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

Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingelanden, um uns beizutreten. Bewerben Sie sich!

A 69-year-old woman presented to the emergency room after experiencing 2 weeks of dizziness. On physical exam she appeared jaundiced, and had hepatomegaly and generalized abdominal tenderness. Rectal exam showed silver-colored stool. She had a hemoglobin level of 7.5 g per deciliter (reference range, 11.0 to 14.5), an elevated total bilirubin level, and an elevated alkaline phosphatase level. What is the diagnosis?

Upper gastrointestinal bleed

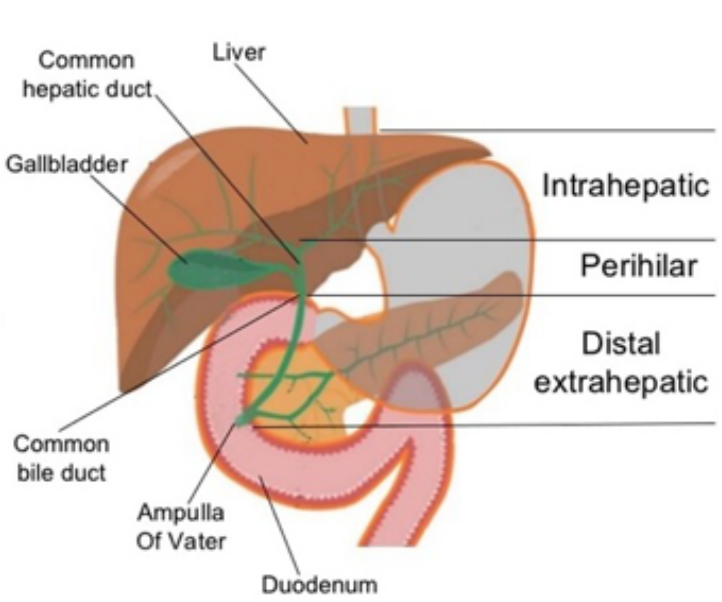
Metastatic colon cancer

Heavy-metal toxicity

Liver cirrhosis

Dubin-Johnson syndrome

Correct!
The correct answer is metastatic colon cancer. The patient was found to have a cecal mass and multiple liver metastases on a computed tomography scan, consistent with metastatic colon cancer. The appearance of silver stool was from a combination of white stool associated with obstructive jaundice and black stool of melena.



Thomas's Sign, or the Silver Stool in Cancer of the Ampulla of Vater

Dr. A. M. Thomas, pathologist to the Royal Masonic Hospital, has pointed out that in cancer involving the ampulla of Vater the patient sometimes passes "silver stools"—that is, motions having the colour of oxidized silver or aluminium paint. The silver or grey stool is a combination of the white stool of obstructive jaundice and the black stool of melaena.

Biliary obstruction, whatever its cause, will produce a clay-coloured stool. Such a stool may contain blood from many sources. If the amount of blood is small it will not colour the stool appreciably. If it is large it will dominate the picture and lead to the typical black stool of melaena, but massive intestinal haemorrhage is either intermittent or fatal. If the blood comes from low down it will be red and not black. The combination of deep jaundice with steady intestinal haemorrhage coming from high up in the intestinal tract is seen regularly in cancer of the ampulla, and only rarely in other conditions.

Case 1

A married woman aged 46 was admitted on September 30, 1952, with a history of intermittent jaundice for three months. She did not appear to have lost weight, but was very anaemic. Tests showed the jaundice to be of the obstructive type, and the stools contained occult blood in large amounts. The barium meal was reported to be normal, apart from spasticity of the pyloric antrum.

A laparotomy was performed on October 16. A carcinoma could be felt at the ampulla. The gall-bladder and common bile duct were grossly distended, and both contained white bile only. Cholecystostomy was performed. The discharge from the drain soon became green in colour. On October 30 pancreatico-duodenectomy was performed with ligature of the stump of the pancreas and implantation of the bile duct in the jejunum. Apart from some blood-stained discharge, convalescence was satisfactory.

Since discharge on January 1, 1953, the patient has remained very well, needing only small doses of insulin. She dislikes fats, but that has benefited two people—her in that she has regained her youthful figure, and me in that she sends me a regular supply of Devonshire cream.

Case 2

A man aged 78 was admitted on February 14, 1954, with a suprapubic fistula, following prostatectomy at another hospital in November, 1953. His haemoglobin level was 50% and his general condition poor. He was given two pints (1,130 ml.) of packed cells, and shortly afterwards developed jaundice which at the time was attributed to the transfusion. His stools were sent for analysis, and Dr. Thomas reported that they had the silvery appearance that he had previously noted in Case 1. On this appearance he made a tentative diagnosis of carcinoma of the ampulla of Vater.

The jaundice deepened and the patient died on February 22 in hepatic failure. At necropsy a carcinoma 3 mm. in diameter was found at the ampulla of Vater. The haemorrhage on which the diagnosis had been made had, however, come from a colonic diverticulum.

Comment

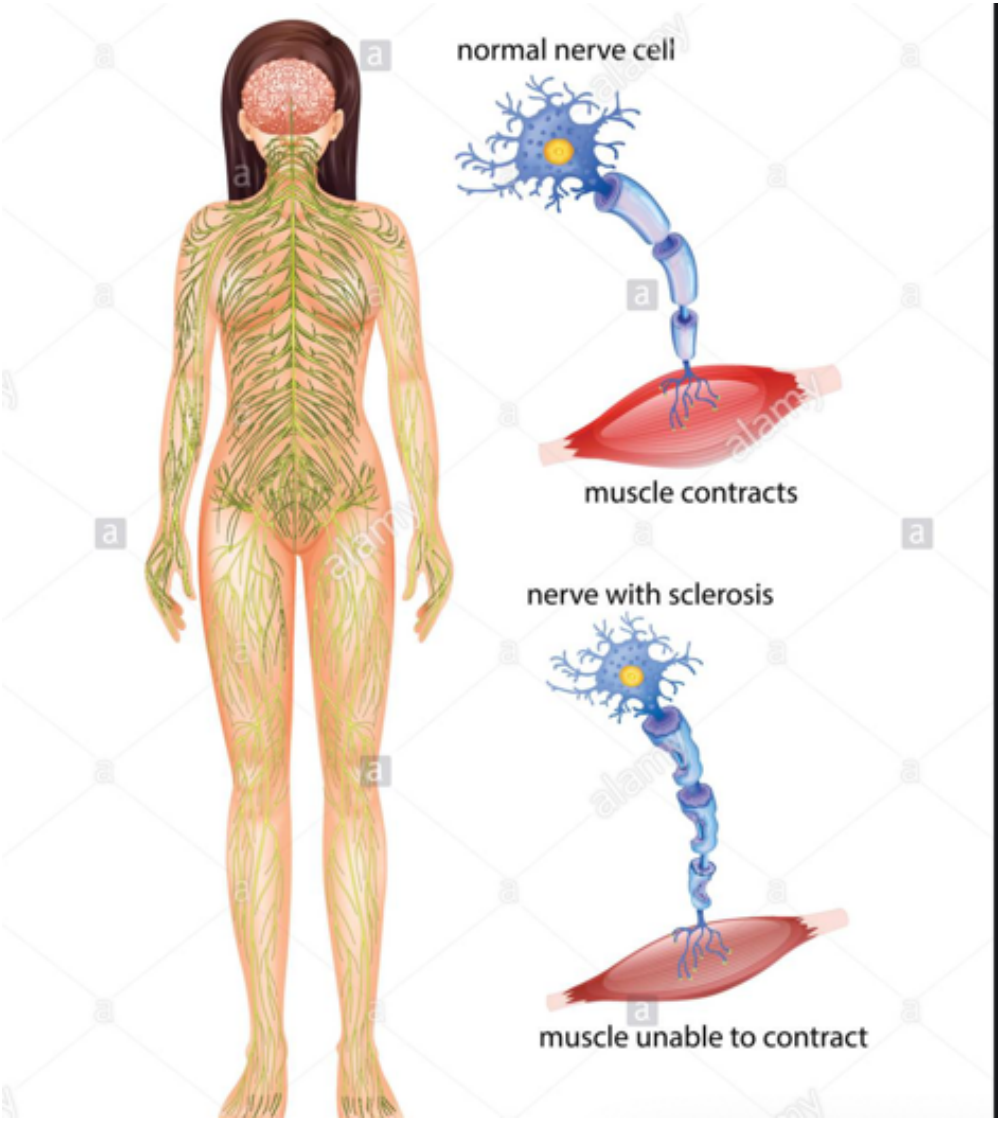
The diagnosis has since been made in two further cases. So far as I am aware the silver stool has never been described before. I bring the sign to the attention of surgeons because Dr. Thomas has not yet reported it himself and, being a pathologist, he is likely to report it in a journal read only by his brother pathologists. Thomas's sign, which can be observed by a house-surgeon or nurse who is aware of its importance, is diagnostic of cancer of the ampulla of Vater, and will enable instances of this eminently curable lesion to be recognized at an early and operable stage.

Heneage Ogilvie, D.M., M.Ch.,
Consulting Surgeon,
Guy's Hospital and Royal Masonic Hospital.

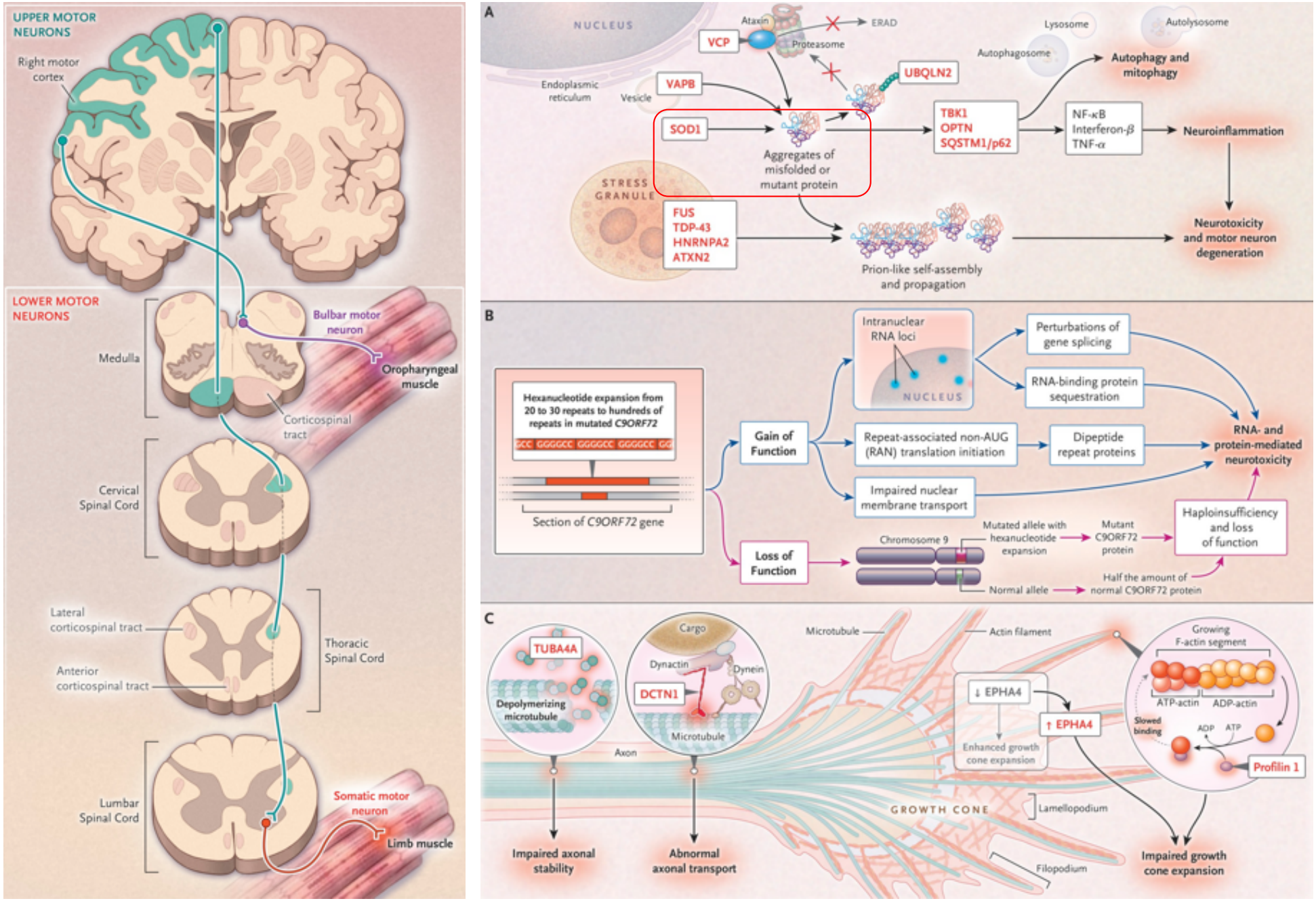
Die amyotrophe Lateralsklerose (ALS) gehört zur Gruppe der Motoneuron-Krankheiten und ist eine nicht heilbare degenerative Erkrankung des motorischen Nervensystems. Das Degenerieren der ersten Motoneurone führt zu einem erhöhten Muskeltonus (spastische Lähmung). Durch Schädigung der zweiten Motoneurone kommt es zu zunehmender Muskelschwäche (Parese bis Plegie), die mit Muskelschwund einhergeht. Dies führt zu einer fortschreitenden Einschränkung bei den Aktivitäten des täglichen Lebens.
Motoneurone bezeichnet. Es können sowohl die so genannten ersten Motoneurone betroffen sein, motorische Nervenzellen, die sich in der motorischen Hirnrinde (motorischer Kortex) befinden, als auch die als zweite Motoneurone bezeichneten Vorderhornzellen des Rückenmarks oder die motorischen Zellen des Hirnstamms in den Hirnnervenkernen. Die Fortsätze (Axone) der ersten Motoneurone ziehen zu den zweiten Motoneuronen, die wiederum mit ihren Fortsätzen zur Skelettmuskulatur ziehen und diese innervieren. Die beiden Formen führen zu etwas unterschiedlichen Symptomen. Das Degenerieren der ersten Motoneurone führt zu einem erhöhten Muskeltonus (spastische Lähmung). Durch Schädigung der zweiten Motoneurone kommt es zu zunehmender Muskelschwäche (Parese bis Plegie), die mit Muskelschwund (Amyotrophie) einhergeht. Durch die Lähmungen der Muskulatur kommt es unter anderem zu Gang-, Sprech- und Schluckstörungen, eingeschränkter Koordination und Schwäche der Arm- und Handmuskulatur und dadurch zu einer fortschreitenden Einschränkung bei den Aktivitäten des täglichen Lebens.

Die amyotrophe Lateralsklerose hat ein – vor allem im Anfangsstadium – sehr variables Krankheitsbild, das durch Degeneration und damit einhergehende Funktionsstörung des ersten und zweiten Motoneurons gekennzeichnet ist. Dies hat Ausfallerscheinungen der Muskulatur zur Folge. Die klinische Symptomatik ist dementsprechend geprägt durch eine Kombination von spastischen und schlaffen Lähmungen der Muskulatur. Je nach Lokalisation der Schädigung der motorischen Bahnen kommt es zur Funktionseinschränkung der Muskulatur der oberen und unteren Extremität,
der bulbären Muskulatur und der Rumpfmuskulatur.

Die Ursache (Ätiologie) der Erkrankung ist unklar. Genetische Faktoren werden bei den meisten ALS-Patienten festgestellt; ob sie die alleinigen Auslöser sind, ist unbekannt. Die meisten Fälle treten sporadisch, das heißt ohne familiäre Häufung, auf (sporadische ALS, sALS). In einem kleinen Teil der Fälle (5–10 %) kommt es jedoch zu einer familiären Häufung (familiäre ALS, fALS). Drei Gruppen von Mutationen in verschiedenen Genen *(TARDBP, C9ORF72, VAPB, FUS, SOD1)* werden in einem Großteil der Fälle gefunden. Sie führen zur pathologischen Anhäufung oder zum vorzeitigen Abbau jeweils eines falsch gefalteten Proteine (TDP-43, FUS oder SOD1), was letztendlich (wie bei den Tautopatien das tau-Protein) die Neurodegeneration auslöst.

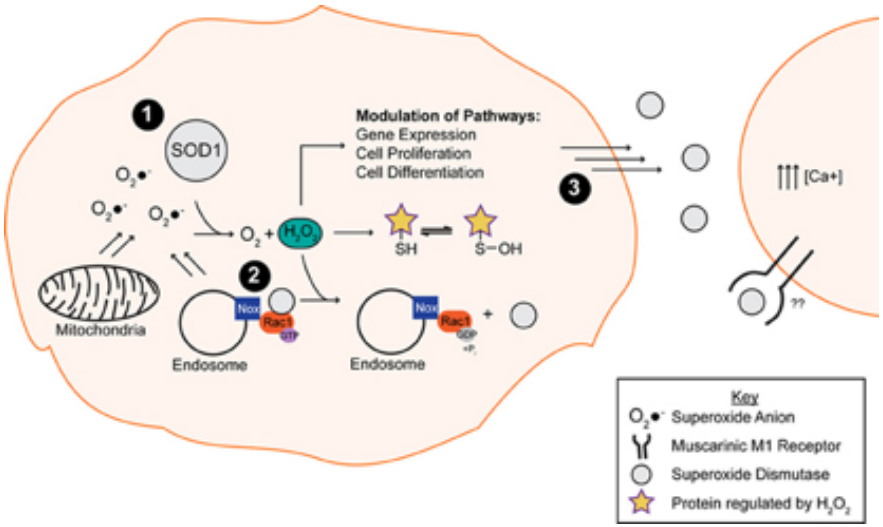


Amyotrophic Lateral Sclerosis N Engl J Med 2017



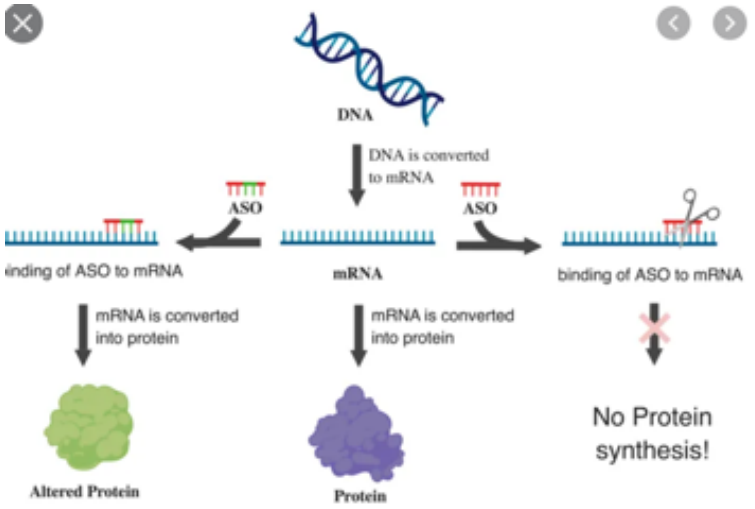
Superoxide dismutase [Cu-Zn] also known as superoxide dismutase 1 or SOD1 is an enzyme that in humans is encoded by the SOD1 gene, located on chromosome 21. SOD1 is one of three human superoxide dismutases. It is implicated in apoptosis and familial amyotrophic lateral sclerosis. SOD1 binds copper and zinc ions and is one of three superoxide dismutases responsible for destroying free superoxide radicals in the body. The encoded isozyme is a soluble cytoplasmic and mitochondrial intermembrane space protein, acting as a homodimer to convert naturally occurring, but harmful, superoxide radicals to molecular oxygen and hydrogen peroxide. Hydrogen peroxide can then be broken down by another enzyme called catalase. Most notably, SOD1 is pivotal in reactive oxygen species (ROS) release during oxidative stress by ischemia-reperfusion injury, specifically in the myocardium as part of a heart attack (also known as ischemic heart disease). Ischemic heart disease, which results from an occlusion of one of the major coronary arteries, is currently still the leading cause of morbidity and mortality in western society. Mutations (over 150 identified to date) in this gene have been linked to familial amyotrophic lateral sclerosis. However, several pieces of evidence also show that wild-type SOD1, under conditions of cellular stress, is implicated in a significant fraction of sporadic ALS cases, which represent 90% of ALS patients. The most frequent mutation are A4V (in the U.S.A.) and H46R (Japan).

Up to 2% of all cases of amyotrophic lateral sclerosis (ALS) result from mutations in the gene encoding superoxide dismutase 1 (*SOD1*). More than 180 different *SOD1* mutations have been identified in ALS. The mechanisms by which mutations in *SOD1* cause degeneration of motor neurons in genetic ALS are not fully understood; a toxic gain of function has been considered to be the most likely mechanism in ALS caused by *SOD1* mutations. Lowering the concentration of mutant SOD1 protein may be a potential target for therapeutic intervention. Antisense oligonucleotides (ASOs) have been generally safe for the treatment of other diseases, including spinal muscular atrophy.



Als Antisense-Oligonukleotide, kurz ASO, bezeichnet man synthetische, kurzkettige, einzelsträngige Nukleinsäuren, die aus wenigen Nukleotiden aus einer frei wählbaren Abfolge von Basen aufgebaut sind. ASO binden über komplementäre Basenpaarung an eine Nukleinsäure, deren Basenabfolge zu ihnen passt (entgegengesetzte Basenpaare - "Anti-Sense"). Antisense-Oligonukleotide finden Verwendung in der Gentechnik und in der Therapie genetisch bedingter Erkrankungen. Durch die spezifische Bindung an die komplementäre Zielsequenz der RNA eines Proteins wird dessen Bildung verhindert. Auch die Modulation von prä-mRNA ist möglich. Exon-Skipping ist momentaner Stand der Forschung zur Heilung verschiedener Erkrankungen, wie der spinalen Muskelatrophie (SMA). Es werden fehlerhafte Mutationen in Exons verändert, sodass das Exon beim Splicing nicht entfernt wird.

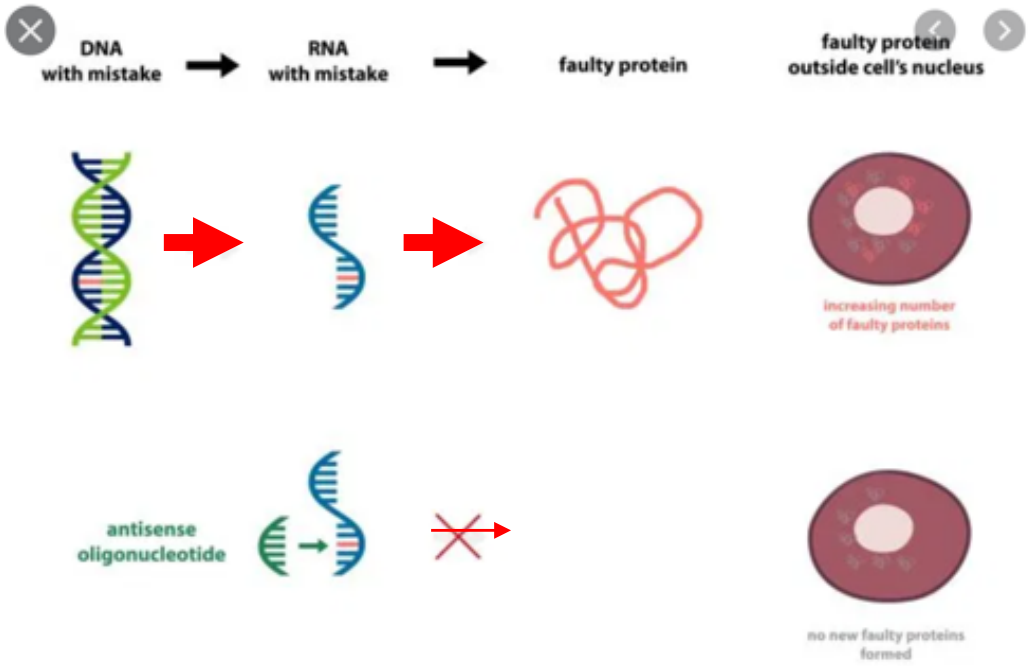
- Eteplirsen
- Fomivirsen
- Inotersen
- Mipomersen
- Nusinersen
- Volanesorsen



Antisense-Oligonucleotide binden nach Einbringung in die Zielzellen an entsprechend komplementäre mRNA, wodurch die Translation und somit auch die Biosynthese des Zielproteins spezifisch verhindert wird.
Der Komplex aus Antisense-DNA-Olignucleotid und dem gebundenen RNA-Strang wird von der RNase H erkannnt, die die RNA enzymatisch spaltet, wodurch das Antisense-DNA-Oligonucleotid frei wird und somit erneut zur Bindung komplementärer RNA zur Verfügung steht.
Kritische Aspekte sind zum einen die Einbringung in die Zellen, denn die negativ geladene DNA überwindet nur schlecht Zellmembranen. Verschiedene lipophile Moleküle haben sich hierbei als hilfreich erwiesen.
Zum anderen werden ungeschützte, kurze DNA-Oligonucleotide in Zellen schnell abgebaut. Um den Abbau zu verhindern oder zumindest zu verlangsamen, werden neben Phosphothioaten verschiedene 2´-Modifikationen erfolgreich eingesetzt.

ALS is a progressive neurodegenerative disorder where damage to and death of motor neurons (the nerve cells that control the movement of muscles) leads to a loss of muscle control and paralysis. The exact cause of the disease is unknown, but some inherited forms of ALS are caused by a mutation in the *superoxide dismutase-1 gene*. *SOD1* encodes for a protein, which neutralizes harmful radical oxygen molecules. Mutations in *SOD1* can cause the enzyme to misfold as it is being made, which may lead to a toxic buildup of misfolded protein.

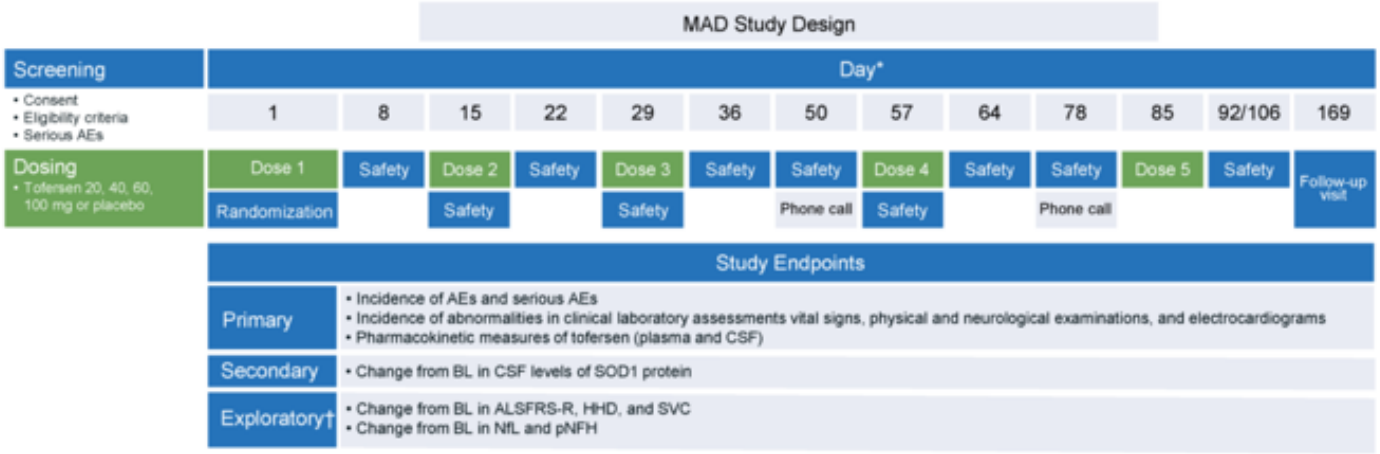
Tofersen is a type of antisense therapy. It is an artificially created piece of DNA that is designed to specifically bind to *SOD1* mRNA (mRNA is a temporary copy of a gene that is used by the machinery of the cell to make protein). By binding to the *SOD1* mRNA, tofersen targets it for degradation and prevents it from being read, thereby stopping SOD1 protein production. By reducing levels of SOD1 protein, tofersen may be able to slow the progression of this form of ALS.



Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS

Tofersen is an antisense oligonucleotide that mediates the degradation of superoxide dismutase 1 (SOD1) messenger RNA to reduce SOD1 protein synthesis. Intrathecal administration of tofersen is being studied for the treatment of amyotrophic lateral sclerosis (ALS) due to *SOD1* mutations. We conducted a phase 1–2 ascending-dose trial evaluating tofersen in adults with ALS due to *SOD1* mutations. In each dose cohort (20, 40, 60, or 100 mg), participants were randomly assigned in a 3:1 ratio to receive five doses of tofersen or placebo, administered intrathecally for 12 weeks. The primary outcomes were safety and pharmacokinetics. The secondary outcome was the change from baseline in the cerebrospinal fluid (CSF) SOD1 concentration at day 85. Clinical function and vital capacity were measured.

Event	Placebo (N=12)	Tofersen, 20 mg (N=10)	Tofersen, 40 mg (N=9)	Tofersen, 60 mg (N=9)	Tofersen, 100 mg (N=10)
	number of participants (percent)				
Any adverse event	12 (100)	10 (100)	9 (100)	9 (100)	10 (100)
Headache	7 (58)	4 (40)	2 (22)	4 (44)	6 (60)
Procedural pain	5 (42)	4 (40)	1 (11)	4 (44)	7 (70)
Post–lumbar puncture syndrome	3 (25)	4 (40)	3 (33)	3 (33)	3 (30)
Fall	3 (25)	3 (30)	3 (33)	2 (22)	5 (50)
Back pain	0	1 (10)	1 (11)	1 (11)	5 (50)
Nasopharyngitis	1 (8)	2 (20)	1 (11)	3 (33)	1 (10)
Upper respiratory tract infection	0	4 (40)	0	2 (22)	0
CSF protein concentration increased	1 (8)	0	0	4 (44)	1 (10)
CSF white-cell count increased	0	0	1 (11)	3 (33)	0
Pain in arm or leg	2 (17)	0	1 (11)	0	3 (30)
Dizziness	3 (25)	0	0	0	1 (10)
Neck pain	3 (25)	0	0	1 (11)	0

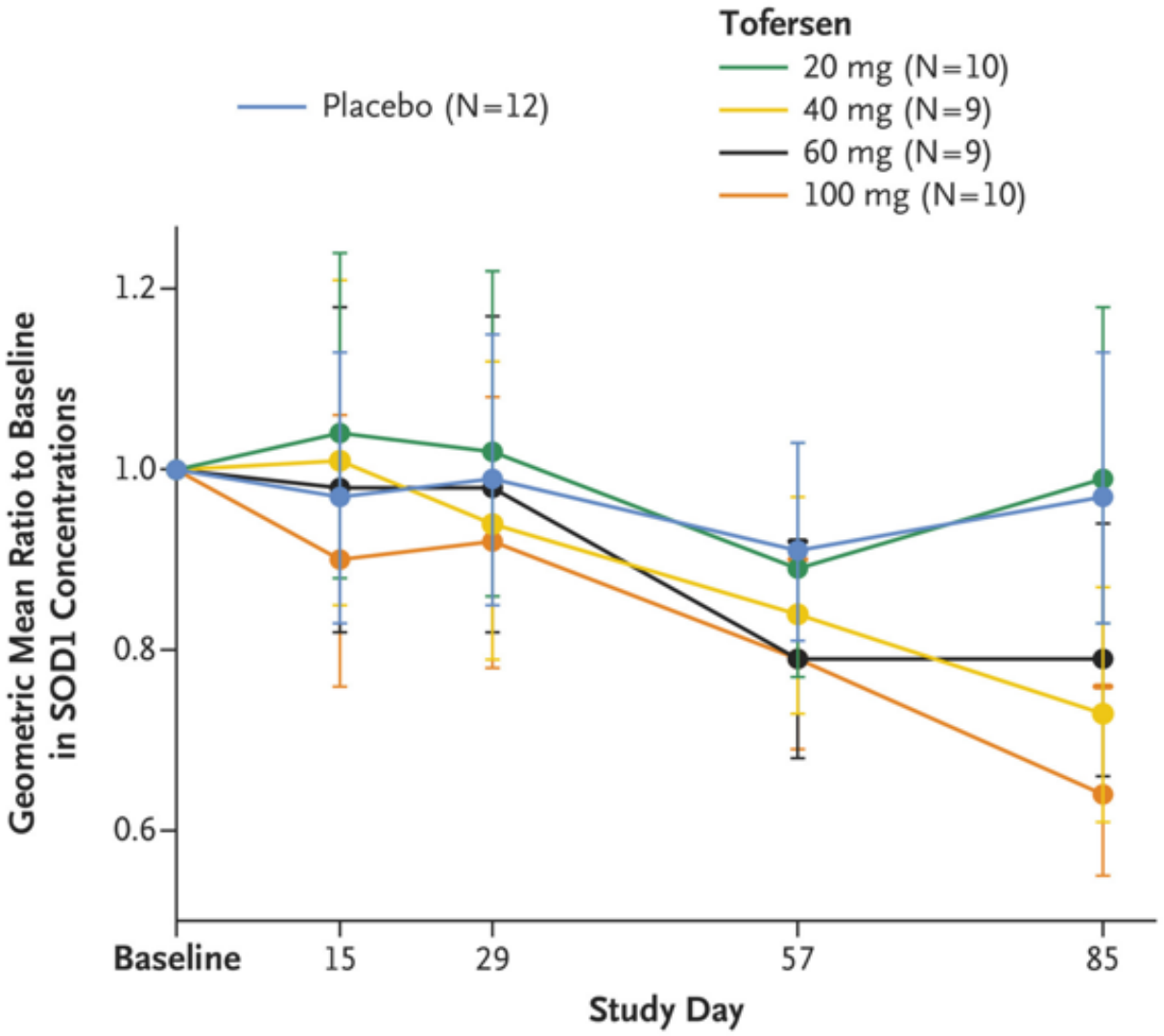


MAD Study Design.

*Single ascending dose study was performed first. †Exploratory outcomes shown were analyzed in this study. Additional exploratory outcomes include changes from baseline (BL) in electrical impedance myography, motor unit number index, ALS Assessment Questionnaire scores, Fatigue Severity Scale scores, EuroQol Five-Dimension Three-Level Questionnaire scores, 36-Item Short Form Health Survey, and Zarit Burden Interview scores, and possible relationships between tofersen pharmacokinetics, CSF SOD1 protein concentrations, and potential biomarker measures including misfolded or mutant *SOD1*, phosphorylated neurofilament heavy chains (pNfH), and neurofilament light chains (NfL). Analyses of these exploratory outcomes are ongoing. Two participants in MAD received an initial dose in the single ascending dose study and enrolled in MAD after a washout period of approximately 20 weeks.

