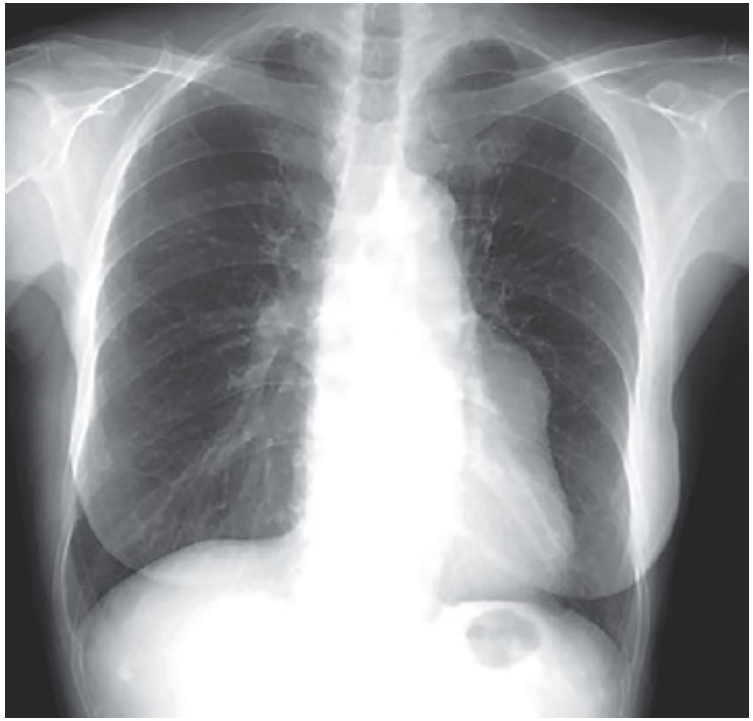
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club


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 eingelanden, um uns beizutreten. Bewerben Sie sich!

A 79-year-old woman with a history of prior stroke was referred for an abnormal X-ray finding along the left heart border, first noticed 6 years prior. In the absence of symptoms, the patient was monitored with serial radiographs which showed a gradual increase in size of the finding. Which of the following is the most likely diagnosis?



Giant Coronary Aneurysm

Left Atrial Appendage Thrombus

Mediastinal Hematoma

Pericardial Cyst

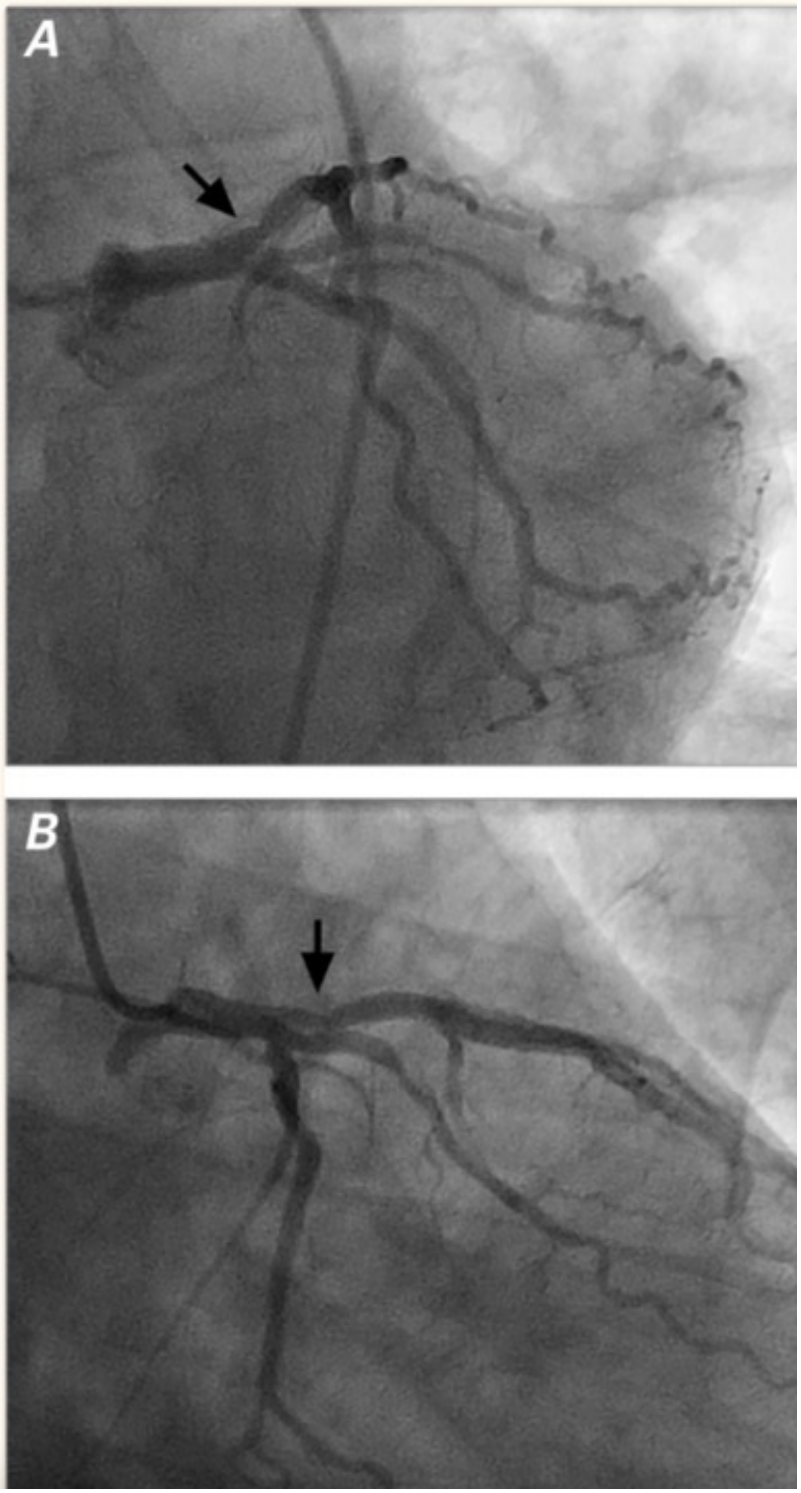
Teratoma

The correct answer is giant coronary aneurysm. Subsequent coronary computed tomography revealed an aneurysm measuring 45 mm in the greatest dimension arising from the left coronary artery, consistent with a diagnosis of coronary artery aneurysm. Following cardiac catheterization, which revealed an additional fistula, the patient underwent cardiac surgery and was discharged 16 days later.

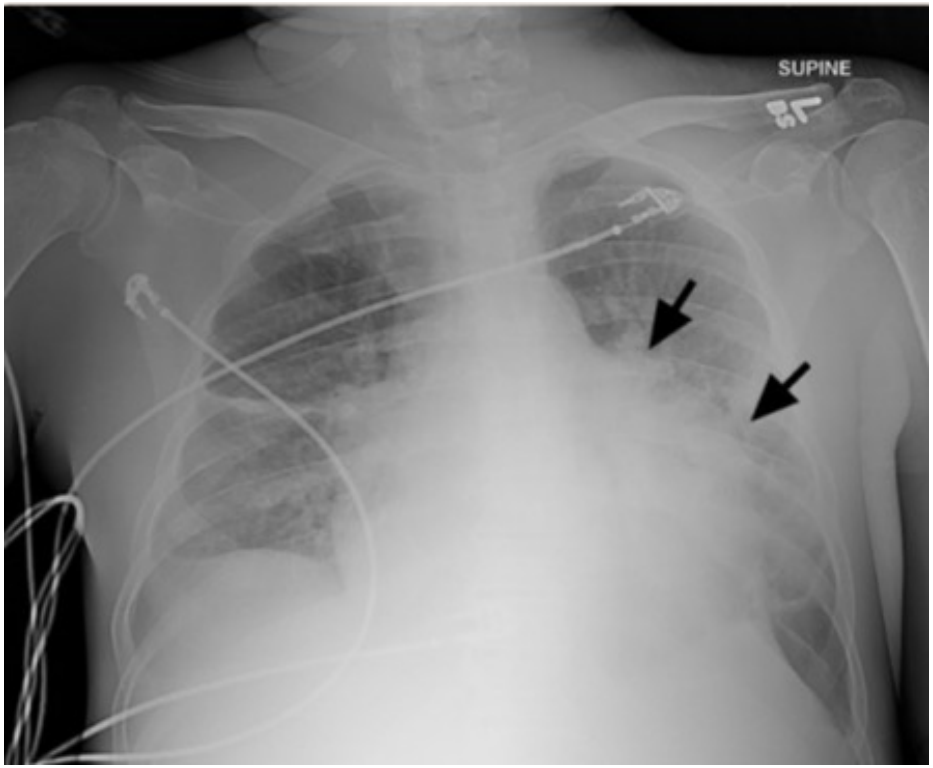
Giant coronary artery aneurysms are rare, with a reported prevalence of 0.02% to 0.2%. Causative factors include atherosclerosis, Takayasu arteritis, congenital disorders, Kawasaki disease, and percutaneous coronary intervention. Most giant coronary artery aneurysms are asymptomatic, but some patients present with angina pectoris, sudden death, fistula formation, pericardial tamponade, compression of surrounding structures, or congestive heart failure. Clinical sequelae include thrombus formation, embolization, fistula formation, and rupture. Surgical correction is generally accepted as the preferred treatment for giant coronary artery aneurysms.

