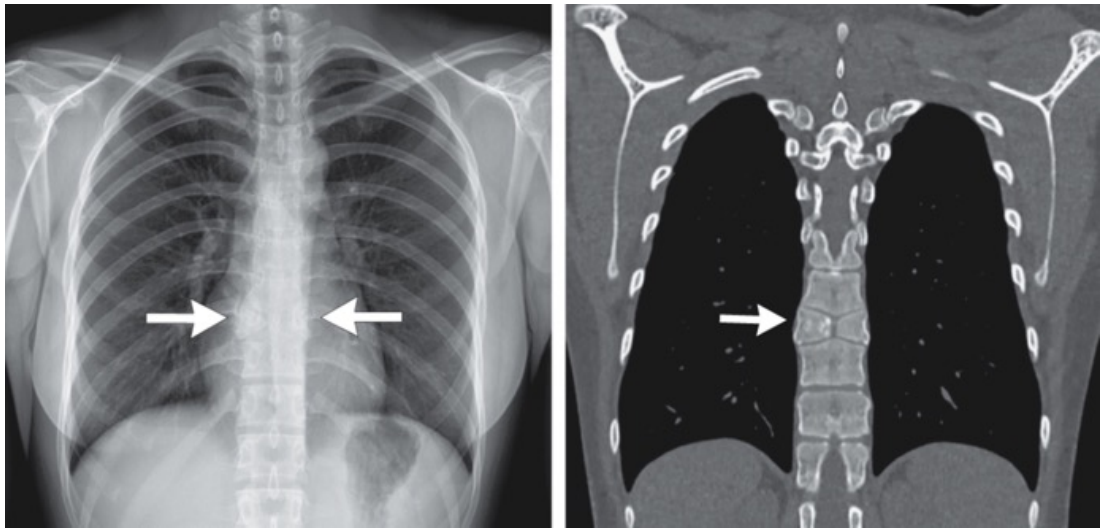
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club


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



A 21-year-old woman who had presented to the pulmonary clinic with a 7-day history of sore throat and cough was noted to have a vertebral abnormality on chest radiograph. She reported no history of back pain. Computed tomography of the chest is shown. What is the most likely underlying etiology?

Congenital anomaly

Decreased bone mineralization

Increased bone turnover

Malignancy

Prior trauma

A diagnosis of a butterfly vertebra was made. A butterfly vertebra is a rare congenital anomaly that results from a lack of fusion of the two lateral ossification centers during embryonic development. It is usually asymptomatic and discovered incidentally on imaging. A butterfly vertebra may occur in isolation or be associated with other congenital anomalies. Reassurance regarding the benign nature of the vertebral finding was provided.

# Volume-depleted infants (Diarrheal illnesses)

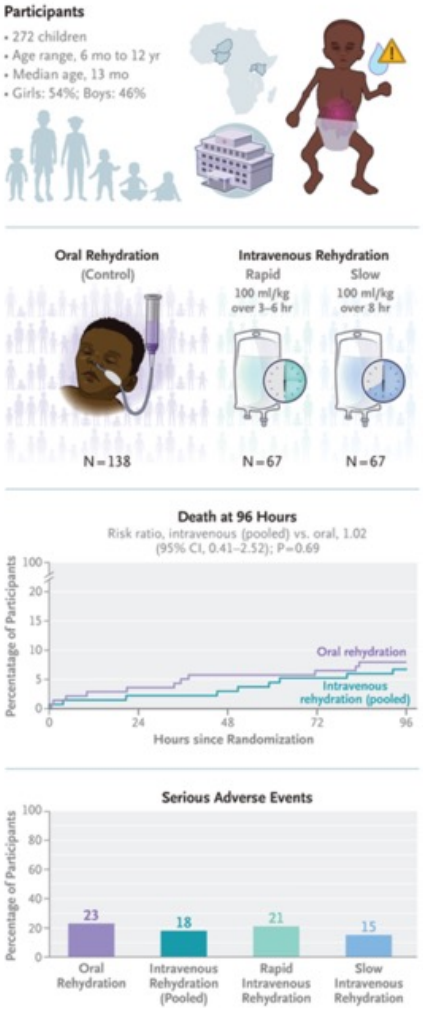
Sick


Not Sick

# Intravenous Rehydration for Severe Acute Malnutrition with Gastroenteritis

International recommendations advise against the use of intravenous rehydration therapy in children with severe acute malnutrition because of the concern about fluid overload, but evidence to support this concern is lacking. Given the high mortality associated with the current recommendations, the adoption of intravenous rehydration strategies might improve outcomes.

We conducted a factorial, open-label superiority trial in four countries in Africa. Children 6 months to 12 years of age with severe acute malnutrition with gastroenteritis and dehydration underwent randomization in a 2:1:1 ratio to one of three rehydration strategies: oral rehydration, plus intravenous boluses for shock; a rapid intravenous strategy that consisted of lactated Ringer's solution (100 ml per kilogram of body weight) administered over a period of 3 to 6 hours, with boluses for shock; or a slow intravenous strategy that consisted of the same solution administered over a period of 8 hours, with no boluses. The primary end point was death at 96 hours.



In 2016, the World Health Organization (WHO), United Nations Children's Fund, and World Bank Group Interagency estimated that 17 million children younger than 5 years of age were severely undernourished. Severe acute malnutrition, the most extreme form of undernourishment, is a leading cause of hospital admissions among children in Africa. Many children with severe malnutrition have additional complications such as severe dehydration due to diarrhea, which is associated with high in-hospital mortality (27 to 41%). Current recommendations for rehydration in children with severe acute malnutrition differ from those for children without malnutrition. Intravenous rehydration is not recommended in severe acute malnutrition because malnourished children are at high risk for compromised cardiac function and sodium overload. Low-sodium oral rehydration solutions are not recommended for similar reasons. Although such guidance documents have been in place for more than two decades, no previous or subsequent evidence has supported these recommendations. Therefore, oral rehydration is the recommended option, with intravenous boluses provided only in the event of shock. This approach often necessitates the use of a nasogastric tube to administer oral rehydration, since most children with severe acute malnutrition are unable to take or retain oral fluids. In addition, most children receive care in busy, overcrowded pediatric units or in dedicated nutrition units with limited nursing staff available to ensure safe implementation of oral nasogastric rehydration and to monitor for signs of shock. Shock is a complication in approximately 25% of children with severe dehydration, and in-hospital mortality among children with shock is high (>40%).

## Methods

### Trial Design and Oversight

We conducted an investigator-initiated, multicenter, factorial, open-label, randomized superiority trial at six hospitals: two in Uganda, two in Kenya, one in Niger, and one in Nigeria.

### Trial Population

Children were eligible if they were 6 months to 12 years of age and were hospitalized with severe acute malnutrition (defined by a weight-for-height z score ≤3, mid-upper-arm circumference <11.5 cm, or presentation with edematous malnutrition [kwashiorkor] with edema in both feet or more generalized edema) with gastroenteritis (with more than three loose stools per day) and signs of severe dehydration. Signs of severe dehydration, according to WHO criteria, included two or more of the following: altered level of consciousness, sunken eyes, reduced skin turgor (slow abdominal skin pinch return [>2 seconds]), or inability to take or retain oral fluids.

### End Points

The primary end point was death at 96 hours. Secondary efficacy end points were death at 28 days, the change in weight at 3 days and 7 days, the change in mid-upper-arm circumference at 3 days and 7 days, and urine output at 8 hours. Safety end points were evidence of pulmonary edema or heart failure, the change in the sodium level from 8 hours to 24 hours, and correction of electrolyte abnormalities (severe hyponatremia [sodium level <125 mmol per liter] or severe hypokalemia [potassium level <2.5 mmol per liter]).

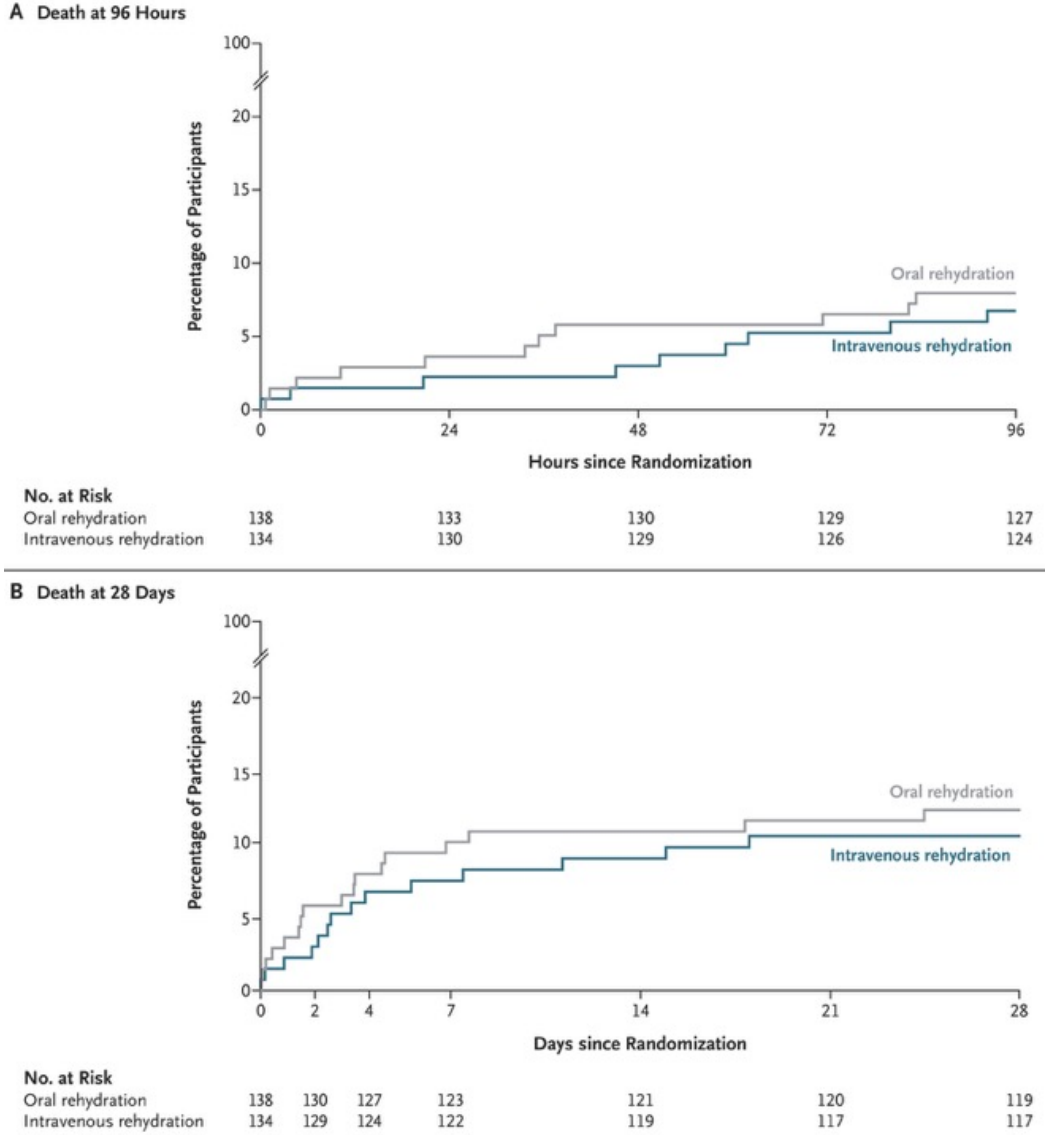
| Characteristic | Oral Rehydration | Intravenous Rehydration | | |
|---|---|---|---|---|
| | (N=138) | Pooled (N=134) | Rapid (N=67) | Slow (N=67) |
| Male sex — no. (%) | 62 (45) | 64 (48) | 28 (42) | 36 (54) |
| Median age (IQR) — mo | 12 (9 to 22) | 14 (9 to 23) | 16 (9 to 24) | 14 (9 to 22) |
| Median weight (IQR) — kg | 5.3 (4.5 to 6.1) | 5.2 (4.6 to 6.1) | 5.0 (4.5 to 6.1) | 5.3 (4.7 to 6.1) |
| Median weight-for-height z score (IQR) | −4.7 (−5.5 to −4.2) | −4.9 (−5.8 to −4.2) | −5.0 (−5.8 to −4.3) | −4.9 (−5.7 to −4.2) |
| Median mid-upper-arm circumference (IQR) — cm | 10.5 (9.6 to 11.0) | 10.1 (9.5 to 11.0) | 10.0 (9.5 to 10.8) | 10.4 (9.6 to 11.0) |
| Kwashiorkor — no. (%)† | 5 (4) | 6 (4) | 4 (6) | 2 (3) |
| Altered level of consciousness — no. (%)‡ | 50 (36) | 54 (40) | 29 (43) | 25 (37) |
| Restlessness — no. (%) | 44 (32) | 42 (31) | 22 (33) | 20 (30) |
| Sunken eyes — no. (%) | 136 (99) | 131 (98) | 65 (97) | 66 (99) |
| Skin pinch return 1–2 sec — no. (%) | 15 (11) | 12 (9) | 6 (9) | 6 (9) |
| Skin pinch return >2 sec — no. (%) | 120 (87) | 122 (91) | 61 (91) | 61 (91) |
| Unable to take or retain oral fluids — no. (%) | 111 (80) | 104 (78) | 53 (79) | 51 (76) |
| Fever — no./total no. (%) | 49/137 (36) | 45/134 (34) | 16/67 (24) | 29/67 (43) |
| Tachypnea — no. (%) | 34 (25) | 35 (26) | 21 (31) | 14 (21) |
| Median oxygen saturation (IQR) — % | 100 (99 to 100) | 100 (98 to 100) | 100 (98 to 100) | 100 (98 to 100) |
| Median heart rate (IQR) — beats/min | 139 (118 to 155) | 136 (118 to 153) | 132 (114 to 156) | 140 (120 to 152) |
| Tachycardia — no. (%)§ | 12 (9) | 14 (10) | 9 (13) | 5 (7) |
| Capillary refill time >3 sec — no. (%) | 18 (13) | 22 (16) | 14 (21) | 8 (12) |
| Weak pulse — no. (%) | 23 (17) | 28 (21) | 17 (25) | 11 (16) |
| Cold hands or feet — no./total no. (%) | 18/138 (13) | 23/133 (17) | 12/66 (18) | 11/67 (16) |
| Moderate hypotension — no./total no. (%)¶ | 42/134 (31) | 34/127 (27) | 18/62 (29) | 16/65 (25) |
| Shock — no. (%)‖ | 12 (9) | 13 (10) | 8 (12) | 5 (7) |
| Intercostal retraction — no./total no. (%) | 12/138 (9) | 17/132 (13) | 11/66 (17) | 6/66 (9) |
| Deep breathing — no./total no. (%) | 15/138 (11) | 11/132 (8) | 6/66 (9) | 5/66 (8) |
| Lung crackles — no./total no. (%) | 14/134 (10) | 19/129 (15) | 10/65 (15) | 9/64 (14) |
| Bloody diarrhea — no./total no. (%) | 30/136 (22) | 24/133 (18) | 14/66 (21) | 10/67 (15) |
| History of vomiting — no./total no. (%) | 113/137 (82) | 102/133 (77) | 48/66 (73) | 54/67 (81) |
| Median appetite score (IQR)** | 3 (2 to 5) | 3 (2 to 4) | 3 (2 to 4) | 3 (2 to 5) |
| Breastfeeding — no./total no. (%) | 76/135 (56) | 62/132 (47) | 29/65 (45) | 33/67 (49) |
| Receiving nutritional therapy — no./total no. (%) | 9/135 (7) | 19/128 (15) | 10/63 (16) | 9/65 (14) |
| Received oral rehydration solution during current illness — no./total no. (%) | 76/138 (55) | 83/133 (62) | 42/66 (64) | 41/67 (61) |
| Admitted to another facility during current illness — no./total no. (%) | 67/136 (49) | 74/128 (58) | 36/63 (57) | 38/65 (58) |
| Diarrhea in previous 6 mo — no./total no. (%) | 73/137 (53) | 72/132 (55) | 36/65 (55) | 36/67 (54) |
| Previous admission for malnutrition — no./total no. (%) | 29/136 (21) | 50/127 (39) | 21/62 (34) | 29/65 (45) |
| Laboratory measures | | | | |
| Hypoglycemia — no./total no. (%) | 12/135 (9) | 13/131 (10) | 10/64 (16) | 3/67 (4) |
| Median sodium level (IQR) — mmol/liter | 124 (118 to 129) | 124 (119 to 130) | 123 (117 to 130) | 125 (120 to 129) |
| Severe hyponatremia — no./total no. (%) | 70/131 (53) | 67/131 (51) | 35/66 (53) | 32/65 (49) |
| Median potassium level (IQR) — mmol/liter | 2.8 (2.0 to 3.4) | 2.5 (2.0 to 3.2) | 2.4 (2.0 to 3.3) | 2.5 (2.0 to 3.2) |
| Severe hypokalemia — no./total no. (%) | 52/129 (40) | 63/129 (49) | 33/65 (51) | 30/64 (47) |
| Median chloride level (IQR) — mmol/liter | 98 (92 to 103) | 98 (93 to 106) | 98 (92 to 105) | 99 (93 to 106) |
| Median bicarbonate level (IQR) — mmol/liter | 16 (11 to 19) | 13 (10 to 17) | 12 (8 to 14) | 15 (13 to 20) |
| Positive for human immunodeficiency virus — no. (%) | 0 | 2 (1) | 1 (1) | 1 (1) |
| Positive rapid test for malaria — no. (%)†† | 25 (18) | 20 (15) | 9 (13) | 11 (16) |
| Median hemoglobin level (IQR) — g/dl | 11.4 (9.7 to 12.6) | 11.5 (9.6 to 12.9) | 11.6 (9.9 to 12.8) | 11.2 (9.5 to 12.9) |
| Severe anemia — no./total no. (%) | 0/131 (0) | 0/127 (0) | 0/64 (0) | 0/63 (0) |
| Bacteremia — no./total no. (%) | 4/45 (9) | 8/53 (15) | 3/27 (11) | 5/26 (19) |

## Clinical Management and Characteristics during the First 24 Hours after Admission.

| Variable | Oral Rehydration | Intravenous Rehydration | | | Odds Ratio (95% CI)* |
|---|---|---|---|---|---|
| | (N=138) | Pooled (N=134) | Rapid (N=67) | Slow (N=67) | |
| Intravenous fluids initiated within 24 hr after randomization — no. (%) | 31 (22)† | 133 (99) | 66 (99) | 67 (100) | |
| Median time to initiation of intravenous fluids (IQR) — min‡ | 123 (13–470) | 14 (9–24) | 16 (10–28) | 12 (8–22) | |
| Shock at randomization — no. (%) | 12 (9) | 13 (10) | 8 (12) | 5 (7) | |
| Initial bolus administered for shock — no./total no. (%) | 12/12 (100) | 7/13 (54) | 7/8 (88) | 0/5 (0) | |
| Treatment for correction of glucose levels during first 24 hr after admission — no./total no. (%) | 10/138 (7) | 9/133 (7) | 4/66 (6) | 5/67 (7) | 0.93 (0.36–2.37) |
| Nasogastric tube inserted during first 24 hr after randomization — no./total no. (%) | 126/135 (93) | 82/126 (65) | 43/64 (67) | 39/62 (63) | 0.13 (0.06–0.30) |
| Vomiting during first 24 hr after admission — no./total no. (%) | 96/136 (71) | 69/133 (52) | 33/66 (50) | 36/67 (54) | 0.44 (0.27–0.75) |

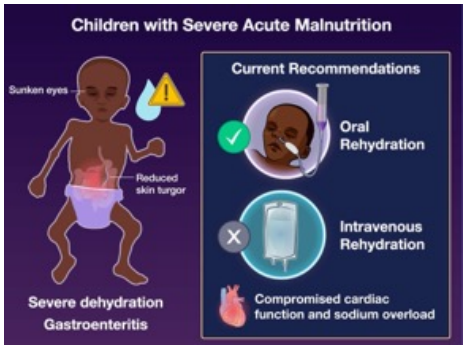
## End Points.

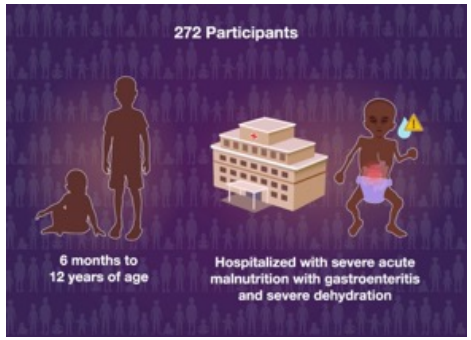
| End Point | Oral Rehydration | Intravenous Rehydration | | | Estimated Treatment Effect, Intravenous vs. Oral (95% CI) |
|---|---|---|---|---|---|
| | (N=138) | Pooled (N=134) | Rapid (N=67) | Slow (N=67) | |
| **Primary end point** | | | | | |
| Death at 96 hours — no. (%) | 11 (8) | 9 (7) | 5 (7) | 4 (6) | 1.02 (0.41 to 2.52)† |
| **Secondary end points** | | | | | |
| Death at 28 days — no. (%) | 17 (12) | 14 (10) | 8 (12) | 6 (9) | 0.85 (0.41 to 1.78)‡ |
| Change in weight at 3 days — kg | 0.4±0.2 | 0.5±0.3 | 0.5±0.2 | 0.5±0.3 | 0.1 (0.1 to 0.2)§ |
| Change in mid-upper-arm circumference at 3 days — cm | 0.2±0.3 | 0.3±0.4 | 0.3±0.5 | 0.3±0.4 | 0.1 (0.0 to 0.2)§ |
| Change in weight at 7 days — kg | 0.6±0.3 | 0.6±0.4 | 0.6±0.4 | 0.7±0.4 | 0.0 (0.0 to 0.1)§ |
| Change in mid-upper-arm circumference at 7 days — cm | 0.6±0.6 | 0.6±0.6 | 0.6±0.7 | 0.6±0.6 | 0.0 (−0.1 to 0.1)§ |
| Urine output at 8 hr — ml | 86±127 | 144±172 | 112±109 | 194±244 | 82 (−27 to 191)§ |
| **Safety end points** | | | | | |
| Suspected pulmonary edema — no. (%) | 0 | 0 | 0 | 0 | |
| Signs consistent with heart failure — no. (%) | 0 | 0 | 0 | 0 | |
| Correction of severe hyponatremia | | | | | 1.55 (1.14 to 2.09)¶ |
| Correction of severe hypokalemia | | | | | 0.82 (0.57 to 1.19)¶ |
| Severe hyponatremia at 8 hr — no./total no. (%) | 58/129 (45) | 20/128 (16) | 13/64 (20) | 7/64 (11) | 0.23 (0.13 to 0.41)‖ |
| Severe hypokalemia at 8 hr — no./total no. (%) | 40/128 (31) | 57/127 (45) | 27/63 (43) | 30/64 (47) | 1.79 (1.07 to 3.01)‖ |
| Change in sodium level from 8 hr to 24 hr — mmol/liter | 2.7±6.5 | 0.7±6.0 | 0.4±6.3 | 1.0±5.8 | 0.1 (−1.4 to 1.6)§ |
| **Other end points** | | | | | |
| Serious adverse event — no. of participants (%) | 32 (23) | 24 (18) | 14 (21) | 10 (15) | 0.73 (0.40 to 1.32)** |
| Development of shock — no./total no. (%)†† | 11/126 (9) | 6/121 (5) | 3/59 (5) | 3/62 (5) | 0.55 (0.19 to 1.53)** |
| Neurologic serious adverse event — no. (%) | 0 | 1 (1) | 0 | 1 (1) | |
| Change in sodium level at 8 hr — mmol/liter | 1.9±6.0 | 7.5±5.0 | 7.4±5.3 | 7.5±4.7 | 5.7 (4.5 to 7.0)§ |
| Hypernatremia at 8 hr — no./total no. (%) | 2/129 (2) | 2/128 (2) | 0/64 (0) | 2/64 (3) | 1.01 (0.14 to 7.29)‖ |
| Change in potassium level at 8 hr — mmol/liter | 0.2±0.8 | −0.1±0.9 | −0.1±1.0 | −0.1±0.8 | −0.3 (−0.5 to −0.2)§ |
| Change in sodium level at 24 hr — mmol/liter | 4.4±7.4 | 8.2±7.2 | 7.8±7.8 | 8.6±6.6 | 4.1 (2.6 to 5.7)§ |
| Severe hyponatremia at 24 hr — no./total no. (%) | 35/129 (27) | 21/127 (17) | 13/64 (20) | 8/63 (13) | 0.53 (0.29 to 0.98)‖ |
| Hypernatremia at 24 hr — no./total no. (%) | 3/129 (2) | 6/127 (5) | 3/64 (5) | 3/63 (5) | 2.08 (0.51 to 8.51)‖ |
| Severe hypokalemia at 24 hr — no./total no. (%) | 26/128 (20) | 36/125 (29) | 17/62 (27) | 19/63 (30) | 1.59 (0.89 to 2.83)‖ |
| Change in potassium level at 24 hr — mmol/liter | 0.6±1.0 | 0.2±0.9 | 0.3±0.9 | 0.1±0.8 | −0.4 (−0.6 to −0.2)§ |

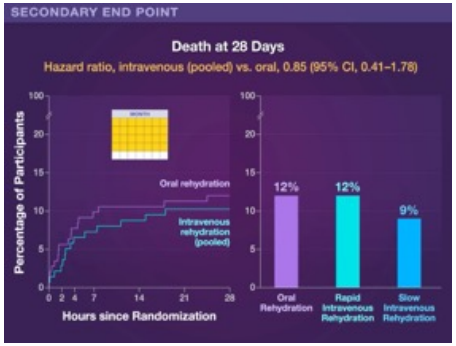


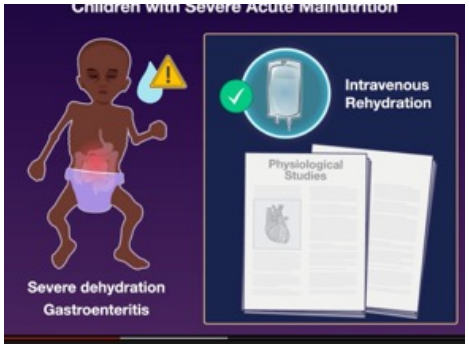

**Death at 96 Hours and at 28 Days.**

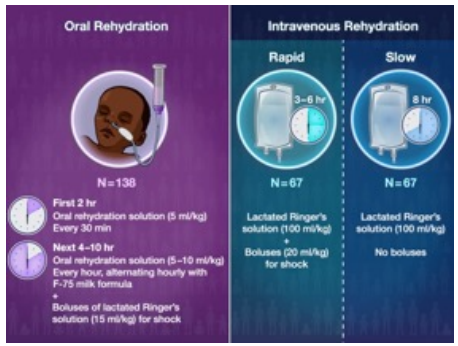
Participants were assigned to an oral rehydration strategy in accordance with the World Health Organization guidelines for children with severe acute malnutrition or to one of two intravenous strategies (a rapid strategy or a slow strategy). The primary end point was death at 96 hours (Panel A). Death at 28 days was a secondary end point (Panel B). Data shown are for the comparison of the oral rehydration group with the pooled intravenous rehydration groups.

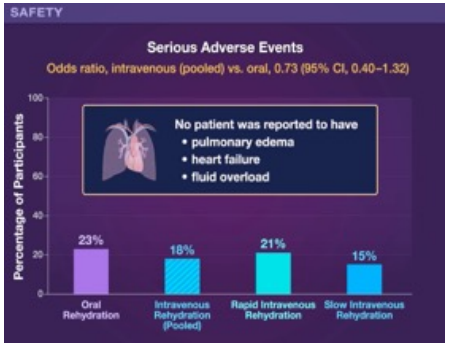

Children with Severe Acute Malnutrition
Sunken eyes
Reduced skin turgor
Severe dehydration
Gastroenteritis
Current Recommendations
Oral Rehydration
Intravenous Rehydration
Compromised cardiac function and sodium overload

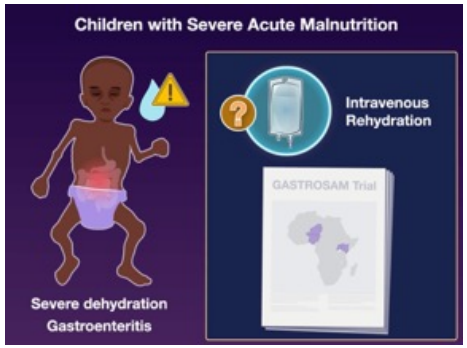

272 Participants
6 months to 12 years of age
Hospitalized with severe acute malnutrition with gastroenteritis and severe dehydration

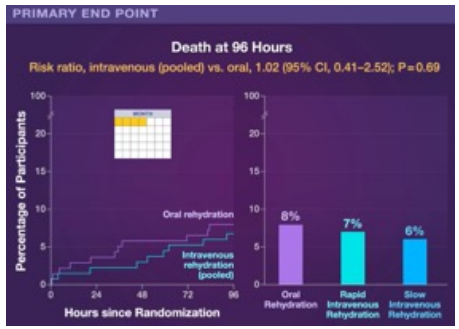

SECONDARY END POINT
Death at 28 Days
Hazard ratio, intravenous (pooled) vs. oral, 0.85 (95% CI, 0.41–1.78)
Percentage of Participants
Oral rehydration
Intravenous rehydration (pooled)
Hours since Randomization
12%
12%
9%
Oral Rehydration
Rapid Intravenous Rehydration
Slow Intravenous Rehydration

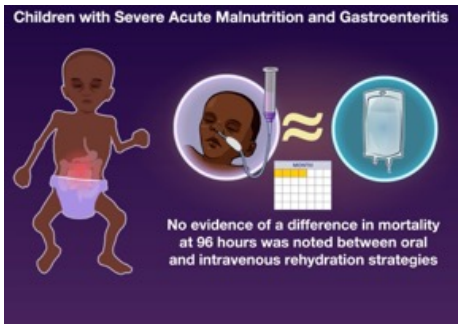

Children with Severe Acute Malnutrition
Intravenous Rehydration
Physiological Studies
Severe dehydration
Gastroenteritis


Oral Rehydration
Intravenous Rehydration
Rapid
Slow
3–6 hr
8 hr
N=138
N=67
N=67
First 2 hr
Oral rehydration solution (5 ml/kg)
Every 30 min
Next 4–10 hr
Oral rehydration solution (5–10 ml/kg)
Every hour, alternating hourly with F-75 milk formula
+
Boluses of lactated Ringer's solution (15 ml/kg) for shock
Lactated Ringer's solution (100 ml/kg)
+
Boluses (20 ml/kg) for shock
Lactated Ringer's solution (100 ml/kg)
No boluses


SAFETY
Serious Adverse Events
Odds ratio, intravenous (pooled) vs. oral, 0.73 (95% CI, 0.40–1.32)
Percentage of Participants
No patient was reported to have
• pulmonary edema
• heart failure
• fluid overload
23%
18%
21%
15%
Oral Rehydration
Intravenous Rehydration (Pooled)
Rapid Intravenous Rehydration
Slow Intravenous Rehydration

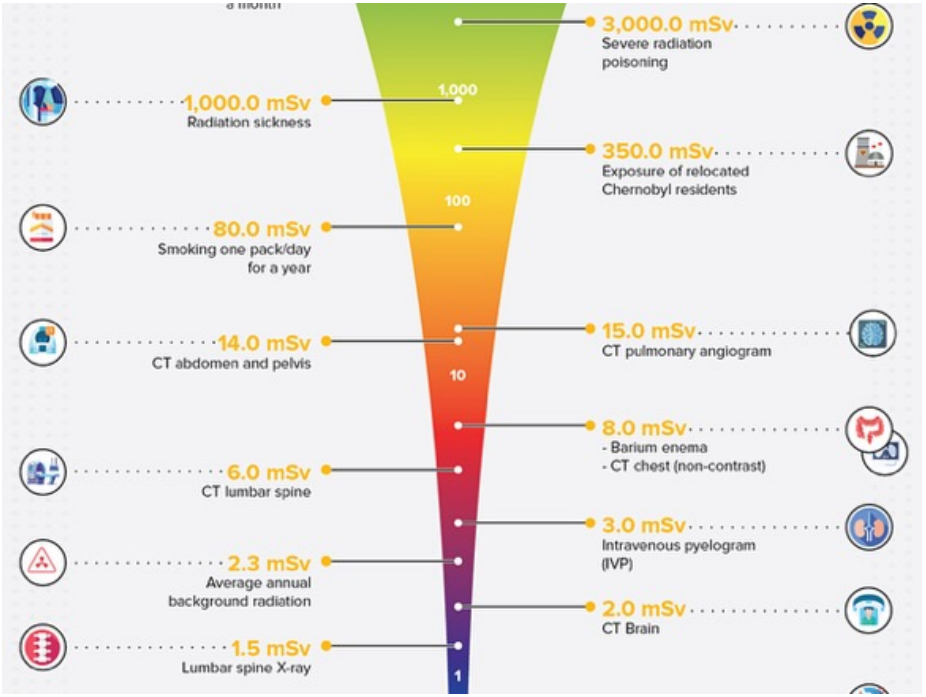

Children with Severe Acute Malnutrition
Intravenous Rehydration
GASTROSAM Trial
Severe dehydration
Gastroenteritis


PRIMARY END POINT
Death at 96 Hours
Risk ratio, intravenous (pooled) vs. oral, 1.02 (95% CI, 0.41–2.52); P=0.69
Percentage of Participants
Oral rehydration
Intravenous rehydration (pooled)
Hours since Randomization
8%
7%
6%
Oral Rehydration
Rapid Intravenous Rehydration
Slow Intravenous Rehydration


Children with Severe Acute Malnutrition and Gastroenteritis
No evidence of a difference in mortality at 96 hours was noted between oral and intravenous rehydration strategies

# Imaging, irradiation, and cancer risk

Imaging and irradiation risks involve a slightly increased lifetime cancer risk, especially for cumulative low doses or younger patients, with the severity linked to dose and patient age. Other less common tissue effects, like skin redness, may occur with high doses during interventional procedures. Most imaging methods using ionizing radiation (like X-rays and CT scans) involve very low doses, and the risks are generally considered very small and outweighed by the benefits of diagnosis. Imaging methods that do not use ionizing radiation, such as ultrasound and MRI, carry no radiation risk.




Millisievert (mSv) ist ein Tausendstel der Einheit Sievert (Sv), die die biologische Wirkung ionisierender Strahlung auf den Menschen misst. Millisievert ist die gängige Einheit im Strahlenschutz, um Dosen und Risiken durch Strahlung im Alltag und bei medizinischen Anwendungen anzugeben, da ein Sievert bereits ein sehr hoher und potenziell tödlicher Wert ist.

# Medical Imaging and Pediatric and Adolescent Hematologic Cancer Risk


**Abstract**

**Background**

Assessing the risk of radiation-induced hematologic cancer from medical imaging in children and adolescents might support informed decisions on the use of imaging.

**Methods**

We followed a retrospective cohort of 3,724,623 children born between 1996 and 2016 in six U.S. health care systems and Ontario, Canada, until the earliest of cancer or benign-tumor diagnosis, death, end of health care coverage, an age of 21 years, or December 31, 2017. Radiation doses to active bone marrow from medical imaging were quantified. Associations between hematologic cancers and cumulative radiation exposure (vs. no exposure), with a lag of 6 months, were estimated with the use of continuous-time hazards models.

**Conclusions**

Our study suggests an association between exposure to radiation from medical imaging and a small but significantly increased risk of hematologic cancer among children and adolescents. (Funded by the National Cancer Institute and others.)

**Calculation of Radiation Dose**

Medical-imaging examinations were identified from administrative databases with the use of codes from Current Procedural Terminology; the *International Classification of Diseases, 9th Revision* (ICD-9-CM and ICD-9-PCS) and *10th Revision* (ICD-10-CM and ICD-10-PCS); the Healthcare Common Procedure Coding System; and the Canadian Classification of Health Interventions. Codes were mapped to an imaging technique and anatomical area. Absorbed doses to the active bone marrow were estimated for each imaging examination with the use of patient characteristics (including sex, height, and weight) extracted from electronic health records, anatomical area imaged, and technical settings used for the imaging. Methods varied according to imaging technique.

