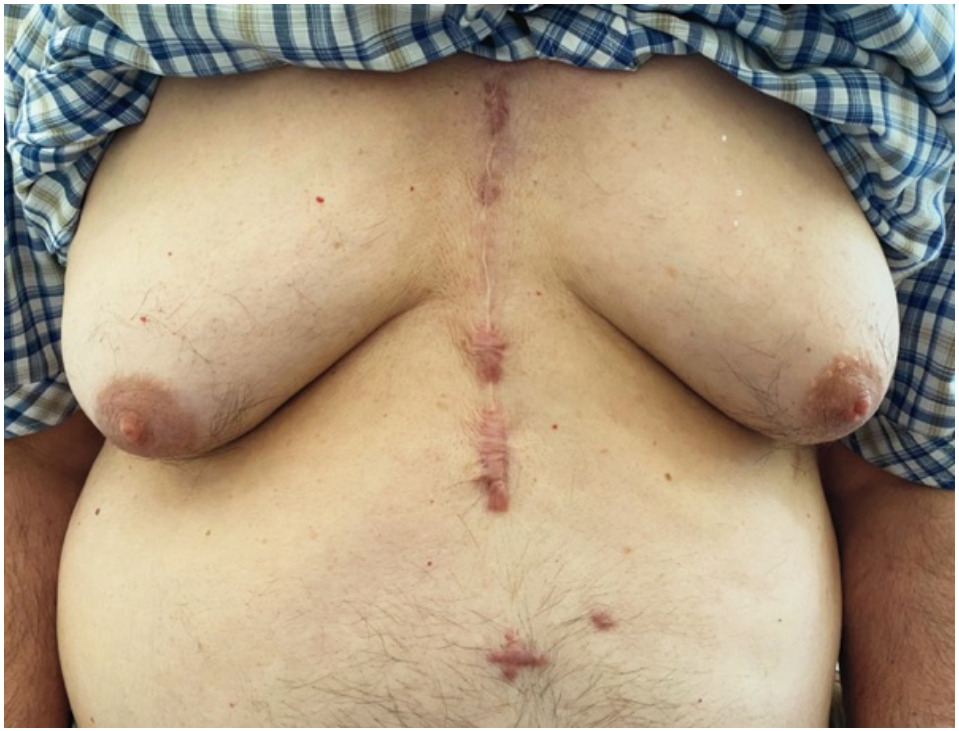
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 76-year-old man with coronary artery disease and heart failure with reduced ejection fraction presented to clinic with an 8-month history of progressive breast enlargement and tenderness. Which of the following is most likely to identify the underlying etiology of this finding?

Computed tomography of the chest, abdomen, and pelvis

Measurement of serum testosterone level

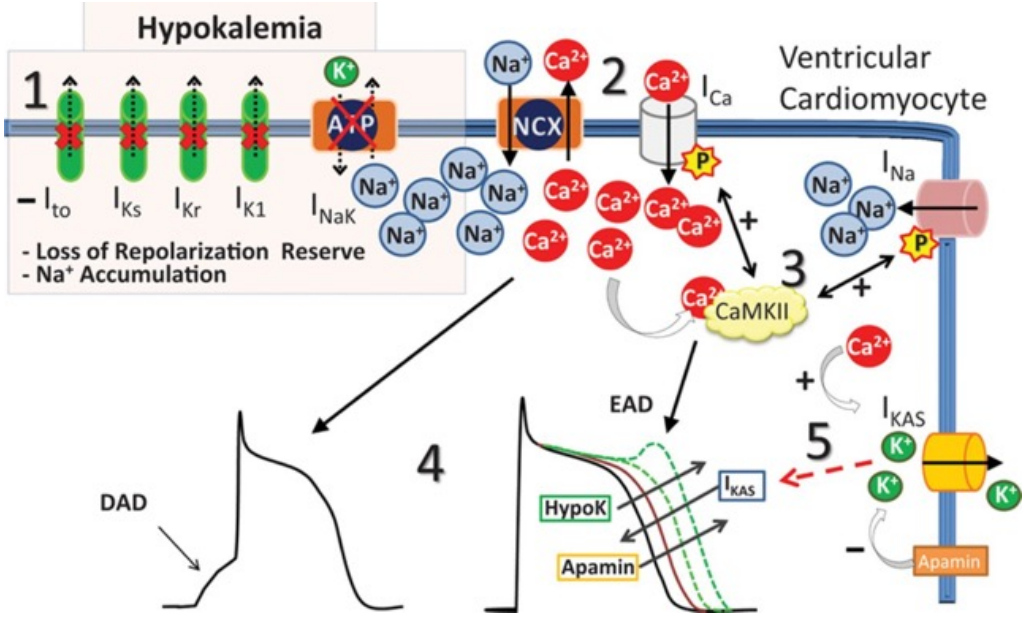
Medication review

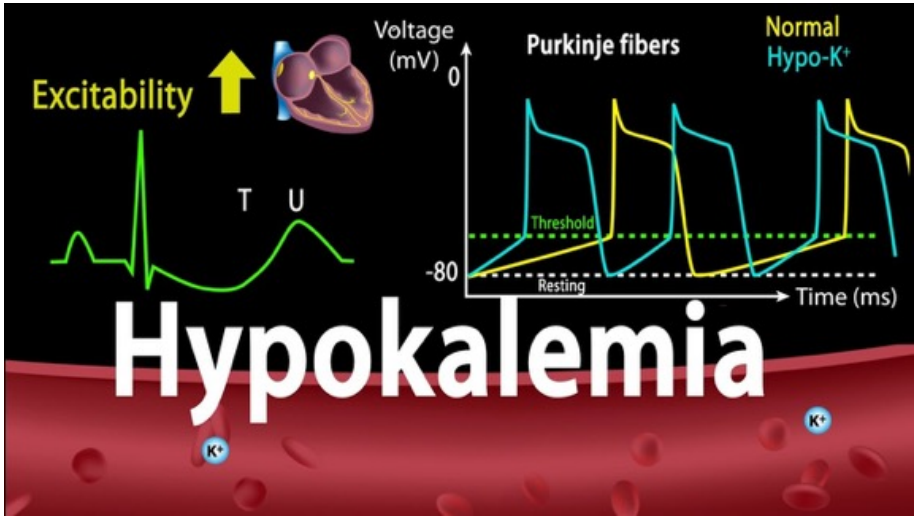
Screening for substance use

Testicular examination

Spironolactone had been started 4 years before presentation as part of the patient's guideline-directed medical therapy for heart failure at a dose of 25 mg daily. It was increased to 100 mg daily 1 year before presentation, and reduced to 25 mg approximately 2 months before presentation due to hyperkalemia. A serum testosterone level was low-normal and serum levels of human chorionic gonadotropin, sex hormone–binding globulin, luteinizing hormone, estradiol, and thyrotropin were normal. A diagnosis of spironolactone-induced gynecomastia was made. Spironolactone was discontinued and eplerenone — a more selective mineralocorticoid receptor antagonist — was started.

Hypokaliämie und Rhythmus Störungen



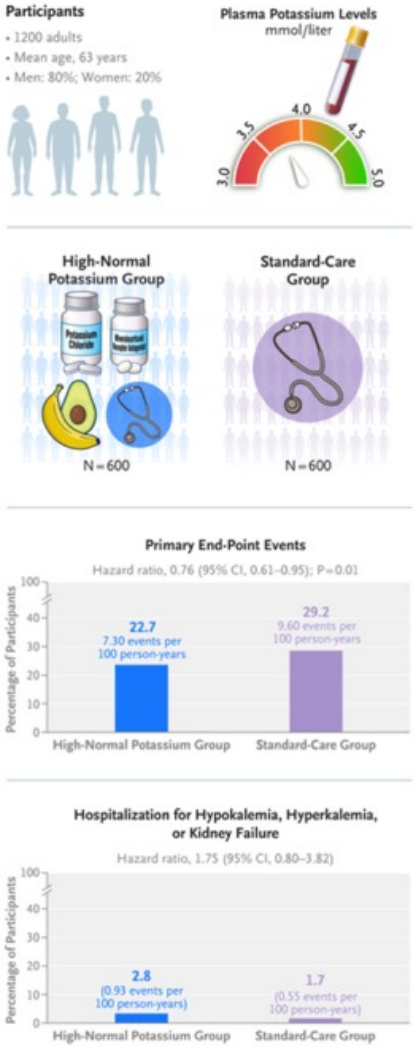


Apamin ist ein neurotoxisches Peptid aus dem Bienengift, das aus 18 Aminosäuren besteht. Es wirkt als selektiver Blocker von kalziumabhängigen Kaliumkanälen (SK-Kanälen) und ist ein wichtiges Werkzeug in der neurowissenschaftlichen Forschung.

Increasing the Potassium Level in Patients at High Risk for Ventricular Arrhythmias

Hypokalemia and even low-normal plasma potassium levels increase the risk of ventricular arrhythmias among patients with cardiovascular disease. An assessment of a strategy of actively increasing plasma potassium levels to the high-normal range is needed.

In this multicenter, open-label, event-driven, randomized superiority trial conducted in Denmark, we enrolled participants at high risk for ventricular arrhythmias (defined as those with an implantable cardioverter–defibrillator [ICD]) and with a baseline plasma potassium level of 4.3 mmol per liter or lower. Participants were randomly assigned, in a 1:1 ratio, to a treatment regimen aimed at increasing the plasma potassium level to a high-normal level (4.5 to 5.0 mmol per liter) by means of potassium supplementation, a mineralocorticoid receptor antagonist, or both plus dietary guidance and standard care (high-normal potassium group) or to standard care only (standard-care group). The primary end point was a composite of documented sustained ventricular tachycardia or appropriate ICD therapy, unplanned hospitalization (>24 hours) for arrhythmia or heart failure, or death from any cause, assessed in a time-to-first-event analysis.



Potassium plays a pivotal role in the electrical and mechanical function of the heart, and a U-shaped relationship has been observed between plasma potassium levels and death. Among patients with cardiovascular disorders, mortality is higher among persons with plasma potassium levels between 3.5 and 4.0 mmol per liter (normal range, 3.5 to 5.0), and plasma potassium levels in the high-normal range (4.5 to 5.0 mmol per liter) are associated with lower mortality.

Among patients with heart failure, mineralocorticoid receptor antagonists and angiotensin-converting–enzyme inhibitors reduce the risk of death, including the risk of sudden death from cardiac causes, as well as the incidence of atrial fibrillation. Both drug classes increase plasma potassium levels and reduce the risk of hypokalemia. A randomized trial showed that among persons at increased risk for cardiovascular events, the substitution of part of the dietary sodium chloride intake with potassium chloride lowered the incidence of cardiovascular events, including death from any cause.

Trial Participants

Adults 18 years of age or older were eligible to enroll in the trial if they had an ICD or a cardiac-resynchronization therapy defibrillator (CRT-D) and had a baseline plasma potassium level of 4.3 mmol per liter or lower. Persons were excluded if the estimated glomerular filtration rate (eGFR) was less than 30 ml per minute per 1.73 m^2 of body-surface area, if they were pregnant, or if they lacked the ability to understand and sign the consent form. All the participants provided written informed consent.

Trial Procedures

The participants were randomly assigned, in a 1:1 ratio, to receive treatment to increase the plasma potassium level in addition to standard care (high-normal potassium group) or to receive standard care only (standard-care group). Appropriate treatment in accordance with society guidelines was ensured for all the participants. All the participants in the high-normal potassium group received written information on a potassium-rich diet and initiated trial medication with potassium supplements, administered as potassium chloride tablets (750 mg [approximately 10 mmol]), a mineralocorticoid receptor antagonist, or both to reach the target plasma potassium level of 4.5 to 5.0 mmol per liter. The maximum daily doses for the mineralocorticoid receptor antagonists were 100 mg for spironolactone and 50 mg for eplerenone; the maximum daily dose for potassium chloride was 4.5 g. If possible, doses of thiazides and loop diuretics were reduced or discontinued. Participants attended visits every other week for blood tests and blood-pressure measurement to evaluate whether increases were needed in the potassium supplement medications and for assessment of adherence and potential side effects.

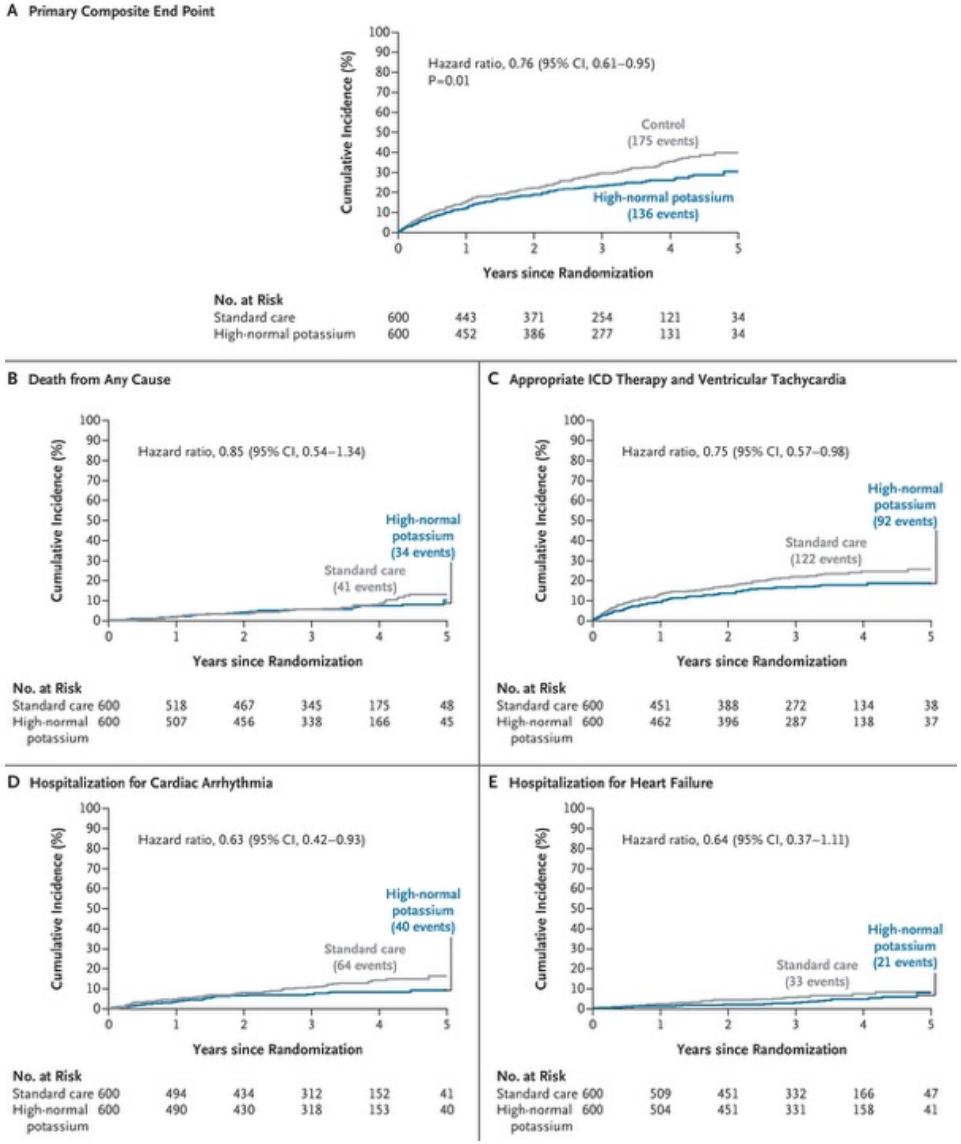
Trial End Points and Safety Measurements

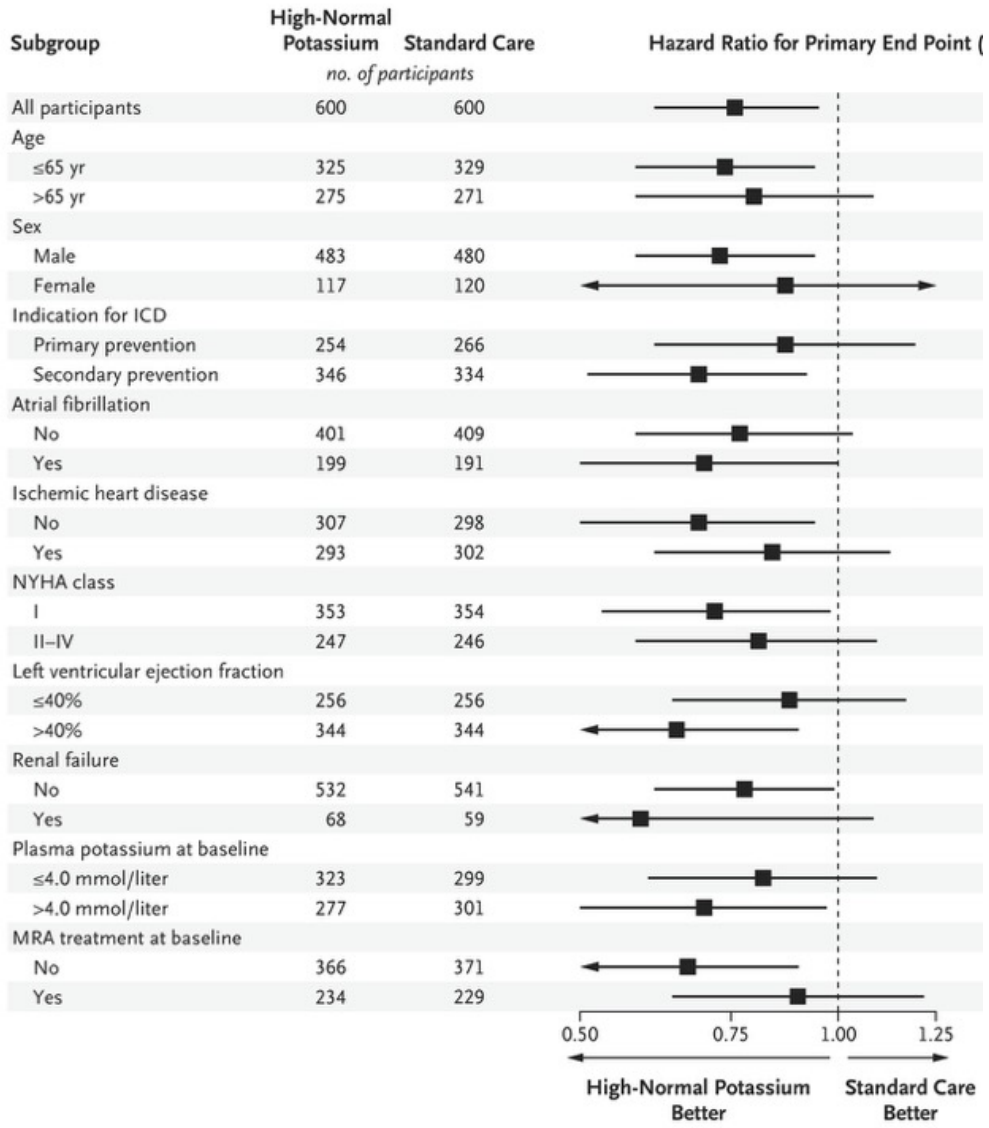
The primary end point was a composite of sustained ventricular tachycardia with a rate of more than 125 beats per minute lasting more than 30 seconds, as documented by electrocardiography (ECG) or observed on the ICD cardiac electrogram; any appropriate ICD therapy as documented by ECG or on the ICD cardiac electrogram; any unplanned hospitalization for more than 24 hours for arrhythmia or heart failure and leading to a change in drug or invasive treatment; or death from any cause.

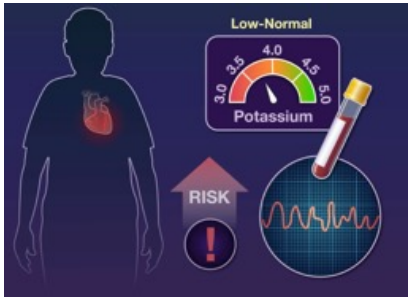
Characteristic	High-Normal Potassium (N=600)	Standard Care (N=600)
Age — yr	62.7±12.1	62.8±11.8
Male sex — no. (%)	483 (80.5)	480 (80.0)
ICD for secondary prevention — no. (%)	346 (57.7)	334 (55.7)
Median left ventricular ejection fraction (IQR) — %	45 (35–55)	45 (30–55)
Left ventricular ejection fraction ≤40% — no. (%)	256 (42.7)	256 (42.7)
NYHA class — no. (%)		
I	353 (58.8)	354 (59.0)
II	213 (35.5)	214 (35.7)
III	34 (5.7)	32 (5.3)
IV	0	0
Plasma potassium level — mmol/liter	4.01±0.24	4.01±0.24
History of ischemic heart disease — no. (%)†		
Ischemic heart disease	293 (48.8)	302 (50.3)
Previous myocardial infarction	208 (34.7)	227 (37.8)
Nonischemic cardiomyopathy and primary arrhythmia — no. (%)†		
Dilated cardiomyopathy	111 (18.5)	90 (15.0)
Nonischemic heart failure, unknown phenotype	40 (6.7)	61 (10.2)
Arrhythmogenic ventricular cardiomyopathy	36 (6.0)	36 (6.0)
Hypertrophic cardiomyopathy	32 (5.3)	34 (5.7)
Primary arrhythmia‡	75 (12.5)	74 (12.3)
Other diagnoses§	23 (3.8)	21 (3.5)
History of heart failure or atrial fibrillation — no. (%)		
Heart failure	390 (65.0)	385 (64.2)
Atrial fibrillation	199 (33.2)	191 (31.8)
History of ventricular tachyarrhythmias		
Previous ventricular tachycardia — no. (%)	414 (69.0)	390 (65.0)
Previous appropriate ICD therapy — no. (%)	181 (30.2)	160 (26.7)
Median time since last ICD therapy (IQR) — days	800 (271–1990)	631 (230–1714)

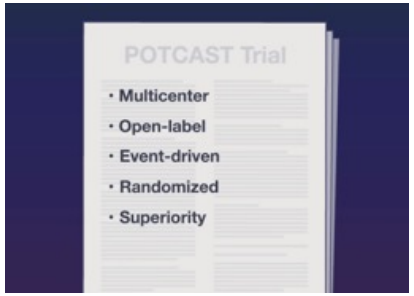
Primary and Secondary End Points and Safety Measurements.

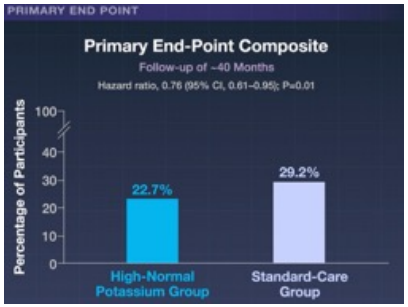
End Point or Measurement	High-Normal Potassium (N=600)		Standard Care (N=600)		Hazard Ratio (95% CI)	P Value
	no. of participants with event (%)	*events per 100 person-years*	*no. of participants with event (%)*	*events per 100 person-years*		
Primary composite end point	136 (22.7)	7.30	175 (29.2)	9.60	0.76 (0.61–0.95)	0.01
Components of the primary end point†						
Appropriate ICD therapy or documented ventricular tachycardia	92 (15.3)	5.05	122 (20.3)	6.69	0.75 (0.57–0.98)	—
Death from any cause	34 (5.7)	1.86	41 (6.8)	2.25	0.85 (0.54–1.34)	—
Hospitalization for cardiac arrhythmia	40 (6.7)	2.19	64 (10.7)	3.51	0.63 (0.42–0.93)	—
Hospitalization for heart failure	21 (3.5)	1.15	33 (5.5)	1.81	0.64 (0.37–1.11)	—
Other secondary end points						
Hospitalization for ventricular arrhythmias	31 (5.2)	1.70	41 (6.8)	2.25	0.76 (0.48–1.22)	—
Hospitalization for supraventricular arrhythmias	12 (2.0)	0.66	27 (4.5)	1.48	0.45 (0.23–0.89)	—
Inappropriate ICD therapy	28 (4.7)	1.54	30 (5.0)	1.65	0.95 (0.57–1.60)	—
Hospitalization for electrolyte disturbances or kidney failure	17 (2.8)	0.93	10 (1.7)	0.55	1.75 (0.80–3.82)	—
Safety measurements						
Hospitalization for other cardiovascular causes	35 (5.8)	1.92	31 (5.2)	1.70	1.15 (0.71–1.87)	0.56
Hospitalization for noncardiovascular causes	111 (18.5)	6.09	127 (21.2)	6.96	0.88 (0.68–1.14)	0.34
Hospitalization for any cause	168 (28.0)	9.21	190 (31.7)	10.42	0.88 (0.71–1.08)	0.21
Hospitalization for any cause or death	177 (29.5)	9.71	199 (33.2)	10.91	0.88 (0.72–1.08)	0.22

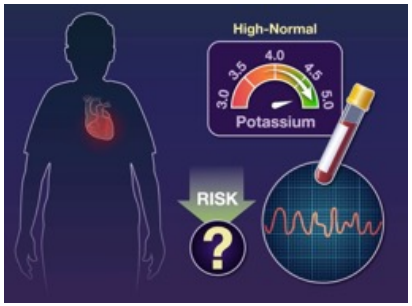

A Primary Composite End Point
Cumulative Incidence (%)
Hazard ratio, 0.76 (95% CI, 0.61–0.95)
P=0.01
Control
(175 events)
High-normal potassium
(136 events)
Years since Randomization
No. at Risk
Standard care 600 443 371 254 121 34
High-normal potassium 600 452 386 277 131 34
B Death from Any Cause
Hazard ratio, 0.85 (95% CI, 0.54–1.34)
High-normal potassium
(34 events)
Standard care
(41 events)
No. at Risk
Standard care 600 518 467 345 175 48
High-normal potassium 600 507 456 338 166 45
C Appropriate ICD Therapy and Ventricular Tachycardia
Hazard ratio, 0.75 (95% CI, 0.57–0.98)
High-normal potassium
(92 events)
Standard care
(122 events)
No. at Risk
Standard care 600 451 388 272 134 38
High-normal potassium 600 462 396 287 138 37
D Hospitalization for Cardiac Arrhythmia
Hazard ratio, 0.63 (95% CI, 0.42–0.93)
High-normal potassium
(40 events)
Standard care
(64 events)
No. at Risk
Standard care 600 494 434 312 152 41
High-normal potassium 600 490 430 318 153 40
E Hospitalization for Heart Failure
Hazard ratio, 0.64 (95% CI, 0.37–1.11)
High-normal potassium
(21 events)
Standard care
(33 events)
No. at Risk
Standard care 600 509 451 332 166 47
High-normal potassium 600 504 451 331 158 41

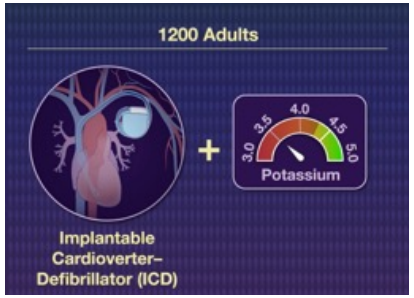

Subgroup
High-Normal Potassium
Standard Care
no. of participants
Hazard Ratio for Primary End Point (
All participants 600 600
Age
≤65 yr 325 329
>65 yr 275 271
Sex
Male 483 480
Female 117 120
Indication for ICD
Primary prevention 254 266
Secondary prevention 346 334
Atrial fibrillation
No 401 409
Yes 199 191
Ischemic heart disease
No 307 298
Yes 293 302
NYHA class
I 353 354
II–IV 247 246
Left ventricular ejection fraction
≤40% 256 256
>40% 344 344
Renal failure
No 532 541
Yes 68 59
Plasma potassium at baseline
≤4.0 mmol/liter 323 299
>4.0 mmol/liter 277 301
MRA treatment at baseline
No 366 371
Yes 234 229
0.50
0.75
1.00
1.25
High-Normal Potassium Better
Standard Care Better

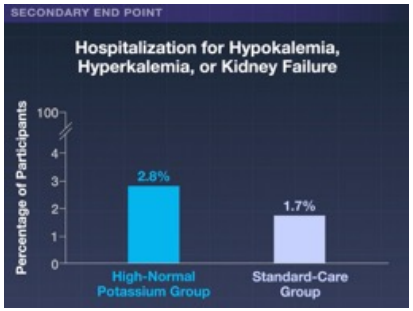

Low-Normal
3.0
3.5
4.0
4.5
5.0
Potassium
RISK

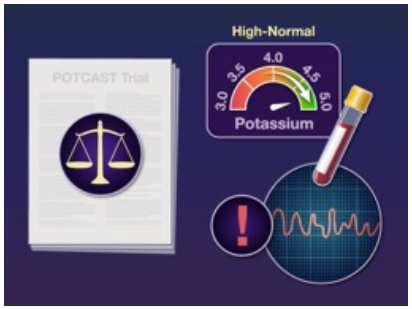

POTCAST Trial
· Multicenter
· Open-label
· Event-driven
· Randomized
· Superiority


PRIMARY END POINT
Primary End-Point Composite
Follow-up of ~40 Months
Hazard ratio, 0.76 (95% CI, 0.61–0.95); P=0.01
Percentage of Participants
100
40
30
20
10
0
22.7%
29.2%
High-Normal Potassium Group
Standard-Care Group

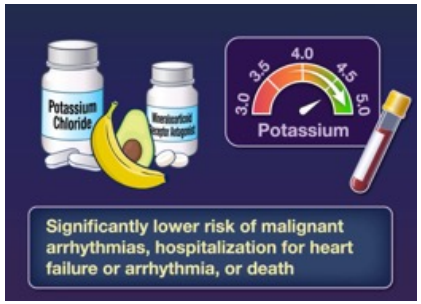

High-Normal
3.0
3.5
4.0
4.5
5.0
Potassium
RISK


1200 Adults
3.0
3.5
4.0
4.5
5.0
Potassium
Implantable Cardioverter–Defibrillator (ICD)


SECONDARY END POINT
Hospitalization for Hypokalemia, Hyperkalemia, or Kidney Failure
Percentage of Participants
100
4
3
2
1
0
2.8%
1.7%
High-Normal Potassium Group
Standard-Care Group


High-Normal
POTCAST Trial
3.0
3.5
4.0
4.5
5.0
Potassium


High-Normal Potassium Group (N=600)
Spironolactone or Eplerenone
Potassium Chloride
Standard-Care Group (N=600)

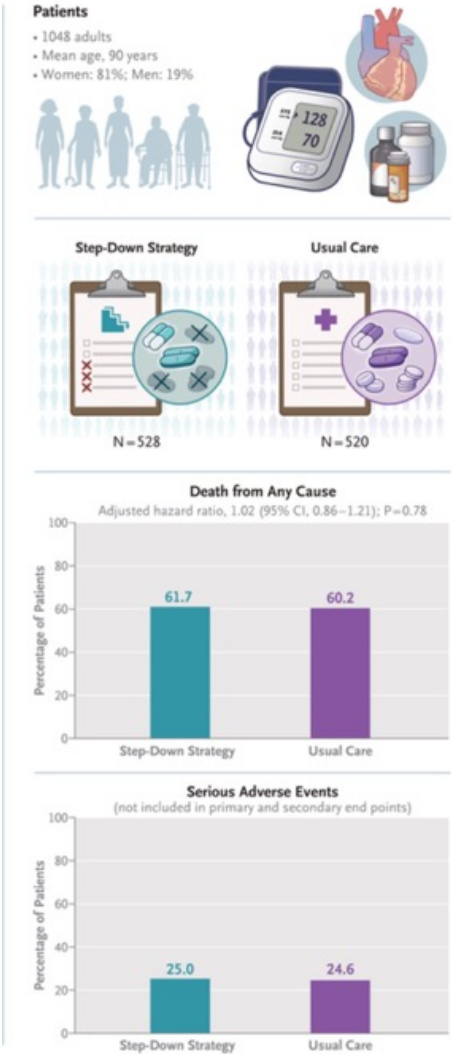

Potassium Chloride
3.0
3.5
4.0
4.5
5.0
Potassium
Significantly lower risk of malignant arrhythmias, hospitalization for heart failure or arrhythmia, or death


VA
Villa Alegría
Skilled Nursing Facility
Hypertension in Older Adults:
Navigating Toward a Healthier Heart

Reduction of Antihypertensive Treatment in Nursing Home Residents

Among older adults with frailty, evidence on the benefits and risks of discontinuing antihypertensive drugs is limited.

In a multicenter, randomized, controlled trial conducted in France, we assigned, in a 1:1 ratio, nursing home residents 80 years of age or older who were receiving more than one antihypertensive drug and had a systolic blood pressure below 130 mm Hg to a protocol-driven strategy of progressive reduction of antihypertensive treatment (step-down group) or to receive usual care (usual-care group). Patients were to be followed for up to 4 years. The primary end point was death from any cause. Secondary end points included the changes in the number of antihypertensive drugs being used from baseline to the last trial visit and the change in systolic blood pressure during the follow-up period.



RETREAT-FRAIL (Reduction of Antihypertensive Treatment in Frail Patients), was a pragmatic, interventional, randomized trial that evaluated the effect of a protocol-driven strategy of progressive reduction of antihypertensive therapies as compared with usual care on all-cause mortality among nursing home residents who were 80 years of age or older and had frailty, had a systolic blood pressure of less than 130 mm Hg, and were receiving at least two antihypertensive agents.

Trial Oversight

This randomized, open-label clinical trial was conducted in 108 nursing homes in France. A coordinating team provided training regarding standardized blood-pressure measurements and training and certification regarding Good Clinical Practice standards.

Trial Design and Interventions

Patients were randomly assigned in a 1:1 ratio to a protocol-driven strategy of progressive discontinuation of antihypertensive drugs (step-down group) or to receive usual care (usual-care group). Randomization was performed with a Web-based randomization system. The randomization list was generated by means of the PLAN procedure in SAS software, version 9.4 (SAS Institute).

End Points

The primary end point was death from any cause. Secondary end points included a composite of major adverse cardiovascular events (defined as the first occurrence of death from cardiovascular causes, stroke, myocardial infarction and other serious coronary artery disease events, acute heart failure, pulmonary embolism, deep-vein thrombosis, atrial fibrillation and major heart-rhythm and conduction disorders, major peripheral vascular events, or transient ischemic attack

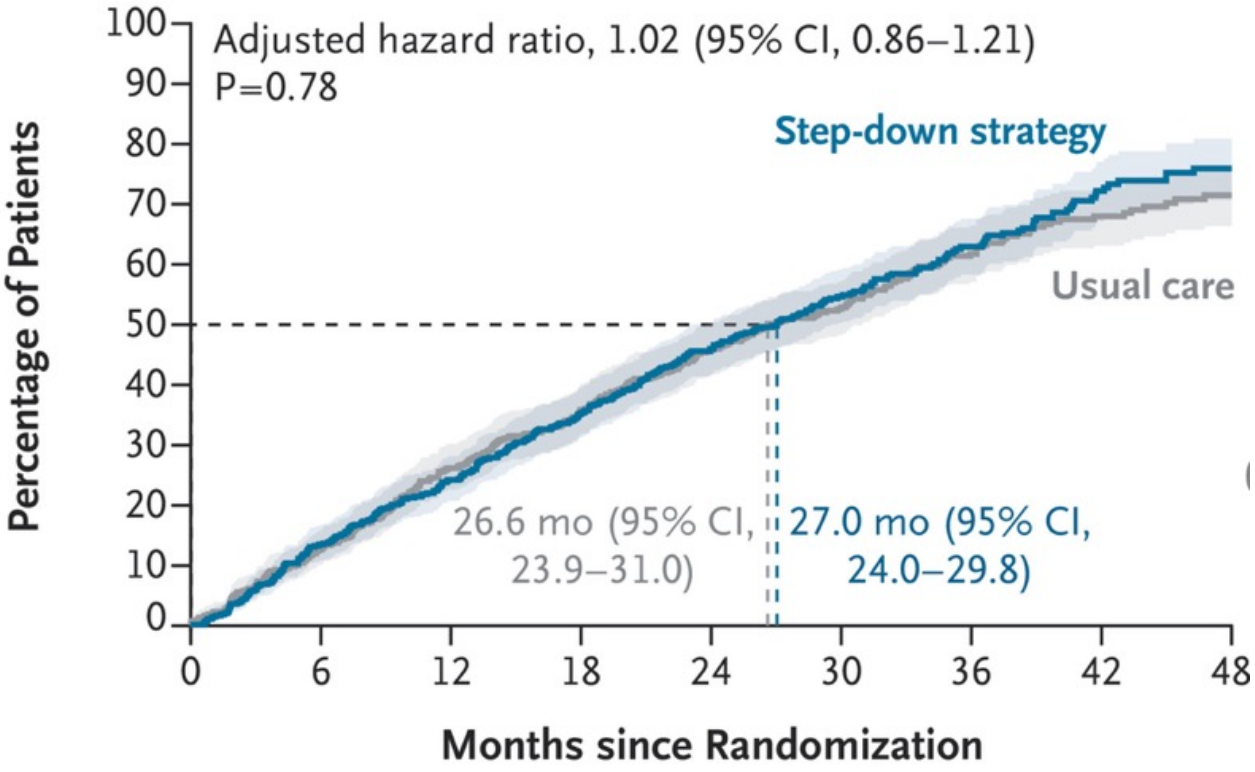
Characteristic	Step-Down Strategy (N=528)	Usual Care (N=520)	Total (N=1048)
Age — yr	90.0±4.8	90.1±5.3	90.1±5.0
Female sex — no. (%)	423 (80.1)	423 (81.3)	846 (80.7)
Weight — kg†	64.9±14.8	65.2±15.0	65.1±14.9
Height — m‡	1.59±0.09	1.58±0.09	1.59±0.09
Body-mass index§	25.9±5.6	26.3±5.8	26.1±5.7
Systolic blood pressure — mm Hg¶	113±11	114±11	114±11
Diastolic blood pressure — mm Hg¶	65±10	65±10	65±10
Heart rate — beats/min¶	72±12	71±12	71±12
MMSE score‖	13.5±10.0	13.3±10.1	13.4±10.0
ADL score**	3.1±2.0	3.2±2.0	3.1±2.0
SPPB score††	1.2 ±1.9	1.2 ±2.0	1.2 ±1.9
EQ-5D-3L questionnaire score ‡‡	0.431±0.407	0.468±0.398	0.449±0.403
Peak muscular force — kg§§	11.7±6.4	12.0±6.8	12.0±6.8
Clinical Frailty Scale score — no./total no. (%)¶¶			
1, 2, or 3	47/525 (9.0)	52/514 (10.1)	99/1039 (9.5)
4 or 5	147/525 (28.0)	164/514 (31.9)	311/1039 (29.9)
6	118/525 (22.5)	111/514 (21.6)	229/1039 (22.0)
7 or 8	213/525 (40.6)	187/514 (36.4)	400/1039 (38.5)
Medications‖‖			
No. of list 1 and list 2 antihypertensive medications	2.6±0.7	2.5±0.7	2.5±0.7
No. of concomitant medications	6.7±3.2	6.7±2.8	6.7±3.0

Medications at Baseline and at the Last Follow-up Visit.

Medications	Step-Down Strategy (N=528)	Usual Care (N=520)	Total (N=1048)
At baseline — no.			
List 1 antihypertensive medications	1.8±0.8	1.8±0.7	1.8±0.8
List 2 antihypertensive medications	0.7±0.7	0.7±0.7	0.7±0.7
List 1 and list 2 antihypertensive medications	2.6±0.7	2.5±0.7	2.5±0.7
Concomitant medications	6.7±3.2	6.7±2.8	6.7±3.0
All medications	9.3±3.4	9.3±2.9	9.3±3.2
At last follow-up visit — no.			
List 1 antihypertensive medications	0.5±0.7	1.2±0.9	0.8±0.9
List 2 antihypertensive medications	1.1±1.0	0.8±0.9	0.9±0.9
List 1 and list 2 antihypertensive medications	1.5±1.1	2.0±1.1	1.8±1.1
Concomitant medications	6.8±3.7	6.6±3.5	6.7±3.6
All medications	8.3±4.1	8.6±3.8	8.5±3.9

Primary and Secondary End Points.

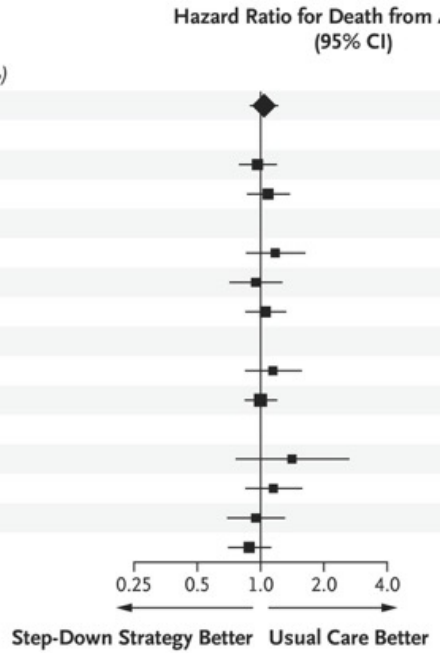
End Points	Step-Down Strategy (N=528)	Usual Care (N=520)	Adjusted Effect Measure (95% CI)	P Value†
Primary end point: death from any cause				
Intention-to-treat analysis — no. (%)	326 (61.7)	313 (60.2)	1.02 (0.86–1.21)‡	0.78
Per-protocol analysis — no./total no. (%)§	311/499 (62.3)	305/497 (61.4)	1.04 (0.87–1.23)‡	
Secondary end points				
Death from noncardiovascular causes — no. (%)	284 (53.8)	278 (53.5)	1.00 (0.83–1.19)¶	
Acute heart failure — no. (%)	67 (12.7)	57 (11.0)	1.19 (0.80–1.78)‖	
Falls				
Overall — no. (%)	264 (50.0)	260 (50.0)	—	
No. of falls per year	0.81±2.08	0.71±1.91	1.14 (0.84–1.51)**	
Fractures				
Overall — no. (%)	41 (7.8)	48 (9.2)	—	
No. of fractures per year	0.03±0.17	0.04±0.17	0.80 (0.51–1.26)††	
Death from Covid-19 — no. (%)	6 (1.1)	16 (3.1)	0.38 (0.10–1.00)‡‡	
Composite of major adverse cardiovascular events — no. (%)§§	102 (19.3)	90 (17.3)	1.15 (0.84–1.56)¶¶	



Kaplan–Meier Analysis of Death from Any Cause (Primary End Point).