The pathologic mechanism of CAAs remains controversial. An inherent defect of the vessel wall can predispose atherosclerotic vessels to aneurysm formation. In areas of marked atherosclerosis, the media of the vessel wall is weakened, and there is a decrease in elasticity. The intraluminal pressure against the weakened wall decreases the stress tolerance and subsequently enables dilation of the vessel. The chronic transmural inflammation seen in atherosclerotic vessels aggravates this process.

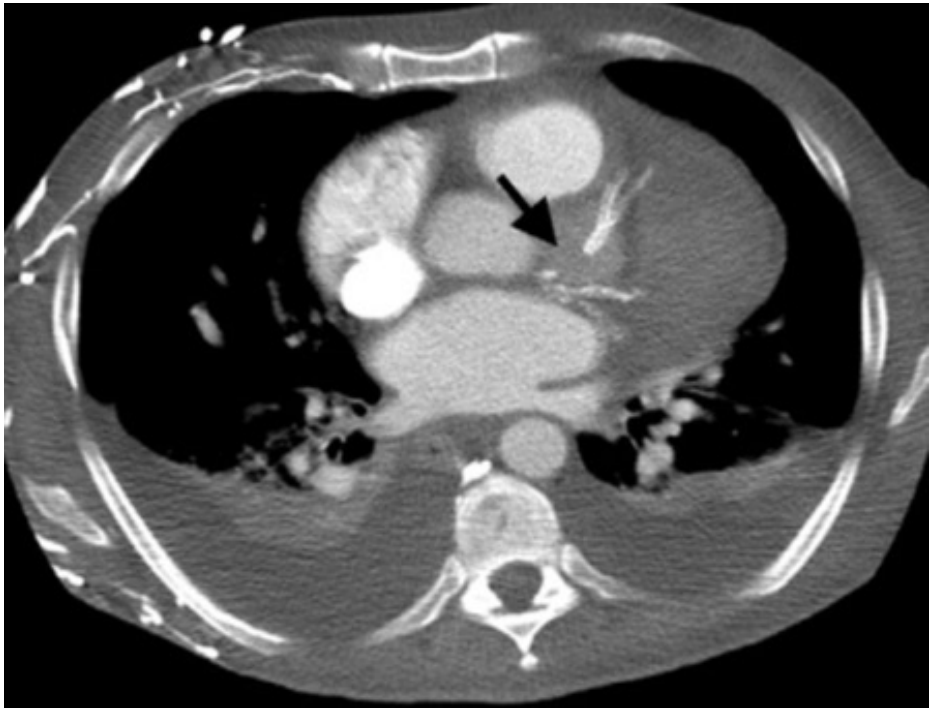
Patient undergoes cath for chest pain:

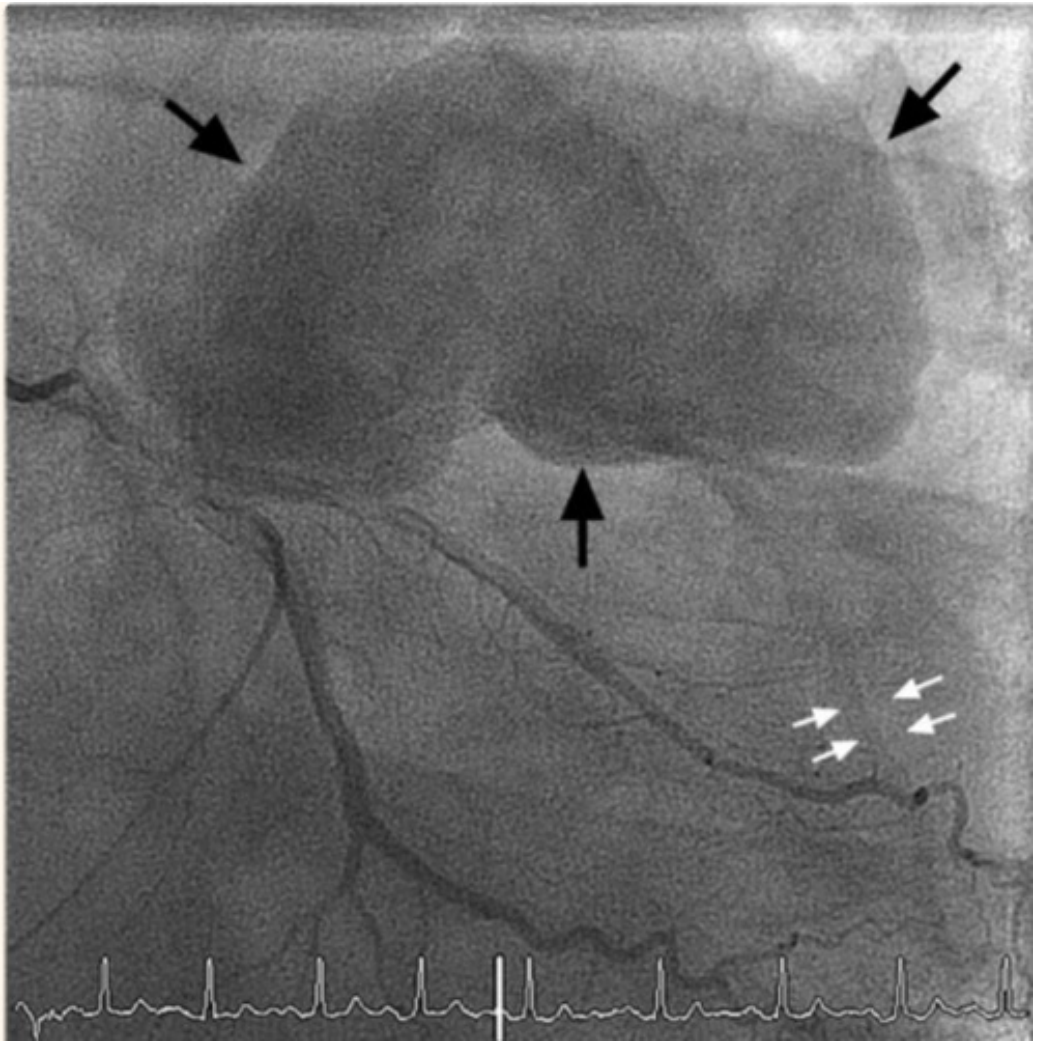


Chest radiograph shows pulmonary vascular congestion, pleural effusions, cardiomegaly, and a left perihilar density (arrows).




Computed tomogram with intravenous contrast medium reveals a contrast-enhanced mass arising from the left main or proximal left anterior descending coronary artery (arrow).





Coronary angiogram shows a 70 × 40-mm aneurysm bulging from the distal left main coronary artery (black arrows). Faint opacification of the distal left anterior descending coronary artery is seen (white arrows).

# Laplace's Law and Aneurysms

## What it shows:

Blow up a long cylindrical balloon and it inflates according to Laplace's law. Arteries, which also need to be flexible, are designed to fight against the kind of aneurysms seen in inflating rubber balloons.

## How it works:

Laplace's law for the gauge pressure inside a cylindrical membrane is given by $\Delta P = \gamma/r$, where $\gamma$ is the surface tension and r the radius of the cylinder. Note the inverse relation between pressure and radius.

When you blow up a balloon, only one part initially expands into an aneurysm. Continue inflating it and the aneurysm grows towards the balloon's end. (A bicycle inner tube behaves similarly.) The *pressure* inside the balloon is the *same* throughout, but when you feel the surface of a partially inflated balloon, the tension of the inflated part is considerably greater than the rest of the balloon. Granted, it's not surface tension, but the analogy to Laplace's relation between tension and radius is clear—for a fixed pressure, a larger radius cylindrical membrane will have a larger tension in the membrane wall and will consequently need to be "stronger" if it is not to burst. A bicycle tire withstands 100 psi with a relatively thin wall compared to automobile tires, which are inflated to only 35 psi. True, the automobile tire must be strong as it suffers all the insults of the road, but the walls of the tire also need to be strong to simply hold the pressure, given the large radius of the interior circle of the torus. Inflating an automobile tire to 100 psi would be disastrous, notwithstanding its thick walls.

**New Dana RS Insulin Pump Embraces #WeAreNotWaiting Open Design!**

A new insulin pump launching outside the United States this week is going where no commercial diabetes product has gone before: it is embracing the do-it-yourself diabetes community by actually including two-way communication capabilities between the pump controller and smartphone apps.

This allows it to interact with do-it-yourself data-viewing technology and the Android version of a homemade closed-loop system, essentially making it easier for the tech-savvy D-Community to use the device in ways that best fit their lives.

This is virtually unheard-of to date in the commercial diabetes industry. While other companies in the U.S. and globally have talked about open interfaces and design and are exploring that for future tech, the new **DANA Diabecare RS insulin pump** from South Korean company SOOIL Development appears to be the first D-device to actually make it happen. They even collaborated with the European DIY community for design advice.

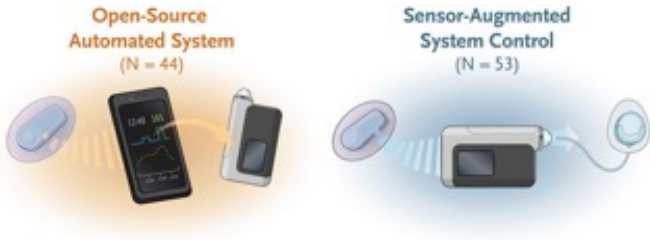
The use of automated insulin delivery (AID) systems that encompass an insulin-delivery algorithm, insulin pump, and continuous glucose monitoring has been shown to improve glycemic control and reduce the care burden for patients with type 1 diabetes. A do-it-yourself AID system, called OpenAPS, was developed by patients with diabetes and was shared freely as an open-source system in February 2015. Since that time, multiple open-source AID systems have evolved, and despite a lack of regulatory approval, such systems have been adopted by approximately 2500 patients with diabetes globally. Data now include the results of more than 55 million hours of real-world open-source AID experience.

