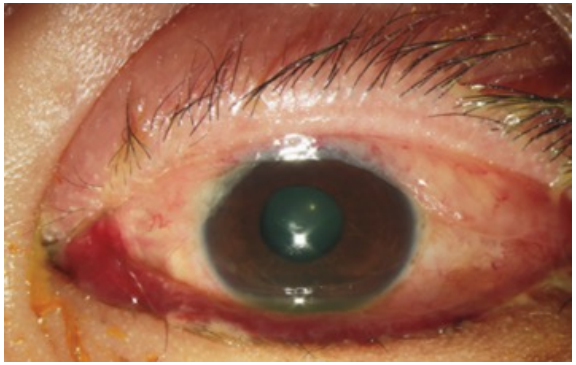
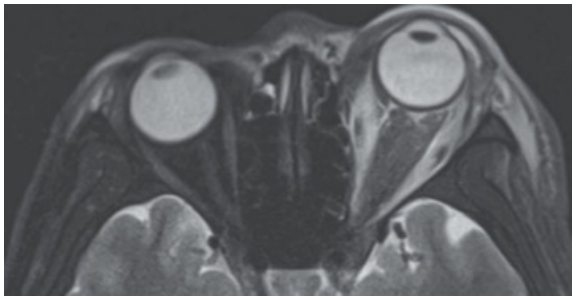
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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, um uns beizutreten. Bewerben Sie sich!





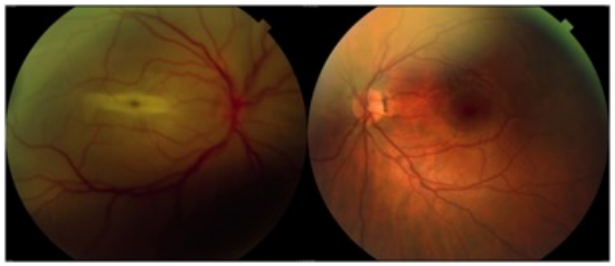
44-year-old man presented to the emergency department with a 3-day history of vision loss and pain in the left eye. The symptoms had started after he had passed out for 3 hours in a position that put pressure on his left eye; before losing consciousness, he had taken insomnia medications and consumed alcohol. An anterior segment examination showed hemorrhagic chemosis and a fixed, mid-dilated pupil (left). The intraocular pressure in the left eye was normal. Funduscopy showed diffuse retinal whitening, a finding consistent with infarction, and optical coherence tomography revealed full-thickness retinal edema. Magnetic resonance imaging of the orbit showed engorgement of the extraocular muscles and orbital tissue (right). A diagnosis of ischemic retinopathy and choroidopathy owing to prolonged orbital compression was made. Which of the following is LEAST likely to be found on physical examination in this patient?

1.Absence of light perception in the left eye
2.A relative afferent pupillary defect
3.Complete ophthalmoplegia of the left eye
4.Proptosis
5.Vertical nystagmus

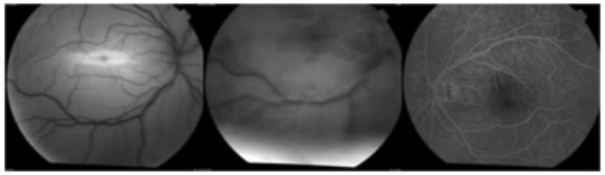
The correct answer is vertical nystagmus; all of the other findings listed were observed in this patient. Historically, this condition has been known as “Saturday night retinopathy” because of its association with the use of alcohol and sedating substances. There is no consensus on management of the condition. The patient received treatment with systemic high-dose glucocorticoids and topical agents to prevent elevation of intraocular pressure; however, during follow-up by telephone 4 months after the initial assessment, the patient reported that he remained blind in his left eye.

Saturday Night Retinopathy with Ophthalmoplegia: A Case Series

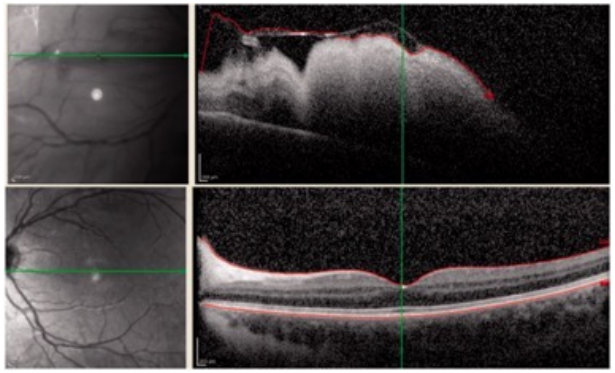
We described three cases who presented to our centre with acute visual loss following intravenous drug abuse and stupor leading to continuous pressure on the orbit while asleep. All cases presented with acute vision loss and had funduscopic evidence of ophthalmic or central retinal artery occlusion. Two of the cases presented with ophthalmoplegia and proptosis. One of the cases had significantly increased intraocular pressure with corneal oedema. All cases had fixed and non-reactive pupils with significant relative afferent pupillary defect. One case also had accompanying peroneal nerve damage. All three cases had poor visual outcomes. Saturday night retinopathy is a blinding condition with either central retinal or ophthalmic artery occlusion, which may present with transient orbital congestion and ophthalmoplegia. It may be accompanied by other nerve damage from compression in other parts of the body and is caused by prolonged positional pressure on the orbit.



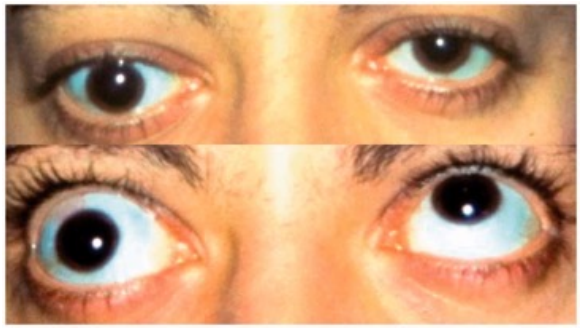
Case 1—3 days after visual loss. (Left) Fundus examination of the right eye revealed significant pallor of the fundus, most notable in the posterior pole, cherry-red spot, engorgement of veins and attenuation of arteries, and slight hyperaemia of the optic disc. (Right) Normal left eye.



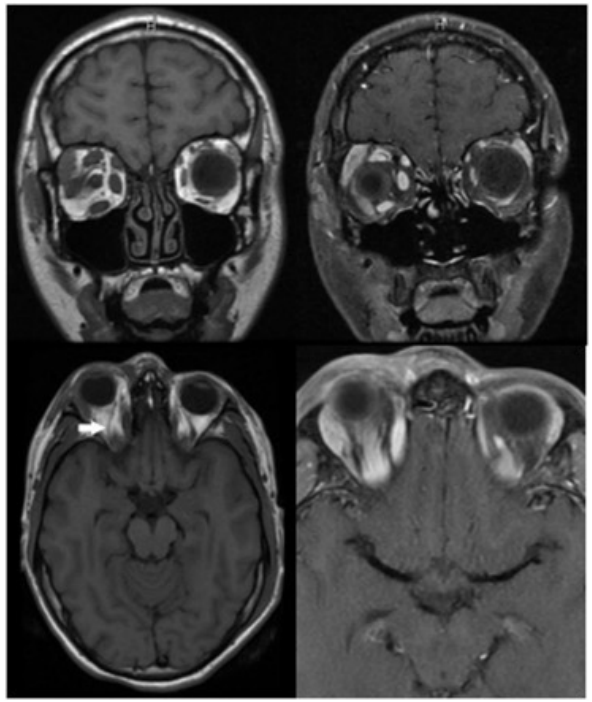
Case 1—3 days after visual loss. (Left) Red free fundus photo, right eye. (Middle) Fluorescein angiography of the right eye at approximately 45 seconds following dye injection confirmed the presence of what had been complete ophthalmic artery occlusion, with significantly delayed and decreased perfusion of the choroid and retinal circulation. (Right) Normal left eye.



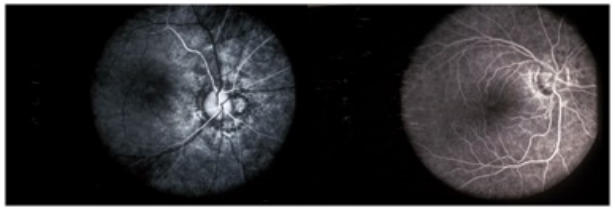
Case 1—3 days after visual loss. OCT of the retina confirmed significant swelling of entire retinal thickness in the right eye extrafoveally (top); normal left eye in the macular area (bottom).



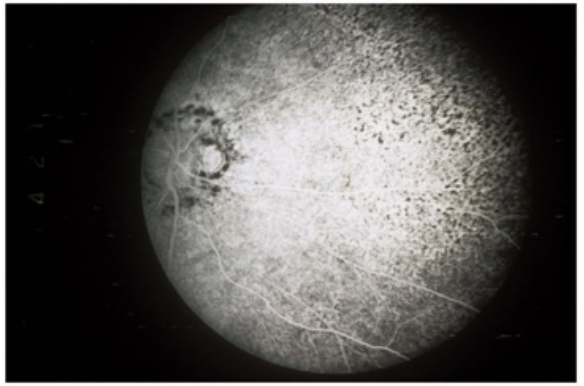
External photograph of patient (case 2) showing proptosis and 4+ underaction in upgaze, OD; OS was normal. Four days after visual loss. (Top) Primary gaze. (Bottom) Upgaze.



Case 1—3 days after visual loss. MRI of orbit revealed engorgement of right extraocular muscles and lacrimal gland. (Top left) Coronal T1. (Top right) Coronal T1 with contrast. (Bottom left) Axial T1. Note normal size of right superior ophthalmic vein (arrow). (Botton right) Axial T1 with contrast.



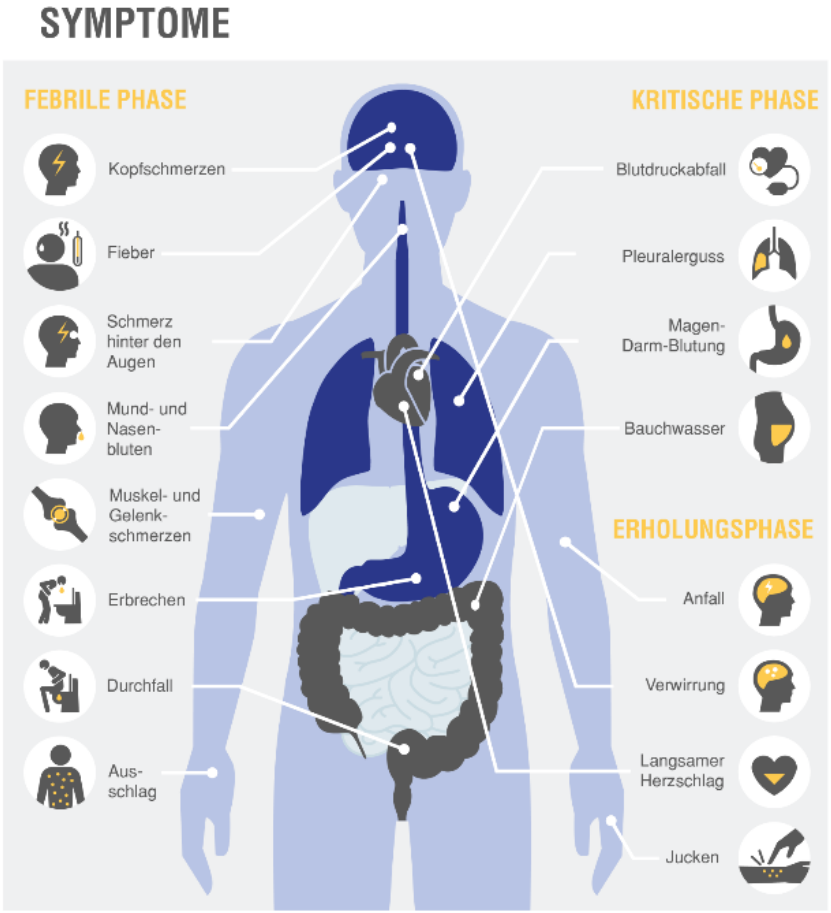
Case 2—4 days after visual loss. Fluorescein angiography of right eye reveals the presence of ophthalmic artery occlusion, with significantly delayed and decreased perfusion of the choroid and retinal circulation.

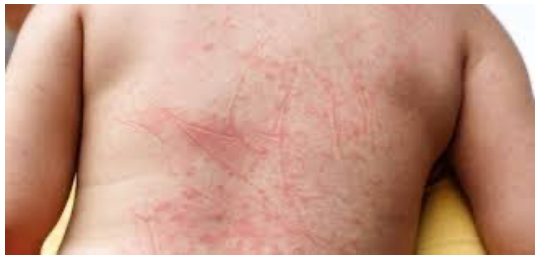


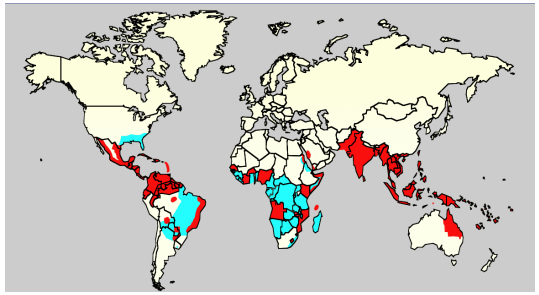
Case 2. Retinal pigment epithelial changes seen 1 month after presentation in the nasal periphery of the fundus further indicate that the ophthalmic artery was involved.

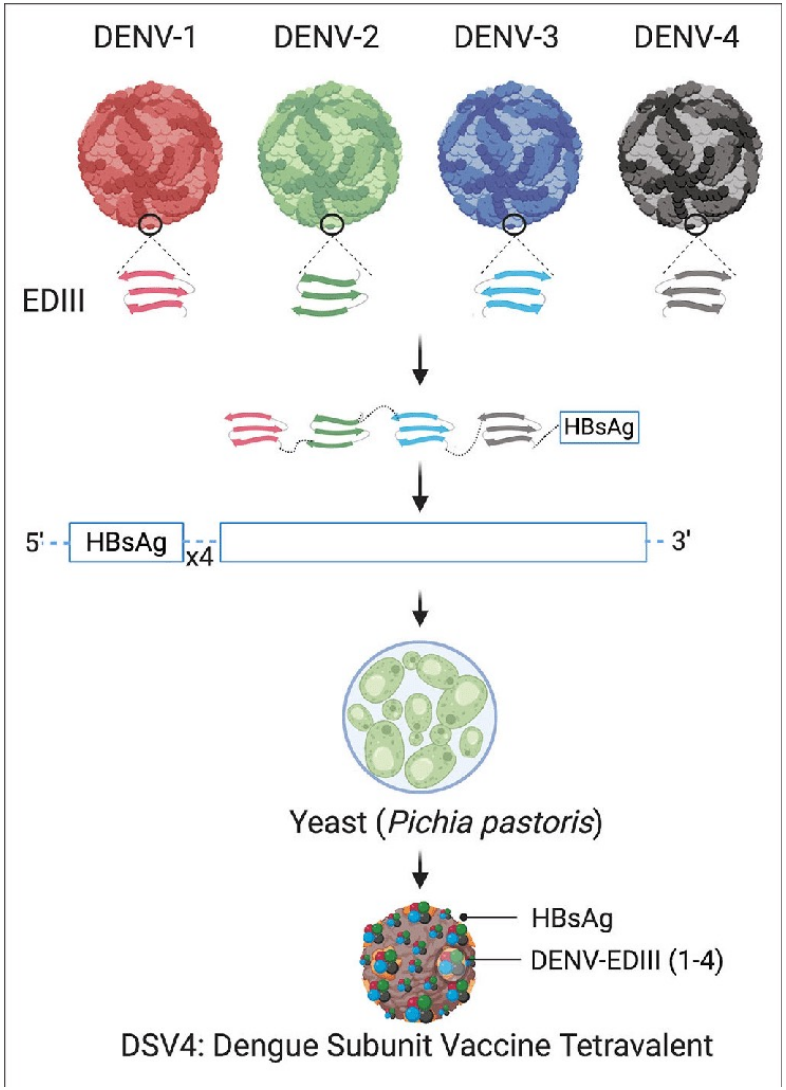
Saturday night retinopathy is a blinding condition with either central retinal or ophthalmic artery occlusion, which may have with transient orbital congestion and ophthalmoplegia. It may be accompanied by other nerve damage from compression in other parts of the body and is caused by prolonged positional pressure on the orbit. Prolonged periods of altered mental status inhibit spontaneous movements, which would ordinarily alleviate the focal compression during normal sleep.

Das Dengue-Fieber ist eine Erkrankung, die durch das Dengue-Virus ausgelöst wird. Das Dengue-Virus wird durch den Stich einer infizierten Stechmücke der Gattung Aedes, hauptsächlich Aedes aegypti (Gelbfiebermücke), aber auch Aedes albopictus (Tigermücke) übertragen und verbreitet.







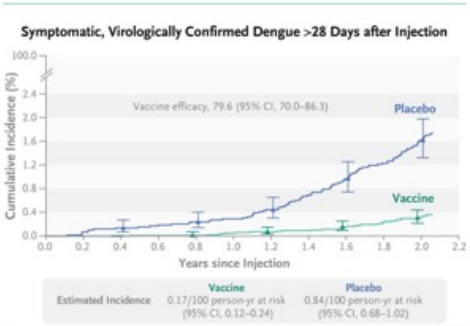


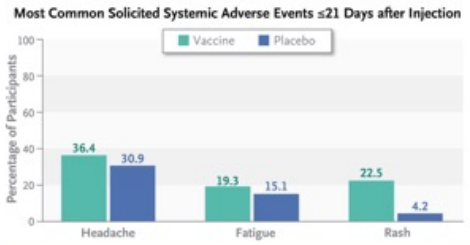
| Design of DSV4. Top panel shows schematic diagram of all four DENV, encircled parts represent envelope domain III (EDIII) component of all four viruses. These EDIIIs components were linked with hexa-glycine linkers, fused to n-terminus of Hepatitis-B surface antigen (HBsAg) and further cloned in the background of four copies of HBsAg. The cloned expression cassette including DENV-EDIIIs, was integrated into the yeast expression host, Pichia pastoris, and DSV4 antigen was purified from the recombinant host for further immunological studies.

ORIGINAL ARTICLE

Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults

Butantan–Dengue Vaccine (Butantan-DV) is an investigational, single-dose, live, attenuated, tetravalent vaccine against dengue disease, but data on its overall efficacy are needed. In an ongoing phase 3, double-blind trial in Brazil, we randomly assigned participants to receive Butantan-DV or placebo, with stratification according to age (2 to 6 years, 7 to 17 years, and 18 to 59 years); 5 years of follow-up is planned. The objectives of the trial were to evaluate overall vaccine efficacy against symptomatic, virologically confirmed dengue of any serotype occurring more than 28 days after vaccination (the primary efficacy end point), regardless of serostatus at baseline, and to describe safety up to day 21 (the primary safety end point). Here, vaccine efficacy was assessed on the basis of 2 years of follow-up for each participant, and safety as solicited vaccine-related adverse events reported up to day 21 after injection. Key secondary objectives were to assess vaccine efficacy among participants according to dengue serostatus at baseline and according to the dengue viral serotype; efficacy according to age was also assessed.





CONCLUSIONS

In an ongoing phase 3 trial in Brazil, a single dose of Butantan-DV prevented symptomatic DENV-1 and DENV-2 in children and adults, regardless of dengue serostatus at baseline, through 2 years of follow-up.

Four serotypes of dengue virus (DENV) circulate worldwide, causing an estimated 390 million infections annually. The largest burden of dengue disease occurs in Southeast Asia and Central and South America. In Brazil, DENV is hyperendemic, with varying incidence across the country. Although most primary DENV infections are asymptomatic or subclinical, DENV can result in severe disease, particularly with secondary heterotypic infection. The goal of a dengue vaccine is to offer protection against all DENV serotypes. An increased risk of severe dengue after CYD-TDV vaccination among persons with no history of dengue infection has been observed. Therefore, the World Health Organization (WHO) has recommended limiting the use of CYD-TDV to persons previously exposed to dengue or, if screening is not available, to areas in which the disease is endemic (with a seroprevalence of at least 80% by 9 years of age).

Methods

Trial Design, Participants, and Oversight

DEN-03-IB is an ongoing phase 3, randomized, double-blind, placebo-controlled trial, with 5 years of planned follow-up, being conducted at 16 sites in Brazil.

Participants underwent randomization according to age (2 to 6 years of age, 7 to 17 years of age, and 18 to 59 years of age) and in a 2:1 ratio to receive a single dose of Butantan-DV or placebo. Enrollment occurred from February 2016 to July 2019, starting with the adult group and proceeding to the remaining age groups in descending order after interim safety analyses were performed by the data and safety monitoring committee.

Vaccine Description

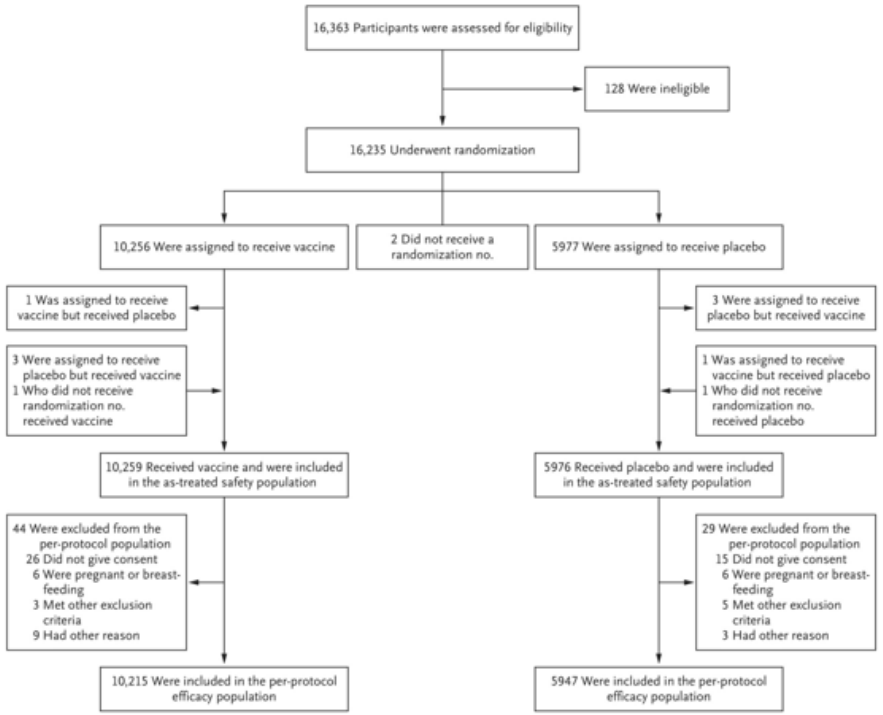
Butantan-DV is composed of attenuated vaccine viruses for DENV-1, DENV-3, and DENV-4 (rDENV1Δ30, rDENV3Δ30/31, and rDENV4Δ30) and a chimeric vaccine virus containing the DENV-2 genes encoding the premembrane (prM) and envelope (E) proteins on the attenuated DENV-4 background (rDENV2/4Δ30[ME]).

Efficacy Assessments and End Points

Vaccine efficacy was assessed on the basis of symptomatic, virologically confirmed dengue occurring more than 28 days after injection. Participants were instructed to seek out the trial team if they had a fever or other symptoms that could be present in a case of dengue. A blood sample was collected, preferably within 9 days after the onset of symptoms, to evaluate the possibility of dengue. Virologic confirmation and determination of serotype were made with the use of a fourplex reverse-transcriptase–polymerase-chain-reaction assay.

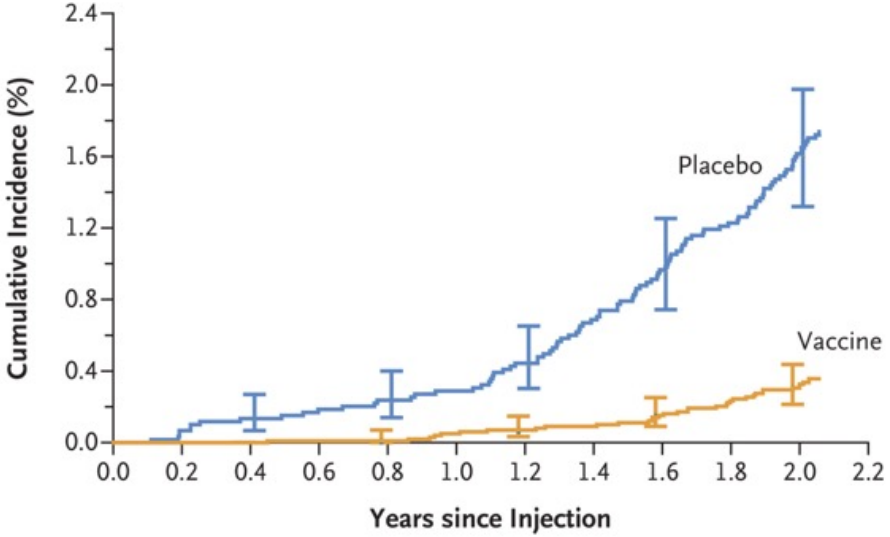
Safety Assessments and End Points

Safety assessments included the monitoring of solicited (administration-site and systemic) and unsolicited adverse events that occurred within 21 days after injection. Unsolicited adverse events, including serious adverse events, were recorded throughout the follow-up period. Participants recorded adverse events in a diary during the 21 days after injection and reported adverse event by means of periodic telephone calls; the investigators evaluated adverse events for severity and causality with respect to the vaccine or placebo.



	Vaccine (N=10,259)	Placebo (N=5976)	Total (N=16,235)
Sex — no. (%)			
Female	5555 (54.1)	3216 (53.8)	8771 (54.0)
Male	4704 (45.9)	2760 (46.2)	7464 (46.0)
Age distribution — no. (%)			
2–6 yr	3337 (32.5)	1679 (28.1)	5016 (30.9)
7–17 yr	3376 (32.9)	1771 (29.6)	5147 (31.7)
18–59 yr	3546 (34.6)	2526 (42.3)	6072 (37.4)
Median age (IQR) — yr	11 (5–31)	14 (6–36)	12 (6–33)
Race or ethnic group — no. (%)†			
Pardo	7017 (68.4)	4036 (67.5)	11,053 (68.1)
White	2410 (23.5)	1402 (23.5)	3812 (23.5)
Black	655 (6.4)	408 (6.8)	1063 (6.5)
Asian	149 (1.5)	114 (1.9)	263 (1.6)
Indigenous or other	28 (0.3)	16 (0.3)	44 (0.3)
Hispanic ethnic group — no. (%)†			
No	10,068 (98.1)	5861 (98.1)	15,929 (98.1)
Yes	191 (1.9)	115 (1.9)	306 (1.9)
Previous exposure to DENV — no. (%)‡			
Yes			
Any serotype	5009 (48.8)	3041 (50.9)	8050 (49.6)
Monovalent	591 (5.8)	304 (5.1)	895 (5.5)
Bivalent	340 (3.3)	173 (2.9)	513 (3.2)
Trivalent	462 (4.5)	318 (5.3)	780 (4.8)
Tetravalent	3616 (35.2)	2246 (37.6)	5862 (36.1)
No	4855 (47.3)	2700 (45.2)	7555 (46.5)
Unknown or missing data§	395 (3.9)	235 (3.9)	630 (3.9)
Previous exposure to DENV, by serotype — no. (%)‡			
DENV-1	4295 (41.9)	2666 (44.6)	6961 (42.9)
DENV-2	4487 (43.7)	2766 (46.3)	7253 (44.7)
DENV-3	3801 (37.1)	2365 (39.6)	6166 (38.0)
DENV-4	4538 (44.2)	2791 (46.7)	7329 (45.1)
Unknown or missing data§	395 (3.9)	235 (3.9)	630 (3.9)

Cumulative Incidence of Virologically Confirmed Dengue through 2-Year Follow-Up.



Shown is the incidence of symptomatic, virologically confirmed dengue occurring more than 28 days after injection through the end of the 2-year follow-up period. Analysis excludes results that did not follow standard operating procedures for the reverse-transcriptase–polymerase-chain-reaction-assay. I bars indicate 95% confidence intervals.

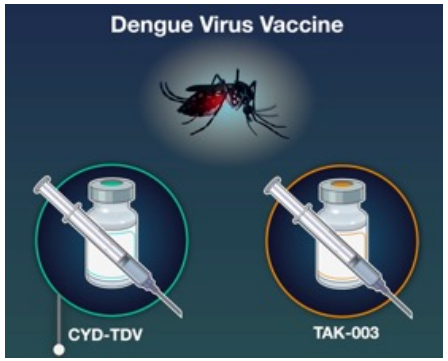
Vaccine Efficacy at 2 Years after Injection.

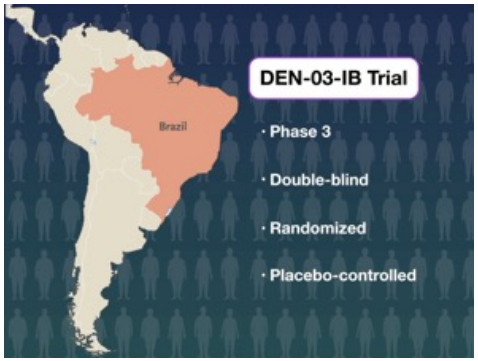
Confirmed Dengue	Vaccine			Placebo			Cumulative
	Cases	Person-Yrs at Risk	Estimated Incidence (95% CI)	Cases	Person-Yrs at Risk	Estimated Incidence (95% CI)	Vaccine Efficacy (95% CI)
	no. (total no.)			*no. (total no.)*			%
Any serotype							
Regardless of serostatus	35/10,215	20,452	0.17 (0.12 to 0.24)	100/5,947	11,927	0.84 (0.68 to 1.02)	79.6 (70.0 to 86.3)
With previous exposure	8/4,994	10,063	0.08 (0.03 to 0.16)	45/3,023	6,092	0.74 (0.54 to 0.99)	89.2 (77.6 to 95.6)
Without previous exposure	26/4,826	9,573	0.27 (0.18 to 0.40)	55/2,690	5,350	1.03 (0.77 to 1.34)	73.6 (57.6 to 83.7)
DENV-1							
Regardless of serostatus	9/10,215	20,463	0.04 (0.02 to 0.08)	50/5,947	11,950	0.42 (0.31 to 0.55)	89.5 (78.7 to 95.0)
With previous exposure	1/4,994	10,065	0.01 (0.00 to 0.06)	19/3,023	6,101	0.31 (0.19 to 0.49)	96.8 (81.0 to 99.8)
Without previous exposure	8/4,826	9,582	0.08 (0.04 to 0.17)	31/2,690	5,365	0.58 (0.39 to 0.82)	85.6 (69.1 to 94.0)
DENV-2							
Regardless of serostatus	26/10,215	20,458	0.13 (0.08 to 0.19)	50/5,947	11,967	0.42 (0.31 to 0.55)	69.6 (50.8 to 81.5)
With previous exposure	7/4,994	10,063	0.07 (0.03 to 0.14)	26/3,023	6,107	0.43 (0.28 to 0.62)	83.7 (63.1 to 93.5)
Without previous exposure	18/4,826	9,579	0.19 (0.11 to 0.30)	24/2,690	5,376	0.45 (0.29 to 0.66)	57.9 (20.8 to 78.1)

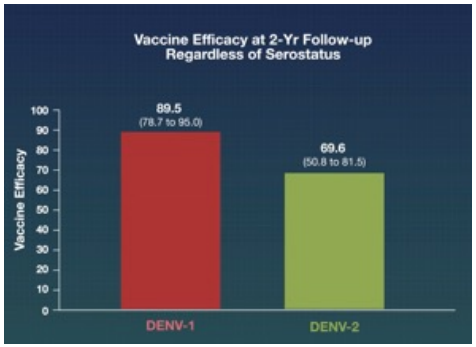
Adverse Event Type	Vaccine (N=10,259)	Placebo (N=5976)
	no. (%)	
Any adverse event	7137 (69.6)	3595 (60.2)
Serious	20 (0.2)	8 (0.1)
Unsolicited	3360 (32.8)	1917 (32.1)
Systemic	6204 (60.5)	2864 (47.9)
Event related to vaccine or placebo†	6527 (63.6)	3109 (52.0)
Serious	3 (<0.1)	2 (<0.1)
Unsolicited	1391 (13.6)	720 (12.0)
Solicited	6395 (62.3)	2998 (50.2)
Administration-site adverse event‡	2012 (19.6)	879 (14.7)
Pain	1527 (14.9)	665 (11.1)
Pruritus	585 (5.7)	239 (4)
Erythema	318 (3.1)	92 (1.5)
Induration	195 (1.9)	94 (1.6)
Swelling	120 (1.2)	63 (1.1)
Systemic adverse event	5980 (58.3)	2725 (45.6)
Headache	3734 (36.4)	1846 (30.9)
Asthenia	1984 (19.3)	905 (15.1)
Exanthema	2312 (22.5)	250 (4.2)
Myalgia	1789 (17.4)	757 (12.7)
Pruritus	1938 (18.9)	526 (8.8)
Retro-orbital eye pain	1618 (15.8)	641 (10.7)
Nausea	1244 (12.1)	631 (10.6)
Arthralgia	1152 (11.2)	487 (8.1)
Photophobia	993 (9.7)	486 (8.1)
Pyrexia§	1047(10.2)	398 (6.7)
Chills	871 (8.5)	328 (5.5)
Vomiting	574 (5.6)	291 (4.9)

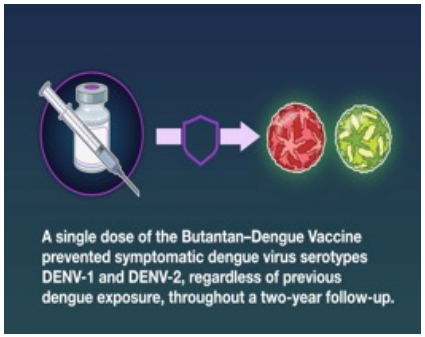
Adverse Events within 21 Days after Injection.

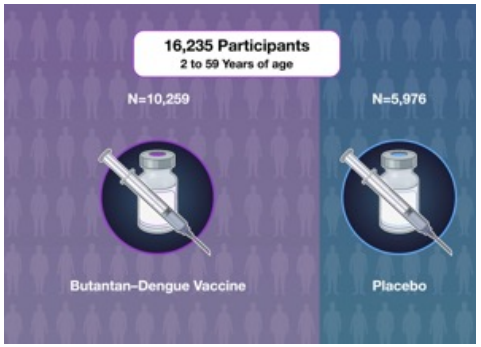
Within 21 days after injection, three participants in the vaccine group and two participants in the placebo group had serious adverse events that were considered to be related to the vaccine or placebo. Two additional participants had vaccine- or placebo-related serious adverse events occurring at 22 days or later after injection, for a total of seven vaccine- or placebo-related serious adverse events (i.e., Bell's palsy, bronchospasm, facial paralysis, Guillain-Barré syndrome, peripheral neuropathy, transverse sinus thrombosis, and viral infection) in the 2 years of follow-up. The trial-group assignments with respect to the participant-level safety data remain concealed; however, the data and safety monitoring committee reviewed all serious adverse events and did not recommend unblinding of the safety data in any case.