**Cancer Assessment**

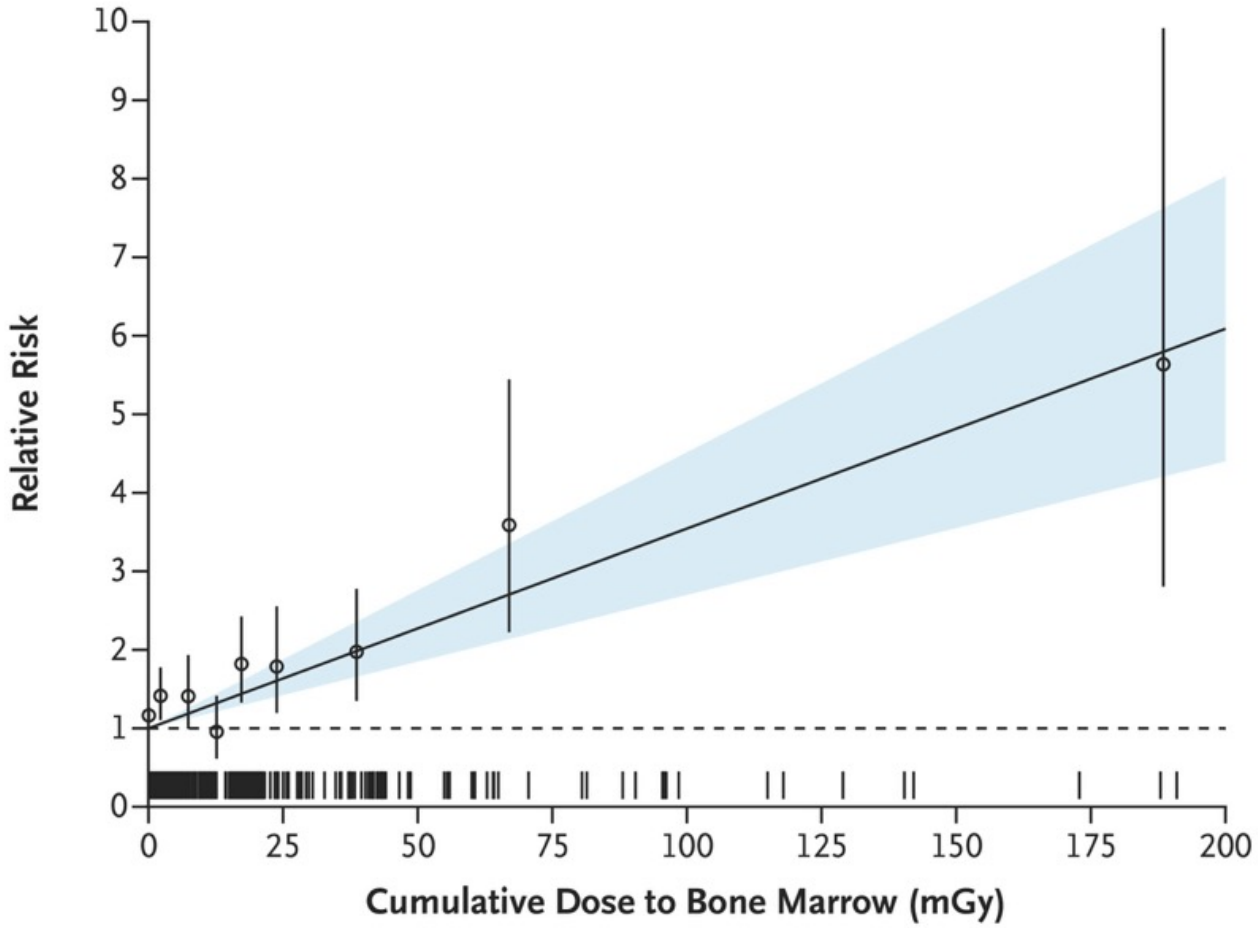
U.S. cancer diagnoses were identified from the cancer registry of each health care system and by linkage with population-based registries participating in the North American Association of Central Cancer Registries. Ontario diagnoses were identified from the Ontario Cancer Registry and the Pediatric Oncology Group of Ontario Networked Information System.

| Characteristic | Entire Cohort (N=3,724,623) | Person-Years of Follow-up (N=35,715,325)† | All Hematologic Cancers (N=2961) |
|---|---|---|---|
| Country — no. (%) | | | |
| Canada | 2,793,503 (75.0) | 30,089,301 (84.2) | 2487 (84.0) |
| United States | 931,120 (25.0) | 5,626,024 (15.8) | 474 (16.0) |
| Sex — no. (%) | | | |
| Male | 1,910,587 (51.3) | 18,315,841 (51.3) | 1722 (58.2) |
| Female | 1,814,036 (48.7) | 17,399,483 (48.7) | 1239 (41.8) |
| Down's syndrome — no. (%) | | | |
| Yes | 4,124 (0.1) | 38,154 (0.1) | 110 (3.7) |
| No | 3,720,499 (99.9) | 35,677,171 (99.9) | 2851 (96.3) |
| Birth cohort — no. (%) | | | |
| 1996 to 1999 | 687,580 (18.5) | 11,342,544 (31.8) | 865 (29.2) |
| 2000 to 2004 | 903,039 (24.2) | 11,337,119 (31.7) | 842 (28.4) |
| 2005 to 2009 | 940,931 (25.3) | 8,268,078 (23.1) | 723 (24.4) |
| 2010 to 2016 | 1,193,073 (32.0) | 4,767,584 (13.3) | 531 (17.9) |
| Age at end of follow-up — no. (%) | | | |
| 6 mo to <5 yr | 1,019,190 (27.4) | 2,503,372 (7.0) | 1506 (50.9) |
| 5 to <10 yr | 953,638 (25.6) | 6,577,018 (18.4) | 695 (23.5) |
| 10 to <15 yr | 789,050 (21.2) | 9,404,954 (26.3) | 430 (14.5) |
| 15 to <21 yr | 962,745 (25.8) | 17,229,980 (48.2) | 330 (11.1) |
| Mean follow-up time — yr | 10.1 | | 6.8 |
| Cumulative radiation dose to bone marrow — no. (%) | | | |
| 0 mGy | 1,406,262 (37.8) | 8,953,308 (25.1) | 1261 (42.6) |
| >0 to <1 mGy | 2,037,813 (54.7) | 22,777,331 (63.8) | 1428 (48.2) |
| 1 to <5 mGy | 84,380 (2.3) | 1,194,532 (3.3) | 77 (2.6) |
| 5 to <10 mGy | 63,552 (1.7) | 1,035,818 (2.9) | 38 (1.3) |
| 10 to <15 mGy | 49,614 (1.3) | 615,186 (1.7) | 23 (0.8) |
| 15 to <20 mGy | 35,266 (1.0) | 443,659 (1.2) | 45 (1.5) |
| 20 to <30 mGy | 21,360 (0.6) | 301,692 (0.8) | 28 (0.9) |
| 30 to <50 mGy | 17,779 (0.5) | 265,994 (0.7) | 31 (1.0) |
| 50 to <100 mGy | 6,462 (0.2) | 96,820 (0.3) | 20 (0.7) |
| ≥100 mGy | 2,135 (0.1) | 30,985 (0.1) | 10 (0.3) |
| Cumulative radiation dose to bone marrow among children who received an exposure of ≥1 mGy | | | |
| Mean — mGy | 14.0±23.1 | | 24.5±36.4 |
| 90th percentile — mGy | 28.7 | | 55.9 |
| Reason for end of follow-up — no. (%)‡ | | | |
| Hematologic cancer | 2,961 (0.1) | 18,765 (0.1) | |
| Other malignant or benign tumor | 3,742 (0.1) | 25,435 (0.1) | |
| Death | 4,916 (0.1) | 27,808 (0.1) | |
| Age of 21 yr | 135,078 (3.6) | 2,768,558 (7.8) | |
| End of health care coverage§ | 611,180 (16.4) | 2,476,343 (6.9) | |
| End of study follow-up | 2,966,746 (79.7) | 30,398,415 (85.1) | |

## Excess Relative Risk per 100-mGy Increase in Exposure and Relative Risks of Hematologic Cancer According to Radiation Dose to Bone Marrow.

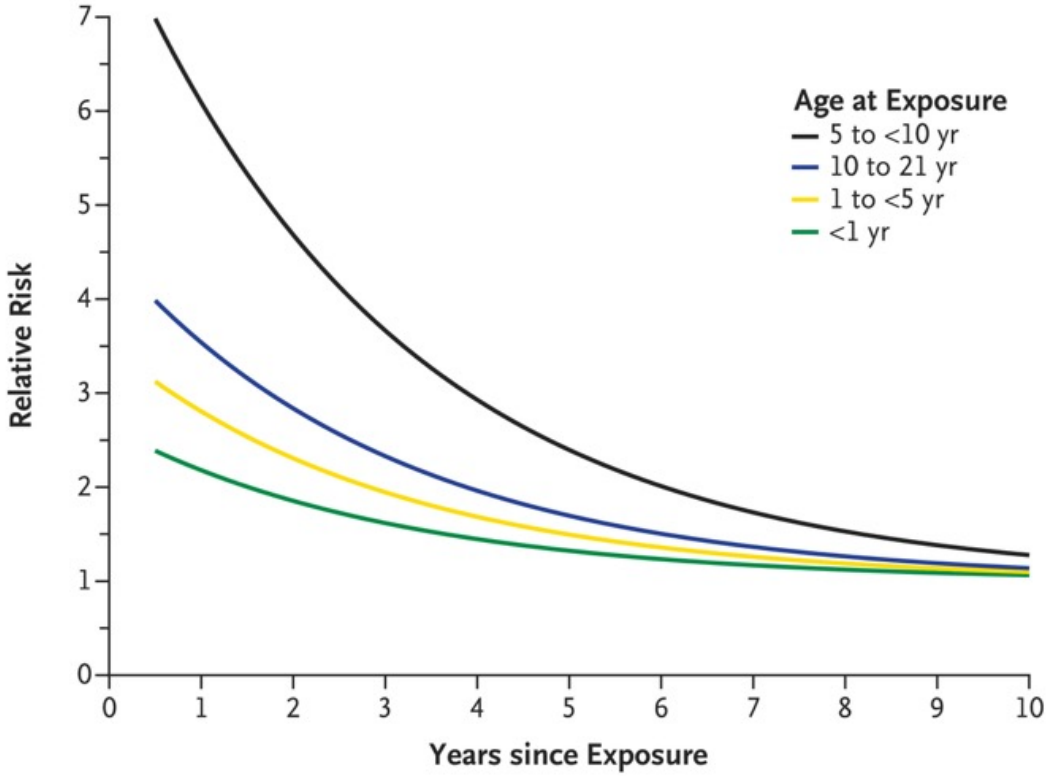
| Cancer Type and Subtype | No. of Cases | Excess Relative Risk per 100 mGy (95% CI) | Relative Risk vs. No Exposure (95% CI) | | |
|---|---|---|---|---|---|
| | | | 10 mGy | 30 mGy | 100 mGy |
| All hematologic cancers† | 2961 | 2.54 (1.70–3.51) | 1.25 (1.17–1.35) | 1.76 (1.51–2.05) | 3.54 (2.70–4.51) |
| Lymphoid cancers‡ | 2349 | 1.95 (1.09–2.97) | 1.20 (1.11–1.30) | 1.59 (1.33–1.89) | 2.95 (2.09–3.97) |
| Non–Hodgkin's lymphoma | 2059 | 2.56 (1.52–3.81) | 1.26 (1.15–1.38) | 1.77 (1.46–2.14) | 3.56 (2.52–4.81) |
| Mature B-cell lymphoma | 229 | 9.68 (5.53–15.38) | 1.97 (1.55–2.54) | 3.90 (2.66–5.61) | 10.68 (6.53–16.38) |
| Mature T-cell or natural-killer-cell lymphoma | 76 | 9.26 (2.86–20.26) | 1.93 (1.29–3.03) | 3.78 (1.86–7.08) | 10.26 (3.86–21.26) |
| Precursor-cell lymphoma§ | 1745 | 0.32 (>0.00–1.22) | 1.03 (1.00–1.12) | 1.09 (1.00–1.37) | 1.32 (1.00–2.22) |
| Hodgkin's lymphoma§ | 279 | 0.00 (0.00–1.10) | 1.00 (1.00–1.11) | 1.00 (1.00–1.33) | 1.00 (1.00–2.10) |
| Myeloid cancer or acute leukemia¶ | 460 | 1.82 (>0.00–4.02) | 1.18 (>1.00–1.40) | 1.55 (>1.00–2.21) | 2.82 (>1.00–5.02) |
| AML, related precursor neoplasm, ALMP, or ALAP§‖ | 304 | 0.00 (0.00–1.49) | 1.00 (1.00–1.15) | 1.00 (1.00–1.45) | 1.00 (1.00–2.49) |
| Myeloproliferative or myelodysplastic syndrome | 124 | 10.19 (3.61–20.82) | 2.02 (1.36–3.08) | 4.06 (2.08–7.24) | 11.19 (4.61–21.82) |
| Histiocytic- or dendritic-cell cancer | 129 | 20.01 (10.00–35.71) | 3.00 (2.00–4.57) | 7.00 (4.00–11.71) | 21.01 (11.00–36.71) |

Milligray (mGy) ist eine Einheit für die Strahlendosis, die angibt, wie viel Energie von ionisierender Strahlung pro Kilogramm Körpergewebe absorbiert wird. Es ist ein Tausendstel eines Grays (Gy), was die SI-Einheit für die Energiedosis ist. Da die Einheit Gray sehr groß ist, werden Messungen oft in Milligray, zum Beispiel bei der Exposition durch Röntgengeräte, angegeben.



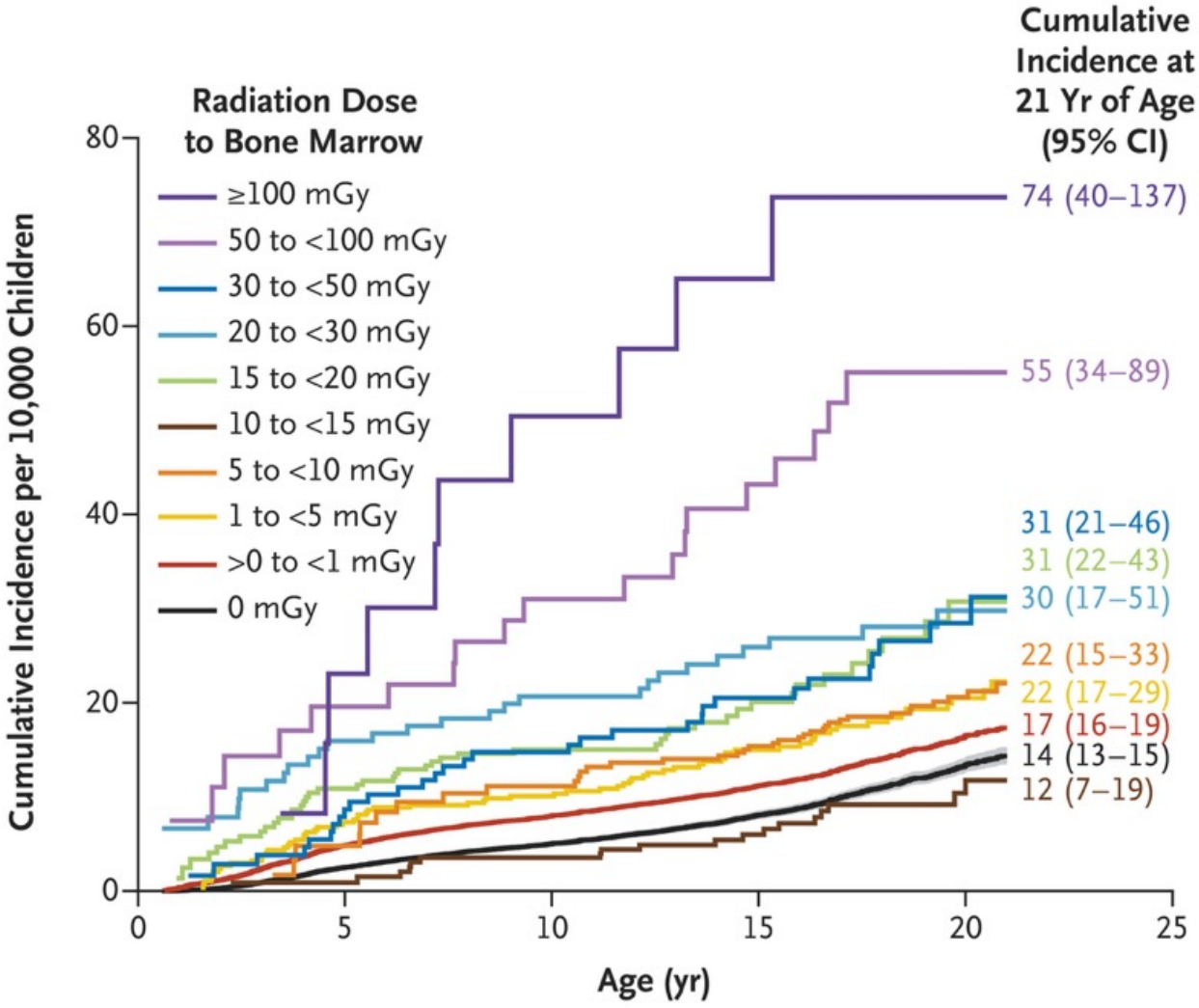

**Relative Risks for All Hematologic Cancers According to Cumulative Radiation Dose to Bone Marrow.**

Dots show estimated relative risks according to categories of cumulative dose (see Table S3 in Supplementary Appendix 2). Vertical bars show 95% confidence intervals. The solid line represents the fitted dose–response relation from the linear model (excess relative risk, 2.54 per 100 mGy exposure). The shaded area represents the upper and lower confidence intervals for the dose–response relation (95% confidence interval for excess relative risk, 1.70 to 3.51). The dashed horizontal line represents the reference value (relative risk, 1.0). The vertical lines at the bottom of the figure show the cumulative doses for children with a hematologic cancer, excluding two children with doses of more than 200 mGy.




**Relative Risk of Hematologic Cancer for a Dose of 30 mGy (vs. No Exposure), According to Time since Exposure and Age at Exposure.**

Time since exposure is modeled as a continuous variable, and age at exposure is modeled as a categorical variable. Results for other dose exposures are shown in Table S5 in Supplementary Appendix 2.




**Cumulative Incidence of Hematologic Cancer According to Attained Age and Radiation Dose to Bone Marrow among Children without Down's Syndrome.**

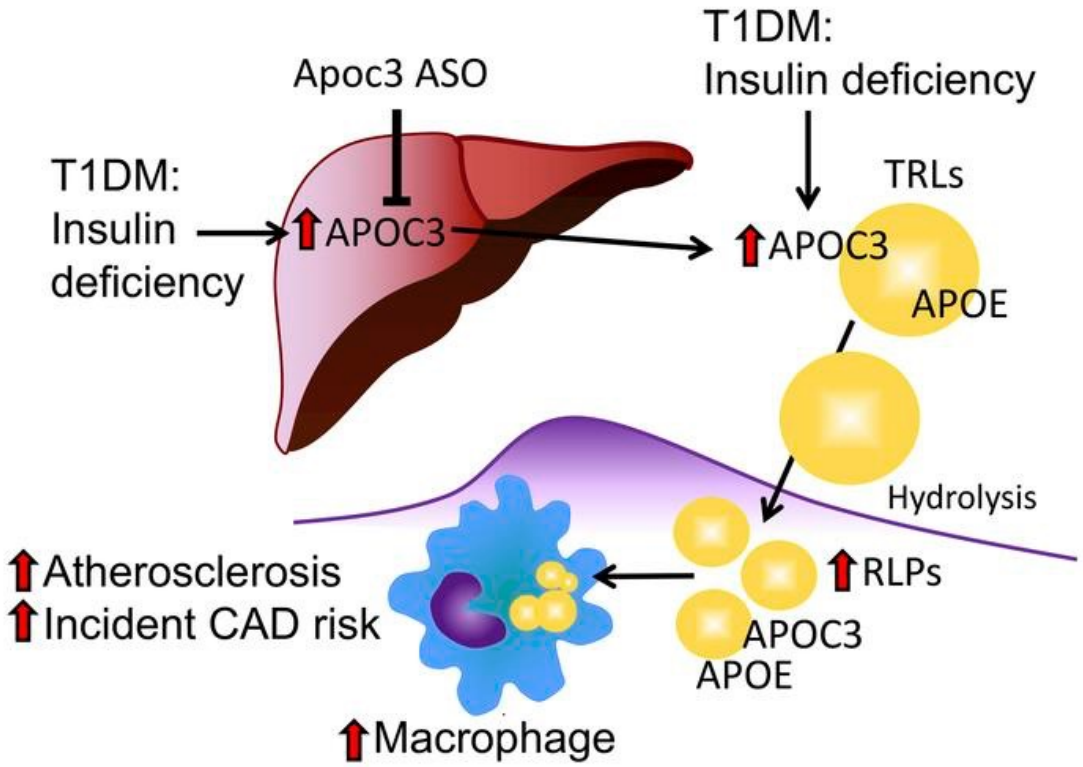
The cumulative incidence and 95% confidence interval are shown for an age of 21 years. The shaded gray area represents the 95% confidence interval for the no-exposure (0 mGy) group. Confidence bands for other groups are omitted for readability.

**Discussion**

In this retrospective cohort study involving more than 3.7 million children born in the United States or Ontario, Canada, we found a significant dose–response relation between cumulative radiation dose to bone marrow and hematologic cancer risk. Exposures that were associated with increased risk are common in clinical practice. For example, a 15-to-30-mGy exposure equivalent to one to two CT scans of the head was associated with an increased risk by a factor of 1.8, rising to a factor of 3.6 for exposures of 50 to less than 100 mGy (Table S3 in Supplementary Appendix 2). The excess cumulative incidence of hematologic cancers by 21 years of age was 25.6 per 10,000 among children exposed to at least 30 mGy and 40.8 per 10,000 among those exposed to 50 to 100 mGy. Excess risks were consistent across most subtypes of hematologic cancer and were robust to sensitivity analyses.

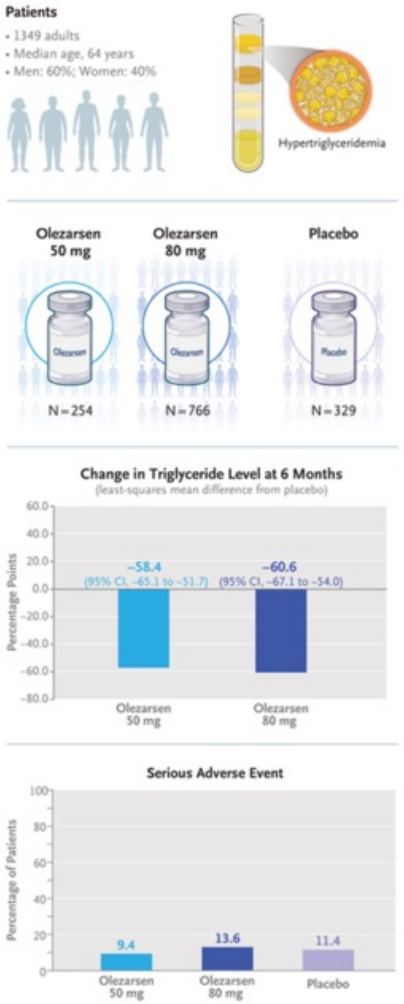
This study provides robust, directly observed evidence that ionizing radiation from medical imaging was associated with an increased risk of hematologic cancer among children, even at doses of less than 50 mGy. These findings underscore the need to carefully weigh benefits and risks when using imaging in children and the need to minimize radiation exposure whenever clinically feasible.

APOC3 (Apolipoprotein C3) ist ein Protein, das eine wichtige Rolle im Fettstoffwechsel spielt, indem es die Funktion von Lipoproteinlipasen hemmt und so den Abbau von Triglyceriden verzögert. Es ist ein Bestandteil von VLDL (Very Low Density Lipoprotein) und Chylomikronen und wird in Leber und Dünndarm produziert. Mutationen im APOC3-Gen können zu Hypertriglyceridämie führen, während eine Hemmung von APOC3, beispielsweise durch Medikamente wie Volanesorsen, den Triglyceridspiegel senken und das Risiko für koronare Herzkrankheiten reduzieren kann.



# Targeting *APOC3* with Olezarsen in Moderate Hypertriglyceridemia

Highly effective therapies to reduce triglyceride levels are lacking. Olezarsen is an *N*-acetylgalactosamine–conjugated antisense oligonucleotide that targets the messenger RNA of apolipoprotein C-III, which inhibits triglyceride clearance. In this phase 3, international, double-blind, randomized, placebo-controlled trial, we enrolled patients with moderate hypertriglyceridemia (triglyceride level, 150 to 499 mg per deciliter) and elevated cardiovascular risk or with severe hypertriglyceridemia (triglyceride level, ≥500 mg per deciliter) and randomly assigned them in a 1:3 ratio to a 50-mg or 80-mg cohort. The patients were then randomly assigned in a 3:1 ratio to receive monthly subcutaneous olezarsen or matching placebo within each cohort. The primary outcome was the least-squares mean percent change in triglyceride level from baseline to 6 months among the patients with moderate hypertriglyceridemia, reported as the difference between each olezarsen dose group and the placebo group (the placebo-adjusted change).



Hypertriglyceridemia is common and is associated with an increased risk of atherosclerosis, yet highly effective therapies for reducing triglyceride levels are lacking. Apolipoprotein C-III is a central regulator of triglyceride metabolism that limits the clearance of triglyceride-rich lipoproteins through inhibition of lipoprotein lipase and hepatic uptake of triglyceride-rich lipoprotein remnants. Olezarsen is an *N*-acetylgalactosamine–conjugated antisense oligonucleotide that targets *APOC3* messenger RNA.
Olezarsen has been shown to decrease triglyceride levels in small phase 2 trials and to reduce triglyceride levels and the risk of acute pancreatitis among patients with familial chylomicronemia syndrome. The Essence–TIMI (Thrombolysis in Myocardial Infarction) 73b trial was designed to evaluate the efficacy and safety of olezarsen in patients with moderate hypertriglyceridemia who are at high cardiovascular risk and in those with severe hypertriglyceridemia.

## Methods

### Trial Design and Oversight

In this phase 3, double-blind, randomized, placebo-controlled trial, we assessed olezarsen at a dose of 50 mg or 80 mg for lowering triglyceride levels.

### Trial Population

Patients were eligible for the trial if they were at least 18 years of age and had either moderate hypertriglyceridemia (triglyceride level, 150 to 499 mg per deciliter [1.7 to 5.6 mmol per liter]) in addition to an elevated risk of cardiovascular events or severe hypertriglyceridemia (triglyceride level, ≥500 mg per deciliter [≥5.6 mmol per liter]). The minimum triglyceride level for eligibility was originally 150 mg per deciliter but was increased to 200 mg per deciliter (2.3 mmol per liter) with a protocol amendment that was made on June 27, 2023, on the basis of regulatory feedback that suggested the trial should be enriched for a population at increased cardiovascular risk.

### Outcomes

The primary outcome was the least-squares mean percent change in triglyceride level from baseline to 6 months among the patients with moderate hypertriglyceridemia, reported as the difference between each olezarsen dose group and the placebo group (the placebo-adjusted change).

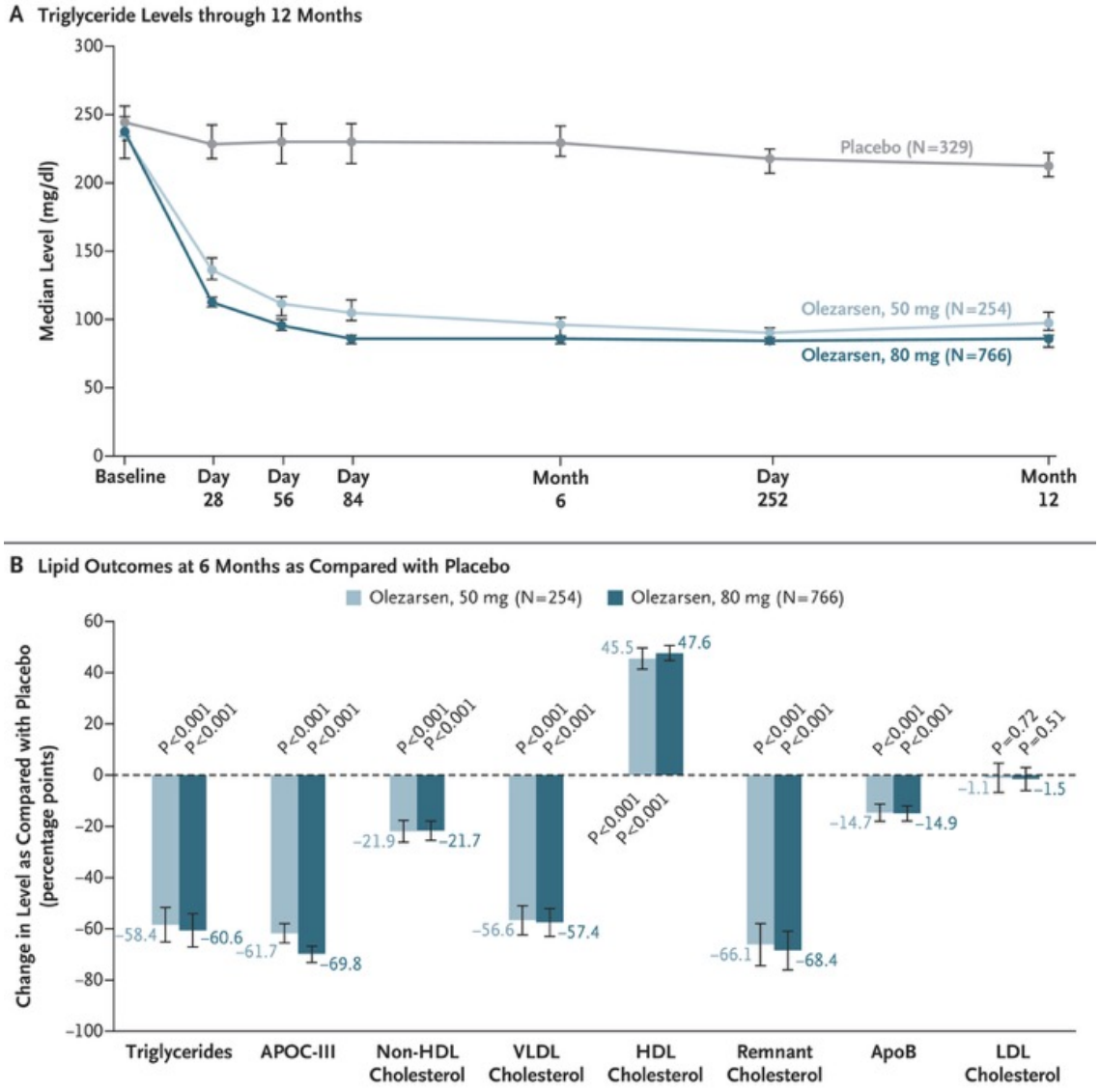
| Characteristic | Olezarsen, 50 mg (N=254) | Olezarsen, 80 mg (N=766) | Placebo (N=329) |
|---|---|---|---|
| Median age (IQR) — yr | 63 (57–69) | 64 (56–70) | 63 (56–70) |
| Female sex — no. (%) | 97 (38.2) | 306 (39.9) | 140 (42.6) |
| Race and ethnic group — no. (%)† | | | |
| White | 240 (94.5) | 713 (93.1) | 299 (90.9) |
| Black | 2 (0.8) | 34 (4.4) | 16 (4.9) |
| Asian | 6 (2.4) | 8 (1.0) | 6 (1.8) |
| Hispanic or Latino | 67 (26.4) | 179 (23.4) | 68 (20.7) |
| Median body-mass index (IQR)‡ | 31.6 (28.3–34.9) | 31.5 (28.5–35.9) | 31.8 (28.1–35.2) |
| Atherosclerotic cardiovascular disease — no. (%) | 115 (45.3) | 307 (40.1) | 128 (38.9) |
| Diabetes mellitus — no. (%) | 151 (59.4) | 468 (61.1) | 190 (57.8) |
| Chronic kidney disease — no. (%) | 27 (10.6) | 64 (8.4) | 30 (9.1) |
| Median triglyceride level (IQR) — mg/dl | 235.3 (186.5–309.5) | 237.3 (191.5–306.0) | 244.0 (191.5–306.5) |
| Median apolipoprotein C-III level (IQR) — mg/dl | 15.2 (12.3–18.8) | 15.3 (12.9–18.3) | 15.4 (12.7–18.8) |
| Median VLDL cholesterol level (IQR) — mg/dl | 40.5 (30.7–53.0) | 42.0 (32.7–53.0) | 41.0 (31.5–55.0) |
| Median remnant cholesterol level (IQR) — mg/dl | 50.7 (36.5–70.3) | 49.4 (36.3–70.2) | 48.8 (34.1–69.6) |
| Median non-HDL cholesterol level (IQR) — mg/dl | 123.3 (97.5–158.0) | 126.0 (99.5–155.5) | 130.5 (106.0–167.0) |
| Median apolipoprotein B level (IQR) — mg/dl | 89.5 (73.1–110.3) | 90.7 (74.0–109.0) | 94.5 (78.2–116.5) |
| Median LDL cholesterol level (IQR) — mg/dl | 79.0 (58.0–112.0) | 81.0 (60.0–107.3) | 87.0 (66.0–117.5) |
| Median glycated hemoglobin level (IQR) — % | 6.3 (5.7–7.1) | 6.2 (5.7–7.0) | 6.2 (5.6–7.1) |
| Median creatinine level (IQR) — mg/dl | 0.9 (0.8–1.1) | 0.9 (0.8–1.1) | 0.9 (0.8–1.1) |
| Median platelet count (IQR) — $\times 10^3/\mu l$ | 236.3 (196.3–273.0) | 232.8 (194.7–271.0) | 232.0 (198.7–282.0) |
| Lipid-lowering therapy — no. (%) | | | |
| Any | 243 (95.7) | 739 (96.5) | 317 (96.4) |
| Statin | 200 (78.7) | 622 (81.2) | 265 (80.5) |
| Ezetimibe | 43 (16.9) | 127 (16.6) | 59 (17.9) |
| Fibrate | 55 (21.7) | 172 (22.5) | 82 (24.9) |
| N–3 fatty acid | 65 (25.6) | 172 (22.5) | 64 (19.5) |
| Niacin | 1 (0.4) | 7 (0.9) | 4 (1.2) |
| PCSK9 inhibitor | 11 (4.3) | 38 (5.0) | 13 (4.0) |
| ≥2 therapies | 100 (39.4) | 326 (42.6) | 138 (41.9) |

## Lipid Levels at Baseline and at 6 Months (Primary Efficacy Population).

| Variable | Olezarsen, 50 mg (N = 254) | Olezarsen, 80 mg (N = 766) | Placebo (N = 329) |
|---|---|---|---|
| **Triglycerides** | | | |
| Level at baseline — mg/dl | 258.7±86.9 | 257.4±85.5 | 260.0±84.9 |
| Level at 6 mo — mg/dl | 109.8±56.3 | 104.8±76.9 | 260.1±177.1 |
| LSM change from baseline (95% CI) — % | −55.6 (−58.0 to −53.2) | −57.8 (−59.6 to −55.9) | 2.8 (−3.5 to 9.0) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −58.4 (−65.1 to −51.7) | −60.6 (−67.1 to −54.0) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **Apolipoprotein C-III** | | | |
| Level at baseline — mg/dl | 16.1±5.1 | 16.2±4.8 | 16.2±4.6 |
| Level at 6 mo — mg/dl | 6.0±3.2 | 4.8±3.6 | 16.0±5.7 |
| LSM change from baseline (95% CI) — % | −61.7 (−64.2 to −59.2) | −69.8 (−71.4 to −68.2) | 0.0 (−2.8 to 2.8) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −61.7 (−65.5 to −57.9) | −69.8 (−73.0 to −66.6) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **Non-HDL cholesterol** | | | |
| Level at baseline — mg/dl | 130.6±43.5 | 132.2±44.8 | 139.3±46.1 |
| Level at 6 mo — mg/dl | 102.6±40.2 | 104.0±44.2 | 138.3±51.4 |
| LSM change from baseline (95% CI) — % | −19.9 (−22.6 to −17.2) | −19.7 (−21.7 to −17.7) | 2.0 (−1.2 to 5.2) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −21.9 (−26.1 to −17.7) | −21.7 (−25.5 to −17.9) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **VLDL cholesterol** | | | |
| Level at baseline — mg/dl | 44.0±16.4 | 44.9±17.7 | 45.7±19.4 |
| Level at 6 mo — mg/dl | 21.4±10.7 | 21.2±14.2 | 46.8±25.8 |
| LSM change from baseline (95% CI) — % | −48.7 (−51.4 to −46.1) | −49.5 (−51.7 to −47.4) | 7.9 (2.8 to 12.9) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −56.6 (−62.3 to −50.9) | −57.4 (−62.9 to −52.0) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **HDL cholesterol** | | | |
| Level at baseline — mg/dl | 39.6±11.7 | 39.7±10.8 | 39.7±10.0 |
| Level at 6 mo — mg/dl | 58.7±18.6 | 59.9±18.5 | 41.2±11.0 |
| LSM change from baseline (95% CI) — % | 50.4 (46.6 to 54.1) | 52.5 (50.3 to 54.7) | 4.9 (2.9 to 6.9) |
| Placebo-adjusted LSM change (95% CI) — percentage points | 45.5 (41.2 to 49.7) | 47.6 (44.7 to 50.5) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **Remnant cholesterol** | | | |
| Level at baseline — mg/dl | 56.7±28.8 | 57.4±31.5 | 57.8±34.6 |
| Level at 6 mo — mg/dl | 21.6±13.3 | 21.8±20.5 | 56.0±36.2 |
| LSM change from baseline (95% CI) — % | −55.5 (−59.3 to −51.7) | −57.7 (−59.9 to −55.5) | 10.7 (3.4 to 17.9) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −66.1 (−74.3 to −57.9) | −68.4 (−76.0 to −60.8) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **Apolipoprotein B** | | | |
| Level at baseline — mg/dl | 93.2±27.0 | 93.9±27.7 | 98.7±27.7 |
| Level at 6 mo — mg/dl | 78.3±24.1 | 78.8±26.9 | 97.1±30.3 |
| LSM change from baseline (95% CI) — % | −14.4 (−16.8 to −12.0) | −14.6 (−16.3 to −13.0) | 0.3 (−2.1 to 2.8) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −14.7 (−18.1 to −11.3) | −14.9 (−17.9 to −11.9) | — |
| P value vs. placebo | <0.001 | <0.001 | — |
| **LDL cholesterol** | | | |
| Level at baseline — mg/dl | 86.6±37.7 | 87.3±38.3 | 93.9±38.5 |
| Level at 6 mo — mg/dl | 82.8±39.0 | 83.2±39.0 | 91.4±41.1 |
| LSM change from baseline (95% CI) — % | 0.1 (−4.5 to 4.7) | −0.4 (−3.2 to 2.4) | 1.1 (−2.4 to 4.7) |
| Placebo-adjusted LSM change (95% CI) — percentage points | −1.1 (−6.9 to 4.7) | −1.5 (−6.0 to 3.0) | — |
| P value vs. placebo | 0.72 | 0.51 | — |

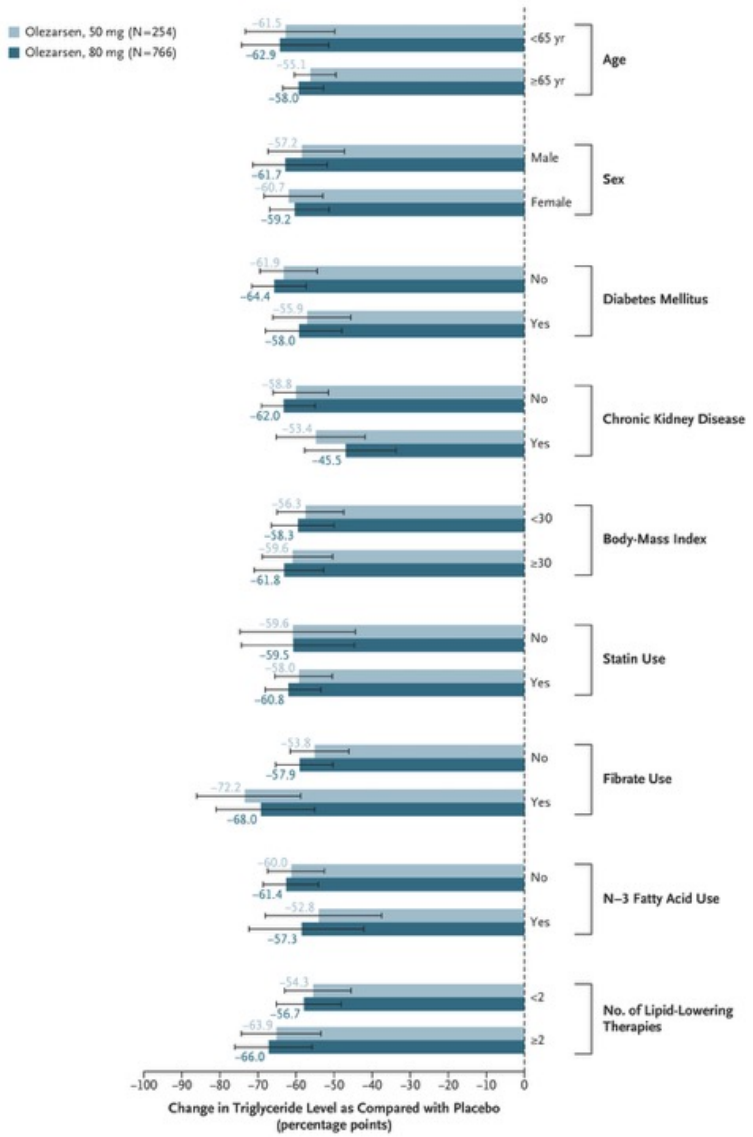
## Key Safety and Laboratory Measures (Safety Population).

| Safety Measure | Placebo (N=369) | Olezarsen, 50 mg (N=276) | P Value vs. Placebo | Olezarsen, 80 mg (N=832) | P Value vs. Placebo |
|---|---|---|---|---|---|
| **Adverse events — no. (%)** | | | | | |
| Any adverse event | 266 (72.1) | 201 (72.8) | 0.84 | 638 (76.7) | 0.09 |
| Adverse event leading to discontinuation of olezarsen or placebo | 18 (4.9) | 12 (4.3) | 0.75 | 56 (6.7) | 0.22 |
| Any serious adverse event | 42 (11.4) | 26 (9.4) | 0.42 | 113 (13.6) | 0.29 |
| Serious adverse event leading to discontinuation of olezarsen or placebo | 5 (1.4) | 2 (0.7) | 0.70 | 18 (2.2) | 0.49 |
| Injection-site reaction† | | | | | |
| Any | 6 (1.6) | 42 (15.2) | <0.001 | 135 (16.2) | <0.001 |
| Mild | 6 (1.6) | 37 (13.4) | <0.001 | 125 (15.0) | <0.001 |
| Moderate | 1 (0.3) | 8 (2.9) | 0.006 | 24 (2.9) | 0.002 |
| Severe | 0 | 0 | — | 0 | — |
| Possible hypersensitivity reaction‡ | 20 (5.4) | 13 (4.7) | 0.69 | 38 (4.6) | 0.53 |
| **Laboratory measures — no./total no. (%)** | | | | | |
| Hepatic abnormality | | | | | |
| ALT or AST level ≥3× ULN | 3/363 (0.8) | 7/272 (2.6) | 0.11 | 17/822 (2.1) | 0.15 |
| ALT or AST level ≥5× ULN | 1/363 (0.3) | 2/272 (0.7) | 0.58 | 2/822 (0.2) | 0.99 |
| Total bilirubin level ≥2× ULN | 1/363 (0.3) | 1/272 (0.4) | 0.99 | 1/822 (0.1) | 0.52 |
| Renal abnormality | | | | | |
| Decrease in eGFR ≥30% | 14/363 (3.9) | 9/272 (3.3) | 0.71 | 33/822 (4.0) | 0.90 |
| Decrease in eGFR ≥50% | 2/363 (0.6) | 1/272 (0.4) | 0.99 | 7/822 (0.9) | 0.73 |
| Urinary protein:creatinine ratio ≥1000§ | 7/363 (1.9) | 4/272 (1.5) | 0.77 | 16/822 (1.9) | 0.98 |
| Urinary protein:creatinine ratio ≥3000§ | 0/363 (0) | 1/272 (0.4) | 0.43 | 1/822 (0.1) | 0.99 |
| Platelet count | | | | | |
| <100,000/μl | 3/363 (0.8) | 6/272 (2.2) | 0.18 | 19/821 (2.3) | 0.10 |
| <75,000/μl | 1/363 (0.3) | 3/272 (1.1) | 0.32 | 6/821 (0.7) | 0.68 |
| <50,000/μl | 1/363 (0.3) | 0/272 (0) | 0.99 | 1/821 (0.1) | 0.52 |



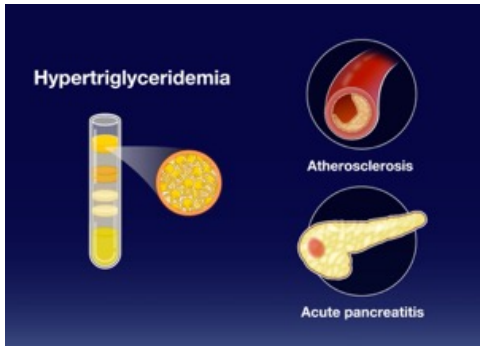

**Triglyceride Levels through 12 Months and Lipid Outcomes at 6 Months.**

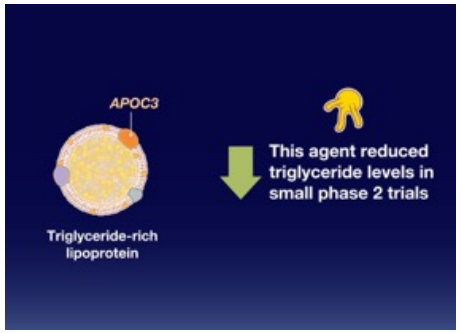
Panel A shows the median triglyceride levels from baseline through 12 months. Panel B shows the primary outcome (the change in triglyceride levels) and secondary lipid outcomes at 6 months; the values are the least-squares mean differences in the percent change in levels from baseline between each olezarsen dose group and the placebo group. Data shown in both panels are for the primary efficacy population, which included the patients with a baseline triglyceride level of less than 500 mg per deciliter who received at least one dose of olezarsen or placebo. I bars indicate 95% confidence intervals. Remnant cholesterol is the cholesterol on triglyceride-rich lipoproteins. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. ApoB denotes apolipoprotein B, APOC-III apolipoprotein C-III, HDL high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.