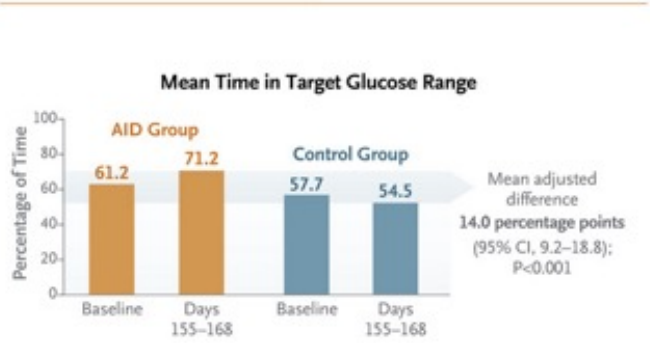
Two widely used open-source AID systems are AndroidAPS (OpenAPS algorithm on an Android device) and Loop (a different algorithm on an iOS device). In a single-group study, investigators found that patients who used the Loop system had a higher percentage of time in range for target glucose control (70 to 180 mg per deciliter [3.9 to 10.0 mmol per liter]), with an increase in control from 67% at baseline to 73% at 6 months. However, this study was limited by a lack of comparative effectiveness and the enrollment of patients who had a high percentage of time in the target range at baseline.

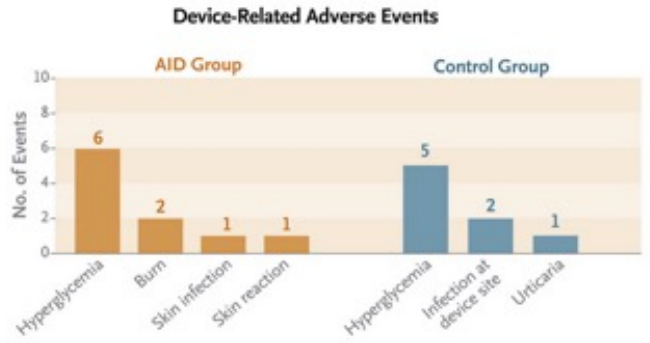
The uptake of open-source AID systems has a number of barriers beyond a lack of regulatory approval, including a lack of trial data regarding safety and efficacy, limited expertise with the system among health care professionals, and a perception that the use of AID systems is technically challenging. In the randomized, controlled trial called CREATE (Community Derived Automated Insulin Delivery), we evaluated the efficacy and safety of an open-source AID system as compared with sensor-augmented insulin-pump therapy in children and adults with type 1 diabetes.

# Open-Source Automated Insulin Delivery in Type 1 Diabetes

Open-source automated insulin delivery (AID) systems are used by many patients with type 1 diabetes. Data are needed on the efficacy and safety of an open-source AID system. In this multicenter, open-label, randomized, controlled trial, we assigned patients with type 1 diabetes in a 1:1 ratio to use an open-source AID system or a sensor-augmented insulin pump (control). The patients included both children (defined as 7 to 15 years of age) and adults (defined as 16 to 70 years of age). The AID system was a modified version of AndroidAPS 2.8 (with a standard OpenAPS 0.7.0 algorithm) paired with a preproduction DANA-i insulin pump and Dexcom G6 CGM, which has an Android smartphone application as the user interface. The primary outcome was the percentage of time in the target glucose range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) between days 155 and 168 (the final 2 weeks of the trial).




**CONCLUSIONS**

Among children and adults with type 1 diabetes, use of an open-source automated insulin delivery system resulted in a significantly higher percentage of time in the target glucose range than use of a sensor-augmented insulin pump, without an increase in adverse events.

## Open-Source AID

The system was a modified version of AndroidAPS 2.8 (which uses the standard OpenAPS 0.7.0 algorithm) paired with a preproduction DANA-i insulin pump and Dexcom G6 CGM. The user interface was an Android smartphone application (AnyDANA-Loop). Modifications reduced the number of objectives and time required to enable closed-loop therapy. Patients used the AnyDANA-Loop application for mealtime insulin administration and AnyDANA-Loop automated insulin delivery in response to the glucose target. Any changes to user-specific settings were made with the patients' involvement, according to the technical manual. Written guidelines and "how to" video demonstrations of key aspects of the applications were provided to all the patients in the AID group.

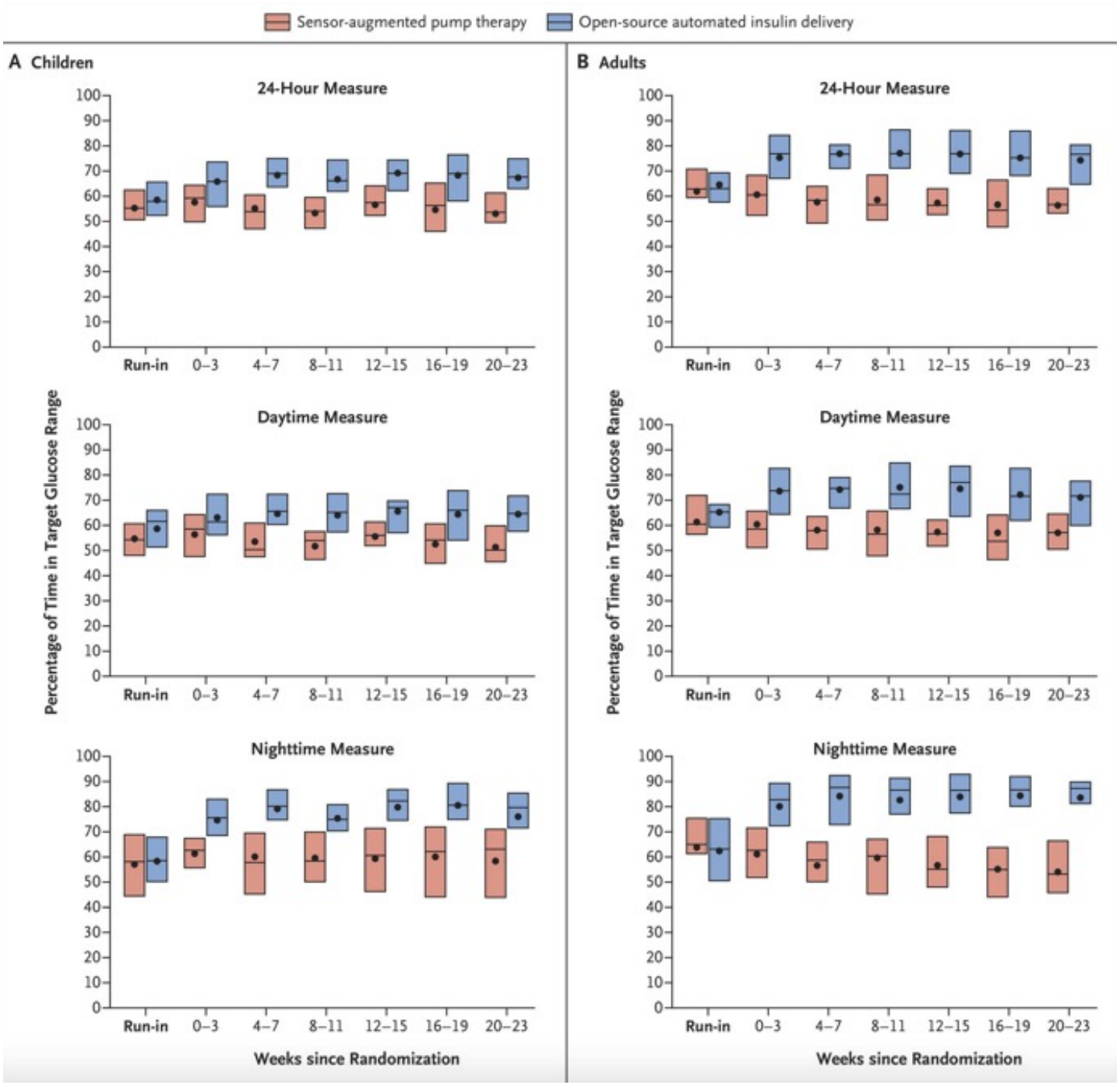
## Sensor-Augmented Insulin-Pump Therapy

Patients in the control group used the Dexcom G6 CGM with high and low glucose alerts and their usual insulin pump or a preproduction DANA-i insulin pump to administer bolus insulin doses. The sensor-augmented insulin-pump therapy was not designed to predict low-glucose levels or to suspend insulin administration. A smartphone application, called Monitor, transmitted data regarding continuous glucose monitoring to Nightscout.

