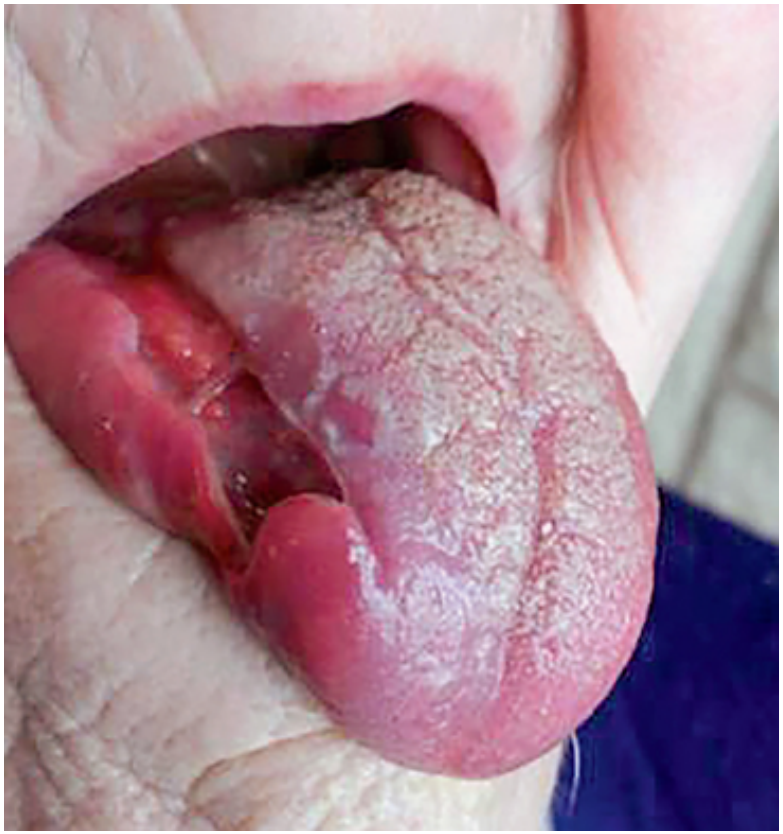
An 86-year-old woman presented to the emergency room with tongue pain 8 days after the diagnosis of giant-cell arteritis by temporal artery biopsy and treatment with glucocorticoids. Exam revealed necrotic ulceration on the right side of the tongue. Cervicofacial CT showed complete thrombosis of which one of the following arteries, on the right side?



Superior thyroid artery

Ascending pharyngeal artery

Posterior auricular artery

Facial artery

Lingual artery

The correct answer is the lingual artery. Tongue necrosis due to lingual artery thrombosis is a rare complication of giant-cell arteritis. With continued glucocorticoid treatment, the patient's symptoms resolved and the tongue healed within 4 weeks.

A Randomized Trial of a Family-Support Intervention in Intensive Care Units

Surrogate decision makers for incapacitated, critically ill patients often struggle with decisions related to goals of care. Such decisions cause psychological distress in surrogates and may lead to treatment that does not align with patients' preferences. We conducted a stepped-wedge, cluster-randomized trial involving patients with a high risk of death and their surrogates in five intensive care units (ICUs) to compare a multicomponent family-support intervention delivered by the interprofessional ICU team with usual care. The primary outcome was the surrogates' mean score on the Hospital Anxiety and Depression Scale (HADS) at 6 months (scores range from 0 to 42, with higher scores indicating worse symptoms). Prespecified secondary outcomes were the surrogates' mean scores on the Impact of Event Scale (IES; scores range from 0 to 88, with higher scores indicating worse symptoms), the Quality of Communication (QOC) scale (scores range from 0 to 100, with higher scores indicating better clinician–family communication), and a modified Patient Perception of Patient Centeredness (PPPC) scale (scores range from 1 to 4, with lower scores indicating more patient- and family-centered care), as well as the mean length of ICU stay.

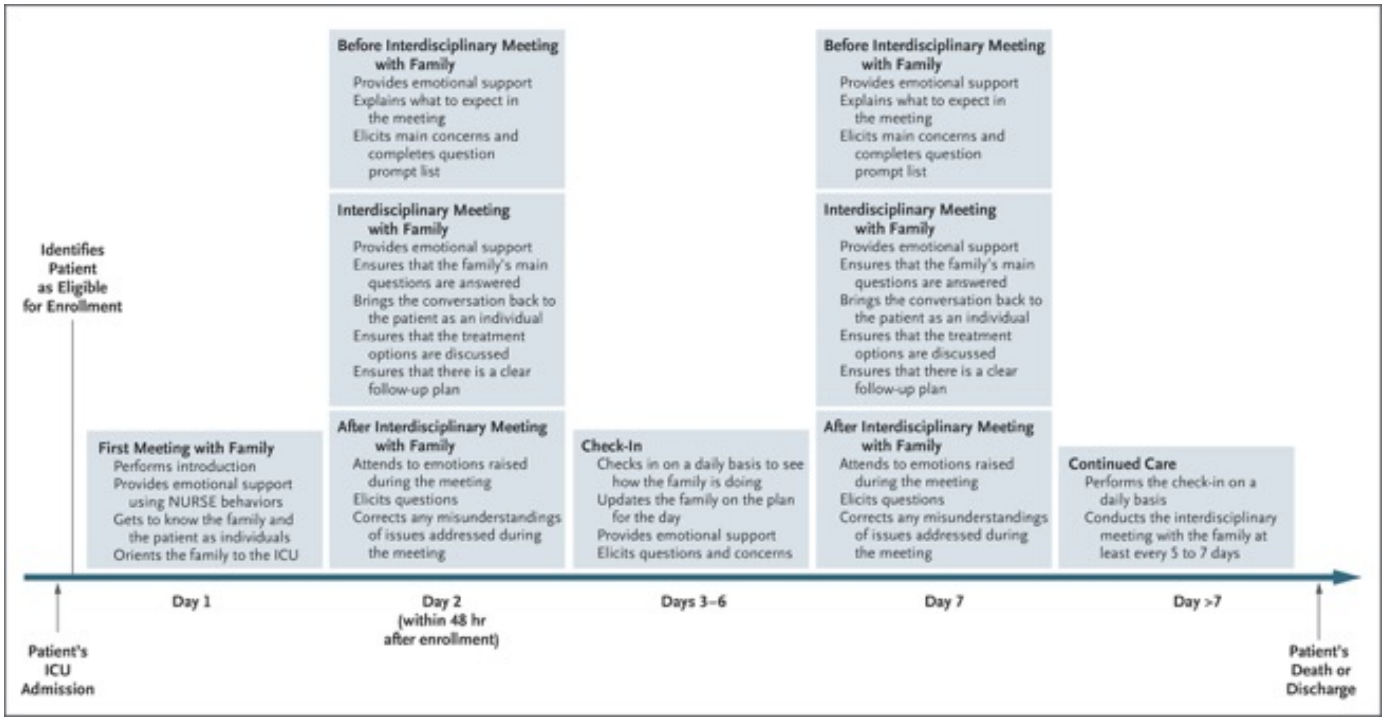


Table 1. Characteristics of the Patients and Surrogates at Baseline.*

Characteristic	Intervention	Control	P Value†
Patients			
Total no.	547	873	
Age — yr	67.5±14.9	63.3±15.5	<0.001
Female sex — no. (%)	290 (53.0)	405 (46.4)	0.02
Primary diagnosis — no. (%)‡			<0.01
Cardiovascular cause	33 (6.0)	36 (4.1)	
Pulmonary cause	107 (19.6)	138 (15.9)	
Gastrointestinal cause	49 (9.0)	94 (10.8)	
Toxicologic cause	18 (3.3)	38 (4.4)	
Infection or sepsis	159 (29.1)	212 (24.4)	
Neurologic cause	106 (19.4)	173 (19.9)	
Oncologic cause	18 (3.3)	59 (6.8)	
Other	56 (10.3)	118 (13.6)	
Source of admission to the ICU — no. (%)			<0.001
Direct admission	50 (9.1)	224 (25.7)	
Transfer from emergency department	422 (77.2)	549 (62.9)	
Transfer from other hospital	73 (13.4)	100 (11.5)	
Transfer from skilled nursing facility	2 (0.4)	0	
Modified SAPS III§	51.0±11.8	49.4±12.0	0.02
Elixhauser Comorbidity Index score¶	5.8±2.4	5.1±2.5	<0.001
Use of mechanical ventilation during hospitalization — no. (%)	479 (87.6)	759 (86.9)	0.73
Surrogates			
Total no.	429	677	
Age — yr	57.1±13.7	56.4±13.6	0.46
Female sex — no. (%)	284 (66.2)	480 (70.9)	0.06
Relationship to patient — no. (%)			0.04
Spouse or partner	161 (37.5)	295 (43.6)	
Parent	28 (6.5)	63 (9.3)	
Child	163 (38.0)	197 (29.1)	
Sibling	53 (12.4)	81 (12.0)	
Other	24 (5.6)	41 (6.1)	

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. ICU denotes intensive care unit. For details, see Table S2 in the Supplementary Appendix.
† P values were calculated with Student's t-test or Pearson's chi-square test.
‡ Data were missing for one patient in the intervention group and five patients in the control group.
§ The modified Simplified Acute Physiology Score (SAPS) III ranges from 0 to 166, with higher scores indicating a greater severity of acute illness.
¶ The Elixhauser Comorbidity Index score ranges from 0 to 29, with higher scores indicating a higher number of chronic coexisting conditions.

Table 2. Primary and Secondary Outcomes.*

Outcome	Unadjusted Analysis		Adjusted Analysis†			
	Intervention	Control	Intervention	Control	Estimated Effect of Intervention (95% CI)	P Value
			mean (95% CI)			
Surrogates' burden of psychological symptoms						
No. of surrogates assessed	308	501				
HADS score‡	11.7±7.9	12.1±8.5	11.7 (10.7 to 12.7)	12.0 (11.3 to 12.8)	−0.34 (−1.67 to 0.99)§	0.61
IES score¶	20.5±18.1	20.7±17.7	21.2 (19.3 to 23.2)	20.3 (18.8 to 21.9)	0.90 (−1.66 to 3.47)§	0.49
Quality of decision making and communication						
No. of surrogates assessed	308	501				
QOC score‖	69.7±23.5	63.0±24.8	69.1 (66.2 to 72.0)	62.7 (60.4 to 65.0)	6.39 (2.57 to 10.20)§	0.001
Modified PPPC score**	1.6±0.6	1.8±0.7	1.7 (1.6 to 1.7)	1.8 (1.8 to 1.9)	−0.15 (−0.26 to −0.04)§	0.006
Health care utilization						
No. of patients assessed	547	873				
Length of ICU stay — days	8.1±8.6	8.8±8.8	6.7 (6.1 to 7.2)	7.4 (7.0 to 7.9)	0.90 (0.81 to 1.00)††	0.045
Length of hospital stay — days	11.8±13.1	15.5±19.2	10.4 (9.5 to 11.3)	13.5 (12.6 to 14.4)	0.77 (0.69 to 0.87)††	<0.001

* Plus–minus values are means ±SD.

† Adjusted analyses were performed with regression models. All models were adjusted for patient's age, modified SAPS III, Elixhauser Comorbidity Index score, use or nonuse of mechanical ventilation, primary diagnosis, and admission source.

‡ Scores on the Hospital Anxiety and Depression Scale (HADS) range from 0 to 42, with higher scores indicating worse symptoms. The adjusted analysis included the following additional covariates: patient's vital status at 6 months after discharge, the surrogate's sex, and the surrogate's relationship to the patient.

§ The result is a beta coefficient calculated with generalized linear mixed modeling.

¶ Scores on the Impact of Event Scale (IES) range from 0 to 88, with higher scores indicating worse symptoms. The adjusted analysis included the following additional covariates: patient's vital status at 6 months after discharge, the surrogate's sex, and the surrogate's relationship to the patient.

‖ Scores on the Quality of Communication (QOC) scale range from 0 to 100, with higher scores indicating better communication. The adjusted analysis included the following additional covariate: patient's race (black vs. nonblack).

** Scores on the modified Patient Perception of Patient Centeredness (PPPC) scale range from 1 to 4, with lower scores indicating more patient- and family-centered care. The adjusted analysis included the following additional covariates: surrogate's age and sex.

†† The result is an incidence rate ratio calculated with zero-truncated negative binomial regression modeling.

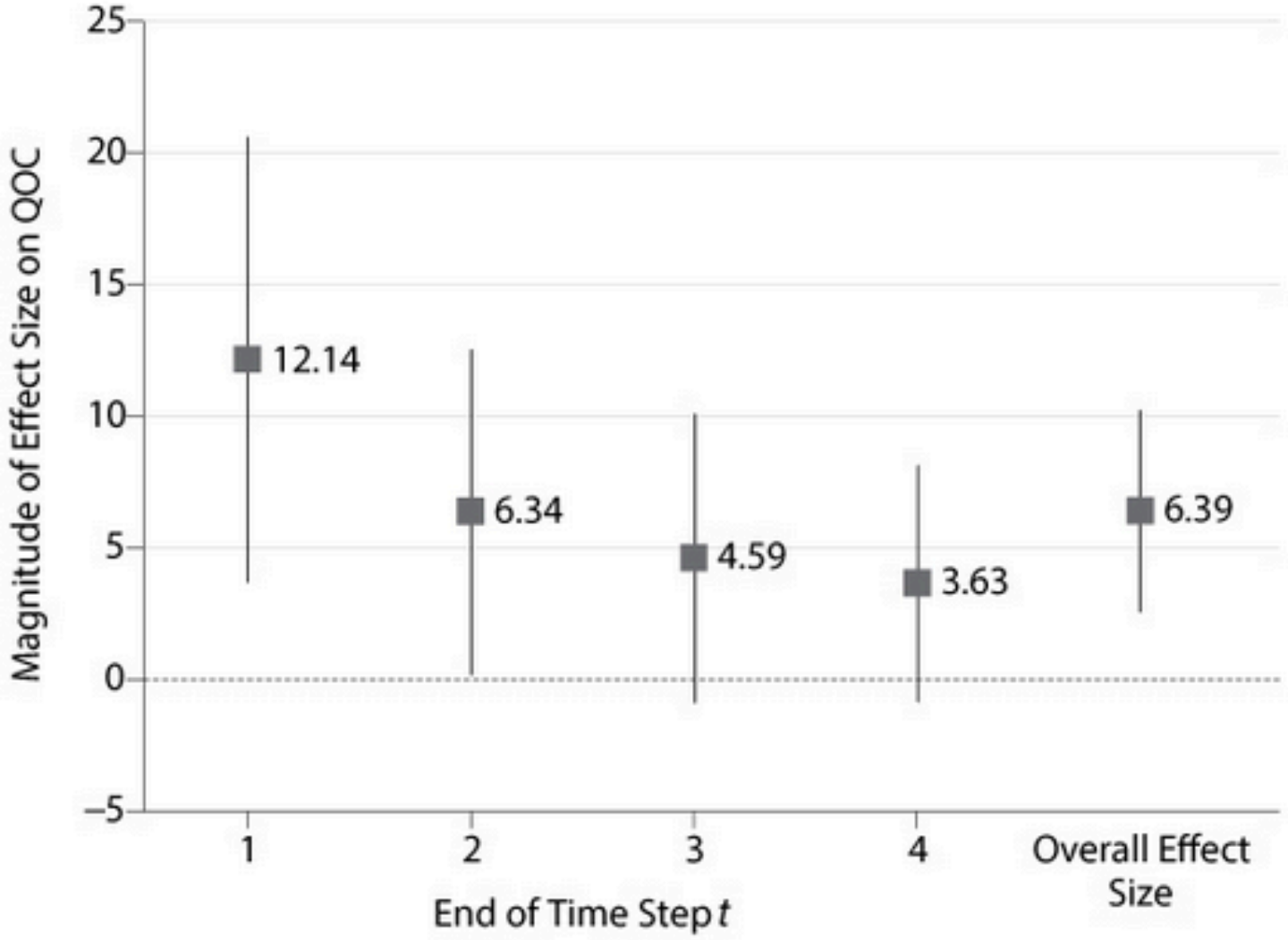

25
20
15
10
5
0
−5
Magnitude of Effect Size on QOC
12.14
6.34
4.59
3.63
6.39
1
2
3
4
Overall Effect Size
End of Time Step t

Table 3. Patients' Clinical Outcomes.

Outcome	Unadjusted Analysis		Adjusted Analysis*			
	Intervention (N=547)	Control (N=873)	Intervention (N=547)	Control (N=873)	Odds Ratio (95% CI)	P Value
	no. of patients (%)		*% (95% CI)*			
In-hospital death	208 (38.0)	264 (30.2)	36.0 (26.2 to 45.7)	28.5 (20.1 to 36.9)	1.43 (1.10 to 1.87)	0.008
Death at 6 mo	339 (62.0)	472 (54.1)	60.4 (56.0 to 64.9)	55.4 (51.9 to 59.0)	1.18 (0.93 to 1.50)	0.17
Living independently at home at 6 mo	3 (1.0)	13 (2.6)	0.8 (−0.5 to 2.2)	0.7 (−0.2 to 1.6)	1.15 (0.13 to 9.89)	0.90

* Adjusted analyses were performed with regression models. All models were adjusted for patient's age, modified SAPS III, Elixhauser Co-morbidity Index score, use or nonuse of mechanical ventilation, primary diagnosis, and admission source. These analyses included the following additional covariate: patient's sex. Odds ratios were calculated with logistic-regression modeling.

In-hospital mortality was higher in the intervention group than in the control group (36.0% vs. 28.5%; odds ratio, 1.43; 95% CI, 1.10 to 1.87; P=0.008), but mortality at 6 months did not differ significantly between the two groups (60.4% and 55.4%, respectively; adjusted odds ratio, 1.18; 95% CI, 0.93 to 1.50; P=0.17). There was no significant difference between the intervention group and the control group in the mean score on the Katz Index of Independence in Activities of Daily Living at 6 months (4.4 and 4.0, respectively; beta coefficient, −0.16 to 1.01; P=0.16), the percentage of patients who were living independently at home at 6 months (0.8% and 0.7%; odds ratio, 1.15; 95% CI, 0.13 to 9.89; P=0.90), or the percentage of patients who were able to live at home at any point during the 6-month follow-up period (5.6% and 7.5%; odds ratio, 0.69; 95% CI, 0.38 to 1.27; P=0.23). The mean cost to use the intervention was $170 per patient

In conclusion, among critically ill patients and their surrogates, a family-support intervention delivered by the existing interprofessional ICU team did not affect the surrogates' symptoms of depression and anxiety at 6 months, but the surrogates' ratings of the quality of communication and the patient- and family-centeredness of care were better and the length of stay in the ICU was shorter with the intervention than with usual care. Our data are not directive, but they suggest that equipoise is present and that a large replication trial may be conducted in multiple geographic regions to establish the generalizability of the findings in different health systems that have potentially different attitudes and practices regarding care for patients with advanced critical illness.

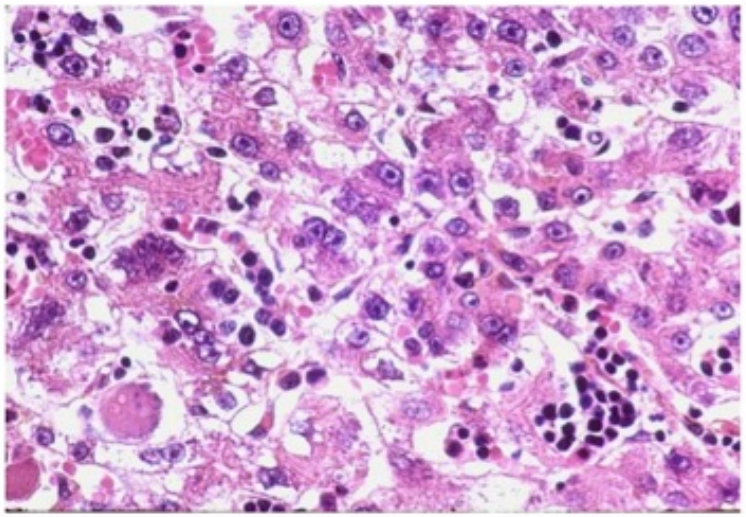
Die HADS-D dient der Erfassung von Angst und Depression bei Patienten mit körperlichen Erkrankungen oder (möglicherweise psychogenen) Körperbeschwerden. Das Verfahren kann als Screeningverfahren sowie zur dimensionalen Schweregradbestimmung, auch in der Verlaufsbeurteilung, eingesetzt werden. Zusätzlich zu den bei kardiologischen Patienten erhobenen Normen werden in der vorliegenden Neuauflage auch repräsentative Bevölkerungsnormen präsentiert.

Erfasst wird mittels Selbstbeurteilung die Ausprägung ängstlicher und depressiver Symptomatik während der vergangenen Woche, die auf zwei Subskalen mit je sieben Items erfasst wird. Der Gesamtsummenwert kann als Maß für die allgemeine psychische Beeinträchtigung eingesetzt werden. Itemauswahl und -formulierung berücksichtigen besonders die spezifischen Anforderungen eines durch körperliche Krankheit bestimmten Settings. Dabei wird gezielt nur auf psychische Angst- und Depressionssymptome fokussiert, um eine Konfundierung durch somatische Komorbidität zu vermeiden. Erfasst werden auch leichtere Ausprägungen psychischer Störungen, die in der somatischen Medizin häufig vorliegen. Schwere psychopathologische Symptome werden bewusst ausgeklammert, was zur sehr hohen Akzeptanz des Verfahrens in den Zielgruppen beiträgt.

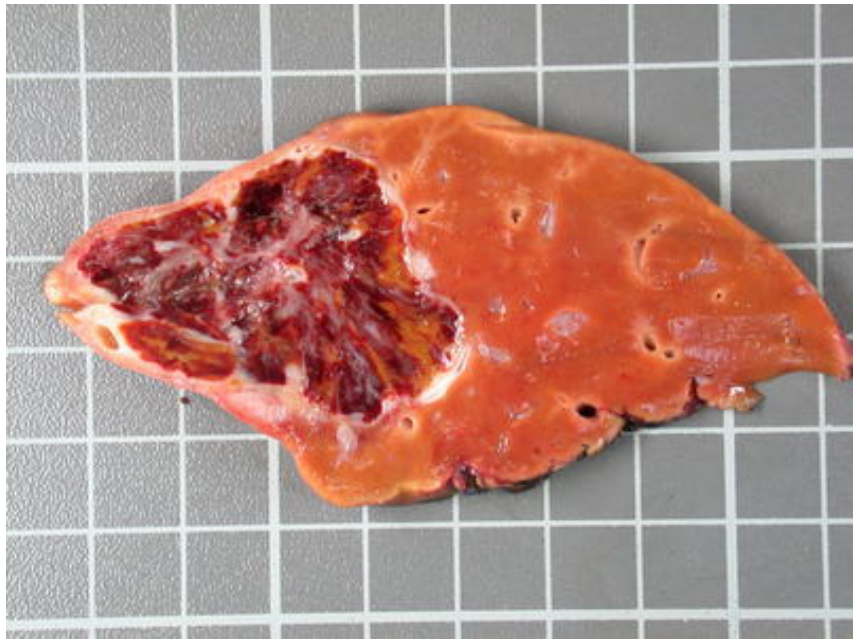
Impact of Event Scale-revidierte Form (IES-R)

Die drei Subskalen „*Intrusionen*“, „*Vermeidung*“ und „*Ubererregung*“ erfassen typische Formen individueller Reaktionen bzw. Symptome auf extrem belastende Ereignisse. Die Frage- (Item-)Formulierungen sind unabhängig von der jeweiligen Fassung im DSM-IV oder ICD-10. Eine Schätzformel (Regressionsgleichung) erlaubt, aus den drei Subskalen das Vorliegen einer PTB-Diagnose abzuschätzen.

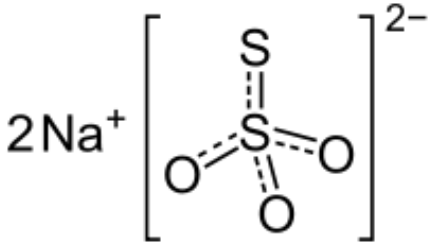
Unter einem Hepatoblastom versteht man einen malignen Lebertumor des Kindesalters. Das Hepatoblastom ist der häufigste maligne Lebertumor im Kindesalter. Die Inzidenz beträgt 0,09 auf 100.000 Kinder, die jünger als fünfzehn Jahre alt sind. Mädchen sind seltener betroffen als Jungen.
Das Hepatoblastom betrifft vor allem Kinder, die das zweite Lebensjahr noch nicht überschritten haben.
Die Ätiologie ist noch nicht geklärt. Das Hepatoblastom kann gemeinsam mit dem Nephroblastom sowie dem Beckwith-Wiedemann-Syndrom auftreten. Es besteht keine Assoziation zu einer Infektion mit dem Hepatitis-B-Virus.
Der Tumor ist in der Mehrzahl der Fälle im rechten Leberlappen lokalisiert. Meistens handelt es sich um einen solitären Tumor. Das Hepatoblastom metastasiert vor allem in die Lunge, seltener in die Knochen.
Grundlage der Therapie ist zunächst die operative Entfernung des Tumors, bei der möglichst keine Reste im Körper verbleiben sollten.
Um eine vollständige Entfernung zu erreichen, kann eine neoadjuvante Zytostatikatherapie mit Cisplatin oder Adriamycin notwenig sein. Es ist möglich, die Zytostatika in die Arteria hepatica zu applizieren.
Acht von zehn Kindern können geheilt werden.
Voraussetzung für eine Heilung ist die komplette Resektion des Tumors.



Fetal tip hepatoblastom



Natriumthiosulfat ist das stabile Natriumsalz der in freiem Zustand instabilen Thioschwefelsäure. Natriumthiosulfat bildet farblose Kristalle, die mit 5 Mol Kristallwasser kristallisieren und gut wasserlöslich sind; beim Auflösen kühlt sich die Flüssigkeit stark ab, da die Hydratationsenthalpie kleiner ist als die Gitterenergie und die fehlende Wärmemenge dem System entzogen wird. Dieses so genannte Pentahydrat $Na_2S_2O_3 \cdot 5H_2O$ ist auch unter dem Namen Fixiersalz bekannt, da es bei der Filmentwicklung zur Fixierung dient. Unter dem Namen Antichlor wird es nach dem Bleichen von Papier- und Textilfasern verwendet, um überschüssiges Chlor zu entfernen.
Die Pentahydrat-Kristalle haben einen Schmelzpunkt von 48,5 ° C, die Schmelze kann unterkühlt werden und gibt beim, durch einen Impfkristall ausgelösten, Erstarren eine große Menge von Kristallisationswärme ab. Wird zur wässrigen Natriumthiosulfat-Lösung Säure hinzugefügt, so scheidet sich nach kurzer Zeit Schwefel in Form einer gelblichen Trübung aus. Die freigesetzte, instabile Thioschwefelsäure ($H_2S_2O_3$) zerfällt nämlich rasch zu Schwefel und Schwefeldioxid. In der Medizin wird es als Gegenmittel bei Cyanidvergiftungen verwendet, dabei wird weniger gefährliches Thiocyanat gebildet.
„Strategies for prevention of chemotherapy-induced toxicity include temporal or anatomical separation of cisplatin or carboplatin from sodium thiosulfate, D-methionine, or N-acetyl-cysteine. Clinical application of these methods has begun. The mechanisms presumably involve free radicals or drug conjugation, or both. Understanding the role of free radicals in medicine is likely to become important in the future.“



In a study involving 53 hemodialysis-dependent patients with calciphylaxis who were treated with intravenous sodium thiosulfate (three times per week [with each dialysis session] for approximately 3 months), calciphylaxis completely resolved in 26% of the patients, and 19% had marked improvement in skin lesions. In another study, involving 27 patients being treated with dialysis, complete remission was observed in 52% of the patients and partial remission in 19% after treatment with intravenous sodium thiosulfate.

Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss

Cisplatin chemotherapy and surgery are effective treatments for children with standard-risk hepatoblastoma but may cause considerable and irreversible hearing loss. This trial compared cisplatin with cisplatin plus delayed administration of sodium thiosulfate, aiming to reduce the incidence and severity of cisplatin-related ototoxic effects without jeopardizing overall and event-free survival. We randomly assigned children older than 1 month and younger than 18 years of age who had standard-risk hepatoblastoma (≤3 involved liver sectors, no metastatic disease, and an alpha-fetoprotein level of >100 ng per milliliter) to receive cisplatin alone (at a dose of 80 mg per square meter of body-surface area, administered over a period of 6 hours) or cisplatin plus sodium thiosulfate (at a dose of 20 g per square meter, administered intravenously over a 15-minute period, 6 hours after the discontinuation of cisplatin) for four preoperative and two postoperative courses. The primary end point was the absolute hearing threshold, as measured by pure-tone audiometry, at a minimum age of 3.5 years. Hearing loss was assessed according to the Brock grade (on a scale from 0 to 4, with higher grades indicating greater hearing loss). The main secondary end points were overall survival and event-free survival at 3 years.

Table 1. Demographic and Clinical Characteristics of the Children at Baseline.*

Characteristic	Cisplatin Alone (N=52)	Cisplatin–Sodium Thiosulfate (N=57)
Age — mo		
Median	13.4	12.8
Range	3.0–70.2	1.2–98.6
Male sex — no. (%)	29 (56)	30 (53)
Alpha-fetoprotein level — ng/ml		
Median	73,760	154,638
Range	187–2,175,690	273–4,536,500
PRETEXT score — no. (%)†		
I or II	31 (60)	41 (72)
III	21 (40)	16 (28)

* Cisplatin was administered at a dose of 80 mg per square meter of body-surface area in a 6-hour intravenous infusion. Sodium thiosulfate was administered at a dose of 20 g per square meter in a 15-minute intravenous infusion 6 hours after cisplatin was stopped. There were no significant differences between the groups in any of the above characteristics.

† Tumor extent was assessed with the use of the Pretreatment Extent of Disease (PRETEXT) system. Scores range from I to IV, with higher scores indicating increased extent of the disease in the liver. Children with a score of IV were not included in this trial.

Hearing Level among 101 Children Who Could Be Evaluated. A Brock grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively.[10] The grade was determined according to the hearing level in the child's better ear.

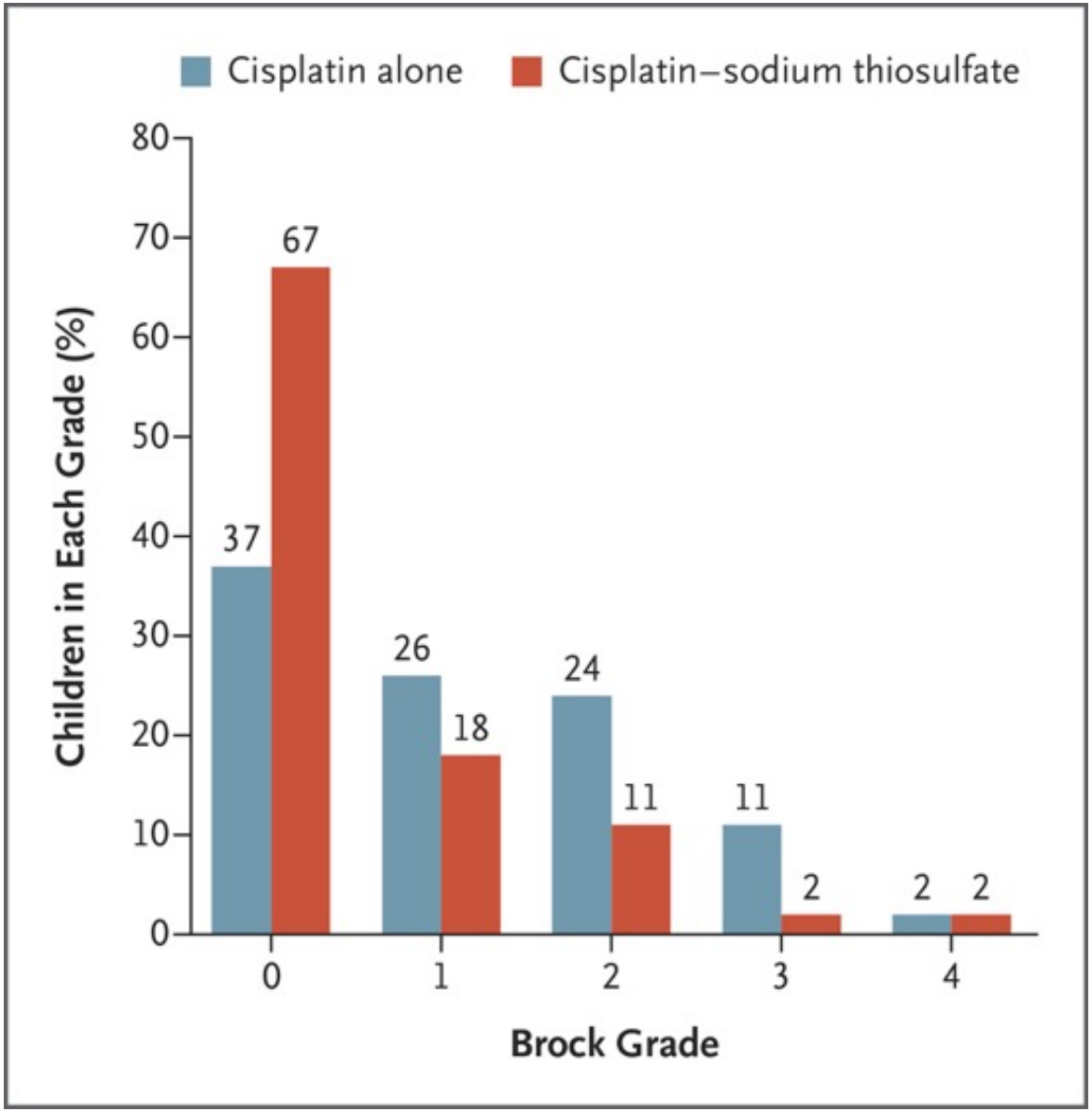


Table 2. Status after Preoperative Chemotherapy.*

Response	Cisplatin Alone (N=52)	Cisplatin–Sodium Thiosulfate (N=57)
	no. of patients (%)	
Response after two cycles		
Partial response	28 (54)	23 (40)
Stable disease	24 (46)	34 (60)
Response after four cycles		
Partial response	39 (75)	38 (67)
Stable disease	5 (10)	11 (19)
Progressive disease	5 (10)	5 (9)
Not evaluated†	3 (6)	3 (5)
Resection after preoperative chemotherapy		
Partial hepatectomy	48 (92)	53 (93)
Liver transplantation	4 (8)	4 (7)
Status at end of treatment		
Complete remission	44 (85)	52 (91)
Partial remission	4 (8)	5 (9)
Progressive disease	2 (4)	0
Died	1 (2)	0
Not evaluated	1 (2)	0
Status at last follow-up		
Complete remission	48 (92)	55 (96)
Partial remission	0	0
Recurrent disease	0	0
Died‡	4 (8)	2 (4)

* The response criteria are explained in the Methods section. Doxorubicin may have been administered in cases of progressive disease (or for other reasons, such as a surgeon's request). A total of 21 children received 1 to 6 courses of doxorubicin during initial therapy, including 9 children in the cisplatin-alone group (who received a total of 30 courses) and 12 in the cisplatin–sodium thiosulfate group (who received a total of 28 courses).