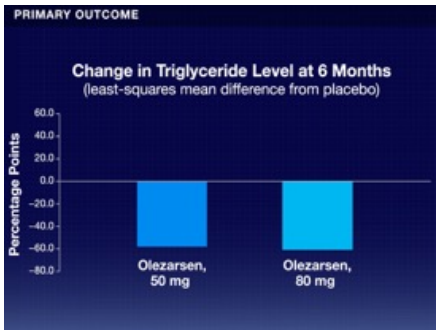

**Changes in Triglyceride Levels at 6 Months in Key Clinical Subgroups.**

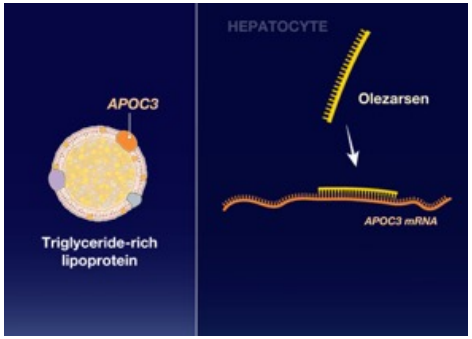
Shown are the least-squares mean differences in the percent change in triglyceride levels from baseline to 6 months between each olezarsen dose group and the placebo group. The body-mass index is the weight in kilograms divided by the square of the height in meters. I bars indicate 95% confidence intervals.


Hypertriglyceridemia
Atherosclerosis
Acute pancreatitis

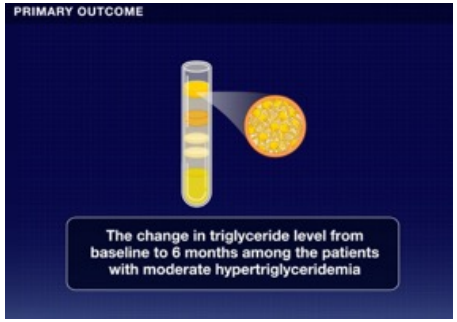

APOC3
Triglyceride-rich lipoprotein
This agent reduced triglyceride levels in small phase 2 trials

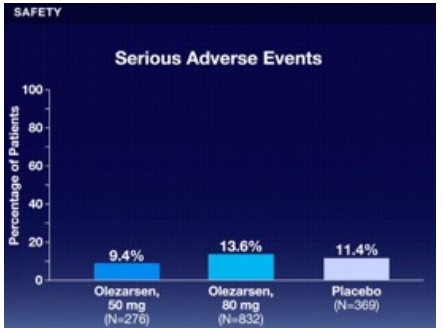

Olezarsen
50 mg monthly
Olezarsen
80 mg monthly
Placebo
N=254
N=766
N=329

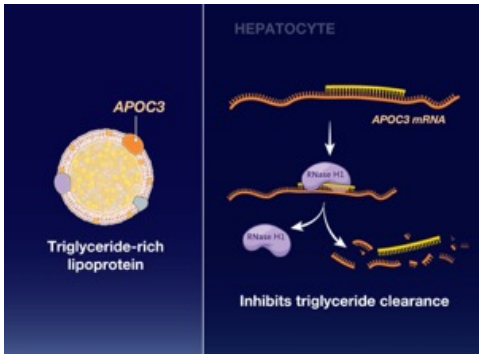

PRIMARY OUTCOME
Change in Triglyceride Level at 6 Months
(least-squares mean difference from placebo)
Percentage Points
60.0
40.0
20.0
0.0
-20.0
-40.0
-60.0
-80.0
Olezarsen, 50 mg
Olezarsen, 80 mg

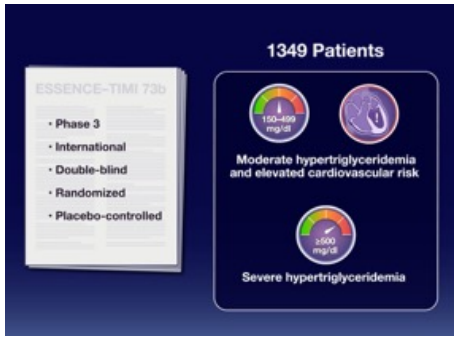

HEPATOCYTE
APOC3
Olezarsen
APOC3 mRNA
Triglyceride-rich lipoprotein


ESSENCE-TIMI 73b
This agent reduced triglyceride levels in small phase 2 trials


PRIMARY OUTCOME
The change in triglyceride level from baseline to 6 months among the patients with moderate hypertriglyceridemia


SAFETY
Serious Adverse Events
Percentage of Patients
100
80
60
40
20
0
9.4%
13.6%
11.4%
Olezarsen, 50 mg (N=276)
Olezarsen, 80 mg (N=832)
Placebo (N=369)

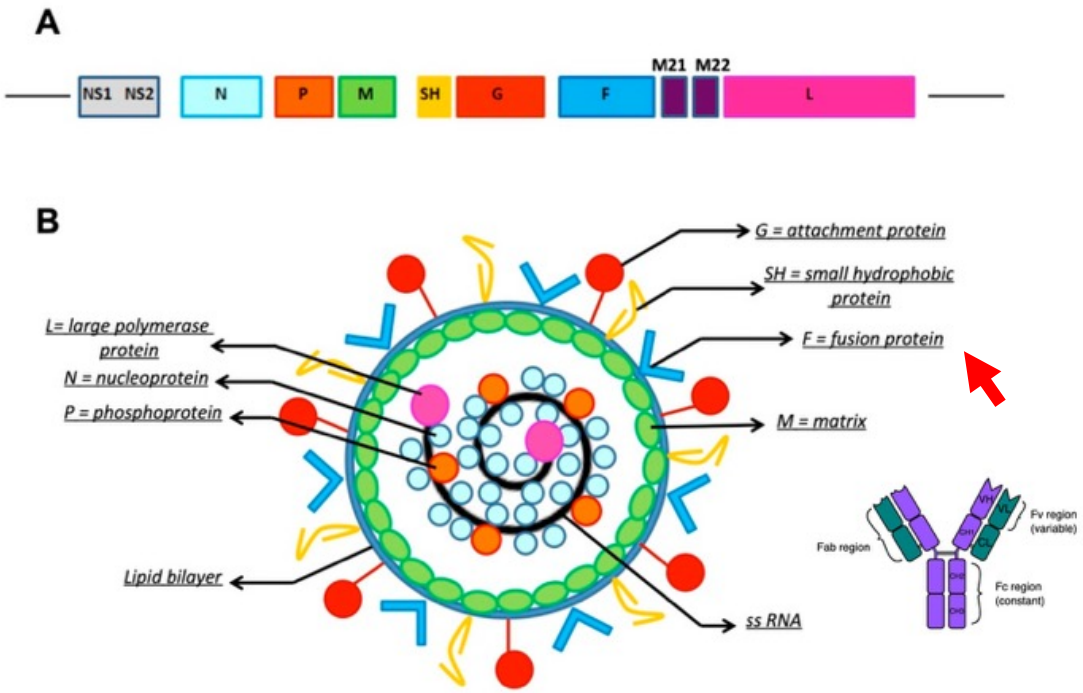

HEPATOCYTE
APOC3
APOC3 mRNA
RNase H1
Triglyceride-rich lipoprotein
Inhibits triglyceride clearance


ESSENCE-TIMI 73b
• Phase 3
• International
• Double-blind
• Randomized
• Placebo-controlled
1349 Patients
150–499 mg/dl
Moderate hypertriglyceridemia and elevated cardiovascular risk
≥500 mg/dl
Severe hypertriglyceridemia


PRIMARY OUTCOME
Reported as the difference between each olezarsen dose group and the placebo group
50 mg
80 mg


Olezarsen
Monthly treatment with olezarsen reduced triglyceride levels at 6 months as compared with placebo

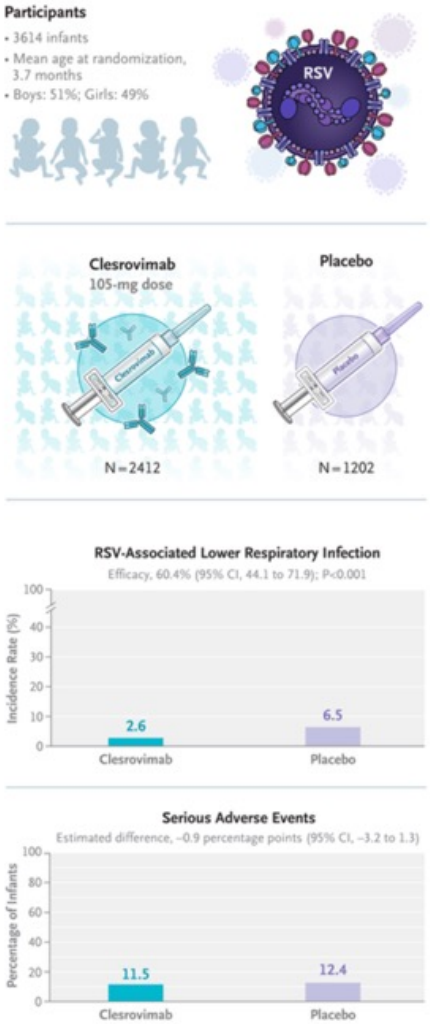
Passive immunity for Respiratory Syncytial Virus (RSV) involves providing a baby with pre-made antibodies for immediate protection, either by administering RSV-specific monoclonal antibodies directly to the infant or by the mother receiving an RSV vaccine during pregnancy, which triggers the transfer of her antibodies to the fetus. This approach offers short-term protection against severe RSV disease, particularly during the first RSV season when infants are most vulnerable.



# Clesrovimab for Prevention of RSV Disease in Healthy Infants

Clesrovimab is a long-acting investigational monoclonal antibody against site IV of the respiratory syncytial virus (RSV) fusion protein. Data regarding the safety and efficacy of clesrovimab in healthy infants are needed.

We randomly assigned healthy preterm and full-term infants entering their first RSV season in a 2:1 ratio to receive one intramuscular 105-mg dose of clesrovimab or placebo. The primary efficacy end point was RSV-associated medically attended lower respiratory infection (including at least one indicator of lower respiratory infection or disease severity) through 150 days after injection. A key secondary efficacy end point was RSV-associated hospitalization during the same period.



Among infants younger than 1 year of age, respiratory syncytial virus (RSV) causes an estimated 12.9 million lower respiratory infections and approximately 2.2 million hospitalizations per year worldwide. RSV is a leading cause of infant hospitalization in high-income countries and is a frequent cause of infant deaths in low- and middle-income countries. Preterm infants and those with underlying medical conditions are predisposed to severe RSV infection, but the majority of RSV hospitalizations occur in full-term healthy infants. The burden of severe RSV infection is highest during the first 6 months after birth, when prevention is needed. Recently, two RSV preventive therapies — the monoclonal antibody nirsevimab (Beyfortus, Sanofi) and the maternal bivalent prefusion F vaccine (ABRYSVO, Pfizer) — have been licensed for use in infants.
Clesrovimab is a human RSV monoclonal antibody with three amino acid substitutions (M252Y, S254T, and T256E, collectively referred to as YTE) in the Fc portion. Clesrovimab binds site IV of the RSV fusion (F) protein, which differs from the RSV antibodies palivizumab (site II) and nirsevimab (site Ø).

## Methods

### Trial Design and Participants

We conducted this double-blind, randomized, placebo-controlled trial in 22 countries. Key exclusion criteria were a recommendation that the infant receive palivizumab, a recent history of febrile illness, and any previous preventive RSV treatment. Palivizumab is licensed in many countries for infants at increased risk for severe RSV disease, including those born at a gestational age of less than 35 weeks and those with coexisting conditions such as chronic lung disease of prematurity and hemodynamically significant congenital heart disease.

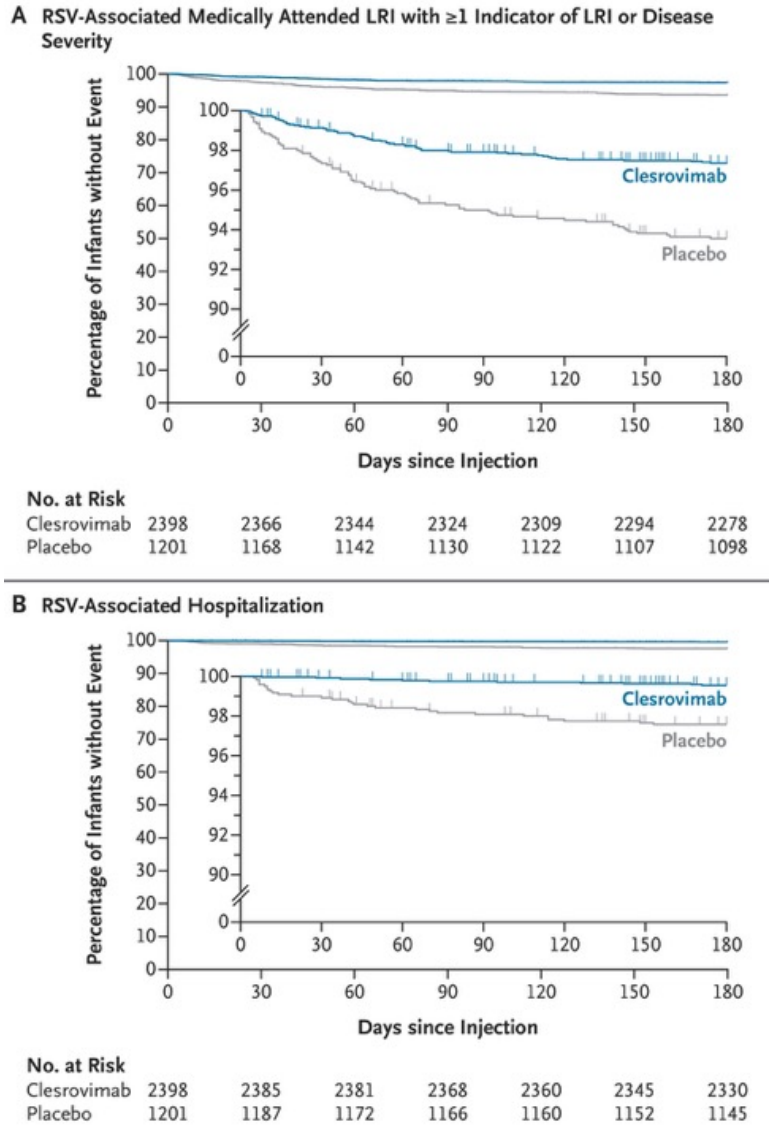
### End Points and Adverse Events

The primary efficacy end point was RSV-associated medically attended (inpatient or outpatient) lower respiratory infection that included at least one indicator of lower respiratory infection or one indicator of disease severity from days 1 to 150 after injection. The case definition that was used for the primary end point required confirmation of RSV infection on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay from a sample obtained within 7 days before or 12 days after symptom onset or worsening of symptoms.

| Characteristic | Clesrovimab (N=2411) | Placebo (N=1203) | Total (N=3614) |
|---|---|---|---|
| Sex — no. (%) | | | |
| Male | 1228 (50.9) | 617 (51.3) | 1845 (51.1) |
| Female | 1183 (49.1) | 586 (48.7) | 1769 (48.9) |
| Age | | | |
| Mean — mo | 3.7±2.6 | 3.7±2.6 | 3.7±2.6 |
| Distribution — no. (%) | | | |
| <6 mo | 1923 (79.8) | 964 (80.1) | 2887 (79.9) |
| 6 to <9 mo | 383 (15.9) | 192 (16.0) | 575 (15.9) |
| ≥9 mo | 105 (4.4) | 47 (3.9) | 152 (4.2) |
| Race or ethnic group — no. (%)† | | | |
| American Indian or Alaska Native | 50 (2.1) | 18 (1.5) | 68 (1.9) |
| Asian | 641 (26.6) | 320 (26.6) | 961 (26.6) |
| Black | 326 (13.5) | 171 (14.2) | 497 (13.8) |
| Multiple | 302 (12.5) | 138 (11.5) | 440 (12.2) |
| Native Hawaiian or other Pacific Islander | 1 (<0.1) | 1 (0.1) | 2 (0.1) |
| White | 1082 (44.9) | 550 (45.7) | 1632 (45.2) |
| Missing data | 9 (0.4) | 5 (0.4) | 14 (0.4) |
| Hispanic or Latino ethnic group — no. (%) | | | |
| Yes | 682 (28.3) | 335 (27.8) | 1017 (28.1) |
| No | 1660 (68.9) | 834 (69.3) | 2494 (69.0) |
| Not reported, unknown, or missing data | 69 (2.9) | 34 (2.8) | 103(2.9) |
| Gestational age — no. (%) | | | |
| ≥29 to <35 wk | 422 (17.5) | 209 (17.4) | 631 (17.5) |
| ≥35 wk | 1989 (82.5) | 994 (82.6) | 2983 (82.5) |
| Geographic region | | | |
| Northern Hemisphere | 1650 (68.4) | 814 (67.7) | 2464 (68.2) |
| Southern Hemisphere | 761 (31.6) | 389 (32.3) | 1150 (31.8) |
| Climate in region | | | |
| Tropical or subtropical | 459 (19.0) | 233 (19.4) | 692 (19.1) |
| Temperate | 1952 (81.0) | 970 (80.6) | 2922 (80.9) |
| Body weight — kg | 5.8±2.0 | 5.9±2.0 | 5.8±2.0 |
| Body length — cm | 59.2±7.6 | 59.3±7.5 | 59.2±7.5 |

## Adverse Events (Safety Population).

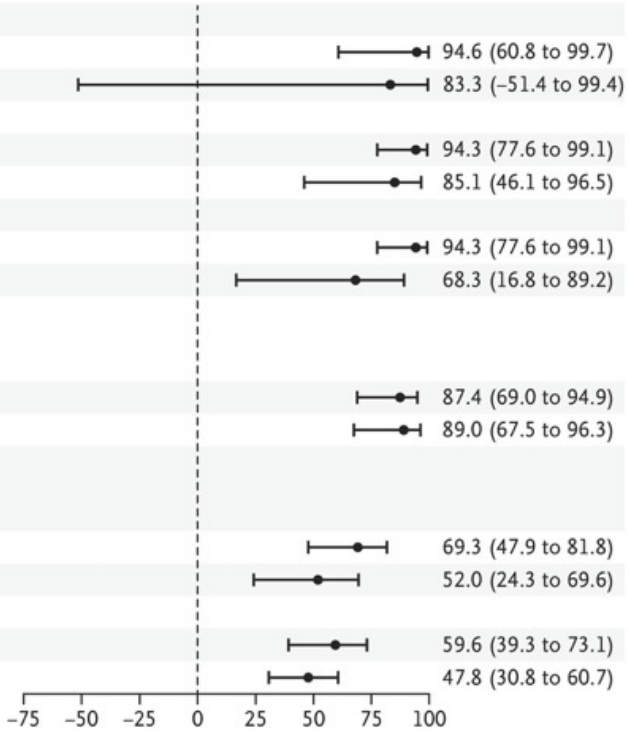
| Adverse Event | Clesrovimab (N=2409) | Placebo (N=1202) | Estimated Difference (95% CI)† |
|---|---|---|---|
| | *no. of infants (%)* | | *percentage points* |
| Overall adverse events‡ | | | |
| Any adverse event | | | |
| ≥1 Adverse event | 1816 (75.4) | 918 (76.4) | −1.0 (−3.9 to 2.0) |
| Related to clesrovimab or placebo | 587 (24.4) | 296 (24.6) | −0.3 (−3.3 to 2.7) |
| Any serious adverse event | 278 (11.5) | 149 (12.4) | −0.9 (−3.2 to 1.3) |
| Related to clesrovimab or placebo | 1 (<0.1) | 1 (0.1) | −0.0 (−0.4 to 0.2) |
| Death§ | 7 (0.3) | 3 (0.2) | 0.0 (−0.5 to 0.4) |
| Solicited adverse event or fever on days 1–5 after injection | | | |
| Injection-site reaction | 223 (9.3) | 117 (9.7) | −0.5 (−2.6 to 1.5) |
| Erythema | 90 (3.7) | 40 (3.3) | 0.4 (−0.9 to 1.6) |
| Pain | 122 (5.1) | 77 (6.4) | −1.3 (−3.1 to 0.2) |
| Swelling | 65 (2.7) | 31 (2.6) | 0.1 (−1.1 to 1.2) |
| Solicited systemic adverse event | 631 (26.2) | 337 (28.0) | −1.8 (−5.0 to 1.2) |
| Decreased appetite | 106 (4.4) | 61 (5.1) | −0.7 (−2.3 to 0.7) |
| Irritability | 450 (18.7) | 237 (19.7) | −1.0 (−3.8 to 1.7) |
| Somnolence | 303 (12.6) | 171 (14.2) | −1.6 (−4.1 to 0.7) |
| With fever | 13 (0.5) | 14 (1.2) | −0.6 (−1.4 to −0.0) |
| Adverse event of special interest on days 1–42 after injection | | | |
| Anaphylaxis or hypersensitivity | 1 (<0.1) | 0 | 0.0 (−0.3 to 0.2) |
| Rash | 11 (0.5) | 4 (0.3) | 0.1 (−0.4 to 0.5) |




**Time-to-Event Analyses.**

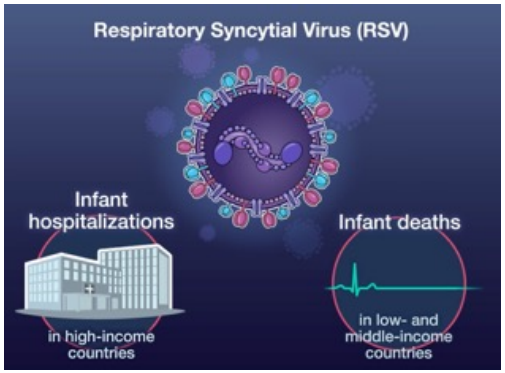
Kaplan–Meier curves are shown for time-to-event analyses of the percentage of infants in the full-analysis population who were free from RSV-associated medically attended LRI with at least one indicator of LRI or disease severity through day 180 (Panel A) or RSV-associated hospitalization through day 180 (Panel B). Tick marks indicate censored data. The inset in each panel shows the same data on an expanded y axis.

| RSV-Associated End Point, According to Body Weight at Randomization | Clesrovimab (<5 kg, N=860; ≥5 kg, N=1538) | Placebo (<5 kg, N=428; ≥5 kg, N=773) | Efficacy (95% CI) |
|---|---|---|---|
| | *no. of cases* | *no. of cases* | *percent* |
| Severe medically attended LRI | | | |
| <5 kg | 1 | 9 | 94.6 (60.8 to 99.7) |
| ≥5 kg | 1 | 3 | 83.3 (−51.4 to 99.4) |
| Hospitalization for LRI | | | |
| <5 kg | 2 | 17 | 94.3 (77.6 to 99.1) |
| ≥5 kg | 3 | 10 | 85.1 (46.1 to 96.5) |
| Hospitalization | | | |
| <5 kg | 2 | 17 | 94.3 (77.6 to 99.1) |
| ≥5 kg | 7 | 11 | 68.3 (16.8 to 89.2) |
| Medically attended LRI with ≥2 indicators of LRI or disease severity | | | |
| <5 kg | 6 | 23 | 87.4 (69.0 to 94.9) |
| ≥5 kg | 4 | 18 | 89.0 (67.5 to 96.3) |
| Medically attended LRI with ≥1 indicator of LRI or disease severity | | | |
| <5 kg | 23 | 36 | 69.3 (47.9 to 81.8) |
| ≥5 kg | 37 | 38 | 52.0 (24.3 to 69.6) |
| Acute respiratory infection | | | |
| <5 kg | 44 | 52 | 59.6 (39.3 to 73.1) |
| ≥5 kg | 104 | 96 | 47.8 (30.8 to 60.7) |

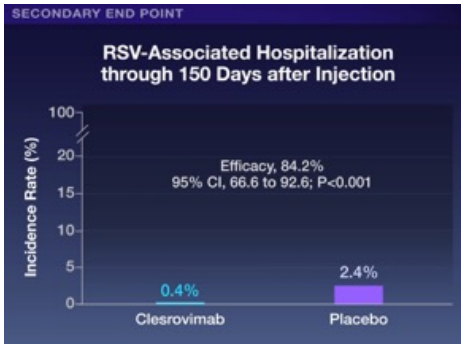


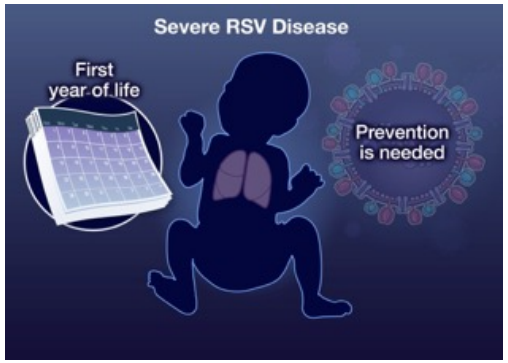

**Efficacy of Clesrovimab through 150 Days after Injection for RSV-Associated End Points, According to Body Weight at Randomization.**

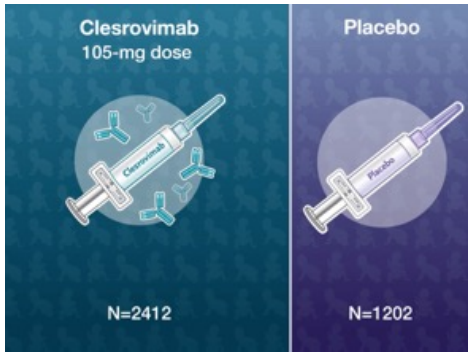
The efficacy of clesrovimab is shown according to body-weight subgroups in the full analysis population. The model included only the trial-group assignment. If the model did not converge or if a confidence interval could not be estimated with the use of the modified Poisson method, an exact binomial method proposed by Chan and Bohidar,[23] along with Blaker's confidence interval,[24] was used.


Respiratory Syncytial Virus (RSV)
Infant hospitalizations
in high-income countries
Infant deaths
in low- and middle-income countries

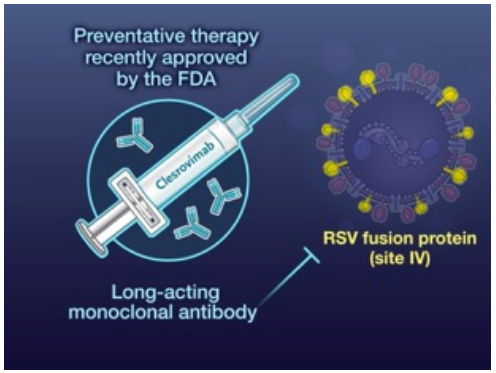

Preventative therapy recently approved by the FDA
Clesrovimab
Safety and efficacy in healthy infants?
Long-acting monoclonal antibody

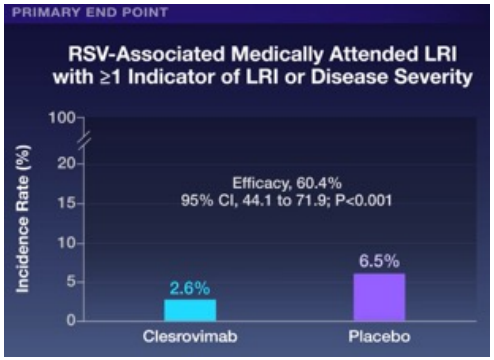

SECONDARY END POINT
RSV-Associated Hospitalization through 150 Days after Injection
Incidence Rate (%)
100
20
15
10
5
0
Efficacy, 84.2%
95% CI, 66.6 to 92.6; P<0.001
0.4%
2.4%
Clesrovimab
Placebo

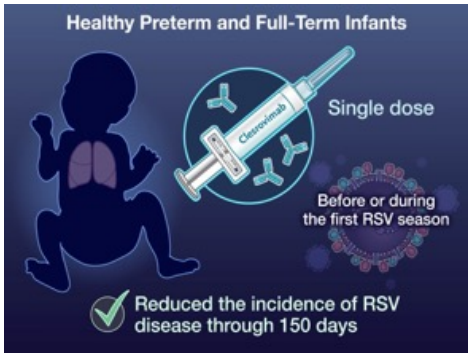

Severe RSV Disease
First year of life
Prevention is needed


Clesrovimab
105-mg dose
Placebo
N=2412
N=1202

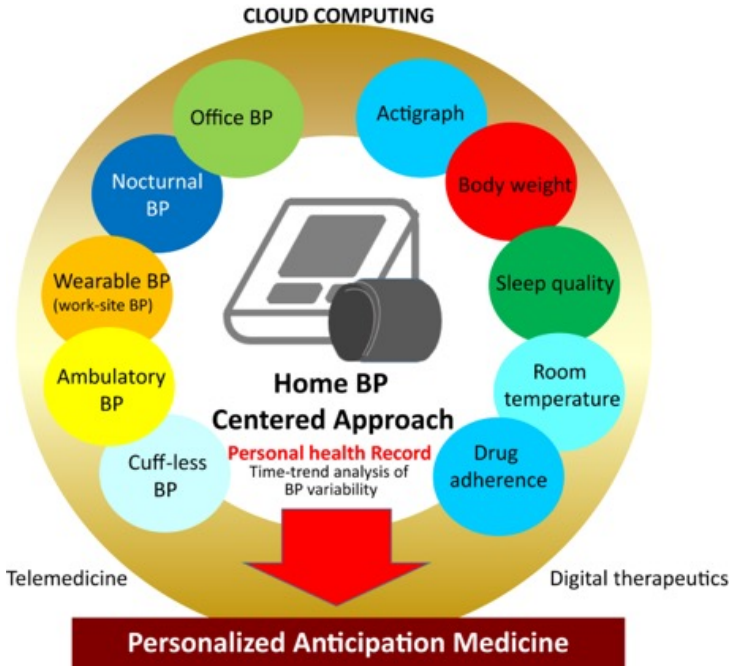

SAFETY
Serious Adverse Events
Percentage of Infants
100
80
60
40
20
0
Estimated difference,
−0.9 percentage points (95% CI, −3.2 to 1.3)
11.5%
12.4%
Clesrovimab
Placebo


Preventative therapy recently approved by the FDA
Clesrovimab
RSV fusion protein (site IV)
Long-acting monoclonal antibody


PRIMARY END POINT
RSV-Associated Medically Attended LRI with ≥1 Indicator of LRI or Disease Severity
Incidence Rate (%)
100
20
15
10
5
0
Efficacy, 60.4%
95% CI, 44.1 to 71.9; P<0.001
2.6%
6.5%
Clesrovimab
Placebo

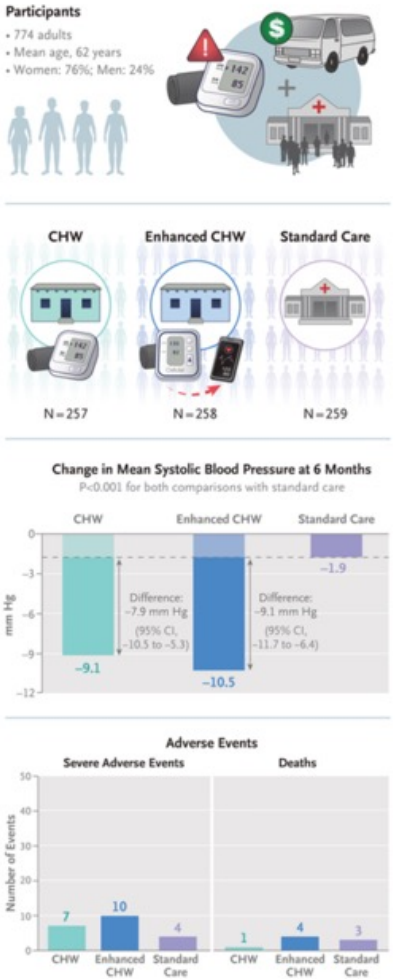

Healthy Preterm and Full-Term Infants
Clesrovimab
Single dose
Before or during the first RSV season
Reduced the incidence of RSV disease through 150 days

Home-based hypertension care involves a comprehensive approach, including taking prescribed medications, self-monitoring blood pressure, adhering to a low-sodium diet rich in fruits and vegetables, getting regular physical activity, maintaining a healthy weight, limiting alcohol, quitting smoking, and managing stress through techniques like meditation or yoga. A healthcare professional can help set up a personalized home-based care plan, according to the Centers for Disease Control and Prevention.



# Home-Based Care for Hypertension in Rural South Africa

Poorly controlled hypertension is a common problem worldwide, particularly in low-resource settings.
We conducted an open-label, randomized, controlled trial of a home-based model of hypertension care in South Africa. Adults with hypertension were assigned to receive home-based care, which consisted of patient monitoring of blood pressure, home visits from a community health worker (CHW) for data collection and medication delivery, and remote nurse-led decision making supported by a mobile application (CHW group); enhanced home-based care, which consisted of the same intervention but with blood-pressure machines transmitting readings automatically (enhanced CHW group); or standard care with clinic-based management (standard-care group). The primary outcome was the systolic blood pressure at 6 months. Secondary outcomes were the systolic blood pressure at 12 months and hypertension control at 6 and 12 months. Safety outcomes included adverse events, deaths, and retention in care.



Elevated blood pressure is the leading risk factor for preventable death, resulting in approximately 10 million deaths each year. Although numerous low-cost, effective therapies are available, poorly controlled hypertension is a common problem, particularly in populations with structural barriers to health care. In the public sector of South Africa, patients' limited involvement in their care, overcrowded clinics, inconsistent availability of sphygmomanometers, and the costs of transportation to a clinic and missed work are commonly cited contributors to suboptimal outcomes. Home-based blood-pressure management with remote monitoring has been proposed to address these barriers, but data on the efficacy of such programs are scarce.

**Outcomes and Assessments**

The primary outcome was the systolic blood pressure at 6 months. Secondary outcomes were the systolic blood pressure at 12 months and hypertension control at 6 and 12 months. Hypertension control was defined by a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg. Safety outcomes included adverse events, hospitalizations, deaths, and retention in care, which was defined as an interaction with a health care worker (nurse, physician, or CHW) for hypertension care within the past 3 months.

**Trial Design and Oversight**

We conducted a parallel-group, open-label, randomized, controlled trial. The trial was designed and implemented as a superiority trial in which two intervention groups were individually compared with a control group.

## Trial Procedures

Participants were randomly assigned to receive home-based care from a CHW (CHW group), enhanced home-based care from a CHW (enhanced CHW group), or standard care with clinic-based management (standard-care group). Participants in all three groups were seen by a nurse on the day of enrollment for determination of initial antihypertensive therapy. Before the trial began, nurses involved in the program had received training on best practices for hypertension care. The three principal antihypertensive therapies that were available in the public sector in South Africa and used in this trial were hydrochlorothiazide, lisinopril, and amlodipine. All the therapies were provided to the participants free of charge.

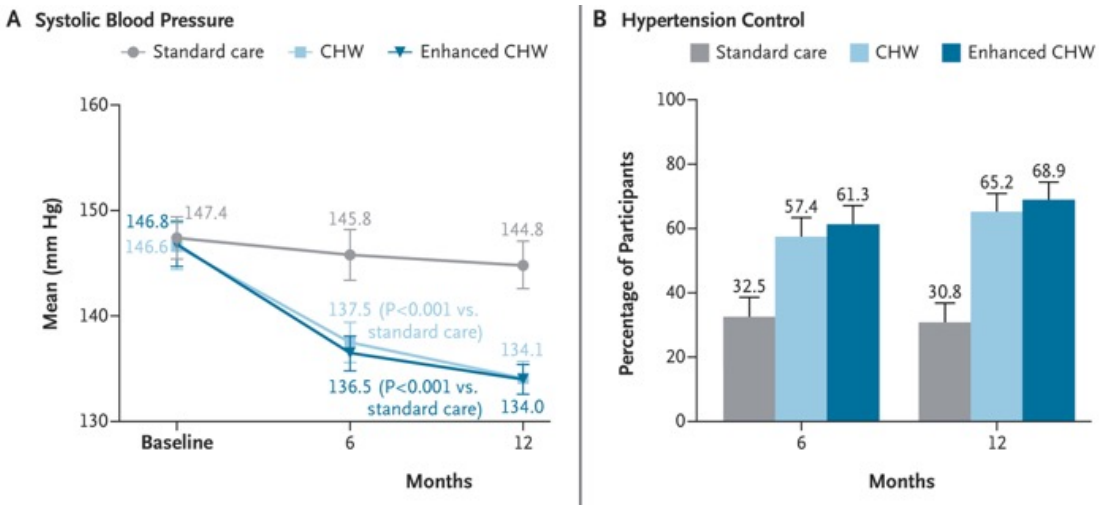
In the standard-care group, participants were asked to return to the clinic approximately monthly for measurement of blood pressure, adjustment of antihypertensive therapy in accordance with the national guidelines, and collection of medication from the clinic pharmacy. In the CHW group, participants received an automated blood-pressure machine (Omron M3), were trained on its use by CHWs, and were advised to take blood-pressure measurements daily.