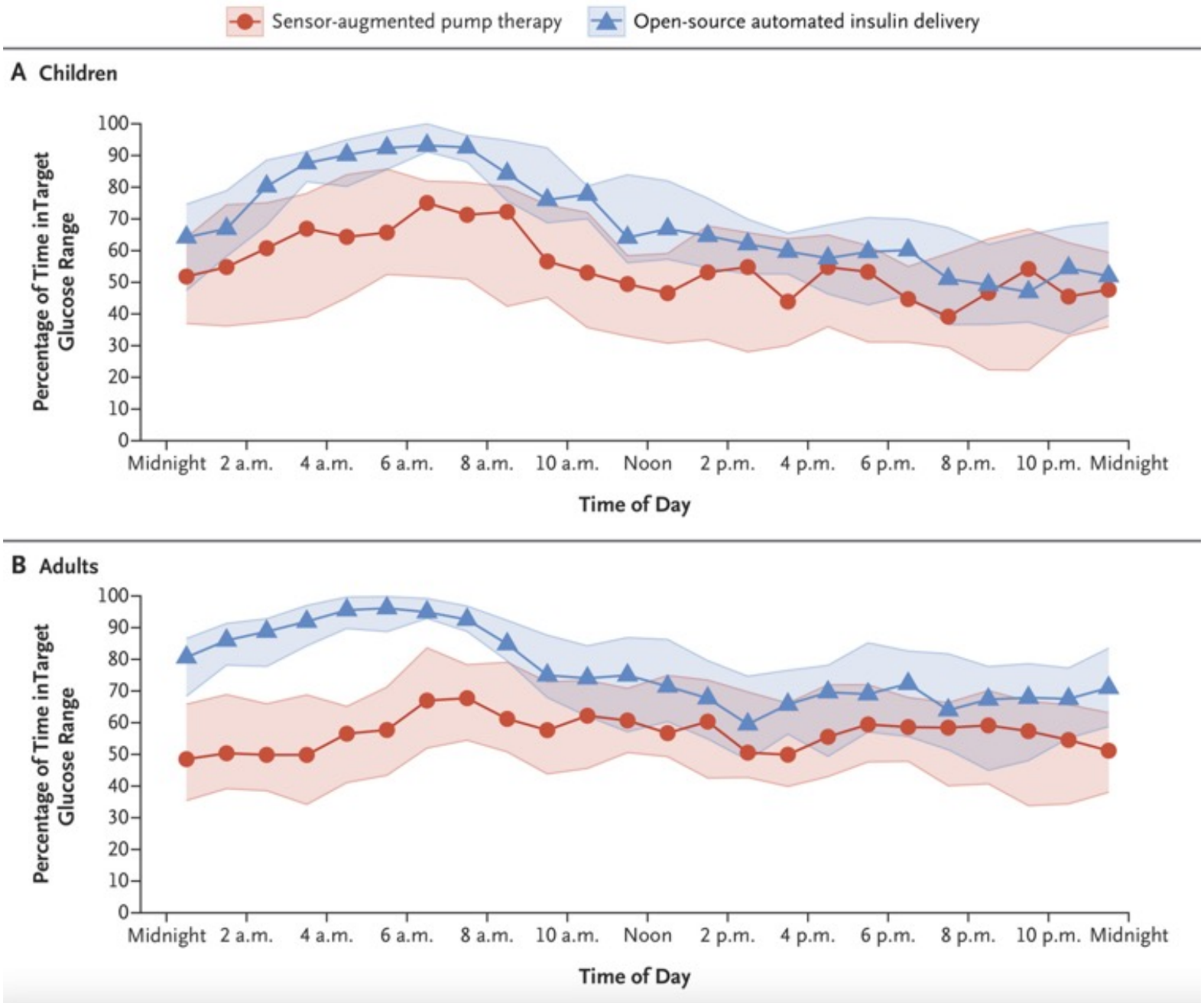
| Characteristic | Automated Insulin Delivery | Control | Total |
|---|---|---|---|
| **Children** | | | |
| No. of patients | 21 | 27 | 48 |
| Median age (IQR) — yr | 14.0 (11.0–15.0) | 11.0 (9.0–14.5) | 13.0 (9.0–15.0) |
| Female sex — no. (%) | 11 (52) | 13 (48) | 24 (50) |
| Ethnic group — no. (%)† | | | |
| Maori | 4 (19) | 4 (15) | 8 (17) |
| Asian | 1 (5) | 0 | 1 (2) |
| European or other | 16 (76) | 23 (85) | 39 (81) |
| New Zealand Deprivation Index — no. (%)‡ | | | |
| Quintile 1 | 9 (43) | 10 (37) | 19 (40) |
| Quintile 2 | 6 (29) | 10 (37) | 16 (33) |
| Quintile 3 | 4 (19) | 3 (11) | 7 (15) |
| Quintile 4 | 2 (10) | 2 (7) | 4 (8) |
| Quintile 5 | 0 | 2 (7) | 2 (4) |
| Diabetes history | | | |
| Glycated hemoglobin§ | | | |
| Value — mmol/mol | 58.3±6.6 | 58.4±9.9 | 58.4±8.5 |
| Mean percent§ | 7.5 | 7.5 | 7.5 |
| Previous use of CGM — no. (%)¶ | 20 (95) | 26 (96) | 46 (96) |
| Previous use of automated insulin delivery — no. (%)‖ | 1 (5) | 2 (7) | 3 (6) |
| Time in glucose range — (%)** | 57.4±10.6 | 55.1±12.6 | 56.1±11.7 |
| **Adults** | | | |
| No. of patients | 23 | 26 | 49 |
| Median age (IQR) — yr | 40.0 (33.0–43.5) | 38.0 (23.2–45.8) | 40.0 (29.0–45.0) |
| Sex — no. (%) | | | |
| Female | 15 (65) | 15 (58) | 30 (61) |
| Male | 7 (30) | 11 (42) | 18 (37) |
| Nonbinary | 1 (4) | 0 | 1 (2) |
| Ethnic group — no. (%)† | | | |
| Maori | 2 (9) | 5 (19) | 7 (14) |
| Asian | 0 | 1 (4) | 1 (2) |
| Middle Eastern, Latin American, or African | 1 (4) | 0 | 1 (2) |
| European or other | 20 (87) | 20 (77) | 40 (82) |
| New Zealand Deprivation Index — no. (%)‡ | | | |
| Quintile 1 | 9 (39) | 4 (15) | 13 (27) |
| Quintile 2 | 3 (13) | 7 (27) | 10 (20) |
| Quintile 3 | 5 (22) | 7 (27) | 12 (24) |
| Quintile 4 | 3 (13) | 6 (23) | 9 (18) |
| Quintile 5 | 3 (13) | 2 (8) | 5 (10) |
| Diabetes history | | | |
| Glycated hemoglobin§ | | | |
| Value — mmol/mol | 60.0±13.7 | 62.1±9.1 | 61.1±11.5 |
| Mean percent | 7.6 | 7.8 | 7.7 |
| Previous use of CGM — no. (%)¶ | 15 (65) | 17 (65) | 32 (65) |
| Previous use of automated insulin delivery — no. (%)‖ | 4 (17) | 5 (19) | 9 (18) |
| Time in target glucose range — %** | 64.7±12.9 | 60.3±15.6 | 62.4±14.4 |