† In the cisplatin-alone group, response in two children was not evaluated after four cycles, and treatment in one child was switched to a dose-dense regimen, on the basis of the International Liver Tumor Strategy Group (SIOPEL) 4 study,[13] at the request of the surgeon. In the cisplatin–sodium thiosulfate group, two children had a response that had been sufficiently good for them to undergo surgery after three cycles, which made them unable to be evaluated for chemotherapy response after four cycles, and response was not evaluated in one child after four cycles.

‡ The deaths in the cisplatin-alone group were due to surgical complications (in one child), due to cardiac arrest after treatment with paclitaxel after progression (in one), and due to disease (in two). The two deaths in the cisplatin–sodium thiosulfate group were due to disease.

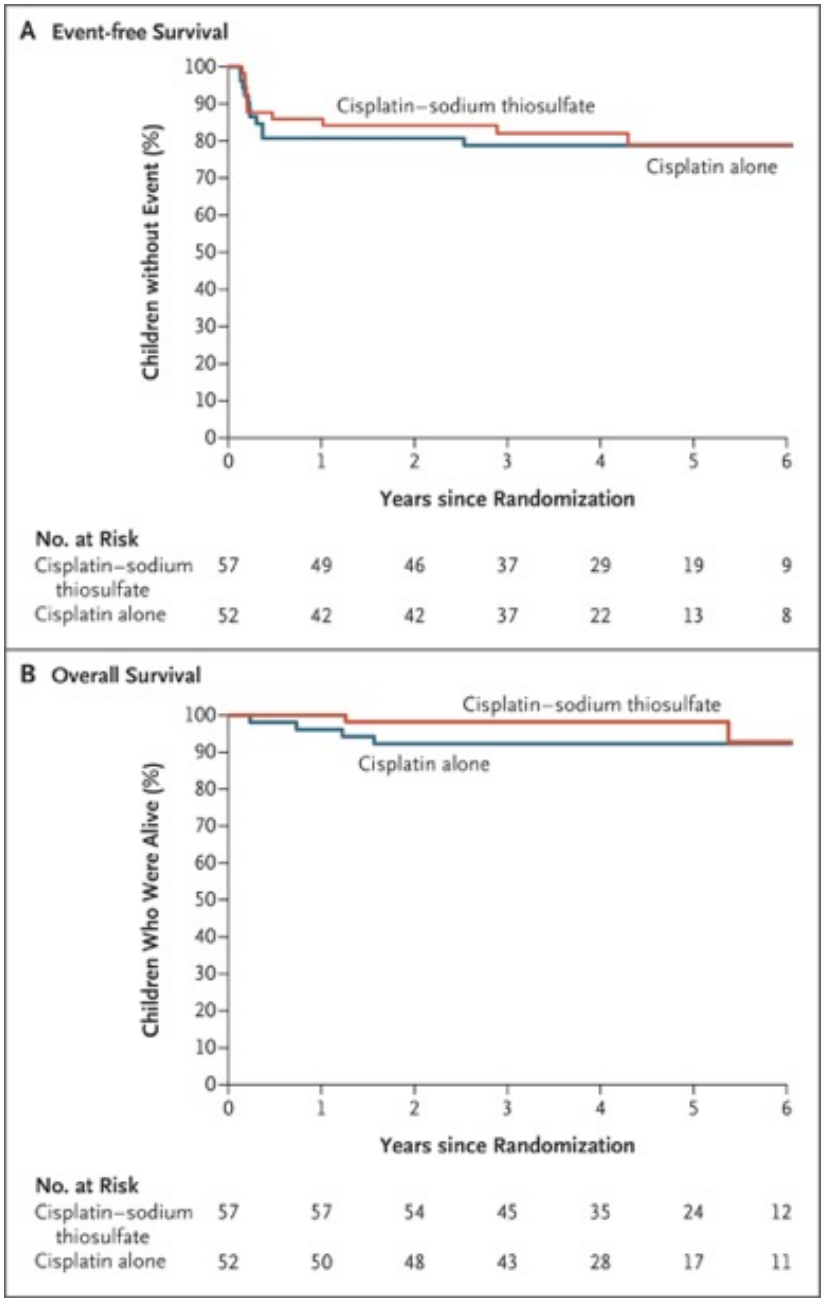


Table 3. Children with Grade 3 or 4 Adverse Events.*

Adverse Event and Grade	Cisplatin Alone (N=52)	Cisplatin–Sodium Thiosulfate (N=57)
	no. of patients (%)	
Allergy, grade 3	1 (2)	0
Febrile neutropenia, grade 3	10 (19)	8 (14)
Infection, grade 3	16 (31)	13 (23)
Hypomagnesemia, grade 3	1 (2)	1 (2)
Hypernatremia, grade 3	0	1 (2)
Vomiting, grade 3	2 (4)	4 (7)
Nausea, grade 3	3 (6)	2 (4)
Left ventricular systolic dysfunction, grade 3 or 4	0	0
Renal event, grade 3 or 4	0	0
Anemia		
Grade 3	8 (15)	10 (18)
Grade 4	0	1 (2)
Leukopenia, grade 3	2 (4)	2 (4)
Neutropenia		
Grade 3	3 (6)	7 (12)
Grade 4	3 (6)	3 (5)
Thrombocytopenia		
Grade 3	1 (2)	1 (2)
Grade 4	1 (2	1 (2)
Gastrointestinal event	2 (4)	3 (5)
Elevated liver-enzyme level		
Grade 3	6 (12)	3 (5)
Grade 4	0	1 (2)
Elevated serum glucose level, grade 3	2 (4)	1 (2)
Hypermagnesemia, grade 3†	2 (4)	5 (9)
Hypophosphatemia, grade 3	0	5 (9)
Hyperkalemia, grade 3	2 (4)	0
Hypokalemia		
Grade 3	0	4 (7)
Grade 4	0	1 (2)
Dyspnea, grade 3	1 (2)	0

* If grade 4 is not shown, there was no grade 4 adverse event. This table includes adverse events that were associated with additional treatment (mostly doxorubicin) given to children in each group.
† The protocol specified the addition of magnesium to the hydration fluid administered with cisplatin therapy.

In this trial, the addition of delayed sodium thiosulfate to cisplatin led to a 48% lower risk of hearing loss. Hearing loss of grade 1 or higher occurred in 63% of the children who did not receive otoprotection, as compared with 33% of those who did. The administration of sodium thiosulfate was associated with a trend toward reduced ototoxicity in all the Brock grades. Children with hearing of grade 0 may not have completely normal hearing but can manage life with little or no additional help. Children with hearing loss of grade 1 or higher typically receive further intervention with each increasing grade of hearing loss, with children with any grade of hearing loss receiving educational support. In the United Kingdom, young children with hearing loss of grade 1 and all children with hearing loss of grade 2 or 3 are offered hearing aids. Children with hearing loss of grade 4 are offered cochlear implants. Similar reductions in the incidence and severity of cisplatin-induced ototoxic effects were reported with the delayed administration of sodium thiosulfate in the ACCL0431 trial. The effect of high-frequency hearing loss and hearing support varies across the world, the reasons for which are multifactorial but include the variation in sound frequencies that are used in different languages. The analysis of these variables was beyond the scope of this trial.

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

Mutations in the gene encoding isocitrate dehydrogenase 1 (*IDH1*) occur in 6 to 10% of patients with acute myeloid leukemia (AML). Ivosidenib (AG-120) is an oral, targeted, small-molecule inhibitor of mutant IDH1. We conducted a phase 1 dose-escalation and dose-expansion study of ivosidenib monotherapy in *IDH1*-mutated AML. Safety and efficacy were assessed in all treated patients. The primary efficacy population included patients with relapsed or refractory AML receiving 500 mg of ivosidenib daily with at least 6 months of follow-up.

Table 1. Baseline Characteristics of the Patients with Relapsed or Refractory AML and All Patients in the Dose-Escalation and Dose-Expansion Phases.*

Characteristic	Ivosidenib, 500 mg Daily		Overall Population (N = 258)
	Primary Efficacy Population (N = 125)†	Relapsed or Refractory AML (N = 179)‡	
Median age (range) — yr	67.0 (18–87)	67.0 (18–87)	68.0 (18–89)
Sex — no. (%)			
Female	60 (48)	89 (50)	121 (47)
Male	65 (52)	90 (50)	137 (53)
AML classification — no./total no. (%)§			
Primary AML	83/125 (66)	120/179 (67)	148/242 (61)
Secondary AML	42/125 (34)	59/179 (33)	94/242 (39)
History of the myelodysplastic syndrome	18/125 (14)	29/179 (16)	52/242 (21)
History of myeloproliferative neoplasm	7/125 (6)	9/179 (5)	13/242 (5)
Treatment-related AML	14/125 (11)	16/179 (9)	22/242 (9)
Other	3/125 (2)	5/179 (3)	7/242 (3)
Median no. of previous therapies (range)	2.0 (1–4)	2.0 (1–4)	1.0 (0–4)
All previous therapies — no. (%)¶			
Intensive chemotherapy	92 (74)	127 (71)	—
Nonintensive chemotherapy	82 (66)	115 (64)	—
Investigational therapy	37 (30)	55 (31)	—
Outcome of previous therapy for AML — no. (%)			
Relapse after transplantation	36 (29)	43 (24)	—
Second or later relapse	20 (16)	26 (15)	—
Disease that was refractory to initial induction or reinduction therapy	86 (69)	106 (59)	—
Relapse within 1 yr after initial therapy	13 (10)	17 (9)	—
Cytogenetic risk status — no. (%)‖			
Favorable	0	0	1 (<1)
Intermediate	66 (53)	105 (59)	147 (57)
Poor	38 (30)	50 (28)	80 (31)
Unknown or missing	21 (17)	24 (13)	30 (12)
Co-occurring mutations — no./total no. (%)**			
In *FLT3*	9/119 (8)	11/172 (6)	17/245 (7)
In *NPM1*	24/119 (20)	44/172 (26)	53/245 (22)
In *CEBPA*	3/119 (3)	4/172 (2)	5/245 (2)
Mutated *IDH* allele — no./total no. (%)			
R132C			
Dose-escalation phase	21/33 (64)	22/35 (63)	47/78 (60)
Dose-expansion phase	55/92 (60)	81/144 (56)	109/180 (61)
R132H			
Dose-escalation phase	5/33 (15)	5/35 (14)	15/78 (19)
Dose-expansion phase	22/92 (24)	39/144 (27)	44/180 (24)
R132G/L/S			
Dose-escalation phase	4/33 (12)	5/35 (14)	12/78 (15)
Dose-expansion phase	15/92 (16)	24/144 (17)	27/180 (15)
Wild-type			
Dose-escalation phase	1/33 (3)	1/35 (3)	1/78 (1)
Dose-expansion phase	—	—	—
Other			
Dose-escalation phase	2/33 (6)	2/35 (6)	3/78 (4)
Dose-expansion phase	0/92	0/144	0/180
Median percentage of bone marrow blasts (range)	55.5 (0–98)	48.0 (0–98)	45.0 (0–98)

* AML denotes acute myeloid leukemia.
† Data are for patients with relapsed or refractory AML who were eligible for group 1 and whose first dose of ivosidenib was at least 6 months before the analysis-cutoff date of May 12, 2017 (including patients from the dose-escalation phase). Group 1 comprised patients who had a second or later relapse, had a relapse after stem-cell transplantation, had disease that was refractory to induction or reinduction chemotherapy, or had a relapse less than 12 months after initial therapy.
‡ Data are for all patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg once daily.
§ Percentages for the overall-population column were calculated according to the number of patients with relapsed or refractory AML.
¶ Patients could be counted in more than one category.
‖ Status was assessed by the investigator, according to National Comprehensive Cancer Network Clinical Practice Guidelines for AML, version 1.2015.
** Percentages were calculated according to the number of patients with a baseline bone marrow sample.

Table 2. Treatment-Related Adverse Events of Grade 3 or Higher Occurring in More than 1% of the Overall Population.*

Event	Relapsed or Refractory AML and Starting Dose of Ivosidenib of 500 mg Daily (N=179)	Overall Population (N=258)
	no. of patients (%)	
≥1 Treatment-related adverse event of grade 3 or higher	37 (20.7)	66 (25.6)
Prolongation of the QT interval on ECG	14 (7.8)	18 (7.0)
IDH differentiation syndrome†	7 (3.9)	12 (4.7)
Anemia	4 (2.2)	6 (2.3)
Thrombocytopenia	3 (1.7)	5 (1.9)
Leukocytosis	3 (1.7)	3 (1.2)
Febrile neutropenia	1 (0.6)	3 (1.2)
Diarrhea	1 (0.6)	3 (1.2)
Platelet count decreased	3 (1.7)	3 (1.2)
Hypoxia	2 (1.1)	3 (1.2)

* Investigators determined relatedness to treatment. ECG denotes electrocardiography, and IDH isocitrate dehydrogenase.
† This adverse event was graded on a scale of 1 to 5 (with higher grades indicating greater severity) by investigators according to National Cancer Institute Common Terminology Criteria for Adverse Events general grading guidelines.

The table shows the most common adverse events of grade 3 or higher that were judged by the investigator to be treatment-related in the overall population and in patients with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg daily. In the latter group, these events included prolongation of the QT interval on ECG (in 14 patients [7.8%]), the IDH differentiation syndrome (in 7 [3.9%]), and anemia (in 4 [2.2%]).

Table 3. Investigator-Reported Hematologic Response, Time to Response, and Response Duration in Patients Receiving 500 mg of Ivosidenib Daily.*

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)	Untreated AML (N=34)†	MDS (N=12)‡
CR or CRh				NA
No. of patients	38	54	12	NA
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)	35.3 (19.7–53.5)	NA
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)	2.8 (1.9–2.9)	NA
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)	NE (1.0–NE)	NA
CR				
No. of patients	27	39	7	5
% (95% CI)	21.6 (14.7–29.8)	21.8 (16.0–28.6)	20.6 (8.7–37.9)	41.7 (15.2–72.3)
Median time to CR (range) — mo	2.8 (0.9–8.3)	2.8 (0.9–8.3)	2.8 (1.9–3.7)	1.9 (1.0–5.6)
Median duration of CR (95% CI) — mo	9.3 (5.6–18.3)	9.3 (5.6–12.5)	NE (5.6–NE)	NE (2.8–NE)
Overall response				
No. of patients	52	70	19	11
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)	55.9 (37.9–72.8)	91.7 (61.5–99.8)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)	1.9 (0.9–2.9)	1.6 (1.0–2.8)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)	9.2 (1.9–NE)	NE (2.3–NE)
Best response — no. (%)				
CR	27 (21.6)	39 (21.8)	7 (20.6)	5 (41.7)
CRi or CRp	16 (12.8)	21 (11.7)	7 (20.6)	0
Partial remission	0	0	1 (2.9)	0
MLFS or bone marrow CR¶	9 (7.2)	10 (5.6)	4 (11.8)	6 (50.0)
Stable disease	44 (35.2)	69 (38.5)	10 (29.4)	0
Progressive disease	13 (10.4)	15 (8.4)	3 (8.8)	1 (8.3)
Could not be evaluated	0	0	0	0
Not assessed	16 (12.8)	25 (14.0)	2 (5.9)	0

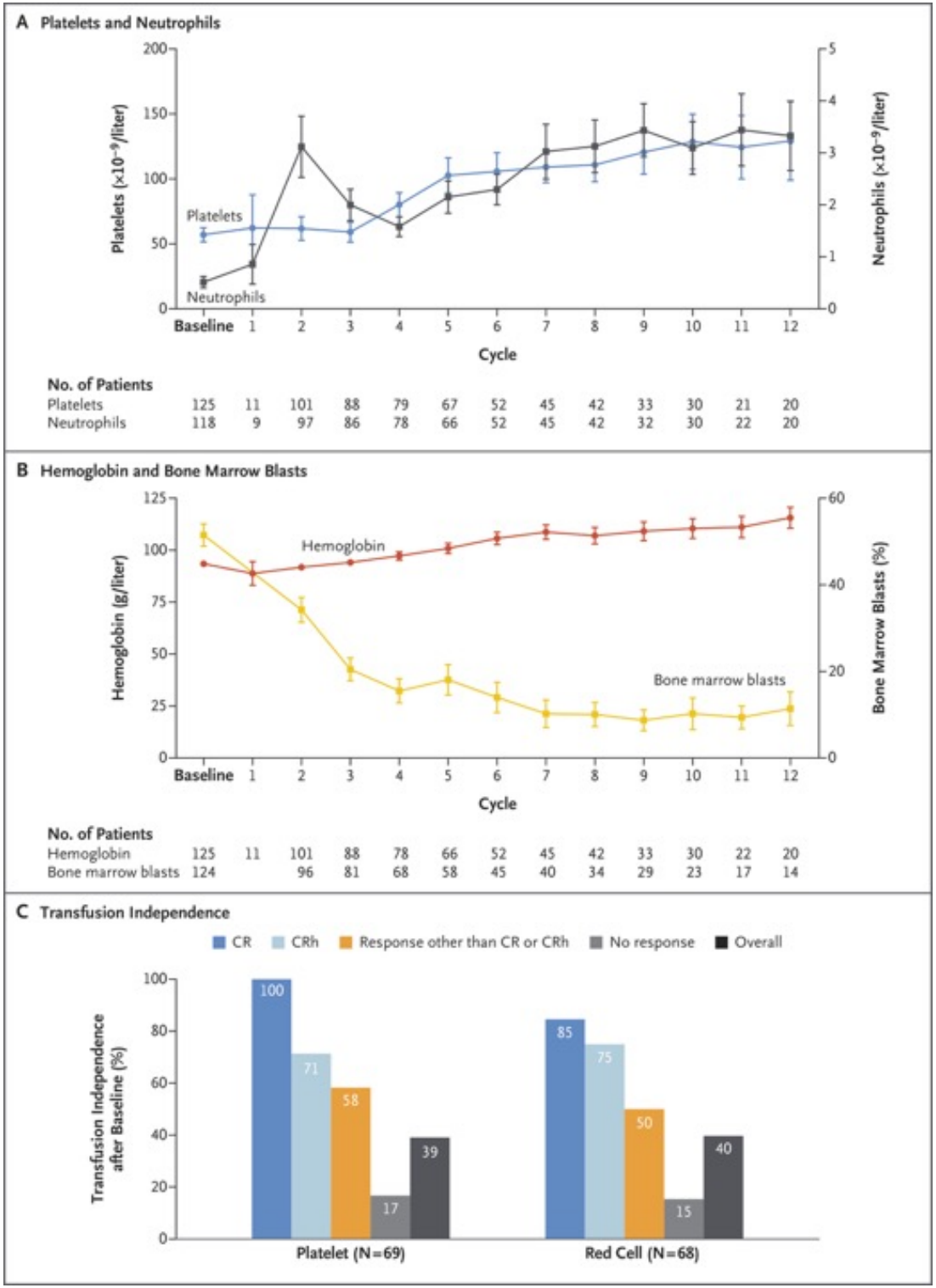
* Complete remission (CR) was assessed by the investigators. Complete remission with partial hematologic recovery (CRh) was assessed by the sponsor. CRi denotes complete remission with incomplete hematologic recovery, CRp complete remission with incomplete platelet recovery, MDS the myelodysplastic syndrome, MLFS morphologic leukemia-free state, NA not applicable, and NE could not be estimated.

† Data are for patients with untreated AML who were not eligible for standard-of-care treatment in dose-expansion group 2 and in the dose-escalation phase whose starting dose of ivosidenib was 500 mg once daily.

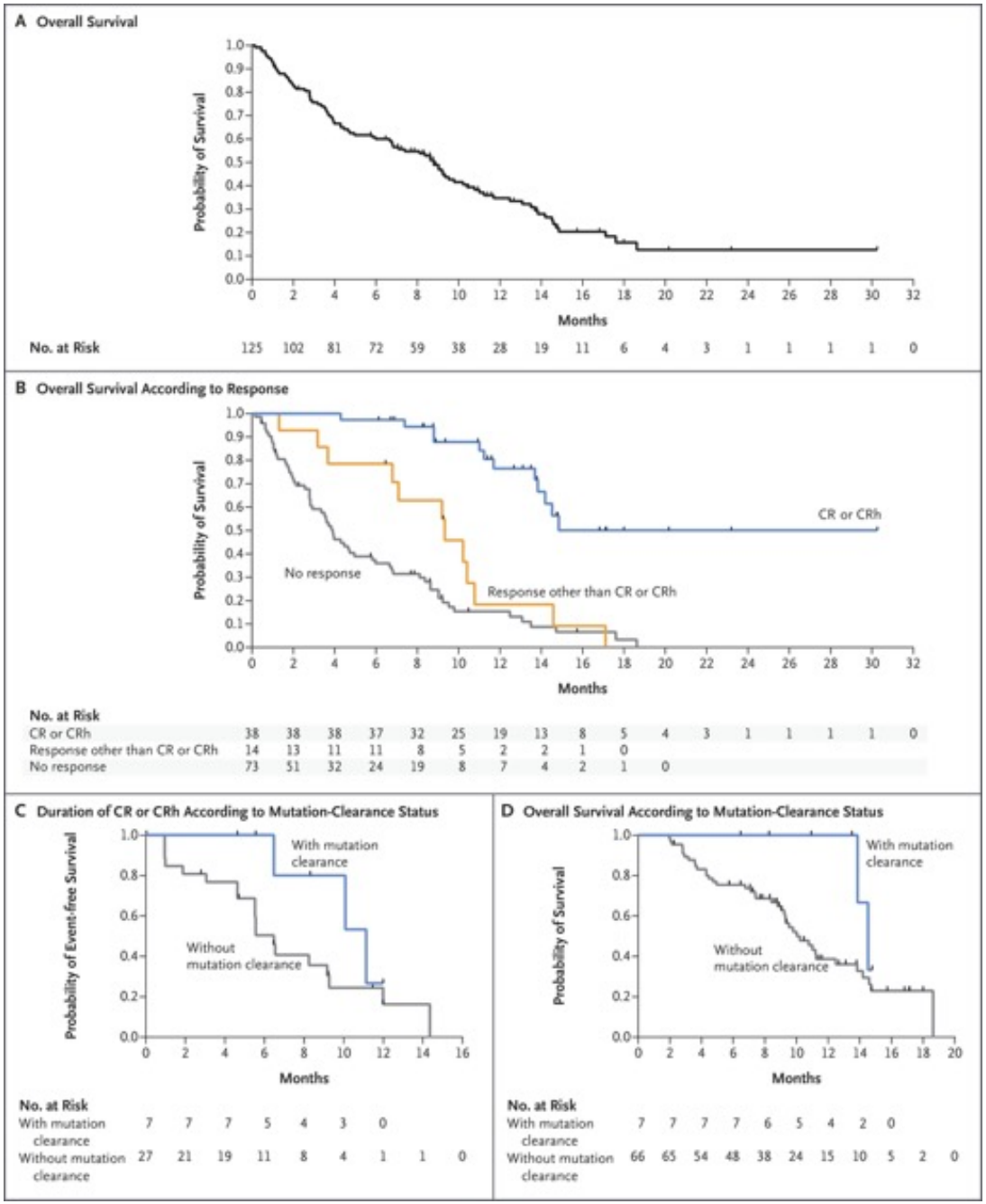
‡ Data are for patients with MDS that was recurrent or refractory after the failure of hypomethylating agents in dose-expansion group 3 and in the dose-escalation phase whose starting dose of ivosidenib was 500 mg once daily.

§ Shown is the time from the first dose to the first occurrence of any response (CR, CRi or CRp, partial remission, or MLFS) among patients who had a response.

¶ The category of bone marrow CR was used only for patients with MDS.



Improvements in Hematologic Variables in the Primary Efficacy Population. Panel A shows the mean platelet count and mean absolute neutrophil count over time. Panel B shows the mean hemoglobin level and mean percentage of bone marrow blasts over time. In Panels A and B, the values are for day 1 of the cycle, and I bars represent the standard error. Values reported at cycle 1 reflect data on day 1 of cycle 1 for patients in the dose-escalation phase for whom data from day 1 of cycle 1 and from 3 days before the first scheduled dose were available. Panel C shows transfusion independence in patients who were dependent at baseline. Patients with a response other than complete remission (CR) or complete remission with partial hematologic recovery (CRh) include patients with CR with incomplete hematologic or platelet recovery and a morphologic leukemia-free state not meeting the criteria for CRh and patients with partial remission. Patients with no response include those with stable disease or progressive disease.



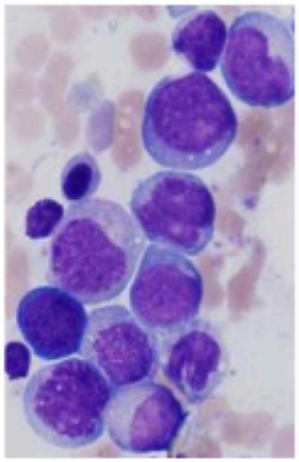
Overall Survival, Response of CR or CRh, and Mutation-Clearance Status. Panel A shows overall survival in the primary efficacy population. Panel B shows overall survival according to response in the primary efficacy population. Panel C shows the duration of CR or CRh in patients with and those without clearance of *IDH1* mutations. Panel D shows the duration of overall survival among patients with and those without clearance of *IDH1* mutations. Data in Panels C and D are for patients in the dose-expansion phase with relapsed or refractory AML whose starting dose of ivosidenib was 500 mg once daily and who received the first dose at least 6 months before the analysis-cutoff date. Tick marks indicate censored data.

Thus, among patients with high-risk, molecularly defined relapsed or refractory AML, ivosidenib monotherapy was associated with a low rate of grade 3 or higher treatment-related adverse events and induced deep and durable remissions and led to favorable outcomes as compared with historical outcomes in patients with advanced relapsed or refractory AML.

Morphologic evidence of myeloid differentiation following ivosidenib treatment (from a patient who achieved complete remission at end of cycle 1).

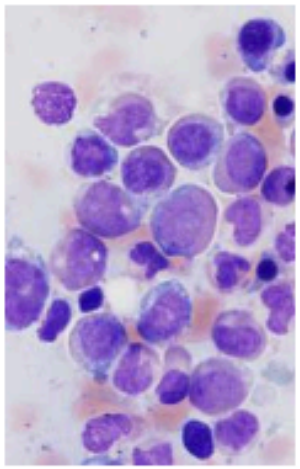
Screening

44% blasts



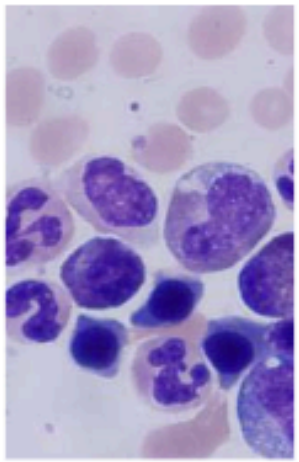
Cycle 1 day 15

3% blasts

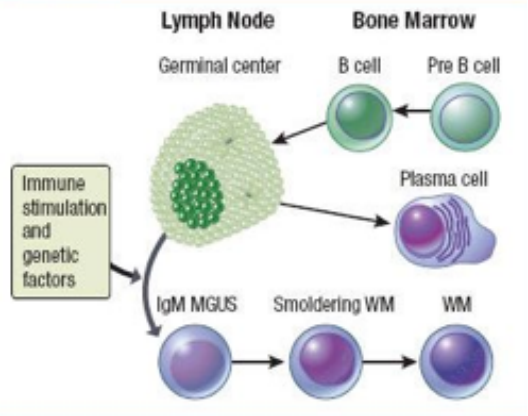


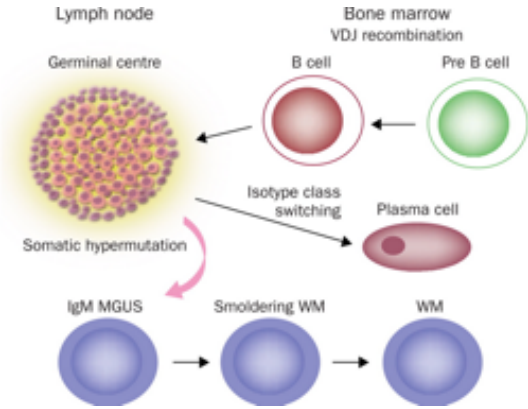
Cycle 1 day 28

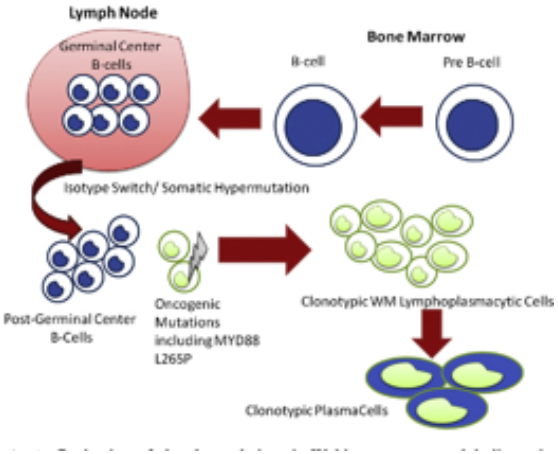
2% blasts



Der Morbus Waldenström (MW), auch Makroglobulinämie oder Immunozytom genannt, ist eine maligne Lymphomerkrankung. Sie wird zu den indolenten (d. h. langsam fortschreitenden und wenig Symptome verursachenden) B-Zell-Non-Hodgkin-Lymphomen gezählt, und zwar unter die Oberkategorie der lymphoplasmozytischen Lymphome.[1] Die Erkrankung ist typischerweise verbunden mit einer abnormen Produktion von monoklonalem Immunglobulin M (IgM) durch die Lymphomzellen. In bestimmten Aspekten hat der Morbus Waldenström Ähnlichkeit mit dem Multiplen Myelom (Plasmozytom), er zeigt jedoch einen wesentlich gutartigeren Verlauf.
Die Erkrankung trägt ihren Namen nach Jan Gösta Waldenström (1906–1996), einem schwedischen Internisten, der die Erkrankung 1944 erstmals wissenschaftlich beschrieb. Die Pathogenese ist im Einzelnen bisher nicht verstanden und ähnelt möglicherweise der chronischen lymphatischen Leukämie. Es kommt zu einer ungehemmten klonalen Vermehrung von reifen plasmazellulär differenzierten aber funktionsgestörten B-Lymphozyten, sowie zu einer Infiltration verschiedener Gewebe und zur Überproduktion von IgM. Betroffen sind von der Infiltration vor allem das Knochenmark, die Milz und die Lymphknoten. Seltener werden andere Organsysteme wie die Leber, die Augen oder das zentrale Nervensystem, was als Bing-Neel-Syndrom bezeichnet wird, befallen. Die Infiltration des Knochenmarks führt unter anderem zur Verdrängung der hämatopoetischen Stammzellen. Dadurch wird die Hämatopoese eingeschränkt, und es kommt zu einer Anämie, zur Infekt- und Blutungsneigung. Die Überproduktion von IgM kann zu einem Hyperviskositätssyndrom führen. Durch die erhöhte Viskosität des Blutes kann die Gewebsdurchblutung beeinträchtigt werden und als Folge treten dann Mikrozirkulationsstörungen, also Durchblutungsstörungen vor allem in den kleinen Gefäßen, auf.