The step-down strategy was a protocol-driven progressive reduction in antihypertensive medications. Dashed lines indicate the median time to death in each trial group. The shaded areas indicate 95% confidence intervals.

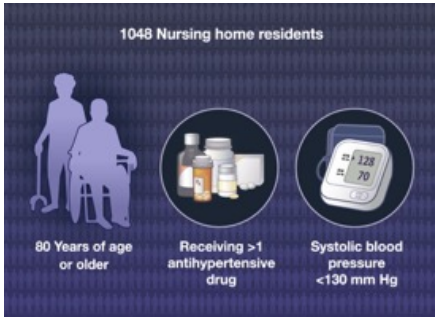
Subgroup	Step-Down Strategy	Usual Care
	no. of patients with event/total no. of patients (%)	
All patients	326/528 (61.7)	313/520 (60.2)
Age		
>90 yr	185/267 (69.3)	176/253 (69.6)
≤90 yr	141/261 (54.0)	137/267 (51.3)
Systolic blood pressure		
<105 mm Hg	76/104 (73.1)	71/104 (68.3)
105–115 mm Hg	97/168 (57.7)	88/154 (57.1)
>115 mm Hg	153/256 (59.8)	154/262 (58.8)
Chronic heart failure		
Yes	87/128 (68.0)	74/118 (62.7)
No	239/400 (59.8)	239/402 (59.5)
Clinical Frailty Scale score		
1, 2, or 3	21/47 (44.7)	19/52 (36.5)
4 or 5	78/147 (53.1)	80/164 (48.8)
6	79/118 (66.9)	76/111 (68.5)
7 or 8	146/213 (68.5)	134/187 (71.7)

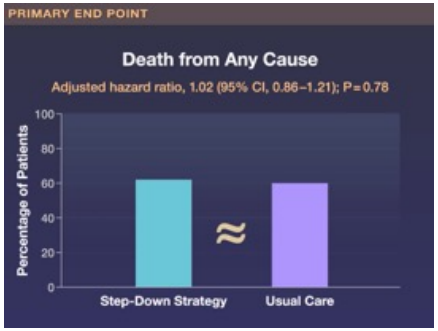


Subgroup Analyses of Death from Any Cause.

All the analyses except those of systolic blood pressure (measured while the patient was seated) were adjusted for baseline systolic blood pressure. The level of frailty was assessed with an algorithm that calculated a composite score. The algorithm included data on functional capacities (autonomy, mobility, and cognitive status) measured in the trial to classify frailty levels according to scores on the validated Clinical Frailty Scale. Scores range from 1 to 9, with a score of 1 indicating fit, 2 well, 3 managing well, 4 vulnerable, 5 mild frailty, 6 moderate frailty, 7 severe frailty, 8 very severe frailty, and 9 terminally ill. Clinical Frailty Scale scores were missing for three patients in the step-down group and six patients in the usual-care group.


Evidence on the benefits and risks of discontinuing antihypertensive drugs is limited
Medications


1048 Nursing home residents
80 Years of age or older
Receiving >1 antihypertensive drug
Systolic blood pressure <130 mm Hg


PRIMARY END POINT
Death from Any Cause
Adjusted hazard ratio, 1.02 (95% CI, 0.86–1.21); P=0.78
Percentage of Patients
Step-Down Strategy
Usual Care


Evidence on the benefits and risks of discontinuing antihypertensive drugs is limited
Medications
Effect of progressive reduction in antihypertensive medications, as compared with usual care, on all-cause mortality


Step-Down Strategy
Usual Care
N=528
N=520


SECONDARY END POINT
Death from Noncardiovascular Causes
Hazard ratio, 1.00 (95% CI, 0.83–1.19)
Percentage of Patients
53.8%
53.5%
Step-Down Strategy
Usual Care


Antihypertensive medication step-down strategy in very old patients with frailty and low blood pressure
Unlikely to have a clinically relevant effect on all-cause mortality


RETREAT-FRAIL Trial
• Randomized
• Controlled
• Open-label
• Multicenter
• France


Step-Down Strategy
Usual Care
N=528
N=520
Followed for up to 4 years

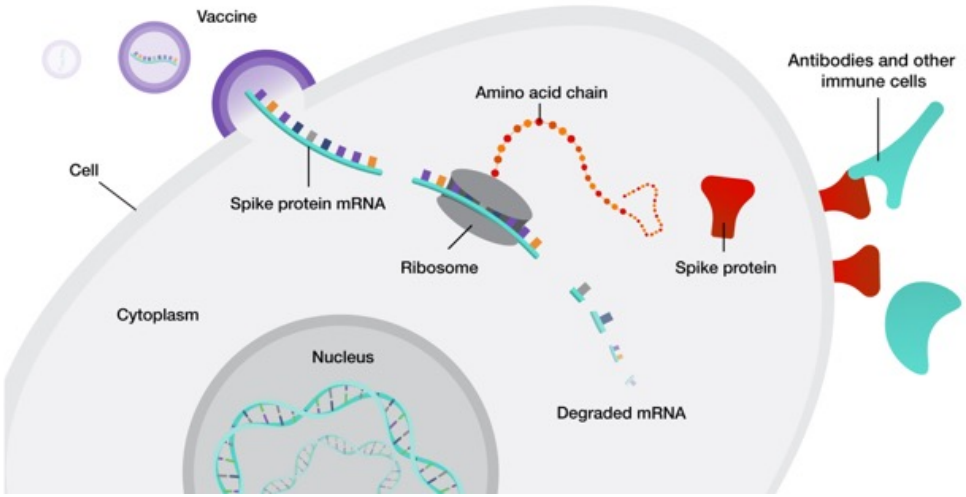

SAFETY
Serious Adverse Events
Other than those included in definitions of the primary and secondary end points
Number of Patients
132
(N=528)
128
(N=520)
Step-Down Strategy
Usual Care

How does an mRNA vaccine work?

mRNA acts as a cellular messenger. DNA, which is stored in a cell's nucleus, encodes the genetic information for making proteins. mRNA transfers a copy of this genetic information outside of the nucleus, to a cell's cytoplasm, where it is translated into amino acids by ribosomes and then folded into complete proteins. mRNA is a short-lived molecule, meaning it degrades easily and does not last long inside cells.

By injecting cells with a synthetic mRNA that encodes a viral spike protein, an mRNA vaccine can direct human cells to make a viral spike protein and evoke an immune response without a person ever having been exposed to the viral material.

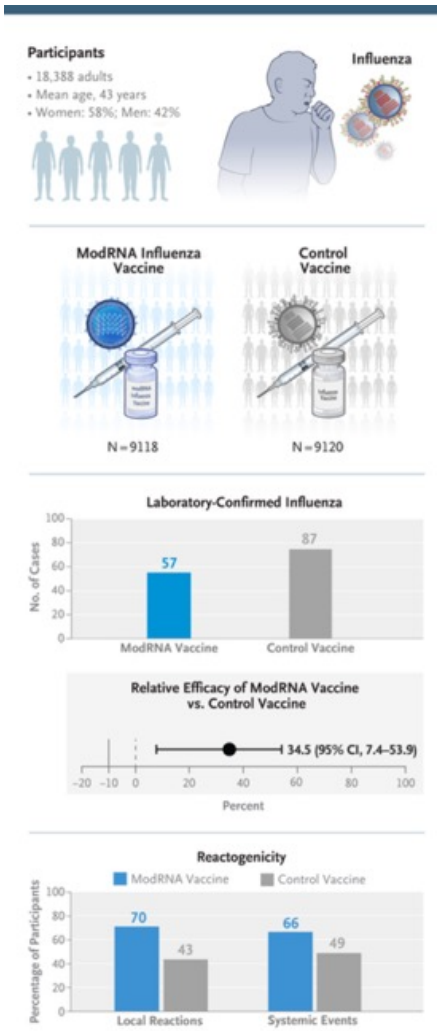
These viral spike proteins, or antigens, normally coat the surface of the virus and are recognized by antibodies and other immune cells that prepare and protect the body against the virus. If a person is later exposed to the virus, antibodies and other parts of the immune system can recognize and attack the virus before it can infect healthy cells or cause illness.



Efficacy, Immunogenicity, and Safety of Modified mRNA Influenza Vaccine

Influenza remains a major health burden despite the use of licensed vaccines. Nucleoside-modified messenger RNA (modRNA) influenza vaccines have shown promising immunogenicity against influenza and an acceptable safety profile in a phase 1–2 trial.

In this phase 3 trial, we randomly assigned healthy adults between the ages of 18 and 64 years to receive either a quadrivalent modRNA influenza vaccine (modRNA group) or a licensed inactivated quadrivalent influenza vaccine (control group) during the 2022–2023 influenza season in the United States, South Africa, and the Philippines. The primary end point was relative efficacy, defined by the reduction in the percentage of participants with laboratory-confirmed influenza associated with influenza-like illness at least 14 days after vaccination with the modRNA vaccine, as compared with the control vaccine, and analyzed for noninferiority and superiority. Immunogenicity was evaluated by means of a hemagglutination inhibition (HAI) assay. We assessed reactogenicity within 7 days after vaccination, adverse events through 1 month, and serious adverse events through 6 months. We assessed vaccine efficacy, immunogenicity, and safety in the modRNA group.



Nucleoside-modified messenger RNA (modRNA)–based vaccines have become integral to vaccine development. During the coronavirus disease 2019 (Covid-19) pandemic, licensed lipid nanoparticle–encapsulated modRNA vaccines encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein were highly effective. ModRNA-based vaccines, in which some nucleosides are replaced by naturally occurring modified nucleosides, decrease innate immune activation and increase translation. The modRNA platform offers unique advantages over traditional egg-based vaccines, including larger-scale production, direct matching of the vaccine to the targeted influenza strain, potential for shorter manufacturing timelines between strain selection and vaccine production, and no risk of egg-adaptive mutations, which can decrease effectiveness.

A quadrivalent modRNA influenza vaccine candidate has shown promising immunogenicity and an acceptable safety profile in a phase 1–2 investigation. We conducted a phase 3 efficacy trial — A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Modified RNA Vaccine against Influenza (Pfizer C4781004 trial) — to determine the relative efficacy of the modRNA vaccine as compared with a standard quadrivalent vaccine against influenza.

Participants and Trial Design

This randomized, blinded trial enrolled participants at 242 sites in the United States, 5 sites in South Africa, and 1 site in the Philippines during the 2022–2023 influenza season.

Efficacy

Our primary objective was to show the noninferiority and superiority of the modRNA vaccine to the control vaccine against laboratory-confirmed influenza associated with influenza-like illness, according to the protocol definition. Relative vaccine efficacy was defined as the relative reduction in the percentage of participants with a first episode of influenza-like illness at least 14 days after vaccination with the modRNA vaccine as compared with the control vaccine.

Secondary efficacy end points were the first episode of laboratory-confirmed influenza-like illness caused by all antigenically matched strains, by unmatched strains, and by each matched strain; culture-confirmed influenza-associated illness (any strain);

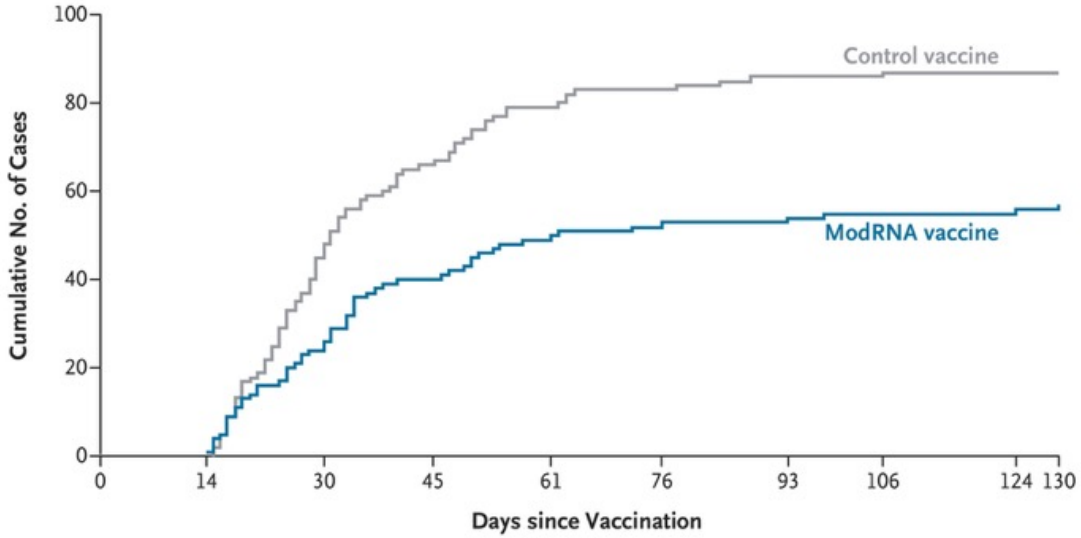
Immunogenicity

We assessed immunogenicity in approximately 4000 participants (immunogenicity subgroup). Blood was collected before vaccination and at 4 weeks and 6 months after vaccination.

Safety

The primary safety objective was to define the safety and side-effect profile for the modRNA vaccine. Safety assessments included solicited local reactions and systemic events (reactogenicity) within 7 days after vaccination (as documented by a subgroup of participants in an electronic diary), adverse events through 4 weeks, and serious adverse events through 6 months.

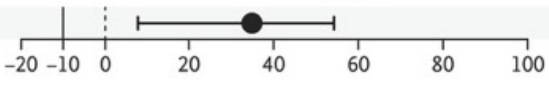
A **Laboratory-Confirmed Cases of Influenza**



Cumulative No. of Events								
Control vaccine	0	48	67	79	83	86	87	87 87
ModRNA vaccine	1	26	40	50	53	54	55	56 57

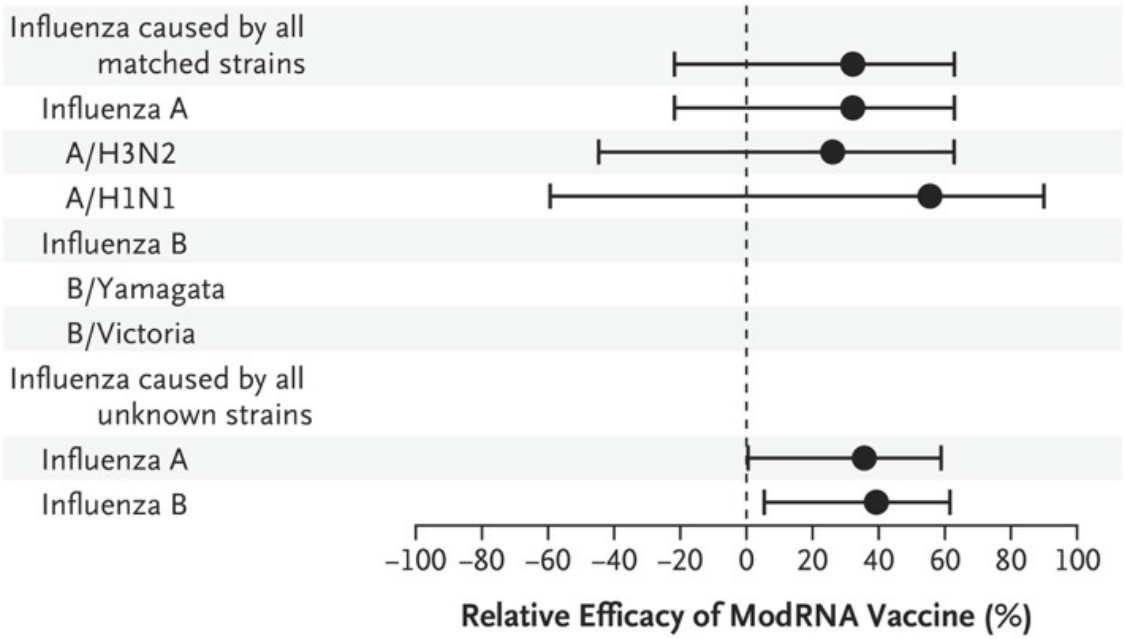
B **Relative Vaccine Efficacy against Influenza in ModRNA Group vs. Control Group**

	ModRNA (N=9118)	Control (N=9120)	Relative Vaccine Efficacy (95% CI)
	no. of cases/attack rate (%)		*percent*
Any influenza strain	57/0.63	87/0.95	34.5 (7.4–53.9)



Relative Vaccine Efficacy (Primary End Point).

Panel A shows the cumulative number of laboratory-confirmed cases of influenza-like illness among participants who received the quadrivalent nucleoside-modified messenger RNA (modRNA) influenza vaccine (modRNA group) or a licensed inactivated quadrivalent influenza vaccine (control group). Panel B shows the relative vaccine efficacy against the first episode of influenza-like illness caused by any strain in the modRNA group as compared with the control group. Data in both panels are for the evaluable efficacy population and include influenza-like illness with symptom onset starting at least 14 days after vaccination through the surveillance data-cutoff date (March 17, 2023). The attack rate was calculated as the total number of cases divided by the number of participants at risk times 100. In Panel B, noninferiority of the modRNA vaccine was shown if the lower boundary of the confidence interval for the relative vaccine efficacy was greater than –10 percentage points (indicated by a solid vertical black line), and superiority was shown if the lower boundary was greater than 0 percentage points (indicated by a dashed vertical black line).

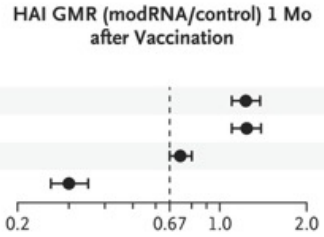


Relative Vaccine Efficacy, According to Influenza Strain.

Shown are data for the relative efficacy of the modRNA vaccine as compared with the licensed quadrivalent influenza (control) vaccine against a first episode of influenza-like illness with symptom onset at least 14 days after vaccination, according to the influenza strain (a secondary efficacy end point). Matched strains were culture-confirmed influenza strains that were antigenically similar to the vaccine strain (difference in hemagglutination inhibition [HAI] titers to a reference virus strain by a factor of 4 or less). Confidence intervals were not adjusted for multiplicity and should not be used to infer effects.

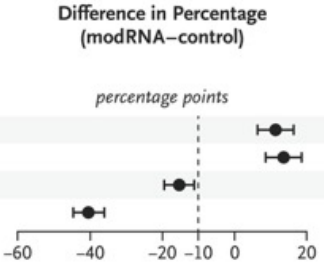
A **Egg-Derived Viral Titers and Ratios on HAI Assay**

	No. of Participants		HAI GMT (95% CI)	
	ModRNA	Control	ModRNA	Control
A/Darwin/9/2021 (A/H3N2)	738	746	222.3 (206.0–240.0)	180.4 (166.6–195.4)
A/Victoria/2570/2019 (A/H1N1)	738	746	397.7 (367.8–430.0)	321.7 (294.6–351.2)
B/Phuket/3073/2013 (B/Yamagata)	736	743	84.5 (79.4–90.0)	115.9 (108.5–123.8)
B/Austria/1359417/2021 (B/Victoria)	734	736	21.3 (19.3–23.6)	70.6 (63.6–78.4)



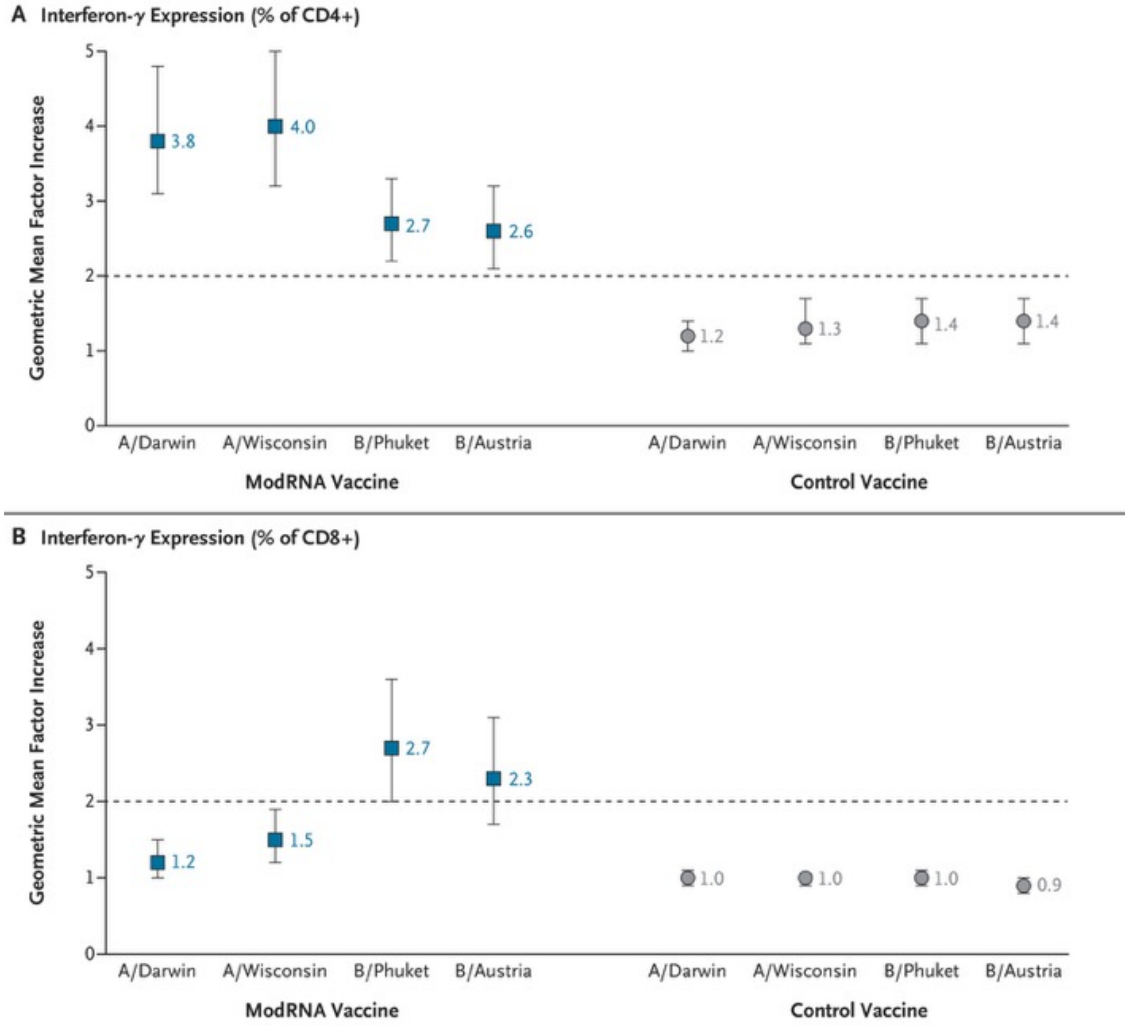
B **Seroresponse Results**

	No. of Participants		Seroresponse (95% CI)	
	ModRNA	Control	ModRNA	Control
			percent	
A/Darwin/9/2021 (A/H3N2)	735	746	64.2 (60.6–67.7)	52.8 (49.2–56.4)
A/Victoria/2570/2019 (A/H1N1)	735	743	66.1 (62.6–69.5)	52.5 (48.8–56.1)
B/Phuket/3073/2013 (B/Yamagata)	736	743	13.9 (11.4–16.6)	29.2 (26.0–32.6)
B/Austria/1359417/2021 (B/Victoria)	731	733	11.4 (9.1–13.9)	51.8 (48.2–55.5)



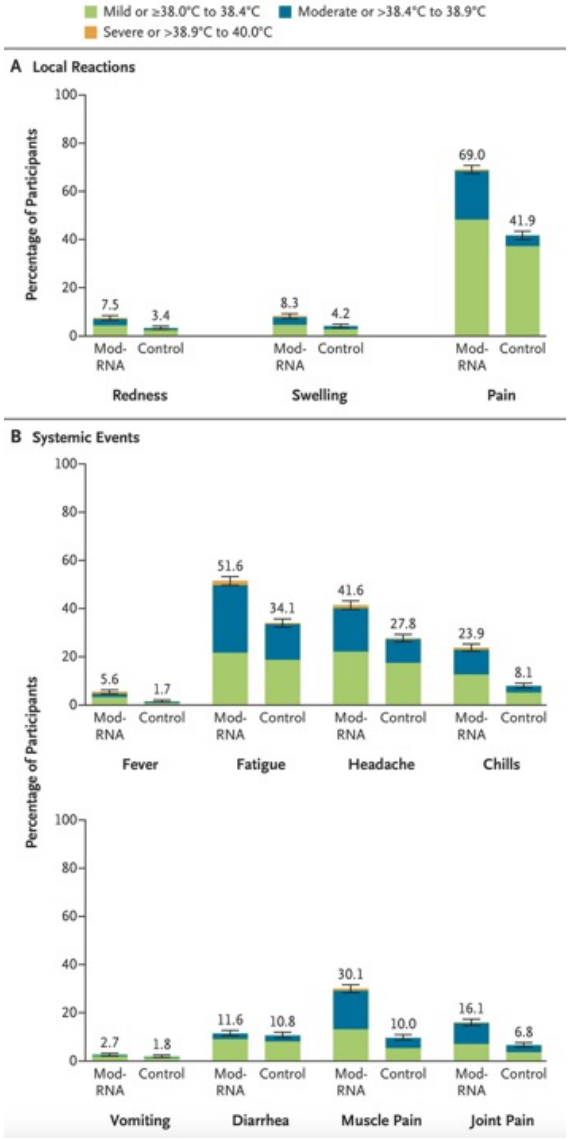
HAI Titer and Seroresponse 4 Weeks after Vaccination, According to Strain.

Shown are HAI geometric mean titers (Panel A) and seroresponse (Panel B) among patients in the evaluable immunogenicity population in the modRNA group and the control group, according to viral strain. The lower limit of quantitation (LLOQ) for each strain-specific HAI titer was 10. Assay results below the LLOQ were set at 0.5×LLOQ for this analysis. The upper limit of quantitation (ULOQ) for A/H3N2, A/H1N1, B/Yamagata, and B/Victoria HAI titers was 5120, 2560, 5120, and 2560, respectively. Assay results above the ULOQ were set to ULOQ+1 for analysis. In Panel A, the geometric mean ratio (GMR) was estimated as the ratio of the HAI titer in the modRNA group to that in the control group. In Panel B, a seroresponse was defined as a titer of less than 1:10 before vaccination and of 1:40 or more at 4 weeks after vaccination or a titer of 1:10 or more before vaccination with a factor increase of four at 4 weeks after vaccination. The difference in seroresponse is expressed as a percentage. In both panels, I bars represent 95% confidence intervals, and the dotted lines represent noninferiority criteria.



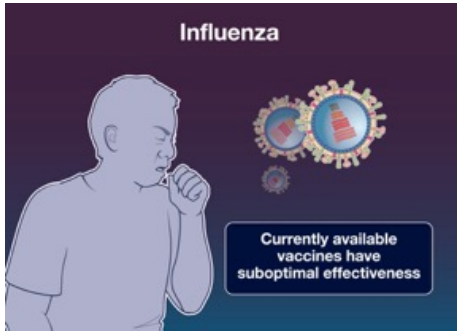
T-Cell Expression of Interferon-γ at 1 Week after Vaccination.

Shown are results in the participants who underwent evaluation of peripheral-blood mononuclear cells for T-cell expression of interferon-γ, according to the percentage of CD4+ and CD8+ cells. The response is reported as the geometric mean factor increase in the T-cell percentage. The LLOQ value for the intracellular cytokine staining assay was 0.00260 for CD4+ cells and 0.01636 for CD8+ cells. Influenza strains that were evaluated included A/Darwin/6/2021 (A/H3N2), A/Wisconsin/588/2019 (A/H1N1), B/Phuket/3073/2013 (B/Yamagata), and B/Austria/1359417/2021 (B/Victoria). Confidence intervals (represented by I bars) were not adjusted for multiplicity and should not be used to infer effects.

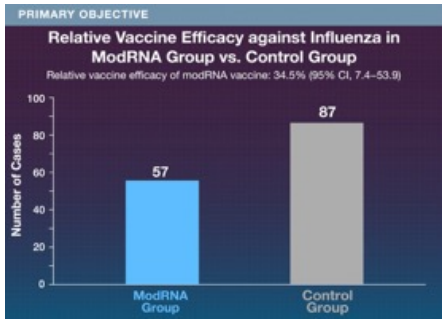


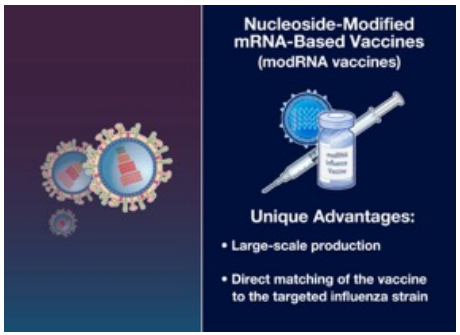
Local Reactions and Systemic Events within 7 Days after Injection.

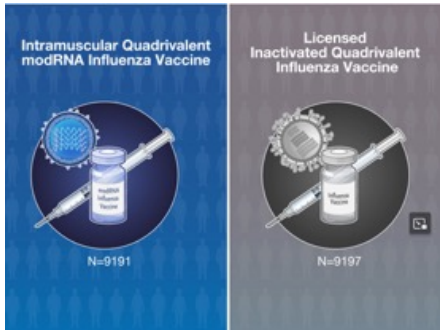
Shown are local reactions (Panel A) and systemic events (Panel B) in 3060 recipients of the modRNA vaccine and in 3067 recipients of the control vaccine. Data are for the participants who kept an electronic diary of reactogenicity events. The demographic characteristics of this population are shown in Table S8. Severity grading scales are summarized in Table S13. The numbers above the bars show the percentage of participants in each group with the specified local reaction (mild, moderate, or severe) or systemic event (temperature range). In the modRNA group, severe redness was reported by 11 participants (0.4%) and severe swelling by 14 participants (0.5%); severe injection-site pain was reported by 17 participants (0.6%) in the modRNA group and 1 participant (<0.1%) in the control group. Fever in a range of 38.9°C to 40.0°C was reported by 24 participants (0.8%) in the modRNA group and 7 participants (0.2%) in the control group; severe fatigue by 51 participants (1.7%) and 13 participants (0.4%), respectively; severe headache by 38 participants (1.2%) and 13 participants (0.4%), respectively; severe chills by 29 participants (0.9%) and 3 participants (<0.1%), respectively; severe diarrhea by 4 participants (0.1%) and 4 participants (0.1%), respectively; severe muscle pain by 25 participants (0.8%) and 7 participants (0.2%), respectively; and severe joint pain by 9 participants (0.3%) and 3 participants (<0.1%), respectively. One participant who received the modRNA vaccine reported having grade 4 diarrhea.

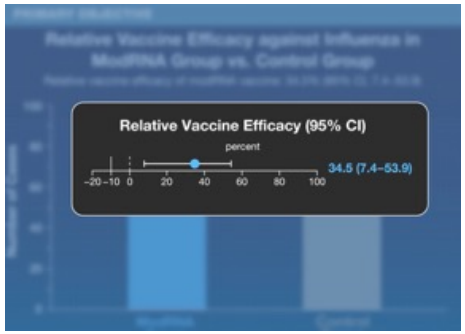

Influenza
Currently available vaccines have suboptimal effectiveness

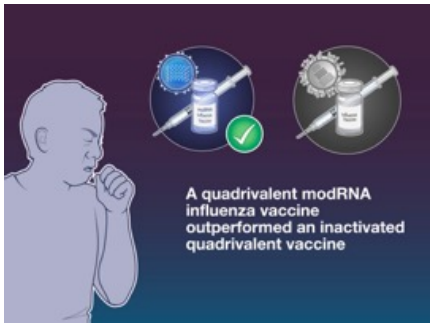

TRIAL
• Phase 3
• Randomized
• Observer-blinded
• U.S.-based trial

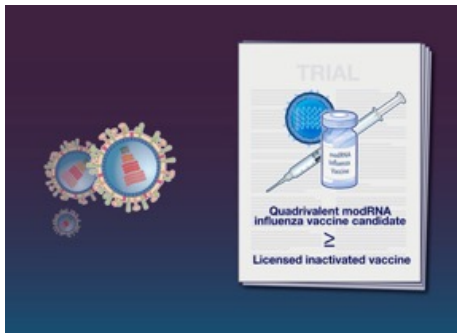

PRIMARY OBJECTIVE
Relative Vaccine Efficacy against Influenza in ModRNA Group vs. Control Group
Relative vaccine efficacy of modRNA vaccine: 34.5% (95% CI, 7.4–53.9)
Number of Cases
100
80
60
40
20
0
57
87
ModRNA Group
Control Group

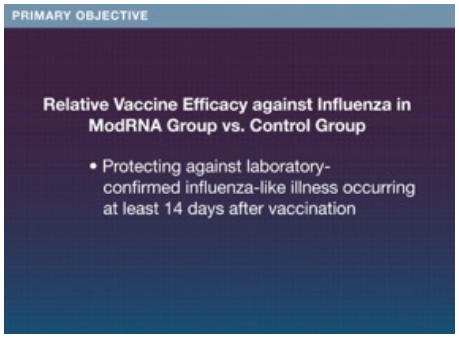

Nucleoside-Modified mRNA-Based Vaccines (modRNA vaccines)
Unique Advantages:
• Large-scale production
• Direct matching of the vaccine to the targeted influenza strain

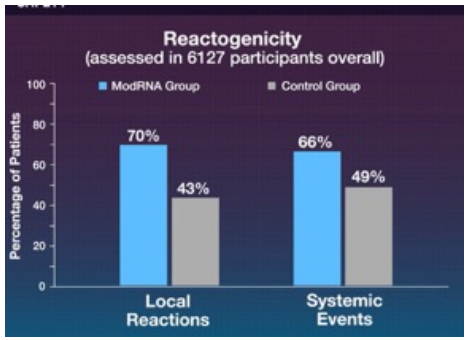

Intramuscular Quadrivalent modRNA Influenza Vaccine
N=9191
Licensed Inactivated Quadrivalent Influenza Vaccine
N=9197


Relative Vaccine Efficacy (95% CI)
percent
34.5 (7.4–53.9)

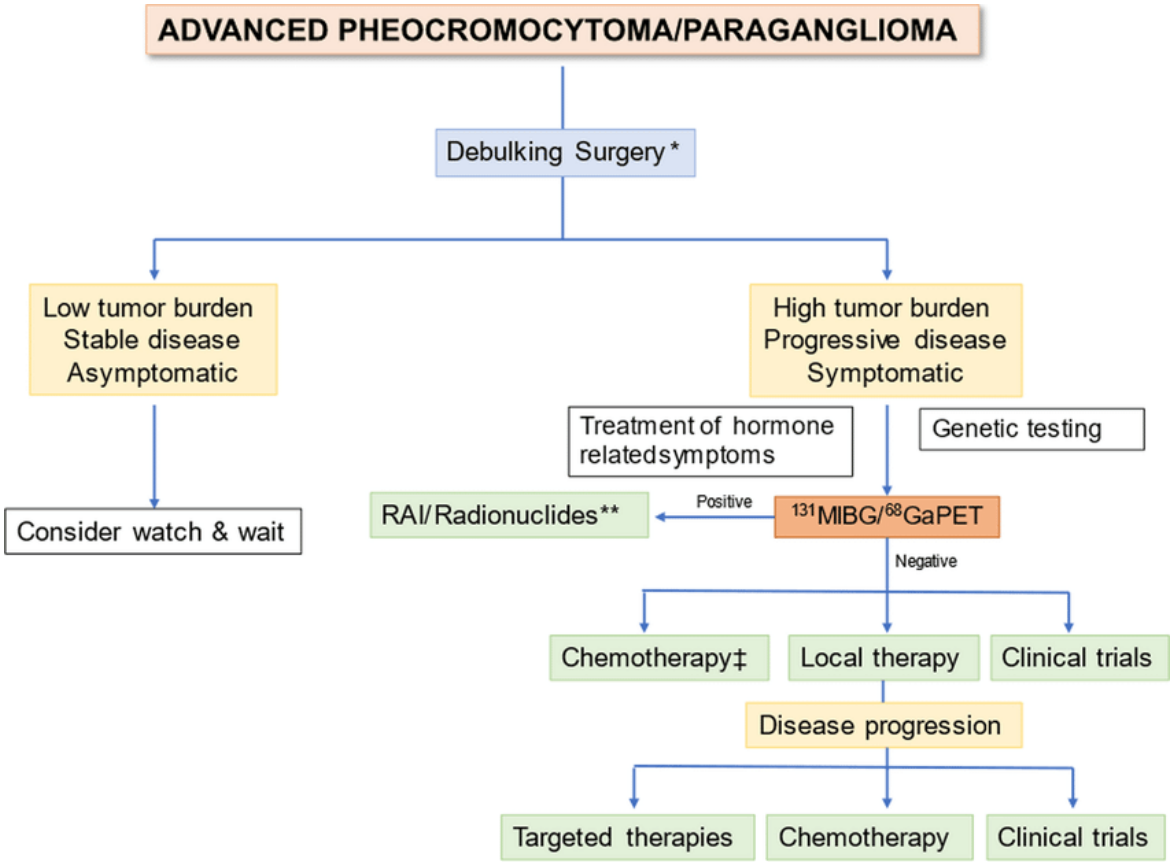

A quadrivalent modRNA influenza vaccine outperformed an inactivated quadrivalent vaccine

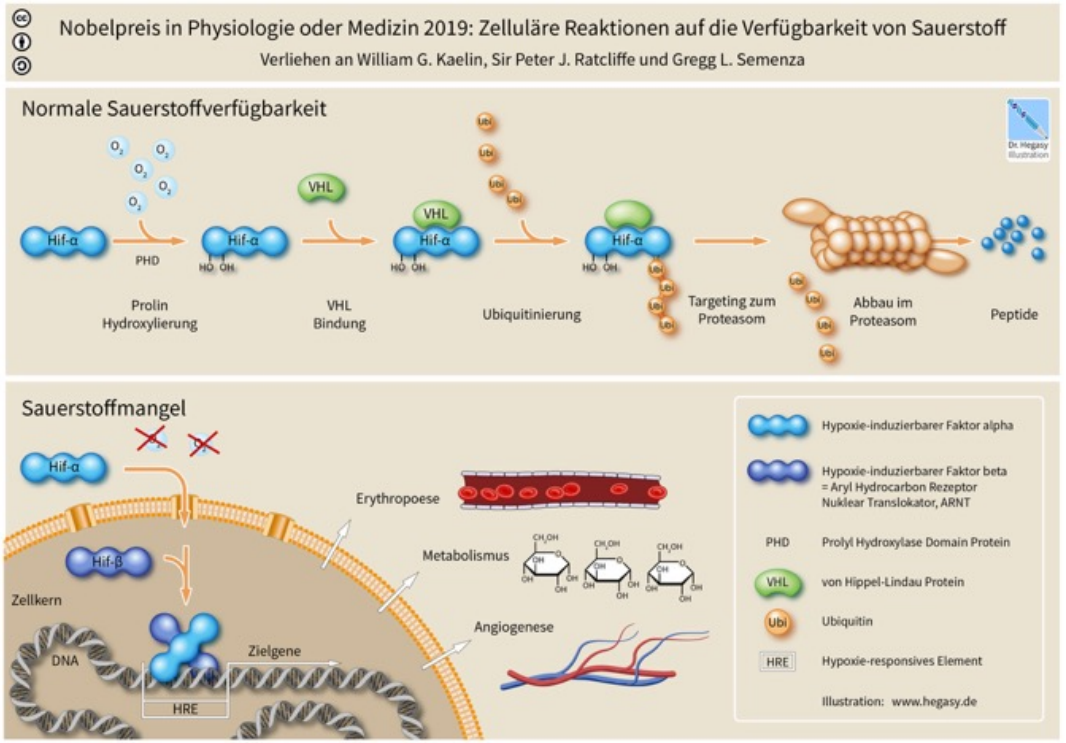

TRIAL
Quadrivalent modRNA influenza vaccine candidate
≥
Licensed inactivated vaccine


PRIMARY OBJECTIVE
Relative Vaccine Efficacy against Influenza in ModRNA Group vs. Control Group
• Protecting against laboratory-confirmed influenza-like illness occurring at least 14 days after vaccination


Reactogenicity
(assessed in 6127 participants overall)
ModRNA Group
Control Group
Percentage of Patients
100
80
60
40
20
0
70%
43%
66%
49%
Local Reactions
Systemic Events

Metastasierendes Phäochromozytom oder Paragangliom, je nach Lokalisation) ist ein seltener, hormonell aktiver Tumor des Nebennierenmarks oder der sympathischen Paraganglien, der durch die Bildung von Fernmetastasen in Organen, die natürlicherweise keine chromaffinen Zellen enthalten (z.B. Knochen, Lunge, Leber), definiert wird.