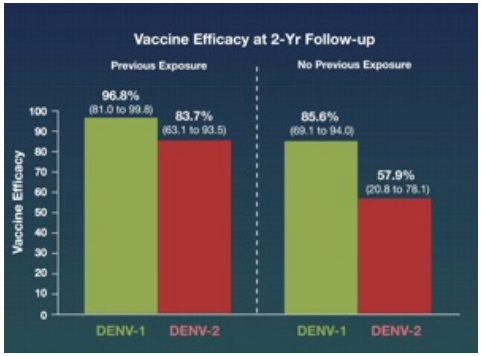


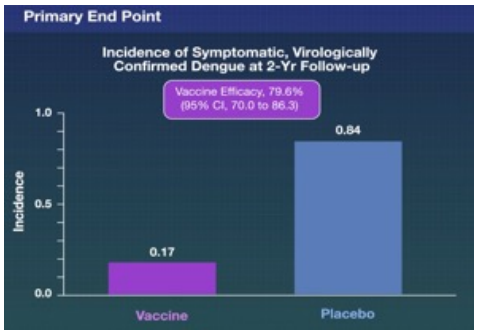


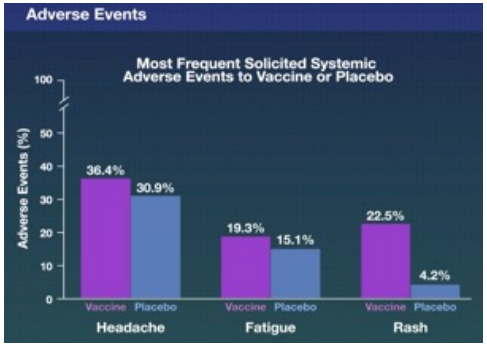






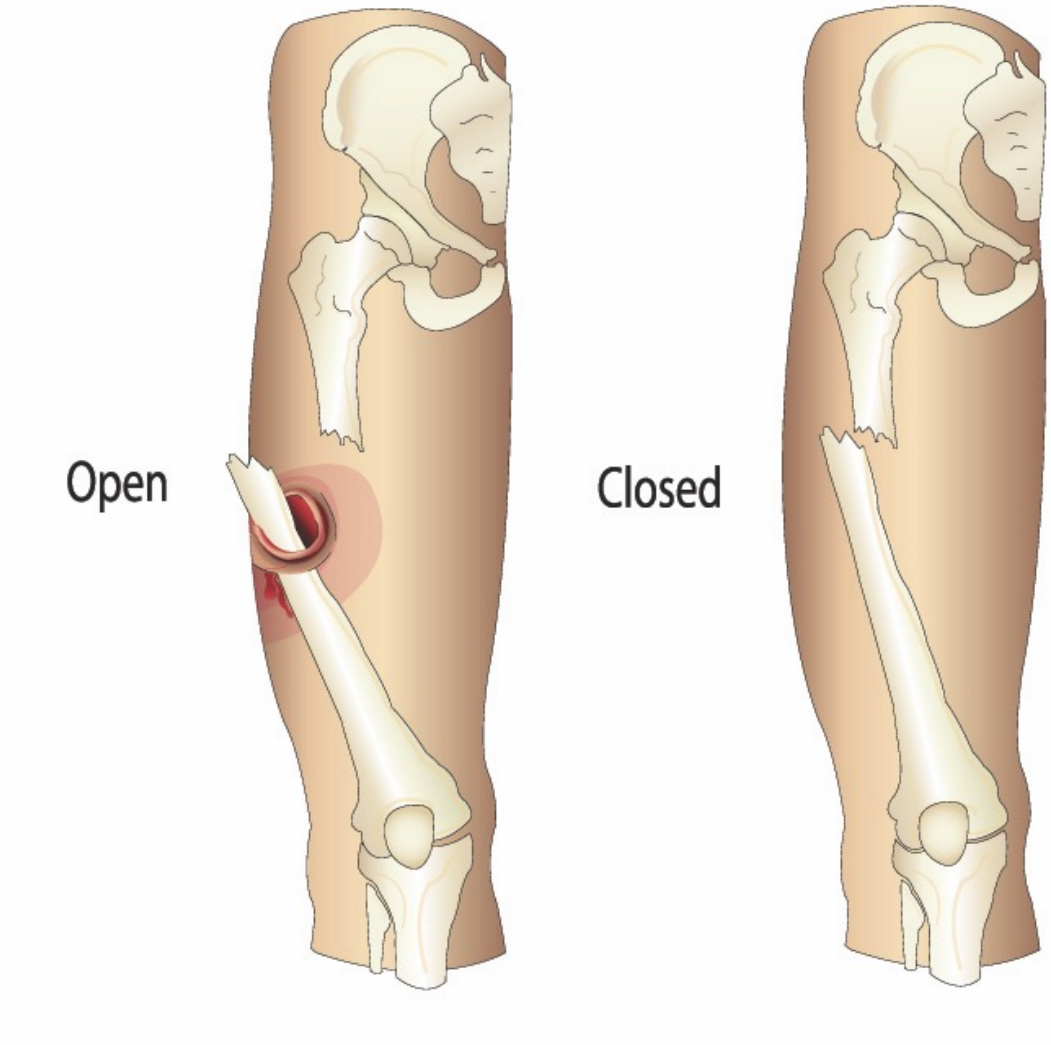






LIMITATIONS AND REMAINING QUESTIONS

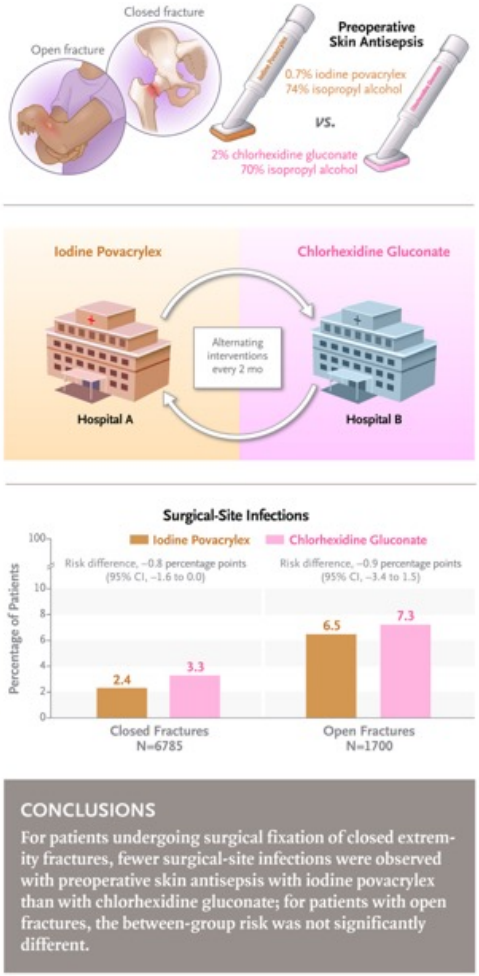
- No DENV-3 or DENV-4 cases occurred, which precluded assessment of vaccine efficacy against these serotypes.
- No safety concerns were identified; careful follow-up through the planned 5 years will be important to confirm this finding.
- The effect of preexisting immunity from other flaviviruses (Zika virus or yellow fever) on subsequent DENV infection or Butantan-DV vaccination requires exploration.
- A low incidence of virologically confirmed dengue precluded meaningful analyses of vaccine efficacy against severe dengue.


Open
Closed

ORIGINAL ARTICLE

Skin Antisepsis before Surgical Fixation of Extremity Fractures

Studies evaluating surgical-site infection have had conflicting results with respect to the use of alcohol solutions containing iodine povacrylex or chlorhexidine gluconate as skin antisepsis before surgery to repair a fractured limb (i.e., an extremity fracture). In a cluster-randomized, crossover trial at 25 hospitals in the United States and Canada, we randomly assigned hospitals to use a solution of 0.7% iodine povacrylex in 74% isopropyl alcohol (iodine group) or 2% chlorhexidine gluconate in 70% isopropyl alcohol (chlorhexidine group) as preoperative antisepsis for surgical procedures to repair extremity fractures. Every 2 months, the hospitals alternated interventions. Separate populations of patients with either open or closed fractures were enrolled and included in the analysis. The primary outcome was surgical-site infection, which included superficial incisional infection within 30 days or deep incisional or organ-space infection within 90 days. The secondary outcome was unplanned reoperation for fracture-healing complications.



CONCLUSIONS

For patients undergoing surgical fixation of closed extremity fractures, fewer surgical-site infections were observed with preoperative skin antisepsis with iodine povacrylex than with chlorhexidine gluconate; for patients with open fractures, the between-group risk was not significantly different.

Clinical practice guidelines universally recommend the use of antiseptic skin solutions containing alcohol to prevent surgical-site infection. Although some guidelines favor antisepsis with chlorhexidine gluconate over an iodophor, all recommendations recognize a lack of consensus with respect to the most effective agent.

Methods

Trial Design and Oversight

In this trial, we used a multiple-period, cluster-randomized, crossover design. A total of 25 hospitals in the United States and Canada participated in the trial. Of these hospitals, 20 recruited patients with either open or closed fractures; 3 hospitals recruited patients with closed fractures only, and 2 recruited those with open fractures only.

Cluster Selection

We selected hospitals for participation in the trial after we had obtained confirmation that their orthopedic surgery practice group had appropriate research personnel infrastructure to implement the protocol, an adequate volume of patients with fractures to meet enrollment targets, a commitment from all surgeons to adhere to the assigned interventions.

Closed-Fracture Population

The closed-fracture population consisted of adults (≥18 years old) who were undergoing surgical fixation of a closed lower-limb or pelvic fracture.

Open-Fracture Population

The open-fracture population consisted of adults (≥18 years old) who had an open upper-limb or lower-limb fracture warranting surgical fixation. In addition, the patient's open fracture must have received surgical débridement within 72 hours after injury.

Randomization and Interventions

Participating hospitals were randomly assigned to use a solution of 0.7% iodine povacrylex in 74% isopropyl alcohol (3M Duraprep Surgical Prepping Solution) or a solution of 2% chlorhexidine gluconate in 70% isopropyl alcohol (BD ChloraPrep; 3M SoluPrep S Sterile Antiseptic Solution) for all eligible patients.

Trial Outcomes

The primary outcome was surgical-site infection, as defined by the 2017 reporting criteria of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network. This outcome included superficial incisional infection within 30 days and deep incisional or organ-space infection within 90 days after definitive fracture-management surgery.

S1.3A Eligibility Criteria for Closed Population

Inclusion Criteria:

1. Patients 18 years of age or older.
2. Closed fracture of the lower extremity or pelvis.
3. Received or will receive definitive fracture treatment with a surgical implant(s) (i.e., internal fixation, external fixation, joint prosthesis, etc.).
4. Fracture management requires a surgical incision (i.e., for fracture reduction or implant insertion).
5. Will have all planned fracture care surgeries performed by a participating surgeon or delegate.
6. Informed consent obtained.
7. Patient enrolled within 6 weeks of their fracture.

Exclusion Criteria:

1. Patients who did not or will not receive the allocated pre-operative surgical preparation solution due to a medical contraindication.
2. Received previous surgical management of their fracture at a non-participating hospital or clinic.
3. Fracture managed outside of the participating orthopaedic service (e.g., foot fracture managed by podiatrist).
4. Chronic or acute infection at or near the fracture site at the time of initial fracture surgery.
5. Burns at the fracture site.
6. Incarceration.
7. Expected injury survival of less than 90 days.
8. Terminal illness with expected survival less than 90 days.
9. Currently enrolled in a study that does not permit co-enrollment.
10. Unable to obtain informed consent due to language barriers.
11. Likely, problems, in the judgment of study personnel, with maintaining follow-up with the patient.
12. Prior or current enrollment in a PREP-IT trial.
13. Enrolled in the PREPARE open trial.
14. Excluded due to random sampling strategy.

Characteristics of the Patients at Baseline.

	Closed-Fracture Population		Open-Fracture Population	
	Iodine Povacrylex (N=3360)	Chlorhexidine Gluconate (N=3425)	Iodine Povacrylex (N=854)	Chlorhexidine Gluconate (N=846)
Age — yr	54.3±20.2	53.6±20.4	45.0±18.3	44.2±18.1
Sex — no. (%)				
Female	1730 (51.5)	1739 (50.8)	312 (36.5)	309 (36.5)
Male	1629 (48.5)	1686 (49.2)	542 (63.5)	537 (63.5)
Missing data	1 (<0.1)	0	0	0
Race or ethnic group — no. (%)†				
White	2652 (78.9)	2706 (79.0)	584 (68.4)	589 (69.6)
Black	501 (14.9)	480 (14.0)	227 (26.6)	214 (25.3)
Asian	140 (4.2)	147 (4.3)	22 (2.6)	17 (2.0)
Indigenous	27 (0.8)	33 (1.0)	9 (1.1)	12 (1.4)
Central or South American	4 (0.1)	7 (0.2)	2 (0.2)	1 (0.1)
Multiracial	3 (0.1)	4 (0.1)	2 (0.2)	4 (0.5)
Native Hawaiian or Pacific Islander	3 (0.1)	5 (0.1)	1 (0.1)	1 (0.1)
Missing data	30 (0.9)	43 (1.3)	7 (0.8)	8 (0.9)
Hispanic ethnic group — no. (%)†	170 (5.1)	181 (5.3)	65 (7.6)	47 (5.6)
Body-mass index — no. (%)‡				
<18.5: underweight	99 (2.9)	80 (2.3)	12 (1.4)	13 (1.5)
18.5–24.9: normal weight	1068 (31.8)	1106 (32.3)	252 (29.5)	250 (29.6)
25.0–29.9: overweight	1082 (32.2)	1024 (29.9)	279 (32.7)	294 (34.8)
≥30: obese	1111 (33.1)	1215 (35.5)	311 (36.4)	289 (34.2)
Diabetes of any type — no. (%)	470 (14.0)	445 (13.0)	80 (9.4)	64 (7.6)
Current smoker — no. (%)	753 (22.4)	722 (21.1)	289 (33.8)	282 (33.3)
Injury severity score§	9.0±6.2	8.9±6.2	13.4±8.5	12.9±8.0
Score on the ASA physical-status classification — no. (%)¶				
Class I or II	1760 (52.4)	1752 (51.2)	440 (51.5)	463 (54.7)
Class III or higher	1600 (47.6)	1673 (48.8)	414 (48.5)	383 (45.3)
No. of included closed fractures per patient — no. (%)				
One	3169 (94.3)	3240 (94.6)	782 (91.6)	771 (91.1)
Two	166 (4.9)	162 (4.7)	62 (7.3)	68 (8.0)
Three	25 (0.7)	23 (0.7)	10 (1.2)	7 (0.8)

Treatment Characteristics of Closed-Fracture Injuries.

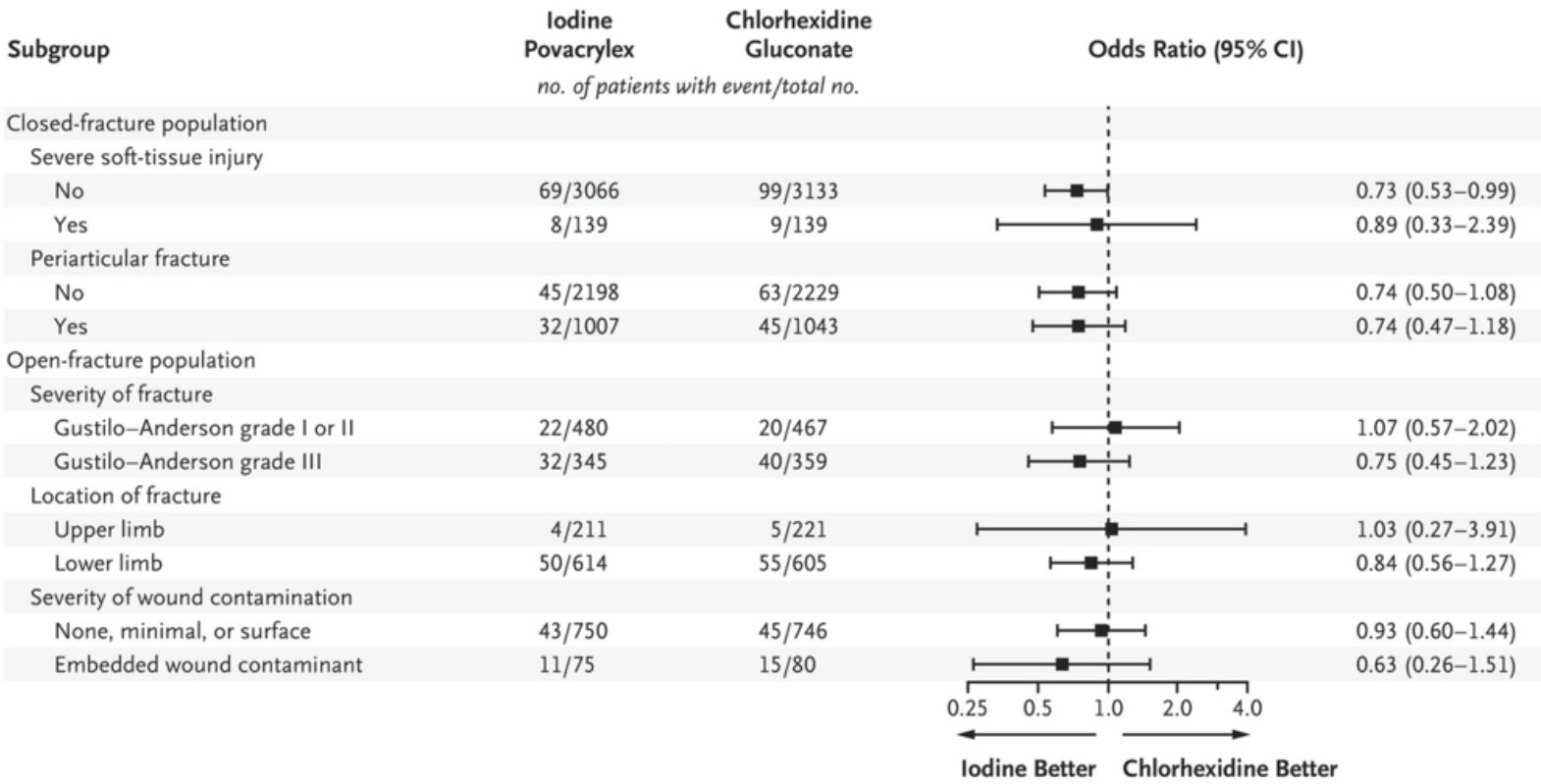
Characteristic	Iodine Povacrylex (N = 3576 fractures)	Chlorhexidine Gluconate (N = 3633 fractures)
Location of fracture — no. (%)		
Proximal femur	865 (24.2)	772 (21.2)
Foot or ankle	778 (21.8)	830 (22.8)
Proximal tibia or fibula	430 (12.0)	443 (12.2)
Pelvis or acetabulum	369 (10.3)	415 (11.4)
Femoral shaft	358 (10.0)	382 (10.5)
Distal tibia or fibula	288 (8.1)	275 (7.6)
Tibia or fibula shaft	241 (6.7)	264 (7.3)
Distal femur	183 (5.1)	183 (5.0)
Patella	64 (1.8)	69 (1.9)
Periarticular fracture — no. (%)†	1122 (31.4)	1155 (31.8)
Severe soft-tissue injury — no. (%)‡	149 (4.2)	149 (4.1)
Temporary fracture stabilization — no. (%)	294 (8.2)	301 (8.3)
No. of planned surgeries — no. (%)		
1	3264 (91.3)	3307 (91.0)
2	284 (7.9)	303 (8.3)
≥3	28 (0.8)	23 (0.6)
Median no. of days of antibiotic administration (IQR)§	1.0 (1.0–2.0)	1.0 (1.0–2.0)

Treatment Characteristics of Open-Fracture Injuries.

	Iodine Povacrylex (N=936 fractures)	Chlorhexidine Gluconate (N=928 fractures)
Gustilo–Anderson severity grade — no. (%)*		
Grade I	219 (23.4)	213 (23.0)
Grade II	316 (33.8)	317 (34.2)
Grade IIIA	361 (38.6)	361 (38.9)
Grade IIIB or IIIC	40 (4.3)	37 (4.0)
Location of fracture — no. (%)		
Lower limb or pelvis	687 (73.4)	672 (72.4)
Upper limb	249 (26.6)	256 (27.6)
Wound contamination — no. (%)		
None or minimal	573 (61.2)	576 (62.1)
Surface only	282 (30.1)	266 (28.7)
Contaminant embedded in bone or deep soft tissue	81 (8.7)	86 (9.3)
Temporary fracture stabilization — no. (%)	184 (19.7)	165 (17.8)
No. of planned surgeries — no. (%)		
1	678 (72.4)	673 (72.5)
2	184 (19.7)	190 (20.5)
3	38 (4.1)	42 (4.5)
4	12 (1.3)	10 (1.1)
≥5	24 (2.6)	13 (1.4)
Median no. of days of antibiotic administration (IQR)†	3.0 (2.0–4.0)	3.0 (2.0–3.3)
Closure method — no. (%)‡		
Primary wound closure	855 (91.3)	859 (92.6)
No closure attempted or secondary wound healing	17 (1.8)	14 (1.5)
Skin graft	35 (3.7)	20 (2.2)
Local flap	12 (1.3)	20 (2.2)
Free flap	17 (1.8)	15 (1.6)

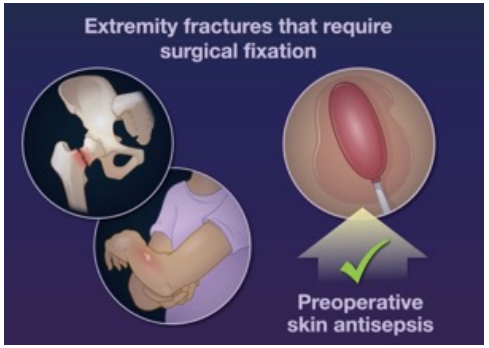
Primary and Secondary Outcomes.

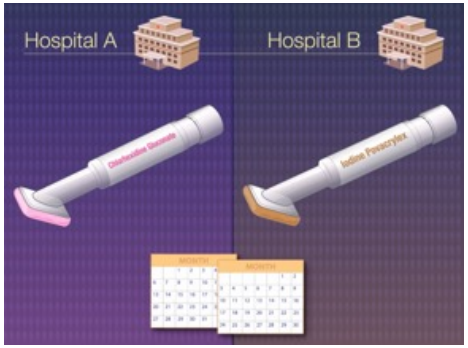
Outcome	Iodine Povacrylex	Chlorhexidine Gluconate	Odds Ratio (95% CI)†	P Value	Risk Difference (95% CI)†‡
	no./total no. (%)				*percentage points*
Closed-fracture population					
Surgical-site infection: primary outcome§	77/3205 (2.4)	108/3272 (3.3)	0.74 (0.55 to 1.00)	0.049	−0.8 (−1.6 to 0.0)
Superficial infection in ≤30 days	20/3205 (0.6)	27/3272 (0.8)			
Deep infection in ≤90 days	29/3205 (0.9)	54/3272 (1.7)			
Organ-space infection in ≤90 days	28/3205 (0.9)	27/3272 (0.8)			
Unplanned reoperation: secondary outcome¶	164/2982 (5.5)	179/3047 (5.9)	0.96 (0.77 to 1.20)	NA	−0.3 (−1.6 to 1.1)
For infection	98/2982 (3.3)	117/3047 (3.8)			
For wound-healing problem	57/2982 (1.9)	65/3047 (2.1)			
For delayed union or nonunion	66/2982 (2.2)	66/3047 (2.2)			
Open-fracture population					
Surgical-site infection: primary outcome§	54/825 (6.5)	60/826 (7.3)	0.86 (0.58 to 1.27)	0.45	−0.9 (−3.4 to 1.5)
Superficial infection in ≤30 days	6/825 (0.7)	9/826 (1.1)			
Deep infection in ≤90 days	21/825 (2.5)	20/826 (2.4)			
Organ-space infection in ≤90 days	27/825 (3.3)	31/826 (3.8)			
Unplanned reoperation: secondary outcome¶	126/784 (16.1)	114/785 (14.5)	1.16 (0.87 to 1.54)	NA	1.8 (−1.7 to 5.3)
For infection	70/784 (8.9)	70/785 (8.9)			
For wound-healing problem	49/784 (6.2)	42/785 (5.4)			
For delayed union or nonunion	61/784 (7.8)	50/785 (6.4)			

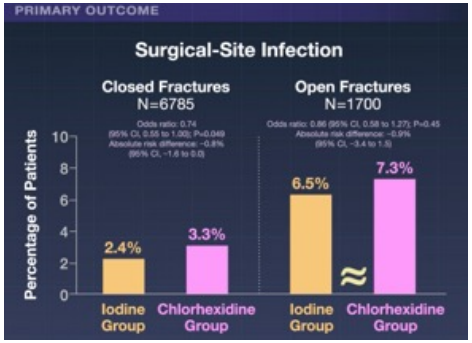


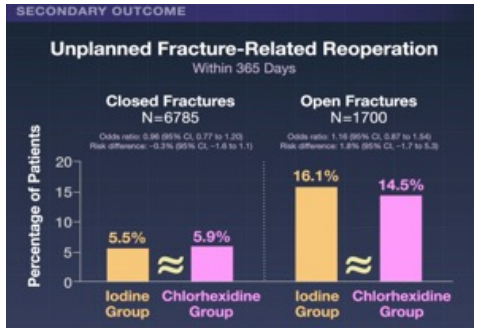
Subgroup Analyses of Surgical-Site Infection.

The presence of a severe soft-tissue injury or periarticular fracture did not substantially modify the effect of iodine povacrylex as compared with chlorhexidine gluconate in the closed-fracture population. Similarly, in the open-fracture population, there was no major differential treatment effect associated with the severity or location of the fracture or with the presence of wound contamination.





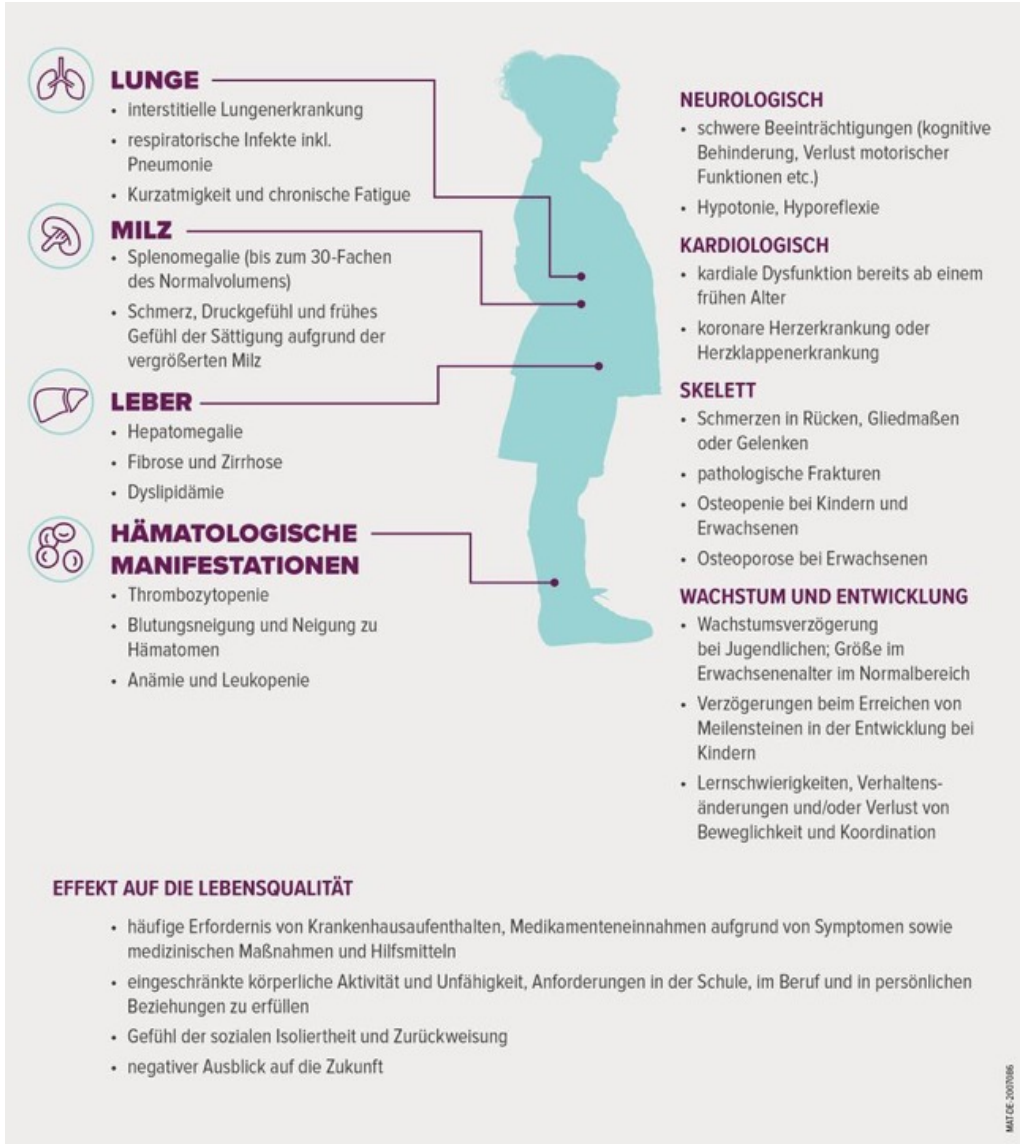


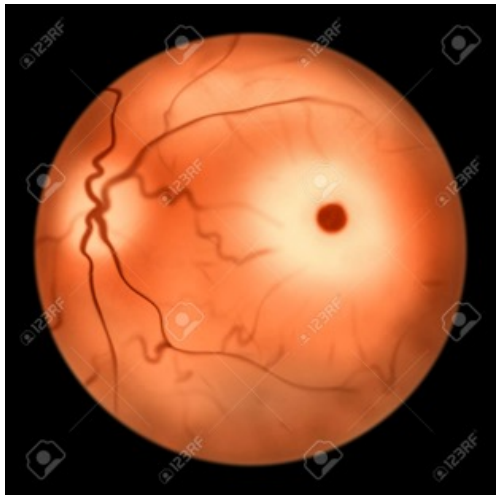


LIMITATIONS AND REMAINING QUESTIONS

- The baseline risk in the open-fracture population was lower than anticipated, which reduced the statistical power for the primary comparison.
- Surgeons and patients were aware of the assigned treatment, although a central adjudication committee reviewed all suspected outcomes in a blinded manner, thereby mitigating potential assessment bias.
- Overall treatment adherence, which exceeded 95% in both fracture populations, was better with chlorhexidine gluconate than with iodine povacrylex.

Beim Morbus Niemann-Pick handelt es sich um eine vererbte Sphingomyelinlipidose.
Morbus Niemann-Pick Typ A und B werden den Sphingolipidosen zugeordnet und gemeinsam auch als ASMD ("acid sphingomeyelinase deficiency“ ASMD) gelabelt. Morbus Niemann-Pick Typ C und D gehört zu den Lipidspeicherkrankheiten. Die klinischen Unterschiede sind jedoch nur sehr gering.
Morbus Niemann-Pick Typ A und B beruhen auf einem Defekt des SMPD1-Gens auf Chromosom 11, das für die saure Sphingomyelinase (ASM) kodiert. Der Gendefekt führt dazu, dass das Sphingomyelin nicht mehr abgebaut werden kann und sich in den Zellen von verschiedenen Organen (z.B. Milz und Leber) anreichert.
Eine Beeinträchtigung des Cholesterolstoffwechsels, bedingt durch einen Gendefekt auf dem Chromosom 18, ist Ursache des Morbus Niemann-Pick Typ C und D. Bei diesen Formen reichern sich Cholesterin und andere Produkte des Stoffwechsels in den Zellen an.
Hauptsymptome des Morbus Niemann-Pick Typ A sind eine Hepatosplenomegalie und ein psychomotorischer Abbau. Die Entwicklung der betroffenen Kinder stagniert. Fähigkeiten, die in den vergangenen Lebensjahren erlernt wurden, gehen im Laufe der Zeit verloren.
Häufig lassen sich noch vor Vollendigung des ersten Lebenshalbjahres eine Gedeihstörung, Erbrechen, eine Gehörminderung, eine Tetraspastik sowie myoklonische Anfälle beobachten. Beim Typ B werden keine zerebralen Symptome beobachtet.
Bei Typ C und D ist die Speicherung von Lipiden in den inneren Organen besonders ausgeprägt. Häufig zeigen schon Neugeborene einen Ikterus.
Im Laufe der Zeit treten neurologische Symptome mit Atrophie des Großhirns, des Kleinhirns, Tremor und Krampfanfällen hinzu. Die Entwicklung einer Aspirationspneumonie ist durch eine Schluckstörung möglich.
Bei jedem zweiten Kind zeigt sich bei der Spiegelung des Augenhintergrunds ein kirschroter Fleck.



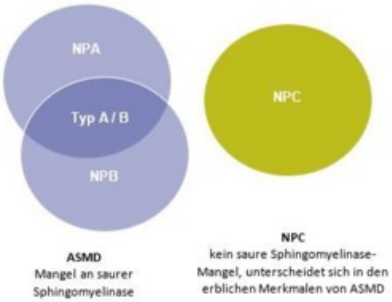


Die zugrundeliegenden Gendefekte sind zur Zeit (2022) nicht therapierbar. Für den Morbus Niemann-Pick Typ A und B ist eine Enzymersatztherapie mit Olipudase alfa verfügbar. Typ C wird symptomatisch mit Iminozucker Miglustat behandelt.

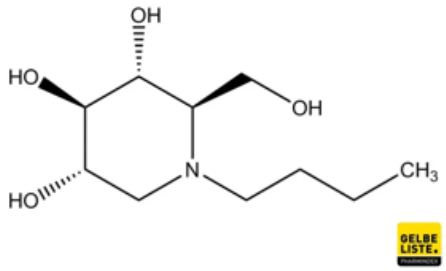
Ein Verlust von Myelin im Zentralnervensystem wird als einer der wichtigsten Faktoren in der Pathogenese der Niemann-Pick-Krankheit gesehen. Zur Erforschung der Krankheit werden Tiermodelle genutzt, die Mutationen tragen, welche der Niemann-Pick-Krankheit zugrunde liegen, beispielsweise eine Mutation im NPC1-Gen, wie sie in Niemann-Pick Typ C vorliegt. In diesem Modell konnte gezeigt werden, dass die Expression des Proteins Myelin Gene Regulatory Factor (MRF) signifikant abnimmt. MRF ist ein Transkriptionsfaktor von kritischer Bedeutung in der Bildung und Aufrechterhaltung von Myelinscheiden. Es ist daher wahrscheinlich, dass Fehler in der Differenzierung von Oligodendrozyten und in der Myelinisierung die neurologischen Defizite bedingen.

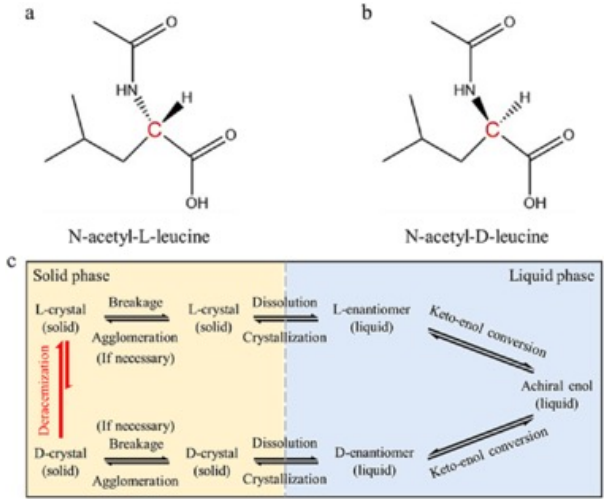
Umfassendes differentialdiagnostisches panel für Morbus Niemann-Pick, Typ C, Differentialdiagnose, mit insgesamt 29 kuratierten Genen je nach klinischer Verdachtsdiagnose. Typ C resultiert aus NPC1- oder NPC2 -Genvarianten, die für den intrazellulären Transport von Lipiden benötigt werden. Diese Mutationen führen zu einer Störung der Lysosomen, die Sphingomyelin und Cholesterin nicht richtig metabolisieren können, was zu einer fortschreitenden intrazellulären Lipidakkumulation und Organschäden führt. Klinische Manifestationen können Gedeihstörung, Hepatosplenomegalie, Thrombozytopenie, interstitielle Lungenerkrankung, kognitive und motorische Beeinträchtigung sowie ein kirschroter Fleck der Makula sein. Bei NPK-A werden eine fortschreitende Neurodegeneration und eine kurze Lebenserwartung beobachtet, während NPK-B sich typischerweise nicht neurologisch manifestiert. Die Diagnose einer NPK basiert auf einem klinischen Verdacht und kann durch die Messung der Sphingomyelinase-Aktivität oder Biomarker, Gentests oder Biopsie bestätigt werden. Derzeit gibt es keine Heilung für NPK, daher ist die Therapie supportiv und konzentriert sich auf die Symptomkontrolle.

Acid sphingomyelinase deficiency (ASMD)



Miglustat ist ein Arzneistoff der zur Behandlung zweier lysosomaler Speicherkrankheiten angewendet wird: Morbus Gaucher des Typs 1 und Niemann-Pick-Krankheit Typ C. Der Arzneistoff ist im Gegensatz zu den anderen Medikamenten, die zur Therapie des Morbus Gaucher verabreicht werden oral bioverfügbar.





N-Acetyl-L-leucine is an endogenous metabolite.

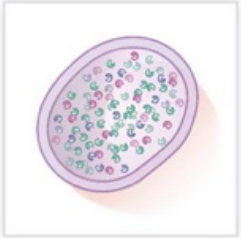
•Miglustat hemmt die Glukosylzeramidsynthase, die für den ersten Schritt in der Synthese der meisten Glykolipide verantwortlich ist.

•Treatment of NPC is currently limited to reducing the rate of disease progression with the substrate reduction therapy drug miglustat (Zavesca™), which is approved in the European Union and several other countries, but not in the USA .