Event	Placebo (N=12)	Tofersen, 20 mg (N=10)	Tofersen, 40 mg (N=9)	Tofersen, 60 mg (N=9)	Tofersen, 100 mg (N=10)
	number of participants (percent)				
Grade†					
1: mild	5 (42)	3 (30)	4 (44)	4 (44)	4 (40)
2: moderate	3 (25)	5 (50)	4 (44)	2 (22)	6 (60)
3: severe or medically significant	3 (25)	1 (10)	1 (11)	2 (22)	0
4: life-threatening	0	0	0	0	0
5: death related to adverse event	1 (8)	1 (10)	0	1 (11)	0
Event related to placebo or tofersen‡	0	2 (20)	2 (22)	6 (67)	4 (40)
Event related to lumbar puncture‡	9 (75)	8 (80)	7 (78)	8 (89)	9 (90)
Serious event	2 (17)	2 (20)	1 (11)	2 (22)	0
Serious event related to placebo or tofersen‡	0	0	0	1 (11)	0
Serious event leading to discontinuation of placebo or tofersen	1 (8)	0	0	0	0
Serious event leading to interruption of trial regimen	0	0	0	0	0
Serious event leading to withdrawal from trial	1 (8)	1 (10)	0	1 (11)	0
Death	1 (8)	1 (10)	0	1 (11)	0

At baseline and during the trial, an elevated CSF protein concentration or CSF pleocytosis (or both) was observed. In the combined placebo group, 1 of 12 participants (8%) had at least one CSF white-cell count of more than 10 cells per cubic millimeter, as compared with 16 of 38 participants (42%) in the combined tofersen groups, with a maximum observed value of 144 white cells per cubic millimeter. Elevations in CSF white-cell count and protein were reported as adverse events in 4 and 5 participants, respectively, who received tofersen; 1 participant who received placebo had an adverse event of elevated CSF protein concentration.

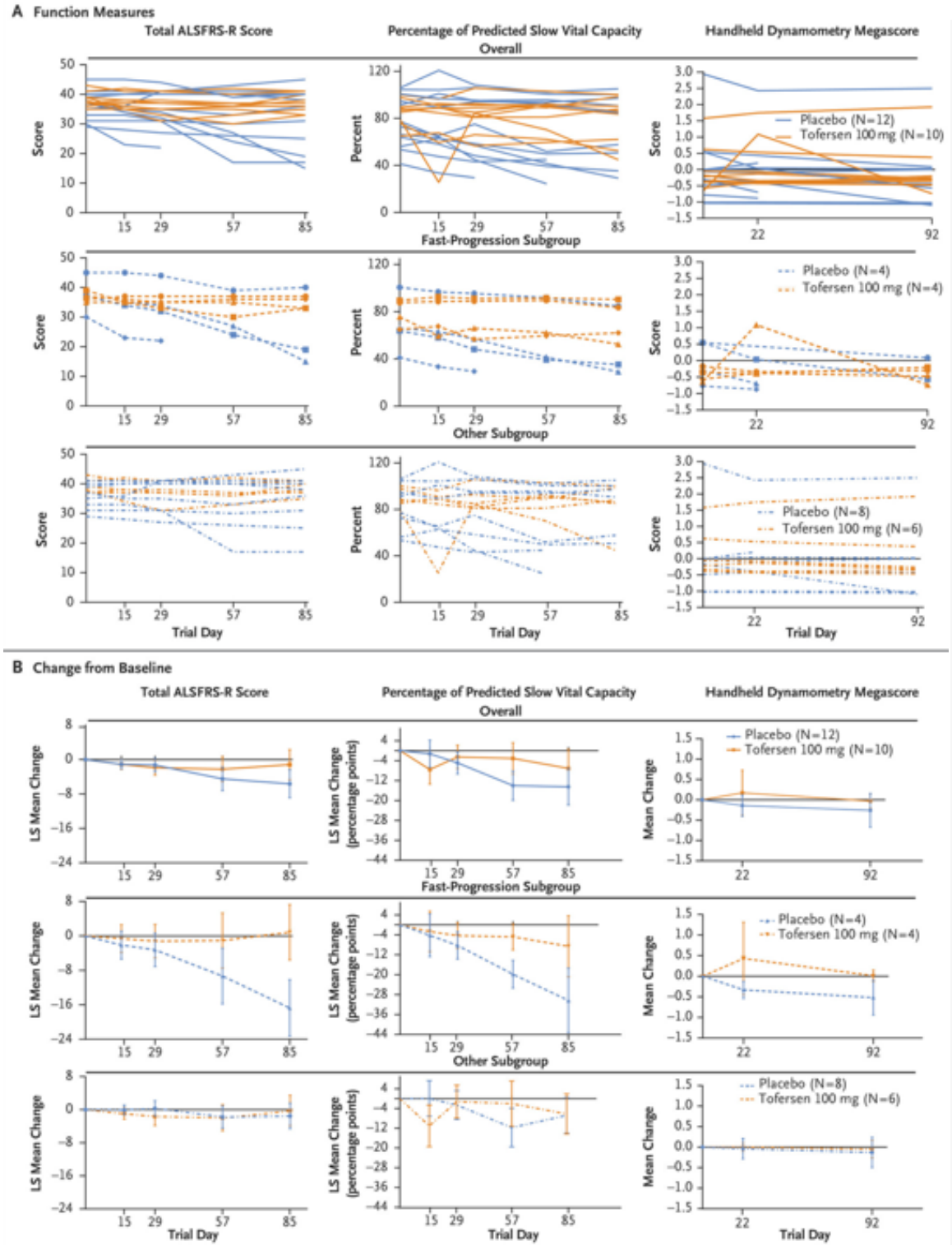


Effect of Tofersen Treatment on Total Superoxide Dismutase 1 (SOD1) Protein Concentrations in Cerebrospinal Fluid.

The geometric mean ratio between the baseline value and the values at the specified time points are shown. Geometric mean ratios were calculated with the use of the least-squares method. I bars indicate 95% confidence intervals. In the combined placebo group, there was one anomaly for a cerebrospinal fluid sample obtained at day 15; the result was below the limit of quantitation and was noted as being missing data. All missing data were imputed with the use of a mixed model for repeated measures.

Clinical Measures of Change in Clinical Function, Respiratory Function, and Muscle Strength.

Outcome	Placebo (N=12)	Tofersen, 20 mg (N=10)	Tofersen, 40 mg (N=9)	Tofersen, 60 mg (N=9)	Tofersen, 100 mg (N=10)
Least-squares mean change in ALSFRS-R score (95% CI) — points					
At day 15	−1.11 (−2.17 to −0.05)	−0.34 (−1.59 to 0.91)	−0.46 (−1.75 to 0.83)	−0.40 (−1.66 to 0.86)	−1.13 (−2.29 to 0.02)
At day 29	−1.29 (−2.88 to 0.30)	−0.88 (−2.73 to 0.96)	−0.69 (−2.56 to 1.19)	−0.82 (−2.68 to 1.04)	−1.91 (−3.65 to 0.17)
At day 57	−4.50 (−7.21 to −1.78)	−0.97 (−4.09 to 2.15)	−1.35 (−4.44 to 1.74)	−1.97 (−5.06 to 1.13)	−2.24 (−5.16 to 0.67)
At day 85	−5.63 (−8.90 to −2.36)	−0.76 (−4.49 to 2.97)	−0.82 (−4.50 to 2.85)	−2.13 (−5.82 to 1.56)	−1.19 (−4.67 to 2.29)
Least-squares mean change in percentage of predicted slow vital capacity (95% CI) — percentage points					
At day 15	−1.21 (−6.66 to 4.25)	0.15 (−5.99 to 6.29)	−2.06 (−8.86 to 4.74)	1.72 (−4.28 to 8.22)	−7.52 (−13.41 to −1.62)
At day 29	−4.88 (−9.29 to −0.47)	0.23 (−4.95 to 5.42)	−1.65 (−7.11 to 3.81)	−0.98 (−6.47 to 4.50)	−2.50 (−7.17 to 2.18)
At day 57	−14.00 (−19.85 to −8.15)	−3.48 (−10.22 to 3.25)	−0.03 (−7.24 to 7.18)	−2.28 (−4.69 to 9.25)	−3.06 (9.32 to 3.20)
At day 85	−14.46 (−21.79 to −7.12)	−9.17 (−17.24 to −1.10)	−6.30 (−15.01 to 2.41)	−0.18 (−8.54 to 8.19)	−7.08 (−14.69 to 0.54)
Mean change in handheld dynamometry megascore — points†					
At day 22	−0.14±0.27	NA	−0.06±0.23	−0.10±0.10	0.17±0.56
At day 92	−0.26±0.42	−0.14±0.20	−0.02±0.30	−0.16±0.26	−0.03±0.18



Panel A shows individual values for the ALSFRS-R scores, the percentage of the predicted slow vital capacity, and handheld dynamometry megascores for all participants over time. The ALSFRS-R measures 12 items in four domains of function, each scored on a scale from 0 to 4, with higher scores indicating better function. Handheld dynamometry measures strength in 16 muscle groups in the arms and legs; z-score normalization was applied to scores, with lower scores indicating worse function. Postbaseline missing values were imputed with the use of a mixed model for repeated measures for the ALSFRS-R score and the percentage of the predicted slow vital capacity; the last-observation-carried-forward method was used for the handheld dynamometry megascore. Baseline values were not carried forward, which resulted in missing data at day 22 for three participants in the placebo group (one in the fast-progression subgroup and two in the other subgroup, which included participants who did not meet the criteria for fast-progressing disease). The two subgroups were defined post hoc, and no conclusions can be drawn from these data. Panel B shows the least-squares (LS) mean total ALSFRS-R scores, the LS mean percentage of the predicted slow vital capacity, and the raw mean handheld dynamometry megascore in the 100-mg dose group and the placebo group, overall and in the two subgroups. In the graphs for the ALSFRS-R score and slow vital capacity, I bars indicate 95% confidence intervals; in the handheld dynamometry megascore graphs, I bars indicate 1 SD.

Discussion

In this trial of the SOD-1 mRNA-targeting ASO tofersen, adverse events were headache, procedural pain, post–lumbar puncture syndrome, falls, back pain, pain in an arm or leg, dizziness, and neck pain, many of which were attributable to the lumbar puncture that was required for administration of tofersen or placebo. Increased CSF protein and white-cell counts were also observed. The cause of CSF pleocytosis and protein elevations remains unclear. Although myelitis with sensory and motor deficits was not seen in this trial, the clinical syndrome has been observed in the context of tofersen administration (unpublished data from the ongoing phase 3 [part C] portion of our trial and the long-term extension study [ClinicalTrials.gov number, NCT03070119. opens in new tab]). The underlying cause of myelitis and the relationship to CSF pleocytosis and protein elevations are unknown. Changes in CSF variables and any manifestations of central nervous system inflammation are being monitored in part C of our trial and in the ongoing extension study.

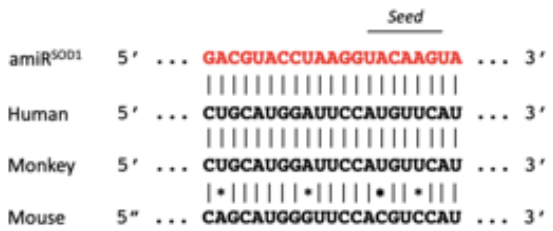
The reduction from baseline in the total CSF SOD1 concentration was 3% in the placebo group and 36% in the group that received 100 mg of tofersen (the highest-dose group), with reductions in the lower-dose tofersen groups ranging from 1% to 27%. There was no multiplicity adjustment of confidence intervals for the CSF SOD1 analyses, so no quantitative inferences can be made from these data. The highest concentrations of tofersen in plasma and CSF were observed with the 100-mg dose of tofersen. In post hoc analyses, there were no apparent differences in the baseline concentrations or magnitude of total reduction in the SOD1 concentration in CSF between participants with fast-progressing disease and other participants. The decrease in the SOD1 protein concentration was most apparent after 57 days. Data from animal models suggest that ASOs can lower SOD1 protein concentrations by more than 75% in the spinal cord, but it is unknown how the reduction in the SOD1 concentration in CSF in the current trial translates into a reduction of SOD1 concentration in central nervous system parenchymal tissues.

This trial was not powered to test an effect on clinical or biologic measures beyond the reduction in SOD1 concentration in CSF. With regard to some exploratory outcomes, there may have been evidence of a slowing in the decrease in the ALSFRS-R score, the slow vital capacity, and the handheld dynamometry megascore with the 100-mg dose of tofersen, although no conclusions can be drawn from these descriptive outcomes. With cessation of the 100-mg dose of tofersen, smaller decreases in the SOD1 concentration in CSF, neurofilament light chains, and phosphorylated neurofilament heavy chains and greater decreases in the ALSFRS-R score were observed than during the intervention period.

SOD1 Suppression with Adeno-Associated Virus and MicroRNA in Familial ALS

Summary

Two patients with familial amyotrophic lateral sclerosis (ALS) and mutations in the gene encoding superoxide dismutase 1 (*SOD1*) were treated with a single intrathecal infusion of adeno-associated virus encoding a microRNA targeting SOD1. In Patient 1, SOD1 levels in spinal cord tissue as analyzed on autopsy were lower than corresponding levels in untreated patients with SOD1-mediated ALS and in healthy controls. Levels of SOD1 in cerebrospinal fluid were transiently and only slightly lower in Patient 1 but were not affected in Patient 2. In Patient 1, meningoradiculitis developed after the infusion; Patient 2 was pretreated with immunosuppressive drugs and did not have this complication. Patient 1 had transient improvement in the strength of his right leg, a measure that had been relatively stable throughout his disease course, but there was no change in his vital capacity. Patient 2 had stable scores on a composite measure of ALS function and a stable vital capacity during a 12-month period. This study showed that intrathecal microRNA can be used as a potential treatment for SOD1-mediated ALS.



Sequence of amiR^{SOD1}. The nucleic acid sequence of amiR^{SOD1} is fully complementary to human and monkey but not mouse SOD1. The asterisks denote mismatches with the mouse sequence. The amiR^{SOD1} sequence is incorporated into the stem of the cellular microRNA mir-155, which is then incorporated into AAVrh10. The label in italics highlights the seed sequence, which is critical for amiR^{SOD1} binding to the target mRNA. Modified from Ref 2.

Patient 1.

During the month of February 2017, Patient 1, a 22-year-old man, began to notice weakness in his left leg. He had the same *SOD1* missense mutation replacing alanine with valine at position 5 (*SOD1*-A5V) as his mother, who had died from ALS at the age of 45 years. In March 2017, his slow vital capacity was 100% of the predicted value, and his ALSFRS-R score was 42.

On July 19, 2017, he received a single intrathecal infusion of 4.2×10^{14} vector genomes of AAV-miR-SOD1 along with an intravenous bolus of methylprednisolone (1.0 g); the latter was repeated the following day.

Three weeks after the infusion, he had transient tingling in both hands, and 1 week later, he reported having a feeling of painful “electric shocks” in his left foot. The prednisone dose, which had been tapered to 10 mg per day, was increased to 30 mg. At 8 weeks, the CSF had 23 white cells per cubic millimeter and a protein level of 342 mg per deciliter.

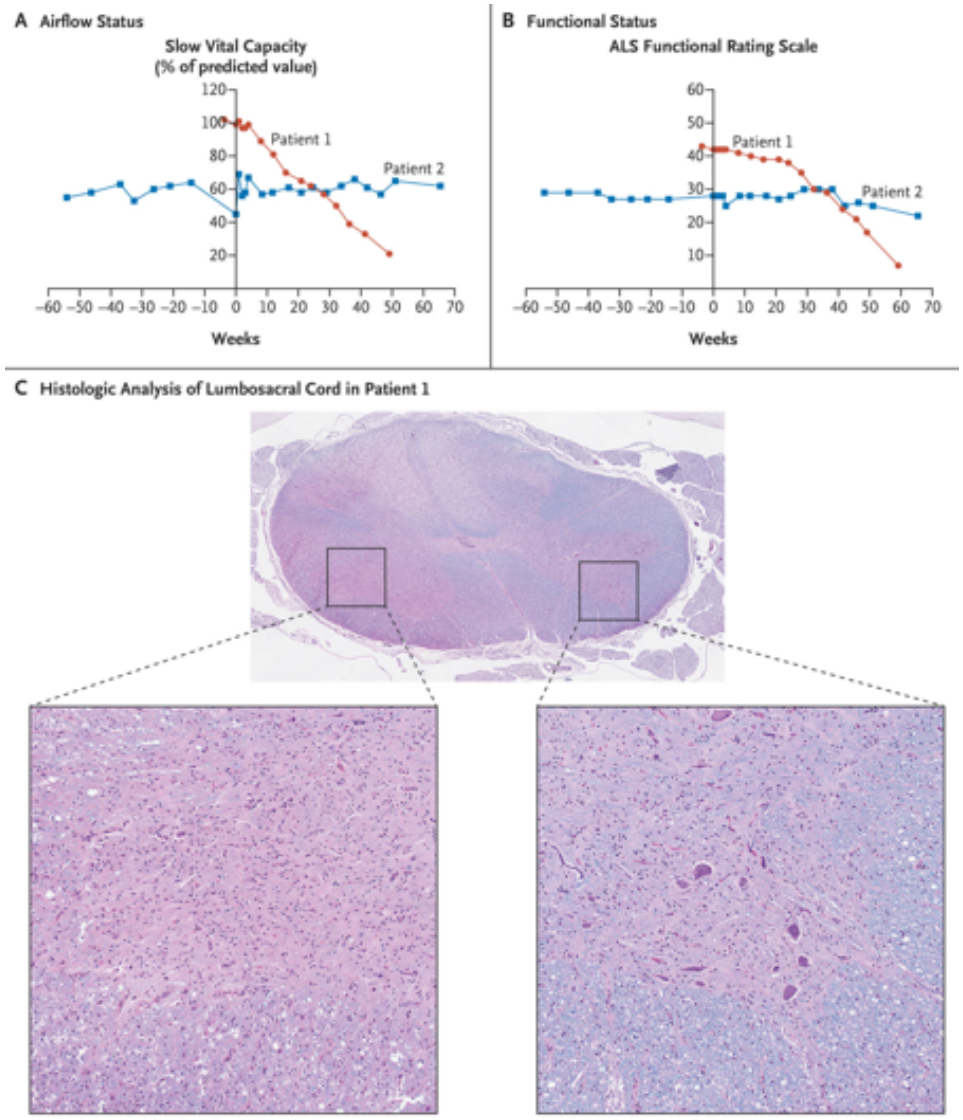
Twenty-four weeks after treatment (46 weeks after the onset of ALS symptoms), the patient’s ALSFRS-R score was reduced to 38 from the baseline level of 42. The loss of strength in the left leg continued, with left hip flexion and extension of MRC grade 0 and grade 2, respectively. Scores for strength of extension and flexion of the left knee were absent, whereas scores for extension and flexion of the right knee were 85% and 61%, respectively, with both scores better than at 20 weeks. At 36 weeks after treatment, flexion of the right knee was 100% of the predicted value on dynamometry.

At 41 weeks, the extension and flexion of the right knee were 90% and 56%, respectively, of the predicted values. The CSF showed 8 white cells per cubic millimeter, and the protein level was 99 mg per deciliter (Table S1). At 12 months after treatment (nearly 18 months after the onset of ALS symptoms), he could propel himself in a wheelchair using the right leg, and vital capacity was reduced to 21% of the predicted value. At 14 months, he regained the ability to extend and flex the fingers of the left hand, a function that had been absent for the previous 20 weeks. Subsequently, he received continuous noninvasive ventilation and died of respiratory arrest 15.6 months after the initiation of treatment and 20.5 months after the onset of ALS symptoms.

The results of autopsy performed 4 hours after death showed a loss of motor neurons in the cervical, thoracic, and left lumbosacral spinal cord but relative sparing of motor neurons in the right lumbosacral spinal cord as gauged visually; this finding corresponded to the preservation of some strength in his right leg.

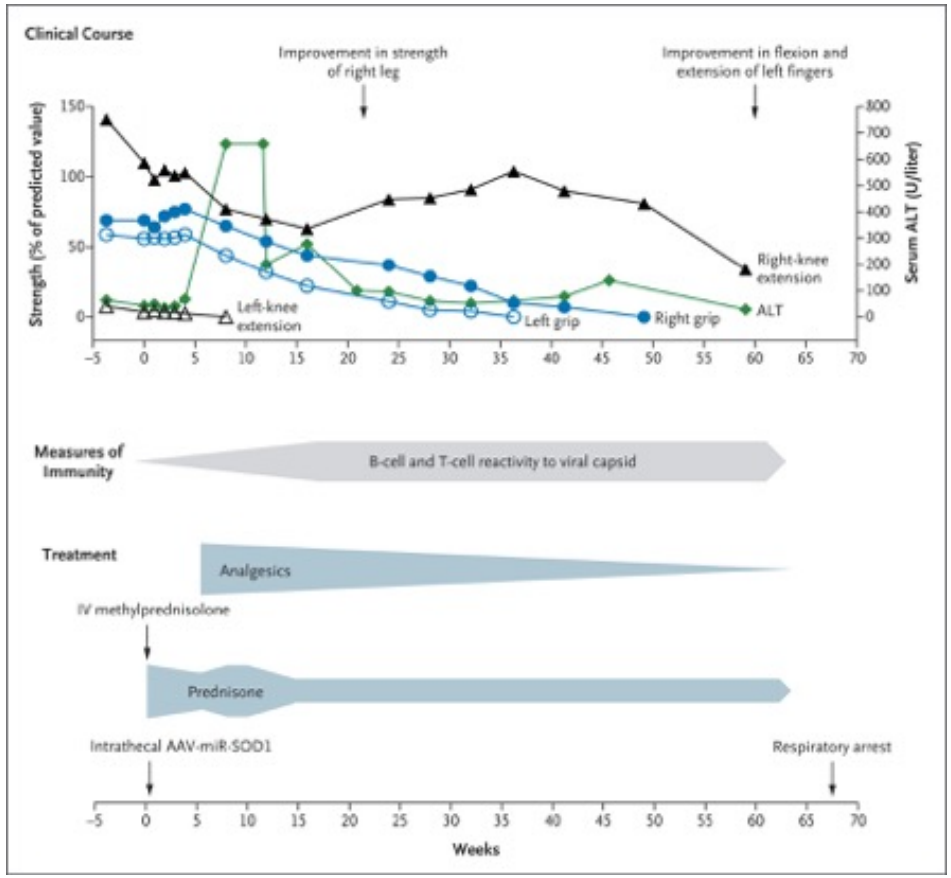
On Western immunoblotting, the ratio of SOD1 to actin in a sample of lumbosacral spinal cord obtained from Patient 1 was 0.25, which was more than 90% lower than the level either in five samples obtained from other patients who had ALS.

Slow Vital Capacity, Functional Status, and Histologic Analysis of Spinal Cord in the Study Patients.

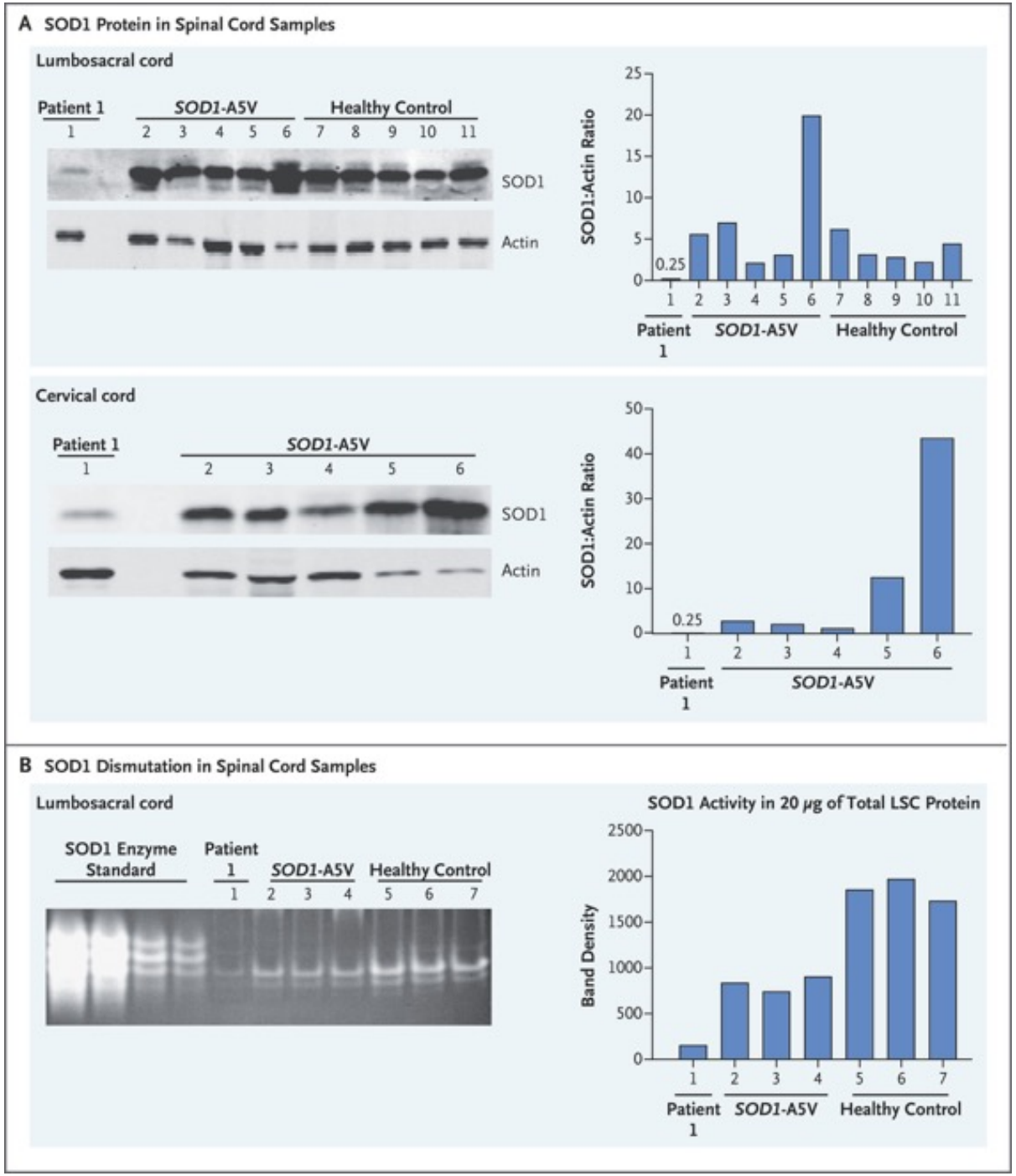


Shown are the results of evaluations involving two patients with familial amyotrophic lateral sclerosis (ALS) and mutations in the gene encoding superoxide dismutase 1 (*SOD1*), who were treated with an intrathecal infusion of an adeno-associated virus rh10 containing anti-SOD1 microRNA (AAV-miR-SOD1). Results are shown for Patients 1 and 2 before and after treatment with respect to slow vital capacity (Panel A) and functional status (Panel B). Scores on the ALS Functional Rating Scale range from 0 to 48 points, with higher scores indicating better function. Panel C shows the results of histologic analysis of a lumbosacral-cord sample obtained from Patient 1 on autopsy. This analysis reveals the relative preservation of motor neurons in the right-side hemisection of the spinal cord (at right) as compared with the left-side hemisection (at left) (hematoxylin and eosin staining).

Time Course of Clinical Events, Immune Reaction, and Treatment in Patient 1.



The top portion of the graph shows the time course of dynamometric measurement on the Accurate Test of Limb Isometric Strength with respect to the patient's grip on the right side (blue solid circles) and left side (blue open circles), as well as knee extension on the right side (black solid triangles) and left side (black open triangles). The dynamometric force is presented as a fraction of the predicted value as compared with normalized data for age- and sex-matched controls. The time course of the increase in the alanine aminotransferase (ALT) level is also shown (green diamonds), as measured on the y axis at right. In the graphs below are shown the time course and approximate extent of the increase in levels of B cells and T cells (gray shading) and the time course of treatments (blue shading). Arrows on the timelines indicate the timing of the intrathecal infusion of AAV-miR-SOD1, the intravenous (IV) administration of methylprednisolone, and the patient's terminal respiratory arrest.



Western Immunoblot Analysis of SOD1 Protein in Spinal Cord.

Panel A shows the results of Western immunoblot analysis of SOD1 and actin proteins (the latter as a control) in samples obtained from Patient 1. The upper portion of the panel shows the results of the analysis of lumbosacral cord (LSC) obtained from Patient 1, from five patients with ALS who had a *SOD1* missense mutation replacing alanine with valine at position 5 (*SOD1*-A5V), and from five controls. The lower portion of the panel shows the results of analysis of cervical cord obtained from Patient 1 and from five patients with *SOD1*-A5V. The histograms at right present the ratios of band densities of SOD1 to actin for each Western blot. Panel B shows the SOD1 dismutation activity in lumbosacral cord obtained from Patient 1, from three patients with *SOD1*-A5V, and from three controls. Gel activity is shown on the left, and gel quantification is shown in the graph on the right. Standard methods were used for Western immunoblotting[12] and for assays of SOD1 enzyme activity.[13]

Patient 2

Patient 2 was a 56-year-old man with a family history of ALS who had a homozygous missense mutation in *SOD1* that replaced aspartate with alanine at position 91 (D91A–D91A). In the autumn of 2013, he first noted distal weakness in both legs; in November 2017, the examination showed bilateral wrist-extension weakness (MRC grade, 3) and reduced hip-flexion strength (MRC grade, 2). He had Babinski signs and excessively reactive finger jerks to percussion. Sensory function was normal. As a result of the meningoradiculitis that developed after treatment in Patient 1, we aimed to suppress B-cell activity and T-cell function with rituximab (at a dose of 375 mg per square meter of body-surface area), which was initiated in late August 2018 in weekly intravenous infusions for 3 weeks and with intravenous methylprednisolone (at a dose of 125 mg before each dose of rituximab and 1 g on the day of AAV-miR-SOD1 infusion). Beginning at the initiation of study treatment, the patient began receiving daily oral sirolimus (6 mg). The day after treatment, oral prednisone (0.5 mg per kilogram of body weight) was initiated; sirolimus and prednisone were continued for 6 months.

On September 17, 2018, he received an intrathecal infusion of 4.2×10^{14} vector genomes of AAV-miR-SOD1. During the year before therapy, his functional status had been stable, with ALSFRS-R scores averaging close to 28; during testing that was conducted 60 weeks after treatment, the score was 24, signifying worse overall function. For a year before treatment, his slow vital capacity had ranged from 42 to 58% of the predicted value; at 65 weeks after therapy, the value was 62%. On the day after treatment and at weeks 12 and 17, he received intravenous immune globulin (at a dose of 0.4 mg per kilogram) in response to a decrease in the serum IgG to a level of less than 700 mg per deciliter, which had been induced by rituximab. In contrast to the clinical course of Patient 1, the immunosuppressive regimen in Patient 2 blunted the generation of neutralizing antibodies, antiviral antibodies, and T-cell response to the viral capsid. Patient 2 did not have elevated hepatic aminotransferase levels, sensory dysfunction, or CSF pleocytosis. As of May 18, 2020, his disease course was stable, with a functional measure of 24 at 90 weeks after treatment.

Discussion

We designed this study to evaluate the safety of the AAV-mediated silencing of mutated genes in two selected patients with ALS, with descriptive and some objective measures of clinical function and biologic effects of SOD1 levels on tissue and CSF. In Patient 1, a single intrathecal dose of AAV-miR–SOD1 resulted in levels of SOD1 in the spinal cord that were lower than levels in samples obtained from other patients with *SOD1* mutations and from controls. However, the viral vector therapy had no effect on SOD1 levels in the CSF. In this patient, we cannot determine whether the strength in his right leg remained stable or improved slightly after treatment, since that limb had normal strength at the beginning of the study and had been relatively strong throughout his course of treatment. There was similar ambiguity in the interpretation of the corresponding preservation of motor neurons on the right side of the lumbosacral spinal cord (as compared with a lack of preservation on the left side) on autopsy.

The experience with this patient indicates that intrathecal infusion of this viral vector can trigger an adverse inflammatory response, as has been reported in some studies after the intravenous administration of AAV9 in animals. In Patient 2, we attenuated this effect with immunosuppression, although viral vector therapy provided him with no clinical benefit. His functional status and vital capacity were relatively stable during a 60-week period, a course that could be typical of the slow disease progression in patients with his *SOD1* genotype, so no clinical conclusions can be made about the treatment effects.

These results suggest that the intrathecal infusion of AAV-delivered microRNAs can be accomplished but may require the use of immunosuppression. Although attenuation of SOD1 protein levels in CSF has been seen with antisense oligonucleotides, we did not find this result at 2 weeks after the initiation of treatment in our study. A theoretical advantage of viral vector–mediated gene suppression is the potential for the sustained effect of a single dose of therapy, which is balanced by the possibility that viral vectors may mediate long-lasting adverse effects. Additional studies are required to determine the results of this method in a larger number of patients who have ALS with *SOD1* mutations.

A Randomized Trial of a Multifactorial Strategy to Prevent Serious Fall Injuries

Injuries from falls are major contributors to complications and death in older adults. Despite evidence from efficacy trials that many falls can be prevented, rates of falls resulting in injury have not declined. We conducted a pragmatic, cluster-randomized trial to evaluate the effectiveness of a multifactorial intervention that included risk assessment and individualized plans, administered by specially trained nurses, to prevent fall injuries. A total of 86 primary care practices across 10 health care systems were randomly assigned to the intervention or to enhanced usual care (the control) (43 practices each). The participants were community-dwelling adults, 70 years of age or older, who were at increased risk for fall injuries. The primary outcome, assessed in a time-to-event analysis, was the first serious fall injury, adjudicated with the use of participant report, electronic health records, and claims data. We hypothesized that the event rate would be lower by 20% in the intervention group than in the control group.