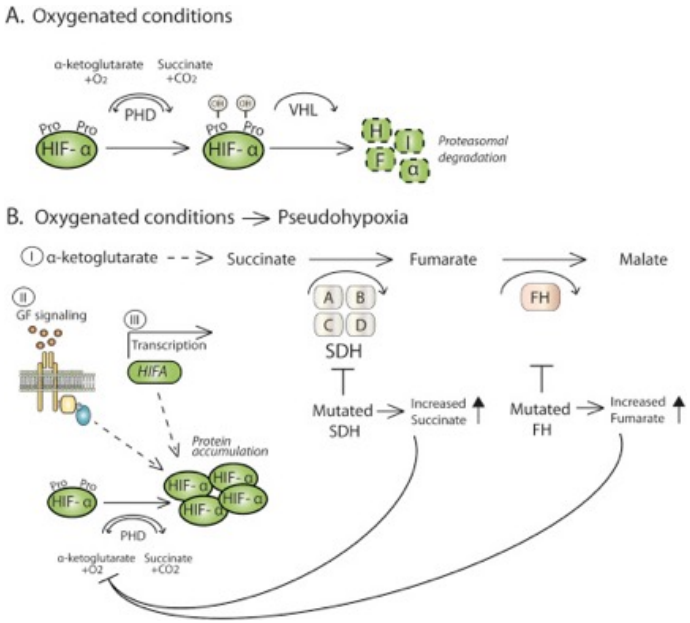


Zelluläre Anpassungsmechanismen an die Verfügbarkeit von Sauerstoff. Bei normaler zellulärer Verfügbarkeit von Sauerstoff wird Hif-1 alpha an zwei Prolin-Resten hydroxyliert und nach der Bindung an VHL und Ubiquitin im Proteasom abgebaut. Bei Sauerstoffmangel transloziert Hif-1 alpha in den Zellkern, wo es als Komplex mit Hif-1 beta an HRE bindet und Gene aktiviert, die z. B. Erythropoese, Glykolyse und Angiogenese steuern. HIF besteht aus einer labilen α-Untereinheit, die in den drei Isoformen HIF-1α, HIF-2α und HIF-3α existiert, und einer β-Untereinheit.

Pseudohypoxia refers to a condition that mimics hypoxia, by having sufficient oxygen yet impaired mitochondrial respiration due to a deficiency of necessary co-enzymes, such as NAD+ and TPP. The increased cytosolic ratio of free NADH/NAD+ in cells (more NADH than NAD+) can be caused by diabetic hyperglycemia and by excessive alcohol consumption. Low levels of TPP results from thiamine deficiency.

The insufficiency of available NAD+ or TPP produces symptoms similar to hypoxia (lack of oxygen), because they are needed primarily by the Krebs cycle for oxidative phosphorylation, and NAD+ to a lesser extent in anaerobic glycolysis. Oxidative phosphorylation and glyocolysis are vital as these metabolic pathways produce ATP, which is the molecule that releases energy necessary for cells to function.

As there is not enough NAD+ or TPP for aerobic glycolysis nor fatty acid oxidation, anaerobic glycolysis is excessively used which turns glycogen and glucose into pyruvate, and then the pyruvate into lactate (fermentation). Fermentation also generates a small amount of NAD+ from NADH, but only enough to keep anaerobic glycolysis going. The excessive use of anaerobic glycolysis disrupts the lactate/pyruvate ratio causing lactic acidosis. The decreased pyruvate inhibits gluconeogenesis and increases release of fatty acids from adipose tissue. In the liver, the increase of plasma free fatty acids results in increased ketone production (which in excess causes ketoacidosis).



Impaired mitochondrial function
Lactate production increased
Ketone production increased

Pseudohypoxia is a key molecular characteristic observed in a specific subgroup of **pheochromocytomas** (PHEOs) and paragangliomas (PPGLs), where cells activate pathways typically associated with low oxygen levels (hypoxia) despite having normal oxygen availability. This is often driven by specific genetic mutations and plays a crucial role in tumor development, behavior, and potential treatment responses.

Mechanism of Pseudohypoxia in Pheochromocytoma

Under normal conditions (normoxia), the hypoxia-inducible factors (HIFs), primarily HIF-1α and HIF-2α, are targeted for degradation by the von Hippel-Lindau (VHL) protein. However, in pseudohypoxia-type (PHT) pheochromocytomas, mutations in certain genes disrupt this process:

- **VHL gene mutations:** Loss-of-function mutations in the *VHL* tumor suppressor gene prevent the VHL protein from binding to HIF-α subunits, leading to their abnormal accumulation and activation, even when oxygen is abundant.
- **SDH gene mutations:** Mutations in genes encoding components of the succinate dehydrogenase (SDH) complex (e.g., *SDHB*, *SDHD*) lead to the accumulation of the oncometabolite succinate. This excess succinate inhibits prolyl-hydroxylase enzymes, which are necessary for HIF-α degradation, thereby stabilizing HIF-α.
- **EPAS1 mutations:** Somatic gain-of-function mutations in the *EPAS1* gene (which encodes HIF-2α) directly lead to the stabilization and activation of HIF-2α.

EPSA1 gene ecodes HIF-2 alpha

The persistent high levels of HIFs, especially HIF-2α, result in the transcription of hypoxia-responsive genes involved in angiogenesis, cell proliferation, and altered metabolism, which contribute to tumorigenesis.

Belzutifan for Advanced Pheochromocytoma or Paraganglioma

Pheochromocytoma and paraganglioma are neoplasms originating in the adrenal medulla and extraadrenal paraganglia, respectively. Most cases of metastatic pheochromocytoma and paraganglioma are driven by dysregulation of the hypoxia-inducible factor 2α (HIF-2α) pathway. Belzutifan is a HIF-2α inhibitor that may provide antitumor activity in patients with advanced pheochromocytoma or paraganglioma.

We conducted a phase 2, international, single-group trial involving 72 participants with locally advanced or metastatic pheochromocytoma or paraganglioma that was not amenable to surgery or curative-intent treatment. Participants received belzutifan at a dose of 120 mg once daily until the occurrence of progression, unacceptable toxic effects, or withdrawal from the trial. The primary end point was confirmed objective response (complete or partial response) as assessed by blinded independent central review. Secondary and other key end points included the duration of response, disease control, progression-free survival as assessed by blinded independent central review, overall survival, safety, and a reduction from baseline in antihypertensive medication.

Conclusions

Belzutifan showed antitumor activity with durable responses in participants with advanced pheochromocytoma or paraganglioma.

Dysregulation of the hypoxia-inducible factor 2α (HIF-2α) pathway is one of the key oncogenic drivers of metastatic pheochromocytoma and paraganglioma. Germline pathogenic variants affecting genes encoding key Krebs cycle enzymes — such as the succinate dehydrogenase subunits (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), *SDHAF2*, fumarate hydratase, and *MDH2* — or affecting components of the hypoxia signaling pathway (*VHL*, *EGLN1*, *EGLN2*, and *HIF2A* [also known as *EPAS1*]) can result in pseudohypoxia and stabilization of HIF-2α. Stable HIF-2α leads to downstream activation of multiple genes that promote tumorigenesis, cell survival, metastasis, and angiogenesis. Most cases of metastatic pheochromocytoma and paraganglioma are characterized by pseudohypoxia, and up to 50% are associated with an *SDHB* germline pathogenic variant. In addition, many pheochromocytomas and paragangliomas that are not associated with the previously described germline pathogenic variants exhibit a similar molecular phenotype of pseudohypoxia.

Belzutifan is a HIF-2α inhibitor that is currently approved for use in adults with von Hippel–Lindau (VHL) disease–associated renal-cell carcinoma, pancreatic neuroendocrine tumors, or hemangioblastomas of the central nervous system, in whom immediate surgery is not clinically indicated. This approval was supported by the results of the LITESPARK-004 trial, in which the objective response with belzutifan was 49% among participants with VHL disease–associated renal cell carcinoma, 83% among those with pancreatic neuroendocrine tumors, and 63% among those with central nervous system hemangioblastomas.

EGLN1 ist ein Gen, das für ein Enzym namens Prolyl-Hydroxylase Domain 2 (PHD2) kodiert, das eine Schlüsselrolle bei der Sauerstoffregulierung im Körper spielt.

Methods

Participants

In the LITESPARK-015 trial, eligible participants were at least 12 years of age, had a documented histopathological diagnosis of pheochromocytoma or paraganglioma that was locally advanced or metastatic and was not amenable to surgery or curative-intent treatment, and had measurable disease as assessed by blinded independent central review.

Trial Design and Treatment

In this phase 2, international, multicenter, open-label, single-group, multicohort trial, eligible participants received belzutifan orally at a dose of 120 mg once daily until the occurrence of progression, unacceptable toxic effects, or withdrawal from the trial by the participant or investigator. The dose of belzutifan could be decreased to 80 mg once daily, and then to 40 mg once daily, to manage unacceptable toxic effects. Treatment beyond the occurrence of radiologic progression was permitted in accordance with the protocol for clinical benefit if the participant's condition was clinically stable.

End Points

The primary end point was objective response, which was defined as a confirmed complete or partial response as assessed by blinded independent central review according to RECIST, version 1.1. Secondary end points were the duration of response, which was defined as the time from the first documented evidence of a complete or partial response until the first documented occurrence of disease progression or death.

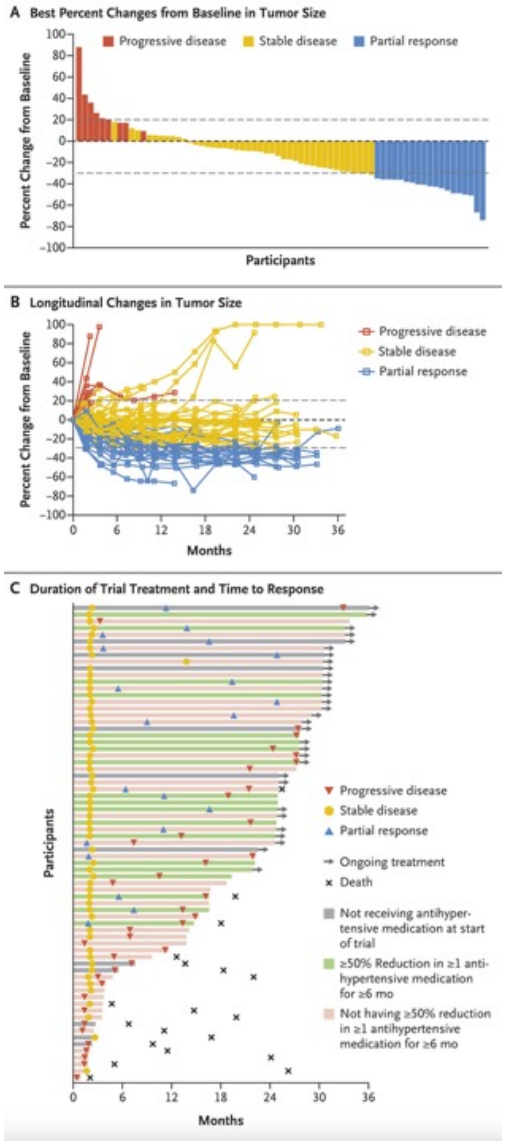
Characteristic	All Participants (N = 72)
Age	
Median (range) — yr	51.5 (22–77)
≥65 yr — no. (%)	9 (12)
Male sex — no. (%)	42 (58)
Geographic region — no. (%)	
North America	21 (29)
Western Europe	46 (64)
Rest of the world	5 (7)
ECOG performance-status score — no. (%)†	
0	39 (54)
1	33 (46)
Previous lines of systemic therapy‡	
Median no. (range)	1 (0–5)
≥1 Previous line of systemic therapy — no. of participants (%)	54 (75)
Previous therapy — no. (%)	
Chemotherapy	36 (50)
Radiopharmaceutical agent	32 (44)
VEGF receptor–tyrosine kinase inhibitor	18 (25)
Other anticancer therapy	5 (7)
Somatostatin-receptor analogue	10 (14)
History of genetic syndrome — no. (%)	
Yes	28 (39)
SDHD-related tumor predisposition syndrome	2 (3)
SDHB-related tumor predisposition syndrome	24 (33)
SDHA-related tumor predisposition syndrome	2 (3)
No	20 (28)
Unknown	24 (33)
Disease type — no. (%)	
Locally advanced	2 (3)
Metastatic	70 (97)
History of hypertension — no. (%)	60 (83)
Diagnosis — no. (%)	
Pheochromocytoma	24 (33)
Paraganglioma	45 (62)
Both pheochromocytoma and paraganglioma	3 (4)
Median tumor burden (range) — mm	84.5 (10–261)
Site of disease or metastasis — no. (%)	
Lymph node	48 (67)
Bone	41 (57)
Liver	23 (32)
Lung	19 (26)
Peritoneum	10 (14)
Other	57 (79)

Antitumor Activity.

Variable	All Participants (N = 72)
Objective response — no.	19
% (95% CI)	26 (17 to 38)
Complete response — no.	0
Partial response — no. (%)	19 (26)
Stable disease — no. (%)	42 (58)
Disease control — no.	61
% (95% CI)	85 (74 to 92)
Median time to response (range) — mo	11.0 (1.7 to 24.8)
Duration of response	
Median (95% CI) (range) — mo	20.4 (8.3 to NR) (5.6+ to 26.6+)†
Kaplan–Meier estimate at 12 mo — %	64
Kaplan–Meier estimate at 24 mo — %	28
Progression-free survival	
Median (95% CI) — mo	22.3 (13.8 to NR)
Kaplan–Meier estimate at 12 mo — %	66
Kaplan–Meier estimate at 24 mo — %	49
Overall survival	
Median (95% CI) — mo	NR (NR to NR)
Kaplan–Meier estimate at 12 mo — %	89
Kaplan–Meier estimate at 24 mo — %	76

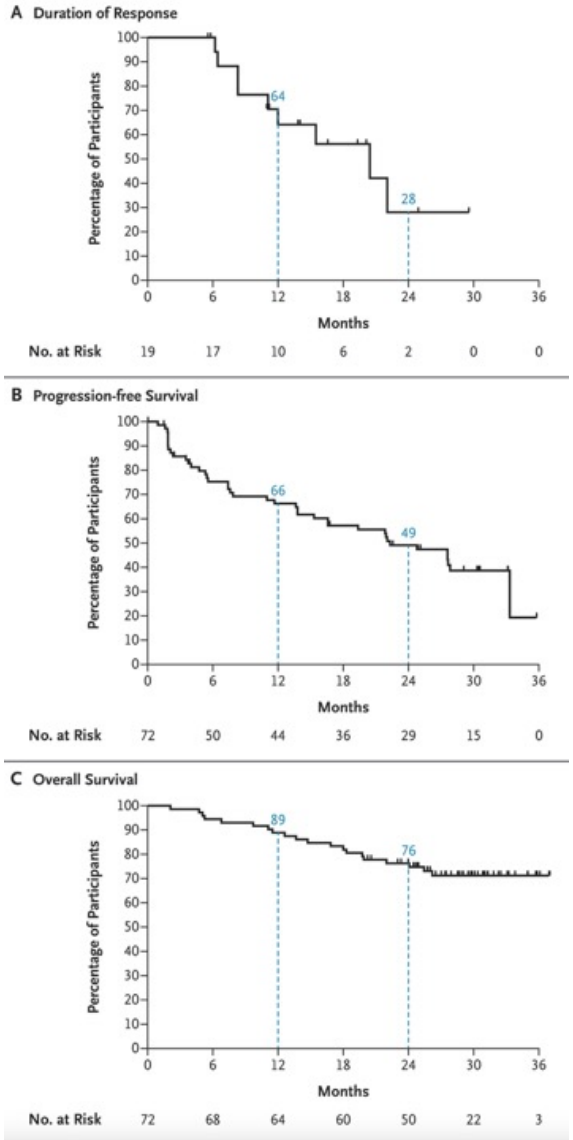
Treatment-Related Adverse Events.

Adverse Event	All Participants (N=72)	
	Any Grade	Grade 3 or 4
	no. (%)	
Any	71 (99)	33 (46)
Led to discontinuation of belzutifan	2 (3)	
Led to dose reduction of belzutifan	9 (12)	
Reported in >10% of participants		
Anemia	63 (88)	16 (22)
Fatigue	23 (32)	3 (4)
Dyspnea	15 (21)	0
Hypoxia	10 (14)	7 (10)
Asthenia	10 (14)	0
Nausea	9 (12)	1 (1)
Peripheral edema	9 (12)	0
Headache	8 (11)	0



Changes in Tumor Size, Duration of Treatment, and Time to Response.

Panel A shows the best percent changes from baseline in pheochromocytoma or paraganglioma tumor size. Panel B shows longitudinal changes in the size of target pheochromocytoma or paraganglioma tumors over time. Panel C shows the duration of the trial treatment and the time to response. In Panel C, the gray bars indicate participants who were not receiving antihypertensive medication at the start of the trial. The green bars indicate participants who were receiving antihypertensive medication at the start of the trial and had a reduction of at least 50% in the total daily dose of at least one antihypertensive medication for at least 6 months. The pink bars indicate participants who were receiving antihypertensive medication at the start of the trial and did not have a reduction of at least 50% in the total daily dose of at least one antihypertensive medication for at least 6 months. One participant had no postbaseline assessment.



Duration of Response, Progression-free Survival, and Overall Survival.

Shown are Kaplan–Meier estimates of duration of response as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Panel A); progression-free survival as assessed by blinded independent central review according to RECIST, version 1.1 (Panel B); and overall survival (Panel C). Tick marks indicate censored data.

Discussion

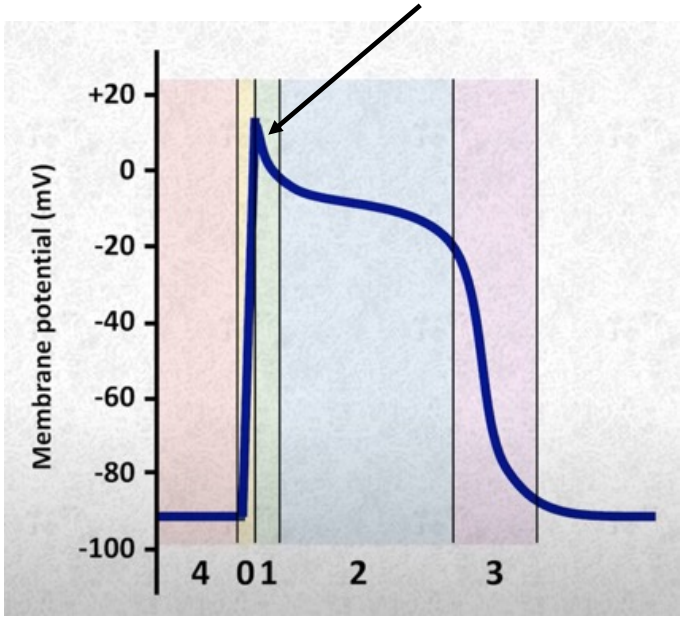
Patients with pheochromocytoma or paraganglioma face substantial health challenges associated with tumor burden, cardiovascular complications related to hypertension, and gastrointestinal symptoms such as constipation due to catecholamine excess. Treatment options for pheochromocytoma and paraganglioma are limited, primarily owing to the paucity of data from small-scale clinical trials, concerns about toxic effects, and the fact that benefits are short-term.

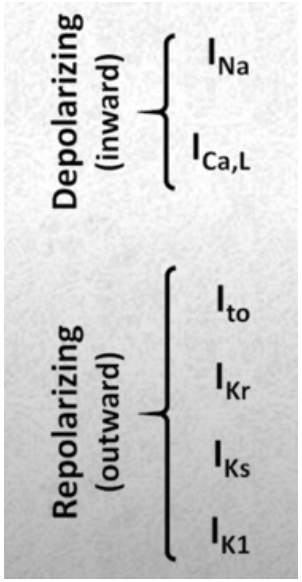
In the current trial, at least one response was noted in prespecified subgroups defined according to age, sex, previous use of tyrosine kinase inhibitors, previous treatment with a radiopharmaceutical agent, number of previous lines of systemic therapy, and a reported history of *SDHB*-related tumor predisposition syndrome. Although the single-group design limits comparative conclusions and interpretation of time-to-event data (progression-free survival and overall survival), the totality of the data shows that belzutifan is clinically active and supports the potential use of belzutifan as a novel treatment option for patients with advanced pheochromocytoma or paraganglioma. Biomarker and genetic analyses are in progress. Pheochromocytoma and paraganglioma remain challenging conditions to manage, but emerging targeted therapies such as belzutifan show promise for improving patient outcomes.

Aktionspotential

„Fast-Response“ wird Numeriert

„Overshoot“





0

2

Depolarisierung

Ionenstrom nach innen

1

3

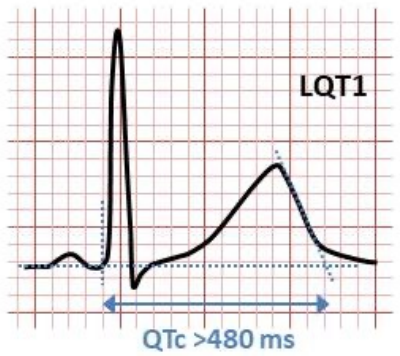
Repolarisierung

3

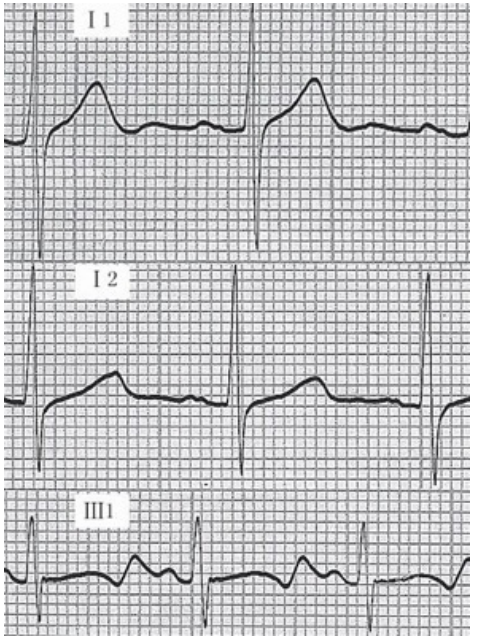
Ionenstrom nach außen

4

Das QT Intervall
(auch Systole genannt)



(25 mm/sek)



Erworbenes Long QT-Syndrom (LQTS)
Erworbene Formen können Arzneimittel-induziert sein, z.B. durch Klasse I- und III-Antiarrhythmika, verschiedene Antibiotika, Psychopharmaka Haloperidol oder infolge einer Hypokaliämie auftreten. Weitere Medikamente, die zu einer Verlängerung der QT-Zeit führen, sind Antihistaminika wie Ebastin, Terfenadin und Astemizol. Auch Arzneistoffe, die bei COVID-19 eingesetzt wurden, wie Chloroquin, Hydroxychloroquin und Azithromycin, können zu einem LQT-Syndrom führen.
Bei einer Hypokaliämie kann die QT-Zeit durch Verschmelzung der T- und U-Wellen nicht bestimmbar sein - man spricht dann von einer "Pseudo-QT-Zeit-Verlängerung".

Long QT Syndrome

To assess a physician's expertise on the basis of whether the doctor checks a patient's QT interval would be excessive, but the fact remains that in many cases, checking it saves lives. The author of a respected textbook on electrocardiography wrote, "The measurement of the QT interval has little usefulness" in 1957 — the same year in which Jervell and Lange-Nielsen published their first report on the association between QT-interval prolongation and sudden death in a family with congenital deafness, which was soon followed by similar findings reported by Romano and colleagues and by Ward in patients with normal hearing. In 1975, Romano–Ward syndrome and Jervell–Lange-Nielsen syndrome were grouped under the name long QT syndrome.

Long QT syndrome is an uncommon disease of genetic origin with a documented prevalence of 1 in 2000 live births; however, the actual prevalence is probably higher because the original prospective study, which involved 44,000 infants, did not include genotype-positive–phenotype-negative persons. The syndrome is characterized by prolongation of the QT interval on an electrocardiogram (ECG) obtained when the patient was at rest and by a propensity for life-threatening arrhythmias that occur mostly under conditions of physical or emotional stress. The clinical importance of the timely diagnosis of the syndrome stems from the fact that sudden cardiac death is often the first symptom, which makes remedying diagnostic or therapeutic errors impossible. Untreated — long QT syndrome is nowadays inexcusable; unfortunately, missed diagnosis is still too often the case.

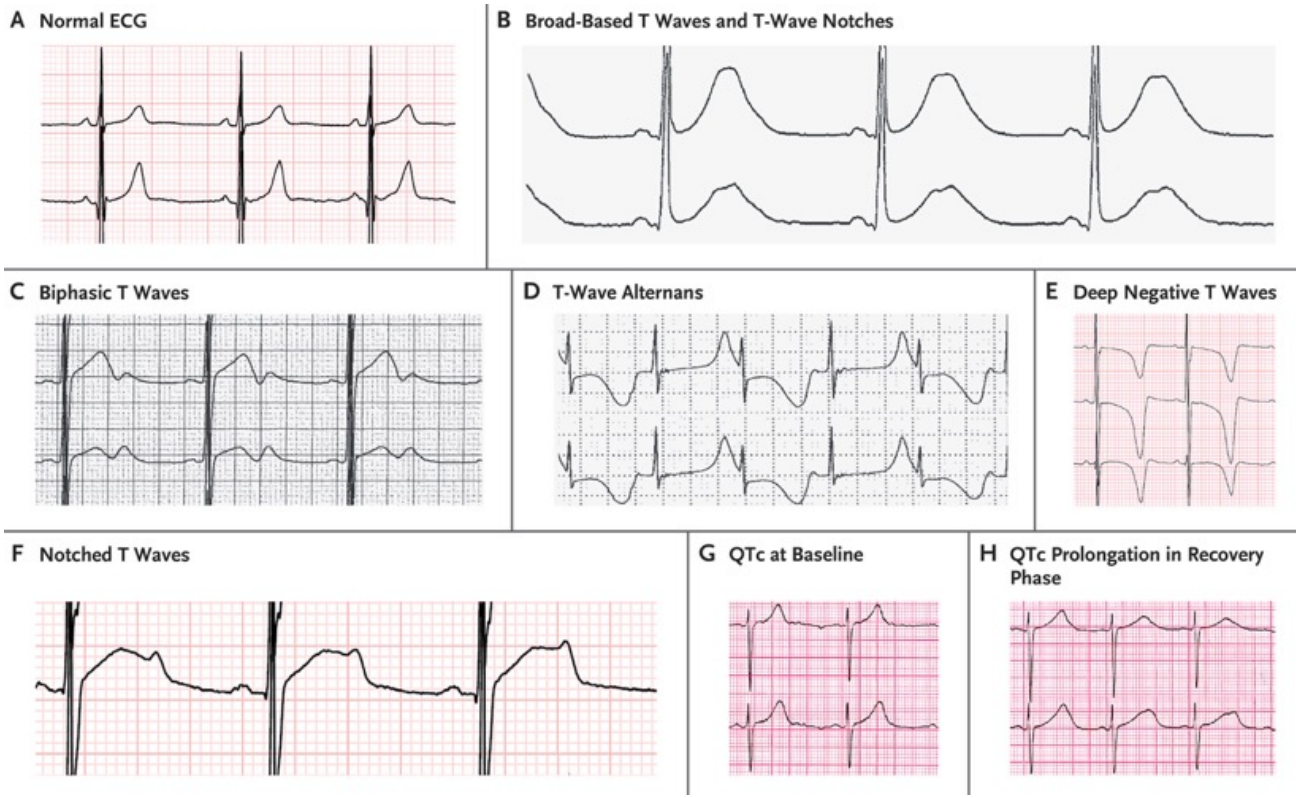
Genetic Basis of Long QT Syndrome

The three major genes associated with long QT syndrome (present in approximately 90% of cases), *KCNQ1, KCNH2*, and *SCN5A*, were identified in 1995 and 1996. Variants in *KCNQ1* and *KCNH2* are the cause of long QT syndrome type 1 and type 2 in approximately 50% and 40% of patients with the syndrome, respectively; these genes encode the potassium channels conducting the outward currents I_{Ks} and I_{Kr}. These channels are critically important for cardiac repolarization, and the reduction in the I_{Ks} and I_{Kr} currents caused by pathogenic variants prolongs the QT interval and causes long QT syndrome. During adrenergic activation, such as during physical activity, the I_{Ks} current becomes the prevalent repolarization current, and this alteration carries major clinical implications — if the QT interval does not appropriately shorten when the heart rate increases, ventricular fibrillation may ensue. The third major gene, *SCN5A*, encodes the voltage-gated sodium channel conducting the major depolarizing inward sodium current I_{Na}. Pathogenic variants of *SCN5A* producing gain of function prolong repolarization and cause long QT syndrome type 3 in approximately 10% of cases. Homozygous or compound heterozygous pathogenic variants in *KCNQ1* and *KCNE1* (encoding subunits of the potassium channel I_{Ks}) cause the recessive Jervell–Lange-Nielsen syndrome associated with congenital deafness.

KEY POINTS

Long QT Syndrome

- Long QT syndrome is a leading cause of sudden death in young persons, with a prevalence exceeding 1 in 2000.
- It is characterized by prolongation of the QT interval, aberrant T-wave morphologic features, and the propensity toward life-threatening arrhythmias triggered mostly by adrenergic activation.
- Long QT syndrome is caused by variants in genes encoding primarily for potassium-ion and sodium-ion channels. Common genetic variants (in modifier genes) increase or decrease the arrhythmic risk linked to the disease-causing variants and can contribute to risk stratification.
- The current therapies — including treatment with beta-blockers, left cardiac sympathetic denervation, and mexiletine — are extremely effective and limit the need for an implantable cardioverter–defibrillator to a small percentage of patients. Genotype-specific management is important. Gene therapy is promising but is not yet ready for clinical use.
- Arrhythmic risk and the approach to therapy need to be reassessed at yearly visits to allow optimization of therapy.

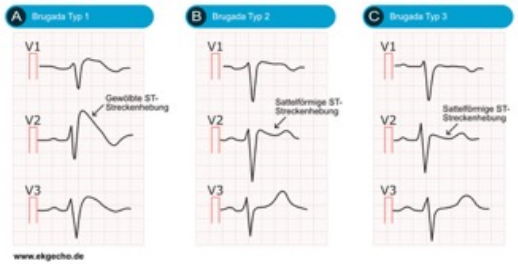


ECG Patterns Suggestive of Long QT Syndrome.

Some electrocardiographic (ECG) patterns are suggestive of long QT syndrome independent of the actual length of the QT interval. Panel A shows a normal ECG and a QT interval corrected for heart rate (QTc) of 417 msec. Panel B shows broad-based T waves and T-wave notches and a QTc of 615 msec. Panel C shows biphasic T waves and a QTc of 577 msec. Panel D shows T-wave alternans, a typical ECG feature of long QT syndrome and a marker of high electrical instability and a QTc of 776 msec. Panel E shows deep negative T waves and a QTc of 673 msec. Panel F shows notched T waves, typical of long QT syndrome type 2, with a QTc of 483 msec. Panel G and Panel H are from the same patient and show QTc prolongation in the recovery phase at the end of an exercise stress test with a QTc of 640 msec (Panel H) as compared with the baseline (Panel G) QTc of 472 msec. The QTc was measured by using the point of return to the baseline of the T wave, and an approximate 10-msec measurement error should be taken into account.

Diagnostic Criteria for LQTS, 1993–2011.

Criteria	Points†
Electrocardiographic results‡	
QTc§	
≥480 msec	3
460 to 479 msec	2
450 to 459 msec, in male patients	1
QTc ≥480 msec at 4 min of recovery from exercise stress test§	1
Torsades de pointes¶	2
T-wave alternans	1
Notched T wave in three leads	1
Low heart rate for age‖	0.5
Clinical history	
Syncope¶	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history**	
≥1 Family member with confirmed LQTS	1
Unexplained sudden cardiac death in immediate family member younger than 30 years of age	0.5



Brugada Syndrom
SCN5A

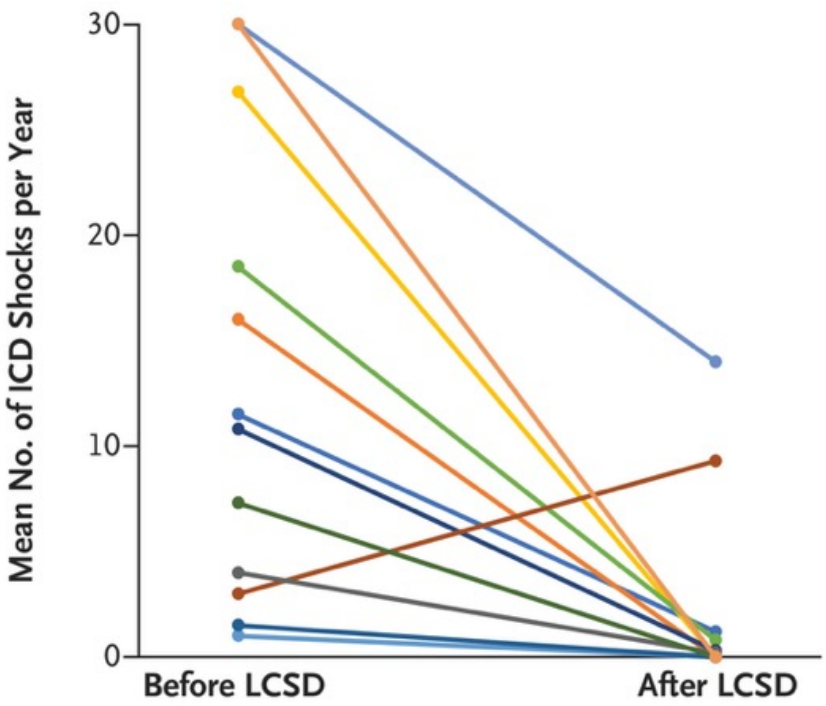
Genotype-Specific Management.

Aspect of Management	LQT1	LQT2	LQT3
Response†			
Beta-blockers	+++	++	++
Left cardiac sympathetic denervation	+++	++	++
Mexiletine	Unknown	++	+++
Triggers or associated events	Adrenergic — strenuous exercise, swimming, and strong emotion	Startle (e.g., sudden, loud noises; alarm clock; telephone ringing), low serum potassium level, in postpartum period	Sleep or rest
Recommendations	Limit strenuous exercise (swimming allowed with supervision by an adult who can swim), avoid verbal or physical confrontations, yearly visit for risk reassessment	Preserve serum potassium level at ≥4 mmol per liter; avoid use of alarm clocks and telephone in the bedroom; beta-blockers taken morning and evening; in postpartum period, share bedroom to provide sleep protection by partner‡; yearly visit for risk reassessment	Potential benefit with home automatic external defibrillator‡ and with bedroom sharing§; yearly visits for risk reassessment

LQT1 ist die häufigste Form des Long-QT-Syndroms, einer genetischen Herzerkrankung, die durch Fehlfunktionen von Kaliumkanälen im Herzen verursacht wird und das Risiko von Herzrhythmusstörungen erhöht. LQT1 wird durch Mutationen im KCNQ1-Gen verursacht, das für die Herstellung des Kaliumkanals verantwortlich ist.

LQT2, mutation im KCNH2-Gen: LQT2 wird durch Mutationen im Gen KCNH2 (auch bekannt als hERG oder HERG1)

LQT3 steht für Long-QT-Syndrom Typ 3, eine seltene, erbliche Herzerkrankung, die durch eine genetische Veränderung im SCN5A-Gen verursacht wird. Dieses Gen ist für den Natriumkanal im Herzen verantwortlich, und bei LQT3 führt eine "Funktionsgewinn"-Mutation dazu, dass dieser Kanal nach einem Herzschlag nicht richtig schließt.



Effects of Left Cardiac Sympathetic Denervation.

Shown are the effects of left cardiac sympathetic denervation (LCSD) on the annual rate of implantable cardioverter–defibrillator (ICD) shocks in 14 patients with long QT syndrome who had recurrent ICD shocks or arrhythmic storms before undergoing LCSD. All 14 patients had more than 1 year of follow-up after undergoing LCSD, 10 (71%) had received at least 10 ICD shocks before LCSD and 11 (79%) were younger than 16 years of age at the time of LCSD.[63,65] These data reflect an overall 90% reduction in the mean yearly number of ICD shocks per patient and a major effect on the patients' quality of life. The number of ICD shocks shown for two patients was capped at 30.

Therapy

The four cornerstones of therapy are beta-blockers, mexiletine, left cardiac sympathetic denervation, and an implantable cardioverter–defibrillator (ICD). These therapies reflect the understanding of the underlying pathophysiology of long QT syndrome. In addition, lifestyle modification, including avoidance of QT-prolonging drugs.

Beta-Blockers

Since the mid-1970s, beta-blockers have represented the mainstay of therapy for patients with long QT syndrome, and their efficacy has been repeatedly confirmed independent of the genotype. The only two beta-blockers that have been confirmed to be effective in the syndrome are propranolol (at a dose of 2.0 to 3.5 mg per kilograms of body weight per day) and nadolol (1.0 to 1.5 mg per kilogram per day). Metoprolol should not be used. Nonadherence to beta-blocker therapy and the use of QT-prolonging drugs are responsible for most life-threatening failures of beta-blocker therapy in persons with long QT syndrome.

Left Cardiac Sympathetic Denervation

Left cardiac sympathetic denervation, now mostly performed by means of thoracoscopy, involves the removal of the lower half of the stellate ganglion to prevent Horner’s syndromeand of the first four thoracic ganglia (T1 to T4).

Mexiletine

In 1995, shortly after the discovery that the *SCN5A* variants causing long QT syndrome were increasing the sodium current, the sodium-channel blocker mexiletine was proposed as the first gene-specific therapy for long QT syndrome type 3, and it is now widely used in these patients with the main goal of shortening the QTc and thereby reducing the risk of arrhythmia.

ICDs

There are large differences in the use of ICDs across the world, with some centers in the United States implanting ICDs in almost 50% of their patients with long QT syndrome, whereas two of the largest clinics in the world treating patients with the syndrome (Mayo Clinic and the Center for Cardiac Arrhythmias of Genetic Origin, Istituto Auxologico Italiano) implant ICDs in approximately 5% of patients with long QT syndrome. An intravenous ICD is preferable to a subcutaneous one because it allows for pacing, which becomes essential whenever an increase in the beta-blocker dose is necessary, either in patients with a very low heart rate or during arrhythmic storms. Implantation of an ICD immediately after a documented cardiac arrest, either with or without beta-blocker therapy, is reasonable. A study that included 233 patients with long QT syndrome who had received an ICD provided critical information and showed that most of the patients had not suffered a cardiac arrest and, moreover, that many had not had a failure of beta-blocker therapy. Asymptomatic patients, almost absent in the long QT syndrome type 1 and type 2 groups, represented 45% of the patient group with type 3, a finding that indicates that the presence of a pathogenic variant in *SCN5A*, even in asymptomatic persons, was deemed to be sufficient for implantation of an ICD. During a mean follow-up of 5 years, an adverse event occurred in 25% of patients.

Acquired Long QT Syndrome

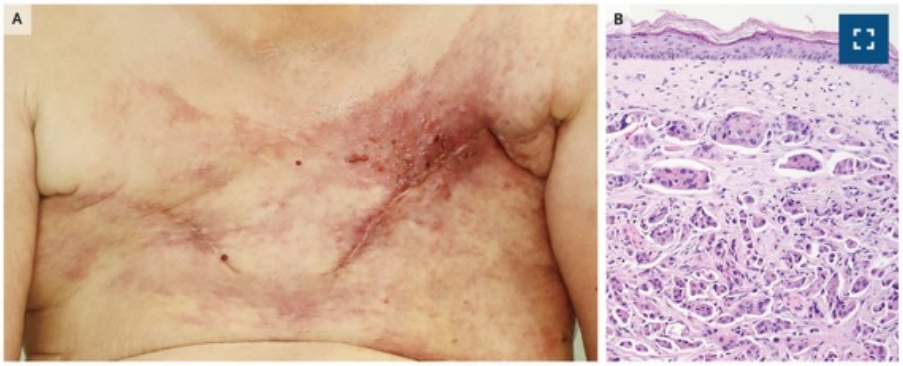
The QT interval may become prolonged under several conditions, including hypokalemia, bradycardia, heart block and, especially, the intake of drugs that share I_{Kr} blocking activity. Acquired long QT syndrome is clinically important because it carries a significant risk for torsades de pointes and sudden cardiac death. Correction of the offending factor prevents recurrences.

Conclusions

Long QT syndrome remains an often-lethal disorder for which effective and safe therapies currently exist, thus allowing normal quality of life for almost all patients. Correct management of the syndrome requires specific expertise, and clinicians should be able to suspect the presence of the disease in order to refer patients to a high-volume center with specific experience in treating patients with long QT syndrome.

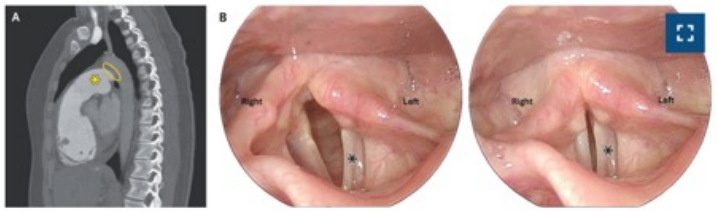
Erworbene Formen können Arzneimittel-induziert sein, z.B. durch Klasse I- und III-Antiarrhythmika, verschiedene Antibiotika, Psychopharmaka Haloperidol oder infolge einer Hypokaliämie auftreten. Weitere Medikamente, die zu einer Verlängerung der QT-Zeit führen, sind Antihistaminika wie Ebastin, Terfenadin und Astemizol. Auch Arzneistoffe, die bei COVID-19 eingesetzt wurden, wie Chloroquin, Hydroxychloroquin und Azithromycin, können zu einem LQT-Syndrom führen. Bei einer Hypokaliämie kann die QT-Zeit durch Verschmelzung der T- und U-Wellen nicht bestimmbar sein - man spricht dann von einer "Pseudo-QT-Zeit-Verlängerung".

Cutaneous Metastases from Breast Carcinoma



A 75-year-old woman with a history of infiltrating ductal carcinoma of the breast presented to the dermatology clinic with a 1-year history of a rash on her chest. Four years before presentation, she had undergone modified radical mastectomy of both breasts, followed by adjuvant hormonal therapy, which was ongoing. Physical examination showed a cluster of papules on an erythematous base along the upper aspect of the surgical scar on the left chest wall (Panel A). Patchy erythema and papules were also scattered across the right chest wall and left anterior shoulder. Histopathological analysis of a skin-biopsy sample obtained from the lesion along the superior aspect of the left chest-wall scar showed large, atypical cells within dermal lymphatic vessels (Panel B, hematoxylin and eosin stain). On immunohistochemical analysis, a specimen stained positive for gross cystic disease fluid protein 15 and GATA3. A diagnosis of cutaneous metastases from breast carcinoma was made. In patients with a history of breast cancer, cutaneous metastases must be considered when a skin eruption resembling erysipelas or cellulitis occurs on the chest wall. The patient was referred to a multidisciplinary team for her recurrent breast cancer. Shortly thereafter, cutaneous metastases spread to her back and a malignant pleural effusion developed. Two months after presentation, the patient died while receiving hospice care.

