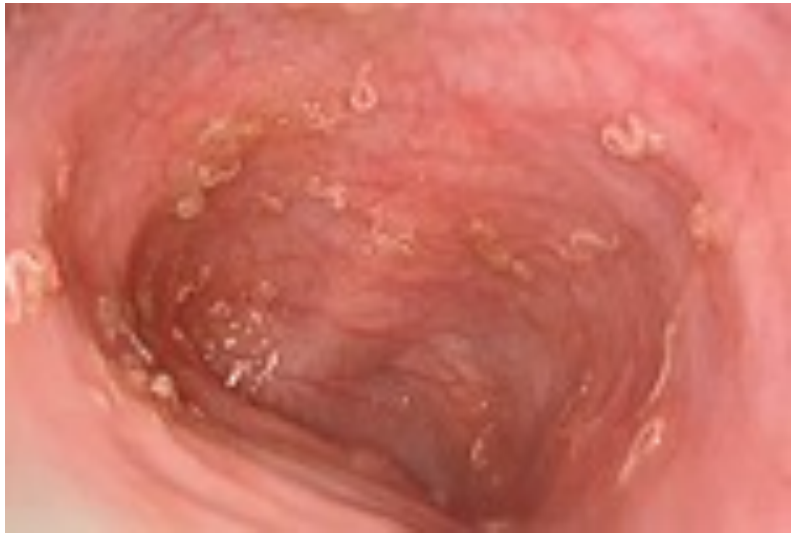
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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 2-year-old boy from a rural village was brought to the pediatric clinic with a 6-month history of diarrhea and poor weight gain. His body weight was 12.1 kg (below the 25th percentile for his age) and height 90 cm (1 SD below the median for his age). Physical examination revealed dry mucous membranes and decreased skin turgor. Laboratory tests showed iron-deficiency anemia, eosinophilia, and occult blood in the stool. Stool samples examined by direct microscopy for ova and parasites were negative. A colonoscopy showed numerous mobile, white worms adherent to the colon wall. What is the most likely culprit organism?

Ascaris lumbricoides

Enterobius vermicularis (pinworm)

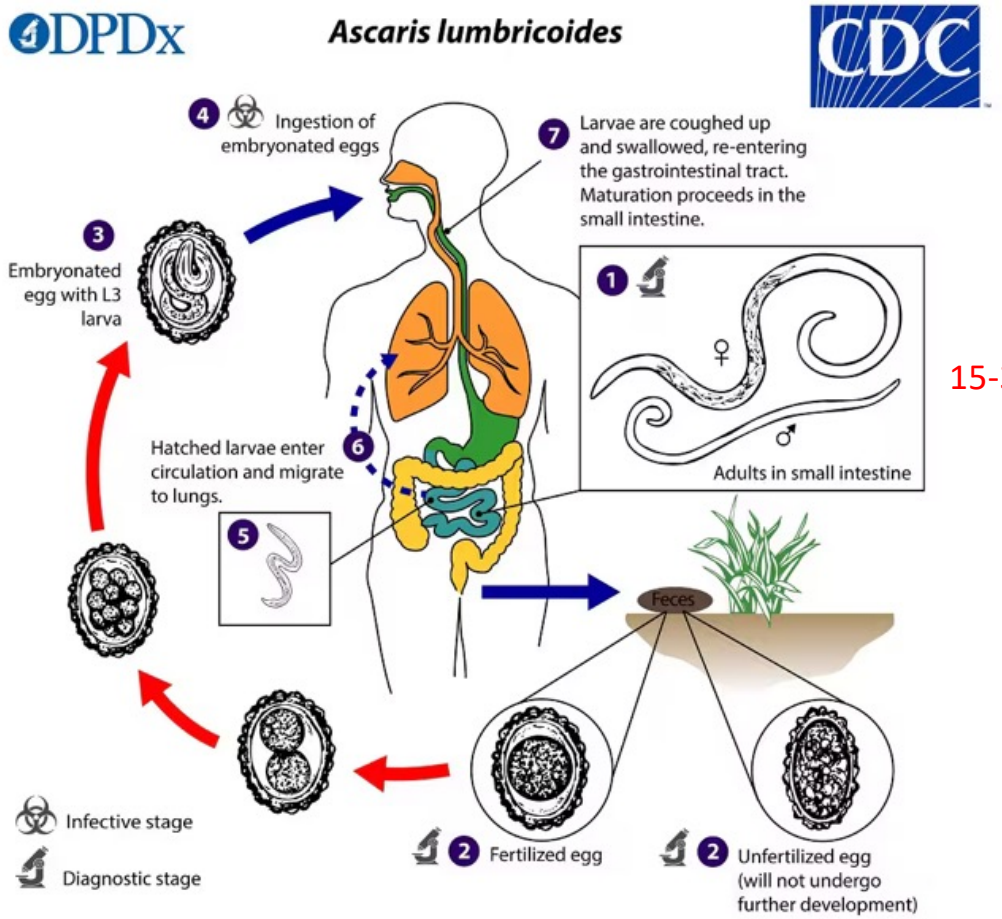
Hymenolepis nana (dwarf tapeworm)

Strongyloides stercoralis

Trichuris trichiura (whipworm) ←

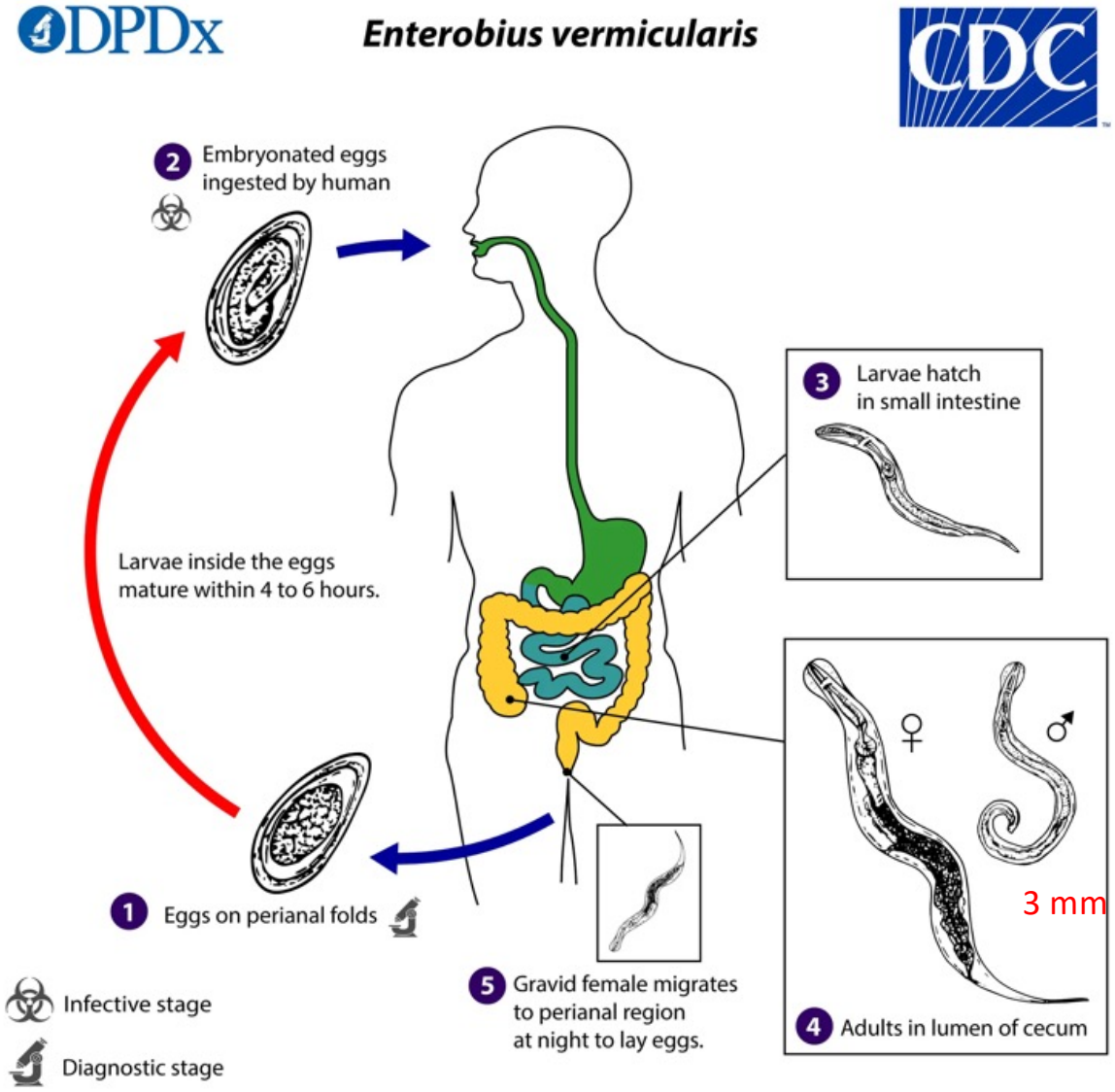
The worms were identified as Trichuris trichiura. A diagnosis of trichuriasis — also known as human whipworm infection — was made. Trichuriasis results from the ingestion of soil contaminated by whipworm eggs. Adult worms mature in the large intestine and affix themselves there by threading into the mucosa. Trichuriasis is usually asymptomatic but may result in diarrhea and growth retardation in cases of heavy infection, especially in young children.

Die Spulwürmer (Ascaris) sind eine Gattung der Fadenwürmer (Nematoda), die im Allgemeinen auch bekannt ist unter dem Sammelbegriff Askariden. Die bekanntesten Vertreter sind der Spulwurm (Ascaris lumbricoides) und der Schweinespulwurm (Ascaris suum).

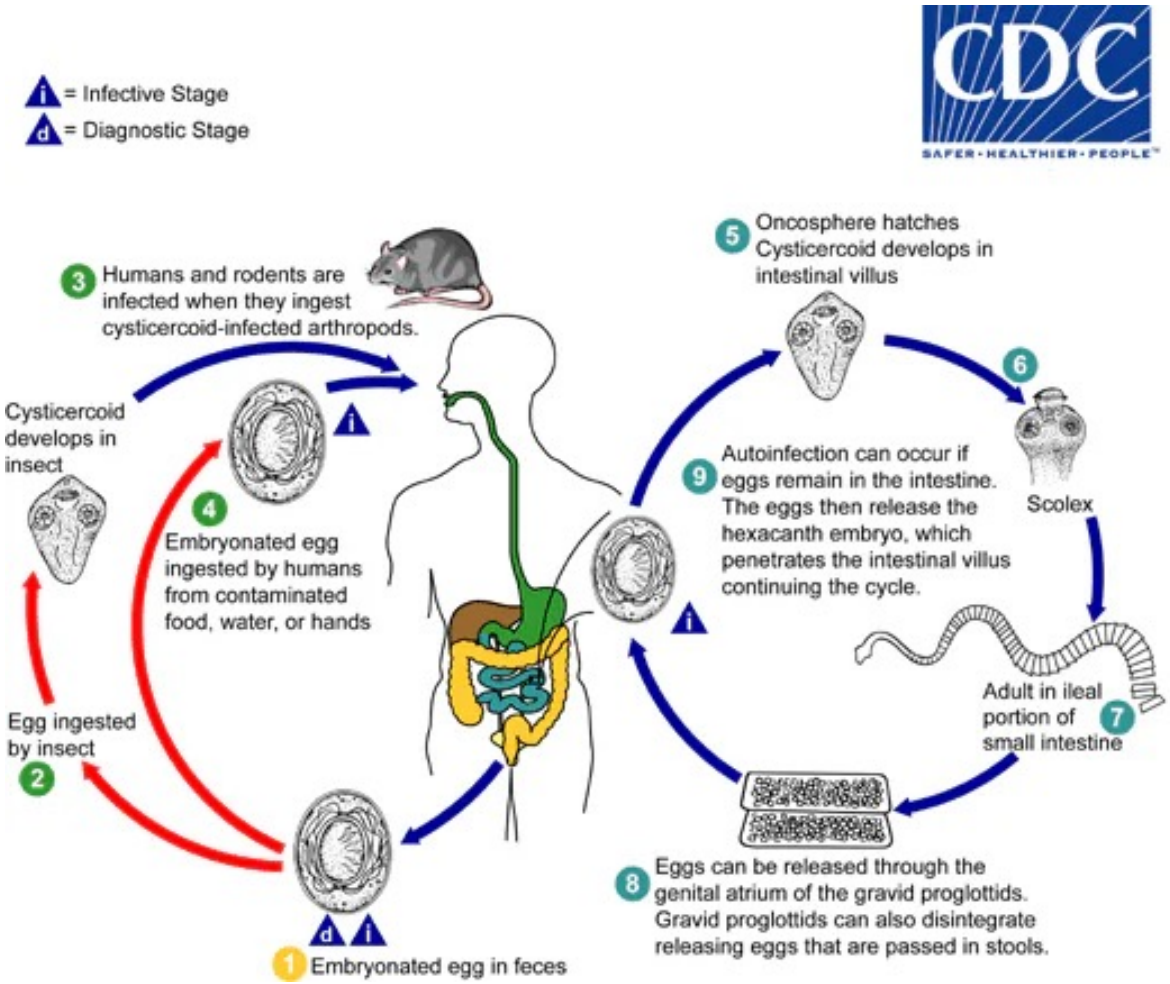


15-30 cm long

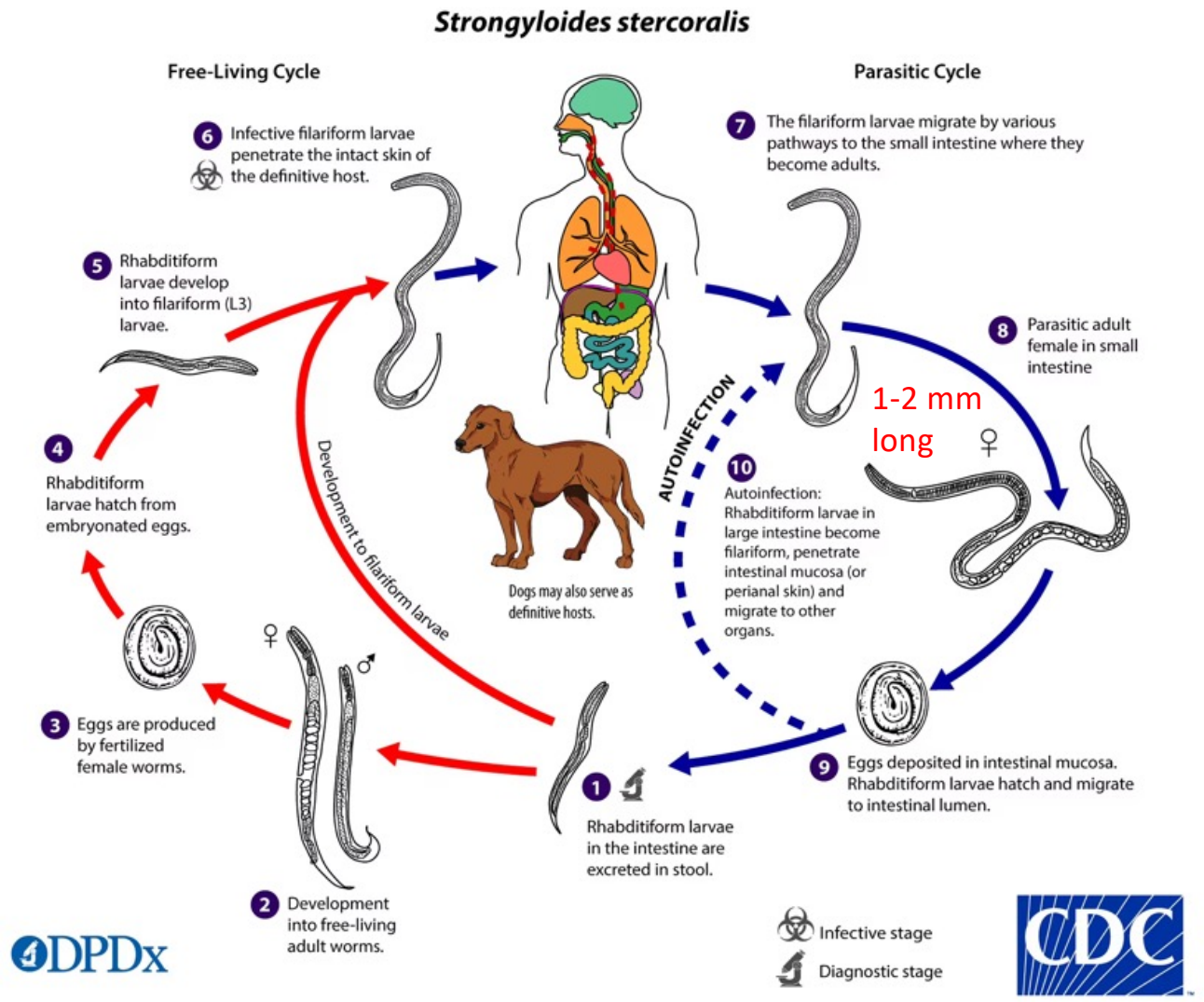
Enterobius (syn. Oxyuris) vermicularis gehört als humanpathogener intestinaler Parasit zum Stamm der Fadenwürmer (Nematoda). Im Deutschen werden neben der Bezeichnung „Madenwurm“ auch die Synonyme „Oxyuren“ (Pluralbegriff), „Springwurm“, „Pfriemenschwanz“ oder „Aftermade“ verwendet.



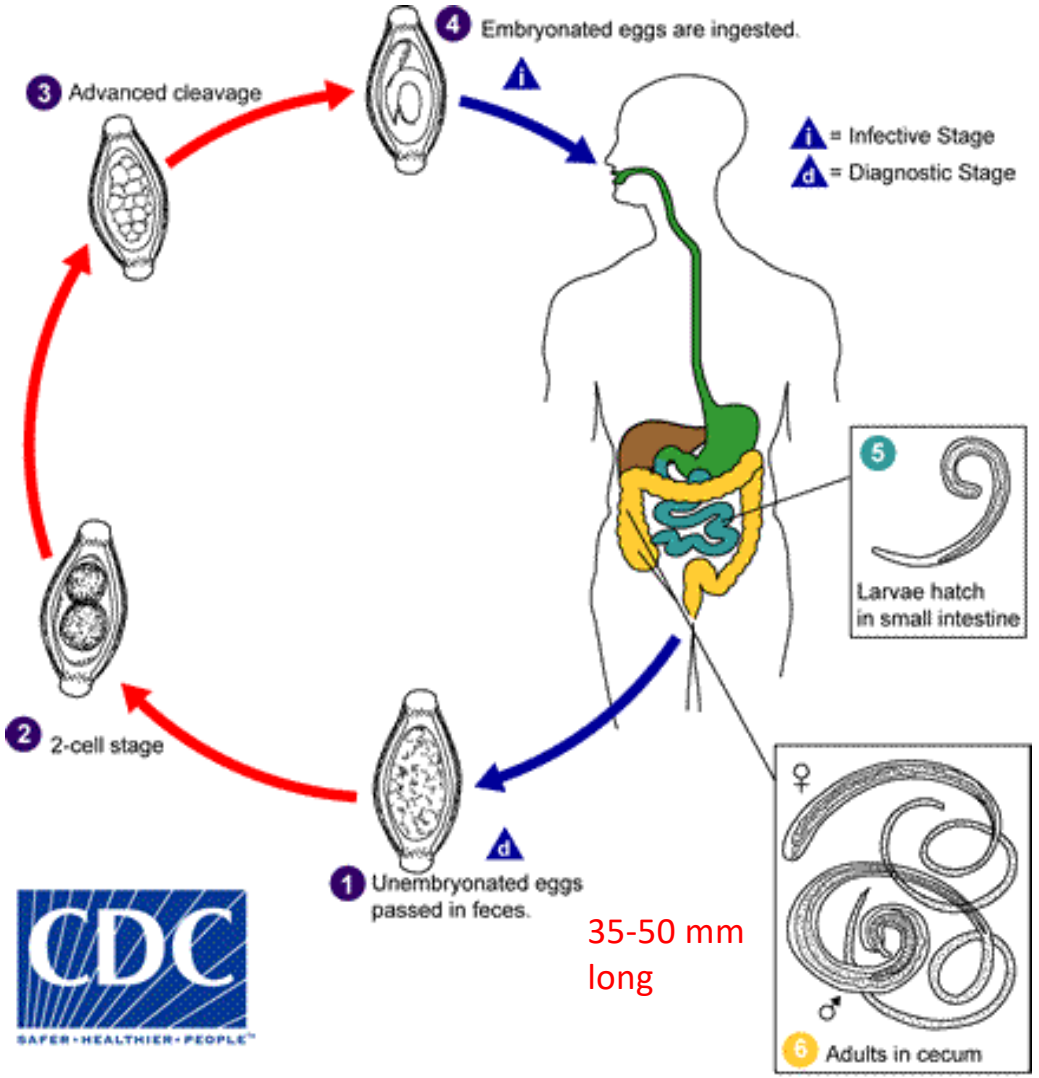
Hymenolepis nana-(Zwergenbandwurm)-Infektion. Hymenolepis nana, ein winzig er Darm Bandwurm, ist einer der häufigsten menschlichen Zestoden; der Lebenszyklus erfordertkeinen Zwischenwirt. Die Infektion wird mit Praziquantel oder Niclosamid behandelt.



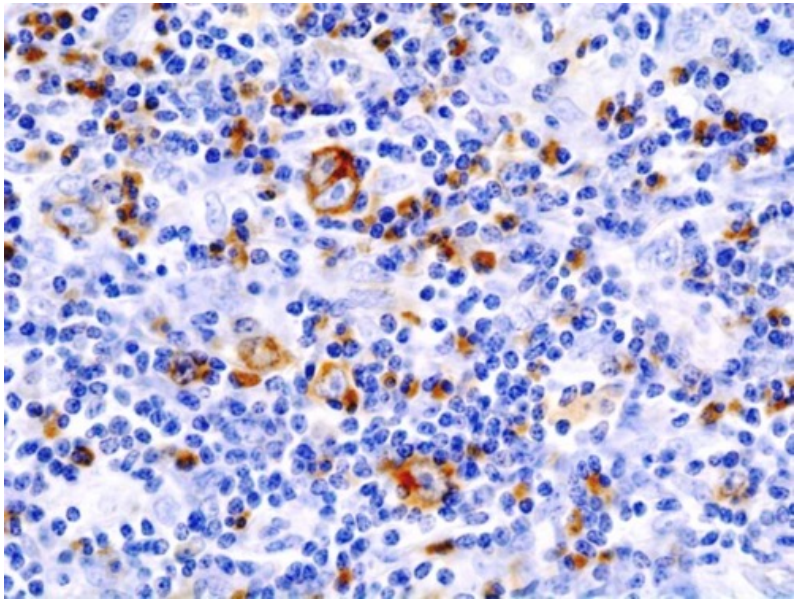
Definition. Unter einer Strongyloides versteht man eine Infektion mit dem Zwergfadenwurm (Strongyloides stercoralis). Dieser Parasit befällt den Darm des Menschen ohne Zwischenwirt, allerdings unterbrochen von einer freilebenden Lebensphase. Zwergfadenwürmer sind im ausgewachsenen Zustand zwei Millimeter lang.

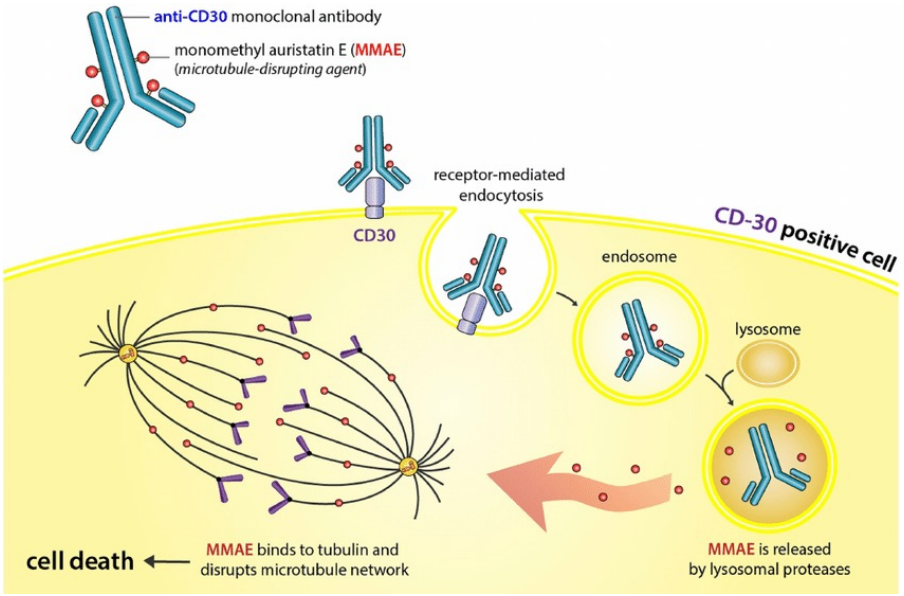


Der Peitschenwurm (Trichuris trichiura; synonym: Trichocephalus dispar) gehört zum Stamm der Fadenwürmer. Er hat einen fadenförmigen Kopfteil und ein kurzes, dickes Schwanzende. Er ist ein Parasit des Menschen und Verursacher der Trichuriasis.



Das Hodgkin-Lymphom ist ein bösartiger Tumor des Lymphsystems. Die Erkrankung macht sich durch schmerzlose Schwellungen von Lymphknoten bemerkbar, begleitend können sogenannte B-Symptome, wie zum Beispiel der für diese Erkrankung fast pathognomonische Alkoholschmerz, auftreten.

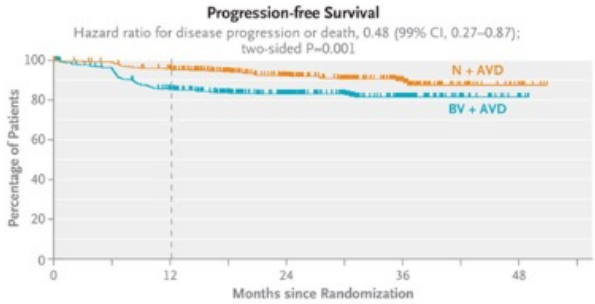




Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma

Incorporating brentuximab vedotin into the treatment of advanced-stage classic Hodgkin's lymphoma improves outcomes in adult and pediatric patients. However, brentuximab vedotin increases the toxic effects of treatment in adults, more than half of pediatric patients who receive the drug undergo consolidative radiation, and relapse remains a challenge. Programmed death 1 blockade is effective in Hodgkin's lymphoma, including in preliminary studies involving previously untreated patients.

We conducted a phase 3, multicenter, open-label, randomized trial involving patients at least 12 years of age with stage III or IV newly diagnosed Hodgkin's lymphoma. Patients were randomly assigned to receive brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine (BV+AVD) or nivolumab with doxorubicin, vinblastine, and dacarbazine (N+AVD). Prespecified patients could receive radiation therapy directed to residual metabolically active lesions. The primary end point was progression-free survival, defined as the time from randomization to the first observation of progressive disease or death from any cause.



Fewer patients discontinued nivolumab than brentuximab vedotin. Most treatment discontinuations were due to adverse events.

Combination chemotherapy has been the standard treatment for advanced-stage Hodgkin's lymphoma for decades. Chemotherapy backbones differ worldwide, with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) being the most commonly used combinations. Divergent approaches are taken for adult and pediatric patients, with modifications to these backbones, positron emission tomography (PET)–based response adaptation, and the use of consolidative radiotherapy after completion of chemotherapy in 55 to 76% of pediatric patients.

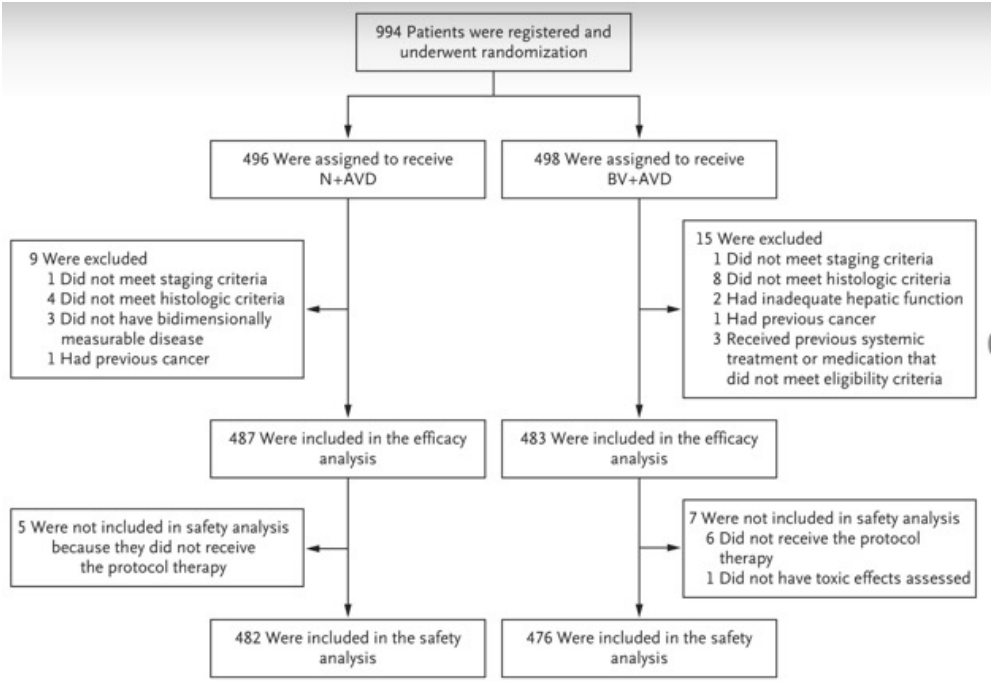
Trial Design

Patients were randomly assigned to receive N+AVD intravenously (nivolumab at a dose of 240 mg in adults and 3 mg per kilogram of body weight in children 12 to <18 years of age [capped at 240 mg], doxorubicin at a dose of 25 mg per square meter of body-surface area, vinblastine at a dose of 6 mg per square meter, and dacarbazine at a dose of 375 mg per square meter) or BV+AVD (brentuximab vedotin at a dose of 1.2 mg per kilogram [capped at 100 kg], and AVD at the doses listed above) on days 1 and 15 of each 28-day cycle for six cycles.

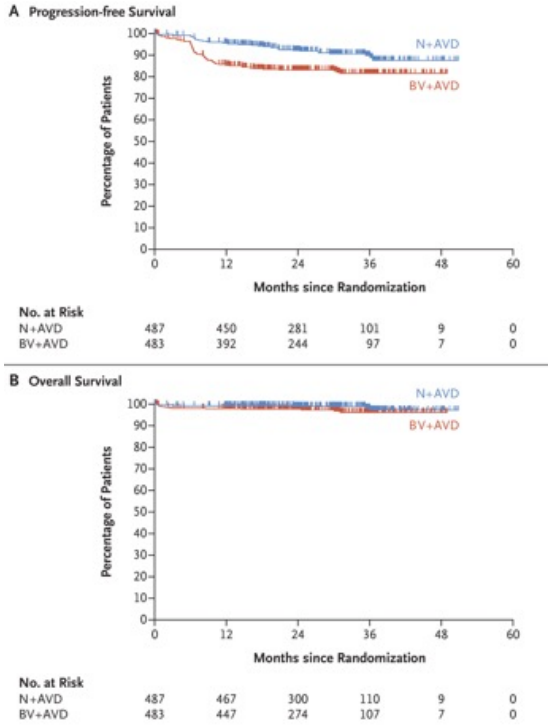
Patients

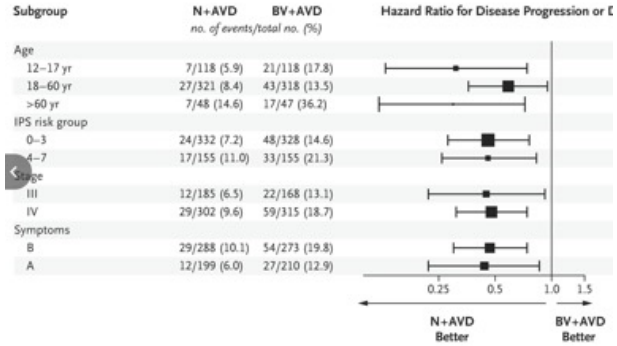
Patients 12 years of age or older were eligible for inclusion in the trial if they had previously untreated stage III or IV classic Hodgkin's lymphoma, Zubrod performance status of 0 to 2 (or Lansky performance status of 50 to 100 in patients 17 years of age or younger), and adequate hematologic and organ function. Zubrod performance status is measured on a 5-point scale, with higher numbers reflecting greater disability, and Lansky performance status is measured on a scale ranging from 0 to 100, with higher numbers indicating better performance on play and activity.