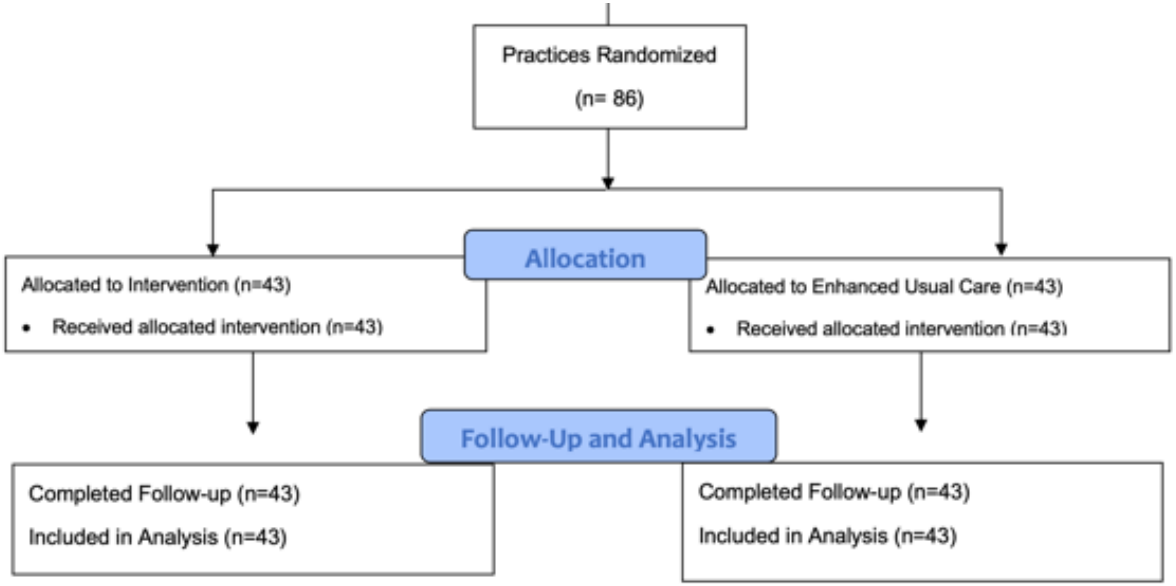


Figure S1 Legend. The enrollment of primary care clinical practices, allocation of practices to the intervention or enhanced usual care arms, and follow-up through the study are shown. All 86 practices completed study follow-up and were included in the analysis.

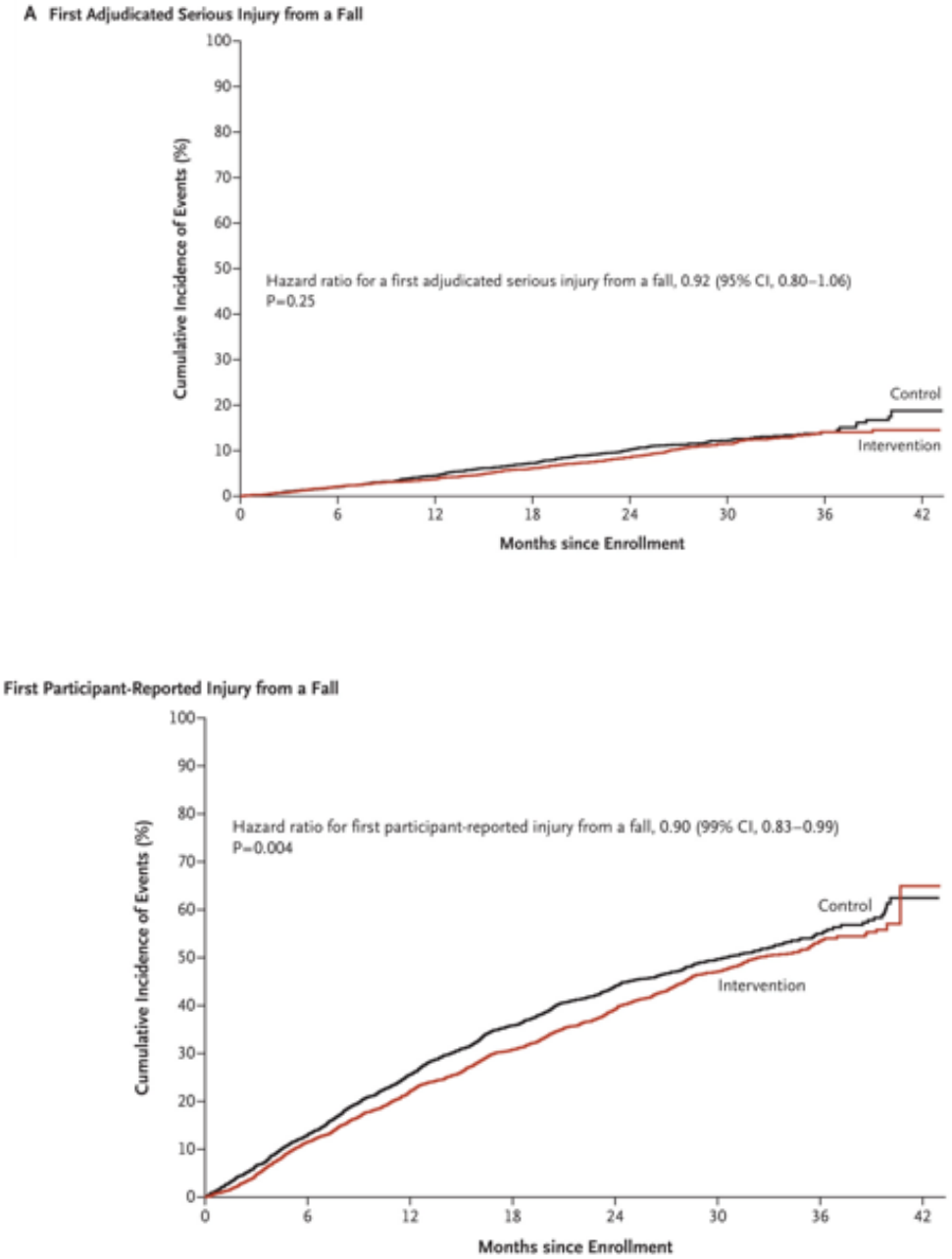
The intervention included five components.

1. The first component was a standardized assessment of seven modifiable risk factors for fall injuries (impairment of strength, gait, or balance; use of certain medications; postural hypotension; problems with feet or footwear; vision impairment; osteoporosis or vitamin D deficiency; and home safety hazards).
2. The second was standardized protocol-driven recommendations for management of risk factors that were explained to the participant, caregiver, or both with the use of motivational interviewing.
3. The third was the development of an individualized care plan, initially focused on one to three risk factors, that was approved by primary care providers.
4. The fourth was implementation of the care plan, including referrals to community-based programs, if needed.
5. The fifth was follow-up care, which was conducted by telephone or in person. The risk factors for fall injuries were reassessed annually, and the care plan was revised, as needed.

Characteristic	Intervention (N = 2802)	Control (N = 2649)
Age — yr	79.9±5.7	79.5±5.8
Female sex — no. (%)	1752 (62.5)	1629 (61.5)
Race — no. (%)†		
White	2571 (91.8)	2394 (90.4)
Black	128 (4.6)	164 (6.2)
Other or unknown	103 (3.7)	91 (3.4)
Hispanic ethnic group — no. (%)†	196 (7.0)	211 (8.0)
Educational level — no. (%)		
High school graduate or less	602 (21.5)	643 (24.3)
Some college or equivalent	697 (24.9)	659 (24.9)
College graduate or higher	1502 (53.6)	1343 (50.7)
Unknown	1 (<0.1)	4 (0.2)
Chronic coexisting conditions‡		
No. per participant	2.1±1.3	2.1±1.3
Fracture other than of the hip after 50 yr of age — no. (%)	918 (32.8)	876 (33.1)
Hip fracture after 50 yr of age — no. (%)	132 (4.7)	119 (4.5)
Clinically significant cognitive impairment — no. (%)§	85 (3.0)	75 (2.8)
Use of a mobility aid or inability to ambulate — no. (%)	972 (34.7)	909 (34.3)
Response to screening questions regarding risk of fall injuries — no. (%)		
Fell two or more times in the past year	1015 (36.2)	896 (33.8)
Had a fall-related injury in the past year	1089 (38.9)	1031 (38.9)
Was afraid of falling because of problems with walking or balance	2405 (85.8)	2273 (85.8)
Had a fear of falling only, with a negative response to the other three questions	1341 (47.9)	1284 (48.5)
No. of positive responses to screening questions regarding fall injuries — no. (%)		
1	1634 (58.3)	1571 (59.3)
2	629 (22.4)	605 (22.8)
3	539 (19.2)	473 (17.9)

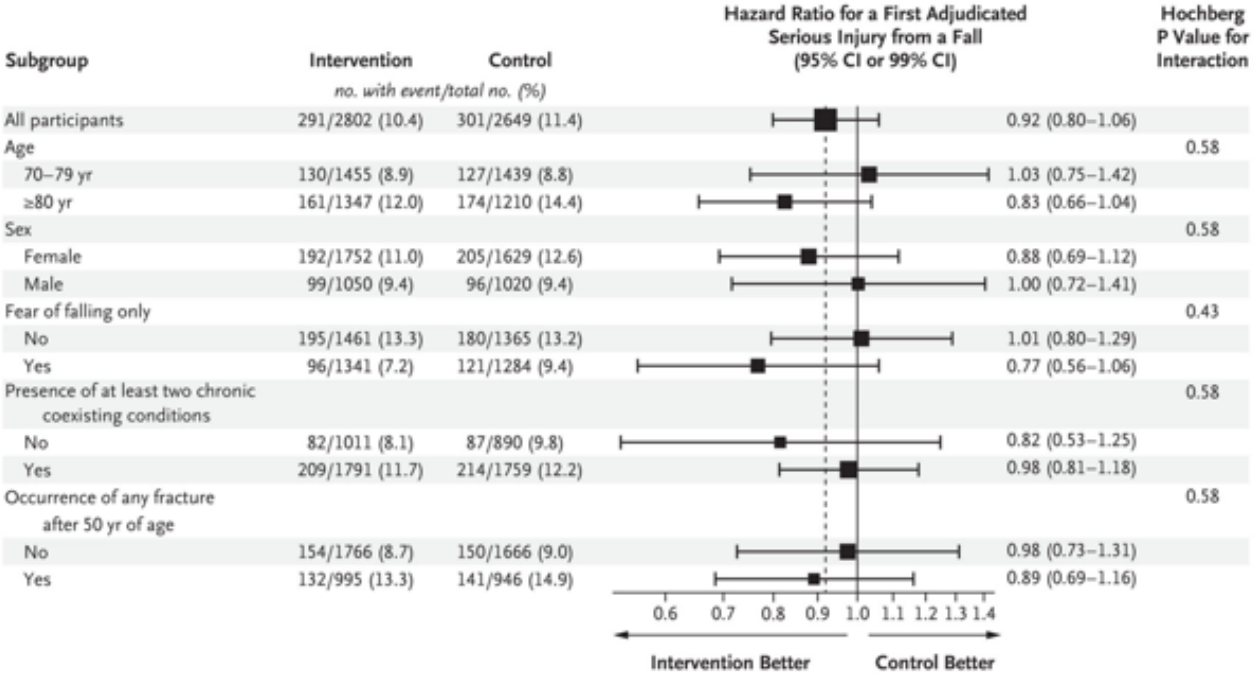
Risk Factor Assessment and Prioritization among Participants in the Intervention Group.

Risk Factor	Participants Assessed for Risk Factors†	Participants Assessed and Determined to Have Risk Factor	Participants Who Had Risk Factor and Prioritized Risk Factor	Participants Who Prioritized Risk Factor and Agreed to Address Risk Factor
		no./total no. (%)		
Use of certain medications	2402/2404 (99.9)	819/2402 (34.1)	429/819 (52.4)	234/429 (54.5)
Impairment of strength, gait, or balance	2354/2404 (97.9)	2354/2354 (100)	2252/2354 (95.7)	2148/2252 (95.4)
Postural hypotension	2331/2404 (97.0)	470/2331 (20.2)	437/470 (93.0)	281/437 (64.3)
Problems with feet or footwear	2375/2404 (98.8)	1478/2375 (62.2)	1226/1478 (82.9)	749/1226 (61.1)
Osteoporosis or vitamin D deficiency	2402/2404 (99.9)	2320/2402 (96.6)	2001/2320 (86.2)	1482/2001 (74.1)
Vision impairment	2399/2404 (99.8)	2086/2399 (87.0)	1831/2086 (87.8)	1403/1831 (76.6)
Home safety hazards	2400/2404 (99.8)	680/2400 (28.3)	548/680 (80.6)	341/548 (62.2)
Any risk factor	2404/2404 (100)	2402/2404 (99.9)	2379/2402 (99.0)	2265/2379 (95.2)



Cumulative Incidence of a First Adjudicated Serious Fall Injury and a First Participant-Reported Fall Injury.

The cumulative incidence curves are plotted to the last event time in each treatment group. The cumulative incidence of a first adjudicated serious fall injury over the course of 3.5 years was 15% in the intervention group (95% bootstrap CI, 13 to 16) and 19% in the control group (95% CI, 14 to 24) (Panel A). The cumulative incidence of a first participant-reported fall injury over the course of 3.5 years was 65% in the intervention group (99% CI, 53 to 80) and 63% in the control group (99% CI, 56 to 71) (Panel B).



The effect of the intervention on the first adjudicated serious fall injury was evaluated in five prespecified subgroups with the use of tests of interaction. Adjustment for multiple comparisons was made with the use of the Hochberg procedure to preserve an overall two-sided type 1 error rate at 0.05. The point estimates of the hazard ratio and the associated confidence intervals (95% for the overall analysis and 99% for each subgroup) are shown. Participants in the "Fear of falling only" subgroup had a negative response to all the fall-related screening questions except the question about whether they had a fear of falling. The dashed vertical line represents the hazard ratio for the overall intervention effect. The size of each black square is proportional to the total number of participants in the subgroup.

Outcome of Serious Adverse Event	Intervention (N=2802)*			Control (N=2649)*			Adjusted Ratio (95% CI)†	P Value
	Participants	Events	Rate‡	Participants	Events	Rate‡		
	no. (%)	*no.*		*no. (%)*	*no.*			
Death	235 (8.4)	235	3.3	220 (8.3)	220	3.3	1.01 (0.84–1.23)	0.88
Hospitalization	1139 (40.6)	2344	32.8	1108 (41.8)	2246	33.3	0.98 (0.92–1.04)	0.47

Fall Injury Prevention in Older Adults

MULTICENTER, CLUSTER-RANDOMIZED, PRAGMATIC TRIAL

86
Primary care practices with patients at risk for fall injuries

Multifactorial Intervention

N=43

Enhanced Usual Care

N=43

Serious fall injury rate
(injuries per 100 person-yr of follow-up)

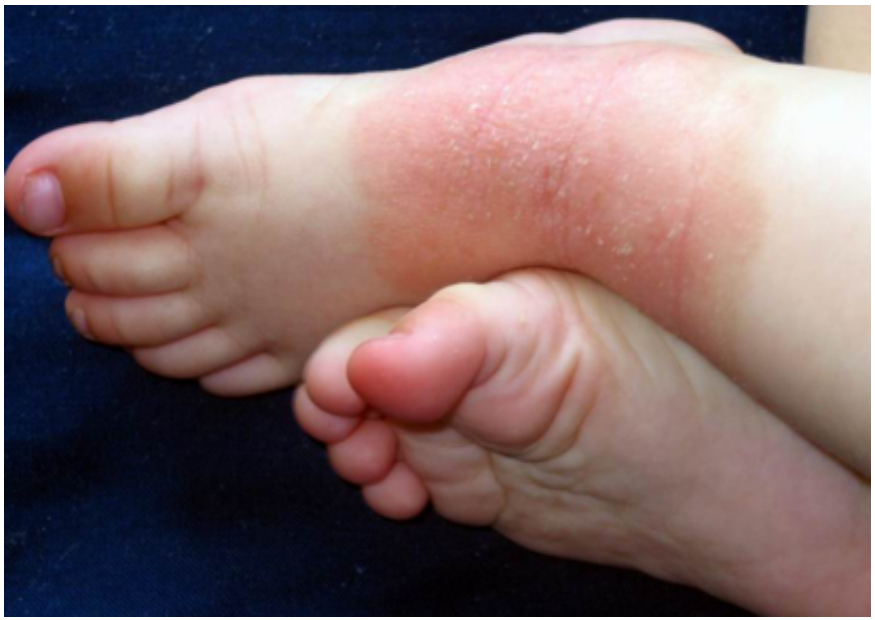
4.9 Fall injuries

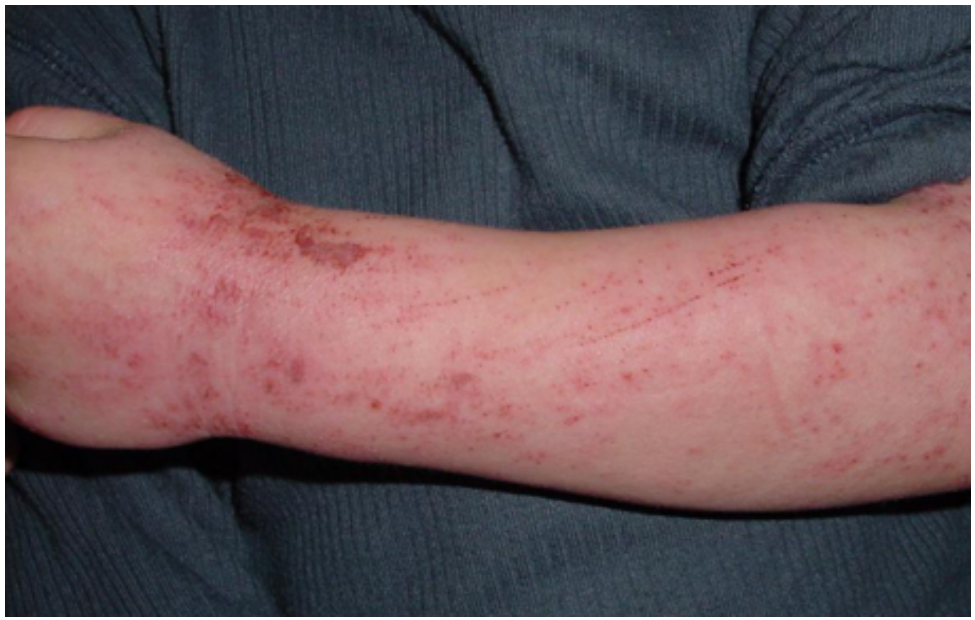
5.3 Fall injuries

HR, 0.92; 95% CI, 0.80 to 1.06

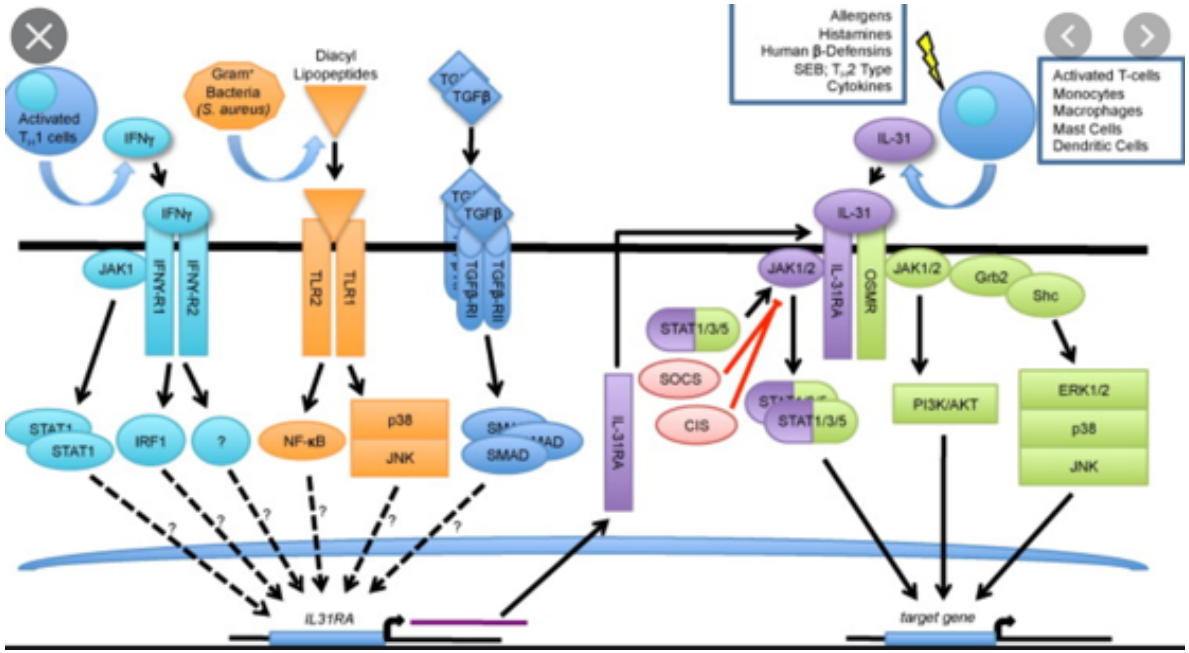
No significant difference in rate of serious fall injury in older adults at risk

Das atopische Ekzem (atopía – „Ortlosigkeit“, „nicht zuzuordnen“, ekzema – „Aufgegangenes“) ist eine chronische, nicht ansteckende Hautkrankheit, die zu den atopischen Erkrankungen gehört. Weitere geläufige Bezeichnungen sind Neurodermitis, atopische Dermatitis und endogenes Ekzem. Außerdem wird die Erkrankung auch als chronisch konstitutionelles Ekzem, Asthmaekzem und Prurigo Besnier bezeichnet. Die Bezeichnung Neurodermitis stammt aus dem 19. Jahrhundert. Damals meinte man, die Ursache der Hauterkrankung sei eine Nervenentzündung. Später wurde diese Ansicht widerlegt, die Bezeichnung ist aber weiterhin geläufig. Hauptsymptome sind rote, schuppende, manchmal auch nässende Ekzeme auf der Haut und ein starker Juckreiz. Die Erkrankung verläuft schubweise und hat ein individuelles, vom Lebensalter abhängiges Erscheinungsbild.
Das atopische Ekzem gilt als nicht heilbar, ist aber behandelbar. Die am meisten verbreitete Behandlung besteht hauptsächlich aus der Bekämpfung der charakteristischen Hauttrockenheit und der äußerlichen Anwendung von entzündungshemmenden Wirkstoffen. Es gibt weitere Therapien, die unter anderem nicht nur äußerliche Behandlungen einschließen, bspw. durch eine Ernährungsumstellung mit Einnahme von B-Vitaminen.





IL-31 is an inflammatory cytokine that helps trigger cell-mediated immunity against pathogens. It has also been identified as a major player in a number of chronic inflammatory diseases, including atopic dermatitis. IL-31 is produced by a variety of cells, namely type 2 helper (TH2) T-cells. IL-31 sends signals through a receptor complex made of IL-31RA and oncostatin M receptor β (OSMRβ) expressed in immune and epithelial cells. These signals activate three pathways: ERK1/2 MAP kinase, PI3K/AKT, and JAK1/2 signaling pathways. IL-31 signals via a receptor complex that is composed of IL-31 receptor A (IL31RA) and oncostatin M receptor (OSMR) subunits. These receptor subunits are expressed in activated monocytes and in unstimulated epithelial cells.[3] IL-31RA binds IL-31 through its cytokine binding domain (CBD). OSMR does not normally bind to IL-31 but it does increase the IL-31 binding affinity to IL-31RA. IL-31RA has an intracellular domain that possesses a box1 motif that mediates association with kinases of the JAK family. Additionally, the intracellular portion of the IL-31RA contains tyrosine residues. When IL-31 binds to the receptor complex, JAK kinases are activated which phosphorylate and activate STAT1, STAT3, and STAT5. IL-31 is believed to play a role in chronic inflammation diseases. One of these diseases is atopic dermatitis, or eczema. When biopsy samples of patients with atopic dermatitis were compared to samples from patients without atopic dermatitis, levels of IL-31 were elevated in patients with atopic dermatitis. IL-31 plays a role in this disease by inducing chemokine genes CCL1, CCL17, and CCL22.



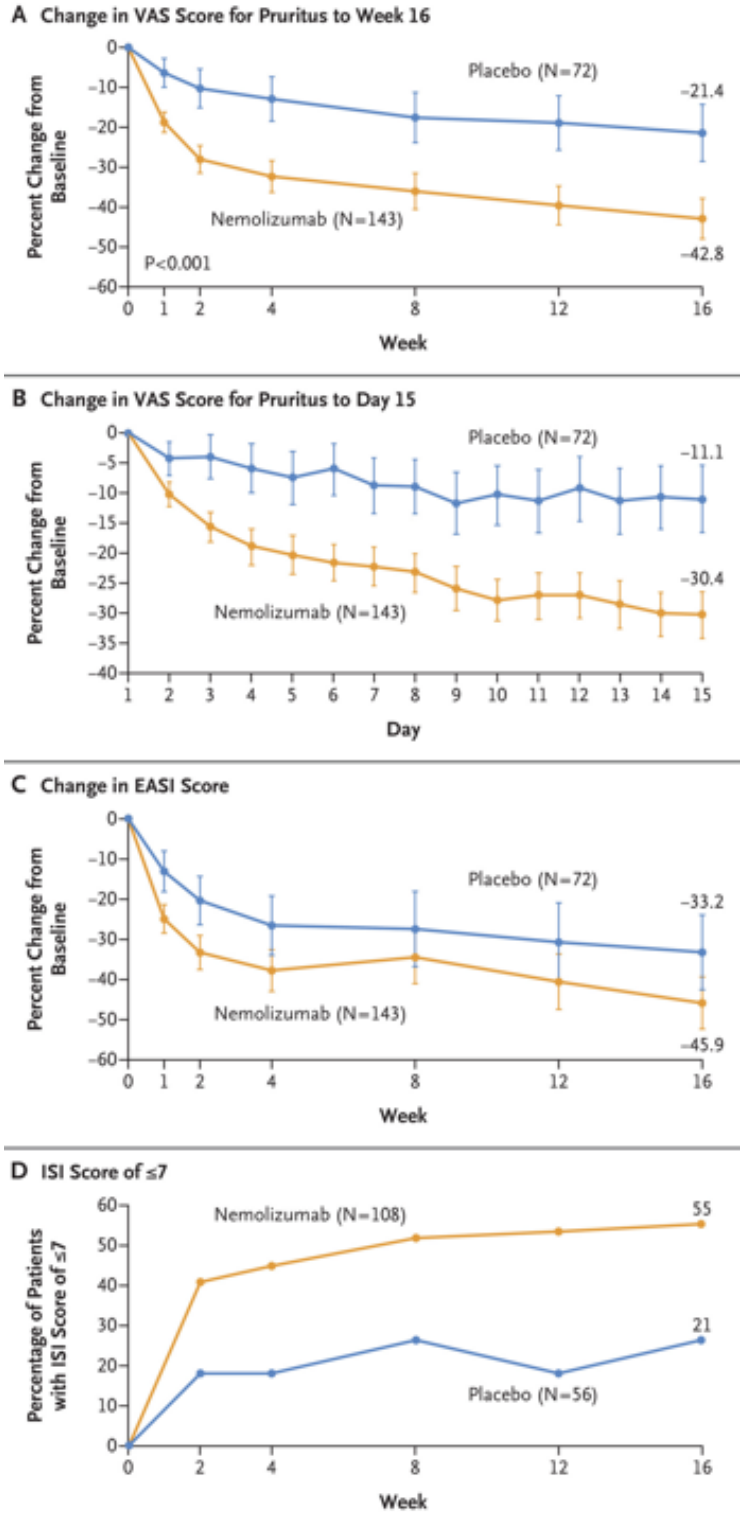
Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus

Nemolizumab is a subcutaneously administered humanized monoclonal antibody against interleukin-31 receptor A, which is involved in pruritus and inflammation in atopic dermatitis. In phase 2 studies, nemolizumab lessened the severity of atopic dermatitis. In a 16-week, double-blind, phase 3 trial, we randomly assigned Japanese patients with atopic dermatitis and moderate-to-severe pruritus and an inadequate response to topical agents in a 2:1 ratio to receive subcutaneous nemolizumab (60 mg) or placebo every 4 weeks until week 16, with concomitant topical agents. The primary end point was the mean percent change in the visual-analogue scale (VAS) score for pruritus (range, 0 to 100, with higher scores indicating worse pruritus) from baseline to week 16. Secondary end points included the time course of change in the VAS score for pruritus up to week 4, the change in the Eczema Area and Severity Index (EASI) score (range, 0 to 72, with higher scores indicating greater severity), a score of 4 or less on the Dermatology Life Quality Index (DLQI; range, 0 to 30, with higher scores indicating a greater effect on daily life), a score of 7 or less on the Insomnia Severity Index (ISI; range, 0 to 28, with higher scores indicating greater severity), and safety.

Characteristic	Nemolizumab (N=143)	Placebo (N=72)
Male sex — no. (%)	93 (65)	48 (67)
Median age (range) — yr	39.0 (13–73)	40.5 (13–80)
Median duration of disease (range) — yr	30.3 (1.1–61.3)	28.9 (1.3–59.9)
Median VAS score for pruritus (range)†	75.7 (49.7–100.0)	75.1 (53.3–100.0)
Median score on five-level itch scale (range)‡	3.0 (2–4)	3.0 (2–4)
Median EASI score (range)§	24.2 (10–65)	22.7 (10–58)
sIGA score — no. (%)¶		
0–3	82 (57)	45 (62)
≥4	61 (43)	27 (38)
DLQI score‖		
No. of patients with available data	136	69
Median (range)	12.0 (2–26)	12.0 (2–30)
ISI score**		
No. of patients with available data	142	72
Median (range)	12.0 (2–28)	12.0 (1–28)
POEM score††		
No. of patients with available data	142	72
Median (range)	22.0 (5–28)	20.5 (8–28)
Median no. of pruriginous lesions and papules (range)‡‡	8.0 (0–270)	11.0 (0–400)
Baseline treatment — no. (%)		
Topical therapy§§	143 (100)	72 (100)
Medium-potency topical glucocorticoid	139 (97)	70 (97)
Topical calcineurin inhibitor	59 (41)	29 (40)
Oral antihistamines§§	127 (89)	63 (88)
Nonsedating	126 (88)	61 (85)
Sedating	17 (12)	11 (15)

Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).

End Point	Nemolizumab (N = 143)	Placebo (N = 72)	Difference (95% CI)
			percentage points
Primary end point: percent change in pruritus VAS score from baseline to wk 16	−42.8±2.6	−21.4±3.6	−21.5 (−30.2 to −12.7)†
Secondary end points‡			
Percent change in pruritus VAS score from baseline to day 29	−34.4±2.2	−15.3±3.0	−19.3 (−26.6 to −11.9)
Percent change in EASI score from baseline to wk 16	−45.9±3.3	−33.2±4.7	−12.6 (−24.0 to −1.3)
Percentage of patients with a DLQI score of ≤4 at wk 16 (no./total no.)§	40 (51/129)	22 (15/67)	17 (2 to 31)
Percentage of patients with a decrease of ≥4 points in the DLQI score from baseline to wk 16 (no./total no.)¶	67 (89/133)	50 (34/68)	17 (3 to 31)
Percentage of patients with an ISI score of ≤7 at wk 16 (no./total no.)‖	55 (59/108)	21 (12/56)	33 (17 to 48)



Panel A shows the primary efficacy end point: the percent change in the weekly mean visual-analogue scale (VAS) score for pruritus (with higher scores indicating worse pruritus) from baseline to week 16. Panel B shows the percent change in the daily mean VAS score for pruritus from baseline to day 15; for the prespecified secondary end point of the percent change up to week 4, the least-squares mean difference between the nemolizumab group and the placebo group was −19.3 percentage points (95% confidence interval, −26.6 to −11.9). Panel C shows the percent change in the Eczema Area and Severity Index (EASI) score (with higher scores indicating greater severity) from baseline to week 16. In Panels A through C, data are shown as least-squares means, and I bars indicate 95% confidence intervals. Panel D shows the percentage of patients with a score of 7 or less on the Insomnia Severity Index (ISI; range, 0 to 28, with higher scores indicating greater severity) from baseline to week 16.

Adverse Event	Nemolizumab (N=143)	Placebo (N=72)
	no. of patients (%)	
Any adverse event	101 (71)	51 (71)
Severe	3 (2)†	0
Moderate	32 (22)	14 (19)
Mild	90 (63)	45 (62)
Serious adverse event	3 (2)	2 (3)
Treatment modification		
Discontinuation	3 (2)	0
Dose interruption	3 (2)	2 (3)
Dose reduction	0	0
Adverse events of special interest		
Injection-related reaction	12 (8)	2 (3)
Asthma	0	0
Worsening of atopic dermatitis‡	34 (24)	15 (21)
Skin infection	10 (7)	7 (10)
Elevated creatine kinase	4 (3)	1 (1)
Musculoskeletal and connective-tissue symptoms	7 (5)	6 (8)
Death	0	0
Adverse events reported by ≥3% of patients in either group§		
Dermatitis atopic‡	33 (23)	15 (21)
Nasopharyngitis	18 (13)	11 (15)
Cytokine abnormal	10 (7)	0
Blood creatine kinase increased	5 (3)	1 (1)
Acne	2 (1)	3 (4)

Discussion

In the current trial, nemolizumab resulted in a greater reduction in pruritus than placebo over a period of 16 weeks in patients with atopic dermatitis who had not had an adequate response to topical agents and antihistamines. The secondary end-point results with respect to quality of life, sleep, and signs or extent of atopic dermatitis were in the same direction as the primary end-point results, but no inferences can be made from these results because there was no plan for adjustment for multiple comparisons. Nemolizumab plus topical agents may ameliorate both pruritus and signs of eczema and may lessen the severity of atopic dermatitis by disrupting the itch–scratch cycle. Safety results in our trial indicated that some patients reported worsening atopic dermatitis as an adverse event, although those patients had reductions in pruritus as measured by the VAS score. This worsening of atopic dermatitis as a safety outcome was not correlated with the efficacy outcome of a reduction in pruritus, and the mechanisms underlying this dichotomy are unclear.