Ortner's Syndrome in Pulmonary Hypertension



A previously healthy 26-year-old woman was referred to the pulmonary hypertension clinic with a 6-month history of exertional dyspnea and hoarseness. Physical examination was notable for hoarseness (Audio 1). Jugular venous distention was also present, in addition to an S3 gallop over the left lower sternal border and an accentuated pulmonic component of S2. Transthoracic echocardiography showed a dilated right atrium and ventricle with an estimated pulmonary artery systolic pressure of 81 mm Hg. A computed tomographic pulmonary angiogram (Panel A) showed marked dilatation of the main pulmonary artery (yellow asterisk). There was no evidence of thromboembolic disease. Right heart catheterization findings were consistent with the hemodynamic profile of precapillary pulmonary hypertension. A laryngoscopic examination showed left vocal-fold paralysis (Panel B [the asterisk indicates the immobile left side] and video). A diagnosis of Ortner's syndrome due to pulmonary hypertension was made. Ortner's syndrome — also known as cardiovocal syndrome — occurs when the left recurrent laryngeal nerve is compressed between an enlarged cardiovascular structure (in this case, the pulmonary artery) and the aortic arch (the oval in Panel A indicates the region of compression). Hoarseness results from impaired innervation of the ipsilateral intrinsic muscles of the larynx. Treatment with tadalafil and macitentan was started. The patient's dyspnea decreased in severity 1 month later. Four months after starting treatment, the patient's hoarseness had abated (Audio 2), and a repeat laryngoscopic examination showed restored mobility of the left vocal fold.

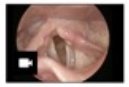
AUDIO

Hoarseness at Presentation
0m 17s
DOWNLOAD

AUDIO

Decreased Hoarseness at 4 Months 0m 18s
DOWNLOAD

VIDEO



Vocal-Fold Paralysis on Laryngoscopy 0m 7s

Case 33-2025: A 27-Year-Old Man with Abnormal Behaviors, Confusion, and Seizure

The patient had been in his usual state of health until 2 months before the current presentation, when his family and outpatient mental health providers noticed abnormal behaviors and an increasing amount of paranoia and confusion after he had independently discontinued his medications prescribed to treat bipolar I disorder. The patient was noted to have repeatedly called his mother; he reported being persecuted, and his mother stated that he had been speaking in nonsensical, cryptic statements. The patient had no recollection of their conversation shortly after each phone call. On the day of admission, the patient became agitated upon trying to sleep, asking for the noise generated by the crickets outside to be silenced, and his partner brought him to the emergency department of this hospital for evaluation.

Discussant

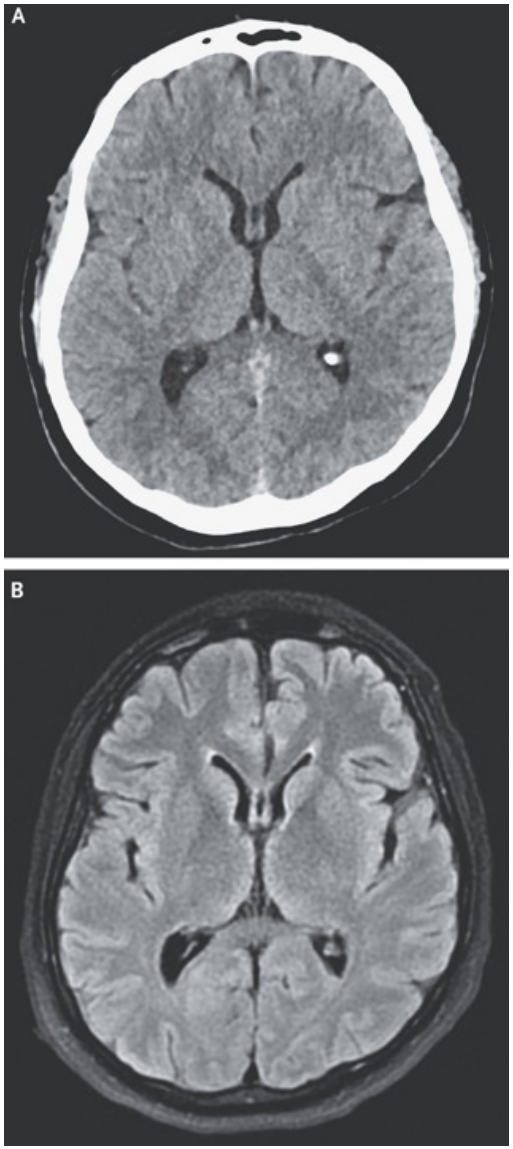
This 27-year-old man with bipolar I disorder, a history of hyperthyroidism, and daily alcohol use presented with a 2-month history of confusion, abnormal behavior, paranoia, nonsensical speech, and short-term memory deficits. The physical examination in the emergency department was notable for disorganized and tangential thinking, impaired orientation and attention, limited short- and long-term recall, and tachycardia.

On the second hospital day, the patient had a tonic–clonic seizure that was witnessed by emergency department personnel. The results of the initial laboratory evaluation, EEG, imaging studies, and CSF analysis were essentially normal except for ketonuria and mild proteinuria. The physical examination was notable for tachycardia and the development of hypertension on the second day of hospitalization. Other features of his medical history to consider include previous lithium therapy and a thyroid disorder for which he had received no treatment other than nonselective beta-blockers. In an attempt to explain this patient's clinical presentation, I will integrate his psychiatric and medical background with the foreground of abnormal behaviors, confusion, new seizure, and ketonuria. To develop a differential diagnosis, I will ask three central questions: First, is this patient having a manic episode? Second, is this patient withdrawing from alcohol? Third, does this patient have thyrotoxicosis?

Variable	Reference Range, Adults, This Hospital†	On Initial Presentation, This Hospital
Blood		
Hemoglobin (g/dl)	13.5–17.5	15.1
Hematocrit (%)	41.0–53.0	47.0
White-cell count (per μl)	4500–11,000	12,600
Differential count (per μl)		
Neutrophils	1800–7700	11,080
Lymphocytes	1000–4800	980
Monocytes	200–1200	420
Eosinophils	0–900	40
Basophils	0–300	50
Immature granulocytes	0–100	40
Platelet count (per μl)	150,000–400,000	363,000
Sodium (mmol/liter)	135–145	143
Potassium (mmol/liter)	3.4–5.0	4.0
Chloride (mmol/liter)	98–108	105
Carbon dioxide (mmol/liter)	23–32	23
Urea nitrogen (mg/dl)	8–25	14
Creatinine (mg/dl)	0.60–1.50	0.87
Glucose (mg/dl)	70–110	148
Globulin (g/dl)	1.9–4.1	3.8
Albumin (g/dl)	3.3–5.0	4.8
Alanine aminotransferase (U/liter)	10–40	13
Aspartate aminotransferase (U/liter)	10–55	16
Alkaline phosphatase (U/liter)	45–115	132
Total bilirubin (mg/dl)	0–1	0.5
Cerebrospinal fluid		
Total protein (mg/dl)	5–55	24
Glucose (mg/dl)	50–75	85
Nucleated-cell count (per μl)	0–5	1
Differential count (%)		
Neutrophils	—	0
Lymphocytes	—	76
Monocytes	—	24
Red-cell count (per μl)	0–5	1
Urine		
Color	Yellow	Yellow
Clarity	Clear	Turbid
pH	5.0–9.0	5.5
Specific gravity	1.001–1.035	1.034
Glucose	Negative	Negative
Ketones	Negative	2+
Leukocyte esterase	Negative	Negative
Nitrite	Negative	Negative
Blood	Negative	Negative
Protein	Negative	1+
Red cells (per high-power field)	0–2	0–2
White cells (per high-power field)	<10	<10
Bacteria	None	None

Bipolar I Disorder

Given the patient's history of bipolar I disorder, we must consider whether this constellation of findings is due to mania. According to the criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), patients with a manic episode with psychotic features must display at least three of the following symptoms (or four if the patient's mood is only irritable), resulting in marked functional impairment: distractibility, impulsivity, grandiosity, flight of ideas, increased activity or agitation, decreased need for sleep, and talkativeness. It is important to note that these phenomena cannot be attributed to substance use or another medical condition. Given his history of psychiatric hospitalizations, and a temporal correlation of symptoms that started after he had discontinued his medications, an affective decompensation of his underlying bipolar I disorder is certainly a possible diagnosis. However, the findings of confusion, impaired attention, short- and long-term recall deficits, seizure, and ketonuria would not be explained by a manic episode related to bipolar I disorder. Taking all these factors into consideration, I wonder whether a medical cause could better explain this patient's presentation.



Alcohol Withdrawal

We are told that this patient has a history of daily alcohol use, and upon arrival at the hospital, he was noted to have an elevated heart rate, for which he received a dose of lorazepam. Subsequently, a generalized tonic–clonic seizure developed within 48 hours after presentation, a critical time period when patients are at peak risk for seizures related to alcohol withdrawal due to a relative γ-aminobutyric acid (GABA) deficiency. Alcohol withdrawal syndrome occurs in patients with consistent, heavy, and daily alcohol use and usually begins within 6 to 12 hours after the last intake of alcohol. Patients commonly present with anxiety, gastrointestinal symptoms, and autonomic manifestations such as diaphoresis, tachycardia, tremor, and hypertension. Complicated alcohol withdrawal is characterized by the development of seizures, perceptual disturbances, agitation, confusion, disorientation, and pyrexia.

Thyrotoxicosis

We are told that the patient has a history of hyperthyroidism and that aside from nonselective beta-blockers, he had received no treatment with antithyroid agents. Multiple features of this patient's case are consistent with a diagnosis of thyrotoxicosis, including the duration of his illness, the presence of maniform symptoms and cognitive impairment, persistent sinus tachycardia, and seizure (a rare finding). In addition, thyroid dysregulation, particularly hyperthyroidism, has been associated with ketonuria, which this patient has, although this is a nonspecific finding in the context of a protracted illness with unclear dietary intake. Furthermore, the remainder of his diagnostic evaluation was largely unrevealing, including normal findings on MRI of the head, EEG, and CSF analysis — all of which would be expected in a patient with hyperthyroidism.

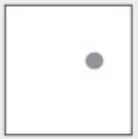
Graves' Disease

Graves' disease is an autoimmune disorder that results in autoantibody-mediated thyroidal activation, which leads to thyrotoxicosis. Neuropsychiatric symptoms of Graves' disease can include anxiety, depression, irritability, emotional lability, and cognitive dysfunction such as memory and concentration problems. More severe neuropsychiatric manifestations, including psychosis, delirium, and seizure, can develop in some patients, but these are rare and usually seen in those with severe thyrotoxicosis.

Lithium-Induced Thyroiditis

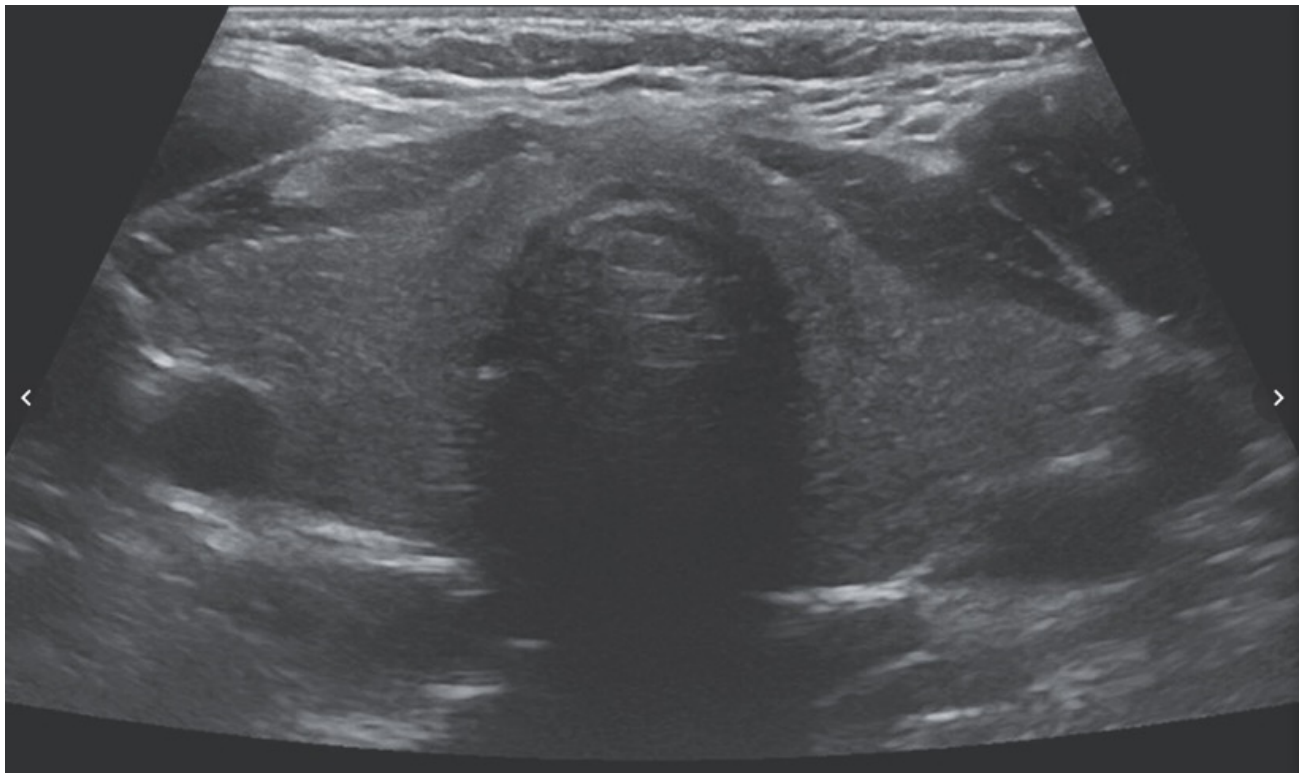
Lithium-induced thyroiditis typically manifests as a painless thyroiditis that is characterized by a triphasic course. First, there is a thyrotoxic phase, during which the thyroid tissue becomes inflamed and releases preformed thyroid hormones, which leads to transient hyperthyroidism. This phase can be asymptomatic or relatively mild and can last for weeks to months, with symptoms and signs including weight loss, tachycardia, heat intolerance, and tremor due to elevated thyroid hormone levels. Neuropsychiatric symptoms of the thyrotoxic phase of thyroiditis are similar to those seen with other causes of hyperthyroidism and include mood symptoms, cognitive changes, sleep disturbance, maniform symptoms, delirium, restlessness, and in rare cases, psychosis or seizures. The thyrotoxic phase is usually followed by the more clinically apparent hypothyroid phase, which is seen once the gland is depleted of hormones or damaged. Most patients then enter the recovery phase, during which thyroid function typically returns to normal within 12 months.

The patient had a thyrotropin level of less than 0.01 mIU per liter (reference range, 0.40 to 5.00), a total thyroxine level of 21.2 µg per deciliter (reference range, 4.5 to 10.9), and a free thyroxine level of 3.7 ng per deciliter (48 pmol per liter; reference range, 0.9 to 1.8 ng per deciliter [12 to 23 pmol per liter]), findings that are consistent with a diagnosis of thyrotoxicosis. From a psychiatric standpoint, the patient's symptoms were most consistent with a diagnosis of psychotic disorder due to another medical condition. Diagnostic criteria include prominent delusions or hallucinations and laboratory evidence confirming that the behavioral disturbance is the direct consequence of another medical condition. In addition, the behavioral disturbance cannot be better explained by another psychiatric condition, does not occur exclusively during delirium, and results in significant distress or impairment — all features that were present in this patient.

	Thyroid Autonomy from Graves' Disease	Thyroid Autonomy from Toxic Nodule	Exogenous Thyroid Hormone	Release of Preformed Hormone	This Patient
T3:T4 ratio	>20	Usually <20	<20	<20	**9.9**
Iodine-123 uptake and scan of the thyroid			No uptake	No uptake	**No uptake**
Thyroid-stimulating immunoglobulin	Present	Absent	Absent	Absent	**Absent**
Thyroid-binding inhibitory immunoglobulin	Present	Absent	Absent	Absent	**Absent**

Identifying the Cause of Hyperthyroidism.

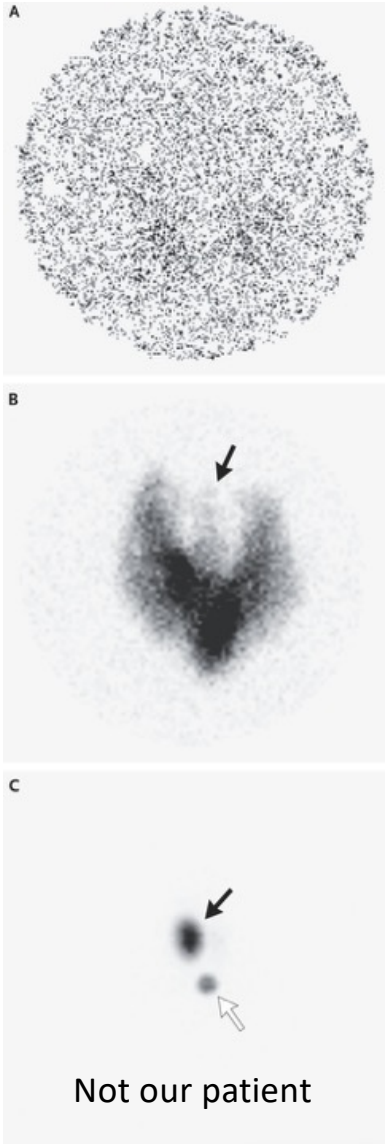
The causes of hyperthyroidism can be distinguished from each other on the basis of the ratio of blood levels of total triiodothyronine (T3, measured in nanograms per deciliter) to thyroxine (T4, measured in micrograms per deciliter), the results of thyroid scintigraphy with measurement of radioactive iodine uptake, and the presence or absence of thyroid-stimulating immunoglobulin and thyrotropin-binding inhibitory immunoglobulin.



Thyroid Ultrasound Image.

A representative screen capture from transverse ultrasonography of the thyroid shows a homogeneous thyroid parenchyma with no defined thyroid nodules.

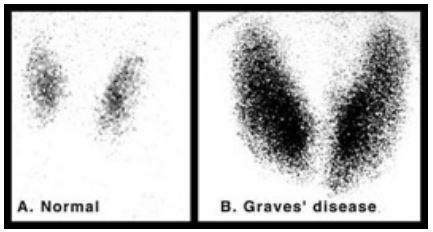
Did this patient's previous lithium use contribute to his current presentation? Typically, lithium exposure confers a high risk of goiter and hypothyroidism. In addition, hyperthyroidism, specifically painless subacute thyroiditis, occurs more often in patients with previous exposure to lithium. It is unclear whether the risk of hyperthyroidism decreases over time after cessation of lithium therapy, and the underlying mechanism remains unknown. Therefore, although it is possible that his painless subacute thyroiditis is linked to lithium use, this is not certain.



Not our patient

Radioactive Iodine Uptake and Scan of the Thyroid.

Thyroid scintigraphy with measurement of radioactive iodine uptake was performed with the use of iodine-123. Panel A shows uniformly decreased uptake of iodine-123 in the thyroid, which could be a result of thyroid hormone release or exogenous thyroid hormone consumption. Panel B shows uniformly increased tracer uptake throughout the thyroid gland and visualization of the thyroid pyramidal lobe (arrow), findings consistent with Graves' disease in the context of hyperthyroidism. Panel C shows a solitary hyperfunctioning autonomous thyroid nodule, also known as a toxic nodule (black arrow), in the right thyroid lobe with suppression of the surrounding thyroid tissue; a sternal notch marker (white arrow) is also shown.



We recommended that the patient continue treatment with beta-blockers, increasing the dose as allowed by his heart rate, to control the symptoms caused by hyperthyroidism. In patients with painless subacute thyroiditis, hyperthyroidism is expected to resolve as preformed thyroid hormone is depleted. Antithyroid agents, such as methimazole and propylthiouracil, interfere with thyrotropin-mediated thyroid hormone production. Given that preformed thyroid hormone drives the symptoms and that production of additional thyroid hormone is suppressed in painless thyroiditis, these agents do not have a role in treatment.

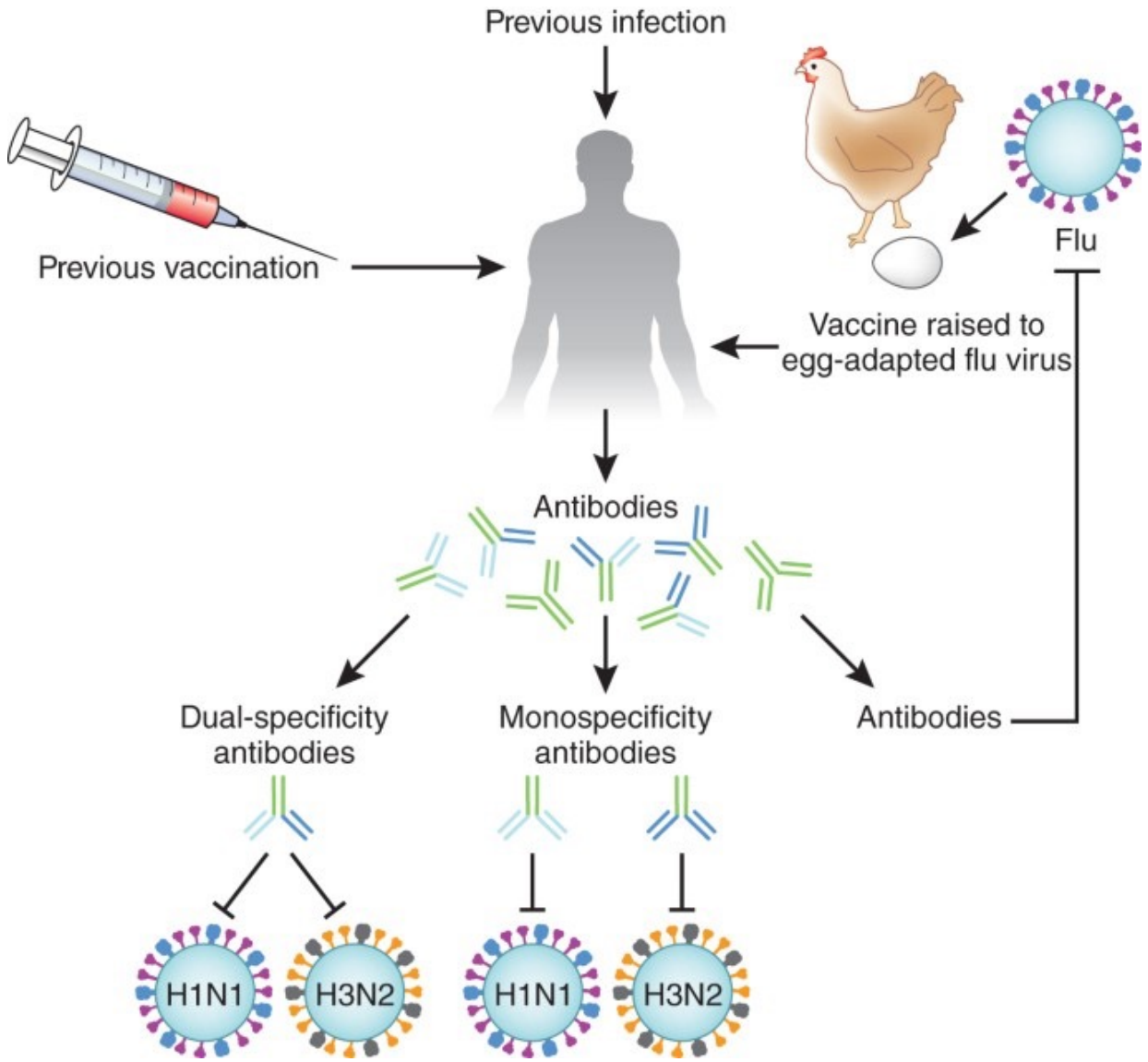
Upon depletion of circulating hormone, temporary hypothyroidism can develop, owing to either delayed recovery from thyrotropin suppression or an inability of the damaged thyroid tissue to produce adequate hormone levels. When hypothyroidism develops in patients with subacute painless thyroiditis, I typically start treatment with levothyroxine. After 6 months, I then stop treatment with levothyroxine and assess whether the patient has normal thyroid function.

Follow-up

The patient's mentation and behavior improved over the next 5 days of hospitalization in the medical service, and no further seizure activity was witnessed. We advised close follow-up in the outpatient endocrine and psychiatric clinics to monitor the results of thyroid-function tests over time and to evaluate him for impending hypothyroidism, as well as to treat his underlying mood disorder. Unfortunately, the patient was lost to follow-up after discharge.

Final Diagnosis

Subacute painless thyroiditis.


Previous infection
Previous vaccination
Flu
Vaccine raised to
egg-adapted flu virus
Antibodies
Dual-specificity
antibodies
Monospecificity
antibodies
Antibodies
H1N1
H3N2
H1N1
H3N2

Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis

Summary

Background Two large-scale trials comparing high-dose inactivated influenza vaccine (HD-IIV) versus standard-dose inactivated influenza vaccine (SD-IIV) against hospitalisation outcomes have been conducted in Denmark and Spain. We aimed to analyse the pooled data from these trials to enhance generalisability and assess the relative vaccine effectiveness (rVE) of HD-IIV versus SD-IIV against severe clinical outcomes in older adults.

Methods FLUNITY-HD was a prespecified, individual-level pooled analysis of two methodologically harmonised pragmatic, individually randomised trials comparing HD-IIV with SD-IIV in older adults. DANFLU-2 included adults aged 65 years or older and GALFLU included community-dwelling adults aged 65–79 years. DANFLU-2 was conducted during the 2022–23, 2023–24, and 2024–25 influenza seasons in Denmark, whereas GALFLU was conducted during the 2023–24 and 2024–25 seasons in Galicia, Spain. In both trials, participants were randomly assigned (1:1) to receive either HD-IIV (60 µg of haemagglutinin [HA] antigen per strain) or SD-IIV (15 µg of HA antigen per strain) and followed up for the occurrence of endpoints from 14 days after vaccination to May 31 the following year in each season. Routine health-care databases were used as primary data source. The primary endpoint of both the pooled analysis and the individual trials was hospitalisation for influenza or pneumonia. Secondary endpoints were tested hierarchically, and consisted of hospitalisation for any cardiorespiratory disease, laboratory-confirmed influenza hospitalisation, all-cause hospitalisation, all-cause mortality, hospitalisation for influenza (ICD-10), and hospitalisation for pneumonia. The pooled analysis is registered with ClinicalTrials.gov, NCT06506812.

Findings The analysis included 466 320 individually randomised participants (233 311 were randomly assigned to HD-IIV and 233 009 to SD-IIV). Mean age was 73·3 years (SD 5·4); 223 681 (48·0%) were female and 242 639 (52·0%) were male. 228 125 (48·9%) participants had at least one chronic condition. The primary endpoint of hospitalisation for influenza or pneumonia occurred in 1312 (0·56%) of 233 311 participants in the HD-IIV group compared with 1437 (0·62%) of 233 009 participants in the SD-IIV group (rVE 8·8%, 95% CI 1·7 to 15·5; one-sided p=0·0082). HD-IIV also reduced the incidence of cardiorespiratory hospitalisation (4720 [2·02%] participants in the HD-IIV group *vs* 5033 [2·16%] participants in the SD-IIV group; rVE 6·3%, 2·5 to 10·0; p=0·0006), laboratory-confirmed influenza hospitalisation (249 [0·11%] participants *vs* 365 [0·16%] participants; rVE 31·9%, 19·7 to 42·2; p<0·0001), and all-cause hospitalisation (19 921 [8·54%] *vs* 20 348 [8·73%]; rVE 2·2%, 0·3 to 4·1; p=0·012). All-cause mortality occurred with similar frequency in both groups (1421 [0·61%] *vs* 1437 [0·62%]; rVE 1·2%, –6·3 to 8·3; p=0·38). ICD-10-coded hospitalisation for influenza occurred in 164 (0·07%) participants in the HD-IIV group and 271 (0·12%) participants in the SD-IIV group (rVE 39·6%, 26·4 to 50·5) and hospitalisation for pneumonia occurred in 1161 (0·50%) participants in the HD-IIV group and 1187 (0·51%) participants in the SD-IIV group (rVE 2·3%, –6·0 to 10·0). The incidence of serious adverse events was similar between groups (16 032 events in the HD-IIV group and 15 857 events in the SD-IIV group).

Interpretation In this prespecified pooled analysis, HD-IIV demonstrated superior protection compared with SD-IIV against hospitalisation for influenza or pneumonia and also reduced the incidence of the secondary endpoints of cardiorespiratory hospitalisation, laboratory-confirmed influenza hospitalisation, and all-cause hospitalisation. Given wide eligibility for influenza vaccination, implementing HD-IIV could result in substantial public health benefits.

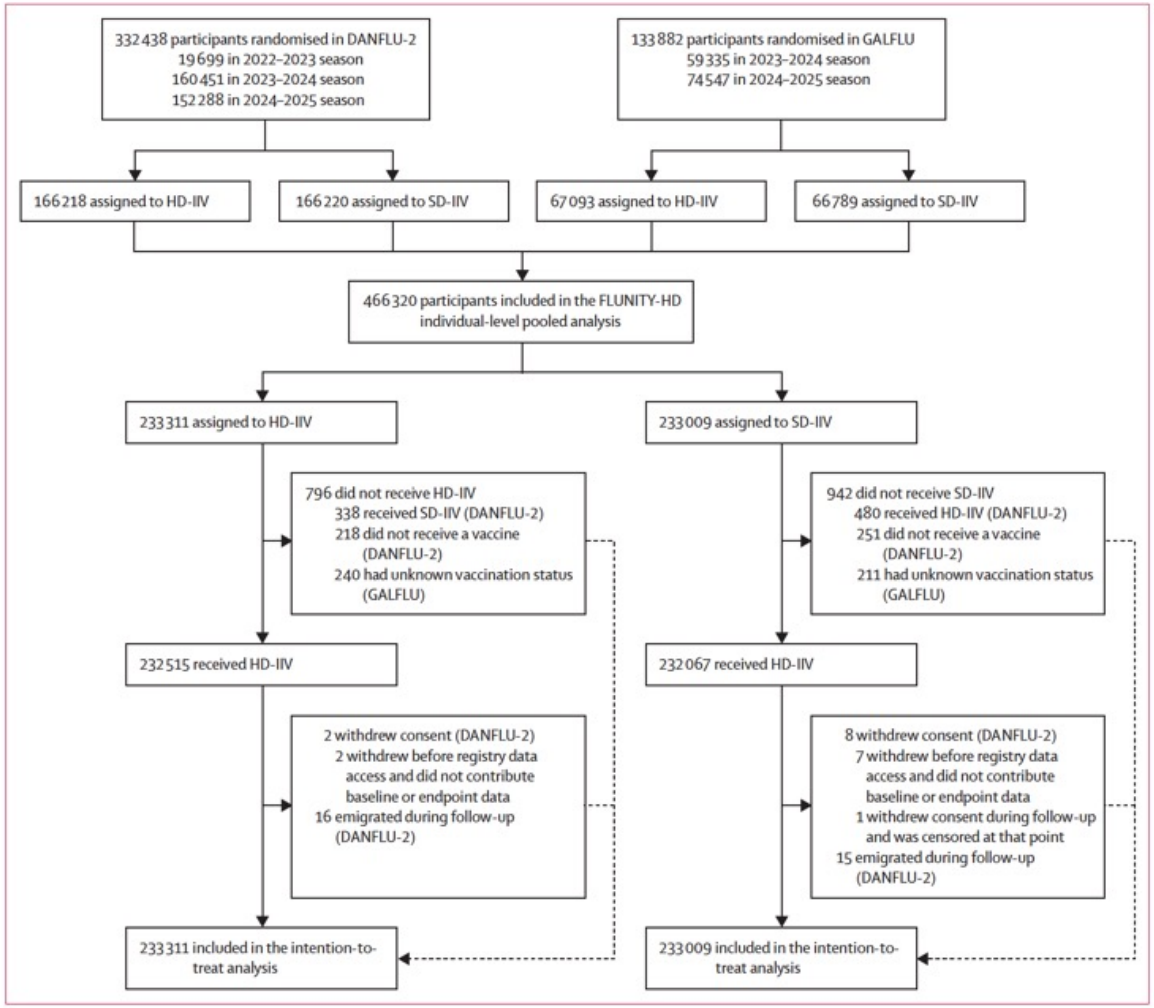


Figure 1: **Study profile**

The individual trials allowed participants to enrol in subsequent seasons, in which case they were randomly assigned to groups again. In DANFLU-2, participants withdrawing consent before registry data access for that particular season did not contribute registry data to the study database, but only contributed data on age, sex, randomisation, and vaccination. HD-IIV=high-dose inactivated influenza vaccine. SD-IIV=standard-dose inactivated influenza vaccine.

	Overall		DANFLU-2		GALFLU	
	HD-IIV group (n=233 311)	SD-IIV group (n=233 009)	HD-IIV group (n=166 218)	SD-IIV group (n=166 220)	HD-IIV group (n=67 093)	SD-IIV group (n=66 789)
Mean age, years (SD)	73·3 (5·4)	73·3 (5·4)	73·7 (5·8)	73·7 (5·8)	72·3 (4·2)	72·3 (4·3)
Female sex	111 809 (47·9%)	111 872 (48·0%)	80 781 (48·6%)	80 757 (48·6%)	31 028 (46·2%)	31 115 (46·6%)
Male sex	121 502 (52·1%)	121 137 (52·0%)	85 437 (51·4%)	85 463 (51·4%)	36 065 (53·8%)	35 674 (53·4%)
Presence of at least one chronic disease	114 073 (48·9%)	114 052 (48·9%)	81 997 (49·3%)	82 166 (49·4%)	25 238 (37·6%)	25 118 (37·6%)
Cardiovascular disease	54 061 (23·2%)	53 639 (23·0%)	45 688 (27·5%)	45 338 (27·3%)	8373 (12·5%)	8301 (12·4%)
Diabetes	32 489 (13·9%)	32 492 (13·9%)	21 929 (13·2%)	21 952 (13·2%)	10 560 (15·7%)	10 540 (15·8%)
Cancer	28 548 (12·2%)	28 455 (12·2%)	22 922 (13·8%)	22 996 (13·8%)	5626 (8·4%)	5459 (8·2%)
Chronic kidney disease	24 062 (10·3%)	24 195 (10·4%)	23 302 (14·0%)	23 486 (14·1%)	760 (1·1%)	709 (1·1%)
Atrial fibrillation	19 179 (8·2%)	19 043 (8·2%)	17 076 (10·3%)	17 009 (10·2%)	2103 (3·1%)	2034 (3·0%)
Ischaemic heart disease	19 033 (8·2%)	18 809 (8·1%)	15 666 (9·4%)	15 446 (9·3%)	3367 (5·0%)	3363 (5·0%)
Chronic lung disease	16 022 (6·9%)	15 954 (6·8%)	13 575 (8·2%)	13 577 (8·2%)	2447 (3·6%)	2377 (3·6%)
Chronic obstructive pulmonary disease	8252 (3·5%)	8100 (3·5%)	6799 (4·1%)	6689 (4·0%)	1453 (2·2%)	1411 (2·1%)
Heart failure	6497 (2·8%)	6536 (2·8%)	5201 (3·1%)	5209 (3·1%)	1296 (1·9%)	1327 (2·0%)
Immunosuppression	12 308 (5·3%)	12 308 (5·2%)	7187 (4·3%)	7128 (4·3%)	5121 (7·6%)	5180 (7·8%)
Co-administration with COVID-19 vaccine	165 412 (70·9%)	165 424 (71·0%)	102 242 (61·5%)	102 481 (61·7%)	63 170 (94·2%)	62 943 (94·2%)
COVID-19 vaccine during same season	224 353 (96·2%)	224 055 (96·2%)	160 436 (96·5%)	160 432 (96·5%)	63 917 (95·3%)	63 623 (95·3%)
Pneumococcal vaccination after age 65 years	184 946 (79·3%)	185 170 (79·5%)	140 432 (84·5%)	140 414 (84·5%)	44 514 (66·3%)	44 756 (67·0%)

Data are n (%), unless otherwise indicated. Baseline characteristics were sourced from nationwide administrative health registries using prespecified definitions (appendix pp 5–14,32–39). In DANFLU-2, nine participants withdrew consent before registry data linkage; therefore, these participants did not contribute baseline data other than age and sex. Due to data availability, DANFLU-2 and GALFLU used different definitions for chronic kidney disease and immunosuppression. COVID-19 co-administration was defined as receiving COVID-19 vaccination on the same day as the study vaccine. HD-IIV=high-dose inactivated influenza vaccine. SD-IIV=standard-dose inactivated influenza vaccine.

Table 1: **Baseline characteristics of participants**

	HD-IIV (n=233 311)	SD-IIV (n=233 009)	Crude relative vaccine effectiveness (95% CI)	Adjusted relative vaccine effectiveness (95% CI)	One-sided p value	Number needed to vaccinate (95% CI)
Primary endpoint						
Hospitalisation for influenza or pneumonia	1312 (0·56%)	1437 (0·62%)	8·8% (1·7 to 15·5)	8·7% (1·7 to 15·3)	0·0082	1839 (1049 to 9756)
Secondary endpoints						
Hospitalisation for any cardiorespiratory disease	4720 (2·02%)	5033 (2·16%)	6·3% (2·5 to 10·0)	6·3% (2·5 to 9·9)	0·0006	730 (463 to 1832)
Laboratory-confirmed influenza hospitalisation	249 (0·11%)	365 (0·16%)	31·9% (19·7 to 42·2)	31·9% (20·0 to 42·0)	<0·0001	2003 (1511 to 3233)
All-cause hospitalisation	19 921 (8·54%)	20 348 (8·73%)	2·2% (0·3 to 4·1)	2·2% (0·3 to 4·0)	0·012	515 (278 to 3929)
All-cause mortality	1421 (0·61%)	1437 (0·62%)	1·2% (–6·3 to 8·3)	1·2% (–6·3 to 8·2)	0·38	..
Hospitalisation for influenza (ICD-10)	164 (0·07%)	271 (0·12%)	39·6% (26·4 to 50·5)	39·6% (26·7 to 50·2)	NA	..
Hospitalisation for pneumonia	1161 (0·50%)	1187 (0·51%)	2·3% (–6·0 to 10·0)	2·2% (–6·0 to 9·8)	NA	..

Endpoints occurring between 14 days after vaccination and May 31 the following year were defined as eligible for analysis. Only first events were considered for each endpoint. Median follow-up was 232 days (IQR 211–239). Endpoints were ascertained using data from Danish and Galician administrative health registries. Prespecified endpoint definitions are shown in the appendix pp 15–22. The endpoint of hospitalisation for influenza required an ICD-10 code for influenza but did not require a positive influenza test, whereas the endpoint of laboratory-confirmed influenza hospitalisation required a positive influenza test between 14 days before and 3 days after hospital admission but no specific ICD-10 code. Relative vaccine effectiveness was calculated as 1 minus the relative risk of the outcome. p values were estimated using binomial tests, corresponding to the crude relative vaccine effectiveness estimates. The adjusted relative vaccine effectiveness estimates are adjusted for trial and for season and generated using log-binomial regression models. NA denotes not applicable since p values are reported only for endpoints formally tested in the hierarchical testing procedure. Number needed to vaccinate describes the number of individuals needed to be vaccinated with HD-IIV instead of SD-IIV to prevent one additional event and is calculated only for endpoints with significant relative vaccine effectiveness estimates. HD-IIV=high-dose inactivated influenza vaccine. NA=not applicable. SD-IIV=standard-dose inactivated influenza vaccine.