One mechanism of action of N-acetyl-L-leucine is the activation of cerebral glucose metabolism in the cerebellum, correlated with enhanced cerebellar activity. In an animal model of NPC, N-acetyl-DL-leucine and its enantiomers significantly reduced ataxia in *Npc1*$^{-/-}$ mice, when treated symptomatically (from 8 to 9 weeks of age) and pre-symptomatically (from 3 weeks of age). These studies specifically identified the L-enantiomer as the neuroprotective isomer, observed to significantly delay the onset of functional decline (gait abnormalities, motor dysfunction), the decline in general health and condition, as well as slowing disease progression and prolonging survival (whereas the D-enantiomer did not).

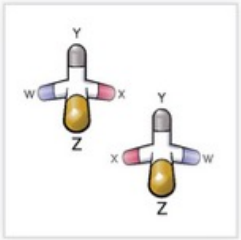
N-Acetyl-L-Leucine and Neurodegenerative Disease

Key Concepts



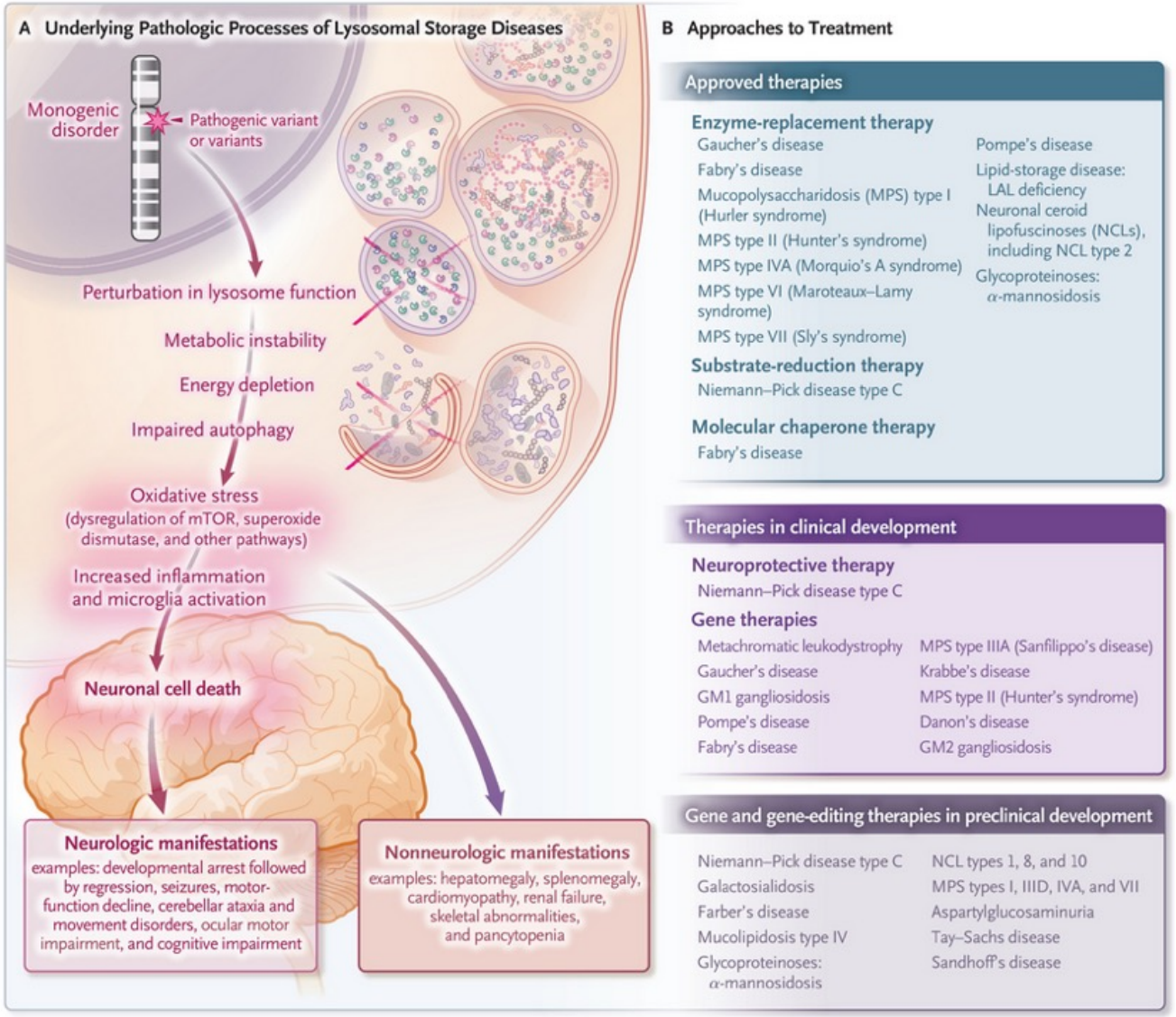
Lysosome

An acidic intracellular organelle, bound by a phospholipid bilayer membrane, that has key functions in cellular homeostasis, including the breakdown and recycling of macromolecules (carbohydrates, lipids, nucleic acids, and proteins), control of nutrient sensing, and calcium signaling. Lysosomes can fuse with endosomes, phagosomes, and autophagosomes and, by fusing with the plasma (cell) membrane, facilitate cell–cell communication.



Enantiomer

One of a pair of molecules, each of which is the mirror image of the other. They cannot, therefore, be superimposed on one another. A racemate is a mixture of the two enantiomers. Biologic molecules may naturally occur in one enantiomeric form that has different properties from its opposing enantiomer. Understanding the properties and effects of each enantiomer is therefore important in pharmacology.



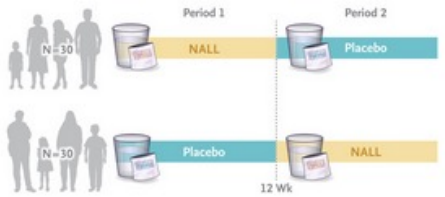
Approaches to Treatment of Lysosomal Storage Diseases.

Bremova-Ertl et al.[3] describe a new approach to the treatment of lysosomal storage diseases that uses a modified amino acid, N-acetyl-L-leucine, as an agent to improve the neurologic function and symptoms in patients with Niemann–Pick disease type C. The neuroprotective potential is currently being evaluated in the extension phase of the reported randomized clinical trial. Approved therapies for lysosomal storage disorders include enzyme-replacement therapy, substrate-reduction therapy, and molecular chaperone therapy. Another approach, gene therapy, is under clinical development for several disorders, and gene and gene-editing therapies are in preclinical development. LAL denotes lysosomal acid lipase, and mTOR mammalian target of rapamycin.

ORIGINAL ARTICLE

Trial of N-Acetyl-L-Leucine in Niemann–Pick Disease Type C

Niemann–Pick disease type C is a rare lysosomal storage disorder. We evaluated the safety and efficacy of *N*-acetyl-l-leucine (NALL), an agent that potentially ameliorates lysosomal and metabolic dysfunction, for the treatment of Niemann–Pick disease type C. In this double-blind, placebo-controlled, crossover trial, we randomly assigned patients 4 years of age or older with genetically confirmed Niemann–Pick disease type C in a 1:1 ratio to receive NALL for 12 weeks, followed by placebo for 12 weeks, or to receive placebo for 12 weeks, followed by NALL for 12 weeks. NALL or matching placebo was administered orally two to three times per day, with patients 4 to 12 years of age receiving weight-based doses (2 to 4 g per day) and those 13 years of age or older receiving a dose of 4 g per day. The primary end point was the total score on the Scale for the Assessment and Rating of Ataxia (SARA; range, 0 to 40, with lower scores indicating better neurologic status). Secondary end points included scores on the Clinical Global Impression of Improvement, the Spinocerebellar Ataxia Functional Index, and the Modified Disability Rating Scale. Crossover data from the two 12-week periods in each group were included in the comparisons of NALL with placebo.



CONCLUSIONS

Among patients with Niemann–Pick disease type C, treatment with NALL for 12 weeks led to better neurologic status than placebo.

Niemann–Pick disease type C is a rare, progressive, debilitating, and prematurely fatal autosomal recessive lysosomal storage disorder, with an incidence of one case per 100,000 persons. The disease manifests with systemic, psychiatric, and neurologic symptoms, and many aspects of neurologic function are impaired. Treatment of Niemann–Pick disease type C is currently limited to slowing the progression of neurologic symptoms with miglustat, a drug used in substrate reduction therapy for glycosphingolipid lysosomal storage disorders. Miglustat has been approved in the European Union and several other countries but not in the United States.

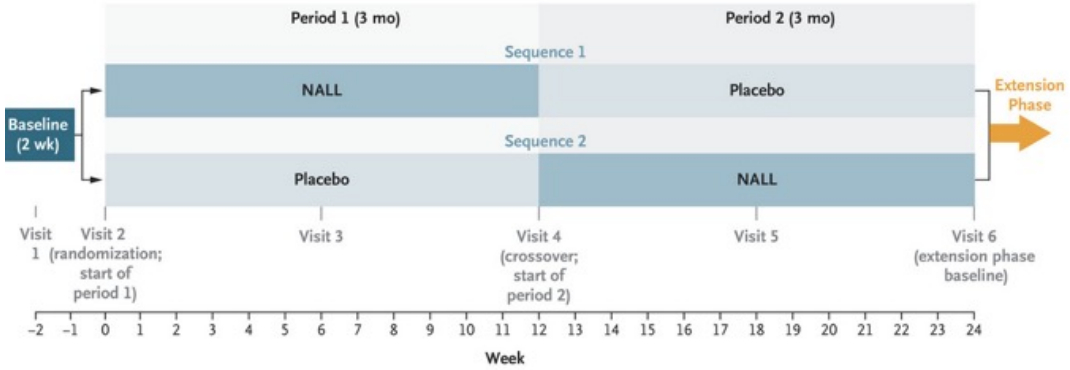
N-acetyl-l-leucine (NALL) is the l-enantiomer of *N*-acetyl-dl-leucine. The agent is administered orally and is taken up by monocarboxylate transporters, which are expressed ubiquitously and thus deliver NALL to all body tissues, including across the blood–brain barrier. The agent enters enzyme-controlled pathways that correct metabolic dysfunction and improves adenosine triphosphate (ATP) energy production. Such correction and improvement have multiple subsequent effects: mitochondrial and lysosomal functions are intrinsically linked, and the normalization of energy metabolism ameliorates lysosomal dysfunction and leads to a reduction in the storage of unesterified cholesterol and sphingolipids. At a cellular level, the depletion of ATP causes neuronal depolarization, leading to the failure of membrane-based ion-transport systems and defective membrane excitability that affects neuronal communication. Treatment with NALL was shown to normalize neuronal membrane potentials in a guinea pig model, thereby ostensibly improving cellular signaling processes and restoring and protecting neuronal circuits. In various animal models, treatment with NALL has led to dampening of neuroinflammation, which indicates a potential neuroprotective effect.

Patients

Patients 4 years of age or older who had received a diagnosis of Niemann–Pick disease type C were eligible for inclusion if they had presented with clinical symptoms and signs referable to Niemann–Pick disease type C, had provided written informed consent (or consent had been provided by a legal representative), and had undertaken a washout of any prohibited medications (i.e., *N*-acetyl-dl-leucine, *N*-acetyl-l-leucine, sulfasalazine, or rosuvastatin) for 42 days before screening. The total score on the Scale for the Assessment and Rating of Ataxia (SARA) had to be between 7 and 34, which represents a range of mild to severe symptoms (scores range from 0 to 40, with lower scores indicating better neurologic status).

Procedures

The trial consisted of a 2-week baseline period followed by two consecutive 12-week treatment periods; the baseline and treatment periods included a 7-day window for the last visit after the intended 2 or 12 weeks, respectively. Two visits (occurring 14 to 21 days apart) were conducted in the baseline period. Safety and efficacy assessments were performed at both visits. At the second baseline visit (visit 2), eligible patients were randomly assigned in a 1:1 ratio to receive NALL in period 1 for 84 to 91 days and then matching placebo in period 2 for 84 to 91 days (sequence 1) or to receive placebo in period 1 for 84 to 91 days and then NALL in period 2 for 84 to 91 days (sequence 2). NALL or placebo was immediately switched at the end of period 1 (visit 4).



Endpoint

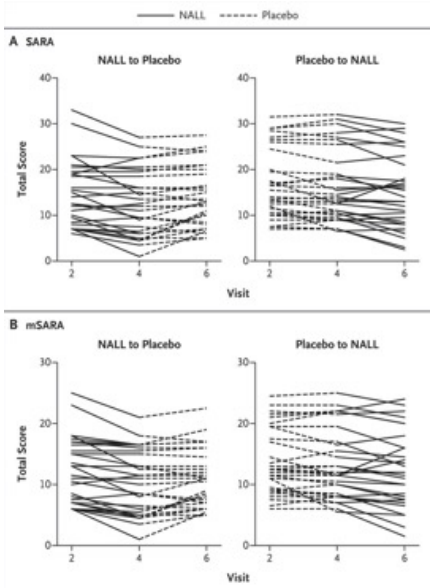
The endpoint was the total score on the SARA, an eight-item clinical rating scale that incorporates assessments of gait, stance, sitting, and speech disturbance, as well as the finger-chase test, the nose-to-finger test, the fast-alternating-hand-movements test, and the heel-along-shin slide test.

5-domain NPCCSS

Domain	Scoring	Minimum–Maximum Score
Ambulation	0 = Normal	0–5
	1 = Clumsy	
	2 = Ataxic unassisted gait or not walking by 18 months	
	4 = Assisted ambulation or not walking by 24 months	
	5 = Wheelchair dependent	
Fine Motor Skills	0 = Normal	0–5
	1 = Slight dysmetria/dystonia (independent manipulation)	
	2 = Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	
	4 = Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self)	
	5 = Severe dysmetria/Dystonia (gross motor limitation, requires assistance for selfcare activities)	
Swallow	0 = Normal, no dysphagia	0–5
	1 = Cough while eating	
	Intermittent dysphagia*	
	+ 1 = w/Liquids	
	+ 1 = w/Solids	
	Dysphagia*	
	+ 2 = w/Liquids	
	+ 2 = w/Solids	
	4 = Nasogastric tube or gastric tube for supplemental feeding	
	5 = Nasogastric tube or gastric tube feeding only	
	5 = Nasogastric tube or gastric tube feeding only	
Cognition	0 = Normal	0–5
	1 = Mild learning delay, grade appropriate for age	
	3 = Moderate learning delay, individualized curriculum or modified work setting	
	4 = Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function^	
	5 = Minimal cognitive function	
Speech	0 = Normal	0–5
	1 = Mild dysarthria (easily Understood	
	2 = Severe dysarthria (difficult to understand)	
	3 = Non-verbal/functional communication skills for needs	
	5 = Minimal communication	
5-domain NPCCSS score	Sum of all scores from the 5 domains above	0–25 (higher score = more severe clinical impairment)

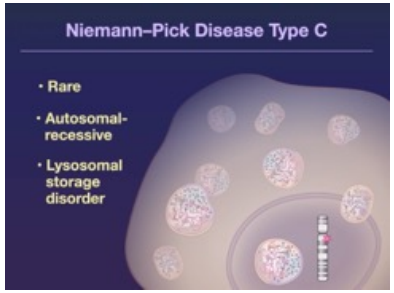
Characteristic	Patients (N = 60)
Age group — no. (%)	
Pediatric, <18 yr	23 (38)
Adult, ≥18 yr	37 (62)
Sex — no. (%)	
Female	27 (45)
Male	33 (55)
Race or ethnic group — no. (%)†	
American Indian or Alaska native	0
Asian	0
Black or African American	2 (3)
Native Hawaiian or other Pacific Islander	0
White	54 (90)
Other	4 (7)
Age at diagnosis — no. (%)	
<2 yr	9 (15)
2 to <6 yr	14 (23)
6 to <15 yr	23 (38)
≥15 yr	14 (23)
Duration of disease — mo‡	
Mean	171.32±116.70
Median	153.43
Minimum–maximum range	19.1 to 514.3
Dose group — no. (%)	
Age 4 to 12 yr	
15 to <25 kg of body weight: 2 g per day	6 (10)
25 to <35 kg of body weight: 3 g per day	3 (5)
25 to ≥35 kg of body weight: 4 g per day	3 (5)
Age ≥13 yr: 4 g per day	48 (80)
Miglustat use — no. (%)§	51 (85)
Assessment tool score¶	
SARA‖	
Before first dose of NALL	15.88±7.50
Before first dose of placebo	15.68±7.39
mSARA‖	
Before first dose of NALL	13.20±5.50
Before first dose of placebo	13.03±5.39
SCAFI**	
Before first dose of NALL	−0.29±1.03
Before first dose of placebo	−0.26±1.01
mDRS††	
Before first dose of NALL	0.480±0.149
Before first dose of placebo	0.477±0.149
NPC-CSS‡‡	
Before first dose of NALL	18.1±7.1
Before first dose of placebo	17.9±7.0

End Point	NALL			Placebo			Difference in Change (95% CI)†
	No. of Patients Assessed at End of Treatment Period	Score at End of Treatment Period	Change from Baseline	No. of Patients Assessed at End of Treatment Period	Score at End of Treatment Period	Change from Baseline	
Primary end point‡							
SARA	59	13.71±7.68	−1.97±2.43	58	15.2±7.27	−0.60±2.39	−1.28 (−1.91 to −0.65)§
mSARA	59	11.37±5.81	−1.66±1.97	58	12.47±5.34	−0.67±1.74	−0.96 (−1.45 to −0.46)
Secondary end points							
CGI-I¶‖							
Investigator-rated	30	3.3±0.9	−0.7	30	3.9±0.9	−0.1	−0.6 (−1.1 to −0.1)
Caregiver-rated	27	3.6±0.9	−0.4	25	4.3±0.9	0.3	−0.7 (−1.2 to 0.2)
Patient-rated	24	3.3±1.0	−0.7	26	3.8±1.1	−0.2	−0.5 (−1.1 to 0.1)
SCAFI	57	−0.17±0.98	0.05±0.27	56	−0.27±0.99	−0.02±0.31	0.07 (−0.0 to 0.15)
mDRS	59	0.447±0.157	−0.030±0.060	58	0.478±0.136	−0.001±0.061	−0.029 (−0.048 to −0.010)
Exploratory end point							
NPC-CSS¶	58	17.6±6.8	−0.3±2.2	58	18.2±6.9	0.1±2.1	−0.5 (−1.2 to 0.2)

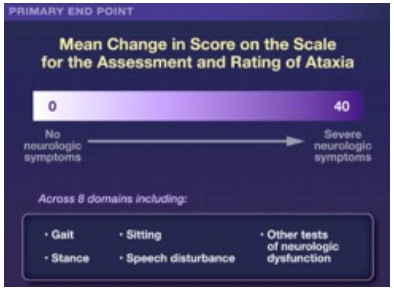


SARA and mSARA Total Scores at Visits 2, 4, and 6.

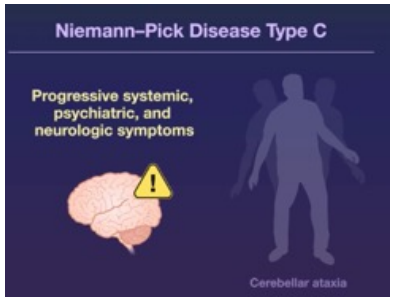
Shown are the total scores on the Scale for the Assessment and Rating of Ataxia (SARA; Panel A) and the modified SARA (mSARA; Panel B) for the individual patients at visits 2, 4, and 6 according to active treatment–placebo treatment. Total scores on the SARA range from 0 to 40, and total scores on the mSARA range from 0 to 30; on both scales, lower scores indicate better neurologic status.

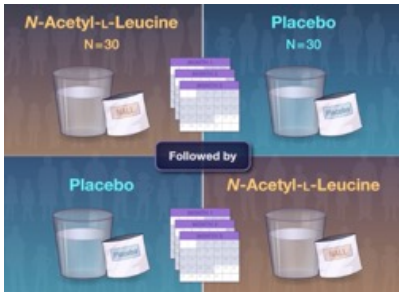

Niemann–Pick Disease Type C
• Rare
• Autosomal-recessive
• Lysosomal storage disorder

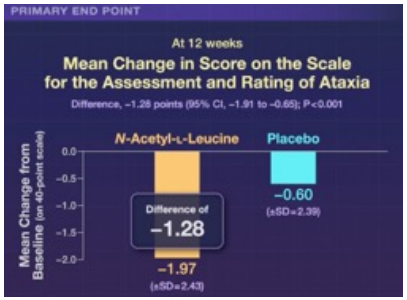

OH
NH
O
? Treatment
Niemann–Pick Disease Type C

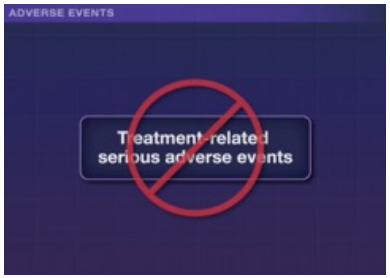

PRIMARY END POINT
Mean Change in Score on the Scale for the Assessment and Rating of Ataxia
0
40
No neurologic symptoms
Severe neurologic symptoms
Across 8 domains including:
• Gait
• Stance
• Sitting
• Speech disturbance
• Other tests of neurologic dysfunction

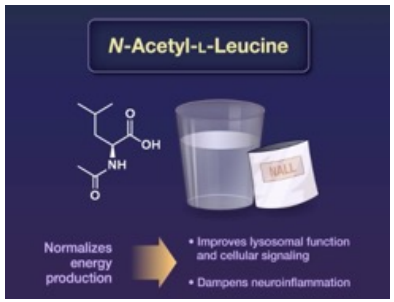

ADVERSE EVENTS
Treatment-Related Adverse Events
Anal incontinence
Restless legs
Rosacea


Niemann–Pick Disease Type C
Progressive systemic, psychiatric, and neurologic symptoms
Cerebellar ataxia

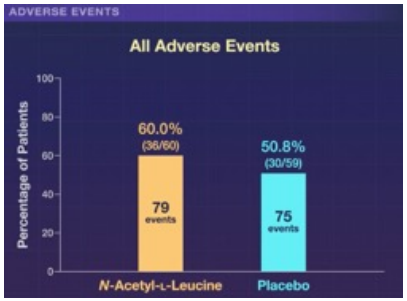

N-Acetyl-L-Leucine
N=30
Placebo
N=30
Followed by
Placebo
N-Acetyl-L-Leucine

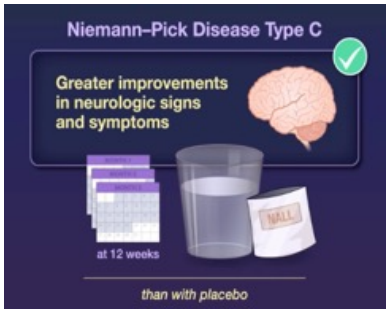

PRIMARY END POINT
At 12 weeks
Mean Change in Score on the Scale for the Assessment and Rating of Ataxia
Difference, −1.28 points (95% CI, −1.91 to −0.65); P<0.001
N-Acetyl-L-Leucine
Placebo
Mean Change from Baseline (on 40-point scale)
0.0
−0.5
−1.0
−1.5
−2.0
Difference of −1.28
−0.60
(±SD=2.39)
−1.97
(±SD=2.43)


ADVERSE EVENTS
Treatment-related serious adverse events

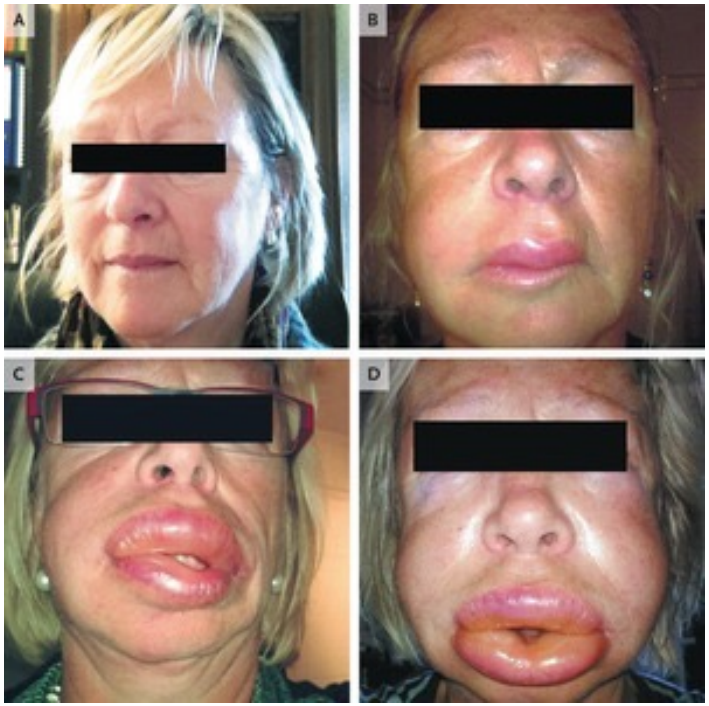

N-Acetyl-L-Leucine
OH
NH
O
Normalizes energy production
• Improves lysosomal function and cellular signaling
• Dampens neuroinflammation

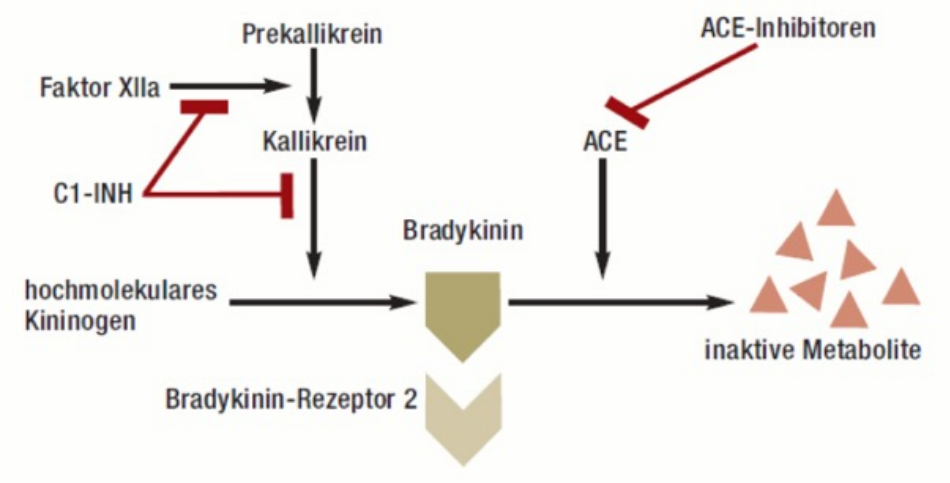

Treatment dose varied by age and weight
2–4 g per day
4 g per day
≥4–12 years of age
≥13 years of age


ADVERSE EVENTS
All Adverse Events
Percentage of Patients
100
80
60
40
20
0
60.0%
(36/60)
79
events
50.8%
(30/59)
75
events
N-Acetyl-L-Leucine
Placebo


Niemann–Pick Disease Type C
Greater improvements in neurologic signs and symptoms
at 12 weeks
than with placebo

Das hereditäre Angioödem (HAE) ist eine genetisch bedingte Erkrankung, die durch attackenhaft auftretende Schwellungen gekennzeichnet ist. Diese Schwellungen können zu einer lebensbedrohlichen Verlegung der Luftwege führen.





The symptoms of hereditary angioedema type I develop due to a deficiency of a protein known as complement component C1 esterase inhibitor. Hereditary angioedema type II is a more uncommon form of the disorder and may occur because of abnormal C1 esterase proteins that do not function properly.

When the target DNA is found, Cas9 – one of the enzymes produced by the CRISPR system – binds to the DNA and cuts it, shutting the targeted gene off. Using modified versions of Cas9, researchers can activate gene expression instead of cutting the DNA.

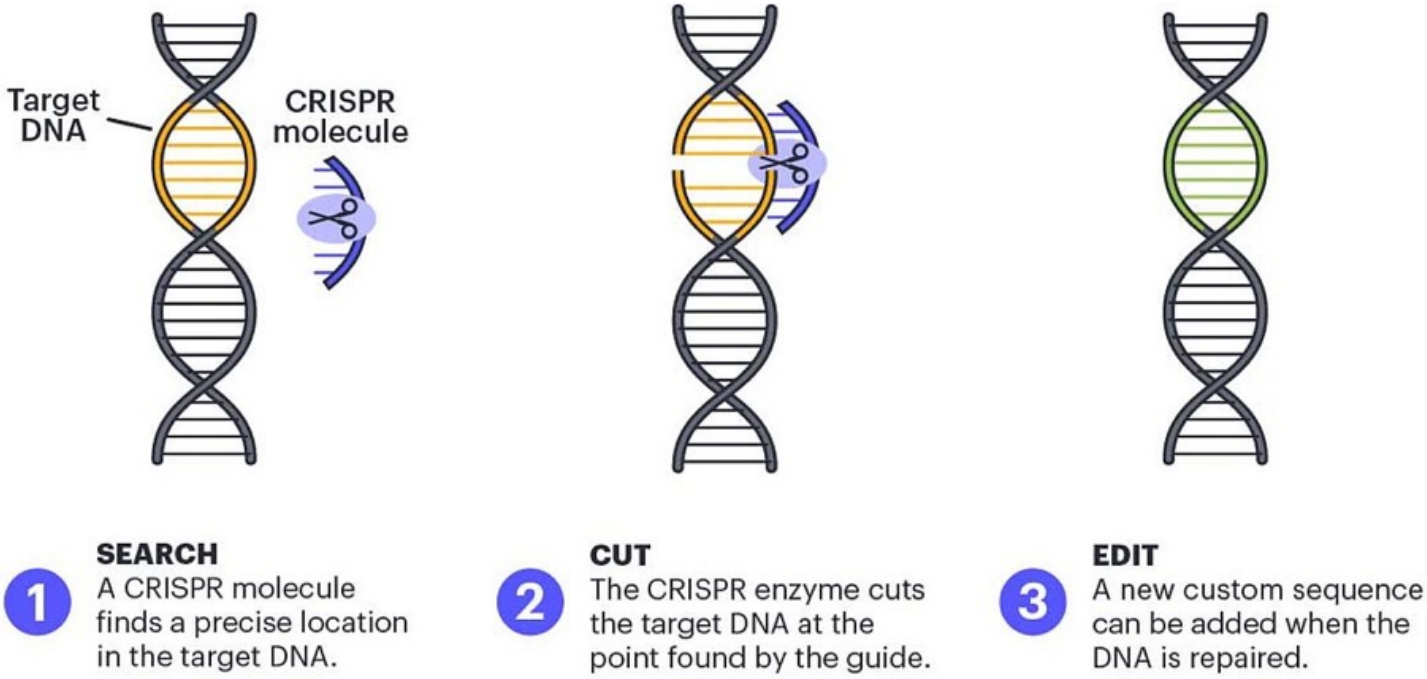
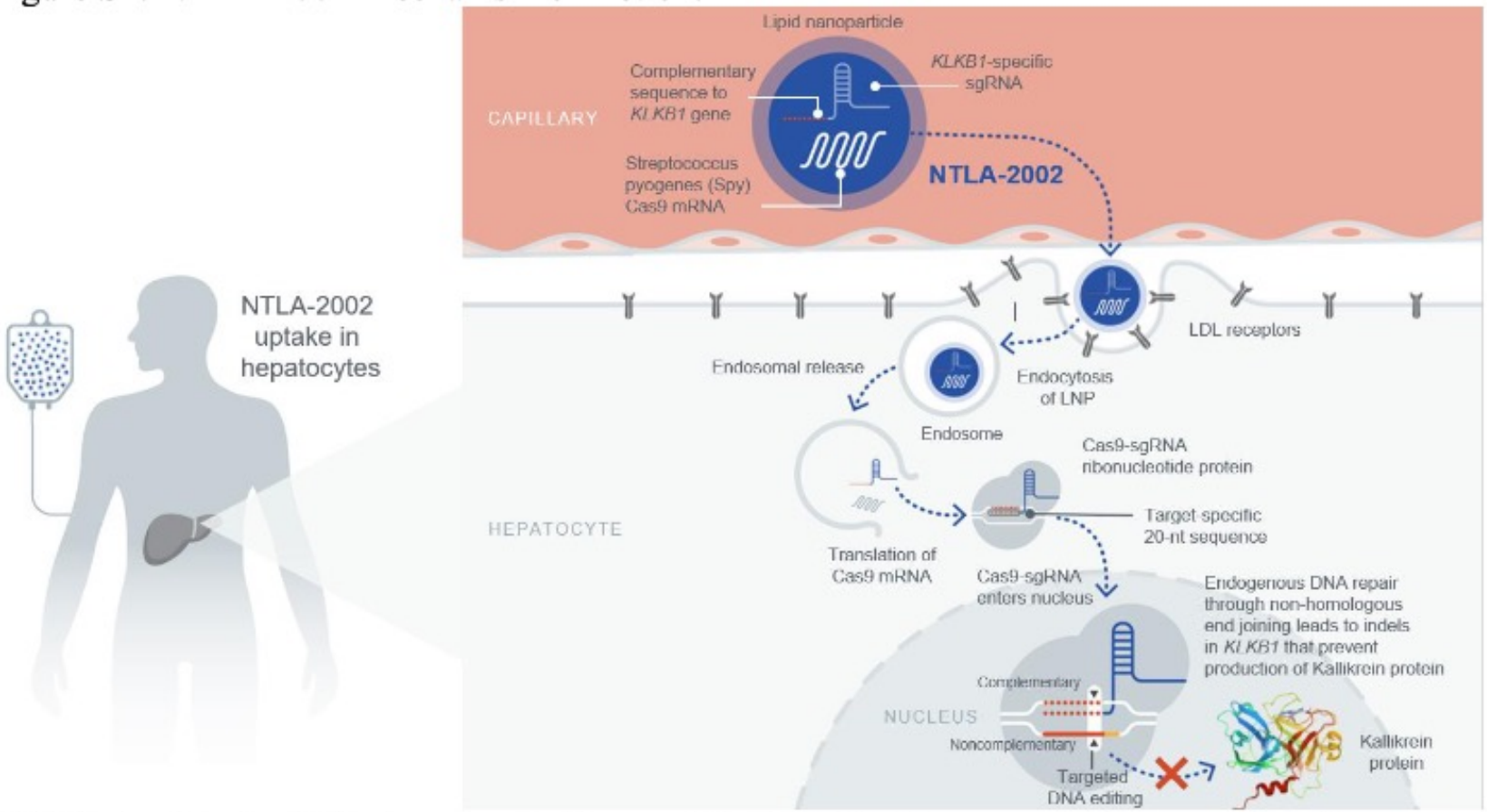


Figure S1. NTLA-2002 Mechanism of Action.



KLKB1, kallikrein; LDL, low density lipoprotein; LNP, lipid nanoparticle; nt, nucleotide.
Schematic depicting the mechanism of action for NTLA-2002, a CRISPR/Cas9-based *in vivo* gene editing therapy targeting *KLKB1* in the liver.

ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing of *KLKB1* for Hereditary Angioedema

Hereditary angioedema is a rare genetic disease that leads to severe and unpredictable swelling attacks. NTLA-2002 is an in vivo gene-editing therapy based on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9. NTLA-2002 targets the gene encoding kallikrein B1 (*KLKB1*), with the goal of lifelong control of angioedema attacks after a single dose. In this phase 1 dose-escalation portion of a combined phase 1–2 trial of NTLA-2002 in adults with hereditary angioedema, we administered NTLA-2002 at a single dose of 25 mg, 50 mg, or 75 mg. The primary end points were the safety and side-effect profile of NTLA-2002 therapy. Secondary and exploratory end points included pharmacokinetics, pharmacodynamics, and clinical efficacy determined on the basis of investigator-confirmed angioedema attacks.

Conclusions

In this small study, a single dose of NTLA-2002 led to robust, dose-dependent, and durable reductions in total plasma kallikrein levels, and no severe adverse events were observed. In exploratory analyses, reductions in the number of angioedema attacks per month were observed at all dose levels.

Methods

Study Design and Oversight

The phase 1 portion of this phase 1–2 trial is an ongoing multicenter, open-label, dose-escalation study with up to 30 patients that is assessing the safety, side-effect profile, pharmacodynamics, pharmacokinetics, and preliminary efficacy of NTLA-2002 therapy in patients with hereditary angioedema.

Patients

Eligible patients were 18 years of age or older, had received a diagnosis of type 1 or type 2 hereditary angioedema, and had had at least three investigator-confirmed attacks during the 90 days before screening (the historical attack period). Patients were excluded if they had a concurrent diagnosis of any other type of recurrent angioedema or if they were known to have had an adverse reaction or hypersensitivity to any LNP component. Full eligibility criteria are listed in the protocol.

Treatment

NTLA-2002 was administered as a single intravenous infusion over a minimum of 2 hours.

Clinical Assessments

Each patient recorded angioedema symptoms, attacks, and treatments in an electronic diary. The investigator reviewed the diary at each study visit to confirm whether an event represented an attack due to angioedema.