| Age Group and Glycemic Metric | Automated Insulin Delivery | | | Control | | | Adjusted Mean Difference between Groups (95% CI)‡ |
|---|---|---|---|---|---|---|---|
| | Run-in Period | Days 155–168† | Mean Change (95% CI) | Run-in Period | Days 155–168† | Mean Change (95% CI) | |
| **Children** | | | | | | | |
| No. of patients | 21 | 20 | 20 | 27 | 27 | 27 | |
| Percentage of time with glucose in 70–180 mg/dl range | 57.4±10.6 | 67.5±11.5 | 9.9 (2.9 to 16.9) | 55.1±12.6 | 52.5±17.5 | −2.6 (−8.1 to 2.8) | 12.6 (5.7 to 19.5) |
| Percentage of time with glucose level <70 mg/dl: level 1 or 2 hypoglycemia | 3.5±2.6 | 2.1±1.5 | −1.5 (−2.5 to −0.4) | 3.7±3.0 | 2.7±2.8 | −1.0 (−1.9 to −0.2) | −0.5 (−1.6 to 0.5) |
| Percentage of time with glucose in 180–250 mg/dl range: level 1 hyperglycemia | 25.3±5.3 | 21.1±6.8 | −4.1 (−8.2 to −0.0) | 25.0±8.0 | 26.0±7.5 | 1.0 (−0.7 to 2.8) | −4.8 (−8.7 to −1.0) |
| Percentage of time with glucose level >250 mg/dl: level 2 hyperglycemia | 13.8±7.3 | 9.3±6.0 | −4.4 (−8.0 to −0.7) | 16.1±7.5 | 18.8±14.7 | 2.6 (−2.2 to 7.4) | −7.2 (−12.0 to −2.4) |
| Mean glucose level — mg/dl | 171.0±19.6 | 156.8±18.8 | −13.6 (−25.2 to −2.1) | 174.1± 22.4 | 182.4±36.4 | 8.3 (−3.4 to 20.0) | −21.4 (−34.4 to −8.4) |
| Glucose standard deviation — mg/dl | 69.6±12.4 | 62.2±10.6 | −7.3 (−13.2 to −1.3) | 70.8±12.2 | 67.6±13.6 | −3.2 (−7.4 to 0.9) | −4.5 (−10.1 to 1.0) |
| Coefficient of variation — % | 40.6±4.7 | 39.7±5.2 | −0.9 (−3.6 to 1.7) | 40.8±6.1 | 37.4±5.9 | −3.4 (−5.4 to −1.4) | 2.1 (−0.4 to 4.6) |
| Glycated hemoglobin§ | | | | | | | |
| Value — mmol/mol | 58.3±6.6 | 52.6±9.8 | −5.9 (−11.4 to −0.4) | 58.4±9.9 | 59.2±10.7 | 0.0 (−3.2 to 3.1) | −5.2 (−10.0 to −0.4) |
| Percent | 7.5±0.6 | 7.0±0.9 | −0.5 (−1.0 to 0.0) | 7.5±0.9 | 7.6±1.0 | 0.0 (−0.3 to 0.3) | −0.5 (−0.9 to −0.0) |
| **Adults** | | | | | | | |
| No. of patients | 23 | 22 | 22 | 26 | 26 | 26 | |
| Percentage of time with glucose in 70–180 mg/dl range | 64.7±12.9 | 74.5±11.9 | 9.6 (4.4 to 14.8) | 60.3±15.6 | 56.5±14.2 | −3.8 (−7.7 to 0.1) | 15.4 (8.6 to 22.1) |
| Percentage of time with glucose level <70 mg/dl: level 1 or 2 hypoglycemia | 2.3±2.2 | 1.6±2.1 | −0.4 (−1.2 to 0.4) | 1.7±2.2 | 1.8±2.5 | 0.1 (−0.3 to 0.5) | −0.4 (−1.4 to 0.6) |
| Percentage of time with glucose in 180–250 mg/dl range: level 1 hyperglycemia | 24.7±9.5 | 18.2±8.4 | −6.6 (−11.2 to −2.1) | 26.3±7.4 | 27.9±8.1 | 1.6 (−0.3 to 3.5) | −8.8 (−12.6 to −5.1) |
| Percentage of time with glucose level >250 mg/dl: level 2 hyperglycemia | 8.2±7.0 | 5.6±4.9 | −2.6 (−5.1 to −0.1) | 11.7±12.1 | 13.8±9.3 | 2.1 (−1.2 to 5.4) | −6.2 (−11.0 to −1.5) |
| Mean glucose level — mg/dl | 159.7±21.6 | 148.4±21.3 | −12.0 (−20.2 to −3.8) | 170.3±28.3 | 175.4±24.5 | 5.1 (−2.5 to 12.7) | −21.4 (−34.3 to −8.6) |
| Glucose standard deviation — mg/dl | 57.0±12.9 | 51.0±10.7 | −5.6 (−10.1 to −1.1) | 59.3±11.9 | 61.4±9.5 | 2.0 (−2.0 to 6.1) | −8.9 (−14.3 to −3.5) |
| Coefficient of variation — % | 35.5±5.0 | 34.1±3.8 | −0.9 (−3.2 to 1.3) | 35.0±5.9 | 35.3±5.3 | 0.3 (−1.3 to 1.9) | −1.2 (−3.7 to 1.2) |
| Glycated hemoglobin¶ | | | | | | | |
| Value — mmol/mol | 60.0±13.7 | 50.7±8.8 | −9.8 (−15.0 to −4.5) | 62.1±9.1 | 59.0±8.3 | −3.4 (−6.2 to −0.7) | −7.7 (−12.3 to −3.2) |
| Percent | 7.6±1.3 | 6.8±0.8 | −0.9 (−1.4 to −0.4) | 7.8±0.8 | 7.5±0.8 | −0.3 (−0.6 to −0.1) | −0.7 (−1.1 to −0.3) |

**Percentage of Time in Target Glucose Range, According to Age Group and Trial Period.**



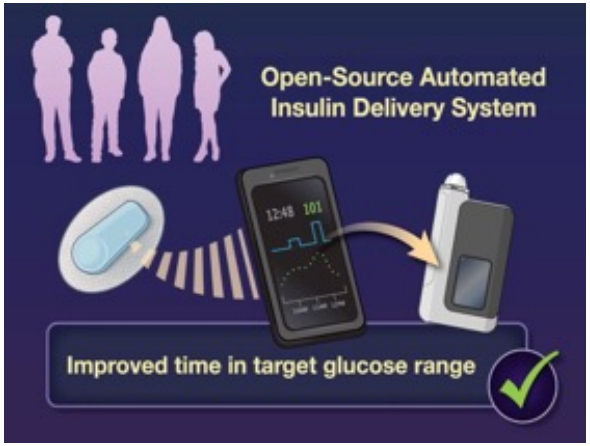
**Percentage of Time in Target Glucose Range, According to Time of Day.**



**Adverse Events, According to Age Group.**

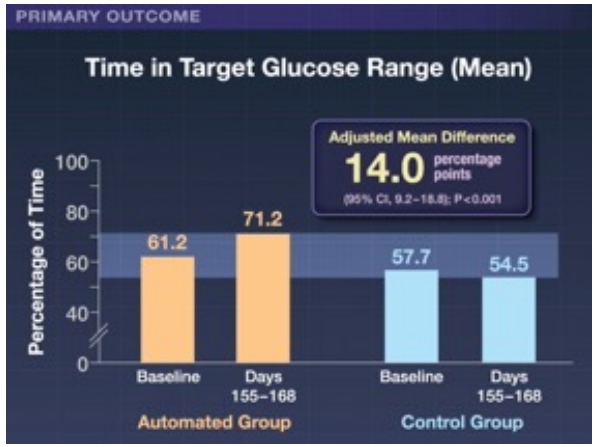
| Adverse Event and Age Group | Automated Insulin Delivery | | Control | | Total | |
|---|---|---|---|---|---|---|
| | Events | Patients | Events | Patients | Events | Patients |
| **Children** | | | | | | |
| Nonserious adverse device effect† | | | | | | |
| Any | 5 | 5 | 4 | 4 | 9 | 9 |
| Hyperglycemia | 3 | 3 | 3 | 3 | 6 | 6 |
| Skin infection | 1 | 1 | 0 | 0 | 1 | 1 |
| Localized skin reaction | 1 | 1 | 0 | 0 | 1 | 1 |
| Urticaria | 0 | 0 | 1 | 1 | 1 | 1 |
| Serious adverse event or serious adverse device effect‡ | | | | | | |
| Any | 2 | 2 | 5 | 5 | 7 | 7 |
| Anaphylactic reaction to food | 0 | 0 | 2 | 2 | 2 | 2 |
| Croup | 1 | 1 | 1 | 1 | 2 | 2 |
| Hyperglycemia | 1 | 1 | 1 | 1 | 2 | 2 |
| Pilonidal cyst with abscess | 0 | 0 | 1 | 1 | 1 | 1 |
| **Adults§** | | | | | | |
| Nonserious adverse device effect | | | | | | |
| Any | 5 | 3 | 4 | 4 | 9 | 7 |
| Burn | 2 | 1 | 0 | 0 | 2 | 1 |
| Hyperglycemia | 3 | 2 | 2 | 2 | 5 | 4 |
| Infection at medical device site | 0 | 0 | 2 | 2 | 2 | 2 |

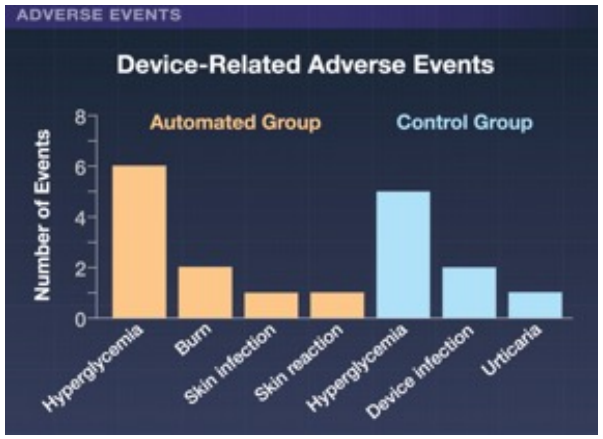







Real-world support may differ from that provided in a trial. The control group did not have an automated system for predicting low-glucose levels or suspending insulin administration, features that have been shown to reduce the incidence of hypoglycemia. The generalizability of our findings may be limited by the enrollment of patients with a relatively low glycated hemoglobin level at baseline, by the underrepresentation of patients with reduced economic resources, and by the increased familiarity with insulin-pump therapy and continuous glucose monitoring among the patients at baseline.