Table 2: **Effectiveness endpoints**

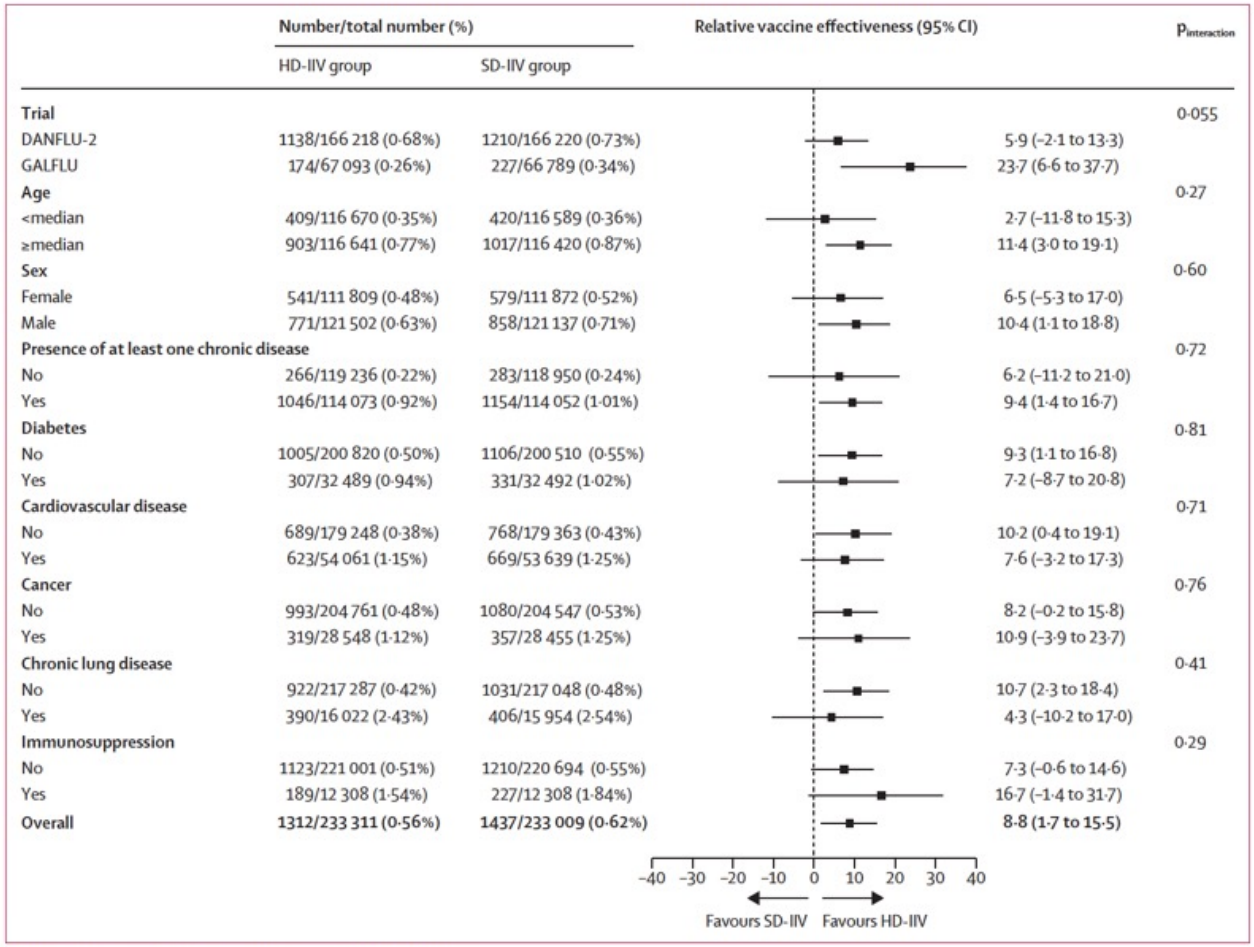


Figure 2: **Primary endpoint in major prespecified subgroups**

The primary endpoint was hospitalisation for influenza or pneumonia. Relative vaccine effectiveness was calculated as 1 minus the relative risk. Median age was 72·7 years. p values for interaction were estimated by including interaction terms in log-binomial regression models adjusted for trial and season. HD-IIV=high-dose inactivated influenza vaccine. SD-IIV=standard-dose inactivated influenza vaccine.

Research in context

Evidence before this study

Older adults (aged ≥65 years) are at increased risk of severe influenza-related complications compared with younger adults. Although vaccination remains the most effective means of reducing burden, traditional standard-dose inactivated influenza vaccines (SD-IIV) confer suboptimal protection in this vulnerable population. High-dose inactivated influenza vaccine (HD-IIV) was developed to improve protection in older adults and has demonstrated superior efficacy compared with SD-IIV against laboratory-confirmed influenza infection. Previous data have suggested benefits of HD-IIV over SD-IIV against severe clinical outcomes, but limited evidence exists from adequately powered individually randomised studies. As part of a previous meta-analysis (Skaarup et al, 2024), we reviewed existing literature on HD-IIV's relative vaccine effectiveness (rVE) versus SD-IIV via a PubMed and Embase search on May 22, 2023, combining groups of search terms for influenza, vaccine, high-dose and trial/randomised using the Boolean "OR" within groups and "AND" between groups (no date or language restrictions; excluded studies conducted during the 2009–10 influenza pandemic). The five smaller randomised trials included were meta-analysed (n=105 685), showing significantly lower incidence of hospitalisation-based outcomes with HD-IIV than with SD-IIV; however, a need remained for high-quality, adequately powered individually randomised studies to confirm these findings.

Added value of this study

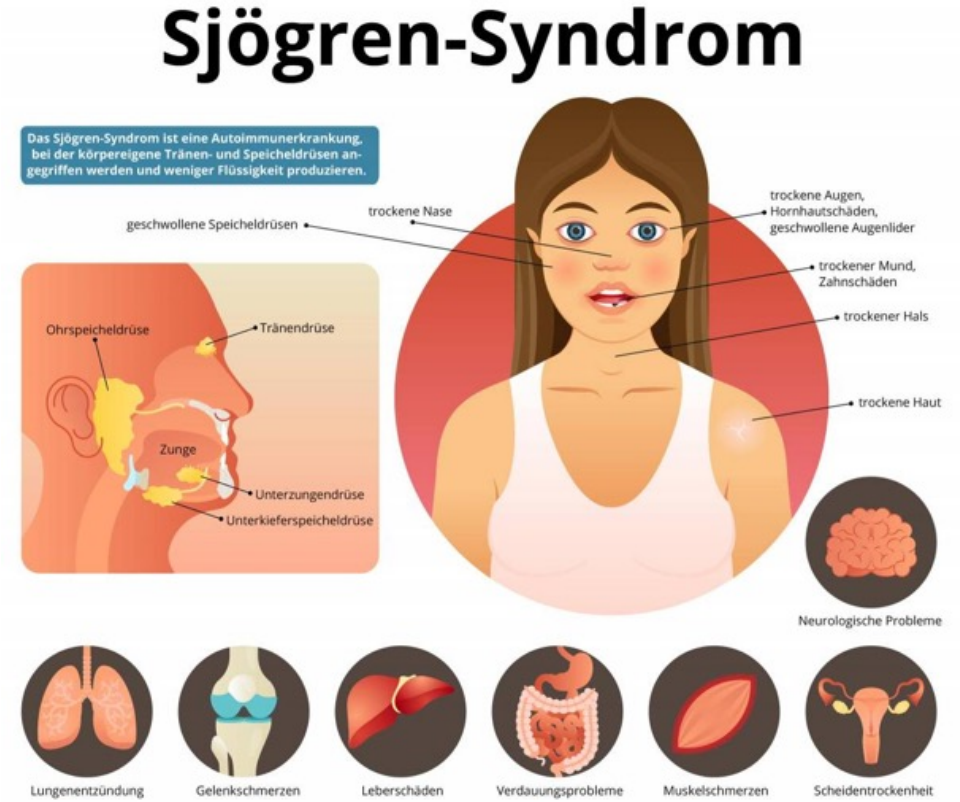
FLUNITY-HD is a large influenza vaccine effectiveness analysis conducted among individually randomised older adults, assessing the rVE of HD-IIV versus SD-IIV against severe clinical outcomes, including hospitalisations, across 466 320 older adults over two geographical areas and three seasons. As a prespecified pooled analysis of two a priori methodologically harmonised individually randomised trials, this study included more than four times the number of randomised older adults as the post-hoc meta-analysis of non-harmonised RCTs (Skaarup et al, 2024). Designed to assess the rVE of HD-IIV versus SD-IIV against severe outcomes beyond influenza infection, the study provides the first definitive evidence of the superior protection of HD-IIV versus SD-IIV against hospitalisation outcomes including due to influenza or pneumonia. HD-IIV also reduced the incidence of the secondary endpoints of cardiorespiratory hospitalisation, laboratory-confirmed influenza hospitalisation, and all-cause hospitalisation—severe outcomes of great importance to patients, clinicians, and decision makers. To our knowledge, no influenza vaccine tailored for older adults has previously demonstrated superior rVE against hospitalisations versus SD-IIV in a powered, individually randomised study to date. These findings confirm the full breadth of protection conferred by HD-IIV beyond influenza infection, from specific laboratory-confirmed influenza hospitalisations to broader all-cause hospitalisations, consistently across seasons.

Implications of all the available evidence

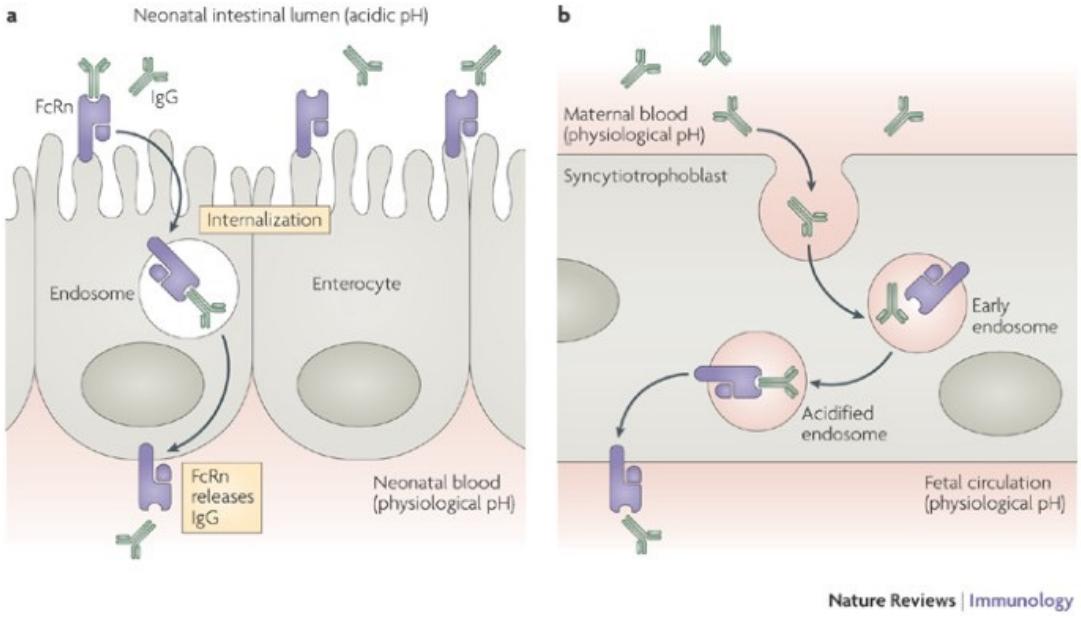
This critical and timely evidence will inform evidence-based decision making by health-care providers, policy makers, and immunisation technical advisory groups, contributing to potential optimisation of influenza vaccination strategies in the vulnerable older adult population globally. At an estimated 515 older adults needed to be vaccinated with HD-IIV instead of SD-IIV to prevent one all-cause hospitalisation, a simple switch from SD-IIV to HD-IIV could substantially reduce the burden of influenza on health systems.

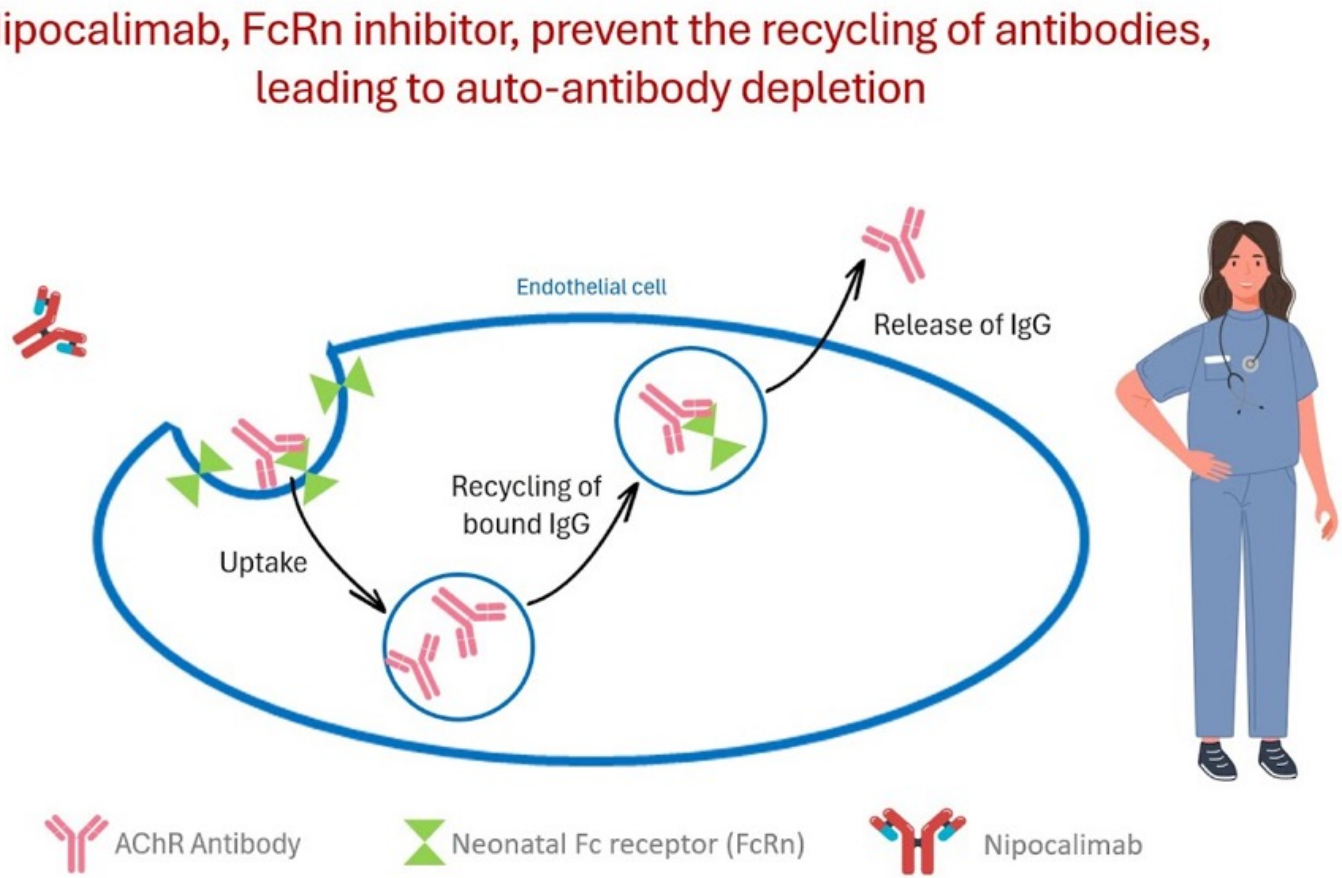
Das Sjögren-Syndrom ist eine chronische, Autoimmunerkrankung, bei der das Immunsystem die eigenen Tränen- und Speicheldrüsen angreift, was zu Symptomen wie trockenen Augen und Mundtrockenheit führt. Es ist eine systemische Erkrankung, die auch andere Organe wie Lunge, Nieren oder Nerven beeinträchtigen und Symptome wie Gelenkentzündungen (Arthritis), Müdigkeit und Hautausschläge verursachen kann. Die Behandlung zielt darauf ab, die Symptome zu lindern, da die Krankheit derzeit nicht heilbar ist.

The main antibodies involved in Sjögren's syndrome are **anti-Ro (SS-A)** and **anti-La (SS-B)** autoantibodies.



Der neonataler Fc-Rezeptor (FcRn) ist ein Protein, das eine zentrale Rolle bei der Regulation der Immunglobulin-G (IgG)- und Albumin-Spiegel im Blutkreislauf spielt. Er ist strukturell mit den MHC-Klasse-I-Molekülen verwandt, bindet jedoch keine Antigene, sondern schützt IgG-Antikörper vor dem Abbau. Er ist strukturell mit den MHC-Klasse-I-Molekülen verwandt, bindet jedoch keine Antigene, sondern schützt IgG-Antikörper vor dem Abbau.
Verlängerung der Halbwertszeit von IgG: IgG-Antikörper haben im Vergleich zu anderen Immunglobulinen eine außergewöhnlich lange Halbwertszeit von etwa 21 Tagen im menschlichen Serum. Dies liegt daran, dass der FcRn sie in Endosomen bindet (bei saurem pH-Wert) und vor dem lysosomalen Abbau schützt, indem er sie zurück in den Blutkreislauf schleust (bei neutralem pH-Wert).





Nipocalimab wirkt, indem er den neonatalen Fc-Rezeptor (FcRn) blockiert, was zu einer Reduzierung der IgG-Antikörperspiegel führt. Dadurch werden die schädlichen Autoantikörper abgebaut, die bei Myasthenia gravis die neuromuskuläre Synapse angreifen.

Efficacy and safety of nipocalimab in patients with moderate-to-severe Sjögren's disease (DAHLIAS): a randomised, phase 2, placebo-controlled, double-blind trial

Summary

Background Sjögren's disease is characterised by mucosal dryness, fatigue, chronic pain, systemic organ involvement, and elevated autoreactive IgG antibodies. There are no approved disease-modifying treatments. Therefore, we aimed to evaluate nipocalimab, a neonatal Fc receptor blocker that reduces circulating IgG, including autoantibodies, in patients with Sjögren's disease.

Methods This phase 2, double-blind, multicentre trial enrolled individuals with moderate-to-severe, active Sjögren's disease (ie, Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index [ClinESSDAI] of at least 6) who were seropositive for anti-Ro IgG autoantibodies. Participants were recruited from 69 centres across France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, Spain, Taiwan, and the USA. These centres included rheumatology centres, hospitals, and clinical research centres with experience conducting pharmaceutical company-sponsored phase 2 and phase 3 studies, which reported an ability to enrol eligible patients. Central randomisation assigned participants to one of three treatment groups using an Interactive Web Response System. Randomised (1:1:1) participants received intravenous nipocalimab 5 mg/kg, intravenous nipocalimab 15 mg/kg, or placebo every 2 weeks for 22 weeks. Schedules for administering the study intervention were the same across treatment groups, and labels on the study interventions were prepared by an unmasked pharmacist and were identical to maintain masking for the participants, investigators, site staff, and sponsor. The primary endpoint was change from baseline in ClinESSDAI score at week 24. The primary endpoint and other efficacy and safety analyses included participants who were randomly assigned and who received at least one dose of study intervention. For the primary endpoint, data from the time of discontinuation and onward were considered missing. The primary analysis approach used a mixed model for repeated measures to estimate the average outcome, taking into account the non-missing data and variability. DAHLIAS was registered with EudraCT (2021-000665-32) and ClinicalTrials.gov (NCT04968912) and has been completed.

Findings 163 participants were recruited between Sept 21, 2021, and April 3, 2023, (53 participants to nipocalimab 5 mg/kg, 54 to nipocalimab 15 mg/kg, and 56 to the placebo). The mean age of participants was 48·1 years (SD 12·12); 151 (93%) participants were female and 12 (7%) were male. The nipocalimab 15 mg/kg group had a significant reduction in ClinESSDAI score at week 24 versus the placebo group (least squares mean difference –2·65, 90% CI –4·03 to –1·28; p=0·0018), and the nipocalimab 5 mg/kg group had a non-significant reduction versus placebo (–0·34, –1·71 to 1·03; p=0·68). The safety profile of nipocalimab was comparable, for both doses, with that of placebo, with generally similar rates of adverse events and serious adverse events across groups.

Interpretation Fc receptor blockade by nipocalimab 15 mg/kg significantly improved clinical disease activity versus placebo and was safe and well tolerated in participants with moderate-to-severe, active Sjögren's disease. Reductions in IgG autoantibodies during nipocalimab treatment support their contribution to Sjögren's disease pathogenesis.

	Placebo (n=56)	Nipocalimab 5 mg/kg every 2 weeks (n=53)	Nipocalimab 15 mg/kg every 2 weeks (n=54)	Nipocalimab combined (n=107)	Total (N=163)
Age, years	47·3 (12·60)	48·3 (11·83)	48·6 (12·07)	48·5 (11·90)	48·1 (12·12)
Sex					
Female	52 (93%)	49 (92%)	50 (93%)	99 (93%)	151 (93%)
Male	4 (7%)	4 (8%)	4 (7%)	8 (7%)	12 (7%)
Race					
Black	0	1 (2%)	1 (2%)	2 (2%)	2 (1%)
White	50 (89%)	49 (92%)	49 (91%)	98 (92%)	148 (91%)
Other	6 (11%)	3 (6%)	4 (7%)	7 (7%)	13 (8%)
Ethnicity					
Hispanic or Latino	1 (2%)	0	2 (4%)	2 (2%)	3 (2%)
Not Hispanic or Latino	55 (98%)	53 (100%)	52 (96%)	105 (98%)	160 (98%)
Time since diagnosis, years	6·85 (6·650)	6·04 (6·617)	5·56 (4·334)	5·80 (5·562)	6·16 (5·959)
ClinESSDAI score	10·0 (3·75)	9·4 (3·05)	10·2 (3·64)	9·8 (3·37)	9·9 (3·49)
ESSDAI score	8·9 (3·51)	8·5 (3·14)	9·2 (3·65)	8·9 (3·41)	8·9 (3·44)
PhGA, mm	60·7 (15·38)	58·5 (17·38)	58·0 (14·38)	58·2 (15·86)	59·1 (15·69)
ESSPRI score	7·04 (1·260)	7·04 (1·259)	7·16 (1·188)	7·10 (1·220)	7·08 (1·230)
PtGA, mm	66·9 (15·38)	64·8 (21·18)	67·5 (15·87)	66·1 (18·65)	66·4 (17·55)
FACIT-Fatigue score	23·6 (9·75)	23·6 (10·13)	26·8 (10·97)	25·2 (10·64)	24·6 (10·34)
Salivary flow rate, mL per min	0·16 (0·130)	0·19 (0·229)	0·15 (0·127)	0·17 (0·185)	0·16 (0·168)
Schirmer's test, mm	6·6 (5·42)	6·9 (6·55)	14·2 (63·81)*	10·6 (45·50)	9·2 (36·99)
Oral corticosteroid use	15 (27%)	15 (28%)	14 (26%)	29 (27%)	44 (27%)
Use of anti-malarials	36 (64%)	34 (64%)	35 (65%)	69 (64%)	105 (64%)
Hydroxychloroquine sulfate	24 (43%)	20 (38%)	23 (43%)	43 (40%)	67 (41%)
Hydroxychloroquine	10 (18%)	11 (21%)	10 (19%)	21 (20%)	31 (19%)
Chloroquine phosphate	2 (4%)	3 (6%)	2 (4%)	5 (5%)	7 (4%)
Use of disease-modifying antirheumatic drugs	12 (21%)	7 (13%)	8 (15%)	15 (14%)	27 (17%)
Methotrexate	7 (13%)	2 (4%)	3 (6%)	5 (5%)	12 (7%)
Azathioprine	1 (2%)	3 (6%)	1 (2%)	4 (4%)	5 (3%)
Methotrexate sodium	1 (2%)	1 (2%)	3 (6%)	4 (4%)	5 (3%)
Mycophenolate mofetil	2 (4%)	0	1 (2%)	1 (1%)	3 (2%)
Leflunomide	1 (2%)	1 (2%)	0	1 (1%)	2 (1%)
Sulfasalazine	0	0	1 (2%)	1 (1%)	1 (1%)
Neutrophils <1·5 × 10^9/L†	5 (9%)	0	3 (6%)	3 (3%)	8 (5%)
Lymphocytes <1·0 × 10^9/L†	13 (23%)	14 (26%)	8 (15%)	22 (21%)	35 (21%)
Haemoglobin <120 g/L†	13 (23%)	7 (13%)	8 (15%)	15 (14%)	28 (17%)
Platelets <150 × 10^9/L†	2 (4%)	0	2 (4%)	2 (2%)	4 (2%)
IgG ≥16·0 g/L†	24 (43%)	20 (38%)	26 (48%)	46 (43%)	70 (43%)

Data are n (%) or mean (SD). ClinESSDAI=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient Reported Index. FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue. PhGA=Physician's Global Assessment of Disease Activity. PtGA=Patient's Global Assessment of Disease Activity. *One participant exhibited high levels of tear production at baseline, resulting in >35 mm strip wetting in <5 min. The total wetting in 5 min was extrapolated to avoid censoring the data, which resulted in high numbers for this participant, skewing the mean and SD results for this treatment group. †Parameter cutoffs represent thresholds defining disease activity in the ESSDAI biological and haematological domains.

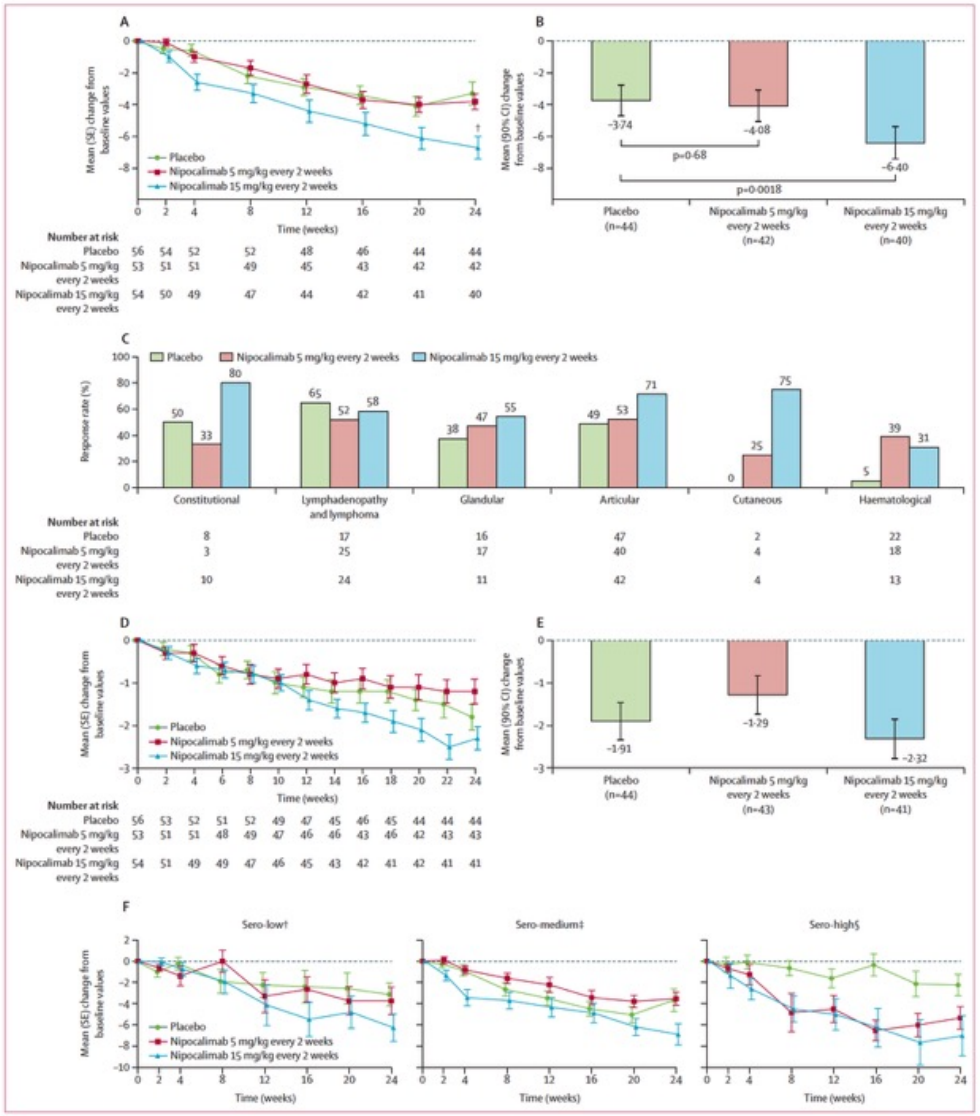
Table 1: **Baseline study population characteristics**

Change from baseline

Response rate

Change from baseline

Response rate



	Placebo (n=56)	Nipocalimab 5 mg/kg every 2 weeks (n=53)	Nipocalimab 15 mg/kg every 2 weeks (n=54)
Primary endpoint			
Change from baseline in ClinESSDAI score, least squares mean (90% CI)	−3·74 (−4·74 to −2·75)	−4·08 (−5·10 to −3·07)	−6·40 (−7·43 to −5·36)
Least squares mean difference (90% CI)*	..	−0·34 (−1·71 to 1·03)	−2·65 (−4·03 to −1·28)
p value*	..	0·68	0·0018
Secondary and exploratory endpoints			
Change from baseline in the Physician's Global Assessment of Disease Activity score, least squares mean (90% CI)	−24·26 (−28·91 to −19·61)	−26·51 (−31·27 to −21·76)	−38·76 (−43·62 to −33·91)
Least squares mean difference (90% CI)*	..	−2·26 (−8·50 to 3·99)	−14·50 (−20·81 to −8·19)
Change from baseline in ESSDAI score, least squares mean (90% CI)	−2·82 (−3·67 to −1·98)	−3·34 (−4·20 to −2·48)	−4·61 (−5·49 to −3·73)
Least squares mean difference (90% CI)*	..	−0·52 (−1·67 to 0·63)	−1·79 (−2·94 to −0·63)
Change from baseline in ESSPRI score, least squares mean (90% CI)	−1·91 (−2·36 to −1·46)	−1·29 (−1·75 to −0·83)	−2·32 (−2·79 to −1·85)
Least squares mean difference (90% CI)*	..	0·62 (0·01 to 1·23)	−0·41 (−1·03 to 0·20)
Number of participants who achieved ESSDAI-4 response	16 (29%)	18 (34%)	25 (46%)
Difference in proportion (90% CI)†	..	5·4 (−9·2 to 20·0)	17·7 (2·8 to 32·7)
Number of participants who achieved ClinESSDAI-4 response	19 (34%)	20 (38%)	28 (52%)
Difference in proportion (90% CI)†	..	3·8 (−11·3 to 18·9)	17·9 (2·6 to 33·2)
Number of participants who achieved ESSPRI response	28 (50%)	21 (40%)	30 (56%)
Difference in proportion (90% CI)†	..	−10·4 (−26·0 to 5·2)	5·6 (−10·1 to 21·2)
Number of participants who achieved Sjögren's Tool for Assessing Response	22 (39%)	27 (51%)	34 (63%)
Difference in proportion (90% CI)†‡	..	11·7 (−3·9 to 27·2)	23·7 (8·4 to 38·9)
Number of participants who achieved CRESS response	10 (18%)	23 (43%)	26 (48%)
Difference in proportion (90% CI)†‡	..	25·5 (11·5 to 39·5)	30·3 (16·3 to 44·3)
Number of participants who achieved disease activity level response§	19 (34%)	28 (53%)	29 (54%)
Difference in proportion (90% CI)†	..	18·9 (3·6 to 34·2)	19·8 (4·5 to 35·0)

ClinESSDAI=Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome. ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient Reported Index. *Compared with the placebo group using a mixed-effects repeated-measures model with baseline score, study treatment, visit, region, baseline steroid use, baseline antimalarial use, and a treatment-by-visit interaction as terms in the model. For continuous endpoints, participants who had an intercurrent event per protocol were considered to have missing data thereafter. †Compared with the placebo group using a Cochran–Mantel–Haenszel test with region, baseline steroid use, and baseline antimalarial use as stratification factors. For binary composite endpoints, participants who had intercurrent events were considered non-responders after the event. ‡Alternative calculations of the Sjögren's Tool for Assessing Response and CRESS were least squares performed by removing the IgG-based criterion, revealing a difference in the proportion of 2·7% (90% CI −8·8 to 14·1) and 0·1% (−15·0 to 15·2) for nipocalimab 5 mg/kg and 28·3% (14·8 to 41·8) and 21·7% (6·4 to 37·0) for nipocalimab 15 mg/kg, respectively. §Disease activity level response is a reduction from baseline in disease activity level by at least one level in at least one of ClinESSDAI or ESSDAI domain (eg, articular, haematological, cutaneous, or constitutional).

Table 2: **Efficacy endpoints for nipocalimab 5 mg/kg and nipocalimab 15 mg/kg versus placebo**

Safety not the issue

	Placebo (n=56)	Nipocalimab 5 mg/kg every 2 weeks (n=53)	Nipocalimab 15 mg/kg every 2 weeks (n=54)	Nipocalimab combined (n=107)
Adverse events	35 (63%)	42 (79%)	43 (80%)	85 (79%)
Related adverse events*	12 (21%)	21 (40%)	18 (33%)	39 (36%)
Related non-serious adverse events*	12 (21%)	21 (40%)	18 (33%)	39 (36%)
Adverse events leading to death†	0	0	0	0
Serious adverse events	3 (5%)	4 (8%)	4 (7%)	8 (7%)
Related serious adverse events*	0	1 (2%)‡	0	1 (1%)
Adverse events leading to discontinuation of study agent	2 (4%)	3 (6%)	3 (6%)	6 (6%)
Related adverse events leading to discontinuation of study agent*	0	2 (4%)	1 (2%)	3 (3%)
Infections that were severe or required intravenous anti-infective or surgical intervention§	1 (2%)	2 (4%)	1 (2%)	3 (3%)
New onset hypoalbuminaemia with albumin <20 g/L	0	0	0	0
Infusion reactions¶	2 (4%)	6 (11%)	1 (2%)	7 (7%)
Infusion-site reactions§	0	0	0	0
Opportunistic infections	0	0	0	0
Hypersensitivity reactions	3 (5%)	6 (11%)	7 (13%)	13 (12%)
Anaphylactic reactions or serum sickness	0	1 (2%)‡	0	1 (1%)
Major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke)	2 (4%)	0	0	0
Activation of latent virus‖	1 (2%)	3 (6%)	3 (6%)	6 (6%)
Headache	8 (14%)	4 (8%)	6 (11%)	10 (9%)
COVID-19 infection	3 (5%)	8 (15%)	3 (6%)	11 (10%)
COVID-19 infection serious adverse events	0	1 (2%)	0	1 (1%)

Data are n (%). *An adverse event is assessed by the investigator as being related to the study agent. †Adverse events leading to death are based on a fatal adverse event outcome. ‡Anaphylactic reaction occurred without a previous history of anaphylaxis or allergy to biological treatments. The participant developed tachycardia, hypertension, dyspnoea, and urticaria during the tenth administration of study treatment. Symptoms improved after stopping treatment and immediate administration of standard anaphylaxis intervention (ie, epinephrine, paracetamol, dexamethasone, and supplemental oxygen). §As assessed by the investigator. ¶Temporally associated with infusion (during or within 1 h after infusion). ‖All instances of activation of latent virus in the placebo and nipocalimab 5 mg/kg groups were reported as herpes simplex 1 reactivation; in the nipocalimab 15 mg/kg group, this adverse event was reported as herpes zoster, herpes simplex 1, and primary genital herpes in three separate participants.

Table 3: **Summary of treatment-emergent adverse events through to the end of the study**

Antibody levels

Antibody levels

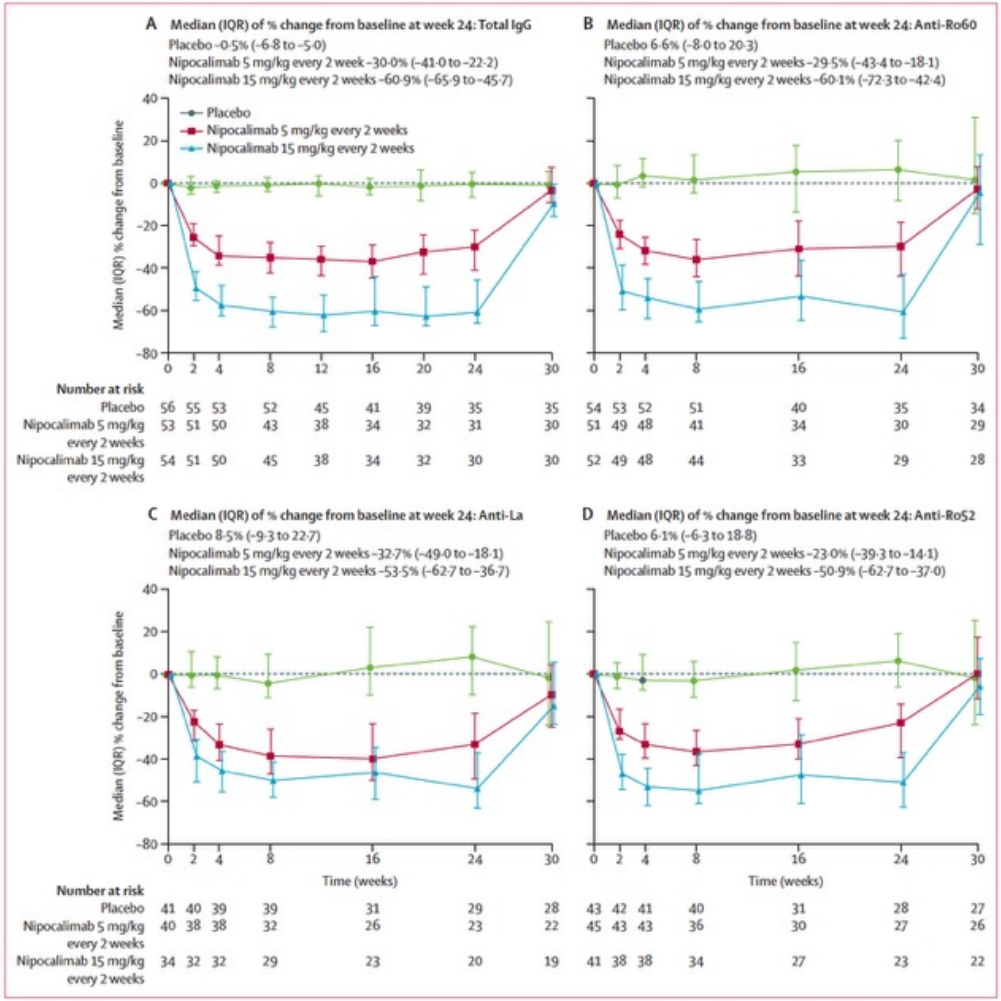


Figure 2: **Nipocalimab mechanism of action: observed (minimum pre-dose) percent change from baseline in (A) total IgG, (B) anti-Ro60, (C) anti-La, and (D) anti-Ro52 IgG autoantibody levels over time through to week 30**

The number of participants is those with no missing value at both baseline and the postbaseline timepoint. If a participant missed a planned dose of the study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Participants were required to have at least one valid post-dose blood sample drawn for pharmacodynamic analysis. Participants included in the anti-Ro60, anti-La, and anti-Ro52 analyses must have been positive for anti-Ro60, anti-La, or anti-Ro52, respectively, at baseline.

Research in context

Evidence before this study

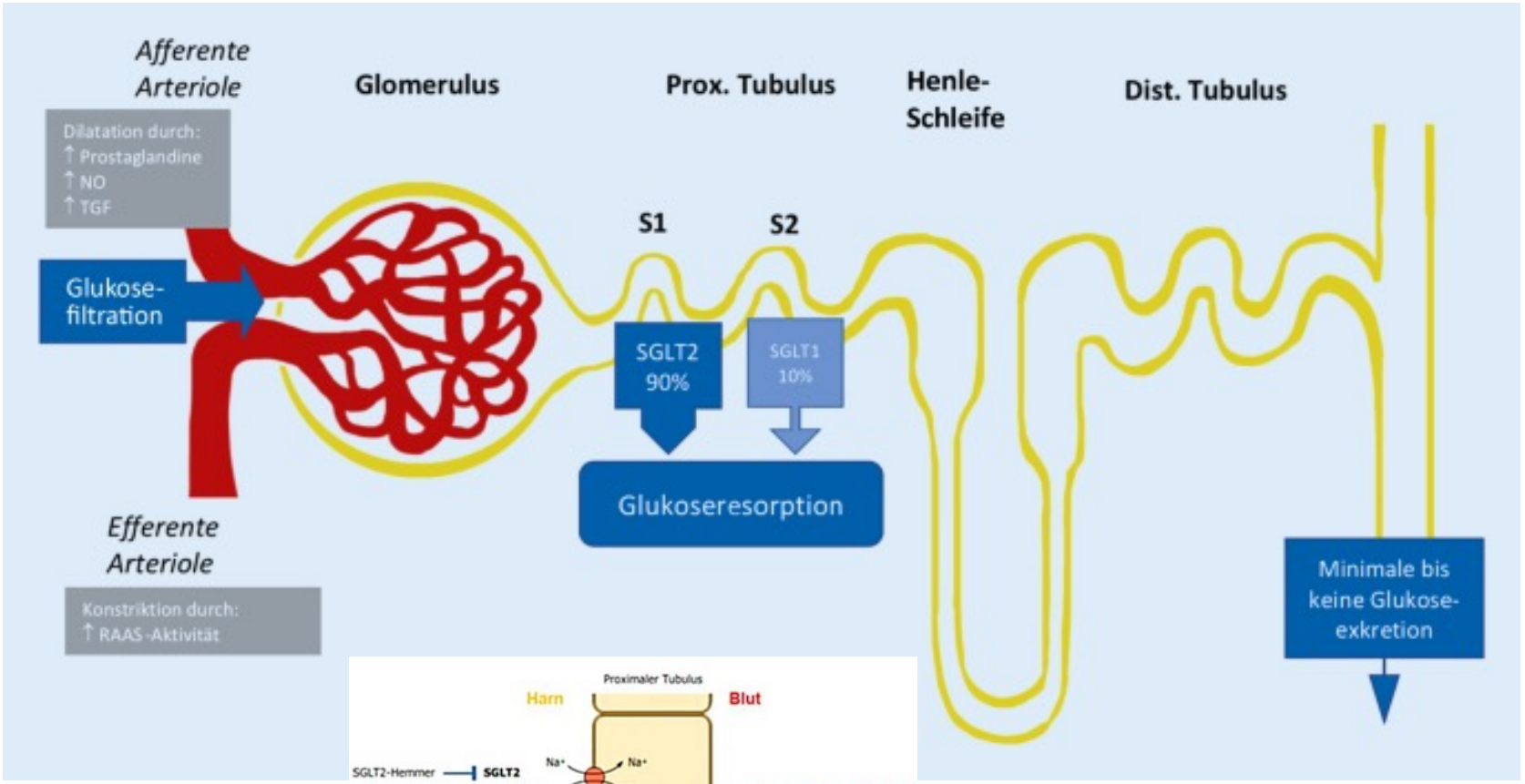
We searched PubMed from database inception to May 14, 2025, using the search terms "("Sjögren's syndrome" OR "Sjögren's disease") AND (targeted therapy OR disease-modifying treatment OR immune-modulating treatment) AND (randomizedcontrolledtrial[Filter])." No language restrictions were applied. This search produced 14 results. 11 results were studies in which all participants had Sjögren's disease.
The studies that met their primary endpoints investigated drugs that cause B-cell depletion (ianalumab), B-cell modulation (ianalumab and telitacicept), Treg enhancement (low-dose IL-2), and/or inhibition of B-cell and T-cell co-stimulation (dazodalibep and iscalimab). In addition to affecting B cells, many of these mechanisms have the potential to affect autoantibody production. A phase 2b, double-blind, multicentre study of ianalumab found improvements in overall disease activity, as measured by the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI), and dose-dependent reductions in IgG levels after 24 weeks of treatment. A phase 2, double-blind study of telitacicept, a B-cell-activating factor and a proliferation-inducing ligand blocker, found improvements in ESSDAI score after 24 weeks of treatment; along with reductions in the Multidimensional Fatigue Inventory (MFI-20); and serum IgM, IgA, and IgG levels. A phase 2, double-blind study of low-dose IL-2 showed improvements in ESSDAI score compared with placebo. In the phase 2, double-blind, multicentre study of the CD40 ligand antagonist dazodalibep, there were improvements in ESSDAI and European League Against Rheumatism Sjögren's Syndrome Patient Reported Index (ESSPRI) score after 24 weeks of treatment. Another phase 2 study, this time a proof-of-concept study, showed an improvement in ESSDAI score with intravenous iscalimab after 12 weeks. Finally, the phase 2b, double-blind, multicentre study of iscalimab showed a significant improvement in ESSDAI score, a tendency towards improvement in ESSPRI score, and a decrease in IgG concentrations after 24 weeks of iscalimab treatment.