Degenerative Cervical Spondylosis

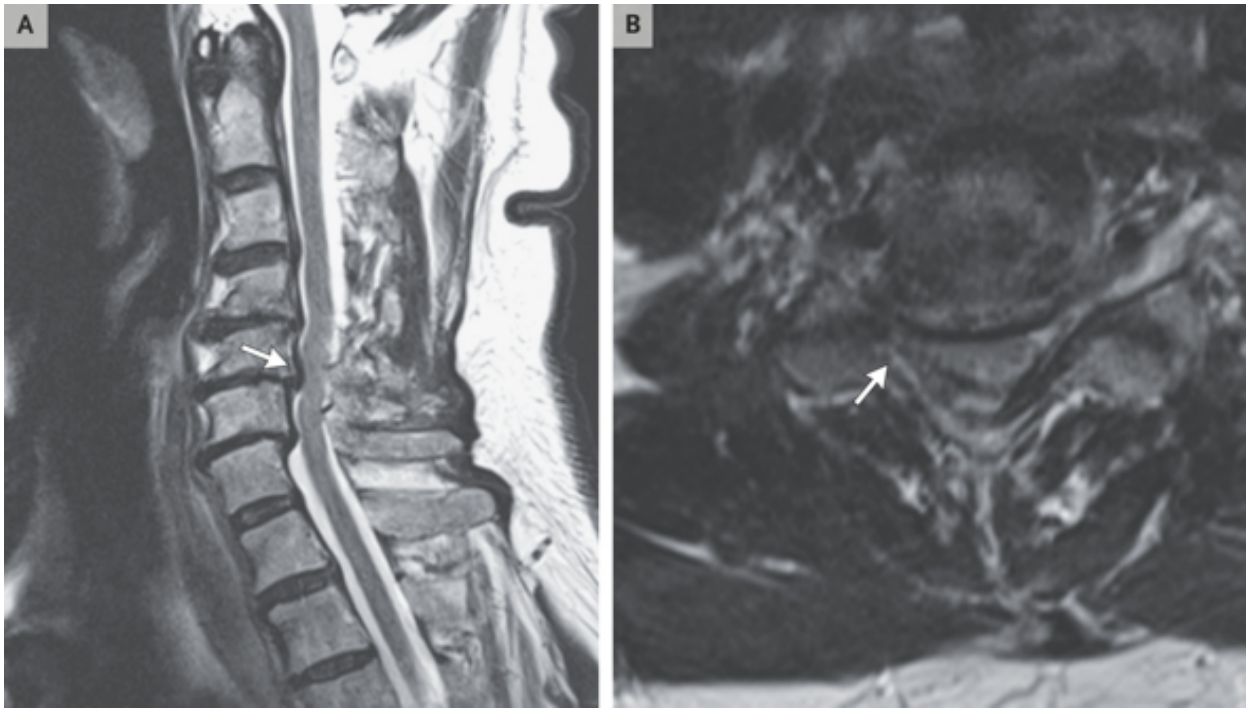
Degenerative cervical spondylosis is a chronic, progressive deterioration of osseocartilaginous components of the cervical spine that is most often related to aging. Radiographic evidence of degeneration of the cervical spine occurs in virtually all persons as they age; however, not all persons have the typical symptoms of neck pain or neurologic deficits that correspond to the mechanical compression of neural elements. Symptomatic cervical spondylosis is initially managed with nonsurgical treatment options, which usually result in abatement of symptoms. Surgical intervention may be indicated if there is clinically significant neurologic dysfunction or progressive instability or deformity of the cervical spine. No currently approved therapy addresses the cause of degenerative cervical spondylosis or reverses the deterioration. In select patients, surgical intervention can lead to favorable outcomes.

Worrisome Signs and Symptoms in the Evaluation of Patients with Degenerative Cervical Spondylosis.

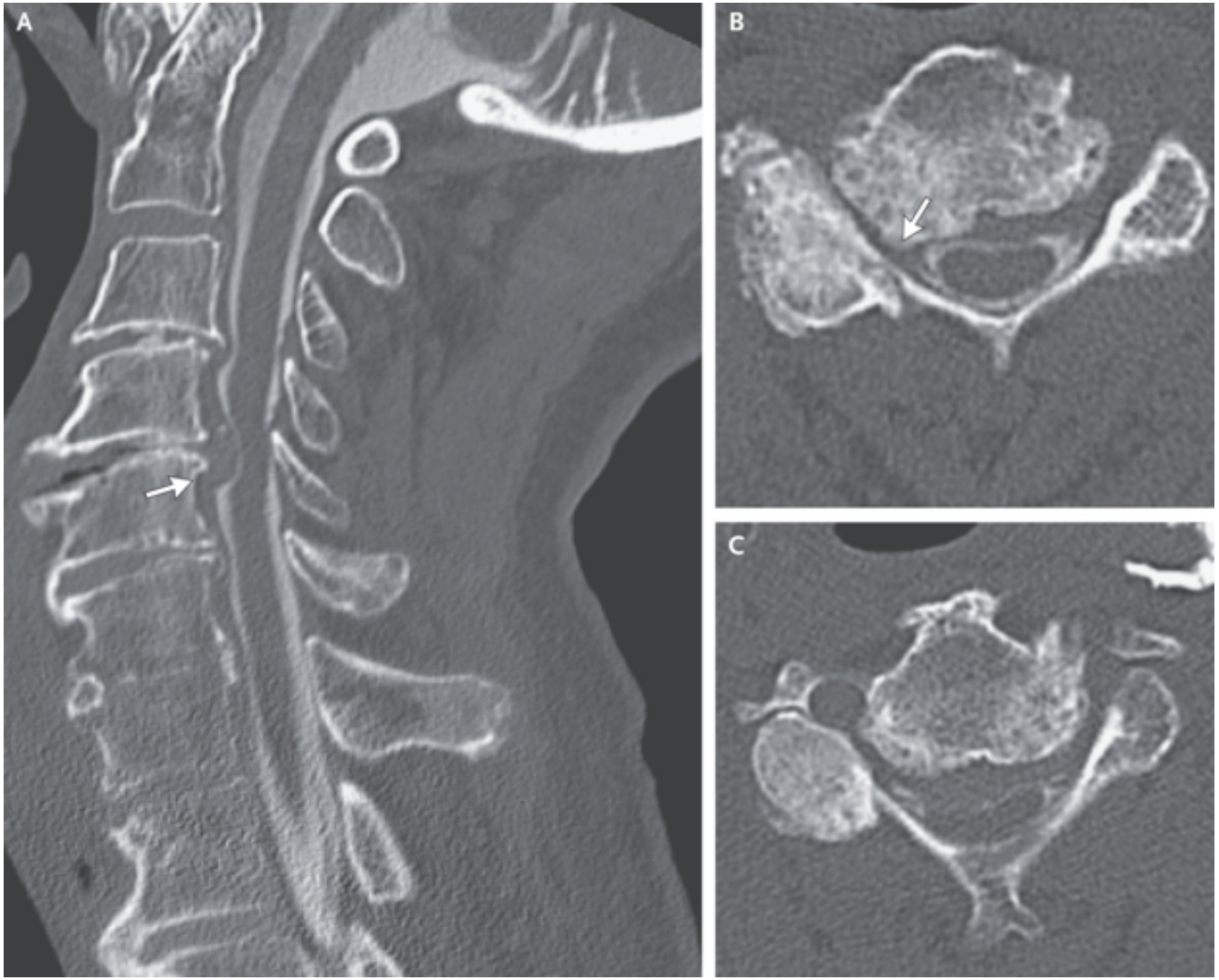
Signs and Symptoms	Cause	Physical Examination
History of cancer (especially breast, prostate, or lung), weight loss, night sweats, fever, nocturnal neck pain	Cancer	Variable findings, neurologic deficit, exquisite tenderness over vertebral body
History of intravenous drug use, immunocompromised status, fever, diabetes, recent sepsis	Spinal abscess	Usually severe local pain
Decreased dexterity in hands or feet, gait and balance instability, increased urinary frequency and urgency	Spondylitic myelopathy	Hyperreflexia, clonus, ataxia, Romberg's sign, atrophy of intrinsic hand muscles

Differential Diagnosis for Cervical Degenerative Spondylosis.

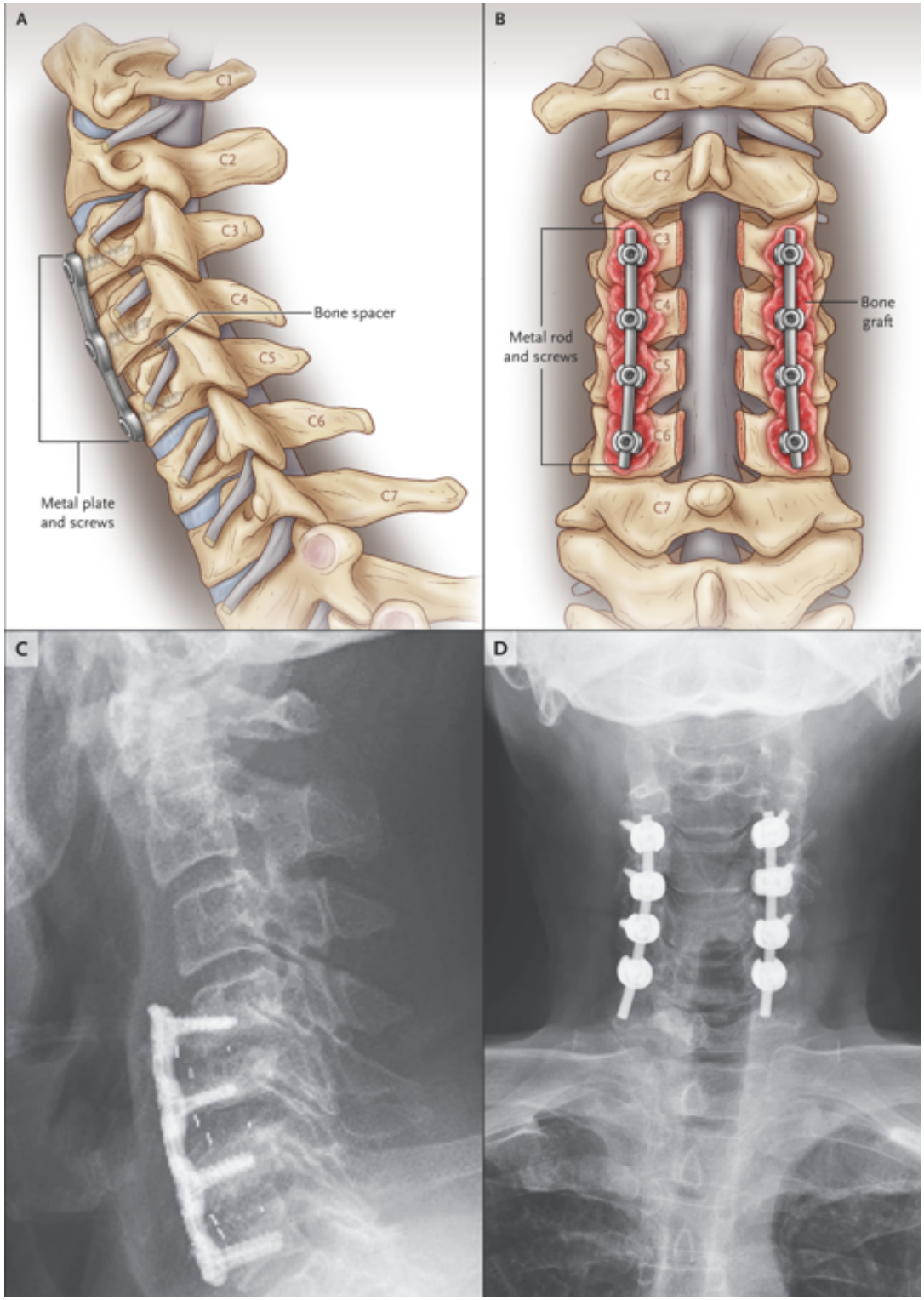
Clinical Feature	Acute Conditions	Chronic Conditions
Neck pain	Cervical strain or sprain, painful intervertebral disk, painful facet joint	Fibromyalgia, failed surgical fusion, referred visceral pain, hypochondriasis and somatoform disorders
Radiculopathy	Intervertebral disk herniation, brachial plexitis	Intervertebral disk herniation, shoulder disorder, entrapment neuropathy, focal facet hypertrophy
Myelopathy	Intervertebral disk herniation, pathologic fracture, Guillain–Barré syndrome	Intervertebral disk herniation, spinal instability, central canal stenosis, multiple sclerosis, neoplasm, infection, myopathies, syringomyelia, arteriovenous malformation, vitamin B_{12} deficiency



A 75-year-old man presented with a 2-year history of progressive upper-extremity paresthesias and radicular pain. He reported having dropped items recently from both hands and noted dexterity and balance deficits but no bowel or bladder incontinence. A sagittal T2-weighted MRI scan shows stenosis of the central spinal canal at C4–C7, with an osteophyte, deformation of the cord, disk material, and spondylolisthesis at C5–C6 (Panel A, arrow). An axial T2-weighted image shows severe foraminal stenosis (Panel B, arrow) and severe encroachment on the spinal canal by osteophyte, ligamentous, and facet hypertrophy.



A 68-year-old woman had increasing hand weakness, intrinsic hand-muscle atrophy, and hand numbness. She had begun falling and had Romberg's sign. She was unable to undergo MRI. A midsagittal CT myelogram (Panel A) shows multilevel cervical spondylosis with osteophytes, disk protrusion, and cord compression at C4–C5 (arrow). An axial image at the C3–C4 disk space shows a right lateral osteophyte (Panel B, arrow) encroaching on the neural foramen, and a similar image at the C4–C5 disk space shows marked cord compression (Panel C).



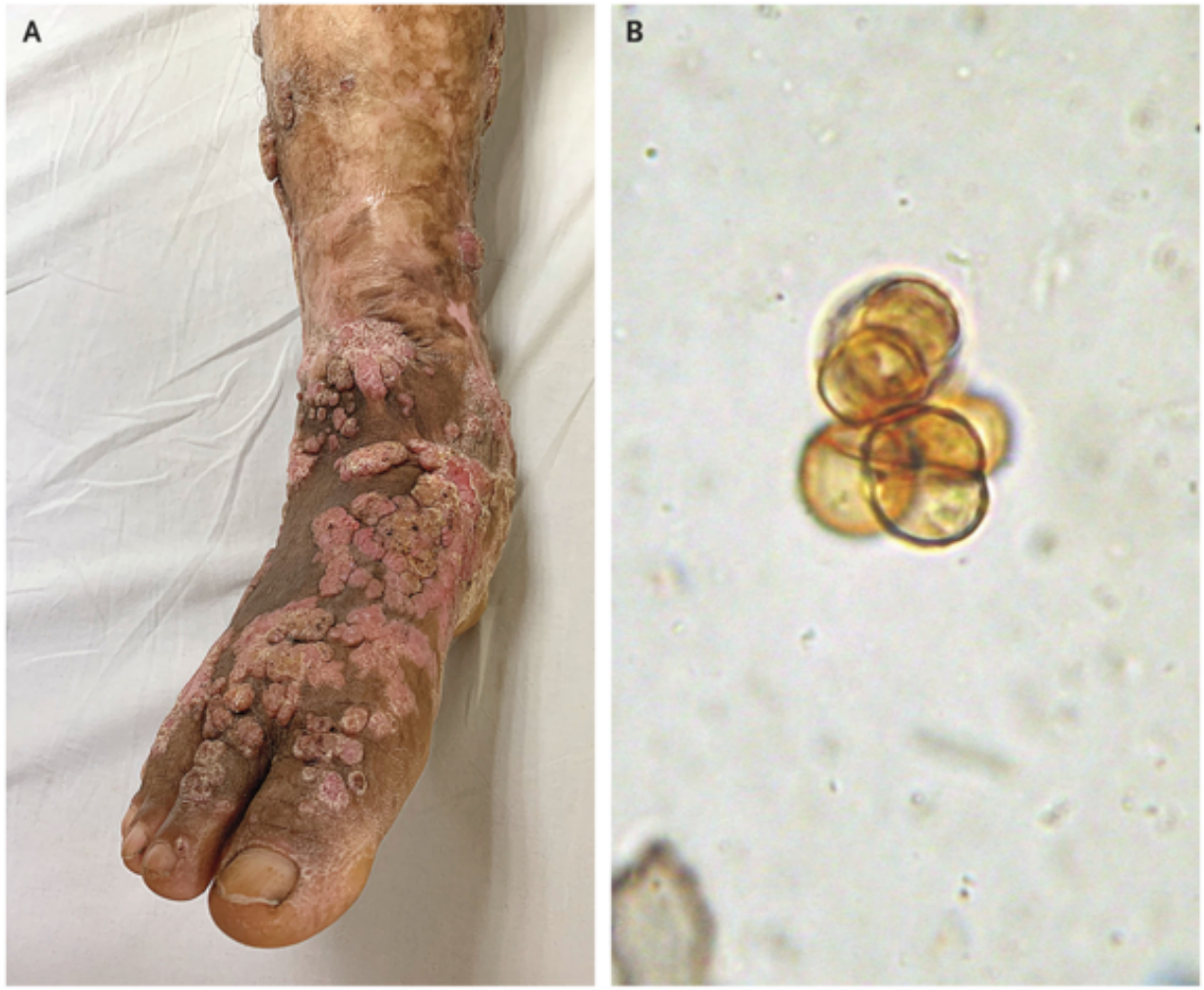
Anterior cervical diskectomies at C3–C4 and C4–C5, with the placement of bone-graft spacers where disks were removed and stabilizing screw–plate instrumentation, are shown schematically in Panel A and in a lateral radiograph in Panel C. Posterior laminectomies and lateral mass screw–rod instrumentation and fusion at C3–C6 are shown schematically in Panel B and in an anteroposterior radiograph in Panel D.

Prevention

In general, virtually all people have some degree of cervical degeneration with age, including intervertebral disk desiccation, neural foraminal narrowing, osteophyte formation, and facet joint hypertrophy. Why only some patients have symptoms after these changes occur is unclear. Certain anatomical configurations, such as a congenitally narrow spinal canal, short pedicles, and small neural foramina, are almost certainly contributors to the development of symptoms for a given degree of spondylosis. Staying physically active, maintaining good posture, and preventing neck injuries may all help prevent symptomatic degenerative cervical spondylosis. In addition, smoking and obesity have been found to be associated with spondylosis; therefore, managing these risk factors may offer benefits.

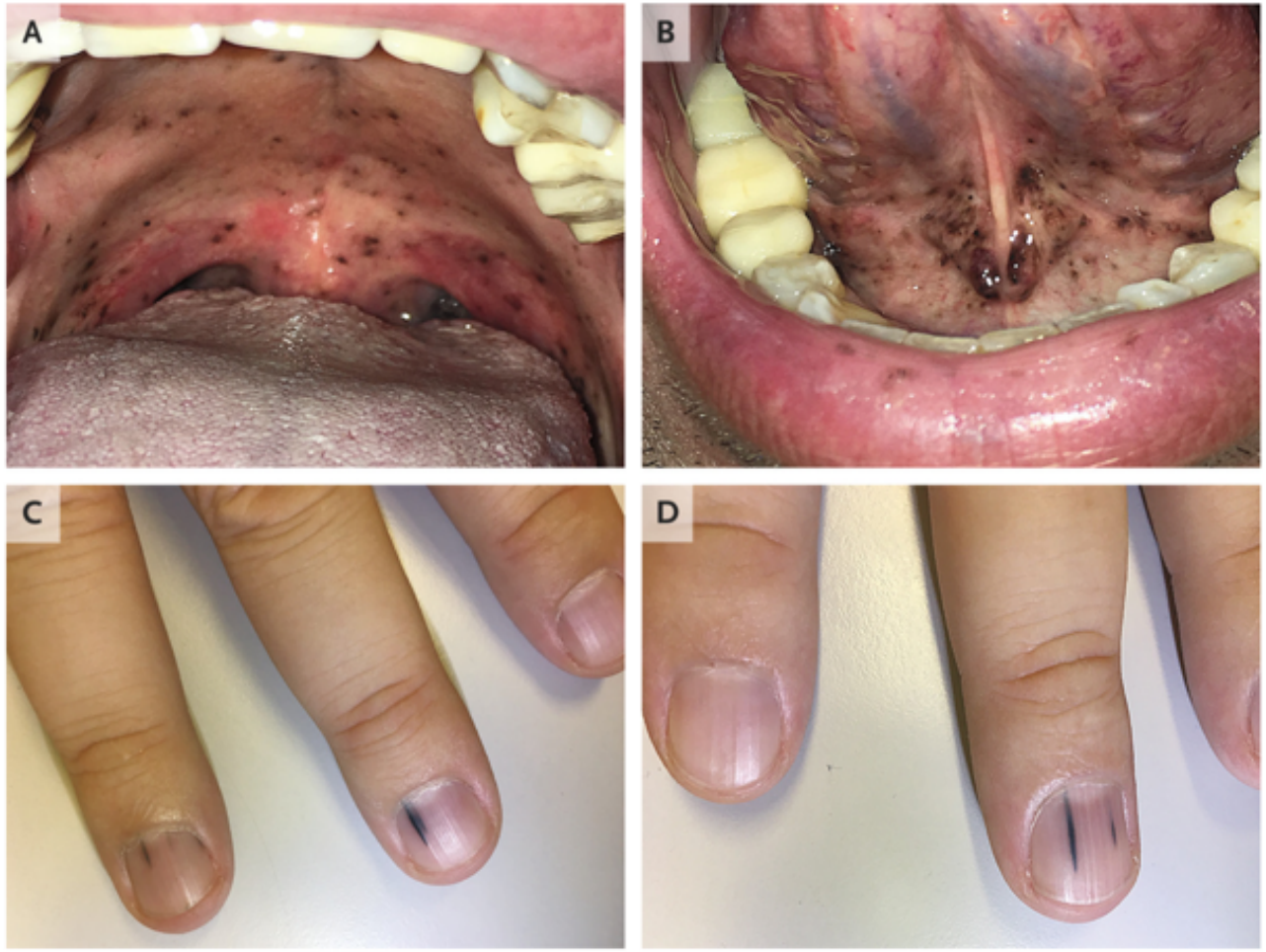
Conclusions and Recommendations

Degenerative cervical spondylosis is caused by arthritic changes in the osseocartilaginous components of the cervical spine, which may compress spinal nerve roots, the spinal cord, or both, causing neck pain, radiculopathy, or myelopathy. Treatment is generally nonsurgical, especially for pain and mild radiculopathy, which are typically self-limiting. However, surgery is generally indicated to treat myelopathy and may be indicated for persistent and severe nerve-root compression.



A 41-year-old farmer presented to the outpatient infectious disease clinic with a 20-year history of slowly growing lesions on the right leg that had progressed over time to cause gait abnormality. The lesions initially began as painless, pruritic papules on the knee and gradually spread to the dorsum of the foot. Physical examination revealed palpable, coalescent, subcutaneous nodules with verrucous lesions and associated skin changes (Panel A). Examination of a skin scraping prepared with 10% potassium hydroxide revealed pigmented, thick-walled, multicellular structures known as Medlar bodies (also called sclerotic cells) (Panel B), a finding that suggested chromoblastomycosis, a chronic, subcutaneous mycosis that can develop at sites of skin trauma. *Fonsecaea pedrosoi*, a saprophyte found in soil and a causative agent of chromoblastomycosis, was grown on culture. Daily treatment with 400 mg of oral itraconazole was initiated and continued for 1 year, with slight abatement of the lesions. Further treatment with cryotherapy is planned.

Chromoblastosis (Peru)

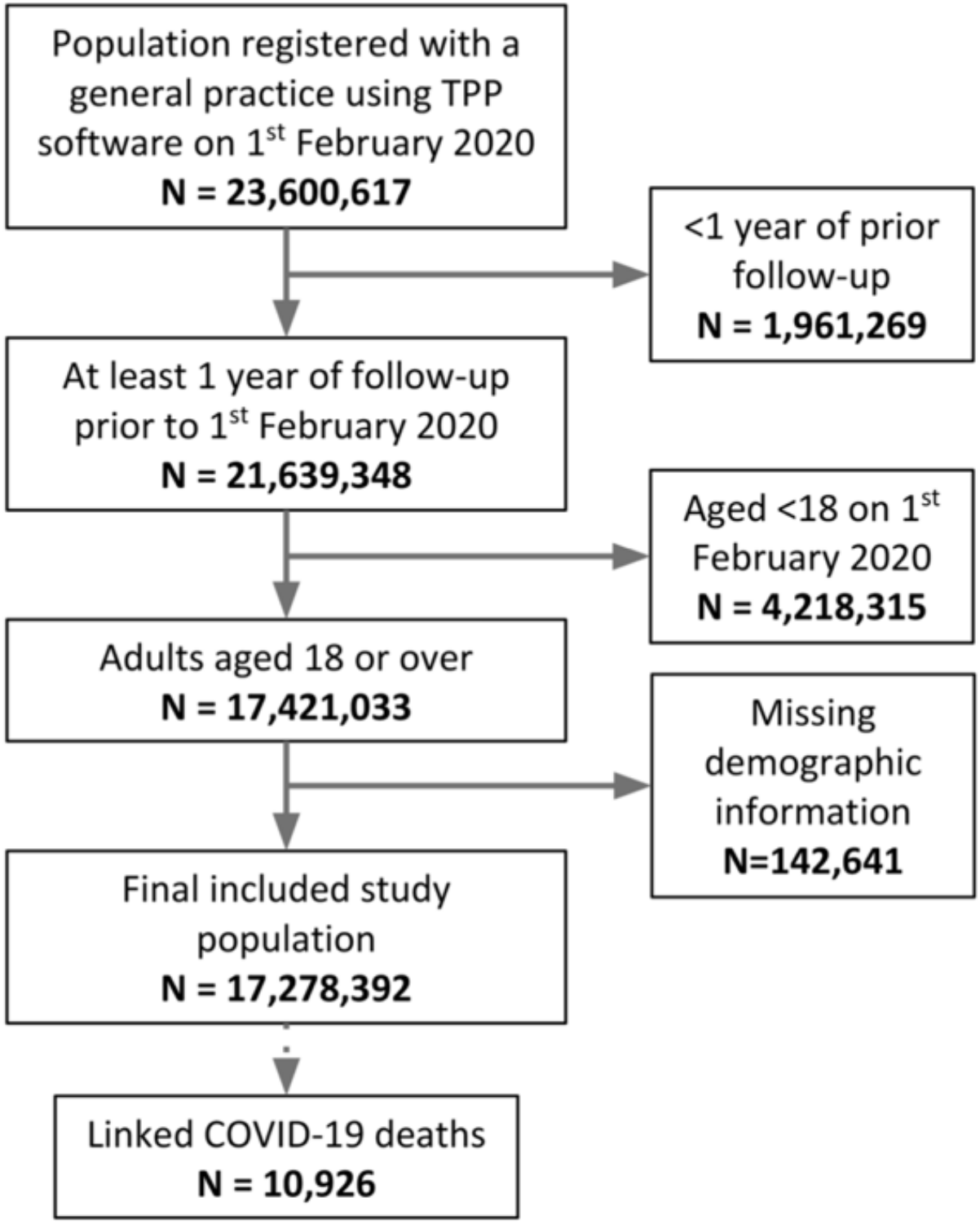


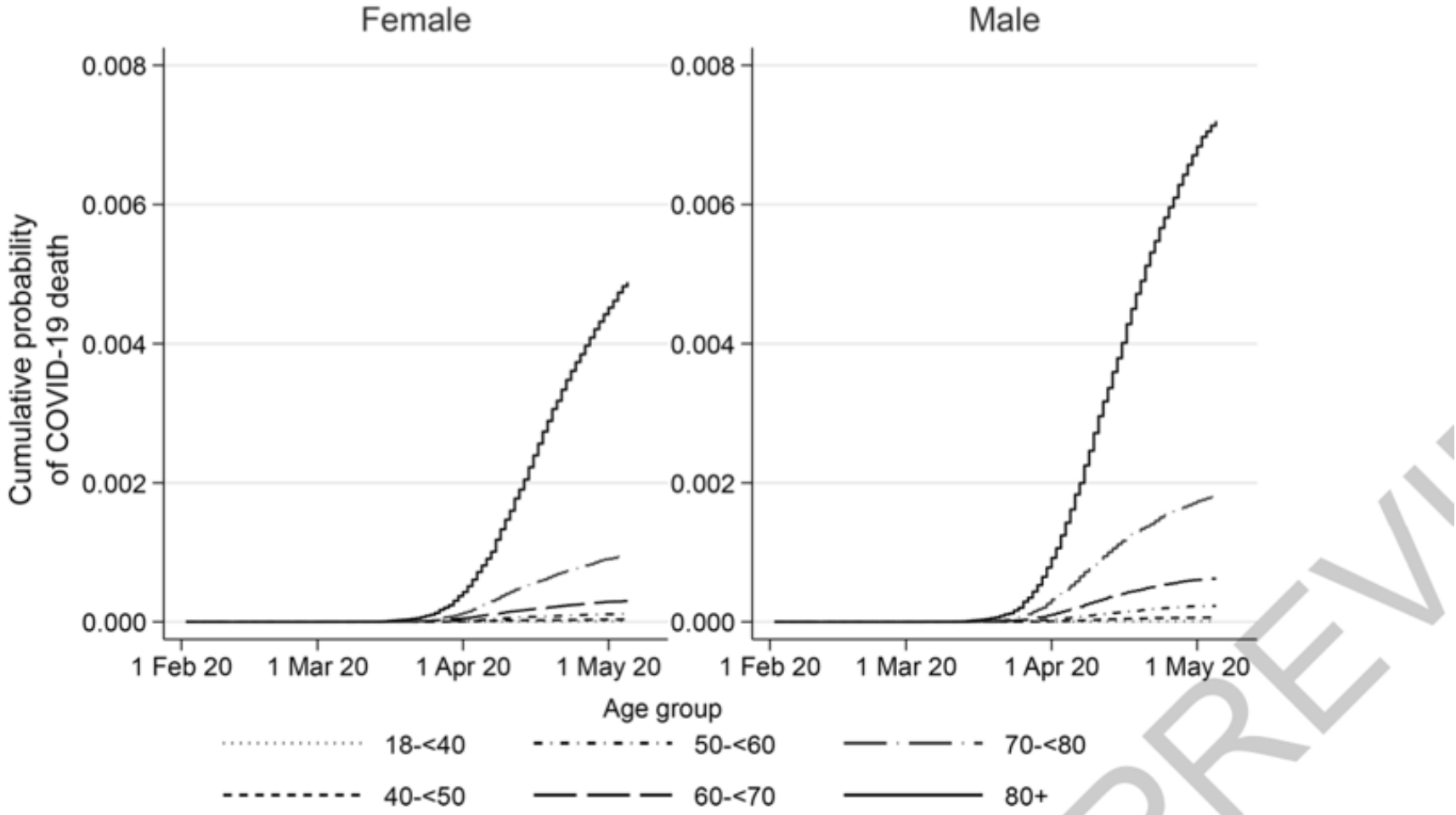
A 47-year-old man presented to the dermatology clinic with a 10-day history of multiple fingernail, oral, and penile lesions associated with fever, decreased appetite, and nausea. His medical history was notable for cutaneous melanoma on the chest that had been treated 11 years earlier with surgical excision. The physical examination showed multiple discrete, pigmented lesions on the hard and soft palates, as well as below the tongue (Panels A and B). He had similar lesions on the penis. Examination of the hands showed numerous longitudinal dark bands on the nail bed of multiple fingers (Panels C and D). A biopsy of one of these lesions confirmed the presence of melanoma cells, a finding consistent with a diagnosis of mucosal and ungual melanoma metastases. Further evaluation of the patient's gastrointestinal symptoms revealed gastric metastases, and a *BRAF* mutation was identified by molecular analysis. The patient was treated with dabrafenib and trametinib, and partial regression of the lesions was seen at a 5-month follow-up visit.

Article

OpenSAFELY: factors associated with COVID-19 death in 17 million patients

COVID-19 has rapidly affected mortality worldwide[1]. There is unprecedented urgency to understand who is most at risk of severe outcomes, requiring new approaches for timely analysis of large datasets. Working on behalf of NHS England, here we created OpenSAFELY: a secure health analytics platform covering 40% of all patients in England, holding patient data within the existing data centre of a major primary care electronic health records vendor. Primary care records of 17,278,392 adults were pseudonymously linked to 10,926 COVID-19-related deaths. COVID-19-related death was associated with: being male (hazard ratio (HR) 1.59, 95% confidence interval (CI) 1.53–1.65); older age and deprivation (both with a strong gradient); diabetes; severe asthma; and various other medical conditions. Compared with people with white ethnicity, Black and South Asian people were at higher risk even after adjustment for other factors (HR 1.48, 1.30–1.69 and 1.44, 1.32–1.58, respectively). We have quantified a range of clinical risk factors for COVID-19-related death in the largest cohort study conducted by any country to date. OpenSAFELY is rapidly adding further patients' records; we will update and extend results regularly.


Population registered with a general practice using TPP software on 1st February 2020
N = 23,600,617
<1 year of prior follow-up
N = 1,961,269
At least 1 year of follow-up prior to 1st February 2020
N = 21,639,348
Aged <18 on 1st February 2020
N = 4,218,315
Adults aged 18 or over
N = 17,421,033
Missing demographic information
N=142,641
Final included study population
N = 17,278,392
Linked COVID-19 deaths
N = 10,926



2 | Kaplan-Meier plots for COVID-19 related death over time by age and sex.

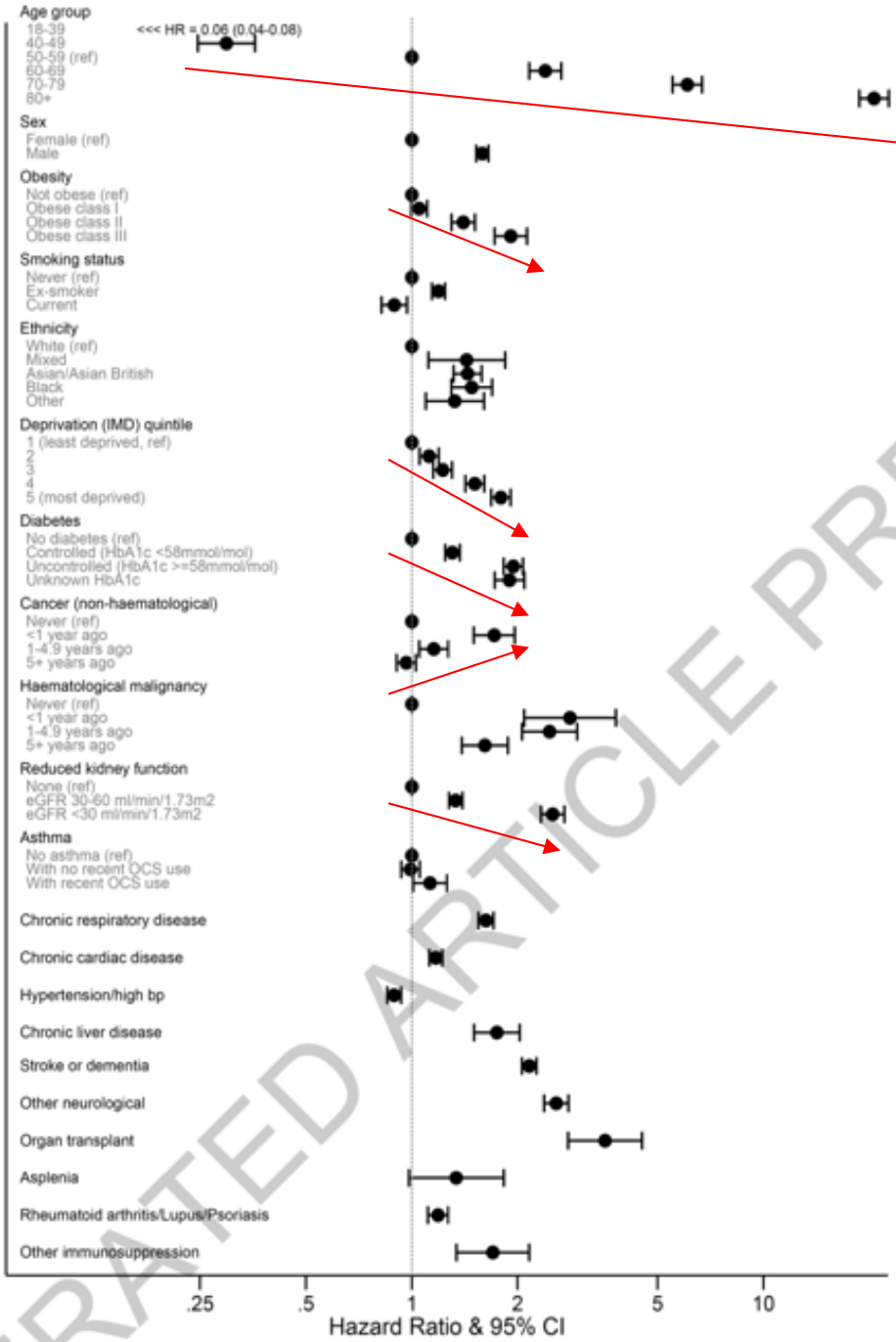


Fig. 3 | Estimated Hazard Ratios (shown on a log scale) for each potential risk factor from a multivariable Cox model. Error bars represent limits of the 95% confidence interval for the hazard ratio. Obese class I: 30-34.9kg/m^2, class II: 35-39.9kg/m^2, class III: >=40kg/m^2. OCS = oral corticosteroid. All HRs are adjusted for all other factors listed other than ethnicity. Ethnicity estimates are from a separate model among those with complete ethnicity data, and are fully adjusted for other covariates. Total n = 17,278,392 for non-ethnicity models, and 12,718,279 for ethnicity model.