Study End Points

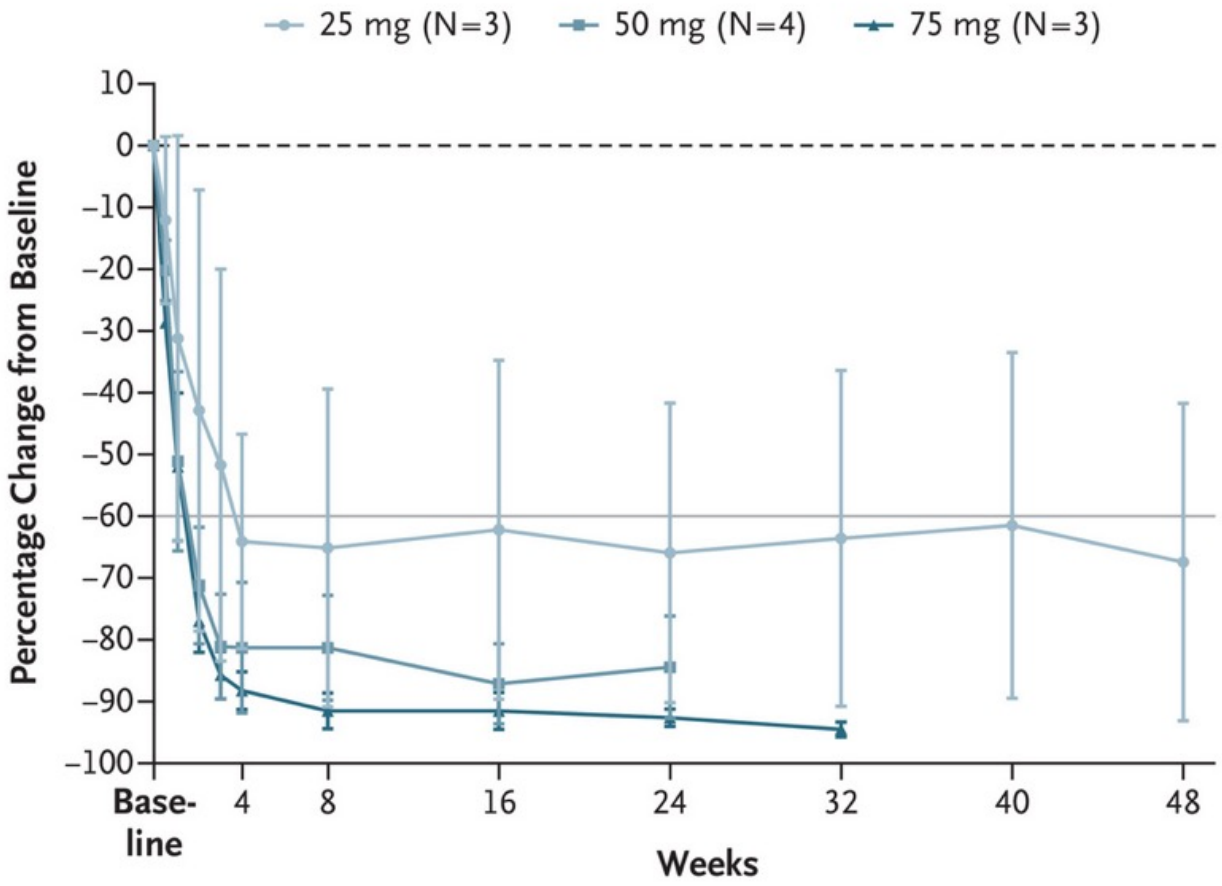
The primary end points of the phase 1 study were the safety and side-effect profile of NTLA-2002 as assessed on the basis of adverse events and the incidence of dose-limiting toxic effects. The secondary end points included the change from baseline in the total plasma kallikrein protein level and the change from baseline in the plasma concentrations of the components of NTLA-2002.

Characteristic	NTLA-2002, 25 mg (N=3)	NTLA-2002, 50 mg (N=4)	NTLA-2002, 75 mg (N=3)	All Patients (N=10)
Median age (range) — yr	30 (26–52)	65 (52–73)	45 (27–49)	51 (26–73)
Male sex — no. (%)	3 (100)	1 (25)	2 (67)	6 (60)
White race — no. (%)†	3 (100)	4 (100)	3 (100)	10 (100)
Median weight (range) — kg	83 (78–135)	86 (74–107)	72 (64–84)	83 (64–135)
Type of hereditary angioedema — no. (%)				
Type I	2 (67)	2 (50)	2 (67)	6 (60)
Type II	1 (33)	2 (50)	1 (33)	4 (40)
Previous receipt of long-term prophylaxis — no. (%)	2 (67)	4 (100)	3 (100)	9 (90)
Concomitant receipt of long-term prophylaxis — no. (%)‡	2 (67)	3 (75)	1 (33)	6 (60)
Typical severity of angioedema attacks — no. (%)				
Mild	1 (33)	2 (50)	1 (33)	4 (40)
Moderate	1 (33)	2 (50)	1 (33)	4 (40)
Severe	1 (33)	0	1 (33)	2 (20)
Previous occurrence of laryngeal attacks — no. (%)	1 (33)	4 (100)	3 (100)	8 (80)
Median no. of angioedema attacks during the historical attack period (range)§	7 (6–45)	3 (3–6)	14 (6–54)	6 (3–54)
Type of angioedema attack during the historical attack period — no. (%)§				
Peripheral	3 (100)	1 (25)	1 (33)	5 (50)
Abdominal	2 (67)	1 (25)	3 (100)	6 (60)
Laryngeal	1 (33)	0	2 (67)	3 (30)

Adverse Events after the Administration of NTLA-2002.

Event	NTLA-2002, 25 mg (N=3)	NTLA-2002, 50 mg (N=4)	NTLA-2002, 75 mg (N=3)	All Patients (N=10)
		number of patients (percent)		
Any event	3 (100)	3 (75)	3 (100)	9 (90)
Infusion-related reaction	2 (67)	2 (50)	3 (100)	7 (70)
Fatigue	1 (33)	3 (75)	2 (67)	6 (60)
Coronavirus disease 2019	3 (100)	1 (25)	1 (33)	5 (50)
Upper respiratory tract infection	1 (33)	1 (25)	2 (67)	4 (40)
Oropharyngeal pain	2 (67)	0	1 (33)	3 (30)
Abdominal pain	1 (33)	0	1 (33)	2 (20)
Headache	0	0	2 (67)	2 (20)
Viral upper respiratory tract infection	0	0	2 (67)	2 (20)

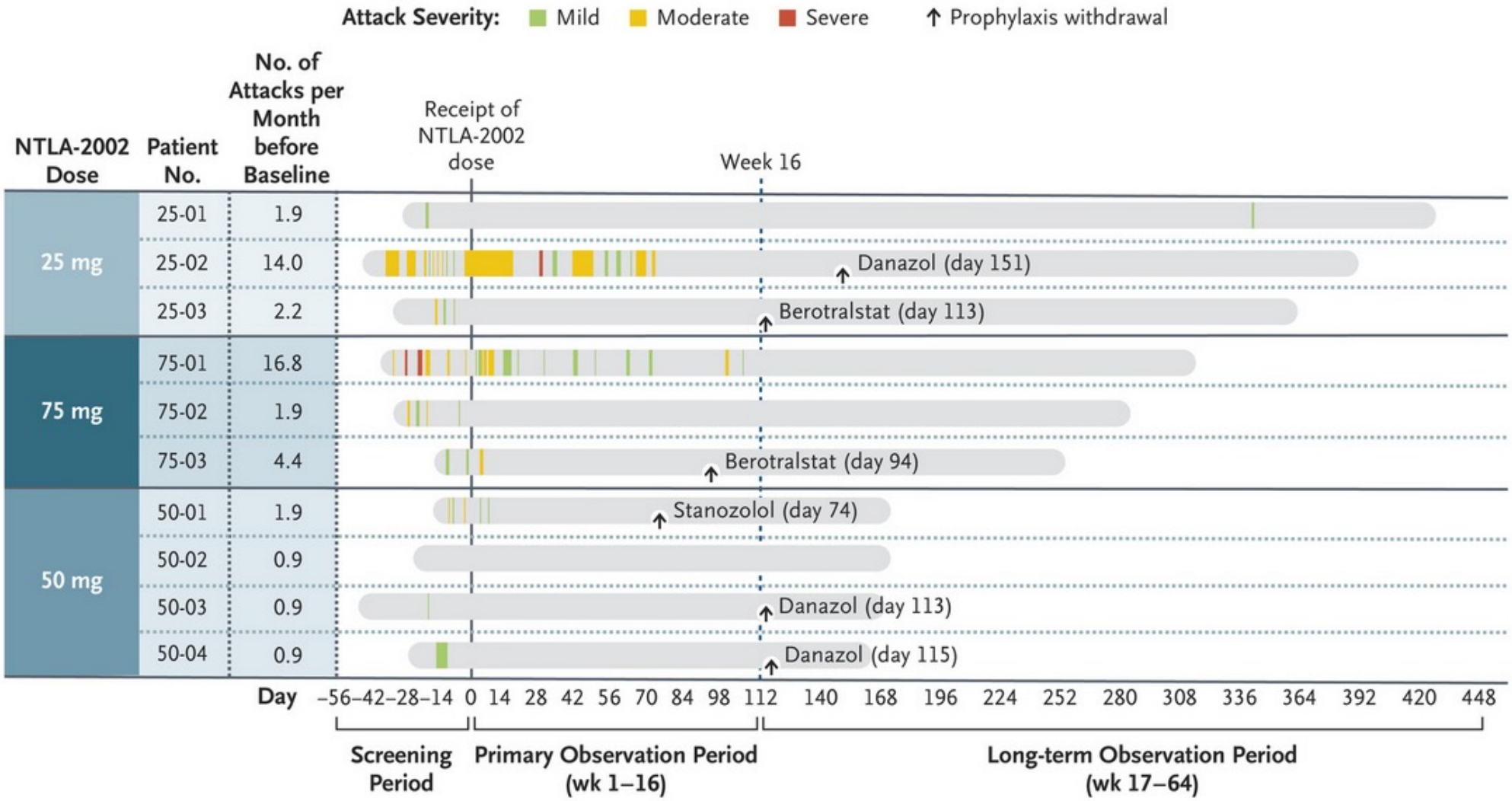
Change from Baseline in the Total Plasma Kallikrein Protein Level According to NTLA-2002 Dose.



Change from Baseline in the Number of Investigator-Confirmed Angioedema Attacks per Month.

Variable	NTLA-2002, 25 mg (N=3)	NTLA-2002, 50 mg (N=4)	NTLA-2002, 75 mg (N=3)	All Patients (N=10)
No. of patients with attacks during the screening period (%)	3 (100)	3 (75)	3 (100)	9 (90)
Percentage change from baseline in no. of attacks per mo†				
To wk 1–16	−91±16	−97±5	−80±30	−89±19
To wk 5–16	−89±19	−100±0	−87±23	−92±16
To wk 1–24	−94±11	−98±3	−86±20	−93±13
Through the latest assessment	−95±4	−98±3	−93±11	−95±6

Angioedema Attacks before and after the Infusion of NTLA-2002.



Discussion

In 10 patients with hereditary angioedema, a single dose of NTLA-2002 resulted in no apparent safety concerns. The safety profile of NTLA-2002 was substantially similar to that of NTLA-2001, which is not surprising because the two drug products differ only with respect to the 20-nucleotide targeting sequence at the 5′ end of the sgRNA. We therefore propose that the short-term safety events associated with the use of each product are caused by the LNP or the expression of Cas9 protein, rather than by the editing activity of the treatment.

Together with previously reported results from an ongoing phase 1 study of NTLA-2001 in patients with transthyretin amyloidosis, these results from our study of NTLA-2002 in patients with hereditary angioedema support the modularity of CRISPR-Cas9–based in vivo gene editing as a therapeutic platform with the potential for broad application in the treatment of genetic diseases. None of the patients who received NTLA-2002 had serious adverse events, and treatment with the drug elicited a dose-dependent reduction in the total plasma kallikrein level. After the receipt of NTLA-2002 therapy, patients had a decreased number of angioedema attacks per month. These results support the continued investigation of NTLA-2002 as a new therapy for the treatment of hereditary angioedema.

Figure 2 Comparison of the size of traditional and next generation pacemakers in relation to a capsule

Figure 3 Size of the leadless pacemaker

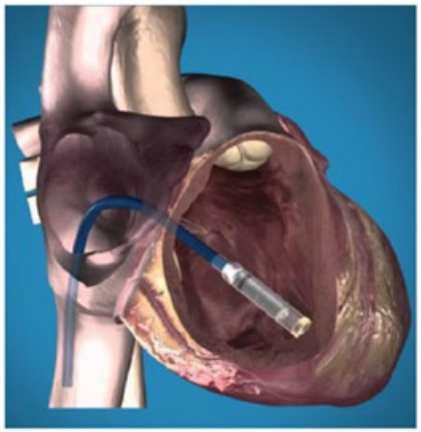


Figure 4 Placement of the leadless pacemaker in the right ventricle using a long delivery sheath from the patient's femoral vein

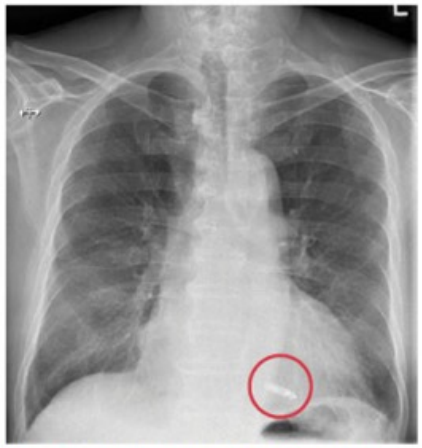


Figure 5 Leadless pacemaker on Chest X-ray (CXR), near the cardiac apex

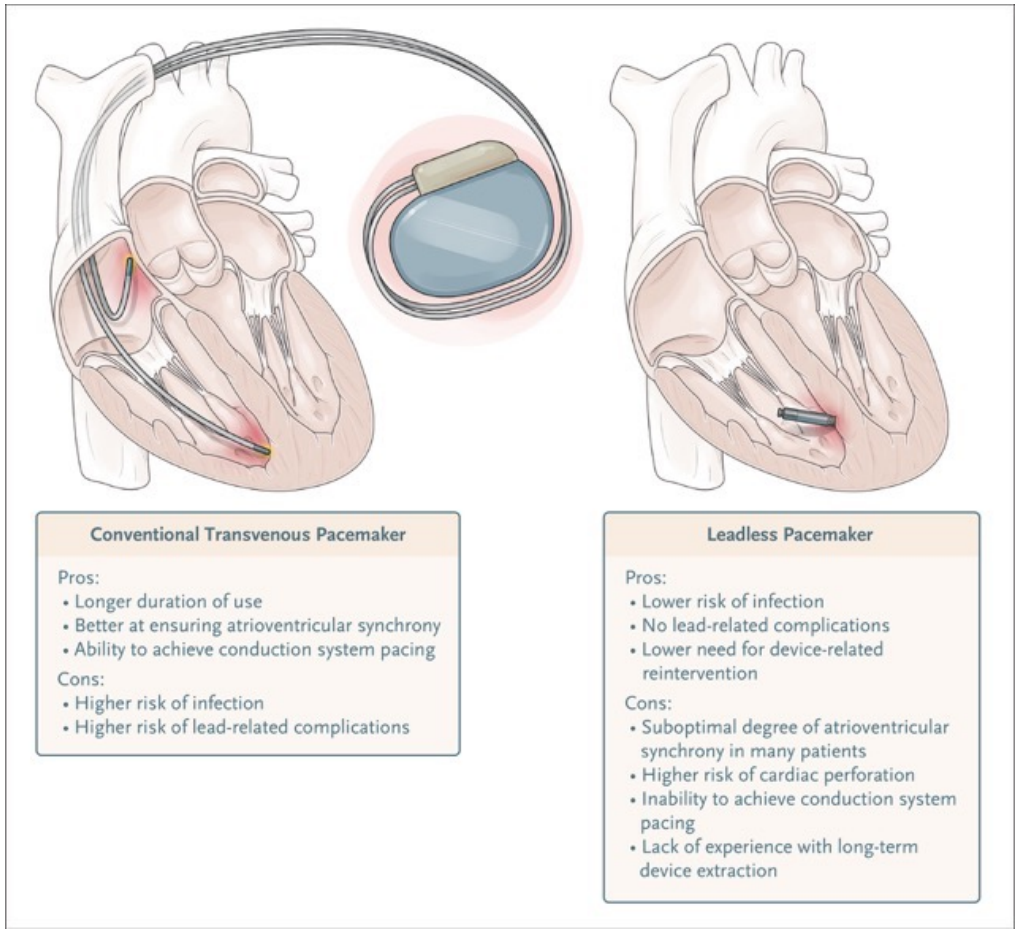
REVIEW ARTICLE

Cardiac Implantable Electronic Devices

Cardiac implantable electronic devices (CIEDs) constitute a major breakthrough in the management of heart rhythm disorders. These devices largely include bradycardia pacemakers, biventricular pacemakers, and implantable cardioverter–defibrillators (ICDs). In the United States, more than 400,000 CIEDs are implanted every year. The increasing number of patients with a CIED has made it necessary for all clinicians to have a basic understanding of what these devices do, the evidence supporting their use, their possible contribution to the overall clinical presentation, and the consideration of how they should be managed when surgery, a nonsurgical procedure, magnetic resonance imaging (MRI), or radiation therapy is planned.

RCT and Year	Sample Size	Follow-up	Patient Population	Primary End Point	Main Findings
	no. of patients	*yr*			
Atrial vs. ventricular pacing,[4] 1994	225	5	Sick sinus syndrome	Atrial fibrillation, thromboembolism, death	Atrial pacing resulted in significantly lower rates of atrial fibrillation and thromboembolic events but not death
Longer follow-up of atrial vs. ventricular pacing,[5] 1997	225	8	Sick sinus syndrome	Atrial fibrillation, thromboembolism, death, heart failure	Atrial pacing resulted in significantly less atrial fibrillation, fewer thromboembolic events, and lower rates of death and heart failure
Pacemaker Selection in the Elderly (PSE),[6] 1998	407	2.5	Age ≥65 yr, sinus rhythm, bradycardia pacing indication	Health-related quality of life per 36-item Medical Outcomes Study Short-Form General Health Survey	Patients with sinus-node dysfunction, but not those with atrioventricular block, had moderately better quality of life and cardiovascular functional status with dual-chamber pacing than with ventricular pacing
Mode Selection Trial in Sinus-Node Dysfunction (MOST),[7] 2002	2010	2.7	Sick sinus syndrome	Death from any cause or nonfatal stroke	Dual-chamber pacing did not improve stroke-free survival, as compared with ventricular pacing but reduced the risk of atrial fibrillation and signs and symptoms of heart failure and slightly improved quality of life
Canadian Trial of Physiological Pacing (CTOPP),[8] 2000	2568	3	Symptomatic bradycardia with no chronic atrial fibrillation	Stroke or death due to cardiovascular causes	The rate of stroke or cardiovascular death was similar with ventricular and physiologic pacing*
CTOPP,[9] 2004	2568	6	Symptomatic bradycardia with no chronic atrial fibrillation	Stroke or death due to cardiovascular causes	The rate of stroke or cardiovascular death was similar with ventricular and physiologic pacing, but the rate of atrial fibrillation was significantly lower with physiologic pacing*
United Kingdom Pacing and Cardiovascular Events (UKPACE),[10] 2005	2021	4.6	Age ≥70 yr; first pacemaker implantation for high-grade atrioventricular block	All-cause mortality	The effect on mortality was similar with single-chamber ventricular pacing and dual-chamber pacing; there were no significant between-group differences in secondary end points of atrial fibrillation, heart failure, stroke, or other thromboembolic events
Comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome (DANPACE),[11] 2011	1415	5.4	Sick sinus syndrome	Death from any cause	There was no significant difference in death from any cause between single-chamber atrial pacing and dual-chamber pacing; atrial pacing was associated with a higher risk of paroxysmal atrial fibrillation and 2 times the risk of pacemaker reoperation

Pros and Cons of Various Pacemaker Types.



Conventional Transvenous Pacemaker

Pros:
- Longer duration of use
- Better at ensuring atrioventricular synchrony
- Ability to achieve conduction system pacing

Cons:
- Higher risk of infection
- Higher risk of lead-related complications

Leadless Pacemaker

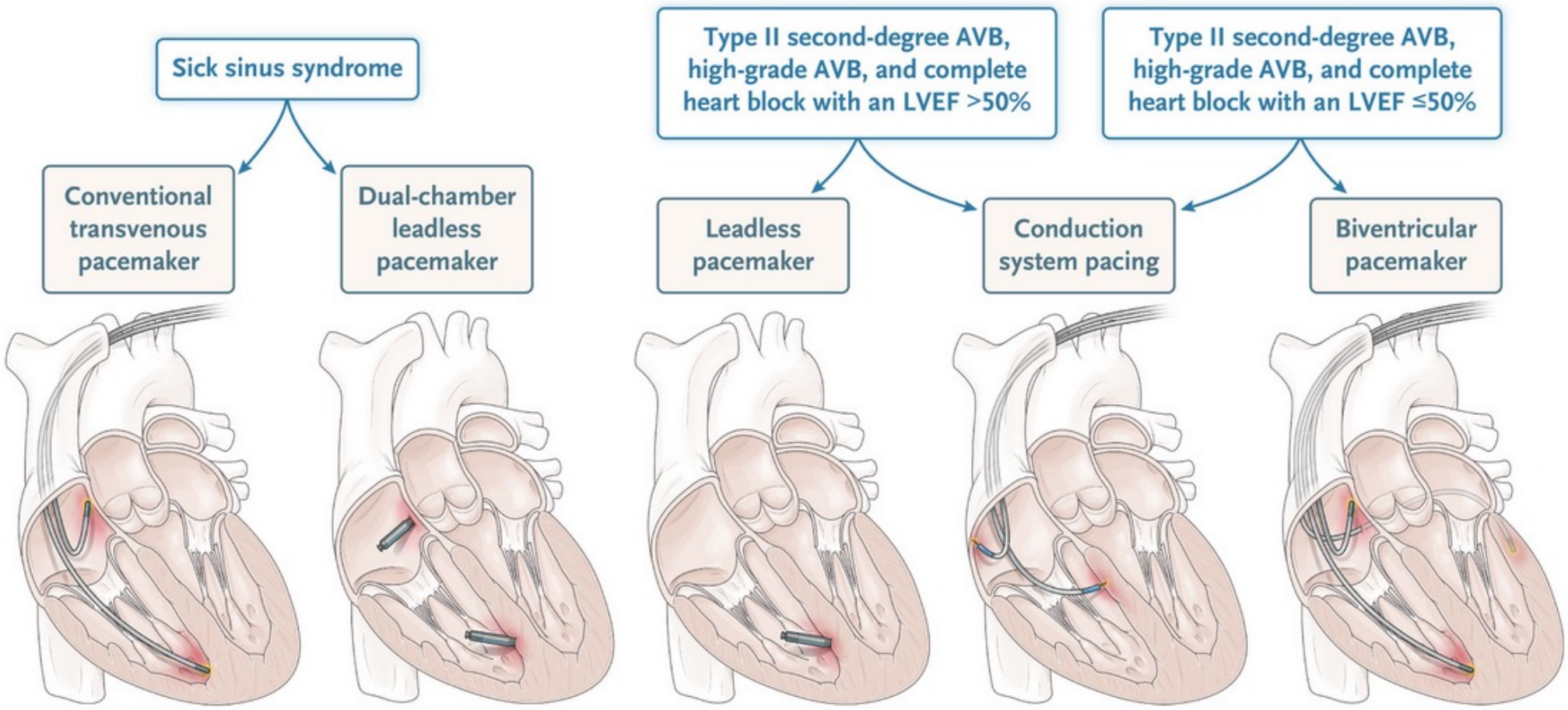
Pros:
- Lower risk of infection
- No lead-related complications
- Lower need for device-related reintervention

Cons:
- Suboptimal degree of atrioventricular synchrony in many patients
- Higher risk of cardiac perforation
- Inability to achieve conduction system pacing
- Lack of experience with long-term device extraction

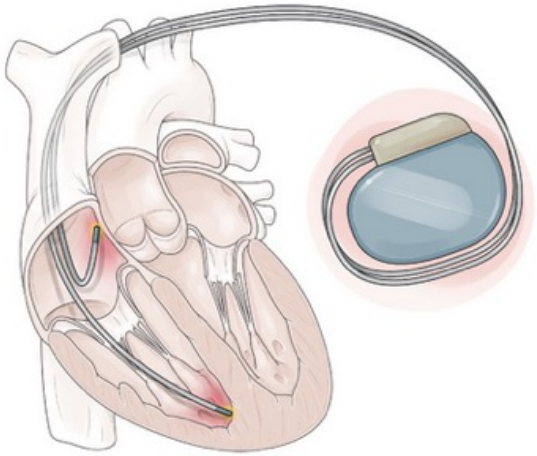
RCTs of Cardiac-Resynchronization Therapy (CRT) and an Implantable Cardioverter–Defibrillator (ICD).

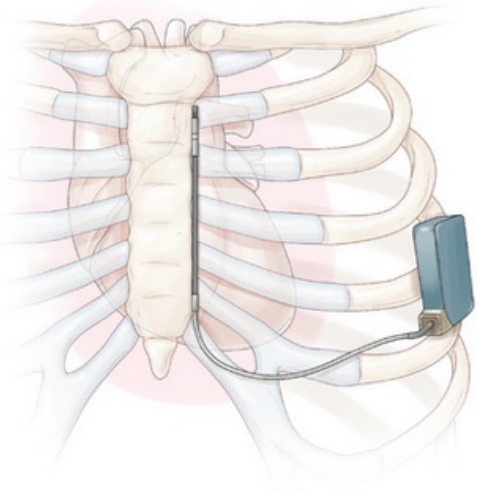
RCT and Year	Sample Size	Follow-up	Patient Population	Primary End Point	Main Findings
	no. of patients	*mo*			
CRT for heart failure with a reduced ejection fraction					
Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION),[34] 2004	1520	11.9–16.2	NYHA class III or IV due to ischemic or nonischemic cardiomyopathy, QRS duration ≥120 msec	Time to death from any cause or hospitalization for any cause	As compared with medical therapy, CRT with a pacemaker reduced the risk of the primary end point (HR, 0.81; P=0.02), as did CRT with a pacemaker–defibrillator (HR 0.80; P=0.01)
Cardiac Resynchronization — Heart Failure (CARE-HF),[35] 2005	813	29.4	NYHA class III or IV heart failure due to systolic dysfunction, cardiac dyssynchrony, on standard pharmacologic therapy	Time to death from any cause or an unplanned hospitalization for a major cardiovascular event	The primary end point occurred in 159 patients in the CRT group vs. 224 patients in the medical therapy group (39% vs. 55%; HR, 0.63; 95% CI, 0.51 to 0.77; P<0.001)
Multicenter Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[36] 2009	1820	28.8	NYHA class I or II symptoms due to ischemic or nonischemic cardiomyopathy, LVEF ≤30%, QRS duration ≥130 msec	Death from any cause or a nonfatal heart failure event	The primary end point was observed in 187 of 1089 patients in the CRT–ICD group (17%) and 185 of 731 patients in the ICD-only group (25%) (HR, 0.66; 95% CI, 0.52 to 0.84; P=0.001)
Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT),[37] 2010	1798	40	NYHA class II or III heart failure, LVEF ≤30%, intrinsic QRS duration ≥120 msec or a paced QRS duration ≥200 msec	Death from any cause or hospitalization for heart failure	The primary outcome was observed in 297 of 894 patients (33%) in the ICD–CRT group and 364 of 904 patients (40%) in the ICD group (HR, 0.75; 95% CI, 0.64 to 0.87; P<0.001)
Transvenous ICDs					
Antiarrhythmics vs. Implantable Defibrillators (AVID) Trial,[38] 1997	1016	18.2	Resuscitated from near-fatal ventricular fibrillation, sustained ventricular tachycardia with syncope, or sustained ventricular tachycardia with LVEF ≤40% and hemodynamic compromise	All-cause mortality	Reductions in mortality with the ICD were 39±20% at 1 yr, 27±21% at 2 yr, and 31±21% at 3 yr
Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II),[39] 2002	1232	20	Prior myocardial infarction and LVEF ≤30%	All-cause mortality	The HR for death from any cause in the ICD group vs. the conventional medical therapy group was 0.69 (95% CI, 0.51 to 0.93; P=0.02)
Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE),[40] 2004	458	29	Nonischemic cardiomyopathy, LVEF ≤ 35%, premature ventricular complexes or nonsustained ventricular tachycardia	All-cause mortality	The HR for death from any cause in the ICD group vs. the medical therapy group was 0.65 (95% CI, 0.40 to 1.06; P=0.08)
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT),[41] 2005	2521	45.5	NYHA class II or III, HF due to ischemic or nonischemic cardiomyopathy, and LVEF ≤35%	All-cause mortality	As compared with placebo, amiodarone resulted in a similar risk of death (HR, 1.06; 97.5% CI, 0.86 to 1.30 P=0.53); the ICD decreased the risk of death by 23% (HR, 0.77; 97.5% CI, 0.62 to 0.96; P=0.007)

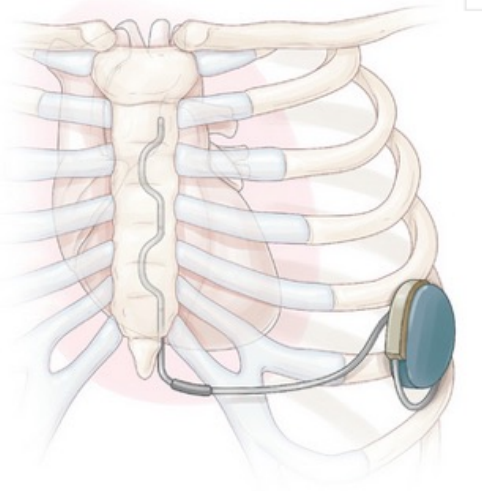
Selecting a Pacemaker Type for a Given Patient.



Pros and Cons of Various ICD Types.







Conventional Transvenous ICD	Subcutaneous ICD	Extravascular ICD
Pros: • Longer duration of use • Supported by the strongest evidence • Capable of bradycardia, antitachycardia, and, in some, biventricular pacing • Longest battery life Cons: • Higher risk of infection • Higher risk of lead-related complications	Pros: • Lower risk of infection • Lower risk of lead-related complications Cons: • Largest size • Shorter battery life • Not capable of bradycardia, antitachycardia, or biventricular pacing	Pros: • Lower risk of lead-related complications • Capable of bradycardia and antitachycardia pacing Cons: • No clinical practice data (not FDA-approved for clinical use in the United States) • Higher risk of inappropriate shocks • Logistic difficulties in aligning electrophysiologist's availability with thoracic surgeon's availability

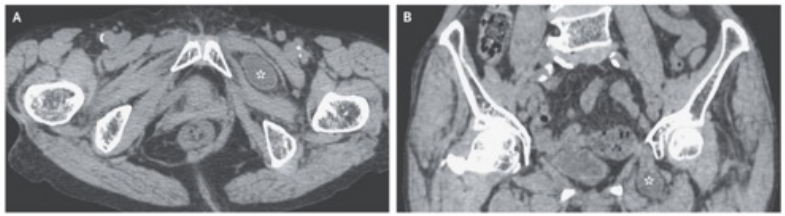
Conclusions and Future Directions

The field of CIEDs has evolved substantially in the past two decades, and evidence is accumulating with respect to which patients benefit most from different methods of pacing and various types of ICD. Despite these major advances, several gaps in knowledge remain. In relation to pacing, we need to determine both how to optimize the effectiveness and safety of dual-chamber, leadless pacemakers and whether leadless pacemakers could be developed that would allow conduction system pacing. More data are needed on how the effectiveness and safety of His or left bundle-branch area pacing compare with those of biventricular pacing. This question is being assessed by the Left vs. Left pragmatic randomized trial, which is enrolling patients with an LVEF of 50% or less and either a wide QRS complex (≥130 msec) or anticipated pacing of 40% or more.

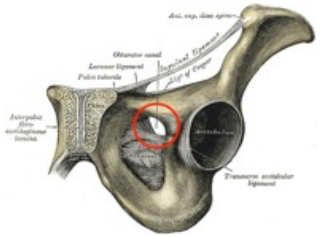
More data are needed on the role of ICDs for primary prevention in patients with nonischemic cardiomyopathy; the outcomes of subcutaneous ICDs in patients not included or not well represented in prior studies, such as patients with hypertrophic cardiomyopathy; and the outcomes of extravascular ICDs. Other data gaps concern the identification of patients who are most likely to benefit from an ICD among all ICD-eligible patients and the development of methods to identify and treat patients at high personal risk for sudden death from cardiac causes who are not identified by current ICD guidelines. Filling these gaps will enable clinicians to deliver personalized care, ensuring that patients receive the type of CIED that will provide the greatest benefit.

IMAGES IN CLINICAL MEDICINE

Incarcerated Obturator Hernia

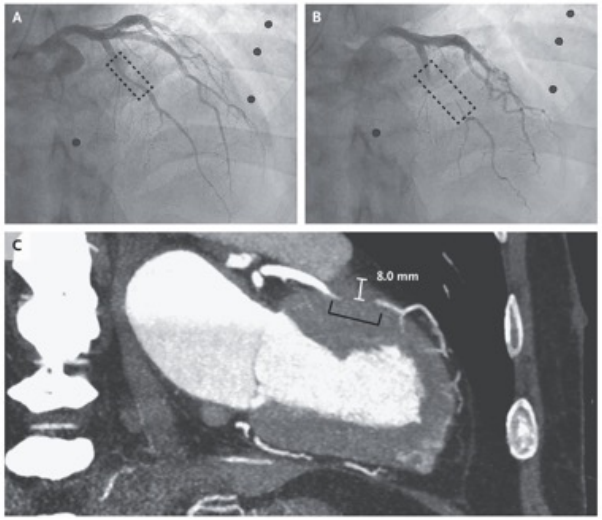


An 84-year-old woman with a history of six vaginal deliveries presented to the gastroenterology department with a 12-hour history of left lower abdominal pain, nausea, and vomiting. Her body-mass index (the weight in kilograms divided by the square of the height in meters) was 16, indicating underweight status. On physical examination, the patient had tenderness to palpation in the left inguinal region. Computed tomography of the abdomen revealed a loop of small bowel protruding through the left obturator canal, between the pectineus muscle anteriorly and the obturator external muscle posteriorly (Panels A [axial view] and B [coronal view], asterisk). Small-bowel dilatation with fluid accumulation proximal to the herniated bowel was also observed. A diagnosis of an incarcerated obturator hernia was made. Emergency laparotomy was performed, during which a part of the ileum located 80 cm from the ileocecal region was found embedded in the left obturator canal. The ileum was manually returned to the peritoneum, and the hernia was repaired. An obturator hernia is a rare type of hernia most commonly identified in thin, multiparous, older women. Owing to the lack of overt findings associated with this pelvic hernia on physical examination, diagnosis may be delayed. The patient recovered well and was discharged home 7 days after surgery.



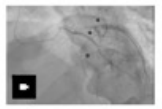
IMAGES IN CLINICAL MEDICINE

Myocardial Bridging



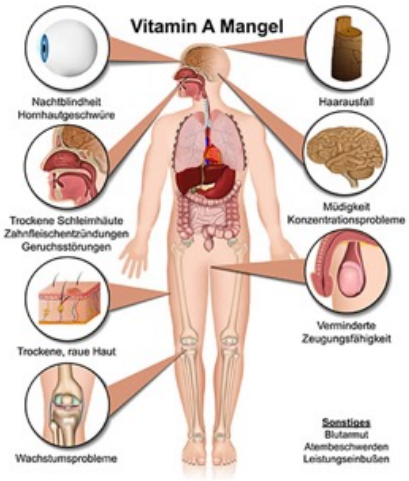
A 66-year-old man with a history of hypertension, diabetes mellitus, and ischemic stroke was transferred to a tertiary hospital after a cardiac arrest. For 6 months before presentation, he had had recurrent exertional angina but had not sought evaluation. On the morning of the cardiac arrest, he had woken with chest pain, lost consciousness, and regained consciousness after brief cardiopulmonary resuscitation by his family. On transfer to the tertiary hospital, findings from a physical examination and a transthoracic echocardiogram were normal. Coronary angiography revealed 50% stenosis in the middle left anterior descending (LAD) coronary artery during diastole (Panel A, dashed box) with complete occlusion during systole (Panel B, dashed box) and sluggish distal flow (see **video**). A diagnosis of myocardial bridging was made. Myocardial bridging is a coronary anomaly in which an epicardial coronary artery takes an intramuscular course. The condition is congenital but may not result in symptoms until later in life when concurrent left ventricular hypertrophy, coronary microvascular disease, or intraluminal stenosis develops from atherosclerosis. Coronary computed tomographic angiography that was performed for surgical planning showed an 8-mm depth of the middle LAD coronary artery in the myocardium (Panel C, bracket). Coronary-artery bypass surgery was performed with a saphenous vein graft. The patient recovered well and had no recurrence of symptoms.