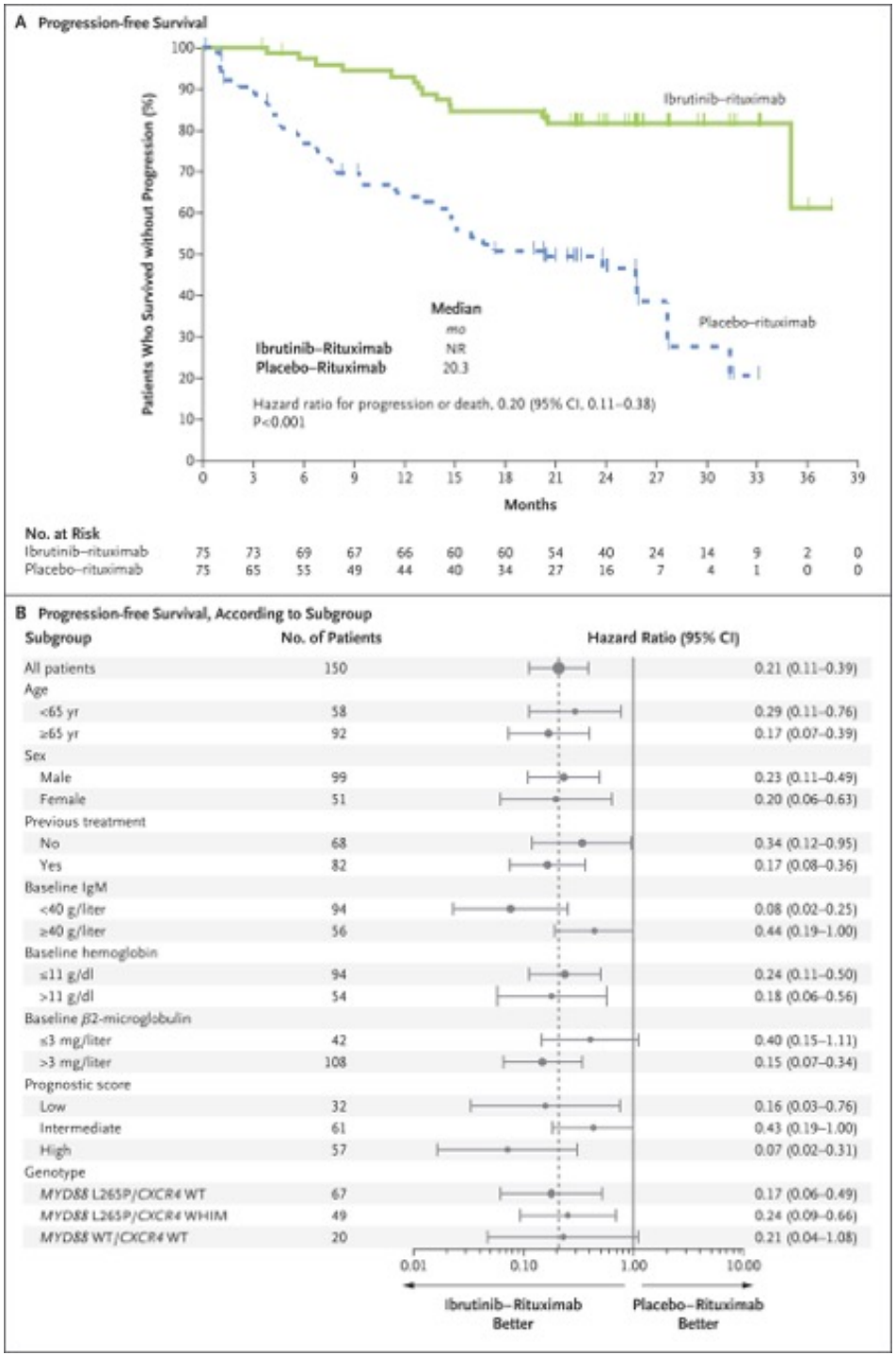
Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

Single-agent ibrutinib has shown substantial activity in patients with relapsed Waldenström's macroglobulinemia, a rare form of B-cell lymphoma. We evaluated the effect of adding ibrutinib to rituximab in patients with this disease, both in those who had not received previous treatment and in those with disease recurrence. We randomly assigned 150 symptomatic patients to receive ibrutinib plus rituximab or placebo plus rituximab. The primary end point was progression-free survival, as assessed by an independent review committee. Key secondary end points were response rates, sustained hematologic improvement from baseline, and safety. The mutational status of *MYD88* and *CXCR4* was assessed in bone marrow samples.

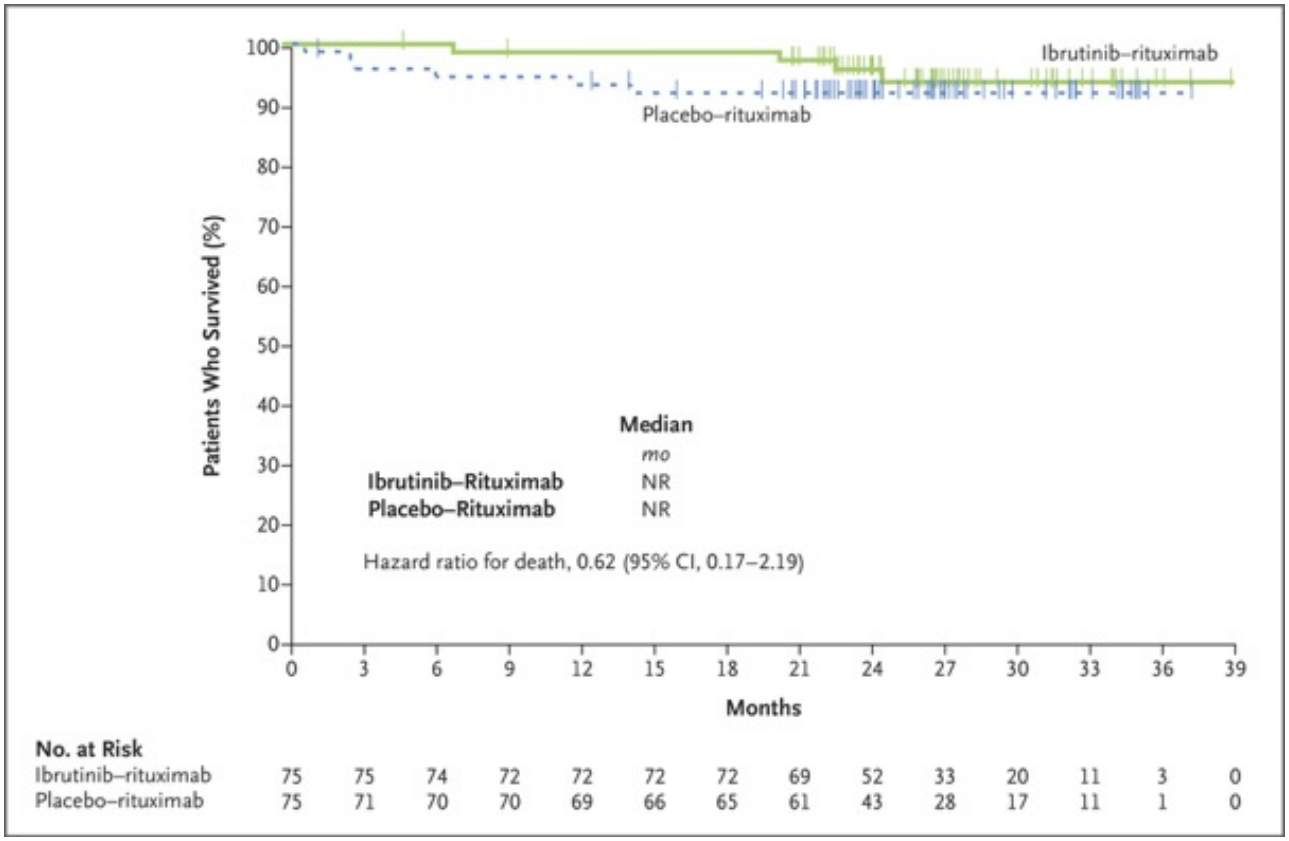
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Ibrutinib–Rituximab (N=75)	Placebo–Rituximab (N=75)
Age		
Median (range) — yr	70 (36–89)	68 (39–85)
≥75 yr — no. (%)	30 (40)	20 (27)
Male sex — no. (%)	45 (60)	54 (72)
Median time from diagnosis (range) — mo	50 (1–257)	56 (1–247)
ECOG performance-status score — no. (%)†		
0	39 (52)	37 (49)
1	32 (43)	32 (43)
2	4 (5)	6 (8)
Prognostic score — no. (%)‡		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Genotype — no./total no. (%)		
*MYD88*WT/*CXCR4* WT	11/69 (16)	9/67 (13)
MYD88 L265P/*CXCR4* WT	32/69 (46)	35/67 (52)
MYD88 L265P/*CXCR4* WHIM	26/69 (38)	23/67 (34)
Cytopenia at baseline — no. (%)		
Hemoglobin of ≤11 g/dl	44 (59)	50 (67)
Platelet count of ≤100,000/mm^3	4 (5)	7 (9)
Absolute neutrophil count of ≤1500/mm^3	4 (5)	1 (1)
Median hemoglobin (range) — g/dl	10.5 (6.9–15.5)	10.0 (6.6–16.1)
Bone marrow infiltration		
Median cellularity (range) — %	80 (25–100)	80 (2–100)
Median intertrabecular space (range) — %	36 (2–95)	40 (1–95)
Serum IgM		
Median (range) — g/liter	32.9 (6.2–77.6)	31.8 (5.9–83.3)
>70 g/liter — no. (%)	2 (3)	4 (5)
Median β_2 microglobulin (range) — mg/liter	3.4 (1.4–27.9)	3.9 (1.5–11.6)
Extramedullary disease — no. (%)	59 (79)	60 (80)
Adenopathy§	56 (75)	58 (77)
Splenomegaly¶	9 (12)	18 (24)
No. of previous systemic therapies — no. (%)		
0	34 (45)	34 (45)
1 or 2	34 (45)	36 (48)
≥3	7 (9)	5 (7)
Previous rituximab-containing regimen — no./total no. (%)	36/41 (88)	34/41 (83)

* There was no significant difference between the groups at baseline. Percentages may not total 100 because of rounding. WT denotes wild type.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability; a score of 5 indicates death.
‡ Scores on the International Prognostic Scoring System for Waldenström's Macroglobulinemia range from 0 to 5, with higher scores indicating a greater risk of death.
§ Adenopathy was defined as the presence of lymph nodes with a long axis of more than 1.5 cm or a short axis of more than 1.0 cm.
¶ Splenomegaly was defined as a spleen depth (cranial to caudal) of more than 13 cm.

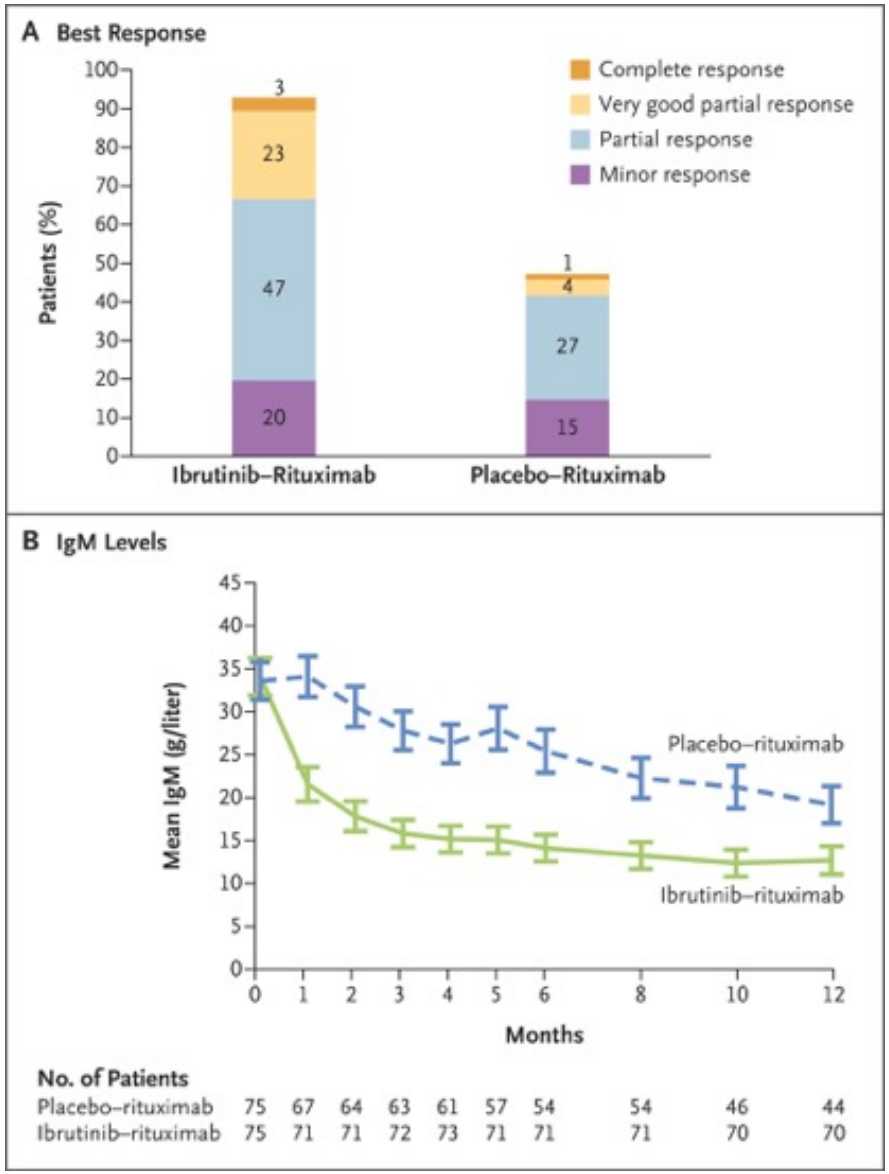


Progression-free Survival among All Patients and According to Subgroup. Shown are the results of the primary analysis of progression-free survival, as assessed by the independent review committee in the overall population (Panel A) and according to subgroup (Panel B). The tick marks indicate censoring of data. NR denotes not reached. In Panel B, the hazard ratios are for disease progression or death. The sizes of the circles are proportional to the sizes of the subgroups. The dashed vertical line represents the overall treatment effect in all patients. The prognostic score was measured on the International Prognostic Scoring System for Waldenström's Macroglobulinemia, which ranges from 0 to 5, with higher scores indicating a greater risk of death.



Overall Survival. Shown are the results of the secondary analysis of overall survival, comparing a combination of ibrutinib plus rituximab with placebo plus rituximab. The tick marks indicate censoring of data.

So what?



Best Response Rates and a Comparison of IgM Levels. Panel A shows the best response to treatment, as assessed by the independent review committee, in the ibrutinib–rituximab group versus the placebo–rituximab group before the initiation of subsequent antineoplastic therapy, disease progression, death, or the date of the interim analysis, whichever was earliest. Categories for response assessments included complete response, very good partial response, partial response, and minor response. Data were unknown, missing, or could not be evaluated for 4 patients in the ibrutinib–rituximab group and for 2 patients in the placebo–rituximab group. The percentages of patients in each category of response may not total the overall proportion with a response because of rounding. Panel B shows the mean IgM levels over time among all the patients in the intention-to-treat population in each treatment group. The I bars represent the standard error.

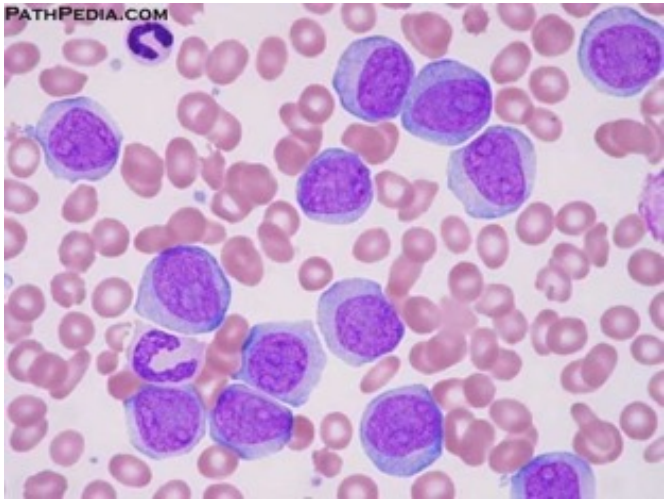
Table 2. Adverse Events and Duration of Treatment.

Variable	Ibrutinib–Rituximab (N=75)	Placebo–Rituximab (N=75)
Median duration of treatment (range) — mo	25.8 (1.0–37.2)	15.5 (0.4–34.3)
Most common adverse events of any grade — no. of patients (%)*		
Infusion-related reaction	32 (43)	44 (59)
Diarrhea	21 (28)	11 (15)
Arthralgia	18 (24)	8 (11)
Nausea	16 (21)	9 (12)
Anemia	14 (19)	22 (29)
Asthenia	12 (16)	19 (25)
Fatigue	10 (13)	20 (27)
Headache	10 (13)	17 (23)
IgM flare	6 (8)	35 (47)
Adverse event of grade ≥3 — no. of patients (%)†	45 (60)	46 (61)
Hypertension	10 (13)	3 (4)
Atrial fibrillation	9 (12)	1 (1)
Anemia	8 (11)	13 (17)
Neutropenia	7 (9)	2 (3)
Pneumonia	7 (9)	2 (3)
Hyponatremia	4 (5)	2 (3)
Infusion-related reaction	1 (1)	12 (16)
Thrombocytopenia	0	4 (5)
Serious adverse event — no. of patients (%)‡	32 (43)	25 (33)
Pneumonia	6 (8)	2 (3)
Atrial fibrillation	5 (7)	1 (1)
Respiratory tract infection	3 (4)	0
Anemia	2 (3)	0
Congestive cardiac failure	2 (3)	0
Fall	2 (3)	0
Gastroenteritis	2 (3)	0
Myocardial ischemia	2 (3)	0
Arthralgia	2 (3)	0

* Listed are adverse events of any grade that occurred in at least 20% of the patients in either treatment group and for which the frequency differed between treatment groups by at least 5 percentage points. Data regarding major hemorrhage (which occurred in 4% of the patients in each group) are not listed because the incidence did not meet the criteria for reporting here.
† Listed are adverse events of grade 3 or higher that occurred in at least 5% of the patients in either treatment group.
‡ Listed are serious adverse events that occurred in at least 2% of the patients in either treatment group.

Best Response Rates and a Comparison of IgM Levels. Panel A shows the best response to treatment, as assessed by the independent review committee, in the ibrutinib–rituximab group versus the placebo–rituximab group before the initiation of subsequent antineoplastic therapy, disease progression, death, or the date of the interim analysis, whichever was earliest. Categories for response assessments included complete response, very good partial response, partial response, and minor response. Data were unknown, missing, or could not be evaluated for 4 patients in the ibrutinib–rituximab group and for 2 patients in the placebo–rituximab group. The percentages of patients in each category of response may not total the overall proportion with a response because of rounding. Panel B shows the mean IgM levels over time among all the patients in the intention-to-treat population in each treatment group. The I bars represent the standard error.

Ibrutinib has shown substantial single-agent activity in patients with Waldenström's macroglobulinemia. In long-term follow-up of a pivotal trial of ibrutinib in patients with advanced Waldenström's macroglobulinemia, the duration of progression-free survival had not been reached at a median follow-up of 47 months. The durable responses, taken together with the established long-term safety profile of ibrutinib in various B-cell cancers, made ibrutinib an attractive option for the treatment of Waldenström's macroglobulinemia. However, questions remain about the efficacy of ibrutinib among patients who have not received previous treatment and about the influence of *MYD88* and *CXCR4* mutations on response, which may affect the course of the disease, as well as the efficacy of a dual-targeting combination to overcome the potential effects of *MYD88* and *CXCR4* genotypes on the response to ibrutinib. We conducted a placebo-controlled trial to evaluate the effect of adding ibrutinib to rituximab.



Retraction and Republication: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. N Engl J Med 2013;368:1279-90.

To the Editor:

Because of irregularities in the randomization procedures, we wish to retract the following article: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. N Engl J Med 2013;368:1279-90. DOI: 10.1056/NEJMoa1200303.[1] We have reanalyzed the data and have published a new report: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. DOI: 10.1056/NEJMoa1800389.[2]

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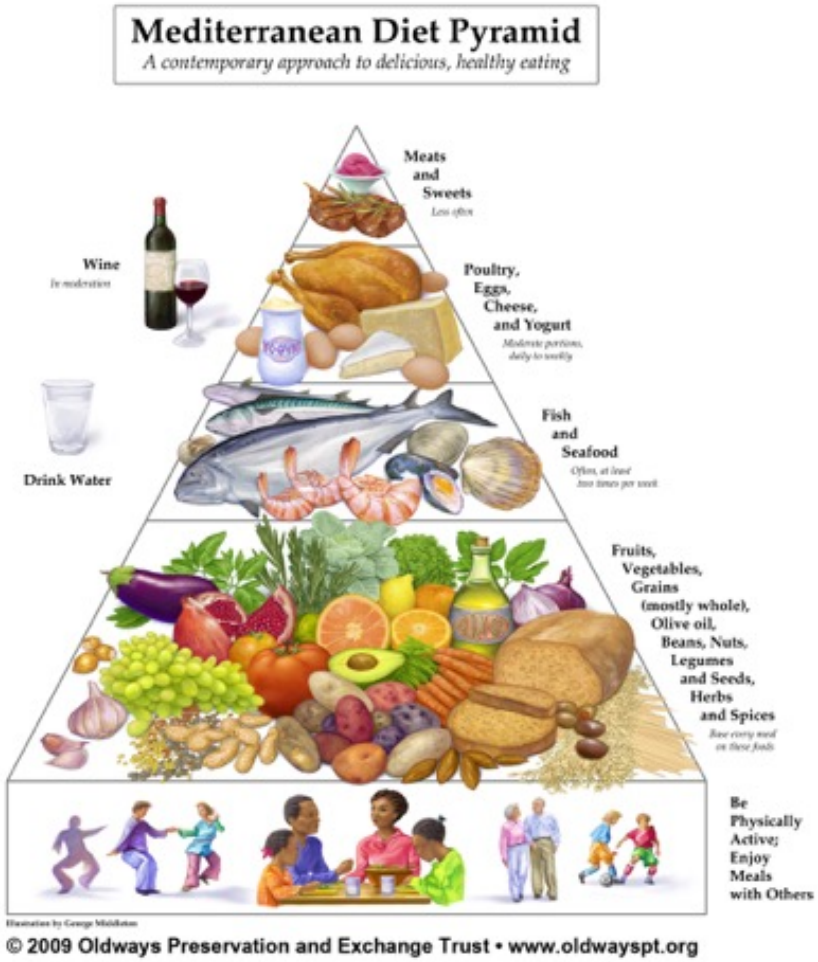


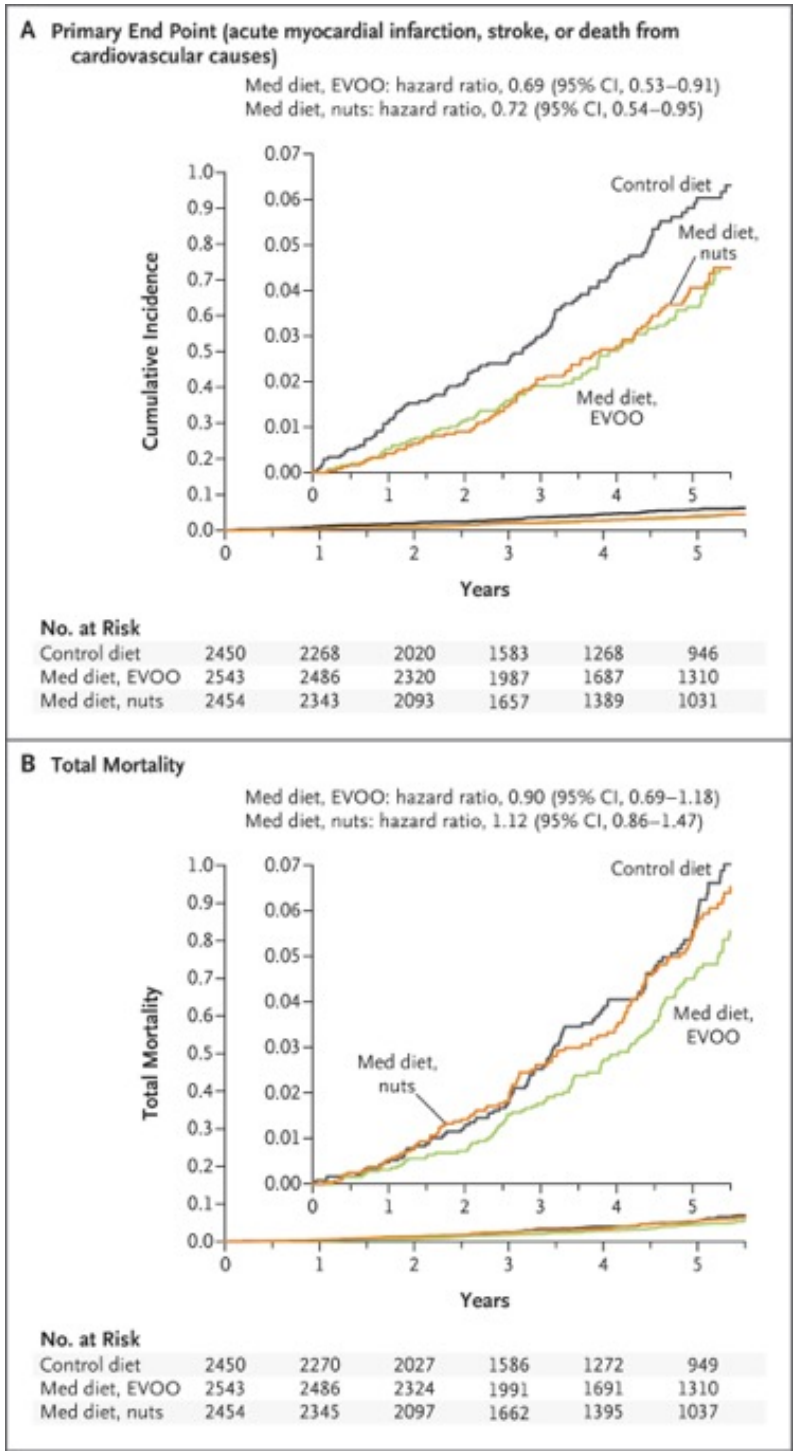
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts

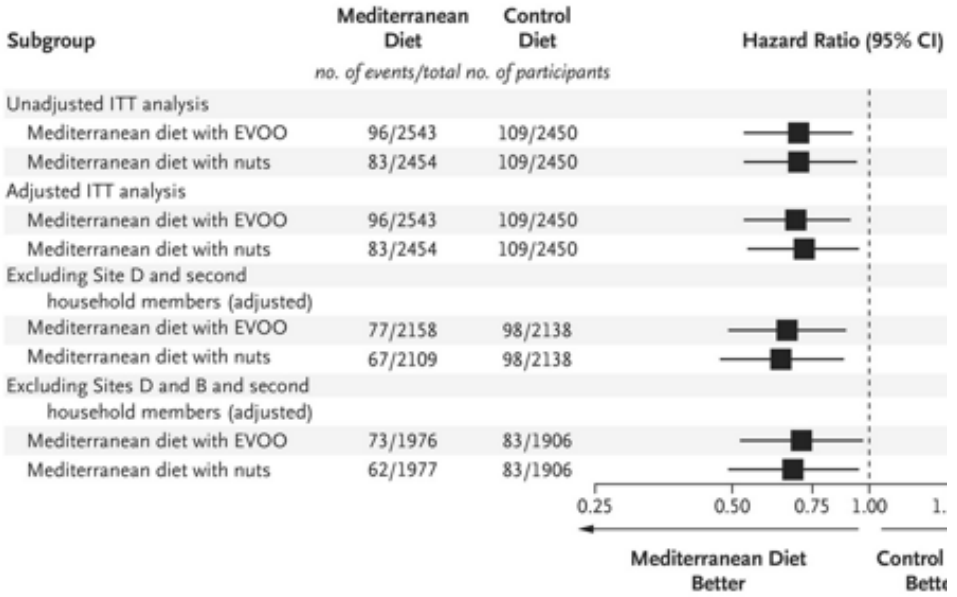
Observational cohort studies and a secondary prevention trial have shown inverse associations between adherence to the Mediterranean diet and cardiovascular risk. The original „Mediterranean diet“ study was withdrawn because there were „irregularities“ in recruitment. The authors ”withdrew” the original study and now publish the same results again.
In a multicenter trial in Spain, we assigned 7447 participants (55 to 80 years of age, 57% women) who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was a major cardiovascular event (myocardial infarction, stroke, or death from cardiovascular causes). After a median follow-up of 4.8 years, the trial was stopped on the basis of a prespecified interim analysis. In 2013, we reported the results for the primary end point in the *Journal*. We subsequently identified protocol deviations, including enrollment of household members without randomization, assignment to a study group without randomization of some participants at 1 of 11 study sites, and apparent inconsistent use of randomization tables at another site. We have withdrawn our previously published report and now report revised effect estimates based on analyses that do not rely exclusively on the assumption that all the participants were randomly assigned.

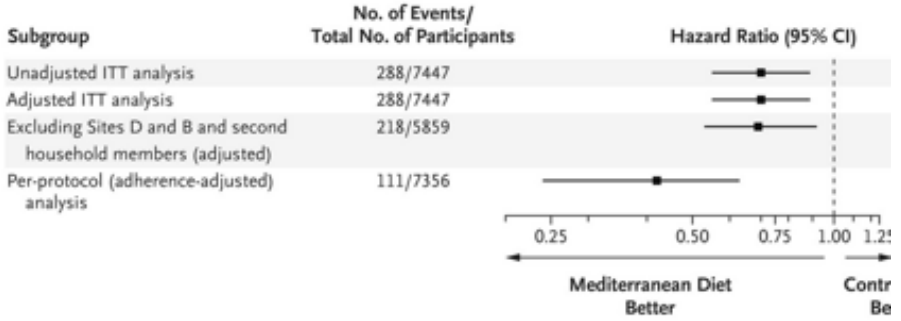
Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<2 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)¶	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Lean fish and seafood	≥3 servings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving/wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups‖	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Female sex — no. (%)†	1493 (58.7)	1326 (54.0)	1463 (59.7)
Age — yr†	67.0±6.2	66.7±6.1	67.3±6.3
Race or ethnic group — no. (%)‡			
White, from Europe	2470 (97.1)	2390 (97.4)	2375 (96.9)
Hispanic, from Central or South America	35 (1.4)	29 (1.2)	38 (1.6)
Other	38 (1.5)	35 (1.4)	37 (1.5)
Smoking status — no. (%)			
Never smoked	1572 (61.8)	1465 (59.7)	1527 (62.3)
Former smoker	618 (24.3)	634 (25.8)	584 (23.8)
Current smoker	353 (13.9)	355 (14.5)	339 (13.8)
Body-mass index†§	29.9±3.7	29.7±3.8	30.2±4.0
Waist circumference — cm	100±10	100±10	101±11
Waist-to-height ratio†¶	0.63±0.06	0.63±0.06	0.63±0.07
Hypertension — no. (%)‖	2088 (82.1)	2024 (82.5)	2050 (83.7)
Type 2 diabetes — no. (%)†**	1282 (50.4)	1143 (46.6)	1189 (48.5)
Dyslipidemia — no. (%)††	1821 (71.6)	1799 (73.3)	1763 (72.0)
Family history of premature CHD — no. (%)‡‡	576 (22.7)	532 (21.7)	560 (22.9)
Medication use — no. (%)			
ACE inhibitors	1236 (48.6)	1223 (49.8)	1216 (49.6)
Diuretics†	534 (21.0)	477 (19.4)	562 (22.9)
Other antihypertensive agents	725 (28.5)	710 (28.9)	758 (30.9)
Statins	1039 (40.9)	964 (39.3)	983 (40.1)
Other lipid-lowering agents	121 (4.8)	145 (5.9)	126 (5.1)
Insulin	124 (4.9)	126 (5.1)	134 (5.5)
Oral hypoglycemic agents†	768 (30.2)	680 (27.7)	757 (30.9)
Antiplatelet therapy	475 (18.7)	490 (20.0)	513 (20.9)
Hormone-replacement therapy§§	42 (2.8)	35 (2.6)	39 (2.7)

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
No. of person-yr of follow-up	11852	10365	9763
Primary end point†			
No. of events	96	83	109
Incidence rate per 1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)
5-yr absolute risk — % (95% CI)‡	3.6 (2.8–4.5)	4.0 (3.1–5.0)	5.7 (4.6–6.9)
Secondary end points			
Stroke			
No. of events	49	32	58
Incidence rate per 1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)
5-yr absolute risk — % (95% CI)	1.7 (1.3–2.4)	1.5 (1.1–2.3)	3.0 (2.3–3.9)
Myocardial infarction			
No. of events	37	31	38
Incidence rate per 1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)
5-yr absolute risk — % (95% CI)	1.4 (1.0–2.1)	1.6 (1.1–2.3)	2.1 (1.5–2.9)
Death from cardiovascular causes			
No. of events	26	31	30
Incidence rate per 1000 person-yr (95% CI)	2.2 (1.4–3.2)	3.0 (2.0–4.2)	3.1 (2.1–4.4)
5-yr absolute risk — % (95% CI)	1.0 (0.6–1.5)	1.4 (0.9–2.1)	1.6 (1.1–2.3)
Death from any cause			
No. of events	118	116	114
Incidence rate per 1000 person-yr (95% CI)	10.0 (8.2–11.9)	11.2 (9.3–13.4)	11.7 (9.6–14.0)
5-yr absolute risk — % (95% CI)	4.4 (3.6–5.4)	5.4 (4.4–6.6)	5.4 (4.4–6.7)
ITT analysis: hazard ratio for each Mediterranean diet vs. control (95% CI)§			
Primary end point			
Unadjusted	0.70 (0.53–0.92)	0.70 (0.53–0.94)	1.00 (ref)
Adjusted¶	0.69 (0.53–0.91)	0.72 (0.54–0.95)	1.00 (ref)
Secondary end points¶			
Stroke	0.65 (0.44–0.95)	0.54 (0.35–0.82)	1.00 (ref)
Myocardial infarction	0.82 (0.52–1.30)	0.76 (0.47–1.25)	1.00 (ref)
Death from cardiovascular causes	0.62 (0.36–1.06)	1.02 (0.63–1.67)	1.00 (ref)
Death from any cause	0.90 (0.69–1.18)	1.12 (0.86–1.47)	1.00 (ref)
ITT analysis: hazard ratio for Mediterranean diets combined vs. control (95% CI)§			
Primary end point			
Unadjusted	0.70 (0.55–0.89)		1.00 (ref)
Adjusted¶	0.70 (0.55–0.89)		1.00 (ref)
Secondary end points¶			
Stroke	0.58 (0.42–0.82)		1.00 (ref)
Myocardial infarction	0.80 (0.53–1.21)		1.00 (ref)
Death from cardiovascular causes	0.80 (0.51–1.24)		1.00 (ref)
Death from any cause	0.98 (0.77–1.24)		1.00 (ref)
Primary end point, excluding Site D and second household members‖			
Each Mediterranean diet and control			
No. of participants	2158	2109	2138
5-year absolute risk — % (95% CI)	3.4 (2.6–4.3)	3.9 (3.0–5.0)	5.9 (4.8–7.2)
Hazard ratio (95% CI)¶	0.66 (0.49–0.89)	0.64 (0.47–0.88)	1.00 (ref)
Mediterranean diets combined and control			
5-year absolute risk — % (95% CI)	3.6 (3.0–4.3)		5.9 (4.8–7.2)
Hazard ratio (95% CI)¶	0.65 (0.50–0.85)		1.00 (ref)







In this study involving high-risk persons without cardiovascular disease, assignment to an energy-unrestricted Mediterranean diet supplemented with either extra-virgin olive oil or nuts was associated with a lower risk of major cardiovascular events over a period of 5 years than assignment to a control (low-fat) diet, with a relative difference of 30% and an absolute difference of 1.7 to 2.1 percentage points.