## Demographic and Clinical Characteristics of the Participants at Enrollment.

| Characteristic | CHW (N=257) | Enhanced CHW (N=258) | Standard Care (N=259) | Total (N=774) |
|---|---|---|---|---|
| Age — yr | 63±12 | 62±11 | 62±12 | 62±12 |
| Female sex — no. (%) | 202 (78.6) | 192 (74.4) | 194 (74.9) | 588 (76.0) |
| Education level — no. (%) | | | | |
| None | 110 (42.8) | 90 (34.9) | 103 (39.8) | 303 (39.1) |
| Primary education | 61 (23.7) | 65 (25.2) | 57 (22.0) | 183 (23.6) |
| Higher than primary education | 85 (33.1) | 103 (39.9) | 99 (38.2) | 287 (37.1) |
| Missing data | 1 (0.4) | 0 | 0 | 1 (0.1) |
| Employment status — no. (%) | | | | |
| Employed | 28 (10.9) | 31 (12.0) | 28 (10.8) | 87 (11.2) |
| Unemployed | 226 (87.9) | 225 (87.2) | 227 (87.6) | 678 (87.6) |
| Missing data | 3 (1.2) | 2 (0.8) | 4 (1.5) | 9 (1.2) |
| Asset index quintile — no. (%) | | | | |
| Most deprived | 43 (16.7) | 55 (21.3) | 64 (24.7) | 162 (20.9) |
| Deprived | 54 (21.0) | 51 (19.8) | 42 (16.2) | 147 (19.0) |
| Moderately deprived | 51 (19.8) | 42 (16.3) | 58 (22.4) | 151 (19.5) |
| Less deprived | 46 (17.9) | 53 (20.5) | 54 (20.8) | 153 (19.8) |
| Least deprived | 57 (22.2) | 55 (21.3) | 40 (15.4) | 152 (19.6) |
| Missing data | 6 (2.3) | 2 (0.8) | 1 (0.4) | 9 (1.2) |
| Access to running water — no. (%) | | | | |
| Yes | 34 (13.2) | 38 (14.7) | 40 (15.4) | 112 (14.5) |
| No | 222 (86.4) | 220 (85.3) | 218 (84.2) | 660 (85.3) |
| Missing data | 1 (0.4) | 0 | 1 (0.4) | 2 (0.3) |
| Travel time to clinic — min | 52±187 | 41±33 | 47±43 | 47±112 |
| Cost of travel to clinic — South African rand† | 30.58±27.17 | 29.11±24.93 | 26.21±16.14 | 28.68±23.37 |
| Systolic blood pressure — mm Hg | 146.6±18.0 | 146.8±17.2 | 147.4±16.4 | 147.0±17.2 |
| Systolic blood pressure ≥160 mm Hg — no. (%) | 53 (20.6) | 53 (20.5) | 50 (19.3) | 156 (20.2) |
| Use of antihypertensive therapy — no. (%) | 249 (96.9) | 251 (97.3) | 251 (96.9) | 751 (97.0) |
| Body-mass index‡ | 29.8±7.1 | 30.0±7.1 | 29.3±7.5 | 29.7±7.2 |
| Estimated glomerular filtration rate — ml/min/1.73 $m^2$§ | 74.5±14.1 | 78.2±15.7 | 75.5±14.9 | 76.1±15.0 |
| Diabetes mellitus — no. (%) | 32 (12.5) | 41 (15.9) | 32 (12.4) | 105 (13.6) |
| HIV status — no. (%) | | | | |
| Negative | 133 (51.8) | 149 (57.8) | 131 (50.6) | 413 (53.4) |
| Positive | 123 (47.9) | 109 (42.2) | 128 (49.4) | 360 (46.5) |
| Unknown | 1 (0.4) | 0 | 0 | 1 (0.1) |

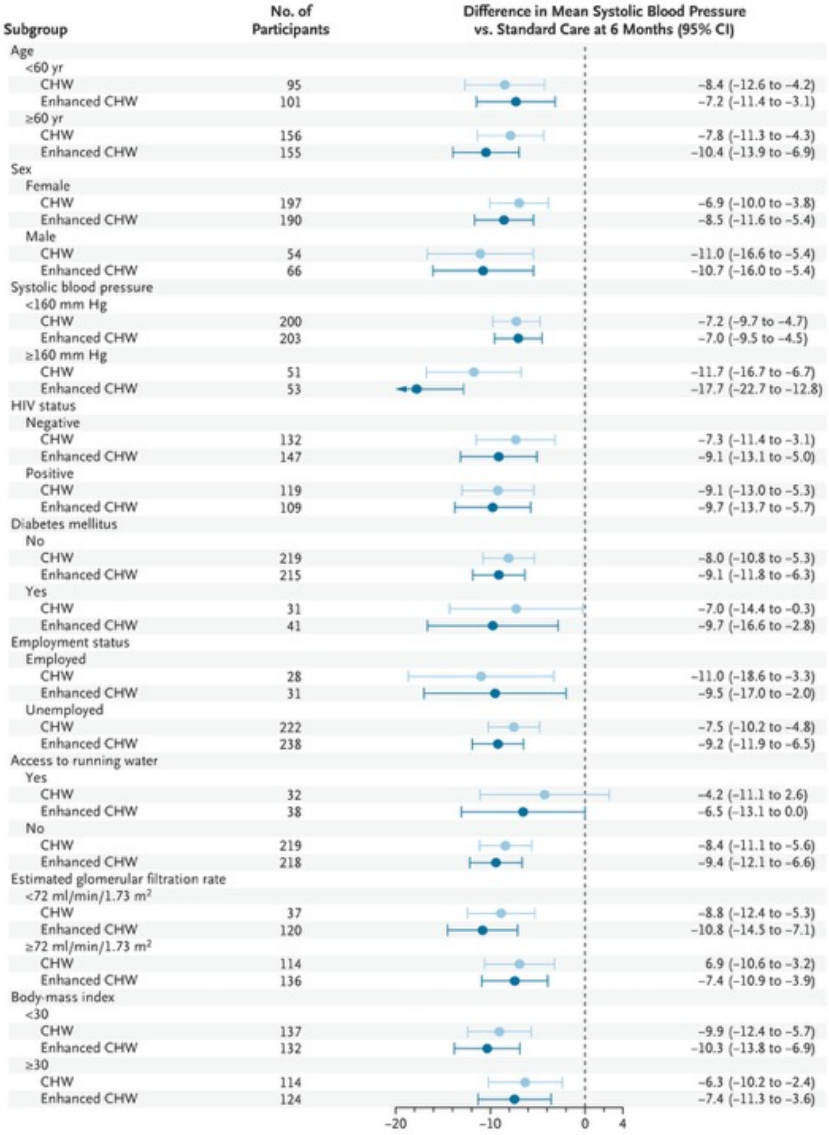
## Efficacy and Safety Outcomes.

| Outcome | CHW (N=257) | Enhanced CHW (N=258) | Standard Care (N=259) |
|---|---|---|---|
| Systolic blood pressure — mm Hg | | | |
| Enrollment | | | |
| Mean (95% CI) | 146.6 (144.4 to 148.8) | 146.8 (144.7 to 149.0) | 147.4 (145.4 to 149.4) |
| 6 Mo | | | |
| Mean (95% CI) | 137.5 (135.6 to 139.4) | 136.5 (134.8 to 138.1) | 145.8 (143.4 to 148.2) |
| Difference vs. enrollment (95% CI) | −9.1 (−11.3 to −6.8) | −10.5 (−12.8 to −8.2) | −1.9 (−4.2 to 0.4) |
| Difference vs. standard-care group (95% CI) | −7.9 (−10.5 to −5.3) | −9.1 (−11.7 to −6.4) | — |
| P value vs. standard-care group | <0.001 | <0.001 | — |
| 12 Mo | | | |
| Mean (95% CI) | 134.1 (132.6 to 135.7) | 134.0 (132.6 to 135.4) | 144.8 (142.6 to 147.1) |
| Difference vs. enrollment (95% CI) | −12.4 (−14.7 to −10.1) | −12.8 (−15.1 to −10.5) | −3.0 (−5.1 to −0.9) |
| Difference vs. standard-care group (95% CI) | −10.3 (−12.6 to −8.0) | −10.5 (−12.8 to −8.2) | — |
| Hypertension control | | | |
| 6 Mo | | | |
| % (95% CI) | 76.9 (71.2 to 81.7) | 82.8 (77.7 to 87.0) | 57.6 (51.5 to 63.6) |
| Relative risk vs. standard-care group (95% CI) | 1.33 (1.18 to 1.51) | 1.44 (1.28 to 1.62) | — |
| 12 Mo | | | |
| % (95% CI) | 82.8 (77.6 to 87.0) | 85.7 (80.7 to 89.5) | 57.7 (51.5 to 63.7) |
| Relative risk vs. standard-care group (95% CI) | 1.43 (1.27 to 1.62) | 1.48 (1.32 to 1.67) | — |
| Adverse events during observation period — no. (%) | | | |
| Total adverse events | 7 (2.7) | 10 (3.9) | 4 (1.6) |
| Severe adverse events | 7 (2.7) | 10 (3.9) | 4 (1.6) |
| Adverse events related to trial procedures | 0 | 0 | 0 |
| Deaths | 1 (0.4) | 4 (1.6) | 3 (1.2) |
| Retention in care — % (95% CI) | | | |
| 6 Mo | 98.1 (95.4 to 99.2) | 99.6 (97.3 to 99.9) | 76.4 (70.9 to 81.2) |
| 12 Mo | 97.3 (94.4 to 98.7) | 97.7 (94.9 to 99.0) | 72.6 (66.8 to 77.7) |




**Systolic Blood Pressure and Hypertension Control at 6 and 12 Months.**

Panel A shows the mean systolic blood pressure, and Panel B shows the percentage of participants with hypertension control. Participants were randomly assigned to receive home-based care, which consisted of patient monitoring of blood pressure, home visits from a community health worker (CHW) for data collection and medication delivery, and remote nurse-led decision making supported by a mobile application (CHW group); enhanced home-based care, which consisted of the same intervention but with blood-pressure machines transmitting readings automatically (enhanced CHW group); or standard care with clinic-based management (standard-care group). I bars indicate 95% confidence intervals.




**Subgroup Analysis of Systolic Blood Pressure at 6 Months.**

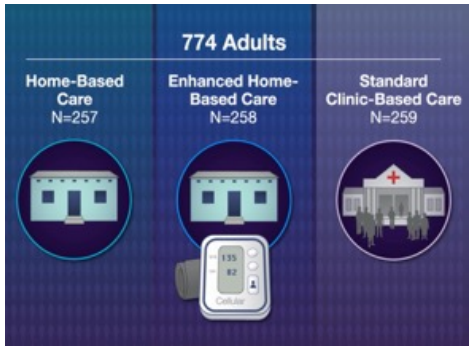
Participants were randomly assigned to receive home-based care from a CHW (CHW group), enhanced home-based care from a CHW (enhanced CHW group), or standard care with clinic-based management (standard-care group). The body-mass index is the weight in kilograms divided by the square of the height in meters. HIV denotes human immunodeficiency virus.

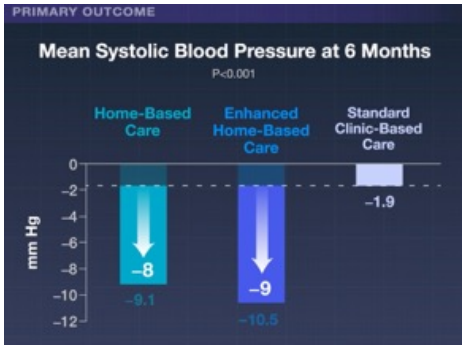

~10 million deaths per year
142
85

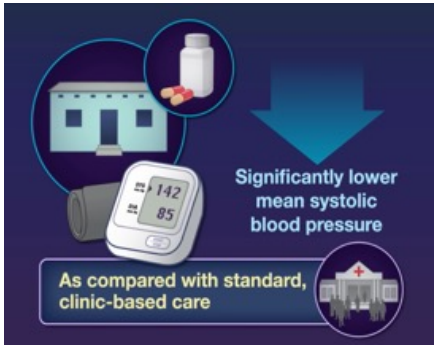

New Trial
?
In populations with numerous barriers to care


Enhanced Home-Based Care
N=258

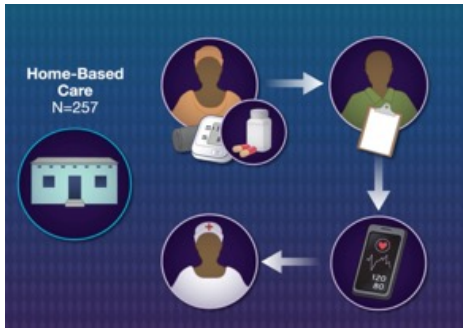

142
85
Low-cost, effective therapies


774 Adults
Home-Based Care N=257
Enhanced Home-Based Care N=258
Standard Clinic-Based Care N=259


PRIMARY OUTCOME
Mean Systolic Blood Pressure at 6 Months
P<0.001
Home-Based Care
Enhanced Home-Based Care
Standard Clinic-Based Care
mm Hg
0
−2
−4
−6
−8
−10
−12
−8
−9.1
−9
−10.5
−1.9

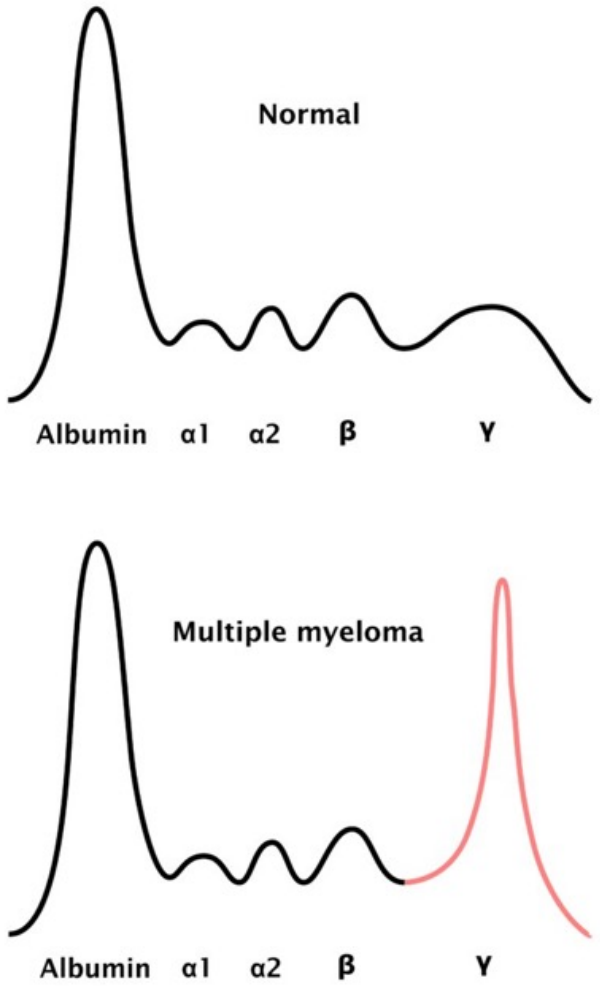

142
85
Significantly lower mean systolic blood pressure
As compared with standard, clinic-based care


Populations with Structural Barriers to Health Care
142
85
$


Home-Based Care
N=257


SAFETY
Adverse Events
Home-Based Care
Enhanced Home-Based Care
Standard Clinic-Based Care
Number of Patients
0
2
4
6
8
10
7
10
4
1
4
3
Severe Adverse Events
Deaths

Serum protein electrophoresis (SPEP) is a lab test that separates proteins in a blood sample based on their charge and size using an electric current, helping to diagnose and monitor diseases by identifying abnormal protein patterns. The test divides proteins into five major fractions—albumin, alpha-1, alpha-2, beta, and gamma globulins—and is particularly useful for detecting monoclonal gammopathies, such as in multiple myeloma.



# Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance (MGUS) is a common premalignant plasma-cell proliferative disorder that is present in approximately 5% of the general population over the age of 50 years. This disorder is important not only because it is the precursor to plasma-cell cancers, including multiple myeloma, solitary plasmacytoma, and Waldenström's macroglobulinemia, but also because it is causally related to numerous serious nonmalignant disorders, collectively referred to as monoclonal gammopathy of clinical significance (MGCS). MGUS is characterized by a limited yet monoclonal proliferation of plasma cells secreting abnormal levels of immunoglobulins (antibodies) that are identical to each other, with the same amino acid sequence, referred to as monoclonal (M) proteins. These secreted M proteins are best appreciated as fully functioning human antibodies present in high concentrations that fortunately lack affinity to self-antigens (autoantibody characteristics) in most persons. As a result, MGUS remains asymptomatic in the absence of malignant transformation in most people. However, there is potential for serious harm if the M protein has or develops affinity for one or more organs in the body, resulting in MGCS.

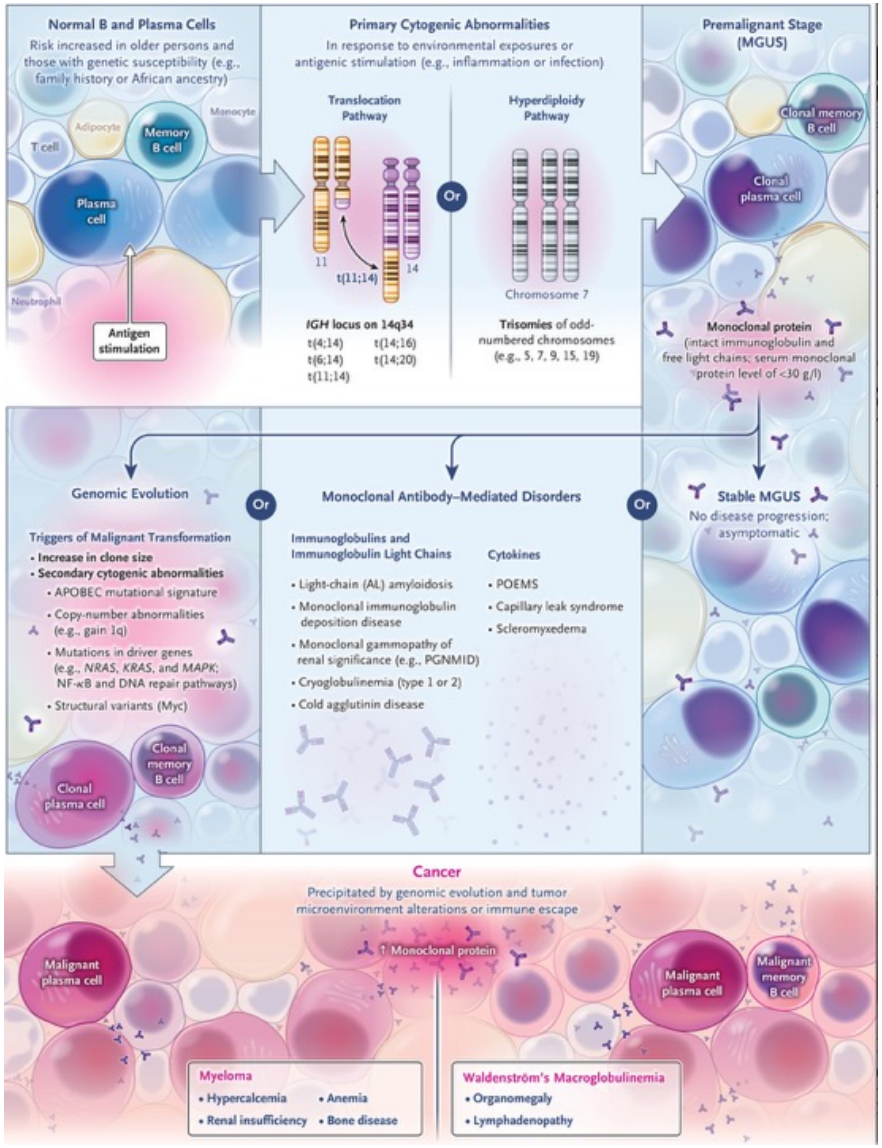
KEY POINTS

## Monoclonal Gammopathy of Undetermined Significance

- Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma-cell disorder present in approximately 5% of the general population over the age of 50 years.
- MGUS is characterized by the presence of detectable monoclonal (M) proteins, which are identical copies of intact immunoglobulins, immunoglobulin light chains, or both that are secreted by the clonal plasma cells.
- MGUS is asymptomatic but can progress to cancer — specifically, multiple myeloma, Waldenström's macroglobulinemia, or solitary plasmacytoma — at a rate of 1% per year.
- A variety of systemic disorders, referred to collectively as monoclonal gammopathy of clinical significance (MGCS), can develop as a result of the secreted monoclonal immunoglobulin in persons with MGUS.
- The diagnosis of progression to cancer or MGCS usually requires histopathological confirmation to ensure that the clinical problem is attributable to the plasma-cell disorder.
- No therapy is needed for MGUS, and the schedule for clinical follow-up is dictated by underlying risk stratification.

**Classification of Monoclonal Gammopathy of Undetermined Significance (MGUS), Diagnostic Criteria, and Major Disorders Associated with Disease Progression.**

| Disorders | Diagnostic Criteria |
|---|---|
| MGUS (IgM MGUS, non-IgM MGUS, light-chain MGUS†) | Serum monoclonal protein level of <3 g/dl (or in the case of light-chain MGUS, an abnormal FLC ratio plus increased level of involved light chain)<br><10% Clonal plasma cells or lymphoplasmacytic cells in bone marrow‡<br>Absence of end-organ damage (e.g., CRAB criteria) that can be attributed to the plasma-cell proliferative disorder |
| Malignant progression of MGUS (multiple myeloma, solitary bone plasmacytoma, solitary extramedullary plasmacytoma, Waldenström's macroglobulinemia) | ≥10% Clonal plasma or lymphoplasmacytic cells in bone marrow or presence of a biopsy-proven bony or extramedullary plasmacytoma<br>For multiple myeloma: one or more myeloma-defining events§<br>For Waldenström's macroglobulinemia: anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly attributable to the underlying clonal proliferative disorder |
| Causally related nonmalignant disorders<br>Multisystem disorders (AL amyloidosis, monoclonal immunoglobulin deposition disease, cryoglobulinemia)<br>Major syndromes (POEMS syndrome¶, Schnitzler's syndrome, TEMPI syndrome, cold agglutinin disease)<br>MGRS (PGNMID, C3 glomerulonephritis, monoclonal immunoglobulin crystalline membranous nephropathy)††<br>MGNS (monoclonal gammopathy–associated IgM neuropathy, monoclonal gammopathy–associated non-IgM neuropathy)<br>MGTS<br>Dermatologic diseases (necrobiotic xanthogranuloma, scleromyxedema) | Monoclonal protein, clonal plasma cells, or both in bone marrow required, with few exceptions‖<br>Likely causal relationship established on the basis of the presence of monoclonal protein (intact, light or heavy chain only, or fragments) or monoclonal plasma-cell or B-cell infiltrate**<br>Specific diagnostic criteria for diagnosis of well-defined disorders and syndromes (e.g., AL amyloidosis, POEMS syndrome, cryoglobulinemia, and cold agglutinin disease) |




**Pathogenesis and Progression of Monoclonal Gammopathy of Undetermined Significance (MGUS).**

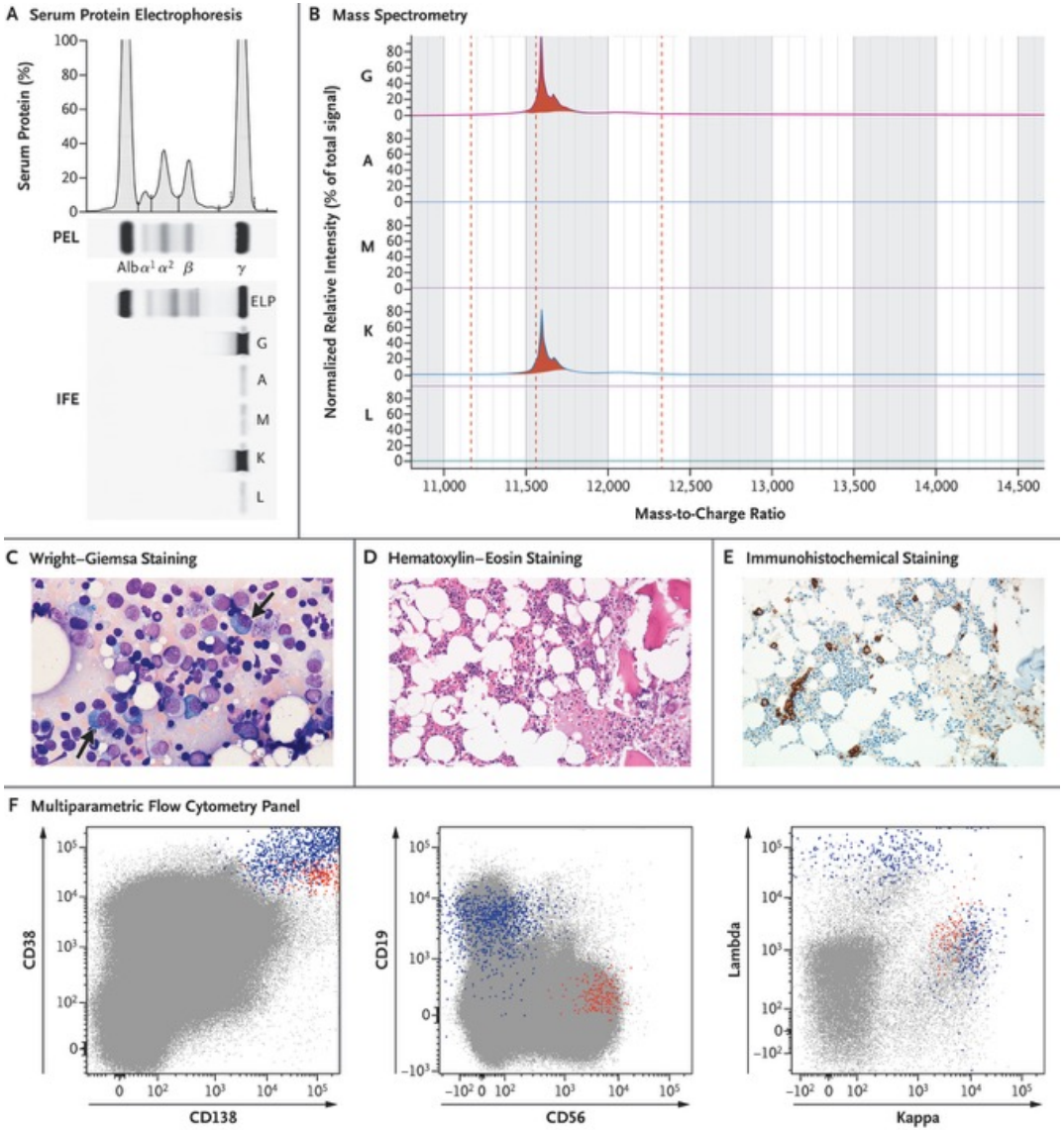
The primary molecular genetic abnormalities that establish the premalignant clonal process, which occur in normal memory B cells and plasma cells responding to infection and inflammation, consist of either trisomies or one of the listed *IGH* translocations. The transition from precancer to cancer is related to acquisition of one or more secondary cytogenetic abnormalities, changes in the bone marrow microenvironment, and defects in immune surveillance. The premalignant clonal expansion clinically referred to as MGUS can progress to overt cancer or to nonmalignant disorders that are typically mediated by the monoclonal protein (immunoglobulin) secreted by these cells. NF-κB denotes nuclear factor κB, PGNMID proliferative glomerulonephritis with monoclonal immunoglobulin deposits, and POEMS polyradiculoneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

**Clinical Presentation**

MGUS is asymptomatic in the absence of progression to cancer or an association with one of the MGCS disorders. The diagnosis of MGUS is usually made incidentally when tests to detect M proteins are ordered as part of a broad workup in patients with fatigue, an elevated erythrocyte sedimentation rate, anemia, bone pain, osteoporosis, or infections. MGUS is also diagnosed when multiple myeloma is considered in the differential diagnosis for patients presenting with osteolytic lesions, bone fractures, hypercalcemia, proteinuria, renal insufficiency, lymphadenopathy, or hepatosplenomegaly. Testing for M proteins should be performed only if there is clinical concern about a plasma-cell cancer or a suspicion that a monoclonal plasma-cell disorder or M protein is the cause of a given clinical problem (i.e., suspected MGCS) or in specific circumstances, such as organ donation. Although MGUS is asymptomatic, some persons have suppression of uninvolved normal immunoglobulins and a slightly blunted response to vaccines.

**Laboratory Testing**

With serum protein electrophoresis, M proteins are detected as an abnormal narrow peak (like a church spire) on the densitometer tracing. For a diagnosis of MGUS, the serum M protein concentration must be less than 3 g per deciliter. The type of M protein can be ascertained with serum immunofixation on the basis of localization of the discrete heavy- and light-chain bands. Mass spectrometry is an alternative to immunofixation and is a more efficient, sensitive, and specific method for detecting M proteins. If an M protein is detected, 24-hour urine electrophoresis is recommended to quantitate M proteins in the urine as a baseline and to detect albuminuria, which can occur with renal injury from MGCS. In approximately 20% of patients with MGUS, there is no expression of the normal immunoglobulin heavy chain, and the clonal cell secretes only free monoclonal light chains (light-chain MGUS). This subtype of MGUS is best identified with the serum free light-chain (FLC) assay, which measures free kappa and lambda light chains that are not bound to intact immunoglobulin. The assay should therefore be performed, along with serum electrophoresis and immunofixation, for all patients in whom a clonal plasma-cell disorder is suspected. Clonality on the serum FLC assay is established by the presence of an abnormal ratio of the two light-chain concentrations.




**Diagnostic Testing for MGUS.**

Serum protein electrophoresis and mass spectrometry can be used to detect monoclonal (M) protein; in serum protein electrophoresis, M protein is detected as an abnormal peak, and the type of protein can be determined by immunofixation. Panel A shows protein electrophoresis (PEL) with a monoclonal spike in the gamma region (top image) and serum immunofixation (IFE) with discrete bands in IgG and kappa (bottom image), indicating the presence of IgG kappa monoclonal protein. Alb denotes albumin; $\alpha^1$, $\alpha^2$, β, and γ denote globulins; ELP indicates the lane in which the total protein was electrophoresed; and G, A, M, K, and L denote antiserum against IgG, IgA, IgM, kappa light chain, and lambda light chain, respectively. Mass spectrometry can be used in place of immunofixation; Panel B shows normal spectrum, characterized by smooth curves and an absence of monoclonal protein spikes, as well as spikes in IgG and kappa, indicating the presence of IgG kappa monoclonal protein. Panel C shows Wright–Giemsa staining of a bone marrow aspirate with a slightly increased percentage of plasma cells (<10%) (arrows). Panel D shows hematoxylin and eosin staining of a bone marrow biopsy specimen with a few scattered plasma cells. Panel E shows CD138 immunohistochemical staining of a bone marrow biopsy specimen with a minimally increased percentage of plasma cells (brown staining). Panel F shows multiparametric flow cytometry with initial gating of plasma cells based on CD38 and CD138 expression (left image) and aberrant loss of CD19 and gain of CD56 expression in abnormal plasma cells (middle image), with confirmation that the abnormal plasma cells are kappa light-chain–restricted (right image). Normal (polyclonal) plasma cells are blue, and abnormal (monoclonal) plasma cells are red.

Bone marrow aspiration and biopsy, if performed, must show less than 10% clonal bone marrow plasma cells. Plasma cells can be easily identified on the basis of morphologic features and positive immunohistochemical staining for CD138. In IgM MGUS, the clonal cells may have lymphoid or mixed lymphoplasmacytic morphologic features. Clonality is established with flow cytometry or immunohistochemistry. Baseline testing of bone marrow samples for cytogenetic abnormalities with the use of fluorescence in situ hybridization or sequencing is recommended, if available, to establish the biologic subtype of MGUS. MGUS is differentiated from multiple myeloma and smoldering multiple myeloma on the basis of the M protein concentration, bone marrow plasma-cell percentage, and presence or absence of related cancer, especially myeloma-defining events such as hypercalcemia, renal insufficiency, anemia, or lytic bone lesions. The presence of end-organ damage does not automatically indicate that MGUS has progressed to cancer or MGCS, since there may be other causes for these findings. End-organ damage must be carefully investigated to determine whether the injury is attributable to a clonal plasma-cell disorder or another, unrelated problem. If indicated, whole-body, low-dose computed tomography (CT) or positron-emission tomography–CT or whole-body magnetic resonance imaging should be performed to rule out multiple myeloma and Waldenström's macroglobulinemia.

**Cancers Resulting from Progression of MGUS**

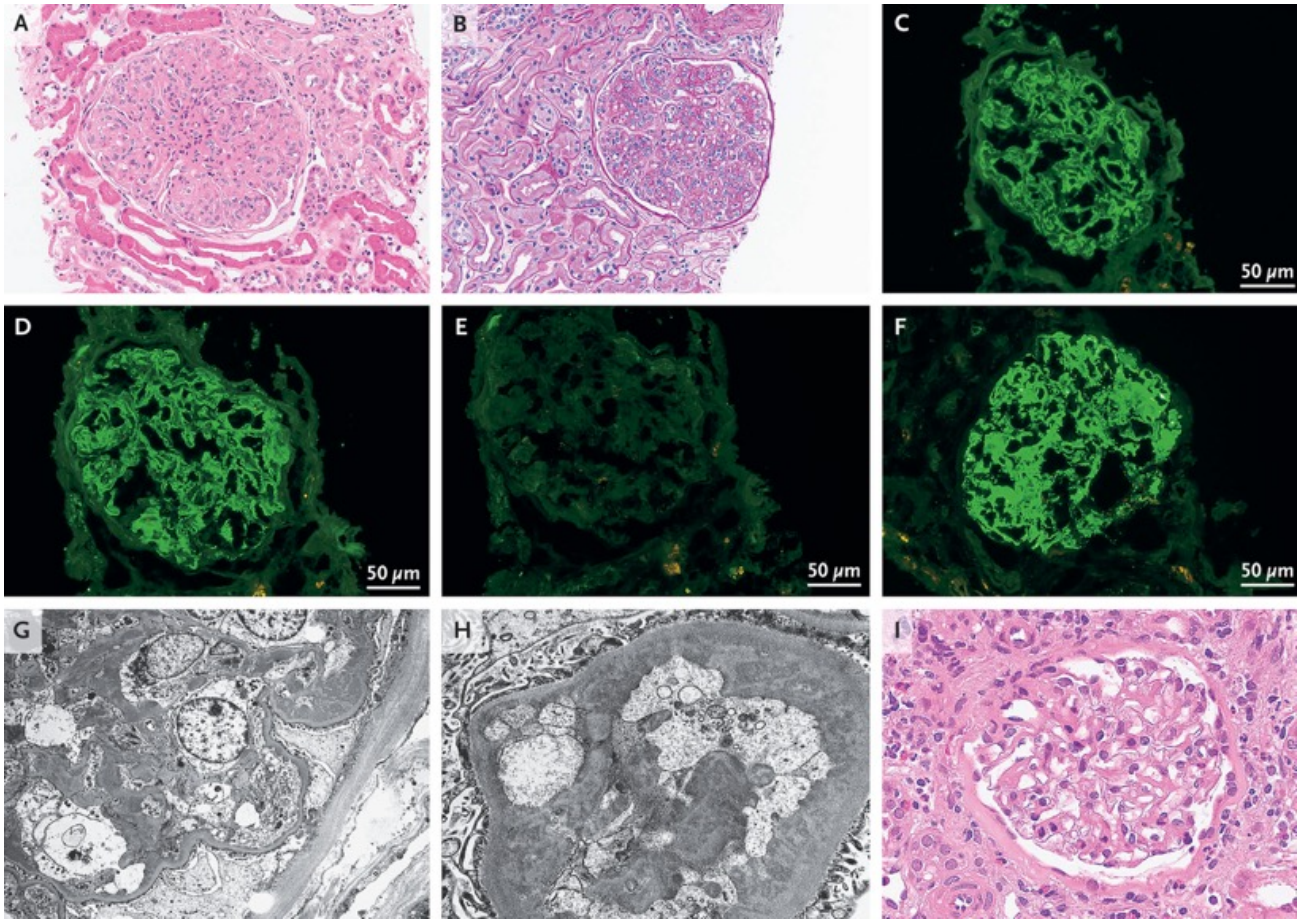
MGUS is the premalignant precursor of myeloma, Waldenström's macroglobulinemia, and solitary plasmacytoma. In almost all patients with multiple myeloma, MGUS has been present for many years before the cancer is diagnosed. The overall risk of progression of MGUS to multiple myeloma or a related cancer is approximately 1% per year, on the basis of a population-based study involving 1384 persons. In the subgroup of patients with light-chain MGUS, the risk of progression appears to be lower, at 0.3% per year.

**Nonmalignant Disorders Causally Related to MGUS**

More than 100 nonmalignant diseases have been reported to be associated with MGUS, but most such associations are coincidental rather than causal. However, several well-defined nonmalignant diseases are known to be causally related to MGUS, and MGCS is the umbrella term for these disorders.

**Monoclonal Gammopathy of Renal Significance**

The kidney is particularly vulnerable in clonal plasma-cell disorders; the classic presentation is acute renal failure due to light-chain cast nephropathy in multiple myeloma. But even without malignant progression to multiple myeloma, many specific renal disorders can occur as a result of M proteins secreted by a premalignant MGUS clone.

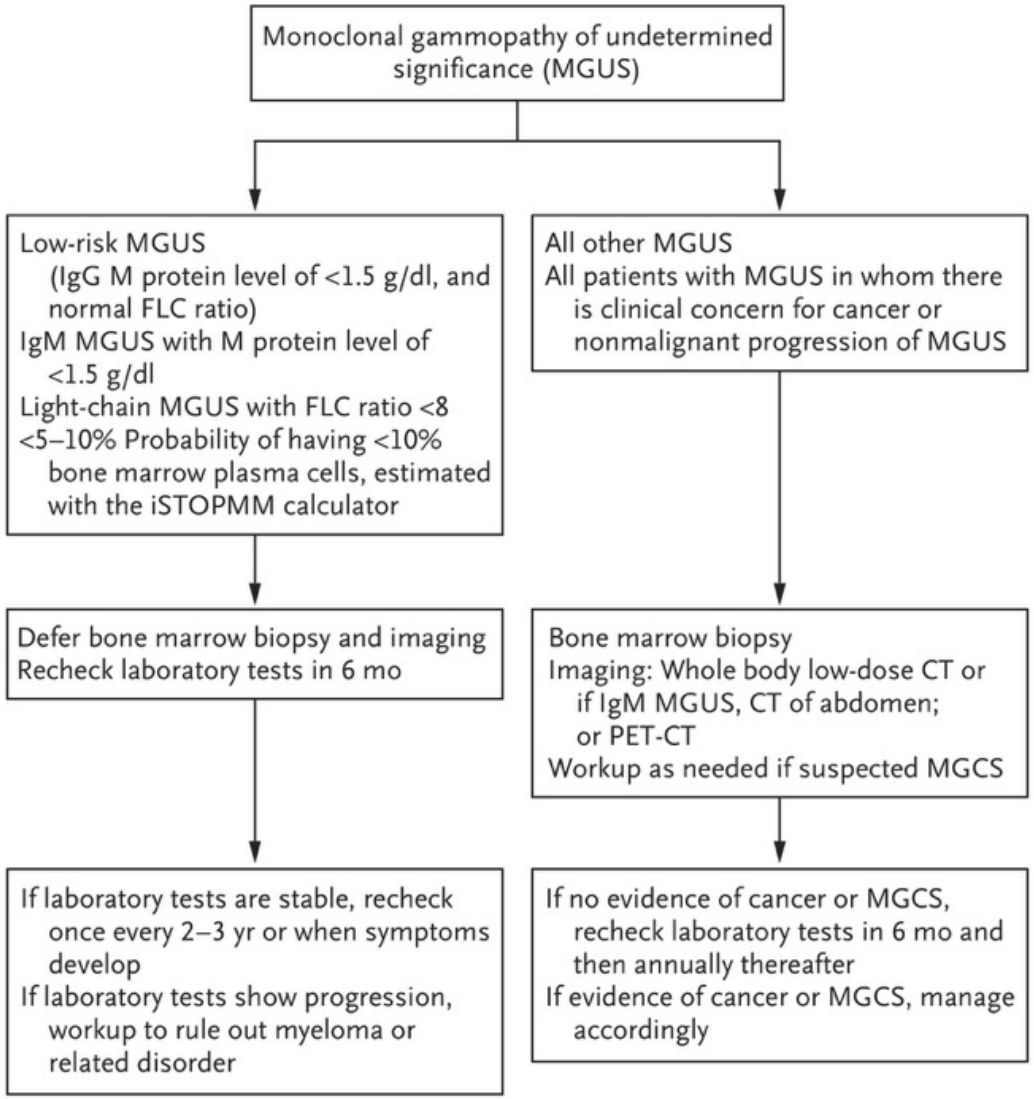



**Kidney-Biopsy Specimen Showing Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits.**

In Panels A and B, light microscopy shows a membranoproliferative pattern of injury (Panel A, hematoxylin and eosin staining; Panel B, periodic acid–Schiff staining), and in Panel C, immunofluorescence microscopy shows granular IgG along the glomerular capillary walls. In Panels D, E, and F, immunofluorescence microscopy shows bright staining for kappa light chains along the glomerular capillary walls (Panel D), negative staining for lambda light chains (Panel E), and bright staining for IgG3 (Panel F); findings for IgG1, IgG2, and IgG4 were negative (not shown). In Panels G and H, electron microscopy shows subendothelial deposits. Normal glomerulus is shown in Panel I (hematoxylin and eosin staining).