Video

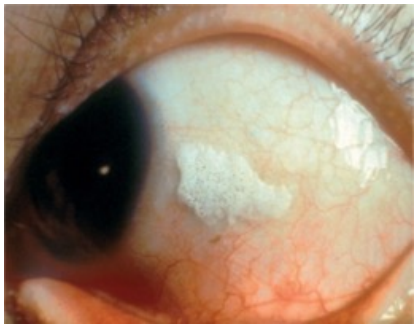


Coronary Angiography in Left Anterior Oblique View (00:15)

Ein Vitamin-A-Mangel ist eine Form der Hypovitaminose, die durch eine zu geringe Zufuhr von Vitamin A bedingt ist. Er tritt vor allem in Entwicklungsländern auf. Frühsymptome eines Vitamin-A-Mangels ist die Nachtblindheit (Nyktalopie) sowie eine Photophobie. Eine Augenbeteiligung kann sich weiterhin in Form einer konjunktivalen Xerose mit Bitot-Flecken (weiße Flecken aus keratinisiertem Epithel auf der Sklera), selten mit Hornhautgeschwüren und -nekrosen bzw. in Form einer Xerophthalmie manifestieren. Die Keratomalazie führt bei ca. 250.000 Kindern pro Jahr zur Erblindung.
Ein symptomatischer Vitamin-A-Mangel geht mit einer erhöhten Sterblichkeit durch Diarrhö, Dysenterie, Masern, Malaria und Atemwegserkrankungen einher. Vitamin-A-Mangel kann die Barrierefunktionen der Epithelien stören und das Immunsystem schwächen.



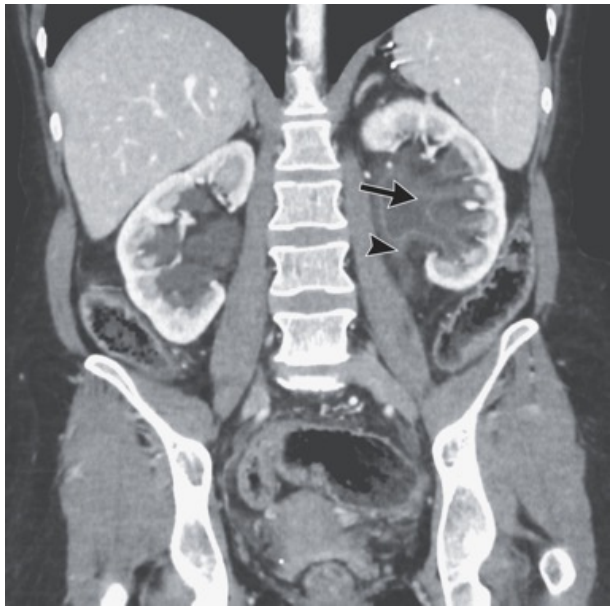
Vitamin A ist wichtig für das Wachstum, Funktion und Aufbau von Haut und Schleimhäuten, Blutkörperchen, Stoffwechsel so wie für den Sehvorgang. Die Verwertung dieses Vitamins im Körper kann durch Leberschäden und die Einnahme von Östrogenpräparaten gestört werden. Neueste Untersuchungen zeigten, dass entgegen der Vermutung selbst durch geringste Mengen Fett in Nahrungsmitteln das Vitamin A vom Körper aufgenommen und verwendet werden kann. Beim Sehvorgang vermittelt 11-cis-Retinal (bei Süßwasserfischen und manchen Amphibien 11-cis-3,4-Dehydroretinal) als lichtempfindliches Chromophor die Phototransduktion. Es kommt in den Sehpigmenten bei den Lichtrezeptoren in der Retina vor. Unter den vielen Vitamin A-Funktionen ist die fürs Sehen am besten untersucht.



CLINICAL PROBLEM-SOLVING

Flipping the Switch

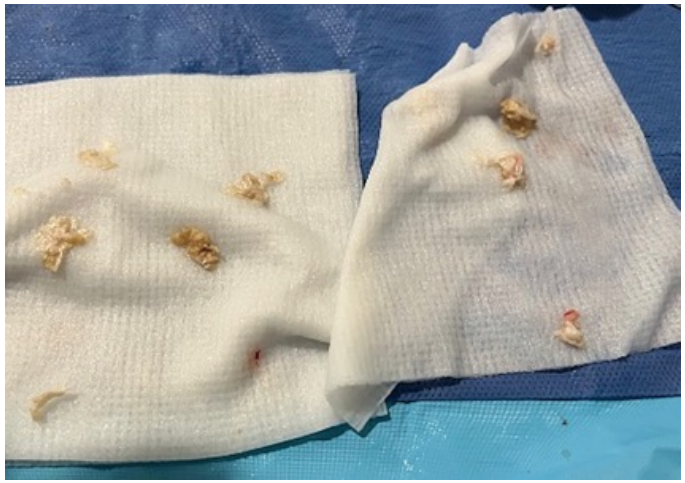
A 43-year-old woman presented to the primary care clinic with a 1-week history of dysuria and lower abdominal pressure. She reported no fevers, hematuria, or flank pain. She had reported similar symptoms several times over the previous 2 years in a different health care system. Each episode had been diagnosed as a urinary tract infection (UTI) with confirmation by culture (all cultures grew either *Escherichia coli* or *Enterococcus faecalis*) and had resolved after antimicrobial treatment. The patient's medical history included severe obesity that had been treated with a biliopancreatic diversion with a duodenal switch procedure 20 years earlier, nephrolithiasis (visualized on computed tomographic [CT] urography, with calcium phosphate and calcium oxalate stones identified on stone analysis), and iron-deficiency anemia. The patient was premenopausal. She had previously been treated with intravenous ferric gluconate infusions but had not received infusions in the past 6 months. Her only medication was a transdermal multivitamin patch; she preferred not to take supplements in pill form. She reported no tobacco smoking or illicit drug use. She drank alcohol twice a year. Her only international travel was a weeklong cruise to Jamaica several years earlier. She worked in an office. She was sexually active with one male partner. All labs, examins were normal. The serum albumin level was 3.4 g per deciliter. The serum ferritin level was 70 ng per milliliter (normal range, 7 to 271). Urinary dipstick analysis was positive for nitrites and leukocyte esterase; the urine pH was 6.0. Urine culture grew more than 100,000 colony-forming units of *E. coli*. Her symptoms resolved with a 7-day course of cefuroxime.



The patient had additional UTIs caused by *E. coli* and *E. faecalis*. One year after her index primary care visit, CT urography revealed urothelial thickening and mild dilatation of the left renal collecting system and ureter with nonenhancing debris involving the majority of the left renal calyces. Kidney size was normal. There was no perinephric fat stranding, bladder-wall thickening, or stones. Flexible ureteroscopy revealed pale, sloughing mucosa with patchy white plaques throughout both renal pelvicalyceal systems, with a greater plaque burden on the left side than on the right side. During ureteroscopic biopsy of the left pelvicalyceal urothelium, scant fragments of keratinaceous debris were obtained, but there was insufficient tissue for further studies. The bladder urothelium was normal.

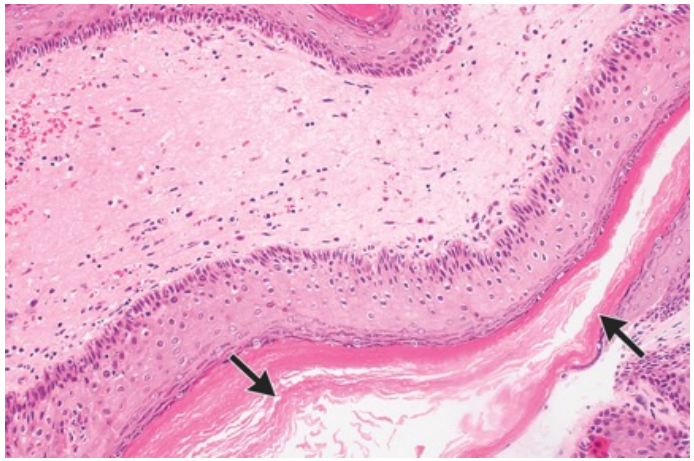
Bacterial and fungal cultures and cytologic testing of aspirated samples (from the left renal pelvis) and clean-catch urine samples were negative. Blastomyces antigen testing and nucleic acid amplification testing for *Neisseria gonorrhea*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Mycoplasma genitalium*, assessed in urine, were also negative. Polymerase-chain-reaction testing for *Ureaplasma parvum* in urine was positive. Serum testing for rapid plasma reagin and an interferon gamma release assay were negative, as were serologic tests for blastomyces, histoplasma, coccidioides, and schistosoma. Levels of IgG4, IgA, IgG, and IgM were normal. Testing for the human immunodeficiency virus was not done. Mycobacterial cultures of the urine were negative. The patient continued to have UTIs caused by *E. coli* and *E. faecalis*.

Percutaneous nephroscopy that was performed 7 months after the flexible ureteroscopy revealed white, pale, sloughing mucosa in the urothelial tract, which was débrided. Histopathological assessment of a urothelial-biopsy sample showed extensive keratinizing squamous metaplasia



Histopathological Sample from the Left Renal Collecting System.

A histopathological assessment of a biopsy sample obtained from the left renal collecting system showed extensively keratinizing squamous metaplasia (arrows; hematoxylin and eosin staining).



Serum levels of copper, selenium, vitamin B_{12}, and folic acid were normal. The serum zinc level was 51 µg per deciliter (7.8 µmol per liter; normal range, 55 to 150 µg per deciliter [8.4 to 23.0 µmol per liter]), the 25-hydroxyvitamin D level was 9 ng per milliliter (normal range, 30 to 100), the vitamin E level was less than 0.2 mg per deciliter (5 µmol per liter; normal range, 0.55 to 1.70 mg per deciliter [13 to 39 µmol per liter]), and the vitamin A level was less than 10 µg per deciliter (0.35 µmol per liter; normal range, 10 to 50 µg per deciliter [0.35 to 1.75 µmol per liter]).
On further questioning after the diagnosis of vitamin A deficiency, the patient reported problems with driving at night owing to difficulty seeing in the dark. She did not undergo a formal ophthalmologic assessment. She reported no pruritus, skin dryness, abdominal pain, or steatorrhea, and no abnormalities on skin examination were noted after the diagnosis.

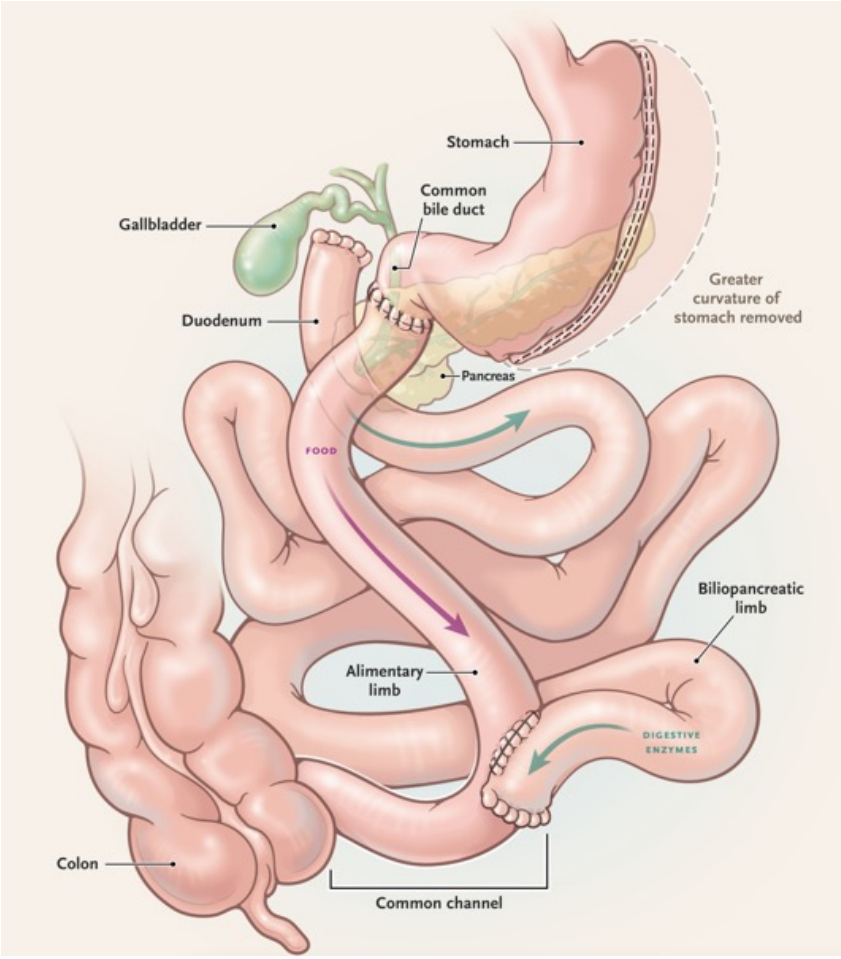
High-dose vitamin A (100,000 IU by mouth daily for 4 days, then 50,000 IU daily) was prescribed, as were oral vitamin D, calcium, zinc, iron supplements, and a multivitamin. Four months later, the serum vitamin A level was 23 µg per deciliter (0.80 µmol per liter), and ureteroscopy revealed a substantial reduction in white plaques and sloughing mucosa. Ureteroscopy that was conducted after 15 months of vitamin A supplementation revealed resolution of the urothelial abnormalities, and the vitamin A level at that time was 13 µg per deciliter (0.45 µmol per liter). Although the patient's vitamin A level had decreased from the previous year, she reported taking oral vitamin A supplementation as prescribed. After 2 years of treatment, she had not had any subsequent UTIs.

Commentary

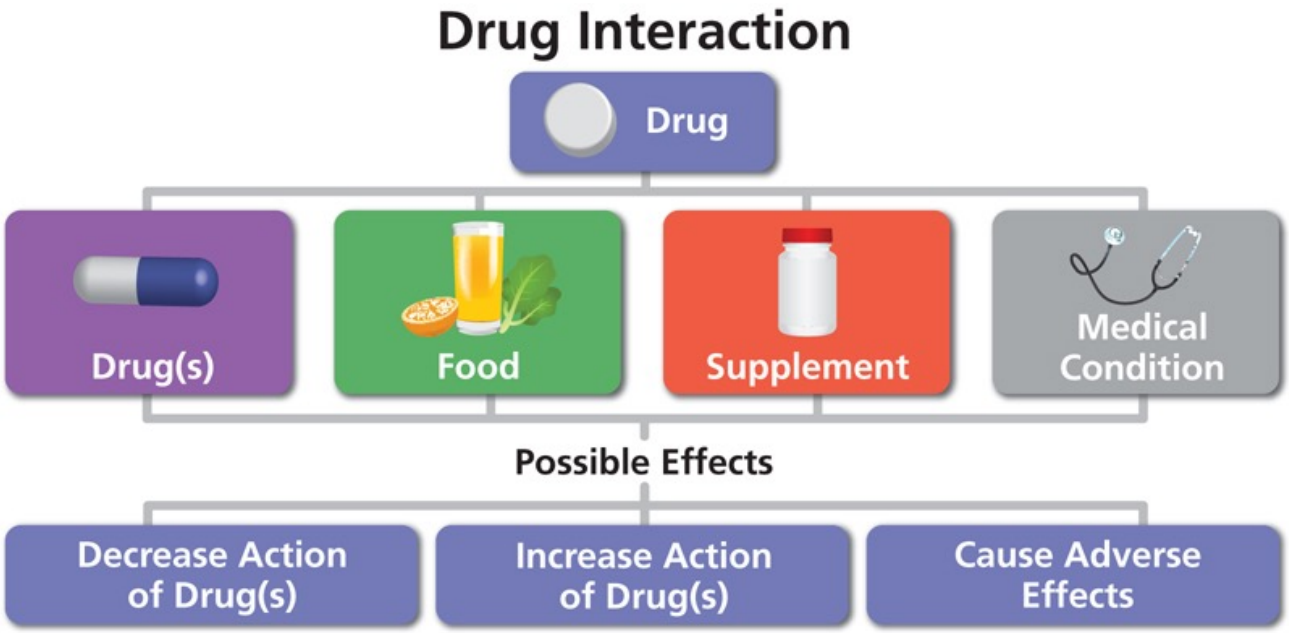
The time between this patient's first UTI and identification of the cause of recurrent UTIs — keratinizing desquamative squamous metaplasia — was approximately 4 years. Keratinizing desquamative squamous metaplasia due to vitamin A deficiency occurred after a bariatric operation that had been performed 20 years earlier, with subsequent insufficient nutritional supplementation.

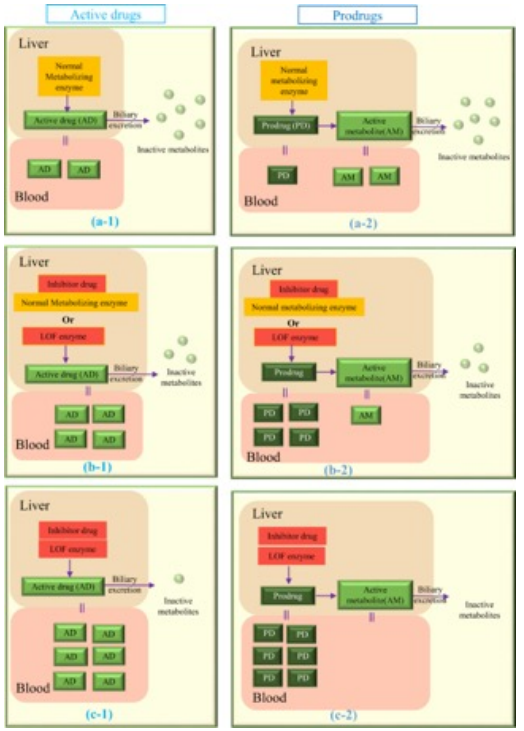
Biliopancreatic Diversion with Duodenal Switch.

In a biliopancreatic diversion with duodenal switch procedure, a portion of the greater curvature of the stomach is removed. The duodenum is then divided, and the intestinal tract is rerouted to create a long limb of bowel that contains only digestive enzymes and another long limb that contains only food. There is a short segment of distal bowel (50 to 100 cm) where food and digestive enzymes mix. This situation leads to a reduced surface area for absorption.



Postsurgical bariatric care requires frequent laboratory testing and multiple encounters with the health care team to review and respond to results; care restrictions that were associated with the coronavirus disease 2019 pandemic made the situation more challenging for this patient. This case highlights the importance of clearly defined and coordinated nutritional care pathways after bariatric surgery and the hazards of fragmented care.
Bariatric procedures such as biliopancreatic diversion with duodenal switch are associated with enduring medical and psychological benefits, but they can induce occult or overt malnutrition, including micronutrient deficiencies. This case reminds us how close attention to postoperative nutritional supplementation and coordination of care can flip the switch.


Drug Interaction
Drug
Drug(s)
Food
Supplement
Medical Condition
Possible Effects
Decrease Action of Drug(s)
Increase Action of Drug(s)
Cause Adverse Effects


Active drugs
Prodrugs
Liver
Blood
Inactive metabolites
(a-1)
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(b-1)
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(c-1)
(c-2)

The effect of computerised decision support alerts tailored to intensive care on the administration of high-risk drug combinations, and their monitoring: a cluster randomised stepped-wedge trial

Summary

Background Drug–drug interactions (DDIs) can harm patients admitted to the intensive care unit (ICU). Yet, clinical decision support systems (CDSSs) aimed at helping physicians prevent DDIs are plagued by low-yield alerts, causing alert fatigue and compromising patient safety. The aim of this multicentre study was to evaluate the effect of tailoring potential DDI alerts to the ICU setting on the frequency of administered high-risk drug combinations.

Methods We implemented a cluster randomised stepped-wedge trial in nine ICUs in the Netherlands. Five ICUs already used potential DDI alerts. Patients aged 18 years or older admitted to the ICU with at least two drugs administered were included. Our intervention was an adapted CDSS, only providing alerts for potential DDIs considered as high risk. The intervention was delivered at the ICU level and targeted physicians. We hypothesised that showing only relevant alerts would improve CDSS effectiveness and lead to a decreased number of administered high-risk drug combinations. The order in which the intervention was implemented in the ICUs was randomised by an independent researcher. The primary outcome was the number of administered high-risk drug combinations per 1000 drug administrations per patient and was assessed in all included patients. This trial was registered in the Netherlands Trial Register (identifier NL6762) on Nov 26, 2018, and is now closed.

Findings In total, 10 423 patients admitted to the ICU between Sept 1, 2018, and Sept 1, 2019, were assessed and 9887 patients were included. The mean number of administered high-risk drug combinations per 1000 drug administrations per patient was 26·2 (SD 53·4) in the intervention group (n=5534), compared with 35·6 (65·0) in the control group (n=4353). Tailoring potential DDI alerts to the ICU led to a 12% decrease (95% CI 5–18%; p=0·0008) in the number of administered high-risk drug combinations per 1000 drug administrations per patient, after adjusting for clustering and prognostic factors.

Interpretation This cluster randomised stepped-wedge trial showed that tailoring potential DDI alerts to the ICU setting significantly reduced the number of administered high-risk drug combinations. Our list of high-risk drug combinations can be used in other ICUs, and our strategy of tailoring alerts based on clinical relevance could be applied to other clinical settings.

Introduction

Drug–drug interactions (DDIs) are an important cause of patient harm.[1] Patient harm occurs when two drugs known to interact are co-administered and subsequently their effect is increased or decreased, causing drug toxicity or therapy failure.[2] Patients admitted to the intensive care unit (ICU) are more prone to adverse drug events compared with patients on non-ICU wards.[3] The observed rate of adverse drug events was 11·5 per 1000 patient-days in general wards compared with 19·4 in the ICU in the USA in 1995.[4] Approximately 16% of all adverse drug events in the ICU are caused by DDIs.[5–7]

A potential DDI refers to the administration of two drugs known to interact. The term potential implies uncertainty regarding whether the exposure will lead to an actual DDI, harming the patient. The occurrence of an interaction depends on factors such as the patient's renal and liver function, and the dose and duration of the co-administration. For potential DDIs that are considered clinically relevant in the ICU, the term high-risk drug combination is used, indicating exposure to a combination that might result in an actual DDI with clinically relevant consequences harming the patient.

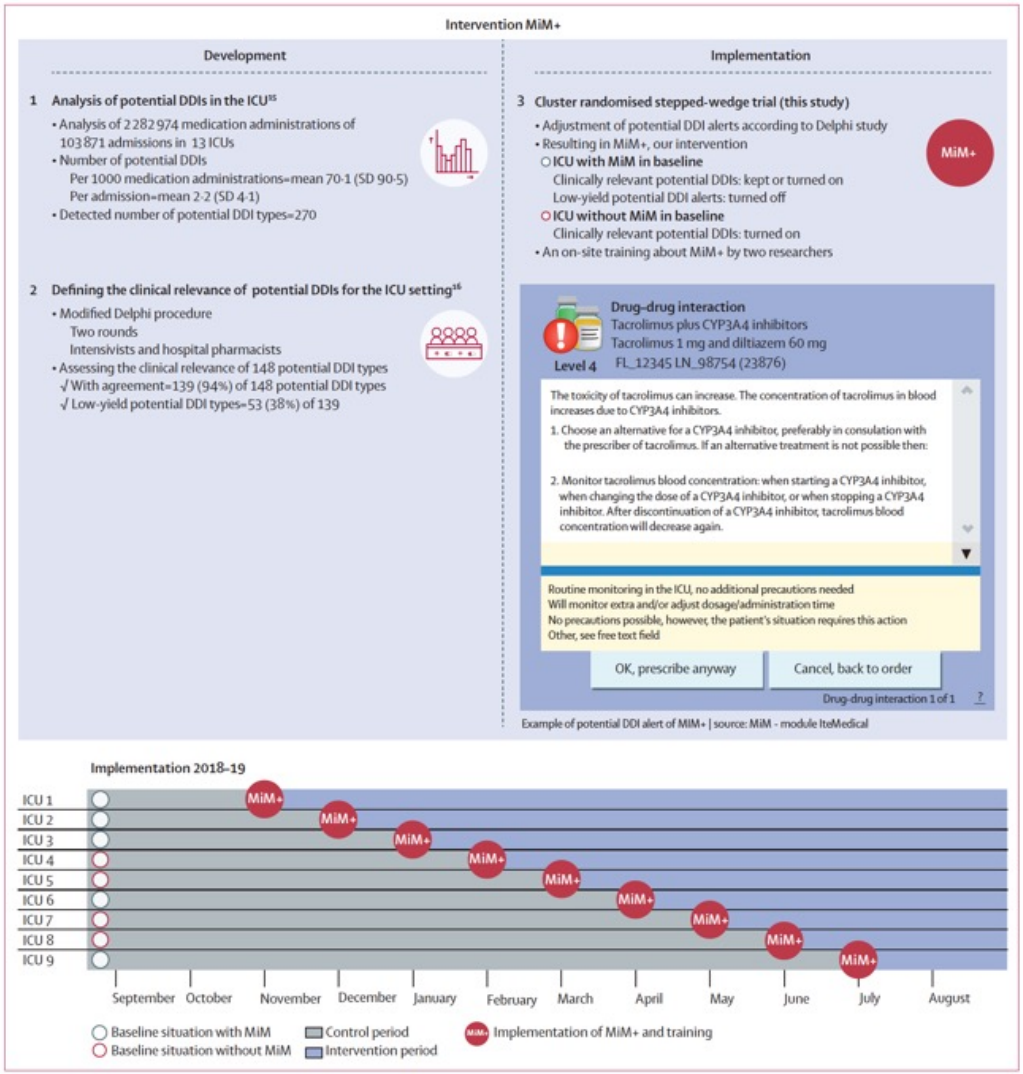


Figure 1: **Graphical summary of the development and implementation of the MiM+ intervention**
DDI=drug–drug interaction. ICU=intensive care unit. MiM+=Medication Interaction Module+.

Intervention

Our intervention was a restricted version of the Medication Interaction Module (MiM), a CDSS developed by ItéMedical. ICUs using the patient data management system MetaVision have the option to use MiM, which provides potential DDI alerts or duplicate order alerts, or both. Five of the nine participating ICUs used the MiM. MiM is based on the G-Standaard, an evidence-based professional database developed by the Scientific Institute of Dutch Pharmacists. The G-Standaard is used in all Dutch hospitals and contains information about potential DDIs and their management.[18] The interactions included in the G-standaard are listed in the appendix (pp 17–29).

Our intervention, referred to as MiM+, provided alerts only for potential DDIs considered clinically relevant to the ICU (ie, high-risk drug combinations). An alert example is shown in the appendix (p 13). To establish clinical relevance, we applied a modified Delphi procedure with an expert panel consisting of intensivists and hospital pharmacists (among which included AK, EdJ, IMP, JtC, MH, PES, SH, and WJV), assessing the clinical relevance of 139 potential DDIs for the ICU setting. We found that 86 of 139 potential DDIs (62%) were considered clinically relevant in the ICU setting (figure 1; appendix pp 30–32). For nine potential DDIs, agreement on clinical relevance was not reached in the Delphi study (appendix p 33). This study is described elsewhere.[16] The adaptation to MiM+ differed for ICUs already using the MiM (n=5) and ICUs not using the MiM (n=4).

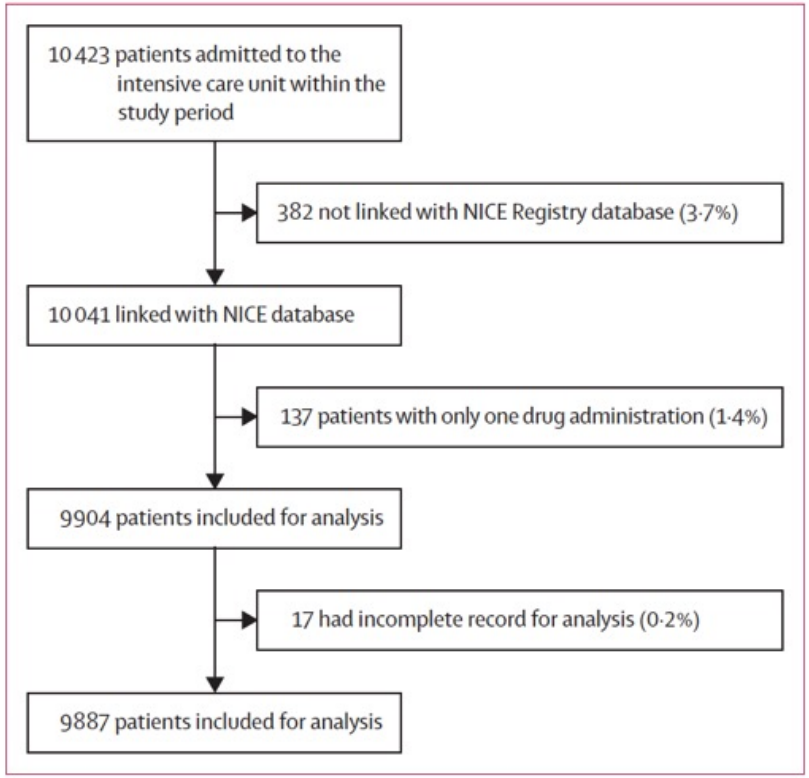


Figure 2: **Flow of patient inclusion**
NICE=National Intensive Care Evaluation.

	Control group (n=5534)	Intervention group (n=4353)
Age, years*		
Mean	63·2 (15·3)	63·2 (15·9)
Median	66·0 (55–74)	66·0 (55–75)
Sex		
Female	2114 (38·2%)	1695 (38·9%)
Male	3420 (61·8%)	2658 (61·1%)
APACHE IV score*		
Mean	57·2 (27·6)	56·5 (27·1)
Median	51·0 (38–71)	51·0 (37–70)
Admission type		
Medical	2480 (44·8%)	2078 (47·7%)
Emergency surgical	670 (12·1%)	451 (10·4%)
Elective surgical	2384 (43·1%)	1824 (41·9%)
Chronic conditions		
Chronic renal failure	286 (5·2%)	252 (5·8%)
Chronic obstructive pulmonary disease	543 (9·8%)	580 (13·3%)
Respiratory failure	182 (3·3%)	139 (3·2%)
Cardiovascular disease	174 (3·1%)	113 (2·6%)
Cirrhosis	89 (1·6%)	53 (1·2%)
Haematological malignancy	92 (1·7%)	74 (1·7%)
AIDS	3 (0·1%)	1 (<0·1%)
Immunodeficiency	586 (10·6%)	487 (11·2%)

Data are n (%), mean (SD), or median (IQR). APACHE IV=Acute Physiology And Chronic Health Evaluation IV. *Age and APACHE IV score were not normally distributed and therefore the median and IQR were reported. For completeness we also reported the mean and SD.

Table 1: **Patient characteristics**

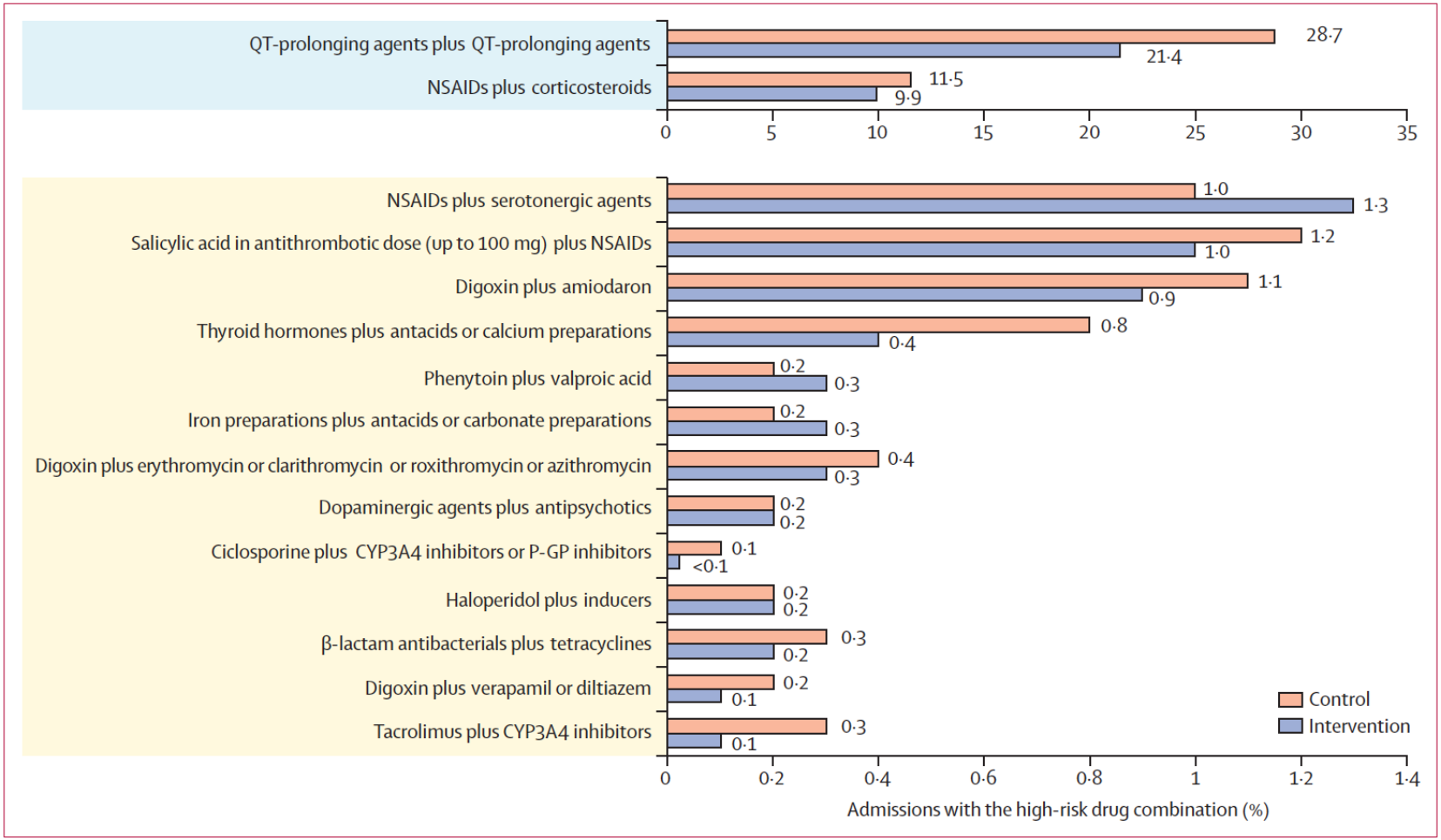


***Figure 3*: Comparison of the percentage of patients with a high-risk drug combination for the 15 most frequent types of high-risk drug combinations in the intervention and control group**

Please note the different scales used for the top two and bottom 13 types of drug combinations. NSAIDs=non-steroidal anti-inflammatory drugs.

	Variable	Estimated incidence rate ratio	95% CI lower bound	95% CI upper bound	p value
Unadjusted M0	MiM+	0·88	0·81	0·94	0·0004*
Adjusted M1	MiM+	0·86	0·80	0·92	<0·0001*
Adjusted M2	MiM+	0·88	0·82	0·95	0·0008*

Model M1 was adjusted for admission type (medical, emergency surgical, or elective surgical) and the presence of chronic obstructive pulmonary disease. Model M2 was adjusted for age, sex, admission type, Acute Physiology And Chronic Health Evaluation IV score, presence of cardiovascular disease, and presence of immunodeficiency. The result was considered significant when $p<0·05$. MiM=Medication Interaction Module. *Significant result.

Table 2: **Output for the unadjusted and adjusted generalised linear mixed-effect models**

Research in context

Evidence before this study

Drug–drug interactions (DDIs) are a notable cause of patient harm. Patients admitted to the intensive care unit (ICU) are more prone to adverse drug events compared with patients on non-ICU wards. We searched MEDLINE for studies in English published from Jan 1, 2010, to April 13, 2017, on information technology-based interventions to improve DDI outcomes. We subsequently conducted an update of this search for studies published in the period April 13, 2017, to Oct 9, 2019. We used the search terms "drug interaction", "medication interaction", "decision support system", "expert system", and "prescribing system". We excluded studies that focused on the feasibility, validity, acceptability, or description of information technology-based applications. We found that clinical decision support systems (CDSSs) are plagued by an overload of low-yield potential DDI alerts. Producing many low-yield alerts desensitises clinicians and leads to alert fatigue, high over-ride rates, and the risk of missing relevant alerts, thereby compromising patient safety. In the ICU, approximately 90% of the potential DDI alerts are over-ridden, and 84% of these over-rides appear justified because of the perceived low yield of the potential DDI alerts. Furthermore, we found no studies that evaluated the effect of tailoring potential DDI alerts to the ICU setting on high-risk drug combination frequency, patient monitoring, or ICU length of stay.