Table 1 | Cohort description with number of COVID-19 deaths by potential risk factors

Characteristic	Category	N (column %)	Number of COVID-19 deaths (% within stratum)
Total		17,278,392 (100.0)	10,926 (0.06)
Age	18-<40	5,914,384 (34.2)	54 (0.00)
	40-<50	2,849,984 (16.5)	140 (0.00)
	50-<60	3,051,110 (17.7)	522 (0.02)
	60-<70	2,392,392 (13.8)	1,101 (0.05)
	70-<80	1,938,842 (11.2)	2,635 (0.14)
	80+	1,131,680 (6.5)	6,474 (0.57)
Sex	Female	8,647,989 (50.1)	4,764 (0.06)
	Male	8,630,403 (49.9)	6,162 (0.07)
BMI (kg/m2)	<18.5	310,721 (1.8)	522 (0.17)
	18.5-24.9	4,763,150 (27.6)	3,364 (0.07)
	25-29.9	4,682,906 (27.1)	3,068 (0.07)
	30-34.9 (Obese class I)	2,384,406 (13.8)	1,813 (0.08)
	35-39.9 (Obese class II)	922,398 (5.3)	762 (0.08)
	≥40 (Obese class III)	463,042 (2.7)	379 (0.08)
	Missing	3,751,769 (21.7)	1,018 (0.03)
Smoking	Never	7,924,739 (45.9)	3,598 (0.05)
	Former	5,690,966 (32.9)	6,531 (0.11)
	Current	2,941,764 (17.0)	708 (0.02)
	Missing	720,923 (4.2)	89 (0.01)
Ethnicity	White	10,866,411 (62.9)	7,119 (0.07)
	Mixed	169,697 (1.0)	62 (0.04)
	South Asian	1,022,130 (5.9)	608 (0.06)
	Black	339,909 (2.0)	250 (0.07)
	Other	320,132 (1.9)	110 (0.03)
	Missing	4,560,113 (26.4)	2,777 (0.06)
IMD quintile	1 (least deprived)	3,497,154 (20.2)	1,908 (0.05)
	2	3,476,668 (20.1)	2,030 (0.06)
	3	3,483,668 (20.2)	2,114 (0.06)
	4	3,480,459 (20.1)	2,388 (0.07)
	5 (most deprived)	3,340,443 (19.3)	2,486 (0.07)
Blood pressure	Normal	3,804,148 (22.0)	2,487 (0.07)
	Elevated	2,482,710 (14.4)	1,899 (0.08)
	High Stage 1	5,548,198 (32.1)	3,281 (0.06)
	High Stage 2	3,728,241 (21.6)	3,229 (0.09)
	Missing	1,715,095 (9.9)	30 (0.00)
High bp or diagnosed hypertension		5,925,492 (34.3)	8,049 (0.14)
Respiratory disease ex asthma		703,917 (4.1)	2,240 (0.32)
Asthma*	With no recent ocs use	2,454,403 (14.2)	1,211 (0.05)
	With recent ocs use	291,670 (1.7)	335 (0.11)
Chronic heart disease		1,167,455 (6.8)	3,811 (0.33)
Diabetes**	With HbA1c<58 mmol/mol	1,038,082 (6.0)	2,391 (0.23)
	With HbA1c>=58 mmol/mol	486,491 (2.8)	1,254 (0.26)
	With no recent HbA1c measure	193,993 (1.1)	444 (0.23)
Cancer (non-haematological)	Diagnosed < 1 year ago	79,964 (0.5)	220 (0.28)
	Diagnosed 1-4.9 years ago	234,186 (1.4)	449 (0.19)
	Diagnosed ≥5 years ago	542,320 (3.1)	1,125 (0.21)
Haematological malignancy	Diagnosed < 1 year ago	8,704 (0.1)	43 (0.49)
	Diagnosed 1-4.9 years ago	27,742 (0.2)	120 (0.43)
	Diagnosed ≥5 years ago	63,460 (0.4)	173 (0.27)
Reduced kidney function***	Estimated GFR 30-60	1,007,383 (5.8)	3,987 (0.40)

Continued

=0.6%

Characteristic	Category	N (column %)	Number of COVID-19 deaths (% within stratum)
	Estimated GFR <30	78,093 (0.5)	864 (1.11)
Kidney dialysis		23,978 (0.1)	192 (0.80)
Liver disease		100,017 (0.6)	181 (0.18)
Stroke/dementia		390,002 (2.3)	2,423 (0.62)
Other neurological disease		170,448 (1.0)	665 (0.39)
Organ transplant		20,001 (0.1)	69 (0.34)
Asplenia		27,917 (0.2)	40 (0.14)
Rheumatoid/Lupus/ Psoriasis		878,475 (5.1)	962 (0.11)
Other immunosuppressive condition		278,948 (1.6)	69 (0.02)

Discussion

This secure analytics platform operating across over 23 million patient records for the COVID-19 emergency was used to identify, quantify, and explore risk factors for COVID-19 related death in the largest cohort study conducted by any country to date. Most comorbidities were associated with increased risk, including cardiovascular disease, diabetes, respiratory disease including severe asthma, obesity, history of haematological malignancy or recent other cancer, kidney, liver, neurological and autoimmune conditions. People from South Asian and black groups had a substantially higher risk of death, only partially attributable to co-morbidity, deprivation or other risk factors. A strong association between deprivation and risk was only partly attributable to co-morbidity or other risk factors.

These analyses provide a preliminary picture of how key demographic characteristics and a range of comorbidities, a priori selected as being of interest in COVID-19, are jointly associated with poor outcomes. These initial results may be used subsequently to inform the development of prognostic models. We caution against interpreting our estimates as causal effects. For example, the fully adjusted smoking hazard ratio does not capture the causal effect of smoking due to the inclusion of comorbidities which are likely to mediate any effect of smoking on COVID-19 death (e.g. COPD). Our study has highlighted a need for carefully designed causal analyses specifically focusing on the causal effect of smoking on COVID-19 death. Similarly, there is a need for analyses exploring the causal relationships underlying the associations observed between hypertension and COVID-19 death.

Future Research

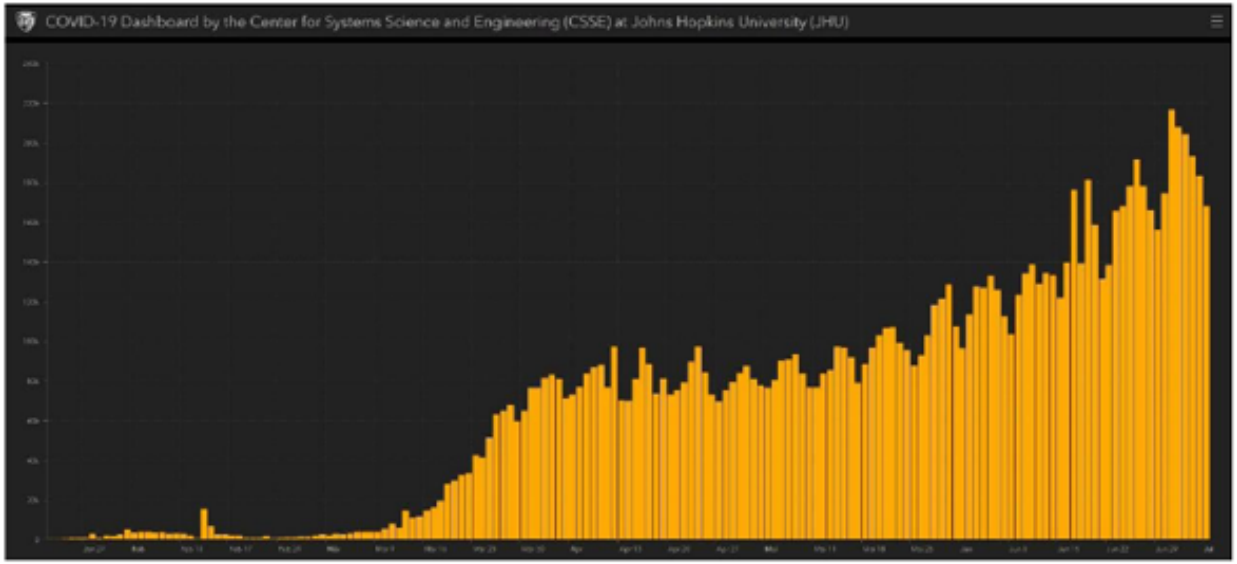
The underlying causes of higher risk of COVID-19 related death among those from non-white backgrounds, and deprived areas, require further exploration; we would suggest collecting data on occupational exposure and living conditions as first steps. The statistical power offered by our approach means that associations with less common risk factors can be robustly assessed in more detail, at the earliest possible date, as the pandemic progresses. We will therefore update our findings and address smaller risk groups as new cases arise over time. The open source reusable codebase on OpenSAFELY supports rapid, secure and collaborative development of new analyses: we are currently conducting expedited studies on the impact of various medical treatments and population interventions on the risk of COVID-19 infection, ITU admission, and death, alongside other observational analyses. OpenSAFELY is rapidly scalable for additional NHS patients' records, with new data sources progressing.

Conclusion

We generated early insights into risk factors for COVID-19 related death using an unprecedented scale of 17 million patients' detailed primary care records, maintaining privacy, in the context of a global health emergency.

In Context

Weltweit positive Testungen (ca. 12 Mio. Johns Hopkins University)



Dunkelziffer 10 bis 50-fach, d.h. 100-500 Mio. infizierte Personen

550.000 Todesfälle: Letalität 0,1-0,5% Nature article =0.6%

zum Vergleich Influenza Grippe 0,1-0,2%

SARS (2003) 9%

Spanische Grippe 5-10%

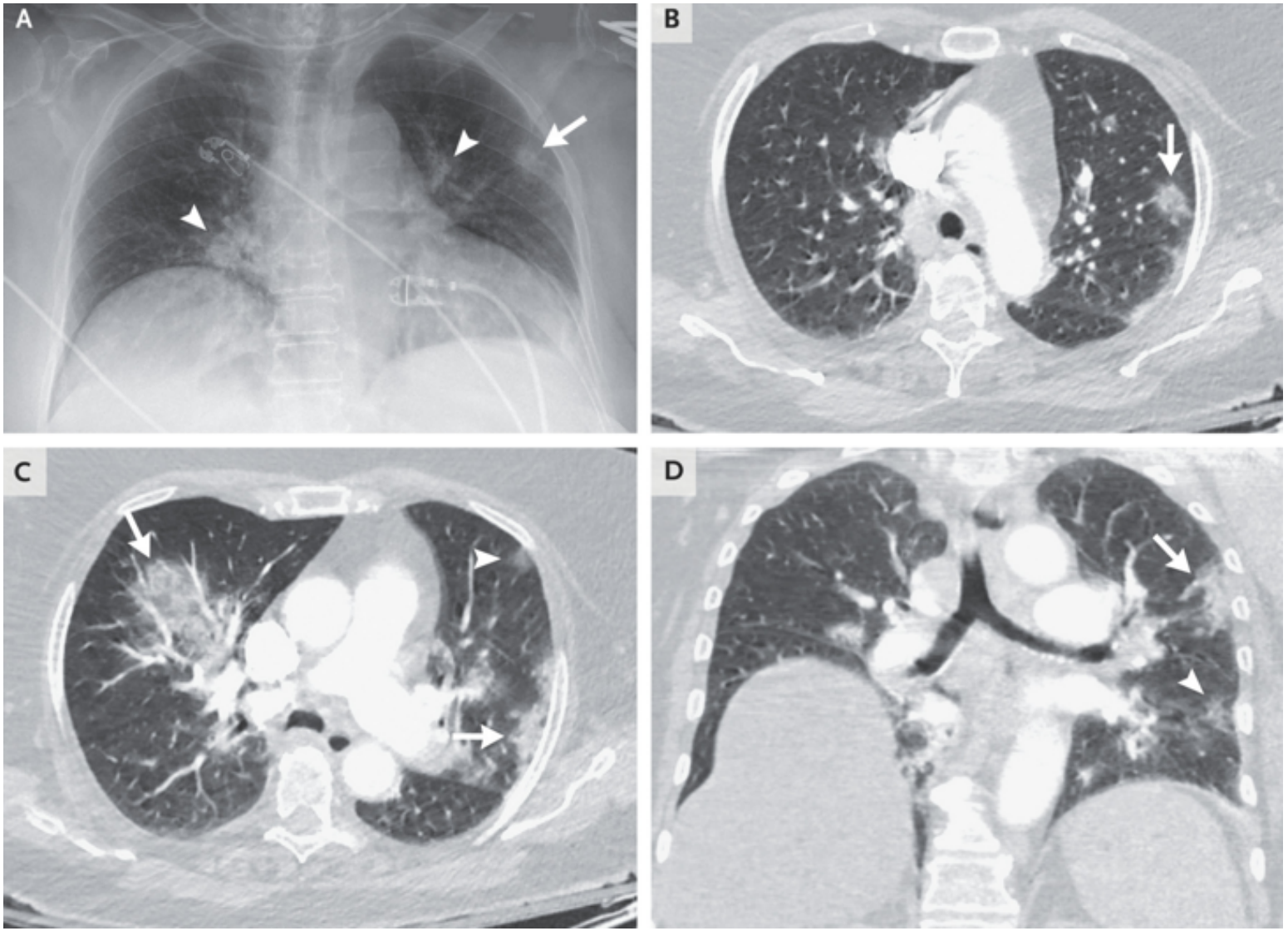
Ebola 30-90%

5 x more lethal than influenza virus today; far less than H1N1 influenza in 1920
Mortality of Germans has not changed because of Covid-19 in 1920 (courtesy Stefan Willich).

A 76-Year-Old Woman Who Died from Covid-19

A 76-year-old woman was admitted to this hospital because of confusion and hypoxemia during the pandemic of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The patient had been well until 6 days before this admission, when nasal congestion developed, with no fever or cough. One day before this admission, she called her primary care physician, who recommended fluticasone nasal spray and nasal rinses and asked her to follow up by telephone in 2 days. However, the next day, the patient's son visited the patient and found her to be confused and incontinent of urine and stool. Emergency medical services were called, and when they arrived at the patient's home, the oxygen saturation was 87% while she was breathing ambient air. The patient was transported by ambulance to this hospital. There was a history of asthma, diabetes, hypertension, hyperlipidemia, osteoporosis, and psoriasis. Medications included atorvastatin, aspirin, hydrochlorothiazide, losartan, insulin, metformin, glipizide, citalopram, acetaminophen, cholecalciferol, folate, fluticasone nasal spray, and topical betamethasone and fluocinonide. The temperature was 38.8° C, the heart rate 94 beats per minute, the blood pressure 176/55 mm Hg, the respiratory rate 24 breaths per minute, and the oxygen saturation 94% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 2 liters per minute.

Variable	Reference Range†	On Admission
Hemoglobin (g/dl)	12.0–16.0	13.9
Hematocrit (%)	36.0–46.0	43.2
White-cell count (per μl)	4500–11,000	7690
Differential count (per μl)		
Neutrophils	1800–7700	6150
Lymphocytes	1000–4800	1270
Monocytes	200–1200	200
Basophils	0–300	70
Platelet count (per μl)	150,000–400,000	149,000
Sodium (mmol/liter)	135–145	136
Potassium (mmol/liter)	3.4–5.0	4.2
Chloride (mmol/liter)	98–108	94
Carbon dioxide (mmol/liter)	23–32	22
Anion gap (mmol/liter)	3–17	20
Urea nitrogen (mg/dl)	8–25	13
Creatinine (mg/dl)	0.60–1.50	0.65
Glucose (mg/dl)	70–110	366
Alanine aminotransferase (U/liter)	7–33	27
Aspartate aminotransferase (U/liter)	9–32	35
Alkaline phosphatase (U/liter)	30–100	54
Creatine kinase (U/liter)	40–150	363
Lactate dehydrogenase (U/liter)	110–210	289
Ferritin (μg/liter)	10–200	675
D-dimer (ng/ml)	<500	3592



Chest Imaging Studies Obtained on Admission. A radiograph (Panel A) shows patchy opacities with rounded contours in the peripheral left upper lobe (arrow) and perihilar patchy opacities (arrowheads), along with evidence of mild cardiomegaly. Axial (Panels B and C) and coronal (Panel D) CT pulmonary angiographic images show multifocal consolidative opacities (arrows) and ground-glass opacities (arrowheads), including some with rounded morphologic features, in both lungs. The distribution of these findings is predominantly peripheral and peribronchial.

Acetaminophen and empirical ceftriaxone, azithromycin, and hydroxychloroquine were administered. Because the patient had acute respiratory failure and Covid-19, goals of care were discussed with her adult children by telephone; the patient was unable to participate meaningfully in the discussion because of confusion. She had recently expressed to her primary care doctor that she would "not want to be on a breathing machine if something were irreversible." A status of "do not resuscitate and do not intubate" was assigned.

During the next day, intermittent episodes of fever occurred, with temperatures as high as 40.3° C, and delirium and hypoxemia worsened. On the third hospital day, new atrial fibrillation with a rapid ventricular response developed, and metoprolol and furosemide were administered.

On the fourth hospital day, the respiratory rate was 36 breaths per minute and the oxygen saturation was 90% while the patient was receiving supplemental oxygen through a nonrebreather mask at a rate of 15 liters per minute. She appeared to be in distress, with increased work of breathing. Goals of care were again discussed with the patient's family, and a status of "comfort measures only" was assigned. The patient died 36 hours later.

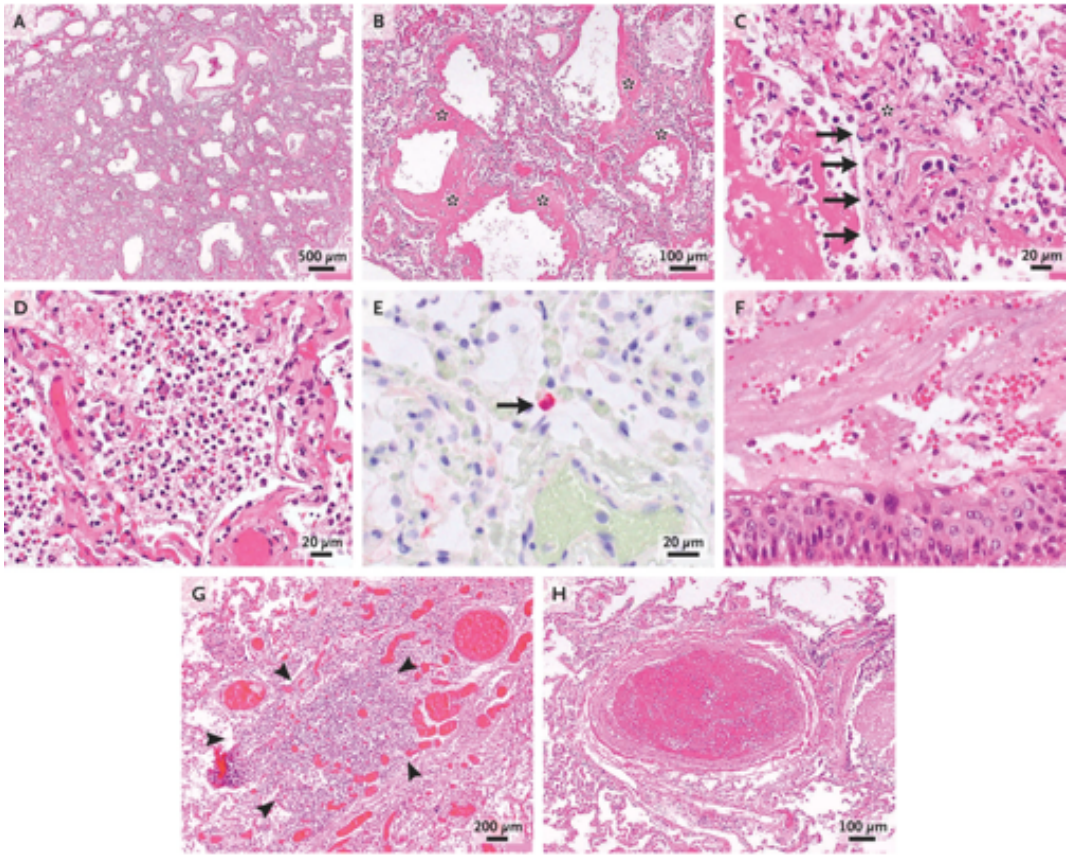
After discussion with the family, an autopsy was performed.

In the 1970s, autopsy was performed after approximately 1 in 5 deaths, but now, it is performed after fewer than 1 in 10. Among the many factors contributing to this trend is the reluctance of clinicians to discuss autopsy with families and patients. Some conversations about autopsy happen in a cursory way out of obligation or do not happen at all.

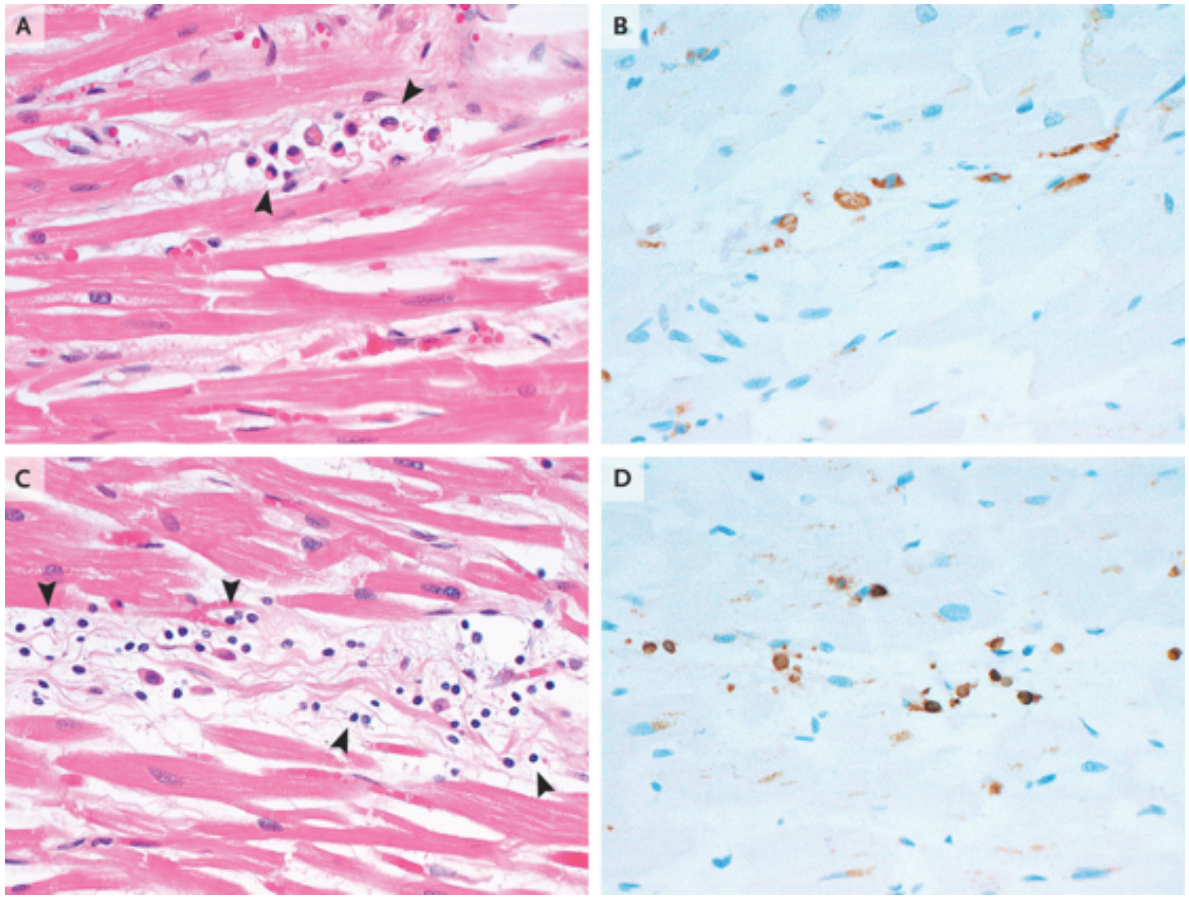
Usually, the clinician will approach the family about autopsy. However, in this case, during discussions that occurred before the patient's death, the daughter expressed sadness that her mother had become a casualty of the Covid-19 pandemic and initiated the conversation about autopsy.

In discussions about autopsy, the words "consent," "permission," and "request" have traditionally been used, but this language may imply that the benefit of autopsy is for clinicians and institutions, rather than patients and families. It may be more appropriate to use the word "offer" to indicate that the family is being informed of their right to an autopsy.

After the results of the autopsy are final, an appointment is typically made with the family to share and discuss the relevant findings. This discussion would be organized by either the clinician who had initially discussed autopsy with the family or another clinician who had been involved in the patient's care, such as the primary care physician. Families are typically understanding of the fact that it can take an extended period of time to receive autopsy results as long as they know that communication will occur in the future.



Lung Autopsy Specimens. On hematoxylin and eosin staining, both lungs show architecturally preserved alveolar parenchyma (Panel A) with thick hyaline membranes (Panel B, asterisks) associated with pneumocyte denudation (Panel C, arrows). In some areas, alveolar walls show increased cellularity with some spindled fibroblast-like cells (Panel C, asterisk). These findings are consistent with an exudative to early proliferative phase of diffuse alveolar damage. There are also rare foci with neutrophilic and histiocytic infiltrates in alveolar spaces (Panel D), features suggestive of a focal pneumonic process. Immunohistochemical staining for SARS nucleocapsid protein highlights scattered pneumocytes (Panel E, arrow) and alveolar macrophages, findings supportive of a diagnosis of SARS-CoV-2 infection in the lungs. Thick mucin and epithelial denudation are seen in the majority of bronchi, and squamous metaplasia with reactive changes is focally replacing the denuded lining (Panel F). Only a few scattered perivascular chronic inflammatory aggregates (Panel G, arrowheads) and rare fibrin thrombi in small pulmonary arteries (Panel H) are present in this case.



Heart Autopsy Specimens. On hematoxylin and eosin staining, there is increased infiltration of the myocardium by macrophages (Panel A, arrowheads); on immunohistochemical staining, the macrophages express the marker CD68 (Panel B, in brown). There is also focal infiltration of the myocardium by lymphocytes (Panel C, arrowheads), which express the marker CD3 (Panel D, in brown). These findings are not associated with myocyte injury.

Role of Autopsy

Dr. Stone: Autopsies can be very important in establishing the cause of death. Even in an era with routine use of high-resolution imaging, published studies have shown that approximately 50% of autopsies reveal findings that were not suspected before death and 20% of autopsies lead to the diagnosis of a primary cause of death that was not established clinically. In the absence of an autopsy, the likelihood that a death certificate will be inaccurate is at least one in three. Just over 100 years ago, during the 1918 influenza pandemic, autopsies facilitated our understanding that the majority of deaths that occurred during that time were due to bacterial pneumonia. Likewise, autopsy studies have highlighted the role of tuberculosis in the death of patients with human immunodeficiency virus type 1 infection. During the Covid-19 pandemic, autopsies are critical to our understanding of the full spectrum of pulmonary changes that can occur in this disease, the mechanisms of healing and long-term pathological consequences of the disease, and the extent and nature of the involvement of different organs by the virus. For example, in this case, although diffuse alveolar damage was the predominant pathological finding in the lungs, there were also focal features of a superimposed pneumonic process.

Follow-up

Dr. Tran: I shared the findings of this patient's autopsy with her family by telephone. The results helped to relieve the guilt that her son felt because he had discovered his mother was ill only just before hospital admission. I also had the opportunity to reassure the patient's son and daughter that the end-of-life decisions they had made on behalf of their mother preserved her comfort near the time of death.

Perhaps the performance of the autopsy itself was more emotionally beneficial to this patient's family than the autopsy results. In our conversation, the patient's daughter reflected on the helplessness she had felt during her mother's illness and death, as well as more broadly during the Covid-19 pandemic. However, she felt uplifted that her mother's autopsy made the experience "part of something bigger."

Anatomical Diagnosis

Diffuse alveolar damage due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study

Summary

Background Some studies, mainly from high-income countries (HICs), report that women receive less care (investigations and treatments) for cardiovascular disease than do men and might have a higher risk of death. However, very few studies systematically report risk factors, use of primary or secondary prevention medications, incidence of cardiovascular disease, or death in populations drawn from the community. Given that most cardiovascular disease occurs in low-income and middle-income countries (LMICs), there is a need for comprehensive information comparing treatments and outcomes between women and men in HICs, middle-income countries, and low-income countries from community-based population studies.

Methods In the Prospective Urban Rural Epidemiological study (PURE), individuals aged 35–70 years from urban and rural communities in 27 countries were considered for inclusion. We recorded information on participants' sociodemographic characteristics, risk factors, medication use, cardiac investigations, and interventions. 168 490 participants who enrolled in the first two of the three phases of PURE were followed up prospectively for incident cardiovascular disease and death.

Findings From Jan 6, 2005 to May 6, 2019, 202072 individuals were recruited to the study. The mean age of women included in the study was 50·8 (SD 9·9) years compared with 51·7 (10) years for men. Participants were followed up for a median of 9·5 (IQR 8·5–10·9) years. Women had a lower cardiovascular disease risk factor burden using two different risk scores (INTERHEART and Framingham). Primary prevention strategies, such as adoption of several healthy lifestyle behaviours and use of proven medicines, were more frequent in women than men. Incidence of cardiovascular disease (4·1 [95% CI 4·0–4·2] for women *vs* 6·4 [6·2–6·6] for men per 1000 person-years; adjusted hazard ratio [aHR] 0·75 [95% CI 0·72–0·79]) and all-cause death (4·5 [95% CI 4·4–4·7] for women *vs* 7·4 [7·2–7·7] for men per 1000 person-years; aHR 0·62 [95% CI 0·60–0·65]) were also lower in women. By contrast, secondary prevention treatments, cardiac investigations, and coronary revascularisation were less frequent in women than men with coronary artery disease in all groups of countries. Despite this, women had lower risk of recurrent cardiovascular disease events (20·0 [95% CI 18·2–21·7] versus 27·7 [95% CI 25·6–29·8] per 1000 person-years in men, adjusted hazard ratio 0·73 [95% CI 0·64-0·83]) and women had lower 30-day mortality after a new cardiovascular disease event compared with men (22% in women versus 28% in men; p<0·0001). Differences between women and men in treatments and outcomes were more marked in LMICs with little differences in HICs in those with or without previous cardiovascular disease.

Interpretation Treatments for cardiovascular disease are more common in women than men in primary prevention, but the reverse is seen in secondary prevention. However, consistently better outcomes are observed in women than in men, both in those with and without previous cardiovascular disease. Improving cardiovascular disease prevention and treatment, especially in LMICs, should be vigorously pursued in both women and men.

	Women (n=119 799)	Men (n=82 273)	p value
Age, distribution, and disease history			
Age	50·8 (9·9)	51·7 (10·0)	p<0·0001
Living in rural communities (%)	51 706 (43·2%)	36 387 (44·2%)	p<0·0001
Living in a high-income country (%)	9679 (8·1%)	8481 (10·3%)	p<0·0001
Living in a middle-income country (%)	86 379 (72·1%)	55 711 (67·7%)	p<0·0001
Living in a low-income country (%)	23 741 (19·8%)	18 081 (22·0%)	p<0·0001
Previous cardiovascular disease (%)	6348 (5·3%)	5310 (6·5%)	p<0·0001
Behavioural, psychosocial, and socioeconomic risk factors			
Current smokers	11 839/118 647 (10·0%)	29 410/81 500 (36·1%)	p<0·0001
High physical activity*	47 925/111 116(43·1%)	34 153/75 586 (45·2%)	p<0·0001
Healthy diet†	30 400/90 245 (33·7%)	21 678/65 016 (33·3%)	p=0·16
Ever consume alcohol	28 786/113 312 (25·4%)	39 191/77 716 (50·4%)	p<0·0001
Probable depression‡	16 351/112 540 (14·5%)	6111/76 644 (8·0%)	p<0·0001
Low education§	50 886/110 842 (45·9%)	28 779/77 627 (37·1%)	p<0·0001
Physical measures and blood pressure, mean (SD)			
Body-mass index, kg/m² (n=190 800)	26·6 (5·6)	25·7 (4·9)	p<0·0001
Waist circumference, cm (n=190 851)	84·3 (13·9)	89·0 (13·6)	p<0·0001
Waist:hip ratio (n=182 985)	0·85 (0·08)	0·92 (0·08)	p<0·0001
Systolic blood pressure, mm Hg (n=189 905)	129·9 (22·3)	133·5 (20·8)	p<0·0001
Diastolic blood pressure, mm Hg (n=189 946)	80·9 (12·1)	82·7 (12·3)	p<0·0001
Lipids and blood glucose, mean (SD)			
Total cholesterol, mmol/L (n=142 428)¶	5·5 (10·6)	5·2 (9·0)	p<0·0001
Triglycerides, mmol/L (n=140 193)¶	1·7 (5·3)	1·9 (4·6)	p<0·0001
LDL-cholesterol, mmol/L (n=138 307)¶	3·2 (1·0)	3·1 (1·0)	p<0·0001
HDL-cholesterol, mmol/L (n=139 631)¶	1·3 (0·4)	1·2 (0·3)	p<0·0001
non-HDL-cholesterol, mmol/L (n=139 625)¶	3·8 (1·1)	3·7 (1·1)	p<0·0001
ApoB, µmol/dL (n=20 940)	1·01 (0·3)	1·03 (0·3)	p<0·0001
ApoA1, mol/dL (n=20 978)	1·6 (0·4)	1·4 (0·3)	p<0·0001
ApoB:ApoA1 ratio (n=20 935)	0·68 (0·24)	0·75 (0·29)	p<0·0001
Total cholesterol:HDL-cholesterol ratio (n=139 625)¶	4·2 (7·0)	4·6 (7·6)	p<0·0001
Fasting blood glucose, mmol/L (n=141 250)	5·3 (1·8)	5·4 (1·9)	p<0·0001

Data are n (%), n/N (%), or mean (SD). *High physical activity was defined as more than 3000 metabolic equivalents × min per week. †Healthy diet was defined as having an alternative healthy eating index score of more than 31 (index scores range from 6 to 70). ‡Probable depression was defined as having five or more symptoms of depression; diagnosis was made on the basis of responses to Short-Form International Diagnostic Interview Schedule for Major Depressive Disorder. §Low education level was defined as no education, primary education only, or unknown education level. ¶Fasting blood samples used.