**Management of MGCS**

The treatment of any of the MGCS disorders requires precise diagnosis of the nature and extent of the injury. In general, once the diagnosis is established, plasma-cell or B-cell clone–directed therapy to reduce or eradicate the M protein should be considered. For well-established systemic disorders such as AL amyloidosis, POEMS syndrome, cryoglobulinemia, and monoclonal immunoglobulin deposition disease, there are clear algorithms for therapy, and a detailed discussion of these disorders is beyond the scope of this review. Patients with MGRS due to proliferative glomerulonephritis with immunoglobulin deposits or C3 glomerulonephritis can benefit from treatments used for multiple myeloma, such as daratumumab or the bortezomib, cyclophosphamide, and dexamethasone regimen, in order to preserve renal function and prevent end-stage renal disease. However, clone-directed therapy in patients with MGUS-associated peripheral neuropathy has had disappointing results and requires more study. For patients with IgM monoclonal gammopathy–associated neuropathy, a trial of intravenous immune globulin, rituximab, or both is reasonable. For non-IgM monoclonal gammopathy–associated neuropathy with a presentation similar to that of chronic inflammatory demyelinating polyneuropathy, treatment usually comprises plasmapheresis, intravenous immune globulin, and glucocorticoids rather than clone-directed therapy.




**Management of MGUS.**

The iSTOPMM (Iceland Screens, Treats, or Prevents Multiple Myeloma) calculator is available at https://istopmm.com/riskmodel/. In low-risk patients who are younger than 50 years of age, bone marrow biopsy and imaging may be considered a baseline evaluation, given the anticipated life expectancy. FLC denotes free light chain, and MGCS monoclonal gammopathy of clinical significance.

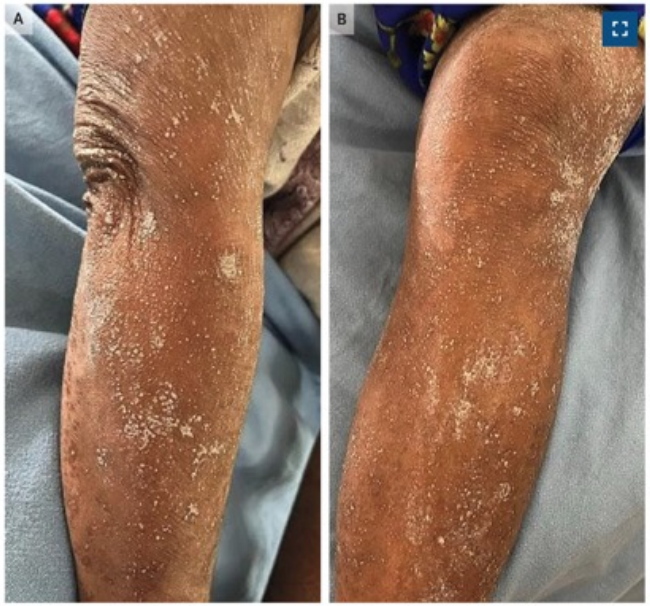
**Management of MGUS**

The approach to management of MGUS is shown. A baseline evaluation is performed to rule out malignant progression, including a complete blood count and serum calcium and creatinine levels. The CT bone survey and bone marrow biopsy can be omitted in persons with a clinical picture that is otherwise consistent with MGUS, since such persons are considered to be at low risk.

No therapy is needed for MGUS. A complete blood count, serum calcium and creatinine measurements, and serum monoclonal protein and FLC studies should be repeated 6 months after the diagnosis has been established. Further follow-up is based on baseline risk status, as shown. The goal of follow-up is to improve outcomes by identifying progression of MGUS to cancer or MGCS before serious end-organ damage occurs. Clinical trials involving selected high-risk persons with MGUS and patients with MGCS are ongoing.

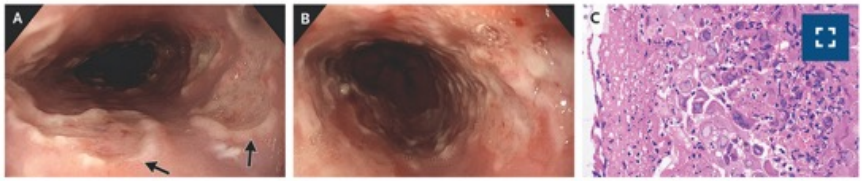
Screening for MGUS in the general population is not recommended. The Iceland Screens, Treats, or Prevents Multiple Myeloma (iSTOPMM) randomized trial is testing the effect of screening for MGUS on malignant and nonmalignant progression, but overall survival results are not expected for several years.

# Uremic Frost



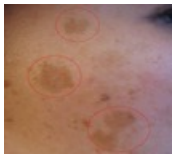

A 52-year-old woman with hypertension presented to the hospital with a 1-month history of fatigue, as well as 6 days of vomiting and 1 day of confusion. Over the past 20 years, she had not received regular treatment for hypertension. Physical examination was notable for pallor of the conjunctiva and oral mucosa, as well as for powdery, crystalline deposits on the arms (Panel A, right arm), legs (Panel B, left leg), trunk, and scalp. Laboratory testing showed a blood urea nitrogen (BUN) level of 375 mg per deciliter (134 mmol per liter; reference range, 5 to 21 mg per deciliter [2 to 7 mmol per liter]), a creatinine level of 22 mg per deciliter (1945 µmol per liter; reference range, 0.5 to 1.5 mg per deciliter [44 to 133 µmol per liter]), and a hemoglobin level of 6.1 g per deciliter (reference range, 13.0 to 16.5). Testing of a skin scraping of the powdery crystals was positive for urea. A diagnosis of advanced end-stage kidney disease with uremic frost was made. Uremic frost is a rare manifestation of end-stage kidney disease that may occur when the BUN level is greater than 200 mg per deciliter (71 mmol per liter). The whitish crystals form on the skin when sweat with a high content of urea evaporates. Treatment with hemodialysis for five consecutive sessions was initiated. Nineteen days after presentation, the patient had a fatal asystolic cardiac arrest in the context of shock secondary to hospital-acquired pneumonia.

# Herpes Simplex Virus Esophagitis




A previously healthy 29-year-old woman presented to the gastroenterology clinic with a 2-day history of painful swallowing of solids and liquids (odynophagia). One week earlier, she had had a fever and sore throat for 3 days. Physical examination was normal. Upper endoscopy revealed multiple discrete, shallow, “volcano-like” ulcers with raised edges in the middle esophagus (Panel A, arrows). In the distal esophagus, widespread whitish exudates and friable mucosa were seen (Panel B). Histopathological testing of a biopsy specimen from an ulcer showed viral cytopathic effects — including chromatin margination, nuclear molding, and multinucleation — in the squamous epithelial cells of the esophageal lining (Panel C, hematoxylin and eosin stain). Immunohistochemical staining for herpes simplex virus and testing for serum IgM antibody against herpes simplex virus were positive. Testing for human immunodeficiency virus was negative. A diagnosis of herpes simplex virus esophagitis, which is more typically seen in persons with immunocompromise, was made. The patient reported no history of herpes simplex virus infection. Treatment with intravenous acyclovir was initiated and later changed to an oral formulation when the patient’s odynophagia abated 7 days after the initiation of treatment. Results of a repeat upper endoscopy that was conducted 4 weeks after the end of treatment were normal.

# Case 12-2023: A 44-Year-Old Woman with Muscle Weakness and Myalgia



Melasma

A 44-year-old woman was evaluated in the rheumatology clinic of this hospital because of proximal muscle weakness and myalgia.

The patient had been in her usual state of health until 5 years before the current presentation, when morning stiffness and pain developed in the small joints of both hands. Laboratory evaluation reportedly revealed elevated blood levels of anti–cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor, as well as an elevated erythrocyte sedimentation rate. Rheumatoid arthritis was diagnosed, but the patient chose not to begin specific therapy for rheumatoid arthritis. Instead, she began taking selenium, cod-liver oil, and turmeric as home remedies for joint pain. Morning stiffness and joint pain resolved after 4 weeks.

Four years before the current presentation, treatment with hydroxychloroquine was started after the occurrence of another episode of morning stiffness and pain in the small joints of the hands.

Three years before the current presentation, treatment with hydroxychloroquine was stopped after melasma developed. Treatment with methotrexate was initiated, but morning hand stiffness and pain recurred; methotrexate was replaced with leflunomide, and the symptoms in the hands subsequently decreased.

Six months before the current presentation, the patient began to have myalgia in the arms and thighs, as well as generalized fatigue. She had difficulty raising her arms above her head, and she could no longer independently brush her hair or apply makeup. Myalgia worsened with exercise and was worst at the end of the day. The patient reported episodes of tingling in the hands and feet, but she had no stiffness or pain in the small joints of her hands.

Three months before the current presentation, the patient was evaluated by a local rheumatologist and laboratory testing was performed. The blood level of creatine kinase was 422 U per liter (reference range, 40 to 150) and the lactate dehydrogenase level 509 U per liter (reference range, 110 to 210). Antinuclear antibodies (ANA) were detected at a titer of 1:320 in a nuclear homogenous pattern, and anti–U1-ribonucleoprotein (U1-RNP) antibodies were present. The blood levels of C3 and C4 were normal, and testing for anti–double-stranded DNA (dsDNA) and anti-Smith antibodies was negative.

Two months before the current presentation, treatment with azathioprine was started, and the patient was referred to the rheumatology clinic of this hospital.

In the rheumatology clinic, the patient reported ongoing myalgia and tingling in the hands and feet but had noticed an improvement in her ability to raise her arms above her head after starting treatment with azathioprine. Two weeks earlier, episodes of muscle spasms in the hands and fingers had developed; massage of the hands had been performed to relax the spasms.

The patient had a history of Graves' disease, which had been complicated by ophthalmoplegia and had been treated with methimazole for 2 years, followed by radioactive iodine ablation 11 years before this presentation; hypothyroidism had developed after radioactive iodine ablation therapy. Other history included latent tuberculosis infection, which had been treated with a 3-month course of isoniazid and rifampin, and hypoparathyroidism that had developed 9 years before this presentation. Medications included azathioprine, levothyroxine, calcium supplements, and calcitriol; the patient was unsure of the formulation and dose of calcium supplementation. She lived outside the United States and traveled intermittently to Boston for specialized medical care. She lived with her mother and worked in information technology. She drank alcohol occasionally, smoked cigarettes, and used no illicit drugs. A sibling had systemic lupus erythematosus (SLE).

On examination, the temporal temperature was 36.3°C, the blood pressure 145/70 mm Hg, the pulse 72 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. She had mild exophthalmos in both eyes. There was an area of hyperpigmentation on the face. The joints had a normal range of motion without tenderness on palpation; there was no synovitis. Neck flexion was mildly weak, as was hip flexion; strength was otherwise normal, as was sensation. There was no rash. The remainder of the examination was normal (Chvostek test was not done).

Diagnostic tests were performed, and management decisions were made.

(no measurements of parathyroid function etc. are given in this protocol).

**Differential Diagnosis**

This 44-year-old woman with seropositive rheumatoid arthritis presented to the rheumatology clinic with a recent onset of fatigue, proximal muscle weakness, myalgia in the arms and legs, paresthesia in the hands and feet, and muscle spasms in the hands. The available laboratory data showed elevated levels of creatine kinase and lactate dehydrogenase, as well as the presence of rheumatoid factor, anti-CCP antibodies, ANA, and anti–U1-RNP antibodies.

**Rheumatoid Arthritis**

When I evaluate a patient with a history of a rheumatic disease, I first establish whether I agree with the previous diagnosis before proceeding with evaluation of the patient's current presentation. Five years before this patient's current presentation, she had symmetric small-joint polyarthritis and was found to have positive tests for rheumatoid factor and anti-CCP antibodies. The specificity of a positive test for anti-CCP antibodies for the diagnosis of rheumatoid arthritis is 95%; in combination with a positive test for rheumatoid factor, the specificity increases to 98%.

**Autoimmune Diseases**

Proximal muscle weakness and myalgia are not characteristic clinical manifestations of rheumatoid arthritis. However, other rheumatic conditions are high on the differential diagnosis in this patient with evidence of autoimmunity, on the basis of her diagnoses of rheumatoid arthritis, Graves' disease, and hypoparathyroidism (which can be caused by an autoimmune process) and given the fact that a first-degree relative has SLE.

**Overlap Syndrome of Rheumatoid Arthritis and SLE**

Could this patient have an overlap syndrome of rheumatoid arthritis and SLE? She is known to have had a positive ANA test; such antibodies can be present in patients with SLE. However, this autoantibody has low specificity and can also be present in patients with rheumatoid arthritis, idiopathic inflammatory myopathies, overlap syndromes, mixed connective-tissue disease, and Graves' disease, as well as in first-degree relatives of patients with SLE.

**Overlap Syndrome of Rheumatoid Arthritis and Idiopathic Inflammatory Myopathy**

The classification criteria for idiopathic inflammatory myopathies include proximal muscle weakness, laboratory abnormalities (e.g., a positive anti–Jo-1 antibody test or elevated blood levels of creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, or aspartate aminotransferase), rash (e.g., Gottron's papules, Gottron's sign, or heliotrope rash), esophageal dysmotility or dysphagia, and pathological findings on muscle biopsy.

**Mixed Connective-Tissue Disease**

Proximal muscle weakness is also a manifestation of mixed connective-tissue disease. Mixed connective-tissue disease is characterized by the presence of anti–U1-RNP antibodies in association with features of several different rheumatic conditions, without meeting classification criteria for any one disease.

**Infiltrative Diseases**

Both amyloidosis and sarcoidosis can be manifested by proximal muscle weakness and can be associated with carpal tunnel syndrome, which could explain the paresthesia in this patient's hands. Although a diagnosis of either amyloidosis or sarcoidosis could explain her proximal muscle weakness and paresthesia, muscle spasms would be an unusual feature of either disease.

## Medications

Many medications have been associated with myalgia or proximal muscle weakness. The patient's current medications included azathioprine (started 2 months before the current presentation for muscle weakness) and longer-standing treatment with leflunomide (for rheumatoid arthritis), calcium supplementation and calcitriol (for hypoparathyroidism), and levothyroxine (for hypothyroidism that developed after treatment for Graves' disease).

## Infections

The bacterial infections that are most commonly associated with myalgia and proximal muscle weakness are those related to contiguous spread of *Staphylococcus aureus* infection.

## Metabolic Derangements

Patients with metabolic myopathies that are related to disorders of carbohydrate, lipid, or purine metabolism often have proximal muscle weakness. However, I would have expected this patient to have had symptoms earlier in life if a metabolic myopathy was the cause.

Proximal muscle weakness can manifest in patients deficient in vitamin D, phosphorus, or calcium, as well as in patients with hypothyroidism or hyperthyroidism. This patient presented with not only muscle symptoms but also nerve symptoms (paresthesia and muscle spasms); therefore, I will focus on conditions that could explain both muscle and nerve symptoms.

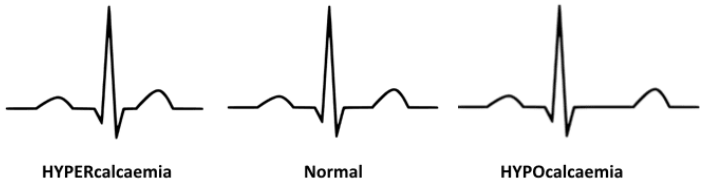
Hypothyroidism can be associated with both muscle symptoms and paresthesia, particularly in the context of carpal tunnel syndrome. This patient's treatment for Graves' disease resulted in hypothyroidism, and her levothyroxine replacement dose could be too low. In addition, she has hypoparathyroidism, for which she was prescribed calcium supplementation and calcitriol. She was uncertain of the formulation and dose of her calcium supplementation regimen, so it is possible that the calcium supplementation has not been adequate. Hypoparathyroidism, with associated hypocalcemia, can be manifested by proximal muscle weakness and myalgia with the additional symptom of muscle spasms. Patients with profound hypocalcemia can have elevated creatine kinase levels. Overall, I suspect that hypocalcemia resulting from hypoparathyroidism is the most likely explanation for her presentation. I suspect that the diagnostic test was a comprehensive metabolic panel, which would include measurement of blood levels of calcium and albumin.

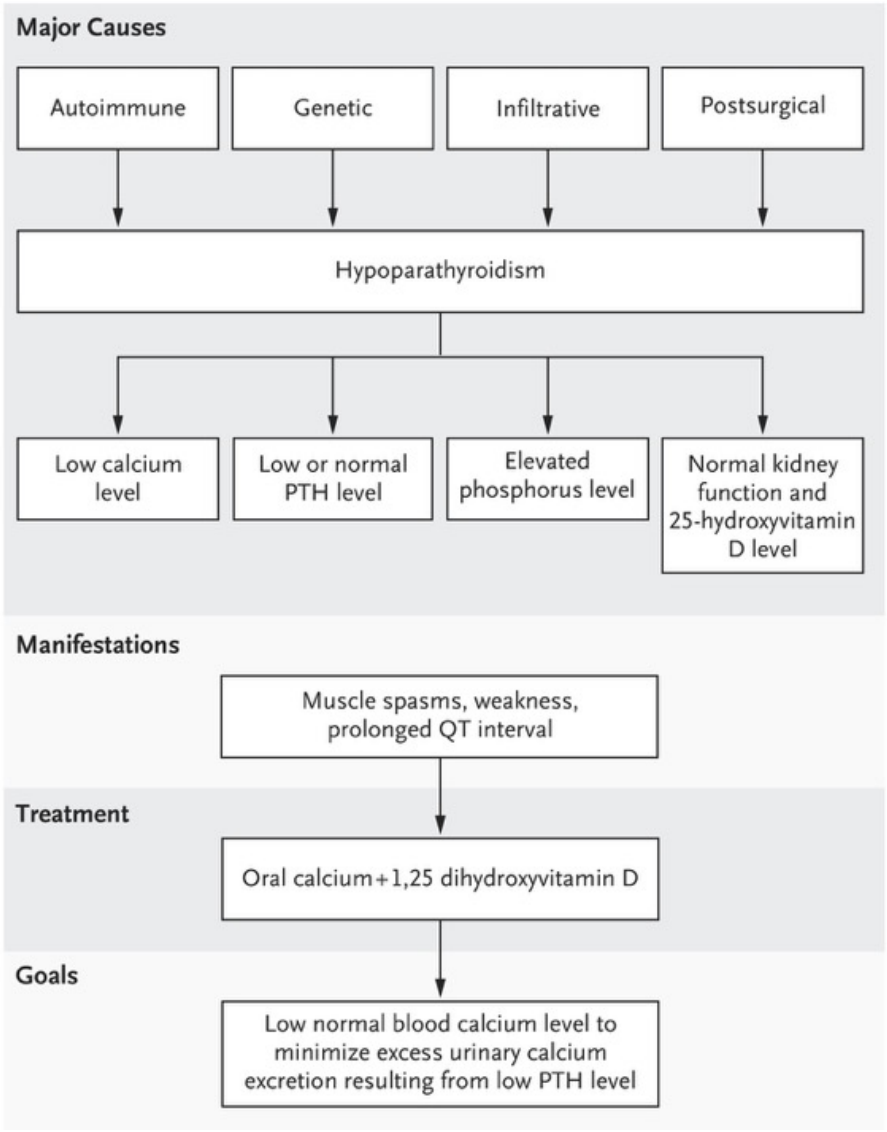
Diagnostic laboratory test results obtained at the rheumatology clinic included a blood calcium level of 5.9 mg per deciliter (1.5 mmol per liter; reference range, 8.5 to 10.5 mg per deciliter [2.1 to 2.6 mmol per liter]) and a blood phosphorus level of 4.5 mg per deciliter (1.5 mmol per liter; reference range, 2.6 to 4.5 mg per deciliter [0.8 to 1.5 mmol per liter]). An ECG would have been nice.

**Discussion of Endocrinology Management**

The patient's severe hypocalcemia with associated symptoms was initially treated with intravenous calcium. Intravenous calcium gluconate is usually used to avoid irritation from extravasation of intravenous fluid.

The cause of the hypoparathyroidism in this patient was not entirely clear. The differential diagnosis of hypoparathyroidism includes neck surgery, infiltrative and destructive diseases, autoimmune diseases, and genetic and developmental conditions. She had no family history of hypocalcemia. There was no history that was consistent with autoimmune polyglandular syndrome type 1, nor was there a history of early development of hypocalcemia in childhood. She was not receiving any medications that were known to be associated with hypocalcemia. She had been treated with radioactive iodine ablation for Graves' disease, and rare case reports have described the development of hypoparathyroidism in such circumstances. Acquired hypoparathyroidism can be due to autoimmune mechanisms, including activating autoantibodies to the calcium-sensing receptor in the context of ongoing autoimmune disease, which may be of relevance to this patient, given her underlying autoimmune diagnosis.






**Major Causes, Manifestations, Treatment, and Goals of Treatment in Patients with Hypoparathyroidism.**

Hypoparathyroidism is commonly caused by neck surgery, infiltrative or destructive diseases, autoimmune diseases, or genetic or developmental conditions, but it can be idiopathic. Typically, the calcium level is low, and parathyroid hormone (PTH) levels are low or inappropriately normal; the phosphorus level is either elevated or at the upper limit of the reference range. Hypocalcemia can lead to muscle spasms, muscle weakness, and myalgia, as well as a prolonged QT interval on electrocardiography. Treatment includes calcium and vitamin D supplementation. In patients with hypoparathyroidism, conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is impaired, and treatment with calcitriol is needed for vitamin D replacement. Treatment of hypoparathyroidism can be difficult because calcium is not reabsorbed in the distal nephron owing to the low PTH levels, and the urinary calcium level can increase and ultimately lead to nephrolithiasis. Patients are often treated with a goal of a low normal calcium level to simultaneously minimize symptoms and avoid excess urinary calcium excretion.

**Rheumatology Diagnostic Testing**

When we first evaluated the patient, the available test results included the calcium level of 5.9 mg per deciliter, as well as a markedly elevated creatine kinase level. Proximal muscle weakness, myalgia, and a substantially elevated creatine kinase level increased our suspicion for idiopathic inflammatory myopathies. However, the presence of hypocalcemia in the context of hypoparathyroidism would explain the patient's muscle spasms and paresthesia, as well as her myopathy. Some endocrinopathies, such as hyperthyroidism, typically cause myopathy in patients with a normal creatine kinase level. In contrast, patients with hypoparathyroid myopathy typically present with an elevated creatine kinase level; thus, hypoparathyroid myopathy was considered to be the most likely diagnosis in this case.

The diagnosis of hypocalcemic hypoparathyroid myopathy could have been confirmed by monitoring the patient's symptoms and creatine kinase level after calcium repletion therapy was started. However, because of the facts that her symptoms resulted in hospitalization, that the morbidity associated with untreated idiopathic inflammatory myopathies is high, and that she lived outside the United States, we chose to further evaluate the possibility of idiopathic inflammatory myopathies.

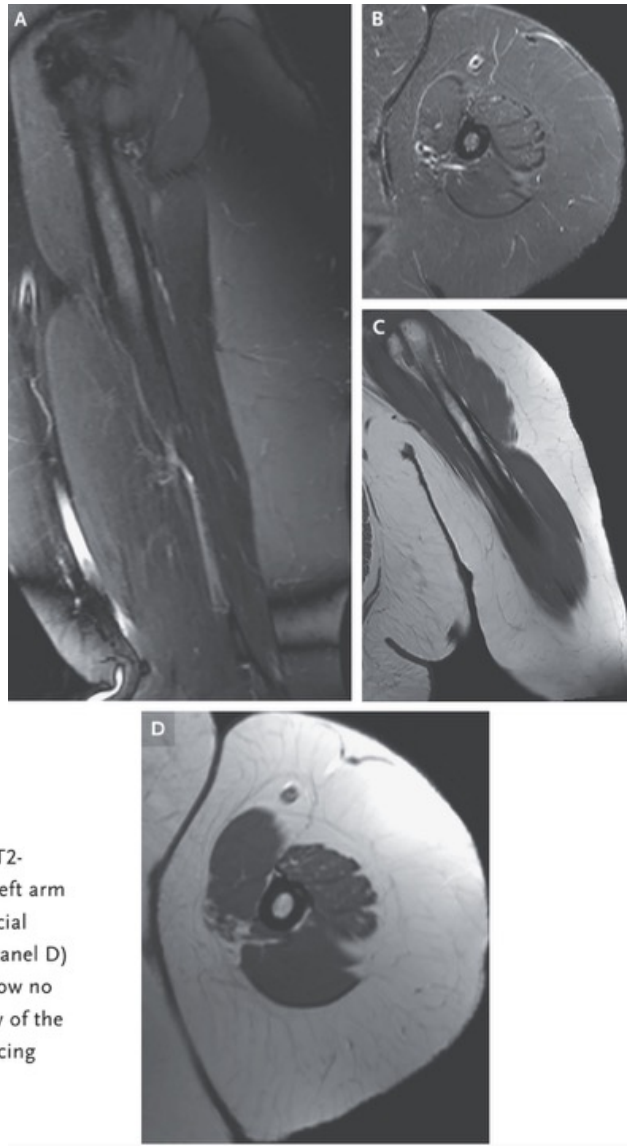
## Myositis-Specific and Myositis-Associated Antibodies.

Myositis-specific antibodies

- Anti-tRNA synthetase antibodies (associated with interstitial lung disease): anti–Jo-1, anti–PL-7, anti–PL-12, anti-EJ, anti-OJ, anti-KS, anti-Ha, and anti-Zo
- Anti–MDA-5 (associated with rapidly progressive interstitial lung disease)
- Anti–TIF-1γ (associated with cancer)
- Anti-SRP (associated with necrotizing myopathy)
- Anti–Mi-2 (associated with frequent cutaneous manifestations)
- Anti–HMG-CoA reductase (associated with statin-induced necrotizing autoimmune myopathy)
- Anti–NXP-2 (associated with frequent cutaneous manifestations)
- Anti-SAE (associated with frequent cutaneous manifestations)
- Anti-cN1A (associated with inclusion-body myositis)

Myositis-associated antibodies

- Anti–U1-RNP
- Anti-Ro
- Anti–PM-Scl
- Anti-Ku




**MRI of the Arm.**

Sagittal (Panel A) and axial (Panel B) T2-weighted fat-saturated images of the left arm show no bone marrow, muscle, or fascial edema. Coronal (Panel C) and axial (Panel D) T1-weighted images of the left arm show no evidence of fatty infiltration or atrophy of the muscles. No fracture or marrow-replacing lesion is present.

Given the negative MRI results, which further decreased the probability of idiopathic inflammatory myopathies, we chose not to pursue a muscle biopsy. After calcium repletion therapy, the patient's symptoms abated rapidly, and by the time she was discharged from the hospital, the creatine kinase level had decreased to 227 U per liter. The results of the myositis panel, which became available after her discharge, did not identify any additional positive antibodies. Therefore, the response to calcium repletion therapy and the negative MRI and myositis panel were all consistent with hypocalcemic hypoparathyroid myopathy. Although the reason she felt better after treatment with azathioprine was unclear, we recommended discontinuation of azathioprine and resumption of leflunomide because her rheumatoid arthritis had been in remission with the use of leflunomide therapy and because her myopathy was not inflammatory in nature.

## Follow-up

The importance of routine appointments with the patient's local endocrinologist was emphasized so that her doses of calcium and calcitriol could be adjusted appropriately, her urinary calcium level could be monitored, and any new prospective therapeutic options, including PTH replacement therapy, could be discussed. We recommended genetic testing for a possible activating mutation in the calcium-sensing receptor and for mutations associated with autoimmune hypoparathyroidism; however, such mutations were probably unlikely to be present, given that symptoms did not develop in this patient until later in life. Autoantibodies to the calcium-sensing receptor in the context of her autoimmune disease might also be useful.

# Budesonide–formoterol versus salbutamol as reliever therapy in children with mild asthma (CARE): a 52-week, open-label, multicentre, superiority, randomised controlled trial


## Summary

**Background** Combination inhaled corticosteroid–formoterol reliever monotherapy reduces the rate of asthma attacks compared to short-acting $\beta_2$-agonist (SABA) reliever monotherapy in adults. Its comparative efficacy in children has not been established.

**Methods** CARE was a 52-week, open-label, parallel-group, multicentre, superiority, randomised controlled trial in children aged 5–15 years with asthma using SABA reliever monotherapy at 15 clinical trials sites in New Zealand. Participants were randomly assigned (1:1) to either budesonide 50 µg–formoterol 3 µg, two actuations as needed, or salbutamol 100 µg, two actuations as needed. The primary outcome was asthma attacks as rate per participant per year. This trial was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12620001091998.

**Findings** From Jan 28, 2021, to June 23, 2023, we assessed 382 participants for eligibility. We randomly assigned 360 (94%) participants to treatment (179 [50%] to the budesonide–formoterol group and 181 [50%] to the salbutamol group). The annualised rate of asthma attacks was lower in the budesonide–formoterol group than in the salbutamol group—cluster-adjusted rates 0·23 versus 0·41 per participant per year (relative rate 0·55 [95% CI 0·35–0·86]; p=0·012). The number of participants with at least one adverse event was 162 (91%) in the budesonide–formoterol group and 167 (92%) in the salbutamol group (odds ratio 0·79 [95% CI 0·35–1·79]).

**Interpretation** In children aged 5–15 years with mild asthma, budesonide–formoterol reliever monotherapy is superior to salbutamol for preventing asthma attacks, with a similar safety profile.



**Funding** Health Research Council of New Zealand, Cure Kids New Zealand, and the Barbara Basham Medical Charitable Trust (managed by Perpetual Guardian).

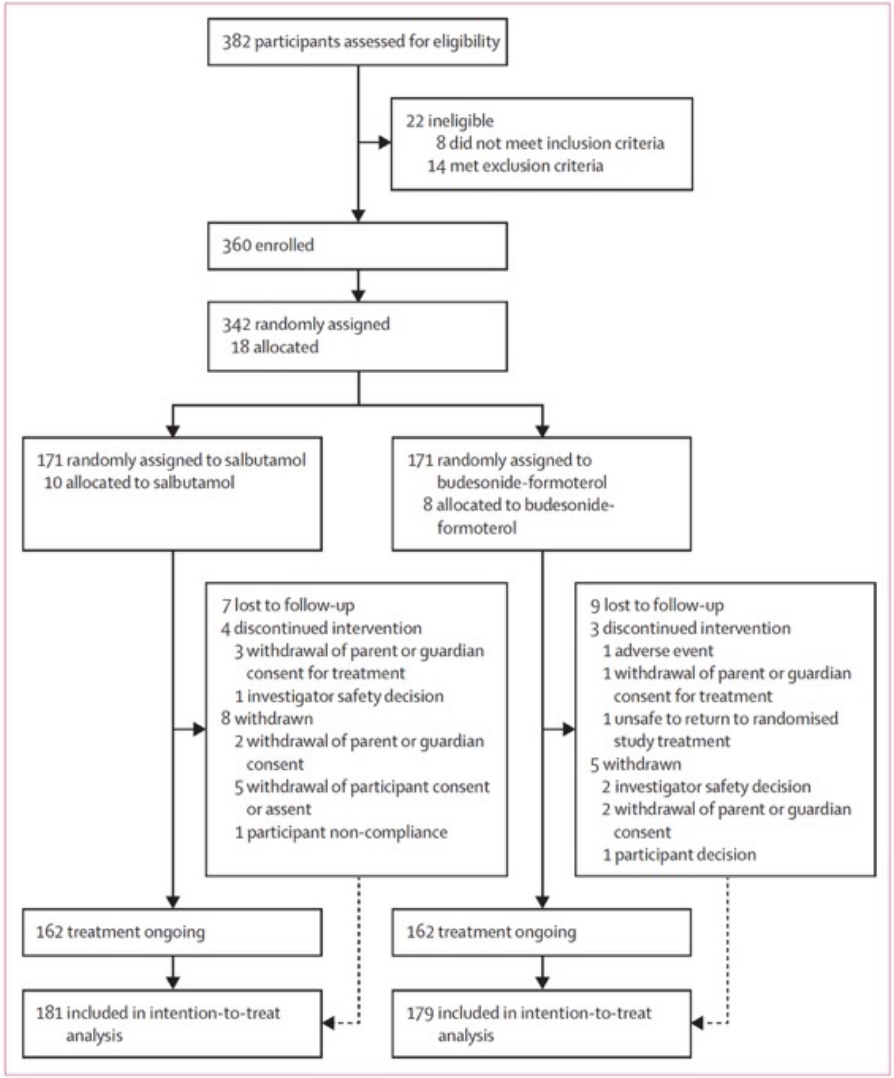



*Figure 1:* **Trial profile**

| | Budesonide–formoterol group (n=179) | Salbutamol group (n=181) |
|---|---|---|
| Age (years) | 10·1 (2·8) | 9·9 (2·9) |
| Age group | | |
| 5–11 years | 127 (71%) | 131 (72%) |
| 12–15 years | 52 (29%) | 50 (28%) |
| Sex | | |
| Female | 94 (53%) | 84 (46%) |
| Male | 85 (47%) | 97 (54%) |
| Ethnicity | | |
| Asian | 15 (8%) | 19 (11%) |
| European | 106 (59%) | 91 (50%) |
| Māori | 44 (25%) | 46 (25%) |
| MELAA | 3 (2%) | 9 (5%) |
| Pacific | 11 (6%) | 16 (9%) |
| BMI, kg/m² | 19·3 (4·2) n=176 | 19·6 (4·5) n=179 |
| Height, cm | 143·0 (18·0) n=176 | 141·7 (18·1) n=179 |
| Age that symptoms started, years | 3·4 (2·7) | 3·5 (2·5) |
| Age at diagnosis, years | 4·5 (2·9) | 4·6 (2·7) n=180 |
| SABA reliever use in the past 12 months | | |
| ≥3 consecutive days | 144 (80%) | 142 (78%) |
| ≥2 days per month | 149 (83%) | 139 (77%) |
| SABA reliever use in the past 4 weeks | | |
| Occasions per week | 2·4 (3·0) | 2·0 (2·9) |
| Actuations per use episode | 2·3 (1·8) | 1·9 (1·6) |
| ≥1 severe asthma attack in the past 12 months | 37 (21%) | 40 (22%) |
| Hospital admission due to asthma ever | 36 (20%) | 36 (20%) |
| History of atopic conditions | 154 (86%) | 141 (78%) |
| Allergic rhinitis | 117 (65%) | 118 (65%) |
| Eczema or dermatitis | 85 (47%) | 84 (46%) |
| Allergies | 82/178 (46%) | 62 (34%) |
| ACQ-5 score | 1·12 (0·81) | 0·99 (0·83) |
| On-treatment $FEV_1$ % of predicted value* | 98·2 (15·6) n=168 | 100·7 (15·4) n=172 |
| Median FeNO, ppb | 37 (11–67) n=159 | 44 (13–78) n=162 |
| FeNO machine used | n=163 | n=169 |
| FENObreath | 23/163 (14%) | 27/169 (16%) |
| Niox Vero | 140/163 (86%) | 142/169 (84%) |
| Household smoke exposure | | |
| Current | 17 (10%) | 23 (13%) |
| Previous | 18 (10%) | 17 (9%) |
| Never | 144 (80%) | 141 (78%) |
| Treatment allocation | | |
| Randomised | 171 (96%) | 172 (95%) |
| Allocated | 8 (4%) | 9 (5%) |

Data are n (%), mean (SD), or median (IQR). ACQ-5=five-question version of the Asthma Control Questionnaire. FeNO=fraction of exhaled nitric oxide. $FEV_1$=forced expiratory volume in 1 s. MELAA= Middle Eastern, Latin American, and African. ppb=parts per billion. SABA=short-acting $\beta_2$-agonist. *Participants received no specific instruction to withhold use of their bronchodilator before measurement of $FEV_1$.

***Table 1:*** **Baseline characteristics**

| | Budesonide–formoterol group (n=179) | Salbutamol group (n=181) |
|---|---|---|
| **Asthma attacks** | | |
| Annualised rate* | 0·23 | 0·41 |
| Relative rate (95% CI)* | 0·55 (0·35 to 0·86) p=0·012 | .. |
| Asthma attack count | | |
| 0 | 149 (83%) | 123 (68%) |
| 1 | 23 (13%) | 40 (22%) |
| 2 | 3 (2%) | 14 (8%) |
| 3 | 2 (1%) | 4 (2%) |
| 4 | 0 | 0 |
| 5 | 2 (1%) | 0 |
| ≥1 asthma attack | 30 (17%) | 58 (32%) |
| Odds ratio (95% CI) | 0·43 (0·24 to 0·75) p=0·0060 | .. |
| Time to first asthma attacks, days | 329 (103) | 295 (122) |
| Hazard ratio (95% CI) | 0·48 (0·31 to 0·74) p=0·0010 | .. |
| Health-care encounters for asthma attacks | | |
| After hours (urgent care) | 9 | 11 |
| Emergency department | 3 | 11 |
| General practice | 34 | 66 |
| Hospitalisation | 3 | 1 |
| Other | 1 | 7 |
| **Severe asthma attacks** | | |
| Annualised rate | 0·11 | 0·18 |
| Relative rate (95% CI) | 0·60 (0·32 to 1·14) p=0·11 | .. |
| Severe attack count | | |
| 0 | 163 (91%) | 153 (85%) |
| 1 | 13 (7%) | 21 (12%) |
| 2 | 2 (1%) | 6 (3%) |
| 3 | 0 | 1 (<1%) |
| 4 | 0 | 0 |
| 5 | 1 (1%) | 0 |
| ≥1 severe attack | 16 (9%) | 28 (16%) |
| Odds ratio (95% CI) | 0·54 (0·26 to 1·11) p=0·086 | .. |
| Time to severe attack, days | 343 (89) | 325 (101) |
| Hazard ratio (95% CI) | 0·55 (0·30 to 1·03) p=0·062 | .. |
| **Asthma control and respiratory testing** | | |
| Treatment step at visit 5 | | |
| Step 1 | 145/167 (87%) | 126/166 (76%) |
| Step 2 | 18/167 (11%) | 28/166 (17%) |
| Step 3 | 1/167 (1%) | 8/166 (5%) |
| Non-study | 3/167 (2%) | 4/166 (2%) |
| Treatment Step 1 vs other or non-treatment steps, odds ratio (95% CI) | 1·86 (1·07 to 3·22) p=0·031 | |
| ACQ-5 score | | |
| Visit 3 | 0·81 (0·69) | 0·75 (0·66) |
| Visit 5 | 0·77 (0·68) | 0·79 (0·72) |
| Mean difference across all timepoints (95% CI) | −0·003 (−0·12 to 0·11) p=0·95 | |

(Table 2 continues on next page)

(Continued from previous page)

| | Budesonide–formoterol group (n=179) | Salbutamol group (n=181) |
|---|---|---|
| FeNO, ppb | 35·2 (13·5 to 65·5) | 42·3 (11·7 to 70) |
| $FEV_1$ % predicted | 99·3 (15·2) | 100·2 (14·8) |
| Mean difference | 0·36 (−2·46 to 3·17) p=0·80 | .. |
| **Growth velocity** | | |
| Height, cm | 148·09 (17·09) | 146·63 (17·21) |
| Mean difference (95% CI) | −0·35 (−0·93 to 0·24) p=0·24 | .. |
| **Time off due to asthma** | | |
| Days lost from school | 1·62 (3·83) | 2·11 (3·54) |
| Relative rate (95% CI) | 0·68 (0·44 to 1·04) p=0·075 | .. |
| Days lost from work due to childcare | 0·68 (2·78) | 0·72 (1·96) |
| Relative rate (95% CI) | 0·87 (0·49 to 1·56) p=0·64 | .. |

Data are n, n/N (%), n (%), mean (SD), or median (IQR), unless stated otherwise. Outcomes are cluster-adjusted, where specified in the methods and trial statistical analysis plan. ACQ-5=five-question version of the Asthma Control Questionnaire. FeNO=fraction of exhaled nitric oxide. $FEV_1$=forced expiratory volume in 1 s. *Primary outcome.