Added value of this study

This cluster randomised stepped-wedge trial showed that tailoring potential DDI alerts to the ICU setting, by only producing alerts that are clinically relevant in this setting, improved CDSS effectiveness and led to a 12% decrease in the number of administered high-risk drug combinations (95% CI 5–18%; p=0·0008). Additionally, patient monitoring for potential consequences of DDIs improved by 9% (6–11%; p<0·0001), and the length of stay in the ICU was reduced by 6% (2–10%; p=0·0021). These findings contribute to the goal of intensivists to avoid high-risk drug combinations if possible and, if not possible, to prescribe them while being aware of and adequately monitoring the potential consequences.

Implications of all the available evidence

Tailoring potential DDI alerts to a specific setting can reduce the administration of high-risk drug combinations and length of stay in the ICU, and improve patient monitoring for the potential consequences of DDIs. Our results are relevant to clinicians, hospital pharmacists, CDSS developers, managers, quality-of-care officers, and researchers in the ICU setting. Other ICUs could use our list of high-risk drug combinations to tailor their potential DDI alerts and improve CDSS effectiveness. Additionally, our results might encourage other medical practitioners to establish a set of high-risk drug combinations for patients in other specific settings, such as in neonatology, paediatrics, or oncology.

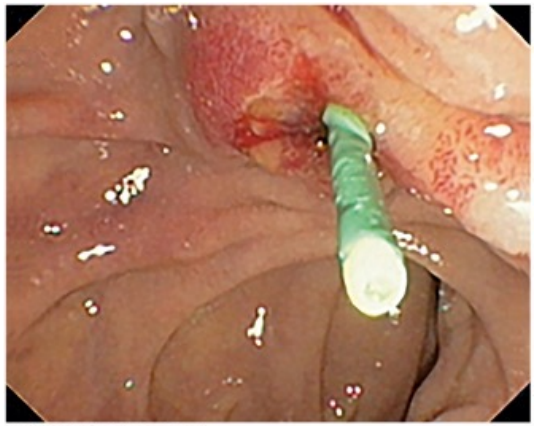
Prophylaxe der Post-ERCP-Pankreatitis

Zusammenfassung

Die Post-ERCP-Pankreatitis ist die häufigste Komplikation einer ERCP und wird durch eine Vielzahl an Faktoren beeinflusst. Zu deren Prophylaxe ist eine strenge Indikationsstellung zur ERCP erforderlich. Sofern keine Gegenanzeigen bestehen, sollen die Patienten vor, während und nach der Untersuchung eine forcierte i.v.-Flüssigkeitszufuhr mit Ringer-Laktat erhalten (in unserer Praxis wird beispielsweise ein Liter Ringer-Laktat vor Beginn der Untersuchung angehängt und zumindest ein weiterer Liter während oder nach der Untersuchung nachgegeben). Vor jeder ERCP sollen ferner 100 mg Diclofenac oder Indometacin rektal verabreicht werden, sofern keine Kontraindikationen bestehen. Je nach Eingriffsart und zusätzlichen intraprozeduralen Risikofaktoren kann schließlich die Platzierung eines Pankreasschutzstents erforderlich sein, um das Risiko weiter minimieren zu können.

Prophylaktischer Pankreasstent

Auch die Platzierung eines sog. Pankreasschutzstents kann dazu beitragen, das Auftreten einer PEP weniger wahrscheinlich zu machen. Dies gilt vor allem bei Vorliegen einer der folgenden Konstellationen, die mit einem besonders hohen PEP-Risiko einhergehen: Hochrisikointerventionen wie beispielsweise eine Papillektomie, Double-wire-Sondierungstechnik, mehr als 3-malige Pankreasgangsondierung oder eine Kontrastierung des Pankreas. Bezüglich des empfohlenen Stentdesigns hat sich ein 5 Fr-Monopigtailstent ohne Flaps als besonders günstig herausgestellt. Eine Spontanmigration nach distal ist in den ersten Tagen nach der Intervention sehr wahrscheinlich und kann bei Verwendung einer röntgendichten Markierung ohne Notwendigkeit eines invasiven Eingriffs verifiziert werden.



Prophylaktischer Pankreas-Stent (3F/flapless)

Indomethacin with or without prophylactic pancreatic stent placement to prevent pancreatitis after ERCP: a randomised non-inferiority trial

Summary

Background The combination of rectally administered indomethacin and placement of a prophylactic pancreatic stent is recommended to prevent pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) in high-risk patients. Preliminary evidence suggests that the use of indomethacin might eliminate or substantially reduce the need for stent placement, a technically complex, costly, and potentially harmful intervention.

Methods In this randomised, non-inferiority trial conducted at 20 referral centres in the USA and Canada, patients (aged ≥18 years) at high risk for post-ERCP pancreatitis were randomly assigned (1:1) to receive rectal indomethacin alone or the combination of indomethacin plus a prophylactic pancreatic stent. Patients, treating clinicians, and outcomes assessors were masked to study group assignment. The primary outcome was post-ERCP pancreatitis. To declare non-inferiority, the upper bound of the two-sided 95% CI for the difference in post-ERCP pancreatitis (indomethacin alone minus indomethacin plus stent) would have to be less than 5% (non-inferiority margin) in both the intention-to-treat and per-protocol populations. This trial is registered with ClinicalTrials.gov (NCT02476279), and is complete.

Findings Between Sept 17, 2015, and Jan 25, 2023, a total of 1950 patients were randomly assigned. Post-ERCP pancreatitis occurred in 145 (14·9%) of 975 patients in the indomethacin alone group and in 110 (11·3%) of 975 in the indomethacin plus stent group (risk difference 3·6%; 95% CI 0·6–6·6; p=0·18 for non-inferiority). A post-hoc intention-to-treat analysis of the risk difference between groups showed that indomethacin alone was inferior to the combination of indomethacin plus prophylactic stent (p=0·011). The relative benefit of stent placement was generally consistent across study subgroups but appeared more prominent among patients at highest risk for pancreatitis. Safety outcomes (serious adverse events, intensive care unit admission, and hospital length of stay) did not differ between groups.

Interpretation For preventing post-ERCP pancreatitis in high-risk patients, a strategy of indomethacin alone was not as effective as a strategy of indomethacin plus prophylactic pancreatic stent placement. These results support prophylactic pancreatic stent placement in addition to rectal indomethacin administration in high-risk patients, in accordance with clinical practice guidelines.

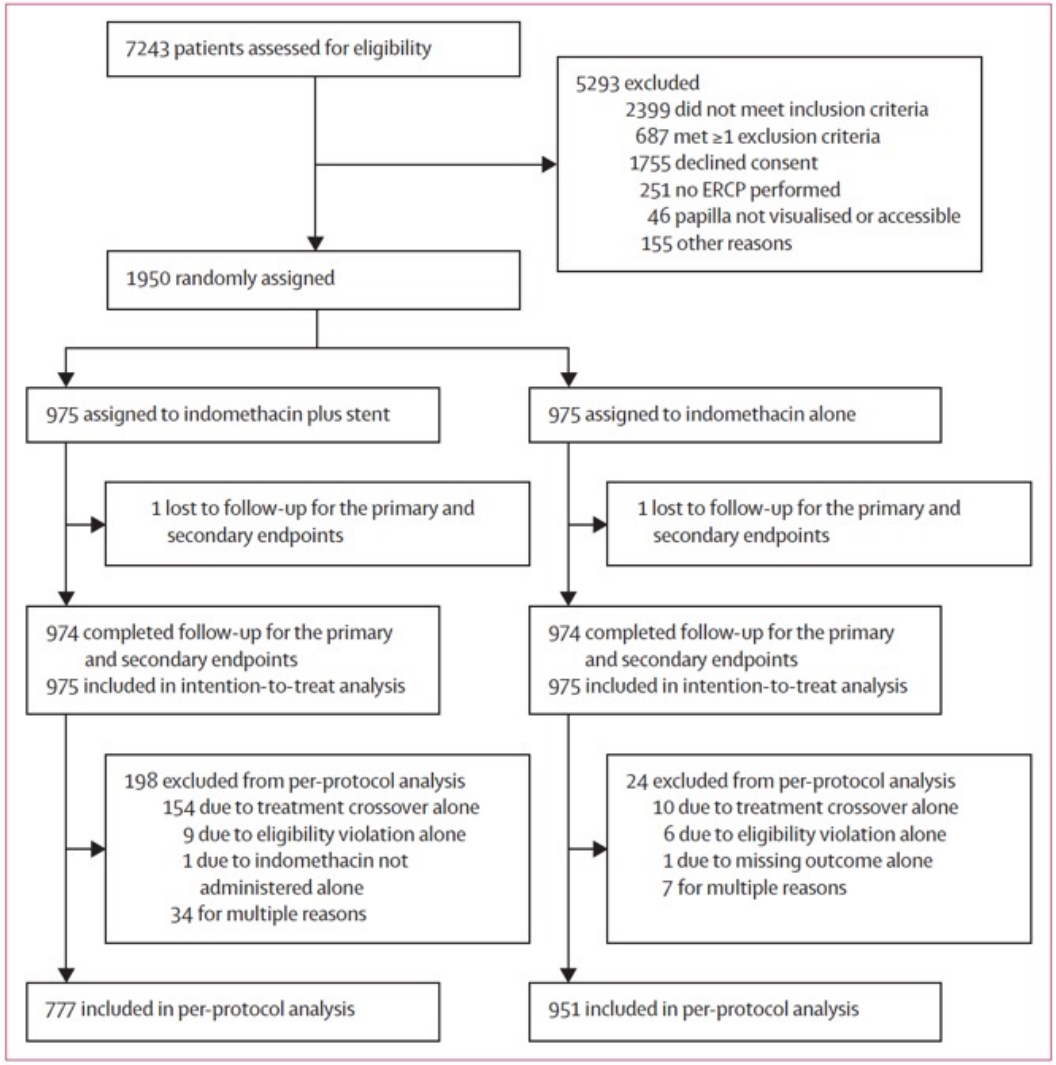


Figure 1: **Trial profile**

	Indomethacin plus stent (n=975)	Indomethacin alone (n=975)
Age, years	55·8 (16·3)	55·6 (16·4)
Sex		
Female	596 (61·1%)	599 (61·4%)
Male	379 (38·9%)	376 (38·6%)
Race		
Asian	19 (1·9%)	17 (1·7%)
Black or African American	102 (10·5%)	115 (11·8%)
White	825 (84·6%)	809 (83·0%)
Other	29 (3·0%)	34 (3·5%)
Ethnicity		
Hispanic or Latino	99 (10·2%)	101 (10·4%)
Not Hispanic or Latino	871 (89·3%)	866 (88·8%)
Unknown	5 (0·5%)	8 (0·8%)
BMI*	29·6 (7·2)	28·6 (6·8)
Antibiotic use in past 3 months†	366 (41·8%)	363 (41·8%)
Clinical suspicion or known sphincter of Oddi dysfunction	252 (25·8%)	262 (26·9%)
History of post-ERCP pancreatitis	24 (2·5%)	36 (3·7%)
History of recurrent pancreatitis	126 (12·9%)	128 (13·1%)
Difficult cannulation	823 (84·4%)	795 (81·5%)
Precut (access) sphincterotomy‡	100 (10·3%)	112 (11·5%)
Number of pancreatic injections, median (IQR; range)§	1 (0–2; 0–15)	0 (0–1; 0–20)
Pancreatic sphincterotomy	66 (6·8%)	58 (5·9%)
Pancreatic acinarisation¶	8 (0·8%)	6 (0·6%)
Biliary sphincterotomy	869 (89·1%)	864 (88·6%)
Trainee involvement	546 (56·0%)	555 (56·9%)
Total intravenous fluid received during periprocedural period, mL‖	1852 (938)	1796 (935)
Total intravenous lactated Ringer's fluid received during periprocedural period, mL**	1606 (1085)	1554 (1052)
Prophylactic pancreatic stent calibre in those who received a stent		
3 French	18/787 (2·3%)	0
4 French	165/787 (21·0%)	4/16 (25·0%)
5 French	586/787 (74·5%)	9/16 (56·3%)
>5 French	18/787 (2·3%)	0
Missing	0	3/16 (18·8%)
Prophylactic pancreatic stent length in those who received a stent		
2–5 cm	455/787 (57·8%)	7/16 (43·8%)
6–8 cm	95/787 (12·1%)	3/16 (18·8%)
>8 cm	237/787 (30·1%)	3/16 (18·8%)
Missing	0	3/16 (18·8%)

Data are n (%), n/N (%), or mean (SD), unless otherwise indicated. Baseline characteristics were similar in the two treatment groups. ERCP=endoscopic retrograde cholangiopancreatography. *Missing in three patients (indomethacin alone group). †Missing in 207 patients (100 in indomethacin plus stent group, 107 in indomethacin alone group) due to question being added in August, 2016. ‡Precut sphincterotomy is performed to facilitate biliary access when standard cannulation techniques are unsuccessful. §Missing in three patients (one in indomethacin plus stent group, two in indomethacin alone group). ¶Pancreatic acinarisation occurs when excessive injection of contrast agent into the pancreatic duct results in opacification of pancreatic acini. ‖Missing in two patients (one in indomethacin plus stent group, one in indomethacin alone group). **Missing in five patients (two in indomethacin plus stent group, three in indomethacin alone group).

Table 1: **Characteristics of the patients at baseline**

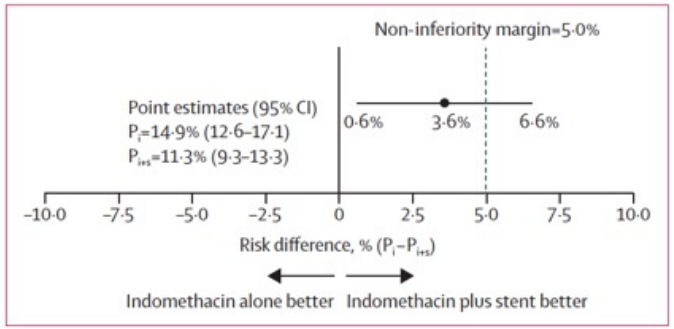


Figure 2: **Risk difference in post-ERCP pancreatitis between indomethacin alone and indomethacin plus a prophylactic stent**

Because the upper bound of the 95% CI around the risk difference in post-ERCP pancreatitis between the groups was more than 5%, non-inferiority was not demonstrated. Since the lower bound of the risk difference favouring the indomethacin plus stent group was more than 0, indomethacin alone was found to be inferior to indomethacin plus a prophylactic stent. $P_i - P_{i+s}$ represents the difference in the primary outcome (the proportion of patients with post-ERCP pancreatitis) between patients assigned to indomethacin alone and those assigned to indomethacin plus stent. ERCP=endoscopic retrograde cholangiopancreatography.

	Intention-to-treat analysis (n=1950)			Per-protocol analysis (n=1728)		
	Indomethacin plus stent (n=975)	Indomethacin alone (n=975)	Risk difference (95% CI)	Indomethacin plus stent (n=777)	Indomethacin alone (n=951)	Risk difference (95% CI)
Primary outcome						
Post-ERCP acute pancreatitis	110 (11·3%; 9·3 to 13·3)	145 (14·9%; 12·6 to 17·1)	3·6% (0·6–6·6)	90 (11·6%; 9·3 to 13·8)	137 (14·4%; 12·2 to 16·6)	2·8% (–0·3 to 6·0)
Secondary and safety outcomes						
Moderate or severe post-ERCP pancreatitis*	58 (6·0%)	78 (8·0%)	2·1% (–0·2 to 4·3)	45 (5·8%)	74 (7·8%)	2·0% (–0·4 to 4·4)
Severe pancreatitis*	14 (1·4%)	20 (2·1%)	0·6% (–0·5 to 1·8)	12 (1·5%)	19 (2·0%)	0·5% (–0·8 to 1·7)
Pancreatitis-related death	0	3 (0·3%)	0·3% (0·0 to 0·7)	0	3 (0·3%)	0·3% (0·0 to 0·7)
Serious adverse events†	352 (36·1%)	355 (36·4%)	–0·3% (–4·6 to 4·0)	282 (36·3%)	345 (36·3%)	0·0% (–4·5 to 4·6)
ICU admission	39 (4·0%)	29 (3·0%)	–1·0% (–2·7 to 0·6)	27 (3·5%)	29 (3·0%)	–0·4% (–2·1 to 1·3)
Hospital length of stay						
Mean (SD)	2·9 (6·7)	3·2 (7·2)	0·4 (–0·3 to 1·0)‡	2·8 (6·7)	3·2 (7·1)	0·3 (–0·3 to 1·0)‡
Median (range)	0·0 (0·0 to 71·0)	0·0 (0·0 to 86·0)	..	0·0 (0·0 to 62·0)	0·0 (0·0 to 86·0)	..

Data are n (%; 95% CI), n (%), or risk difference (95% CI), unless otherwise specified. The intention-to-treat analysis included all randomly assigned patients. The per-protocol analysis excluded randomly assigned participants with any of the following predefined types of protocol deviations: eligibility violations, indomethacin not administered, treatment crossover, or missing outcome data. Risk difference refers to risk in the indomethacin alone group minus risk in the indomethacin plus stent group. ERCP=endoscopic retrograde cholangiopancreatography. ICU=intensive care unit. *Outcome data missing for two patients (one in indomethacin plus stent group, one in indomethacin alone group) and excluded from percentage denominator. †A full list of serious adverse events is provided in the appendix (pp 7–10). ‡These data are difference in means (95% CI).

Table 2: **Incidence of the primary, secondary, and safety outcomes**

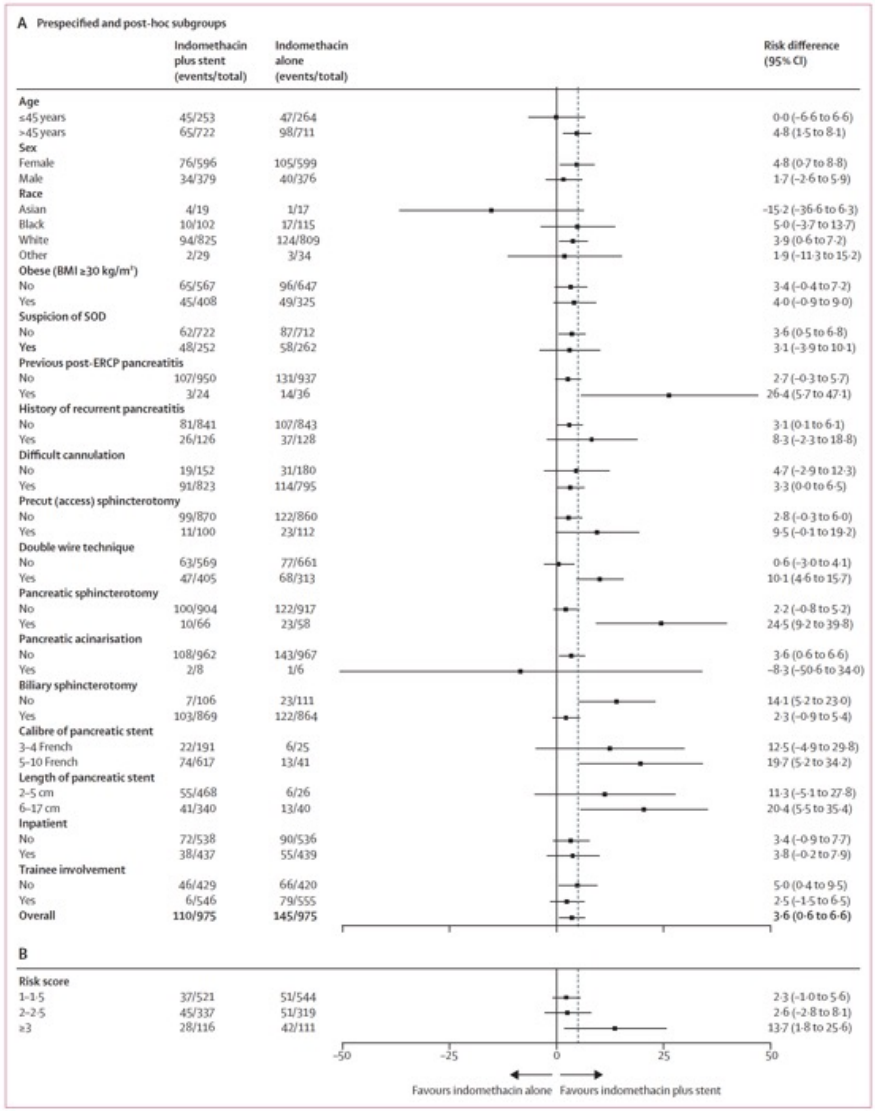


***Figure 3*: Exploratory subgroup analyses**

(A) The primary outcome was generally consistent across the prespecified subgroups. The following subgroups had a statistically significant interaction with indomethacin plus stent: pancreatic sphincterotomy (p=0·0055), double wire technique (p=0·0040), previous post-ERCP pancreatitis (p=0·038), and (absence of) biliary sphincterotomy (p=0·014). (B) The relative benefit of indomethacin plus stent increased with rising pretreatment risk score categories. The absolute risk reduction associated with indomethacin plus stent ranged from a number needed to treat to prevent one case of ERCP-related pancreatitis of 44 when the risk score was 1–1·5, to 38 when the risk score was 2–2·5, to 7 when the risk score was ≥3. Individual patient risk scores were determined by assigning 1·0 point for each major inclusion criterion and 0·5 points for each minor inclusion criterion, as outlined in the Methods section. Two patients were excluded from this analysis because of a risk score of 0 (randomised erroneously). The dashed vertical line indicates the non-inferiority margin of 5% for the risk difference. ERCP=endoscopic retrograde cholangiopancreatography. SOD=sphincter of Oddi dysfunction.

Research in context

Evidence before this study

Acute pancreatitis is the most common and potentially devastating complication of endoscopic retrograde cholangiopancreatography (ERCP). Despite important advances in the prevention of this complication, post-ERCP pancreatitis still occurs in up to 15% of high-risk cases and mortality associated with this condition appears to be rising. We searched PubMed, Ovid, and Cochrane Library electronic databases and ClinicalTrials.gov (to identify ongoing trials) between Jan 1, 1990, and Aug 30, 2023, using the search terms "post-ERCP complications", "post-ERCP pancreatitis", "post-ERCP pancreatitis prevention", "prophylactic pancreatic stent", "NSAIDs", and "indomethacin" with no restrictions on study type or language. Both prophylactic pancreatic stent placement and the administration of rectal indomethacin have independently been shown in clinical trials to reduce the incidence and severity of post-ERCP pancreatitis, and their combination is recommended for patients at elevated risk for this complication. While rectal indomethacin is widely available, safe, and easy to administer, prophylactic pancreatic stent placement is technically complex, time consuming, costly, and potentially harmful in certain situations. On this basis, and because hypothesis-generating studies have suggested that the administration of indomethacin might obviate the need for prophylactic stenting, the use of stents has decreased substantially in clinical practice, perhaps contributing to the rising mortality associated with this condition. A large-scale, methodologically rigorous, comparative effectiveness trial had not been performed but is necessary to provide clarity on the role of prophylactic stent placement in clinical practice.

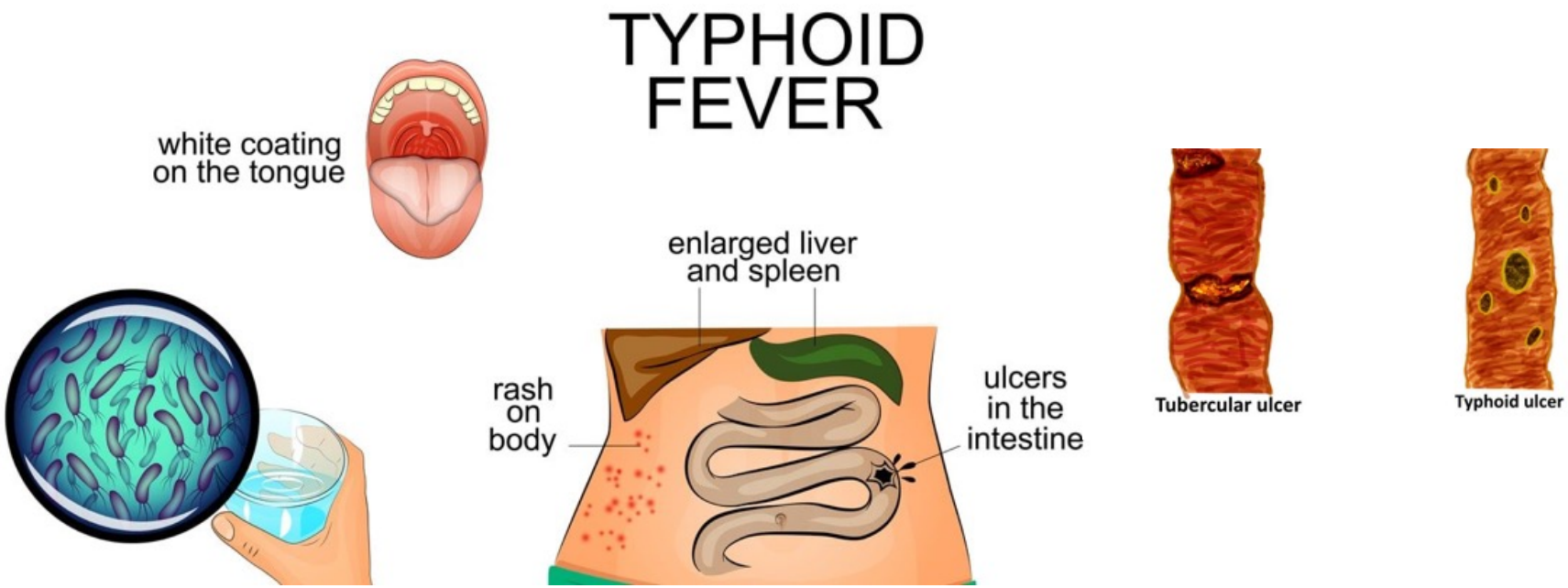
Added value of this study

In this 20-centre, randomised, non-inferiority trial, patients at high risk for post-ERCP pancreatitis were assigned to receive indomethacin alone or the combination of indomethacin plus a prophylactic pancreatic stent. We found that post-ERCP pancreatitis occurred more commonly in the indomethacin alone group compared with the indomethacin plus stent group, and this difference was statistically significant. Thus, non-inferiority was not declared and indomethacin alone was in fact found to be less effective than the combination. The relative benefit of stent placement was generally consistent across study subgroups but appeared to be more prominent among patients at highest risk for pancreatitis. This study addresses two important limitations in the design of previous trials evaluating prophylactic stent placement—their open-label design and conduct at a limited number of expert centres. Because the development of post-ERCP pancreatitis can be affected by unequal co-interventions between study groups and because its definition is somewhat subjective (related to the interpretation of pain and the decision to hospitalise patients), we implemented rigorous study operations that aimed to ensure masking at the level of the participant, clinician caring for the patient after ERCP, and outcomes adjudicator. Additionally, the study was conducted across a large number of medical centres, with more than 100 participating endoscopists, increasing the generalisability of the findings.

Implications of all the available evidence

The findings of this trial support prophylactic pancreatic stent placement in addition to rectal indomethacin administration for preventing pancreatitis in high-risk patients, in accordance with existing international clinical practice guidelines. These findings should reverse the widespread abandonment of prophylactic pancreatic stenting that has been observed recently in the absence of an evidence base to support it. In this trial, stents appeared to be protective in the large subgroup of patients who experienced a difficult cannulation during ERCP—a common situation in which risk is increased to some extent—but those at highest risk for the complication appeared to derive the most benefit, underscoring the importance of this intervention in the most vulnerable patients especially.

What Is Typhoid Fever And How Do You Treat It?



Der deutsche Begriff „Typhus“ stiftet im Ausland gelegentlich Verwirrung. Die Krankheit heißt auf englisch „typhoid fever“ oder auch „enteric fever“. Der englische Begriff „typhus“ bezeichnet hingegen eine andere Gruppe von Infektionskrankheiten.

Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children

Summary

Background Randomised controlled trials of typhoid conjugate vaccines among children in Africa and Asia have shown high short-term efficacy. Data on the durability of protection beyond 2 years are sparse. We present the final analysis of a randomised controlled trial in Malawi, encompassing more than 4 years of follow-up, with the aim of investigating vaccine efficacy over time and by age group.

Methods In this phase 3, double-blind, randomised controlled efficacy trial in Blantyre, Malawi, healthy children aged 9 months to 12 years were randomly assigned (1:1) by an unmasked statistician to receive a single dose of Vi polysaccharide conjugated to tetanus toxoid vaccine (Vi-TT) or meningococcal capsular group A conjugate (MenA) vaccine. Children had to have no previous history of typhoid vaccination and reside in the study areas for inclusion and were recruited from government schools and health centres. Participants, their parents or guardians, and the study team were masked to vaccine allocation. Nurses administering vaccines were unmasked. We did surveillance for febrile illness from vaccination until follow-up completion. The primary outcome was first occurrence of blood culture-confirmed typhoid fever. Eligible children who were randomly assigned and vaccinated were included in the intention-to-treat analyses. This trial is registered at ClinicalTrials.gov, NCT03299426.

Findings Between Feb 21, 2018, and Sept 27, 2018, 28 130 children were vaccinated; 14 069 were assigned to receive Vi-TT and 14 061 to receive MenA. After a median follow-up of 4·3 years (IQR 4·2–4·5), 24 (39·7 cases per 100 000 person-years) children in the Vi-TT group and 110 (182·7 cases per 100 000 person-years) children in the MenA group were diagnosed with a first episode of blood culture-confirmed typhoid fever. In the intention-to-treat population, efficacy of Vi-TT was 78·3% (95% CI 66·3–86·1), and 163 (129–222) children needed to be vaccinated to prevent one case. Efficacies by age group were 70·6% (6·4–93·0) for children aged 9 months to 2 years; 79·6% (45·8–93·9) for children aged 2–4 years; and 79·3% (63·5–89·0) for children aged 5–12 years.

Interpretation A single dose of Vi-TT is durably efficacious for at least 4 years among children aged 9 months to 12 years and shows efficacy in all age groups, including children younger than 2 years. These results support current WHO recommendations in typhoid-endemic areas for mass campaigns among children aged 9 months to 15 years, followed by routine introduction in the first 2 years of life.

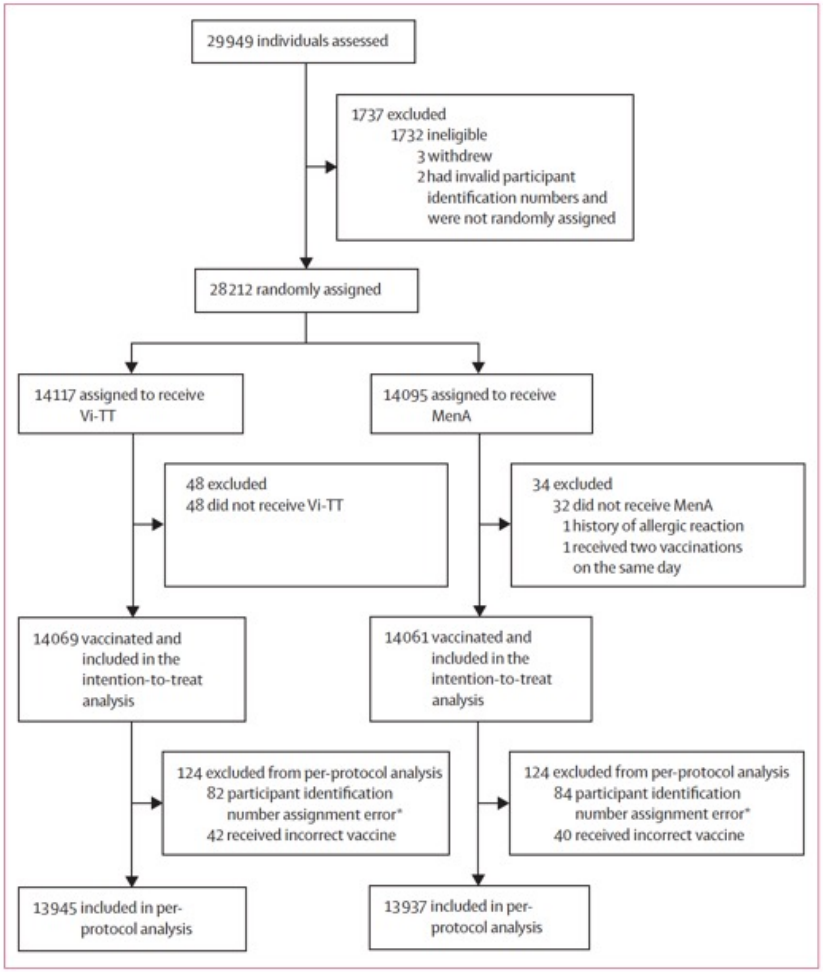


Figure 1: **Trial profile**
248 participants were excluded from the per-protocol analysis due to a participant identification number assignment error or vaccine administration error. MenA=meningococcal capsular group A conjugate vaccine. Vi-TT=Vi polysaccharide tetanus toxoid typhoid conjugate vaccine. *166 pairs of children received the same participant identification number due to a duplicate bar code printing error. The second participant who received the duplicate number within a pair was assigned a new number and excluded from the per-protocol analysis.

	Vi-TT (n=14 069)	MenA (n=14 061)
Age at enrolment (years)		
Mean (SD)	6·1 (3·3)	6·2 (3·3)
Median (range)	6·0 (0·8–12·0)	6·0 (0·8–12·0)
Age group		
<2 years	1555 (11·1%)	1600 (11·4%)
2–4 years	3503 (24·9%)	3579 (25·5%)
≥5 years	9011 (64·1%)	8882 (63·2%)
Sex		
Female	7065 (50·2%)	7231 (51·4%)
Male	7004 (49·8%)	6830 (48·6%)
Ethnicity		
Black African	14 069 (100·0%)	14 061 (100·0%)
Study site		
Ndirande	8863 (63·0%)	8832 (62·8%)
Zingwangwa	5206 (37·0%)	5229 (37·2%)

Data are n (%) unless otherwise specified. Vi-TT=Vi polysaccharide tetanus toxoid typhoid conjugate vaccine. MenA=meningococcal capsular group A conjugate vaccine.

Table 1: **Baseline characteristics of the intention-to-treat population**

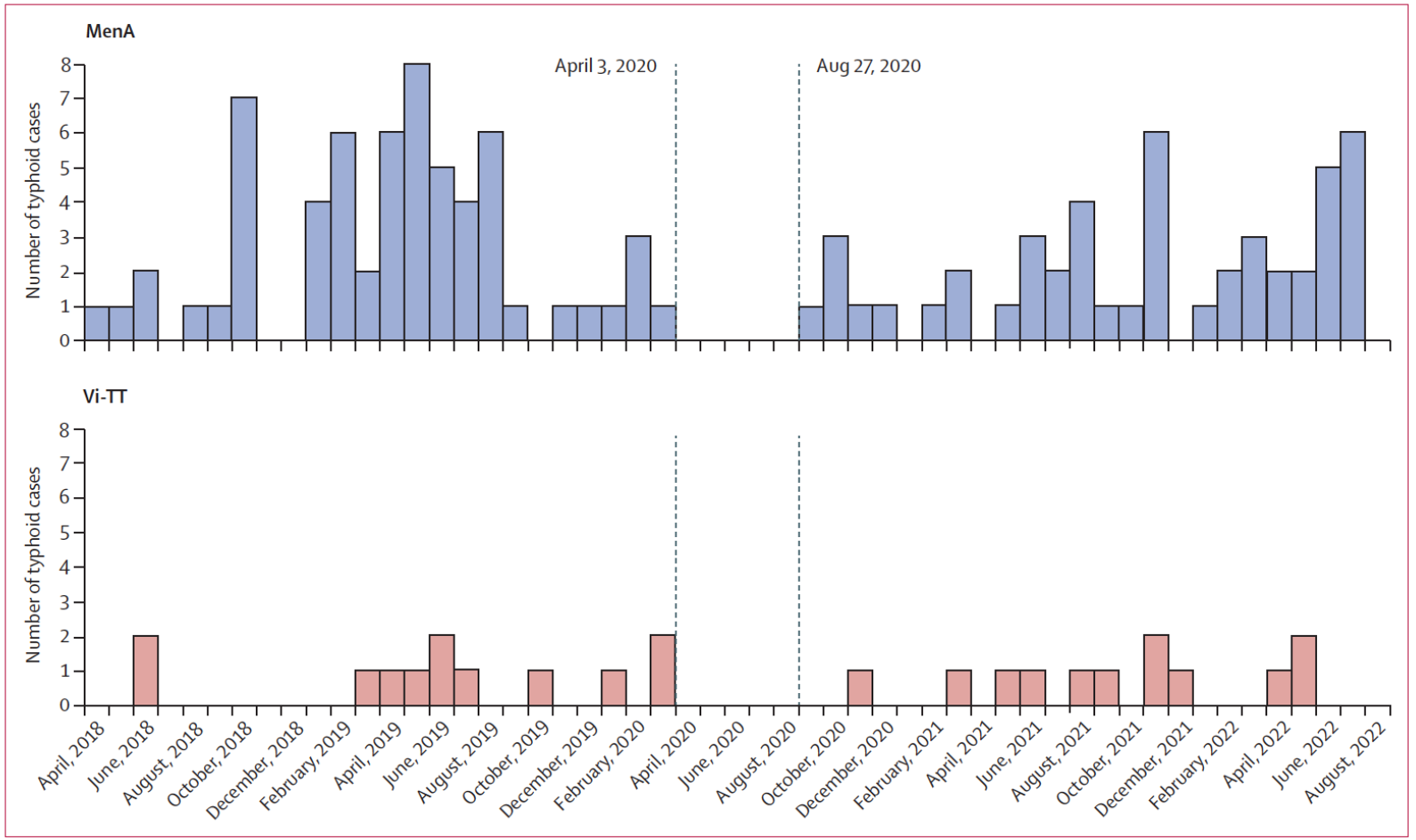


Figure 2: **Number of blood-culture positive typhoid cases in the intention-to-treat population, by date and vaccine group**

Dates of COVID-19 surveillance interruptions are shown with dotted vertical lines. MenA=meningococcal capsular group A conjugate vaccine. Vi-TT=Vi polysaccharide tetanus toxoid typhoid conjugate vaccine.