Subclinical Hyperthyroidism

A 65-year-old woman is seen for routine evaluation. She has a history of paroxysmal atrial fibrillation and osteoporosis, which has been treated with a bisphosphonate. She has no history of thyroid disease and reports no symptoms of hyperthyroidism. Her pulse is 80 beats per minute. The left thyroid lobe is enlarged, but the results of physical examination are otherwise normal, as are the results of electrocardiography. The serum thyrotropin level is 0.2 mU per liter (reference range, 0.5 to 4.5) and the free thyroxine (T_4) level 1.2 ng per deciliter (reference range, 0.8 to 1.8). How should this patient be evaluated and treated? In overt hyperthyroidism, serum levels of free T_4 and triiodothyronine (T_3) or levels of T_3 alone are elevated, and serum thyrotropin levels are suppressed. In subclinical hyperthyroidism, levels of free T_4 and T_3 are normal, thyrotropin levels are suppressed, and thyroid hormone levels are usually in the middle to upper range of normal. The prevalence of overt hyperthyroidism ranges from 0.7 to 1.8% in iodine-sufficient populations and 2 to 15% in persons with mild iodine deficiency. Between 65% and 75% of persons with subclinical hyperthyroidism have serum thyrotropin levels of 0.1 to 0.4 mU per liter (referred to here as mild subclinical hyperthyroidism), and the remainder have thyrotropin levels of less than 0.1 mU per liter (severe subclinical hyperthyroidism).

KEY CLINICAL POINTS

Subclinical Hyperthyroidism

- Subclinical hyperthyroidism, in which serum thyroid hormone levels are within the reference range but serum thyrotropin levels are subnormal (≤0.4 mU per liter), may be caused by overproduction of endogenous thyroid hormone or excessive ingestion of exogenous thyroid hormone.
- Progression to overt hyperthyroidism may occur, especially when serum thyrotropin levels are less than 0.1 mU per liter.
- Even without progression to overt hyperthyroidism, subclinical hyperthyroidism can be associated with adverse outcomes, including cardiovascular disease (e.g., atrial fibrillation, heart failure, and coronary heart disease), bone loss, fractures, and dementia, particularly in persons older than 65 years of age with severe disease.
- Although data are lacking from randomized clinical trials to guide treatment decisions, professional organizations recommend treatment of subclinical hyperthyroidism in persons older than 65 years of age and postmenopausal women, especially when serum thyrotropin levels are less than 0.1 mU per liter.

Table 1. Clinical Outcomes in Mild and Severe Endogenous Subclinical Hyperthyroidism and Possible Benefits of Treatment.*

Outcome	Strength of Association†		Benefits of Treatment
	Mild Subclinical Hyperthyroidism‡	Severe Subclinical Hyperthyroidism‡	
Symptoms	Insufficient data	Possible in young patients; usually absent in patients older than 65 yr	Nonrandomized studies involving young adults with severe subclinical hyperthyroidism suggest benefit
Risk of progression	Progression may occur but less frequently than in patients with severe disease; risk increases after large iodine load	Definite according to prospective studies	Early treatment can prevent development of known adverse effects of overt hyperthyroidism
Cardiovascular manifestations or ectopic rhythm§	Insufficient data	Possible	Nonrandomized studies involving patients with severe subclinical hyperthyroidism suggest benefit
Atrial fibrillation	Definite, especially in middle-aged and elderly patients with risk factors for atrial fibrillation	Definite	Insufficient data
Heart failure	Possible, especially with advanced age and in patients with risk factors for heart failure	Definite	Insufficient data
Death from coronary heart disease	Possible, especially in adults with cardiovascular risk factors	Definite	Insufficient data
Stroke[8]	Available data suggest no statistically significant increase in risk, but data are limited and conflicting	Insufficient data	Insufficient data
Cognitive dysfunction or dementia	Data from prospective studies are limited and conflicting	Definite according to meta-analyses	Insufficient data
Osteoporosis	Possible in patients with risk factors for osteoporosis; unlikely in young adults without risk factors for osteoporosis	Definite	Nonrandomized studies involving postmenopausal women with severe subclinical hyperthyroidism suggest improvement in bone density; data insufficient to inform benefits in elderly men
Fractures	Possible, especially in patients with risk factors for osteoporosis; unlikely in young adults without risk factors for osteoporosis	Definite in postmenopausal women, elderly men, and patients with risk factors for osteoporosis	Insufficient data

* Data on stroke are derived from are derived from Chaker et al.[8]. All other data are derived from Cooper and Biondi,[1] Vadiveloo et al.,[9] Selmer et al.,[10,11] Cappola et al.,[12] Collet et al.,[13] Gencer et al.,[14] Yan et al.,[15] Blum et al.,[16] Yang et al.,[17] Rieben et al.,[18] and Aubert et al.[19]

† Associations are considered to be definite when supported consistently by results of meta-analyses, possible when there are some but inconsistent supporting data (including heterogeneous results of meta-analyses), and insufficient when data are limited.

‡ Mild subclinical hyperthyroidism is defined as a thyrotropin level of 0.1 to 0.4 mU per liter, and severe subclinical hyperthyroidism as a thyrotropin level of less than 0.1 mU per liter.

§ Cardiovascular manifestations include sinus tachycardia while at rest, premature atrial and ventricular beats, reduced variability in heart rate, increased left ventricular mass, diastolic dysfunction, and reduced exercise tolerance.

Table 2. Overt Primary Hyperthyroidism, Subclinical Hyperthyroidism, and Other Causes of Low Serum Thyrotropin Levels.

Overt primary hyperthyroidism

Suppressed thyrotropin levels and elevated levels of free thyroxine (T_4) and triiodothyronine (T_3) or elevated levels of T_3 only

Subclinical hyperthyroidism

In mild cases, low but detectable serum thyrotropin levels (0.1 to 0.4 mU per liter) with normal levels of free T_4 and T_3

In severe cases, undetectable serum thyrotropin level (<0.1 mU per liter) with normal levels of free T_4 and T_3

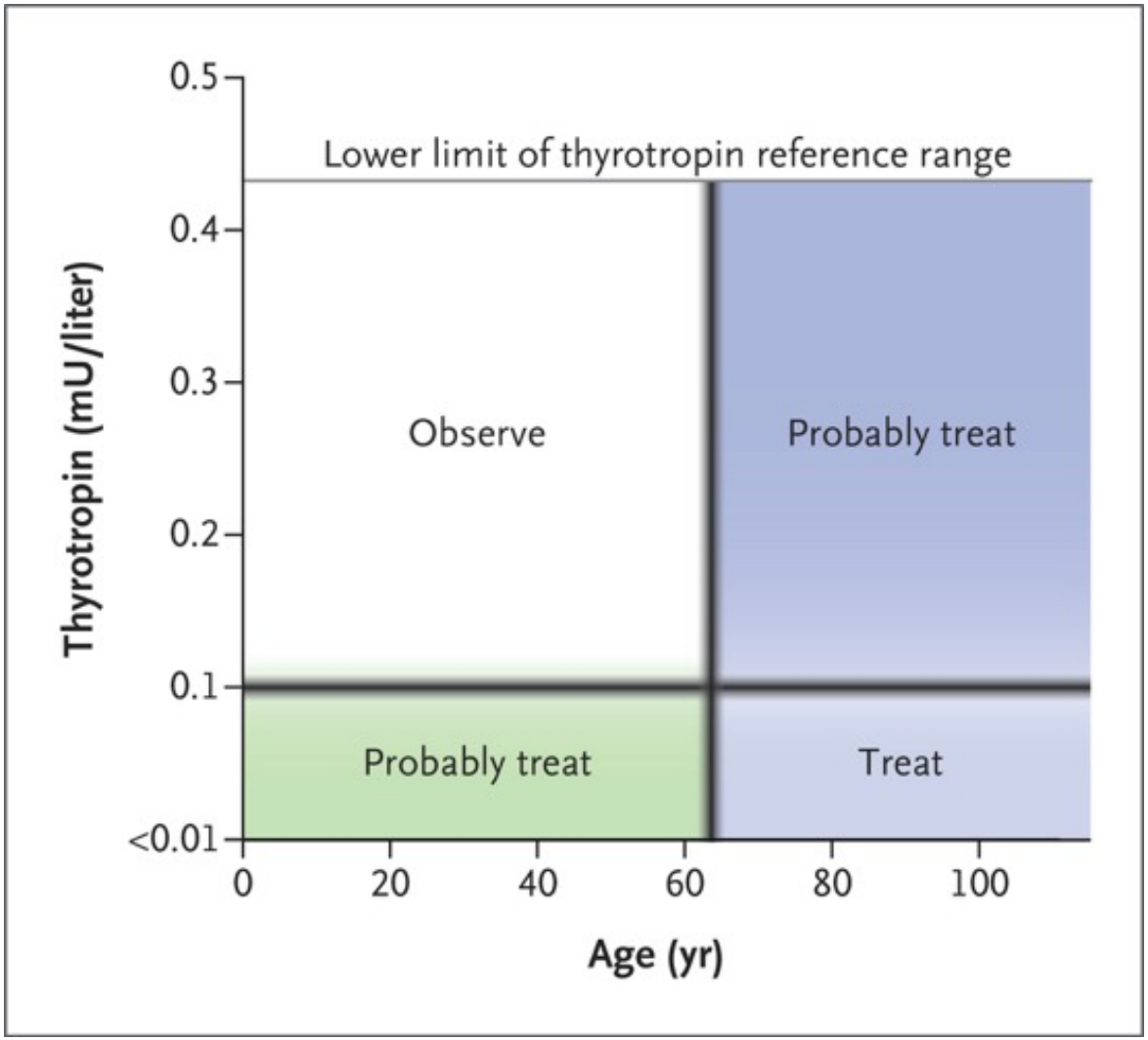
Other causes of low serum thyrotropin levels

The following causes of low serum thyrotropin levels should be ruled out before a diagnosis of subclinical hyperthyroidism is made:

- Severe nonthyroidal illness
- Administration of drugs that suppress serum thyrotropin levels (e.g., dopamine, high doses of glucocorticoids, dobutamine, somatostatin analogues, amphetamines, bromocriptine, and bexarotene)
- Pituitary or hypothalamic disease that causes thyroid hormone or thyrotropin deficiency
- Psychiatric illness
- Late first-trimester of pregnancy
- Hyperemesis gravidarum
- Older age (i.e., age-induced changes in the hypothalamic–pituitary thyroid axis in areas of the world with iodine deficiency)
- African descent (thyrotropin levels are below the reference range in 3 to 4% of patients

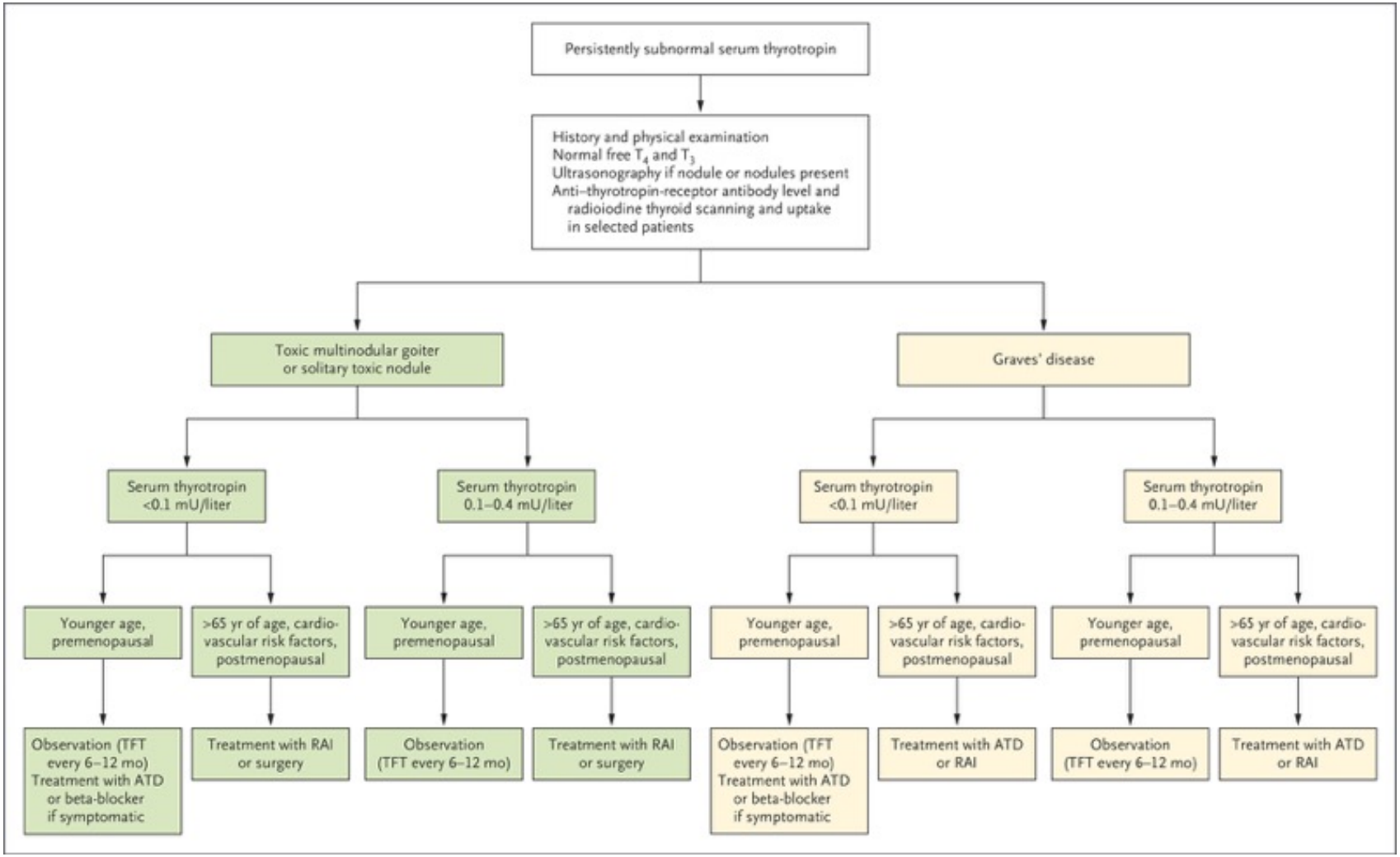
Table 3. Means of Establishing the Cause and Assessing the Risks Associated with Subclinical Hyperthyroidism.

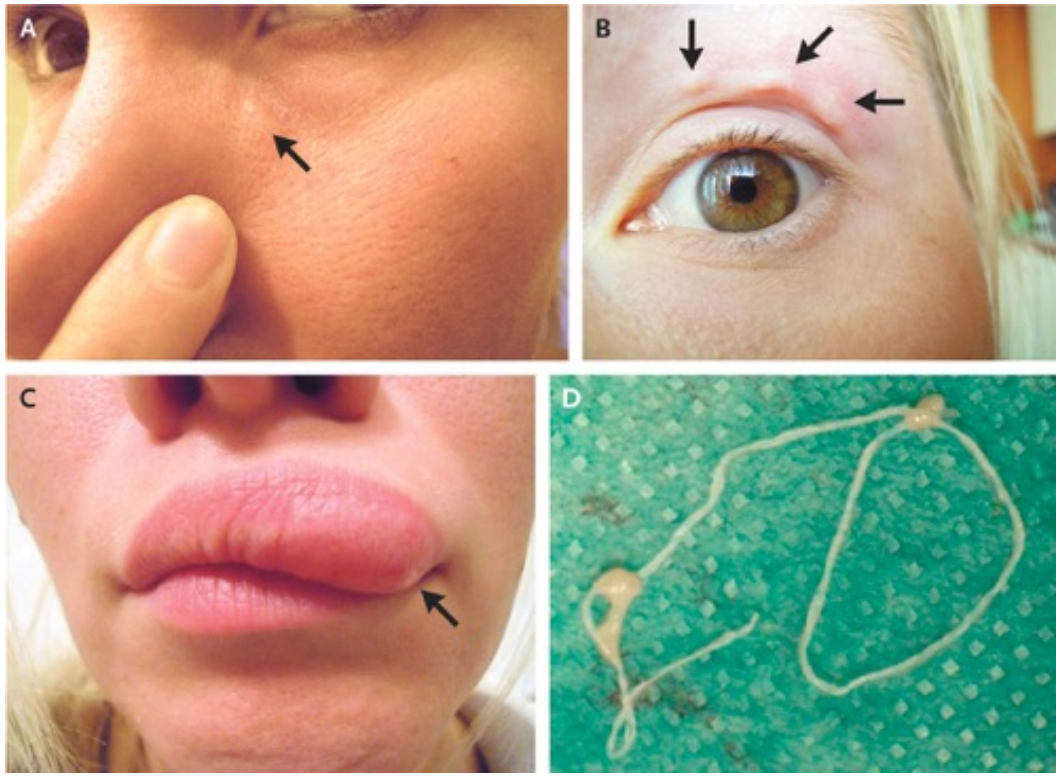
Objective	Patient Population	Rationale or Interpretation
Establishment of cause		
Evaluation of anti–thyrotropin-receptor antibodies (thyroid-stimulating antibody or thyroid-stimulating immunoglobulin)	Patients with normal results on thyroid examination or those in whom Graves' disease is suspected (e.g., diffuse thyroid enlargement, Graves' ophthalmopathy)	Positive result for anti–thyrotropin-receptor antibodies is virtually diagnostic of Graves' disease; however, test is less sensitive in patients with milder disease (e.g., subclinical hyperthyroidism) than in those with overt disease.
Color-flow Doppler ultrasonography of thyroid to document and characterize thyroid nodules and goiter	Patients in whom thyroid nodule or goiter is suspected on physical examination	Documentation of ≥1 nodule on ultrasonography, especially if >2 cm in diameter, suggests one or more autonomous thyroid nodules are causing subclinical hyperthyroidism.
Thyroid scintigraphy and 24-hr radioactive iodine uptake to identify autonomous thyroid tissue	Patients with one or more thyroid nodules or goiter detected on ultrasonography	Documentation of functional thyroid nodules establishes the likely cause of subclinical hyperthyroidism (radioiodine is the preferred therapy). Low uptake suggests thyroiditis or iodine exposure.
Assessment of 24-hr urinary iodine excretion	Patients with suspected or known excessive exposure to iodine, usually from iodinated contrast agents	Patients with nodular thyroid disease are susceptible to iodine-induced thyrotoxicosis (the Jod–Basedow phenomenon), especially in areas of the world with iodine insufficiency.
Assessment of risks		
Evaluation for cardiovascular risk factors, underlying cardiovascular disease, or both	All patients, especially those >65 yr	Patients >65 yr may be at increased risk for cardiac consequences of chronic subclinical hyperthyroidism, especially if they have underlying cardiovascular disease.
Electrocardiography	Patients with symptoms of cardiovascular disease (e.g., palpitations)	Assessment of heart rate and detection of arrhythmias.
Holter monitoring	Patients with symptoms of cardiovascular disease and patients with underlying heart disease or new-onset atrial fibrillation, heart failure, or coronary heart disease	Assessment of heart rate and detection of arrhythmias.
Echocardiography	Patients with symptoms of cardiovascular disease and patients with underlying heart disease, heart failure, atrial fibrillation, or coronary heart disease	Assessment of cardiac structure and ventricular function.
Assessment for risk factors for stroke	Patients with atrial fibrillation	Hypertension, diabetes mellitus, history of congestive heart failure, older age (≥65 yr), history of stroke or transient ischemic attack are associated with increased risk of stroke.
Dual-energy radiographic absorptiometry (bone-density test)	Postmenopausal women, men >65 yr, and patients with other risk factors for low bone mineral density	If bone mineral density is low, intake of calcium and vitamin D should be increased. Antiresorptive therapy should be considered in patients with osteoporosis after assessment of the risks and benefits of therapy.



General Therapeutic Approach to Endogenous Subclinical Hyperthyroidism. Postmenopausal women and patients older than 65 years of age should be treated if serum thyrotropin levels are persistently lower than 0.1 mU per liter. Older patients with serum thyrotropin levels between 0.1 and 0.4 mU per liter should be considered for treatment. Premenopausal women and younger patients should be considered for treatment if serum thyrotropin levels are less than 0.1 mU per liter and they have symptoms of hyperthyroidism or coexisting conditions such as osteopenia, osteoporosis, or cardiovascular disease. There is no indication for treatment in younger patients who do not have coexisting conditions if the serum thyrotropin level is 0.1 mU per liter or higher. The blurring of the boundaries between the quadrants is intended to illustrate that the cutoffs of age and thyrotropin level for therapy are not precisely defined.

Management of Endogenous Subclinical Hyperthyroidism. Once subclinical hyperthyroidism is verified with normal levels of free thyroxine (T_4) and triiodothyronine (T_3) and a persistently subnormal level of serum thyrotropin, a diagnosis should be made on the basis of laboratory tests for antithyrotropin-receptor antibodies (to test for Graves' disease), imaging studies (radionuclide scanning or ultrasonography), or both, depending on the clinical circumstances. The decision to treat and the nature of the treatment depend on the underlying diagnosis, the degree of thyrotropin suppression, patient age, and any coexisting conditions. Antithyroid drugs or radioiodine are the preferred treatment in patients with Graves' disease, whereas radioiodine is preferred in patients with toxic nodular disease. Surgery is an option in patients with large goiters that are causing obstructive symptoms when the patient has no major coexisting conditions. ATD denotes antithyroid drug, RAI radioactive iodine, and TFT thyroid function test.



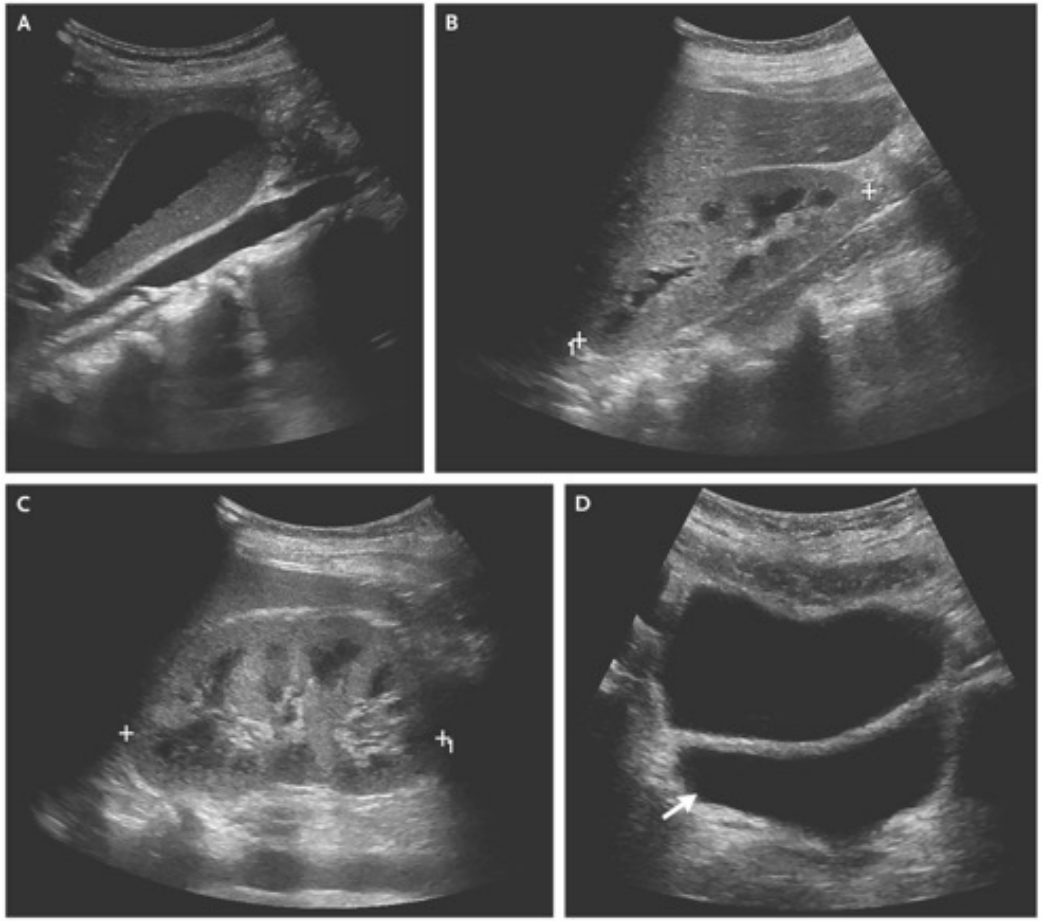


A 32-year-old woman presented to an ophthalmologist with a 2-week history of nodules that moved around her face. She had first noted a nodule below her left eye (Panel A). Five days later, it had moved to above her left eye (Panel B), and 10 days after that to the upper lip (Panel C). She documented these changes by taking photographs of her face (i.e., “selfies”). The nodules occasionally caused a localized itching and burning sensation, but otherwise she had no symptoms. She had recently traveled to a rural area outside Moscow and recalled being frequently bitten by mosquitoes. A physical examination showed a superficial moving oblong nodule at the left upper eyelid. A parasite was fixed with forceps and removed surgically (Panel D). The parasite was identified by means of a polymerase-chain-reaction assay as *Dirofilaria repens*, which is a zoonotic filarial nematode. Dogs and other carnivores are the definitive hosts, and mosquitoes serve as vectors. Humans can become aberrant hosts. Surgical excision of the worm is curative. After removal of the worm, the patient had a full recovery.

A 15-year-old girl was admitted to this hospital during the summer because of acute kidney injury.
The patient had been well until 8 days before admission, when painful cramping in the lower abdomen and bloody diarrhea developed. Bowel movements occurred approximately every hour, and the patient was unable to sleep. She took ibuprofen but had no relief of the abdominal pain.
On the third day of illness, two episodes of nonbloody, nonbilious emesis occurred. The following day, the patient was seen by her primary care pediatrician. She reported that she felt fatigued and that the diarrhea, abdominal cramping, and vomiting had persisted; she had not had a fever. The results of a physical examination were normal. Stool samples were obtained for cultures for salmonella, shigella, campylobacter, aeromonas, plesiomonas, and *Escherichia coli* O157:H7, and antigen-detection tests were performed for rotavirus, giardia, and *Clostridium difficile* toxin. The patient was advised to stop taking ibuprofen, to take loperamide and acetaminophen as needed, and to drink an electrolyte-containing oral rehydration solution.
During the next 3 days, the diarrhea resolved, but the patient continued to vomit several times each day and the abdominal cramping became localized to the epigastrium. The stool cultures and antigen-detection tests were negative. Her mother called the pediatrician's office on the seventh day of illness, and ondansetron (Antiemetikum) was prescribed.