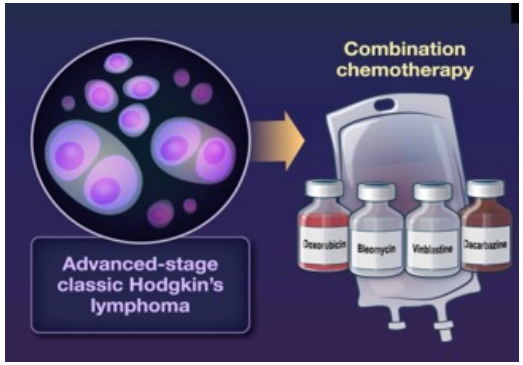
Characteristic	N+AVD (N = 487)	BV+AVD (N = 483)
Age		
Median (range) — yr	27.6 (12.0–83.7)	26.8 (12.0–81.7)
Distribution — no. (%)		
12–17 yr	118 (24)	118 (24)
18–60 yr	321 (66)	318 (66)
>60 yr	48 (10)	47 (10)
Female sex — no. (%)	216 (44)	210 (43)
Race or ethnic group — no. (%)†		
White	372 (76)	361 (75)
Black	58 (12)	56 (12)
Asian	11 (2)	17 (4)
Other or unknown	46 (9)	49 (10)
Hispanic	66 (14)	58 (12)
Disease stage — no. (%)		
III	185 (38)	168 (35)
IV	302 (62)	315 (65)
B symptoms present — no. (%)‡	288 (59)	273 (57)
IPS — no. (%)§		
0–3	332 (68)	328 (68)
4–7	155 (32)	155 (32)
Bulky disease — no. (%)¶	156 (32)	127 (26)
HIV-positive status — no. (%)	11 (2)	5 (1)



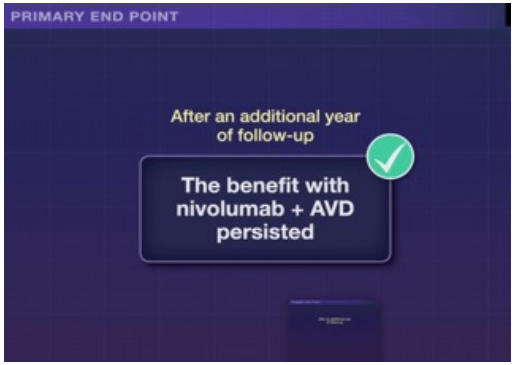
Event	N+AVD (N=482)	BV+AVD (N=476)
	number (percent)	
Nausea	312 (65)	331 (70)
Fatigue	228 (47)	242 (51)
Neutrophil count decreased	272 (56)	160 (34)
Anemia	190 (39)	217 (46)
Peripheral sensory neuropathy	139 (29)	266 (56)
Constipation	193 (40)	204 (43)
ALT increased	160 (33)	201 (42)
White-cells decreased	197 (41)	128 (27)
Vomiting	134 (28)	157 (33)
AST increased	125 (26)	160 (34)
Diarrhea	100 (21)	129 (27)
Alopecia	103 (21)	124 (26)
Lymphocyte count decreased	103 (21)	109 (23)
Mucositis, oral	107 (22)	100 (21)
Anorexia	61 (13)	106 (22)
Abdominal pain	58 (12)	107 (22)
Headache	69 (14)	75 (16)
Platelet count decreased	52 (11)	86 (18)
Bone pain	40 (8)	96 (20)
Alkaline phosphatase increased	54 (11)	81 (17)
Fever	62 (13)	61 (13)
Arthralgia	64 (13)	58 (12)
Hyperglycemia	57 (12)	63 (13)
Maculopapular rash	54 (11)	58 (12)
Myalgia	52 (11)	57 (12)
Dyspnea	42 (9)	58 (12)
Weight loss	25 (5)	71 (15)
Dysgeusia	35 (7)	59 (12)



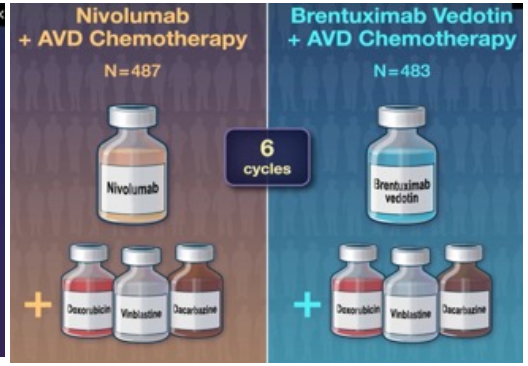


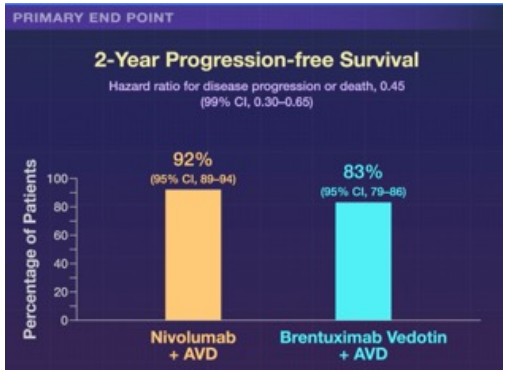

Combination chemotherapy
Advanced-stage classic Hodgkin's lymphoma
Doxorubicin
Bleomycin
Vinblastine
Dacarbazine


? Efficacy and Safety
Nivolumab
Brentuximab vedotin
Doxorubicin
Vinblastine
Dacarbazine
Advanced-stage classic Hodgkin's lymphoma


PRIMARY END POINT
After an additional year of follow-up
The benefit with nivolumab + AVD persisted

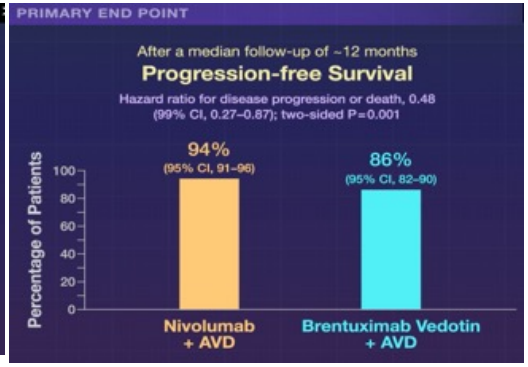

Doxorubicin
Brentuximab vedotin
Vinblastine
Dacarbazine
vs.
Bleomycin
Standard ABVD regimen
Improves outcomes


Nivolumab + AVD Chemotherapy
N=487
Brentuximab Vedotin + AVD Chemotherapy
N=483
6 cycles
Nivolumab
Brentuximab vedotin
Doxorubicin
Vinblastine
Dacarbazine


PRIMARY END POINT
2-Year Progression-free Survival
Hazard ratio for disease progression or death, 0.45
(99% CI, 0.30–0.65)
Percentage of Patients
92%
(95% CI, 89–94)
83%
(95% CI, 79–86)
Nivolumab + AVD
Brentuximab Vedotin + AVD

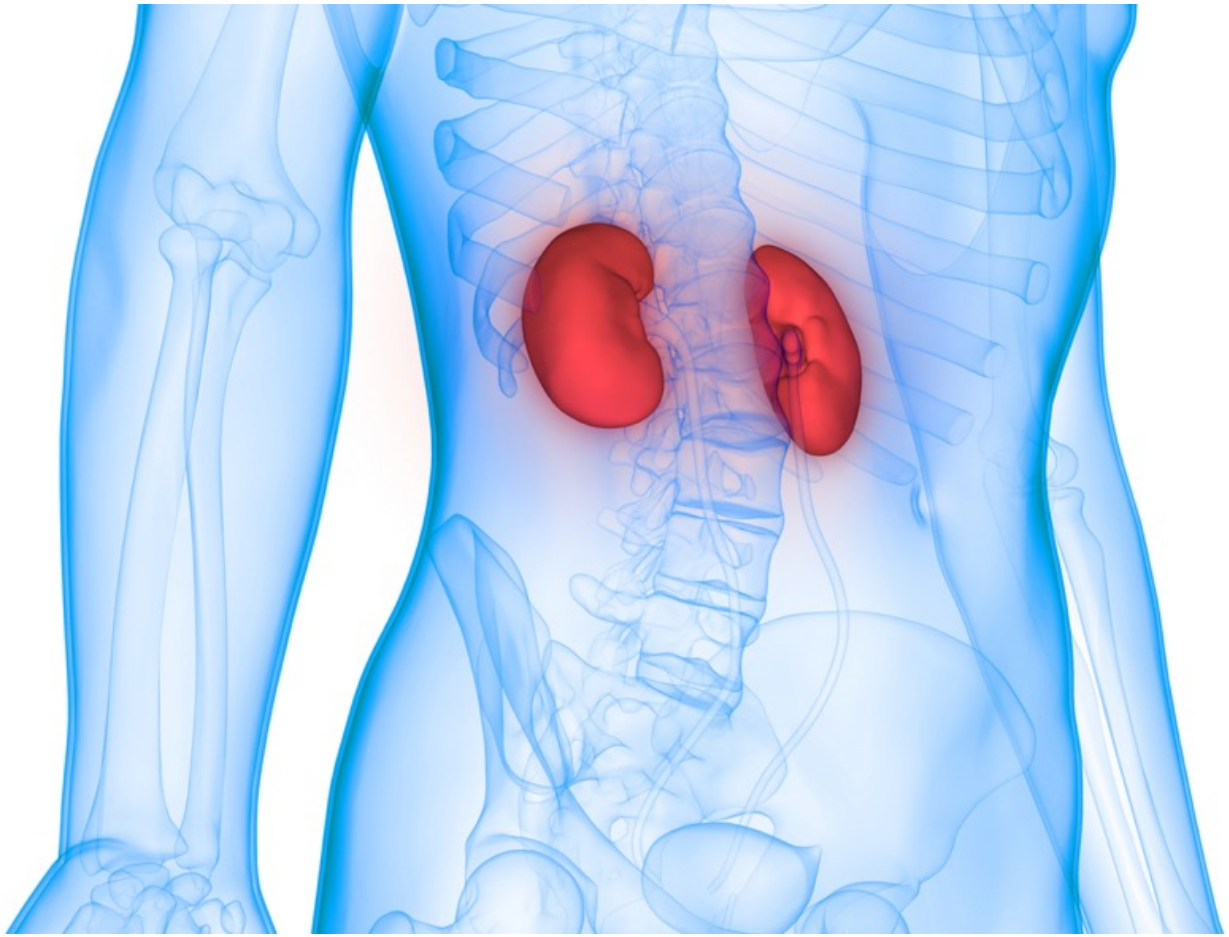

Nivolumab
Doxorubicin
Vinblastine
Dacarbazine
Improved progression-free survival
over ~2 years of follow-up
as compared with brentuximab vedotin + AVD


Doxorubicin
Brentuximab vedotin
Vinblastine
Dacarbazine
• Adults have increased toxic effects
• More than half of children still receive radiation therapy
• Relapses remain problematic
Improves outcomes


PRIMARY END POINT
After a median follow-up of ~12 months
Progression-free Survival
Hazard ratio for disease progression or death, 0.48
(99% CI, 0.27–0.87); two-sided P=0.001
Percentage of Patients
94%
(95% CI, 91–96)
86%
(95% CI, 82–90)
Nivolumab + AVD
Brentuximab Vedotin + AVD


TREATMENT DISCONTINUATION
Any Discontinuation
Percentage of Patients
9.4%
22.2%
Nivolumab
Brentuximab Vedotin

Kidney Transplantation Between People with HIV is Safe, NIH Study Finds



Safety of Kidney Transplantation from Donors with HIV

Kidney transplantation from donors with human immunodeficiency virus (HIV) to recipients with HIV is an emerging practice. It has been performed since 2016 under the U.S. congressional HIV Organ Policy Equity Act and is currently approved for research only. The Department of Health and Human Services is considering expanding the procedure to clinical practice, but data are limited to small case series that did not include donors without HIV as controls.

In an observational study conducted at 26 U.S. centers, we compared transplantation of kidneys from deceased donors with HIV and donors without HIV to recipients with HIV. The primary outcome was a safety event (a composite of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection), assessed for noninferiority (margin for the upper bound of the 95% confidence interval, 3.00). Secondary outcomes included overall survival, survival without graft loss, rejection, infection, cancer, and HIV superinfection.

Conclusions

In this observational study of kidney transplantation in persons with HIV, transplantation from donors with HIV appeared to be noninferior to that from donors without HIV.

Kidney transplantation provides a survival benefit for persons with human immunodeficiency virus (HIV) and end-stage renal disease, but access is limited by a shortage of available organs. In particular, persons with HIV who are receiving dialysis have a higher risk of death and less access to kidney transplantation than persons without HIV. Kidney transplantation from donors with HIV to recipients with HIV is a strategy that addresses the organ shortage and mitigates disparities in mortality among candidates on the waiting list and in transplantation access. Good outcomes from a series in South Africa involving transplantation from donors with HIV to recipients with HIV provided preliminary evidence to support this practice.

Study Design and Oversight

Our observational, noninferiority study compared kidney transplantation from deceased donors with HIV to recipients with HIV with that from deceased donors without HIV to recipients with HIV at 26 transplantation centers in the United States

tudy Participants

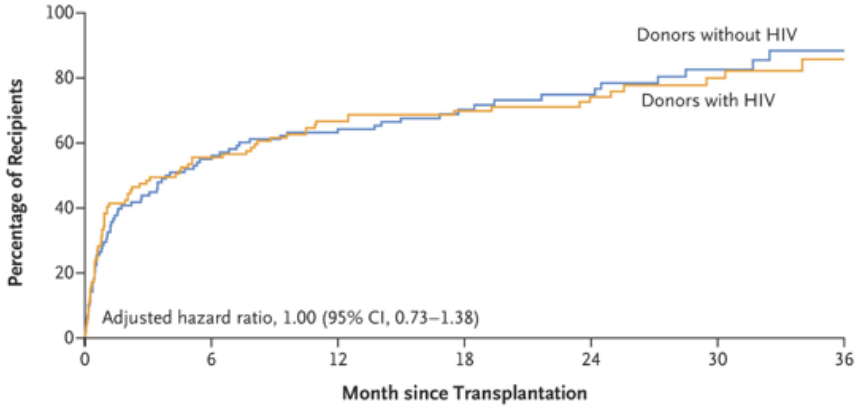
Persons with HIV and end-stage renal disease were eligible if they were 18 years of age or older, met local criteria for kidney transplantation, and consented to consider receiving a kidney from a deceased donor with HIV. Additional criteria included a CD4+ cell count of at least 200 cells per microliter, active antiretroviral therapy, and an HIV RNA level of less than 50 copies per milliliter. Exclusion criteria were an active opportunistic infection, previous progressive multifocal leukoencephalopathy, and central nervous system lymphoma.

Intervention

All the participants provided consent and were eligible to receive a kidney from a donor with or without HIV, whichever was available first. Allocation could not be randomized because of constraints of the national OPTN (e.g., blood type, HLA matching, and geographic location).

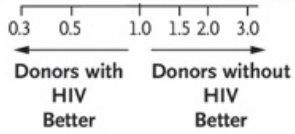
Characteristic	Donors with HIV	Donors without HIV	Absolute SMD
Recipients			
No. of recipients	99	99	
Median age (IQR) — yr	53 (45–60)	57 (50–63)	0.264
Female sex — no. (%)	16 (16)	19 (19)	0.080
Race or ethnic group — no. (%)†			0.296
Black	72 (73)	69 (70)	
White, non-Hispanic	10 (10)	13 (13)	
Hispanic or Latino	10 (10)	15 (15)	
Other	7 (7)	2 (2)	
Hepatitis C antibody–positive — no. (%)	9 (9)	17 (17)	0.241
Positive hepatitis C nucleic acid test — no./total no. (%)	1/9 (11)	6/17 (35)	0.598
HIV RNA level <200 copies/ml at transplantation — no. (%)‡	98 (99)	98 (99)	0
Median CD4+ cell count (IQR) — cells/μl	511 (375–652)	492 (362–686)	0.021
Antiretroviral therapy — no. (%)			
Containing a protease inhibitor or cobicistat	6 (6)	6 (6)	0
Containing integrase strand transfer inhibitor	98 (99)	95 (96)	0.194
Cause of kidney failure — no. (%)§			0.092
HIV-associated nephropathy	34 (34)	36 (36)	
Diabetes	23 (23)	25 (25)	
Hypertension	20 (20)	17 (17)	
Median duration of renal-replacement therapy (IQR) — yr	4.1 (2.6–6.1)	4.8 (2.6–7.6)	0.359
Induction immunosuppression — no. (%)			0.187
ATG or ATGAM	61 (62)	63 (64)	0.042
Basiliximab	34 (34)	33 (33)	0.021
ATG or ATGAM plus basiliximab	4 (4)	2 (2)	0.118
Maintenance immunosuppression — no. (%)			
Tacrolimus	96 (97)	98 (99)	0.144
Mycophenolate mofetil or mycophenolic acid	96 (97)	95 (96)	0.054
Glucocorticoids	77 (78)	82 (83)	0.127
Participation in CCR5 trial — no. (%)	30 (30)	23 (23)	0.160
Donors			
No. of donors	64	82	
Median age (IQR) — yr	36 (28–45)	40 (30–49)	0.305
Female sex — no. (%)	18 (28)	26 (32)	0.078
Race or ethnic group — no. (%)¶			0.480
Black	25 (39)	17 (21)	
White, non-Hispanic	30 (47)	47 (57)	
Hispanic or Latino	9 (14)	15 (18)	
Other	0	3 (4)	
Median Kidney Donor Profile Index score (IQR)‖	38 (26–54)	53 (35–69)	0.407
Hepatitis C antibody virus–positive — no. (%)	3 (5)	10 (12)	0.273
Hepatitis C RNA detectable — no. (%)	2 (3)	8 (10)	0.273
False positive HIV test — no. (%)	NA	27 (33)	NA

A Cumulative Incidence of Composite Primary-Outcome Event among Recipients with HIV

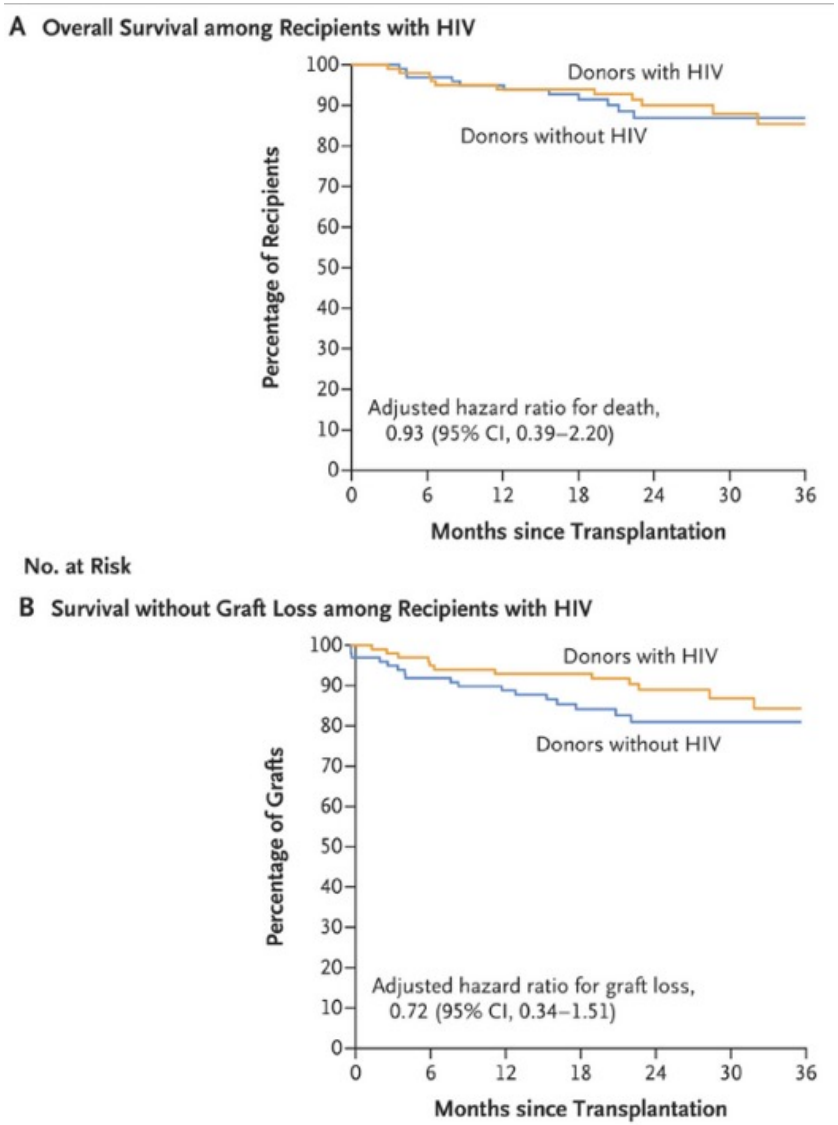


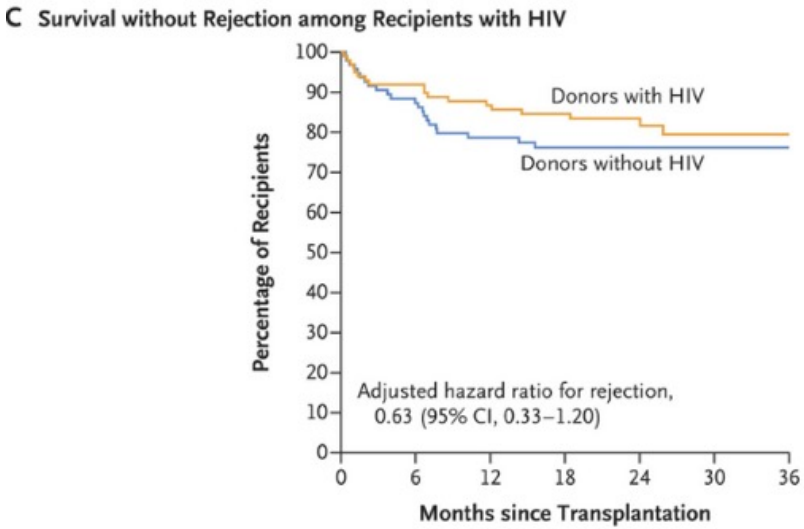
B Adjusted Relative Risks of Primary- and Secondary-Outcome Event among Recipients with HIV

Outcome	Donors with HIV	Donors without HIV	Adjusted Relative Risk (95% CI)
	no. of events/no. of recipients		
Primary outcome: composite safety event	79/99	77/99	1.00 (0.73–1.38)
Composite safety event, with additional adjustment	79/99	77/99	1.05 (0.75–1.47)
Death	12/99	11/99	0.93 (0.39–2.20)
Death or graft loss	14/99	17/99	0.72 (0.34–1.51)
Death, graft loss, or first serious adverse event	74/99	76/99	0.96 (0.68–1.34)
Death, graft loss, first serious adverse event, or first opportunistic infection	75/99	76/99	1.00 (0.71–1.40)
Secondary outcome: opportunistic infection	11/99	8/99	1.28 (0.51–3.18)



Outcome	Donors with HIV (N=99)		Donors without HIV (N=99)		Crude Incidence Rate Ratio (95% CI)
	Participants with Event	Total No. of Events	Participants with Event	Total No. of Events	
Serious adverse event — no. (%)	74 (75)	206	76 (77)	222	0.90 (0.74–1.08)
Allograft rejection — no. (%)	18 (18)	21	22 (22)	32	0.63 (0.37–1.10)
Allograft rejection at 1 yr — no. (%)	13 (13)	13	20 (20)	25	0.52 (0.26–1.01)
HIV breakthrough infection — no. (%)	10 (10)	13	4 (4)	4	3.14 (1.02–9.63)
Persistent failure of HIV treatment — no.	0	0	0	0	NA
Any infection — no. (%)	81 (82)	273	71 (72)	229	1.15 (0.97–1.37)
Opportunistic infection — no. (%)	8 (8)	11	7 (7)	8	1.33 (0.53–3.30)
Any infection with hospitalization — no. (%)	43 (43)	94	43 (43)	97	0.94 (0.70–1.24)
Surgical or vascular complication — no. (%)	12 (12)	17	19 (19)	23	0.71 (0.38–1.34)
Cancer — no. (%)	8 (8)	9	6 (6)	6	1.45 (0.52–4.07)
New donor-specific antibodies at 1 yr — no./total no. (%)*	9/67 (13)	9	13/59 (22)	13	0.61 (0.28–1.33)

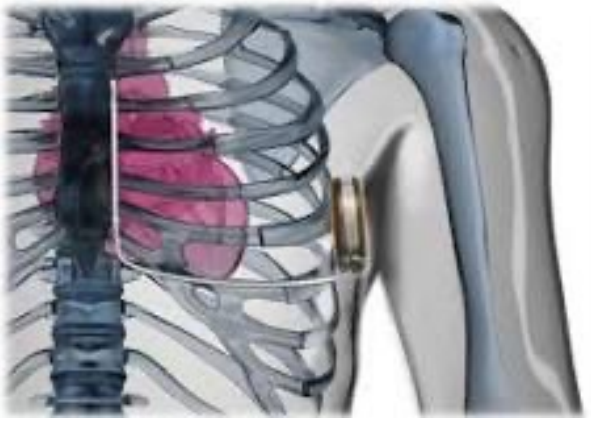




Discussion

In this multicenter, noninferiority, observational study involving transplantation candidates with HIV, we found that kidney transplantation from donors with HIV was noninferior to kidney transplantation from donors without HIV with respect to the primary safety outcome (a composite of death from any cause, graft loss, serious adverse event, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection).

A subcutaneous implantable cardioverter-defibrillator (S-ICD) is a less invasive alternative to a traditional ICD . The S-ICD device is placed under the skin at the side of the chest below the armpit. It connects it to a sensor that runs along the breastbone.



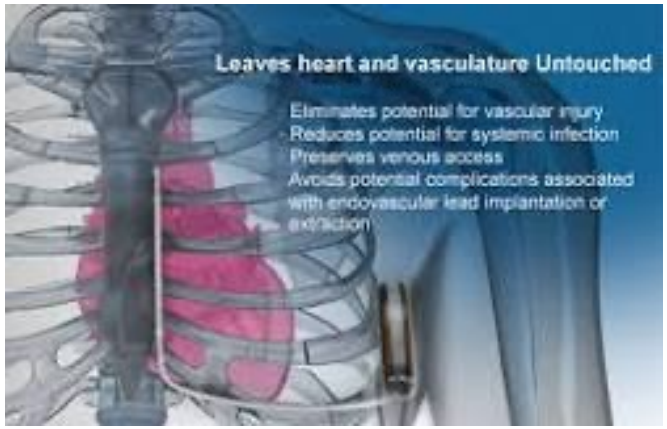
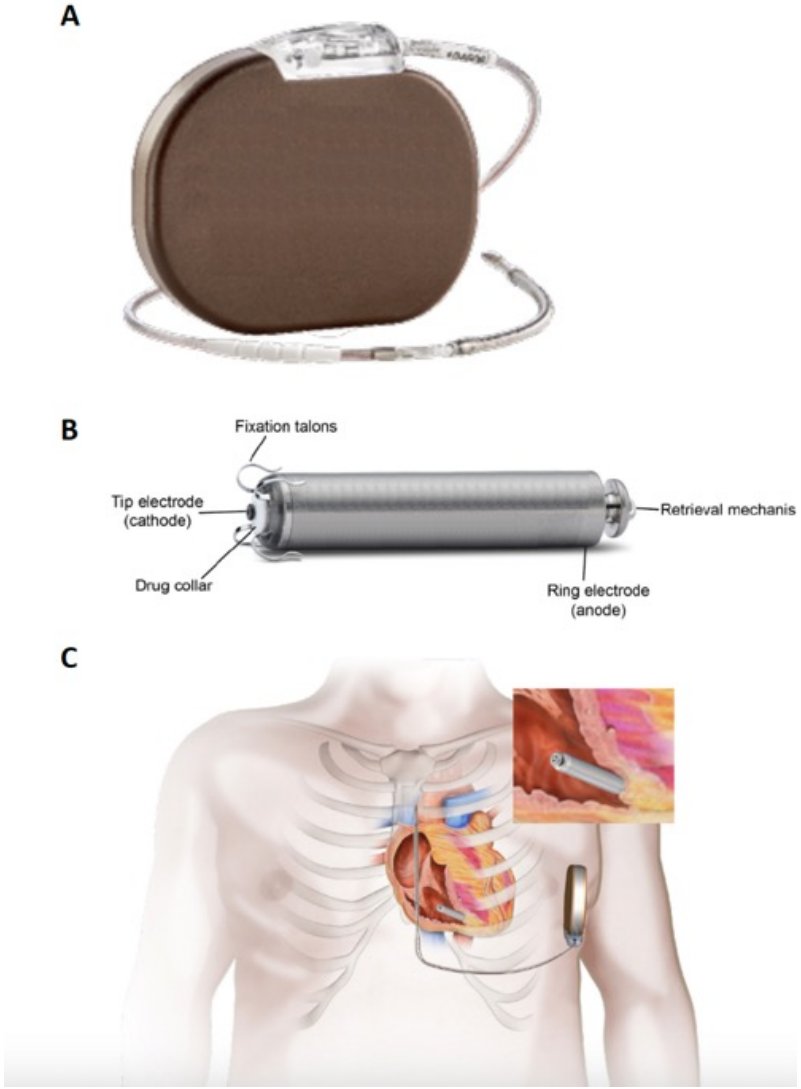


Figure S1: The Modular Pacemaker Defibrillator System



Panels A and B show the components of the modular pacing-defibrillator system—the subcutaneous implantable defibrillator (subcutaneous-ICD) and the ventricular leadless pacemaker (LP), respectively. The system is designed to enable delivery of antitachycardia pacing (ATP) as well as shock therapy. The LP measures 32 mm long and 6 mm in diameter and affixes to the endocardium via active-fixation nitinol tines. When device therapy is warranted to treat a ventricular arrhythmia, the subcutaneous-ICD has one-way inductive communication capabilities to transmit an ATP request signal to the LP. Panel C illustrates the modular pacing-defibrillator system in situ with an inset showing the LP implanted in the right ventricle. In addition to working in concert with the subcutaneous-ICD to provide a wireless pacing-defibrillator system, the LP can be employed as a stand-alone, rate-responsive, single chamber ventricular pacemaker. Images provided courtesy of Boston Scientific.

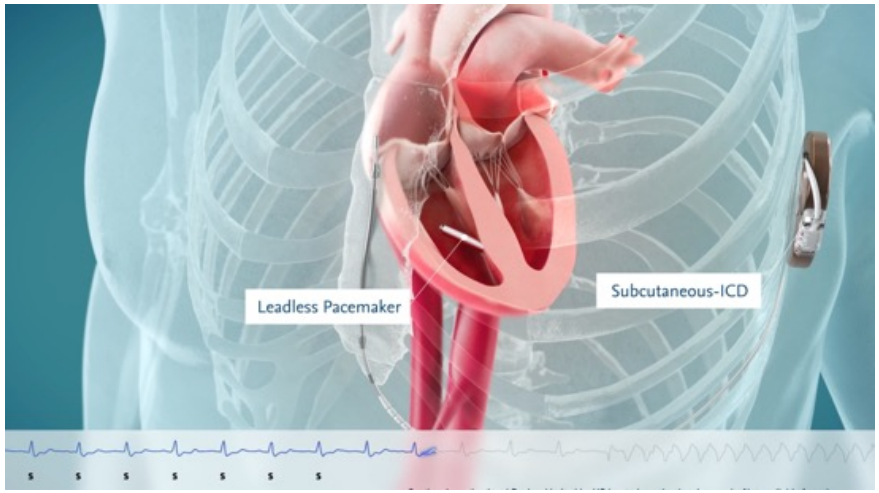
A Modular Communicative Leadless Pacing–Defibrillator System

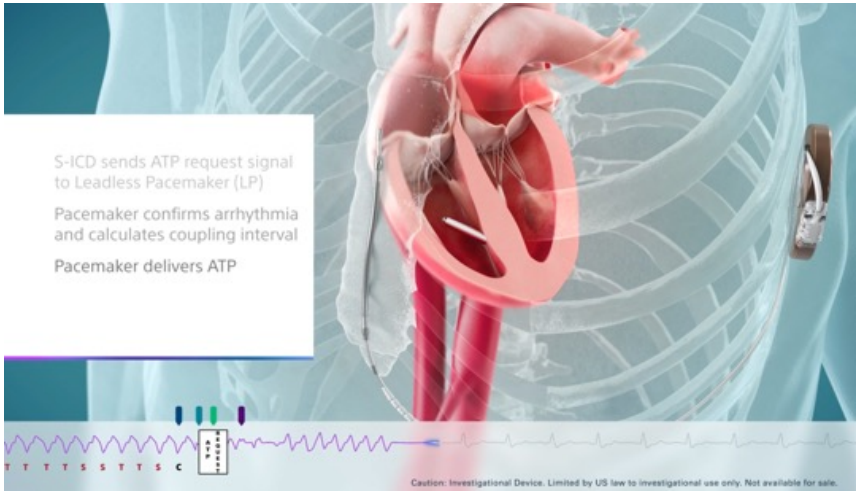
The subcutaneous implantable cardioverter–defibrillator (ICD) is associated with fewer lead-related complications than a transvenous ICD; however, the subcutaneous ICD cannot provide bradycardia and antitachycardia pacing. Whether a modular pacing–defibrillator system comprising a leadless pacemaker in wireless communication with a subcutaneous ICD to provide antitachycardia and bradycardia pacing is safe remains unknown. We conducted a multinational, single-group study that enrolled patients at risk for sudden death from ventricular arrhythmias and followed them for 6 months after implantation of a modular pacemaker–defibrillator system. The safety end point was freedom from leadless pacemaker–related major complications, evaluated against a performance goal of 86%. The two primary performance end points were successful communication between the pacemaker and the ICD (performance goal, 88%) and a pacing threshold of up to 2.0 V at a 0.4-msec pulse width (performance goal, 80%).

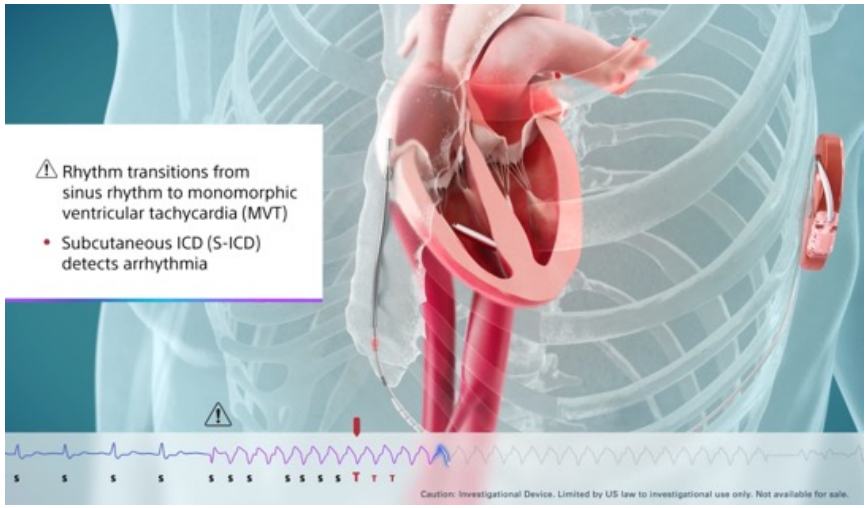
Conclusions

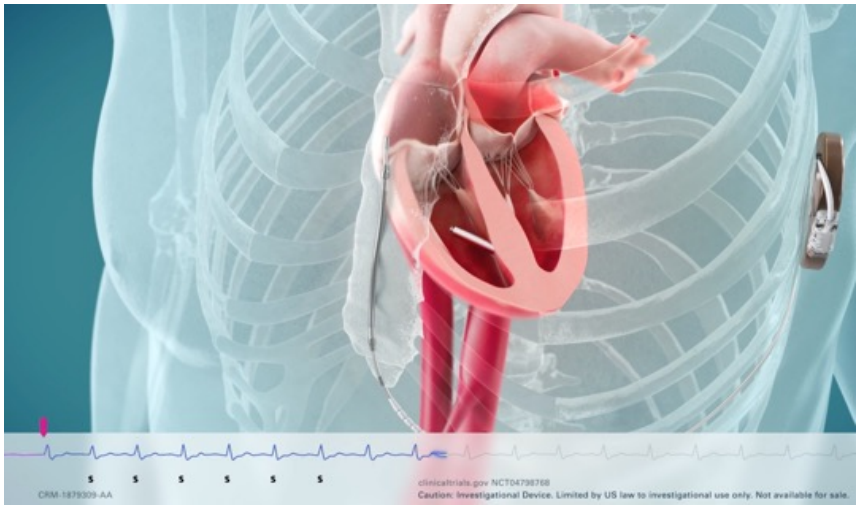
The leadless pacemaker in wireless communication with a subcutaneous ICD exceeded performance goals for freedom from major complications related to the leadless pacemaker, for communication between the leadless pacemaker and subcutaneous ICD, and for the percentage of patients with a pacing threshold up to 2.0 V at a 0.4-msec pulse width at 6 months.