***Table 2:*** **Summary of outcomes**

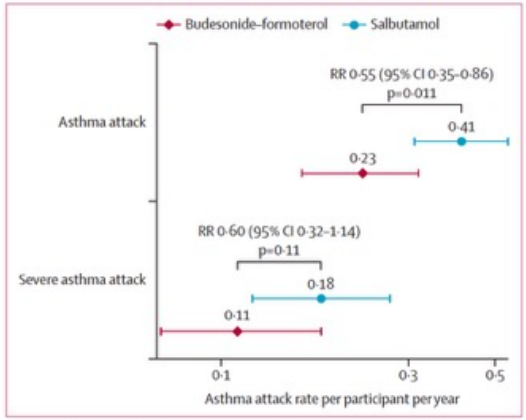



***Figure 2:*** **Annualised asthma attack rates**
X-axis is displayed on the logarithm scale. RR=relative rate.

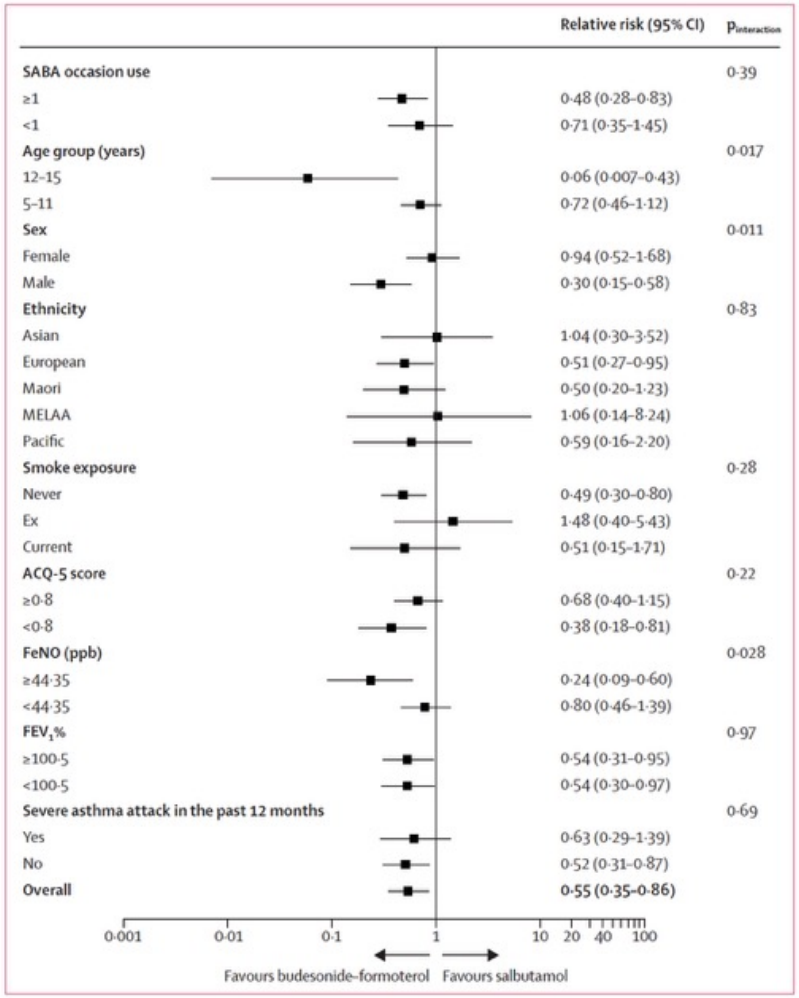



***Figure 3:*** **Differential effect of treatment on asthma attack outcomes**
Data shown by potential effect-modifying baseline variables for the relative rate of asthma attacks. ACQ-5=five-question version of the Asthma Control Questionnaire. FeNO=fraction of exhaled nitric oxide (units expressed as parts per billion). $FEV_1$%=forced expiratory volume in 1 s, percentage predicted. MELAA=Middle Eastern, Latin American, and African. ppb=parts per billion. SABA=short-acting $\beta_2$-agonist.

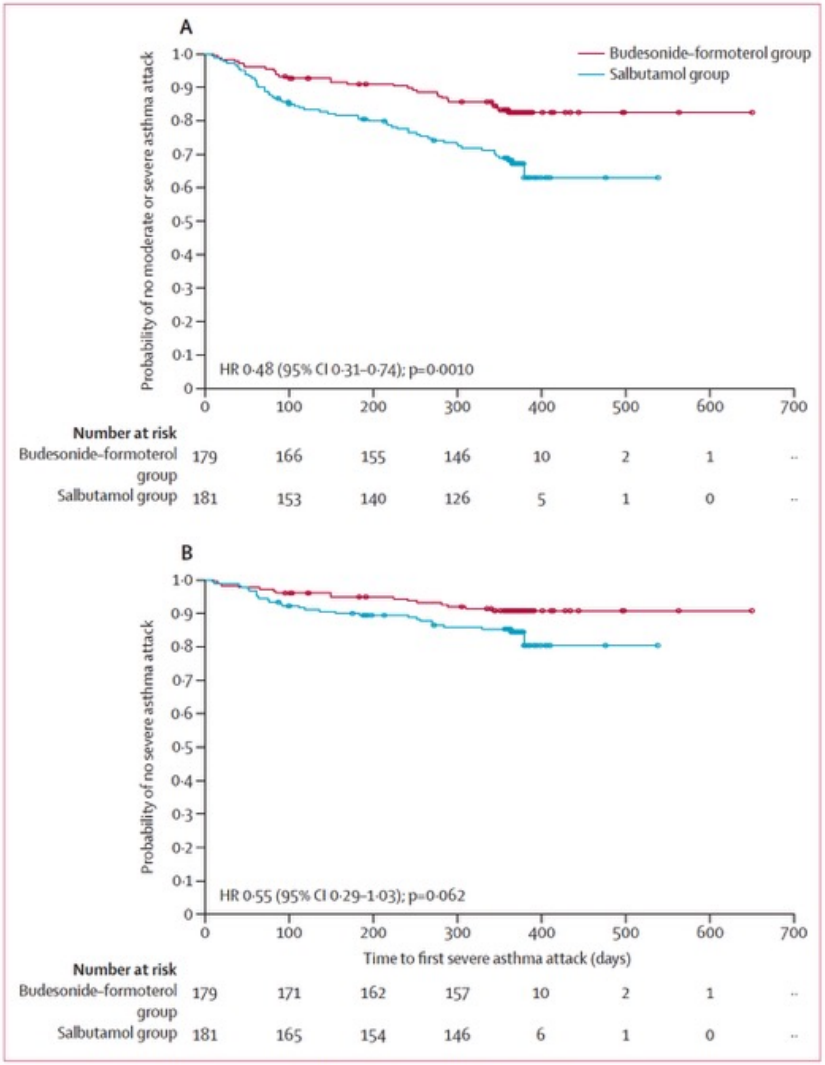



***Figure 4:*** **Estimates of the occurrence of asthma attacks in a time-to-event analysis**
Graphs show time to first moderate or severe attack (A) and time to first severe attack (B). HR=hazard ratio.

| | Budesonide–formoterol group (n=179) | | | Salbutamol group (n=181) | | |
|---|---|---|---|---|---|---|
| | All | Treatment related | Not treatment related | All | Treatment related | Not treatment related |
| Adverse events | 952 | 6 | 946 | 993 | 1 | 992 |
| At least one adverse event | 162 (90%) | 6 (3%) | 161 (90%) | 167 (92%) | 1 (1%) | 167 (92%) |
| Adverse events that occurred in ≥5% of participants in either group | | | | | | |
| Upper respiratory tract infection | 90 (50%) | 0 | 90 (50%) | 92 (51%) | 0 | 92 (51%) |
| Asthma | 84 (47%) | 0 | 84 (47%) | 110 (61%) | 0 | 110 (61%) |
| COVID-19 | 62 (35%) | 0 | 62 (35%) | 67 (37%) | 0 | 67 (37%) |
| Vaccination site pain | 26 (15%) | 0 | 26 (15%) | 19 (10%) | 0 | 19 (10%) |
| Viral upper respiratory tract infection | 21 (12%) | 0 | 21 (12%) | 22 (12%) | 0 | 22 (12%) |
| Vaccination complication | 21 (12%) | 0 | 21 (12%) | 16 (9%) | 0 | 16 (9%) |
| Gastroenteritis | 20 (11%) | 0 | 20 (11%) | 19 (10%) | 0 | 19 (10%) |
| Respiratory tract infection | 17 (9%) | 0 | 17 (9%) | 17 (9%) | 0 | 17 (9%) |
| Oropharyngeal pain | 17 (9%) | 2 (1%) | 15 (8%) | 8 (4%) | 0 | 8 (4%) |
| Headache | 13 (7%) | 1 (1%) | 12 (6%) | 14 (8%) | 0 | 14 (8%) |
| Viral infection | 13 (7%) | 0 | 13 (7%) | 12 (7%) | 0 | 12 (7%) |
| Ligament sprain | 13 (7%) | 0 | 13 (7%) | 11 (6%) | 0 | 11 (6%) |
| Cough | 10 (6%) | 0 | 10 (6%) | 7 (4%) | 0 | 7 (4%) |
| Seasonal allergy | 9 (5%) | 0 | 9 (5%) | 7 (4%) | 0 | 7 (4%) |
| Abdominal pain | 7 (4%) | 0 | 7 (4%) | 10 (6%) | 0 | 10 (6%) |
| Fall | 5 (3%) | 0 | 5 (3%) | 13 (7%) | 0 | 13 (7%) |
| Croup infectious | 3 (2%) | 0 | 3 (2%) | 9 (5%) | 0 | 9 (5%) |
| Serious adverse event | 6 | 0 | 6 | 9 | 0 | 9 |
| ≥1 serious adverse event | 5 (3%) | 0 | 5 (3%) | 8 (2%) | 0 | 8 (2%) |
| All serious adverse events | | | | | | |
| Asthma | 3 (2%) | 0 | 3 (2%) | 1 (1%) | 0 | 1 (1%) |
| Abdominal pain | 0 | 0 | 0 | 1 (1%) | 0 | 1 (0·6%) |
| Cellulitis | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Concussion | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Constipation | 1 (1%) | 0 | 1 (1%) | 0 | 0 | 0 |
| Gastroenteritis | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Localised coinfection | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Lymphadenitis | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Neck injury | 0 | 0 | 0 | 1 (1%) | 0 | 1 (0%) |
| Osteomyelitis | 0 | 0 | 0 | 1 (1%) | 0 | 1 (1%) |
| Skin laceration | 1 (1%) | 0 | 1 (1%) | 0 | 0 | 0 |
| Testicular torsion | 1 (1%) | 0 | 1 (1%) | 0 | 0 | 0 |

Data are n or n (%).

***Table 3:*** **Adverse events**

## Research in context

### Evidence before this study

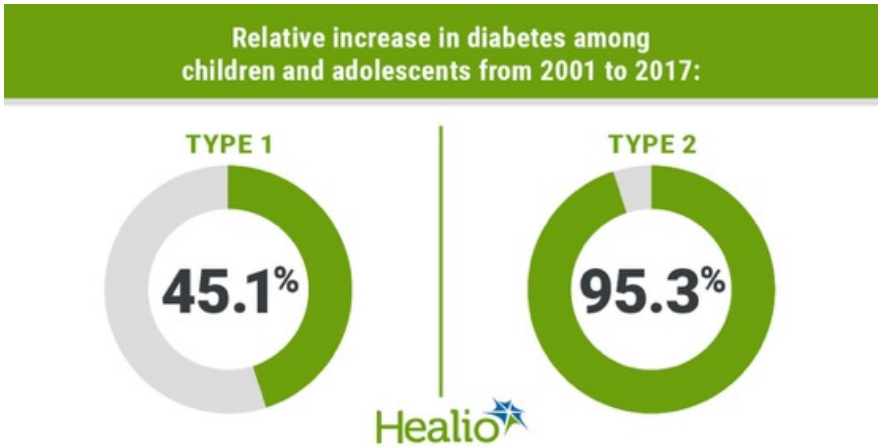
In adults and adolescents with mild asthma, combination inhaled corticosteroid (ICS)–formoterol reliever monotherapy reduces the risk of asthma attacks compared to treatment with short-acting $\beta_2$-agonist (SABA) reliever monotherapy. The treatment's efficacy in children has not been reported. We searched MEDLINE on Nov 22, 2024, for studies using the terms (child* OR pedi* OR paed* OR adolescent) AND ("ICS–formoterol" OR "budesonide–formoterol") AND (Asthma) AND (reliever OR "as-needed" OR "as-required"), with the filters "randomized controlled trial". We found a single double-blind, placebo-controlled, randomised controlled trial (SYGMA 1), which investigated the efficacy of budesonide–formoterol reliever monotherapy in adolescents and adults aged 12 years and older. In a post hoc analysis of adolescents (aged 12–17 years) enrolled in this trial, budesonide–formoterol reliever monotherapy reduced the rate of severe attacks by 77% compared with terbutaline reliever monotherapy. The relative rate of moderate and severe attacks in this subgroup was not reported. We found no evidence of the efficacy and safety of ICS–formoterol reliever monotherapy in children aged 5–11 years.

### Added value of this study

This is the first randomised controlled trial of ICS–formoterol versus SABA as reliever monotherapy in children aged 5–15 years with asthma in a real-world setting. Budesonide–formoterol resulted in a lower rate of asthma attacks than salbutamol, with rates of 0·23 versus 0·41 per participant per year (relative rate [RR] 0·55 [95% CI 0·35–0·86]; p=0·012). The findings from pre-specified subgroup analyses were consistent with a greater treatment effect in those aged 12–15 years versus children aged 5–11 years, boys versus girls, and those with a higher baseline fractional exhaled nitric oxide (FeNO). The rate of severe asthma attacks with budesonide–formoterol was 0·11 per participant per year versus 0·18 per participant per year with salbutamol (RR 0·60 [95% CI 0·32–1·14]; p=0.11). Growth velocity, asthma symptom control, lung function, FeNO, and the proportion of participants with adverse events were similar in the two regimens.

### Implications of all the available evidence

The available evidence suggests that for patients aged 5–75 years with asthma currently using SABA reliever monotherapy, switching to budesonide–formoterol reliever monotherapy is more effective at preventing asthma attacks.


Relative increase in diabetes among
children and adolescents from 2001 to 2017:
TYPE 1
45.1%
TYPE 2
95.3%
Healio

# Efficacy and safety of tirzepatide in children and adolescents with type 2 diabetes (SURPASS-PEDS): a randomised, double-blind, placebo-controlled, phase 3 trial


## Summary

**Background** Current treatment options for youth-onset type 2 diabetes are limited and have demonstrated lower glycaemic efficacy than those for adult-onset type 2 diabetes. We aimed to assess the safety and efficacy of tirzepatide, a glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, compared with placebo in youth-onset type 2 diabetes.

**Methods** We conducted a phase 3, double-blind, placebo-controlled, multicentre (39 sites), multinational (eight countries) trial over 30 weeks, followed by an open-label extension for 22 weeks in which all participants received tirzepatide. Participants aged 10 to <18 years with youth-onset type 2 diabetes inadequately controlled with metformin and/or basal insulin were randomly assigned (1:1:1) to receive tirzepatide 5 mg, 10 mg, or placebo administered by subcutaneous injection with a single-dose pen. Randomisation was stratified by age group (≤14 years or >14 years) and antihyperglycaemic medication use (metformin, basal insulin, or both). All participants, investigators, and the sponsor were masked to treatment assignment during the 30-week double-blind period. The primary endpoint was change in glycated haemoglobin ($HbA_{1c}$) from baseline to week 30. Data from all participants who received at least one dose of study drug were used to analyse efficacy and safety. This completed trial is registered with ClinicalTrials.gov (NCT05260021).

**Findings** Between April 12, 2022, and Dec 27, 2023, 146 participants were screened, of whom 99 (60 [61%] female, 39 [39%] male; mean age 14·7 years [SD 1·8]; mean baseline $HbA_{1c}$ 8·04% [1·23]) were randomly assigned to tirzepatide 5 mg (n=32), tirzepatide 10 mg (n=33), or placebo (n=34). At week 30, tirzepatide was superior to placebo in reducing $HbA_{1c}$, with a mean reduction of 2·23% in the pooled tirzepatide group versus an increase of 0·05% in the placebo group (estimated treatment difference −2·28%; 95% CI −2·87 to −1·69; p<0·0001). Glycaemic efficacy was sustained up to 52 weeks with tirzepatide treatment. Tirzepatide also resulted in significant reductions in BMI of 7·4% and 11·2% for the 5 mg and 10 mg groups, respectively, compared with 0·4% in the placebo group at 30 weeks. The most common adverse events with tirzepatide treatment were gastrointestinal, all mild to moderate in severity, and decreased over time. Two (6%) patients in the tirzepatide 5 mg group discontinued study drug due to an adverse event. The safety profile of tirzepatide was consistent with that reported in adults. No deaths were reported during the study period.

**Interpretation** Tirzepatide demonstrated significant improvements in glycaemic control and BMI compared with placebo. These effects were sustained over 1 year.

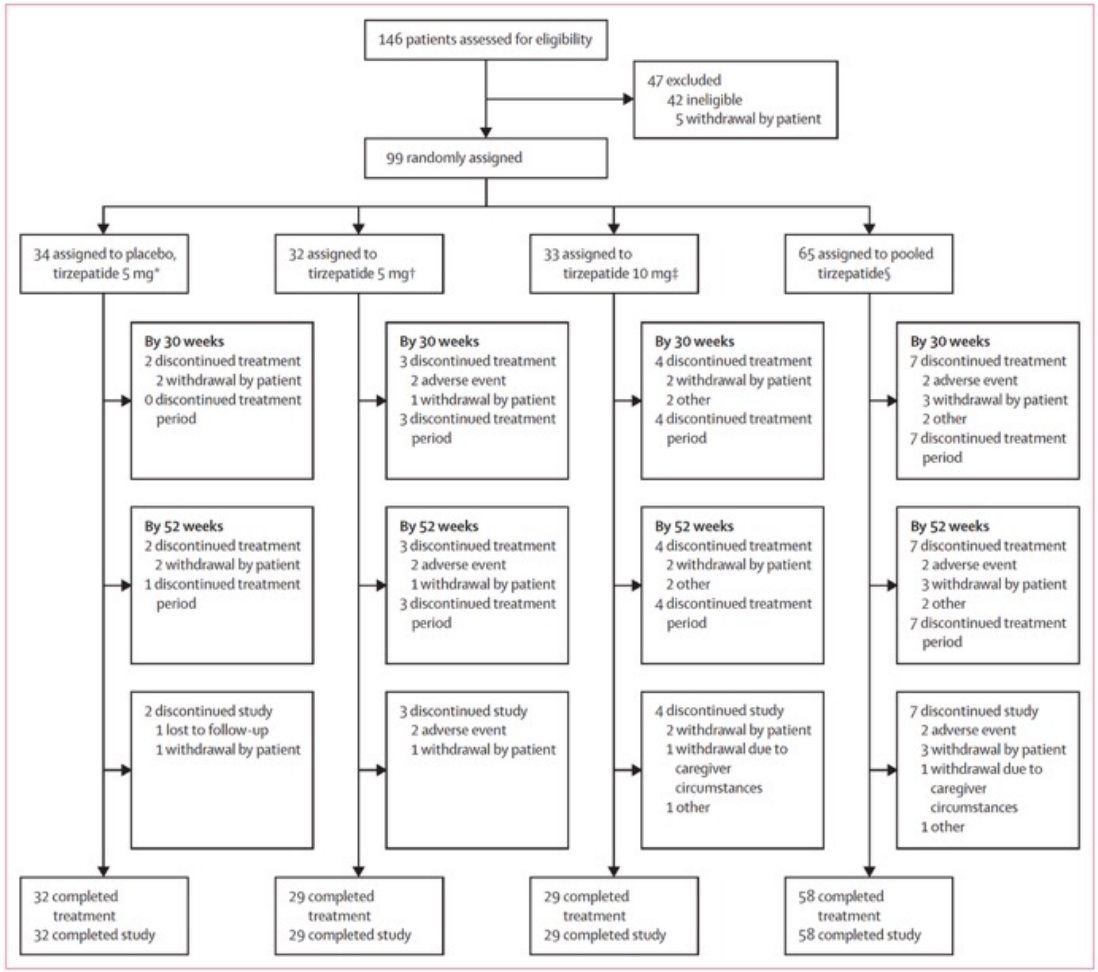



***Figure 1:*** **Trial profile**

The reasons for participants who discontinued the study treatment period are the same as the reasons for study treatment discontinuation during the 30-week double-blind treatment period. The two participants who discontinued treatment for reasons listed as "other" discontinued due to inadvertent enrolment and lack of efficacy. After week 30 to the end of week 52, no new participant discontinued the study treatment. *Placebo treatment in the double-blind period and tirzepatide 5 mg treatment in the open-label period. †Tirzepatide 5 mg in both the double-blind and open-label periods. ‡Tirzepatide 10 mg in both the double-blind and open-label periods. §Pooled groups of tirzepatide 5 mg and 10 mg in the double-blind and open-label periods.

| | Placebo (n=34) | Tirzepatide 5 mg (n=32) | Tirzepatide 10 mg (n=33) | Pooled tirzepatide (n=65) | Total (n=99) |
|---|---|---|---|---|---|
| Age, years | 14·6 (1·8) | 15·0 (1·9) | 14·6 (1·8) | 14·8 (1·9) | 14·7 (1·8) |
| Age category | | | | | |
| ≥10 to ≤14 years | 16 (47%) | 13 (41%) | 15 (45%) | 28 (43%) | 44 (44%) |
| ≥15 to <18 years | 18 (53%) | 19 (59%) | 18 (55%) | 37 (57%) | 55 (56%) |
| Duration of diabetes, years | 2·7 (2·3) | 2·5 (1·6) | 1·9 (1·3) | 2·2 (1·5) | 2·4 (1·8) |
| Sex | | | | | |
| Female | 21 (62%) | 21 (66%) | 18 (55%) | 39 (60%) | 60 (61%) |
| Male | 13 (38%) | 11 (34%) | 15 (45%) | 26 (40%) | 39 (39%) |
| Race | | | | | |
| American Indian or Alaska Native | 8 (24%) | 7 (22%) | 5 (15%) | 12 (18%) | 20 (20%) |
| Asian | 3 (9%) | 1 (3%) | 2 (6%) | 3 (5%) | 6 (6%) |
| Black or African American | 2 (6%) | 5 (16%) | 4 (12%) | 9 (14%) | 11 (11%) |
| Multiple | 0 | 1 (3%) | 1 (3%) | 2 (3%) | 2 (2%) |
| White | 21 (62%) | 17 (53%) | 19 (58%) | 36 (55%) | 57 (58%) |
| Missing | 0 | 1 (3%) | 1 (3%) | 2 (3%) | 2 (2%) |
| Ethnicity | | | | | |
| Hispanic or Latino | 24 (71%) | 24 (75%) | 17 (52%) | 41 (63%) | 65 (66%) |
| Not Hispanic or Latino | 9 (26%) | 8 (25%) | 16 (48%) | 24 (37%) | 33 (33%) |
| Not reported | 1 (3%) | 0 | 0 | 0 | 1 (1%) |
| Diabetes therapy at baseline | | | | | |
| Basal insulin only | 2 (6%) | 3 (9%) | 3 (9%) | 6 (9%) | 8 (8%) |
| Metformin plus basal insulin | 8 (24%) | 7 (22%) | 8 (24%) | 15 (23%) | 23 (23%) |
| Metformin only | 24 (71%) | 22 (69%) | 22 (67%) | 44 (68%) | 68 (69%) |
| $HbA_{1c}$ concentration | | | | | |
| % | 8·02 (1·30) | 8·22 (1·17) | 7·89 (1·22) | 8·05 (1·20) | 8·04 (1·23) |
| mmol/mol | 64·2 (14·2) | 66·3 (12·8) | 62·8 (13·4) | 64·5 (13·1) | 64·4 (13·4) |
| FSG concentration | | | | | |
| mg/dL | 156·1 (77·8) | 147·8 (52·3) | 151·6 (68·3) | 149·8 (60·9) | 152·0 (66·9) |
| mmol/L | 8·66 (4·3) | 8·20 (2·9) | 8·42 (3·8) | 8·32 (3·4) | 8·44 (3·7) |
| BMI, kg/m² | 34·7 (7·7) | 33·9 (7·2) | 37·7 (8·4) | 35·8 (8·0) | 35·4 (7·9) |
| BMI percentile | 98·0 (3·4) | 98·3 (3·0) | 99·3 (1·3) | 98·8 (2·3) | 98·6 (2·8) |
| BMI SDS | 2·99 (1·18) | 2·86 (1·01) | 3·48 (1·23) | 3·17 (1·16) | 3·11 (1·17) |
| Height, cm | 163·2 (8·4) | 164·6 (10·2) | 164·6 (9·3) | 164·6 (9·6) | 164·1 (9·2) |
| Height SDS | −0·05 (0·91) | 0·21 (1·10) | 0·18 (1·20) | 0·20 (1·14) | 0·11 (1·07) |
| Bodyweight, kg | 93·5 (25·7) | 93·2 (27·1) | 103·2 (29·6) | 98·3 (28·6) | 96·6 (27·6) |
| Tanner stage 1* | | | | | |
| Female | 0 | 0 | 0 | 0 | 0 |
| Male | 1/13 (8%) | 1/11 (9%) | 1/15 (7%) | 2/26 (8%) | 3/39 (8%) |
| Tanner stage 2–4* | | | | | |
| Female | 8/21 (38%) | 5/21 (24%) | 7/18 (39%) | 12/39 (31%) | 20/60 (33%) |
| Male | 5/13 (39%) | 3/11 (27%) | 6/15 (40%) | 9/26 (35%) | 14/39 (36%) |
| Tanner stage 5* | | | | | |
| Female | 13/21 (62%) | 16/21 (76%) | 11/18 (61%) | 27/39 (69%) | 40/60 (67%) |
| Male | 7/13 (54%) | 7/11 (64%) | 8/15 (53%) | 15/26 (58%) | 22/39 (56%) |
| Blood pressure, mm Hg | | | | | |
| Systolic | 113·7 (9·2) | 112·6 (10·3) | 117·8 (11·1) | 115·2 (11·0) | 114·7 (10·4) |
| Diastolic | 74·5 (10·3) | 72·1 (9·2) | 73·3 (9·2) | 72·7 (9·2) | 73·3 (9·5) |
| Pulse rate, beats per min | 80·0 (8·8) | 82·3 (11·1) | 79·0 (8·3) | 80·7 (9·8) | 80·4 (9·5) |

Data are mean (SD), n (%), or n/N (%). FSG=fasting serum glucose. $HbA_{1c}$=glycated haemoglobin. SDS=standard deviation score. *Tanner stages are used to evaluate pubertal development. Tanner stage was determined on the basis of the female breast score and the male genital score.

**Table 1: Baseline characteristics**

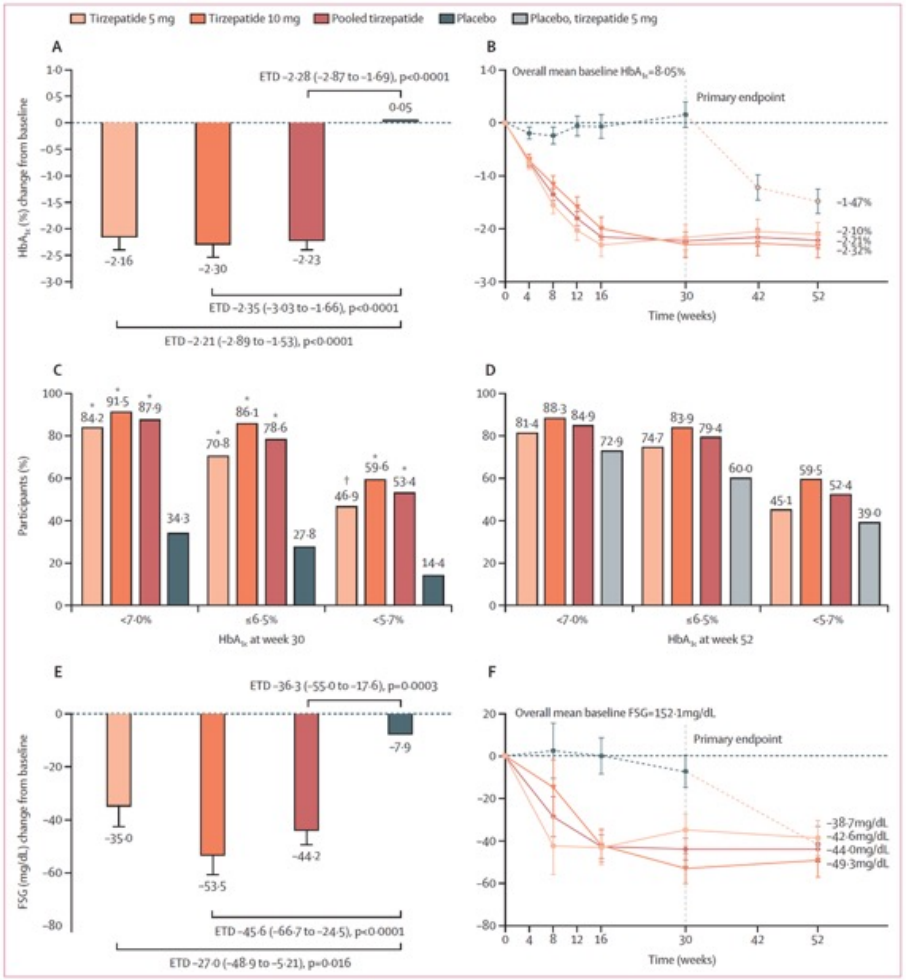



***Figure 2:* Change in $HbA_{1c}$, participants with $HbA_{1c}$ <7%, ≤6·5%, or <5·7%, and change in FSG**

Data presented are for the efficacy estimand and are least-squares mean (SE) unless otherwise stated. ETDs are least-squares mean (95% CI) and p value, in the modified intention-to-treat population (efficacy analysis set); baseline values of the endpoint were included in the model as covariates. Panels A and B show the change from baseline in $HbA_{1c}$ at week 30 (A) and over 52 weeks (B). Panels C and D show the proportion of patients with $HbA_{1c}$ of <7%, ≤6·5%, or <5·7% at week 30 (C) and week 52 (D). Panels E and F show the change from baseline in FSG (central laboratory) concentrations at week 30 (E) and over 52 weeks (F). Change from baseline in $HbA_{1c}$ at week 30, the proportion of patients with $HbA_{1c}$ ≤6·5% at week 30, and change from baseline in FSG at week 30 were controlled for type I error. Other endpoints were not controlled for type I error and nominal p values are presented. ETD=estimated treatment difference. FSG=fasting serum glucose. $HbA_{1c}$=glycated haemoglobin. *p<0·001 versus placebo. †p<0·01 versus placebo.

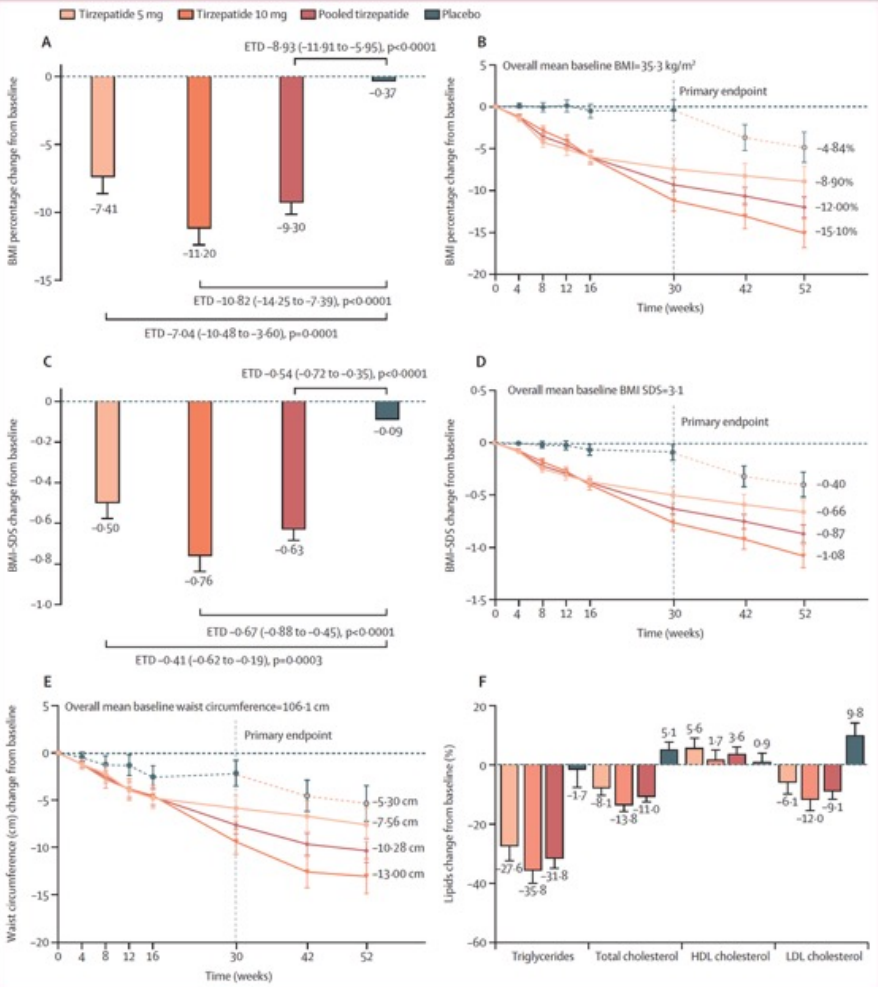



***Figure 3*: Change in BMI, BMI-SDS, waist circumference, and fasting lipids**

Data presented are for the efficacy estimand and are least-squares mean (SE) unless otherwise stated. Estimated treatment differences are least-squares mean (95% CI) and p value, in the modified intention-to-treat population (efficacy analysis set). Panel A and B show the percentage change from baseline in BMI at week 30 (A) and over 52 weeks (B). Panel C and D show the change from baseline in BMI-SDS at week 30 (C) and over 52 weeks (D). Panel E shows the change from baseline in waist circumference, and panel F shows the change from baseline in lipids at week 30 (data from safety analysis set 1). Percentage change from baseline in BMI and change from baseline in BMI-SDS at week 30 were controlled for type I error. Other endpoints were not controlled for type I error and nominal p values are presented. ETD=estimated treatment difference. SDS=standard deviation score.

| | Placebo (n=34) | Tirzepatide 5 mg (n=32) | Tirzepatide 10 mg (n=33) | Pooled tirzepatide (n=65) |
|---|---|---|---|---|
| **Adverse events** | | | | |
| Any adverse event | 15 (44%) | 21 (66%) | 23 (70%) | 44 (68%) |
| Serious adverse events | 1 (3%) | 1 (3%) | 1 (3%) | 2 (3%) |
| Adverse events causing treatment discontinuation* | 0 | 2 (6%) | 0 | 2 (3%) |
| Adverse events occurring in at least 5% of participants in any treatment group | | | | |
| Diarrhoea | 2 (6%) | 8 (25%) | 8 (24%) | 16 (25%) |
| Nausea | 3 (9%) | 7 (22%) | 6 (18%) | 13 (20%) |
| Vomiting | 1 (3%) | 5 (16%) | 4 (12%) | 9 (14%) |
| Abdominal pain upper | 3 (9%) | 2 (6%) | 4 (12%) | 6 (9%) |
| Abdominal pain | 1 (3%) | 5 (16%) | 1 (3%) | 6 (9%) |
| Dyspepsia | 0 | 2 (6%) | 4 (12%) | 6 (9%) |
| Headache | 1 (3%) | 2 (6%) | 3 (9%) | 5 (8%) |
| Oropharyngeal pain | 2 (6%) | 3 (9%) | 1 (3%) | 4 (6%) |
| Cough | 1 (3%) | 3 (9%) | 1 (3%) | 4 (6%) |
| Hyperglycaemia | 5 (15%) | 0 | 0 | 0 |
| Nasopharyngitis | 2 (6%) | 1 (3%) | 2 (6%) | 3 (5%) |
| Decreased appetite | 0 | 0 | 4 (12%) | 4 (6%) |
| Anxiety | 0 | 1 (3%) | 2 (6%) | 3 (5%) |
| Gastroenteritis | 2 (6%) | 0 | 0 | 0 |
| Injection site reaction | 0 | 0 | 2 (6%) | 2 (3%) |
| Tonsillitis | 0 | 2 (6%) | 0 | 2 (3%) |
| **Hypoglycaemia** | | | | |
| Severe hypoglycaemia (level 3) | | | | |
| Incidence | 0 | 0 | 0 | 0 |
| Blood glucose <54 mg/dL (level 2) | | | | |
| Incidence | 2 (6%) | 5 (16%) | 5 (15%) | 10 (15%) |
| Rate per year | 0·15 | 1·11 | 0·51 | 0·81 |
| Blood glucose <54 mg/dL in participants with baseline basal insulin use | | | | |
| Incidence | 1/10 (10%) | 3/10 (30%) | 3/11 (27%) | 6/21 (29%) |
| Rate per year | 0·35 | 2·79 | 1·12 | 1·98 |
| Blood glucose <54 mg/dL in participants with baseline metformin use only | | | | |
| Incidence | 1/24 (4%) | 2/22 (9%) | 2/22 (9%) | 4/44 (9%) |
| Rate per year | 0·07 | 0·33 | 0·24 | 0·28 |

Data are n (%) or n/N (%) unless otherwise stated. For data presented as n (%) or n/N (%), n refers to number of participants with events meeting specified criteria. Data are shown for the modified intention-to-treat population (safety analysis set 1). Participants might be counted in >1 category. Hypoglycaemia data exclude events after initiating new antihyperglycaemic therapy. *One participant assigned to tirzepatide 5 mg discontinued study treatment due to nausea and one participant discontinued study treatment due to suicidal ideation.

***Table 2*: Adverse events and hypoglycaemia**

## Research in context

### Evidence before this study

We searched PubMed on July 15, 2025, using the terms "type 2 diabetes", "youth", "youth-onset", "young", "children", "adolescents", "paediatric", "tirzepatide", and "GLP-1 RA" with no date restrictions or language restrictions. Youth-onset type 2 diabetes constitutes a particularly aggressive disease phenotype, marked by a more rapid progression than adult-onset type 2 diabetes. Data from pivotal studies of youth-onset type 2 diabetes such as TODAY and RISE reveal that affected youth experience pronounced reductions in insulin sensitivity. This is exacerbated during puberty by heightened growth hormone secretion and a hyper-responsiveness of β cells, leading to an accelerated deterioration of β-cell function and, ultimately, a rapid decline in endogenous insulin production. While new agents including GLP-1 receptor agonists and SGLT-2 inhibitors have been approved in recent years for youth-onset type 2 diabetes, pharmacotherapeutic treatment options for youth-onset type 2 diabetes remain limited compared with those for adult-onset type 2 diabetes. Among the available treatments, GLP-1 receptor agonists such as dulaglutide and liraglutide have demonstrated early efficacy in lowering glycaemia in youth. Despite initial responses, these agents have not sustained durable long-term glycaemic control, likely reflecting the progressive and aggressive nature of youth-onset type 2 diabetes. Moreover, clinical trials indicate that these agents do not deliver clinically meaningful weight reduction in this population, further highlighting the gap in effective treatment options.