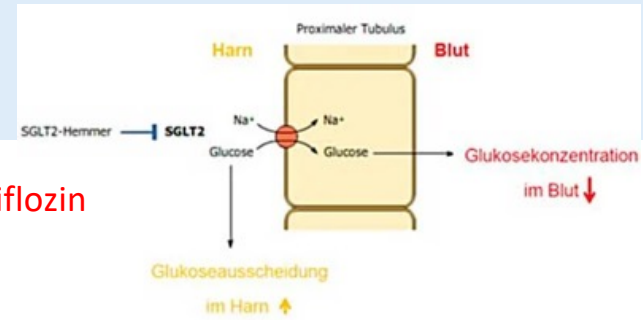
Added value of this study

To the best of our knowledge, this phase 2, multicentre, randomised, placebo-controlled, double-blind study is the first randomised controlled trial of a neonatal Fc receptor blocker in patients with Sjögren's disease. Although most other drugs have targeted B-cell depletion or suppression, nipocalimab targets the neonatal Fc receptor to specifically reduce the abnormally high levels of circulating IgG antibodies and autoantibodies present in most patients with Sjögren's disease. This trial is also the largest study to the best of our knowledge to evaluate efficacy using the Clinical ESSDAI (ClinESSDAI) as the primary endpoint, which excludes the ESSDAI's potentially confounding biological domain that includes B-cell and IgG-based criteria. Furthermore, this study explores the potential pathogenic role of IgG autoantibodies in the progression of Sjögren's disease and shows proof of concept for nipocalimab treatment for patients with Sjögren's disease.

Implications of all the available evidence

There are no targeted or disease-modifying therapies approved for systemic Sjögren's disease. The results of this study, along with all the available evidence, suggest that drugs that target high levels of autoantibodies and associated pathways have the potential to be effective treatments for Sjögren's disease.

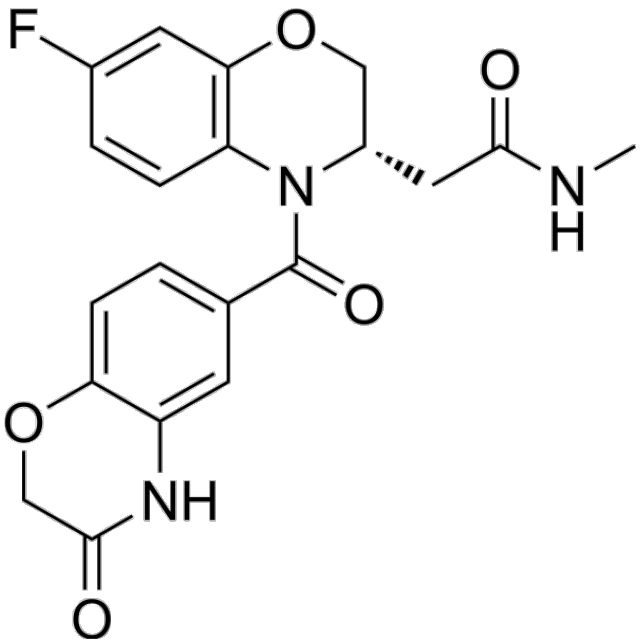




Dapagliflozin

MR Blocker

Balcinrenone (AZD9977) ist ein experimenteller, selektiver Modulator des Mineralokortikoidrezeptors, der von AstraZeneca für die Behandlung von Herzinsuffizienz und chronischer Nierenerkrankung entwickelt wird. Es ist ein oral aktiver Wirkstoff, der darauf abzielt, die Vorteile herkömmlicher Medikamente beizubehalten, aber das Risiko einer Hyperkaliämie (hoher Kaliumspiegel im Blut) zu verringern. Balcinrenone wird in der Forschung oft in Kombination mit Dapagliflozin untersucht.



Balcinrenone in combination with dapagliflozin compared with dapagliflozin alone in patients with chronic kidney disease and albuminuria: a randomised, active-controlled

Summary

Background Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce albuminuria and risk of progression of chronic kidney disease. Non-steroidal mineralocorticoid receptor antagonists (MRA) have similar effects in patients with type 2 diabetes with chronic kidney disease. We aimed to assess efficacy and safety of the novel MRA balcinrenone combined with the SGLT2 inhibitor dapagliflozin in a randomised controlled trial.

Methods MIRO-CKD was a multicentre, randomised, double-blind, active controlled, dose-finding phase 2b trial conducted in 106 clinical practice sites in 15 countries in America, Asia, and Europe. Adults with estimated glomerular filtration rate (eGFR) of 25–<60 mL/min per 1·73 m², a urine albumin-to-creatinine ratio (UACR) of >100–≤5000 mg/g, and a serum potassium concentration 3·5–5·0 mmol/L were randomly assigned (1:1:1) via an interactive response technology system to treatment with combined balcinrenone 15 mg plus dapagliflozin 10 mg, balcinrenone 40 mg plus dapagliflozin 10 mg, or dapagliflozin 10 mg plus placebo (double-dummy technique) once daily as adjunct to renin angiotensin system inhibitors, if tolerated, for 12 weeks, followed by an 8-week wash-out period. The primary efficacy endpoint was relative change in UACR from baseline to week 12, analysed in all participants who were randomly assigned and received at least one dose of study drug. Missing values were not imputed, assuming that any missing UACR values were missing at random. Other endpoints included safety and tolerability. The MIRO-CKD trial was registered at ClinicalTrials.gov, NCT06350123, and is completed.

Findings Between May 1 and Dec 18, 2024, 613 participants were assessed for eligibility, 289 were excluded due to not meeting eligibility criteria or withdrawing, and 324 were randomly assigned to receive balcinrenone 15 mg plus dapagliflozin 10 mg (n=108), balcinrenone 40 mg plus dapagliflozin 10 mg (n=110), or dapagliflozin plus placebo (n=106). Participants had a mean age of 64·6 years (SD 12·4), a mean eGFR of 42·2 mL/min per 1·73 m² (SD 10·5), median UACR of 365 mg/g (IQR 157 to 825), and 56% were taking SGLT2 inhibitors. 110 (34%) participants were female and 214 (66%) were male. A globally diverse population was included with 103 (32%) Asian, 23 (7%) Black or African American, and 183 (56%) White participants. Balcinrenone 15 mg plus dapagliflozin 10 mg and balcinrenone 40 mg plus dapagliflozin 10 mg were superior in reducing UACR versus dapagliflozin 10 mg plus placebo throughout the treatment period. At week 12, the UACR difference versus dapagliflozin 10 mg plus placebo was –22·8% (90% CI –33·3 to –10·7; p=0·0038) for balcinrenone 15 mg plus dapagliflozin 10 mg and –32·8% (–42·0 to –22·1; p<0·0001) for balcinrenone 40 mg plus dapagliflozin 10 mg. Investigator-reported adverse events of hyperkalaemia were reported in 6% (seven of 108) of the balcinrenone 15 mg plus dapagliflozin 10 mg group, 7% (eight of 110) of the balcinrenone 40 mg plus dapagliflozin 10 mg group, and 5% (five of 106) of the dapagliflozin 10 mg plus placebo group. Adverse events of hypotension and renal events were few, balanced across the treatment groups, and none were serious. Two deaths occurred during the study, both more than 28 days after the last dose of study drug.

Interpretation In participants with chronic kidney disease at increased risk of disease progression, a fixed dose combination of balcinrenone and dapagliflozin was superior to dapagliflozin alone in reducing albuminuria. Balcinrenone plus dapagliflozin was well tolerated, effects on potassium were minor, and no unexpected safety concerns were identified.

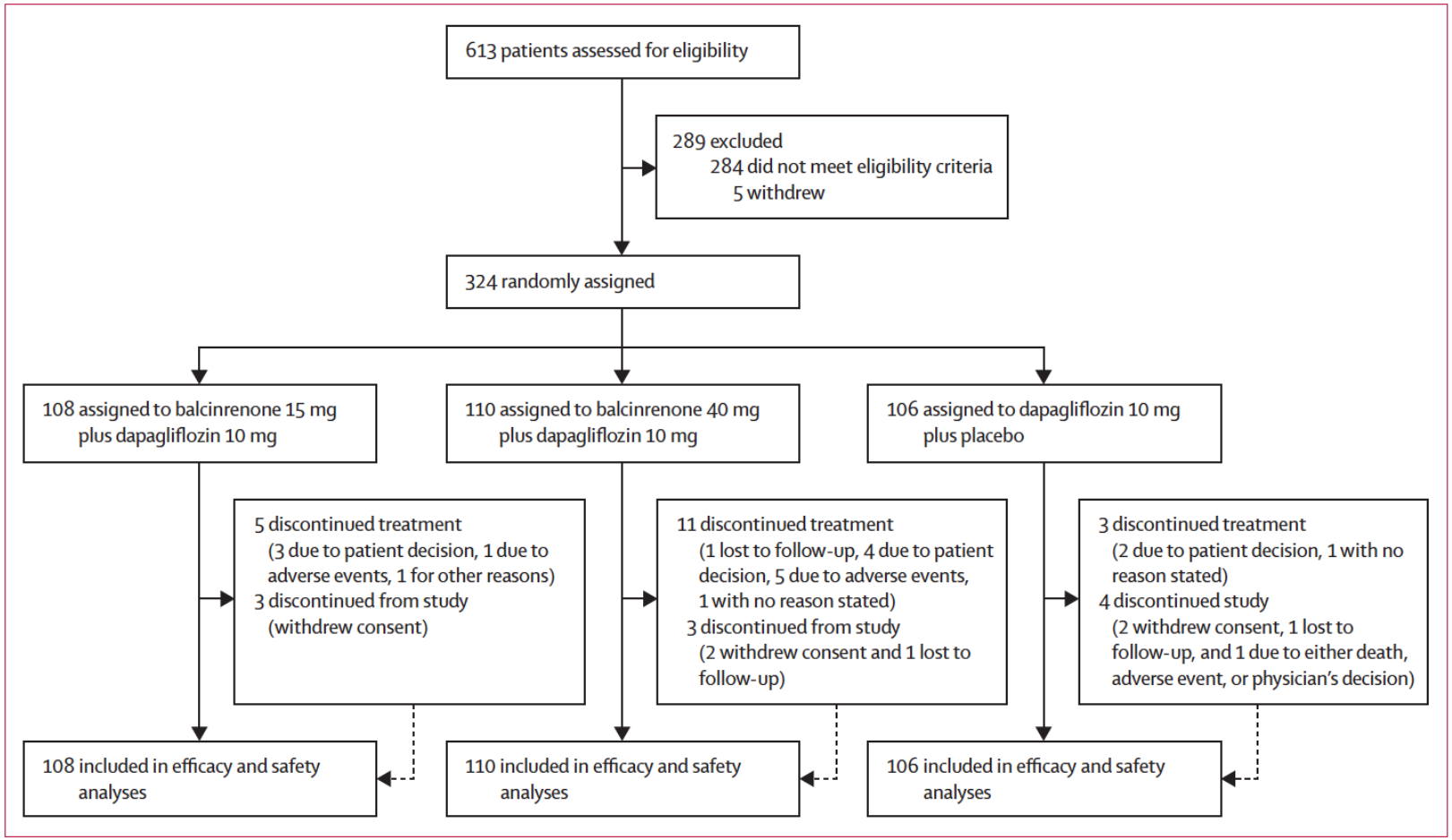


Figure 1: **Trial profile**

	Balcinrenone 15 mg plus dapagliflozin 10 mg (n=108)	Balcinrenone 40 mg plus dapagliflozin 10 mg (n=110)	Dapagliflozin 10 mg plus placebo (n=106)	Total (N=324)
Age, years	64·7 (12·4)	65·2 (12·3)	63·9 (12·5)	64·6 (12·4)
Sex				
Female	37 (34%)	39 (35%)	34 (32%)	110 (34%)
Male	71 (66%)	71 (65%)	72 (68%)	214 (66%)
Race				
Asian	35 (32%)	39 (35%)	29 (27%)	103 (32%)
Black or African American	5 (5%)	11 (10%)	7 (7%)	23 (7%)
White	60 (56%)	58 (53%)	65 (61%)	183 (56%)
Other	8 (7%)	1 (1%)	5 (5%)	14 (4%)
Not reported	0	1 (1%)	0	1 (<1%)
BMI, kg/m²	28·0 (5·4)	28·9 (5·4)	30·1 (6·5)	29·0 (5·8)
eGFR, mL/min per 1·73 m²	41·3 (10·8)	42·2 (9·9)	43·1 (10·8)	42·2 (10·5)
≥45	43 (40%)	44 (40%)	48 (45%)	135 (42%)
≥30 to <45	47 (44%)	57 (52%)	48 (45%)	152 (47%)
<30	18 (17%)	9 (8%)	10 (9%)	37 (11%)
UACR, mg/g	305 (157–706)	406 (184–1085)	375 (137–874)	365 (157–825)
≥1000	16 (15%)	29 (26%)	22 (21%)	67 (21%)
Serum potassium, mmol/L	4·5 (0·5)	4·5 (0·5)	4·5 (0·5)	4·5 (0·5)
≥4·8	36 (33%)	34 (31%)	27 (25%)	97 (30%)
≥4·5 to <4·8	20 (19%)	24 (22%)	27 (25%)	71 (22%)
≥3·5 to <4·5	50 (46%)	51 (46%)	49 (45%)	150 (46%)
<3·5	2 (2%)	1 (1%)	3 (3%)	6 (2%)
Type 2 diabetes	60 (56%)	62 (56%)	61 (58%)	183 (56%)
Glycated haemoglobin	6·5% (1·4)	6·6% (1·3)	6·6% (1·4)	6·6% (1·4)
Blood pressure, mmHg				
Systolic	132·8 (14·4)	134·1 (16·3)	131·9 (17·7)	132·9 (16·1)
Diastolic	76·1 (9·7)	75·2 (11·2)	77·8 (11·1)	76·4 (10·7)
Medication				
SGLT2 inhibitors	63 (58%)	60 (55%)	59 (56%)	182 (56%)
Diuretics	38 (35%)	41 (37%)	43 (41%)	122 (38%)
RAS inhibitors	92 (85%)	94 (85%)	94 (89%)	280 (86%)*
ACE inhibitors	26 (24%)	26 (24%)	36 (34%)	88 (27%)
ARB	67 (62%)	68 (62%)	58 (55%)	193 (60%)
SGLT2 inhibitor and RAS inhibitor	54 (50%)	47 (43%)	54 (51%)	155 (48%)

Data are n (%), mean (SD), or median (IQR). ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. eGFR=estimated glomerular filtration rate. RAS=renin-angiotensin system. SGLT2=sodium-glucose co-transporter 2. UACR=urinary albumin-to-creatinine ratio. *Use of both ACE inhibitor and ARB was recorded for one participant.

Table 1: **Baseline characteristics**

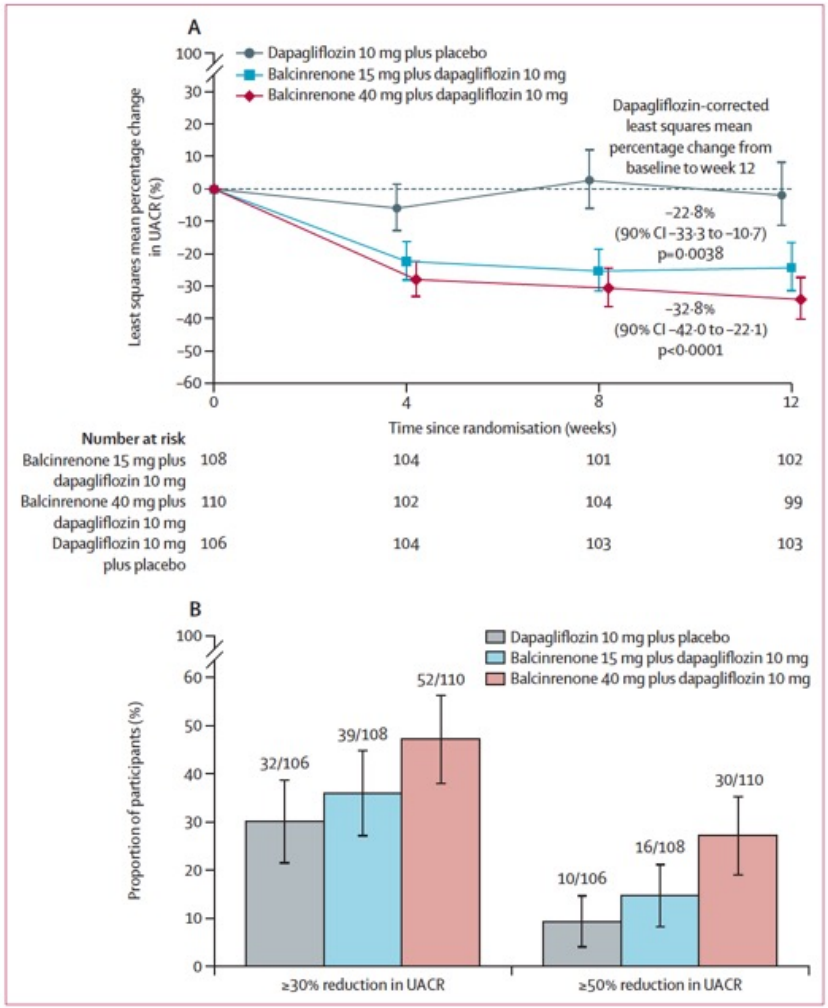


Figure 2: **Mean percentage change from baseline in UACR (A) and proportion of participants with a reduction in UACR from baseline to week 12 of at least 30% or 50% (B)**

Data for least squares mean percentage change are presented with 90% CIs. Data for proportion of participants are presented with 95% CIs. UACR=urine albumin-to-creatinine ratio.

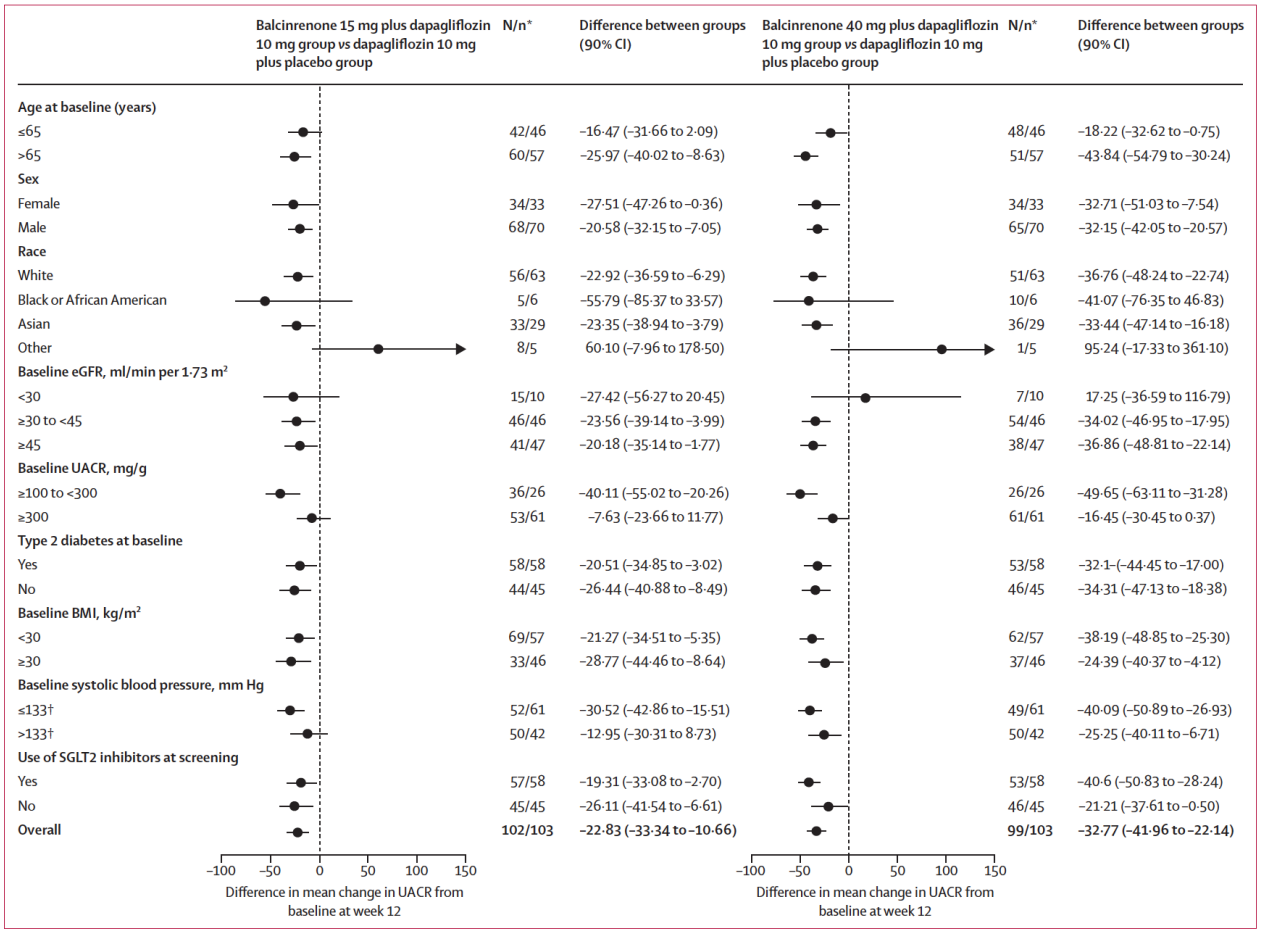


Figure 3: **Effects of balcinrenone plus dapagliflozin groups versus dapagliflozin 10 mg plus placebo group on UACR at week 12 in patient subgroups**
Whiskers represent 90% CIs. eGFR=estimated glomerular filtration rate. UACR=urine albumin-to-creatinine ratio. SGLT2=sodium–glucose cotransporter-2. *Number of participants in the balcinrenone plus dapagliflozin versus dapagliflozin plus placebo groups. †133 mm Hg was the median systolic blood pressure value at baseline.

Plasma K

Blood pressure values

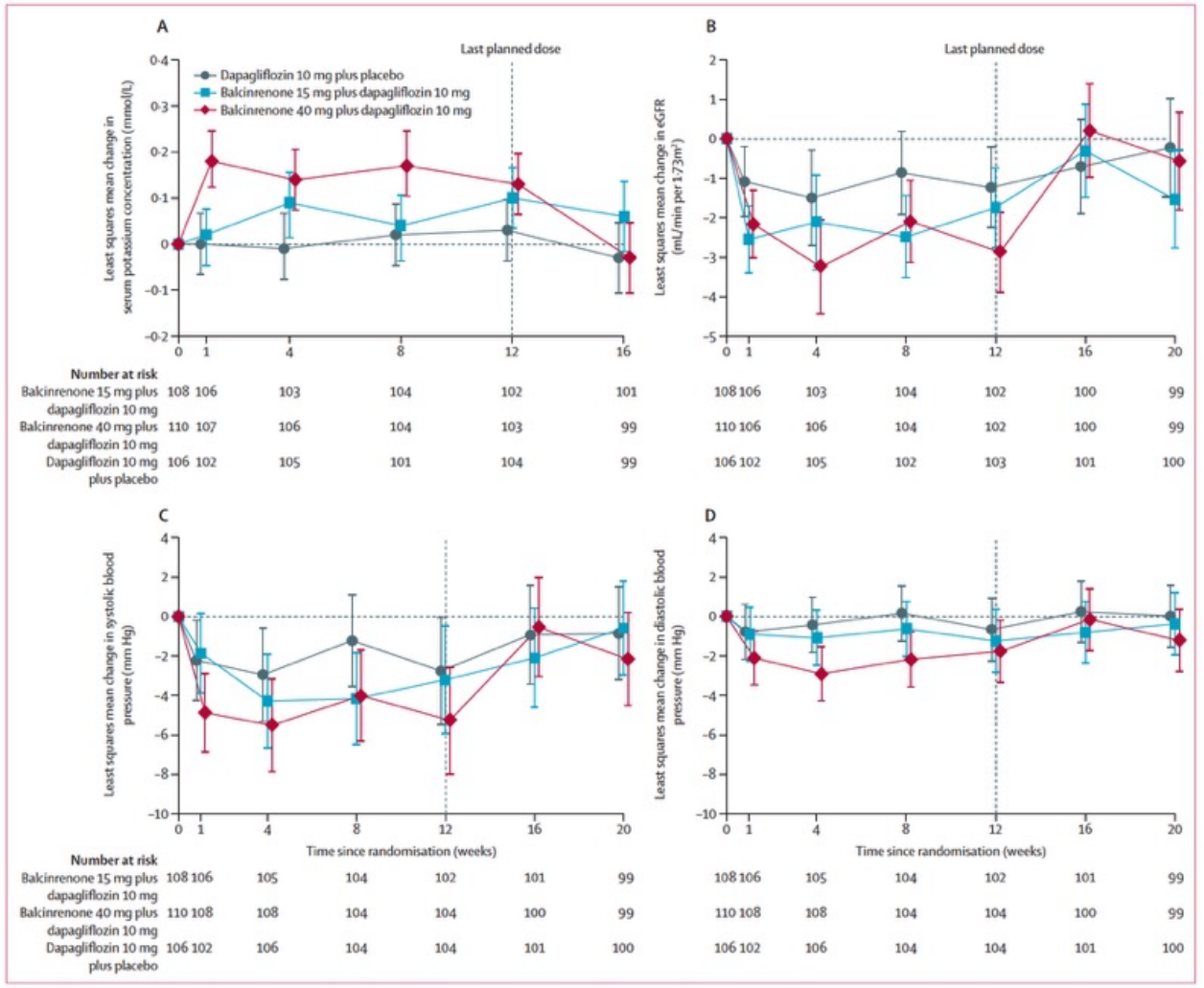


Figure 4: **Mean change from baseline in serum potassium (A), eGFR (B), systolic blood pressure (C) and diastolic blood pressure (D)**
Data for least square mean changes are presented with 95% CIs. eGFR=estimated glomerular filtration rate.

	Balcinrenone 15 mg plus dapagliflozin 10 mg (n=108)	Balcinrenone 40 mg plus dapagliflozin 10 mg (n=110)	Dapagliflozin 10 mg plus placebo (n=106)	Total (N=324)
Any treatment-emergent adverse events	45 (42%)	50 (45%)	51 (48%)	146 (45%)
Any treatment-emergent adverse event leading to study drug discontinuation	1 (1%)	5 (5%)	0	6 (2%)
Any treatment-emergent serious adverse event	1 (1%)	8 (7%)	8 (8%)	17 (5%)
Treatment-emergent adverse events of special interest				
Hyperkalaemia				
Investigator-reported adverse events of hyperkalaemia*	7 (6%)	8 (7%)	5 (5%)	20 (6%)
Investigator-reported serious adverse event of hyperkalaemia	0	0	0	0
Hyperkalaemia adverse events leading to study drug discontinuation	1 (1%)	2 (2%)	0	3 (1%)
Any serum potassium >5·5 mmol/L†	8 (7%)	14 (13%)	5 (5%)	27 (8%)
Hypotension	2 (2%)	2 (2%)	1 (1%)	5 (2%)
Dizziness	0	1 (1%)	1 (1%)	2 (1%)
Hypotension	2 (2%)	1 (1%)	0	3 (1%)
Investigator-reported serious adverse event of hypotension	0	0	0	0
Renal events	1 (1%)	4 (4%)	0	5 (2%)
Renal impairment	1 (1%)	2 (2%)	0	3 (1%)
Acute kidney injury	0	2 (2%)	0	2 (1%)
Investigator-reported serious adverse event of renal event	0	0	0	0

Data are n (%). The table includes adverse events and serious adverse events with an onset date, or worsening, on or after the first dose of study drug and within 28 days after the last dose of study drug. Participants with multiple occurrences are counted once per preferred term regardless of the number of occurrences. *Investigator-reported adverse events of hyperkalaemia include adverse events with preferred term of hyperkalaemia or blood potassium increase, the latter occurring in one participant in the balcinrenone 40 mg plus dapagliflozin 10 mg group and one participant in the dapagliflozin 10 mg plus placebo group. †Analysed at central or local laboratory, reported by the investigator. Preferred terms are based on *Medical Dictionary for Regulatory Activities* version 28.0.

Table 2: **Summary of treatment-emergent adverse events**

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published in English between Jan 1, 1990, and July 1, 2025, with the terms "chronic kidney disease" AND "albuminuria" AND mineralocorticoid receptor" AND "mineralocorticoid receptor antagonist" AND "randomized controlled trial". Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce albuminuria, slow chronic kidney disease progression, and reduce the risk of kidney and heart failure in patients with chronic kidney disease regardless of diabetes status. Similar evidence exists for the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone in patients with type 2 diabetes with chronic kidney disease. Accordingly, clinical practice guidelines for the management of chronic kidney disease recommend SGLT2 inhibitors as first-line therapy regardless of diabetes status and finerenone as an add-on therapy to renin–angiotensin system inhibition in patients with type 2 diabetes. Post-hoc analyses from kidney outcome trials reported that the benefits of SGLT2 inhibitors in reducing kidney and heart failure are consistent in patients who use and do not use traditional MRAs (spironolactone or eplerenone). A post-hoc analysis from two kidney outcome trials with finerenone showed that the clinical benefits of finerenone are present irrespective of whether patients use or do not use SGLT2 inhibitors, although participants were restricted to those having serum potassium concentrations of less than 4·8 mmol/L at screening in these trials. A small prospective study of short duration suggested that combined treatment with dapagliflozin and finerenone reduced albuminuria more than either treatment alone. However, this small study and the previous post-hoc analyses were only hypothesis-generating and did not adequately answer the question whether simultaneous initiation of SGLT2 inhibitors and finerenone is safe and further reduces albuminuria compared with either treatment alone. The CONFIDENCE trial was designed to assess the albuminuria lowering effects and safety of simultaneous initiation of empagliflozin and finerenone in patients with type 2 diabetes and chronic kidney disease. The study showed that combined initiation of empagliflozin and finerenone exerts additive effects on albuminuria, resulting in a 32% greater reduction in albuminuria from baseline at day 180 than empagliflozin alone. The study also showed that this combination therapy was safe and well-tolerated, although it was associated with increases in serum potassium concentrations. Balcinrenone is another novel non-steroidal MRA currently being investigated in combination with SGLT2 inhibitors in patients with heart failure and in patients with chronic kidney disease. Balcinrenone reduced albuminuria and improved kidney histopathology similar to traditional MRAs in animal models of chronic kidney disease and diabetic kidney disease. However, balcinrenone has a differential mechanism of action, supported by the lack of effect on the urinary sodium/potassium ratio in rats compared with the increase typically seen with other MRAs, suggesting a low risk of hyperkalaemia. This is particularly relevant for patients with chronic kidney disease with reduced estimated glomerular filtration rate (eGFR) who often do not tolerate renin–angiotensin system inhibition due to hyperkalaemia. The phase 2b MIRACLE trial of balcinrenone plus the SGLT2 inhibitor dapagliflozin in patients with heart failure and chronic kidney disease showed a trend towards albuminuria-lowering effects with a low risk of hyperkalaemia, but the study was terminated early due to slow recruitment, precluding definitive conclusions.

Added value of this study

The MIRO-CKD trial was a phase 2b randomised, active-controlled, double-blind clinical trial designed to assess the efficacy, safety, and dose–response of a fixed-dose combination of balcinrenone 15 mg or 40 mg and dapagliflozin 10 mg compared with dapagliflozin 10 mg in participants with chronic kidney disease (eGFR ≥25 to <60 mL/min per 1·73 m^2) and albuminuria, serum potassium concentrations within normal range without further restrictions, and with or without type 2 diabetes. Participants were eligible irrespective of whether they were already using SGLT2 inhibitors. The study demonstrated that 12-week combination treatment with balcinrenone 15 mg plus dapagliflozin 10 mg and balcinrenone 40 mg plus dapagliflozin 10 mg reduced albuminuria by 23% and 33%, respectively, compared with dapagliflozin 10 mg. Balcinrenone plus dapagliflozin was well tolerated in patients with chronic kidney disease with a minor increase in serum potassium concentrations and a low incidence of hyperkalaemia.

Implications of all the available evidence

The MIRO-CKD clinical trial showed a robust and clinically meaningful reduction in albuminuria with a fixed-dose combination of the novel MRA balcinrenone and the SGLT2 inhibitor dapagliflozin in participants with or without SGLT2 inhibitors at study entry, for both doses of balcinrenone. This combination was generally well tolerated with no unexpected safety events. In the context of the previous post-hoc analyses and prospective clinical trials, the totality of the available evidence indicates that combined treatment with balcinrenone and dapagliflozin confers additive effects on albuminuria with minor effects on serum potassium concentrations and a low risk of hyperkalaemia. These findings support the conduct of a long-term phase 3 clinical trial to assess the efficacy and safety of the combination of balcinrenone and dapagliflozin in reducing the risk of adverse kidney and cardiovascular outcomes in patients with chronic kidney disease at high risk of progression.

Epidemiology of chronic kidney disease: an update 2022

kidney INTERNATIONAL supplements

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Extremely common

843,6 Million in 2017

Approximately **1** in 10

Increasing death rate

+41.5% 1990 to 2017

Rank in cause of death

Large burden in low- and middle-income countries

Among the **top 10 causes** of death in Singapore, Greece, and Israel

Kovesdy, 2022

CONCLUSION

Chronic kidney disease (CKD) occurs frequently and has devastating consequences. This should prompt major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

Global, regional, and national burden of chronic kidney disease in adults, 1990–2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023

Summary

Background Chronic kidney disease (CKD) is common and ranks among the leading causes of mortality and morbidity. This analysis aimed to present global CKD estimates using the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2023 to inform evidence-based policies for CKD identification and treatment.

Methods This analysis focused on adults aged 20 years and older over the period 1990 to 2023, from 204 countries and territories. Data sources used were published literature, vital registration systems, kidney failure treatment registries, and household surveys. Estimates of CKD burden, including deaths, incidence, prevalence, and disability-adjusted life-years (DALYs), were produced using a Cause of Death Ensemble model and a Bayesian meta-regression analytical tool. A comparative risk assessment approach estimated the proportion of cardiovascular deaths attributable to impaired kidney function and estimated risk factors for CKD.

Findings Globally, in 2023, 788 million (95% uncertainty interval 743–843) people aged 20 years and older were estimated to have CKD, up from 378 million (354–407) in 1990. The global age-standardised prevalence of CKD in adults was 14·2% (13·4–15·2), a relative rise of 3·5% (2·7–4·1) from 1990. The region with the highest age-standardised prevalence was north Africa and the Middle East (18·0%; 16·9–19·4). Most people had stage 1–3 CKD, with a combined prevalence of 13·9% (13·1–15·0). In 2023, CKD was the ninth leading cause of death globally, accounting for 1·48 million (1·30–1·65) deaths, and the 12th leading cause of DALYs, with an age-standardised DALY rate of 769·2 (691·8–857·4) per 100 000. Impaired kidney function as a risk factor accounted for 11·5% (8·4–14·5) of cardiovascular deaths. High fasting plasma glucose, body-mass index, and systolic blood pressure were all leading risk factors for CKD DALYs.

Interpretation CKD is a major global health issue, with rising prevalence and increasing importance as a cause of death and as a risk factor for cardiovascular death. A better understating of aetiology, appropriate screening, and implementation programmes are needed to translate advances in CKD treatment into improved patient outcomes.