Table 1: **Participant baseline characteristics**

	Women (n=113 451)	Men (n=76 963)	p value
Overall	8·44 (8·43–8·46)	11·44 (11·41–11·46)	p<0·0001
Economic status			
High-income countries	11·44 (11·37–11·51)	14·38 (14·29–14·46)	p<0·0001
Middle-income countries	8·62 (8·59–8·66)	11·84 (11·79–11·89)	p<0·0001
Low-income countries	6·61 (6·57–6·64)	8·93 (8·88–8·97)	p<0·0001
Region			
North America and Europe	10·04 (10·00–10·09)	13·85 (13·78–13·92)	p<0·0001
South America	9·60 (9·56–9·64)	11·58 (11·53–11·64)	p<0·0001
Middle East	10·03 (9·96–10·10)	12·92 (12·83–13·01)	p<0·0001
China	7·27 (7·24–7·30)	11·47 (11·42–11·52)	p<0·0001
Southeast Asia	8·94 (8·89–8·99)	11·77 (11·69–11·84)	p<0·0001
South Asia	6·76 (6·73–6·80)	9·18 (9·14–9·23)	p<0·0001
Africa	8·02 (7·95–8·10)	8·73 (8·61–8·85)	p<0·0001
Russia and Central Asia	7·26 (7·18–7·34)	10·40 (10·23–10·56)	p<0·0001

All data are mean (95% CI). Participants with a history of cardiovascular diseases were excluded. Higher scores of the INTERHEART score indicate a higher risk factor burden. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity. The estimated 10-year cardiovascular disease risk based on the Framingham risk score indicates that 10·5% of women and 37·3% of men are at high risk (≥20%) of developing the disease (appendix p 25).

Table 2: **Mean non-laboratory INTERHEART risk score for women and men for the entire cohort and each economic and regional subgroup**

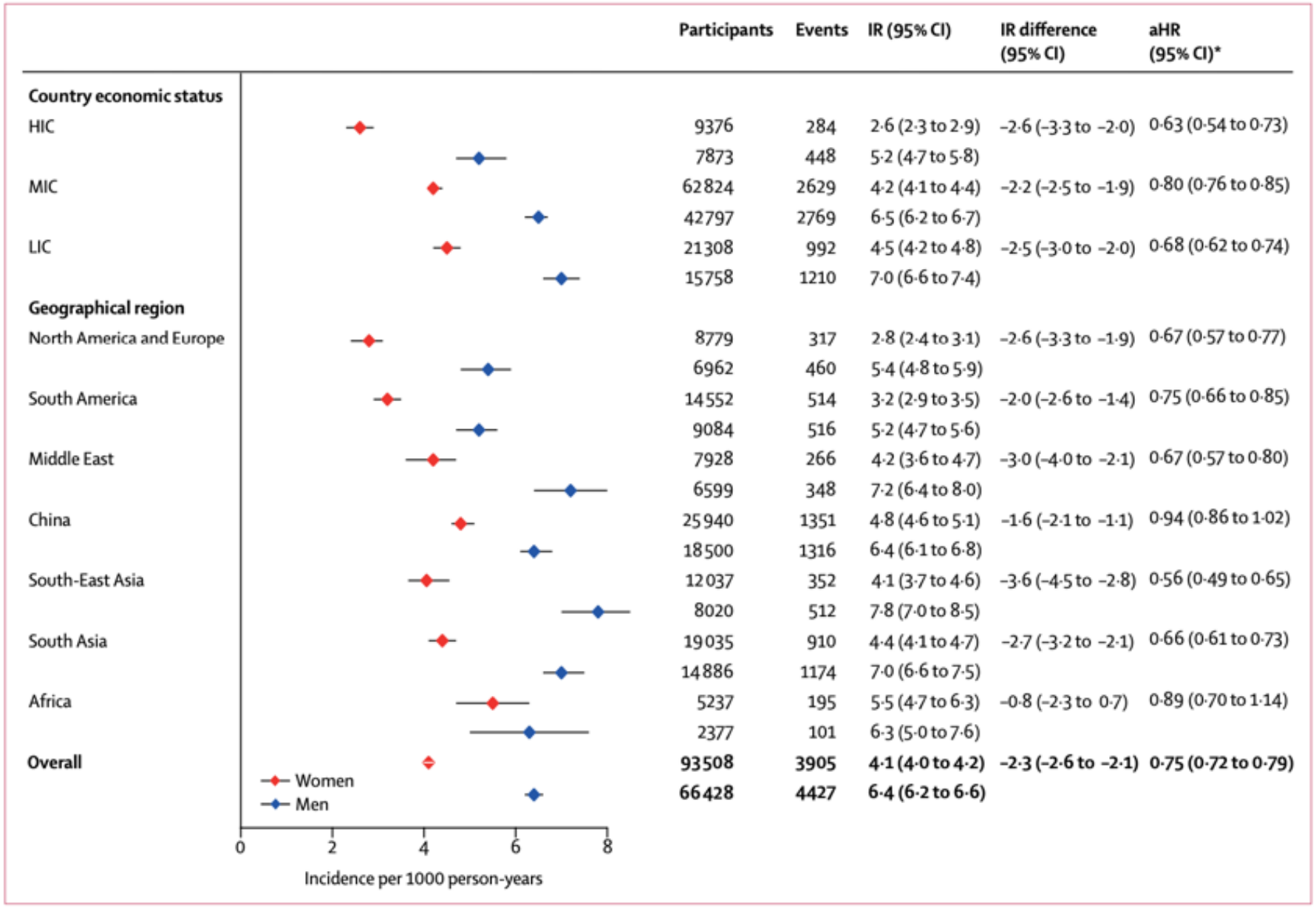


Figure 1: **Age-standardised incidence rates per 1000 person-years of major cardiovascular disease in those without a history of previous cardiovascular disease**
Major cardiovascular disease includes cardiovascular death, myocardial infarction, stroke, heart failure, and other major cardiovascular disease events. Errors bars represent 95% CIs. Participants with a history of cardiovascular diseases are excluded. Interaction between economic status and sex p<0·0001; interaction between geographic region and sex p<0·0001. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios are adjusted for location, education, INTERHEART risk score, and a random intercept for centre. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.

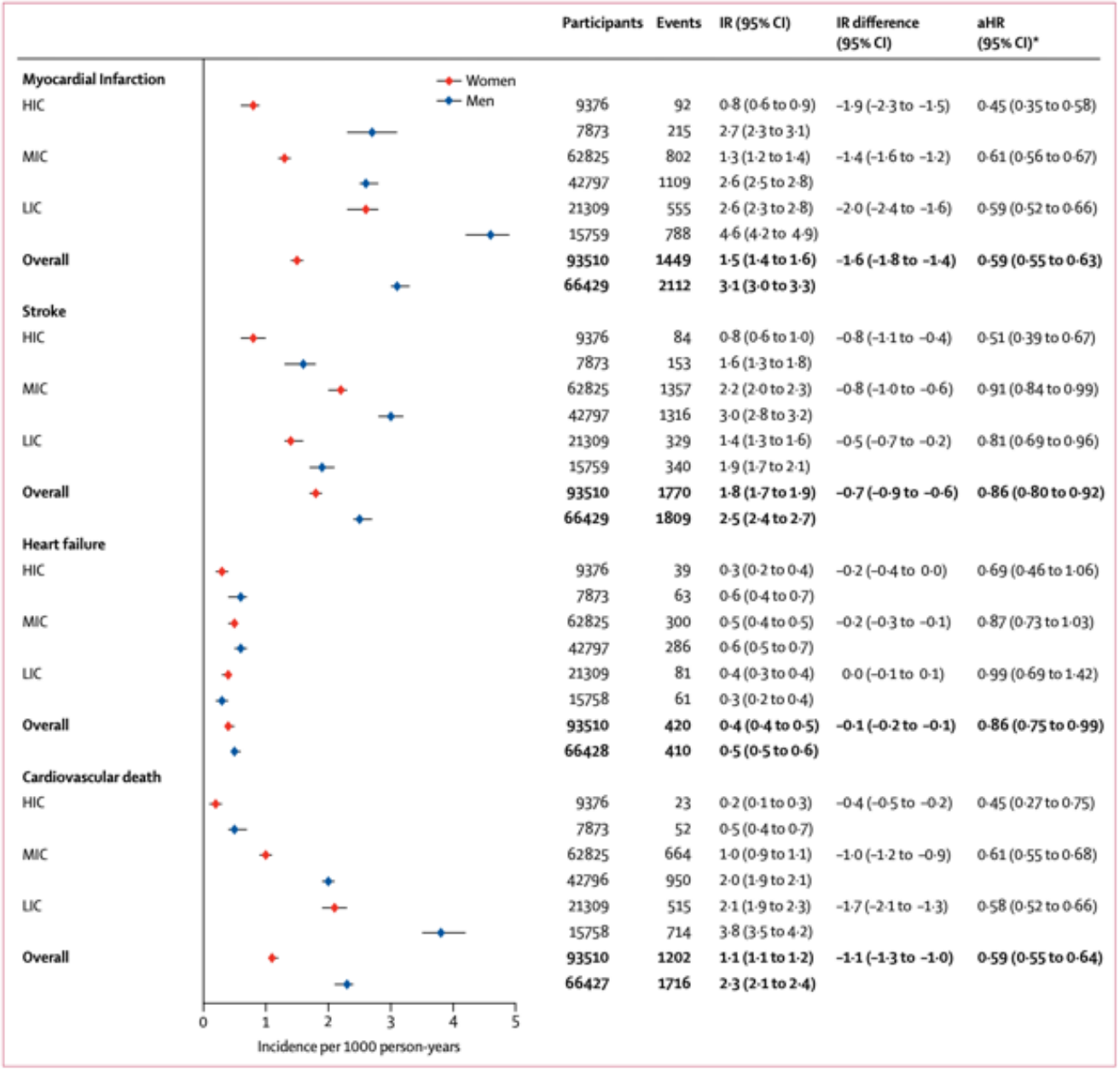


***Figure 2*: Age-standardised incidence rates per 1000 person-years of myocardial infarction, stroke, heart failure, and cardiovascular death in those without previous cardiovascular disease**

Errors bars represent 95% CIs. Of note, 385 other major cardiovascular events (261 in women and 124 in men) included in major cardiovascular are not presented above. Data are not presented by geographical region because the numbers of events of myocardial infarction, stroke, and heart failure are substantially reduced resulting in unstable estimates. Interaction between country economic status and sex p=0·0001 for myocardial infarction events; p=0·0001 for stroke events; p=0·3006 for heart failure events. Interaction between country economic status and sex p=0·0001 for cardiovascular deaths. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios are adjusted for location, education, INTERHEART risk score, and a random intercept for centre ID. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.

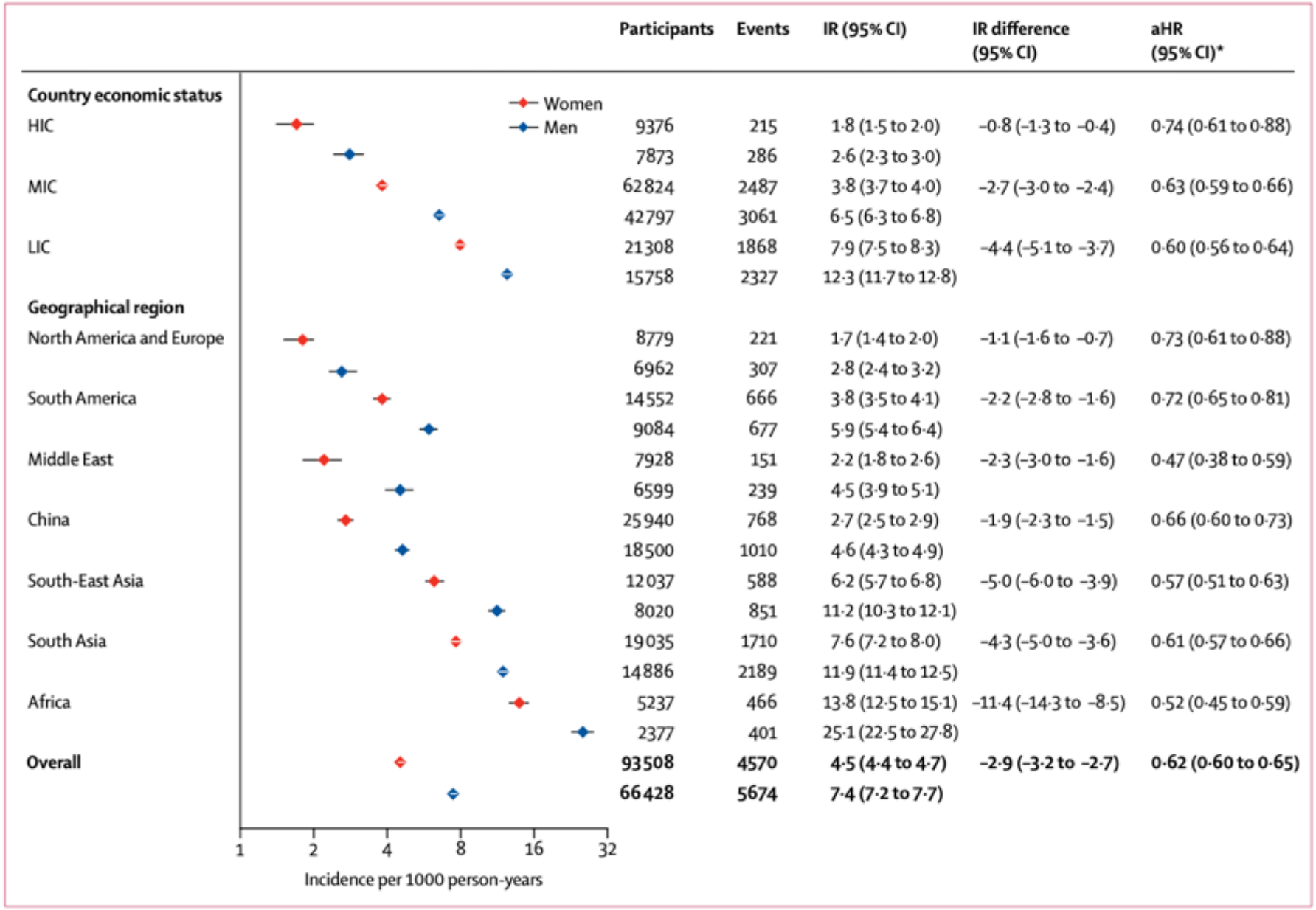
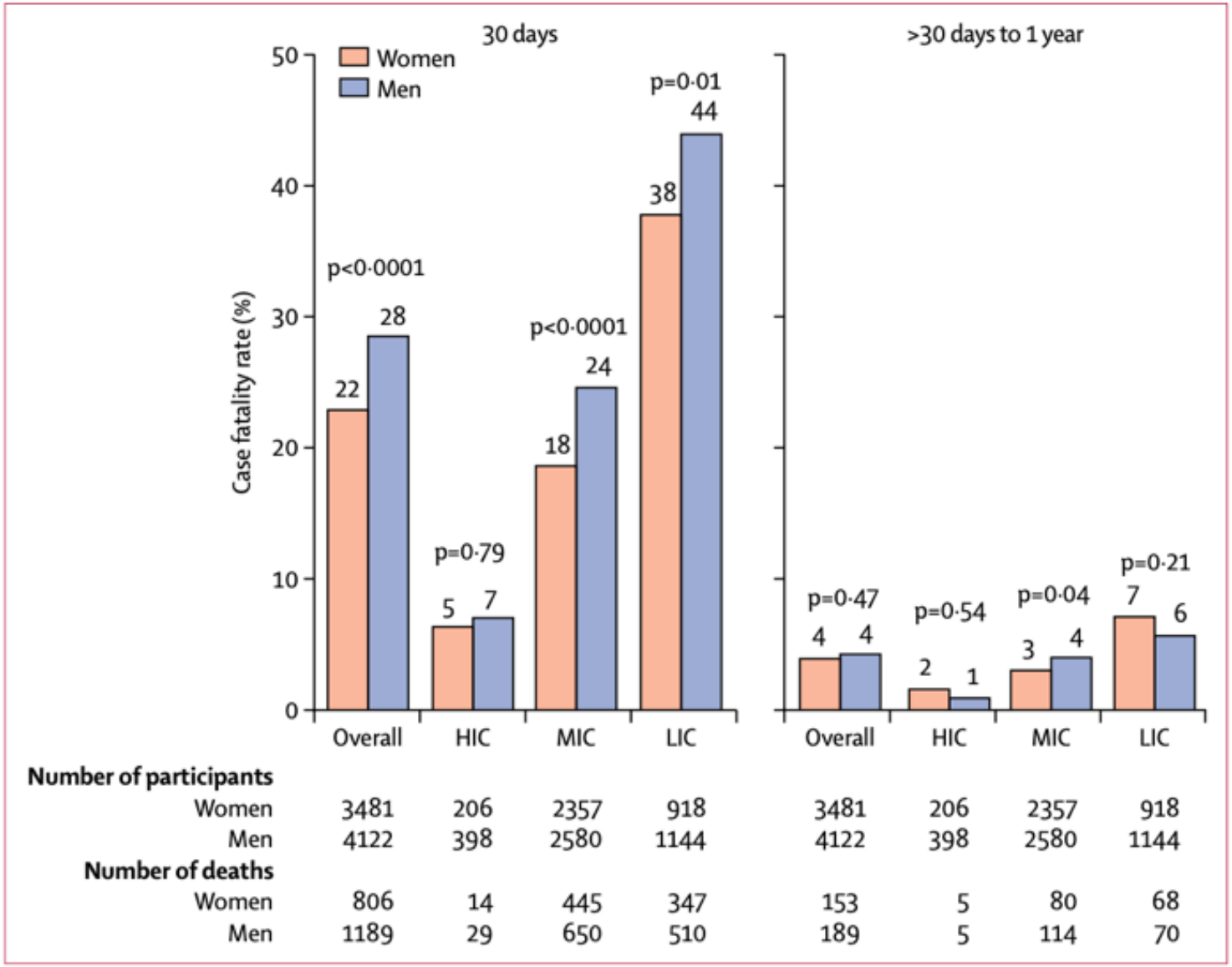


***Figure 3*: Age-standardised incidence rates per 1000 person-years of all-cause death in those without previous cardiovascular disease**

Participants with a history of cardiovascular diseases are excluded. Interaction between sex and country economic status p<0·0001; Interaction between sex and geographic region p<0·0001. Errors bars represent 95% CIs. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios adjusted for location, education, INTERHEART risk score, and a random intercept for centre. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.



Number of participants								
Women	3481	206	2357	918	3481	206	2357	918
Men	4122	398	2580	1144	4122	398	2580	1144
Number of deaths								
Women	806	14	445	347	153	5	80	68
Men	1189	29	650	510	189	5	114	70

Figure 4: **Case fatality rates after an incident myocardial infarction, stroke, or heart failure event in women and men by country economic status**

Case fatality rates adjusted for age. Participants with a history of cardiovascular diseases were excluded.

	Participants without a history of cardiovascular disease				Participants with a history of cardiovascular disease			
	Women, n/N (%)	Men, n/N (%)	Women vs men OR (95% CI)*	Women vs men OR (95% CI)†	Women, n/N (%)	Men, n/N (%)	Women vs men OR (95% CI)*	Women vs men OR (95% CI)†
Medication								
Antiplatelet drugs	3621/113 451 (3·2%)	2684/76 963 (3·5%)	0·96 (0·91–1·01)	1·34 (1·26–1·42)	1357/6348 (21·4%)	1660/5310 (31·3%)	0·67 (0·60–0·75)	0·65 (0·59–0·72)
β blockers	4410/113 451 (3·9%)	2070/76963 (2·7%)	1·53 (1·44–1·62)	2·34 (2·20–2·49)	1022/6348 (16·1%)	1020/5310 (19·2%)	0·73 (0·66–1·81)	0·93 (0·83–1·04)
ACE inhibitors or ARBs	7549/113 451 (6·7%)	4472/76963 (5·8%)	1·17 (1·12–1·22)	1·91 (1·82–2·00)	1280/6348 (20·2%)	1323/5310 (24·9%)	0·66 (0·59–0·73)	0·86 (0·77–0·96)
Diuretics	4669/113 451 (4·1%)	2345/76963 (3·0%)	1·47 (1·39–1·55)	2·20 (2·07–2·33)	896/6348 (14·1%)	579/5310 (10·9%)	1·27 (1·12–1·44)	1·56 (1·37–1·77)
Calcium-channel blockers	3495/113 451 (3·1%)	2123/76963 (2·8%)	1·25 (1·18–1·33)	1·80 (1·70–1·92)	755/6348 (11·9%)	629/5310 (11·8%)	1·04 (0·92–1·17)	1·28 (1·12–1·45)
Blood-pressure lowering medicines among those with known hypertension‡	13 932/21 878 (63·7%)	7584/12 285 (61·7%)	1·01 (0·96–1·06)	1·21 (1·15–1·28)	2308/3513 (65·7%)	1847/2703 (68·3%)	0·71 (0·63–0·80)	0·82 (0·72–0·92)
Statins	3952/113 451 (3·5%)	2509/ 76963 (3·3%)	1·08 (1·02–1·14)	1·60 (1·50–1·69)	951/6348 (15·0%)	1200/5310 (22·6%)	0·54 (0·48–0·60)	0·70 (0·62–0·79)
Use of glucose-lowering agents among those with known diabetes	4050/8090 (50·1%)	2977/5902 (50·4%)	1·02 (0·95–1·10)	1·19 (1·11–1·28)	668/1303 (51·3%)	572/1288 (44·4%)	1·03 (0·87–1·23)	1·31 (1·09–1·56)
Hypertension control and healthy lifestyle behaviours								
Hypertension controlled among those with known hypertension	6922/21 878 (31·6%)	3177/12 285 (25·9%)	1·34 (1·27–1·42)	NA	1205/3513 (34·3%)	860/2703 (31·8%)	1·11 (0·98–1·25)	NA
Quit smoking among ever smokers	9644/20 880 (46·2%)	14 606/42 541 (34·2%)	1·57 (1·51–1·63)	NA	770/1373 (56·1%)	1767/3242 (54·5%)	1·01 (0·87–1·18)	NA
Healthy eating	28 765/86 132 (33·4%)	20 284/61 182 (33·2%)	1·05 (1·03 to –1·07)	NA	1635/4113 (39·8%)	1394/3834 (36·4%)	1·21 (1·10–1·33)	NA
Physically active§	45 482/105 042 (43·3%)	32 259/70 546 (45·7%)	0·91 (0·89–0·93)	NA	2443/6074 (40·2%)	1894/5040 (37·6%)	1·21 (1·11–1·31)	NA

OR=odds ratio. ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. *OR adjusted for age, education, urban versus rural location. †OR adjusted for age, education, urban versus rural location, and INTERHEART risk score. ‡Blood-pressure lowering medicines include any of β blockers, ACE inhibitors, ARBs, diuretics, calcium-channel blockers, and alpha-antagonist. §High physical activity was defined as having performed more than 3000 metabolic equivalent × min per week.

Table 3: **Use of preventive medicines, risk factor control, and healthy lifestyle behaviours in participants without and with a history of cardiovascular disease**

	Cardiac tests									Revascularisation procedures (PCI or CABG)		
	Cardiac echocardiogram			Stress test			Coronary angiogram			Women, n/N (%)	Men, n/N (%)	Women vs Men OR* (95% CI)
	Women, n/N (%)	Men, n/N (%)	Women vs Men OR* (95% CI)	Women, n/N (%)	Men, n/N (%)	Women vs Men OR* (95% CI)	Women, n/N (%)	Men, n/N (%)	Women vs Men OR* (95% CI)			
Overall	1796/3930 (45·7%)	2155/3712 (58·1%)	0·77 (0·69–0·86)	829/3929 (21·1%)	1269/3706 (34·2%)	0·72 (0·62–0·85)	990/3935 (25·2%)	1538/3721 (41·3%)	0·62 (0·54–0·70)	477/3959 (12·1%)	1180/3759 (31·4%)	0·37 (0·32–0·42)
High-income countries	214/273 (78·4%)	499/600 (83·2%)	0·72 (0·49–1·04)	194/274 (70·8%)	494/604 (81·2%)	0·64 (0·40–1·02)	167/273 (61·2%)	444/605 (73·4%)	0·59 (0·42–0·82)	103/277 (37·2%)	424/623 (68·1%)	0·29 (0·22–0·40)
Middle-income countries	1408/3109 (45·3%)	1377/2580 (53·4%)	0·81 (0·71–0·93)	597/3107 (19·2%)	702/2570 (27·3%)	0·74 (0·62–0·88)	742/3113 (23·8%)	918/2582 (35·6%)	0·64 (0·55–0·74)	323/3129 (10·3%)	625/2592 (24·1%)	0·37 (0·31–0·44)
Low-income countries	174/548 (31·8%)	279/532 (52·4%)	0·63 (0·47–0·85)	38/548 (6·9%)	73/532 (13·7%)	0·72 (0·45–1·15)	81/549 (14·8%)	176/534 (33·0%)	0·54 (0·38–0·75)	51/553 (9·2%)	131/544 (24·1%)	0·50 (0·34–0·76)

PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. OR=odds ratio. *OR adjusted for age, education, urban versus rural location, and random intercept for centre.

Table 4: **Number of participants who received cardiac tests and coronary revascularisation procedures in women and men with coronary artery disease overall and by economic status**

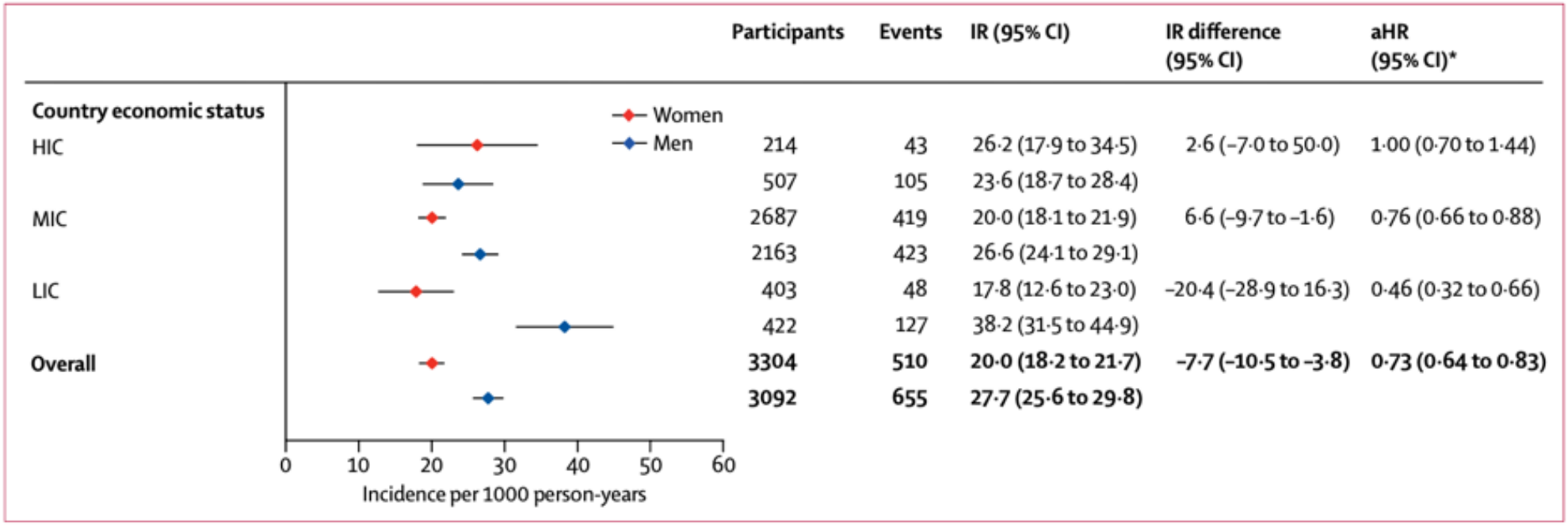


***Figure 5*: Age-standardised incidence rates per 1000 person-year of major cardiovascular disease in those with a history of coronary artery disease**

Major cardiovascular disease includes cardiovascular death, myocardial infarction, stroke, heart failure, and other major cardiovascular disease events. Errors bars represent 95% CIs. Interaction between sex and country economic status p=0·0018. IR=age standardised incidence rates per 1000 person-years. aHR=adjusted hazard ratio. HIC=high-income country. MIC=middle-income country. LIC=low-income country. *Hazard ratios adjusted for location, education, INTERHEART risk score, and a random intercept for centre. The INTERHEART risk score includes age, smoking, diabetes, blood pressure, family history of heart disease, waist:hip ratio, psychosocial factors, dietary factors, and physical activity.

Research in context

Evidence before this study

We searched the MEDLINE database, without language or publication date restrictions, for estimates of differences between women and men in cardiovascular disease risk factors, incidence, deaths, and use of treatments on Sept 15, 2019, and again on Nov 30, 2019. Our search terms were "gender" OR "sex" OR "women" AND "cardiovascular" OR "coronary heart disease" OR "coronary artery disease" OR "risk factor" OR "revascularization" OR "percutaneous coronary intervention" OR "coronary artery bypass grafting" OR "primary prevention" OR "statin" OR "secondary prevention".

Studies have emphasised that women are less likely to undergo revascularisation procedures and receive fewer guideline recommended therapies than men upon having a cardiovascular disease event. These findings, when viewed in isolation, have raised concerns that women are disadvantaged when it comes to cardiovascular disease care. However, much of the existing evidence was from North America and Europe, and most of the published literature are based on hospital registries, outpatient clinics, or administrative databases. We did not find any comprehensive report on differences between women and men in risk factors, management, and outcomes in those with and without a history of cardiovascular disease drawn from community-based populations.

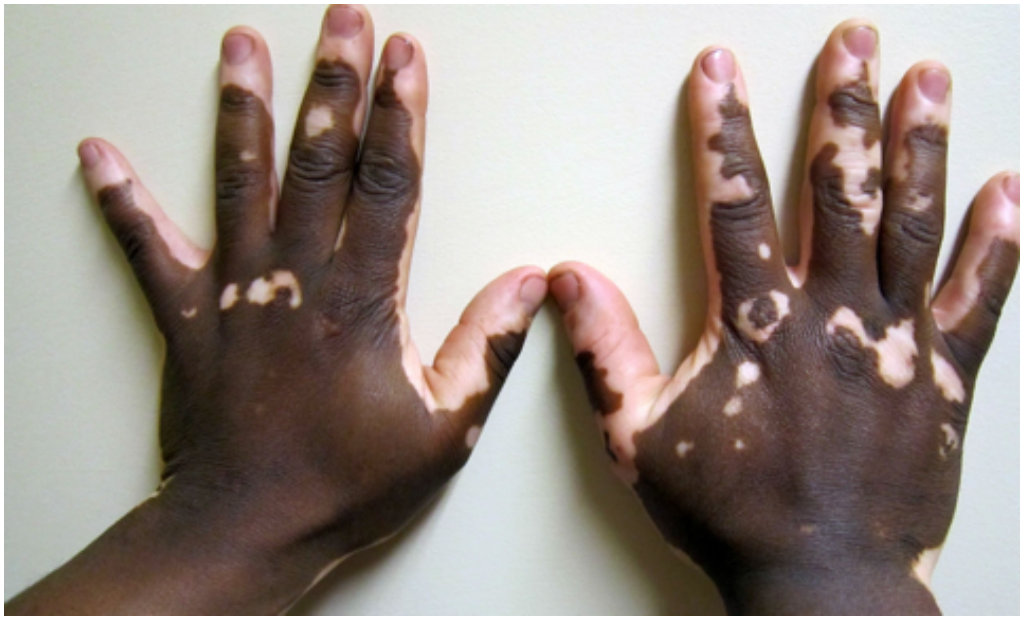
Added value of this study

We systematically examine differences in risk factors, treatments, cardiovascular disease incidence, and mortality in a large population with and without previous cardiovascular disease between women and men from high-income, middle-income, and low-income countries. Our findings indicate that the cardiovascular disease risk factor burden is lower in women; this is consistent across countries at all economic levels and geographical regions. Moreover, primary prevention strategies are used more frequently in women than in men, and are accompanied by lower incidence of cardiovascular disease and mortality. By contrast, use of secondary prevention treatments, cardiac investigations, and coronary interventions, are less frequent in women than in men, but are not associated with a higher rate of recurrent cardiovascular disease or death in women over a median follow-up time of 9·5 (IQR 8·5–10·9) years. The differences in treatments and in outcomes in both women and men from low-income and middle-income countries compared with high-income countries are much larger than the differences between sexes globally or within groups of countries.

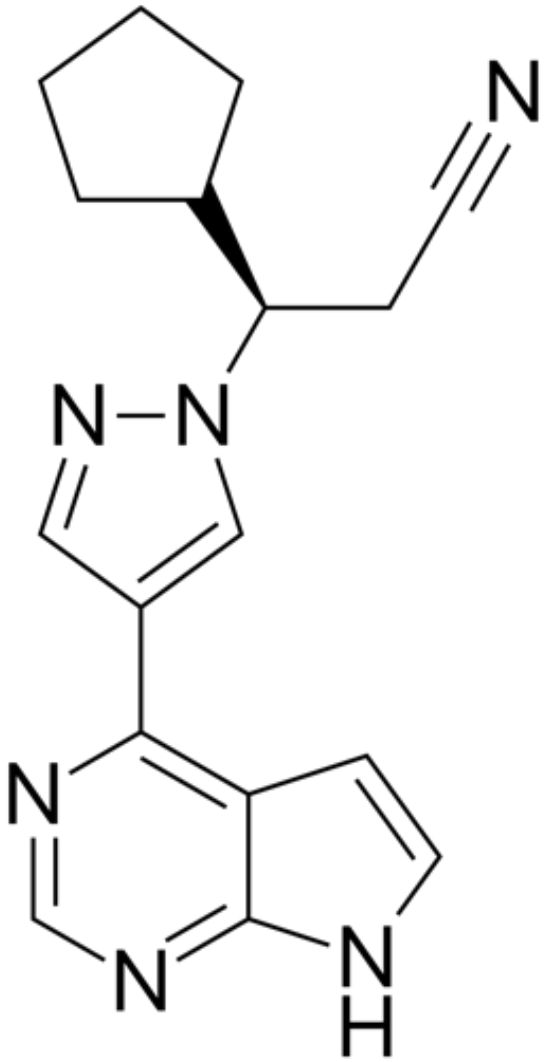
Implications of all the available evidence

Although there are contrasting patterns in the differences in treatment rates between women and men in those with and without previous cardiovascular disease, our data indicate that women do not have worse cardiovascular disease outcomes compared with men. The differences in cardiovascular disease incidence, death, and use of treatments in both women and men between high-income compared with low-income and middle-income countries, and North America and Europe versus other regions is much larger. Understanding and narrowing these gaps deserve greater attention.