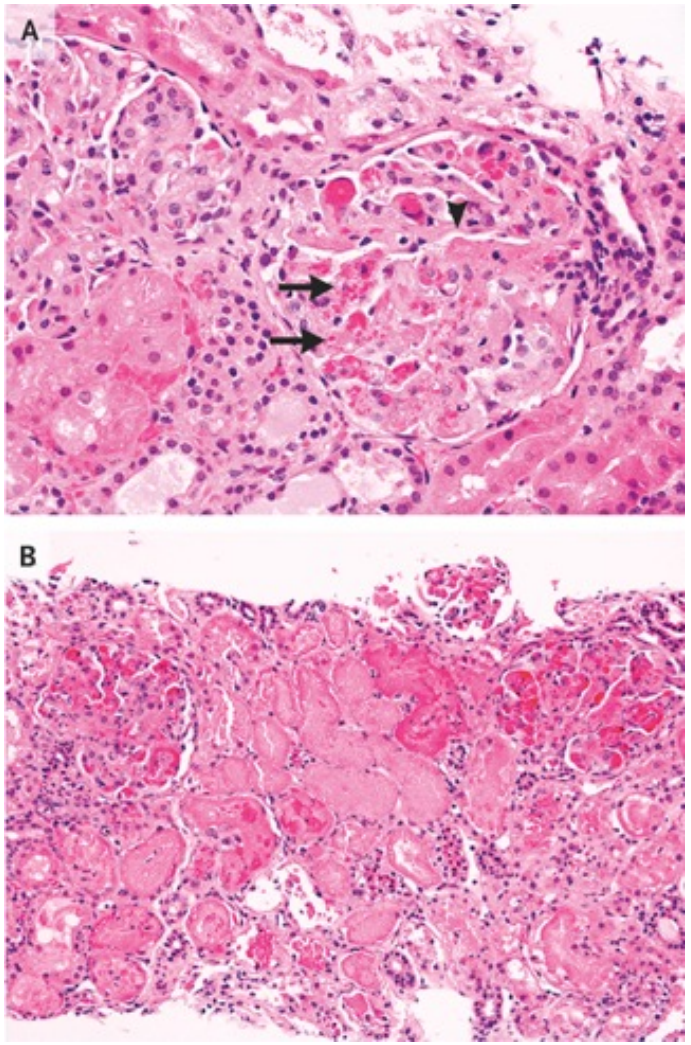
Variable	Reference Range, Other Hospital	On Presentation, Other Hospital	Reference Range, This Hospital†	On Presentation, This Hospital
Hemoglobin (g/dl)	12.0–16.0	12.9	12.0–16.0	11.1
Hematocrit (%)	36.0–46.0	36.4	36.0–46.0	30.9
White-cell count (per mm^3)	4500–11,000	9340	4500–13,500	9310
Differential count (%)				
Neutrophils	54.0–62.0	75.6	40–59	66.1
Bands	0.0–7.0	0.9		
Metamyelocytes	0.0	0.9		
Immature granulocytes			0.0–0.3	3.4
Lymphocytes	25.0–50.0	10.4	33–48	16.1
Monocytes	4.7–12.0	7.8	4–11	12.5
Eosinophils	0.0–3.0	3.5	0–8	1.4
Basophils	0.0–1.0	0.9	0–3	0.5
Platelet count (per mm^3)	140,000–440,000	65,000	150,000–450,000	53,000
Red-cell count (per mm^3)	4,500,000–5,300,000	4,970,000	4,100,000–5,100,000	4,230,000
Mean corpuscular volume (fl)	78.0–102.0	73.2	78.0–102.0	73.0
Mean corpuscular hemoglobin (pg)	27.0–31.0	26.0	25.0–35.0	26.2
Mean corpuscular hemoglobin level (g/dl)	32.0–36.0	35.4	31.0–37.0	35.9
Red-cell distribution width (%)	11.5–14.5	12.6	11.5–14.5	12.7
Reticulocyte count (%)			0.5–2.5	1.1
Description of peripheral-blood smear		Anisocytosis, microcytosis, 1+ polychromasia, large platelets		
Haptoglobin (mg/dl)			16–199	<6
Sodium (mmol/liter)	133–145	131	135–145	132
Potassium (mmol/liter)	3.4–4.7	4.0	3.4–5.0	3.9
Chloride (mmol/liter)	98–107	89	98–108	95
Carbon dioxide (mmol/liter)	22–32	18	23–32	17
Anion gap (mmol/liter)	3–17	24	3–17	20
Calcium (mg/dl)	8.9–10.3	8.0	8.5–10.5	7.5
Phosphorus (mg/dl)			3.0–4.5	5.2
Glucose (mg/dl)	65–99	89	70–110	87
Urea nitrogen (mg/dl)	4–18	101	8–25	97
Creatinine (mg/dl)	0.3–1.0	7.53	0.60–1.50	7.71
Protein (g/dl)				
Total	6.1–8.1	6.0	6.0–8.3	4.9
Albumin	3.1–4.8	3.2	3.3–5.0	2.7
Globulin		2.8	1.9–4.1	2.2
Alanine aminotransferase (U/liter)	7–35	249	7–33	186
Aspartate aminotransferase (U/liter)	14–37	161	9–32	120
Alkaline phosphatase (U/liter)	67–372	300	15–350	232
Bilirubin (mg/dl)				
Total	0.0–1.2	1.0	0.0–1.0	0.8
Direct	0.0–0.2	0.3		
Lipase (U/liter)	13–60	115		
Lactic acid (mmol/liter)			0.5–2.0	0.9
Uric acid (mg/dl)			2.3–6.6	9.0
Lactate dehydrogenase (U/liter)			110–210	2249
Creatine kinase (U/liter)			40–150	108
Parathyroid hormone (pg/ml)			10–60	150
C3 (mg/dl)			81–157	97

On arrival, the patient rated her abdominal pain at 3 on a scale of 0 to 10, with 10 indicating the most severe pain. She reported that, during the past week, her weight had decreased by 3 kg and then increased by 1 kg. She had a history of attention deficit–hyperactivity disorder, anxiety, and labial adhesions. During the previous 7 months, she had been seen by her pediatrician on three occasions because of intermittent dysuria; tests for urinary tract infection, chlamydia, and gonorrhea had been negative. Medications included citalopram and methylphenidate; she had an allergy to azithromycin, which had caused a rash. The patient lived with her parents and siblings in New England. Just before the onset of the current illness, she had spent several days in New York City, where she had eaten food purchased from street vendors. Urinalysis revealed turbid, amber urine, with 2+ blood, 3+ albumin, 3+ leukocyte esterase, a specific gravity of 1.012, and a pH of 5.0 by dipstick; microscopic examination of the sediment revealed transitional cells, squamous cells, amorphous crystals, mucin, bacteria, and white-cell clumps, as well as 20 to 50 red cells per high-power field and more than 100 white cells per high-power field. A urine pregnancy test was negative. Ultrasonography of the bladder, performed at the bedside, revealed that the bladder was collapsed. Ondansetron was administered intravenously.



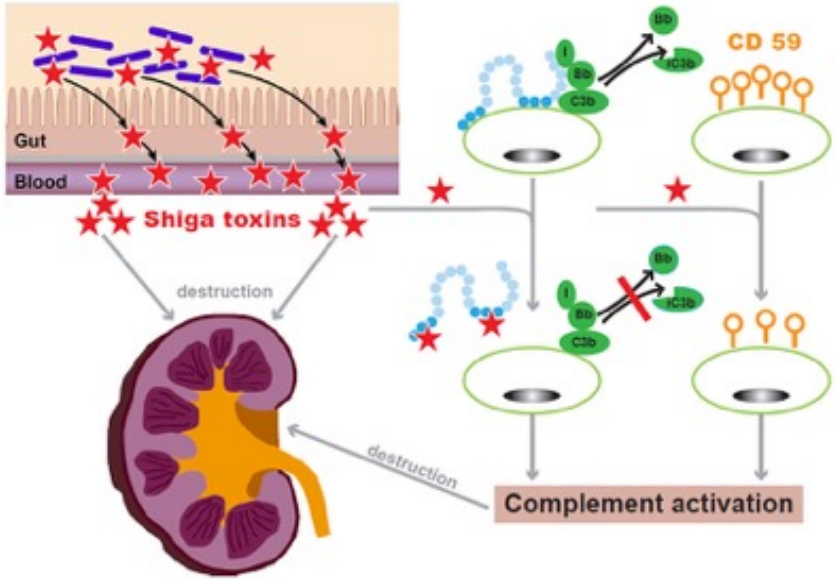
The gallbladder contains a large amount of layering sludge, without wall thickening (Panel A). Both kidneys are normal in size, with mildly echogenic renal parenchyma and without urinary tract dilatation (Panels B and C). The urinary bladder is partially distended, and simple ascites is visible in the pelvis (Panel D, arrow).

Shortly after the patient was admitted to the hospital, examination of a peripheral-blood smear revealed 2+ schistocytes. An enzyme immunoassay of a stool specimen for Shiga toxins 1 and 2 was negative. Histopathological examination of a kidney-biopsy specimen revealed evidence of thrombotic microangiopathy. To rule out thrombotic thrombocytopenic purpura, an assay for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was performed; the result was 64% (normal range, ≥70). This mild reduction in ADAMTS13 activity is inconsistent with thrombotic thrombocytopenic purpura, which is often associated with levels of less than 10%, whereas mildly reduced ADAMTS13 activity may be present in patients with atypical hemolytic–uremic syndrome. Another laboratory finding that is commonly seen in cases of atypical hemolytic–uremic syndrome is low activity in the alternative complement pathway, according to the AH50 assay, which indicates either a deficiency of an alternative or terminal complement pathway component or complement consumption. In this patient, the result of the AH50 assay was less than 10% (normal range, ≥46), which is consistent with atypical hemolytic–uremic syndrome. In this patient, a heterozygous *CFHR3* mutation of unknown significance (c.839_840delTA) was identified. This frameshift mutation results in the substitution of lysine for isoleucine at codon 280 in exon 6 of the *CFHR3* gene and ultimately results in a premature stop codon further downstream.



Hematoxylin and eosin staining of a kidney-biopsy specimen shows evidence of thrombotic microangiopathy, including fragmented red cells (Panel A, arrows) and fibrin deposition (Panel A, arrowhead), as well as tubular necrosis (Panel B).

Das hämolytisch-urämische Syndrom, kurz HUS, ist eine seltene, postinfektiöse Erkrankung der Endothelzellen. Es zählt wie die thrombotisch-thrombozytopenische Purpura zu den thrombotischen Mikroangiopathien. Das Syndrom ist durch die Symptomtrias aus mikroangiopathischer hämolytischer Anämie, Thrombozytopenie und akutem Nierenversagen mit Urämie charakterisiert. Die Inzidenz des HUS wird in Mitteleuropa auf 1 bis 1,5 Fälle pro 100.000 Patienten unter 16 Jahren geschätzt. Obwohl das Syndrom in jedem Lebensalter auftreten kann, liegt der Erkrankungsgipfel zwischen dem zweiten und dritten Lebensjahr. In Deutschland ist das HUS die häufigste Ursache für ein akutes Nierenversagen im Kindesalter. Am häufigsten tritt das hämolytisch-urämische Syndrom postinfektiös nach einer (meist blutigen) Gastroenteritis mit Shigatoxin (Stx, Verotoxin) bildenden Keimen auf. Bekannte Erreger sind hierbei EHEC (Subtyp von Escherichia coli) der Serogruppe O157:H7, verotoxinproduzierende Shigellen, Salmonellen, Yersinien und Campylobacter-Arten. Neben Durchfallerregern können in seltenen Fällen auch bestimmte neuraminidasebildende Pneumokokken Auslöser sein. Ebenfalls seltene infektiöse Auslöser sind Viren (Coxsackie-Virus, Varizella-Zoster-Virus, Echovirus, HIV).
Das typische (durch das Shigatoxin "Stx" ausgelöste) HUS wird auch als "STEC-HUS" (für Shiga-Toxin bildende Escherichia Coli) bezeichnet.



Treten zerebrale Symptome hinzu, handelt es sich in der Regel um eine thrombotisch-thrombozytopenische Purpura (TTP, Moschcowitz-Syndrom) mit petechialen Blutungen und Thrombosenbildung in der Mikrozirkulation. In diesen Fällen ist regelhaft eine gestörte Funktion (familiär oder durch Autoantikörper) des ADAMTS-13-Proteins nachweisbar, das als Protease für die Spaltung und somit Regulation des von-Willebrand-Faktors zuständig ist.

NEJM Knowledge+

Question of the Week

A 39-year-old woman with known bronchiectasis presents to the emergency department with dyspnea, mild hypoxemia, and stable vital signs. A chest radiograph is normal; a chest CT reveals chronic bilateral bronchiectasis with new ground-glass opacities in the left lower lobe. Shortly after hospitalization, the patient has an episode of hemoptysis that produces 300 mL of blood. What is the most appropriate initial management?

- (●) Pulmonary consultation for flexible bronchoscopy
- ( ) Observation of respiratory status and sputum analysis for acid-fast stain
- ( ) Angiography by interventional radiology
- ( ) Observation of respiratory status and serial hemoglobin levels
- ( ) Thoracic surgery consultation for video-assisted thoracoscopic surgery

SUBMIT

Your answer is correct.

Pulmonary consultation for flexible bronchoscopy
Observation of respiratory status and sputum analysis for acid-fast stain
Angiography by interventional radiology
Observation of respiratory status and serial hemoglobin levels
Thoracic surgery consultation for video-assisted thoracoscopic surgery

Key Learning Point

View Case Presentation ›

In a patient with chronic bronchiectasis who presents with massive hemoptysis, stable vital signs, and localized changes on imaging, the most important initial management is emergency angiography by interventional radiology.

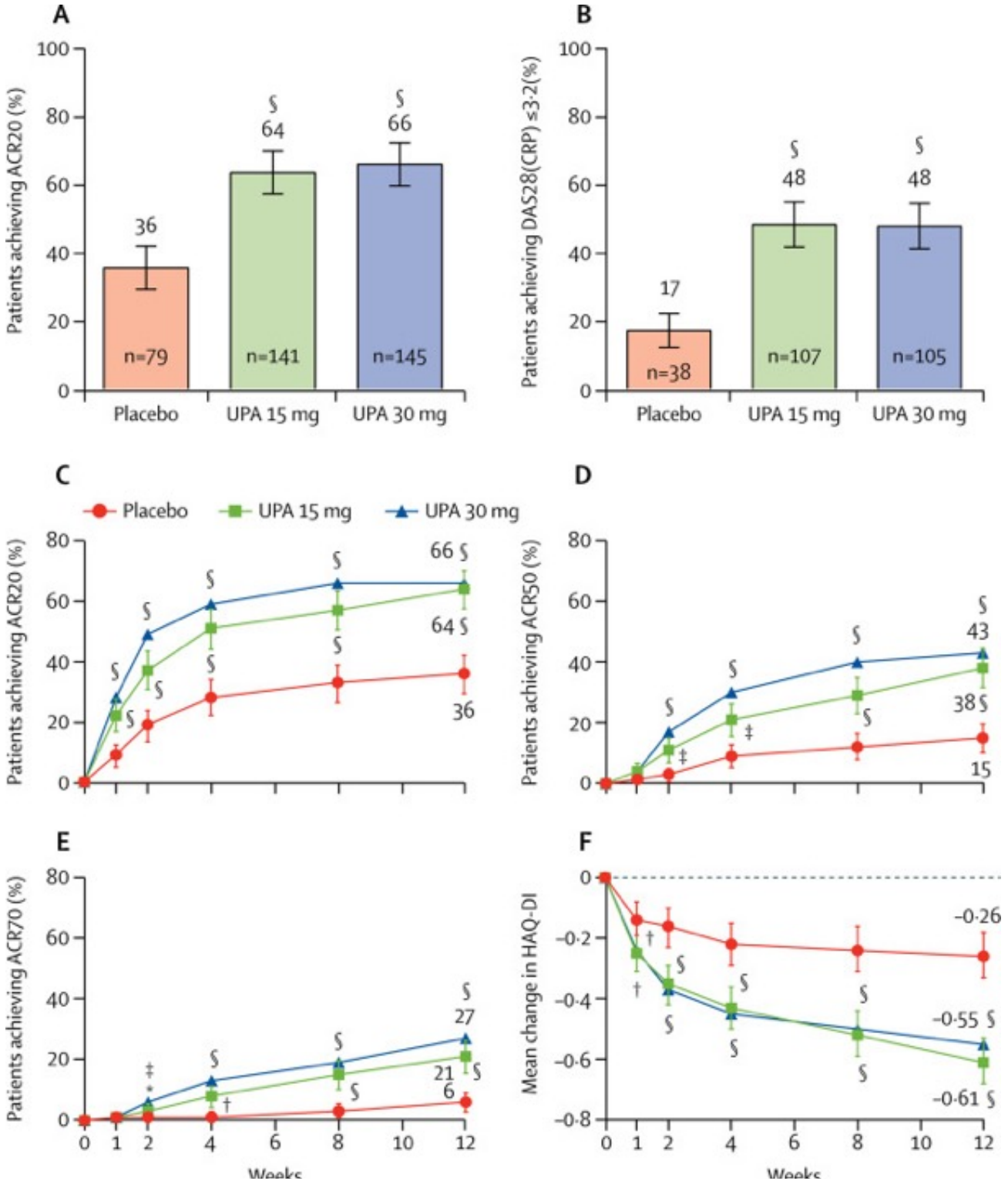
Detailed Feedback

This patient has massive hemoptysis, a medical emergency that requires prompt evaluation. There are varying definitions of "massive" hemoptysis, ranging from 200 mL to 1000 mL of blood produced in 24 hours or more than 100 mL in a single setting. Once the diagnosis is recognized, the patient needs emergency evaluation to help localize the site of bleeding and attempt hemostasis. The most common causes of hemoptysis are bronchiectasis, tuberculosis and other infections, malignancy, autoimmune diseases, arteriovenous malformations, and medications (particularly chemotherapy).

Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial

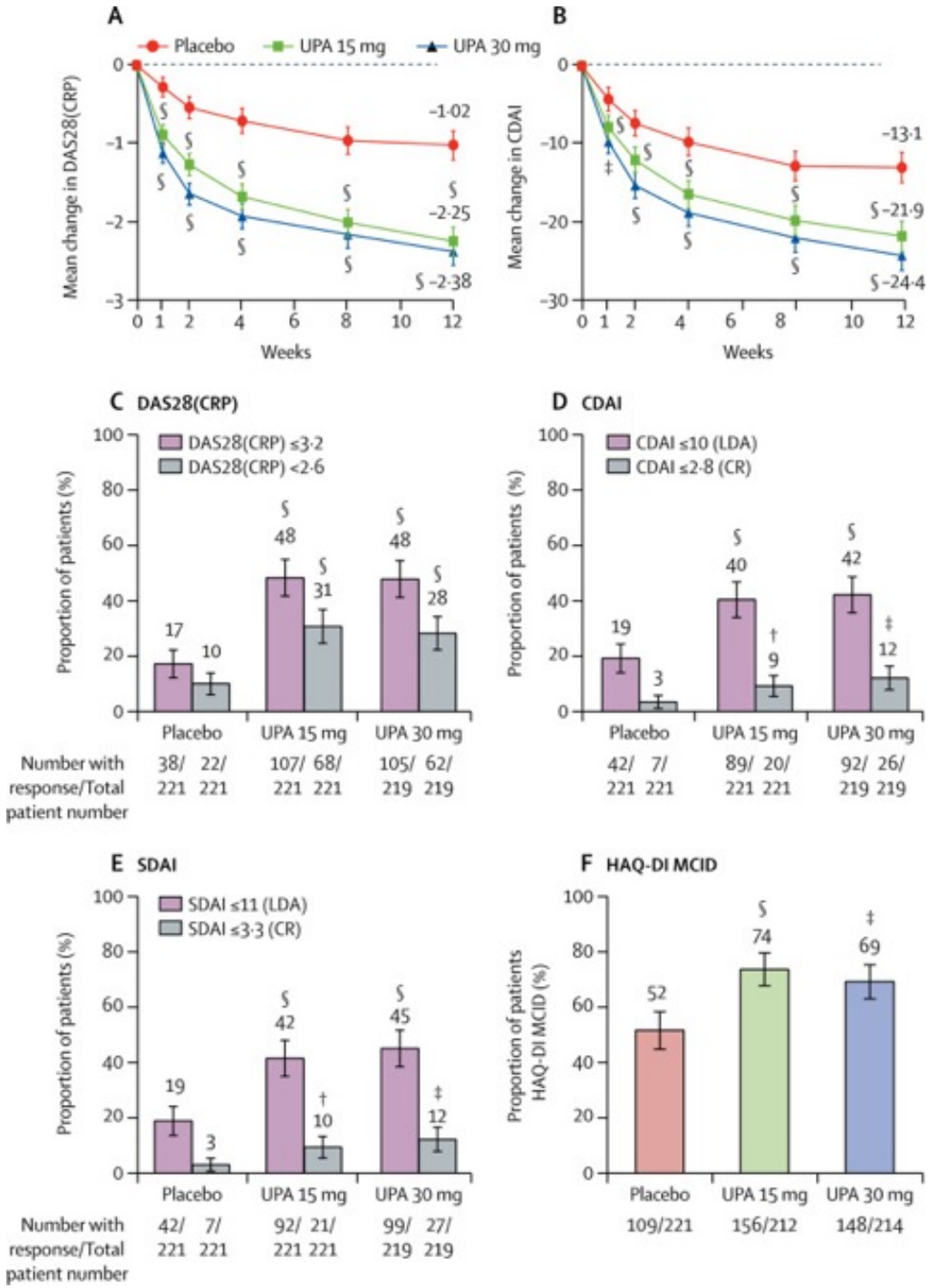
Upadacitinib is a selective inhibitor of Janus kinase 1 and was efficacious in phase 2 studies in patients with moderate-to-severe rheumatoid arthritis. We aimed to assess the efficacy of upadacitinib in patients with inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). We enrolled patients aged 18 years or older with active rheumatoid arthritis for 3 months or longer, who had received csDMARDs for at least 3 months with a stable dose for at least 4 weeks before study entry, and had an inadequate response to at least one of the following csDMARDs: methotrexate, sulfasalazine, or leflunomide. Using interactive response technology, we randomly assigned patients receiving stable background csDMARDs (2:2:1:1) to receive a once-daily extended-release formulation of upadacitinib 15 mg or 30 mg, or placebo, for 12 weeks. Patients, investigators, and the funder were masked to allocation. After 12 weeks, patients taking placebo received 15 mg or 30 mg of upadacitinib once daily, according to the prespecified randomisation assignment. The primary endpoints were the proportion of patients at week 12 who achieved 20% improvement in American College of Rheumatology criteria (ACR20), and a 28-joint disease activity score using C-reactive protein (DAS28[CRP]) of 3·2 or less.

	Placebo (n=221)	Upadacitinib 15 mg once daily (n=221)	Upadacitinib 30 mg once daily (n=219)
Time since rheumatoid arthritis diagnosis, years	7·2 (7·5)	7·3 (7·9)	7·3 (7·9)
Sex			
Female	166 (75%)	182 (82%)	172 (79%)
Male	55 (25%)	39 (18%)	47 (21%)
Mean age, years	56·0 (12·2)	55·3 (11·5)	55·8 (11·3)
Geographical distribution of patients			
North America	90 (41%)	88 (40%)	89 (41%)
Western Europe	24 (11%)	22 (10%)	23 (11%)
Eastern Europe	74 (33%)	76 (34%)	73 (33%)
Asia	16 (7%)	17 (8%)	15 (7%)
Latin and South America	8 (4%)	10 (5%)	11 (5%)
Other*	9 (4%)	8 (4%)	8 (4%)
Previous bDMARD exposure	29 (13%)	27 (12%)	28 (13%)
Oral glucocorticoid use	106 (48%)	96 (43%)	103 (47%)
Oral glucocorticoid dose, mg†	6·3 (2·6)	6·0 (2·4)	6·3 (2·6)
csDMARD use at baseline			
Methotrexate alone	141 (64%)	122 (55%)	136 (62%)
Methotrexate plus other csDMARD	49 (22%)	47 (21%)	39 (18%)
csDMARD other than methotrexate	30 (14%)	51 (23%)	44 (20%)
Data missing	1 (<1%)	1 (<1%)	0
Methotrexate dose, mg	16·3 (4·9)	17·0 (4·9)	16·8 (4·3)
Disease characteristics			
Rheumatoid factor positive or ACPA positive	181 (82%)	184 (83%)	164 (75%)
Tender joint count of 68 joints	24·7 (15·0)	25·2 (13·8)	26·2 (14·3)
Swollen joint count of 66 joints	15·4 (9·2)	16·0 (10·0)	16·2 (10·6)
Patient's GA, 0–100 mm VAS	60·3 (20·5)	63·1 (21·9)	62·8 (20·3)
Physician's GA, 0–100 mm VAS	64·4 (17·7)	64·3 (16·2)	63·0 (18·0)
Pain, 0–100 mm VAS	61·5 (20·8)	64·1 (19·5)	64·0 (19·8)
High-sensitivity C-reactive protein, mg/L	12·6 (14·0)	16·6 (19·2)	14·8 (16·9)
DAS28(CRP)	5·6 (0·8)	5·7 (1·0)	5·7 (0·9)
HAQ-DI	1·4 (0·6)	1·5 (0·6)	1·5 (0·6)
Clinical disease activity index	37·8 (11·8)	38·3 (11·9)	38·6 (12·7)
Simplified disease activity index	39·0 (11·9)	39·9 (12·5)	40·0 (13·1)
Morning stiffness duration, min	138·9 (214·0)	152·4 (241·9)	128·6 (156·0)
Morning stiffness severity, 0–10 scale	6·1 (2·2)	6·1 (2·4)	6·2 (2·2)
FACIT-F	28·3 (11·5)	28·1 (11·1)	27·5 (12·6)
SF-36 PCS	33·1 (7·7)	33·4 (7·4)	32·6 (7·9)



ACR20 and DAS28(CRP) at week 12, and ACR and HAQ-DI over time

Proportion of patients achieving (A) ACR20 and (B) DAS28(CRP) of 3·2 or less at week 12. Responses for (C) ACR20 (D) ACR50, and (E) ACR70 over 12 weeks, with non-responder imputation. (F) HAQ-DI mean change from baseline over 12 weeks (mixed-effect model repeat measurement). Bars are 95% CIs and p values are for comparisons with the placebo group. ACR=American College of Rheumatology. ACR20=20% improvement in ACR score. ACR50=50% improvement in ACR score. ACR70=70% improvement in ACR score. DAS28(CRP)=28-joint disease activity score using C-reactive protein. HAQ-DI=health assessment questionnaire–disability index. UPA=upadacitinib. *p≤0·05. †p≤0·01. ‡p≤p·001. § p≤0·0001.



Disease activity and physical function
Mean change from baseline in (A) DAS28(CRP) and (B) CDAI over 12 weeks, using mixed-effect model repeat measurement. Patients achieving (C) DAS28(CRP)of ≤3·2 or DAS28(CRP) <2·6, (D) CDAI LDA (≤10) or clinical remission (≤2·8), (E) SDAI LDA (≤11) or clinical remission (≤3·3), and (F) HAQ-DI MCID (improvement ≥0·22) at week 12, with non-responder imputation. Only patients with baseline HAQ-DI at least 0·22 are included. Bars are 95% CIs and p values are from comparison with the placebo group. DAS28(CRP)=28-joint disease activity score using C-reactive protein. CDAI=clinical disease activity index. SDAI=simplified disease activity index. HAQ-DI=health assessment questionnaire–disability index. MCID=minimum clinically important difference. LDA=low disease activity. CR=clinical remission. UPA=upadacitinib. *p≤0·05. †p≤0·01. ‡p≤p·001. § p≤0·0001.

	Placebo (n=221)	UPA 15 mg once daily (n=221)	UPA 30 mg once daily (n=219)
Any adverse event	108 (49%)	125 (57%)	118 (54%)
Serious adverse event	5 (2%)	9 (4%)	6 (3%)
Adverse event leading to discontinuation of study drug	7 (3%)	7 (3%)	13 (6%)
Adverse events ocurring in ≥5% of patients in any treatment group			
Nausea	7 (3%)	16 (7%)	3 (1%)
Nasopharyngitis	9 (4%)	12 (5%)	13 (6%)
Upper respiratory tract infection	9 (4%)	12 (5%)	12 (6%)
Headache	12 (5%)	9 (4%)	7 (3%)
Infection	47 (21%)	64 (29%)	69 (32%)
Serious infection	1 (<1%)	1 (<1%)	3 (1%)
Opportunistic infection	1 (<1%)	0	3 (1%)
Herpes zoster virus	1 (<1%)	1 (<1%)	2 (1%)*
Tuberculosis	0	0	0
Hepatic disorder	5 (2%)	4 (2%)	6 (3%)
Malignancy (non-melanoma skin cancer)	0	0	1 (<1%)
Malignancy (excluding non-melanoma skin cancer)	0	0	1 (<1%)
Gastrointestinal perforation	0	0	0
Anaemia	3 (1%)	0	3 (1%)
Neutropenia	1 (<1%)	4 (2%)	8 (4%)
Lymphopenia	1 (<1%)	1 (<1%)	5 (2%)
Creatine phosphokinase increase	0	5 (2%)	6 (3%)
Venous thromboembolic events	0	0	0
Cardiovascular event (adjudicated)	0	2 (1%)	1 (<1%)
Major adverse cardiovascular event	0	0	1 (<1%)†
Other adjudicated cardiovascular events	0	2 (1%)‡	0

*Includes one case of primary varicella zoster virus infection.
†Ischaemic stroke.
‡One case of congestive cardiac failure, one cardiovascular procedure.

In this csDMARD-IR population with moderate-to-severe rheumatoid arthritis, once-daily doses of upadacitinib (15 mg or 30 mg), when administered in combination with csDMARDs, showed improvements in clinical signs and symptoms of rheumatoid arthritis. In keeping with the goals of the treat-to-target strategy, a significantly larger proportion of patients in the upadacitinib groups achieved a state of low disease activity or clinical remission, compared with placebo.
Overall, upadacitinib showed a favourable benefit-to-risk profile; however, the proportions of participants with infections or premature discontinuation due to adverse events were higher in the upadacitinib groups than in the placebo group.

Added value of this study

SELECT-NEXT, RA-BUILD, and ORAL-SYNC were done in similar patient populations with established rheumatoid arthritis, who had inadequate response to csDMARDs. Most patients were receiving background methotrexate alone or methotrexate in combination with another csDMARD (ORAL SYNC >82% of patients, RA-BUILD >72%, and SELECT-NEXT >76%). Although direct comparisons cannot be made, RA-BUILD and ORAL-SYNC reported similar findings at week 12 to SELECT-NEXT, with a significant difference in ACR20 and improvements in function for participants receiving the intervention. SELECT-NEXT also met the primary endpoint of DAS28(CRP) of 3·2 or less. The SELECT-NEXT trial assessed the effect of upadacitinib treatment on the achievement of several stringent efficacy endpoints, such as remission and low disease activity (measured by clinical and simplified disease activity indices). Upadacitinib treatment resulted in almost 50% of this population of patients with inadequate response to csDMARDs (csDMARD-IR) reaching DAS28(CRP) of 3·2 or less by week 12, which is aligned with the recommendations of the treat-to-target strategy. Similar to the RA-BUILD trial, treatment with a JAK inhibitor in SELECT-NEXT (upadacitinib) resulted in rapid, significant improvements in clinical outcomes, as well as in multiple patient-reported outcomes (pain, patient's global assessment of disease activity, Health Assessment Questionnaire-Disability Index, and morning stiffness duration and severity).

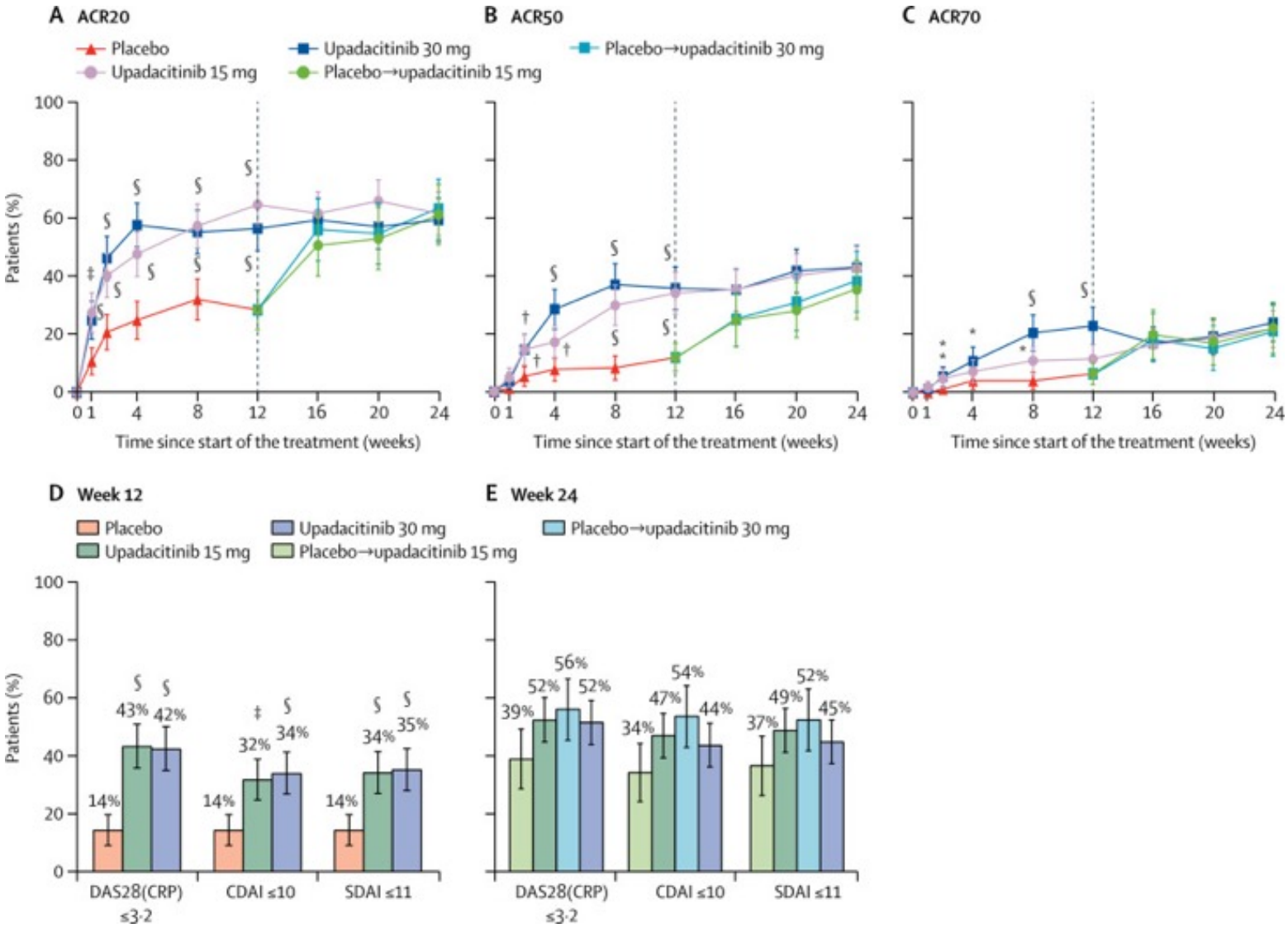
Implications of all the available evidence

The results of SELECT-NEXT support the evidence that JAK inhibitors could be considered as an alternative treatment option for patients with long-term disease who are csDMARD-IR, or those for whom biological DMARDs are not a good option. Treatment with JAK inhibitors could help these patients achieve rapid responses and disease control, as specified by the European League Against Rheumatism recommendations.