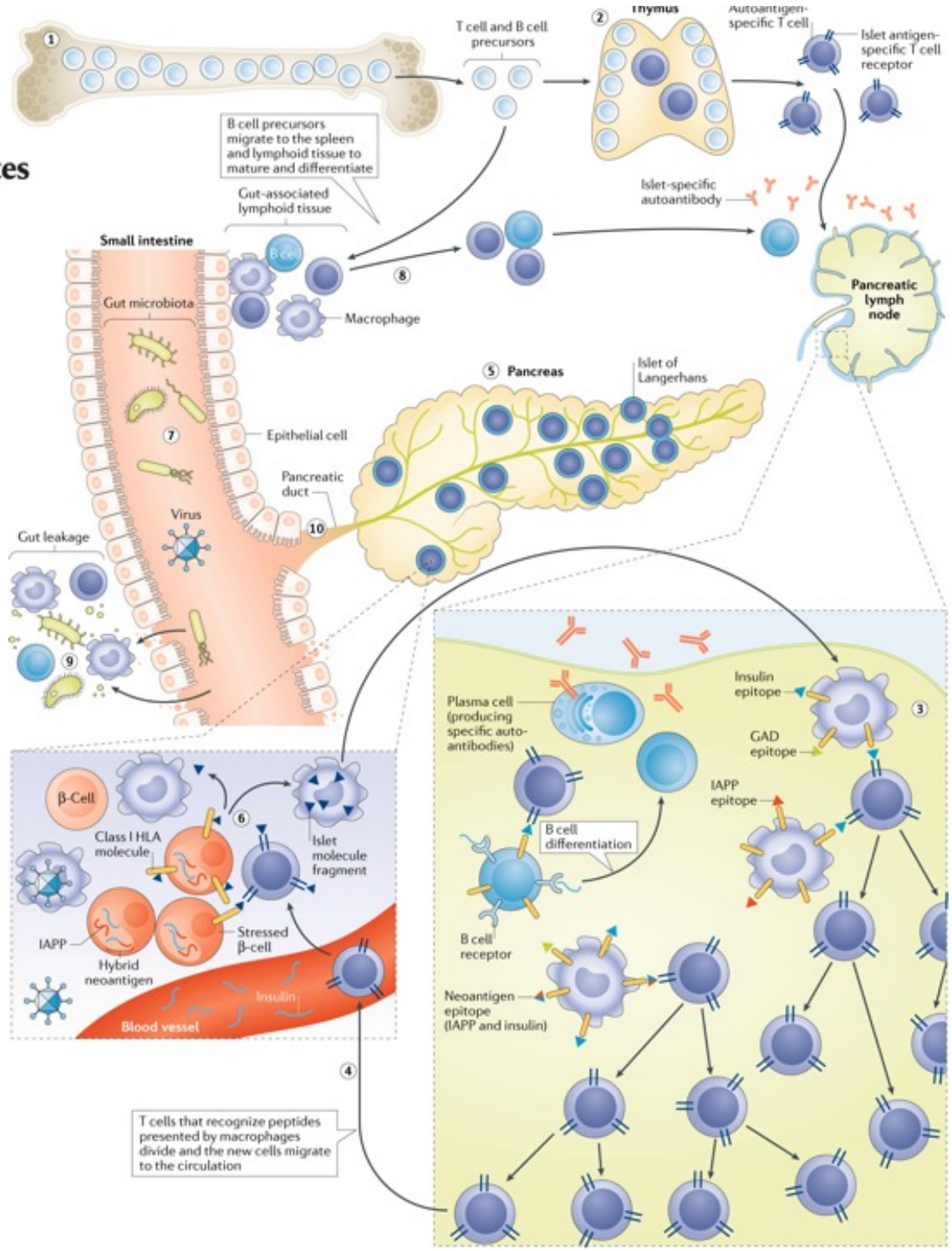


# The heterogeneous pathogenesis of type 1 diabetes mellitus

## Key points

- The incidence of type 1 diabetes mellitus in childhood has increased, and the age at diagnosis has decreased due to environmental changes during the last half of the twentieth century.
- Inherited defects in central and peripheral immune tolerance allow the generation of autoimmune responses directed against pancreatic islets.
- Environmental factors that modify the immune system, such as microbiota composition, microbial infections and nutrition, affect the development and course of the autoimmune response.
- Type 1 diabetes mellitus is a heterogeneous disease with multiple different features, but two major pathways can be discerned with either insulin autoantibodies or glutamic acid decarboxylase autoantibodies as the first autoantibody indicating initiation of the autoimmune process.
- Multiple trials aiming to prevent development of the disease in different phases of the autoimmune process are ongoing or being planned.

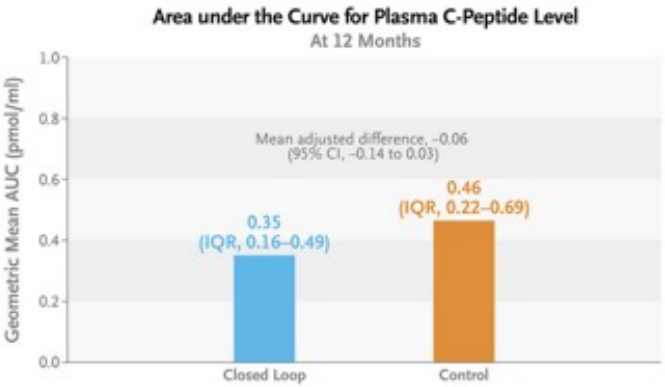


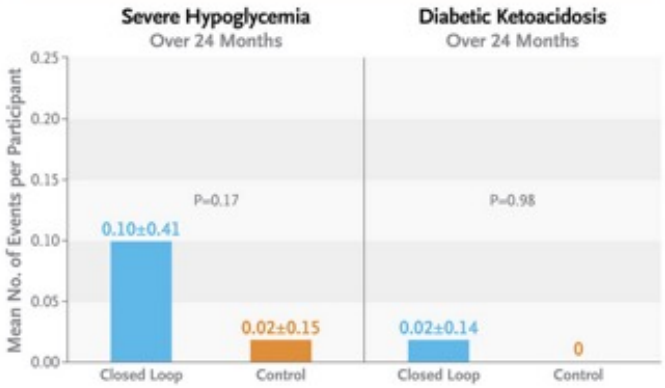

glutamic acid decarboxylase (GAD)

insulin-IAPP hybrid peptide

# Closed-Loop Therapy and Preservation of C-Peptide Secretion in Type 1 Diabetes

Whether improved glucose control with hybrid closed-loop therapy can preserve C-peptide secretion as compared with standard insulin therapy in persons with new-onset type 1 diabetes is unclear. In a multicenter, open-label, parallel-group, randomized trial, we assigned youths 10.0 to 16.9 years of age within 21 days after a diagnosis of type 1 diabetes to receive hybrid closed-loop therapy or standard insulin therapy (control) for 24 months. The primary end point was the area under the curve (AUC) for the plasma C-peptide level (after a mixed-meal tolerance test) at 12 months after diagnosis. The analysis was performed on an intention-to-treat basis.



**CONCLUSIONS**

Among youths with new-onset type 1 diabetes, intensive glucose control with hybrid closed-loop therapy for 24 months did not appear to prevent the decline in residual C-peptide secretion.

## Trial Procedures

Participants and their families received structured diabetes education and training on the regimen of multiple daily insulin injections according to standard clinical practice in the United Kingdom.[16] Within 21 days after diagnosis, participants underwent a baseline mixed-meal tolerance test. After randomization, participants assigned to the closed-loop group were trained to use the trial insulin pump and glucose sensor before starting closed-loop insulin delivery within 6 weeks after diagnosis. Participants continued with closed-loop therapy for 24 months with no remote monitoring or trial-related restrictions. Participants assigned to standard insulin therapy received additional training to complement the core training and to match contact time with the closed-loop group. Participants continued with standard insulin therapy for 24 months but could switch to insulin-pump therapy or use flash or continuous glucose monitoring or approved closed-loop systems if clinically indicated, with application of National Institute for Health and Care Excellence criteria. The recommended glycemic target for both groups was a glycated hemoglobin level of less than 48 mmol per mole (<6.5%), according to the National Institute for Health and Care Excellence guidelines.

## Trial End Points

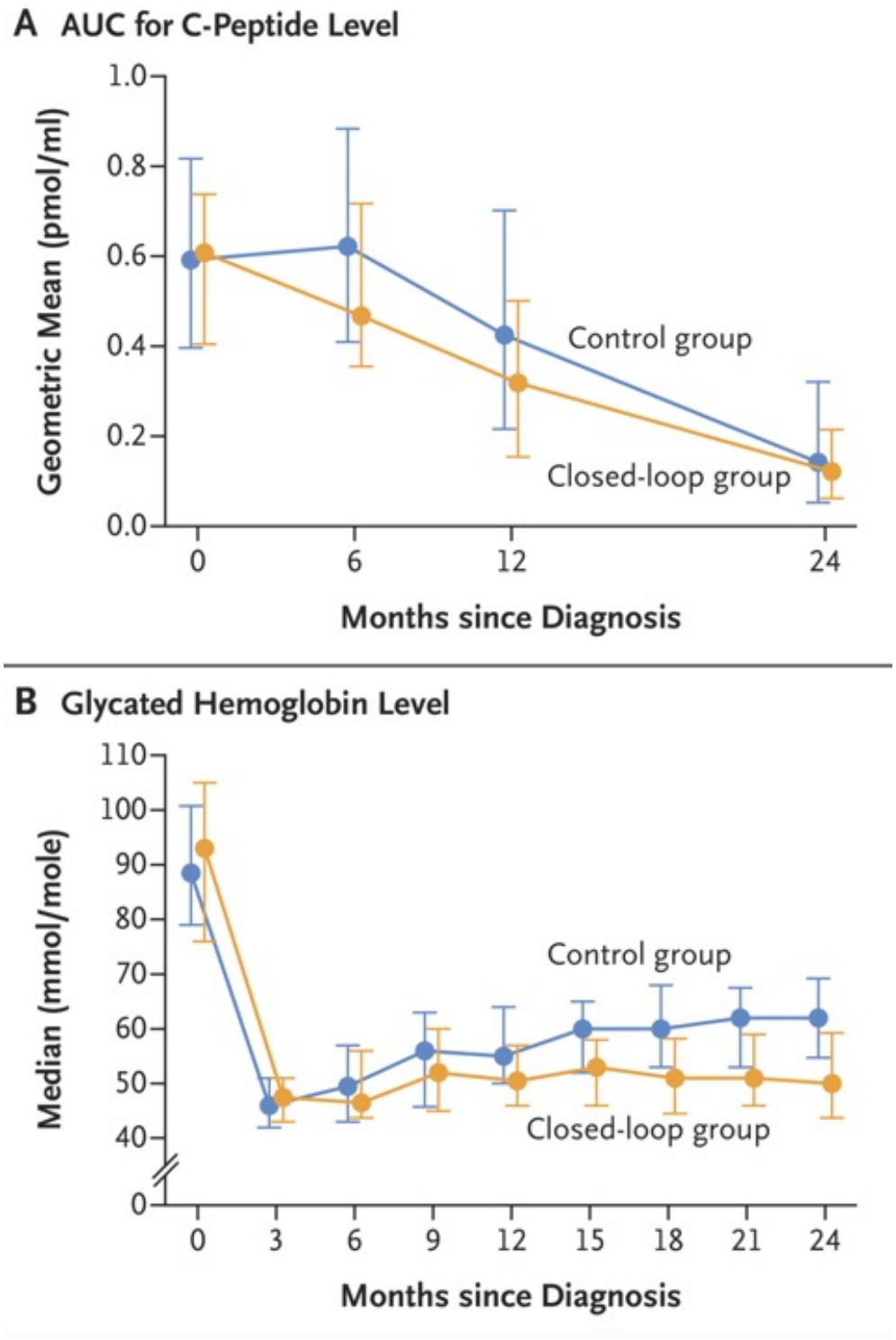
The primary end point was the mean area under the curve (AUC) for the plasma C-peptide level (after a mixed-meal tolerance test) at 12 months after diagnosis. Key secondary end points included the percentage of time in the target glucose range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), the glycated hemoglobin level, and the percentage of time with a glucose level of less than 70 mg per deciliter at 12 months tested with the use of a hierarchical gatekeeping procedure to control the type I error. Sensor glucose end points were based on data from a masked glucose sensor worn for 14 days.