Vitiligo (lateinisch vitilīgō ‚Flechte', ‚Hautkrankheit'; med. Leucopathia acquisita, griechisch λευκός ‚weiß' πάθος ‚Leiden' lat. acquisita ‚erworben') oder auch Weißfleckenkrankheit sowie Scheckhaut genannt ist eine chronische, nicht ansteckende Hauterkrankung, die etwa 0,5 bis 2 % der Menschen weltweit betrifft. Typisch sind Pigmentstörungen in Form weißer, pigmentfreier Hautflecken, die sich langsam ausweiten können, aber nicht unbedingt müssen. Die Ursache ist unbekannt, es werden permanente oder vorübergehende autoimmune Blockierungen bzw. Zerstörung der Melanozyten angenommen. Die Erkrankung tritt oft zusammen mit anderen Autoimmunerkrankungen wie Hashimoto-Thyreoiditis, Diabetes mellitus Typ 1 oder perniziöser Anämie auf. Die Krankheit kann in jedem Alter und auch in anscheinend genetisch nicht vorbelasteten Familien auftreten. Die Vererblichkeitsrate liegt bei ca. 33 %. Statistisch am häufigsten betroffen sind Unterarme, Handgelenke, Hände, Finger, Ellenbogen, Füße und Genitalien. In der Regel sind die gedehnten Hautpartien betroffen, z. B. Ellenbogen. Die unpigmentierten Flächen können sich ausbreiten oder in ihrer Größe konstant bleiben. Spontane Repigmentierungen treten auf.



Ruxolitinib ist
ein Enzymhemmstoff (Tyrosinkinaseinhibitor), der
bei bestimmten Blutbildungskrankheiten
(Myeloproliferativen Neoplasien) wie
der idiopathischen (oder primären)
Myelofibrose oder der Polycythämie eingesetzt wird.
Der Wirkstoff ist seit 2012 zugelassen
(Handelsnamen Jakafi, Jakavi) und hemmt selektiv
die beiden Januskinasen JAK-1 und JAK-2, die über
den JAK-STAT-Signalweg die Wirkung pro-
inflammatorischer Mediatoren und Zytokine,
z. B. Interferon-γ in die Zelle und
den Zellkern vermitteln. Die Anwendung von
Ruxolitinib ist angezeigt bei der Behandlung der
primären Myelofibrose, Polycythaemia vera und bei
Post-Essentieller-Thrombozythämie-Myelofibrose
oder Post-Polycythaemia-vera-Myelofibrose. Auch
bei Behandlung der akuten und Cortison-
refraktären Graft-versus-Host-Reaktion, also einer
Immunreaktion der Stammzellen
nach allogener Stammzelltransplantation gegen den
Empfänger, zeigt Ruxolitinib gute Ergebnisse. In
einer offenen randomisierten kontrollierten
Studie (Phase-III-Studie) zeigte sich unter
Ruxolitinib nach 28 Tagen in 62 % (gegen 39 % in
der Kontrollgruppe) eine Reaktion (Odds ratio 2,64)
mit einer medianen Überlebenszeit von 11 Monaten
(gegen 7 Monate). Ruxolitinib ist für diese Indikation
bisher nicht zugelassen.



Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial

Summary

Background Vitiligo is a chronic autoimmune disease resulting in skin depigmentation and reduced quality of life. There is no approved treatment for vitiligo repigmentation and current off-label therapies have limited efficacy, emphasising the need for improved treatment options. We investigated the therapeutic potential of ruxolitinib cream in patients with vitiligo and report the efficacy and safety results up to 52 weeks of double-blind treatment.

Methods We did a multicentre, randomised, double-blind, phase 2 study for adult patients with vitiligo in 26 US hospitals and medical centres in 18 states. Patients with depigmentation of 0·5% or more of their facial body surface area (BSA) and 3% or more of their non-facial BSA were randomly assigned (1:1:1:1:1) by use of an interactive response technology system to receive ruxolitinib cream (1·5% twice daily, 1·5% once daily, 0·5% once daily, or 0·15% once daily) or vehicle (control group) twice daily on lesions constituting 20% or less of their total BSA for 24 weeks. Patients in the control group in addition to patients in the 0·15% once daily group who did not show a 25% or higher improvement from baseline in facial Vitiligo Area Scoring Index (F-VASI) at week 24 were re-randomised to one of three higher ruxolitinib cream doses (0·5% once daily, 1·5% once daily, 1·5% twice daily). Patients in the 0·5% once daily, 1·5% once daily, or 1·5% twice daily groups remained at their original dose up to week 52. Patients, investigators, and the study sponsor (except members of the interim analysis and primary endpoint analysis data monitoring teams) remained masked to treatment assignment throughout the study. The primary endpoint was the proportion of patients achieving a 50% or higher improvement from baseline in F-VASI (F-VASI50) at week 24, assessed in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT03099304.

Findings Between June 7, 2017, and March 21, 2018, 205 patients were screened for eligibility, 48 were excluded and 157 patients (mean age, 48·3 years [SD 12·9]; 73 [46%] male and 84 [54%] female) were randomly assigned to either an intervention group or the control group. 32 (20%) of 157 were assigned to the control group, 31 (20%) to the 0·15% once daily group, 31 (20%) to the 0·5% once daily group, 30 (19%) to the 1·5% once daily group, and 33 (21%) to the 1·5% twice daily group. F-VASI50 at week 24 was reached by significantly more patients given ruxolitinib cream at 1·5% twice daily (15 [45%] of 33) and 1·5% once daily (15 [50%] of 30) than were treated with vehicle (one [3%] of 32). Four patients had serious treatment-emergent adverse events (one patient in the 1·5% twice daily group developed subdural haematoma; one patient in the 1·5% once daily group had a seizure; one patient in the 0·5% once daily group had coronary artery occlusion; and one patient in the 0·5% once daily group had oesophageal achalasia), all of which were unrelated to study treatment. Application site pruritus was the most common treatment-related adverse event among patients given ruxolitinib cream (one [3%] of 33 in the 1·5% twice daily group; three [10%] of 30 in the 1·5% once daily group; three [10%] of 31 in the 0·5% once daily group; and six [19%] of 31 in the 0·15% once daily group) with three [9%] of 32 patients showing application site pruritis in the control group. Acne was noted as a treatment-related adverse event in 13 (10%) of 125 patients who received ruxolitinib cream and one (3%) of 32 patients who received vehicle cream. All treatment-related adverse events were mild or moderate in severity and similar across treatment groups.

Interpretation Treatment with ruxolitinib cream was associated with substantial repigmentation of vitiligo lesions up to 52 weeks of treatment, and all doses were well tolerated. These data suggest that ruxolitinib cream might be an effective treatment option for patients with vitiligo.

	Control (vehicle twice daily; n=32)	Ruxolitinib cream				Total (n=157)
		0·15% once daily group (n=31)	0·5% once daily group (n=31)	1·5% once daily group (n=30)	1·5% twice daily group (n=33)	
Age, years	46·3 (13·1)	45·1 (11·5)	53·8 (14·3)	46·7 (11·7)	49·5 (12·3)	48·3 (12·9)
≤30	4 (13%)	2 (6%)	3 (10%)	2 (7%)	4 (12%)	15 (10%)
>30	28 (88%)	29 (94%)	28 (90%)	28 (93%)	29 (88%)	142 (90%)
Sex						
Male	12 (38%)	13 (42%)	19 (61%)	11 (37%)	18 (55%)	73 (46%)
Female	20 (63%)	18 (58%)	12 (39%)	19 (63%)	15 (45%)	84 (54%)
Race						
White	26 (81%)	29 (94%)	25 (81%)	23 (77%)	29 (88%)	132 (84%)
Black	5 (16%)	0	4 (13%)	2 (7%)	3 (9%)	14 (9%)
Asian	1 (3%)	0	1 (3%)	2 (7%)	1 (3%)	5 (3%)
Other	0	2 (6%)	1 (3%)	3 (10%)	0	6 (4%)
Baseline F-VASI	1·21 (0·85)	1·19 (0·75)	1·22 (0·71)	1·45 (0·98)	1·26 (0·81)	1·26 (0·82)
Baseline T-VASI	19·40 (18·51)	14·57 (9·05)	18·43 (15·36)	20·55 (18·49)	16·94 (14·26)	17·96 (15·45)
Facial BSA*	1·44 (0·84)	1·35 (0·86)	1·40 (0·76)	1·67 (0·95)	1·55 (0·89)	1·48 (0·86)
Total BSA	23·54 (20·96)	17·56 (10·93)	22·96 (21·45)	24·81 (20·06)	21·46 (16·82)	22·05 (18·38)
Duration of disease, years	15·4 (1·5–37·6)	13·7 (0·3–67·9)	10·8 (1·7–59·0)	14·7 (0·3–56·0)	13·5 (0·8–47·8)	14·0 (0·3–67·9)
Diagnosed in childhood†	8 (25%)	7 (23%)	6 (19%)	4 (13%)	10 (30%)	35 (22%)
Type of vitiligo						
Segmental	5 (16%)	2 (6%)	2 (6%)	0	2 (6%)	11 (7%)
Non-segmental	27 (84%)	29 (94%)	29 (94%)	30 (100%)	31 (94%)	146 (93%)
Disease stability‡						
Progressive	21 (66%)	20 (65%)	12 (39%)	16 (53%)	20 (61%)	89 (57%)
Stable	11 (34%)	11 (35%)	19 (61%)	14 (47%)	13 (39%)	68 (43%)
Skin type						
I	1 (3%)	1 (3%)	1 (3%)	2 (7%)	1 (3%)	6 (4%)
II	7 (22%)	11 (35%)	12 (39%)	8 (27%)	12 (36%)	50 (32%)
III	10 (31%)	9 (29%)	9 (29%)	9 (30%)	13 (39%)	50 (32%)
IV	8 (25%)	8 (26%)	4 (13%)	7 (23%)	4 (12%)	31 (20%)
V	2 (6%)	2 (6%)	2 (6%)	3 (10%)	1 (3%)	10 (6%)
VI	4 (13%)	0	3 (10%)	1 (3%)	2 (6%)	10 (6%)
Other autoimmune disorders						
Thyroid disorders	11 (34%)	6 (19%)	5 (16%)	9 (30%)	8 (24%)	39 (25%)
Juvenile diabetes	0	0	0	0	2 (6%)	2 (1%)
Pernicious anaemia	1 (3%)	0	0	0	0	1 (1%)
Previous therapy						
Topical corticosteroids	16 (50%)	16 (52%)	12 (39%)	14 (47%)	14 (42%)	72 (46%)
Calcineurin inhibitors	18 (56%)	14 (45%)	13 (42%)	11 (37%)	14 (42%)	70 (45%)
Phototherapy	14 (44%)	5 (16%)	13 (42%)	11 (37%)	12 (36%)	55 (35%)
Excimer laser therapy	4 (13%)	2 (6%)	6 (19%)	5 (17%)	3 (9%)	20 (13%)
Photochemotherapy	1 (3%)	1 (3%)	2 (6%)	4 (13%)	4 (12%)	12 (8%)
Vitamin D derivatives	2 (6%)	1 (3%)	2 (6%)	1 (3%)	1 (3%)	7 (4%)
Surgical techniques	0	0	0	0	1 (3%)	1 (1%)
Other	8 (25%)	3 (10%)	2 (6%)	1 (3%)	3 (9%)	17 (11%)

Data are n (%), mean (SD), or median (range). BSA=body surface area. F-VASI=facial Vitiligo Area Scoring Index. T-VASI=total Vitiligo Area Scoring Index. *Percentage of total BSA. †Data missing for one patient in the 1·5% twice daily group. ‡Determination of disease stability was based on investigator judgment.

Table 1: Baseline characteristics

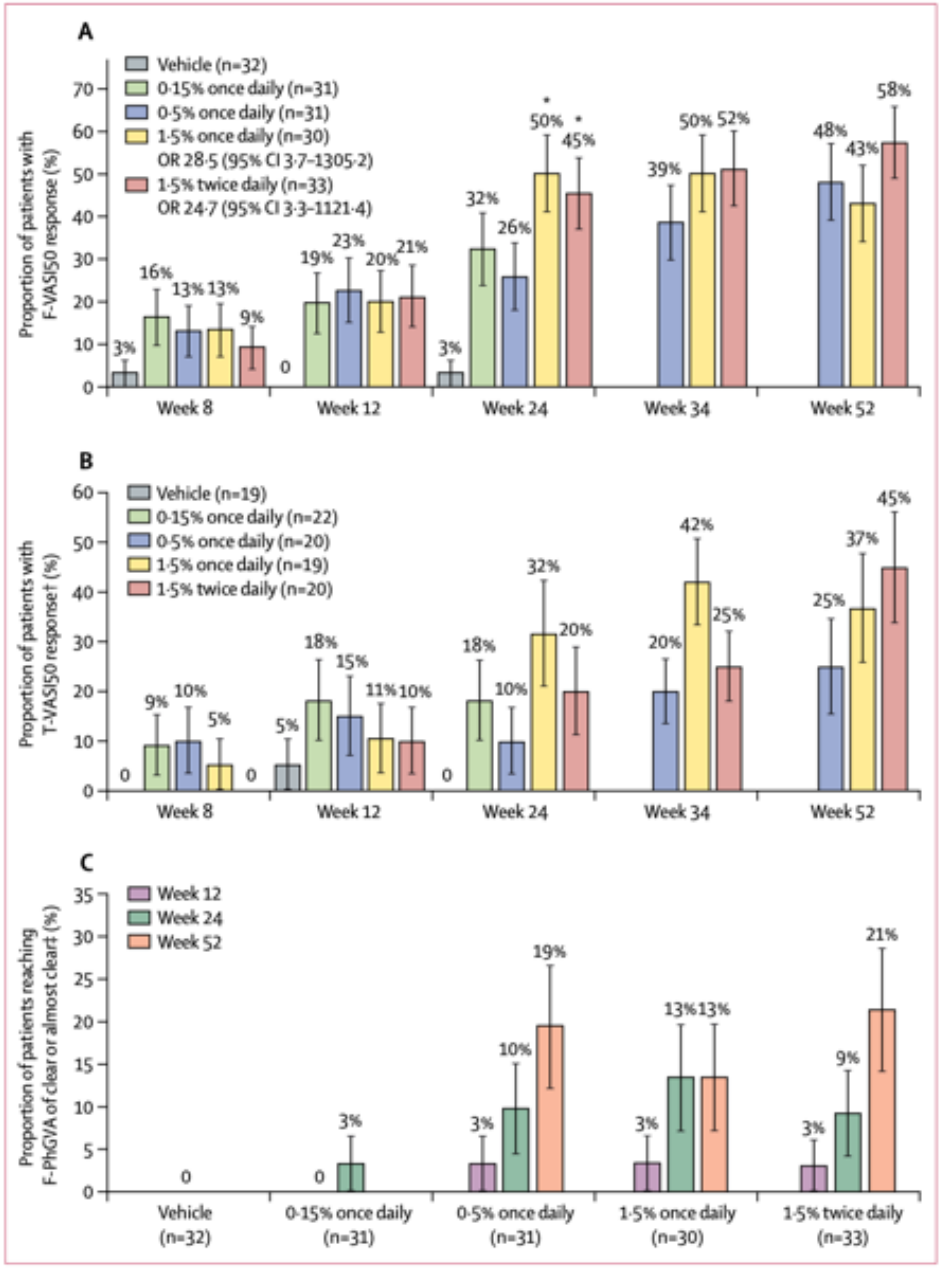


Figure 2: **Efficacy of varying doses of ruxolitinib cream or vehicle cream**

(A) F-VASI50 response. (B) T-VASI50 response. (C) F-PhGVA of clear or almost clear. Part 1 of the study was double-blind vehicle-controlled (up to week 24) and part 2 was a double-blind extension period (up to week 52). Error bars indicate SE. F-PhGVA=facial Physician's Global Vitiligo Assessment. F-VASI50=facial Vitiligo Area Scoring Index improvement of 50% or more. OR=odds ratio. T-BSA=total body surface area. T-VASI50=total Vitiligo Area Scoring Index improvement of 50% or more. *p<0·0001 *vs* vehicle at week 24. †T-VASI50 response is reported for the subset of patients with baseline T-BSA of 20% or less because treatment was limited to lesions constituting 20% or less of T-BSA. ‡No patients had F-PhGVA values of clear or almost clear at baseline.

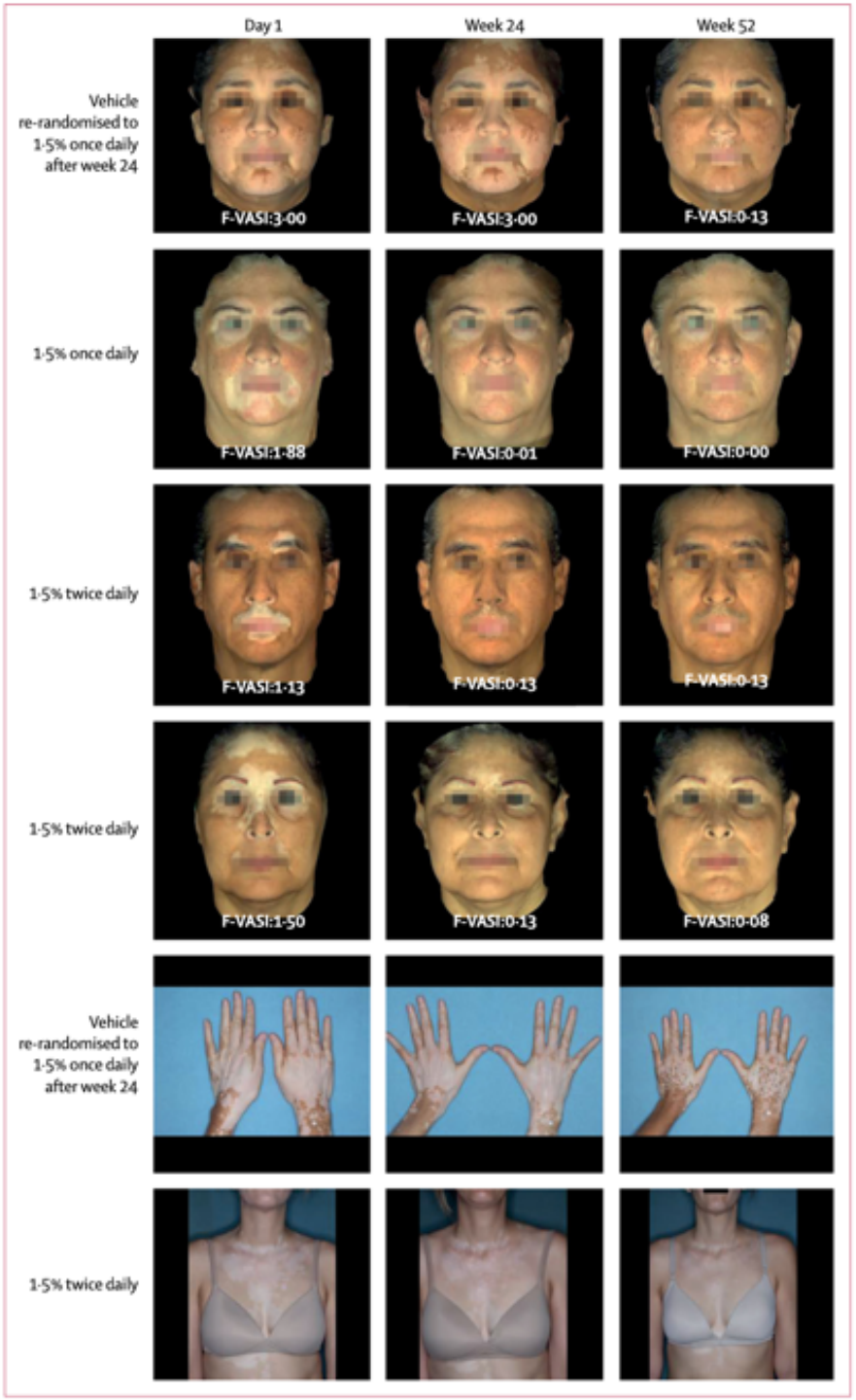


***Figure 3*: Representative clinical images of patients during double-blind treatment with ruxolitinib**
F-VASI=facial Vitiligo Area Scoring Index. Patients provided consent to use their images.

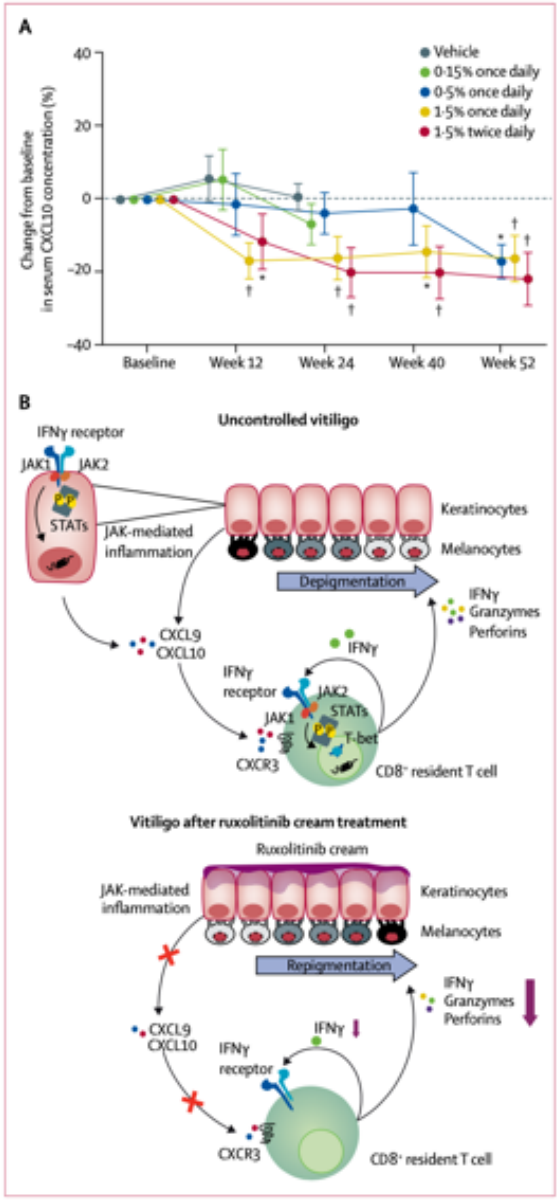


***Figure 4*: Effect of ruxolitinib cream on biomarkers in vitiligo**
(A) Percentage change in CXCL10 serum concentrations following 52 weeks of treatment. (B) Proposed mechanism of action for ruxolitinib cream in vitiligo. Data are mean percentage change (SE). Ruxolitinib cream reduces skin inflammation by inhibiting IFNγ-mediated activation of keratinocytes leading to a reduction of IFNγ, CXCL9, and CXCL10 in circulation. Subsequent reduction of $CD8^+$ T cells trafficking to the skin and the corresponding reduction of inflammatory mediators allows for recovery of melanocyte number and function, facilitating endogenous repigmentation. CXCL=C-X-C motif chemokine ligand. CXCR3=C-X-C motif chemokine receptor 3. IFNγ=interferon γ. JAK=Janus kinase. STAT=signal transducer and activator of transcription. T-bet=T-box transcription factor expressed in T cells. *p<0·05 *vs* baseline; †p<0·01 *vs* baseline. Exact p values for all comparisons are presented in the appendix (p 16).

	Control (vehicle twice daily; n=32)	Ruxolitinib cream			
		0·15% once daily group (n=31)	0·5% once daily group (n=31)	1·5% once daily group (n=30)	1·5% twice daily group (n=33)
Patients with treatment-emergent adverse events	20 (63%)	20 (65%)	26 (84%)	23 (77%)	23 (70%)
Most common treatment-emergent adverse events*					
Acne	1 (3%)	4 (13%)	5 (16%)	3 (10%)	6 (18%)
Viral upper respiratory tract infection	5 (16%)	3 (10%)	3 (10%)	6 (20%)	1 (3%)
Application site pruritus	3 (9%)	6 (19%)	3 (10%)	3 (10%)	1 (3%)
Pruritus	3 (9%)	1 (3%)	5 (16%)	4 (13%)	3 (9%)
Upper respiratory tract infection	0	1 (3%)	5 (16%)	1 (3%)	3 (9%)
Headache	3 (9%)	1 (3%)	0	3 (10%)	2 (6%)
Sinusitis	1 (3%)	2 (6%)	1 (3%)	2 (7%)	2 (6%)
Patients with treatment-related adverse events	12 (38%)	11 (35%)	12 (39%)	12 (40%)	10 (30%)
Most common treatment-related adverse events*					
Application site pruritus	3 (9%)	6 (19%)	3 (10%)	3 (10%)	1 (3%)
Acne	1 (3%)	1 (3%)	3 (10%)	3 (10%)	6 (18%)
Pruritus	2 (6%)	1 (3%)	4 (13%)	3 (10%)	2 (6%)
Patients with treatment-emergent adverse events leading to discontinuation†	1 (3%)	1 (3%)‡	0	1 (3%)	0
Patients with serious treatment-emergent adverse events§	0	0	2 (6%)	1 (3%)	1 (3%)

Data are n (%). *Occurring in more than 5% of the total patient population. †Treatment-emergent adverse events leading to discontinuation were not related to treatment unless otherwise indicated. ‡Headache related to treatment. §No serious treatment-emergent adverse events were related to treatment.

Table 2: **Treatment-emergent adverse events up to 52 weeks of treatment**

Research in context

Evidence before this study

A PubMed search for publications of clinical trials between Jan 1, 1997, and April 4, 2017, using the terms "vitiligo" and "repigmentation" with an emphasis on topical therapy yielded few results in large patient populations. No language restrictions were applied to the search. Among prospective studies evaluating treatment of vitiligo lesions with topical therapies, the majority evaluated corticosteroids or calcineurin inhibitors, or both. Few studies evaluated targeted immunotherapy for the treatment of vitiligo, but promising preliminary results, especially facial repigmentation, were reported with the use of Janus kinase (JAK) inhibitors. Controlled studies reporting the use of topical corticosteroids and calcineurin inhibitors, currently used off-label, included relatively small patient populations, and results indicated inadequate repigmentation with safety limitations on duration of use.

Added value of this study

This phase 2 study is the first, to our knowledge, to report results from a large, prospective, randomised, vehicle-controlled study evaluating the efficacy and safety of any targeted immunomodulatory agent (including JAK inhibitors) in adult patients with vitiligo. A greater proportion of patients receiving any dose of ruxolitinib cream than vehicle met the primary endpoint of a 50% or greater improvement from baseline in facial Vitiligo Area Scoring Index (F-VASI50) at week 24, compared with vehicle. Continuous improvement was seen following 52 weeks of ruxolitinib cream monotherapy. Additionally, 45% of patients with baseline total body surface area 20% or less (and could therefore treat all depigmented skin) who received 1·5% ruxolitinib cream twice daily had a 50% or greater improvement from baseline in total Vitiligo Area Scoring Index (T-VASI50; total body assessment, including the face) at week 52. Ruxolitinib cream was well tolerated and application site reactions during treatment were few.

Implications of all the available evidence

There is no approved treatment for repigmentation of vitiligo lesions. Results from this randomised, double-blind, phase 2 study provide support for the use of JAK inhibitors in the treatment of vitiligo and a rationale for continued investigation of ruxolitinib cream in randomised phase 3 trials. The data generated in this study could provide additional evidence for the use of F-VASI and T-VASI instruments for quantification of repigmentation in future vitiligo clinical trials, on the basis of post-hoc confirmation of instrument validity and reliability using phase 2 data reported here. Identification of biomarkers predictive of patients expected to respond to ruxolitinib cream treatment would be of considerable value and worthy of continued investigation. The use of ruxolitinib cream monotherapy in patients with vitiligo could lead to effective and sustained repigmentation.

Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

Summary

Background Three drug classes (mineralocorticoid receptor antagonists [MRAs], angiotensin receptor–neprilysin inhibitors [ARNIs], and sodium/glucose cotransporter 2 [SGLT2] inhibitors) reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF) beyond conventional therapy consisting of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and β blockers. Each class was previously studied with different background therapies and the expected treatment benefits with their combined use are not known. Here, we used data from three previously reported randomised controlled trials to estimate lifetime gains in event-free survival and overall survival with comprehensive therapy versus conventional therapy in patients with chronic HFrEF.

Methods In this cross-trial analysis, we estimated treatment effects of comprehensive disease-modifying pharmacological therapy (ARNI, β blocker, MRA, and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and β blocker) in patients with chronic HFrEF by making indirect comparisons of three pivotal trials, EMPHASIS-HF (n=2737), PARADIGM-HF (n=8399), and DAPA-HF (n=4744). Our primary endpoint was a composite of cardiovascular death or first hospital admission for heart failure; we also assessed these endpoints individually and assessed all-cause mortality. Assuming these relative treatment effects are consistent over time, we then projected incremental long-term gains in event-free survival and overall survival with comprehensive disease-modifying therapy in the control group of the EMPHASIS-HF trial (ACE inhibitor or ARB and β blocker).

Findings The hazard ratio (HR) for the imputed aggregate treatment effects of comprehensive disease-modifying therapy versus conventional therapy on the primary endpoint of cardiovascular death or hospital admission for heart failure was 0·38 (95% CI 0·30–0·47). HRs were also favourable for cardiovascular death alone (HR 0·50 [95% CI 0·37–0·67]), hospital admission for heart failure alone (0·32 [0·24–0·43]), and all-cause mortality (0·53 [0·40–0·70]). Treatment with comprehensive disease-modifying pharmacological therapy was estimated to afford 2·7 additional years (for an 80-year-old) to 8·3 additional years (for a 55-year-old) free from cardiovascular death or first hospital admission for heart failure and 1·4 additional years (for an 80-year-old) to 6·3 additional years (for a 55-year-old) of survival compared with conventional therapy.

Interpretation Among patients with HFrEF, the anticipated aggregate treatment effects of early comprehensive disease-modifying pharmacological therapy are substantial and support the combination use of an ARNI, β blocker, MRA, and SGLT2 inhibitor as a new therapeutic standard.

	EMPHASIS-HF[6] (n=2737)	PARADIGM-HF[9] (n=8399)	DAPA-HF[8] (n=4744)
Comparison	Eplerenone *vs* placebo	Sacubitril–valsartan *vs* enalapril	Dapagliflozin *vs* placebo
Enrolment period	2006–10	2009–12	2017–18
Median follow-up, months	21 (10–33)	27 (19–36)	18 (13–21)
Age, years	69 (8)	64 (11)	66 (11)
Sex			
Men	2127 (78%)	6567 (78%)	3635 (77%)
Women	610 (22%)	1832 (22%)	1109 (23%)
Systolic blood pressure, mm Hg	124 (17)	121 (15)	122 (16)
Heart rate, beats per min	72 (13)	72 (12)	72 (12)
Left ventricular ejection fraction, %	26 (5)	30 (6)	31 (7)
New York Heart Association class			
1	0	389 (5%)	0
2	2737 (100%)	5919 (70%)	3203 (68%)
3	0	2018 (24%)	1498 (32%)
4	0	60 (1%)	43 (1%)
Atrial fibrillation	844 (31%)	3091 (37%)	1818 (38%)
Diabetes	859 (31%)	2907 (35%)	1983 (42%)
Previous hospital admission for heart failure	1440 (53%)	5274 (63%)	2251 (47%)
Diuretics	2326 (85%)	6738 (80%)	4008 (84%)
ACE inhibitor, ARB, or ARNI*	2557 (93%)	8379 (100%)	4442 (94%)
β blocker	2374 (87%)	7811 (93%)	4558 (96%)
Mineralocorticoid receptor antagonist	..	4671 (56%)	3370 (71%)

Data are n (%) or mean (SD) unless otherwise stated. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. *DAPA-HF is the only trial that enrolled patients on background ARNIs (n=508).