	Number at risk	Total follow-up time (person-years)	Number of cases of blood-culture-confirmed typhoid fever	Incidence rate (per 100 000 person-years; 95% CI)	Protective efficacy of Vi-TT (95% CI)	Absolute risk reduction per 1000 children (95% CI)*	Number needed to vaccinate (95% CI)†
Intention-to-treat population							
Vi-TT	14 069	60 500	24	39·7 (25·4–59·0)	78·3% (66·3–86·1)	6·1 (4·5–7·7)	163 (129–222)
MenA	14 061	60 220	110	182·7 (150·1–220·2)	Ref	Ref	Ref
Age at vaccination							
<2 years							
Vi-TT	1555	6586	4	60·7 (22·8–161·8)	70·6% (6·4–93·0)	6·2 (1·0–11·4)	162 (88–1035)
MenA	1600	6773	14	206·7 (122·4–349·0)	Ref	Ref	Ref
2–4 years							
Vi-TT	3503	15 007	5	33·3 (13·9–80·1)	79·6% (45·8–93·9)	5·6 (2·6–8·6)	180 (117–391)
MenA	3579	15 297	25	163·4 (110·4–241·9)	Ref	Ref	Ref
≥5 years							
Vi-TT	9011	38 907	15	38·6 (23·2–64·0)	79·3% (63·5–89·0)	6·3 (4·3–8·4)	158 (120–233)
MenA	8882	38 151	71	186·1 (147·5–234·8)	Ref	Ref	
Per-protocol population							
Vi-TT	13 945	59 942	22	36·7 (23·0–55·6)	80·0% (68·3–87·3)	6·2 (4·6–7·8)	160 (127–216)
MenA	13 937	59 662	109	182·7 (150·0–220·4)	Ref	Ref	Ref

Vi-TT=Vi polysaccharide tetanus toxoid typhoid conjugate vaccine. MenA=meningococcal capsular group A conjugate vaccine. *Absolute risk reduction (risk in the MenA group minus risk in the Vi-TT group) is the total reduction in the risk of blood-culture-confirmed typhoid fever that resulted from vaccination with TCV. †Number needed to vaccinate is the number of children that would need to be vaccinated to prevent one case of blood-culture-confirmed typhoid fever.

Table 2: **Blood-culture-confirmed typhoid fever and vaccine efficacy**

	Number at risk	Total follow-up time (person-years)	Number of cases of blood-culture-confirmed typhoid fever	Incidence rate (per 100 000 person-years; 95% CI)	Protective efficacy of Vi-TT (95% CI)
Cumulative time since vaccination					
0–1 years					
Vi-TT	14 069	14 058	6	42·7 (19·2–95)	83·4% (60·1–94·3)
MenA	14 061	14 036	36	256·5 (185·0–355·6)	Ref
0–2 years					
Vi-TT	14 069	28 104	12	42·7 (24·2–75·2)	80·7% (63·8–90·5)
MenA	14 061	28 021	62	221·3 (172·5–283·8)	Ref
0–3 years					
Vi-TT	14 069	42 135	15	35·6 (21·5–59·1)	80·1% (65·0–89·4)
MenA	14 061	41 983	75	178·6 (142·5–224·0)	Ref
0–4 years					
Vi-TT	14 069	56 121	23	41·0 (27·2–61·7)	77·1% (63·7–86·1)
MenA	14 061	55 889	100	178·9 (147·1–217·7)	Ref
0–4·61 years					
Vi-TT	14 069	60 500	24	39·7 (25·4–59·0)	78·3% (66·3–86·1)
MenA	14 061	60 220	110	182·7 (150·1–220·2)	Ref
Discrete time since vaccination					
First year					
Vi-TT	14 069	14 058	6	42·7 (19·2–95·0)	83·4% (60·1–94·3)
MenA	14 061	14 036	36	256·5 (185·0–355·6)	Ref
Second year					
Vi-TT	14 050	14 046	6	42·7 (19·2–95·1)	77·0% (42·9–92·3)
MenA	14 006	13 985	26	185·9 (126·6–273·1)	Ref
Third year					
Vi-TT	14 043	14 031	3	93·1 (54·1–160·3)	77·0% (16·4–95·8)
MenA	13 976	13 963	13	93·1 (54·1–160·3)	Ref
Fourth year					
Vi-TT	13 996	13 986	8	57·2 (28·6–114·4)	68·2% (27·2–87·6)
MenA	13 928	13 906	25	179·8 (121·5–266·1)	Ref
Fifth year (up to 4·61 years)					
Vi-TT	13 980	4379	1	22·8 (3·2–162·1)	90·1% (30·5–99·8)
MenA	13 893	4331	10	230·9 (124·2–429·1)	Ref

Vi-TT=Vi polysaccharide tetanus toxoid typhoid conjugate vaccine. MenA=meningococcal capsular group A conjugate vaccine.

Table 3: **Blood-culture-confirmed typhoid fever and vaccine efficacy over time in the intention-to-treat population**

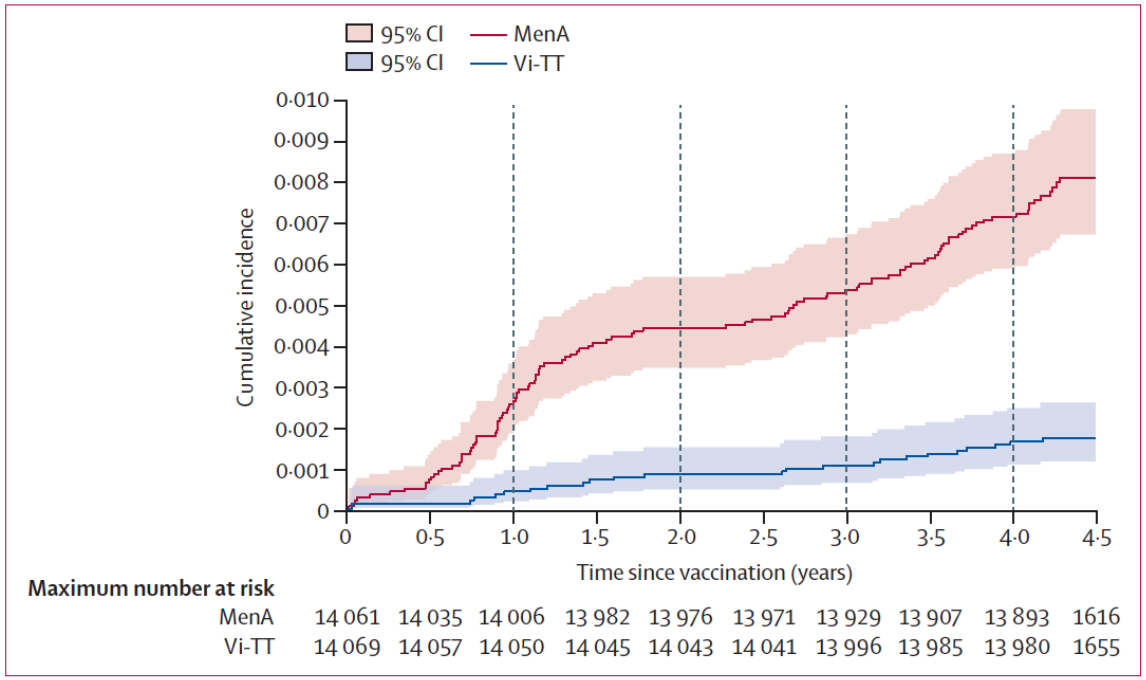


Figure 3: **Kaplan-Meier estimates of the cumulative incidence of blood-culture positive typhoid fever**
Curves begin on vaccination day 0 and are for the intention-to-treat population by vaccine group. MenA=meningococcal capsular group A conjugate vaccine. Vi-TT=Vi polysaccharide tetanus toxoid typhoid conjugate vaccine.

Research in context

Evidence before this study

Until 2018, the only WHO-recommended vaccines available were Vi polysaccharide or Ty21a live oral vaccines, which were not suitable for children younger than 2 years and were accordingly rarely used in low-income settings. WHO recommended typhoid conjugate vaccine (TCV) in 2018 for mass catch-up campaigns for those up to 15 years of age and routine introduction at age 9–15 months in endemic countries, with priority to countries with high typhoid incidence or high antimicrobial resistance among *S* Typhi isolates. Randomised controlled trials in Nepal, Bangladesh, and Malawi established the efficacy of the vaccine at 18–36 months after vaccination. We searched PubMed and the Cochrane Central Register of Controlled Trials for clinical trials involving children using the terms "typhoid conjugate vaccine" and "efficacy" between Jan 1, 1970, and March 29, 2023, with no language restrictions and filters for the following age ranges: 1–23 months, 2–5 years, 6–12 years, and 13–18 years. Five clinical trials evaluating the efficacy of TCV in children in Malawi, Nepal, Bangladesh, Viet Nam, and India were identified. The TCV efficacy trials conducted in Malawi, Nepal, and Bangladesh used single-dose Vi-TT and reported vaccine efficacy against blood culture-confirmed typhoid fever of 80·7% (95% CI 64·2–89·6) at 18–24 months in Malawi, 79·0% (61·9–88·5) at 24 months in Nepal, and 85% (97·5% CI 76–91) at 18 months in Bangladesh.

The other two trials identified in the search used two-dose regimens of Vi polysaccharide conjugated to Pseudomonas aeruginosa exotoxin A (Vi-rEPA; in Viet Nam) and Vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph; in India). The trial of Vi-rEPA began in 1998 and found a vaccine efficacy of 91·5% (95% CI 77·1–96·6) against blood culture-confirmed typhoid fever through 27 months of follow-up in children aged 2–5 years. After unmasking, passive surveillance was conducted for another 19 months, with a vaccine efficacy of 82·4% (22·3–99·1) during that period. The Vi-rEPA did not progress further in development and was not marketed. The PedaTyph trial reported a vaccine efficacy of 100% (97·6–100) for a two-dose regimen over a 12-month surveillance period in children aged 6 months to 12 years. In addition to the short follow-up, this trial enrolled a small sample size, was not individually randomised, and did not include a control vaccine.

Added value of this study

This is the first randomised, controlled, double-blind trial to evaluate the longer-term efficacy of single-dose TCV in a typhoid fever-endemic setting from 9 months of age. Our study provides evidence that Vi-TT provides durable overall protection beyond 48 months after vaccination among children vaccinated between 9 months and 12 years of age, with little decline in efficacy over time. We estimated that vaccine efficacy reduced over time by only 1·3% per year over 4 years. The longer durability of protection translates into a lower number needed to vaccinate to prevent each case of blood culture-confirmed typhoid fever. An age-stratified analysis found that the vaccine is efficacious in all age groups, including children younger than 2 years old.

Implications of all the available evidence

Our data support robust and durable overall protection—for at least 4 years—in children vaccinated according to the WHO recommendation of a single dose of TCV for infants and children in typhoid-endemic areas. The results from this longer term trial support the high estimated cost-effectiveness of these vaccines, generated using assumptions that were based on previous trials of shorter duration. Further long-term data to assess the durability of protection, particularly in young children following WHO-recommended routine introduction of TCV, are warranted.

Anti-$GABA_A$ receptor encephalitis 14 months after allogeneic haematopoietic stem-cell transplant for acute myeloid leukaemia

A 61-year-old man was admitted to our hospital with a 5-day history of sudden-onset, persistent myocloni in his left leg and the left side of his abdomen. Previously, the patient had been fit and well. He reported no recent fever, headache, or trauma.

14 months before admission, the patient had an allogeneic haematopoietic stem cell transplantation for acute myeloid leukaemia with mutated *nucleophosmin 1* which resulted in full remission.

On examination, we found the patient generally well; he had painless, rhythmic myocloni, with a frequency of 0·5–1·0 per s, of the proximal left leg and abdomen. The movements were continuous and would not be triggered or suppressed by any specific movements. The patient had no other atypical findings and cognitively was fully alert and conscious.

Laboratory investigations—apart from a previously described macrocytosis—were within typical range.

On day 1 after admission, an MRI of the patient's brain showed multiple cortico-subcortical fluid-attenuated-inversion-recovery hyperintense lesions without diffusion restrictions or contrast-enhancement (figure).

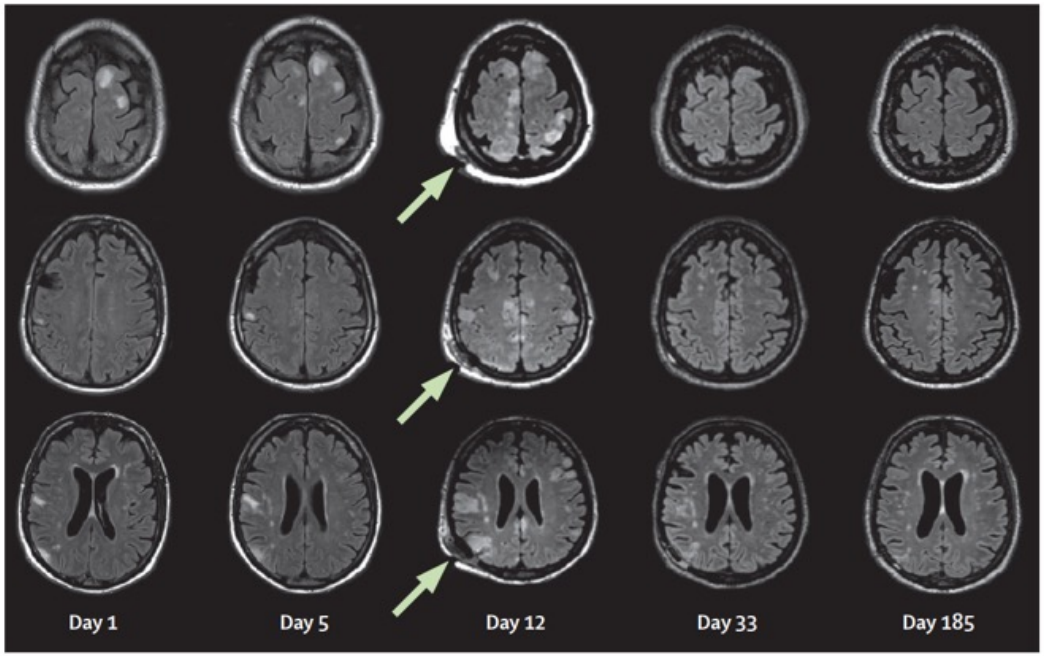


Figure: **Anti-$GABA_A$ receptor encephalitis 14 months after allogeneic haematopoietic stem-cell transplant for acute myeloid leukaemia**

Serial axial fluid-attenuated-inversion-recovery MRIs done on the day of admission (day 1), day 5, day 12, day 33, and at follow-up on day 185, showing supratentorial, bi-hemispheric, multifocal, non-confluent cortico-subcortical hyperintense lesions without diffusion restriction or contrast-enhancement (not shown). Notably, lesion progression decreased after treatment initiation on day 15. The focal tissue swelling in the right parietal region on day 12 is attributed to a brain biopsy (arrows).

On day 2 after admission, cerebrospinal fluid (CSF) analyses showed normal cell and protein count; microbial multiplex PCR testing and cytology tests for malignancies were negative.

On day 3, a scalp electroencephalogram (EEG) showed no epileptiform discharges that correlated with the myocloni. Further investigations found no neoplasms.

On day 5, the myocloni extended to the proximal part of the left arm despite the patient being given multiple antiseizure medications.

On day 8 after admission, a biopsy of the brain was done and histopathological analysis of a sample of the biopsy showed T-cell-dominated perivascular lymphocyte infiltrates and endothelial proliferations without evidence of viral infection, demyelination, graft-versus-host disease, or neoplasia.

From day 9 after admission, the patient's condition deteriorated; he became disorientated and confused, then drowsy and stuporous; the myocloni continued.

Repeated MRIs, from days 5 to 12 after admission, showed progression of the multiple cortico-subcortical lesions (figure); the EEG showed right-hemispheric temporo-parietal focal slowing independent of the worsening of the patient's condition.

On day 15 after admission, he developed electroclinical super-refractory status epilepticus, which was finally terminated by continuous intravenous thiopental. At this stage autoimmune encephalitis was suspected and immunosuppressive treatment with prednisolone, plasmapheresis, intravenous immunoglobulins, and rituximab started; serum and CSF—collected prior to initiation of the treatments—was subsequently found to be positive for $GABA_A$ receptor antibodies (serum titre 1:320; normal <1:20; CSF titre 1:1), confirming the diagnosis of anti-$GABA_A$ receptor encephalitis.

On day 33 and day 185, MRIs showed improvement (figure) with concomitant decreases in serum antibody titres (day 79, 1:20; day 186, <1:20) and serum neurofilament light chain concentrations—day 34, 511·5 pg/mL (99·995 percentile); day 233, 25·4 pg/mL (97·20 percentile).

During the period of hospitalisation, the patient experienced multiple complications, including asystole, which required resuscitation, and critical-illness polyneuromyopathy. After a prolonged stay in the intensive care unit, the patient was transferred to a neurorehabilitation unit.

HIV epidemiology, prevention, treatment, and implementation strategies for public health

The global HIV response has made tremendous progress but is entering a new phase with additional challenges. Scientific innovations have led to multiple safe, effective, and durable options for treatment and prevention, and long-acting formulations for 2-monthly and 6-monthly dosing are becoming available with even longer dosing intervals possible on the horizon. The scientific agenda for HIV cure and remission strategies is moving forward but faces uncertain thresholds for success and acceptability. Nonetheless, innovations in prevention and treatment have often failed to reach large segments of the global population (eg, key and marginalised populations), and these major disparities in access and uptake at multiple levels have caused progress to fall short of their potential to affect public health. Moving forward, sharper epidemiologic tools based on longitudinal, person-centred data are needed to more accurately characterise remaining gaps and guide continued progress against the HIV epidemic. We should also increase prioritisation of strategies that address socio-behavioural challenges and can lead to effective and equitable implementation of existing interventions with high levels of quality that better match individual needs. We review HIV epidemiologic trends; advances in HIV prevention, treatment, and care delivery; and discuss emerging challenges for ending the HIV epidemic over the next decade that are relevant for general practitioners and others involved in HIV care.

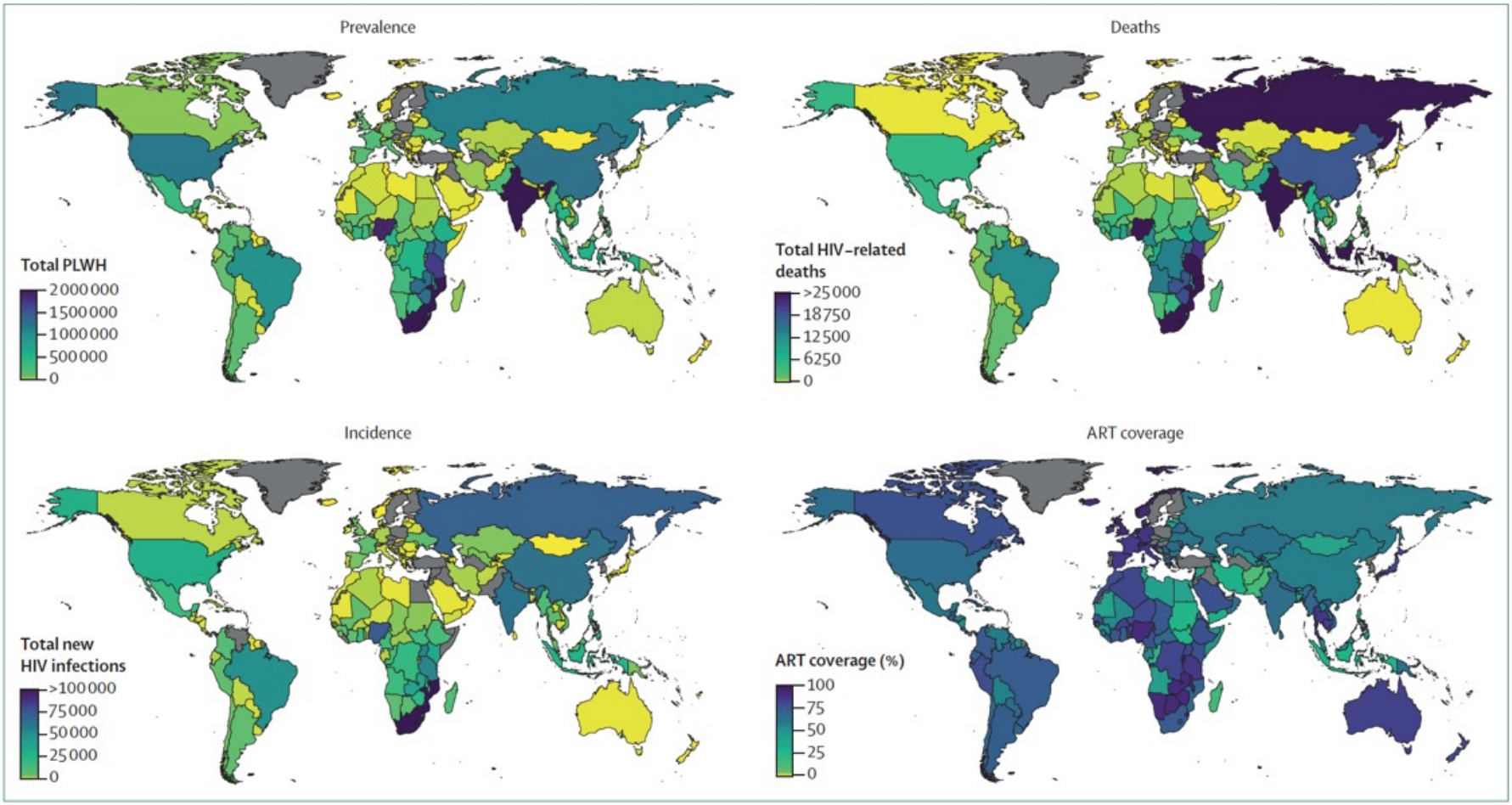


Figure 1: **Estimated numbers of people living with HIV, HIV-related deaths, new HIV infections, and antiretroviral therapy coverage**

Country data were consolidated from UNAIDS 2018 to 2021 datasets[5,6] with the most recent data for each respective country. For countries with missing data, we calculated estimates with other available indicators (eg, incidence rate and total population to estimate new infections) or sourced estimates from the respective country's government data (eg, Canada,[7] China,[8] Japan,[9] Russia,[10] UK,[11] and the USA).[12,13] ART=antiretroviral therapy. PLWH=people living with HIV.

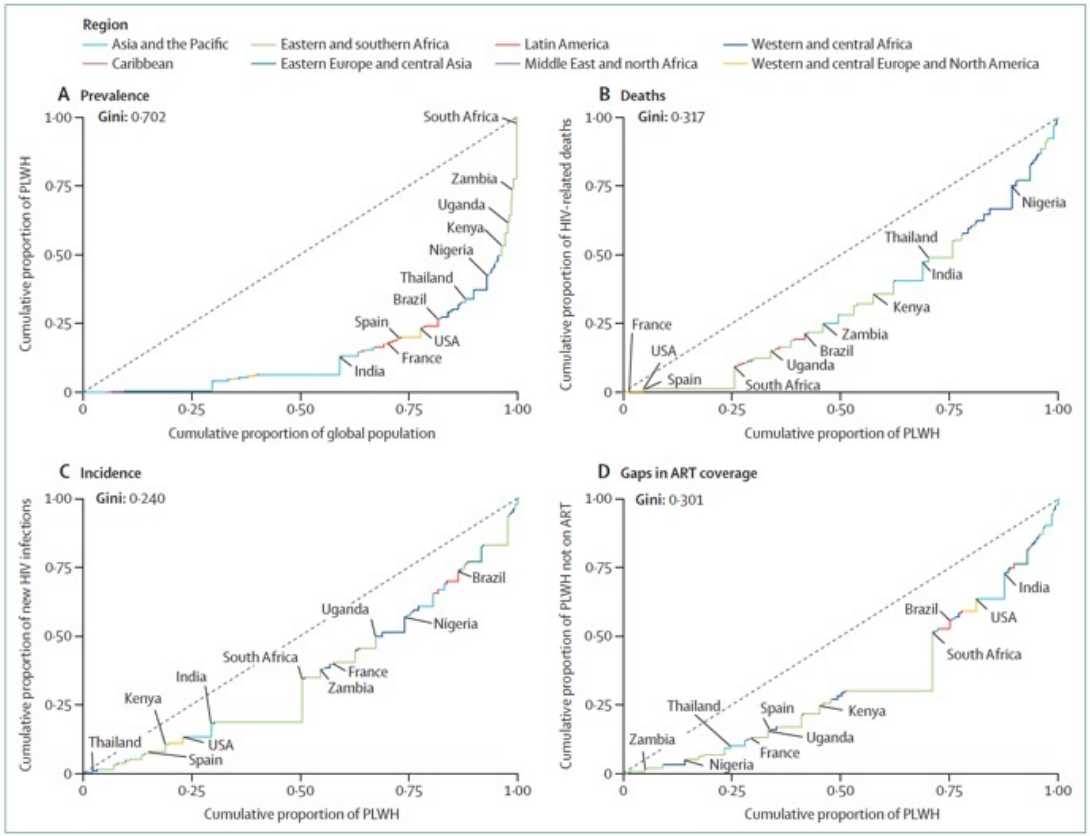


***Figure 2*: Lorenz curves of disparities in prevalence, mortality, incidence, and gaps in antiretroviral therapy coverage across countries**

This figure shows modified Lorenz curves examining disparities in HIV outcomes and service delivery. Each line segment represents a country colour-coded by region that is sorted by the slope of the connecting line, with countries performing better relative to each metric sorted to the left of the each figure and countries doing worse sorted to the right. Country labels correspond to line segments immediately before the label. The dashed line represents equitable distribution if HIV prevalence, mortality, incidence, or ART coverage was evenly distributed across countries. For example, equitable distribution would occur if 50% of morbidity and mortality occurred in countries accounting for 50% of the population. The further the Lorenz curve moves from the line of equity, the more disparities there are across countries. The Lorenz curves measure disparities in the distribution of (A) prevalence (PLWH relative to the overall population), (B) mortality (HIV-related deaths relative to PLWH), (C) incidence (new HIV infections relative to PLWH [ie, slope equals the incidence to prevalence ratio]), and (D) gaps in ART Coverage (PLWH not on ART relative to PLWH). Gini coefficients are a measure of equality or inequality, with 0 indicating perfect equality and 1 indicating perfect inequality (ie, all morbidity or mortality concentrated in a single country). Country data were consolidated from UNAIDS 2018 to 2021 datasets[5,6] with the most recent data for each respective country. For countries with missing data, we calculated estimates from other available indicators (eg, incidence rate and total population to estimate new infections) or sourced estimates from the respective country's government data (eg, Canada,[7] China,[8] Japan,[9] Russia,[10] UK,[11] and the USA),[12,13] to the extent possible.
ART=antiretroviral therapy. PLWH=people living with HIV.

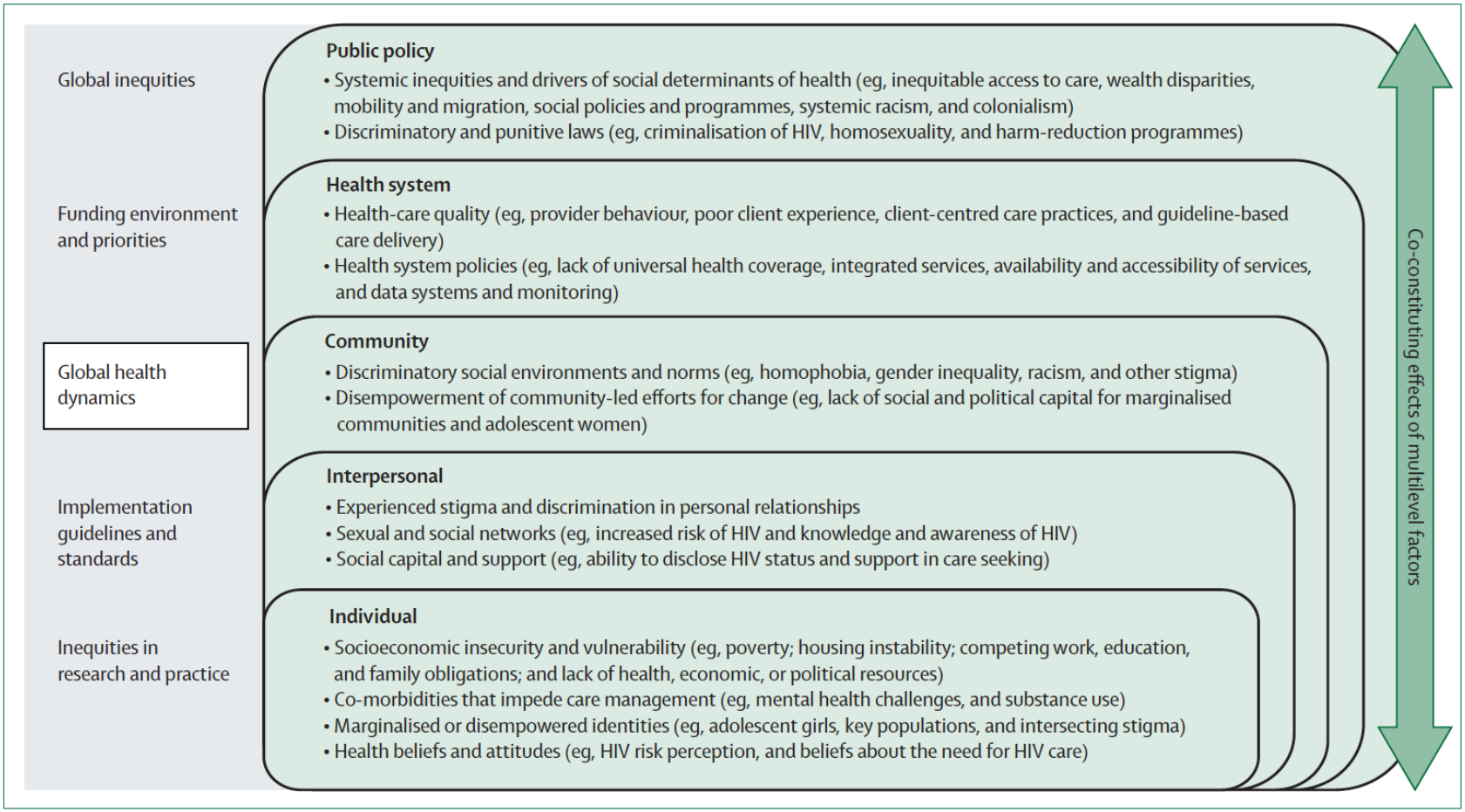


***Figure 3*: Socioecological model of drivers of equitable access, implementation, and outcomes for HIV treatment and prevention**

	Example drugs	Clinical evidence	Clinical and implementation considerations
Prevention			
VMMC	..	Rakai,[59] ANRS 1265,[51] and Kisumu[52]	Permanent but partial protection; one-time procedure allows for novel strategies to reach populations (eg, community-based strategies); and consider preference for circumcisions
Daily oral PrEP	TDF/FTC	iPrex,[53] Partners PrEP,[54] Botswana TDF2,[55] Bangkok TDF,[56] FemPrEP,[57] VOICE,[58] iPrex OLE,[59] and PROUD[60]	Requires daily adherence and ongoing engagement in care; at least 4 doses per week might offer sufficient protection for receptive anal sex, and daily recommended for vaginal sex; cost and comorbidities can drive choice: TDF/FTC renal and bone side-effects, TAF/FTC weight gain and increased lipids; no evidence for TAF/FTC in females; and novel care models might be used to help overcome structural, psychosocial, and clinic-based barriers to long-term engagement in care
	TAF/FTC	Discover[61]	Same as above
Event-driven oral PrEP	TDF/FTC	Ipergay[62]	Essential to be able to plan to take pills at least 2 hours in advance of sex; might be preferable for some patients who have sex infrequently; requires ongoing engagement in care; evidence only among SMM and transgender women; and no evidence for event-driven oral PrEP in females
Long-acting PrEP formulations	CAB injection every 2 months	HPTN 083[63] and HPTN 084[64]	Does not require daily adherence; concerns for transmissions and resistance with long tail after missed injections; client should receive daily oral PrEP after discontinuation; viral load recommended for monitoring and considerations to align injections with lab monitoring; preferable for some clients, others might not desire due to frequency of visits to clinic or injection site reactions (depending on formulation and duration); and cost, cold-chain, and injection administration logistics remain challenges
	Lenacapavir injection every 6 months	Purpose 1 and 2 (ongoing trials NCT04994509 and NCT04925752)	Same as above
	Islatravir as monthly or yearly implant	No longer being developed due to declines in total lymphocyte and CD4 T-cell counts	Same as above
Vaginal ring	Dapivirine	RING[65] and ASPIRE[66]	Decreased efficacy in trials possibly due to adherence; might be preferable for some patients; primary roll-out focused in Africa; and no longer under consideration in the USA
Vaginal or rectal microbicide	TDF gel	Vaginal TDF gels[68,67] and rectal formulation in development	No currently approved products due to a lack of efficacy observed in trials (adherence-related)
Multi-prevention technologies	Dual prevention pill (TDF/FTC + oral contraceptive)	In development[68]	Might be more preferable for some patients; and decreased stigma associated with using a combination product
Monoclonal antibody	VRC01 monoclonal antibody every 2 months	AMP trials[69]	Proof of concept that appropriately matched bNAbs might offer longer durations of protection (27% effect overall, but 75% effective for VRC01-sensitive viruses); and should consider cost and logistics for infusion if further developed
HIV vaccine	..	RV144[70] 31.2% efficacy; VAX003[71] and VAX004[72] no efficacy; HVTN502,[73] HVTN503,[74] and HVTN505[75] no efficacy; Uhambo (HVTN 702) no effect,[76] stopped February 2020; Imbokodo (HVTN 705) no effect, stopped August 2021; Mosaico (HVTN 706) no effect, stopped January 2023; and PrEPVacc ongoing	No effective vaccines to date
Treatment			
Daily three-drug oral tablets	DTG or BIC combined with TXF (TDF or TAF) + XTC (FTC or 3TC)	First line: SINGLE,[77] ADVANCE,[78] NAMSAL,[79] VESTED,[80] DOLPHIN2,[81] ODYSSEY,[82] FLAMINGO,[83] ARIA,[84] and SPRING-2;[85] Bictegravir studies;[86–89] second line: NADIA,[90] D2EFT,[91] DAWNING,[92] SAILING,[93] and VIKING[94]	Safe and effective with high barrier to resistance, including during pregnancy; effective as second-line regimen even with non-active NRTIs, but risk of INSTI resistance in small proportion who are unresponsive to treatment (compared with PI-based regimen); INSTIs associated with weight gain, particularly in combination with TAF; requires daily adherence and ongoing engagement in care; and novel care models might be used to help overcome structural, psychosocial, and clinic-based barriers to long-term engagement in care
	DOR combined with TDF + FTC	DRIVE-AHEAD,[95] DRIVE-FORWARD,[96] and DRIVE-SHIFT[97]	Lower barrier to resistance with DOR; not co-formulated with TAF (exposure to TDF-associated bone and renal side-effects); and might be a good option for INSTI +/- TAF associated weight gain
	DRV/c or DRV/r combined with TXF (TDF or TAF) + XTC (FTC or 3TC)	NADIA,[90] DRV meta-analysis,[98] and Flamingo[83]	Consider use with adherence challenges and drug resistance; effective as second-line regimen even with non-active NRTIs; limited risk of developing PI resistance in small proportion who are unresponsive; and decreased tolerability and drug interactions with PI-based regimen

(Table 1 continues on next page)

	Example drugs	Clinical evidence	Clinical and implementation considerations
(Continued from previous page)			
Daily two-drug regimens	DTG/RPV	SWORD-1 and SWORD-2[99]	DTG/RPV and DTG/3TC not inferior to three-drug regimen, but more INSTI resistance among those who do not respond to treatment; potentially fewer long-term side-effects with NRTI-sparing regimen; and DTG/DRV/r highly effective for second-line therapy
	DTG/3TC	GEMINI-1 and GEMINI-2,[100] TANGO,[101] and SALSA[102]	Same as above
	Islatravir/Doravirine daily	ILLUMINATE studies[103,104]	Same as above
	DTG/DRV/r	D2EFT[91]	Same as above
Long-acting formulations	CAB/RPV injectable every 2 months	FLAIR[105] and ATLAS[106]	Does not require daily adherence; might be important option for patients with adherence challenges; concerns for resistance with CAB/RPV (including to INSTI) with long tail after missed injections, lower barrier to resistance, and missed previous NNRTI resistance; elevated BMI (≥30 kg/m2) and HIV-1 subtype A6/A1 also associated with increased risk of failure and resistance; preferable for some clients, others might not prefer due to frequency of visits to clinic or injection site reactions (depending on formulation and duration); full regimen (not just single medication) should be long-acting to achieve maximum benefits (CAB/RPV currently only full regimen available); considerations to align injections with laboratory monitoring and clinical visits; and cost, cold-chain, and injection administration logistics remain challenges
	Lenacapavir injection every 6 months	CALIBRATE[107] (ongoing)	Same as above
	Islatravir/lenacapavir oral weekly	Phase 2 study ongoing (NCT05052996)	Same as above
Medications for salvage therapy in heavily treatment-experienced patients	Fostemsavir oral daily	BRIGHTE[108]	Consider ease of administration, adherence concerns, other active ART, and patient preference when selecting
	Ibalizumab infusion every 2 weeks	TMB-301[109]	Same as above
	Lenacapavir injection every 6 months	CAPELLA[110]	Same as above
bNab combination	bNAb combination infusion	Sneller et al[111]	Proof of concept that passive infusion bNAbs with long half-lives can maintain viral suppression for sensitive isolates (up to 6 months); and should consider cost and logistics for infusion if further developed

3TC=lamivudine. ART=antiretroviral therapy. bNab=broadly neutralising antibody. BIC=bictegravir. CAB=cabotegravir. DOR=doravirine. DRV=darunavir. DRV/c=darunavir/cobicistat. DRV/r=darunavir/ritonavir. DTG=dolutegravir. FTC=emtricitabine. INSTI=integrase strand transfer inhibitor. SMM=sexual minority men. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. PrEP=pre-exposure prophylaxis. RPV=rilpivirine. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate. TXF=TAF or TDF. VMMC=voluntary medical male circumcision. XTC=lamivudine or emtricitabine.