The transvenous implantable cardioverter–defibrillator (ICD) is the established method for treating life-threatening ventricular arrhythmias in patients at risk for sudden death from cardiac causes. However, patients are at risk for lead-related complications caused by conductor failure, breakdown of insulation, and infection. The subcutaneous ICD was developed to circumvent transvenous lead-related complications. The safety and performance of subcutaneous ICDs are well established. Lead-related complications happen less frequently and overall device-related complications, including infections, are less serious among patients with subcutaneous ICDs than among patients with transvenous ICDs. However, the subcutaneous ICD can provide neither prolonged bradycardia nor antitachycardia pacing therapy. Antitachycardia pacing can terminate ventricular arrhythmias, particularly ventricular tachycardia, thereby possibly allowing avoidance of painful shock delivery. Because it does not have the capability to provide antitachycardia pacing, the subcutaneous ICD is contraindicated in patients who require antitachycardia pacing for arrhythmia termination. The MODULAR ATP (Effectiveness of the EMPOWER Modular Pacing System and EMBLEM Subcutaneous ICD to Communicate Antitachycardia Pacing) study investigated the safety and performance of a modular pacing–defibrillator system — the subcutaneous ICD in wireless communication with a leadless pacemaker — in patients with an indication for ICD implantation who were at risk for sudden death caused by ventricular arrhythmias that could be terminated by antitachycardia pacing.


Leadless Pacemaker
Subcutaneous-ICD
S S S S S S S


S-ICD sends ATP request signal to Leadless Pacemaker (LP)
Pacemaker confirms arrhythmia and calculates coupling interval
Pacemaker delivers ATP
ATP request
T T T T S S T T S C
Caution: Investigational Device. Limited by US law to investigational use only. Not available for sale.

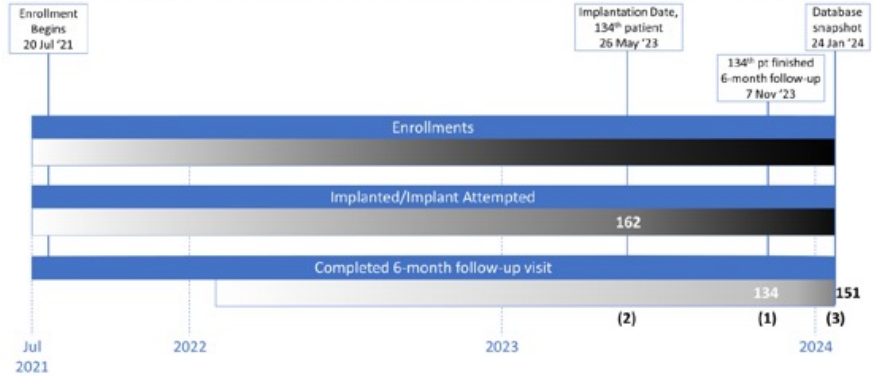

⚠ Rhythm transitions from sinus rhythm to monomorphic ventricular tachycardia (MVT)
• Subcutaneous ICD (S-ICD) detects arrhythmia
S S S S S S S S S S T T T
Caution: Investigational Device. Limited by US law to investigational use only. Not available for sale.


S S S S S S
CRM-1879309-AA
clinicaltrials.gov NCT04738708
Caution: Investigational Device. Limited by US law to investigational use only. Not available for sale.

Patients

Patients 18 years of age or older with an indication for ICD implantation[16,17] who had a preexisting subcutaneous or transvenous ICD that was to be extracted and who were considered to be at high risk for monomorphic ventricular tachycardia were eligible for enrollment if they did not require pacing at baseline, had chronotropic incompetence, or required pacing for ventricular dyssynchrony. The risk of monomorphic ventricular tachycardia was defined as a history of nonsustained monomorphic ventricular tachycardia with a left ventricular ejection fraction of up to 50% or a substantial cardiac scar, a history of sustained ventricular tachycardia or ventricular fibrillation with a left ventricular ejection fraction of up to 50%, a history of syncope that was arrhythmic in origin, a history of ischemic cardiomyopathy with a left ventricular ejection fraction of up to 35%, or a history of nonischemic cardiomyopathy with a left ventricular ejection fraction of up to 35% and a substantial cardiac scar.

Figure S4: The Identification of the 6-month End Point Cohort and Creation of the Database Snapshot



Steps to create 6-month interim cohort and database snapshot:

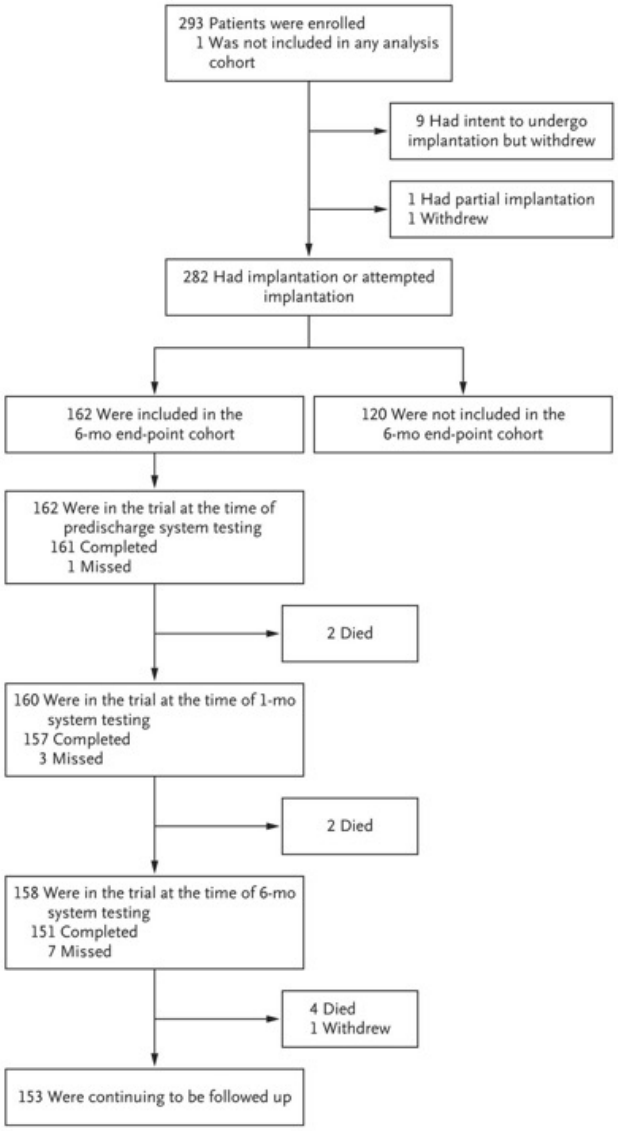
(1) The 134th patient completes 6-month follow-up visit, meeting criteria for early evaluation of 6-month end points.
(2) Due to variable timing of the 6 month follow up visit, patients with attempted implant/implant dates on/before the 134th patient were identified.
(3) After completing database cleaning activities, the database snapshot was created. At this time, 151 of the 162 patients in the end point cohort had completed their 6-month follow-up visit.

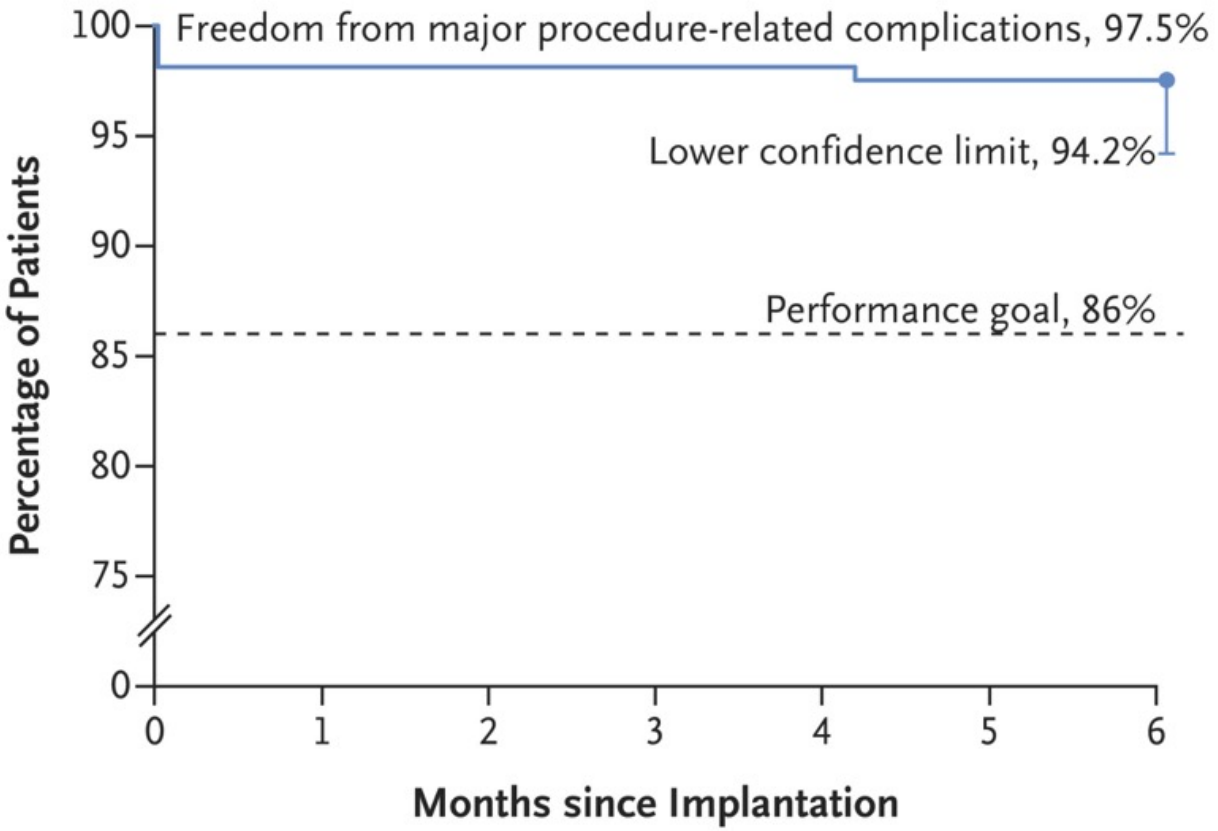
TIMELINE DRAWN TO SCALE

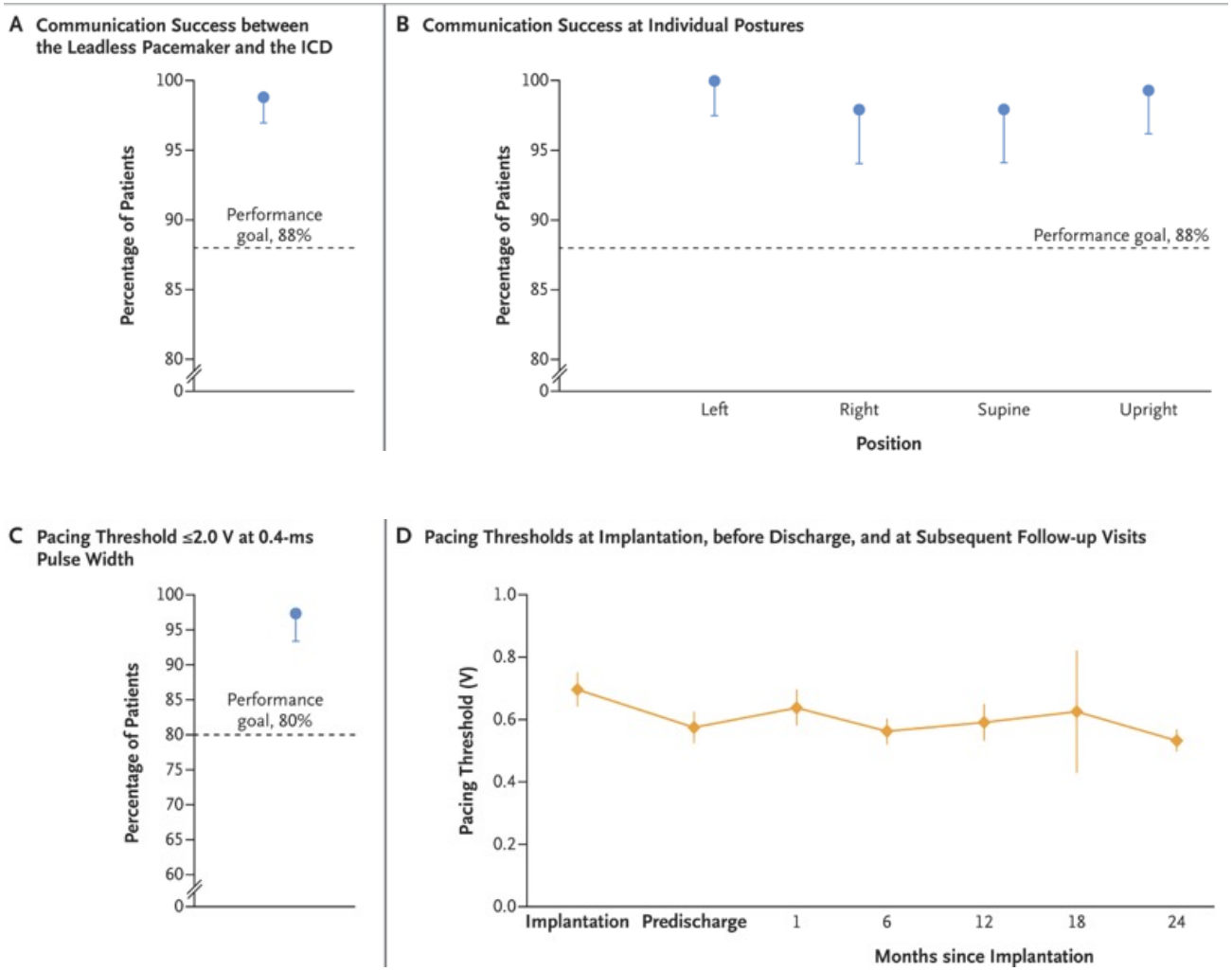
Shown is a graphical depiction of patient enrollments, implanted/attempted implants, and completing the 6-month follow-up visits in the ongoing MODULAR ATP trial. The data cutoff date is the date that the database snapshot was created.

Characteristic	Patients (N=162)
Age — yr	60±12
Sex — no (%)	
Female	27 (16.7)
Male	135 (83.3)
Body-mass index†	29.8±5.9
Race — no. (%)‡	
White	110 (67.9)
Black or African heritage	12 (7.4)
Other	10 (6.2)
Not disclosed	31 (19.1)
Indication for ICD — no. (%)	
Primary prevention	87 (53.7)
Secondary prevention	75 (46.3)
New York Heart Association classification — no. (%)	
Class I	40 (24.7)
Class II	82 (50.6)
Class III	38 (23.5)
Class IV	2 (1.2)
Left ventricular ejection fraction — %	33.1±12.6
Diabetes — no. (%)	57 (35.2)
Hyperlipidemia — no. (%)	103 (63.6)
Renal dysfunction — no. (%)	32 (19.8)
History of cardiac disease — no. (%)§	
Ischemic cardiomyopathy	99 (61.1)
Nonischemic cardiomyopathy	59 (36.4)
Other cardiac diseases	52 (32.1)
No history of cardiac disease	9 (5.6)
Ventricular arrhythmias — no. (%)¶	
Ventricular tachycardia	86 (53.1)
Sustained and nonsustained	19 (11.7)
Monomorphic, nonsustained	35 (21.6)
Monomorphic, sustained	31 (19.1)
Stable	24 (14.8)
Ventricular fibrillation	28 (17.3)
Sustained and nonsustained	2 (1.2)
Nonsustained	3 (1.9)
Sustained	23 (14.2)
No ventricular arrhythmias	67 (41.4)
Previous cardiovascular implantable electronic device — no. (%)‖	
Transvenous pacemaker	0
Transvenous defibrillator	16 (9.9)
Subcutaneous defibrillator	69 (42.6)

Complication	Events	Patients (N=162)
	no.	*no. (%)*
Any complication	18	16 (9.9)
Related to leadless pacemaker or procedure, during procedure	6	5 (3.1)
Myocardial perforation with tamponade†	2	2 (1.2)
Leadless pacemaker inadvertently implanted in left ventricle†	1	1 (0.4)
Adverse reaction, respiratory	1	1 (0.6)
Venous access site bleeding	1	1 (0.6)
Atrial fibrillation	1	1 (0.6)
Related to S-ICD system or procedure, during procedure	3	3 (1.9)
Adverse reaction, vasovagal syncope†‡	1	1 (0.6)
Adverse reaction, respiratory	1	1 (0.6)
Hypotension attributed to IV antibiotic	1	1 (0.6)
Hematoma, S-ICD pocket at ≤30 days after implantation	1	1 (0.6)
Related to S-ICD programmable generator	2	2 (1.2)
Premature cell-battery depletion	1	1 (0.6)
S-ICD migration or revision	1	1 (0.6)
Related to S-ICD electrode	2	2 (1.2)
Invasive intervention to address inappropriate tachycardia therapy, noise (noncardiac), electrode	1	1 (0.6)
Electrode migration or revision	1	1 (0.6)
Related to S-ICD system, therapy: invasive intervention to address ventricular tachycardia below rate cutoff with oversensing	1	1 (0.6)
Related to S-ICD system, diagnosis: random component failure, memory corruption	1	1 (0.6)
Related to S-ICD system, patient related: incisional or superficial infection >30 days after implantation, without explantation	1	1 (0.6)
Cardiovascular	0	0
Noncardiovascular	2	2 (1.2)
Unclassified	0	0


293 Patients were enrolled
1 Was not included in any analysis cohort
9 Had intent to undergo implantation but withdrew
1 Had partial implantation
1 Withdrew
282 Had implantation or attempted implantation
162 Were included in the 6-mo end-point cohort
120 Were not included in the 6-mo end-point cohort
162 Were in the trial at the time of predischarge system testing
161 Completed
1 Missed
2 Died
160 Were in the trial at the time of 1-mo system testing
157 Completed
3 Missed
2 Died
158 Were in the trial at the time of 6-mo system testing
151 Completed
7 Missed
4 Died
1 Withdrew
153 Were continuing to be followed up


Freedom from major procedure-related complications, 97.5%
Lower confidence limit, 94.2%
Performance goal, 86%
Percentage of Patients
100
95
90
85
80
75
0
0
1
2
3
4
5
6
Months since Implantation


A Communication Success between the Leadless Pacemaker and the ICD
Percentage of Patients
100
95
90
85
80
0
Performance goal, 88%
B Communication Success at Individual Postures
Percentage of Patients
100
95
90
85
80
0
Performance goal, 88%
Left
Right
Supine
Upright
Position
C Pacing Threshold ≤2.0 V at 0.4-ms Pulse Width
Percentage of Patients
100
95
90
85
80
75
70
65
60
0
Performance goal, 80%
D Pacing Thresholds at Implantation, before Discharge, and at Subsequent Follow-up Visits
Pacing Threshold (V)
1.0
0.8
0.6
0.4
0.2
0.0
Implantation
Predischarge
1
6
12
18
24
Months since Implantation

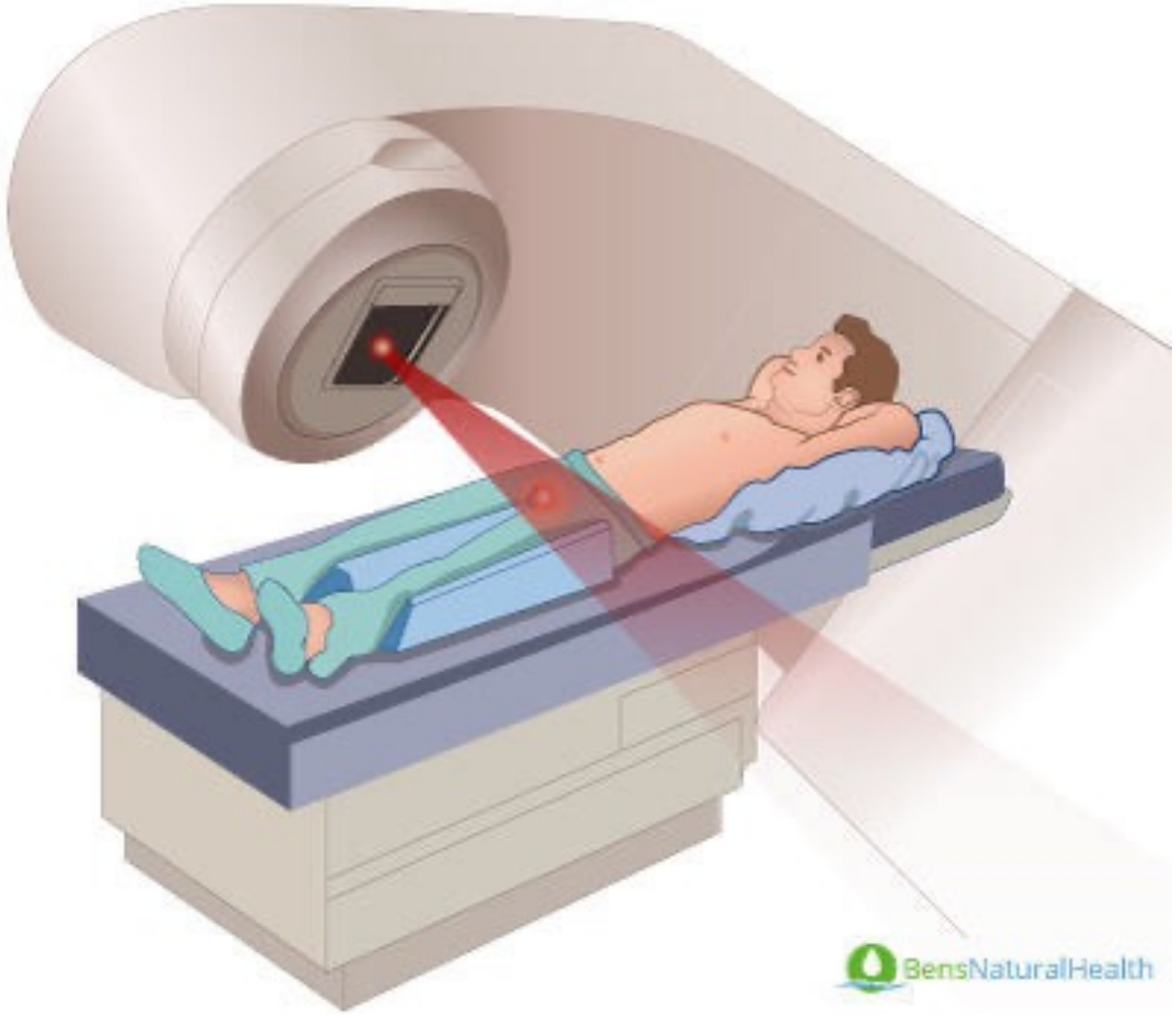
Discussion

In this prospective, multinational, single-group study, a modular pacing–defibrillator system comprising a leadless pacemaker receiving wireless communication from a subcutaneous ICD met the prespecified safety end point of freedom from major complications related to the leadless pacemaker and met the performance end points of successful communication between the pacemaker and the ICD and a pacing threshold of up to 2.0 V at a 0.4-msec pulse width. System implantation was successful in all the patients; 97.5% of the patients were free from major leadless pacemaker–related complications at 6 months, and 91.4% were free from overall system-related complications. Ventricular perforation occurred in 1.2% of the patients, a percentage similar to that reported with implantation of other single-chamber leadless pacemakers, and was resolved with pericardiocentesis. There were no pacemaker dislodgments up to 6 months after implantation, a finding that contrasts with reports for other leadless pacemakers. In two patients, device retrieval at a time remote from implantation was performed successfully.

The study is limited by the inherent disadvantages of a prospective, longitudinal, nonrandomized design with no comparator group. We evaluated the end points against prespecified goals for safety and performance on the basis of benchmarks from previously published literature. Therefore, we can report only on performance and not on efficacy. Our study enrolled patients with a high risk of ventricular tachycardia who were intentionally selected, and our findings may not be generalizable to others who require ICDs or who have ICDs already implanted.

The MODULAR ATP clinical study prospectively showed that the leadless pacemaker in wireless communication with a subcutaneous ICD exceeded performance goals for freedom from major leadless pacemaker–related complications, for communication between the leadless pacemaker and subcutaneous ICD, and for the percentage of patients with a pacing threshold of up to 2.0 V at a 0.4-msec pulse width at 6 months.

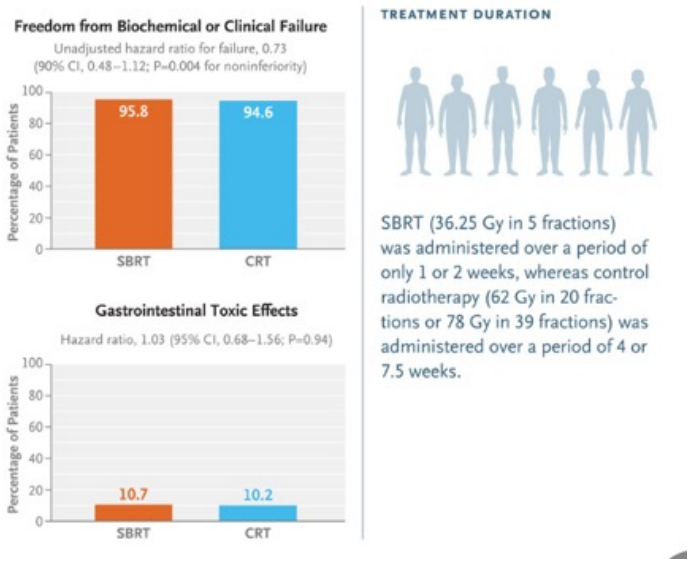
Radiation Therapy for Prostate Cancer



Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer

Whether stereotactic body radiotherapy (SBRT) is noninferior to conventionally or moderately hypofractionated regimens with respect to biochemical or clinical failure in patients with localized prostate cancer is unclear.

We conducted a phase 3, international, open-label, randomized, controlled trial. Men with stage T1 or T2 prostate cancer, a Gleason score of 3+4 or less, and a prostate-specific antigen (PSA) level of no more than 20 ng per milliliter were randomly assigned (in a 1:1 ratio) to receive SBRT (36.25 Gy in 5 fractions over a period of 1 or 2 weeks) or control radiotherapy (78 Gy in 39 fractions over a period of 7.5 weeks or 62 Gy in 20 fractions over a period of 4 weeks). Androgen-deprivation therapy was not permitted. The primary end point was freedom from biochemical or clinical failure, with a critical hazard ratio for noninferiority of 1.45. The analysis was performed in the intention-to-treat population.



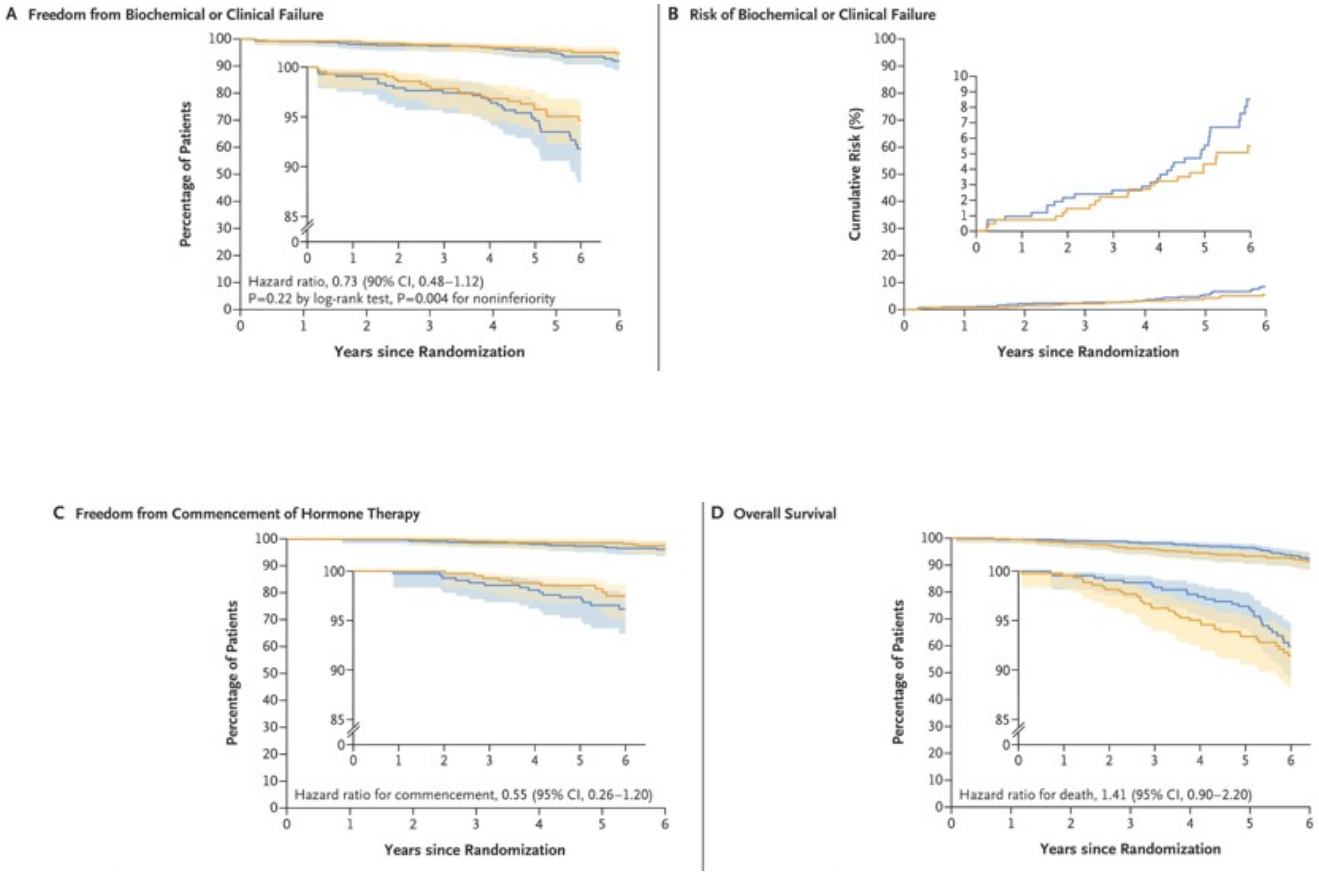
Prostate cancer is a considerable global health care challenge, with nearly 1.5 million men receiving a diagnosis annually. In England in 2021, a total of 12% of newly diagnosed prostate cancers were low risk and 29% were intermediate risk. These men have a number of treatment options, including radiotherapy, which is considered to be curative in the majority of patients.

Innovations in image guidance and radiotherapy treatment delivery have enabled the delivery of higher biologic doses of radiation, significantly improving oncologic outcomes while reducing side effects associated with treatment. Hypofractionation, involving higher doses per treatment session, is appealing because of its potential to maintain the efficacy of the treatment but reduce the total number of treatment sessions, which could make the treatment more attractive to patients and health care systems. Previous studies have confirmed the noninferiority of moderately hypofractionated radiotherapy as compared with conventionally fractionated radiotherapy, and moderate hypofractionation has been established as a standard-care option. Stereotactic body radiotherapy (SBRT) builds on these developments to allow ultrahypofractionated radiotherapy to be delivered with precision.

Patients

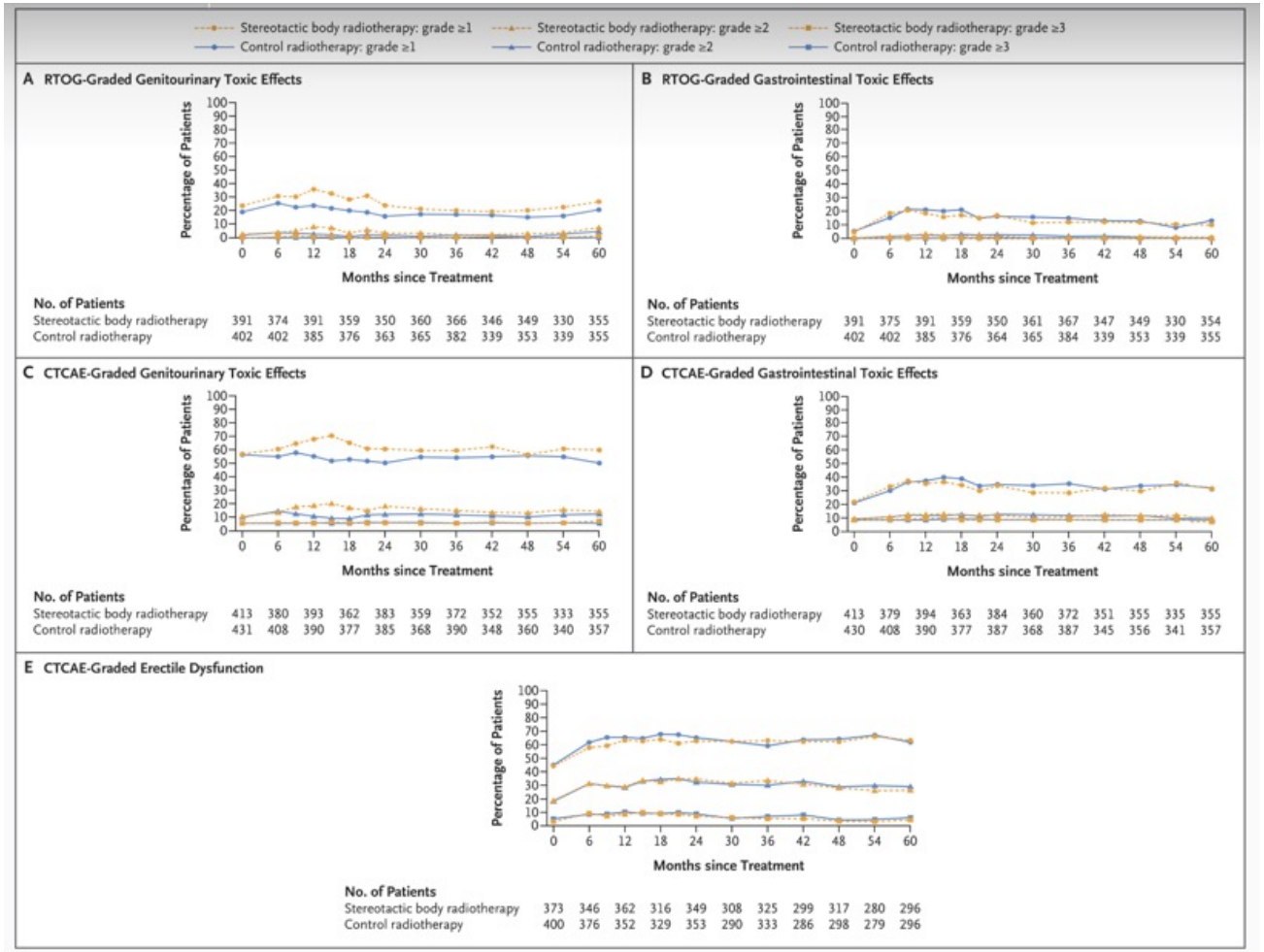
Eligible patients were 18 years of age or older and had histologically confirmed prostate adenocarcinoma, a World Health Organization performance-status score of 0 to 2 (on a scale of 0 to 5, with higher scores indicating greater disability), and a life expectancy of more than 5 years. All the patients had clinical or magnetic resonance imaging (MRI)–defined T1 or T2 disease categorized according to NCCN criteria as low risk (Gleason score of 3+3 and a prostate-specific antigen [PSA] level of ≤10 ng per milliliter) or intermediate risk (Gleason score of 3+4, PSA level of 10.1 to 20.0 ng per milliliter, or both). Among the exclusion criteria were primary Gleason grade 4 or higher disease, any NCCN high-risk factors, previous pelvic radiotherapy, previous treatment for prostate cancer, or prostheses in both hips.