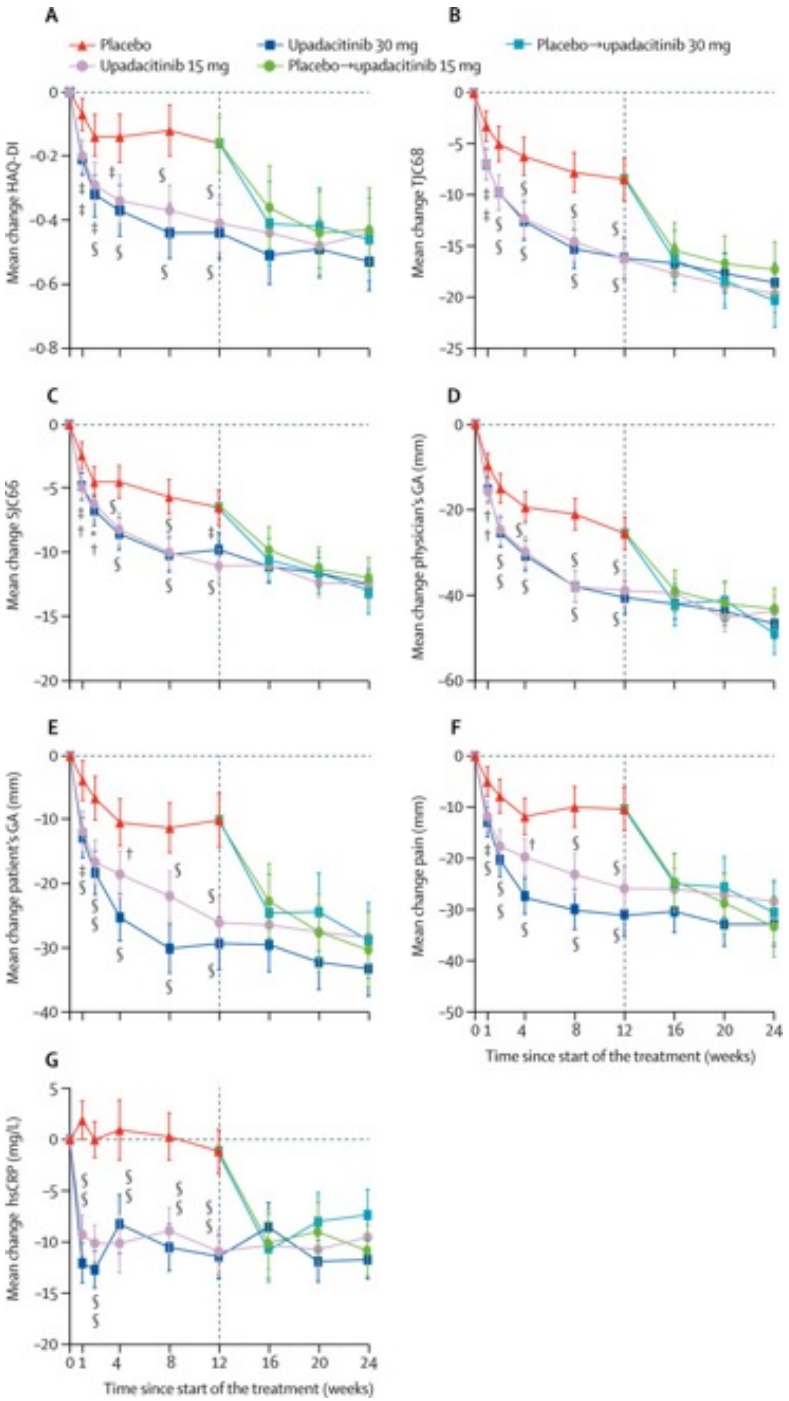
Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial

Phase 2 studies with upadacitinib, a selective Janus kinase 1 (JAK1) inhibitor, have shown safety and efficacy in the treatment of patients with active rheumatoid arthritis. We did this study to further assess the safety and efficacy of upadacitinib in patients with an inadequate response to biologic disease-modifying anti-rheumatic drugs (bDMARDs). Patients were aged 18 years or older, had active rheumatoid arthritis and previous inadequate response or intolerance to bDMARDs, and were receiving concomitant background conventional synthetic DMARDS (csDMARDs). We randomly assigned patients (2:2:1:1) by interactive response technology to receive once-daily oral extended-release upadacitinib 15 mg or 30 mg or placebo for 12 weeks, followed by upadacitinib 15 mg or 30 mg from week 12 onwards. The two separate primary endpoints were the proportions of patients achieving a 20% improvement in American College of Rheumatology criteria (ACR20) at week 12 and the proportion of patients achieving a 28-joint disease activity score using C-reactive protein (DAS28[CRP]) of 3·2 or less at week 12. Efficacy and safety analyses were done in the modified intention-to-treat population of all patients who received at least one dose of study drug. Data are presented up to week 24 of this ongoing study.

	Placebo (n=169)	Upadacitinib 15 mg (n=164)	Upadacitinib 30 mg (n=165)
Time since rheumatoid arthritis diagnosis, years	14·5 (9·2)	12·4 (9·4)	12·7 (9·7)
Sex			
Female	143 (85%)	137 (84%)	138 (84%)
Male	26 (15%)	27 (16%)	27 (16%)
Age, years	57·6 (11·4)	56·3 (11·3)	57·3 (11·6)
Geographical distribution of patients			
North America	110 (65%)	109 (67%)	109 (66%)
Western Europe	33 (20%)	32 (20%)	32 (19%)
Eastern Europe	23 (14%)	22 (13%)	22 (13%)
Asia	0	0	1 (1%)
Other*	3 (2%)	1 (1%)	1 (1%)
Previous bDMARD received			
1	83 (49%)	86 (52%)	66 (40%)
2	46 (27%)	40 (24%)	51 (31%)
≥3	40 (24%)	38 (23%)	47 (28%)
Stratum 1: inadequate response or intolerance to 1–2 bDMARDs of same MoA	117 (69%)	116 (71%)	111 (67%)
Stratum 2: inadequate response or intolerance to ≥3 bDMARDs of same MoA or ≥2 of multiple MoA	52 (31%)	48 (29%)	54 (33%)
Inadequate response or intolerance to ≥1 anti-TNF drug	152 (90%)	146 (89%)	151 (92%)
Lack of efficacy with ≥1 bDMARD	159 (94%)	146 (89%)	139 (85%)†
Lack of efficacy with ≥1 anti-interleukin 6	30 (18%)	27 (16%)	31 (19%)
csDMARD use at baseline‡			
Methotrexate alone§	122 (73%)	118 (73%)	124 (76%)
Methotrexate plus other csDMARD¶	17 (10%)	19 (12%)	11 (7%)
Methotrexate dose‖, mg	16·6 (4·7)	17·3 (4·6)	17·1 (5·1)
csDMARD other than methotrexate	29 (17%)	24 (15%)	29 (18%)
Sulfasalazine	8 (5%)	6 (4%)	9 (5%)
Leflunomide	13 (8%)	15 (9%)	10 (6%)
Hydroxychloroquine	11 (7%)	7 (4%)	14 (8%)
Chloroquine	1 (1%)	0	0
Missing	1	3	1
Oral glucocorticoid use	74 (44%)	83 (51%)	87 (53%)
Oral glucocorticoid dose, mg (prednisone equivalent)	6·3 (2·4)	5·7 (2·4)	6·4 (5·8)
Disease characteristics			
Rheumatoid factor positive	113 (67%)	119 (73%)	113 (68%)
ACPA positive	117 (69%)	119 (73%)	120 (73%)
Rheumatoid factor and ACPA positive	102 (60%)	107 (66%)**	101 (61%)
Rheumatoid factor or ACPA positive, or both	128 (76%)	131 (80%)	132 (80%)
Tender joint count of 68 joints	28·5 (15·3)	27·8 (16·3)	27·3 (15·2)
Swollen joint count of 66 joints	16·3 (9·6)	17·0 (10·8)	17·2 (11·4)
Patient's GA, 0–100 mm VAS	66·3 (22·7)	67·2 (19·6)	64·7 (21·1)
Pain, 0–100 mm VAS	68·9 (21·0)	68·2 (19·8)	65·3 (20·7)
Physician's GA, 0–100 mm VAS	66·9 (16·9)	68·7 (16·6)	66·4 (15·6)
DAS28(CRP)	5·8 (1·0)	5·9 (1·0)	5·8 (0·9)
Clinical disease activity index	41·0 (13·3)	41·7 (13·3)	40·1 (12·3)
Simplified disease activity index	42·6 (13·9)	43·3 (13·8)	41·7 (12·8)
High-sensitivity C-reactive protein, mg/L	16·3 (21·1)	16·2 (18·6)	16·0 (21·2)
HAQ-DI	1·6 (0·6)	1·7 (0·6)	1·6 (0·6)
Morning stiffness severity, 0–10 scale	6·8 (2·3)	6·8 (2·1)	6·5 (2·2)
Morning stiffness duration, min	138·4 (178·6)	140·4 (189·7)	184·5 (284·9)



Primary and secondary endpoint results of ACR, DAS28(CRP), CDAI, and SDAI
(A) ACR20, (B) ACR50, and (C) ACR70, with non-responder imputation. DAS28(CRP) of 3·2 or less, CDAI of 10 or less, and SDAI of 11 or less at week 12 (D) and week 24 (E), with non-responder imputation. Statistical comparisons of upadacitinib 15 mg and upadacitinib 30 mg with the combined placebo group were done up to week 12. ACR=American College of Rheumatology. ACR20=20% improvement in ACR criteria. ACR50=50% improvement in ACR criteria. ACR70=70% improvement in ACR criteria. CDAI=clinical disease activity index. DAS28(CRP)=28-joint disease activity score using C-reactive protein. HAQ-DI=health assessment questionnaire–disability index. SDAI=simplified disease activity index. *p≤0·05. †p≤0·01. ‡p≤0·001. § p≤0·0001.



Least squares mean change from baseline in individual core components of the ACR criteria over 24 weeks (A) HAQ-DI,(B) TJC68, (C) SJC66, (D) physician's GA, (E) patient's GA, (F) pain, and (G) hsCRP (mixed-effect model repeat measurement). Statistical comparisons of upadacitinib 15 mg and upadacitinib 30 mg with the combined placebo group were done up to week 12. GA=global assessment of disease activity. HAQ-DI=health assessment questionnaire–disability index. hsCRP=high-sensitivity C-reactive protein. SJC66=swollen joint count of 66 joints. TJC68=tender joint count of 68 joints. *p≤0·05. †p≤0·01. ‡p≤0·001. § p≤0·0001.

No patients reported tuberculosis, non-melanoma skin cancer, or lymphoma.

	Weeks 0–12			Weeks 12–24			
	Placebo (n=169)	Upadacitinib 15 mg (n=164)	Upadacitinib 30 mg (n=165)	Placebo to upadacitinib 15 mg (n=72)	Placebo to upadacitinib 30 mg (n=75)	Upadacitinib 15 mg (n=156)	Upadacitinib 30 mg (n=148)
Adverse events	95 (56%)	91 (55%)	111 (67%)	30 (42%)	50 (67%)	82 (53%)*	83 (56%)
Adverse event leading to discontinuation	9 (5%)	4 (2%)	15 (9%)	2 (3%)	3 (4%)	5 (3%)*	5 (3%)
Serious adverse events	0	8 (5%)	12 (7%)	5 (7%)	5 (7%)	5 (3%)*	5 (3%)
Infection	51 (30%)	54 (33%)	55 (33%)	16 (22%)	31 (41%)	43 (28%)	47 (32%)
Serious infection	0	1 (1%)	4 (2%)	2 (3%)	1 (1%)	1 (1%)	2 (1%)
Opportunistic infection†	0	1 (1%)	2 (1%)	0	0	0	1 (1%)
Herpes zoster ‡	1 (1%)	1 (1%)	4 (2%)	0	1 (1%)	2 (1%)	2 (1%)
Malignancy (excluding non-melanoma skin cancer)§	0	1 (1%)	2 (1%)	0	0	1 (1%)	0
Hepatic disorder	2 (1%)	2 (1%)	3 (2%)	0	2 (3%)	4 (3%)	4 (3%)
Gastrointestinal perforation	0	0	0	0	0	0	1 (1%)
Pulmonary embolism events* (adjudicated)	0	1 (1%)	0	2 (3%)¶	1 (1%)	0	0
Cardiovascular events (adjudicated)‖	0	1 (1%)	0	0	1 (1%)	2 (1%)	0
Major adverse cardiovascular event	0	1 (1%)	0	0	1 (1%)	0	0
Other cardiovascular events	0	0	0	0	0	1 (1%)	0
Undetermined or unknown cause of death	0	0	0	0	0	1 (1%)	0
Deaths**	0	0	1 (1%)	0	0	1 (1%)	0

Added value of this study

The SELECT-BEYOND study enrolled patients who had inadequate response or intolerance to any bDMARD, not only anti-TNF drugs, thus differing from ORAL-STEP and RA-BEACON in including a broader population of refractory patients. In SELECT-BEYOND, 89% had lack of efficacy with at least one previous bDMARD and 25% had been treated with at least three bDMARDs. The study had two separate primary endpoints to meet the requirements of regulators both in the USA and EU: 20% improvement in American College of Rheumatology criteria (ACR20) at week 12 for the USA and 28-joint disease activity score using C-reactive protein (DAS28[CRP]) of 3·2 or less at week 12 for the EU. Although not directly comparable, in all three studies, the primary endpoint ACR20 at week 12 (about 3 months) was met. In SELECT-BEYOND, the primary endpoint of DAS28(CRP) of 3·2 or less at week 12 was also met. In all three studies, significant improvements from baseline in health assessment questionnaire–disability index and DAS28(CRP) were observed at 12 weeks. The rapid onset of response occurred in SELECT-BEYOND and RA-BEACON as early as 1 week; this timepoint was not assessed in ORAL-STEP. SELECT-BEYOND assessed the effect of upadacitinib treatment on severity and duration of morning stiffness, which was not assessed in ORAL STEP and is considered a common and prominent symptom of rheumatoid arthritis. Although responses in patients with an inadequate response to bDMARDs are usually lower than in less refractory patients, in SELECT-BEYOND, the treatment effect with upadacitinib was similar to that in the less refractory population with inadequate response to csDMARDs in the SELECT-NEXT study. The number and mechanism of action of previous bDMARDs did not affect the achievement of ACR20 at week 12. A high proportion of patients originally assigned to upadacitinib treatment achieved low disease activity by week 12 and the proportion further increased by week 24. Similar results were achieved at week 24 in those patients who switched from placebo treatment to upadacitinib treatment at week 12. Further, patients had significant reductions in the duration and severity of morning stiffness, which have been shown to affect patients' ability to work.

Implications of all available evidence

The data presented in our study expand the available evidence on treatment with JAK inhibitors in patients with refractory disease, and show that with upadacitinib treatment, these patients can achieve significant, rapid improvement in clinical, functional, and patient-reported outcomes.

Robotic-assisted radical cystectomy continues to evolve as a surgical option in the management of muscle-invasive bladder cancer. Current oncologic outcomes appear comparable in the short-term with open radical cystectomy. Long-term follow-up, however, remains lacking for this emerging technique. Modern robotic technology allows a comparable extent of pelvic lymph node dissection as open surgery, a previous criticism of the procedure. Complications compare very favorably to open surgery in comparative series, and blood loss and transfusion rates are routinely lower. Length of stay has been shortened in some series, though not uniformly. Finally, robotic assistance can increase the cost of radical cystectomy.

Key issues

- Radical cystectomy for muscle-invasive bladder cancer is a morbid procedure.
- Robotic cystectomy appears best suited for nonbulky tumors.
- Robotic assistance achieves comparable short-term oncologic outcomes to open surgery in carefully selected patients with low-stage disease.
- Robotic cystectomy is associated with less blood loss than open surgery.
- The extent of pelvic lymph node dissection is comparable between robotic and open surgery.
- Length of stay may be improved by robotic assistance.
- Robotic systems add to the cost of cystectomy, although improved outcomes may offset some of those costs.
- Five-year oncologic outcomes have not been reported for this technique.

Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial

Radical cystectomy is the surgical standard for invasive bladder cancer. Robot-assisted cystectomy has been proposed to provide similar oncological outcomes with lower morbidity. We aimed to compare progression-free survival in patients with bladder cancer treated with open cystectomy and robot-assisted cystectomy. The RAZOR study is a randomised, open-label, non-inferiority, phase 3 trial done in 15 medical centres in the USA. Eligible participants (aged ≥18 years) had biopsy-proven clinical stage T1–T4, N0–N1, M0 bladder cancer or refractory carcinoma in situ. Individuals who had previously had open abdominal or pelvic surgery, or who had any pre-existing health conditions that would preclude safe initiation or maintenance of pneumoperitoneum were excluded. Patients were centrally assigned (1:1) via a web-based system, with block randomisation by institution, stratified by type of urinary diversion, clinical T stage, and Eastern Cooperative Oncology Group performance status, to receive robot-assisted radical cystectomy or open radical cystectomy with extracorporeal urinary diversion. Treatment allocation was only masked from pathologists. The primary endpoint was 2-year progression-free survival, with non-inferiority established if the lower bound of the one-sided 97·5% CI for the treatment difference (robotic cystectomy minus open cystectomy) was greater than −15 percentage points. The primary analysis was done in the per-protocol population. Safety was assessed in the same population.

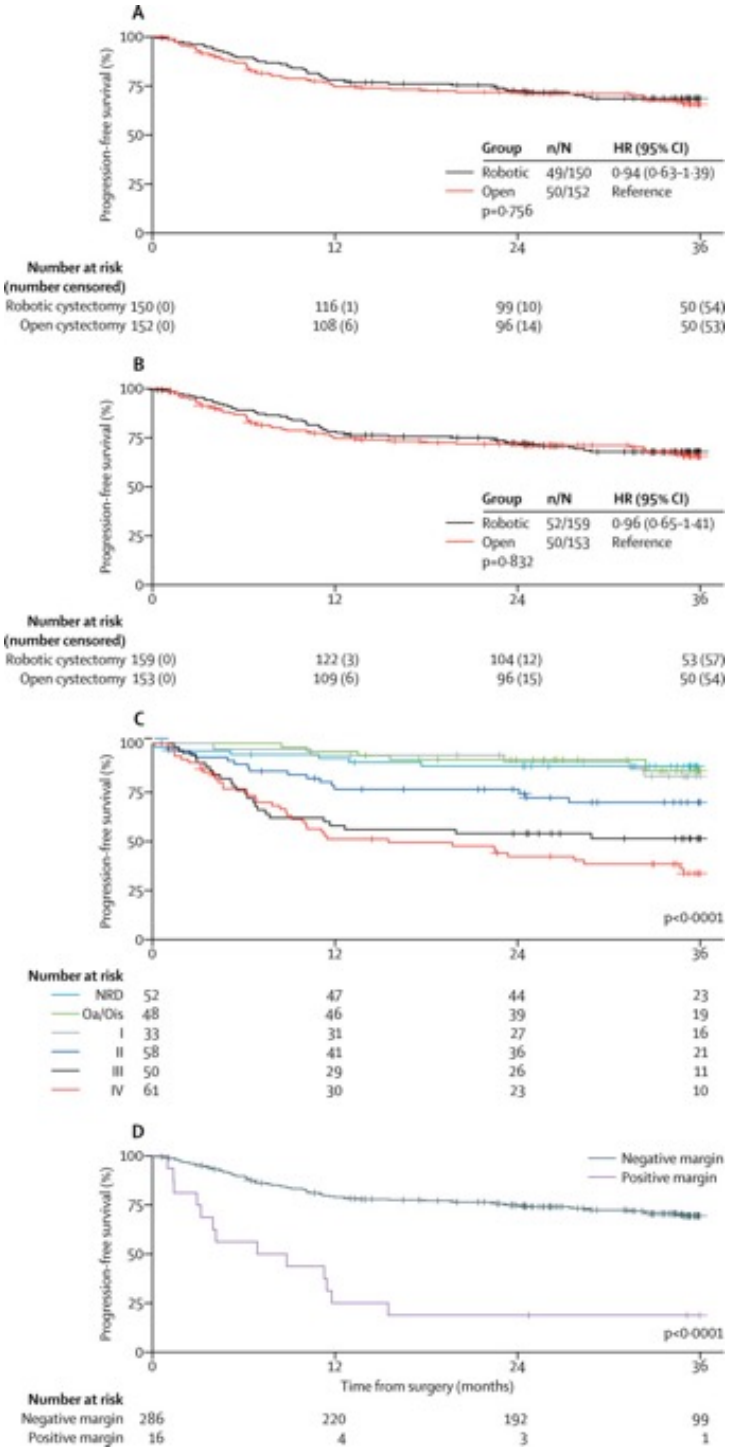
	Robotic cystectomy (n=150)	Open cystectomy (n=152)
Median age, years (range)	70 (43–90)	67 (37–85)
Sex		
Men	126 (84%)	128 (84%)
Women	24 (16%)	24 (16%)
Body-mass index (kg/m²)		
Median (IQR)	27·8 (25·0–30·8)	28·2 (24·9–31·7)
<25	38 (25%)	39 (26%)
25–29·9	60 (40%)	64 (42%)
≥30	52 (35%)	49 (32%)
ECOG performance status		
0	117 (78%)	109 (72%)
1	29 (19%)	39 (26%)
2–3	4 (3%)	4 (3%)
Clinical and TURBT stage*		
Tis	6 (4%)	6 (4%)
Ta	1 (1%)	4 (3%)
T1	41 (27%)	41 (27%)
T2	82 (55%)	81 (53%)
T3	16 (11%)	16 (11%)
T4	4 (3%)	4 (3%)
Perioperative chemotherapy	62 (41%)	70 (46%)
Neoadjuvant chemotherapy†	41 (27%)	55 (36%)
Adjuvant chemotherapy†	25 (17%)	17 (11%)
Urinary diversion procedure‡		
Neobladder	36 (24%)	30 (20%)
Ileal conduit	113 (75%)	122 (80%)
Continent cutaneous reservoir	1 (1%)	..
Baseline haemoglobin (g/dL), mean (SD)	13·05 (1·87)	12·81 (1·87)

Analysis of progression-free survival

	Robotic cystectomy	Open cystectomy	Difference (95% CI)	p value*
Per-protocol analysis set				
Patients with disease progression within 2 years of surgery	41/150 (27%)	42/152 (28%)	..	..
2-year progression-free survival (95% CI)	72·3% (64·3 to 78·8)	71·6% (63·6 to 78·2)	0·7% (−9·6 to 10·9)	0·001
Patients with disease progression (total events)†	49/150 (33%)	50/152 (33%)	..	..
Modified intention-to-treat analysis set				
Patients with disease progression within 2 years of surgery	43/159 (27%)	42/153 (27%)	..	..
2-year progression-free survival (95% CI)	72·3% (64·5 to 78·6)	71·8% (63·8 to 78·3)	0·5% (−9·7 to 10·6)	0·001
Patients with disease progression (total events)†	52/159 (33%)	50/153 (33%)	..	..

Data are % (95% CI) or n/N (%), unless otherwise specified.

*One-sided p value for non-inferiority.
†Total events that had occurred by the data cutoff.



Progression-free survival
Kaplan-Meier curves for comparison of progression-free survival by treatment group in the per-protocol population (A), and the modified intention-to-treat population (B) and by pathological stage (C) and margin status (D) in the per-protocol population. Follow-up is truncated at 36 months. Vertical lines indicate censored patients. n=patients with progression. N=group size. HR=hazard ratio. NRD=no residual disease.

	Robotic cystectomy (n=150)	Open cystectomy (n=152)	Difference (95% CI)	p value
Patients with blood loss data	148 (99%)	149 (98%)	..	..
Blood loss, mL	300 (200–500)	700 (500–1000)	..	<0·0001
Perioperative transfusion	35/143 (24%)	65/143 (45%)	−21·0 (−31·8 to −10·2)	0·0002
Units of blood transfused	3 (2–5)	4 (2–5)	..	0·46
Intraoperative transfusion	18/139 (13%)	46/136 (34%)	−20·8 (−30·6 to −11·2)	<0·0001
Postoperative transfusion	33/132 (25%)	54/135 (40%)	−15·0 (−26·1 to −3·9)	0·0089
Hospital stay ≤5 days	40/139 (29%)	27/146 (18%)	10·3 (0·5 to 20·1)	0·0407
Length of stay, days	6 (5–10)	7 (6–10)	..	0·0216
Operating time, min	428 (322–509)	361 (281–450)	..	0·0005
Surgical complications within 90 days*				
0	49 (33%)	47 (31%)	..	0·80
I	24 (16%)	20 (13%)	..	..
II	44 (29%)	51 (34%)	..	..
III	29 (19%)	28 (18%)	..	..
IV	0	2 (1%)	..	..
V	4 (3%)	4 (3%)	..	..
Grades I–V *vs* 0	101 (67%)	105 (69%)	−1·8 (−12·3 to 8·8)	0·75
Grades III–V *vs* 0–II	33 (22%)	34 (22%)	−0·4 (−9·0 to 9·8)	0·94
Histopathology classification				
Urothelial	123 (82%)	116 (76%)	..	0·50
Non-urothelial	5 (3%)	4 (3%)	..	..
Negative	19 (13%)	29 (19%)	..	..
Undetermined	3 (2%)	3 (2%)	..	..
T stage†				
T0	22 (15%)	31 (20%)	..	0·70
Ta, Tis	25 (17%)	25 (16%)	..	..
T1	19 (13%)	15 (10%)	..	..
T2	38 (25%)	33 (22%)	..	..
T3	35 (23%)	32 (21%)	..	..
T4a	10 (7%)	14 (9%)	..	..
T4b	1 (1%)	3 (2%)	..	..
N stage†				
Nx or missing	5 (3%)	7 (5%)	..	0·55
N0	110 (73%)	121 (80%)	..	..
N1	13 (9%)	8 (5%)	..	..
N2	17 (11%)	13 (9%)	..	..
N3	5 (3%)	3 (2%)	..	..
Pathological stage†				
No residual disease	22 (15%)	30 (20%)	..	0·45
0is/0a	24 (16%)	24 (16%)	..	..
I	18 (12%)	15 (10%)	..	..
II	29 (19%)	29 (19%)	..	..
III	21 (14%)	29 (19%)	..	..
IV	36 (24%)	25 (16%)	..	..
Lymph node dissection‡				
Extended	76/149 (51%)§	84/152 (55%)	−4·3 (−15·5 to 7·0)	0·46
Standard	73/149 (49%)	68/152 (45%)	..	..
Lymph nodes removed, mean (SD)	23·3 (12·5)	25·7 (14·5)	..	0·13
Positive surgical margin	9 (6%)	7 (5%)¶	1·4 (−3·7 to 6·5)	0·59
Positive bladder margin	6 (4%)	5 (3%)	0·7 (−3·5 to 4·9)	0·74
Positive urethral margin	3 (2%)	4 (3%)	−0·6 (−4·0 to 2·8)	1·00

Estimated blood loss was significantly lower in the robotic cystectomy group than the open cystectomy group (p<0·0001). The proportion of patients who required intraoperative blood transfusion and postoperative blood transfusion was significantly lower in the robotic cystectomy group than the open cystectomy group (p=0·0002 and p=0·0089, respectively). Median length of hospital stay was significantly lower in the robotic cystectomy group than the open cystectomy group (p=0·0216; table 3). 40 (29%) of 150 patients in the robotic cystectomy group and 27 (18·5%) of 152 patients in the open cystectomy group stayed in hospital for less than 5 days after surgery (p=0·0407). Median operating time was significantly longer in the robotic cystectomy group than the open cystectomy group (p=0·0005).

	Baseline		3 months		6 months	
	Robotic cystectomy	Open cystectomy	Robotic cystectomy	Open cystectomy	Robotic cystectomy	Open cystectomy
Physical wellbeing, n	116	115	104	102	99	99
Estimated mean score (95% CI)	22·9 (21·8–24·0)	23·4 (22·3–24·6)	23·2 (22·1–24·3)	22·8 (21·6–24·0)	23·2 (22·0–24·3)	23·9 (22·7–25·0)
Social wellbeing, n	113	115	105	100	99	98
Estimated mean score (95% CI)	23·5 (22·2–24·7)	23·5 (22·2–24·8)	23·1 (21·9–24·3)	22·6 (21·3–23·9)	23·3 (22·1–24·5)	23·3 (22·1–24·6)
Emotional wellbeing, n	111	112	98	95	96	91
Estimated mean score (95% CI)	17·5 (16·4–18·6)	17·7 (16·5–18·8)	19·5* (18·4–20·5)	19·9* (18·8–21·0)	19·4* (18·3–20·5)	20·0* (18·9–21·2)
Functional wellbeing, n	115	115	105	100	98	97
Estimated mean score (95% CI)	18·4 (16·8–20·0)	18·4 (16·7–20·1)	17·9 (16·3–19·5)	19·3 (17·6–21·0)	18·5 (16·9–20·1)	19·7 (18·0–21·4)
FACT-BL-Cys, n	115	114	105	100	98	97
Estimated mean score (95% CI)	37·4 (35·0–39·8)	36·7 (34·2–39·2)	37·9 (35·8–40·0)	38·2 (36·0–40·5)	39·3 (37·1–41·4)	39·4 (37·1–41·6)
Trial outcome index, n	115	114	104	100	98	97
Estimated mean score (95% CI)	78·9 (74·6–83·2)	78·9 (74·3–83·5)	79·3 (75·1–83·4)	80·7 (76·3–85·2)	81·1 (77·0–85·3)	83·2 (78·8–87·6)
FACT-G, n	108	112	97	94	95	91
Estimated mean score (95% CI)	82·4 (78·6–86·1)	83·5 (79·5–87·4)	84·2 (80·4–88·1)	85·8 (81·8–89·9)	85·9 (82·1–89·7)	87·4* (83·5–91·4)
FACT-BL-Cys Total, n	108	111	97	94	95	91
Estimated mean score (95% CI)	120·1 (114·5– 125·8)	120·9 (115·0–126·8)	122·8 (117·2–128·3)	125·2 (119·3–131·1)	126·0* (120·4–131·6)	127·5* (121·7–133·3)

In the robotic cystectomy group, the mean estimated score for emotional wellbeing was significantly higher at 3 months (p=0·0007) and 6 months (p=0·0014) than at baseline. Similarly, in the open cystectomy group, the mean estimated emotional wellbeing score was significantly higher at 3 months (p=0·0007) and at 6 months (p=0·0007) than at baseline. Cost data was specified as a secondary endpoint in the protocol, but data could not be collected from all sites due to proprietary reasons. Additionally, considerable heterogeneity was identified between the institutions that shared cost data, and thus the available data was unsuitable for analysis. 101 (67%) of 150 patients in the robotic cystectomy group and 105 (69%) of 152 patients in the open cystectomy group had adverse events. The most common adverse events were urinary tract infection (53 [35%] in the robotic cystectomy group *vs* 39 [26%] in the open cystectomy group) and postoperative ileus (33 [22%] in the robotic cystectomy group *vs* 31 [20%] in the open cystectomy group).

Added value of this study

This is the first phase 3 trial comparing robot-assisted cystectomy with open cystectomy for any urological cancer. We found that 2-year progression-free survival in patients with bladder cancer who had robotic cystectomy was non-inferior to that of patients who had open cystectomy. Estimated blood loss, blood transfusion rates, and median length of hospital stay were also significantly lower in the robotic cystectomy group than the open cystectomy group. However, no significant differences were identified between groups in major complications (Clavien-Dindo grade ≥3), lymph node yield, positive surgical margins, and patient-reported health related quality-of-life (QoL) outcomes. Duration of surgery was significantly longer for robotic surgery than open surgery.

Our data suggest that robotic cystectomy is non-inferior to open cystectomy with regard to oncological outcomes and reinforces the fact that such trials are possible and should be attempted across other surgical specialties.

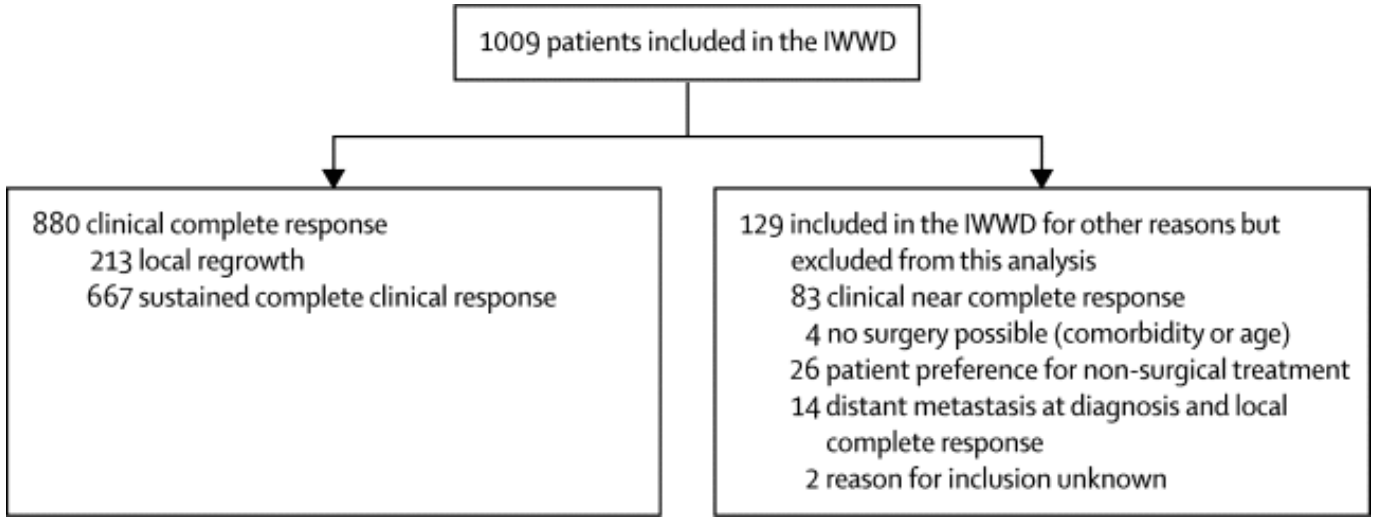
Implications of all the available evidence

This trial provides the first multicentre randomised evidence of the oncological efficacy of robotic cystectomy. In the setting of previous studies, robotic cystectomy did not compromise oncological outcomes compared with open cystectomy. Our results showed that robotic cystectomy is associated with an improvement in perioperative parameters, such as blood loss and length of stay, without significant differences in complication rates and patient-reported QoL outcomes. These findings provide high level evidence to inform discussion between patients and their physicians regarding the benefits and risks of various approaches for a complex and often morbid surgery, such as radical cystectomy. Our results also underscore the need for further high-quality trials to assess surgical innovation before this surgical technique is widely adopted in clinical practice.