Table 1: **Evidence-based interventions for HIV prevention and treatment**

	Example studies	Potential mechanisms and effects on reach, effectiveness, adoption, implementation, or maintenance (RE-AIM)
Streamlined facility-based models		
Health service delivery and implementation process*		
Cascade target: Testing	Implementation of HIV self-testing at facilities[174-176]	Improved acceptability and uptake (adoption), numbers tested (reach), and improved efficiency (implementation and maintenance)
Cascade target: Prevention	Drop-in clinic with same-day PrEP[177]	Improved acceptability (adoption), efficiency (implementation), and increased opportunity to initiate (reach and effectiveness)
Cascade target: Treatment	Facility-based adherence clubs[178-180] and extending refill duration[181,182]	Decrease burden of receiving care (acceptability and efficacy) and increased efficiency of clinic flows (implementation)
Community-based models		
Health service delivery and implementation process*		
Cascade target: Testing	Implementing HIV testing at community health fairs[183,184]	Increased access to testing (reach new populations), increased efficiency (rapid, high-volume testing-implementation), and improved acceptability (adoption)
Cascade target: Prevention	Pharmacy-based PreP programmes[185,186]	Increased availability in community (reach and adoption) and lower barrier to access care (efficacy)
Cascade target: Treatment	Community-based ART delivery[178,179,187-190]	Decreased burden of receiving care and medications (acceptability and efficacy) and care able to reach new populations (reach)
Home-based models		
Health service delivery and implementation process*		
Cascade target: Testing	HIV testing during home visits[183,191-195]	Increased access to testing (adoption) and reach populations that do not routinely access health care
Cascade target: Prevention	Home delivery for PrEP and monitoring[196]	Lower barrier to access care (reach) and more acceptable (adoption)
Cascade target: Treatment	Home-based ART delivery[197]	Decreased burden for receiving care, increased accessibility and reach, and improved acceptability
Low barrier treatment initiation		
Health service delivery and implementation process*		
Cascade target: Prevention	Same day PrEP with drop-in clinics,[177] pharmacy,[198] or community-based models[199]	Decreased barriers to starting and increased opportunity to initiate treatment (reach) with increased acceptability (adoption)
Cascade target: Treatment	Same day ART initiation[200-202]	Decreased barriers to starting and increased opportunity to initiate treatment (reach) with increased acceptability (adoption)
Navigation and care coordination		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Prevention	Navigation for PrEP initatiation[204]	Provide support for barriers to care (efficacy), increase flexibility of care and access (reach and efficacy), and develop relationships with patients (efficacy and acceptability)
Cascade target: Treatment	Patient navigation and care coordination to promote engagement in care[205-214] and tracing and outreach to promote re-engagement[205-217]	Provide support for barriers to care (efficacy), increase flexibility of care and access (reach and efficacy), develop relationships with patients (efficacy and acceptability)
Tailored care models		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Prevention	Youth-friendly PrEP,[218] PrEP delivery with youth-specific community-based mobile clinic,[219] and integrated community-based harm-reduction programmes for people who inject drugs[220]	Increased acceptability of care delivery (adoption and efficacy) and address specific needs for population (efficacy and reach)
Cascade target: Treatment	Care models tailored to meet specific needs of youth,[221-223] individuals re-engaging back into care,[206,215,224] and drop-in clinics for individuals who experience unstable housing[225] or complex needs[226]	Increased acceptability of care delivery (adoption and efficacy) and address specific needs for population (efficacy and reach)
Telehealth or mHealth strategies		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Testing	Promoting testing using mHealth[227,228]	Increased awareness, reach, and adoption of testing
Cascade target: Prevention	PrEP delivery using telehealth[229-231] and two-way SMS messaging to promote PrEP adherence and retention[232]	Decreased burden of receiving care (reach), increased accessibility (reach and efficacy), increased acceptability, foster connection with clinic (acceptability), and provider support (efficacy)
Cascade target: Treatment	Telehealth for HIV treatment[233-235] and SMS reminders and outreach[195]	Decreased burden of receiving care (reach), increased accessibility (reach and efficacy), increased acceptability, foster connection with clinic (acceptability), provider support (efficacy), and deliver theory-backed behavioural interventions (efficacy)
Leveraging social networks		
Health service delivery and implementation process*		
Cascade target: Testing	Index testing, assisted partner services; secondary distribution of HIV self-tests through social, family,[192,236-238] and sexual networks[239-241]	Reach populations not otherwise reached by testing and increased acceptability (adoption)

(Table 2 continues on next page)

	Example studies	Potential mechanisms and effects on reach, effectiveness, adoption, implementation, or maintenance (RE-AIM)
(Continued from previous page)		
Use of non-traditional actors and providers		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Testing	HIV testing with cultural (traditional healers)[240] or religious (churches)[243,244] institutions	Increase reach to populations who do not routinely access health care (reach), leverage social capital and trust to improve acceptability and uptake (adoption), and engage new HCW cadres (implementation and maintenance)
Cascade target: Prevention	Educating religious leaders to promote voluntary medical male circumcision[245] and leveraging key populations to deliver testing and PrEP[246,247]	Increase reach to populations who do not routinely access health care (reach), leverage social capital and trust to improve acceptability and uptake (adoption), and engage new HCW cadres (implementation and maintenance)
Cascade target: Treatment	Key-population led HIV services[248] and traditional healers as adherence partners[249]	Increase reach to populations who do not routinely access health care (reach), leverage social capital and trust to improve acceptability and uptake (adoption), and engage new HCW cadres (implementation and maintenance)
Delivering care at hotspots and targeted venues		
Health service delivery and implementation process*		
Cascade target: Testing	Venue-based for key populations (female sex workers[250–252] and men who have sex with men or transgender people)[252–255] and mobile testing at hotspots[253,256]	Bring testing to areas where target populations gather (reach), increase accessibility (increase reach), and increase acceptability (adoption)
Cascade target: Prevention	PrEP delivery with community-based mobile clinic at targeted locations[259]	Bring preventive services to areas where target populations gather (reach), increase accessibility (increase reach), and increase acceptability and uptake (adoption)
Cascade target: Treatment	Roadside wellness clinics for truck drivers and sex workers[257,258]	Bring treatment services to areas where target populations gather (reach), increase accessibility (increase reach), and increase acceptability and uptake (adoption)
Integration with other services		
Health service delivery, implementation process, and capacity building and support*		
Cascade target: Testing	Integrating HIV testing with hypertension and diabetes screening,[180] primary care visits,[259] emergency room visits,[260] or key population-specific care services[261]	Increase acceptability (adoption), increase access and opportunities to test (reach), and improved efficiency (implementation and maintenance)
Cascade target: Prevention	Integrating PrEP with family planning[262,263] or antenatal and postnatal care[264] and integrated sexual health services specific to sexualised substance use or chemsex[265]	Increase acceptability (adoption), increase access and opportunities for prevention (reach), and improved efficiency (implementation and maintenance)
Cascade target: Treatment	Integrating HIV and non-communicable disease care[266,267]	Increase acceptability (adoption), increase access and opportunities for comprehensive treatment (reach), and improved efficiency (implementation and maintenance)
Incentives		
Financial arrangement*		
Cascade target: Testing	Incentives or lotteries for testing[268–270] and retesting[271]	Increase motivation for testing uptake (adoption)
Cascade target: Prevention	Incentives for linkage to prevention services[272] or PrEP adherence[273]	Increase motivation for using prevention services (adoption)
Cascade target: Treatment	Incentives for linkage to care,[272] ART initiation,[274] or retention[266,275]	Increase motivation for engaging in treatment (adoption)
Strategies to optimise systems-level implementation		
Capacity building and support, implementation process, and governance*		
Cascade target: Testing, prevention, and treatment	Community-led monitoring for best practices for care,[276,277] targeting key opinion leaders and leadership,[277,278] implementing practice champions,[277,279–281] use of audit-and-feedback or dashboards,[277,281–285] and developing networks of practice for cross-learning[286]	Increased knowledge of quality and implementation gaps (implementation), increased motivation to improve care (implementation), and facilitation of quality improvement programmes (implementation and efficacy)

ART=antiretroviral therapy. HCW=health-care workers. mHealth=mobile health. PrEP=pre-exposure prophylaxis. *Implementation strategy typologies based on those used for the Living Database of HIV Implementation Research Project.[287]

Table 2: **Public health and implementation strategies for HIV testing, prevention, and treatment**

Conclusion

The tremendous progress in the global HIV response has been fuelled by innovations in prevention and treatment and scale-up of HIV programmes across the globe, but have not yet been matched by similar innovations in service delivery and implementation. To sustain and expand these accomplishments, new science is needed to learn how to optimally implement the available tools in ways that achieve the greatest effect on public health. Increasing attention to the inequities within the global HIV response and the systems that create them is essential for reaching all populations and addressing new infections, morbidity, and mortality. Innovations are on the horizon, but these might fall short of aspirations without considerable attention to issues of implementation and equity from the outset. HIV providers and programmes also face an ageing population living with HIV and will need to be prepared to also face growing epidemics of NCDs, including hypertension, diabetes, obesity, cardiovascular disease, cancer, neurocognitive diseases, and other ageing-related challenges. In this next phase of the global HIV response, we should consider emerging scientific questions, develop technologies, and adapt approaches to using the tools we already have so that evidence-generation and public health efforts maximise the effect and remain relevant, useful, and focused on the evolving challenges to ending the HIV epidemic.

NEJM Knowledge+

Question of the Week

Which one of the following empiric intravenous antibiotic regimens is most appropriate for a young woman who presents with a septic knee, has a history of injection-drug use, and reports no recent sexual activity?

- ○ Nafcillin and cefepime
- ○ Nafcillin and ertapenem
- ○ Ceftriaxone
- ● Vancomycin and cefepime
- ○ Vancomycin and ceftriaxone

SUBMIT

Question of the Week

For January 30, 2024

Your answer is correct.

Nafcillin and cefepime
Nafcillin and ertapenem
Ceftriaxone
✓ **Vancomycin and cefepime**
Vancomycin and ceftriaxone

Key Learning Point

View Case Presentation ›

Empiric antibiotic therapy for septic arthritis in a patient who injects drugs should include coverage for common organisms and for these two possible sources of infection: methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Detailed Feedback

This patient's physical examination and laboratory findings are consistent with septic arthritis. Septic bacterial arthritis is most commonly caused by *Staphylococcus aureus* and *Streptococcus spp*. Patients who are sexually active are also at risk for gonococcal arthritis, and those who inject drugs are at increased risk for *Pseudomonas aeruginosa* infection.

Given that methicillin-resistant *S. aureus* (MRSA) infection is a possibility in this case, vancomycin should be included in the empiric treatment regimen. An antipseudomonal agent, such as cefepime or piperacillin–tazobactam, is appropriate for patients who are considered to be at risk for pseudomonal infection.

Ceftriaxone, whether used alone or in combination with vancomycin, is not appropriate because it does not cover *P. aeruginosa*.

Nafcillin is not adequate because it lacks coverage for MRSA.

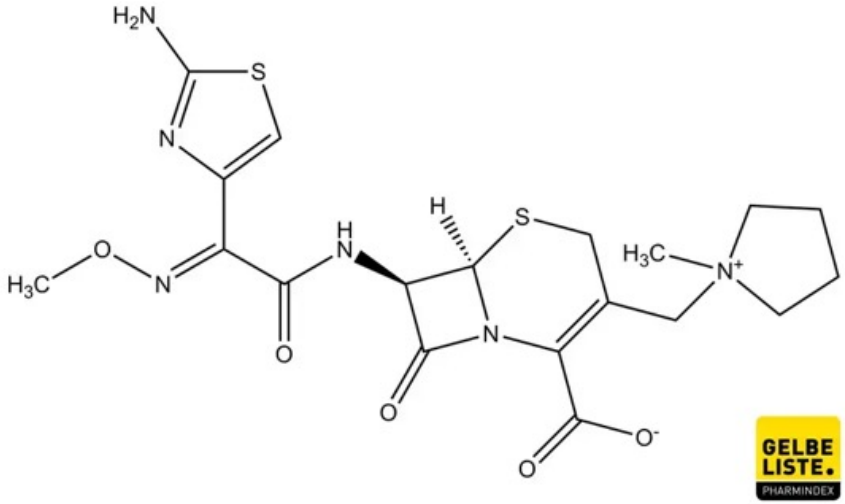
Ertapenem would not be a good choice because it does not cover MRSA or *Pseudomonas*.

Once culture results from the joint aspiration are available, antibiotic therapy should be narrowed to cover the responsible organism.

Cefepim ist ein Cephalosporin-Antibiotikum der vierten Generation, das zur Behandlung von Infektionen angewendet wird, die durch Cefepim-empfindliche Bakterien verursacht werden, wie Lungenentzündung, Harnwegsinfektionen oder Hautinfektionen.

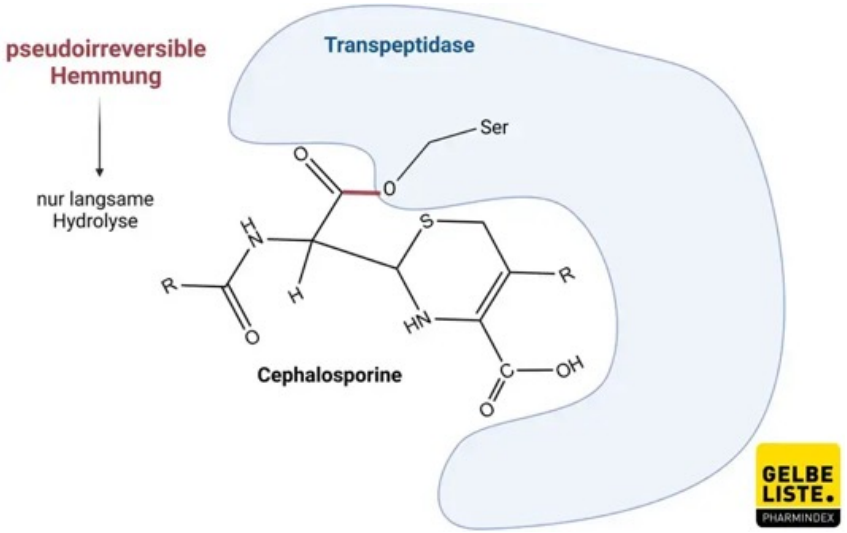
Anwendung

Cefepim ist ein Cephalosporin-Antibiotikum der vierten Generation. Es wirkt gegen gramnegative Bakterien wie Enterobacter spp., Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis und Pseudomonas aeruginosa sowie gegen grampositive Bakterien wie Staphylococcus aureus (nur Methicillin-empfindliche Isolate), Streptococcus pneumoniae, Streptococcus pyogenes und Viridans-Streptokokken.

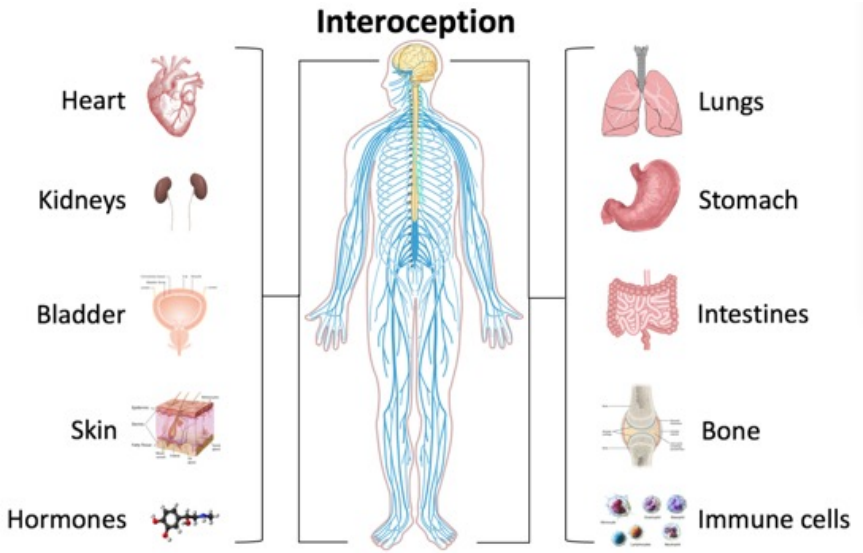


Wirkmechanismus

Cefepim ist ein bakterizides Cephalosporin mit einer ähnlichen Wirkweise wie andere Beta-Laktam-Antibiotika. Cefepim zerstört bakterielle Zellwände, indem es Transpeptidasen, die als Penicillin-bindende Proteine (PBPs) bekannt sind, bindet und hemmt. Diese Enzyme sind an den Endstadien der Synthese der Peptidoglykanschicht beteiligt. Ihre Hemmung führt zur Lyse und zum Tod anfälliger Mikroorganismen.

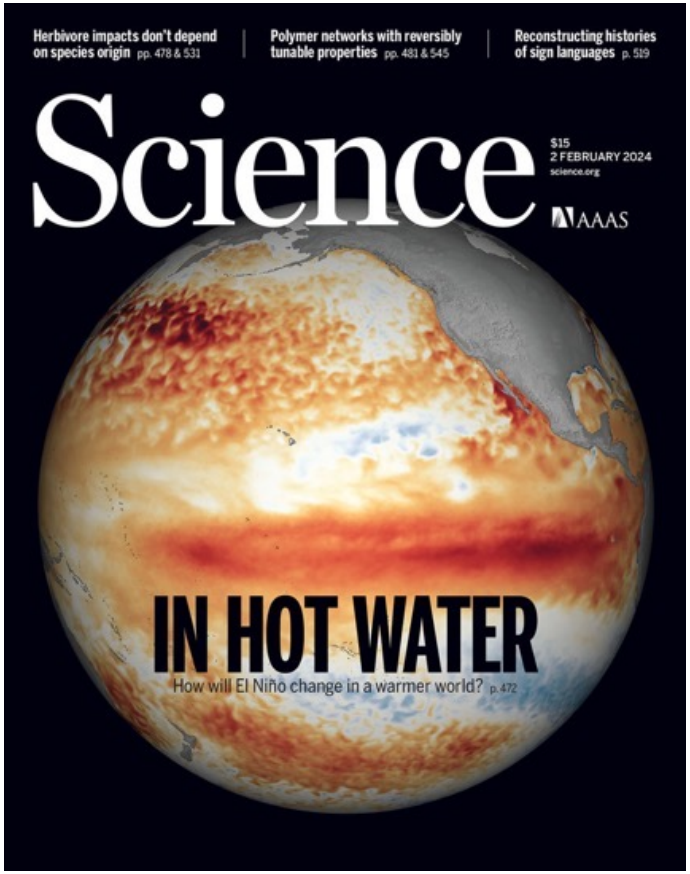


Interoception is the collection of senses providing information to the organism about the internal state of the body. This can be both conscious and subconscious. It encompasses the brain's process of integrating signals relayed from the body into specific subregions—like the brainstem, thalamus, insula, somatosensory, and anterior cingulate cortex—allowing for a nuanced representation of the physiological state of the body. This is important for maintaining homeostatic conditions in the body and, potentially, facilitating self-awareness.



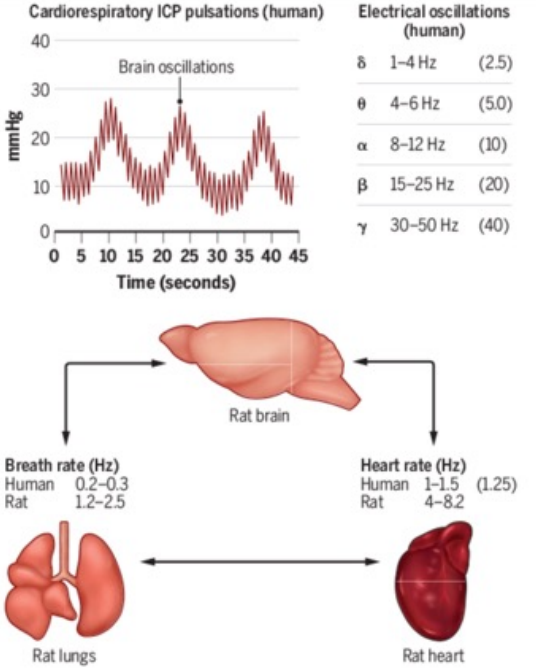
The contemporary definition of interoception is not synonymous with the term "visceroception". Visceroception refers to the perception of bodily signals arising specifically from the viscera: the heart, lungs, stomach, and bladder, along with other internal organs in the trunk of the body.

Misrepresentations of internal states, or a disconnect between the body's signals and the brain's interpretation and prediction of those signals, have been suggested to underlie conditions such as anxiety, depression, panic disorder, anorexia nervosa, bulimia nervosa, posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), alexithymia, somatic symptom disorder, and illness anxiety disorders.



Arterial pulses link heart-brain oscillations

Pressure pulses link breathing, heartbeat, and brain rhythmicity
Heartbeat- and respiratory-related intracranial pressure (ICP) pulsations are transduced by Piezo-type mechanosensitive ion channels (PIEZO2 channels) to generate electrical oscillations. These oscillations may show coupling to the major brain oscillations (δ, θ, α, β, and γ) that are relatively conserved in rats and humans, in contrast to their heart rate and breathing frequencies. Center frequencies (shown in parentheses) support a binary hierarchical brain-body model in humans in which heart rate is the fundamental frequency. Polysynaptic pathways also contribute to lung-heart, lung-brain, and heart-brain coupling. GRAPHIC: A. MASTIN/*SCIENCE*



NEUROSCIENCE

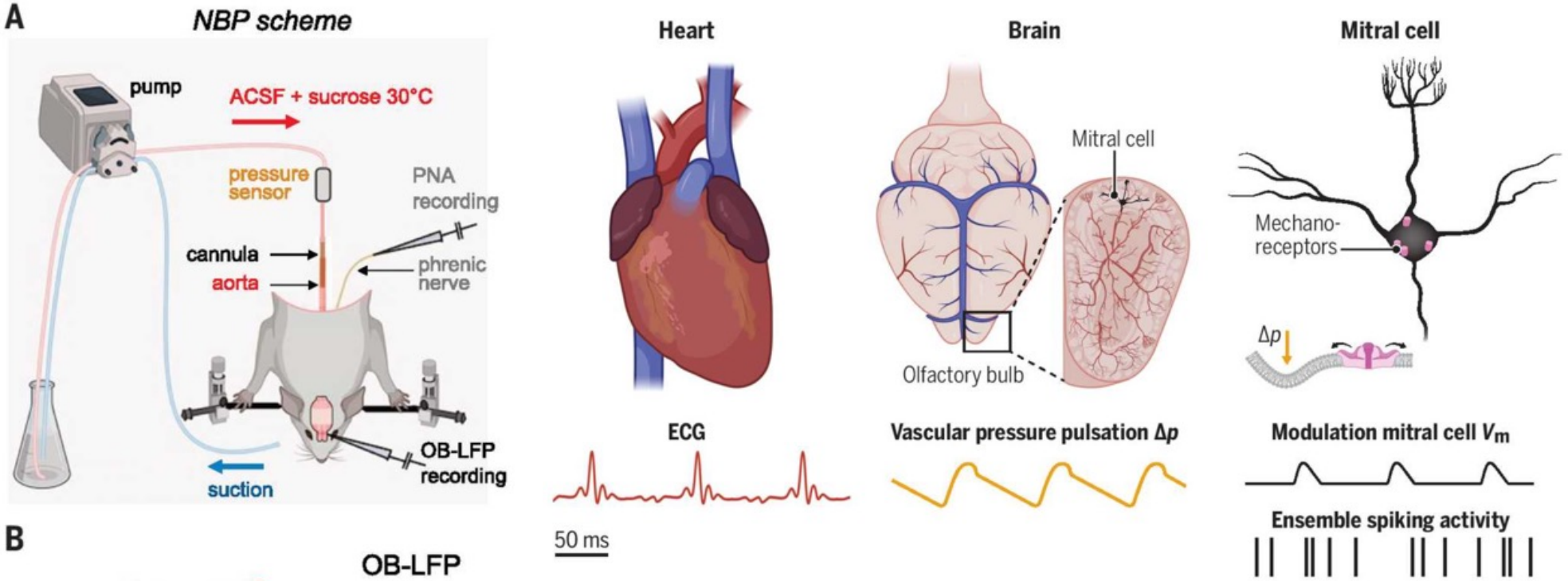
Blood pressure pulsations modulate central neuronal activity via mechanosensitive ion channels

The transmission of the heartbeat through the cerebral vascular system causes intracranial pressure pulsations. We discovered that arterial pressure pulsations can directly modulate central neuronal activity. In a semi-intact rat brain preparation, vascular pressure pulsations elicited correlated local field oscillations in the olfactory bulb mitral cell layer. These oscillations did not require synaptic transmission but reflected baroreceptive transduction in mitral cells. This transduction was mediated by a fast excitatory mechanosensitive ion channel and modulated neuronal spiking activity. In awake animals, the heartbeat entrained the activity of a subset of olfactory bulb neurons within ~20 milliseconds. Thus, we propose that this fast, intrinsic interoceptive mechanism can modulate perception—for example, during arousal—within the olfactory bulb and possibly across various other brain areas.

Interoception is the sensing of internal body signals without outer sensory perception

INTRODUCTION: Neural electrical oscillations are considered fundamental to how the brain processes information. Various modes of oscillation reflect processing in local or brain-wide networks and occur spontaneously or are associated with sensory and cognitive processing. Accumulating evidence suggests that such neural oscillations can also be modulated by the interoception of body rhythms, such as respiration or the heartbeat. Interoception is the sensing of internal body signals—as opposed to the sensory perception of the outer world—and thus informs the brain about the state of the organism.

RATIONALE: To investigate the mechanisms of local oscillations within a restricted network, we had developed a semi-intact preparation of the rat olfactory bulb—the first station of olfactory processing in the brain, noted for its strong oscillatory activity. In this type of reduced preparation, there is no heart, lung, or input from other brain areas, and the vasculature of the bulb is perfused with artificial blood by a peristaltic pump. This pump generates pressure pulsations within the cerebral vascular system that, in our setup, happen to fit within the physiological range of heartbeat-induced pulsations of intracranial pressure in vivo. Notably, these pump-induced mechanical pulsations were precisely followed by local electrical field oscillations that originated from mitral cells, the principal neurons of the olfactory bulb. On the basis of recent evidence for the expression of mechanosensitive ion channels in subsets of principal neurons across the brain, we then hypothesized that these neurons may be capable of directly sensing the vascular blood pressure pulsations associated with the heartbeat.



How neurons can feel the pulse within the brain. (Left) Rat heart (top) and schematic rat electrocardiogram (ECG) (bottom). (Middle) Schematic rat brain and coronal section through the olfactory bulb and its blood vessels with exemplary mitral cell (top) and intracranial pressure pulsations (Δp) caused by the heartbeat (bottom). (Right) Mitral cell with mechanoreceptors (top); weak excitatory modulation of the mitral cell membrane potential V_m by mechanosensitive ion channel currents, with the ion channels (most likely Piezo2) gated by deflections of the mitral cell membrane caused by the pulsations Δp (middle); and the ensuing subtle modulation of the timing of spontaneous spikes in an ensemble of mitral cells (bottom). [Created in part with www.biorender.com]

RESULTS: The pump-induced pressure pulsations provided an adequate stimulus for a vibrations within similar-frequency regimes. Its gating properties could well underlie the transformation of the sinusoidal waveform of the pressure stimulus into the more complex waveform of the local field oscillations observed in our preparation. Although this fast transduction pathway did not involve synaptic transmission, the vascular pressure pulsation rhythm entrained the spontaneous spiking activity of the mitral cells. Thus, the mechanosensory transduction exerted a direct modulatory influence on spike timing. Can this pathway allow the brain to sense the heartbeat in vivo? In awake mice, we found that neuronal spiking activity was in fact modulated by the heartbeat, with ~15% of olfactory bulb neurons being entrained by this rhythm, mostly within 20 ms. This effect was considerably weaker than the known coupling of neuronal activity to the respiration rhythm, which explains why it has not been observed until now. We observed similar heartbeat-induced modulations of neuronal activity also in the hippocampus and prefrontal cortex.

CONCLUSION: The role of interoception in brain function is one of the major challenges in current neuroscience. In humans, recent experimental evidence supports the modulation of autonomous and conscious perception and cognition by the cardiac cycle. Although this modulation is partially mediated by the classical ascending multisynaptic pathway originating from aortic baroreceptors, the present results reveal that heartbeat-induced pulsations of cerebral blood vessels can directly affect central neuronal activity through the activation of mechanosensitive channels. Although currently the function of this immediate pathway is a matter of speculation, we propose that a brain-wide network of "heartbeat sentinel neurons" mediates interoceptive modulation of cognition, mood, and autonomic status. For example, the occurrence of certain states of arousal might correlate with activation of this network. Our finding adds a fast transmission line to the interoceptive body-brain axis, whereby central neurons can feel the pulse within the brain. ■

The surprisingly simple exercise that can lower your blood pressure

The wall sit, a simple bodyweight exercise that can be done virtually anywhere, isn't just for building strength. It can help your cardiovascular health, too.

A recent study in the British Journal of Sports Medicine suggests that isometric exercises, like wall sits (also known as wall squats), can help reduce blood pressure even more effectively than other forms of exercise, including aerobic activity, weight training or high-intensity interval workouts.

The research is good news for people who struggle to meet physical activity guidelines that recommend at least 150 minutes of weekly moderate-intensity exercise, like brisk walking or bicycling. The new analysis found that about eight minutes of isometric exercise, three times a week, can lead to a meaningful reduction in blood pressure.

This means holding a wall sit for two minutes and resting for two minutes. Repeat for a total of four wall sits with breaks in between. A single session, including rest, will take only 14 minutes.

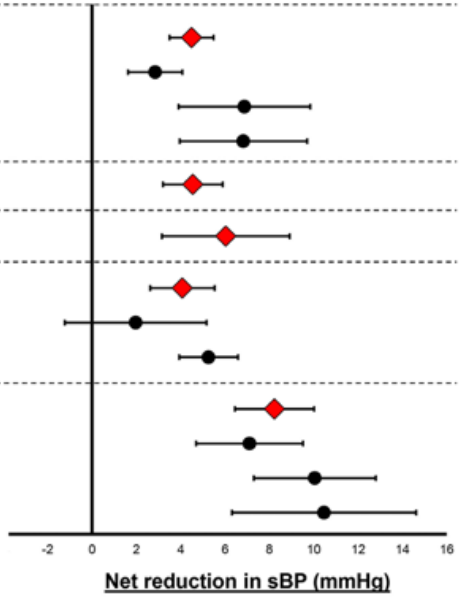
Exercise training and resting blood pressure: a large-scale pairwise and network meta-analysis of randomised controlled trials

To cite: Edwards JJ, Deenmamode AHP, Griffiths M, *et al*. *Br J Sports Med* 2023;**57**:1317–1326.

Systematic review

Pairwise Analysis, sBP (mmHg) Weighted Mean Difference, 95% CI

Exercise Mode	MD [95%CI]	N. Effect Sizes	I^2%	P-Value
Aerobic Exercise Training	4.49 [3.5-5.5]	182	91.5	<0.001
Walking	2.85 [1.6-4.1]	89	77.4	<0.001
Cycling	6.88 [3.9-9.8]	28	92.1	<0.001
Running	6.83 [4.0-9.7]	21	88.4	<0.001
Dynamic Resistance Training	4.55 [3.2-5.9]	57	58.4	<0.001
Combined Training	6.04 [3.2-8.9]	46	92.8	<0.001
High-Intensity Interval Training	4.08 [2.6-5.5]	49	82.4	<0.001
Aerobic Interval Training	1.97 [-1.2-5.2]	13	66.9	0.227
Sprint Interval Training	5.26 [3.9-6.6]	7	0	<0.001
Isometric Exercise Training	8.24 [6.5-10.0]	24	68.8	<0.001
Isometric Handgrip	7.10 [4.7-9.5]	17	68.8	<0.001
Isometric Leg Extension	10.05 [7.3-12.8]	3	0	<0.001
Isometric Wall Squat	10.47 [6.3-14.6]	4	81.0	<0.001



ABSTRACT

Objective To perform a large-scale pairwise and network meta-analysis on the effects of all relevant exercise training modes on resting blood pressure to establish optimal antihypertensive exercise prescription practices.

Design Systematic review and network meta-analysis.

Data sources PubMed (Medline), the Cochrane library and Web of Science were systematically searched.

Eligibility criteria Randomised controlled trials published between 1990 and February 2023. All relevant work reporting reductions in systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) following an exercise intervention of ≥2 weeks, with an eligible non-intervention control group, were included.

Results 270 randomised controlled trials were ultimately included in the final analysis, with a pooled sample size of 15 827 participants. Pairwise analyses demonstrated significant reductions in resting SBP and DBP following aerobic exercise training (−4.49/−2.53 mm Hg, p<0.001), dynamic resistance training (−4.55/−3.04 mm Hg, p<0.001), combined training (−6.04/−2.54 mm Hg, p<0.001), high-intensity interval training (−4.08/−2.50 mm Hg, p<0.001) and isometric exercise training (−8.24/−4.00 mm Hg, p<0.001). As shown in the network meta-analysis, the rank order of effectiveness based on the surface under the cumulative ranking curve (SUCRA) values for SBP were isometric exercise training (SUCRA: 98.3%), combined training (75.7%), dynamic resistance training (46.1%), aerobic exercise training (40.5%) and high-intensity interval training (39.4%). Secondary network meta-analyses revealed isometric wall squat and running as the most effective submodes for reducing SBP (90.4%) and DBP (91.3%), respectively.

Conclusion Various exercise training modes improve resting blood pressure, particularly isometric exercise. The results of this analysis should inform future exercise guideline recommendations for the prevention and treatment of arterial hypertension.

Central illustration. AET, aerobic exercise training; CT, combined training; HIIT, high-intensity interval training; IET, isometric exercise training; RT, dynamic resistance training.