| Characteristic | Overall (N=97) | Closed-Loop Group (N=51) | Control Group (N=46) |
|---|---|---|---|
| Age | | | |
| Mean — yr | 12±2 | 12±2 | 12±2 |
| Distribution — no. (%) | | | |
| 10 to 13 yr | 79 (81) | 41 (80) | 38 (83) |
| 14 to <17 yr | 18 (19) | 10 (20) | 8 (17) |
| Sex — no. (%) | | | |
| Female | 43 (44) | 25 (49) | 18 (39) |
| Male | 54 (56) | 26 (51) | 28 (61) |
| BMI percentile† | 52±31 | 53±29 | 51±34 |
| Race — no. (%)‡ | | | |
| White | 79 (81) | 44 (86) | 35 (76) |
| Black | 3 (3) | 1 (2) | 2 (4) |
| Asian | 6 (6) | 2 (4) | 4 (9) |
| More than one race | 5 (5) | 4 (8) | 1 (2) |
| Unknown or not reported | 4 (4) | 0 | 4 (9) |
| Glycated hemoglobin level | | | |
| In millimoles per mole | 93±18 | 94±20 | 91±17 |
| As a percentage | 10.6±1.7 | 10.7±1.8 | 10.5±1.6 |
| Diabetic ketoacidosis at diagnosis — no. (%) | 28 (29) | 17 (33) | 11 (24) |

**Primary, Key Secondary, and Other Secondary End Points at 12 and 24 Months.**

The percentage of time in the target glucose range of 70 to 180 mg per deciliter on the basis of sensor glucose data at 12 months was higher by 10 percentage points (95% CI, 2 to 17) in the closed-loop group (64±14%) than in the control group (54±23%). Because the P value for this end point did not reach the threshold of 0.01 in the hierarchical analysis, other key secondary end points were not tested for statistical significance. The arithmetic mean glycated hemoglobin level was lower in the closed-loop group than in the control group by 4 mmol per mole (0.4 percentage points; 95% CI, 0 to 8 mmol per mole [0.0 to 0.7 percentage points]) at 12 months. The mean between-group difference in the percentage of time with a glucose level of less than 70 mg per deciliter was 0.9 percentage points (95% CI, −1.0 to 2.8).

| End Point | Baseline | | 12 Months | | Mean Adjusted Between-Group Difference (95% CI)† | 24 Months (all end points secondary) | | Mean Adjusted Between-Group Difference (95% CI)† |
|---|---|---|---|---|---|---|---|---|
| | Closed-Loop Group | Control Group | Closed-Loop Group | Control Group | | Closed-Loop Group | Control Group | |
| **Primary end point at 12 mo** | | | | | | | | |
| AUC for C-peptide level | | | | | | | | |
| No. of participants evaluated | 49 | 45 | 46 | 37 | | 43 | 32 | |
| Geometric mean (IQR) — pmol/ml‡ | 0.56 (0.41 to 0.74) | 0.64 (0.43 to 0.81) | 0.35 (0.16 to 0.49) | 0.46 (0.22 to 0.69) | −0.06 (−0.14 to 0.03) | 0.18 (0.06 to 0.22) | 0.24 (0.05 to 0.30) | −0.04 (−0.14 to 0.06) |
| **Key secondary end points at 12 mo** | | | | | | | | |
| Time in the target glucose range of 70–180 mg/dl§ | | | | | | | | |
| No. of participants evaluated | 50 | 43 | 44 | 33 | | 42 | 30 | |
| Mean — % | 74±14 | 72±13 | 64±14 | 54±23 | 10 (2 to 17) | 64±15 | 49±18 | 14 (6 to 21) |
| Glycated hemoglobin level | | | | | | | | |
| No. of participants evaluated | 51 | 46 | 46 | 39 | | 47 | 36 | |
| Mean — mmol/mole | 94±20 | 91±17 | 52±8 | 56±12 | −4 (−8 to 0) | 52±11 | 63±16 | −11 (−15 to −7) |
| Mean — % | 10.7±1.8 | 10.5±1.6 | 6.9±0.7 | 7.3±1.1 | −0.4 (−0.7 to 0.0) | 6.9±1.0 | 8.0±1.4 | −1.0 (−1.5 to −0.5) |
| Time with a glucose level of <70 mg/dl§¶ | | | | | | | | |
| No. of participants evaluated | 50 | 43 | 44 | 33 | | 42 | 30 | |
| Mean — % | 9.1±6.3 | 10.7±7.1 | 6.2±3.8 | 5.4±4.7 | 0.9 (−1.0 to 2.8) | 11.2±7.3 | 7.5±6.7 | 2.8 (−0.6 to 6.2) |
| **Other secondary end points** | | | | | | | | |
| Sensor glucose end points§ | | | | | | | | |
| No. of participants evaluated | 50 | 43 | 44 | 33 | | 42 | 30 | |
| Glucose level — mg/dl | 130±29 | 125±29 | 152±29 | 176±59 | −28 (−46 to −9) | 142±34 | 176±47 | −31 (−50 to −11) |
| Standard deviation of the glucose level — mg/dl | 49±13 | 49±15 | 64±16 | 67±25 | −3 (−11 to 4) | 66±24 | 72±24 | −8 (−18 to 3) |
| Coefficient of variation of the glucose level — % | 38±7 | 39±7 | 42±7 | 39±8 | 4 (1 to 8) | 46±9 | 41±8 | 4 (0 to 8) |
| Time spent at glucose level — %¶ | | | | | | | | |
| <63 mg/dl | 5.2±4.8 | 6.6±5.2 | 3.6±2.6 | 3.3±3.1 | 0.3 (−1.0 to 1.6) | 7.0±5.3 | 5.0±5.0 | 1.1 (−1.4 to 3.7) |
| <54 mg/dl | 2.0±2.5 | 2.8±2.8 | 1.4±1.2 | 1.5±1.6 | −0.2 (−0.8 to 0.5) | 3.1±3.0 | 2.3±2.7 | 0.2 (−1.2 to 1.6) |
| <50 mg/dl | 1.3±1.8 | 1.9±2.2 | 0.9±0.9 | 1.1±1.4 | −0.3 (−0.8 to 0.2) | 2.0±2.0 | 1.7±2.1 | −0.1 (−1.1 to 0.9) |
| >180 mg/dl | 15±9 | 14±10 | 29±14 | 40±25 | −11 (−19 to −3) | 22±11 | 42±19 | −19 (−26 to −13) |
| >300 mg/dl | 1.0±1.6 | 1.0±1.5 | 4.2±3.8 | 10.0±12.4 | −5.9 (−9.7 to −2.1) | 3.5±4.0 | 8.7±10.7 | −5.9 (−9.3 to −2.4) |
| Area above curve of 70 mg/dl — mg/dl | 18±17 | 23±19 | 12±9 | 11±11 | 1 (−4 to 5) | 25±20 | 18±19 | 3 (−6 to 12) |
| Area above curve of 63 mg/dl — mg/dl | 9±10 | 12±11 | 6±5 | 6±6 | 0 (−3 to 2) | 13±11 | 9±10 | 1 (−4 to 6) |
| Glycated hemoglobin level of <7.5% — no./total no. (%) | 0/51 | 1/46 (2) | 36/46 (78) | 22/39 (56) | 21 (−1 to 42) | 35/47 (74) | 14/36 (39) | 33 (13 to 52) |
| Insulin end points | | | | | | | | |
| No. of participants evaluated | 47 | 44 | 46 | 39 | | 47 | 37 | |
| Total daily insulin — U/kg | 0.87±0.33 | 0.82±0.38 | 0.96±0.45 | 0.84±0.39 | 0.10 (−0.11 to 0.30) | 1.14±0.52 | 1.09±0.42 | 0.04 (−0.21 to 0.29) |
| Total daily basal insulin — U/kg | 0.33±0.12 | 0.36±0.21 | 0.52±0.31 | 0.37±0.26 | 0.14 (−0.01 to 0.29) | 0.62±0.35 | 0.49±0.21 | 0.14 (−0.01 to 0.30) |
| Total daily bolus insulin — U/kg | 0.54±0.24 | 0.46±0.28 | 0.44±0.22 | 0.46±0.23 | −0.06 (−0.17 to 0.05) | 0.52±0.31 | 0.60±0.32 | −0.11 (−0.27 to 0.06) |
| Other end points | | | | | | | | |
| No. of participants evaluated | 49 | 45 | 44 | 36 | | 43 | 31 | |
| Fasting C-peptide level divided by fasting glucose level‖** | 2.4±1.3 | 2.7±1.7 | 1.4±1.1 | 1.7±1.4 | −0.4 (−1.0 to 0.3) | 0.8±0.7 | 0.8±1.0 | −0.1 (−0.6 to 0.3) |
| AUC for plasma glucose level — mg/dl‖ | 227±46 | 221±37 | 255±41 | 260±54 | −8 (−34 to 18) | 260±39 | 293±64 | −35 (−69 to −2) |
| BMI percentile | | | | | | | | |
| No. of participants evaluated | 51 | 46 | 43 | 37 | | 47 | 33 | |
| Mean | 53±29 | 51±34 | 70±26 | 68±29 | 0.0 (−0.1 to 0.1) | 77±20 | 77±21 | 0.0 (−0.1 to 0.1) |
| Blood pressure¶ | | | | | | | | |
| No. of participants evaluated | 51 | 46 | 44 | 37 | | 46 | 32 | |
| Systolic — mm Hg | 110±9 | 108±8 | 113±8 | 111±9 | 2 (−2 to 6) | 112±9 | 108±9 | 3 (−2 to 8) |
| Diastolic — mm Hg | 65±6 | 66±8 | 65±7 | 64±8 | 1 (−2 to 4) | 67±7 | 65±5 | 1 (−2 to 5) |
| Lipid profile¶ | | | | | | | | |
| No. of participants evaluated | 46 | 44 | 42 | 38 | | 44 | 33 | |
| Total cholesterol — mg/dl | 172±28 | 172±29 | 149±19 | 153±26 | −3 (−11 to 5) | 148±21 | 149±27 | 1 (−10 to 12) |
| Triglycerides — mg/dl | 74±23 | 73±26 | 64±19 | 68±30 | −5 (−16 to 7) | 63±19 | 66±28 | −6 (−29 to 16) |
| HDL cholesterol — mg/dl | 60±10 | 59±9 | 55±9 | 57±12 | −2 (−8 to 4) | 55±10 | 55±11 | 0 (−6 to 7) |
| LDL cholesterol — mg/dl†† | 96±24 | 97±25 | 80±12 | 82±23 | 0 (−6 to 7) | 81±19 | 81±19 | 3 (−18 to 24) |