Characteristic	Stereotactic Body Radiotherapy (N=433)	Control Radiotherapy (N=441)	Total (N=874)
Age at randomization — yr			
Median (IQR)	69.8 (65.4–74.1)	69.7 (65.5–73.9)	69.8 (65.4–74.0)
Range	45.8–84.5	48.1–86.7	45.8–86.7
Race or ethnic group — no. (%)†			
Black	35 (8.1)	26 (5.9)	61 (7.0)
East Asian	4 (0.9)	3 (0.7)	7 (0.8)
Mixed heritage	2 (0.5)	2 (0.5)	4 (0.5)
Southern Asian	20 (4.6)	10 (2.3)	30 (3.4)
White	367 (84.8)	393 (89.1)	760 (87.0)
Other	5 (1.2)	7 (1.6)	12 (1.4)
Family history of prostate cancer — no. (%)			
No	312 (72.1)	326 (73.9)	638 (73.0)
Yes	89 (20.6)	88 (20.0)	177 (20.3)
Unknown	32 (7.4)	27 (6.1)	59 (6.8)
WHO performance-status score — no. (%)‡			
0	389 (89.8)	391 (88.7)	780 (89.2)
1	44 (10.2)	48 (10.9)	92 (10.5)
2	0	2 (0.5)	2 (0.2)
T stage — no. (%)§			
T1c	82 (18.9)	81 (18.4)	163 (18.6)
T2a	105 (24.2)	133 (30.2)	238 (27.2)
T2b	81 (18.7)	59 (13.4)	140 (16.0)
T2c	162 (37.4)	168 (38.1)	330 (37.8)
Unknown	3 (0.7)	0	3 (0.3)
Method of staging — no. (%)			
≥1 Staging method performed	430 (99.3)	441 (100)	871 (99.7)
Digital rectal examination	156 (36.0)	166 (37.6)	322 (36.8)
Transrectal ultrasonography	280 (64.7)	264 (59.9)	544 (62.2)
MRI of the pelvis	339 (78.3)	359 (81.4)	698 (79.9)
Gleason score — no. (%)¶			
3+3	63 (14.5)	90 (20.4)	153 (17.5)
3+4	370 (85.5)	351 (79.6)	721 (82.5)
Prostate-specific antigen level			
Median (IQR) — ng/ml	7.9 (5.5–10.9)	8.1 (6.3–11.0)	8.0 (5.9–11.0)
Range — ng/ml	0.5–20.0	0.8–20.0	0.5–20.0
Distribution — no. (%)			
<10 ng/ml	297 (68.6)	303 (68.7)	600 (68.6)
10–20 ng/ml	136 (31.4)	138 (31.3)	274 (31.4)
Percentage of positive biopsy cores — no. (%)			
<50%	287 (66.3)	304 (68.9)	591 (67.6)
≥50%	146 (33.7)	137 (31.1)	283 (32.4)
NCCN risk category — no. (%)			
Low	32 (7.4)	41 (9.3)	73 (8.4)
Intermediate	401 (92.6)	400 (90.7)	801 (91.6)
Favorable	86 (21.4)	106 (26.5)	192 (24.0)
Unfavorable	315 (78.6)	294 (73.5)	609 (76.0)
Prostate volume — no. (%)			
<40 ml	192 (44.3)	163 (37.0)	355 (40.6)
40 to <80 ml	198 (45.7)	223 (50.6)	421 (48.2)
≥80 ml	23 (5.3)	28 (6.3)	51 (5.8)
Unknown	20 (4.6)	27 (6.1)	47 (5.4)
Testosterone level			
No. of patients evaluated	403	407	810
Median (IQR) — μmol/liter	11.5 (9.0–15.0)	11.3 (8.7–15.0)	11.3 (8.9–15.0)
Range — μmol/liter	0.4–30.5	0.4–30.6	0.4–30.6
International Prostate Symptom Score grade — no. (%)‖			
No symptoms: score of 0	16 (3.7)	21 (4.8)	37 (4.2)
Mild symptoms: score of 1–7	202 (46.7)	197 (44.7)	399 (45.7)
Moderate symptoms: score of 8–19	136 (31.4)	141 (32.0)	277 (31.7)
Severe symptoms: score of 20–35	20 (4.6)	23 (5.2)	43 (4.9)
Unknown	59 (13.6)	59 (13.4)	118 (13.5)
Time from diagnosis to randomization — wk**			
Median (IQR)	9.9 (6.6–16.1)	11.0 (6.9–17.0)	10.1 (6.7–16.6)
Range	0.1–225.0	0.9–335.0	0.1–335.0



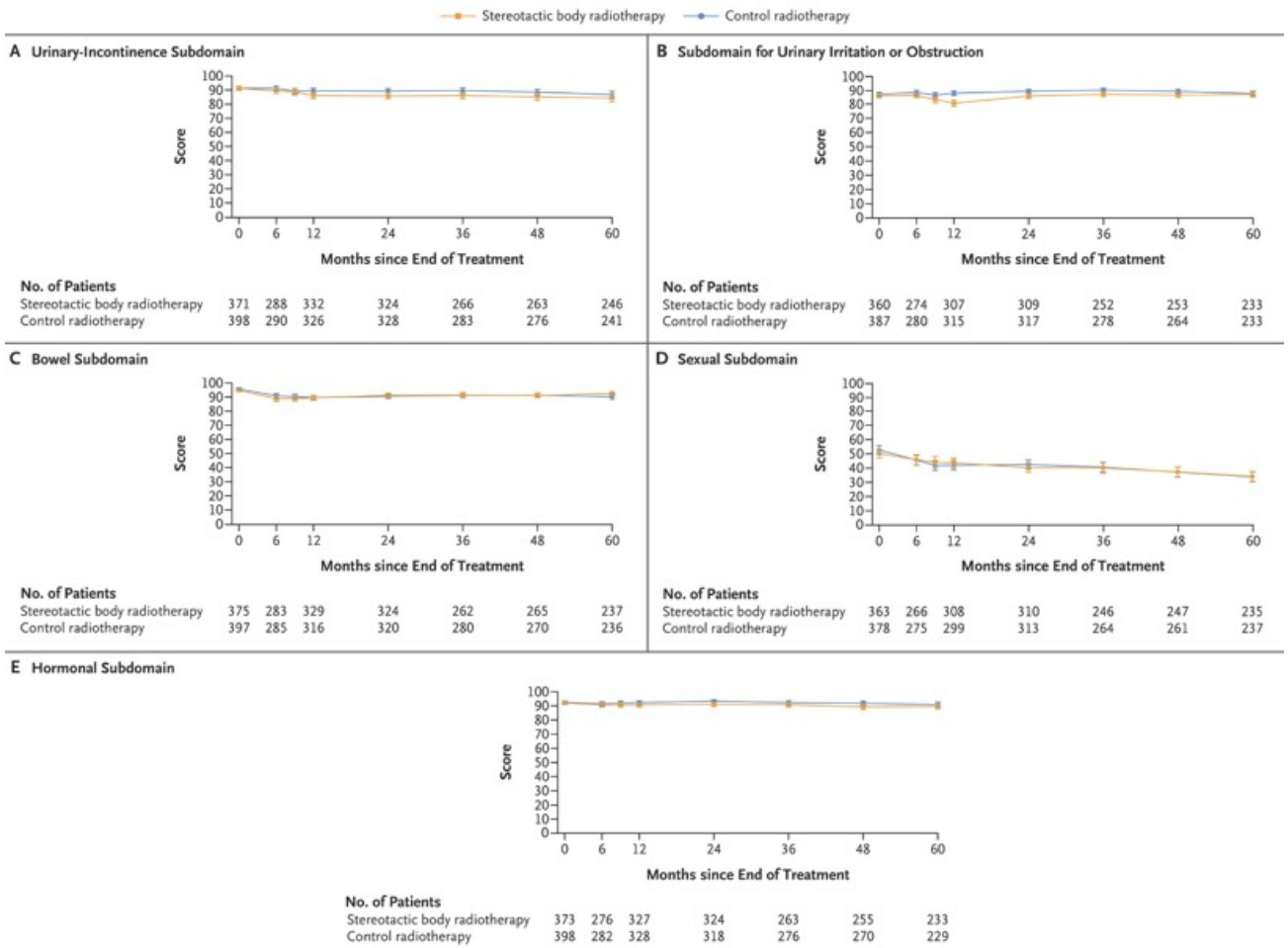
Efficacy Outcomes.

Panel A shows Kaplan–Meier curves for freedom from biochemical or clinical failure, Panel B Nelson–Aalen curves for the cumulative risk of biochemical or clinical failure, Panel C Kaplan–Meier curves for freedom from commencement of hormone therapy, and Panel D Kaplan–Meier curves for overall survival. The shaded areas indicate 95% confidence intervals. Insets show the same data on an expanded y axis.



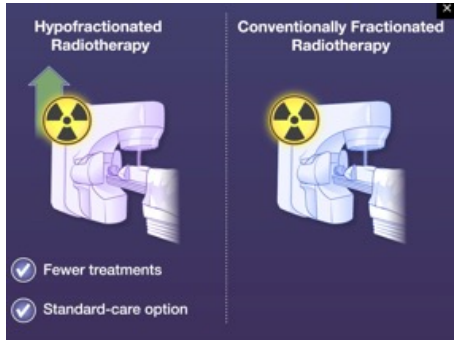
Genitourinary and Gastrointestinal Toxic Effects and Erectile Dysfunction.

Shown are Radiation Therapy Oncology Group (RTOG)–graded or Common Terminology Criteria for Adverse Events (CTCAE)–graded events at each time point assessed according to treatment received.

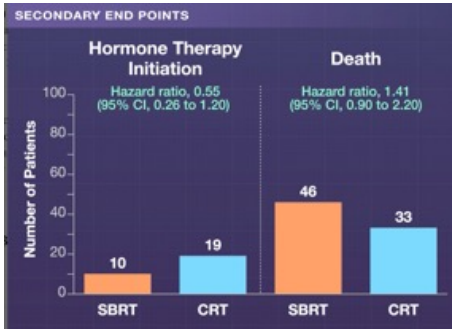


EPIC-26 Subdomain Scores.

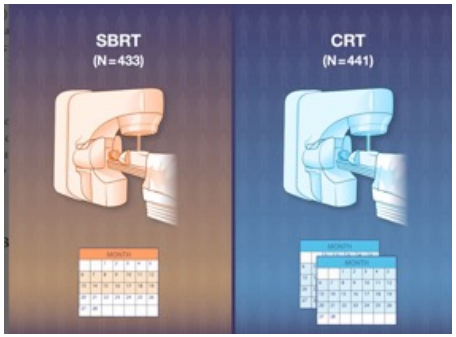
Shown are patient-reported mean scores at each time point assessed according to treatment received. Scores for each subdomain of the 26-question Expanded Prostate Cancer Index Composite (EPIC-26) instrument range from 0 to 100, with higher scores indicating better quality of life. Scores at week 0 are the baseline scores obtained before the start of radiotherapy. I bars indicate 95% confidence intervals.

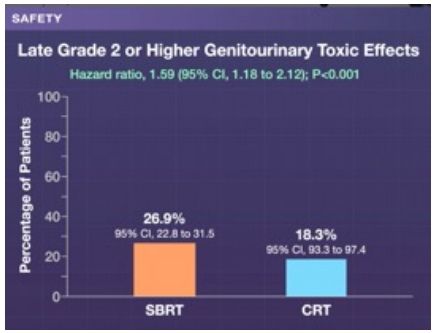

Hypofractionated Radiotherapy
Conventionally Fractionated Radiotherapy
Fewer treatments
Standard-care option

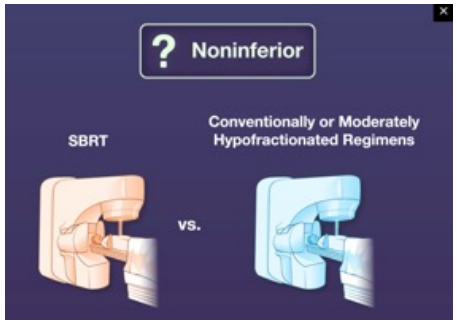

874 Men
Low-to-intermediate-risk localized prostate cancer
Did not warrant hormone therapy

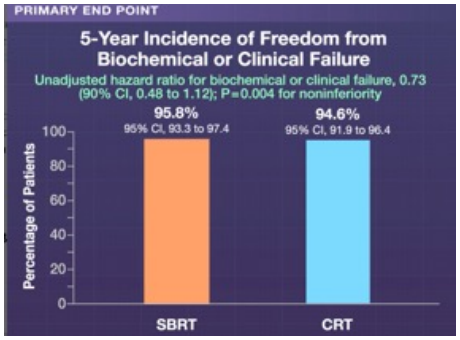

SECONDARY END POINTS
Hormone Therapy Initiation
Hazard ratio, 0.55 (95% CI, 0.26 to 1.20)
Death
Hazard ratio, 1.41 (95% CI, 0.90 to 2.20)
Number of Patients
100
80
60
40
20
0
10
19
46
33
SBRT
CRT
SBRT
CRT

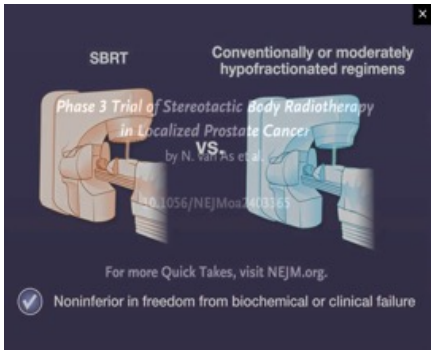

Stereotactic Body Radiotherapy (SBRT)
Ultrahypofractionated radiotherapy


SBRT
(N=433)
CRT
(N=441)

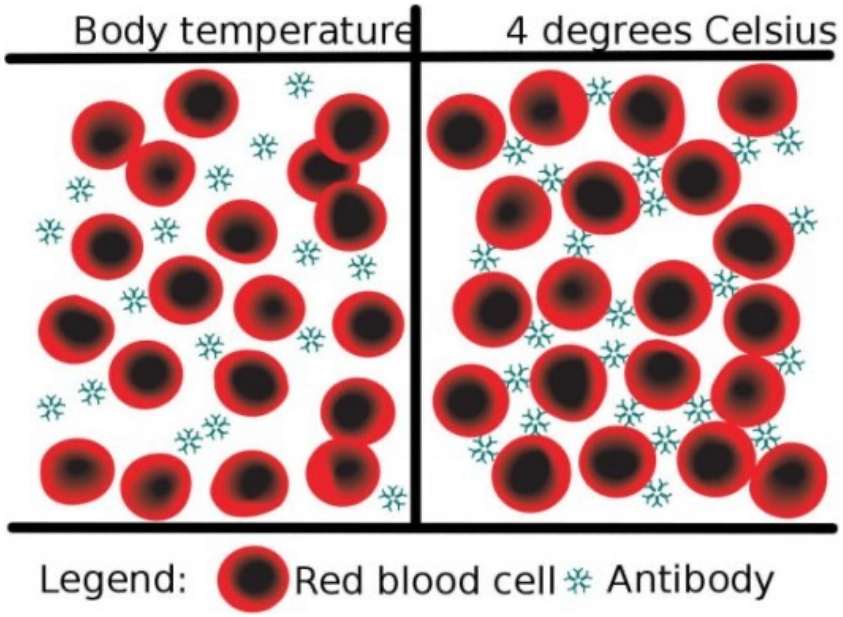

SAFETY
Late Grade 2 or Higher Genitourinary Toxic Effects
Hazard ratio, 1.59 (95% CI, 1.18 to 2.12); P<0.001
Percentage of Patients
100
80
60
40
20
0
26.9%
95% CI, 22.8 to 31.5
18.3%
95% CI, 93.3 to 97.4
SBRT
CRT

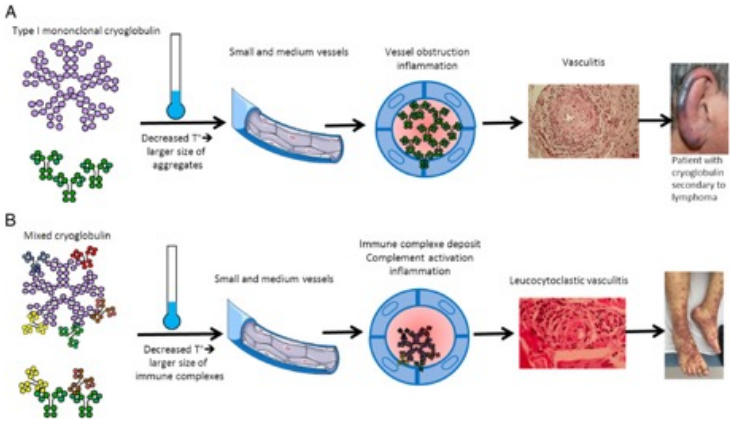

Noninferior
SBRT
Conventionally or Moderately Hypofractionated Regimens
vs.


PRIMARY END POINT
5-Year Incidence of Freedom from Biochemical or Clinical Failure
Unadjusted hazard ratio for biochemical or clinical failure, 0.73 (90% CI, 0.48 to 1.12); P=0.004 for noninferiority
Percentage of Patients
100
80
60
40
20
0
95.8%
95% CI, 93.3 to 97.4
94.6%
95% CI, 91.9 to 96.4
SBRT
CRT


SBRT
Conventionally or moderately hypofractionated regimens
Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer
vs.
For more Quick Takes, visit NEJM.org.
Noninferior in freedom from biochemical or clinical failure

Cold agglutinin disease (CAD) is a rare autoimmune disease characterized by the presence of high concentrations of circulating cold sensitive antibodies. Symptoms of cold agglutinin disease (CAD) are often triggered or made worse by cold temperatures or a viral infection.





Cryoglobulinemia is a medical condition in which the blood contains large amounts of pathological cold sensitive antibodies called **cryoglobulins** – proteins

Cryoglobulinemia — One Name for Two Diseases

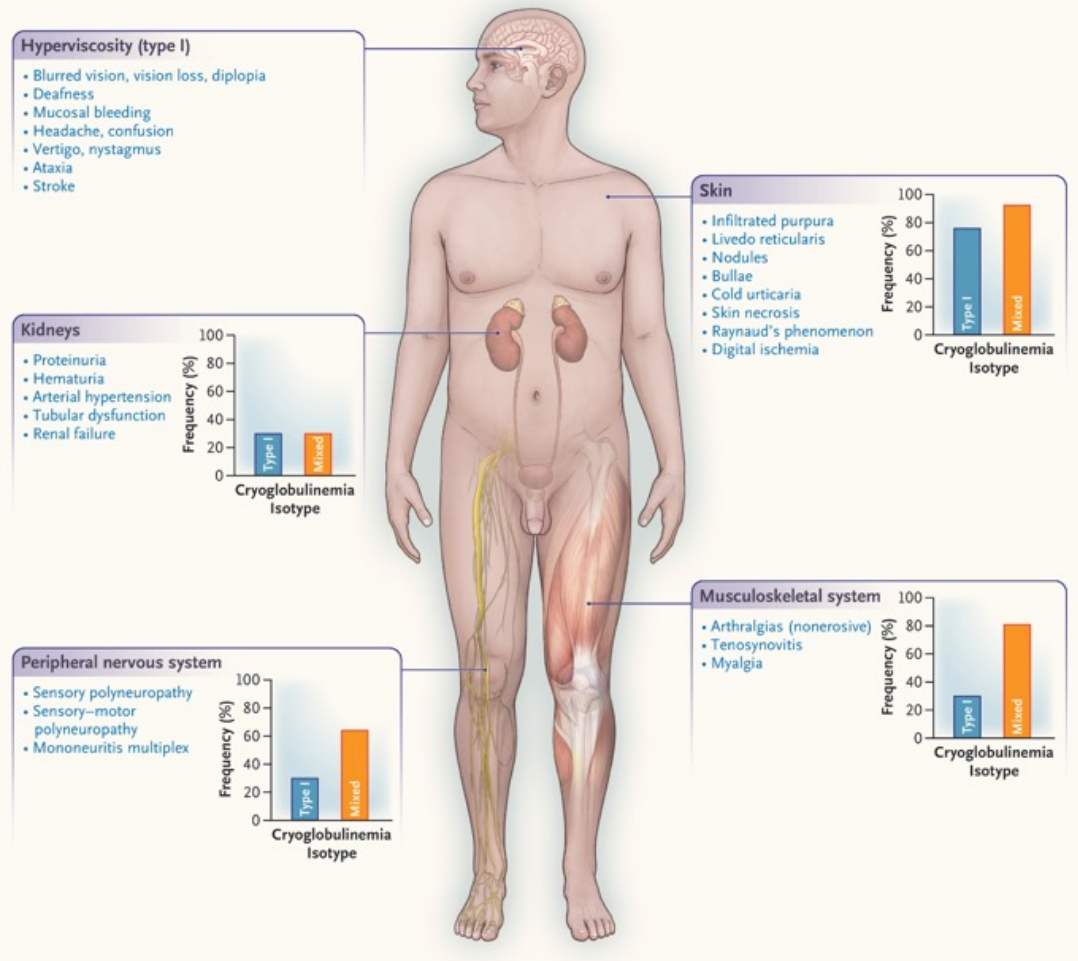
Cryoglobulinemia is a pathologic condition characterized by the precipitation of circulating immunoglobulins from human serum when cooled below 4°C; the immunoglobulins are reversibly soluble when reheated. These proteins were discovered by Wintrobe and Buell in 1933. Lerner and Watson later identified these proteins as gamma globulins and introduced the term cryoglobulins (i.e., cold precipitable serum globulins). Since the initial descriptions of clinical manifestations associated with the in vitro cryoprecipitation of immunoglobulins emerged in the late 1960s, our understanding of cryoglobulinemia, which is characterized by circulating cryoglobulins in the serum, has undergone considerable change. The conditions associated with this unique biologic phenomenon were categorized into three groups of similar importance: lymphomas, Waldenström's macroglobulinemia, and the so-called essential forms, which occur in the absence of any known underlying disease. In 1974, Brouet and colleagues described a classification system, which is still used today, based on the isotype (or isotypes) of immunoglobulins constituting the cryoglobulinemia: type I consists of a monoclonal immunoglobulin (IgM, IgG, or IgA), type II includes polyclonal IgG plus monoclonal IgM with rheumatoid-factor activity, and type III comprises polyclonal IgG, polyclonal IgM, or both. Both type II and type III are known as mixed cryoglobulinemias. Empirical therapeutic approaches have involved different combinations of glucocorticoids, conventional immunosuppressants, and plasma exchange and have yielded inconsistent outcomes and a poor prognosis.

Main Causes of Cryoglobulinemia.

Cause	Disorders
Hematologic disorders	Waldenström's macroglobulinemia Multiple myeloma Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Monoclonal gammopathy of clinical significance
Systemic autoimmune diseases	Sjögren's syndrome Systemic lupus erythematosus Rheumatoid arthritis
Chronic viral infections	Hepatitis C Hepatitis B Human immunodeficiency virus
Others (very rare)	Viral infections (e.g., adenovirus, herpes viruses, Epstein–Barr virus, varicella–zoster virus, human T-cell leukemia virus type 1, influenza virus, parvovirus B19, rubella virus) Bacterial infections (e.g., brucella, infective endocarditis, Lyme disease, rickettsia, syphilis) Fungal infections (e.g., coccidioidomycosis) Parasitic infections (e.g., echinococcosis, leishmaniasis, malaria, schistosomiasis, toxoplasmosis, trypanosomiasis)

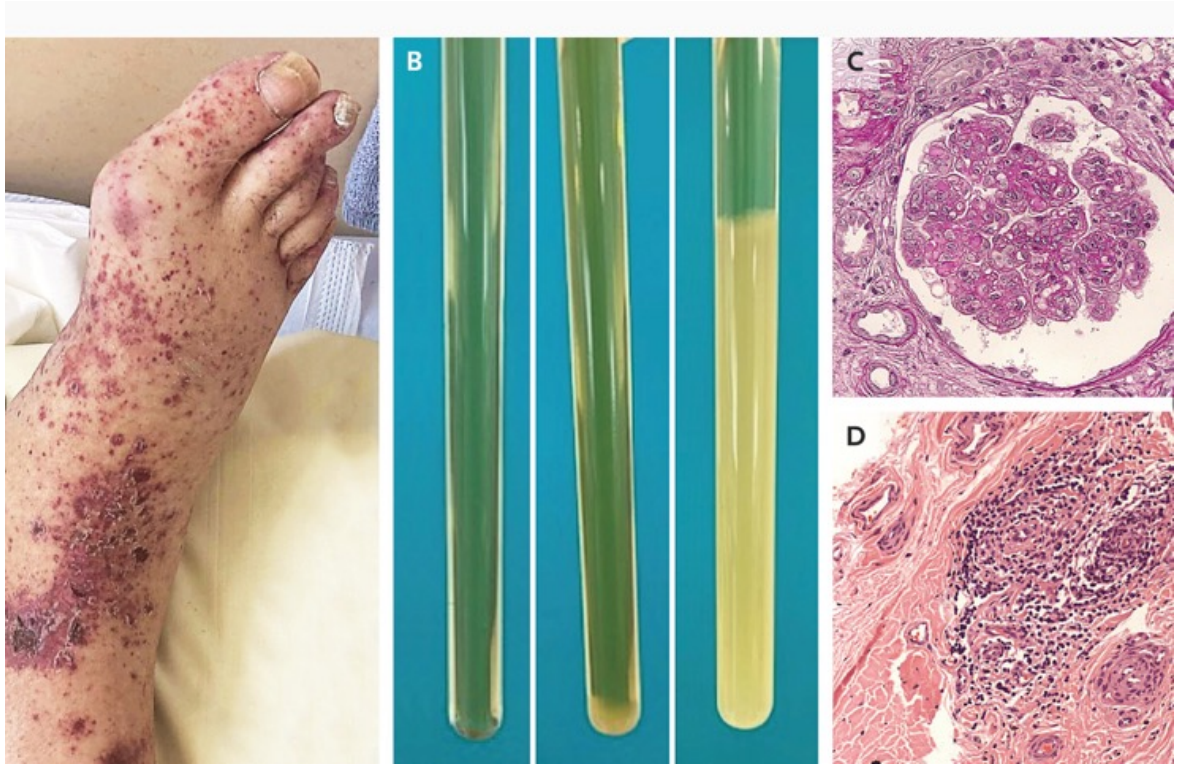
Cryoglobulinemia

- The causes of cryoglobulinemias are currently restricted to a few hematologic disorders, systemic autoimmune diseases, and chronic infections.
- The cryoglobulinemia clinical syndrome comprises two major phenotypes.
- Type I cryoglobulinemia is a genuine hemostasis disorder that leads to mechanical obstruction of multiple small and medium-sized vessels (hyperviscosity, thrombosis, or both); patients with this condition sometimes show signs of vascular inflammation.
- Type II and III mixed cryoglobulinemias are characterized as autoimmune small-vessel vasculitis caused by complement-mediated immune-complex deposition.
- Whereas type I cryoglobulinemia typically arises from a hematologic cancer, mixed cryoglobulinemia is characterized by indolent B-cell lymphoproliferation that may eventually lead to overt lymphoma transformation.
- When pharmacologic therapy is indicated, the underlying disease must first be identified, and then the B-cell lineage clone can be targeted.



The Clinical Presentation of Cryoglobulinemia Syndrome.

Shown are the most frequent clinical manifestations occurring with cryoglobulinemia syndrome, along with the frequency of each category of clinical features according to cryoglobulinemia isotype. Skin involvement includes vascular purpura, which is typically gravity-dependent and which starts on the lower limbs and spreads to the upper limbs while avoiding the trunk and face. Recurrent flares may leave a trace of dermatitis with an ochre color. Skin involvement may also include livedo reticularis, subcutaneous nodules, bullae, vesicles, cold urticaria, and paresthesia in the fingers and toes, rather than true Raynaud's phenomenon. These features of skin involvement are closely linked to physical effort and orthostatism in type II and III mixed cryoglobulinemias, whereas the role of external cold is substantial in type I cryoglobulinemia. Skin manifestations seen in type I



Diagnosis of Cryoglobulinemia.
The diagnosis of cryoglobulinemia is suspected on the basis of characteristic clinical features, such as vascular purpura of the lower limbs (Panel A). The diagnosis is confirmed through the detection of cold-induced precipitates on laboratory testing (Panel B). After centrifugation of blood at 37°C, serum is stored at 4°C for 7 days and then centrifuged at 4°C: tests might be negative (Panel B, left), positive with a low cryocrit (Panel B, middle), or positive with a very high cryocrit (cryoglobulin serum level) (Panel B, right). In cases in which a biologic diagnosis is not possible, targeted tissue biopsies may be helpful. Renal biopsy typically identifies lesions consistent with type I membranoproliferative glomerulonephritis, which is characterized by immunoglobulin deposition (the same isotype as cryoglobulinemia) and complement deposition (C3 and C1q) on immunofluorescence.

Main Causes of Cryoglobulinemia.

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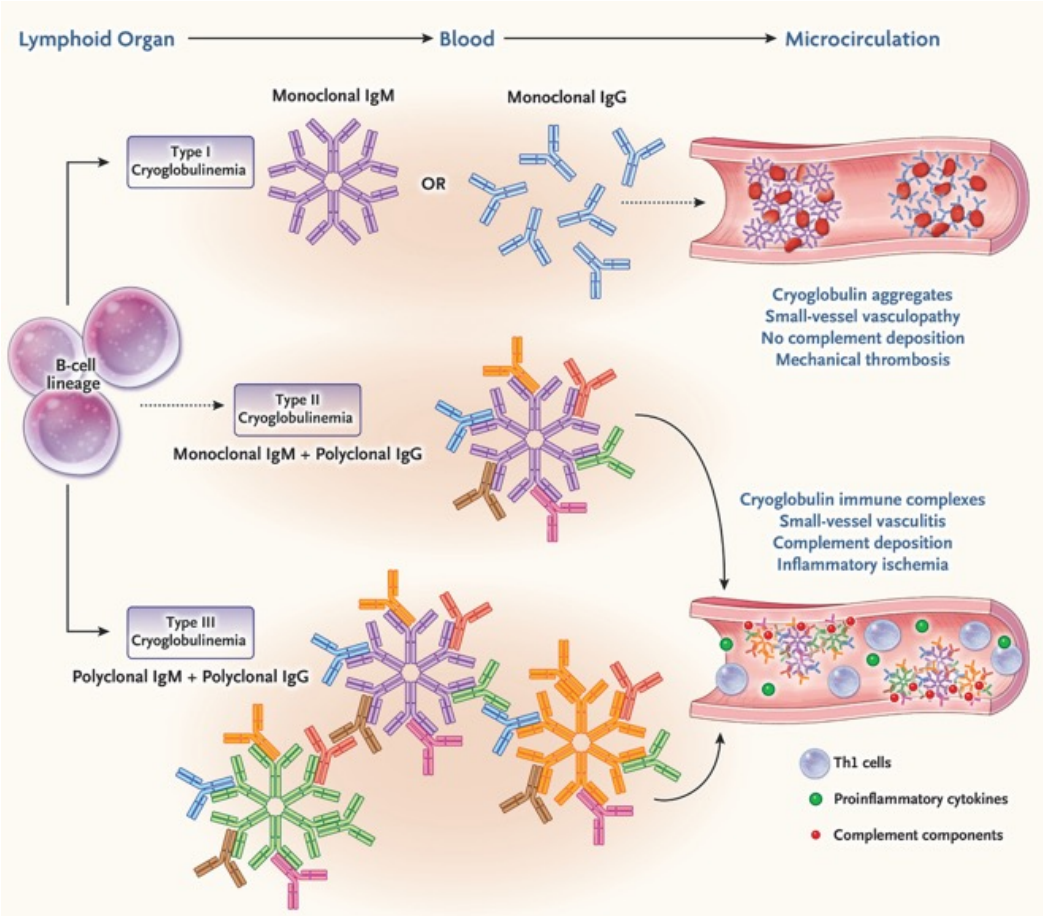


Mechanisms of Cryoglobulinemia.
Cryoglobulinemia has two distinct underlying mechanisms: type I cryoglobulinemia evolves as a vasculopathy affecting small and medium-sized arteries, whereas type II and III mixed cryoglobulinemias manifest as a true autoimmune vasculitis affecting small-to-medium-sized vessels. In both types, lymphocytes from the B-cell lineage (such as memory B cells or plasma cells) produce cryoglobulins in a monoclonal or polyclonal manner. Type I cryoglobulins are monoclonal IgM or IgG produced in large amounts by plasma cells, forming tightly compacted macromolecular nets that physically trap cells within blood vessels, a process known as *rouleaux* formation. Because type I cryoglobulins rarely have rheumatoid-factor activity, complement-mediated inflammatory vasculitis is infrequent. Instead, the primary mechanism in type I cryoglobulinemia involves mechanical vascular obstruction by cold-induced aggregates within the microcirculation, which leads to microthromboses of small vessels.