Table: **Baseline patient characteristics and background medical therapy**

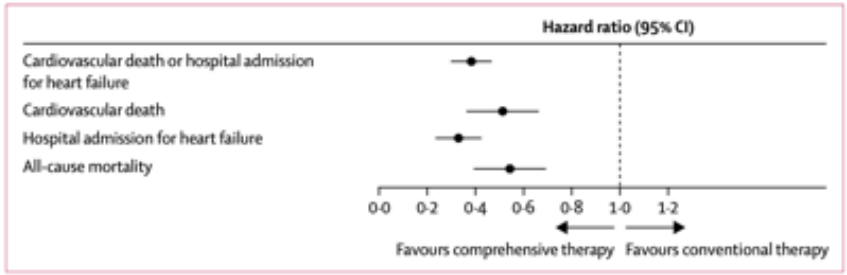


Figure 1: **Estimation of relative treatment effects of comprehensive disease-modifying pharmacological therapy on key cardiovascular events**

Comprehensive therapy consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

See Online for appendix

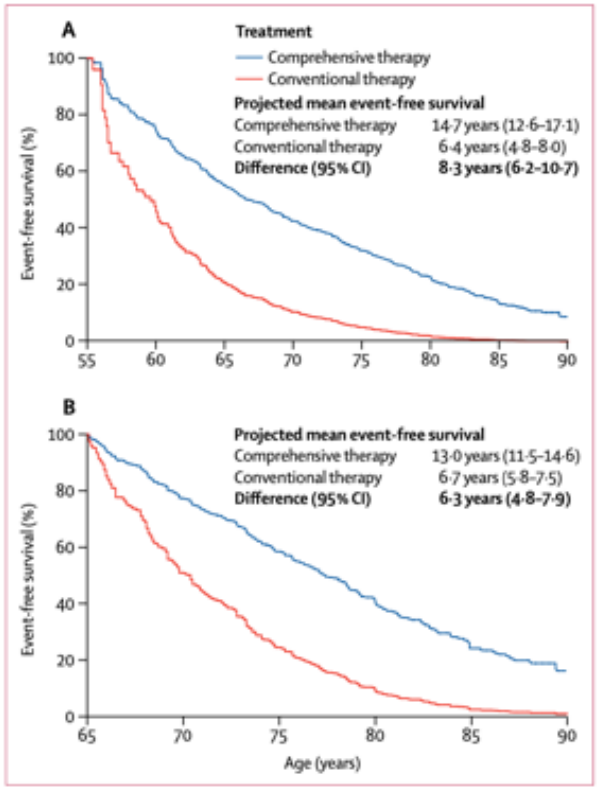


Figure 2: **Event-free survival with comprehensive disease-modifying therapy *vs* conventional therapy**

Kaplan-Meier estimated curves for patients starting at age 55 years (A) and 65 years (B) for primary endpoint event-free survival. Comprehensive therapy (simulated) consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy (EMPHASIS-HF[5] control group) consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

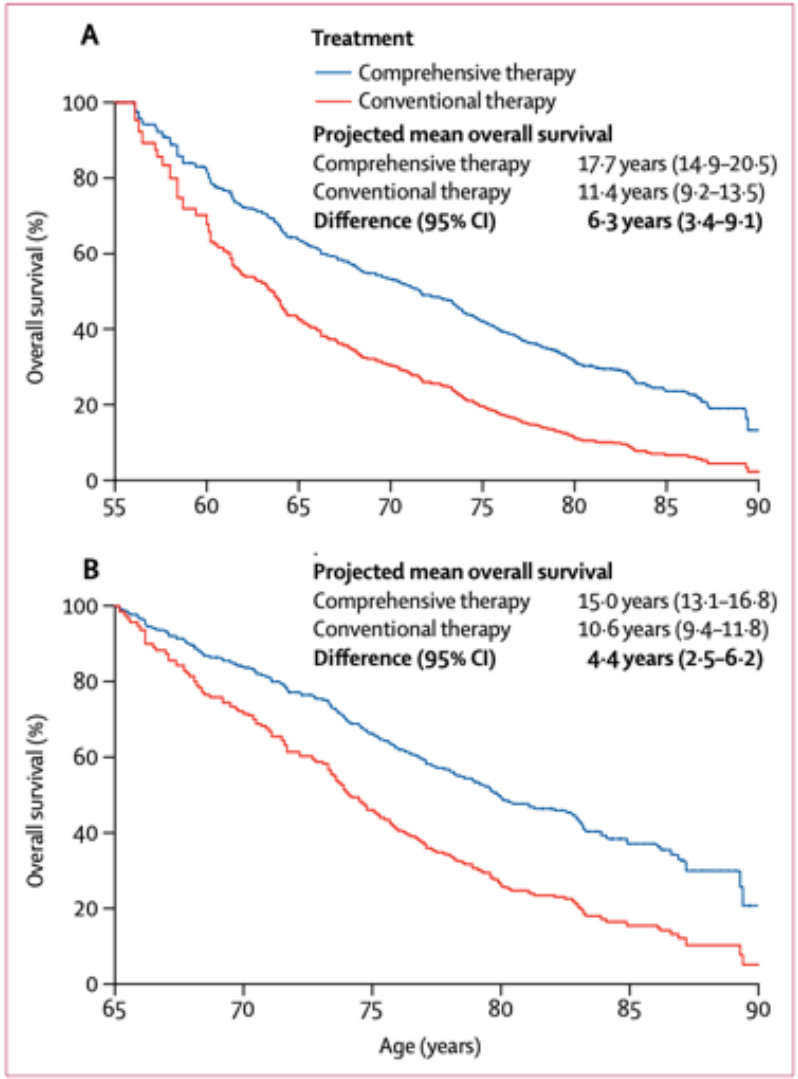


Figure 3: **Long-term overall survival with comprehensive disease-modifying therapy *vs* conventional therapy**

Kaplan-Meier estimated curves for patients starting at age 55 years (A) and 65 years (B) for overall survival. Residual lifespan was estimated using the area under the survival curve up to a maximum of 90 years. Comprehensive therapy (simulated) consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy (EMPHASIS-HF[6] control group) consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

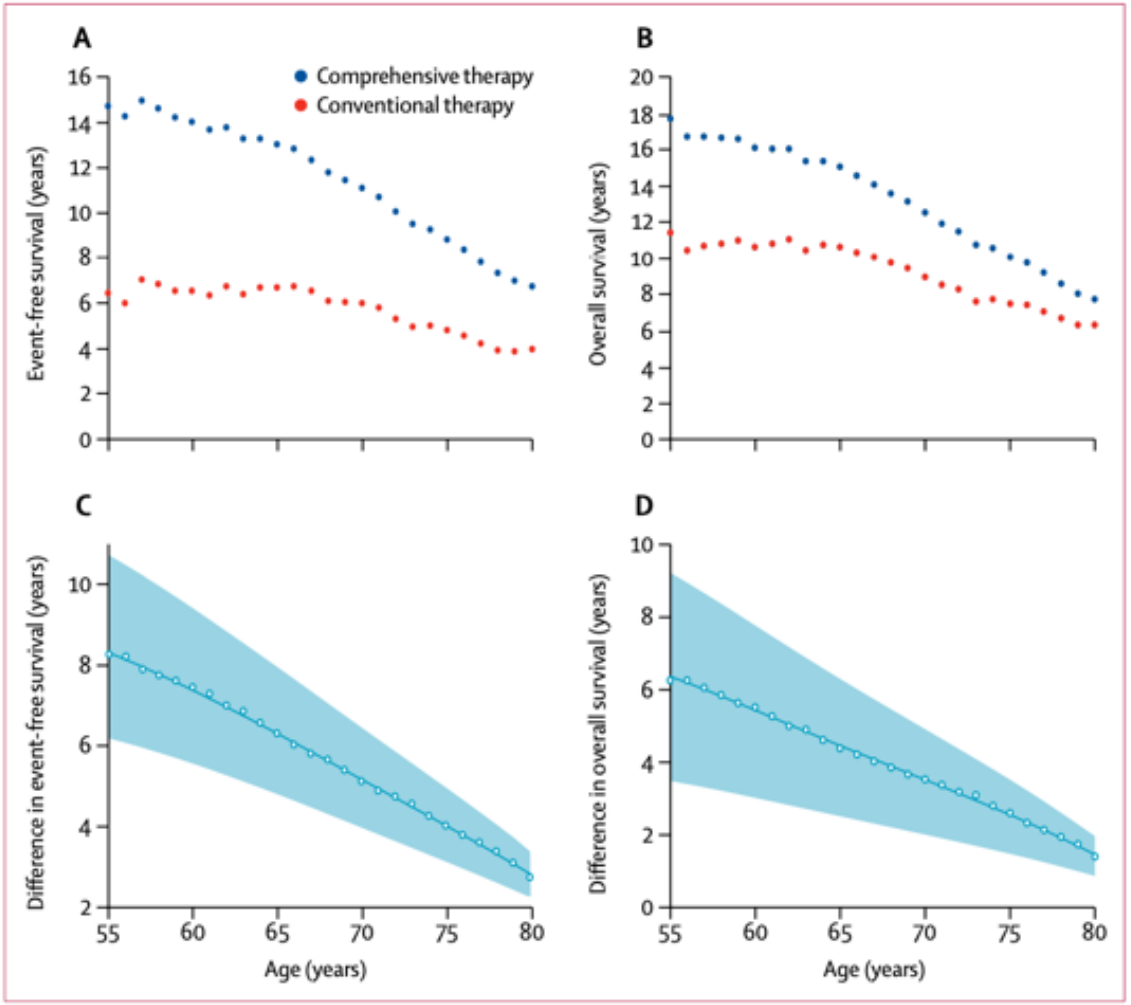


Figure 4: **Treatment benefits on overall survival and event-free survival with comprehensive disease-modifying therapy *vs* conventional therapy**

Estimated mean primary endpoint event-free survival (A) and overall survival (B) in the EMPHASIS-HF control group and the simulated comprehensive therapy group for every age between 55 years and 80 years. Comprehensive therapy (simulated) consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy (EMPHASIS-HF[6] control group) consisted of an ACE inhibitor or ARB and β blocker. Treatment differences (data points), smoothed estimate (solid line), and 95% CI of the smoother estimate (shaded outer area) estimated for mean event-free survival (C) and overall survival (D) with the comprehensive therapy *vs* conventional therapy after application of a locally weighted scatterplot smoothing procedure. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

Research in context

Evidence before this study

Patients with heart failure with reduced ejection fraction (HFrEF) have substantially shorter life expectancies than the general population of a similar age. Multiple therapies are now known to individually extend survival of patients with chronic HFrEF. Although most patients are treated with renin–angiotensin-system inhibitors and β blockers, three drug classes (angiotensin receptor–neprilysin inhibitors [ARNIs], mineralocorticoid receptor antagonists [MRAs], and SGLT2 inhibitors) have additionally been shown to reduce mortality in these patients beyond the effects of the previously established core therapeutic elements. Real-world data have highlighted incomplete use of these more recent additions to the therapeutic armamentarium.

Added value of this study

Although recently introduced therapies have each individually been tested in randomised controlled trials, our study estimates their aggregate benefits when used in a combination multidrug regimen. We used data from three contemporary randomised clinical trials of patients with chronic HFrEF, each with a median follow-up of less than 3 years. Our actuarial analysis projects long-term benefits of these therapies if used over a lifetime. We estimated that comprehensive disease-modifying pharmacological therapy (consisting of an ARNI, β blocker, MRA, and SGLT2 inhibitor) reduces the hazard of cardiovascular death or hospital admission for heart failure significantly (hazard ratio 0·38 [95% CI 0·30–0·47]) compared with conventional therapy (consisting of an angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB] and β blocker). Depending on the age of therapeutic optimisation, treatment with comprehensive disease-modifying pharmacological therapy was estimated to afford 1·4 to 6·3 additional years of survival and 2·7 to 8·3 additional years free from cardiovascular death or hospital admission for heart failure compared with treatment with ACE inhibitor or ARB and β blocker alone.

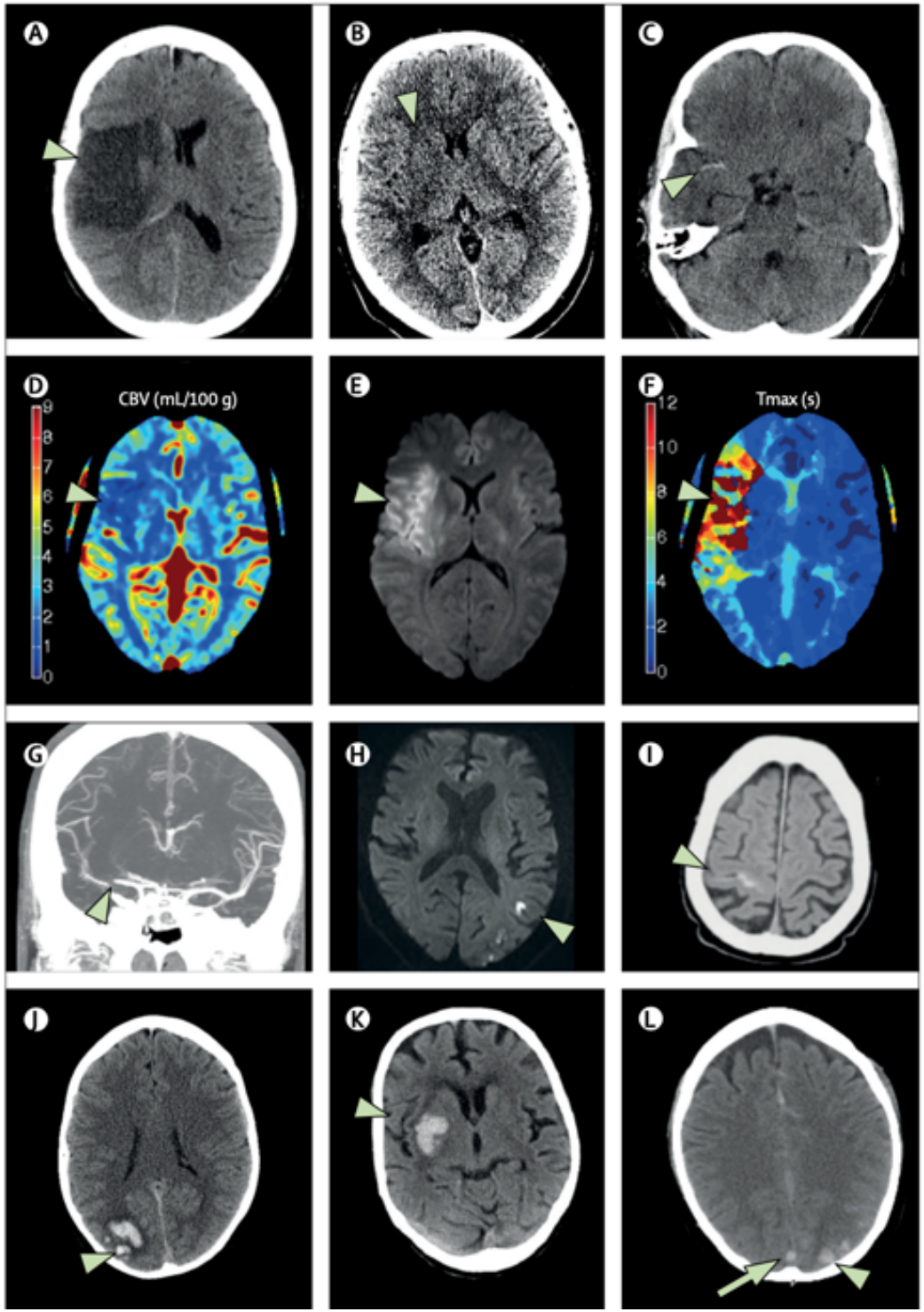
Implications of all the available evidence

Compared with the conventional neurohormonal medical therapies commonly used in clinical practice, our data support the central role of comprehensive disease-modifying pharmacological therapy to halt or delay clinical progression and extend survival of patients with HFrEF. Given incomplete uptake of well established and novel therapies, innovative and disruptive implementation strategies are urgently needed to facilitate use of combination multidrug regimens in appropriately selected patients with HFrEF. The survival benefits estimated with comprehensive disease-modifying pharmacological therapy might be important in shared therapeutic decision making and future health system valuation.

Stroke

Bruce C V Campbell, Pooja Khatri

Stroke is a major cause of death and disability globally. Diagnosis depends on clinical features and brain imaging to differentiate between ischaemic stroke and intracerebral haemorrhage. Non-contrast CT can exclude haemorrhage, but the addition of CT perfusion imaging and angiography allows a positive diagnosis of ischaemic stroke versus mimics and can identify a large vessel occlusion target for endovascular thrombectomy. Management of ischaemic stroke has greatly advanced, with rapid reperfusion by use of intravenous thrombolysis and endovascular thrombectomy shown to reduce disability. These therapies can now be applied in selected patients who present late to medical care if there is imaging evidence of salvageable brain tissue. Both haemostatic agents and surgical interventions are investigational for intracerebral haemorrhage. Prevention of recurrent stroke requires an understanding of the mechanism of stroke to target interventions, such as carotid endarterectomy, anticoagulation for atrial fibrillation, and patent foramen ovale closure. However, interventions such as lowering blood pressure, smoking cessation, and lifestyle optimisation are common to all stroke subtypes.



(A) Ischaemic stroke established in the territory of the right middle cerebral artery 12 h after onset (arrowhead). A patient with left hemiparesis onset 2 h before scan (B–G) showing subtle loss of differentiation between grey and white matter (arrowhead) in the basal ganglia (B) and hyperdense thrombus (arrowhead) in the right middle cerebral artery (C). CT perfusion showing reduced CBV (arrowhead) in the right insular region (D) corresponding to region of diffusion restriction (arrowhead; most likely irreversibly injured) on MRI (E). CT perfusion showing delayed Tmax (arrowhead; substantially delayed Tmax [ie, >6 s] indicates brain tissue that is critically hypoperfused, functionally impaired, and potentially at risk of infarction in the absence of reperfusion) in the right middle cerebral artery territory (F) corresponding to intracranial occlusion of the right middle cerebral artery (arrowhead) on CT angiogram (G). (H) Diffusion MRI lesions (arrowhead) in a patient with two 5 min episodes of aphasia that fully resolved—now defined as ischaemic stroke rather than transient ischaemic attack. (I) Focal subarachnoid haemorrhage (arrowhead) related to amyloid angiopathy presenting as transient parasthesias on the left side (differential diagnosis of transient ischaemic attack). Lobar intracerebral haemorrhage (arrowhead) in a patient with amyloid angiopathy (J) and intracerebral haemorrhage (arrowhead) in the right basal ganglia most likely resulting from deep perforating vasculopathy (K). (L) Thrombosis in the cerebral venous sinus with hyperdense sagittal sinus (arrow) and haemorrhagic venous infarction (arrowhead). CBV=cerebral blood volume. Tmax=time to maximum.

Panel: Major causes of stroke

Atherosclerosis:

- Aortic arch or cervical arteries
- Intracranial arteries

Cardioembolism:

- Atrial fibrillation
- Akinetic myocardial segment
- Patent foramen ovale
- Endocarditis

Small vessel disease

Other causes:

- Other arterial diseases (eg, dissection, vasculitis)
- Haematological diseases (eg, antiphospholipid syndrome, polycythaemia rubra vera, essential thrombocytosis)

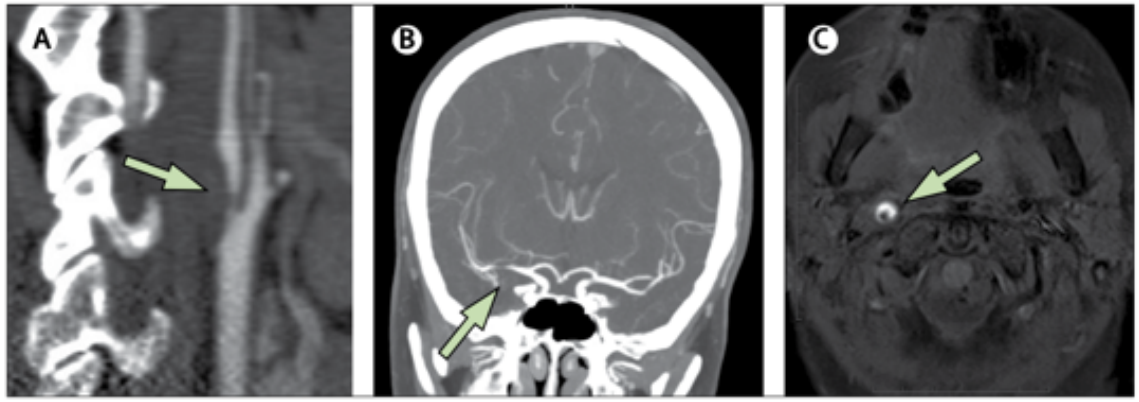


Figure 2: **Determining stroke mechanism**
(A) CT angiography showing atherosclerosis of the internal carotid artery. (B) Intracranial atherosclerotic disease. (C) Fat saturated T1 MRI showing intramural hyperintensity diagnostic of carotid artery dissection.

	Treatment patients with outcome, %	Control patients with outcome, %	Odds ratio (95% CI)	Absolute difference, %
Care in a stroke unit				
Death or dependency (mRS 3–6)[11]	52·4%	60·9%	0·75 (0·66–0·85)	8·5%
Ischaemic stroke				
Alteplase thrombolysis, non-contrast CT brain selection[12,13]				
mRS 0–1 in patients treated 0·0–3·0 h after stroke onset	32·9%	23·1%	1·75 (1·35–2·27)	9·8%
mRS 0–1 in patients treated 3·0–4·5 h after stroke onset	35·3%	30·1%	1·26 (1·05–1·51)	5·2%
SICH	3·7%	0·6%	6·67 (4·11–10·84)	3·1%
Fatal SICH	2·7%	0·4%	7·14 (3·98–12·79)	2·3%
Mortality in patients treated 0·0–3·0 h after stroke onset	22·2%	21·8%	1·00 (0·81–1·24)	0·4% (p=0·70)
Mortality in patients treated 3·0–4·5 h after stroke onset	16·9%	15·9%	1·14 (0·95–1·36)	1·0% (p=0·96)
Alteplase thrombolysis >4·5 h after stroke onset in patients selected by use of perfusion imaging[17]				
mRS 0–1	36·2%	25·8%	2·06 (1·17–3·62)	10·4%
mRS 0–2	50·7%	39·7%	2·22 (1·25–3·94)	11·0%
SICH	4·6%	0·7%	7·29 (0·88–60·18)	3·9% (p=0·067)
Mortality	13·2%	10·5%	1·28 (0·60–2·73)	2·7% (p=0·52)
Endovascular thrombectomy initiated 0·0–6·0 h after stroke onset[14]				
mRS 0–1	26·9%	12·9%	2·72 (1·99–3·71)	14·0%
mRS 0–2	46·0%	26·5%	2·71 (2·07–3·55)	19·5%
SICH	4·4%	4·3%	1·07 (0·62–1·84)	0·1% (p=0·81)
Mortality	15·3%	18·9%	0·73 (0·47–1·13)	3·6% (p=0·16)
Endovascular thrombectomy initiated 6·0–24·0 h after stroke onset in patients selected by the use of perfusion imaging[15]				
mRS 0–2	46·7%	14·8%	5·01 (3·07–8·17)	31·9%
SICH	6·0%	3·7%	1·67 (0·64–4·35)	2·3% (p=0·29)
Mortality	16·6%	21·7%	0·71 (0·34–1·51)	5·1% (p=0·38)
Hemicraniectomy[16]				
mRS 4–6	56·9%	78·6%	0·33 (0·13–0·86)	21·7%
Mortality	21·6%	71·4%	0·10 (0·04–0·27)	49·8%
Aspirin administered <48·0 h after stroke onset[17]				
mRS 0–2	54·4%	53·1%	1·05 (1·01–1·10)	1·3%
Intracerebral haemorrhage				
Intensive blood pressure lowering[18]				
mRS 3–6	52·0%	55·6%	0·87 (0·75–1·01)	3·6% (p=0·059)
Surgical evacuation overall[19]				
Death or disability	59·4%	67·4%	0·72 (0·61–0·84)	8·0%
Mortality	27·3%	31·8%	0·82 (0·69–0·97)	4·5%
Surgery commenced within 0·0–8·0 h of stroke onset[19]				
Death or disability*	70·3%	79·2%	0·59 (0·42–0·84)	8·9%
Minimally invasive surgery[20]				
Death or disability†	47·4%	65·4%	0·59 (0·42–0·84)	18·0%

SICH is defined as parenchymal haematoma occupying >30% of the infarcted territory with substantial mass effect combined with an increase of ≥4 points in National Institutes of Health Stroke Scale score, as used in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study.[11] mRS=modified Rankin scale. SICH=symptomatic intracerebral haemorrhage. *Component studies used different outcomes: composite of death, vegetative or severe disability outcome on Glasgow Outcomes Score; mRS ≥3; or Barthel Index ≤90 in the 0·0–8·0 h analysis. †Component studies used different outcomes: composite of mRS ≥3; or Barthel Index ≤60.

Table: Patient outcomes following acute interventions for stroke

Acute treatments for ischaemic stroke

Intravenous thrombolysis with recombinant human tissue plasminogen activator (alteplase) aims to reperfuse the ischaemic brain by converting plasminogen (PLG) to plasmin, which can dissolve the thrombus that is causing the stroke. Alteplase was first shown to reduce disability in the NINDS part A and B trials[34] when administered within 3·0 h of stroke onset. The treatment window was subsequently extended to 4·5 h, although the benefit reduces rapidly with increasing time after stroke onset (table).[22] When alteplase is delivered within 3·0 h of onset, approximately one in four patients have reduced disability, which decreases to one in seven patients between 3·0 h and 4·5 h.[35] This benefit includes the effect of the approximately 2% absolute risk of fatal intracerebral haemorrhage. A large meta-analysis of individual patient data established that, although age and clinical severity measured by use of the National Institutes of Health Stroke Scale are strongly prognostic, the treatment benefit of alteplase is preserved across the spectrum of these variables.[22] Patients with mild but disabling symptoms benefit from thrombolysis. However, the prematurely terminated 2018 PRISMS trial[36] showed no evidence of benefit in patients with symptoms that were judged to be non-disabling at presentation, and who were selected on the basis of non-contrast CT brain imaging and clinical characteristics. Trials selecting patients with non-disabling symptoms but with arterial occlusion or perfusion abnormality are ongoing (eg, TEMPO-2, NCT02398656).

In 2019, the use of CT or perfusion MRI was established to select patients between 4·5 h and 9·0 h from the time that they were last seen to be well (or within 9·0 h of the midpoint of sleep if they awoke with stroke) if they had imaging evidence of salvageable brain tissue.[37,38] This subset of patients derives at least as much benefit with similar risk of fatal intracerebral haemorrhage to those treated 0·0–3·0 h after stroke onset, and the ability to select patients using CT-based imaging puts this treatment approach within reach of most hospitals that are capable of thrombolysis intervention. Thrombolysis also improved outcomes in patients with unknown time of stroke onset (including those waking up with stroke) in whom MRI showed diffusion lesions that were not yet hyperintense on fluid-attenuated inversion recovery (FLAIR).[18] This diffusion-FLAIR mismatch indicates that the patient is likely to be within 4·5 h of stroke onset. Compared with CT perfusion, MRI diffusion-FLAIR mismatch is more likely to detect patients with lacunar stroke, and who could benefit from thrombolysis.[39] However, the requirement for urgent MRI reduces the applicability of the MRI diffusion-FLAIR technique in many regions.

The 0·9 mg/kg licensed dose of alteplase in most regions was based on data from small studies, and the licensed dose in Japan is 0·6 mg/kg.[40] A randomised trial comparing these two doses did not show non-inferiority

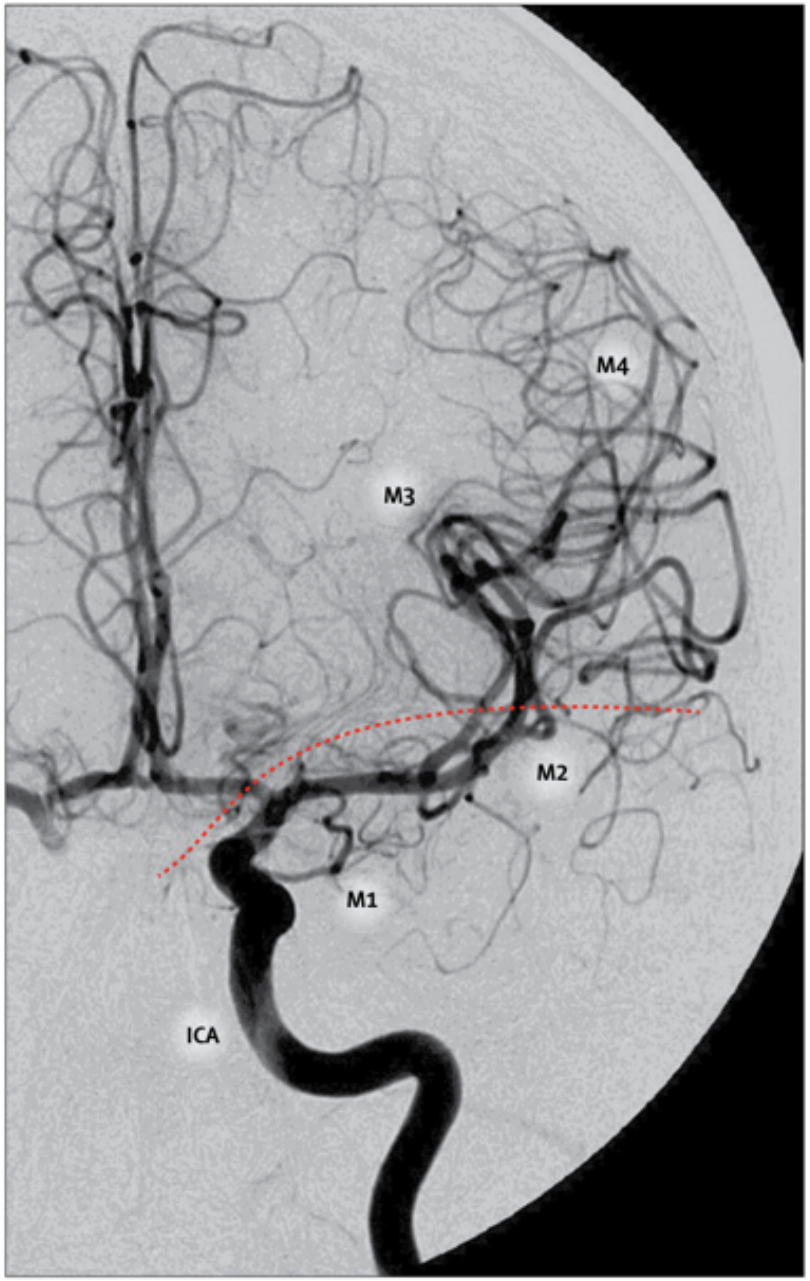


Figure 3: **Intracranial vasculature**
The evidence supports endovascular thrombectomy in the internal carotid artery, M1 segment of the middle cerebral artery, and selected patients with proximal M2 segment occlusion (approximated by the dotted red line). Distal vessels could become more accessible with technological developments. ICA=internal carotid artery.

Conclusions

Care for patients with stroke has transformed over the past 5 years, particularly with reperfusion therapies for ischaemic stroke and improved secondary prevention, although large gaps between evidence and practice still exist. Interventions for intracerebral haemorrhage might similarly revolutionise our approach to that condition in the future. There is reinvigorated interest in the fields of cytoprotection and recovery enhancement. Improved implementation of our existing knowledge about prevention and rapid treatment of patients with stroke could substantially reduce the major global burden of disability related to stroke.

A rare cause of left-sided weakness in an elderly woman: amoebic encephalitis

An 85-year-old Gujarati woman with a 1-day history of confusion, left-sided weakness, and slurred speech attended our hospital. She had a history of headaches, which had been extensively investigated for 2 years from 2013. She also had hypertension. She had no history of recent travel.

On examination, she was afebrile. She had a dense left hemiparesis; cranial nerves, visual fields, and fundoscopy examinations were normal. She was also in atrial fibrillation.

A CT scan of the patient's brain showed multiple cortical and subcortical, hypodense lesions; an MRI showed the lesions to be ring-enhancing, with surrounding vasogenic oedema (figure). A CT of the chest, abdomen, and pelvis found no abnormalities and a transthoracic echo was normal.

Blood investigations found her haemoglobin concentration was 12·4 g/dL (normal range 12·0–15·5); her white cell count was $9{\cdot}4\times10^9$ per L (normal range $4{\cdot}3\times10^9$–$10{\cdot}8\times10^9$); neutrophil count was $7{\cdot}9\times10^9$ per L (normal range $1{\cdot}5\times10^9$–8×10^9); lymphocyte count was $0{\cdot}7\times10^9$ per L (normal range $1{\cdot}0\times10^9$–$4{\cdot}8\times10^9$); C-reactive protein concentration was 4·6 mg/L (normal range <3); and eosinophil count was $0{\cdot}1\times10^9$ per L (normal range $<0{\cdot}45\times10^9$). Blood cultures were negative. HIV, syphilis, and *Brucella* spp serology were negative. An autoimmune screen was negative and serum immunoglobulins were not raised.

A lumbar puncture showed an opening pressure of 22 cm water (normal range 10–25), cerebrospinal fluid (CSF) was clear, with 98% lymphocytes (60 cells per µL; normal range 0–5), a normal glucose concentration (3·1 mg/L; normal range 2·8–4·2), and a total protein concentration of 0·66 g/L (normal 0·15–0·45). GeneXpert MTB/RIF Ultra (Xpert Ultra; Cepheid, Sunnyvale, CA, USA) of the CSF—for diagnosis of tuberculous meningitis—was negative. However, we still suspected the diagnosis to be tuberculous meningoencephalitis because of the patient's ethnicity, and we started empirical treatment with rifampicin, isoniazid, ethambutol, moxifloxacin, and prednisolone.

The patient's condition deteriorated and on day 3 of the admission, she had tonic–clonic seizures, which were initially controlled with lorazepam and levetiracetam. However, her Glasgow Coma Scale steadily dropped to 4 by the afternoon; she had an extensor response to pain stimuli, tachypnoea, pinpoint pupils, and absent doll's head and corneal reflexes. An urgent meeting between the family and clinicians was held; a consensus was made to stop active treatment—including a decision not to carry out a brain biopsy—and to keep the patient comfortable. She died 11 days after admission. A post-mortem examination found multiple haemorrhagic lesions in the brain (figure). Histopathology showed large amoebic cysts in the perivascular spaces and blood vessel lumens (figure). PCR for brain amoebae—*Acanthamoeba* spp, *Naegleria fowleri*, and *Balamuthia mandrillaris*—on formalin-fixed paraffin embedded tissue was negative. However, colleagues with expertise in parasitology from the Centers for Disease Control and Prevention, USA, using both real-time PCR and conventional genotyping PCR of the samples, were able to make a positive diagnosis for *B mandrillaris* (appendix). The family was informed.

Amoebic encephalitis is a difficult diagnosis to confirm and may need both diagnostic real-time PCR and conventional genotyping PCR. Often a definitive diagnosis can only be made by brain biopsy or post-mortem examination. *B mandrillaris* was first isolated in 1986 from the brain tissue of a mandrill. It causes serious cutaneous infections and encephalitis and is fatal in more than 98% of patients (video).

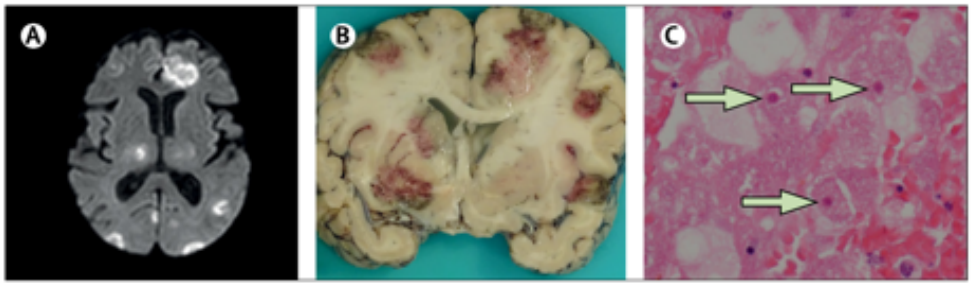


Figure: **A rare cause of left-sided weakness in an elderly woman**
(A) Diffusion weighted MRI shows multiple ring-enhancing lesions with surrounding vasogenic oedema. (B) Post-mortem macroscopic pathology shows multiple irregular solid, haemorrhagic lesions. (C) Histopathology of the brain shows organisms, 30–50 µm in size, with round, eosinophilic nuclei, and prominent karyosomes (arrows; haematoxylin and eosin stain). Original magnification ×400.

Gujarati gehört zum indoarischen Zweig der indoiranischen Untergruppe der indogermanischen Sprachen. Das Verbreitungsgebiet des Gujarati deckt sich weitgehend mit dem indischen Bundesstaat Gujarat, dessen Grenzen 1960 entlang der Sprachgrenze des Gujarati gezogen wurden. (Die Aria kommen aus Indien, nicht aus Deutschland)