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

The strategy of watch and wait (W&W) in patients with rectal cancer who achieve a complete clinical response (cCR) after neoadjuvant therapy is new and offers an opportunity for patients to avoid major resection surgery. However, evidence is based on small-to-moderate sized series from specialist centres. The International Watch & Wait Database (IWWD) aims to describe the outcome of the W&W strategy in a large-scale registry of pooled individual patient data. We report the results of a descriptive analysis after inclusion of more than 1000 patients in the registry. Participating centres entered data in the registry through an online, highly secured, and encrypted research data server. Data included baseline characteristics, neoadjuvant therapy, imaging protocols, incidence of local regrowth and distant metastasis, and survival status. All patients with rectal cancer in whom the standard of care (total mesorectal excision surgery) was omitted after neoadjuvant therapy were eligible to be included in the IWWD. For the present analysis, we only selected patients with no signs of residual tumour at reassessment (a cCR). We analysed the proportion of patients with local regrowth, proportion of patients with distant metastases, 5-year overall survival, and 5-year disease-specific survival.

	Total number of patients (N=880)	Instituto Angelita e Joaquim Gama, São Paolo, Brazil (n=192)	Antoni van Leeuwenhoek and Maastricht University Medical Center, Netherlands (n=239)	OncoRe research database, UK (n=149)	Other participating institutes (n=300)
Country					
Argentina	46 (5%)	..	..	..	46 (15%)
Belgium	27 (3%)	..	..	..	27 (9%)
Brazil	201 (23%)	192 (100%)	..	..	9 (3%)
Germany	25 (3%)	..	..	..	25 (8%)
Denmark	40 (5%)	..	..	..	40 (13%)
France	42 (5%)	..	..	..	42 (14%)
UK	150 (17%)	..	..	149 (100%)	1 (0%)
Ireland	35 (4%)	..	..	..	35 (12%)
Netherlands	252 (29%)	..	239 (100%)	..	13 (4%)
Poland	15 (2%)	..	..	..	15 (5%)
Portugal	21 (2%)	..	..	..	21 (7%)
Russia	5 (1%)	..	..	..	5 (2%)
Sweden	15 (2%)	..	..	..	15 (5%)
Turkey	6 (1%)	..	..	..	6 (2%)
Age, mean (SD)	63·6 (11·7)	59·7 (12·6)	63·5 (9·92)	65·9 (9·4)	65·0 (13·0)
BMI, mean (SD)	26·7 (4·9)	26·1 (3·9)	26·3 (5·4)	27·5 (6·2)	26·4 (4·3)
Sex					
Male	603 (69%)	126 (66%)	161 (67%)	110 (74%)	206 (69%)
Female	277 (32%)	66 (34%)	78 (33%)	39 (26%)	94 (31%)
Comorbidity					
Yes	252 (29%)	58 (30%)	74 (31%)	0 (0%)	120 (40%)
No	337 (38%)	131 (68%)	103 (43%)	17 (11%)	86 (29%)
Unknown	291 (33%)	3 (2%)	62 (26%)	132 (89%)	94 (31%)
Year of decision for W&W					
Before 2010	177 (20%)	113 (59%)	10 (4%)	11 (7%)	43 (14%)
2010–14	450 (51%)	73 (38%)	95 (40%)	131 (88%)	151 (50%)
2015–17	253 (29%)	6 (3%)	134 (56%)	7 (5%)	106 (35%)
Median follow-up time, years (95% CI)	3·3 (3·1–3·6)	7·1 (6·3–8·0)	2·1 (1·9–2·3)	3·7 (3·4–4·1)	2·8 (2·4–3·3)
Clinical T stage baseline*					
cT1	14 (2%)	5 (3%)	1 (0%)	0 (0%)	8 (3%)
cT2	226 (26%)	21 (11%)	50 (21%)	36 (24%)	119 (40%)
cT3	451 (51%)	26 (14%)	170 (71%)	104 (70%)	151 (50%)
cT4	30 (3%)	0 (0%)	15 (6%)	7 (5%)	8 (3%)
Unknown	159 (18%)	140 (73%)	3 (1%)	2 (1%)	14 (5%)
Clinical N stage baseline					
cN0	309 (35%)	59 (31%)	62 (26%)	47 (32%)	141 (47%)
cN1	271 (31%)	22 (12%)	79 (33%)	63 (42%)	107 (36%)
cN2	167 (19%)	2 (1%)	96 (40%)	37 (25%)	32 (11%)
Unknown	133 (15%)	109 (57%)	2 (1%)	2 (1%)	20 (7%)
Local regrowth					
Yes	213 (24%)	70 (37%)	35 (15%)	59 (40%)	49 (16%)
No	667 (76%)	122(64%)	204 (85%)	90 (60%)	251 (84%)
Distant metastasis					
Yes	71 (8%)	27 (14%)	9 (4%)	14 (9%)	21 (7%)
No	809 (92%)	165 (86%)	230 (96%)	135 (91%)	279 (93%)
Last study status					
In follow-up	660 (75%)	98 (51%)	202 (85%)	127 (85%)	233 (78%)
Follow-up completed	57 (7%)	28 (15%)	17 (7%)	0 (0%)	12 (4%)
Lost to follow-up	64 (7%)	28 (15%)	14 (6%)	1 (1%)	21 (7%)
Deceased	99 (11%)	38 (20%)	6 (3%)	21 (14%)	34 (11%)



Diagnostic procedures at baseline and at reassessment after induction therapy

	Baseline (n=880)	Reassessment
Endoscopy	848 (96%)	779 (89%)
MRI pelvis	678 (77%)	620 (71%)
CT pelvis	378 (43%)	261 (30%)
Endorectal ultrasound	146 (17%)	67 (8%)
PET scane	116 (13%)	39 (4%)
CEA	540 (61%)	196 (22%)
Local excision	..	45 (5%)
ypT0	..	40 (4%)
ypT+	..	5 (1%)

Data are n (%). CEA=carcinoembryonic antigen.

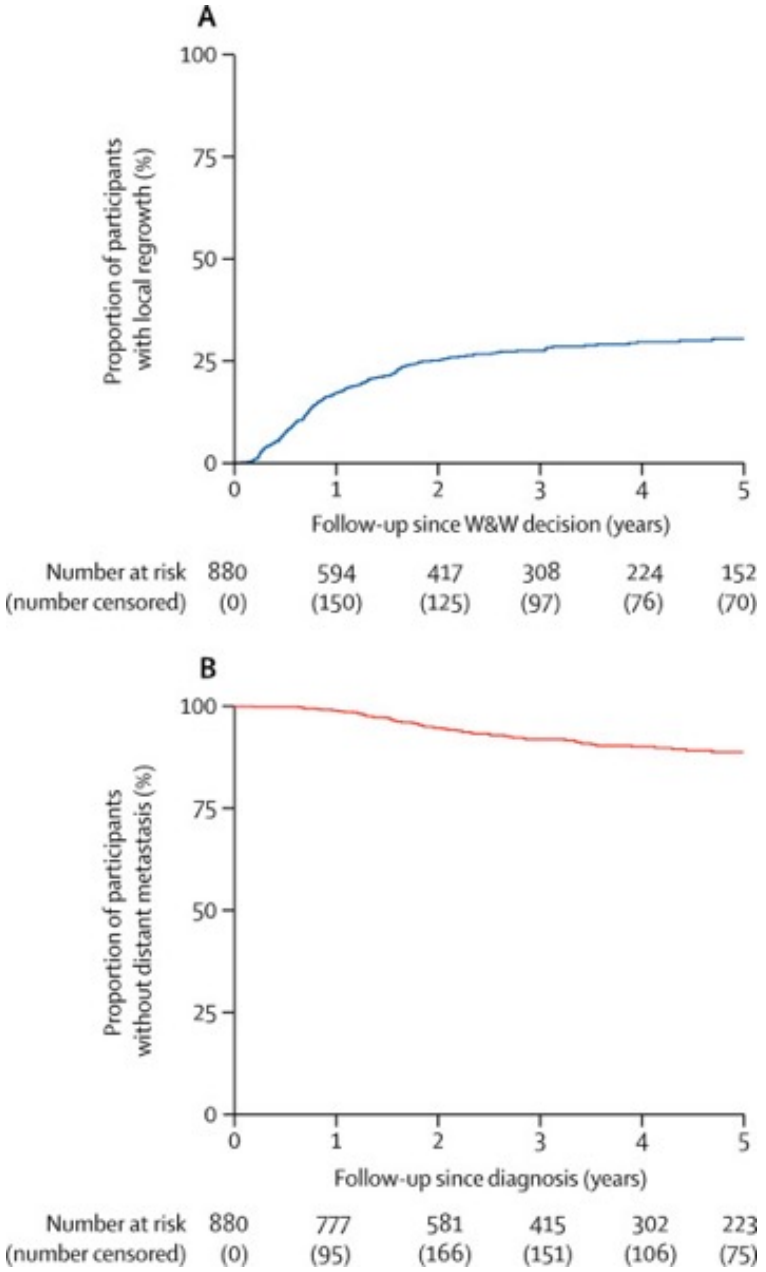
Different types and combinations of induction therapy

	Patients
Single therapy	
Chemoradiotherapy	738
Brachyradiotherapy	5
External beam radiotherapy	35
Chemotherapy	3
Total for single therapy	781
Different combinations	
Chemoradiotherapy and brachyradiotherapy	57
Chemoradiotherapy and chemotherapy	7
Brachyradiotherapy and external beam radiotherapy	19
External beam radiotherapy and chemotherapy	7
Chemoradiotherapy, brachyradiotherapy, and external beam radiotherapy	2
Total for different combination	92
Missing	7
Total	880

Data are n.

This study shows that in strictly selected patients with a clinical complete response, W&W can be a good alternative to major surgery with very little oncological risk. At least at present, selection and surveillance of these patients should be done in dedicated centres. Through the ongoing collaborative effort, the IWWD consortium will address a number of remaining questions regarding W&W in the future, to the benefit of patients with rectal cancer.

Local tumour regrowth (A) and distant metastasis-free period (B). W&W=watch and wait.



Added value of this study

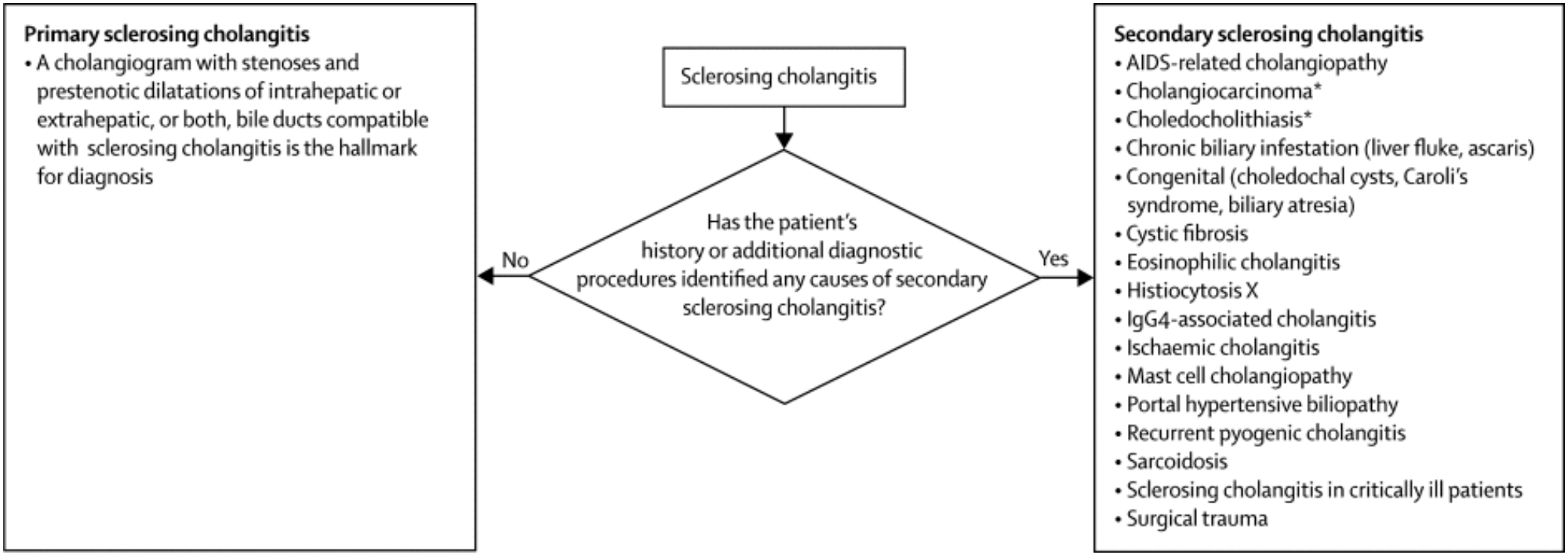
This is the first large registry-based study on international W&W strategies for patients with rectal cancer, consisting of pooled individual patient data of approximately 50% patients from previously published series and 50% unpublished data. Despite the heterogeneity, this study provides a reliable reflection of the real-world risks and benefits of W&W. Local regrowth was most frequently diagnosed in the first 2 years of follow-up and was located in the bowel wall in most patients. Nodal local tumour regrowth was very uncommon. This indicates that strict endoscopic surveillance in W&W protocols is essential and enables early detection followed by curative treatment. In this series, survival was excellent and the risk of local unsalvageable disease was small.

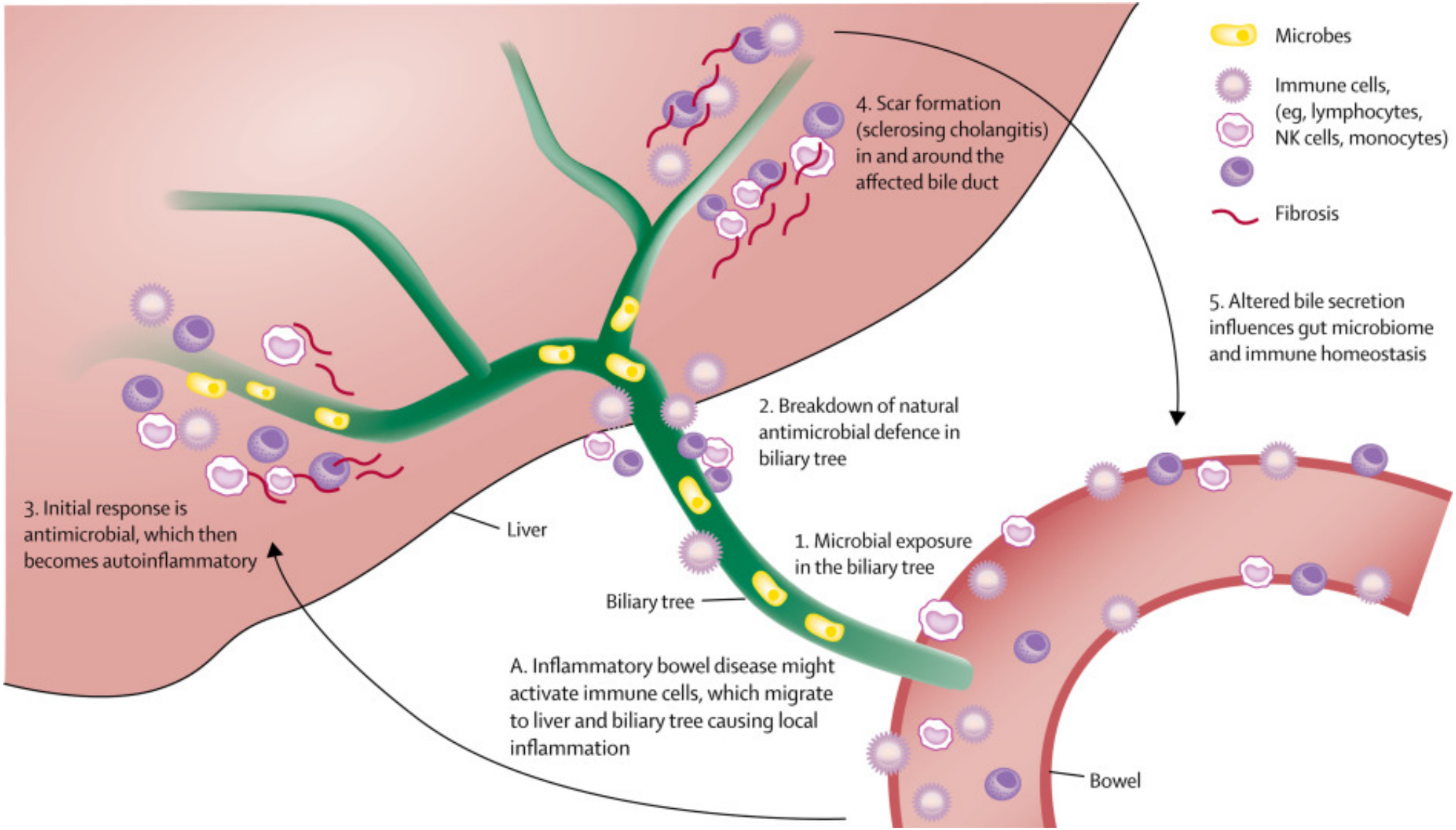
Implications of all the available evidence

This study provides a valuable insight into W&W strategies worldwide. However, further expansion of the network and prospective data collection are essential to learn more on long-term outcomes of W&W, including functional outcomes. The IWWD Consortium will focus on the development of uniform protocols for selection and follow-up of patients on the W&W strategy. All interested clinicians who perform organ-preserving strategies on patients with rectal cancer are welcome to join our network.

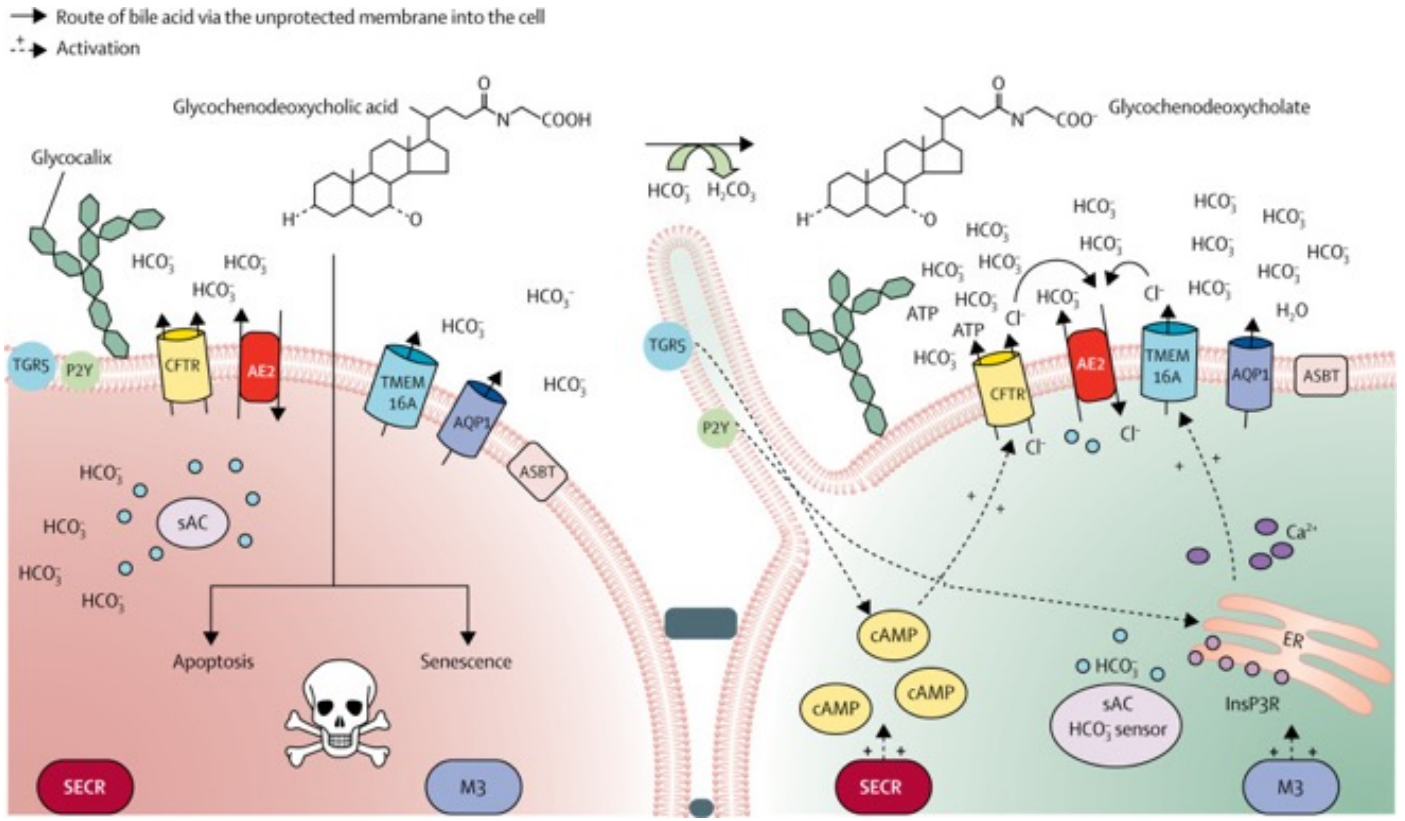
Primary sclerosing cholangitis

Primary sclerosing cholangitis is a rare, chronic cholestatic liver disease characterised by intrahepatic or extrahepatic stricturing, or both, with bile duct fibrosis. Inflammation and fibrosis of bile ducts and the liver are followed by impaired bile formation or flow and progressive liver dysfunction. Patients might be asymptomatic at presentation or might have pruritus, fatigue, right upper quadrant pain, recurrent cholangitis, or sequelae of portal hypertension. The key diagnostic elements are cholestatic liver biochemistry and bile duct stricturing on cholangiography. Genetic and environmental factors are important in the cause of the disease, with the intestinal microbiome increasingly thought to play a pathogenetic role. Approximately 70% of patients have concurrent inflammatory bowel disease and patients require colonoscopic screening and surveillance. Primary sclerosing cholangitis is associated with increased malignancy risk and surveillance strategies for early cholangiocarcinoma detection are limited. No single drug has been proven to improve transplant-free survival. Liver transplantation is effective for advanced disease but at least 25% of patients develop recurrent disease in the graft.

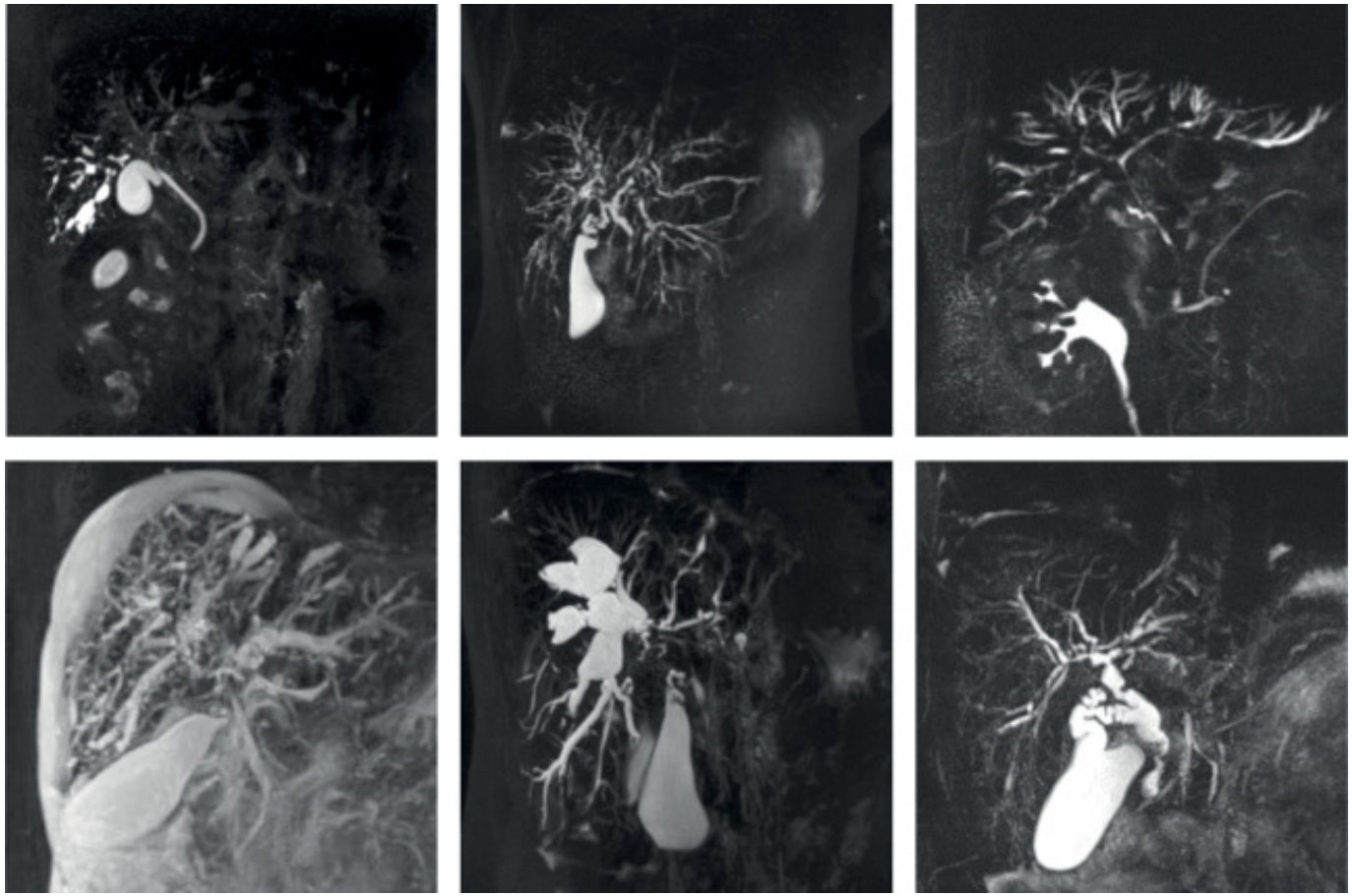




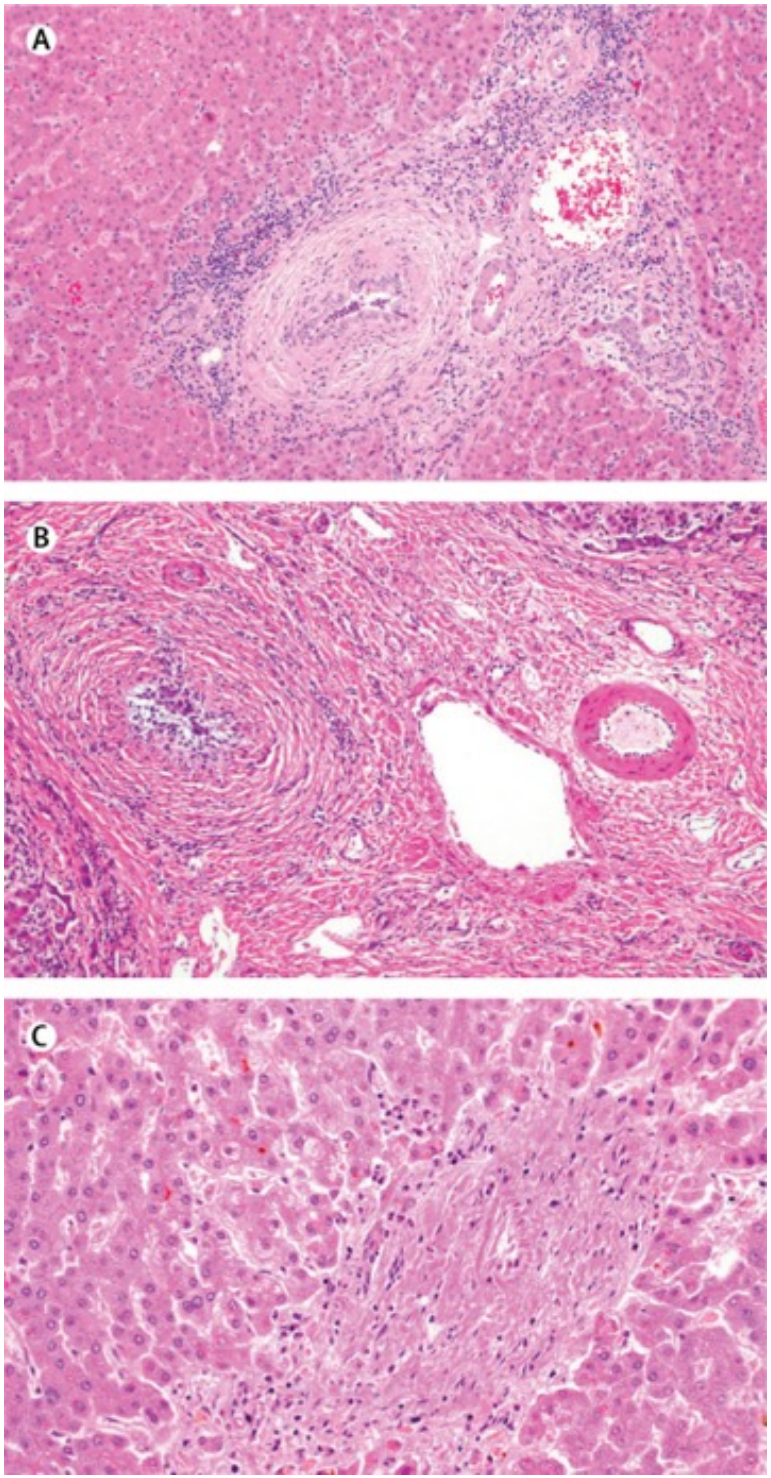
Possible pathogenesis of primary sclerosing cholangitis
Genetic susceptibility and environmental, possibly dietary, factors contribute to pathogenesis, which are not depicted in this figure. A=alternative or additional hypothesis for initiation of the peribiliary inflammatory process. NK=natural killer.



The biliary bicarbonate umbrella hypothesis
Dysfunction of TGR5 (involved in HCO_3^- secretion) or the glycocalyx-stabilising enzyme FUT2 (involved in umbrella formation) have been discussed as weakening the biliary HCO_3^- umbrella in some but not all cohorts of patients with primary sclerosing cholangitis. AE2=anion exchanger 2. AQP1=aquaporin-1. ASBT=apical sodium-dependent bile acid transporter. Ca^{2+}=calcium ion. cAMP=cyclic adenosine monophosphate. CFTR=cystic fibrosis transmembrane conductance regulator. Cl^-=chloride ion. ER=endoplasmic reticulum. H_2O=water molecule. HCO_3^-=bicarbonate. H_2CO_3=carbonic acid. InsP3R=inositol trisphosphate receptor. M3=muscarinic receptor type 3. P2Y=purinergic G protein-coupled receptors. sAC=soluble adenylyl cyclase. SECR=secretin receptor. TGR5=G-protein-coupled bile acid receptor. TMEM16A=transmembrane member 16A (a calcium-dependent chloride channel).



Typical features of large duct primary sclerosing cholangitis
Three-dimensional-gated T2 turbospinecho magnetic resonance cholangiopancreatography maximum intensity projection images showing typical features of large duct primary sclerosing cholangitis with irregular narrowing of bile ducts, stenoses, and focal dilatation of bile ducts.



Histology of primary sclerosing cholangitis
Reproduced with permission from Yvonne Bury, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK. (A) A medium-sized portal tract with bile ducts surrounded by periductal onion-skin concentric fibrosis and oedema with a mild portal inflammatory cell infiltrate (haematoxylin and eosin stain [H&E]; reduced by 25% from × 100 magnification). (B) The bile duct epithelium shows degenerative and atrophic changes and the bile ducts assume an irregular outline. Such characteristic lesions are present only in fewer than half of biopsy specimens because such medium-sized to large ducts are sampled uncommonly in biopsy specimens (H&E; reduced by 25% from × 100 magnification). (C) Progressively, bile ducts are lost and portal tracts contain unpaired arteries without an associated bile duct. This represents ductopenia when seen in more than half of portal tracts. Ductopenia is present in the later stages of primary sclerosing cholangitis and is commonly associated with portal, periportal, or bridging fibrosis (H&E; reduced by 25% from × 200 magnification).