Mechanisms of Mixed Cryoglobulinemic Vasculitis

As both a hepatotropic and lymphotropic virus, HCV is capable of inducing a range of B-cell lymphoproliferative disorders, from isolated polyclonal hypergammaglobulinemia with detectable cryoglobulins in the serum to cryoglobulinemic vasculitis and, ultimately, B-cell cancer. This spectrum is substantiated by robust data and has been extensively reviewed elsewhere.

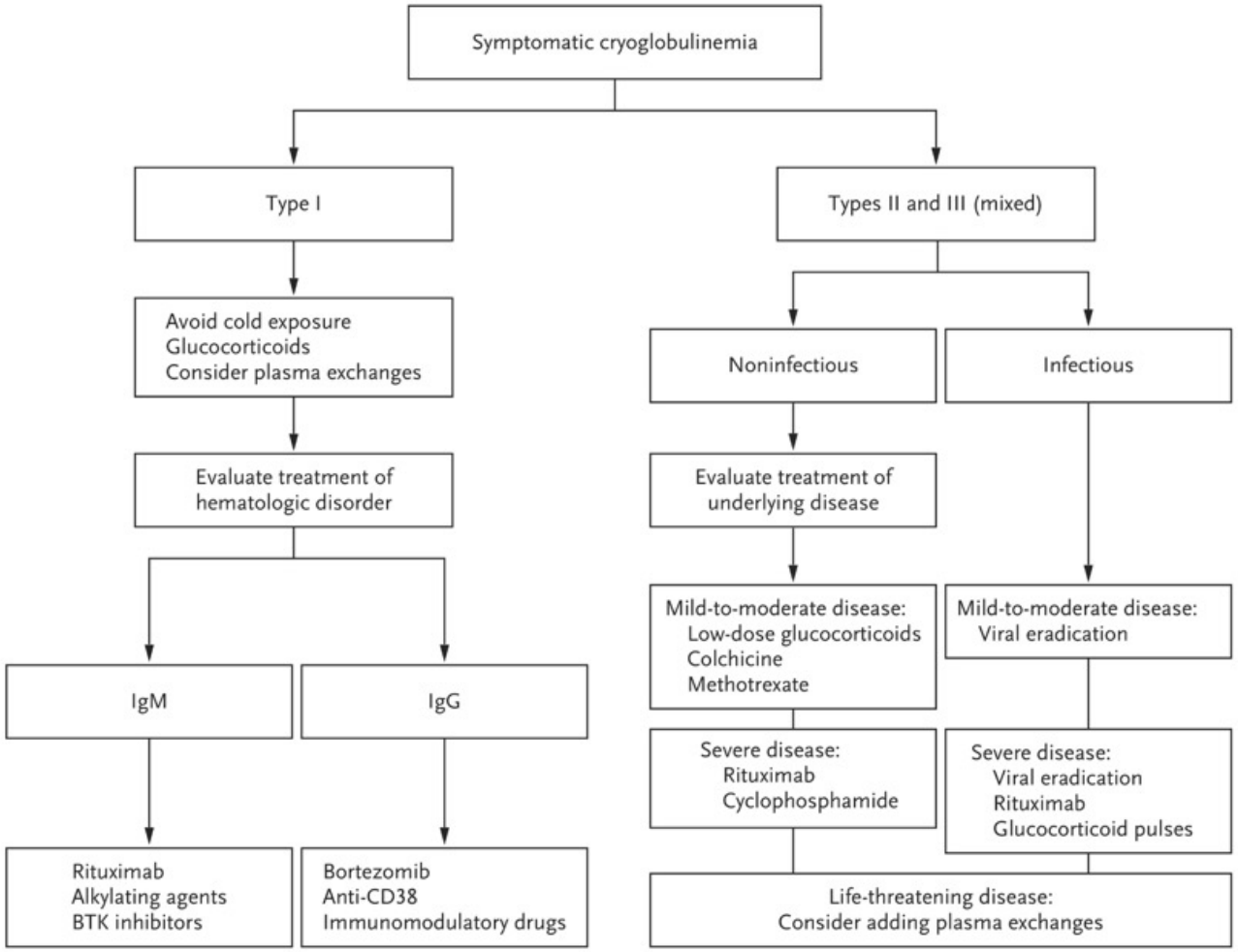
Mechanisms of Type I Cryoglobulinemia

Type I cryoglobulinemic vasculopathy has more similarities to plasma-cell–associated disorders than to autoimmune diseases. When not associated with an overt lymphoproliferative disorder, type I cryoglobulinemia is considered a monoclonal gammopathy of clinical significance. Monoclonal IgG cryoglobulins have finely structured morphologic features and have been shown to form highly structured macromolecular nets capable of physically entrapping cells, a process known as *rouleaux* formation within blood vessels.

Therapeutic Approaches

In the past two decades, therapeutic strategies for cryoglobulinemia have become increasingly targeted because of advancements in our understanding of the underlying mechanisms of the disease. Treatment of mixed cryoglobulinemia often involves direct-acting antiviral agents against HCV, with or without rituximab (an anti-CD20 monoclonal antibody), and much less frequently involves the use of glucocorticoids. For type I cryoglobulinemia, treatment regimens may include glucocorticoids, plasma exchange, and immunosuppressants. Plasmapheresis is a therapeutic option in the context of IgM disease because 80% of IgM antibodies remain in the circulation.

Treatment Algorithm for Cryoglobulinemias.



Type I Cryoglobulinemia

In patients with an indication for systemic treatment (usually because of skin ulceration), targeting the plasma cell clone or lymphoplasmacytic cell clone is crucial, because either will eventually lead to other severe hematologic manifestations.

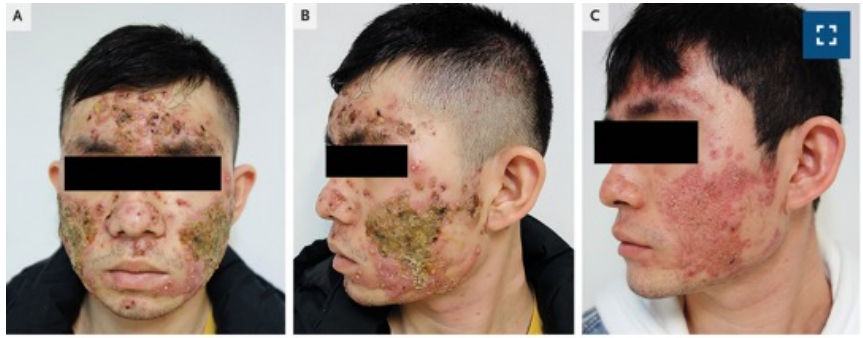
Future Perspectives

Although treatment with rituximab leads to a satisfactory clinical response in patients with mixed cryoglobulinemia, it may not effectively restore defective early B-cell tolerance checkpoints. Elevated serum concentrations of B-lymphocyte stimulator in patients with mixed cryoglobulinemia are associated with increased B-cell proliferation, serum cryoglobulin levels, and vasculitis activity and therefore may contribute to relapse. In light of retrospective observations in patients with mixed cryoglobulinemia who had disease that was refractory to rituximab alone, ongoing clinical trials involving patients with noninfectious mixed cryoglobulinemia are evaluating the sequential therapeutic combination of rituximab and belimumab (an anti–B-lymphocyte stimulator monoclonal antibody.

Conclusion

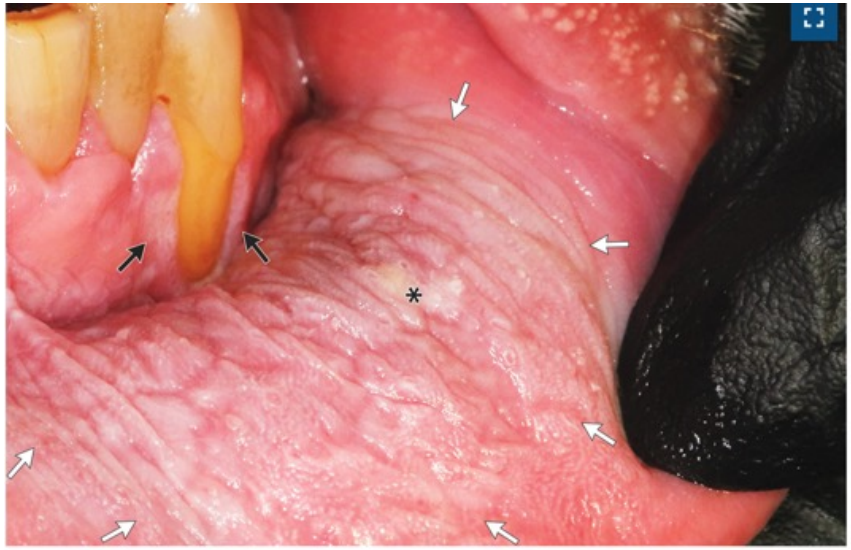
More than a half century after their initial description, mixed and type I cryoglobulinemias should be regarded as two distinct entities, each characterized by unique underlying mechanisms, therapeutic approaches, and prognoses. Pathophysiological and therapeutic advances in HCV-related cryoglobulinemia over the past three decades have been considerable and have led to substantial improvements in patient care. The increased emphasis on underlying autoimmune diseases has underscored the existing knowledge gap in this domain. The range of underlying hematologic conditions in patients with type I cryoglobulinemia highlights the challenges inherent in studying this condition. Future efforts should concentrate on translational research and multicenter, randomized trials focusing on noninfectious mixed cryoglobulinemia and type I cryoglobulinemia, with the ultimate goal of improving prognosis.

Acne Fulminans



A 19-year-old man with a history of mild acne vulgaris presented to the dermatology clinic with a 10-day history of rapidly worsening acne, along with fever, muscle aches, and knee pain. His temperature was 38.5°C. On physical examination, diffuse papulonodular and pustular lesions with areas of overlying crusting were noted across the forehead, nose, cheeks, and chin (Panels A and B). There were similar lesions on the neck, shoulders, chest, back, and thighs. Laboratory studies were notable for neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate and C-reactive protein level. A culture of a skin swab grew only *Cutibacterium acnes*. Histopathological examination of a skin-biopsy specimen taken from behind the left ear showed suppurative folliculitis with adjacent dermal edema. A diagnosis of acne fulminans — an acute, severe variant of inflammatory acne — was made. Acne fulminans may be associated with systemic symptoms, such as fever, myalgias, arthralgias, and even osteolytic bone lesions. Bone imaging showed no osteolytic lesions in this patient. The condition may be induced by isotretinoin therapy or occur spontaneously, as in this case. Treatment with oral glucocorticoids, isotretinoin, and a topical antimicrobial agent was initiated. At the 6-week follow-up, the systemic symptoms had resolved and the acne had abated (Panel C).

Smokeless Tobacco Keratosis



A 55-year-old man with a 40-year history of smokeless tobacco use was referred to the oral medicine clinic for evaluation of a white patch on his left inner lip. The patch was asymptomatic and had been present for years at the site at which he placed moist snuff tobacco. On physical examination, a velvety, fissured patch of mucosa was present on the inner aspect of the left lip, with a small ulcer at the center (asterisk). When stretched, this area of labial mucosa formed a pouch (outlined by white arrows). Brown discoloration of the teeth and gingival recession bordered by leukoplakia (black arrows) were also noted. A diagnosis of smokeless tobacco keratosis — also known as tobacco pouch keratosis — was made. Smokeless tobacco keratosis occurs when a thickened layer of keratin develops at the site of tobacco contact. The lesion may be associated with an increased risk of oral cancer, so referral for an incisional biopsy is warranted. Counseling regarding oral care and tobacco cessation were provided to this patient, and a referral to an oral surgeon for a biopsy was made. Unfortunately, the patient was lost to follow-up.

Case 32-2024: A 72-Year-Old Woman with Dyspnea, Dysphagia, and Dysarthria

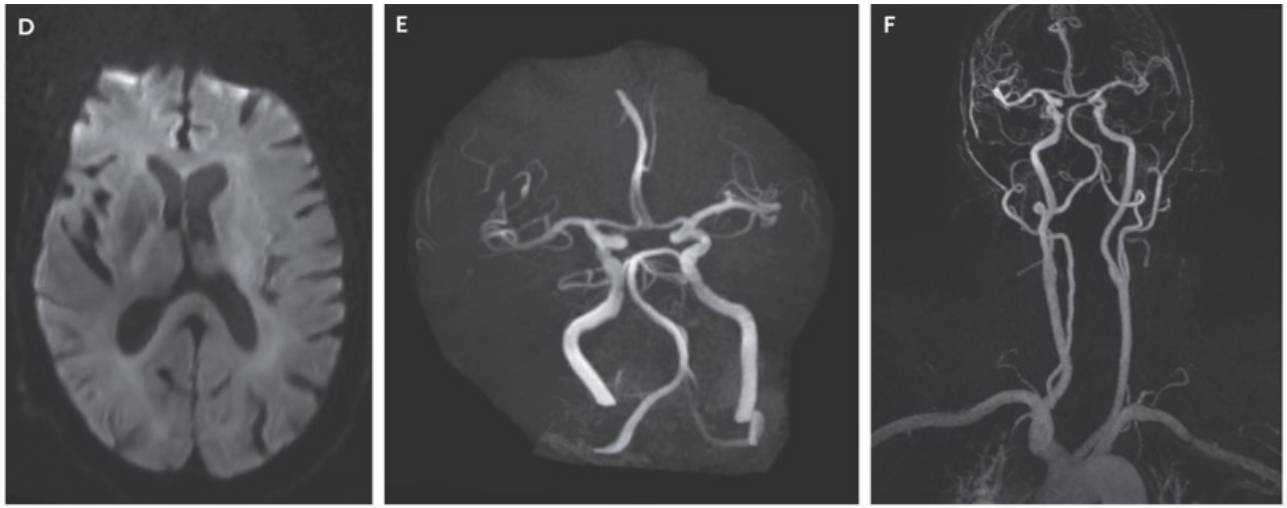
Two years before the current evaluation, the patient presented to her primary care physician at this hospital with subacute exertional dyspnea, which had been present for more than a year but had progressively worsened during the past several months. The oxygen saturation was 91 to 94% while she was walking. She had edema in both legs. The white-cell count, platelet count, and blood levels of electrolytes, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, and hemoglobin were normal, as were test results for kidney function. Hydrochlorothiazide was prescribed. At a follow-up evaluation 2 weeks later, the patient's weight had decreased by 5 kg, but the exertional dyspnea and bilateral leg edema were unchanged. The N-terminal pro–B-type natriuretic peptide level was normal, and the d-dimer level was 3259 ng per milliliter (reference value, <500). Computed tomographic angiography (CTA) of the chest, performed after the administration of intravenous contrast material, showed no pulmonary emboli. A dilated main pulmonary artery, mosaic attenuation of the lungs, and coronary-artery calcifications were present. Four weeks later, the patient presented to her primary care physician with increased exertional dyspnea. Her weight had decreased by 2 kg. The peak expiratory flow was 220 liters per second (expected value according to age, sex, and height, 350). A tapering course of prednisone and inhaled albuterol were prescribed, and her condition improved initially. The patient was lost to follow-up; her next visit took place 10 months before the current evaluation. At that time, the patient reported recurrent exertional dyspnea, which occurred when she moved from room to room. She reported an episode of transient facial asymmetry with saliva dripping from the left side of her mouth that had developed while she was washing herself; later that day, her sister had noticed that she was slurring words during a telephone call. The white-cell count, platelet count, and blood levels of thyrotropin, glycated hemoglobin, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, and hemoglobin were normal.

Variable	Reference Range, Adults†	10 Mo before Admission, Outpatient Clinic	On Presentation, Emergency Department	Hospital Day 2	Hospital Day 3
Sodium (mmol/liter)	135–145	143	139	142	142
Potassium (mmol/liter)	3.4–5.0	3.8	4.7	3.5	3.4
Chloride (mmol/liter)	98–108	99	98	98	94
Carbon dioxide (mmol/liter)	23–32	30	22	28	32
Urea nitrogen (mg/dl)	8–25	29	16	17	16
Creatinine (mg/dl)	0.60–1.50	0.89	0.86	0.83	0.78
Glucose (mg/dl)	70–110	171	120	110	156
N-terminal pro–B-type natriuretic peptide (pg/ml)	<900	1908	2000	—	—
High-sensitivity troponin T (ng/liter)	0–9	—	16	18	—
Erythrocyte sedimentation rate (mm/hr)	0–20	—	—	39	—
Venous blood gas					
pH	7.30–7.40	—	7.33	7.33	—
Partial pressure of carbon dioxide (mm Hg)	38–50	—	63	71	—
Arterial blood gas					
Fraction of inspired oxygen	—	—	—	—	0.45
pH	7.35–7.45	—	—	—	7.32
Partial pressure of carbon dioxide (mm Hg)	35–42	—	—	—	74
Partial pressure of oxygen (mm Hg)	80–100	—	—	—	89

Two months later, the patient presented to her primary care physician with throat pain and dyspnea that had been present for 3 weeks. An examination was notable for diffuse crackles in both lung fields. A chest radiograph showed pulmonary edema and a small right pleural effusion. Intravenous furosemide was administered. Transthoracic echocardiography showed normal biventricular wall thickness, size, and function. Mild biatrial enlargement, a patent foramen ovale with mild left-to-right shunting, moderate tricuspid regurgitation, and a right ventricular systolic pressure of 60 mm Hg were noted. On the day before the current evaluation, the patient called her primary care physician to report sore throat with difficulty swallowing that had started 2 days earlier. Because she had slurred speech over the phone, she was referred to the emergency department of this hospital.

In the emergency department, the patient reported dysphagia with food, liquids, and medications. Her daughter reported that her voice had sounded “garbled” and “soft” during the preceding days and also during an episode of transient dysarthria that had developed a few months earlier. Dyspnea and mild leg edema had been present for at least 3 years, along with some orthopnea and an intermittent nonproductive cough. The patient had started using a walker in the past year owing to exertional fatigue, arthritic pain, and weakness in both legs. Two falls had occurred in the previous 8 months. In addition, the patient reported increased generalized weakness and limb weakness, daytime somnolence, and fatigue. She had no diplopia, numbness, dizziness, headache, chest pain, palpitations, bleeding, nausea, abdominal pain, constipation, diarrhea, or urinary symptoms.

The patient’s medical history was notable for severe obesity, coronary-artery calcifications, hypertension, hyperlipidemia, atrial flutter, and hyperparathyroidism. Medications included furosemide, apixaban, aspirin, amlodipine, lisinopril, metoprolol, lovastatin, metformin, and sertraline. She had had no known adverse drug reactions. The patient was retired and divorced, and she lived alone in an assisted-living community. She had smoked two packs of cigarettes daily for 15 years but had quit smoking 20 years earlier, and she did not drink alcohol or use other substances. Her family history was notable for ischemic heart disease. Her father had had myocardial infarctions; a paternal cousin had systemic lupus erythematosus.



An axial diffusion-weighted image from MRI of the head (Panel D) shows no restricted diffusion that would be suggestive of acute infarction. Maximum-intensity-projection images from three-dimensional time-of-flight magnetic resonance angiography (MRA) of the head (Panel E) and from gadolinium-enhanced MRA of the neck (Panel F) show no high-grade stenosis or occlusion of the major intracranial or cervical arteries.

Magnetic resonance imaging (MRI) of the head and magnetic resonance angiography (MRA) of the head and neck showed findings similar to those seen on CT. No evidence of acute infarction was noted. Scattered foci of susceptibility signal were present in the cerebral hemispheres, basal ganglia, and thalami, findings consistent with chronic microhemorrhages. MRA showed widely patent intracranial and cervical arteries.

On the third day, the patient was somnolent and was using accessory muscles for breathing until bilevel positive airway pressure was initiated. An evaluation revealed weak cough and delayed swallow initiation. Owing to the degree of dysphagia, it was recommended that the patient avoid oral medications and food. The thyrotropin level was normal; other laboratory test results are shown. Direct laryngoscopy showed an impaired swallow, normal vocal cords, and no mass or other source of obstruction. Intravenous furosemide and piperacillin–tazobactam and inhaled ipratropium were administered.

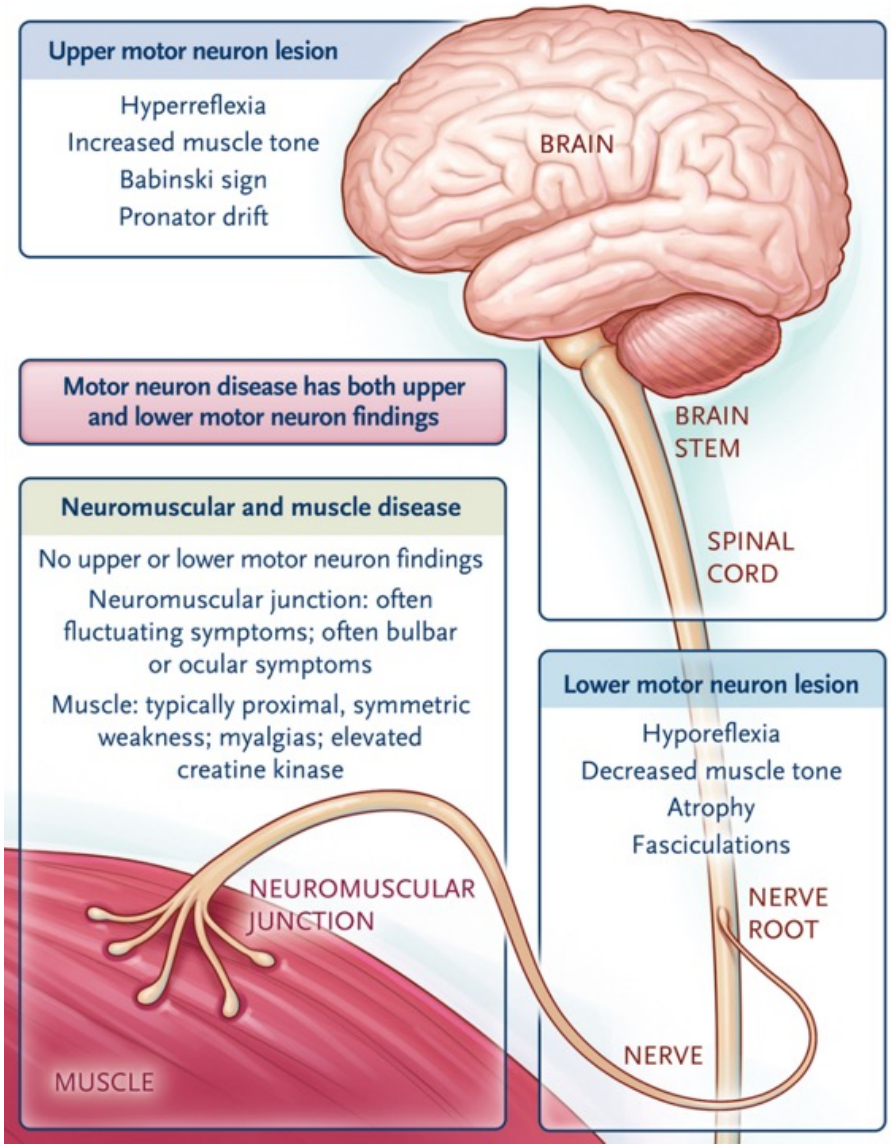
Diagnostic tests were performed, and management decisions were made.

Differential Diagnosis

In a complex case, it can be helpful to identify the features in the background, middle ground, and foreground that form the overall clinical landscape. This 72-year-old woman presented with dyspnea and leg swelling that had occurred for several years and had prompted consideration of multiple cardiopulmonary conditions (background). During the months preceding the current evaluation, episodes of slurred speech, facial asymmetry, and falls had occurred (middle ground). At the time of the current evaluation, sore throat, difficulty swallowing, and increased generalized weakness, including dysarthria, facial droop and ptosis on the right side, and weakness in both legs, had been present for several days (foreground). Neuroimaging showed no acute changes, and the respiratory status rapidly worsened despite the administration of diuretic agents and noninvasive positive-pressure ventilation.

Neuroanatomical Localization of Weakness.

Upper and lower motor neuron findings can be used to localize where the problem lies neuroanatomically.



Neuroanatomical Localization of Weakness

In neurology, one diagnostic approach is to first localize where the problem lies neuroanatomically, according to the upper or lower motor neuron findings present on examination.

Brain and Brain Stem

Could this patient's weakness be caused by acute strokes? The previous bouts of dysarthria could be consistent with transient ischemic attacks, owing to her risk factors for stroke (age, hypertension, hyperlipidemia, obesity, and atrial flutter). However, to account for this patient's weakness, the pattern of the strokes would need to be multifocal, involving territories in both the cerebral cortex and the brain stem.

Motor Neurons

The patient's prominent dysphagia and dysarthria prompt consideration of motor neuron disease. Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder that manifests with bulbar, limb, and respiratory-muscle weakness. The presentation of ALS is heterogeneous; a pure brain-stem variant manifests with progressive bulbar symptoms.

Nerve Roots

When the nerves exit the central nervous system at the brain stem or spinal cord, they traverse the subarachnoid space. Inflammation of the meninges can cause neuropathies that result in weakness. Could leptomeningeal disease, such as that caused by cancer, be a consideration in this patient?

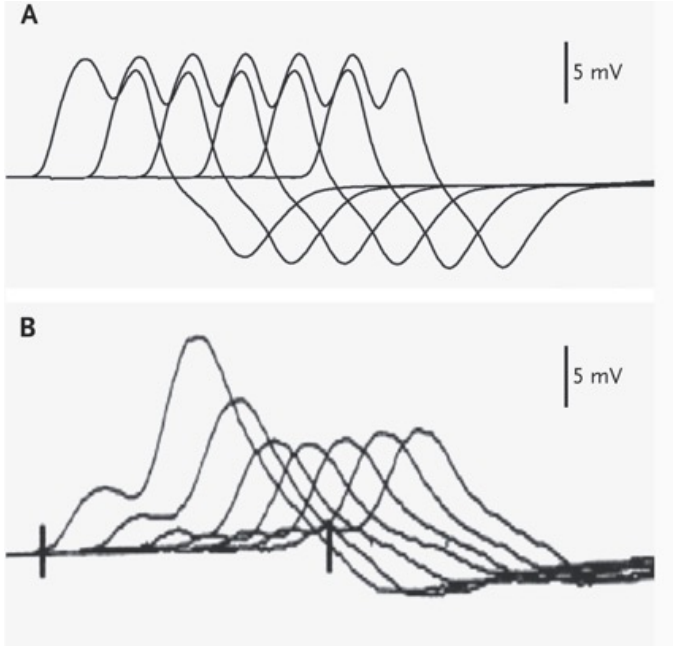
Peripheral Nerves

A few peripheral nerve diseases could explain the bulbar, ocular, facial, and limb weakness observed in this case. Sarcoidosis results in multisystem granulomatous inflammation that could unify the cardiac, pulmonary, and neurologic symptoms. However, the patient's presentation does not fit well with neurosarcoidosis, in which bulbar cranial neuropathies are rare and sensory deficits are common.

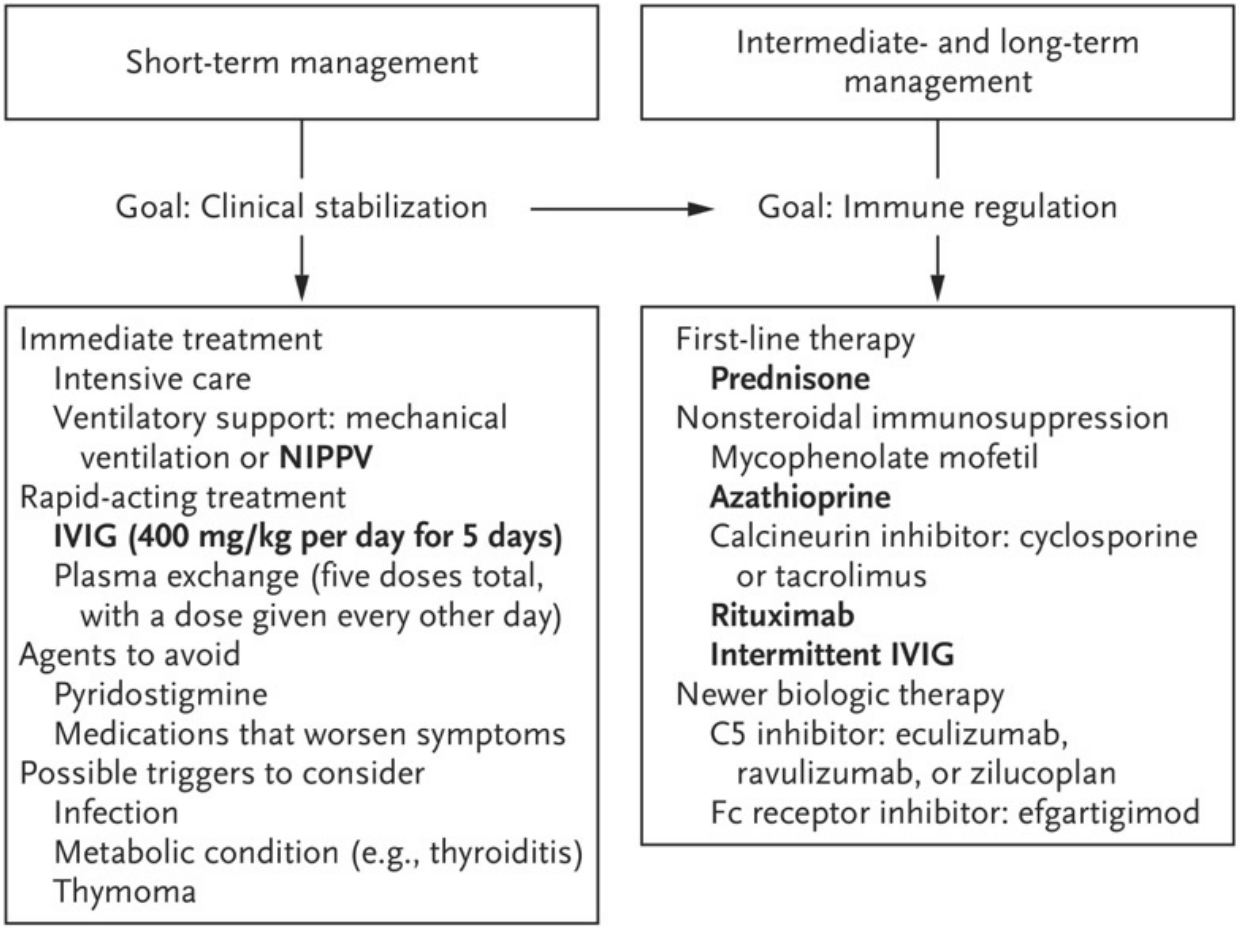
Neuromuscular Junction

Myasthenia gravis and the Lambert–Eaton myasthenic syndrome (LEMS) are two autoimmune neuromuscular junction disorders to consider in this case. Myasthenia gravis is caused by antibodies against the postsynaptic acetylcholine receptor and is characterized by bulbar, ocular, facial, limb, and axial weakness. In 60% of patients,

Myasthenia-related autoantibodies were measured. The level of acetylcholine receptor–binding antibodies was 12.5 nmol per liter (reference value, ≤0.02). Acetylcholine receptor–binding antibodies have high sensitivity (85%) and specificity (90%) for the diagnosis of generalized myasthenia gravis. These pathogenic antibodies lead to dysfunction of the acetylcholine receptor through functional blocking of the receptor and complement-mediated destruction of the postsynaptic membrane. Other pathogenic antibodies directed against structural proteins of the acetylcholine receptor include anti–muscle-specific kinase antibodies, which were not detected in this patient. The titer of antistriational antibodies was 1:30,720 (reference value, <1:120). These nonpathogenic antibodies are seen in approximately 36% of patients with myasthenia gravis and correlate with increased age and disease severity; in younger patients, these antibodies correlate with the presence of thymoma. Given that myasthenia gravis can be associated with thymoma (in approximately 10% of all patients with myasthenia gravis), this patient underwent screening with mediastinal CT, which was negative for a thymic mass.

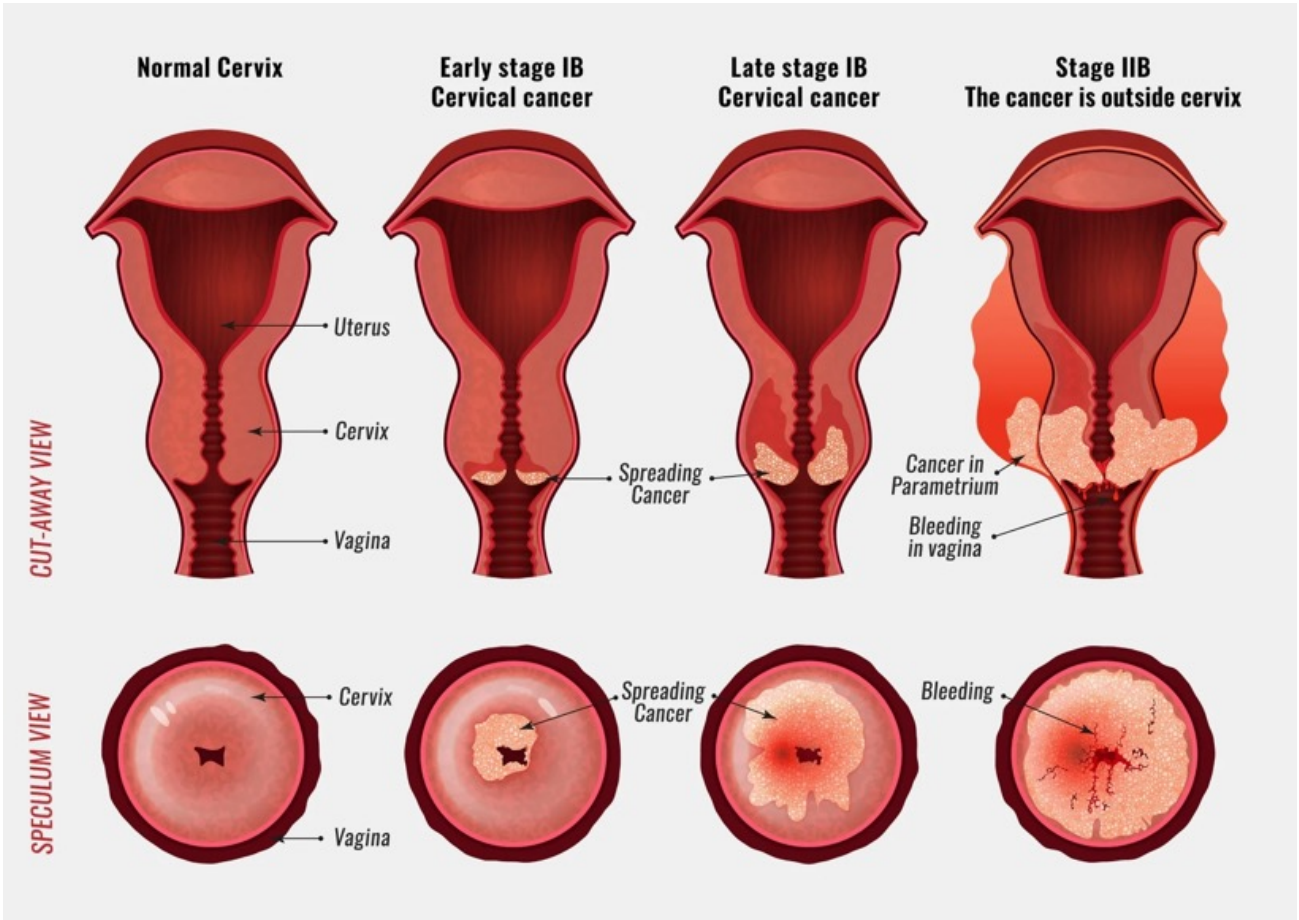


Electrodiagnostic Studies.
Panel A shows an example tracing of the normal response to stimulation. Panel B shows an example tracing of the myasthenic response. When presynaptic neuromuscular transmission disorders are a clinical consideration, additional testing may be performed to distinguish between presynaptic and postsynaptic disorders. The panels are courtesy of Dr. Pushpa Narayanaswami of Beth Israel Deaconess Medical Center.