Previous research has demonstrated clinically meaningful improvements in glycaemic control and bodyweight with tirzepatide treatment in adults with type 2 diabetes, but there remains a gap in clinical evidence on the use of tirzepatide in children and adolescents.

### Added value of this study

This is the first study assessing the safety and efficacy of tirzepatide in youth. The findings demonstrate that tirzepatide provides substantial and superior improvements in glycaemic control compared with placebo in youth-onset type 2 diabetes. To our knowledge, tirzepatide is the first agent to demonstrate sustained glycaemic control up to 1 year and show significant and clinically meaningful improvements in weight-related parameters. The safety profile of tirzepatide in youth was consistent with that established in adults.

### Implications of all the available evidence

Current management for glycaemic control in youth-onset type 2 diabetes remains constrained by the limited number of approved pharmacological options. The American Diabetes Association's standards of care emphasise targeting weight reduction of 7–10% and a stringent glycaemic target of glycated haemoglobin ($HbA_{1c}$) less than 6·5% for most individuals with youth-onset type 2 diabetes, provided the risk of hypoglycaemia is low. However, the aggressive pathophysiology of the disease often challenges the durability of glycaemic control achieved by existing therapies. Findings from the SURPASS-PEDS study suggest that tirzepatide could represent a significant advancement in the therapeutic landscape. Metformin continues to be recommended as first-line therapy for youth-onset type 2 diabetes and an $HbA_{1c}$ below 8·5% at diagnosis. Nevertheless, if approved for use in this population, tirzepatide could emerge as a first-line option, given its robust glycaemic efficacy and substantial impact on BMI reduction. Additional head-to-head trials of tirzepatide compared with metformin and basal insulin are warranted to reassess the treatment guidelines for youth-onset type 2 diabetes.

# SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP) RISK FACTORS

Early age of epilepsy onset

Generalized tonic-clonic seizures

Uncontrolled or frequent seizures

Not taking medication as prescribed

CURE EPILEPSY

# Risk markers for sudden unexpected death in epilepsy: an observational, prospective, multicentre cohort study


## Summary

**Background** Sudden unexpected death in epilepsy (SUDEP) is the leading cause of epilepsy-related mortality. Generalised—particularly nocturnal—convulsive seizures, longstanding epilepsy, and solitary living have been identified retrospectively as risk factors. No definitive electroclinical biomarkers have been prospectively ascertained. This study aimed to identify SUDEP risk markers using multimodality data with long-term follow-up.

**Methods** This prospective, multicentre, observational cohort study, conducted at nine centres (eight in the USA and one in the UK), recruited children and adults with epilepsy who were undergoing prolonged video-electroencephalographic (EEG) monitoring. Inclusion criteria were diagnosis of epilepsy by an epilepsy specialist, with or without drug resistance; age older than 2 months; admission to the epilepsy monitoring unit of a participating centre, with video-EEG monitoring; and completion of at least one 6-month follow-up. Demographic, electroclinical, and cardiorespiratory data were collected at baseline. Participants were followed up long term through routine clinic visits, review of electronic health records, and telephone interviews to collect information about seizure frequency, medication status, and mortality. The primary endpoint was time to SUDEP. Cox proportional hazards models were used to assess significant risk factors.

**Findings** Between Sept 17, 2011, and Dec, 30, 2021, 2632 children and adults with epilepsy were enrolled in this study; 164 were lost to follow-up. 38 (1·54%) of 2468 participants died from SUDEP (12 definite, 18 probable, and eight possible SUDEP cases) and two had near-SUDEP events. Incident SUDEP mortality rate was 4·76 (95% CI 3·37–6·53) cases per 1000 person-years, from a cohort of 7982 person-years. Living alone (hazard ratio 7·62, 95% CI 3·94–14·71), three or more generalised convulsive seizures in the previous year (3·1, 1·64–5·87]), longer ictal central apnoea (1·11, 1·05–1·18), and longer postictal central apnoea (1·32, 1·14–1·54]) were significant predictors of increased SUDEP risk. In a subanalysis excluding possible and near-SUDEP cases, longer ictal central apnoea was not significant.

**Interpretation** This study shows an association between premortem peri-ictal apnoea and increased SUDEP risk. Cardiorespiratory monitoring during seizures might benefit assessments of epilepsy mortality risk. Together with solitary living and convulsive seizure frequency, peri-ictal apnoea (>14 s for postictal central apnoea and >17 s for ictal central apnoea) could inform the development of a validatable SUDEP risk index.

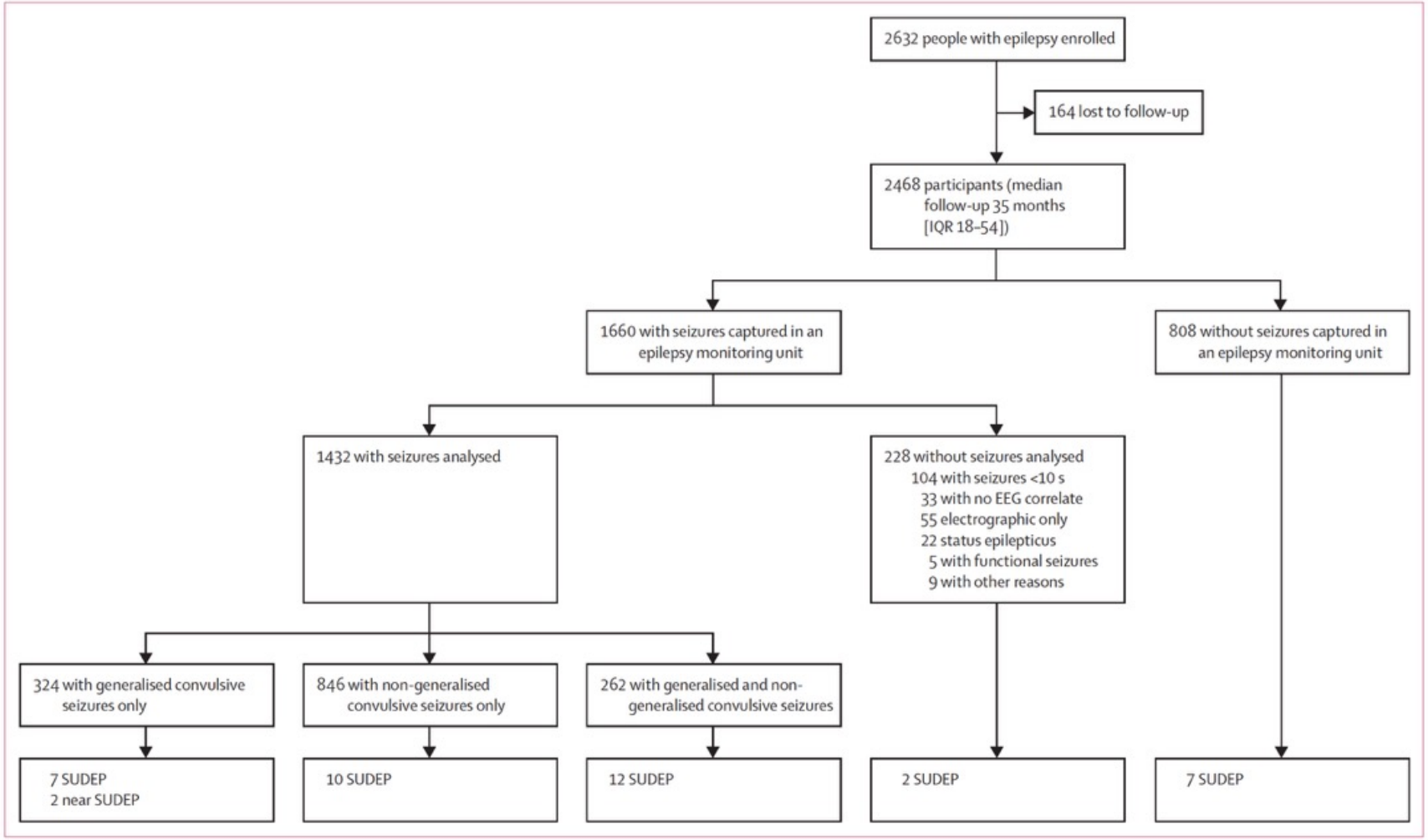



***Figure 1:*** **Cohort enrolment, follow-up, and analysis**
The two near-SUDEP cases were included in the primary analysis. EEG=electroencephalographic. SUDEP=sudden unexpected death in epilepsy.

| | Overall cohort (N=2468) | Non-SUDEP (n=2428) | SUDEP or near SUDEP (n=40) |
|---|---|---|---|
| Age at epilepsy onset, years | 15 (7–27) | 15 (7–27) | 14 (8–33) |
| Adult | 18 (9–30) | 18 (9–30) | 17 (9–40) |
| Paediatric | 3 (0·7–8) | 3 (0·6–7) | 4 (0·1–8) |
| Missing data | 115 (5%) | 115 (5%) | 0 |
| Epilepsy duration at baseline, years | 12 (4–22) | 12 (4–22) | 12 (5–30) |
| Missing data | 123 (5%) | 123 (5%) | 0 |
| Follow-up time, months | 35 (18–54) | 35 (18–54) | 33 (18–60) |
| Sex | | | |
| Male | 1086 (44%) | 1064 (44%) | 22 (55%) |
| Female | 1382 (56%) | 1364 (56%) | 18 (45%) |
| Age, years | | | |
| At first admission to an epilepsy monitoring unit* | 32 (0·17–86) | 32 (0·17–86) | 43 (2–72) |
| Paediatric | 11 (0·17–17) | 11 (0·17–17) | 6 (2–16) |
| Adult | 35 (18–86) | 35 (18–86) | 48 (19–72) |
| Age group at first admission to an epilepsy monitoring unit | | | |
| Paediatric | 309 (13%) | 302 (12%) | 7 (18%) |
| Adult | 2159 (87%) | 2126 (87%) | 33 (83%) |
| Living status | | | |
| Alone | 138/1687 (8%) | 124/1648 (8%) | 14/39 (36%) |
| Not alone | 1549/1687 (92%) | 1524/1648 (92%) | 25/39 (64%) |
| Missing data | 781/2468 (32%) | 780/2428 (32%) | 1 (3%) |
| Number of generalised convulsive seizures in the previous year | | | |
| <3 | 1510/2255 (67%) | 1494/2216 (67%) | 16/39 (41%) |
| ≥3 | 745/2255 (33%) | 722/2216 (33%) | 23/39 (59%) |
| Missing data | 213/2468 (9%) | 212/2428 (8·7%) | 1/40 (3%) |
| Antiseizure medication | | | |
| No medication | 90 (4%) | 90 (4%) | 0 |
| Monotherapy | 728 (30%) | 719 (30%) | 9 (22%) |
| Polytherapy | 1650 (67%) | 1619 (67%) | 31 (78%) |
| Drug-resistant epilepsy | | | |
| Yes | 1592/2467 (65%) | 1565/2427 (64%) | 27 (68%) |
| No | 875/2467 (35%) | 862/2427 (36%) | 13 (33%) |
| Missing data | 1/2468 (<1%) | 1/2428 (<1%) | 0 |
| Epilepsy type | | | |
| Focal | 1937 (78%) | 1902 (78%) | 35 (88%) |
| Combined | 86 (3%) | 86 (4%) | 0 |
| Generalised | 442 (18%) | 437 (18%) | 5 (13%) |
| Unknown | 3 (<1%) | 3 (<1%) | 0 |
| Cardiac comorbidities | | | |
| Yes | 163/2460 (7%) | 157/2421 (6%) | 6/39 (15%) |
| No | 2297/2460 (93%) | 2264/2421 (94%) | 33/39 (85%) |
| Missing data | 8/2468 (<1%) | 7/2428 (<1%) | 1/40 (3%) |
| Respiratory comorbidities | | | |
| Yes | 253/2461 (10%) | 246/2422 (10%) | 7/39 (18%) |
| No | 2208/2461 (90%) | 2176/2422 (90%) | 32/39 (82%) |
| Missing data | 7/2468 (<1%) | 6/2428 (<1) | 1/40 (3%) |

(Table 1 continues on next page)

| | Overall cohort (N=2468) | Non-SUDEP (n=2428) | SUDEP or near SUDEP (n=40) |
|---|---|---|---|
| (Continued from previous page) | | | |
| Intellectual disability | | | |
| Yes | 406/2423 (17%) | 396/2384 (17%) | 10/39 (26%) |
| No | 2017/2423 (83%) | 1988/2384 (83%) | 29/39 (74%) |
| Missing data | 45/2468 (2%) | 44/2428 (2%) | 1/40 (3%) |

Data are median (IQR), n (%), or n/N (%) unless otherwise indicated. Age data are provided to two decimal places for paediatric participants younger than 1 year. Percentages might not total 100% due to rounding. SUDEP=sudden unexpected death in epilepsy. *Data are median (minimum to maximum).

***Table 1:*** **Clinical characteristics**

| | Overall (N=1432) | Non-SUDEP (n=1401) | SUDEP or near SUDEP (n=31) |
|---|---|---|---|
| Number of seizures during admission* | | | |
| Generalised convulsive seizures | 1091/3208 (34%) | 1026/2935 (35%) | 65/273 (24%) |
| Non-generalised convulsive seizures | 2117/3208 (66%) | 1909/2935 (65%) | 208/273 (76%) |
| Any arrhythmia?† | | | |
| Yes | 761/1413 (54%) | 734/1382 (53%) | 27/31 (87%) |
| No | 652/1413 (46%) | 648/1382 (47%) | 4/31 (13%) |
| Missing data | 19/1432 (1%) | 19/1401 (1%) | 0 |
| Any postictal generalised EEG suppression?†‡ | | | |
| Yes | 416/560 (74%) | 400/540 (74%) | 16/20 (80%) |
| Duration, s | 38 (27–47) | 37 (27–46) | 49 (44–64) |
| No | 144/560 (26%) | 140/540 (26%) | 4/20 (20%) |
| Missing data | 26/586 (4%) | 23/565 (4%) | 1/21 (5%) |
| Any postictal central apnoea?† | | | |
| Yes | 211/1031 (20%) | 198/1001 (20%) | 13/30 (43%) |
| Duration, s | 14 (9–25) | 13 (9–24) | 21 (14–50) |
| No | 820/1031 (80%) | 803/1001 (80%) | 17/30 (57%) |
| Missing data | 401/1432 (28%) | 400/1401 (29%) | 1/31 (3%) |
| Any ictal central apnoea?† | | | |
| Yes | 353/824 (43%) | 344/799 (43%) | 9/25(36%) |
| Duration, s | 17 (10–28) | 17 (10–27) | 44 (28–49) |
| No | 471/824 (57%) | 455/799 (57%) | 16/25 (64%) |
| Missing data | 608/1432 (42%) | 602/1401 (43%) | 6/31 (19%) |
| Any hypoxaemia?† | | | |
| Yes | 367/375 (98%) | 354/362 (98%) | 13/13 (100%) |
| Duration, s | 62 (35–103) | 62 (35–101) | 69 (40–159) |
| No | 8/375 (2%) | 8/362 (2%) | 0 |
| Missing data | 1057/1432 (74%) | 1039/1401 (74%) | 18/31 (58%) |
| Hypoxaemia severity† | | | |
| $SpO_2$ signal available but no desaturation | 205/573 (36%) | 202/557 (36%) | 3/16 (19%) |
| $SpO_2$ 75–89% | 187/573 (33%) | 180/557 (32%) | 7/16 (44%) |
| $SpO_2$ <75% | 181/573 (32%) | 175/557 (31%) | 6/16 (38%) |
| Missing data | 859/1432 (60%) | 844/1401 (60%) | 15/31 (48%) |
| Postictal posturing† | | | |
| Yes | 59/554 (11%) | 53/534 (10%) | 6/20 (30%) |
| No | 495/554 (89%) | 481/534 (90%) | 14/20 (70%) |
| Missing data | 32/586 (5%) | 31/565 (5%) | 1/21 (5%) |

(Table 2 continues on next page)

| | Overall (N=1432) | Non-SUDEP (n=1401) | SUDEP or near SUDEP (n=31) |
|---|---|---|---|
| (Continued from previous page) | | | |
| Low-frequency power_awake, normalised units | 51 (33–71) | 51 (33–71) | 55 (28–78) |
| Missing data | 264 (19%) | 260 (19%) | 4 (13%) |
| High-frequency power_awake, normalised units | 45 (28–61) | 45 (28–61) | 41 (25–61) |
| Missing data | 276 (19%) | 272 (19%) | 4 (13%) |
| Low-frequency power_sleep, normalised units | 46 (27–65) | 46 (27–64) | 48 (24–75) |
| Missing data | 288 (20%) | 284 (20%) | 4 (13%) |
| High-frequency power_sleep, normalised units | 52 (35–67) | 52 (35–67) | 50 (27–61) |
| Missing data | 298 (21%) | 294 (21%) | 4 (13%) |

Data are n/N (%), n (%), or median (IQR). Percentages may not sum to 100% due to rounding. Postictal generalised EEG suppression data were only available for generalised convulsive seizures. EEG=electroencephalographic. $SpO_2$=peripheral oxygen saturation. SUDEP=sudden unexpected death in epilepsy. *1117 patients, including 1091 (78%) participants without SUDEP and 26 (84%) who died from SUDEP or had a near-SUDEP event, had more than one seizure during EMU admission to an epilepsy monitoring unit; number of seizures can exceed number of patients. †Most severe features of each patient were reported. ‡Feature only encountered in generalised convulsive seizures.

***Table 2:*** **Electroclinical features of patients who had analysable seizures during admission to an epilepsy monitoring unit**

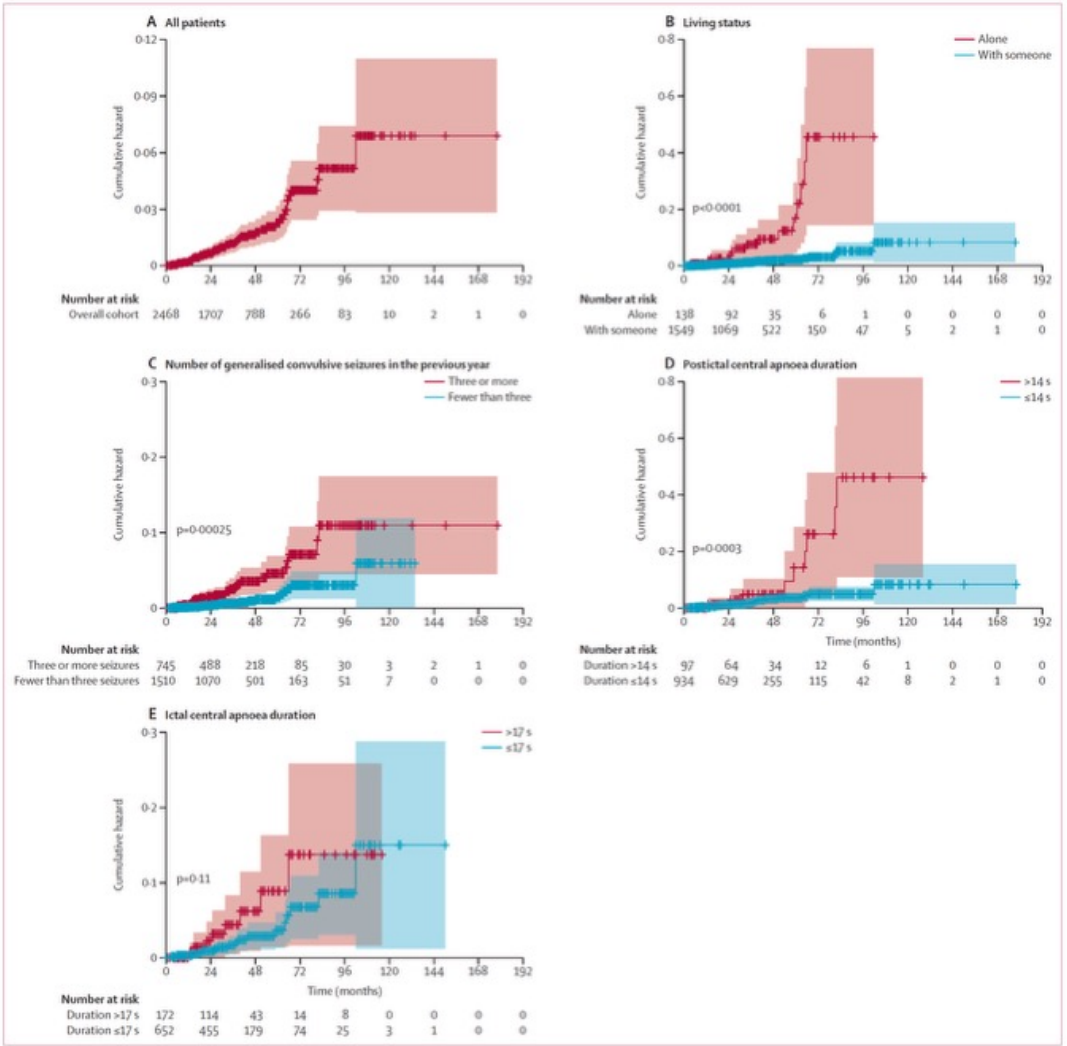



***Figure 2:*** **Cumulative hazard of SUDEP and near SUDEP estimated with the Kaplan–Meier method**
Cumulative hazards are shown for the full cohort (A) and subgroups by living status (B), number of generalised convulsive seizures in the previous year (C), postictal central apnoea duration of 14 s or longer, and ictal central apnoea duration of 17 s or longer (E). Median durations of 14 s and 17 s for postictal central apnoea and ictal central apnoea, respectively (table 2), were used as cutoffs. Shaded areas represent 95% CIs. The graphs are scaled differently to accommodate for differences in CIs.

| | HR (95% CI) | p value* |
|---|---|---|
| Age at epilepsy onset, per 1 year increment | 1·01 (0·99–1·02) | 0·52 |
| Epilepsy duration at baseline, per 1 year increment | 1·01 (0·99–1·04) | 0·21 |
| Sex | .. | 0·10 |
| Female | 1 (ref) | .. |
| Male | 1·68 (0·90–3·13) | .. |
| Living status | .. | <0·0001† |
| Living with someone | 1 (ref) | .. |
| Living alone | 7·62 (3·94–14·71) | .. |
| Number of generalised convulsive seizures in the previous year | .. | 0·0005† |
| <3 | 1 (ref) | .. |
| ≥3 | 3·10 (1·64–5·87) | .. |
| Antiseizure medication | .. | 0·26 |
| Monotherapy | 1 (ref) | .. |
| Polytherapy | 1·53 (0·73–3·21) | .. |
| Drug-resistant epilepsy | .. | 0·40 |
| No | 1 (ref) | .. |
| Yes | 1·33 (0·68–2·58) | .. |
| Cardiac comorbidities | .. | 0·055 |
| No | 1 (ref) | .. |
| Yes | 2·34 (0·98–5·59) | .. |
| Respiratory comorbidities | .. | 0·16 |
| No | 1 (ref) | .. |
| Yes | 1·80 (0·80–4·09) | .. |
| Intellectual disability | .. | 0·35 |
| No | 1 (ref) | .. |
| Yes | 1·41 (0·68–2·89) | .. |
| Any arrhythmia | .. | 0·0028 |
| No | 1 (ref) | .. |
| Yes | 4·96 (1·74–14·2) | .. |
| Postictal central apnoea duration, per 10 s increment | 1·32 (1·14–1·54) | 0·0002† |
| Ictal central apnoea duration, per 10 s increment | 1·11 (1·05–1·18) | 0·0001† |
| Postictal generalised EEG suppression duration, per 10 s increment | 1·12 (1·03–1·22) | 0·0071 |
| Total hypoxaemia duration, per 10 s increment | 1·03 (0·95–1·12) | 0·45 |
| Postictal posturing | .. | 0·013 |
| No | 1 (ref) | .. |
| Yes | 3·36 (1·29–8·77) | .. |
| Low-frequency power_awake | 1·00 (0·99–1·02) | 0·76 |
| High-frequency power_awake | 1·00 (0·98–1·01) | 0·74 |
| Low-frequency power_sleep | 1·01 (0·99–1·02) | 0·45 |
| High-frequency power_sleep | 0·99 (0·98–1·01) | 0·46 |

HRs were estimated with individual Cox proportional hazards models (one per risk factor). No estimates were available for participants who were not treated with antiseizure medication as SUDEP did not occur in this subgroup. EEG=electroencephalographic. HR=hazard ratio. SUDEP=sudden unexpected death in epilepsy. *Uncorrected p values. †Remained significant after Bonferroni correction.

***Table 3:*** **HRs for SUDEP**

| | Adjusted HR (95% CI), no covariate adjustment | HR (95% CI), adjusted for treatment centre | HR (95% CI), adjusted for centre, age of onset, epilepsy duration, and sex |
|---|---|---|---|
| Living condition | | | |
| Living with someone | 1 (ref) | 1 (ref) | 1 (ref) |
| Living alone | 8·25 (3·39–20·10) | 7·71 (3·08–19·30) | 9·07 (3·17–25·90) |
| Number of generalised convulsive seizures in the previous year | | | |
| <3 | 1 (ref) | 1 (ref) | 1 (ref) |
| ≥3 | 2·75 (1·10–6·88) | 2·76 (1·10–6·94) | 2·84 (1·12–7·23) |
| Postictal central apnoea duration, per 10 s increment | 1·04 (0·82–1·33) | 1·03 (0·80–1·32) | 1·05 (0·81–1·36) |
| Ictal central apnoea duration, per 10 s increment | 1·09 (1·01–1·17) | 1·10 (1·01–1·19) | 1·07 (0·98– 1·16) |

Raw CIs are reported. HR=hazard ratio. SUDEP=sudden unexpected death in epilepsy.

***Table 4:*** **Adjusted HRs for SUDEP predictors**

## Research in context

### Evidence before this study

Sudden unexpected death in epilepsy (SUDEP) occurs primarily in people with drug-resistant epilepsy who have generalised convulsive seizures. Active epilepsy with generalised convulsive seizures, frequent seizures of this type, and living alone status have been identified as important risk factors in retrospective studies. Seizure-related electroclinical phenomena, namely post-convulsive breathing cessation, bradyarrhythmias, and postictal general electroencephalographic (EEG) suppression, have been observed in a retrospective case series of patients with epilepsy who died while being monitored in epilepsy monitoring units. Such cardiorespiratory and EEG phenomena can occur premortem in habitual seizures. Peri-ictal central apnoea can manifest as ictal central apnoea and/or postictal central apnoea, both of which have been implicated in the pathogenesis of SUDEP. Because SUDEP is a rare phenomenon, occurring in about one in 1000 patients with epilepsy annually, sufficiently powered prospective studies to identify electroclinical risk markers for SUDEP have been cost prohibitive. This lack of studies has hindered precise risk stratification of individuals with epilepsy, development of pathogenesis-targeted interventions, and randomised clinical trials for SUDEP prevention.

### Added value of this study

This study was the first prospective, observational, multicentric cohort study of SUDEP in people with epilepsy who were undergoing multimodality assessments (including video-EEG and cardiorespiratory measurements) of their seizures in an epilepsy monitoring unit and had long-term follow-up. The unique value of the study lies in its large-scale prospective recruitment of individuals with epilepsy, its use of cardiorespiratory monitoring (including oximetry, breathing rate, and multichannel electrocardiogram), and identification of 40 cases of ascertained SUDEP and near SUDEP. This study is, to our knowledge, the first to prospectively observe SUDEP outcomes in individuals found to have cardiorespiratory dysfunction, in the form of peri-ictal central apnoea and peri-ictal cardiac arrhythmia, specific seizure semiological features such as postictal posturing, and postictal generalised EEG suppression. Of these features, prolonged ictal central apnoea and prolonged postictal central apnoea were particularly associated with SUDEP. The study also prospectively acquired evidence supporting previous retrospective observations of the risk posed by frequent, active generalised convulsive seizures and living alone status.

### Implications of all the available evidence

In addition to the presence and frequency of generalised convulsive seizures and living alone status as SUDEP risk factors, this study identified specific, clinically identifiable peri-ictal respiratory risk markers. Importantly, this study provides evidence for the development of a validatable SUDEP risk index based on these risk markers to precisely identify those most at risk of death, enabling heightened observation and monitoring of such individuals, with proactive treatment changes to reduce seizure frequency. Furthermore, peri-ictal central apnoeas, which occur more frequently than SUDEP, could serve as surrogate markers of SUDEP in preventive clinical trials, thereby reducing cost and increasing feasibility. Lastly, this study paves the way for potential future interventions that target breathing rescue, whether pharmacological or mechanical, to prevent SUDEP.

# Shigellosis

*Shigella* is a Gram-negative, facultative intracellular, gastric acid-resistant bacterium of the Enterobacteriaceae family, which includes four serogroups: *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, and *Shigella boydii*. Globally, shigellosis is the most common cause of invasive bloody diarrhoea in children younger than 5 years. Humans are the only natural reservoir and an inoculum of only 10–100 organisms is required for infection. Rising antibiotic resistance rates increasingly reduce the ability to adequately treat severe disease. The prevention of infection with vaccination and sanitation strategies remains a crucial step in reducing worldwide morbidity and mortality.

| | Approximate turnaround time to result (h) | Technology |
|---|---|---|
| RidaGene-kits (R-Biopharm, Darmstadt, Germany) | 1·5 | Multiplex real-time PCR |
| EntericBio real-time Gastro Panel I (Serosep, Limerick, Ireland) | 1·5 | Multiplex real-time PCR |
| Seeplex Diarrhea ACE detection (Seegene, Seoul, South Korea) | 10·0 | Multiplex real-time PCR |
| xTAG gastrointestinal pathogen panel (Luminex, Austin, TX, USA) | 5·0 | Multiplex real-time PCR and suspension array detection |
| CLART EnteroBac (Tabasmed, Tehran, Iran) | 5·0 | Multiplex PCR and array detection |
| Filmarray gastrointestinal panel (Biofire, Salt Lake City, UT, USA) | 1·0 | Nested PCR, multiplex real-time PCR, and melting curve analysis |

***Table 1:*** **Commercially available molecular tests that include *Shigella* spp**

## *Panel:* Recommendations to prevent the spread of *Shigella* as per the US Centers for Disease Control and Prevention[3,73]

- Wash hands with soap and water (including parents, children, and caretakers) for at least 20 s after using the bathroom, changing nappies, or assisting anyone in the bathroom
- Avoid preparing food for others during illness
- Avoid swimming during illness
- Attempt to stay home during illness and if working in health care, childcare, or food service industries, follow guidance from the local health department on returning to work
- Children should not attend childcare, school, or group activities while having active diarrhoea and follow local health department guidelines on when it is safe to resume these activities
- Wait to have sex until 1 week after diarrhoea stops. When sex resumes, wash body and hands after sex and use barrier condoms

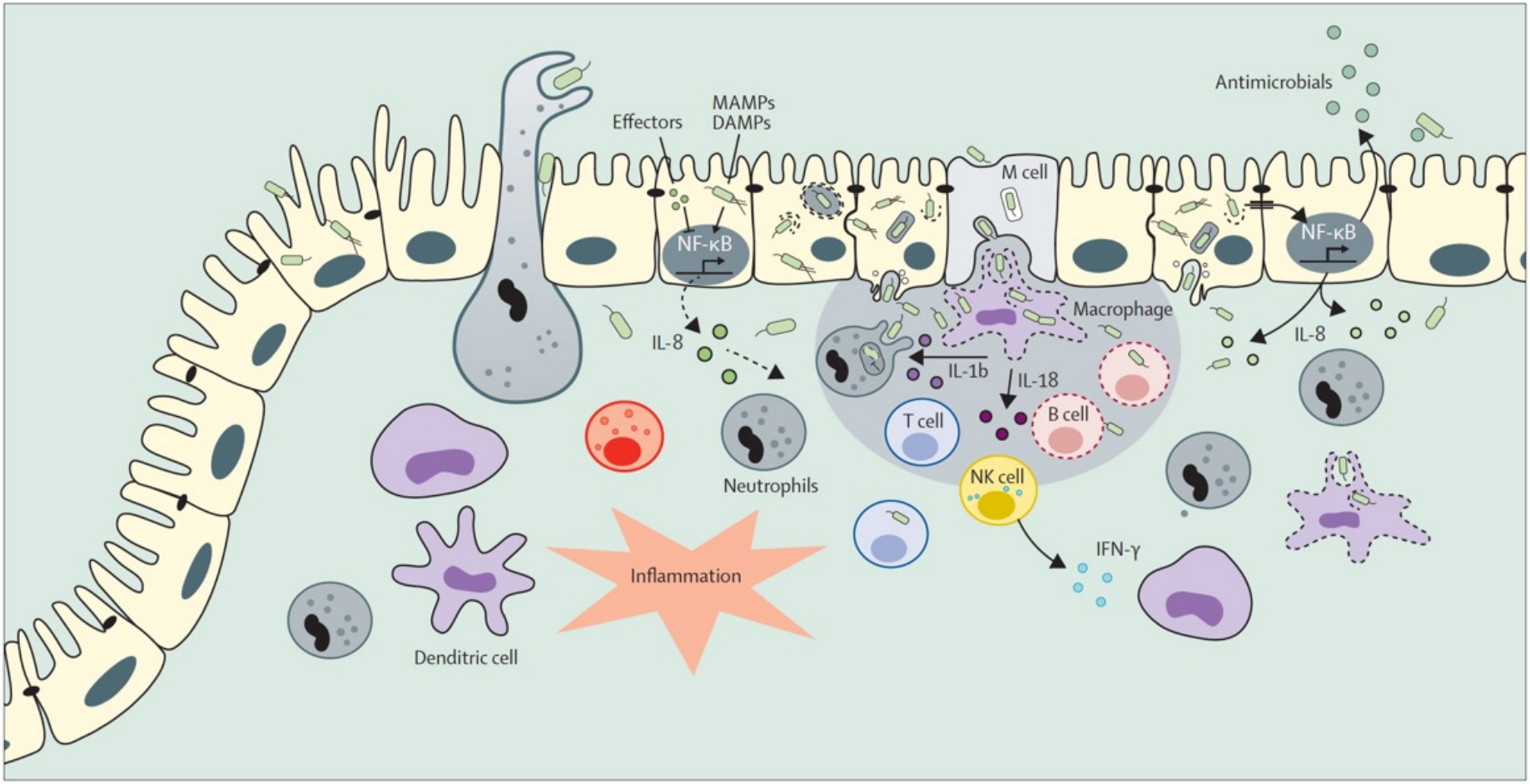



***Figure:*** **The immunopathogenesis of *Shigella* infection in the colon**

MAMPs=microbe-associated molecular patterns. DAMPs=damage-associated molecular patterns. NK=natural killer. Adapted from Schnupf and Sansonetti.[82]

| | Composition | Serotype, serogroup, or strain | Most recent clinical studies and findings |
|---|---|---|---|
| **Attenuated** | | | |
| WRSs2 and WRSs3[128,129] | Δ*virG*, *senA*, and *senB* genes | *S sonnei* Moseley | Completed phase 1 trial in healthy adult participants in the USA (no safety concerns, induced robust and functional serotype-specific anti-LPS antibodies, response correlated with faecal shedding) |
| ShigETEC[130,131] | Δ*rfbF*, *ipaBC*, and *setBA* expressing fusion protein B subunit of ETEC | *S flexneri 2a* 2457T | Completed phase 1 trial in healthy adults in Hungary (no safety concerns, induced robust and functional serotype-specific anti-ShigETEC and anti-LTB antibodies, response correlated with faecal shedding) |
| **Subunit** | | | |
| S4V-EPA[127] | OAg-EPA conjugate | *S sonnei*; *S flexneri* 2a; *S flexneri* 3a; *S flexneri* 6 | Monovalent version (Flexyn2a-EPA) completed phase 1 and 2b (CHIM) in healthy adults in the USA (no safety concerns, robust and functional anti-2a serum IgG response); quadrivalent S4V currently undergoing phase 2 study in Kenya and CHIM study in the USA |
| SF2a-TT15[132–134] | OAg-TT conjugate | *S flexneri* 2a | Completed phase 1 study in Israeli healthy adults (no safety concerns, induced high titre of anti-SF2a LPS IgG antibodies); currently undergoing a dose-finding study in Kenya and CHIM study in the USA |
| ZF0901[135,136] | OAg-TT conjugate | *S sonnei*; *S flexneri* 2a | Completed preliminary phase 1 study in an age-descending order from adults to infants aged 3 months (no safety concerns); completed phase 2 safety and immunogenicity RCT in children aged 3 months to 5 years (robust serotype-specific anti-LPS IgG levels); currently undergoing phase 3 trial in China and Bangladesh |
| altSonflex1–2-3[135,136] | OAg in GMMA | *S sonnei*; *S flexneri* 2a; *S flexneri* 3a; *S flexneri* 1b | Completed phase 1 of a two-stage phase 1/2 RCT in European healthy adults (no safety concerns, induced robust and functional serotype-specific anti-LPS antibodies) |
| $Invaplex_{AR\text{-}Detox}$[119,137] | Ipp proteins and LPS with artificial InvaPlex | Conserved IpaB and IpaC; *S flexneri 2a* 2457T | Completed phase 1 trial in adult participants in the USA (no safety concerns; high anti-LPS, anti-IpaB, and anti-IpaC antibody IgG titres); currently recruiting for phase 1a/1b dose-escalation RCT trial using vaccine adjuvanted with dmLT in healthy Dutch and Zambian adults |

*S*=*Shigella*. ETEC=enterotoxigenic *Escherichia coli*. OAg=O antigen. EPA=exotoxin A of *Pseudomonas aeruginosa*. TT=tetanus toxoid. CDC=Centers for Disease Control and Prevention. GMMA=generalised modules for membrane antigens. Ipa=invasion plasmid antigen. LPS=lipopolysaccharide. RCT=randomised controlled trial. dmLT=double mutant enterotoxigenic *Escherichia coli* heat-labile toxin. CHIM=controlled human infection model. Δ=deletion. LTB=heat-labile toxin B subunit.

***Table 2:*** **Shigella vaccine candidates furthest along in development**

## Controversies and outstanding research questions

The increased sensitivity of qPCR-based multipathogen diagnostic panels for diarrhoeal illness has revealed a larger burden of disease than previously recognised, as well as identifying asymptomatic qPCR-positive infections and co-infections. The clinical significance of these findings needs to be better understood and their existence considered in the design of vaccine and surveillance trials for shigellosis.[61,148]

With the rise of multidrug-resistant strains of *Shigella* limiting the ability to treat infection, particularly with oral antibiotics in low-resource settings, there is an even greater demand to develop preventive strategies for infection. Improved access to clean water, sanitation, and hygiene can substantially reduce morbidity and mortality due to diarrhoeal diseases, particularly in LMICs; however, developing the associated infrastructure is costly and can be difficult to achieve, being closely linked to the economic growth of the country itself. Vaccination remains the most promising approach for a practical, cost-effective, sustainable, and long-lasting means to prevent these diseases.

Vaccine development against *Shigella* spp has proven to be challenging for several reasons: observational and experimental studies have shown that immunity to shigellosis is serotype specific (based on the O polysaccharide antigen of lipopolysaccharides in the outer membrane) and there are about 50 distinct serotypes. Therefore, exposure to one serotype does not protect against another serotype. A desirable balance between reactogenicity and immunogenicity is difficult to achieve, particularly in young children (aged <5 years) living in *Shigella*-endemic countries.