	Prevalence			Deaths		
	Count (thousands), 2023	Age-standardised prevalence (%), 2023	Percentage change in age-standardised prevalence between 1990 and 2023 (%)	Count (thousands), 2023	Age-standardised rate per 100 000, 2023	Percentage change in age-standardised rates between 1990 and 2023 (%)
Global	**788 000 (743 000 to 843 000)**	**14·2% (13·4 to 15·2)**	**3·5% (2·7 to 4·1)**	**1480 (1300 to 1650)**	**26·5 (23·1 to 29·5)**	**6·1% (–7·6 to 25·5)**
Low SDI	**111 000 (103 000 to 120 000)**	**15·2% (14·4 to 16·2)**	**–3·2% (–3·8 to –2·5)**	**200 (154 to 243)**	**35·4 (27·3 to 43·0)**	**–5·2% (–27·5 to 45·6)**
Low-middle SDI	**106 000 (99 000 to 114 000)**	**16·1% (15·2 to 17·3)**	**–6·5% (–7·1 to –5·8)**	**185 (146 to 223)**	**33·8 (26·7 to 40·8)**	**2·9% (–22·0 to 37·6)**
Middle SDI	**96 800 (90 600 to 104 000)**	**16·3% (15·3 to 17·6)**	**4·3% (3·7 to 5·0)**	**207 (171 to 240)**	**39·7 (32·4 to 46·0)**	**–4·5% (–24·5 to 24·0)**
High-middle SDI	**185 000 (175 000 to 197 000)**	**15·1% (14·3 to 16·2)**	**3·0% (2·0 to 3·9)**	**282 (251 to 310)**	**23·0 (20·5 to 25·3)**	**–23·8% (–36·0 to –7·8)**
High SDI	**283 000 (267 000 to 303 000)**	**12·2% (11·5 to 13·1)**	**4·4% (3·4 to 5·3)**	**594 (508 to 654)**	**20·7 (17·9 to 22·6)**	**14·3% (1·0 to 26·4)**
Central Europe, eastern Europe, and central Asia	**48 100 (45 100 to 51 200)**	**13·0% (12·2 to 13·8)**	**1·4% (0·8 to 2·1)**	**49·2 (45·7 to 52·7)**	**12·0 (11·1 to 12·8)**	**16·9% (6·3 to 28·0)**
Central Asia	9240 (8620 to 9860)	16·0% (15·0 to 17·0)	4·0% (2·6 to 5·4)	10·6 (9·77 to 11·6)	20·8 (18·9 to 22·5)	27·1% (11·3 to 44·8)
Armenia	444 (411 to 474)	15·8% (14·7 to 16·8)	3·2% (–0·5 to 6·8)	0·336 (0·303 to 0·375)	10·6 (9·5 to 11·8)	17·6% (–2·6 to 42·0)
Azerbaijan	1110 (1040 to 1190)	15·7% (14·7 to 16·7)	1·8% (0·0 to 3·8)	0·999 (0·774 to 1·25)	15·6 (11·9 to 19·6)	–8·9% (–34·3 to 35·9)
Georgia	535 (504 to 567)	16·3% (15·3 to 17·3)	4·0% (1·4 to 6·8)	0·597 (0·521 to 0·695)	16·2 (14·2 to 18·8)	101·6% (53·3 to 167·0)
Kazakhstan	2060 (1930 to 2190)	16·2% (15·2 to 17·2)	2·9% (–0·1 to 5·5)	2·75 (2·47 to 3·03)	23·6 (21·0 to 26·0)	109·0% (85·2 to 134·4)
Kyrgyzstan	588 (548 to 632)	16·0% (15·1 to 17·0)	2·8% (0·9 to 4·9)	0·479 (0·427 to 0·531)	15·8 (14·1 to 17·4)	–14·0% (–29·6 to 2·9)
Mongolia	279 (261 to 300)	15·9% (14·9 to 16·9)	0·5% (–1·4 to 2·5)	0·291 (0·236 to 0·359)	20·1 (15·6 to 25·0)	–24·7% (–44·0 to 7·1)
Tajikistan	691 (640 to 748)	14·8% (13·9 to 15·8)	–1·0% (–2·6 to 0·6)	0·606 (0·446 to 0·753)	18·9 (14·2 to 23·9)	17·2% (–18·7 to 76·6)
Turkmenistan	489 (457 to 523)	16·5% (15·4 to 17·6)	2·5% (0·9 to 4·4)	0·689 (0·597 to 0·792)	25·0 (21·8 to 28·7)	37·5% (17·3 to 64·0)
Uzbekistan	3040 (2810 to 3260)	16·2% (15·1 to 17·1)	8·2% (5·9 to 10·6)	3·89 (3·55 to 4·26)	25·1 (22·8 to 27·5)	–6·9% (–20·9 to 9·5)
Central Europe	10 200 (9540 to 10 800)	8·5% (8·0 to 9·0)	–1·2% (–2·0 to –0·4)	21·9 (20 to 23·3)	14·9 (13·7 to 15·8)	–5·5% (–12·4 to 2·9)
Albania	191 (178 to 203)	8·1% (7·6 to 8·7)	–1·5% (–3·4 to 0·1)	0·402 (0·303 to 0·541)	15·2 (11·6 to 20·3)	–31·8% (–45·9 to –4·2)
Bosnia and Herzegovina	277 (260 to 297)	8·5% (7·9 to 9·0)	3·6% (1·6 to 5·6)	0·605 (0·436 to 0·764)	15·4 (11·3 to 19·5)	–15·9% (–42·0 to 15·7)
Bulgaria	663 (619 to 707)	8·5% (8·0 to 9·0)	3·9% (2·1 to 5·9)	1·97 (1·76 to 2·19)	21·1 (18·9 to 23·6)	118·3% (91·0 to 147·5)
Croatia	373 (350 to 399)	8·4% (7·9 to 9·0)	1·4% (–0·4 to 3·2)	1·22 (1·09 to 1·33)	20·1 (18·0 to 22·0)	52·5% (36·4 to 74·1)
Czechia	909 (848 to 969)	8·0% (7·5 to 8·6)	–0·3% (–2·2 to 1·3)	1·64 (1·47 to 1·83)	11·4 (10·2 to 12·6)	–10·8% (–21·0 to 1·0)
Hungary	831 (777 to 882)	8·1% (7·7 to 8·6)	0·2% (–1·6 to 2·2)	2·61 (2·36 to 2·85)	19·8 (17·9 to 21·4)	117·8% (101·0 to 135·5)
Montenegro	52·5 (49·2 to 56·3)	8·7% (8·2 to 9·3)	4·5% (2·5 to 6·4)	0·165 (0·125 to 0·213)	24·5 (18·6 to 31·8)	5·9% (–23·7 to 55·3)
North Macedonia	176 (164 to 187)	9·8% (9·1 to 10·4)	1·8% (0·1 to 3·7)	0·378 (0·272 to 0·477)	19·0 (13·8 to 24·0)	–2·8% (–42·9 to 52·1)
Poland	3550 (3320 to 3790)	8·9% (8·4 to 9·5)	–5·4% (–6·1 to –4·8)	5·54 (4·91 to 6·12)	11·2 (9·9 to 12·3)	–42·7% (–49·9 to –35·4)

(Table continues on next page)

	Prevalence			Deaths		
	Count (thousands), 2023	Age-standardised prevalence (%), 2023	Percentage change in age-standardised prevalence between 1990 and 2023 (%)	Count (thousands), 2023	Age-standardised rate per 100 000, 2023	Percentage change in age-standardised rates between 1990 and 2023 (%)
(Continued from previous page)						
Romania	1730 (1640 to 1820)	8·5% (8·1 to 8·9)	−1·2% (−4·2 to 2·3)	3·43 (3·14 to 3·74)	14·2 (13·0 to 15·4)	3·2% (−5·4 to 13·3)
Serbia	634 (596 to 676)	7·4% (7·0 to 7·9)	3·5% (1·1 to 6·9)	2·53 (1·82 to 3·17)	26·6 (19·9 to 33·3)	3·0% (−24·6 to 43·2)
Slovakia	428 (398 to 457)	8·1% (7·6 to 8·6)	−0·4% (−1·9 to 1·5)	0·714 (0·61 to 0·854)	11·8 (10·1 to 14·0)	−33·1% (−46·8 to −15·8)
Slovenia	190 (178 to 203)	8·1% (7·6 to 8·6)	0·2% (−1·7 to 2·0)	0·356 (0·307 to 0·402)	10·5 (9·1 to 11·8)	−3·2% (−15·7 to 11·2)
Eastern Europe	28 700 (26 900 to 30 600)	14·6% (13·7 to 15·6)	0·1% (−0·5 to 0·7)	16·7 (15·2 to 18·4)	7·5 (6·8 to 8·3)	22·2% (5·7 to 40·7)
Belarus	1380 (1290 to 1470)	15·5% (14·5 to 16·5)	2·5% (0·6 to 4·5)	0·492 (0·435 to 0·559)	4·9 (4·3 to 5·6)	14·7% (−5·3 to 38·2)
Estonia	235 (222 to 250)	16·4% (15·3 to 17·5)	2·2% (0·4 to 4·1)	0·773 (0·677 to 0·864)	37·5 (32·9 to 41·7)	101·6% (74·1 to 134·9)
Latvia	331 (309 to 351)	16·1% (15·2 to 17·2)	4·4% (2·6 to 6·5)	0·46 (0·412 to 0·509)	16·9 (15·3 to 18·8)	110·5% (78·2 to 146·3)
Lithuania	489 (458 to 519)	16·2% (15·1 to 17·3)	3·8% (2·0 to 5·7)	0·403 (0·365 to 0·446)	10·4 (9·5 to 11·5)	55·6% (35·0 to 77·6)
Moldova	638 (601 to 677)	18·4% (17·3 to 19·6)	6·4% (3·1 to 9·4)	0·207 (0·185 to 0·232)	5·3 (4·8 to 5·9)	4·9% (−9·7 to 22·8)
Russia	19 300 (18 100 to 20 700)	14·2% (13·3 to 15·2)	−0·3% (−0·8 to 0·3)	12·8 (11·7 to 14·2)	8·3 (7·5 to 9·2)	10·0% (−4·9 to 26·5)
Ukraine	6330 (5900 to 6730)	15·2% (14·2 to 16·3)	1·0% (−0·8 to 2·9)	1·52 (1·35 to 1·7)	3·5 (3·1 to 3·9)	48·0% (17·3 to 76·8)
High income	**130 000 (123 000 to 138 000)**	**10·8% (10·2 to 11·5)**	**0·6% (0·0 to 1·2)**	**400 (330 to 448)**	**23·2 (19·6 to 25·8)**	**49·4% (33·0 to 67·4)**
Australasia	2820 (2640 to 3020)	8·9% (8·3 to 9·5)	−1·3% (−4·2 to 1·9)	6·72 (5·57 to 7·45)	15·6 (13·1 to 17·2)	14·0% (1·5 to 28·4)
Australia	2380 (2220 to 2550)	8·8% (8·3 to 9·5)	−1·6% (−5·2 to 2·3)	5·56 (4·58 to 6·19)	14·9 (12·4 to 16·5)	10·2% (−1·8 to 24·5)
New Zealand	444 (414 to 473)	9·2% (8·5 to 9·8)	0·4% (−1·2 to 2·1)	1·16 (1·01 to 1·29)	19·5 (17·0 to 21·6)	32·8% (18·0 to 51·8)
High-income Asia Pacific	35 300 (33 500 to 37 200)	14·2% (13·4 to 15·1)	−5·4% (−6·3 to −4·6)	67·6 (51 to 79·2)	15·4 (12·1 to 17·8)	−33·2% (−45·7 to −21·5)
Brunei	45·1 (41·9 to 48·6)	15·6% (14·7 to 16·6)	0·5% (−1·5 to 2·4)	0·0965 (0·0762 to 0·118)	46·4 (36·3 to 57·6)	−28·1% (−46·5 to 11·4)
Japan	28 600 (27 000 to 30 300)	15·6% (14·6 to 16·6)	0·4% (−0·2 to 1·0)	56 (42·1 to 65·8)	14·9 (11·7 to 17·3)	−32·8% (−43·7 to −20·9)
Singapore	868 (821 to 914)	16·3% (15·5 to 17·1)	−1·9% (−9·8 to 2·9)	1 (0·856 to 1·11)	17·2 (14·7 to 19·1)	−22·5% (−31·4 to −13·0)
South Korea	5780 (5530 to 6050)	10·5% (10·0 to 11·0)	−18·2% (−22·2 to −14·8)	10·5 (6·1 to 13·7)	16·7 (9·8 to 21·9)	−38·3% (−74·6 to −0·8)
High-income North America	42 100 (39 400 to 44 900)	11·5% (10·8 to 12·3)	3·5% (2·5 to 4·8)	156 (132 to 175)	34·9 (29·7 to 38·8)	177·5% (143·3 to 221·1)
Canada	3780 (3600 to 3960)	9·6% (9·2 to 10·1)	−6·9% (−12·3 to −2·1)	9·67 (8·21 to 10·6)	17·5 (15·0 to 19·1)	73·3% (57·9 to 90·6)
Greenland	4·47 (4·18 to 4·84)	10·9% (10·2 to 11·7)	2·4% (0·4 to 4·5)	0·00842 (0·00501 to 0·0118)	30·4 (17·4 to 43·3)	3·1% (−36·3 to 72·0)
USA	38 300 (35 800 to 40 900)	11·7% (11·0 to 12·6)	5·0% (4·0 to 6·2)	147 (124 to 164)	37·2 (31·5 to 41·4)	189·1% (152·4 to 235·9)
Southern Latin America	6420 (5980 to 6950)	11·8% (10·9 to 12·8)	5·0% (3·1 to 6·8)	25·7 (22·6 to 28·4)	40·3 (35·7 to 44·4)	−9·4% (−18·5 to 0·0)
Argentina	4160 (3860 to 4520)	11·6% (10·7 to 12·6)	6·5% (4·4 to 8·8)	19·2 (16·8 to 21·6)	46·2 (40·5 to 51·9)	−13·6% (−25·7 to −1·7)

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	Prevalence			Deaths		
	Count (thousands), 2023	Age-standardised prevalence (%), 2023	Percentage change in age-standardised prevalence between 1990 and 2023 (%)	Count (thousands), 2023	Age-standardised rate per 100 000, 2023	Percentage change in age-standardised rates between 1990 and 2023 (%)
(Continued from previous page)						
Chile	1880 (1740 to 2030)	12·0% (11·2 to 13·0)	2·1% (−1·1 to 6·7)	5·3 (4·6 to 5·77)	29·5 (25·8 to 32·0)	19·1% (7·4 to 33·1)
Uruguay	379 (354 to 408)	12·6% (11·7 to 13·6)	2·6% (0·1 to 5·2)	1·21 (1·05 to 1·37)	29·1 (25·5 to 32·9)	11·7% (−3·0 to 28·2)
Western Europe	43 700 (41 300 to 46 300)	8·5% (8·0 to 9·1)	−3·4% (−4·1 to −2·6)	144 (117 to 161)	17·6 (14·6 to 19·6)	35·7% (22·1 to 49·9)
Andorra	8·79 (8·25 to 9·4)	9·3% (8·8 to 10·0)	0·2% (−1·7 to 2·0)	0·0216 (0·0159 to 0·0286)	14·2 (10·7 to 18·4)	−14·8% (−39·3 to 33·2)
Austria	977 (921 to 1040)	9·6% (9·0 to 10·2)	3·3% (1·2 to 5·3)	3·96 (3·34 to 4·44)	26·7 (22·6 to 29·9)	163·7% (139·0 to 187·9)
Belgium	1180 (1110 to 1260)	9·4% (8·8 to 10·0)	7·4% (4·7 to 10·7)	3 (2·47 to 3·44)	15·2 (12·6 to 17·3)	−3·1% (−15·8 to 10·7)
Cyprus	116 (108 to 124)	9·8% (9·3 to 10·6)	0·7% (−1·2 to 2·7)	0·42 (0·315 to 0·548)	36·2 (27·5 to 46·9)	−13·1% (−41·2 to 41·7)
Denmark	625 (582 to 668)	9·6% (8·9 to 10·3)	3·0% (0·7 to 5·3)	1·99 (1·69 to 2·25)	21·6 (18·3 to 24·4)	181·8% (143·8 to 222·5)
Finland	683 (641 to 726)	10·1% (9·5 to 10·8)	−4·0% (−6·0 to −2·0)	0·869 (0·706 to 0·995)	8·3 (6·8 to 9·5)	61·1% (42·7 to 80·6)
France	5420 (5100 to 5800)	7·2% (6·7 to 7·8)	3·5% (0·1 to 7·0)	15·6 (13 to 18)	12·4 (10·4 to 14·3)	16·4% (0·6 to 33·0)
Germany	8850 (8450 to 9290)	8·4% (7·9 to 8·9)	−1·5% (−4·5 to 2·1)	42·4 (34·2 to 47·8)	24·2 (19·8 to 27·1)	67·2% (45·9 to 90·1)
Greece	1290 (1210 to 1370)	9·6% (9·0 to 10·2)	0·7% (−1·6 to 2·8)	7·26 (6·33 to 8·06)	34·6 (30·4 to 38·3)	0·3% (−10·8 to 13·6)
Iceland	28·1 (26·2 to 30·1)	8·1% (7·5 to 8·7)	0·8% (−1·8 to 3·5)	0·0443 (0·0363 to 0·0511)	10·3 (8·5 to 11·8)	70·7% (46·1 to 100·6)
Ireland	538 (513 to 568)	11·2% (10·6 to 11·9)	−1·4% (−4·9 to 2·7)	0·652 (0·536 to 0·76)	11·2 (9·2 to 13·0)	−8·3% (−21·4 to 6·3)
Israel	737 (692 to 785)	9·8% (9·2 to 10·5)	0·1% (−1·7 to 2·0)	2·91 (2·45 to 3·34)	31·0 (26·4 to 35·4)	−11·1% (−21·1 to 0·1)
Italy	6120 (5760 to 6560)	8·2% (7·7 to 8·8)	−3·9% (−4·5 to −3·2)	19·3 (15·2 to 22·2)	14·8 (11·9 to 17·0)	11·1% (−4·3 to 26·5)
Luxembourg	50·7 (48 to 53·6)	8·4% (8·0 to 8·9)	−2·4% (−5·8 to 1·3)	0·158 (0·135 to 0·179)	21·0 (18·0 to 23·8)	30·3% (12·4 to 52·8)
Malta	55 (51·6 to 58·5)	9·4% (8·9 to 10·1)	−3·0% (−5·0 to −1·4)	0·148 (0·125 to 0·172)	21·0 (17·8 to 24·3)	9·9% (−5·8 to 28·2)
Monaco	4·83 (4·51 to 5·18)	9·3% (8·7 to 10·0)	0·6% (−1·5 to 2·6)	0·0164 (0·0113 to 0·0234)	20·7 (14·3 to 29·6)	57·9% (0·6 to 169·6)
Netherlands	1650 (1540 to 1770)	9·0% (8·4 to 9·7)	−3·6% (−10·3 to 1·4)	4·46 (3·69 to 5·04)	16·3 (13·6 to 18·4)	57·4% (38·5 to 80·0)
Norway	555 (523 to 592)	10·0% (9·4 to 10·8)	9·2% (8·1 to 10·2)	0·869 (0·704 to 0·998)	11·1 (9·0 to 12·7)	97·1% (66·9 to 130·3)
Portugal	946 (890 to 1020)	7·7% (7·1 to 8·3)	−1·2% (−3·5 to 0·8)	4·73 (3·85 to 5·34)	21·9 (18·1 to 24·6)	14·5% (−1·8 to 30·9)
San Marino	3·83 (3·59 to 4·11)	9·1% (8·5 to 9·8)	−0·5% (−2·2 to 1·6)	0·00744 (0·00528 to 0·0102)	11·3 (8·0 to 15·3)	−16·7% (−43·6 to 36·8)
Spain	4860 (4500 to 5200)	8·6% (8·0 to 9·3)	0·6% (−2·6 to 3·1)	16·8 (13·5 to 19·2)	17·9 (14·6 to 20·5)	−12·7% (−23·2 to −0·6)
Sweden	1440 (1360 to 1520)	11·8% (11·1 to 12·6)	−4·7% (−6·3 to −2·8)	2·82 (2·31 to 3·13)	15·4 (12·8 to 17·1)	151·7% (116·9 to 187·0)
Switzerland	1170 (1100 to 1250)	11·7% (11·1 to 12·5)	4·8% (1·5 to 8·1)	3·13 (2·49 to 3·59)	19·7 (15·7 to 22·5)	73·0% (51·7 to 98·2)
UK	6330 (5910 to 6790)	8·4% (7·8 to 9·0)	−17·6% (−18·3 to −16·9)	12 (10·2 to 13·3)	11·3 (9·7 to 12·5)	68·4% (50·7 to 83·9)

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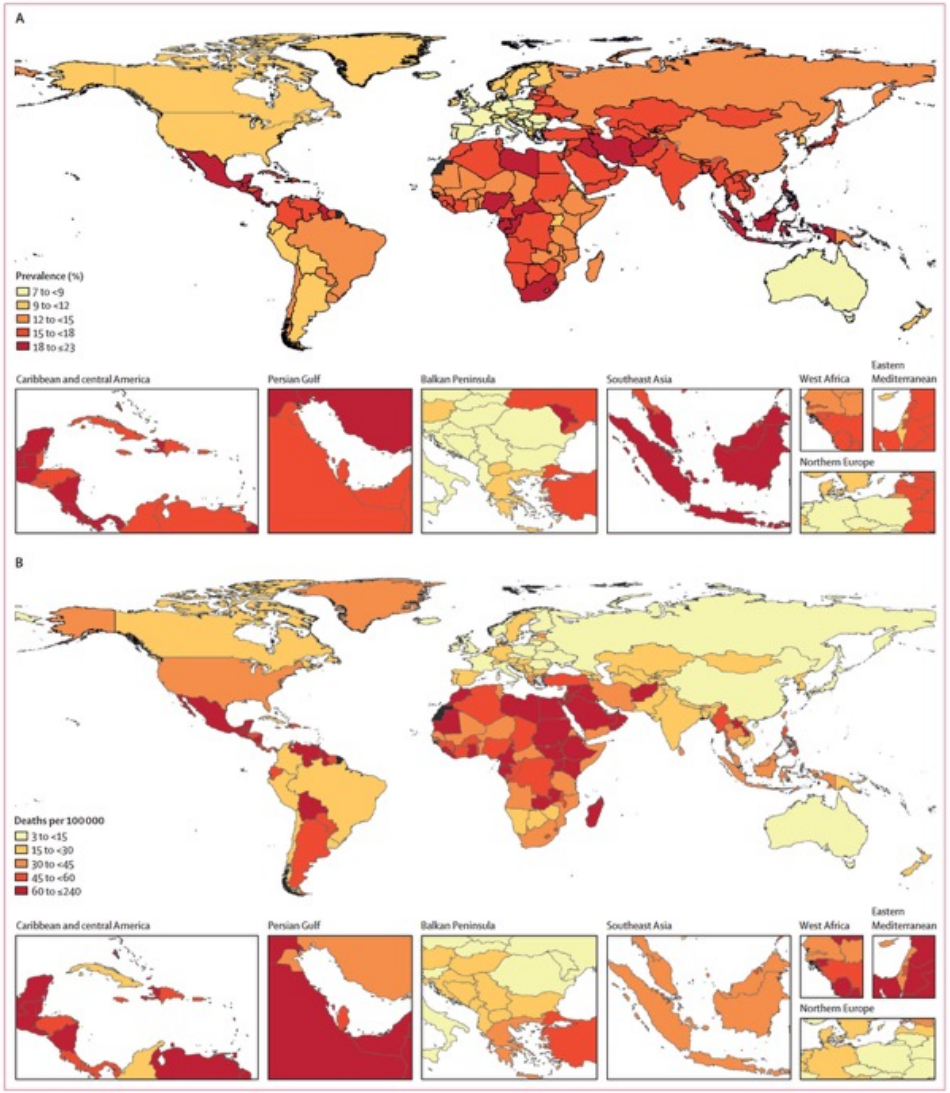


Figure 1: Global age-standardised total chronic kidney disease prevalence (A) and death rates per 100 000 (B) in 2023 in people aged 20 years and older

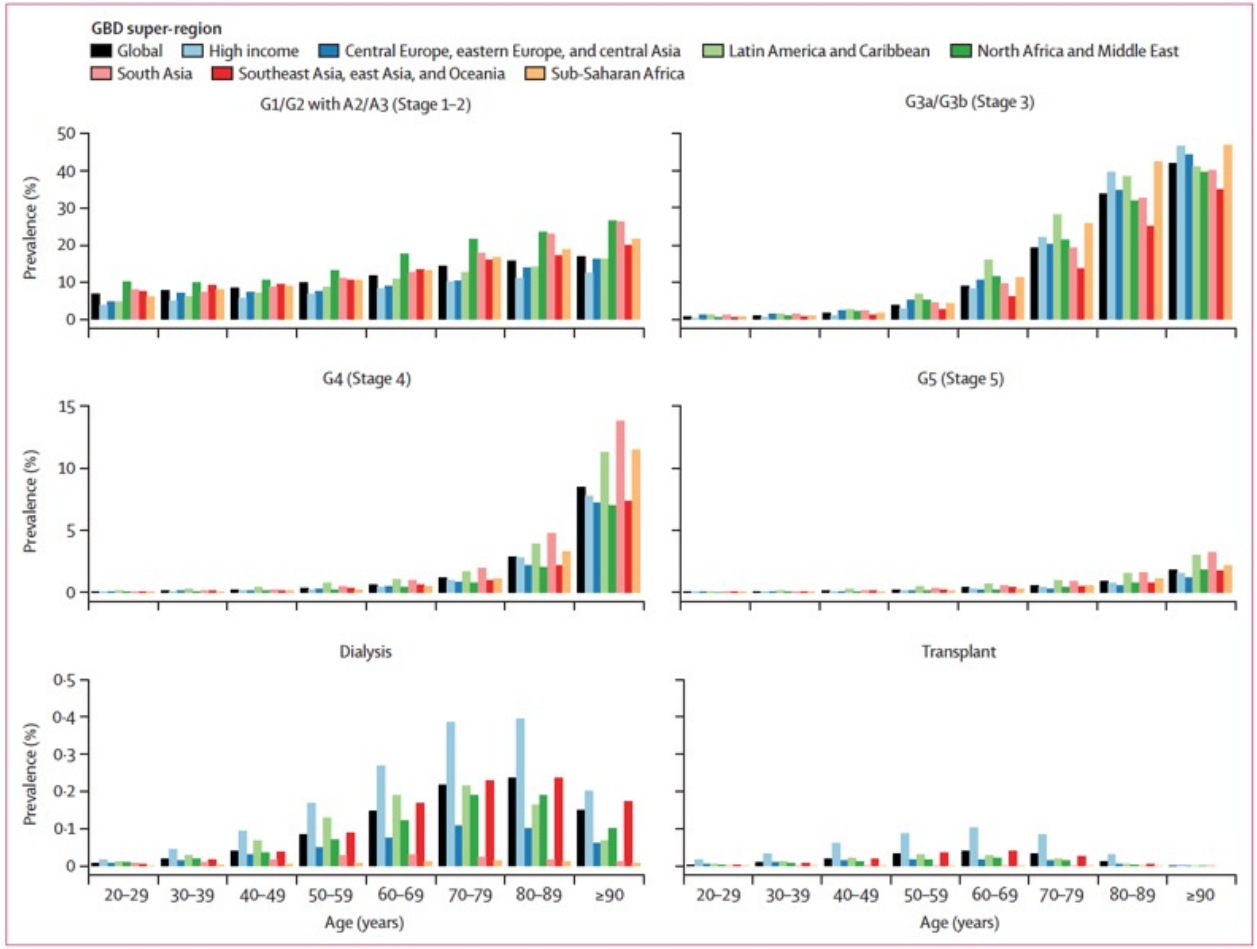


***Figure 2*: Chronic kidney disease stage prevalence by age, globally, and by GBD super-region in 2023**

GBD super-regions are created by grouping countries based on epidemiological and geographical similarity into 21 regions, with these regions further grouped into seven, mutually exclusive super-regions. The high-income super-region includes Australasia, high-income Asia Pacific, high-income North America, southern Latin America and western Europe (see appendix section 6, table S17, for the full GBD location hierarchy). GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

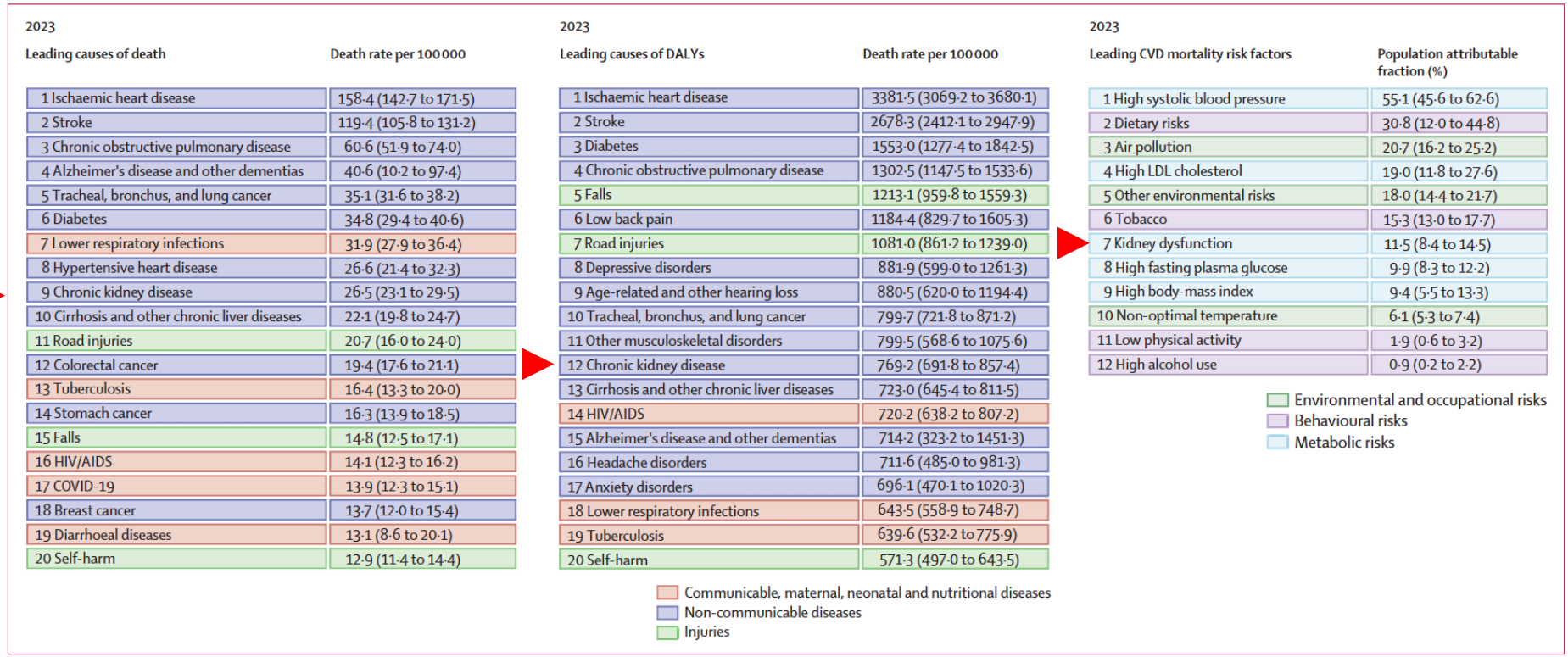


Figure 3: **Leading causes of global deaths, DALYs, and leading CVD mortality risk factors in 2023, age-standardised for people aged 20 years and older**

The listed population attributable fractions do not take into account mediation between risk factors. Therefore, the sum of the population attributable fractions might exceed 100%. CVD=cardiovascular disease. DALY=disability-adjusted life-year.

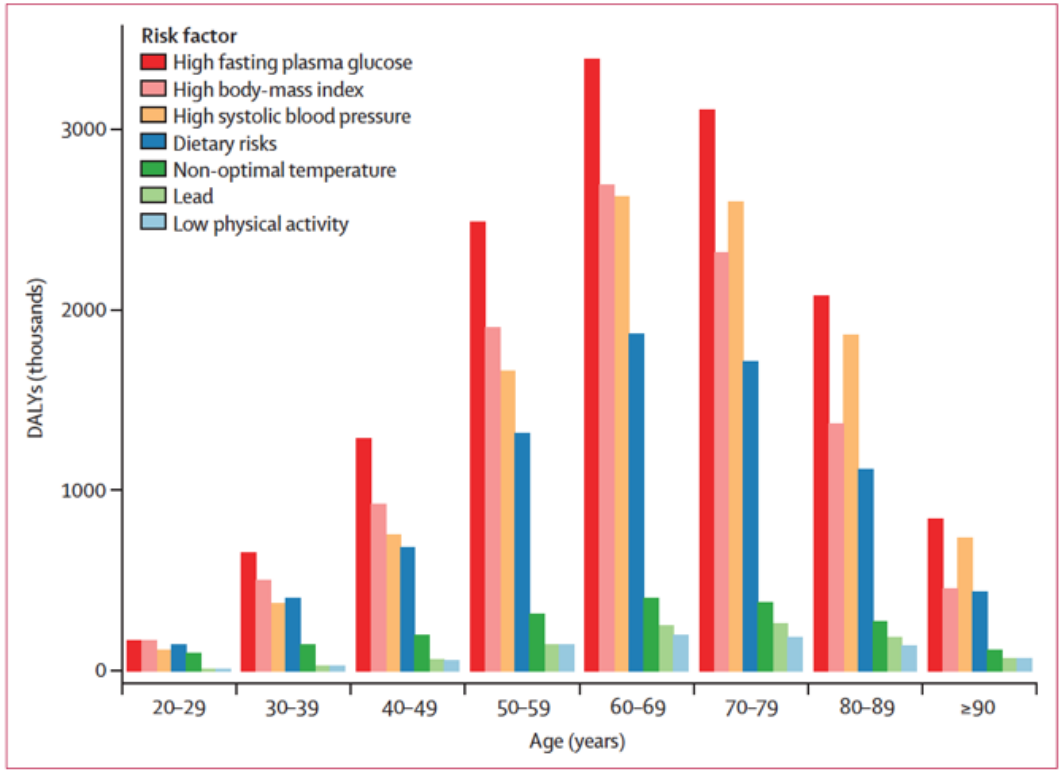


Figure 4: **Number of chronic kidney disease DALYs attributable to risk factors globally by age in 2023**
DALYs might be attributed to more than one risk factor or not be attributed to any risk factor. Therefore, the sum of the attributable DALYs might not be equal to the total chronic kidney disease DALYs. DALY=disability-adjusted life-year.

Research in context

Evidence before this study

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has generated publicly available estimates of chronic kidney disease deaths, prevalence, years of life lost, years lived with disability, and disability-adjusted life-years across age, sex, and location since 1990. GBD produces estimates of CKD with each new cycle, but there has not been a comprehensive description and analysis of data, methods, and estimates since GBD 2017. Although several systematic reviews and meta-analyses have been done by other research groups, these analyses have not been as granular demographically and they have focused exclusively on prevalence or deaths. In this study, we present estimates of morbidity, mortality, and the burden of chronic kidney disease by severity. We conducted systematic reviews in PubMed from Jan 1, 1990, to Sep 13, 2022 (appendix 1 section 3.1), carrying out opportunistic searches of renal registries and incorporating data shared by country collaborators. To estimate the burden of cardiovascular disease due to kidney dysfunction, we acquired data on the risk relationship from a systematic review done from Jan 1, 1990, to April 25, 2023, and relative risk data from the Chronic Kidney Disease Prognosis Consortium (appendix 1 section 4.1).

Added value of this study

This study updates and expands on previously published estimates from GBD. We report epidemiological patterns from 1990 to 2023 and describe CKD patterns for adults by stages—a feature that was not included in the previous analysis and is not otherwise publicly available. We also explicitly quantify the proportion of the cardiovascular disease burden attributable to kidney dysfunction and chronic kidney disease burden attributable to selected risk factors. This information is essential to policy makers, health-care professionals, health researchers, and individuals with chronic kidney disease to understand the scale, magnitude, and trajectory of this disease and to guide resource allocation.

Implications of all the available evidence

Chronic kidney disease is a major health condition that both serves as a risk factor for diseases with high morbidity and mortality and is an important cause of disease burden in its own right. Despite its prominent role among non-communicable diseases, it does not engender the same type of attention as other leading causes of health loss from policy makers. This study serves to underscore and quantify the growing impact of chronic kidney disease across age, year, sex, and location that can be used to understand future research needs and areas for intervention as well as societal costs.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is increasingly recognised and diagnosed in clinical practice. Over the past two decades, a substantial amount of new knowledge on this condition has been accrued, including a better understanding of the pathophysiology, genetic predisposition for a proportion of patients, diagnostic tools, management with a disease-specific therapy, and predictors of outcome. Peripartum cardiomyopathy occurs globally in all ethnic groups and should be suspected in any women who are peripartum presenting with symptoms and signs indicative of heart failure towards the end of pregnancy or in the months following delivery. Verification of left ventricular systolic dysfunction (ejection fraction <45%) is crucial for the diagnosis of peripartum cardiomyopathy and the exclusion of other causes of heart failure, such as pre-existing cardiomyopathy, valvular heart disease, or congenital heart disease. Peripartum cardiomyopathy is a disease with considerable maternal and neonatal morbidity and mortality, with only half of women experiencing complete myocardial recovery within 6 months of the onset of symptoms. This Seminar summarises current knowledge of peripartum cardiomyopathy genetics, pathophysiology, diagnostic approaches, medical management, and outcome. Furthermore, we provide guidance on both risk stratification by use of a novel score to predict recovery and on the outcomes of a subsequent pregnancy.

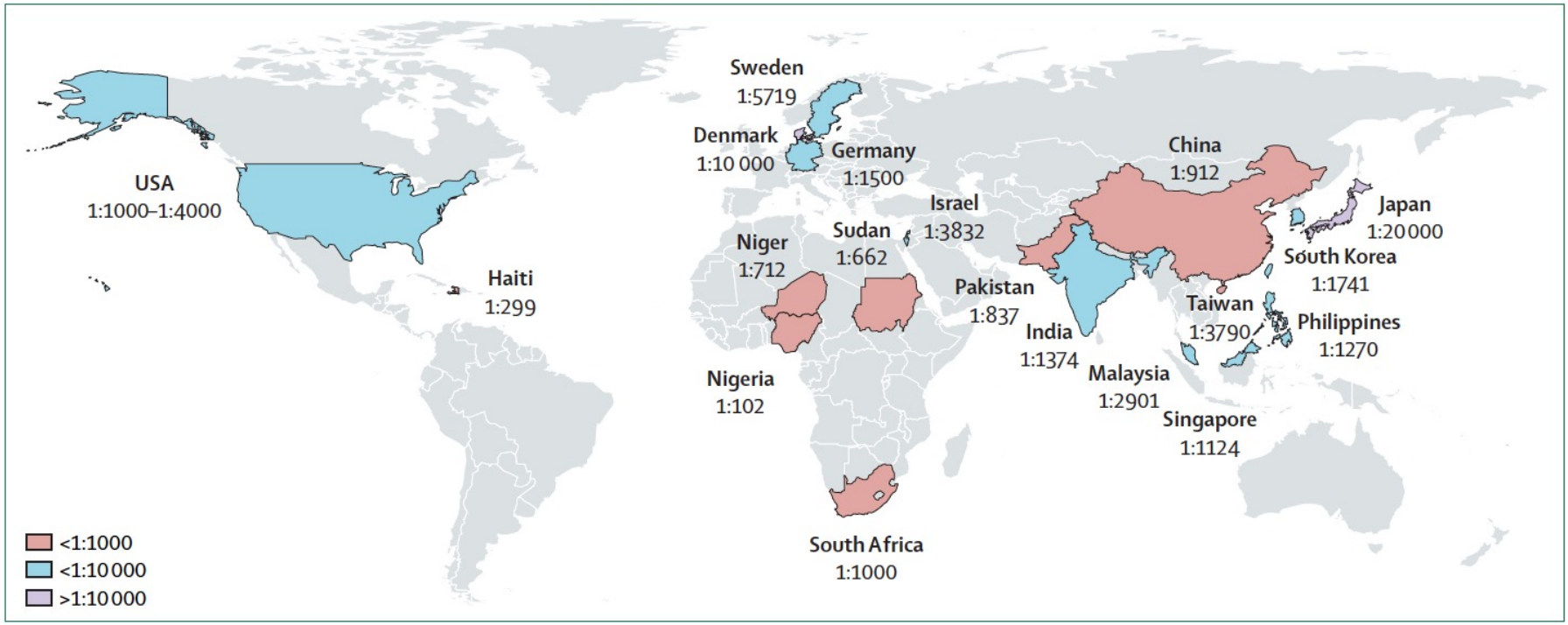


Figure 1: **Global incidence**
Adapted from Viljoen et al,[7] by permission of Wolters Kluwer Health.

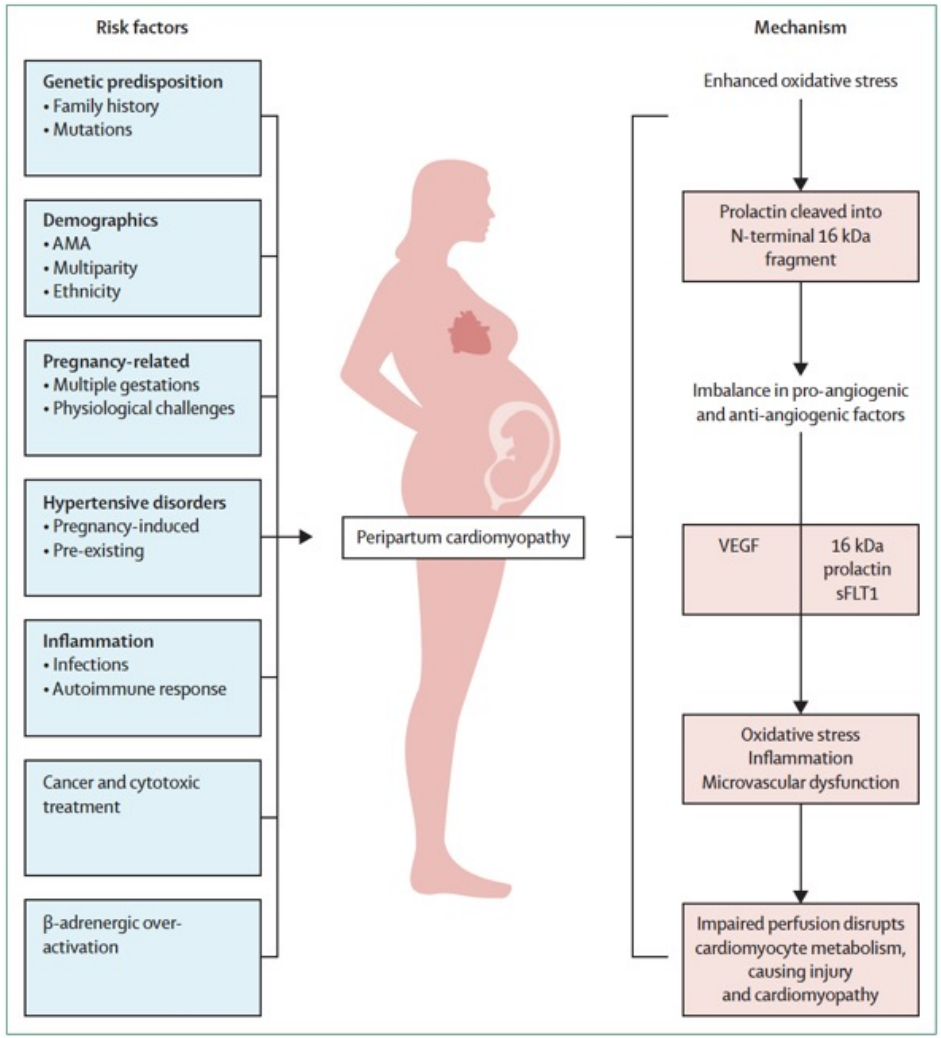


Figure 2: **Multiple hit model**
AMA=advanced maternal age. sFLT1=soluble fms-like tyrosine kinase-1. VEGF=vascular endothelial growth factor.

	History	Onset	Biomarkers	Echocardiography or CMRI	Differentiation from peripartum cardiomyopathy
Peripartum cardiomyopathy	No known cardiac disease; no heart failure signs or symptoms before pregnancy	Towards the end of pregnancy and in the months following delivery	Elevated natriuretic peptides	Reduced systolic left ventricular function; LVEF <45%	NA
Myocarditis	Previous viral infection (eg, respiratory)	Acute or subacute onset after viral infection	Elevated troponin; elevated C-reactive protein	Normal or reduced systolic left ventricular function; typical myocardial LGE pattern; pericardial effusion	CMRI (LGE pattern); myocardial biopsy
Pre-existing idiopathic or familial DCM or acquired cardiomyopathy	Heart failure signs or symptoms or known heart disease before pregnancy	During the second trimester of pregnancy	Elevated natriuretic peptides	Reduced systolic left ventricular function; right ventricular dysfunction possible; typical myocardial late enhancement pattern (DCM)	History; echocardiography; CMRI (LGE pattern)
Takotsubo syndrome	Chest pain; stressful delivery or emergency due to fetal complications	Acute onset during delivery or immediately after	Elevated natriuretic peptides	Regional wall motion irregularities with typical anatomical patterns	History; echocardiography
Pregnancy-associated myocardial infarction	Chest pain; epigastric pain	Acute onset during pregnancy or after delivery	Elevated troponin	Regional wall motion irregularities; ischaemic myocardial scar	History; echocardiography; coronary angiography; CMRI (LGE pattern)
Pulmonary embolism	Chest pain; unilateral leg swelling; acute dyspnoea	Acute onset during pregnancy or after delivery	Elevated natriuretic peptides or troponin; elevated D-dimer	Right ventricular dysfunction; right ventricular dilation; left ventricular function usually normal	CT; ventilation or perfusion scan
Amniotic fluid embolism	Chest pain during or immediately after delivery; acute dyspnoea	Acute onset during delivery or immediately after	Elevated natriuretic peptides possible	Reduced systolic right ventricular function; right ventricular dilatation	History; echocardiography
Hypertensive heart disease or severe pre-eclampsia	Pre-existing or new-onset hypertension; proteinuria	During the second trimester of pregnancy	Elevated natriuretic peptides	Left ventricular hypertrophy; diastolic dysfunction; transient left ventricular dysfunction	History; echocardiography
Hypertrophic cardiomyopathy	Familial predisposition	During the second trimester of pregnancy	Elevated natriuretic peptides	Left ventricular hypertrophy; typical myocardial LGE pattern; LVOTO (HOCM)	History; echocardiography; CMRI (LGE pattern)
HIV/AIDS cardiomyopathy	HIV infection; AIDS	During the second trimester of pregnancy	Elevated natriuretic peptides	Reduced systolic left ventricular function; left ventricle or right ventricle often not dilated	HIV serology; test
Pre-existing (unknown) congenital heart disease	Heart failure signs or symptoms before pregnancy; known heart disease; previous cardiac surgery	During the second trimester of pregnancy	Elevated natriuretic peptides	(Corrected) Congenital heart defects; cardiac shunts	History; echocardiography
Pre-existing valvular heart disease	Heart failure signs or symptoms before pregnancy; known heart disease	During the second trimester of pregnancy	Elevated natriuretic peptides	Valvular stenosis or regurgitation; prosthetic heart valves	History; echocardiography

CMRI=cardiac magnetic resonance imaging. DCM=dilative cardiomyopathy. HOCM=hypertrophic obstructive cardiomyopathy. LGE=late gadolinium enhancement. LVEF=left ventricular ejection fraction. LVOTO=left ventricular outflow tract obstruction. NA=not applicable.