Treatment Strategy for Myasthenic Crisis.

Approaches to the short-term management of myasthenic crisis (left side) and to the intermediate- and long-term management of myasthenia gravis (right side) are shown. The therapies administered to this patient are shown in bold. For patients with previously untreated myasthenia gravis who have moderate-to-severe weakness but are not in myasthenic crisis, the same approach to the intermediate- and long-term management can be used. Drug choice is individualized on the basis of the expected time to clinical effect, the side-effect profile, and the patient's risk with respect to coexisting conditions. IVIG denotes intravenous immune globulin, and NIPPV noninvasive positive-pressure ventilation.


Normal Cervix
Early stage IB
Cervical cancer
Late stage IB
Cervical cancer
Stage IIB
The cancer is outside cervix
CUT-AWAY VIEW
Uterus
Cervix
Vagina
Spreading
Cancer
Cancer in
Parametrium
Bleeding
in vagina
SPECULUM VIEW
Cervix
Vagina
Spreading
Cancer
Bleeding

Induction chemotherapy is the initial chemotherapy a person receives before undergoing additional cancer treatment, such as maintenance chemotherapy, radiation therapy, or surgery. The goal of induction chemotherapy is to destroy as many cancer cells as possible to offer the best possible chance of disease remission.

Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally advanced cervical cancer (GCIG INTERLACE): an international, multicentre, randomised phase 3 trial

Summary

Background Locally advanced cervical cancer is treated with chemoradiotherapy (standard of care), but many patients still relapse and die from metastatic disease. We investigated chemoradiotherapy with or without induction chemotherapy to determine whether induction chemotherapy improves both progression-free survival and overall survival.

Methods The INTERLACE trial was a multicentre, randomised phase 3 trial done at 32 medical centres in Brazil, India, Italy, Mexico, and the UK. Adults (aged ≥18 years) with locally advanced cervical cancer (FIGO 2008 stage IB1 disease with nodal involvement, or stage IB2, IIA, IIB, IIIB, or IVA disease) were randomly assigned (1:1), by minimisation, using a central electronic system, to standard cisplatin-based chemoradiotherapy (once-a-week intravenous cisplatin 40 mg/m² for 5 weeks with 45·0–50·4 Gy external beam radiotherapy delivered in 20–28 fractions plus brachytherapy to achieve a minimum total 2 Gy equivalent dose of 78–86 Gy) alone or induction chemotherapy (once-a-week intravenous carboplatin area under the receiver operator curve 2 and paclitaxel 80 mg/m² for 6 weeks) followed by standard cisplatin-based chemoradiotherapy. Stratification factors were recruiting site, stage, nodal status, three-dimensional conformal radiotherapy or intensity modulated radiotherapy, age, tumour size, and histology (squamous *vs* non-squamous). Primary endpoints were progression-free survival and overall survival within the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT01566240, and EUDRACT, 2011-001300-35.

Findings Between Nov 8, 2012, and Nov 17, 2022, 500 eligible patients were enrolled and randomly assigned to the chemoradiotherapy alone group (n=250) or the induction chemotherapy with chemoradiotherapy group. Of 500 patients, 354 (70%) had stage IIB disease and 56 (11%) stage IIIB disease. Pelvic lymph nodes were positive in 215 (43%) patients. 230 (92%) patients who received induction chemotherapy had at least five cycles. Median interval between induction chemotherapy and chemoradiotherapy was 7 days. Four or more cycles of cisplatin were given to 212 (85%) participants in the induction chemotherapy with chemoradiotherapy group and to 224 (90%) of participants in the chemoradiotherapy alone group. 462 (92%) participants received external beam radiotherapy and brachytherapy with a median overall treatment time of 45 days. After a median follow-up of 67 months, 5-year progression-free survival rates were 72% in the induction chemotherapy with chemoradiotherapy group and 64% in the chemoradiotherapy alone group with a hazard ratio (HR) of 0·65 (95% CI 0·46–0·91, p=0·013). 5-year overall survival rates were 80% in the induction chemotherapy with chemoradiotherapy group and 72% in the chemoradiotherapy alone group, with an HR of 0·60 (95% CI 0·40–0·91, p=0·015). Grade 3 or greater adverse events were reported in 147 (59%) of 250 individuals in the induction chemotherapy with chemoradiotherapy group versus 120 (48%) of 250 individuals in the chemoradiotherapy alone group.

Interpretation Short-course induction chemotherapy followed by chemoradiotherapy significantly improves survival of patients with locally advanced cervical cancer.

Introduction

Globally, there were 660 000 new cases and 350 000 deaths due to cervical cancer in 2022.[1] Although the incidence has decreased in high-income countries due to the implementation of successful screening and HPV vaccination programmes, cervical cancer is the most common cancer type in 23 countries and the leading cause of cancer death in 36 low-income countries. Even in high-income countries health inequalities exist where, for example, the US cervical cancer death rate is 2-fold higher in the most versus least deprived areas.[2] Patients often present with locally advanced disease for which chemoradiotherapy has been the standard treatment for nearly 25 years.[3–5] Improvements in local control have been driven by the delivery of high-quality radiotherapy,[6] but still up to 30% of patients will relapse and die within 5 years.[7] Adjuvant carboplatin and paclitaxel chemotherapy after chemoradiotherapy did not improve progression-free survival or overall survival in the international phase 3 OUTBACK trial.[8]

The aim of short-course induction chemotherapy before definitive radiotherapy or chemoradiotherapy is to reduce tumour volume and micrometastatic disease. In a meta-analysis of 18 trials, neoadjuvant chemotherapy based on a shorter platinum-based chemotherapy cycle length (≤14 days) and increased cisplatin dose density (>25 mg/m² per week) improved overall survival, but there was substantial heterogeneity in the design and outcome of these trials.[9] A single arm multicentre phase 2 trial was conducted to investigate neoadjuvant short-course weekly carboplatin and paclitaxel (CXII study) before chemoradiotherapy and showed a high tumour response rate.[10] The CXII results led to the INTERLACE trial, a multicentre international randomised trial, to evaluate whether the addition of the same short-course induction chemotherapy (induction chemotherapy) before chemoradiotherapy is more effective than chemoradiotherapy alone.

	Induction chemotherapy with chemoradiotherapy (n=250)	Chemoradiotherapy alone (n=250)
Age, years*	46 (26–78)	46 (24–78)
ECOG status		
0	214 (86%)	221 (88%)
1	36 (14%)	29 (12%)
Country		
UK	190 (76%)	190 (76%)
Mexico	49 (20%)	51 (20%)
Italy	5 (2%)	3 (1%)
India	5 (2%)	5 (2%)
Brazil	1 (<1%)	1 (<1%)
FIGO stage (2008)		
IB1	2 (1%)	2 (1%)
IB2	19 (8%)	23 (9%)
IIA	17 (7%)	14 (6%)
IIB	178 (71%)	176 (70%)
IIIB	26 (10%)	30 (12%)
IVA	8 (3%)	5 (2%)
Cell stage		
Non-squamous	44 (18%)	45 (18%)
Squamous	206 (82%)	205 (82%)
Nodal status		
Negative	144 (58%)	141 (56%)
Positive	106 (42%)	109 (44%)
FIGO stage (2018)		
I and II	128 (51%)	126 (50%)
IIIB and IVA	22 (9%)	16 (6%)
IIIC	100 (40%)	108 (43%)
Longest tumour diameter, cm†	4·8 (1·3–13·5)	4·9 (1·8–12·8)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. *25–75 percentiles 27–75 for chemoradiotherapy with induction chemotherapy and 26–73 for chemoradiotherapy alone. †25–75 percentiles 2·0–9·1 for chemoradiotherapy with induction chemotherapy and 2·0–8·3 for chemoradiotherapy alone.

Table 1: **Baseline characteristics**

	Induction chemotherapy (n=250)
Paclitaxel with carboplatin cycles completed	
Six cycles	211 (84%)
At least five cycles	230 (92%)
Main reasons for fewer than six cycles	
Adverse events	29 (12%)
Haematological	9
Non-haematological	17
Both	3
Withdrawal or other reasons not due to toxicity	10 (4%)
Median interval from induction chemotherapy to radiotherapy, days	7 (5–54)

Table 2: **Adherence to induction chemotherapy among patients randomly assigned to this group**

	Induction chemotherapy with chemoradiotherapy (n=250)	Chemoradiotherapy alone (n=250)
Cisplatin cycles completed		
Five cycles	169 (68%)	197 (79%)
At least four cycles*	212 (85%)	224 (90%)
Main reasons for fewer than five cycles		
Adverse events leading to discontinuation	68 (27%)	33 (13%)
Haematological	34	4
Non-haematological	20	25
Both	14	4
Other reasons not due to toxicity	13 (5%)	20 (8%)
Radiotherapy		
Received definitive EBRT on or off trial†	246 (98%)	239 (96%)
Received EBRT on trial	242 (97%)	231 (92%)
IMRT	102 (42%)	93 (40%)
3DCRT	140 (58%)	138 (60%)
Received extended field EBRT	22 (9%)	20 (9%)
Received brachytherapy	238 (98%)	224 (97%)
2D point A	46 (19%)	49 (22%)
3D point A	120 (50%)	107 (48%)
3D HRCTV D90	72 (30%)	68 (30%)
Did not receive brachytherapy on trial	4 (2%)	7 (3·0%)
Received EBRT boost	3 (1%)	6 (2·6%)
No boost	1 (<1%)	1 (<1%)
Did not receive EBRT on trial	8 (3%)	19 (8%)
Had radiotherapy outside trial	4 (50%)	8 (42%)
Ineligible or discontinued	1 (13%)	5 (26%)
No EBRT	1 (13%)	1 (5%)
Unknown	2 (25%)	5 (26%)
Median overall treatment time, days	45 (36–70)	45 (37–88)
Median total EQD2, Gy (% ≥78 Gy)‡	79·4 (69·8)	80·0 (71·4)
Median total HRCTV D90 EQD2 (IGABT), Gy‡	86·6	86·8

Data are n (%) or median (range), unless otherwise indicated. 2D=two-dimensional. 3DCRT=three-dimensional conformal radiotherapy. D90=the total dose to 90%. EBRT=external beam radiotherapy. EQD2=2 Gy equivalent dose. HRCTV=high-risk clinical target volume. IGABT=image-guided adaptive brachytherapy. IMRT=intensity modulated radiation therapy. *38 patients in the chemoradiotherapy with induction chemotherapy group and 26 patients in the chemoradiotherapy alone group completed fewer than four cycles, which is not significant (Fisher's exact test p=0·14). †2% of patients in the chemoradiotherapy with induction chemotherapy group and 4% of patients in the chemoradiotherapy alone group did not have EBRT, which is not significant (Fisher's exact test p=0·11). ‡The total EQD2 is the dose to Point A for all patients including those where the dose was prescribed to the HRCTV whereas total HRCTV D90 refers only to patients who received IGABT.

Table 3: **Adherence to cisplatin and radiation during chemoradiotherapy**

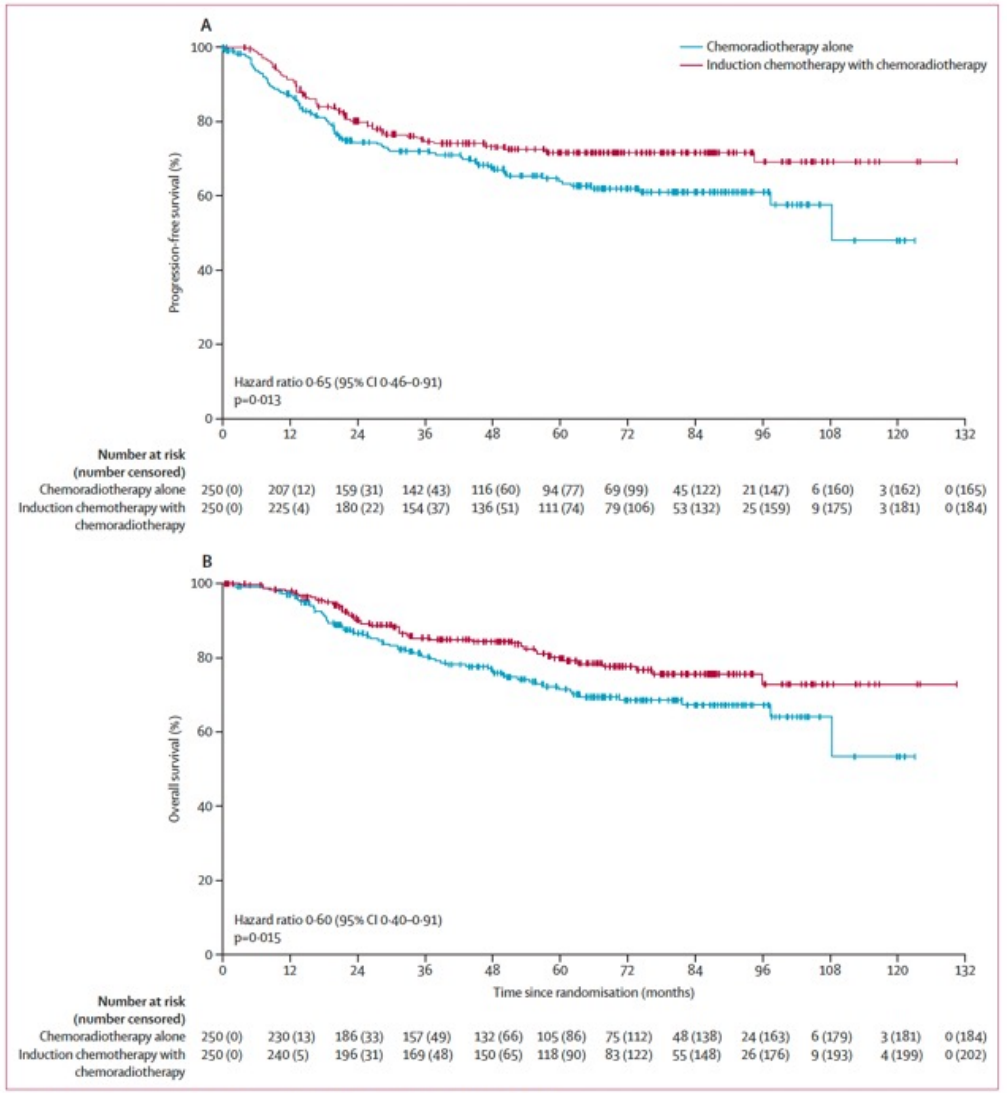


Figure 2: **Kaplan–Meier estimates of progression-free survival (A) and overall survival (B)**

	Induction chemotherapy with chemoradiotherapy (n=250)		Chemoradiotherapy alone (n=250)
	Occurred at any time	Occurred after induction chemotherapy	
Any grade 3–4 event during induction chemotherapy	54 (22%)	NA	NA
Any adverse event	247 (99%)	243 (97%)	237 (95%)
Any grade 3–4 event	147 (59%)	131 (52%)	120 (48%)
Any haematological grade 3–4 event	74 (30%)	60 (24%)	32 (13%)
Neutropenia	48 (19%)	37 (15%)	13 (5%)
Anaemia	13 (5%)	9 (4%)	9 (4%)
Thrombocytopenia	13 (5%)	13 (5%)	5 (2%)
Any non-haematological grade 3–4 event	109 (44%)	98 (39%)	107 (43%)
Abdominal or pelvic pain	13 (5%)	11 (4%)	18 (7%)
Diarrhoea	20 (8%)	19 (8%)	31 (12%)
Fatigue, muscle weakness, or joint pain	28 (11%)	25 (10%)	14 (6%)
Infection	14 (6%)	12 (5%)	13 (5%)

There were three deaths within 30 days of completing treatment, one (respiratory failure) in the induction chemotherapy with chemoradiotherapy group, and two in the chemoradiotherapy alone group (sepsis and pulmonary embolism); none were considered treatment-related. NA=not applicable.

Table 4: **Adverse events**

Research in context

Evidence before this study

We searched PubMed for clinical trials and systematic reviews published in English between Jan 1, 2003, and March 1, 2024, that assessed induction chemotherapy in patients with cervical cancer, using the terms "cervical or cervix cancer", "induction chemotherapy", or "neoadjuvant chemotherapy". Induction chemotherapy was associated with variable efficacy in locally advanced cervical cancer, which was influenced by study design. Two large trials evaluating neoadjuvant chemotherapy before surgery and standard chemoradiotherapy did not show improvements in survival. Many previous studies did not minimise the time interval between finishing neoadjuvant chemotherapy and definitive radiation, chemoradiotherapy, or surgery. Overall, chemotherapy regimens with shorter cycle duration and higher platinum dose intensity were associated with improved outcomes. We had conducted a single arm multicentre phase 2 trial (CXII study) which showed a high tumour response rate using neoadjuvant short-course once-a-week carboplatin and paclitaxel, and this was used to help design the INTERLACE trial.

Added value of this study

The results of INTERLACE show that a short course of chemotherapy using 6 weeks of carboplatin and paclitaxel immediately before standard chemoradiotherapy provided a clinically meaningful and statistically significant improvement in both progression-free survival and overall survival in women with locally advanced cervical cancer. The drugs are cheap and widely available and therefore this approach can be readily adopted in all health-care settings. This is the first randomised phase 3 study to show a significant survival advantage with the addition of induction chemotherapy before chemoradiotherapy in locally advanced cervical cancer. Although chemoradiotherapy is curative treatment for about 75% of patients (80% in INTERLACE), increasing this by 7–10% (at 3–5 years) represents a clinically meaningful improvement and at a relatively low cost.

Implications of all the available evidence

Induction chemotherapy delivered according to the INTERLACE protocol should be included in clinical guidelines as an option to improve outcomes in patients with locally advanced cervical cancer. This approach could be included in the design of future clinical trials of immunotherapy or other targeted drugs in the front-line setting. The study findings presented here also refute the perception that chemotherapy administered before radiotherapy or chemoradiotherapy is detrimental to outcome.

George Medicines developed GMRx2 with telmisartan/amlodipine/indapamide in three strengths (mg): 10/1.25/0.625, 20/2.5/1.25; 40/5/2.5.

Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial

GMRx2 (amlodipine, indapamide and telmisartan) is a single pill, triple combination of existing medicines in development for the treatment for hypertension, including initiation of treatment. Hypertension (high blood pressure) occurs when the force of blood flowing through the blood vessels is too high (≥140/90 mmHg).

Summary

Background Single-pill combinations (SPCs) of three low-dose antihypertensive drugs can improve hypertension control but are not widely available. A key issue for any combination product is the contribution of each component to efficacy and tolerability. This trial compared a new triple SPC called GMRx2, containing telmisartan, amlodipine, and indapamide, with dual combinations of components for efficacy and safety.

Methods In this international, randomised, double-blind, active-controlled trial, we enrolled adults with hypertension receiving between zero and three antihypertensive drugs, with a screening systolic blood pressure (SBP) ranging from 140–179 mm Hg (on no drugs) to 110–150 mm Hg (on three drugs). Participants were recruited from Australia, the Czech Republic, New Zealand, Poland, Sri Lanka, the UK, and the USA. In a 4-week active run-in, existing medications were switched to GMRx2 half dose (telmisartan 20 mg, amlodipine 2·5 mg, and indapamide 1·25 mg). Participants were then randomly allocated (2:1:1:1) to continued GMRx2 half dose or to each possible dual combination of components at half doses (telmisartan 20 mg with amlodipine 2·5 mg, telmisartan 20 mg with indapamide 1·25 mg, or amlodipine 2·5 mg with indapamide 1·25 mg). At week 6, doses were doubled in all groups, unless there was a clinical contraindication. The primary efficacy outcome was mean change in home SBP from baseline to week 12, and the primary safety outcome was withdrawal of treatment due to an adverse event from baseline to week 12. Secondary efficacy outcomes included differences in clinic and home blood pressure levels and control rates. This study is registered with ClinicalTrials.gov, NCT04518293, and is completed.

Findings The trial was conducted between July 9, 2021 and Sept 1, 2023. We randomly allocated 1385 participants to four groups: 551 to GMRx2, 276 to telmisartan–indapamide, 282 to telmisartan–amlodipine, and 276 to amlodipine–indapamide groups. The mean age was 59 years (SD 11), 712 (51%) participants self-reported as female and 673 (48·6%) male, and the mean clinic blood pressure at the screening visit was 142/85 mm Hg when taking an average of 1·6 blood pressure medications. Following the run-in on GMRx2 half dose, the mean clinic blood pressure level at randomisation was 133/81 mm Hg and the mean home blood pressure level was 129/78 mm Hg. At week 12, the mean home SBP was 126 mm Hg in the GMRx2 group, which was lower than for each of the dual combinations: –2·5 (95% CI –3·7 to –1·3, p<0·0001) versus telmisartan–indapamide, –5·4 (–6·8 to –4·1, p<0·0001) versus telmisartan–amlodipine, and –4·4 (–5·8 to –3·1, p<0·0001) versus amlodipine–indapamide. For the same comparisons, differences in clinic blood pressure at week 12 were 4·3/3·5 mm Hg, 5·6/3·7 mm Hg, and 6·3/4·5 mm Hg (all p<0·001). Clinic blood pressure control rate below 140/90 mm Hg at week 12 was superior with GMRx2 (74%) to with each dual combination (range 53–61%). Withdrawal of treatment due to adverse events occurred in 11 (2%) participants in the GMRx2 group, four (1%) in telmisartan–indapamide, three (1%) in telmisartan–amlodipine, and four (1%) in amlodipine–indapamide, with none of the differences being statistically significant.

Interpretation A novel low-dose SPC product of telmisartan, amlodipine, and indapamide provided clinically meaningful improvements in blood pressure reduction compared with dual combinations and was well tolerated. This SPC provides a new therapeutic option for the management of hypertension and its use could result in a substantial improvement in blood pressure control in clinical practice.

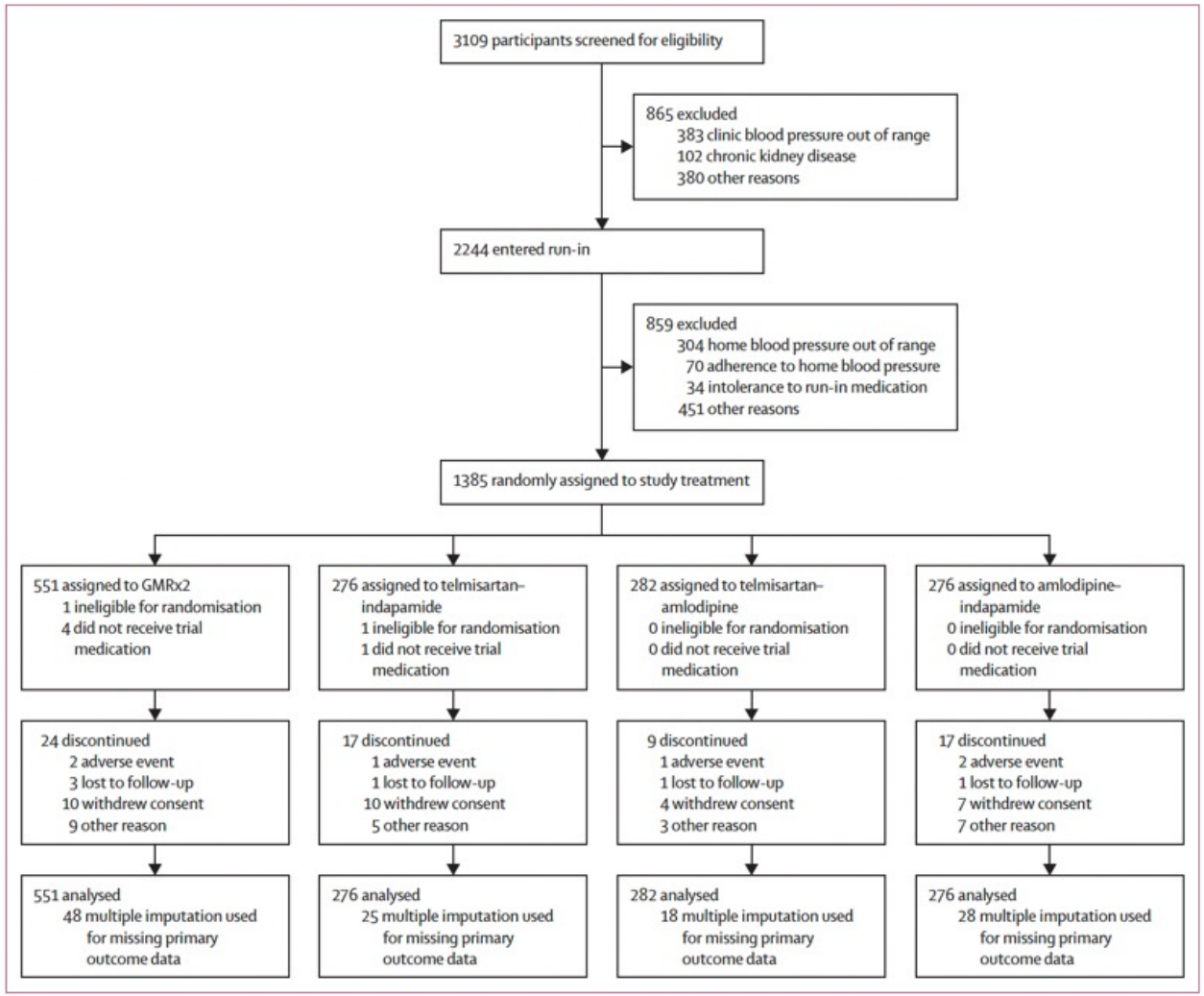


Figure 1: **CONSORT diagram**

	GMRx2 (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)
Age, years	59 (11)	59 (10)	59 (11)	59 (11)
Sex				
Female	276 (50%)	143 (52%)	145 (51%)	148 (54%)
Male	275 (50%)	133 (48%)	137 (49%)	128 (46%)
Weight, kg	79 (21)	79 (21)	78 (20)	78 (21)
Height, cm	165 (11)	165 (12)	165 (11)	164 (12)
BMI, kg/m²	29 (6)	29 (6)	29 (6)	29 (6)
Race				
American Indian or Alaskan Native	0	0	1 (<1%)	0
Asian	272 (49%)	132 (48%)	135 (48%)	134 (49%)
Black or African American	30 (5%)	13 (5%)	11 (4%)	16 (6%)
Native Hawaiian or Other Pacific Islander	2 (<1%)	3 (1%)	3 (1%)	1 (<1%)
White	246 (45%)	128 (46%)	132 (47%)	125 (45%)
Other	1 (<1%)	0	0	0
Ethnicity				
Non-Hispanic or Latino	487 (88%)	246 (89%)	250 (89%)	241 (87%)
Hispanic or Latino	63 (11%)	30 (11%)	31 (11%)	35 (13%)
Country				
Australia	54 (10%)	25 (9%)	26 (9%)	25 (9%)
Czech Republic	4 (<1%)	3 (1%)	2 (<1%)	2 (<1%)
New Zealand	8 (1%)	4 (1%)	4 (1%)	4 (1%)
Poland	4 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Sri Lanka	260 (47%)	128 (46%)	131 (46%)	127 (46%)
UK	138 (25%)	72 (26%)	73 (26%)	68 (25%)
USA	83 (15%)	42 (15%)	44 (16%)	49 (18%)
Education				
No formal education	10 (2%)	6 (2%)	2 (<1%)	1 (<1%)
Primary school	109 (20%)	61 (22%)	53 (19%)	51 (18%)
Secondary school	229 (42%)	100 (36%)	124 (44%)	126 (46%)
Tertiary education	133 (24%)	71 (26%)	79 (28%)	66 (24%)
Vocational training	70 (13%)	38 (14%)	24 (9%)	32 (12%)
Smoking				
Never	431 (78%)	198 (72%)	207 (73%)	211 (76%)
Ex-smoker	92 (17%)	64 (23%)	60 (21%)	50 (18%)
Current smoker	28 (5%)	14 (5%)	15 (5%)	15 (5%)
Alcohol consumption				
Currently drink alcohol	179 (32%)	96 (35%)	101 (36%)	105 (38%)
Standard drinks per week	7 (8)	9 (8)	8 (8)	7 (8)
Prescreening electrocardiogram				
Normal	402 (73%)	215 (78%)	214 (76%)	210 (76%)
Hypertension status				
Clinic blood pressure <140/90 mm Hg at screening	197 (36%)	96 (35%)	92 (33%)	104 (38%)
Clinic blood pressure <140/90 mm Hg at randomisation	356 (65%)	188 (68%)	181 (64%)	171 (62%)
Home blood pressure <135/85 mm Hg at randomisation	352 (64%)	168 (61%)	176 (62%)	160 (58%)

(Table 1 continues on next page)

	GMRx (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)
(Continued from previous page)				
Number of previous blood pressure treatments at screening				
0	65 (12%)	28 (10%)	27 (10%)	24 (9%)
1	193 (35%)	83 (30%)	110 (39%)	87 (32%)
2	217 (39%)	112 (41%)	105 (37%)	121 (44%)
3	76 (14%)	53 (19%)	40 (14%)	44 (16%)
SBP/DBP levels				
Clinic blood pressure at screening	142 (12)/85 (10)	142 (12)/85 (11)	142 (11)/86 (11)	141 (12)/85 (11)
Home blood pressure at randomisation	127 (10)/78 (9)	129 (11)/77 (9)	128 (10)/78 (9)	129 (10)/78 (9)
Clinic blood pressure at randomisation	133 (13)/81 (11)	132 (14)/81 (10)	133 (13)/81 (10)	133 (13)/81 (10)

Data are n (%) or mean (SD). SBP=systolic blood pressure. DBP=diastolic blood pressure.

Table 1: **Baseline characteristics of randomly assigned participants**

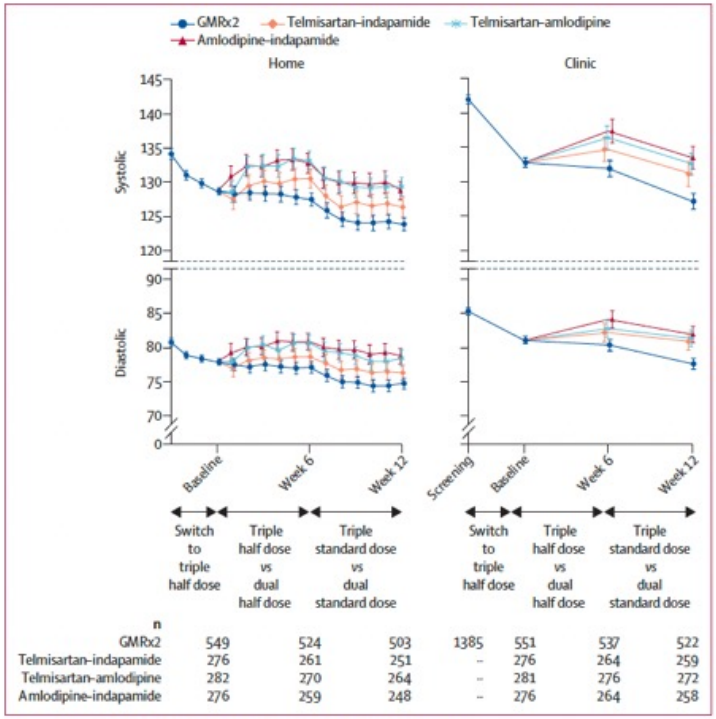


Figure 2: **Home and clinic systolic and diastolic blood pressure over time**

	GMRx2 *vs* telmisartan–indapamide (N=827)	GMRx2 *vs* telmisartan–amlodipine (N=832)	GMRx2 *vs* amlodipine–indapamide (N=827)
Home systolic			
Week 6	–3·0 (–4·1 to –1·9)	–6·1 (–7·1 to –5·1)	–5·1 (–6·3 to –3·9)
Week 12	–2·5 (–3·7 to –1·3)	–5·4 (–6·8 to –4·1)	–4·4 (–5·8 to –3·1)
Home diastolic			
Week 6	–2·1 (–2·8 to –1·4)	–3·5 (–4·1 to –2·9)	–3·6 (–4·4 to –2·7)
Week 12	–2·1 (–3·0 to –1·2)	–3·4 (–4·1 to –2·6)	–3·6 (–4·6 to –2·6)
Clinic systolic			
Week 6	–3·5 (–5·3 to –1·7)	–5·0 (–6·7 to –3·3)	–5·4 (–7·3 to –3·4)
Week 12	–4·3 (–6·7 to –1·9)	–5·6 (–7·3 to –3·9)	–6·3 (–8·0 to –4·7)
Clinic diastolic			
Week 6	–2·3 (–3·4 to –1·2)	–2·4 (–3·4 to –1·5)	–3·8 (–4·9 to –2·7)
Week 12	–3·5 (–4·9 to –2·1)	–3·7 (–4·7 to –2·8)	–4·5 (–5·8 to –3·2)

Data are difference (95% CI). All differences in home and clinic blood pressure were p<0·0001 and all differences in clinic blood pressure were p<0·001.