Prognostic factors in primary sclerosing cholangitis

Good prognostic factors

- Younger age at diagnosis[140]
- Female sex[140]
- Reduced or normal alkaline phosphatase concentrations (whether given ursodeoxycholic acid or not)[141, 142, 143, 144, 145, 146]
- Small duct disease[140, 147, 148]
- Primary sclerosing cholangitis with features of autoimmune hepatitis (worse than classic autoimmune hepatitis, better than classic primary sclerosing cholangitis)[12, 13]

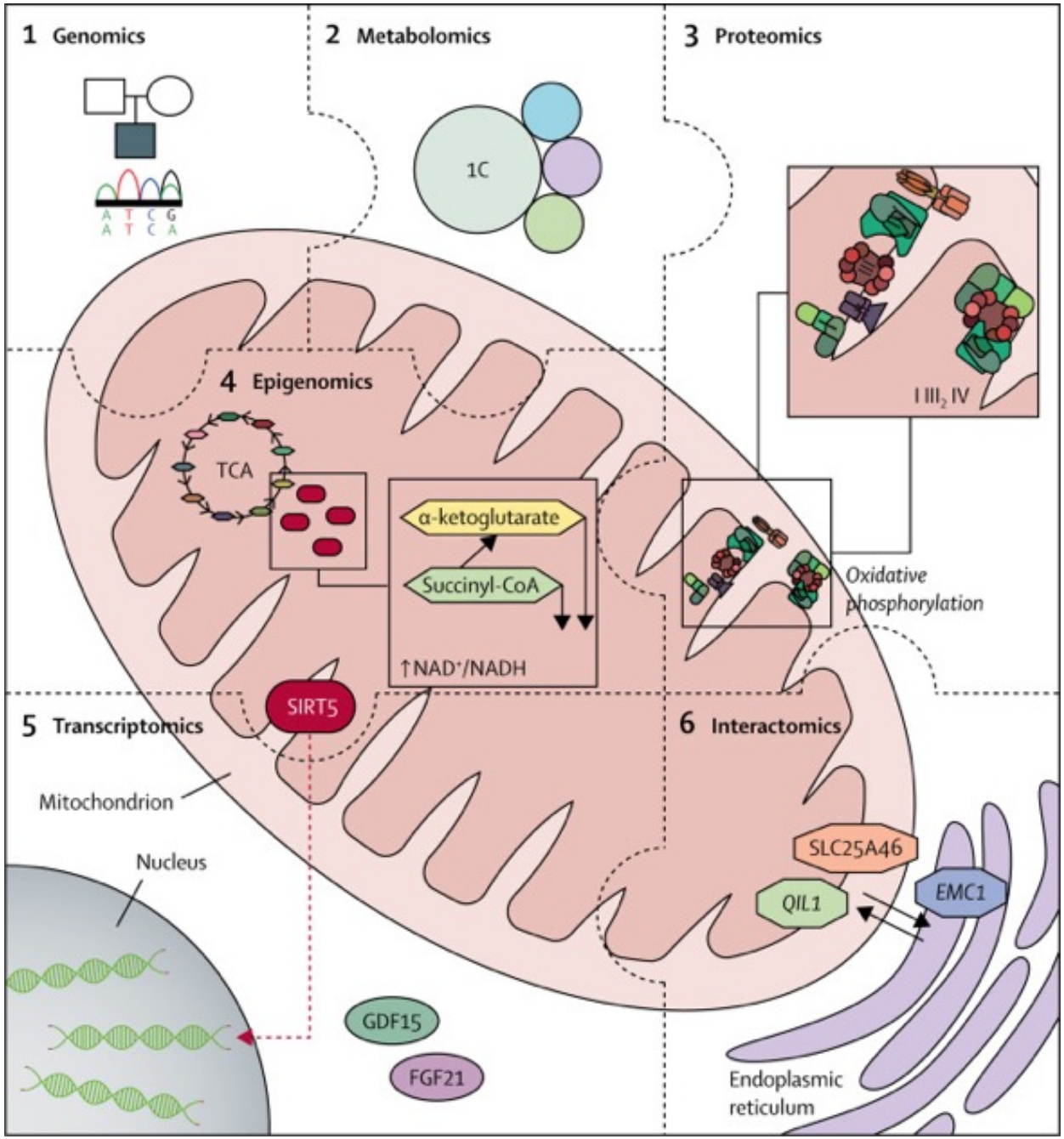
Poor prognostic factors

- Extensive intrahepatic or extrahepatic biliary strictures
- Dominant strictures[149]
- Recurrent cholangitis[39]
- Ulcerative colitis (as opposed to Crohn's disease)[140]
- Evidence of liver synthetic dysfunction
- Cirrhosis with portal hypertension

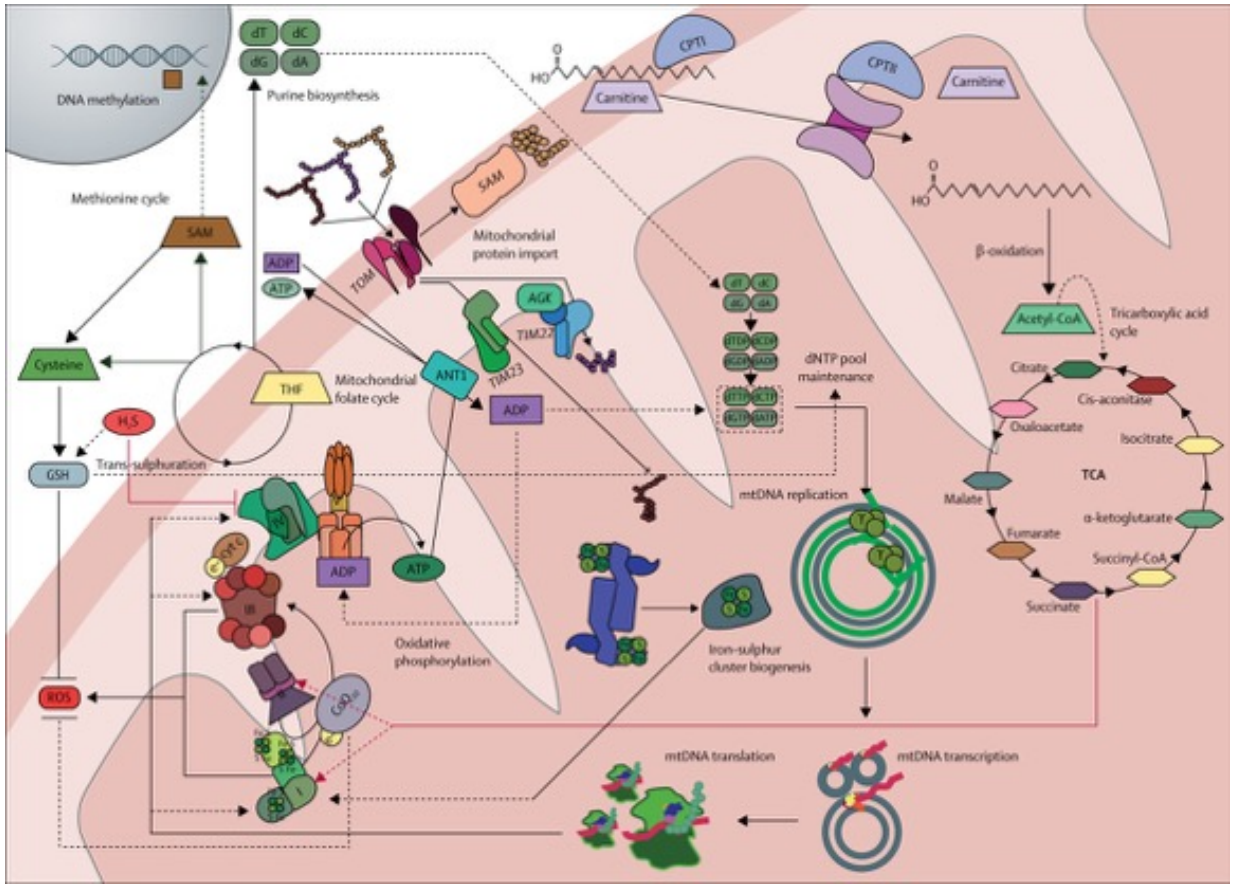
Mitochondrial medicine in the omics era

Mitochondria are dynamic bioenergetic organelles whose maintenance requires around 1500 proteins from two genomes. Mutations in either the mitochondrial or nuclear genome can disrupt a plethora of cellular metabolic and homoeostatic functions. Mitochondrial diseases represent one of the most common and severe groups of inherited genetic disorders, characterised by clinical, biochemical, and genetic heterogeneity, diagnostic odysseys, and absence of disease-modifying curative therapies. This Review aims to discuss recent advances in mitochondrial biology and medicine arising from widespread use of high-throughput omics technologies, and also includes a broad discussion of emerging therapies for mitochondrial disease. New insights into both bioenergetic and biosynthetic mitochondrial functionalities have expedited the genetic diagnosis of primary mitochondrial disorders, and identified novel mitochondrial pathomechanisms and new targets for therapeutic intervention. As we enter this new era of mitochondrial medicine, underpinned by global unbiased approaches and multifaceted investigation of mitochondrial function, omics technologies will continue to shed light on unresolved mitochondrial questions, paving the way for improved outcomes for patients with mitochondrial diseases.

	Gene(s)
Oxidative phosphorylation deficiency	
Complex I subunits and assembly factors	*NDUFA1, NDUFA2, NDUFA6, NDUFA9, NDUFA10, NDUFA11, NDUFA12, NDUFA13 NDUFB3, NDUFB8, NDUFB9, NDUFB10, NDUFB11, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF7, NDUFAF8, ACAD9, ECSIT, FOXRED1, NUBPL, TIMMDC1, TMEM126B, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6*
Complex II subunits and assembly factors	*SDHA, SDHB, SDHC, SDHD, SDHAF1, SDHAF2*
Complex III subunits and assembly factors	*UQCRB, UQCRC2, UQCRFS1, UQCRQ, CYC1, BCS1L, HCCS, TTC19, LYRM7, UQCC2, UQCC3, MT-CYB*
Complex IV subunits and assembly factors	*COX4I1, COX4I2, COX5A, COX6A1, COX6B1, COX7B, COX8A, NDUFA4, SURF1, SCO1, SCO2, COX10, COX15, COA3, COA5, COA6, COA7, COX14, COX20, FASTKD2, PET100, PET117, CEP89, MT-CO1, MT-CO2, MT-CO3*
Complex V subunits and assembly factors	*ATP5A1, ATP5D, ATP5E, ATPAF2, TMEM70, USMG5, MT-ATP6, MT-ATP8*
Disorders of mitochondrial DNA maintenance	
Nucleotide pool maintenance	*ABAT, AK2, DGUOK, RRM2B, SAMHD1, SUCLA2, SUCLG1, TK2, TYMP*
Replication, maintenance, and transcription of mtDNA	*DNA2, FBXL4, MGME1, MPV17, POLG, POLG2, SSBP1, SLC25A4, TWNK*
Mitochondrial translation defects	
Mitochondrial tRNAs	*MT-TA, MT-TC, MT-TD, MT-TD, MT-TE, MT-TF, MT-TG, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TL2, MT-TM, MT-TN, MT-TP, MT-TQ, MT-TR, MT-TS, MT-TT, MT-TV, MT-TW, MT-TY*
Mitochondrial aminoacyl-tRNA synthetases	*AARS2, CARS2, DARS, DARS2, EARS2, FARS2, GARS, HARS2, IARS, IARS2, KARS, LARS, LARS2, MARS2, NARS2, PARS2, QARS, RARS2, SARS2, TARS2, VARS2, WARS2, YARS2*
tRNA modification	*ELAC2, MTFMT, NSUN3, PDE12, QRSL1, TRIT1, TRMT5, TRMT10C, TRNT1*
Mitochondrial rRNA	*MT-RNR1, MT-RNR2*
RNA processing	*PNPT1*
Mitoribosome subunits and assembly	*ERAL1, MRPL3, MRPL12, MRPL44, MRPS2, MRPS7, MRPS16, MRPS22, MRPS23, MRPS34, MRM2, RMND1*
Protein synthesis	*C12orf65, GFM1, GFM2, GTPBP3, GUF1, LRPPRC, MTO1, MTPAP, PUS1, TACO1, TRMU, TSFM, TUFM*
Mitochondrial quality control defects	
Mitochondrial membrane phospholipid and import machinery	*AGK, CHKB, DNAJC19, GFER, MIPEP, PAM16, PLA2G6, PMPCA, SERAC1, SLC25A3, SLC25A10, SLC25A12, SLC25A22, TAZ, TIMM8A, TIMM50, XPNPEP3*
Mitochondrial dynamics	*DNM1L, GDAP1, MFF, MFN2, MSTO1, OPA1, STAT2, TRAK1, YME1L1*
MICOS complex	*CHCHD10, QIL1, SLC25A46*
ER–mitochondrial tethering	*EMC1*
Mitochondrial protein quality control	*AFG3L2, ATAD3A, CLPB, CLPP, CLPX, HSPA9, HSPD1, HSPE1, LONP1, PITRM1, SACS, SPG7, TRAP1*
Toxicity	*ECHS1, ETHE1, HIBCH*
Antioxidant defence	*NNT, TXN2*
Metabolic defects	
Tricarboxylic acid cycle enzymes	*ACO2, DHTKD1, FH, IDH3A, IDH3B, MDH2, OGDH*
Pyruvate metabolism	*DLAT, DLD, MPC1, PC, PDHA1, PDHB, PDHX, PDK3, PDP1, PDPR*
Fatty acid metabolism	*CRAT, ETFA, ETFB, ETFDH, FA2H, HSD17B10, PYCR1, SLC25A1*
CoA metabolism and transport	*COASY, PANK2, SLC25A42*
Vitamin and cofactor metabolism defects	
Coenzyme Q_{10} biosynthesis	*COQ2, COQ4, COQ5, COQ6, COQ7, COQ8A, COQ8B, COQ9, PDSS1, PDSS2*
Iron–sulphur cluster protein biosynthesis	*ABCB7, FDXR, FDX1L, FXN, ISCA1, ISCA2, ISCU, LYRM4, NFS1, NFU1*
Lipoic acid biosynthesis	*BOLA3, GLRX5, IBA57, LIAS, LIPT1, LIPT2, MECR*
Cytochrome *c*	*CYCS*
Biotin metabolism	*BTD, HLCS*
Thiamine metabolism and transport	*SLC19A2, SLC19A3, SLC25A19, TPK1*
Mitochondrial one-carbon metabolism	*SLC25A26, SLC25A32*
Heavy metal metabolism	*SLC25A24, SLC33A1, SLC39A8*
Selenoprotein biosynthesis	*SECISBP2, SEPSECS*
NADPH metabolism	*NADK2, NAXD, NAXE*
Riboflavin metabolism and transport	*FLAD1, SLC52A2, SLC52A3*
Other cellular defects associated with mitochondrial dysfunction	
Ca^{2+} homoeostasis	*ANO10, C19ORF70, CISD2, CYP24A1, MICU1, MICU2, WFS1*
Haem biosynthesis	*ABCB6, ALAS2, SFXN4, SLC25A38*
Apoptosis defects	*AIFM1, APOPT1, DIABLO, HTRA2, PTRH2*
DNA repair	*APTX, XRCC4*
Miscellaneous or unknown function	*ALDH1B1, ALDH18A1, BDH1, CA5A, CTBP1, C1QBP, C19ORF12, DCC, DIAPH1, FHF1, KIF5A, OPA3, PNPLA4, PNPLA8, POP1, PPA2, ROBO3, RTN4IP1, SLC44A1, STXBP1, TANGO2, TMEM65, TMEM126A*

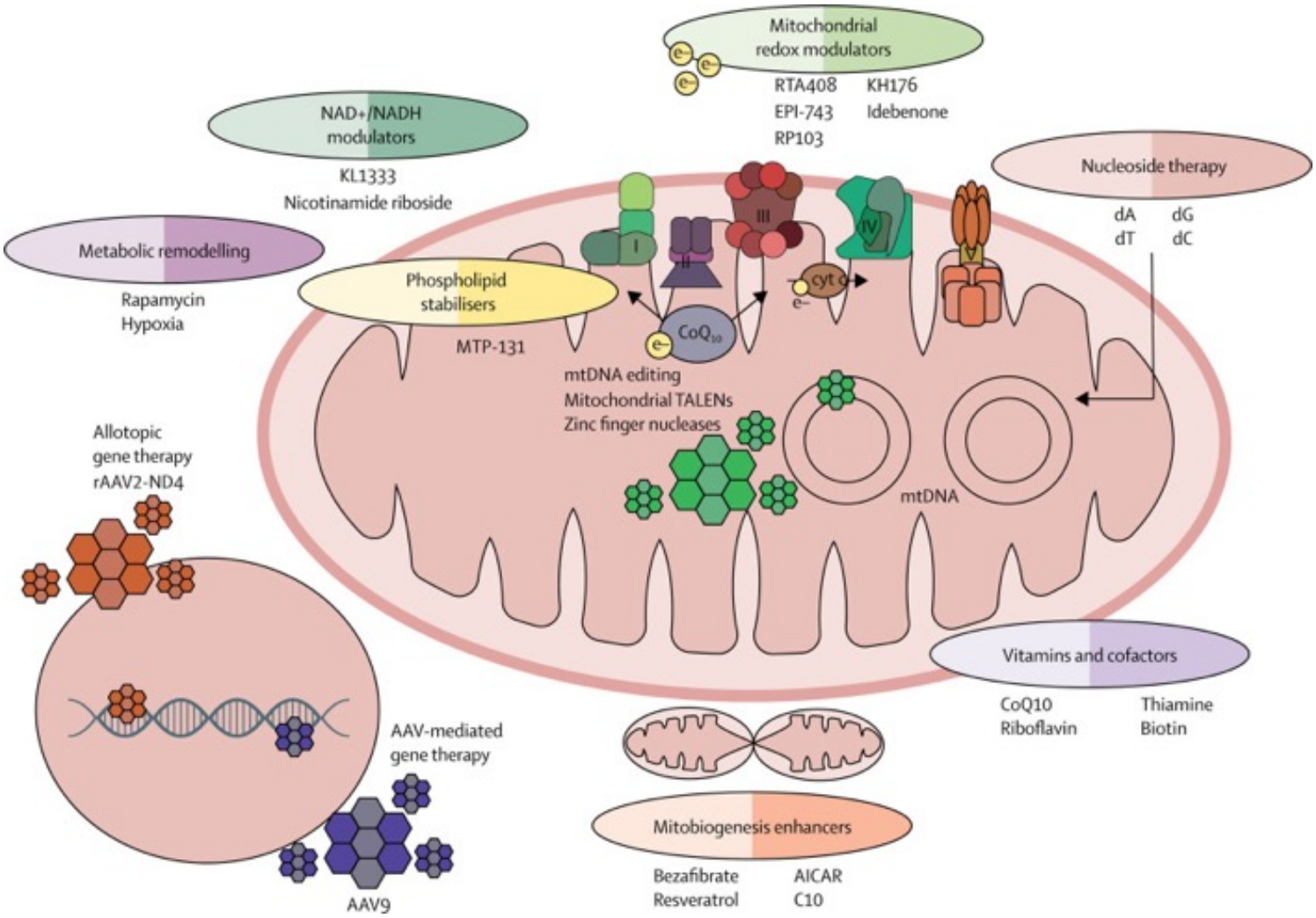


In recent years, high-throughput omics technologies coupled with sophisticated bioinformatic analyses have made substantial contributions to the mitochondrial field. The genomic revolution (1) has increased diagnostic yield for patients with mitochondrial disease and has also expedited the discovery of dozens of novel disease genes. Metabolomics has been a valuable tool in disentangling novel mitochondrial disease pathomechanisms, such as changes to one-carbon cycle metabolism in certain mitochondrial disorders (2). The structure and function of OXPHOS complexes within multimeric supercomplexes has greatly benefited from the use of quantitative proteomics (3). In addition to producing reducing equivalents for OXPHOS, the metabolites and enzymes in the TCA cycle also affect redox ratios in the mitochondrion, thereby modulating downstream epigenetic regulation through the actions of NAD^+-dependent sirtuins (4). Transcriptomics has been a valuable tool in analysing gene expression and has been responsible for the identification of novel mitochondrial disease biomarkers (5). A global analysis of the mitochondrial interactome has revealed novel links between mitochondrial dynamics, mitochondrial cristae organisation, and endoplasmic reticulum–mitochondrial communication (6). OXPHOS=oxidative phosphorylation. TCA=tricarboxylic acid.



Mitochondrial maintenance and function

The mitochondria serve a multitude of biosynthetic and bioenergetic functions. The process of OXPHOS requires the coordinated effort of numerous metabolic reactions and structural components including: the maintenance of mtDNA so that it can be effectively replicated, transcribed, and translated to produce structural components of OXPHOS enzymes; the production of iron–sulphur cofactors with vital redox properties; and the production of reducing equivalents and other metabolites from the TCA cycle. Mitochondria also serve several biosynthetic functions necessary for a variety of cellular processes. These include one-carbon metabolism, which feeds into pathways responsible for antioxidant defence, DNA methylation, and purine biosynthesis. OXPHOS=oxidative phosphorylation. mtDNA=mitochondrial DNA. TCA=tricarboxylic acid.

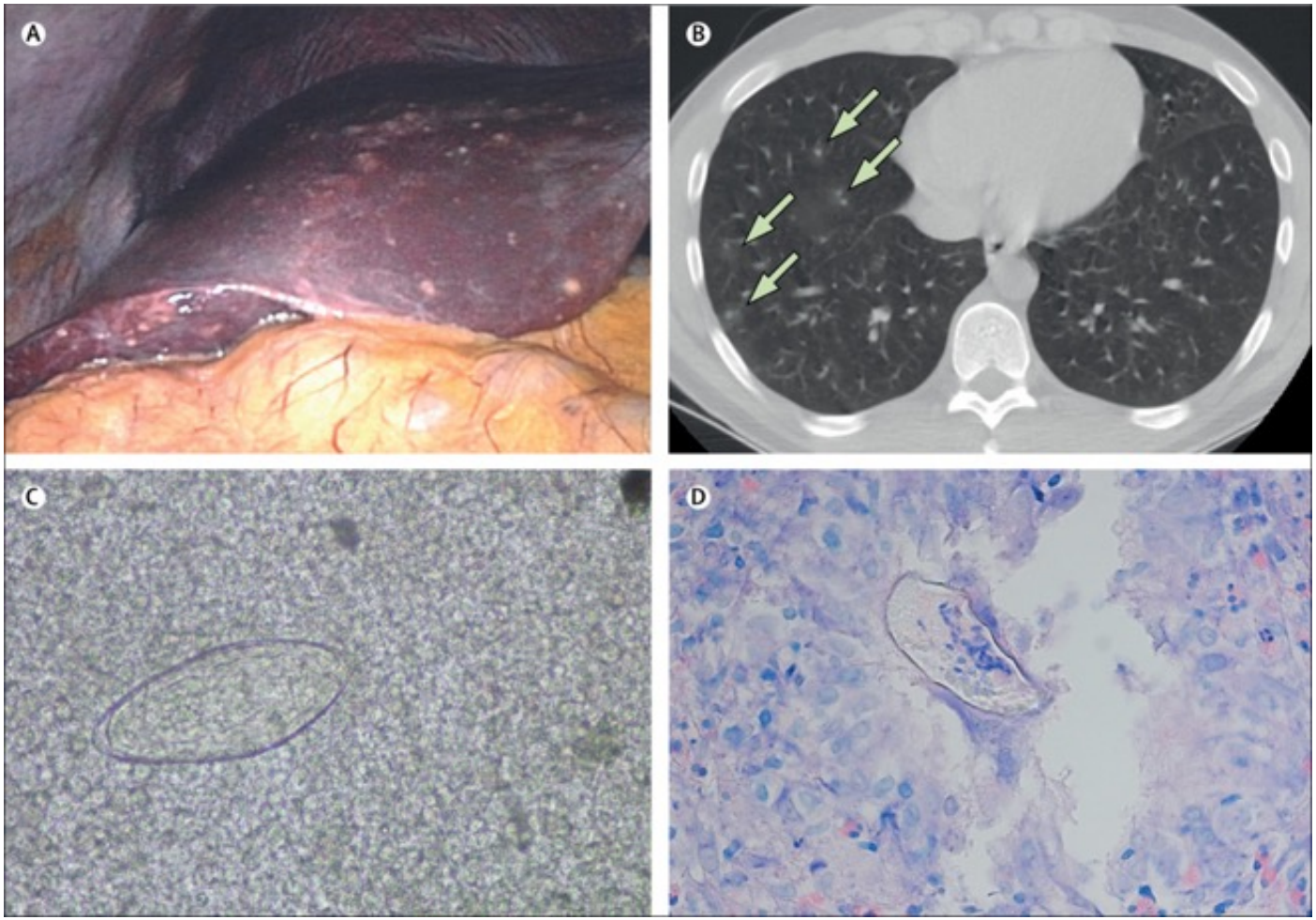


Mitochondrial therapies in development
Despite the absence of approved curative therapies for mitochondrial disease, several pharmacological and genetic approaches to ameliorating the pathology of mitochondrial disease are under investigation.
mtDNA=mitochondrial DNA.

	Mechanism of action	Inclusion criteria		Clinical trial identifier	Primary outcome measure(s)
		Disorder	Age range (years)		
EPI-743 (Vatiquinone, BioElectron, Mountain View, CA, USA)					
Phase 2 study	Mitochondrial redox modulator	PMD	≥1	NCT01370447	Change in neuromuscular function, IAE, NPMDS
Phase 2 study	Mitochondrial redox modulator	LS	1–18	NCT02352896	NPMDS
Idebenone (Raxone, Santhera Pharmaceuticals, Liestal, Switzerland)					
Phase 2 study	Mitochondrial redox modulator	MELAS	8–65	NCT00887562	Mean change in cerebral lactate concentration
Phase 4 study	Mitochondrial redox modulator	LHON	≥12	NCT02774005	BCVA
KH176					
Phase 2 study	Mitochondrial redox modulator	PMD, MM, MELAS, MIDD	≥18	NCT02909400	Movement disorders
RTA408 (Omavexalone, Reata Pharmaceuticals, Irving, TX, USA)					
Phase 2 study	Anti-oxidant and Anti-inflammatory	MM	18–75	NCT02255422	Change in peak workload
Bezafibrate					
Phase 2 study	PPARα activator	MM	16–74	NCT02398201	Change in respiratory chain enzyme activity
Ciclosporin					
Phase 2 study	Immunomodulator	LHON	≥18	NCT02176733	BCVA
KL1333					
Phase 1 study	NAD+ modulator	MRCD, MELAS	19–45	NCT03056209	IAE
MTP-131 (Elamipretide, Stealth BioTherapeutics, Newton, MA, USA)					
Phase 2 study	Cardiolipin stabiliser	PMD	≥16	NCT02805790	IAE
Phase 2 study	Cardiolipin stabiliser	MM	16–65	NCT02367014	IAE
Phase 2 study	Cardiolipin stabiliser	LHON	18–50	NCT02693119	IAE
Arginine and citrulline					
Phase 2 study	Nitric oxide precursors	PMD	3–18	NCT02809170	Reactive hyperaemia index
Allogeneic haemopoietic stem cell transplant					
Phase 1 study	Cellular therapy	MNGIE	5–55	NCT02427178	Neutrophil count
rAAV2-ND4 (GS010)					
Phase 3 study	Gene therapy	LHON	≥15	NCT03293524	BCVA

The mitochondrion is a complex organelle where many pathways and cell functions overlap. Furthermore, critical crosstalk with other subcellular organelles contributes to the remarkable complexity and heterogeneity of mitochondrial disorders. Recent advances in multifaceted omics technologies have, and will continue to, disentangle enigmatic features of mitochondrial disease, revolutionise the field of mitochondrial medicine, and hopefully pave the way for the development of effective therapies at long last.

A 17-year-old German student with acute abdominal pain attended a regional hospital in northern Germany. During interview, he said that 2 weeks earlier his ejaculate had changed to a yellowish brown colour. Laboratory analysis showed leucocytosis (21·9 × 10^9 per L) with a marked eosinophilia (78%, 15·3 × 10^9 per L) and slightly elevated liver enzymes (alanine aminotransferase 101 U/L). An acute appendicitis was suspected and laparoscopic appendectomy was performed. Unexpectedly, intraoperative macroscopic inspection of the liver showed raised white spots on its surface. A biopsy of the liver was done and necrotic granulomas with mainly eosinophils were seen.



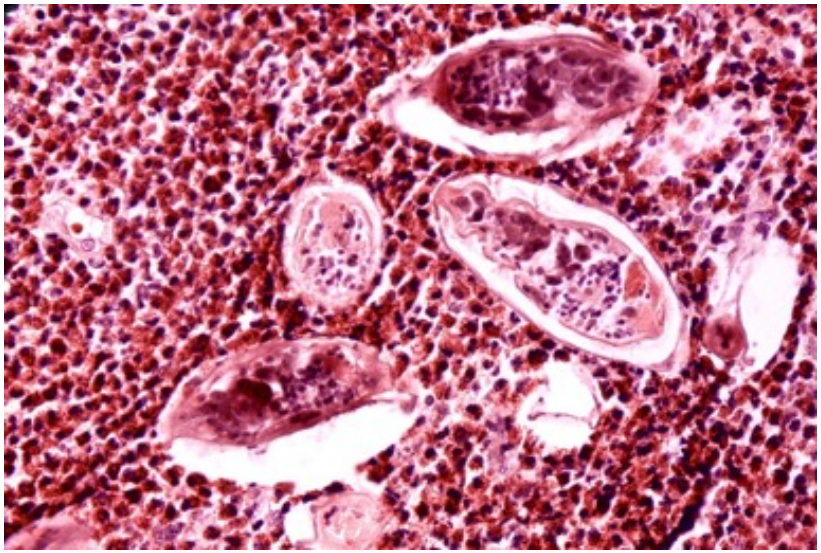
A CT scan of the thorax and abdomen after the appendectomy showed nodular pulmonary infiltrates and hepatomegaly without any specific lesions. The patient was then referred to our hospital, where in a further interview, he said he had recently completed a 2-month trip to Malawi, where he had frequently been in contact with the fresh water in Lake Malawi; the last time was 5 months before the onset of his symptoms. We diagnosed *Schistosoma haematobium* using multiplex real-time PCR of the ejaculate and blood. Examination of the ejaculate under light microscope showed vital *S haematobium* eggs. Re-examination of histopathological samples from the appendix and the liver showed granulomas with a predominance of eosinophils surrounding *S haematobium* eggs.

The antiparasitic drug praziquantel was administered at a dose of 40 mg/kg, orally, for 3 days and the patient made a full clinical recovery.

Schistosomiasis affects more than 250 million people worldwide. Global travel and migration have led to an increase in cases presenting in non-endemic regions. The lengthy delay between exposure and the development of non-specific symptoms means that the disease is commonly misdiagnosed at initial presentation. The discovery of macroscopic white spots on the liver and the accidental detection of *S haematobium* eggs on liver biopsy are uncommon presentations of *S haematobium*.

When taking a medical history, questions about travel and migration are—as always—of paramount importance.

Schistosoma haematobium ist eine Art der Saugwürmer aus der Gattung der Pärchenegel.
Der Erreger kann besonders in Afrika die für zahlreiche Todesfälle verantwortliche Infektionskrankheit Schistosomiasis hervorrufen.
Die erwachsenen Organismen finden sich in Venen, die die Harnblase umschließen. Dort geben sie Eier ab durch die Blasenwand und rufen Hämaturie im Urin hervor. In der Blase lagert sich zu viel Calcium ein, was eine Hydronephrose zur Folge hat. Schistosoma haematobium gehört zu den zehn häufigsten Ursachen für durch Infektionen ausgelöste Krebserkrankungen.
In verunreinigtem Wasser schwimmen die Zerkarien und dringen durch die Haut in das Blutsystem der Patienten. In der Leber werden dann erwachsene Saugwürmer daraus. Diese weisen außen Antigene des Wirtes auf, sodass sie dessen Immunsystem entkommen. Die Eier gelangen mit der Miktion in die Gewässer in der Umgebung der Siedlungen. Dort bilden mehrere Eier ein Miracidium, das eine Bulinus-Schnecke als Zwischenwirt befällt, wo das Epithel abgestreift wird und eine Sporozyste entsteht. Innerhalb weniger Wochen entwickeln sich daraus Tochter-Sporozysten, die bald die Schnecken verlassen und dann im Wasser wieder für Wirte infektiös sind.
Zur Diagnose wird der Urin untersucht, die Eier sind ungefähr 112–180 × 40–70 Mikrometer groß. Zur Prävention müssten die Grundregeln der Hygiene beachtet werden. Zur Behandlung kommt Praziquantel in Frage, wenn es zur Verfügung steht.



Der Erreger in histopathogischer Untersuchung, umgeben von Eosinophilen Granulozyten