Table: **Differential diagnosis of peripartum cardiomyopathy.**

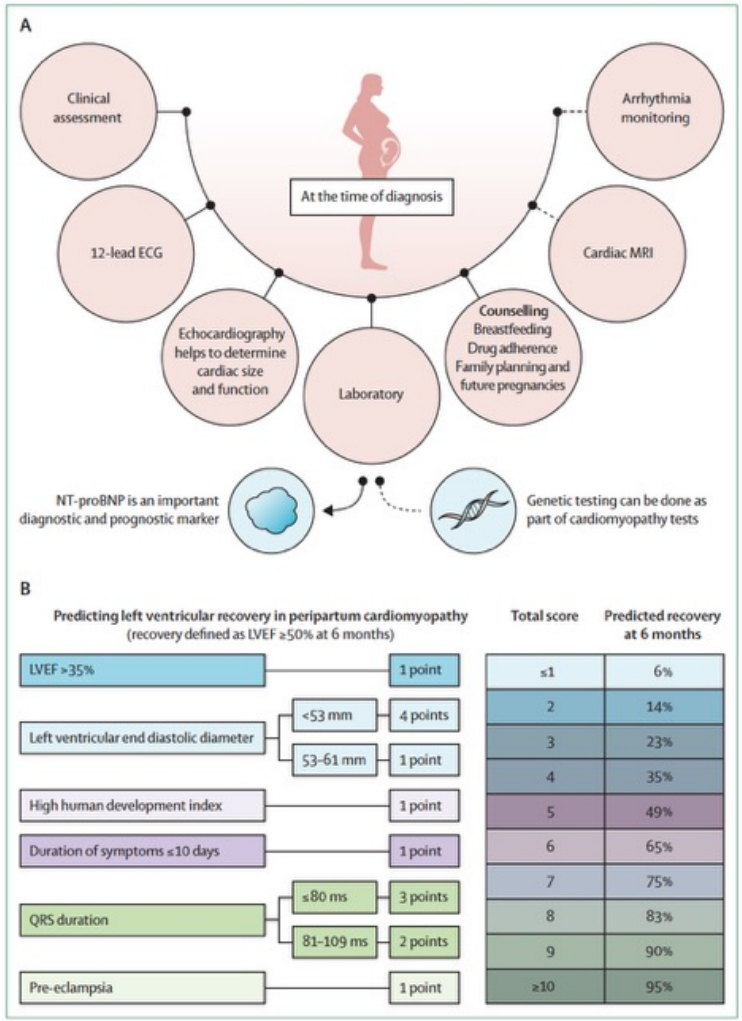


Figure 3: **Testing and scoring**
(A) Diagnosis testing for peripartum cardiomyopathy. Adapted from Sliwa et al.[60] (B) The Peripartum Cardiomyopathy Recovery Score. Adapted from Jackson et al.[44] ECG=electrocardiography. LVEF=left ventricular ejection fraction.

BOARD scheme

Bromocriptine (dose according to severity of the disease)	**Oral heart failure drugs** (β blockers, ACE inhibitor or ARB, MRA)	**Anticoagulation** (at least in prophylactic dose)	**Relaxants** (intravenous vasodilators if SBP >110 mm Hg)	**Diuretics** (in case of fluid overload)

Drug	Heart failure and absence of complete left ventricular recovery	Complete and sustained recovery (LVEF >55% and NYHA functional class I)
β blocker	Essential for all patients in standard or maximally tolerated dosages	Continue all drugs for at least 6–12 months or lifelong after full recovery; individual approach or discuss with patient. Discontinue stepwise and monitor symptoms and left ventricular function: 1) MRA 2) SGLT2 inhibitor 3) ARNI, ACE inhibitor, or ARB 4) β blocker
ARNI	Essential for all patients in standard or maximally tolerated dosages	
ACE inhibitor	Recommended for all patients in standard or maximally tolerated dosages when ARNI is not available or contraindicated	
ARB	Recommended in patients who do not tolerate ACE inhibitor	
MRA	Recommended for all patients in standard or maximally tolerated dosages; preferably eplerenone due to less hormonal side-effects and less blood pressure reduction compared with spironolactone	
SGLT2 inhibitor	Essential for all patients in standard dosage (dapagliflozin 10 mg or empagliflozin 10 mg once daily)	
Ivabradine	Recommended in patients in sinus rhythm with a persisting heart rate >70 bpm at rest despite maximal tolerated β blocker dose	Discontinue if heart rate <50 bpm or in case of complete recovery
Diuretics	Recommended in patients with fluid overload	Taper dose or discontinue if no signs of fluid overload; maintain only if part of antihypertensive therapy

Figure 4: **Drug treatment for patients with peripartum cardiomyopathy during the acute phase (upper panel) and during the subacute or chronic phase (lower panel)**
ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blockers. ARNI=angiotensin receptor neprilysin inhibitors. bpm=beats per minute. LVEF=left ventricular ejection fraction. MRA=mineralocorticoid receptor antagonist. NYHA=New York Heart Association. SBP=systolic blood pressure. SGLT2=sodium-glucose co-transporter-2.

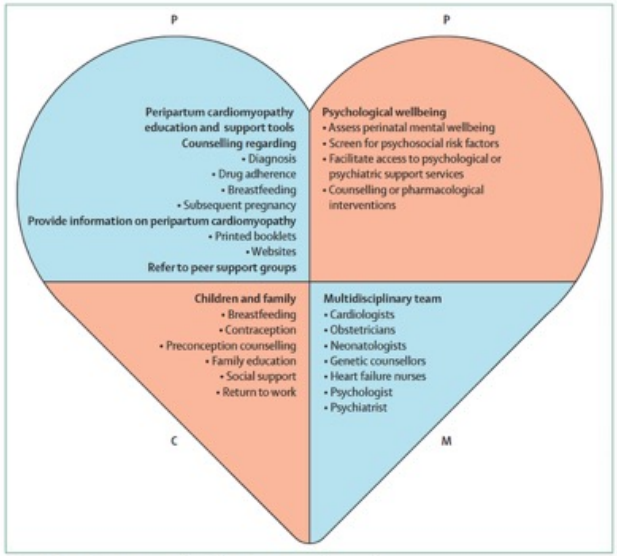


Figure 5: **Supporting women to live with peripartum cardiomyopathy**
Adapted from Sliwa et al.[66] PPCM=peripartum cardiomyopathy.

Conclusion and future research

Peripartum cardiomyopathy is a global disease in which the diagnosis is often delayed, leading to considerable morbidity and mortality. It is a substantial contributor to early (<42 days) and late (up to 1 year) postpartum maternal death. In the past two decades, remarkable advances in understanding the pathogenesis of the condition and patient management have been reached, including a disease-specific therapeutic option, bromocriptine, which should be considered in all cases of peripartum cardiomyopathy, in addition to GDMT for heart failure. In the USA, bromocriptine is not prescribed for peripartum cardiomyopathy—the ongoing REBIRTH research study will provide randomised data regarding its value. Studies such as the P-CARE MRI in peripartum cardiomyopathy study and the observational or peer-to-peer network peripartum cardiomyopathy-R study might further expand the understanding of peripartum cardiomyopathy care, specifically for US patients. How to downtitrate or even stop heart failure GDMT in patients with peripartum cardiomyopathy will be investigated in a dedicated future study. Referral for genetic testing should be discussed, especially in patients with a family history of a cardiomyopathy or sudden death. With increasing awareness and better diagnostic tools, the disease has moved from rare to a frequent pregnancy complication, thereby raising research interest in this field. Despite ongoing research, numerous uncertainties persist regarding the incidence, pathophysiology, differences in mode and presentation, treatment, and prognosis of patients with peripartum cardiomyopathy, indicating the need for further investigation. Most importantly, global awareness of peripartum cardiomyopathy should be increased to improve detection rates and outcomes.

Non-coeliac gluten sensitivity

Non-coeliac gluten sensitivity (NCGS) refers to individuals who report intestinal and extraintestinal symptoms related to the ingestion of gluten-based or wheat-based foods, in the absence of coeliac disease or wheat allergy. Gluten is found in multiple cereals, including wheat, rye, and barley, although the precise trigger of symptoms in NCGS remains unclear. Although approximately 10% of adults worldwide self-report gluten or wheat sensitivity, meta-analyses suggest that, during controlled challenge studies, 16–30% of these individuals have symptoms specifically triggered by gluten. However, methodological variability—including the presence of fermentable carbohydrates in challenge preparations—limits interpretation. Current evidence suggests that fermentable carbohydrates and nocebo effects contribute considerably to symptom generation in many cases. The substantial size of the gluten-free market raises questions about commercial and media influences on how NCGS is portrayed, and on the direction of related research. Definitive diagnosis of NCGS remains elusive due to the absence of biomarkers, significant overlap with disorders of gut–brain interaction, and methodological challenges in dietary evaluation. Until causative agents are identified and diagnostic tests developed, NCGS remains a diagnosis of exclusion, requiring careful systematic evaluation. Management approaches should balance dietary modification with recognition of psychological factors while ensuring nutritional adequacy. This Review critically examines current evidence regarding NCGS as a distinct entity, explores potential mechanisms, and provides practical guidance for assessment and management, while acknowledging major uncertainties in the field.

Glutenhaltiges Getreide sind Weizen, Gerste, Roggen und Hafer sowie ihre Urformen und Kreuzungen wie Dinkel,

The main antibodies used to diagnose celiac disease are anti-tissue transglutaminase (tTG), anti-endomysial (EMA), and anti-deamidated gliadin peptide (DGP). The most common initial test is the tTG-IgA test, but a doctor will also test for total IgA to ensure the results are accurate, especially in cases of IgA deficiency.

	Study design	Primary outcome	Evidence quality	Key finding	Importance to field
de Graaf (2024)[4]	DBPC parallel, randomised	Gastrointestinal symptom severity on VAS	High	Increased symptom scores in those expecting gluten, regardless of actual content (p<0·001)	Landmark study showing that expectancy effects are more influential than actual gluten content; strong evidence for nocebo mechanisms
Cooper (1980)[15]	DBPC crossover	Gastrointestinal symptom response after gluten challenge	Low	Significant worsening of intestinal symptoms with gluten (p<0·01)	First clinical report identifying gluten sensitivity without coeliac disease; historical foundation
Biesiekierski (2013)[22]	DBPC crossover, randomised	Change in overall symptom score	High	No gluten-specific symptom response; all groups similarly increased symptoms *vs* low-FODMAP run-in (p<0·0001)	Highlighted nocebo effects and suggested that FODMAPs, not gluten, might trigger symptoms in suspected NCGS
Skodje (2018)[23]	DBPC crossover, randomised	IBS-symptom severity scale score during challenges	High	Fructans, not gluten, increased IBS symptoms *vs* placebo (p=0·04)	First controlled trial directly comparing gluten and fructans, verifying FODMAP sensitivity as likely mechanism
Peters (2014)[26]	DBPC crossover, randomised	State depression scores	High	Significant increase in depression scores with gluten *vs* placebo (p=0·02)	First study to show extraintestinal psychological effects of gluten
Zanini (2015)[51]	DBPC crossover, randomised	Ability to correctly identify gluten flour	Moderate	Only 34% of participants correctly identified gluten flour; 49% incorrectly identified gluten-free flour as containing gluten	Showed poor reliability of self-reported gluten sensitivity
Biesiekierski (2011)[75]	DBPC parallel, randomised	Proportion with inadequately controlled symptoms	High	68% of participants in the gluten group reported inadequately controlled symptoms *vs* 40% with placebo (p=0·0001)	First randomised controlled trial showing gluten-specific symptom induction; established NCGS as potential clinical entity
Di Sabatino (2015)[78]	DBPC crossover, randomised	Change in overall symptom scores	High	Significant increase in overall symptoms with gluten *vs* placebo (p=0·034), but only three of 59 patients showed gluten sensitivity	Highlighted heterogeneity of NCGS population with only a small number showing clear gluten sensitivity
Francavilla (2018)[129]	DBPC crossover, randomised	Decrease in global VAS score	High	Significant increase in IBS symptom score with gluten *vs* placebo in 11 (39%) of 28 children with suspected NCGS	First paediatric DBPC study showing existence of NCGS in children

For complete methodological details and the full list of DBPC studies, see appendix 1 (pp 1–6). Evidence quality rating was based on methodological criteria, including adequate sample size, appropriate randomisation and blinding procedures, handling of dropout rates, appropriateness of controls and washout periods, clarity of predefined endpoints, and appropriate statistical analysis. DBPC=double-blind, placebo-controlled. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. IBS=irritable bowel syndrome. NCGS=non-coeliac gluten sensitivity. VAS=visual analogue scale.

Table: **Double-blind, placebo-controlled dietary re-challenge studies investigating gluten reactivity in self-reported NCGS**

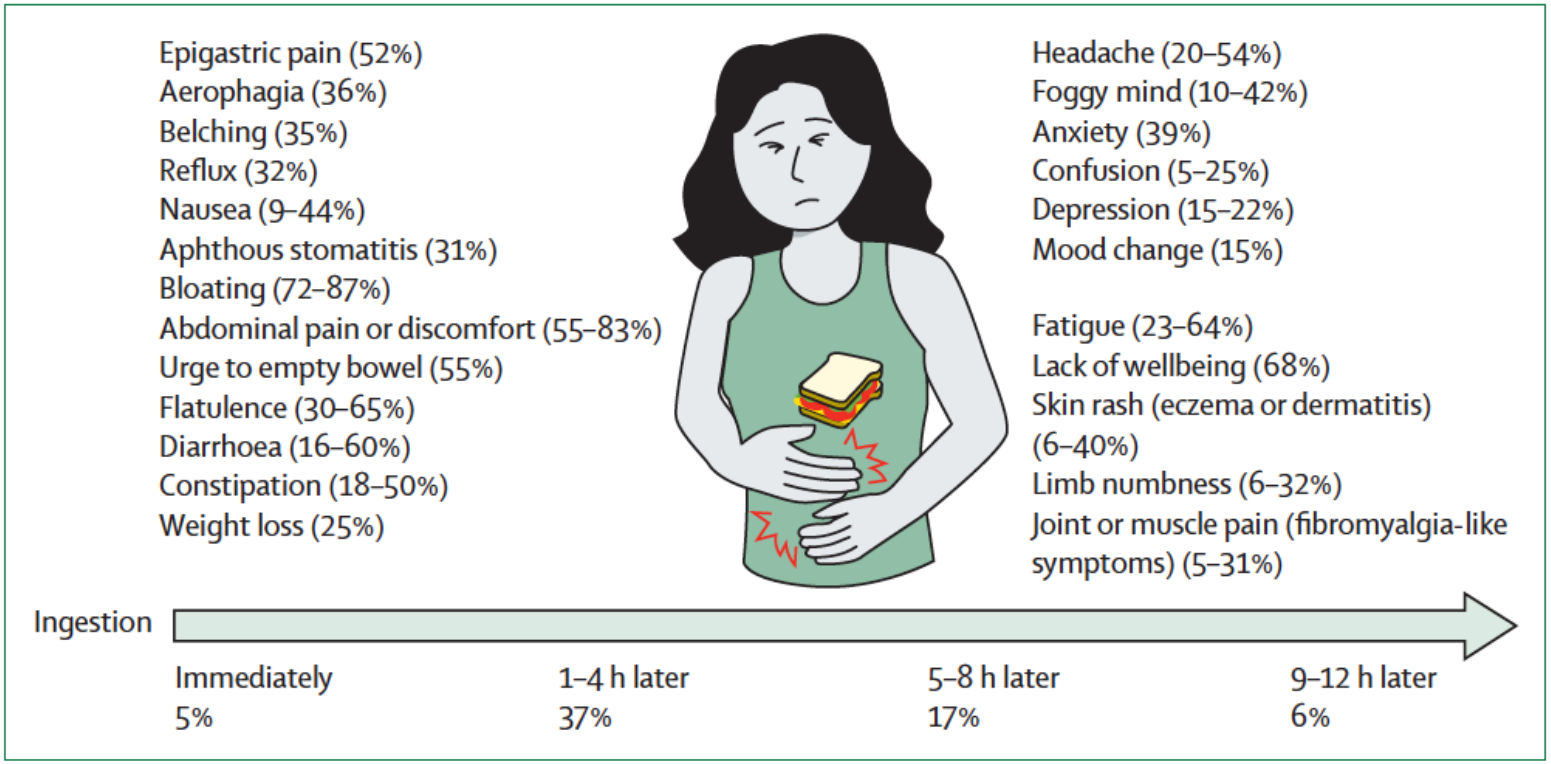


Figure 1: **Symptoms and onset times**

Data from questionnaires completed by individuals with self-reported non-coeliac gluten sensitivity, according to multiple reports: Aziz and colleagues[24] (UK n=1002), Volta and colleagues[25] (Italy n=486), Biesiekierski and colleagues[40] (Australia n=147), and de Graaf and colleagues[4] (prescreening data from the UK and the Netherlands n=301).

Diagnosis

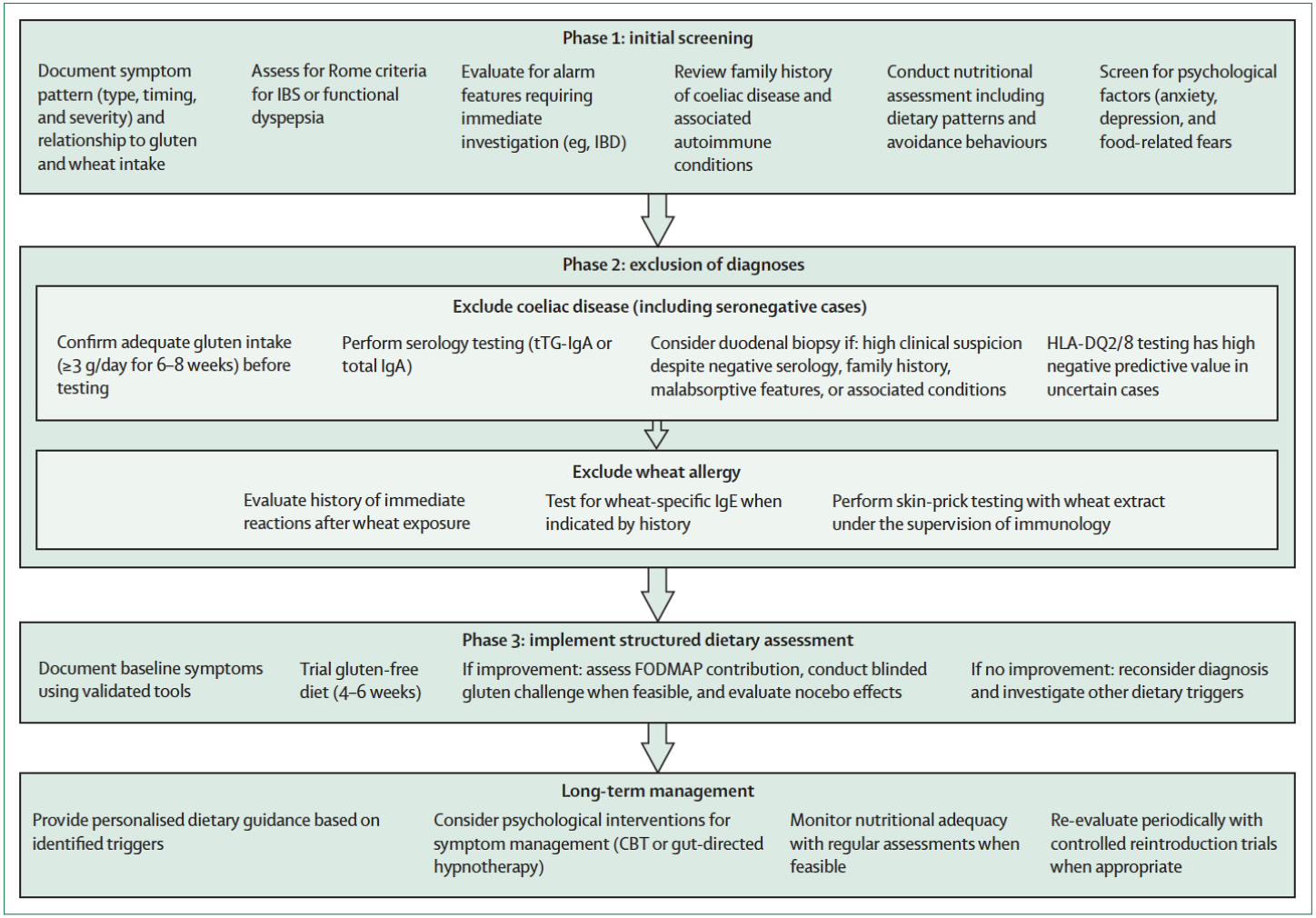


Figure 2: **Three-phase diagnostic pathway**
IBS=irritable bowel syndrome. IBD=inflammatory bowel disease. tTG=tissue transglutaminase. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. CBT=cognitive behavioural therapy.

Patho-
physiology

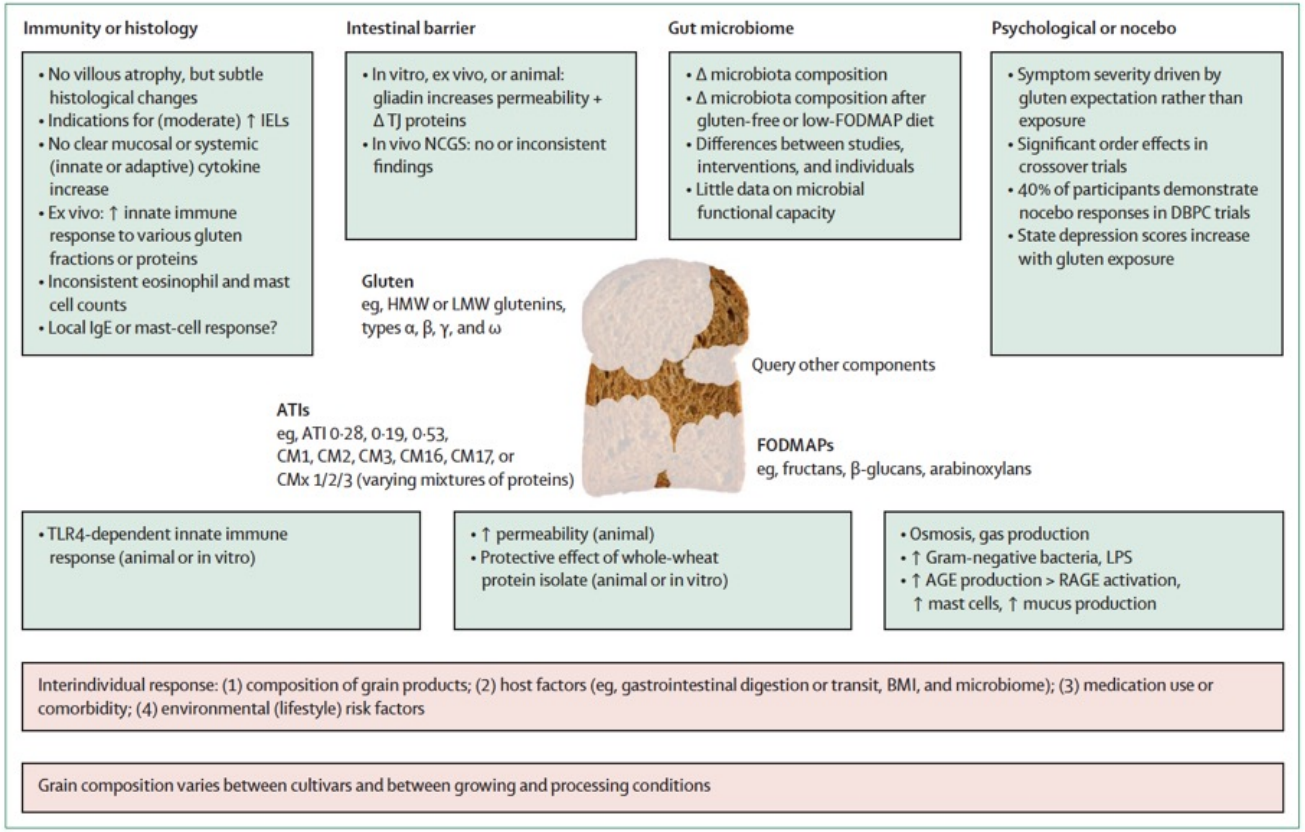


Figure 3: **Potential pathophysiological mechanisms**
For ATIs, the evidence is from preclinical studies only. IEL=intraepithelial lymphocyte. TJ=tight junction. NCGS=non-coeliac gluten sensitivity. FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. DBPC=double-blind, placebo-controlled. HMW=high molecular weight. LMW=low molecular weight. ATI=amylase trypsin inhibitor. LPS=lipopolysaccharide. AGE=advanced glycation endproducts. RAGE=receptor for advanced glycation endproducts.

FODMAPs sind kurzkettige Kohlenhydrate, die im Dünndarm schlecht aufgenommen und im Dickdarm von Bakterien fermentiert (vergoren) werden, was zu Gasbildung, Blähungen und anderen Verdauungssymptomen führen kann. Die Abkürzung steht für fermentierbare Oligo-, Di-, Monosaccharide und **(a)**nd Polyole. Eine FODMAP-arme Diät kann bei Menschen mit Reizdarmsyndrom (RDS) die Symptome lindern, sollte aber unter professioneller Anleitung durchgeführt werden.

Panel: **Key challenges and proposed solutions in non-coeliac gluten sensitivity research, diagnosis, and management**

Methodological limitations in clinical trials

Challenge

Double-blind placebo-controlled (DBPC) trials in non-coeliac gluten sensitivity (NCGS) are hampered by inconsistent coeliac disease screening,[74,77] poor control of nocebo effects, and non-standard protocols

Suggested solutions

- Implement uniform diagnostic criteria for coeliac disease exclusion
- Standardise challenge protocols (vehicle, washout periods, and blinding verification)
- Develop measures to account for nocebo responses
- Establish consistent outcome assessment across trials

Lack of reliable diagnostic criteria

Challenge

Current diagnostic criteria are complex; the absence of biomarkers for NCGS leads to self-diagnosis, unclear prevalence estimates, and heterogenous study populations

Suggested solutions

- Develop validated diagnostic criteria with expert consensus
- Identify objective biomarkers for accurate NCGS diagnosis
- Do population-based studies with standardised assessment methods

Dietary restriction consequences

Challenge

Self-directed dietary restriction often leads to nutritional inadequacies and unnecessary restrictions

Suggested solutions

- Involve dietitians early in the diagnostic process
- Implement systematic dietary challenge protocols controlling for fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)
- Monitor nutritional status during restriction diets
- Consider psychological or gastroenterological referral when features of disordered eating or avoidant/restrictive food intake disorder are present

Commercial influences

Challenge

Commercial and media influences can distort research priorities, diagnostic criteria, and patient management

Suggested solutions

- Require transparent declaration of funding sources
- Develop independent diagnostic criteria
- Consider commercial determinants in guideline development

Heterogeneous research method

Challenge

Inconsistent study designs and diagnostic criteria prevent meaningful comparison across studies

Suggested solutions

- Implement standardised diagnostic criteria and study designs
- Do multicentre studies with consistent protocols
- Use strategies to minimise nocebo effects

Mechanisms of action

Challenge

Multiple pathways likely contribute to symptom generation, with substantial individual variability

Suggested solutions

- Investigate wheat components with standardised protocols
- Study individual response variations and gut-brain interactions
- Compare findings with relevant control groups
- Develop integrated models of biological and psychological factors
- Replicate existing studies and explore symptom responses to varied FODMAP sources and doses

Interpretation of gluten challenges

Challenge

Challenges are confounded by wheat complexity and poor standardisation of protocols

Suggested solutions

- Develop best-practice guidelines for gluten challenges
- Control for confounding dietary factors
- Establish clinically significant endpoints
- Test dose–response relationships

Minimising dietary restriction risks

Challenge

Unnecessary dietary restrictions can lead to nutritional deficiencies and misdiagnosis

Suggested solutions

- Raise proper diagnostic testing before gluten-free diet recommendations
- Incorporate nutritional counselling with dietary modification
- Implement education about the risks of self-diagnosis

Management and follow-up

Challenge

The long-term health impacts of NCGS remain unknown, with insufficient evidence-based guidelines

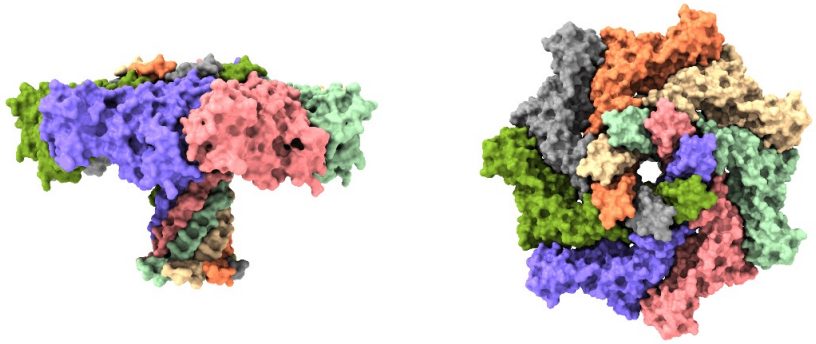
Suggested solutions

- Develop multidisciplinary management approaches
- Do longitudinal cohort studies of health outcomes
- Create and validate NCGS-specific outcome measures

Conclusion

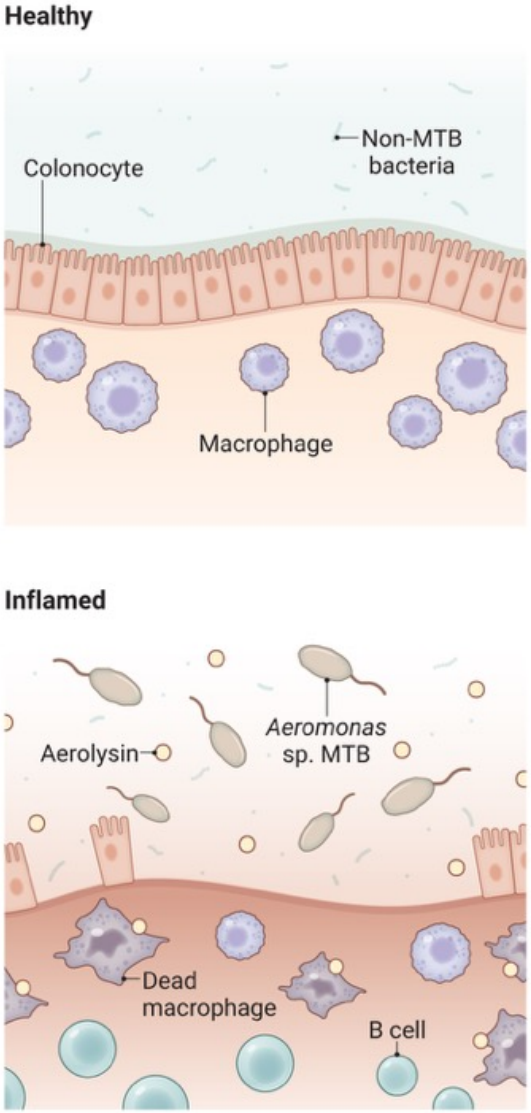
The term NCGS is used to describe a heterogeneous group of individuals reporting intestinal and extraintestinal symptoms related to gluten or wheat ingestion, in the absence of coeliac disease or wheat allergy. However, whether NCGS represents a distinct clinical entity remains unclear. Meta-analyses indicate that only a small subgroup of people show gluten-specific responses in controlled trials, with evidence suggesting that FODMAPs and nocebo effects contribute significantly to symptom generation. Commercial influences, particularly from the growing gluten-free market, can subtly shape research priorities and narrative construction around NCGS. Definitive diagnosis remains elusive due to the absence of biomarkers, considerable overlap with DGBI, and methodological challenges in dietary evaluation. The role of specific wheat components, such as gluten, fructans, and ATIs, in triggering symptoms requires further investigation in well designed, independent studies. Until causative agents are identified and diagnostic tests developed, NCGS remains a diagnosis of exclusion, requiring careful systematic evaluation. Current evidence supports a multidisciplinary approach that integrates dietary modifications with psychological support while ensuring nutritional adequacy.

In molecular biology, Aerolysin is a cytolytic pore-forming toxin exported by *Aeromonas hydrophila*, a Gram-negative bacterium associated with diarrhoeal diseases and deep wound infections.



Aerolysin is also produced by the caterpillar of the moth Megalopyge opercularis, sometimes called the Tree Asp. The mature toxin binds to eukaryotic cells and aggregates to form holes (approximately 3 nm in diameter) leading to the destruction of the membrane permeability barrier and osmotic lysis. The structure of proaerolysin has been determined to 2.8A resolution and shows the protoxin to adopt a novel fold. High-resolution cryo-EM atomic models of aerolysin in membrane-like environment (lipid copolymer Nanodiscs) as well as some prepore-like mutant have been elucidated, permitting the identification of important interactions required for pore formation and revealing four constriction rings in the pore lumen. Aerolysin has also been used as a biosensor due to its narrow lumen and four constrictions points, which could be easily mutated, rendering aerolysin very sensitive for the detection of small molecules, (cyclic) peptides, polymers, biopolymers such as DNA] or RNA, different sugars and also some proteins.

Koch's postulates, formulated in 1884 by Robert Koch and Friedrich Loeffler, state that a microorganism causes a disease if it is found in all disease cases, can be isolated and grown in culture, causes the disease when introduced into a healthy host, and can be reisolated from that host. These criteria have been revised to account for "unculturable" microbes, such as viruses, and to recognize microbial genes as disease agents rather than the microbes themselves. No microorganism that fits Koch's revised postulates has been identified as the cause of ulcerative colitis. Jiang *et al*. report that a bacterial strain isolated from patients with ulcerative colitis drives gut inflammation in mice by producing aerolysin, which is toxic to protective immune cells. The findings suggest a previously unidentified mechanism by which a microbe might contribute to the progression of ulcerative colitis.



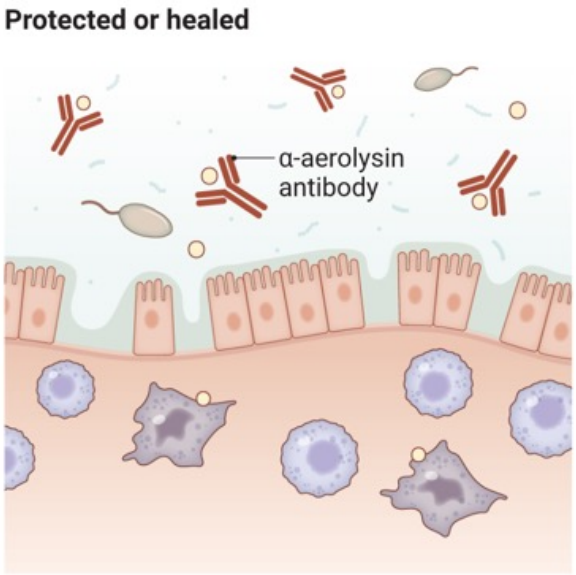
Inflammatory bowel disease (IBD) is an umbrella term for a group of chronic conditions in which the body's immune system attacks the digestive tract, causing inflammation and symptoms such as abdominal pain, diarrhea, and fatigue. The most common types of IBD are Crohn's disease and ulcerative colitis.

Jiang et al. studied biopsies of tissue from the colons of patients with ulcerative colitis using histology and analysis of immune cell populations. The authors observed that tissue-resident macrophages—a type of immune cell that surveys mucosal tissues to detect infections or damage—were nearly absent from the subepithelial mucosa (the layer of tissue beneath the epithelial layer) in the colons of these patients. Chemical or genetic depletion of these gut-resident macrophages in mice revealed that these cells were crucial to protect the colon from chemically induced inflammation. Jiang et al. hypothesized that an agent produced by the gut microbiota might be responsible for the depletion of mucosal-resident macrophages in patients with ulcerative colitis. They found that fecal matter from these patients, but not that from healthy donors, contained aerolysin, a substance secreted by bacteria from the *Aeromonas* genus. Aerolysin forms pores in target cells, which leads to cell death.

Experiments in cultured mouse and human cells showed that aerolysin is highly toxic to macrophages but not to intestinal epithelial cells. The authors dubbed the aerolysin-producing bacterial strain *Aeromonas* sp. macrophage-toxic bacteria (MTB).

To assess the effects of MTB on gut tissue, Jiang *et al*. used mouse models of colonic inflammation. Infection with MTB worsened clinical symptoms of colonic inflammation, such as weight loss, rectal bleeding, and colonic ulcerations, in these animals. Genetically engineered microbes lacking the gene encoding aerolysin did not have a proinflammatory effect when they were orally given to mice. Notably, MTB did not aggravate colitis in mice chemically treated to lack gut-resident macrophages. Furthermore, administering antibodies targeting aerolysin into the abdominal cavities of MTB-infected mice relieved signs of colonic inflammation. Thus, MTB infection renders the colon susceptible to inflammation by destroying gut-resident macrophages with aerolysin.

Jiang et al. also assessed whether MTB and aerolysin were present in fecal samples and colonic biopsies from a cohort of 117 patients with IBD and 430 healthy controls across 12 provinces in China. The authors detected aerolysin-producing MTB in more than 70% of patients with ulcerative colitis, whereas these microbes were only present in ~12% of healthy individuals. Aerolysin was present in the mucosa of all patients with ulcerative colitis but not in that of healthy individuals. Notably, only 1 of the 38 patients with Crohn's disease had MTB.

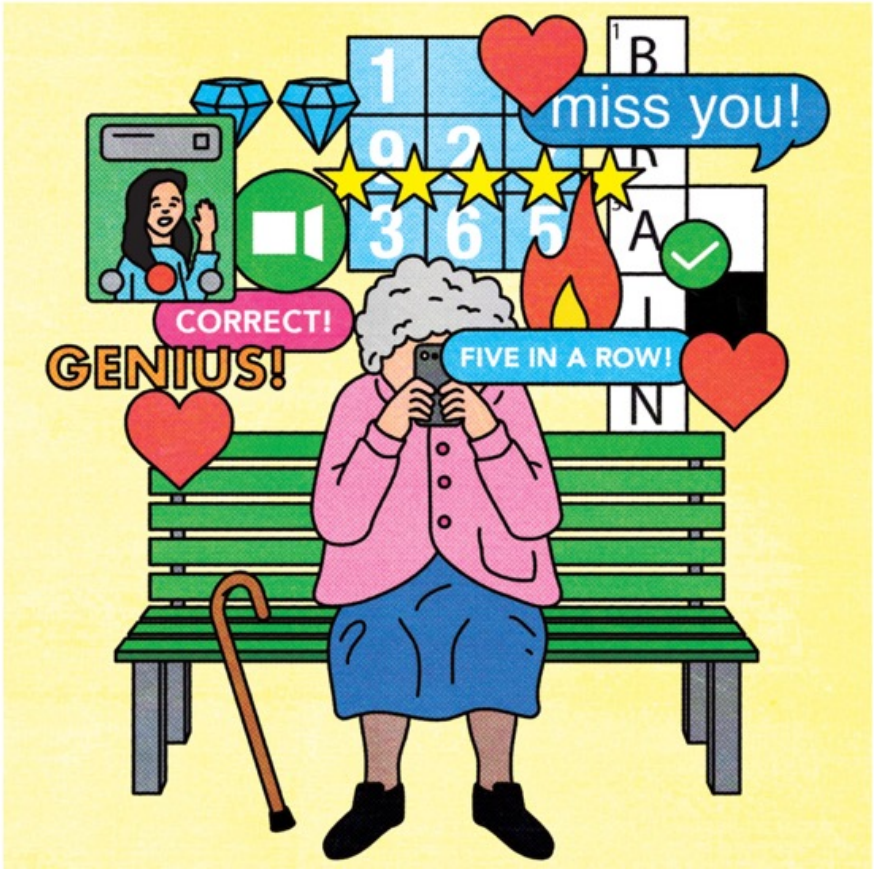


Aerolysin makes the colon susceptible to inflammation

Aeromonas sp. macrophage-toxic bacteria (MTB) isolated from patients with ulcerative colitis produce aerolysin, which is toxic to gut macrophages. Loss of macrophages leads to inflammation and accumulation of B cells and other components of the immune system, which weakens the colon's defenses. Anti-aerolysin (α-aerolysin) antibodies restore the gut mucosa to a healthy state.

The Washington Post
Democracy Dies in Darkness

Why you should embrace new technology as you age



You might think spending time on your smartphone or computer is bad for your brain. Indeed, "brain rot" — the slang term for a mental decline caused by mindlessly consuming social media or digital dreck — was Oxford Dictionary's 2024 Word of the Year.

But new research suggests that older adults who spend time engaging with technology may get a cognitive benefit.

"We saw that older adults who are engaging with technologies overall seem to be having less diagnoses of dementia, mild cognitive impairment, better scores on cognitive measures," said Jared Benge, an associate professor at Dell Medical School at the University of Texas at Austin and an author of the paper, a meta-analysis of 57 studies, which was published in Nature Human Behaviour.

Across the studies, more use of everyday digital technologies such as computers, smartphones and the internet was associated with a 58 percent lower risk of cognitive impairment in people older than 50.

Because the studies were observational, they cannot show causality. But longitudinal studies that tracked participants for an average of six years found that more technology use is associated with better cognitive health in the future.