Table 2: **Difference in change in home and clinic blood pressure from randomisation to week 6 (GMRx2 triple half-dose *vs* dual half-dose comparators) and week 12 (GMRx2 triple standard-dose *vs* dual standard-dose comparators)**

conducted for each of the three GMRx2 versus dual therapy comparisons.

Reductions in clinic SBP and DBP were also seen for all comparisons of GMRx2 versus dual combinations at each timepoint, and on average these were about 20% greater than those for home blood pressure. There was also broad

	Participants with blood pressure control				Risk difference		
	GMRx2 (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)	GMRx2 *vs* telmisartan–indapamide	GMRx2 *vs* telmisartan–amlodipine	GMRx2 *vs* amlodipine–indapamide
Clinic blood pressure control <140/90 mm Hg							
Week 6	346 (63%)	151 (55%)	148 (53%)	122 (44%)	8% (1–15), p=0·026	10% (3–18), p=0·004	19% (11–26), p<0·0001
Week 12	407 (74%)	167 (61%)	173 (61%)	146 (53%)	13% (6–20), p=0·0001	13% (6–20), p=0·0003	21% (14–28), p<0·0001
Clinic blood pressure control <130/80 mm Hg							
Week 6	167 (30%)	59 (21%)	65 (23%)	59 (21%)	9% (2–15), p=0·0046	10% (4–16), p=0·0007	12% (6–18), p<0·0001
Week 12	218 (40%)	76 (28%)	126 (45%)	123 (45%)	12% (5–19), p=0·0004	17% (10–23), p<0·0001	18% (11–24), p<0·0001
Home blood pressure control <135/85 mm Hg							
Week 6	346 (63%)	155 (56%)	74 (26%)	79 (29%)	7% (–1–14), p=0·067	18 (11–25), p<0·0001	18% (11–25), p<0·0001
Week 12	398 (72%)	176 (64%)	109 (39%)	91 (33%)	9% (2–16), p=0·015	15 (8–22), p<0·0001	16% (9–23), p<0·0001
Home blood pressure control <130/80 mm Hg							
Week 6	247 (45%)	90 (33%)	173 (61%)	146 (53%)	12% (5–19), p=0·0005	19% (12–25), p<0·0001	16% (9–23), p<0·0001
Week 12	308 (56%)	121 (44%)	56 (20%)	50 (18%)	12% (5–19), p=0·0010	17% (10–24), p<0·0001	23% (16–30), p<0·0001

Data are n (%) or risk difference (95% CI), p compared with GMRx2.

Table 3: **Home and clinic blood pressure control at week 6 (GMRx2 triple half-dose *vs* dual half-dose comparators) and week 12 (GMRx2 triple standard-dose *vs* dual standard-dose comparators)**

	GMRx2 (N=551)	Telmisartan–indapamide (N=276)	Telmisartan–amlodipine (N=282)	Amlodipine–indapamide (N=276)
Treatment withdrawal due to adverse events	11 (2%)	4 (1%)	3 (1%)	4 (1%)
Adverse events of special interest	184 (34%)	75 (27%)	71 (25%)	79 (29%)
Symptomatic hypotension	32 (6%)	11 (4%)	5 (2%)	4 (1%)
Abnormal laboratory findings*	139 (25%)	59 (22%)	57 (20%)	69 (25%)
Headache	16 (3%)	8 (3%)	5 (2%)	5 (2%)
Peripheral oedema	7 (1%)	1 (0.4%)	6 (2%)	2 (<1%)
Other reason for discontinuation of trial medication	6 (1%)	0	2 (<1%)	1 (<1%)
At least one serious adverse event†	17 (3%)	7 (3%)	6 (2%)	6 (2%)

Data are n (%). Results are for people with one or more event type in the randomised phase, which included 6 weeks of half-dose combination therapy followed by 6 weeks of standard-dose combination therapy. Five participants did not start the study medication and not all were uptitrated at week 6. *Abnormalities of sodium, potassium, uric acid, glucose, lipids, creatinine, or estimated glomerular filtration rate. †All cases of COVID-19 were designated as serious adverse events, and these comprised 21 (57%) of 37 serious adverse events. There were no deaths and only one cardiovascular event: a non-ST segment elevation myocardial infarction occurring in the telmisartan–indapamide group.

Table 4: **Treatment withdrawal due to adverse events, adverse events of special interest, and serious adverse events from baseline to week 12**

Research in context

Evidence before this study

We conducted an updated systematic review of randomised trials that compared triple-combination with dual-combination blood pressure-lowering drugs. Through searching MEDLINE, Cochrane Central Register of Controlled Trials, and the US Food and Drug Administration website from database inception to Dec 31, 2023, we identified randomised, double-blind trials involving adults with hypertension that compared triple versus dual combinations of antihypertensive drugs from five major classes (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β blockers, and diuretics) over a minimum of 4 weeks. Primary outcomes were reduction in blood pressure and withdrawal of treatment due to adverse events. Meta-analyses were conducted using a random-effects model. 24 trials (15533 participants) were included, and baseline systolic/diastolic blood pressure averaged 161/100 mm Hg in trials among people not on treatment and 150/94 mm Hg among people receiving dual therapy. Of the 58 triple-combination versus dual-combination comparisons, 53 (91%) involved one or more standard-dose or maximal-dose components. Overall, triple combination reduced clinic blood pressure by 5·1/3·7 mm Hg compared with dual combination ($p<0·001$ for both) and improved blood pressure control at 140/90 mm Hg from 54% to 69% ($p<0·0001$). Overall, mean final blood pressure was 134/83 mm Hg for triple versus 140/85 mm Hg for dual combination. Incidence of withdrawal of treatment due to adverse events was 4·2% versus 2·9% (relative risk 1·9 [95% CI 1·3–2·4], $p=0·0042$).

Added value of this study

This study provides the first large-scale comparison of triple half-dose versus dual half-dose combinations of any polypill, showing that the average triple versus dual blood pressure reduction of 4·6/2·8 mm Hg is clinically and statistically significantly superior. This trial also assesses the efficacy and tolerability of triple-combination therapy at baseline blood pressure levels considerably lower than those in previous trials. This is of relevance to the increasing emphasis in guideline recommendations on lower blood pressure targets and hence treatment initiation or intensification for individuals at lower blood pressure levels.

Implications of all the available evidence

Treatment with three or more blood pressure-lowering drugs is needed for many individuals to reach and maintain a target blood pressure of below 140/90 mm Hg and for most individuals to reach targets of below 130/80 mm Hg. The addition of a third drug to dual therapy leads to a clinically significant increase in blood pressure control rates and is well tolerated.

Die Infektion mit RSV betrifft alle Altersgruppen

RSV verursacht wiederholte Infektionen während des gesamten Lebens, nicht nur in der Kindheit

Fast alle Kinder werden bis zum Alter von 2 Jahren infiziert[1]

Nur unvollständige & unbeständige Immunantwort nach natürlichen Infektionen[2,3].

RSV-Reinfektionen treten lebenslang auf[3]

Ältere Erwachsene mit hohem Risiko für schwere RSV-Infektionen.
Personen mit medizinischen Vorerkrankungen haben ein noch höheres Risiko[4,5]

1. Centers for Disease Control and Prevention (CDC), 2020;
2. Openshaw PJM *et al. Annu Rev Immunol* 2017;35:501–532
3. Walsh E *et al. Clin Chest* Med 2017;38(1):29–36;
4. Branche AR *et al. Clin Infect Dis* 2022;74(6):1004-1011

Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis

Summary

Background Respiratory syncytial virus vaccines first recommended for use during 2023 were efficacious against lower respiratory tract disease in clinical trials. Limited real-world data regarding respiratory syncytial virus vaccine effectiveness are available. To inform vaccine policy and address gaps in evidence from the clinical trials, we aimed to assess the effectiveness against respiratory syncytial virus-associated hospitalisations and emergency department encounters among adults aged at least 60 years.

Methods We conducted a test-negative design analysis in an electronic health records-based network in eight states in the USA, including hospitalisations and emergency department encounters with respiratory syncytial virus-like illness among adults aged at least 60 years who underwent respiratory syncytial virus testing from Oct 1, 2023, to March 31, 2024. Respiratory syncytial virus vaccination status at the time of the encounter was derived from electronic health record documentation, state and city immunisation registries, and, for some sites, medical claims. Vaccine effectiveness was estimated by immunocompromise status, comparing the odds of vaccination among respiratory syncytial virus-positive case patients and respiratory syncytial virus-negative control patients, and adjusting for age, race and ethnicity, sex, calendar day, social vulnerability index, number of underlying non-respiratory medical conditions, presence of respiratory underlying medical conditions, and geographical region.

Findings Among 28 271 hospitalisations for respiratory syncytial virus-like illness among adults aged at least 60 years without immunocompromising conditions, vaccine effectiveness was 80% (95% CI 71–85) against respiratory syncytial virus-associated hospitalisations, and vaccine effectiveness was 81% (52–92) against respiratory syncytial virus-associated critical illness (ICU admission or death, or both). Among 8435 hospitalisations for respiratory syncytial virus-like illness among adults with immunocompromising conditions, vaccine effectiveness was 73% (48–85) against associated hospitalisation. Among 36 521 emergency department encounters for respiratory syncytial virus-like illness among adults aged at least 60 years without an immunocompromising condition, vaccine effectiveness was 77% (70–83) against respiratory syncytial virus-associated emergency department encounters. Vaccine effectiveness estimates were similar by age group and product type.

Interpretation Respiratory syncytial virus vaccination was effective in preventing respiratory syncytial virus-associated hospitalisations and emergency department encounters among adults aged at least 60 years in the USA during the 2023–24 respiratory syncytial virus season, which was the first season after respiratory syncytial virus vaccine was approved.

	All hospitalisations	Assay for respiratory syncytial virus*—negative	Assay for respiratory syncytial virus*—positive	Standardised mean difference†	Vaccination status‡—unvaccinated	Vaccination status‡—vaccinated	Standardised mean difference§
All hospitalisations	36706	34780	1926	..	33431	3275	..
Site	..	..	..	0·29	..	..	0·24
A	3391 (9%)	3270 (9%)	121 (6%)	..	3022/3391 (89%)	369/3391 (11%)	..
B	4954 (13%)	4755 (14%)	199 (10%)	..	4486/4954 (91%)	468/4954 (9%)	..
C	13686 (37%)	13038 (37%)	648 (34%)	..	12642/13686 (92%)	1044/13686 (8%)	..
D	1728 (5%)	1632 (5%)	96 (5%)	..	1571/1728 (91%)	157/1728 (9%)	..
E	9057 (25%)	8358 (24%)	699 (36%)	..	8365/9057 (92%)	692/9057 (8%)	..
F	3890 (11%)	3727 (11%)	163 (8%)	..	3345/3890 (86%)	545/3890 (14%)	..
Age, years	76 (69-84)	76 (69-83)	76 (69-84)	0·02	76 (69-83)	78 (72-84)	0·17
Age, years	..	..	..	0·04	..	..	0·24
60-64	4380 (12%)	4134 (12%)	246 (13%)	..	4168/4380 (95%)	212/4380 (5%)	..
65-74	11675 (32%)	11091 (32%)	584 (30%)	..	10737/11675 (92%)	938/11675 (8%)	..
≥75	20651 (56%)	19555 (56%)	1096 (57%)	..	18526/20651 (90%)	2125/20651 (10%)	..
Sex	..	..	..	0·10	..	..	0·01
Male	17424 (47%)	16600 (48%)	824 (43%)	..	15889/17424 (91%)	1535/17424 (9%)	..
Female	19282 (53%)	18180 (52%)	1102 (57%)	..	17542/19282 (91%)	1740/19282 (9%)	..
Race and ethnicity	..	..	..	0·04	..	..	0·30
Non-Hispanic White	27057 (74%)	25624 (74%)	1433 (74%)	..	24299/27057 (90%)	2758/27057 (10%)	..
Hispanic	3160 (9%)	2996 (9%)	164 (9%)	..	3009/3160 (95%)	151/3160 (5%)	..
Non-Hispanic Black	2789 (8%)	2656 (8%)	133 (7%)	..	2664/2789 (96%)	125/2789 (4%)	..
Non-Hispanic Other¶	3395 (9%)	3212 (9%)	183 (10%)	..	3164/3395 (93%)	231/3395 (7%)	..
Unknown‖	305 (1%)	292 (1%)	13 (1%)	..	295/305 (97%)	10/305 (3%)	..
Social Vulnerability Index of census tract of residence**	..	..	..	0·04	..	..	0·22
Quartile 1	7988 (22%)	7584 (22%)	404 (21%)	..	7162/7988 (90%)	826/7988 (10%)	..
Quartile 2	7179 (20%)	6816 (20%)	363 (19%)	..	6533/7179 (91%)	646/7179 (9%)	..
Quartile 3	6420 (17%)	6077 (17%)	343 (18%)	..	5968/6420 (93%)	452/6420 (7%)	..
Quartile 4	3815 (10%)	3619 (10%)	196 (10%)	..	3608/3815 (95%)	207/3815 (5%)	..
Unable to Geocode or missing	11304 (31%)	10684 (31%)	620 (32%)	..	10160/11304 (90%)	1144/11304 (10%)	..
Month of hospital admission††	..	..	..	0·48	..	..	0·47
October, 2023	3005 (8%)	2959 (9%)	46 (2%)	..	2938/3005 (98%)	67/3005 (2%)	..
November, 2023	5545 (15%)	5327 (15%)	218 (11%)	..	5297/5545 (96%)	248/5545 (4%)	..
December, 2023	7841 (21%)	7281 (21%)	560 (29%)	..	7221/7841 (92%)	620/7841 (8%)	..
January, 2024	7915 (22%)	7298 (21%)	617 (32%)	..	7120/7915 (90%)	795/7915 (10%)	..
February, 2024	6291 (17%)	5969 (17%)	322 (17%)	..	5542/6291 (88%)	749/6291 (12%)	..
March, 2024	6029 (16%)	5866 (17%)	163 (8%)	..	5242/6029 (87%)	787/6029 (13%)	..
April, 2024	80 (<1%)	80 (<1%)	0 (0)	..	71/80 (89%)	9/80 (11%)	..
ICU admission	7285 (20%)	7003 (20%)	282 (15%)	0·15	6713/7285 (92%)	572/7285 (8%)	0·07
In-hospital death	2888 (8%)	2794 (8%)	94 (5%)	0·13	2694/2888 (93%)	194/2888 (7%)	0·08
Number of underlying medical condition categories‡‡	3 (2-4)	3 (2-4)	3 (2-4)	0·18	3 (2-4)	3 (2-4)	0·08
Number of underlying medical condition categories	..	..	..	0·19	..	..	0·12
0	2111 (6%)	1948 (6%)	163 (8%)	..	1985/2111 (94%)	126/2111 (6%)	..
1	3845 (10%)	3607 (10%)	238 (12%)	..	3550/3845 (92%)	295/3845 (8%)	..
2-3	15420 (42%)	14552 (42%)	868 (45%)	..	14008/15420 (91%)	1412/15420 (9%)	..
≥4	15330 (42%)	14673 (42%)	657 (34%)	..	13888/15330 (91%)	1442/15330 (9%)	..

(Table 1 continues on next page)

	All hospitalisations	Assay for respiratory syncytial virus*—negative	Assay for respiratory syncytial virus*—positive	Standardised mean difference†	Vaccination status‡—unvaccinated	Vaccination status‡—vaccinated	Standardised mean difference§
(Continued from previous page)							
Presence of underlying medical condition category							
Respiratory disease	17 541 (48%)	16 546 (48%)	995 (52%)	0·08	15 717/17 541 (90%)	1824/17 541 (10%)	0·17
Non-respiratory disease	33 160 (90%)	31 519 (91%)	1641 (85%)	0·17	30 153/33 160 (91%)	3007/33 160 (9%)	0·06
Cardiovascular disease	28 822 (79%)	27 410 (79%)	1412 (73%)	0·13	26 180/28 822 (91%)	2642/28 822 (9%)	0·06
Cerebrovascular disease	2346 (6%)	2246 (6%)	100 (5%)	0·05	2189/2346 (93%)	157/2346 (7%)	0·08
Neuromuscular disease	14 008 (38%)	13 380 (38%)	628 (33%)	0·12	12 801/14 008 (91%)	1207/14 008 (9%)	0·03
Haematological disease	3449 (9%)	3322 (10%)	127 (7%)	0·11	3114/3449 (90%)	335/3449 (10%)	0·03
Endocrine or metabolic disease	23 486 (64%)	22 334 (64%)	1152 (60%)	0·09	21 275/23 486 (91%)	2211/23 486 (9%)	0·08
Renal disease	13 905 (38%)	13 224 (38%)	681 (35%)	0·06	12 692/13 905 (91%)	1213/13 905 (9%)	0·02
Gastrointestinal disease	2992 (8%)	2900 (8%)	92 (5%)	0·14	2767/2992 (92%)	225/2992 (8%)	0·05
Documented presence of immunocompromising condition	8435 (23%)	8111 (23%)	324 (17%)	0·16	7615/8435 (90%)	820/8435 (10%)	0·05
Haematological malignancy	1310 (4%)	1237 (4%)	73 (4%)	0·01	1150/1310 (88%)	160/1310 (12%)	0·07
Solid malignancy	3643 (10%)	3535 (10%)	108 (6%)	0·17	3319/3643 (91%)	324/3643 (9%)	<0·01
Transplant	546 (1%)	519 (1%)	27 (1%)	0·01	484/546 (89%)	62/546 (11%)	0·04
Rheumatological or inflammatory disorders	2347 (6%)	2235 (6%)	112 (6%)	0·03	2083/2347 (89%)	264/2347 (11%)	0·07
Other intrinsic immune condition or immunodeficiency	2804 (8%)	2703 (8%)	101 (5%)	0·10	2542/2804 (91%)	262/2804 (9%)	0·02
HIV	103 (<1%)	100 (<1%)	3 (<1%)	0·03	93/103 (90%)	10/103 (10%)	0·01
Respiratory syncytial virus-positive	1926 (5%)	NA	1926 (100%)	NA	1881/1926 (98%)	45/1926 (2%)	0·23
Respiratory syncytial virus vaccination status	..	..	..	0·30	..	..	NA
Unvaccinated	33 431 (91%)	31 550 (91%)	1881 (98%)	..	33 431/33 431 (100%)	..	..
Vaccinated	3275 (9%)	3230 (9%)	45 (2%)	..	..	3275/3275 (100%)	..
Respiratory syncytial virus vaccine type§§	..	..	..	0·17	..	..	NA
GSK, Arexvy	2409 (7%)	2380 (7%)	29 (2%)	..	..	2409/2409 (100%)	..
Pfizer, Abrysvo	865 (2%)	850 (2%)	15 (1%)	..	..	865/865 (100%)	..

Data are n (%) or median (IQR), or n/N (%), unless stated otherwise. NA=not applicable. *Respiratory syncytial virus test results from tests conducted within 10 days before to less than 72 h after the date of hospital admission. If multiple tests were conducted, positive results were prioritised over negative results, followed by the most proximal test to the date of admission, followed by viral culture test results over molecular assay test results, molecular assay test results over rapid molecular assay test results, rapid molecular assay test results over rapid antigen test results, rapid antigen test results over fluorescent antibody test results, and fluorescent antibody test results over serology test results. One site did not capture fluorescent antibody test results or serology test results. Test results for all viral culture, molecular, and rapid molecular tests and positive rapid antigen tests were included. Test results for negative rapid antigen tests and fluorescent antibody and serology tests were excluded. †The standardised mean difference is the difference between the distribution of respiratory syncytial virus-positive encounters and the distribution of negative encounters. ‡Encounters were excluded if the patient received: more than one vaccine; a vaccine before June 21, 2023; a vaccine 0–13 days before the index date; or the immunisation type was missing or unknown. §The standardised mean difference is the difference between the distribution of unvaccinated encounters and the distribution of vaccinated encounters. ¶Includes patients with missing race and ethnicity in their electronic health records. ||Includes patients reporting non-Hispanic ethnicity and any of the following for race: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, other races not listed, and multiple races. Because of small numbers, these categories were combined. **The Social Vulnerability Index is defined based on the census tract of residence. The Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry Social Vulnerability Index uses 16 US census variables to determine social vulnerability for each census tract. Higher Social Vulnerability Index values correspond to higher social vulnerability, which refers to the potential negative effects on communities caused by external stresses on human health. ††The index date for each encounter was defined as either the date of collection of a respiratory specimen associated with the most recent positive or negative respiratory syncytial virus test result before the encounter or the date of the encounter (if testing occurred only after the encounter date). Thus, some hospital admissions could have occurred after March 31, 2024. ‡‡Underlying medical condition categories were pulmonary, cardiovascular, cerebrovascular, musculoskeletal, neurological, haematological, endocrine, renal, and gastrointestinal. §§Excludes N=1 with unknown vaccine type.

Table 1: **Characteristics of respiratory syncytial virus-tested hospital encounters for respiratory syncytial virus-like illness by test result and vaccination status from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) from Oct 1, 2023, to March 31, 2024**

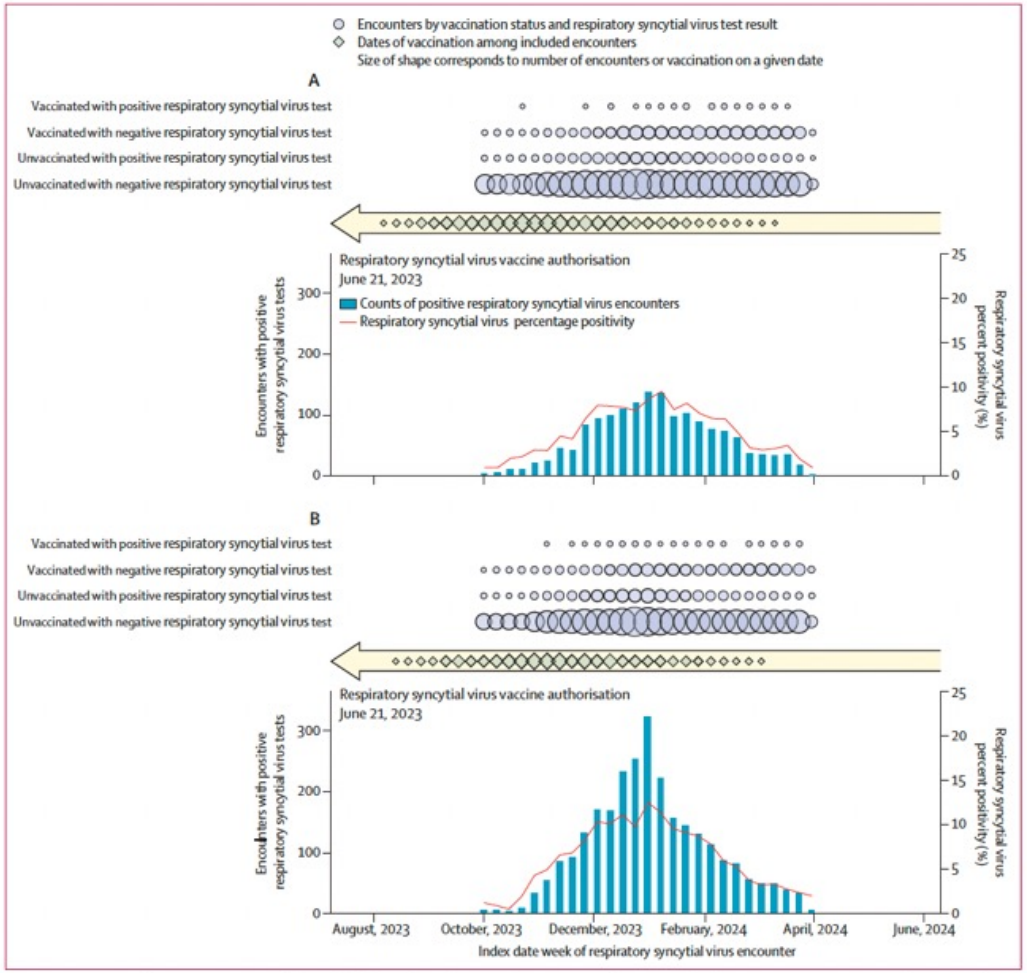


Figure 1: **Encounters for respiratory syncytial virus-like illness, from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) from Oct 1, 2023, to March 31, 2024**

The figure shows the distribution of hospitalisations for respiratory syncytial virus-like illness among adults aged at least 60 years by vaccination and respiratory syncytial virus-positive status (A) and distribution of emergency department encounters for respiratory syncytial virus-like illness among adults aged at least 60 years by vaccination and respiratory syncytial virus-positive status (B).

	All emergency department encounters	Assay for respiratory syncytial virus*—negative	Assay for respiratory syncytial virus*—positive	Standardised mean difference†	Vaccination status‡—unvaccinated	Vaccination status‡—vaccinated	Standardised mean difference§
All emergency department encounters	37 842	35 082	2760	..	34 676	3166	..
Site	..	..	..	0·27	..	..	0·13
A	5193 (14%)	4962 (14%)	231 (8%)	..	4656/5193 (90%)	537/5193 (10%)	..
B	5203 (14%)	4895 (14%)	308 (11%)	..	4746/5203 (91%)	457/5203 (9%)	..
C	21 003 (56%)	19 362 (55%)	1641 (59%)	..	19 405/21 003 (92%)	1598/21 003 (8%)	..
D	3067 (8%)	2877 (8%)	190 (7%)	..	2778/3067 (91%)	289/3067 (9%)	..
E	3376 (9%)	2986 (9%)	390 (14%)	..	3091/3376 (92%)	285/3376 (8%)	..
Age, years	75 (67–82)	75 (67–82)	75 (68–83)	0·03	74 (67–82)	77 (71–83)	0·27
Age, years	..	..	..	0·03	..	..	0·35
60–64	6064 (16%)	5649 (16%)	415 (15%)	..	5848/6064 (96%)	216/6064 (4%)	..
65–74	12 819 (34%)	11 874 (34%)	945 (34%)	..	11 832/12 819 (92%)	987/12 819 (8%)	..
≥75	18 959 (50%)	17 559 (50%)	1400 (51%)	..	16 996/18 959 (90%)	1963/18 959 (10%)	..
Sex	..	..	..	0·08	..	..	0·02
Male	17 072 (45%)	15 931 (45%)	1141 (41%)	..	15 673/17 072 (92%)	1399/17 072 (8%)	..
Female	20 770 (55%)	19 151 (55%)	1619 (59%)	..	19 003/20 770 (91%)	1767/20 770 (9%)	..
Race and ethnicity	..	..	..	0·07	..	..	0·33
Non-Hispanic White	24 832 (66%)	23 069 (66%)	1763 (64%)	..	22 359/24 832 (90%)	2473/24 832 (10%)	..
Hispanic	4562 (12%)	4196 (12%)	366 (13%)	..	4342/4562 (95%)	220/4562 (5%)	..
Non-Hispanic Black	3235 (9%)	3023 (9%)	212 (8%)	..	3103/3235 (96%)	132/3235 (4%)	..
Non-Hispanic Other¶	4810 (13%)	4421 (13%)	389 (14%)	..	4484/4810 (93%)	326/4810 (7%)	..
Unknown‖	403 (1%)	373 (1%)	30 (1%)	..	388/403 (96%)	15/403 (4%)	..
Social Vulnerability Index of census tract of residence**	..	..	..	0·04	..	..	0·23
Quartile 1	10 166 (27%)	9449 (27%)	717 (26%)	..	9118/10 166 (90%)	1048/10 166 (10%)	..
Quartile 2	9603 (25%)	8895 (25%)	708 (26%)	..	8722/9603 (91%)	881/9603 (9%)	..
Quartile 3	8696 (23%)	8063 (23%)	633 (23%)	..	8084/8696 (93%)	612/8696 (7%)	..
Quartile 4	4995 (13%)	4641 (13%)	354 (13%)	..	4728/4995 (95%)	267/4995 (5%)	..
Unable to Geocode or missing	4382 (12%)	4034 (11%)	348 (13%)	..	4024/4382 (92%)	358/4382 (8%)	..
Month of emergency department visit††	..	..	..	0·52	..	..	0·51
October, 2023	1971 (5%)	1951 (6%)	20 (1%)	..	1934/1971 (98%)	37/1971 (2%)	..
November, 2023	5576 (15%)	5222 (15%)	354 (13%)	..	5404/5576 (97%)	172/5576 (3%)	..
December, 2023	9042 (24%)	8119 (23%)	923 (33%)	..	8419/9042 (93%)	623/9042 (7%)	..
January, 2024	8546 (23%)	7657 (22%)	889 (32%)	..	7774/8546 (91%)	772/8546 (9%)	..
February, 2024	6360 (17%)	5973 (17%)	387 (14%)	..	5636/6360 (89%)	724/6360 (11%)	..
March, 2024	6287 (17%)	6100 (17%)	187 (7%)	..	5455/6287 (87%)	832/6287 (13%)	..
April, 2024	60 (<1%)	60 (<1%)	0	..	54/60 (90%)	6/60 (10%)	..
Number of underlying medical condition categories‡‡	0 (0–1)	0 (0–1)	0 (0–1)	0·07	0 (0–1)	1 (0–1)	0·05

(Table 2 continues on next page)

	All emergency department encounters	Assay for respiratory syncytial virus*—negative	Assay for respiratory syncytial virus*—positive	Standardised mean difference†	Vaccination status‡—unvaccinated	Vaccination status‡—vaccinated	Standardised mean difference§
(Continued from previous page)							
Number of underlying medical condition categories	--	--	--	0·08	--	--	0·06
0	19 756 (52%)	18 239 (52%)	1517 (55%)	--	18 178/19 756 (92%)	1578/19 756 (8%)	--
1	11 851 (31%)	11 010 (31%)	841 (30%)	--	10 836/11 851 (91%)	1015/11 851 (9%)	--
2–3	5104 (13%)	4763 (14%)	341 (12%)	--	4634/5104 (91%)	470/5104 (9%)	--
≥4	1131 (3%)	1070 (3%)	61 (2%)	--	1028/1131 (91%)	103/1131 (9%)	--
Presence of underlying medical condition category							
Respiratory disease	9038 (24%)	8382 (24%)	656 (24%)	<0·01	8146/9038 (90%)	892/9038 (10%)	0·11
Non-Respiratory disease	12 280 (32%)	11 487 (33%)	793 (29%)	0·09	11 250/12 280 (92%)	1030/12 280 (8%)	<0·01
Cardiovascular disease	8526 (23%)	7973 (23%)	553 (20%)	0·07	7801/8526 (91%)	725/8526 (9%)	0·01
Cerebrovascular disease	231 (1%)	219 (1%)	12 (<1%)	0·03	217/231 (94%)	14/231 (6%)	0·03
Neuromuscular disease	2421 (6%)	2288 (7%)	133 (5%)	0·07	2243/2421 (93%)	178/2421 (7%)	0·04
Haematological disease	313 (1%)	296 (1%)	17 (1%)	0·03	277/313 (88%)	36/313 (12%)	0·04
Endocrine or metabolic disease	4131 (11%)	3839 (11%)	292 (11%)	0·01	3775/4131 (91%)	356/4131 (9%)	0·01
Renal disease	2367 (6%)	2195 (6%)	172 (6%)	<0·01	2173/2367 (92%)	194/2367 (8%)	0·01
Gastrointestinal disease	300 (1%)	286 (1%)	14 (1%)	0·04	271/300 (90%)	29/300 (10%)	0·02
Documented presence of immunocompromising condition§§	1321 (3%)	1263 (4%)	58 (2%)	0·09	1185/1321 (90%)	136/1321 (10%)	0·05
Respiratory syncytial virus-positive	2760 (7%)	NA	2760 (100%)	NA	2699/2760 (98%)	61/2760 (2%)	0·28
Respiratory syncytial virus vaccination status	--	--	--	0·29	--	--	NA
Unvaccinated	34 676 (92%)	31 977 (91%)	2699 (98%)	--	34 676/34 676 (100%)	--	--
Vaccinated	3166 (8%)	3105 (9%)	61 (2%)	0·29	--	3166/3166 (100%)	NA
Respiratory syncytial virus vaccine type¶¶	--	--	--	<0·01	--	--	NA
GSK, Arexvy	2634 (7%)	2584 (7%)	50 (2%)	--	--	2634/2634 (100%)	--
Pfizer, Abrysvo	530 (1%)	520 (1%)	10 (<1%)	--	--	530/530 (100%)	--

Data are n (%) or median (IQR), or n/N (%), unless stated otherwise. NA=not applicable. *Respiratory syncytial virus test results from tests conducted within 10 days before to less than 72 h after the date of hospital admission. If multiple tests were conducted, positive results were prioritised over negative results, followed by the most proximal test to the date of admission, followed by viral culture test results over molecular assay test results, molecular assay test results over rapid molecular assay test results, rapid molecular assay test results over rapid antigen test results, rapid antigen test results over fluorescent antibody test results, and fluorescent antibody test results over serology test results. One site did not capture fluorescent antibody test results or serology test results. Test results for all viral culture, molecular, and rapid molecular tests and positive rapid antigen tests were included. Test results for negative rapid antigen tests and fluorescent antibody and serology tests were excluded. †The standardised mean difference is the difference between the distribution of respiratory syncytial virus-positive encounters and the distribution of negative encounters. ‡Encounters were excluded if the patient received: more than one vaccine; a vaccine before June 21, 2023; a vaccine 0–13 days before the index date; or the immunisation type was missing or unknown. §The standardised mean difference is the difference between the distribution of unvaccinated encounters and the distribution of vaccinated encounters. ¶Includes patients with missing race and ethnicity in their electronic health records. ||Includes patients reporting non-Hispanic ethnicity and any of the following for race: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, other races not listed, and multiple races. Because of small numbers, these categories were combined. **The Social Vulnerability Index is defined based on the census tract of residence. The Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry Social Vulnerability Index uses 16 US census variables to determine social vulnerability for each census tract. Higher Social Vulnerability Index values correspond to higher social vulnerability, which refers to the potential negative effects on communities caused by external stresses on human health. ††The index date for each encounter was defined as either the date of collection of a respiratory specimen associated with the most recent positive or negative respiratory syncytial virus test result before the encounter or the date of the encounter (if testing occurred only after the encounter date). Thus, some emergency department encounters could have occurred after March 31, 2024. ‡‡Underlying medical condition categories were pulmonary, cardiovascular, cerebrovascular, musculoskeletal, neurological, haematological, endocrine, renal, and gastrointestinal. §§ Immunocompromising conditions included haematological malignancy, solid malignancy, transplant, rheumatological or inflammatory disorders, other intrinsic immune condition or immunodeficiency, or HIV. ¶¶Excludes N=8 with unknown vaccine type.