The majority of the live attenuated *Shigella* vaccines tested to date have been designed to induce serotype-dependent immune response. Thus, to generate protection against commonly circulating strains globally, multiple strains would be required in single-dose vaccines, which can be a major challenge.[12,152,153] Based on the GEMS, a multivalent vaccine including *S flexneri* 2a, 3a, and 6, in addition to *S sonnei*, would provide direct protection against at least 72% of circulating strains and cross protection for up to 89% of strains.[154] Other challenges include, but are not limited to, the minimal amount of suitable small animal models, little understanding of host protection mechanisms, and the ability of *Shigella* to subvert the host innate and adaptive immune responses.[124] Lastly, although there are observational and clinical trial studies that show correlates of protection against shigellosis, particularly with regard to serum IgG anti-lipopolysaccharide,[133,155–157] there is little consensus on the crucial immunological correlates of protection, which reduces comparisons across studies.[141,158]

# The future of type 1 diabetes therapy

The treatment of type 1 diabetes is entering a transformative era. Teplizumab, the first immunotherapy treatment to delay the onset of clinical type 1 diabetes, has been approved by the US Food and Drug Administration. Other immune-based therapies show promise in preserving β-cell function. Public health screening using islet autoantibodies is expanding, enabling earlier diagnosis, reducing diabetic ketoacidosis, and allowing timely introduction of disease-modifying treatments before the need for insulin therapy. β-cell replacement is shifting from traditional transplantation of organ donor islets and the pancreas to stem cell-derived β cells. Bioengineering methods, such as encapsulation, and gene editing to create hypoimmune cells could reduce the need for immunosuppression that has hampered β-cell replacement, and patient-derived stem cells open doors to personalised therapies. Although these innovations have been made available to a small number of patients, scaling them to widespread use remains a challenge. Meanwhile, glucose regulation is improving through the use of automated insulin delivery systems that combine glucose monitoring with insulin pumps. New-generation insulins (those that are ultrarapid, ultralong, and glucose-responsive) improve outcomes by minimising blood sugar fluctuations. Together, these breakthroughs offer renewed hope for improving long-term management and quality of life for people living with type 1 diabetes.

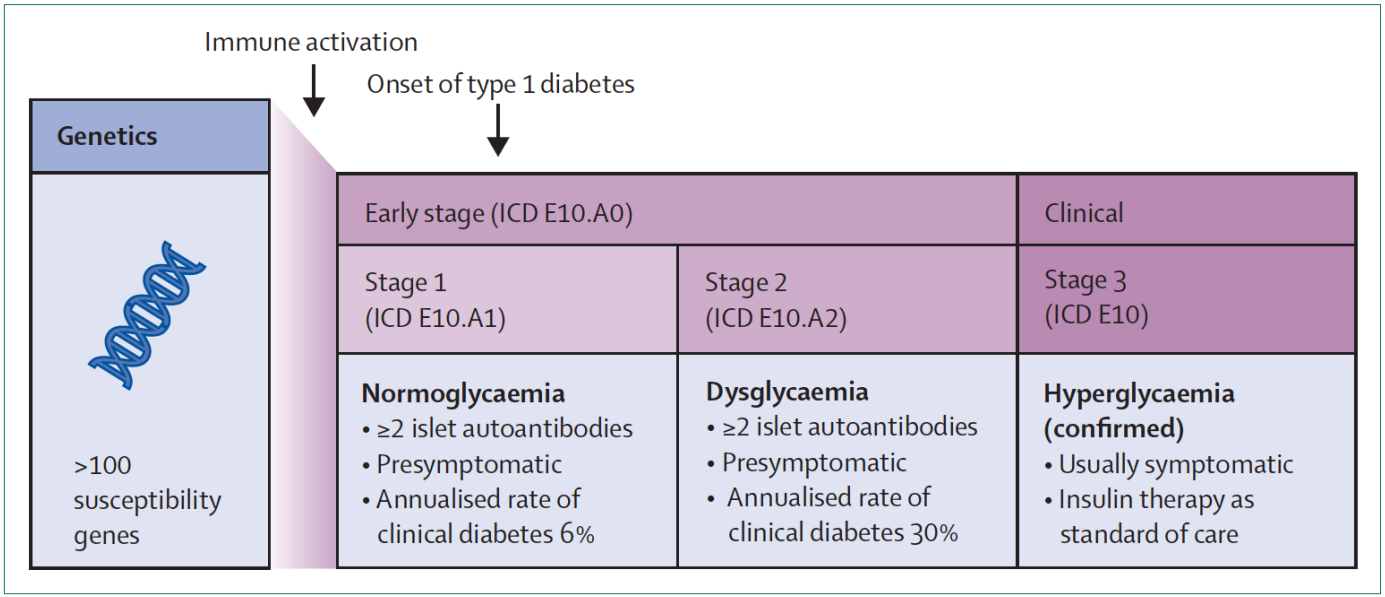



***Figure 1:*** **Stages of type 1 diabetes**

Stage 1 and stage 2 are presymptomatic periods of islet autoimmunity and distinguished by glycaemic criteria. Stage 3 diabetes is the onset of clinical disease. Individuals with stage 3 diabetes usually have diabetes-related symptoms and require insulin. Of individuals identified with presymptomatic diabetes, approximately 85% have stage 1 and 15% stage 2.[4] Normoglycaemia and hyperglycaemia are defined by standard glycaemic criteria.[4,5] Hyperglycaemia is characterised by a fasting plasma glucose of ≥126 mg/dL (7·0 mmol/L), 2-hour oral glucose tolerance test score of ≥200 mg/dL (11·1 mmol/L), $HbA_1c$ measurement ≥6·5% (≥48 mmol/mol), or, in patients with symptoms of hyperglycaemia, a random glucose concentration of ≥200 mg/dL (11·1 mmol/L). Dysglycaemia is defined by impaired fasting plasma glucose of 100–125 mg/dL (5·6–6·9 mmol/L), impaired 2-hour glucose of 140–199 mg/dL (7·8–11·0 mmol/L), high glucose concentrations at intermediate time points on the oral glucose tolerance test (30 min, 60 min, and 90 min measurements of ≥200 mg/dL [11·1 mmol/L]), $HbA_1c$ concentration of 5·7–6·4% (39–47 mmol/mol), or ≥10% increase in $HbA_1c$ concentration.

### *Panel 1:* Key considerations for prescribers

**Overview**

In the past 5 years, substantial advancements have been made in the treatment of type 1 diabetes, including breakthroughs in screening and diagnosis, disease-modifying therapies, β-cell replacement via stem cells, new insulin formulations and delivery, and adjunctive treatments. Health equity and new treatments intersect at the crucial goal of ensuring all individuals with diabetes have access to these innovative treatments for diabetes regardless of race, income or insurance status.

Screening for islet autoantibodies is recommended for healthy individuals at increased disease risk, such as relatives of people with type 1 diabetes. Certified tests for islet autoantibodies, international consensus guidelines, and master protocols on screening and monitoring early-stage type 1 diabetes are available, with screening increasingly applied to children in the general population.

**Disease-modifying therapies**

Teplizumab is approved by the US Food and Drug Admistration (FDA) for delaying the clinical onset of type 1 diabetes in individuals aged 8 years and older with advanced (stage 2) early-stage type 1 diabetes in the USA, and is available through compassionate use programmes in Germany, France, Belgium, Spain, and the UK.

Few β-cell replacement options that include allogeneic transplantation for defined indications and stem cell-based cell therapy are available within clinical trials at selected sites.

**New-generation insulins**

In the past 20 years, innovations have focused on faster absorption and action, prolonged duration, and glucose-responsive properties. Ultrarapid-acting insulins offer improved post-meal control and improved performance in automated insulin delivery (AID) systems. Longer-acting, once-weekly basal insulins reduce daily injection burdens and improve treatment adherence.[4]

**Adjunctive treatments**

Adjunctive treatments can help improve metabolic control and prevent complications, but important questions about their risk-to-benefit profile limit regulatory approval. The amylin analogue pramlintide is the only US FDA-approved adjunctive therapy for type 1 diabetes. Although pramlintide offers weight loss and glucagon inhibition, it is not widely used for treatment of type 1 diabetes given the burden of injections and the risk of hypoglycaemia. SGLT2 inhibitors are associated with a statistically significant increased risk of ketoacidosis.[5]

**AID systems**

AID systems reduce glycated haemoglobin concentrations and improve time in range in people with type 1 diabetes. These systems have proven to be safe and effective when used from the point of diagnosis and during pregnancy together with adequate training and clinical support.[6] Next-generation AID systems that offer smaller devices, longer wear times, better connectivity, and increased precision are expected to reduce the burden faced by people with type 1 diabetes.

| | | | | | |
|---|---|---|---|---|---|
| **Stage 3** | | | | | |
| Abatacept,[19] CTLA4-Ig (TN09) | IV infusions on days 1, 14, 28, and then monthly over 2 years | 112 | 6–45 years | Higher stimulated C-peptide at 2 years (p=0·0029) | $HbA_{1c}$ over 2 years (p=0·007) |
| ATG–GCSF[20,21] | IV infusions of low-dose ATG or ATG followed by SC GCSF biweekly for 12 weeks | 89 | 12–45 years | Higher stimulated C-peptide at 1 year in ATG (p=0·0003) and in ATG–GCSF (p=0·031) | $HbA_{1c}$ at 1 year in ATG (p=0·002), in ATG–GCSF (p=0·011) |
| ATG[22] | IV infusions on 2 consecutive days | 117 | 5–25 years | Higher stimulated C-peptide at 1 year with 2·5 mg/kg dose (p=0·003) and with 0·5 mg/kg dose (p=0·014) | HbA1c at 1 year with 0·5 mg/kg dose (p=0·024) |
| Baricitinib,[23] JAK inhibitor (BANDIT) | Oral, once daily for 48 weeks | 91 | 10–30 years | Higher stimulated C-peptide at 48 weeks (p=0·001) | NA |
| GAD-alum[24] | SC injections on days 1 and 30 | 70 | 10–18 years | Higher fasting C-peptide at 15 months (no significant effect) | Fasting C-peptide at 30 months (p=0·045), stimulated C-peptide at 15 months (p=0·01) and 30 months (p=0·04) |
| GAD-alum[25] (TN08) | Two or three SC injections at weeks 0, 4, and 12 | 145 | 3–45 years | Higher stimulated C-peptide at 1 year (no significant effect) | NA |
| GAD-alum,[26] vitamin D (DIAGNODE-2) | Three intralymphatic injections on days 30, 60, and 90, plus oral vitamin D (2000 IE) for 4 months daily from day 1 | 109 | 12–24 years | Higher stimulated C-peptide at 15 months (no significant effect; p=0·50) | Stimulated C-peptide sub-analysis in HLA DR3-DQ2 subgroup (p=0·0078), insulin dose-adjusted $HbA_{1c}$ (p=0·031) |
| Golimumab,[27] TNF inhibitor (T1GER) | SC injections fortnightly for 52 weeks | 84 | 6–21 years | Higher stimulated C-peptide at week 52 (p<0·001) | Less increase in insulin dose over 52 weeks (p=0·001) |
| Imatinib,[28] tyrosine kinase inhibitor | Oral, once daily for 26 weeks | 64 | 18–45 years | Higher stimulated C-peptide at 12 months (90% CI −0·003 to 0·191, p=0·048) | NA |
| Pleconaril and ribavirin,[29,30] antiviral (DiViDInt) | Oral pleconaril and ribavirin, twice daily for 6 months | 96 | 6–15 years | Higher stimulated C-peptide at 12 months (p=0·037; no effect after 2 years) | $HbA_{1c}$ at 3 and 6 months (p<0·0001), no effect after 2 years |
| Rituximab,[31] anti-CD20 (TN05) | IV infusions at weeks 0, 1, 2, and 3 | 87 | 8–40 years | Higher stimulated C-peptide at 12 months (p=0·03); C-peptide over all time points (p<0·001) | $HbA_{1c}$ over the 12 months (p<0·001), insulin dose (p<0·001) |
| Teplizumab,[32] anti-CD3 (PROTECT) | IV infusions (12 days) at weeks 1 and 26* | 328 | 8–17 years | Higher stimulated C-peptide at week 78 (p<0·001) | NA |
| Teplizumab,[33,34] anti-CD3 (Protégé) | IV infusions (6 full dose, or 14 days low dose or high dose) | 516 | 8–35 years | Lower composite of insulin use <0·5 units per kg/day and $HbA_{1c}$ <6·5% at year 1 (no significant effect) | Stimulated C-peptide at 2 years in full-dose 14-day course (p=0·027) |
| Ustekinumab,[35] IL-12 and IL-23 inhibitor (USTEK1D) | SC injections at weeks 0, 4, 12, 20, 28, 36 and 44 | 72 | 12–18 years | Higher stimulated C-peptide at 12 months (p=0·02) | NA |
| Verapamil,[36] calcium channel blocker | Oral, once daily for 12 months | 24 | 18–44 years | Higher stimulated C-peptide at 3 months (p=0·033) and 12 months (p=0·038) | Total daily dose of insulin at 12 months (p=0·031) |
| Verapamil,[37] calcium channel blocker (CLVer) | Oral, once daily for 12 months (60 mg/day or 120 mg/day with dose escalation) | 88 | 7–17 years | Higher stimulated C-peptide at 52 weeks (p=0·04) | NA |
| **Stage 2** | | | | | |
| Teplizumab,[38] anti-CD3 (TN10) | IV infusions on 14 consecutive days | 76 | 8–45 years | Lower rates of stage 3 type 1 diabetes (p=0·006), average delay of 24 months | NA |
| **Stage 1** | | | | | |
| Abatacept,[39] CTLA4-Ig (TN18) | IV infusions at 0, 2, 4 and weeks, and then monthly for 12 months | 212 | 6–45 years | Lower rates of AGT or stage 3 type 1 diabetes (p=0·11) | Stimulated C-peptide at 12 months (p=0·03) |
| Intranasal insulin (DIPP)[39] | Intranasal, daily for median 1·8 years (IQR 0·9–7) | 264 | 1–15 years | Lower rates of stage 3 type 1 diabetes (HR 0·98, 95% CI 0·67–1·43, p=0·91) | NA |
| Oral insulin[40] (DPT-1) | Oral (7·5 mg), daily for median 4·3 years (IQR 2·5–5·5) | 372 | 3–45 years | Lower rates of stage 3 type 1 diabetes (HR 0·764, 95% CI 0·51–1·14, p=0·189) | Subgroup with IAA ≥80 nU/mL (HR 0·57, 95% CI 0·36–0·89, p=0·015) |
| Oral insulin[40] (TN07) | Oral (7·5 mg), daily for median 2·7 years (IQR 1·5–4·6) | 389 | 3–45 years | Lower rates of stage 3 type 1 diabetes (HR 0·87, 95% CI 0·1–2, p=0·21) | Secondary stratum with low first-phase insulin secretion (HR 0·45, 95% CI 0·0·82, p=0·006) |

(Table 1 continues on next page)

| | Treatment | Participants | Age | Primary outcome *vs* placebo (effect size, if applicable) | Other effects (effect size, if applicable) |
|---|---|---|---|---|---|
| (Continued from previous page) | | | | | |
| **Before islet autoimmunity** | | | | | |
| Oral insulin[42] (POInT) | Oral (7·5 mg for 2 months, then 22·5 mg for 2 months, then 67·5 mg until third birthday), daily for a median of 2·5 years (IQR 2·45–2·55) | 1050 | 4–7 months | Data soon to be reported | Data soon to be reported |

Trial names are listed in the first column in parentheses if available. AGT=abnormal glucose tolerance. ATG=anti-thymocyte globulin. GAD-alum=GAD formulated with aluminium hydroxide. GCSF=granulocyte colony-stimulating factor. $HbA_{1c}$=glycated haemoglobin. HR=hazard ratio. IAA=insulin autoantibody. IE=international unit. IV=intravenous. JAK=Janus kinase. NA=not applicable. SC=subcutaneous. *Participants who were unable to receive the second 12-day course due to COVID-19 pandemic restrictions were given the second course at the week 52 visit.

***Table 1:*** **Summary of major randomised placebo-controlled clinical trials for drugs aiming to prevent or delay islet autoantibodies, the loss of β-cell function, or clinical type 1 diabetes**

| | Trial name, if available (registration number) | Treatment administration | Participants | Inclusion criteria | Primary outcome |
|---|---|---|---|---|---|
| **Stage 3** | | | | | |
| Abatacept (CTLA4-Ig), nasal insulin *vs* placebo | IAA (NCT05742243) | SC weekly or nasal 10 days daily and twice weekly | 62 | Age 6–21 years, random C-peptide >0·3 pmol/mL, stage 3 ≤100 days, and weight ≥20 kg | Stimulated C-peptide at week 48 |
| Abrocitinib (JAK inhibitor) and ritlecitinib (JAK inhibitor) *vs* placebo | JAKPOT T1D (TN31) (NCT05743244) | Oral daily | 78 | Age 12–35 years, stimulated C-peptide >0·2 pmol/mL, and stage 3 ≤100 days | Stimulated C-peptide AUC at week 52 |
| ATG and verapamil *vs* placebo | (NCT06455319) | IV days 1 and 2, or oral daily | 60 | Age 6–35 years, stimulated C-peptide >0·2 pmol/mL, and stage 3 ≤100 days | Stimulated C-peptide AUC at week 26 and 52 |
| ATG, verapamil, or golimumab (anti-TNF) *vs* placebo | T1D-PLUS (IRAS ID 1006723) | Oral daily, IV 2 days, oral, or SC | Adaptive | Age 18–44 years and stage 3 <90 days | Stimulated C-peptide AUC at week 52 |
| CNP-103 (autoantigen nanoparticles) *vs* placebo | (NCT06783309) | IV on days 1, 8, and 90 | 36 | Age 12–35 years, stimulated C-peptide ≥0·2 pmol/mL, and stage 3 <180 days | Safety |
| DFMO (polyamine biosynthesis inhibitor) *vs* placebo | TADPOL (NCT05594563) | Oral twice daily | 70 | Age 4–40 years, non-fasting C-peptide >0·2 pmol/mL, and stage 3 <100 days | Stimulated C-peptide AUC at week 26 |
| Diamyd ($rhGAD_{65}$), colecalciferol *vs* placebo | DIAGNODE-3 (NCT05018585) | Intralymphatic on days 0, 30, and 60, and oral daily | 330 | Age 12–28 years, fasting C-peptide ≥0·12 pmol/mL, stage 3 ≤6 months, and HLA DR3-DQ2 | Stimulated C-peptide AUC at week 104 |
| Frexalimab (anti-CD40L) *vs* placebo | FABULINUS (NCT06111586) | IV day 1, SC bi-weekly | 192 | Age 12–35 years, random C-peptide ≥0·2 pmol/mL, and stage 3 <90 days | Stimulated C-peptide AUC at week 52 |
| NNC0361-0041 (rh pre-proinsulin, TGF-β1, IL-10, and IL-2 plasmid) *vs* placebo | TOPPLE T1D (TN27) (NCT04279613) | SC once weekly | 48 | Age 18–45 years, stimulated C-peptide >0·2 pmol/mL, and stage 3 <48 months | Safety |
| Rituximab-pvvr (anti-CD20), abatacept (CTLA-4 Ig) *vs* placebo | T1D RELAY (TN25) (NCT03929601) | IV 4 weekly doses, SC weekly | 74 | Age 8–45 years, stimulated C-peptide of >0·2 pmol/mL, and stage 3 ≤100 days | Stimulated C-peptide response at week 104 |
| SAR442970 (dual anti-TNF and anti-OX40L nanobody) *vs* placebo | T1D OBTAIN (NCT06812988) | SC | 84 | Age 12–35 years, random C-peptide ≥0·2 pmol/mL, and stage 3 ≤90 days | Stimulated C-peptide AUC at week 26 |
| Verapamil *vs* placebo | Ver-A-T1D (NCT04545151) | Oral daily | 138 | Age 18–44 years, fasting C-peptide ≥0·1 pmol/mL, and stage 3 ≤6 weeks | Stimulated C-peptide AUC at week 52 |
| **Stage 2** | | | | | |
| ATG *vs* placebo | ATG (TN28) (NCT04291703) | IV days 1 and 2 | 101 | Age 6–34 years, multiple islet autoantibodies, and dysglycaemia | Stage 3 |
| Liraglutide (GLP-1 receptor agonist) *vs* placebo | INVESTDIA (NCT02898506) | SC daily | 10 | Age 10–30 years, multiple islet autoantibodies, and dysglycaemia | β-cell function (first-phase insulin response during 10 min IVGTT at week 52) |
| **Stage 1** | | | | | |
| Liraglutide (GLP-1 receptor agonist) *vs* placebo | INVESTDIA (NCT02611232) | SC daily | 10 | Age 18–30 years, multiple islet autoantibodies, and normoglycaemia | β-cell function (first-phase insulin response during 10 min IVGTT at weeks 26 and 104) |
| Oral insulin (67·5 mg) *vs* placebo | Fr1da (NCT02620072) | Oral daily | 220 | Age 2–12 years, multiple islet autoantibodies, and normoglycaemia | Dysglycaemia or diabetes, composite of $CD4^+$ T cell or antibody response to insulin |
| **Before islet autoimmunity** | | | | | |
| *Bifidobacteria infantis* EVC001 *vs* placebo | GPPAD-SINT1A (NCT04769037) | Oral daily | 1149 | Age 7 days to 6 weeks and >10% genetic risk for islet autoantibodies by age 6 years | Multiple islet autoantibodies or diabetes |
| COVID-19 vaccine *vs* placebo | GPPAD-AVAnT1A (NCT06452654) | IM, 3 single doses | 2252 | Age 3–4 months and >10% genetic risk for islet autoantibodies by age 6 years | Multiple islet autoantibodies or diabetes |

ATG=anti-thymocyte globulin. AUC=area under the curve. IV=intravenous. IL=intralymphatic. IM=intramuscular. IV=intravenous. IVGTT=intravenous glucose tolerance test. JAK=Janus kinase. rh=recombinant human. SC=subcutaneous.

***Table 2:*** **Ongoing clinical trials for preventing and delaying the loss of β-cell function**

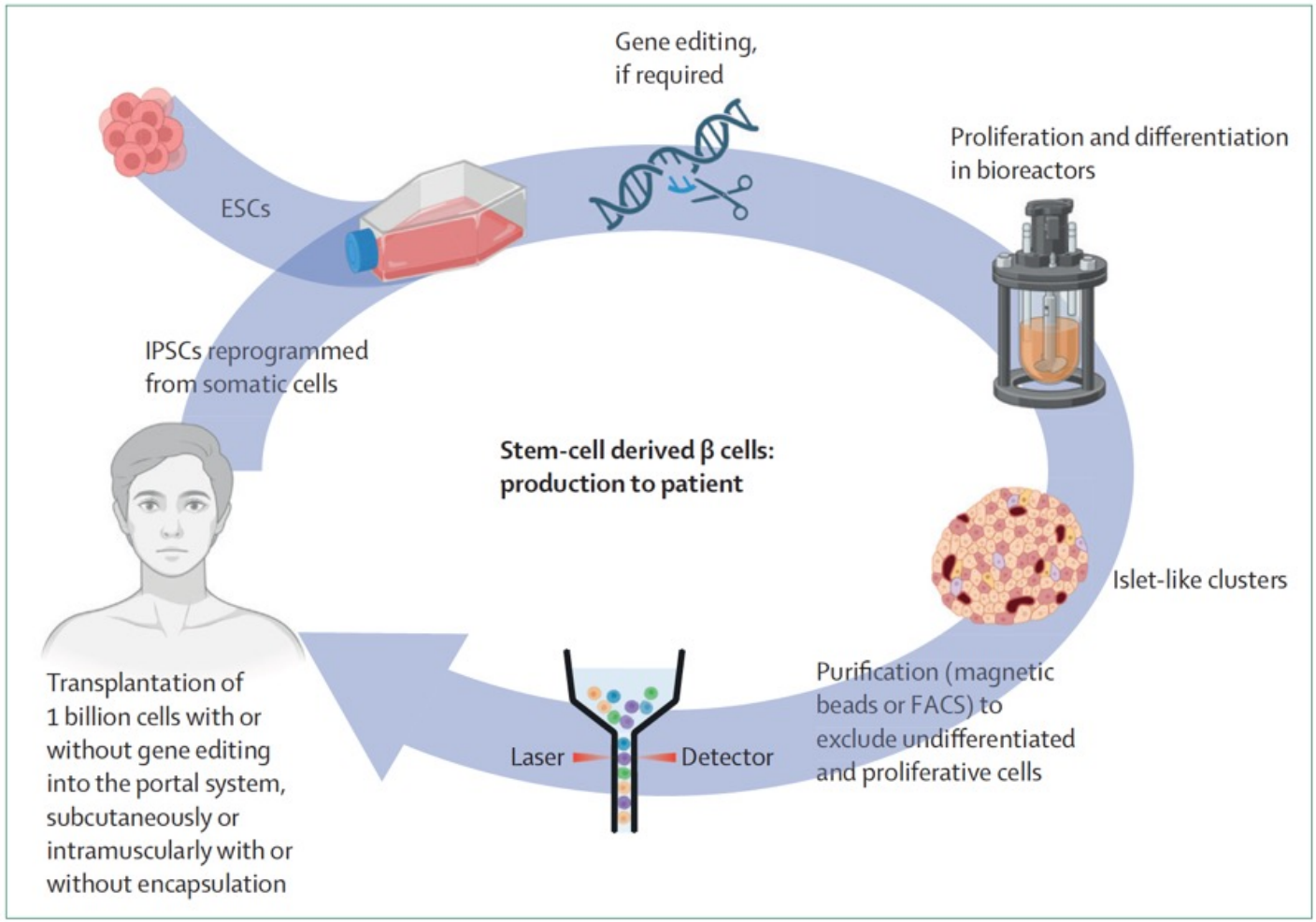



***Figure 2:*** **Production and transplantation of β cells derived from embryonic or induced pluripotent stem cells**
ESCs=embryonic stem cells. FACS=fluorescence-activated cell sorter. IPSCs=induced pluripotent stem cells.

| | Affiliated company | Trial registration number | Immunosuppression | Indication | Site | Origin |
|---|---|---|---|---|---|---|
| Vertex-880 | Vertex (Boston, MA, USA) | NCT04786262 | Full | Hypoglycaemia | Portal vein | Embryonic stem cells |
| Vertex-264 | Vertex (Boston, MA, USA) | NCT05791201 | Encapsulation | Type 1 diabetes | Sub-cut | Embryonic stem cells |
| Hypoimmune islets | Sana (Seattle, WA, USA) | NCT06239636 | Nil | Type 1 diabetes | Muscle | Primary islets |
| Pancreatic endocrine clusters | Seraxis (Germantown, MD, USA) | NCT06651515 | Full | Hypoglycaemia | Omentum | Induced pluripotent stem cells |
| Autologous stem cell-derived β-cells | HangZhou Reprogenix (Hangzhou, China) | ChiCTR2300072200 | Full | Hypoglycaemia | Anterior abdominal wall | Chemically induced pluripotent cells |

***Table 3:*** **Trials in β-cell replacement**

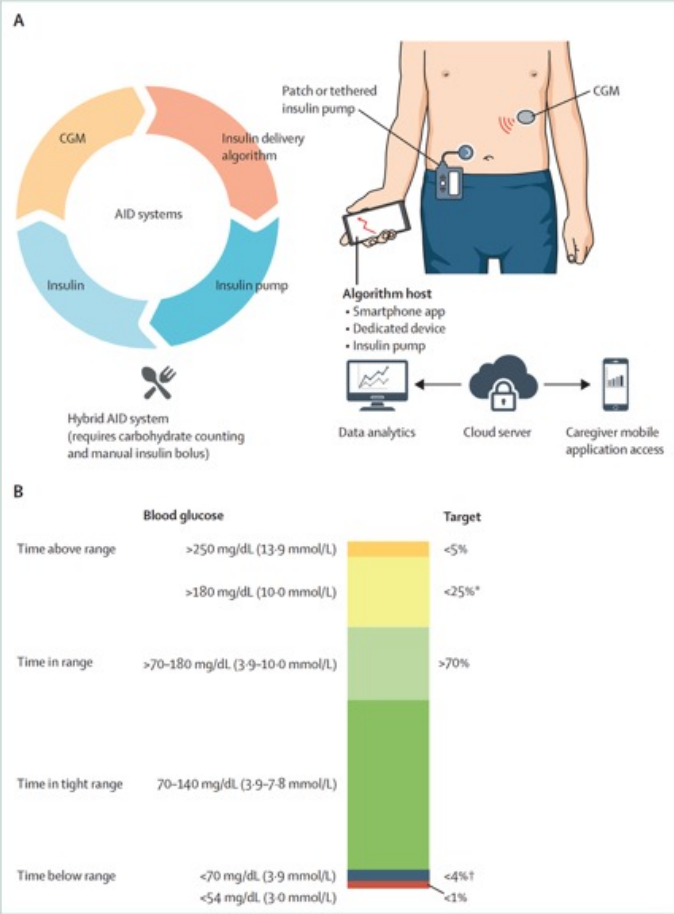



*Figure 3:* **AID systems and CGM-based glycaemia targets**
(A) AID system with its connected components. Insulin dose is calculated on the basis of CGM values using an insulin delivery algorithm, and insulin is infused by the insulin infusion pump (tethered or patch pump). Dual-hormone systems (investigational and not depicted in the figure) infuse other hormones such as glucagon in addition to insulin. Hybrid AID requires meal-time carbohydrate counting and meal bolus input. CGM and insulin delivery data are uploaded to the cloud server for data analytics and can be accessed by parents, caregivers, and clinicians of people with diabetes. (B) Percentage of readings and time per day within target glucose range, time below target glucose range, time above target glucose range, and time in tight range. AID=automated insulin delivery. CGM=continuous glucose monitor. *Includes percentage of values <250 mg/dL (13·9 mmol/L). †Includes percentage of values <54 mg/dL (3·0 mmol/L).

## Future aspects

Future efforts in type 1 diabetes care should shift towards more personalised immunotherapies with durable efficacy and towards combination therapies that target complementary pathways. Subanalyses of trials in individuals with early-stage type 1 diabetes or with stage 3 type 1 diabetes suggest greater efficacy in distinct genetic and phenotypic subgroups. An important step in this direction will be personalised response analyses across trials that lead to robust conclusions and the identification of biomarkers predictive of therapy response. Although stem-cell therapy has shown remarkable results in a few people,[71,72] its promise as a therapy for broad application is dependent on the safe engineering of cells that avoid both alloimmunity and autoimmunity, and on production methods that meet the global demand for cell-based therapy at affordable costs. Insulin therapy will be an integral part of treatment for most people. Advances will be driven by AID systems, and by bihormonal or trihormonal therapies and the development and testing of new glucose-responsive insulins, all of which will optimise and enhance AID systems.

# This scientist studies ultra-processed foods. Here's what he eats in a day.

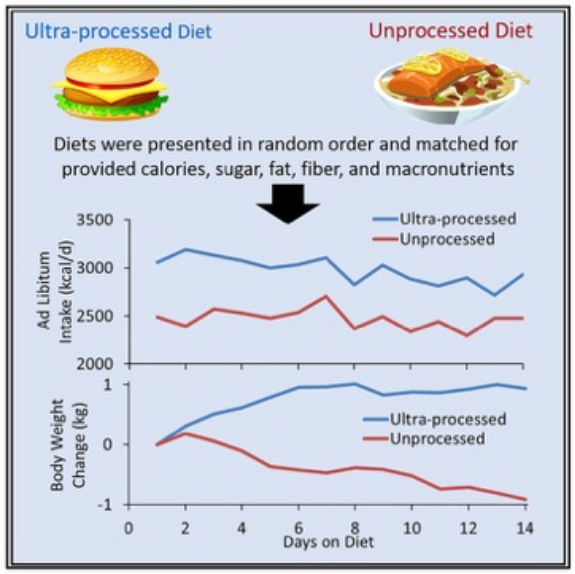

**I have to ask: Do you eat ultra-processed foods?**

I do. I eat some of the bad ones — the tasty treats — but I treat them as recreational substances. I also eat ultra-processed foods that from a nutritional perspective are pretty good even though they contain certain additives. I use, for example, a marinara sauce that's low in sugar and sodium, but when I'm making a nice pasta dish it cuts down the preparation time. I'm not going to make a marinara sauce from scratch. Just because something is ultra-processed doesn't necessarily mean it's bad for you.

Cell Metabolism

# Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of *Ad Libitum* Food Intake

Graphical Abstract

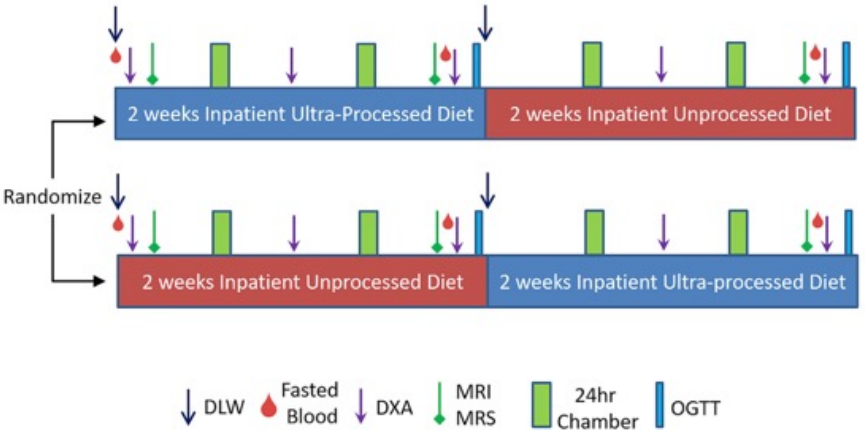


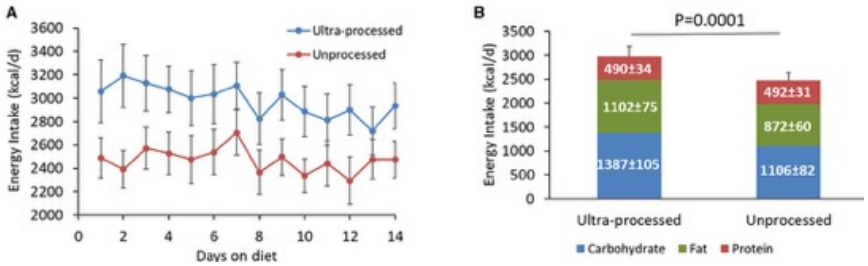

## Highlights

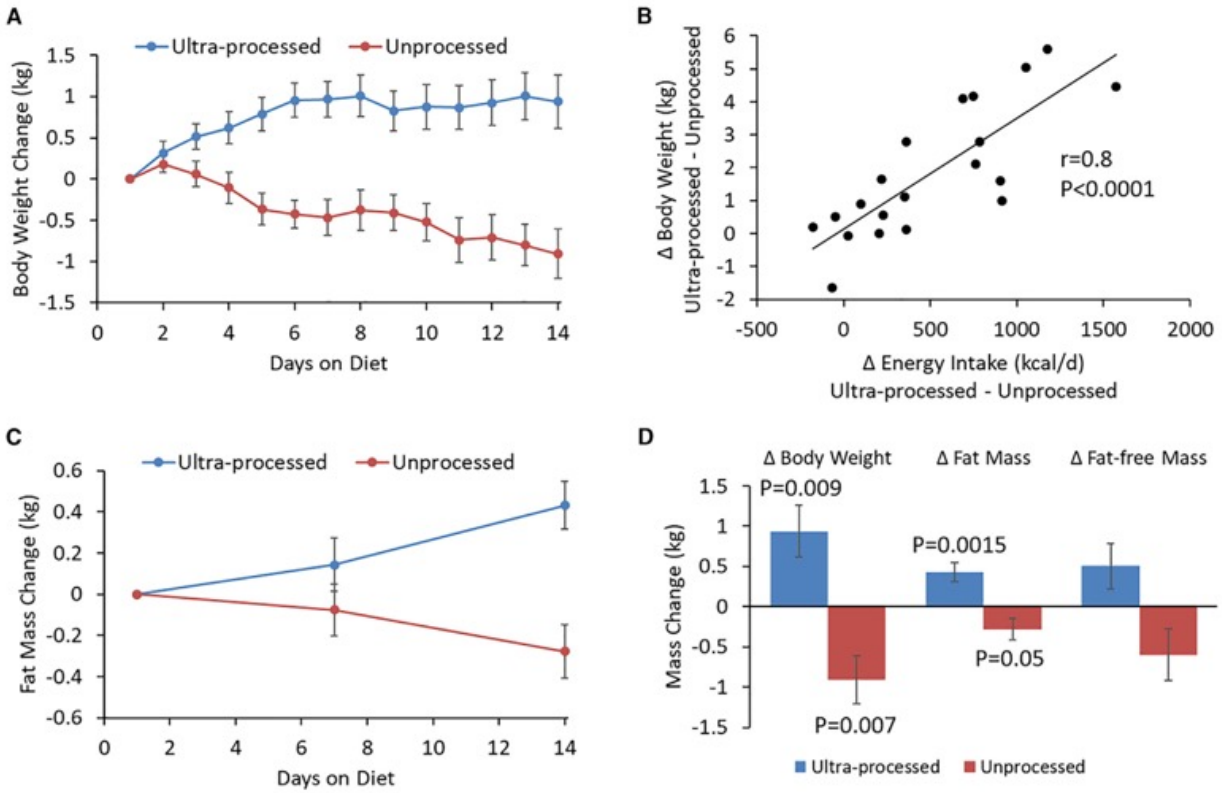
- 20 inpatient adults received ultra-processed and unprocessed diets for 14 days each
- Diets were matched for presented calories, sugar, fat, fiber, and macronutrients
- *Ad libitum* intake was ~500 kcal/day more on the ultra-processed versus unprocessed diet
- Body weight changes were highly correlated with diet differences in energy intake

## SUMMARY

We investigated whether ultra-processed foods affect energy intake in 20 weight-stable adults, aged (mean ± SE) 31.2 ± 1.6 years and BMI = 27 ± 1.5 kg/m$^2$. Subjects were admitted to the NIH Clinical Center and randomized to receive either ultra-processed or unprocessed diets for 2 weeks immediately followed by the alternate diet for 2 weeks. Meals were designed to be matched for presented calories, energy density, macronutrients, sugar, sodium, and fiber. Subjects were instructed to consume as much or as little as desired. Energy intake was greater during the ultra-processed diet (508 ± 106 kcal/day; p = 0.0001), with increased consumption of carbohydrate (280 ± 54 kcal/day; p < 0.0001) and fat (230 ± 53 kcal/day; p = 0.0004), but not protein (−2 ± 12 kcal/day; p = 0.85). Weight changes were highly correlated with energy intake (r = 0.8, p < 0.0001), with participants gaining 0.9 ± 0.3 kg (p = 0.009) during the ultra-processed diet and losing 0.9 ± 0.3 kg (p = 0.007) during the unprocessed diet. Limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment.


A
Ultra-processed
Unprocessed
Body Weight Change (kg)
Days on Diet
B
Δ Body Weight (kg)
Ultra-processed - Unprocessed
r=0.8
P<0.0001
Δ Energy Intake (kcal/d)
Ultra-processed - Unprocessed
C
Ultra-processed
Unprocessed
Fat Mass Change (kg)
Days on Diet
D
Δ Body Weight
Δ Fat Mass
Δ Fat-free Mass
P=0.009
P=0.0015
P=0.05
P=0.007
Mass Change (kg)
Ultra-processed
Unprocessed

# Prominent ultra-processed-food researcher leaves NIH, alleges censorship


After 21 years at my dream job, I'm very sad to announce my early retirement from the National Institutes of Health. My life's work has been to scientifically study how our food environment affects what we eat, and how what we eat affects our physiology. Lately, I've focused on unravelling the reasons why diets high in ultra-processed food are linked to epidemic proportions of chronic diseases such as diabetes and obesity. Our research leads the world on this topic. Given recent bipartisan goals to prevent diet-related chronic diseases, and new agency leadership professing to prioritize scientific investigation of ultra-processed foods, I had hoped to expand our research program with ambitious plans to more rapidly and efficiently determine how our food is likely making Americans chronically sick. Unfortunately, recent events have made me question whether NIH continues to be a place where I can freely conduct unbiased science. Specifically, I experienced censorship in the reporting of our research because of agency concerns that it did not appear to fully support preconceived narratives of my agency's leadership about ultra-processed food addiction.