Table 2: **Characteristics of respiratory syncytial virus-tested emergency department encounters for respiratory syncytial virus-like illness by test result and vaccination status from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) Oct 1, 2023, to March 31, 2024**

	Total	Positive RSV test result (number [%])	Median interval since dose (days [IQR])	Unadjusted vaccine effectiveness (% [95% CI])	Adjusted* vaccine effectiveness (% [95% CI])
Immunocompetent—hospitalisation					
≥60 years					
Unvaccinated	25816	1567 (6%)	NA	0 (ref)	0 (ref)
Vaccinated†	2455	35 (1%)	74 (44-109)	78 (69-84)	80 (71-85)
14-59 days earlier	934	7 (1%)	37 (26-48)	88 (75-94)	90 (79-95)
≥60 days earlier	1520	27 (2%)	100 (79-125)	72 (59-81)	73 (60-82)
GSK, Arexvy	1812	21 (1%)	73 (43-105)	82 (72-88)	83 (73-89)
Pfizer, Abrysvo	642	13 (2%)	81 (48-116)	68 (44-82)	73 (52-85)
60-74 years					
Unvaccinated	11048	670 (6%)	NA	0 (ref)	0 (ref)
Vaccinated	836	11 (1%)	75 (46-110)	79 (62-89)	81 (66-90)
≥75 years					
Unvaccinated	14768	897 (6%)	NA	0 (ref)	0 (ref)
Vaccinated	1619	24 (1%)	74 (43-108)	77 (65-85)	79 (68-86)
Critical illness					
≥60 years					
Unvaccinated	24506	257 (1%)	NA	0 (ref)	0 (ref)
Vaccinated	2425	5 (<1%)	74 (44-109)	81 (53-92)	81 (52-92)
With immunocompromise-hospitilisation					
≥60 years					
Unvaccinated	7615	314 (4%)	NA	0 (ref)	0 (ref)
Vaccinated	820	10 (1%)	72 (43-108)	71 (46-85)	73 (48-85)

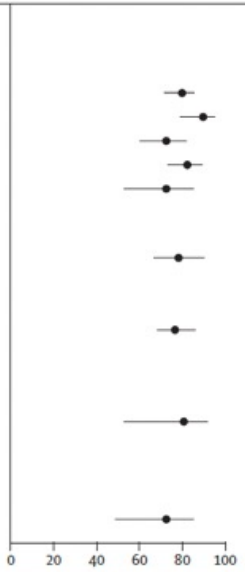


Figure 2: **Estimated vaccine effectiveness against respiratory syncytial virus-associated hospitalisation among adults aged at least 60 years, from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) from Oct 1, 2023, to March 31, 2024**

Patients who were vaccinated received one dose of an approved respiratory syncytial virus vaccine at least 14 days before the index date for the hospitalisation. NA=not applicable. RSV=respiratory syncytial virus. *Adjusted for age, race and ethnicity, sex, underlying medical conditions, Social Vulnerability Index, site, calendar day, and geographical region. †Vaccine effectiveness estimates by vaccine type excludes N=1 with unknown vaccine type.

	Total*	Positive RSV test result (number [%])	Median interval since dose (days [IQR])	Unadjusted vaccine effectiveness (% [95% CI]	Adjusted† vaccine effectiveness, (% [95% CI])
≥60 years					
Unvaccinated	33 491	2645 (8%)	NA	0 (ref)	0 (ref)
Vaccinated‡	3030	57 (2%)	67 (40–101)	78 (71–83)	77 (70–83)
14–59 days earlier	1300	19 (1%)	36 (26–47)	83 (73–89)	85 (77–91)
≥60 days earlier	1728	37 (2%)	95 (76–119)	74 (65–82)	70 (58–78)
GSK, Arexvy	2522	47 (2%)	67 (40–99)	78 (70–83)	77 (70–83)
Pfizer, Abrysvo	506	9 (2%)	71 (40–108)	79 (59–89)	79 (59–89)
60–74 years					
Unvaccinated	16 985	1303 (8%)	NA	0 (ref)	0 (ref)
Vaccinated	1139	23 (2%)	66 (40–100)	75 (62–84)	75 (62–84)
≥75 years					
Unvaccinated	16 506	1342 (8%)	NA	0 (ref)	0 (ref)
Vaccinated	1891	34 (2%)	69 (40–101)	79 (71–85)	78 (69–85)

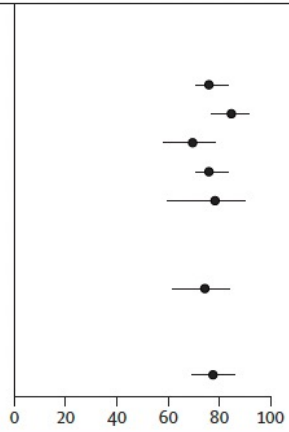


Figure 3: **Estimated vaccine effectiveness against respiratory syncytial virus-associated emergency department encounters among adults aged at least ≥60 years without documented immunocompromise, from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) from Oct 1, 2023, to March 31, 2024**

Patients who were vaccinated received one dose of an approved respiratory syncytial virus vaccine at least 14 days before the index date for the emergency department encounter. NA=not applicable. *Excludes N=1321 encounters with documented immunocompromise. †Adjusted for age, race and ethnicity, sex, underlying medical conditions, Social Vulnerability Index, site, calendar day, and geographical region. ‡Vaccine effectiveness estimates by vaccine type excludes N=2 with unknown vaccine type.

Research in context

Evidence before this study

Respiratory syncytial virus causes substantial morbidity and mortality among older adults in the USA. Respiratory syncytial virus vaccines first recommended for use during 2023 were efficacious against lower respiratory tract disease in clinical trials; however, limited real-world data regarding respiratory syncytial virus vaccine effectiveness are available. Furthermore, clinical trials were underpowered to assess efficacy against severe respiratory syncytial virus outcomes (eg, respiratory syncytial virus-associated hospitalisations) and efficacy among those at highest risk of severe respiratory syncytial virus disease (eg, adults aged at least 75 years). We searched PubMed on Oct 1, 2024, using the search terms (("RSV") OR ("respiratory syncytial")) AND ("vaccine effectiveness") AND (adult). We searched all available literature between June 21, 2023, (which was the date the vaccination was recommended in the USA) and Oct 1, 2024 with no language restrictions, and found 11 relevant publications, with only one study describing real-world effectiveness of respiratory syncytial virus vaccination among adults aged at least 60 years. This study found respiratory syncytial virus vaccination was 75% against respiratory syncytial virus-associated hospitalisation. To inform vaccine policy and address gaps in evidence from the clinical trials, we aimed to assess vaccine effectiveness against respiratory syncytial virus-associated hospitalisations and emergency department encounters among adults aged at least 60 years in the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) during the 2023–24 respiratory virus season, by encounter setting, immunocompromise status, age group, time since vaccination, and vaccine type.

Added value of this study

In this multisite analysis of hospitalisations and emergency department encounters identified in VISION from Oct 1, 2023, to March 31, 2024, among adults aged at least 60 years who presented with respiratory syncytial virus-like illness and were clinically tested for respiratory syncytial virus, vaccination provided protection with effectiveness of 77–81% against respiratory syncytial virus-associated critical illness, hospitalisation, and emergency department encounters during the first respiratory syncytial virus season after vaccine approval. Vaccine effectiveness estimates were similar by age group and vaccine type. These findings are among the first, to our knowledge, to show real-world effectiveness of respiratory syncytial virus vaccination against severe respiratory syncytial virus disease in the USA and indicate that the vaccination has the potential to reduce morbidity and mortality from severe respiratory syncytial virus disease among adults aged at least 60 years.

Implications of all the available evidence

Respiratory syncytial virus vaccination was effective against respiratory syncytial virus-associated hospitalisation and emergency department encounters among adults aged at least 60 years during the first season after vaccine approval, including those at highest risk for severe disease because of advanced age or immunocompromise. Estimates of vaccine effectiveness against respiratory syncytial virus-associated emergency department encounters and hospitalisation from VISION are similar to estimates of clinical trial efficacy against respiratory syncytial virus-associated lower respiratory tract disease during the first season after vaccination. These findings provide additional context regarding the benefit of respiratory syncytial virus vaccination among adults aged at least 60 years.

Hypertrophic cardiomyopathy secondary to hydroxychloroquine toxicity in a patient with rheumatoid arthritis

A 46-year-old woman attended our emergency department reporting a 3-month history of dyspnoea and, in the last 2 weeks, lower limb oedema. The patient had a history of rheumatoid arthritis, which had been diagnosed 13 years before, and had been treated with oral hydroxychloroquine 200 mg twice a day. 1 year earlier, she had presented with syncope; an electrocardiogram (ECG) had showed paroxysmal third-degree atrioventricular block, and a dual-chamber pacemaker had been fitted. An echocardiogram had shown normal biventricular systolic function and mild to moderate left ventricular hypertrophy with an interventricular septum diameter of 13 mm (normal range 6–9); no further investigations were done.

On examination, at our hospital, the patient was generally unwell; her blood pressure was 80/40 mm Hg, she had peripheral oedema, jugular venous distension, pulmonary crackles, and cold extremities. An ECG showed atrial fibrillation with ventricular pacing at 69 beats per min (appendix). Laboratory tests showed a significantly raised N-terminal pro-B-type natriuretic peptide concentration of 31255 ng/L (normal range 0–86) and high-sensitivity cardiac troponin concentration of 543 ng/L (normal range 0–14); and signs of hepatic injury with alanine aminotransferase concentration of 126 U/L (normal range 3–45), aspartate aminotransferase concentration of 92 U/L (normal range 0–40), total bilirubin concentration of 2·51 mg/dL (normal range 0·25–1). Echocardiography showed severe biventricular systolic dysfunction—left ventricular ejection fraction of 20%—and a restrictive filling pattern. Severe concentric hypertrophy was evident with an interventricular septum diameter of 17 mm and heterogeneous myocardial texture (figure).

The differential diagnoses we considered included inflammatory and infiltrative cardiomyopathies—specifically reactive systemic (AA) amyloidosis related to the long-lasting autoimmune disorder—or a hydroxychloroquine-induced cardiomyopathy.

Inotropic support was immediately started, the hydroxychloroquine was discontinued, and the patient was admitted to our intensive care unit. Despite all these measures, 3 days after admission, the patient developed cardiogenic shock and required haemodynamic support with venous-arterial extracorporeal membrane oxygenation.

An endomyocardial biopsy was done with the patient on temporary mechanical support; we hoped the results would inform ongoing treatment. Histopathological examination of a sample obtained at biopsy showed vacuolisation of multiple cardiomyocytes with no inflammatory infiltrate; no amyloid was found (figure). Transmission electron microscopy showed lamellar lysosomal structures—myeloid bodies—and curvilinear inclusions consistent with drug-induced myocardial toxicity. Considering these classic findings, a diagnosis of hydroxychloroquine-induced cardiomyopathy was made.

8 days after admission, despite maximal pharmacological and mechanical support, the patient died due to refractory cardiogenic shock while heart transplantation screening was ongoing. The results of metabolic testing, available after the patient's death, showed no evidence of lysosomal storage disorders—including Fabry's disease and mucopolysaccharidoses. Additionally, the heart postmortem showed concentric left ventricular hypertrophy: septal thickness 16 mm (normal value 13·6 mm [SD 2·0 mm]) and an increased thickness of the right ventricle free wall of 8 mm (normal value 3·8 mm [SD 0·9 mm]). The cardiac mass was also increased (weight 500 g; typical range 190–360; figure).

Chronic use of hydroxychloroquine can result in a drug-induced cardiomyopathy characterised by concentric hypertrophy and conduction abnormalities. Early clinical suspicion is essential, since the condition is potentially reversible. Delay in discontinuation of the drug may not improve the pathology, especially in patients—as in this case—with advanced heart failure.

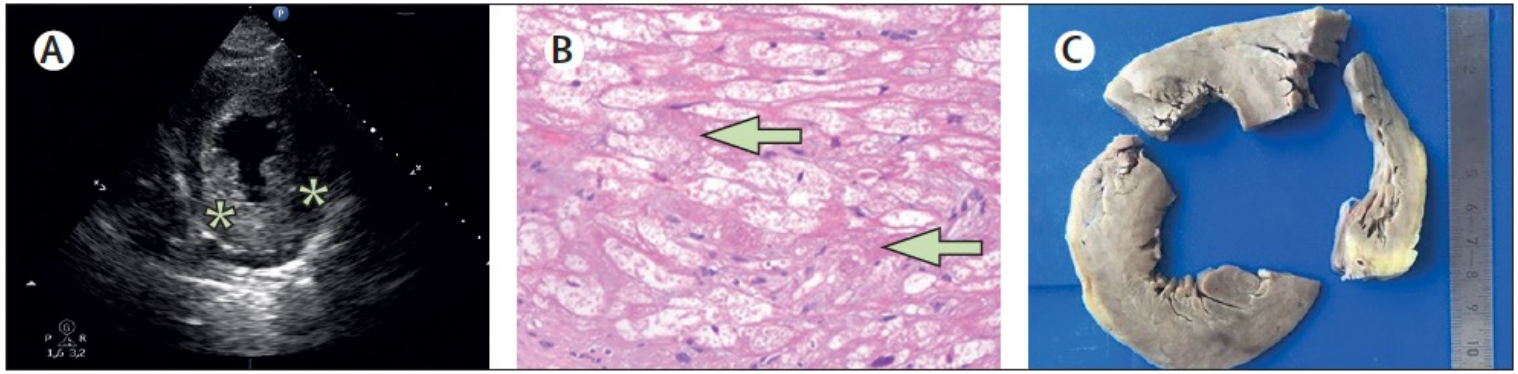


Figure: **Hypertrophic cardiomyopathy secondary to hydroxychloroquine toxicity in a patient with rheumatoid arthritis**

(A) Echocardiographic exam shows severe concentric hypertrophy of the left ventricular walls with inhomogeneous myocardial texture (asterisks). (B) Histopathological examination of a sample obtained after endomyocardial biopsy shows vacuolisation of the cardiac myocytes (arrows), a typical finding of hydroxychloroquine cardiac toxicity. Haematoxylin and eosin stain. High magnification ×40. (C) Photograph of heart post-mortem shows concentric left ventricular hypertrophy, increased thickness of the right ventricle free wall, and increased cardiac mass.

Global health 2050: the path to halving premature death by mid-century

Panel 1: Measuring survival progress—shifting from life expectancy at birth to PPD

Life expectancy at birth is a commonly used measure to monitor progress in population health. It is often misunderstood—"People think it means that when they're reporting life expectancy for 2022 that this is how long a baby who is born in 2022 will live"[8]—but the actual definition is the expected number of years a newborn would live if prevailing patterns of age-specific mortality at the time of birth were to remain throughout its life. Despite such misunderstandings, life expectancy at birth is widely used—including occasionally in this Commission—because as a concept it is easy to communicate.[9]

In this Commission, the main metric that we use is PPD, defined as the probability of dying before age 70 years under the current age-specific mortality rates. PPD is related to life expectancy at birth, and both measures are independent of the age structure of the underlying population. We chose PPD as our main indicator for two reasons. First, PPD encapsulates improvements in survival across all age groups before age 70 years more effectively than life expectancy at birth, which is crucial as more deaths shift to older ages in most countries. As of 2019, the global median age at death was 76 years, with projections indicating a rise to 81 years by 2050.[10] The highest median age at death in 2019 was in the North Atlantic region (84 years) and the lowest median age at death was in the sub-Saharan Africa region (at 65 years), both of which are projected to increase (to 88 years and 69 years, respectively).[10]

Second, although life expectancy at birth is influenced by both age-specific death rates and the remaining life-years of each age group, PPD is affected only by age-specific death rates. For example, a reduction in the number of deaths at younger ages will have a greater impact on life expectancy at birth than a reduction in deaths at older ages because the younger age groups would have more remaining life-years. Life expectancy at birth is thus commonly used to show changes in younger age mortality, but modest declines in life expectancy at birth could mask large reductions in mortality at older ages.

The differences between the two measures in terms of reflecting progress in survival become more evident as overall premature mortality falls.[11] In sub-Saharan Africa between 2000 and 2019, life expectancy at birth rose from 51·2 to 60·7 years (an 18% increase), whereas the PPD fell from 66% to 52% (a 20% decrease)—broadly similar relative improvements (appendix p 7). By contrast, in the North Atlantic region during that same period, life expectancy at birth increased from 78·6 years to 82·4 years (a 5% increase), whereas PPD fell from 21% to 15% (a 27% decrease). Thus, changes in PPD are in close agreement with life expectancy at birth in regions with high premature mortality, but more sensitively characterise the magnitude of change in countries with low premature mortality.

PPD=probability of premature death.

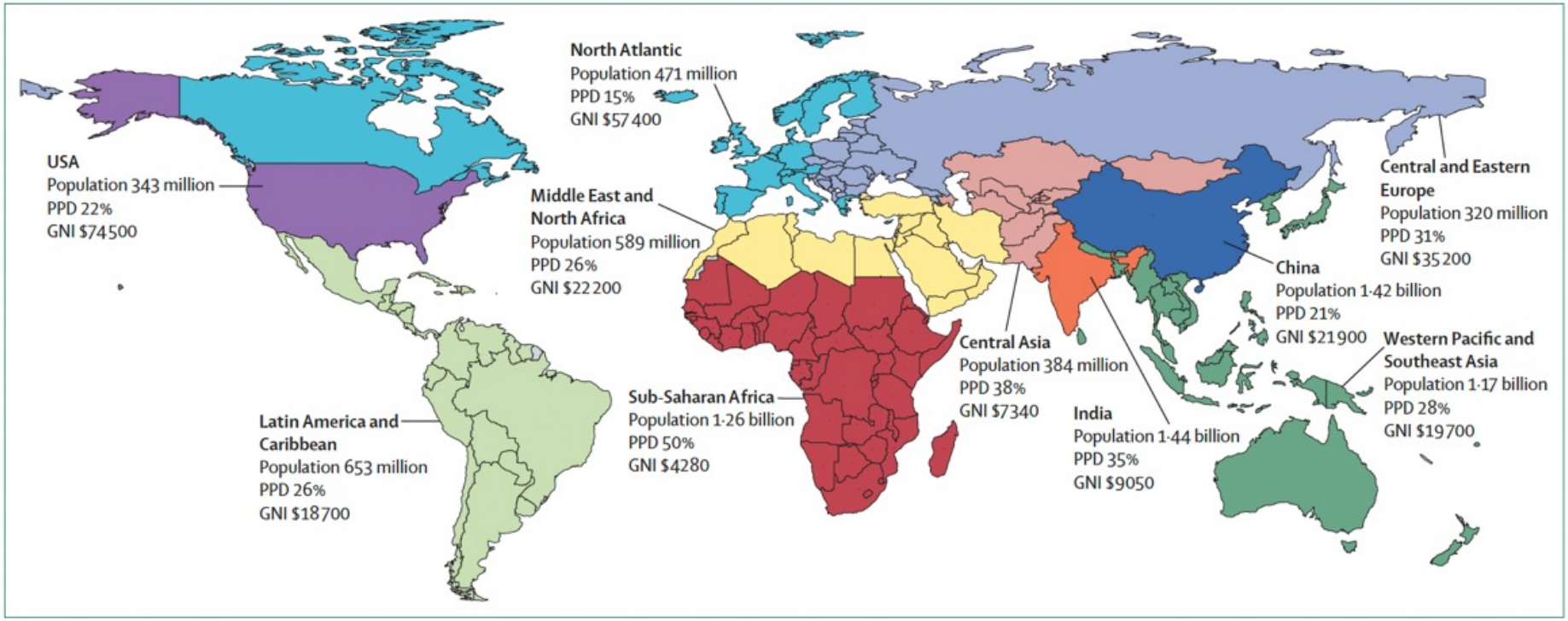


***Figure 1*: Commission on Investing in Health regions with basic statistics**

As of 2023, the global population was 8·09 billion, the PPD was 30%, and the GNI per capita was $20 400. The appendix includes a list of countries in each region (p 3) and basic health, economic, and demographic indicators for each region (p 6). PPD=probability of premature death (ie, death before age 70 years at the prevailing [2023] age-specific mortality rates). GNI=gross national income per capita (in 2021 international dollars—ie, dollars adjusted for purchasing power).

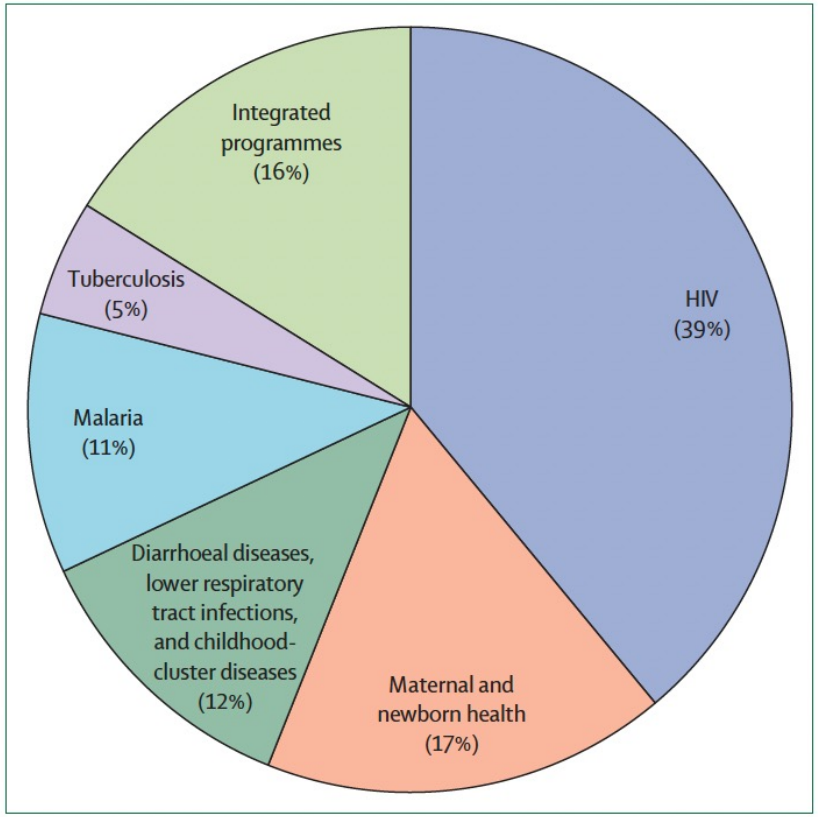


Figure 14: **Country-specific funding for the infectious and maternal health priority conditions**

The chart shows gross disbursements in constant 2021 prices (US$). Source: Schäferhoff et al (2024).[41]

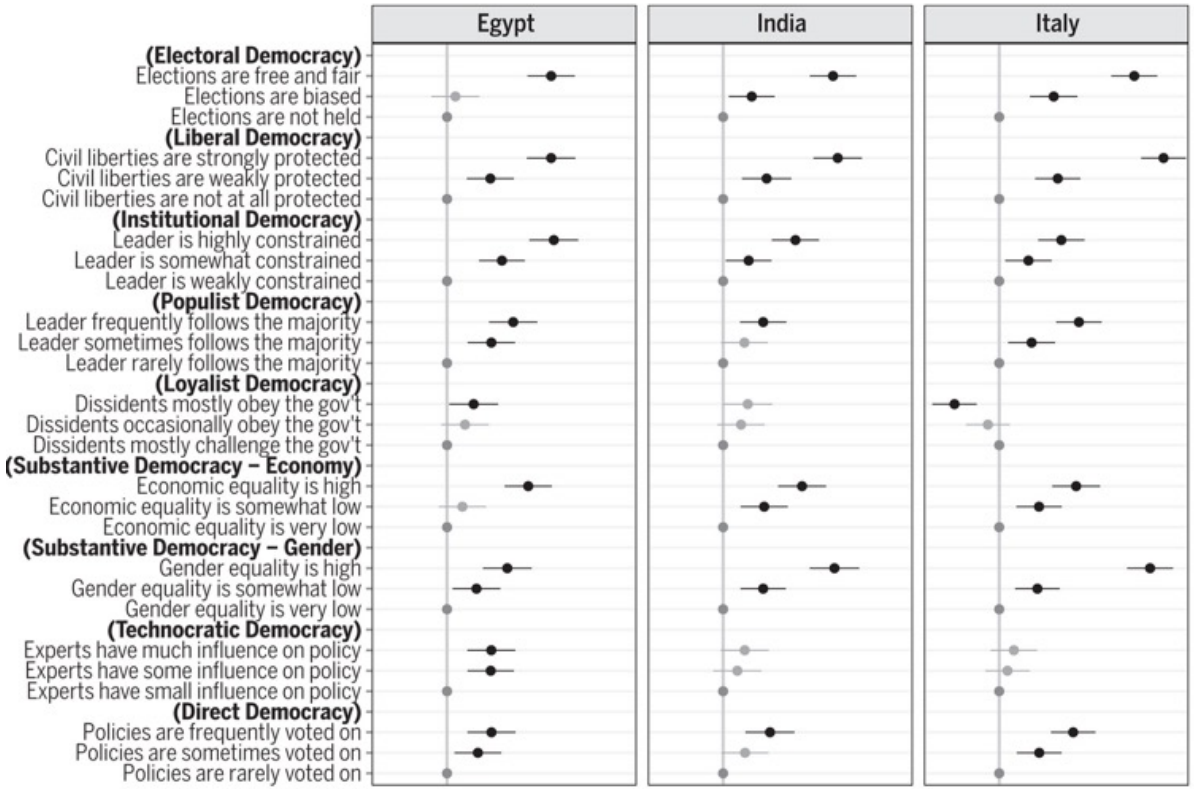
We acknowledge that rising geopolitical tensions, increasingly manifest climate change, growth in nationalistic populism, slowed progress towards UHC, and rising health-care costs are all having an impact on global health progress. Despite these challenges, our analysis shows that a practical pathway to halving PPD by 2050 is within reach. By focusing resources on a narrow set of conditions and scaling up financing to develop new health technologies, we believe that the global health landscape can be utterly transformed within our lifetimes.

GH2035 provided systematic evidence for the high value of mortality declines in much of the world—a value that was often a substantial fraction of GDP growth. We have updated those findings up to 2019 and reiterate the high economic value of actually experienced mortality declines. Today, the case is better than ever for the value of investing in health for reducing mortality and morbidity, alleviating poverty, and improving human welfare.

Contributors

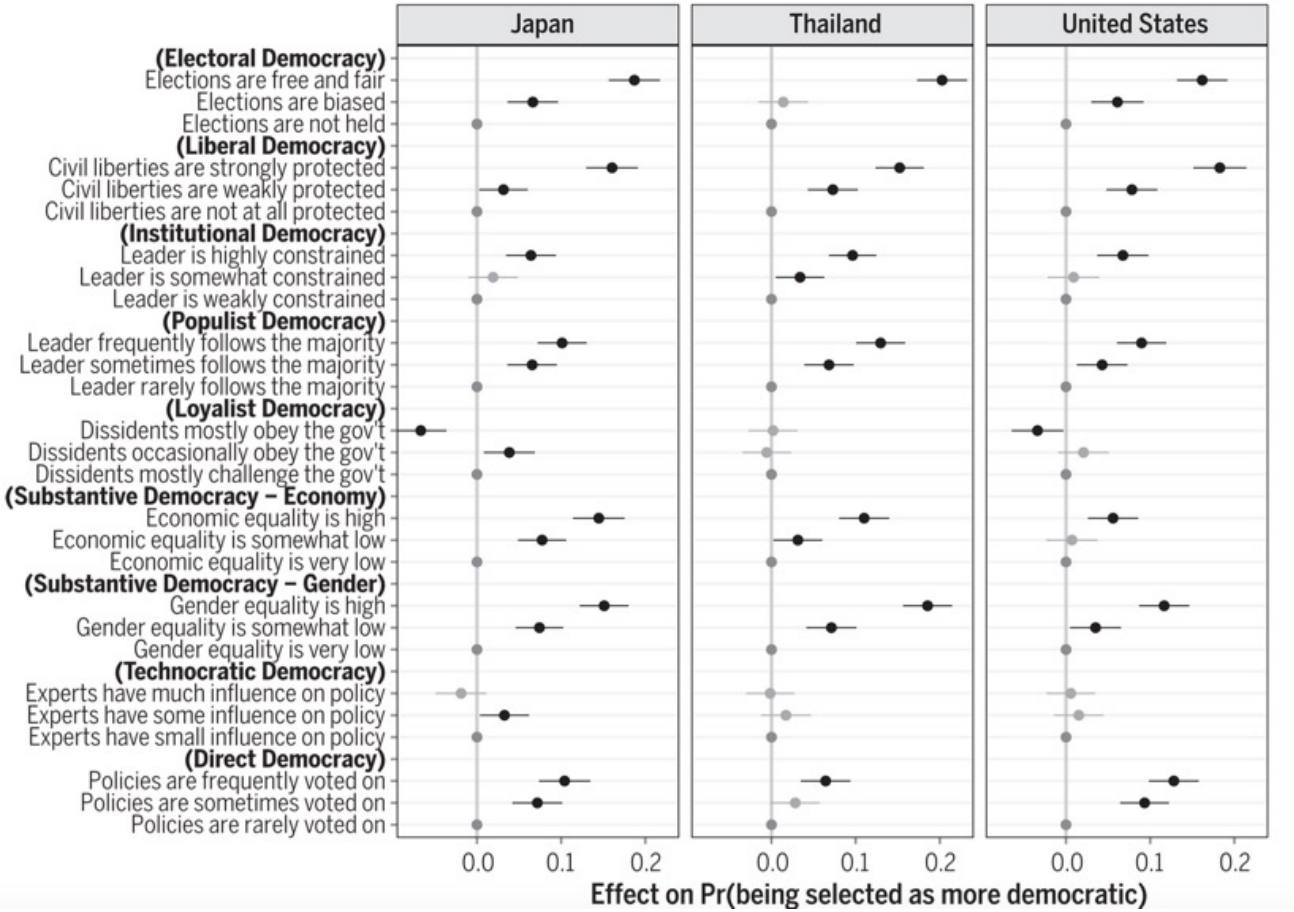
Editor's summary

Most people around the world desire democratic governance, but is there a global consensus on what constitutes a democracy? To defend and strengthen democracy, citizens must share a common understanding of democracy's distinguishing features. Chu *et al*. examined what people considered the most important attributes of a democracy in six distinct countries that are considered well-functioning democracies (Italy and Japan), deteriorating or backsliding democracies (US and India), and nondemocracies (Egypt and Thailand). Across and within countries, people consistently ranked free and fair elections and protection of civil liberties such as free speech as being most important. Gender equality was ranked the third most important attribute everywhere except the US and Egypt. Economic equality was ranked fourth overall. —Ekeoma Uzogara



Factors influencing people's evaluation of democracy in each of six countries.

Estimates represent average marginal component effects. Error bars indicate 95% confidence intervals calculated based on SEs clustered at the individual level. Statistically significant estimates at the 0.05 level after adjustments for multiple comparisons using the Benjamini-Hochberg procedure are displayed in black.



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Research Article | Interventions

Megastudy testing 25 treatments to reduce antidemocratic attitudes and partisan animosityIn Section Research Article | Interventions

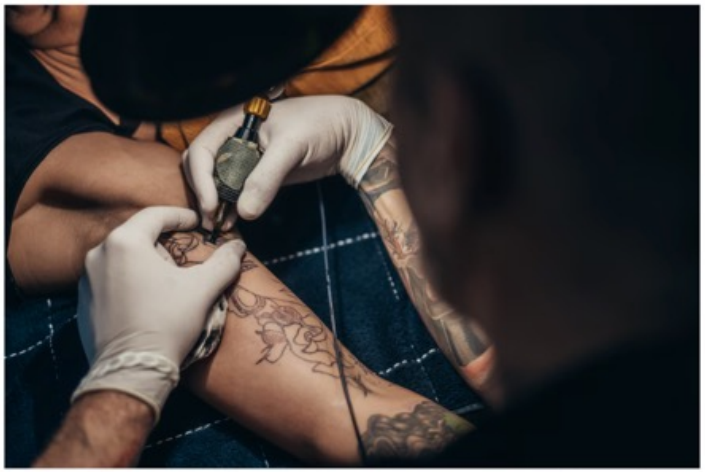
Scholars warn that partisan divisions in the mass public threaten the health of American democracy. We conducted a megastudy (*n* = 32,059 participants) testing 25 treatments designed by academics and practitioners to reduce Americans' partisan animosity and antidemocratic attitudes. We find that many treatments reduced partisan animosity, most strongly by highlighting relatable sympathetic individuals with different political beliefs or by emphasizing common identities shared by rival partisans. We also identify several treatments that reduced support for undemocratic practices—most strongly by correcting misperceptions of rival partisans' views or highlighting the threat of democratic collapse—which shows that antidemocratic attitudes are not intractable. Taken together, the study's findings identify promising general strategies for reducing partisan division and improving democratic attitudes, shedding theoretical light on challenges facing American democracy.

Discussion

We found that people across six very different countries consistently emphasize competitive elections and civil liberties as key determinants of what makes a country democratic. Gender equality and economic equality are the third and fourth most important attributes across most countries, respectively. The relevance of the first two factors, elections and civil liberties, also persists regardless of people's age, gender, education, minority status, political ideology, or preferences for a democratic or authoritarian hegemon in the international system.

More women are discovering the power of tattoos

A higher percentage of women have tattoos than men, and many use them to make statements.



According to Pew Research Center, 38 percent of American women have tattoos, compared with 27 percent of men. (iStock)

Not FDA-regulated

Tattoos are created by injecting colored inks into the second layer of the skin, known as the dermis, a process that can be mildly uncomfortable to seriously painful. It's usually performed without topical anesthesia.

The dyes are not regulated by the Food and Drug Administration and can be taken off the market only if they cause problems, which usually result from bacteria, contamination or adulteration with other ingredients.

The FDA also does not regulate tattoo parlors, which come under the authority of state and local health departments.

"A tattoo is an open wound that results from applying multiple jabs with a needle," making it susceptible to infection, causing redness, swelling or more serious complications if the infection spreads to the bloodstream, says Farley, who co-wrote a paper with Van Hoover describing the potential harm.