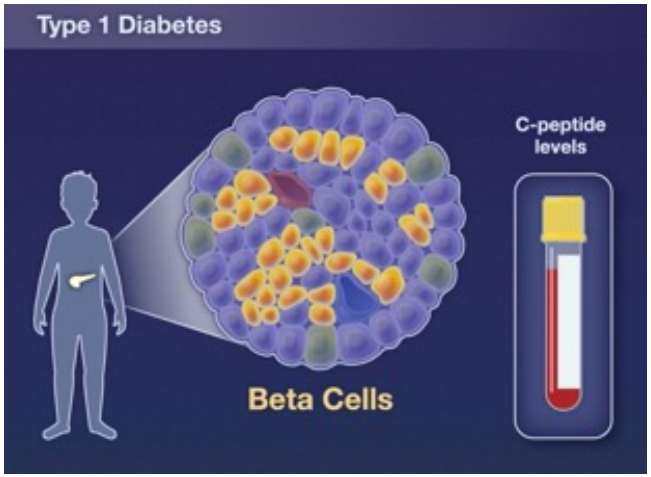

**Plasma C-Peptide Level and Glycated Hemoglobin Level.**

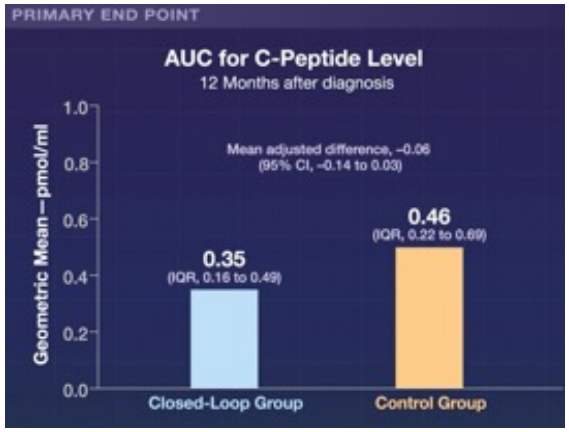
Panel A shows the area under the curve (AUC) for the plasma C-peptide level in response to a mixed-meal tolerance test at baseline and at 6, 12, and 24 months after the diagnosis of type 1 diabetes, and

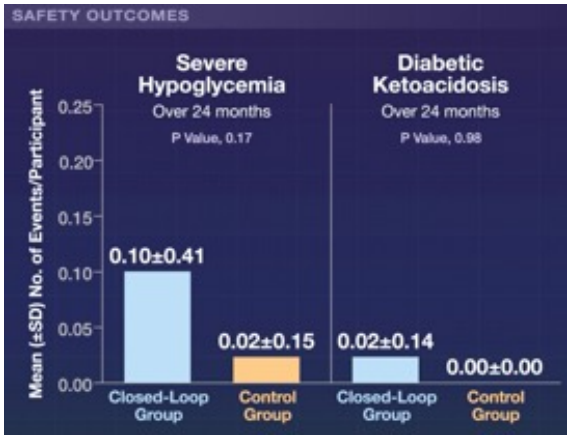
Panel B shows the glycated hemoglobin level from baseline to 24 months. The I bars represent interquartile ranges.

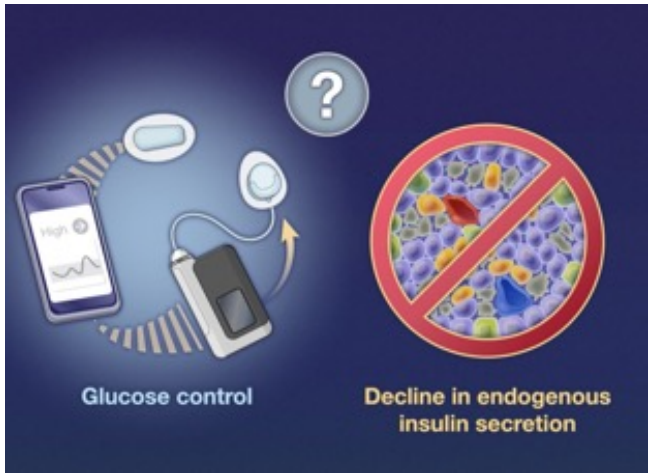
**Safety Outcomes during the 24-Month Intervention Period.**

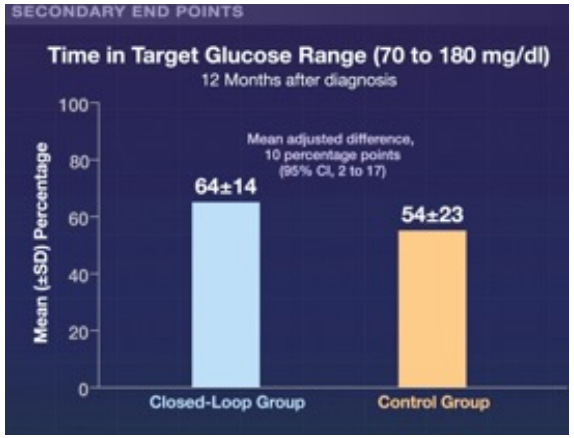
| Event | Closed-Loop Group (N=51) | Control Group (N=46) | P Value† |
|---|---|---|---|
| Severe hypoglycemia | | | |
| Total no. of events | 5 | 1 | |
| No. of events per participant | 0.10±0.41 | 0.02±0.15 | 0.17 |
| Incidence rate per 100 person-yr | 5.4 | 1.2 | 0.18 |
| No. of participants with ≥1 event (%) | 3 (6) | 1 (2) | 0.62 |
| Diabetic ketoacidosis | | | |
| Total no. of events | 1 | 0 | |
| No. of events per participant | 0.02±0.14 | 0.00±0.00 | 0.98 |
| Incidence rate per 100 person-yr | 1.1 | 0.0 | 0.98 |
| No. of participants with ≥1 event (%) | 1 (2) | 0 | >0.99 |
| Serious adverse events | | | |
| Total no. of events | 6 | 4 | |
| No. of events per participant | 0.12±0.38 | 0.09±0.28 | 0.64 |
| Other adverse events | | | |
| Total no. of events | 62 | 61 | |
| No. of events per participant | 1.22±1.84 | 1.33±2.09 | 0.63 |



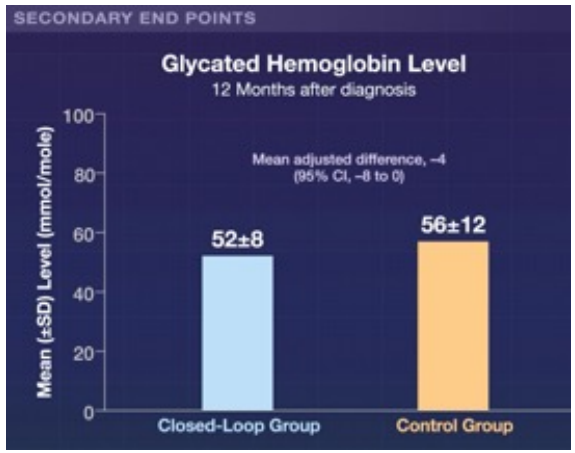





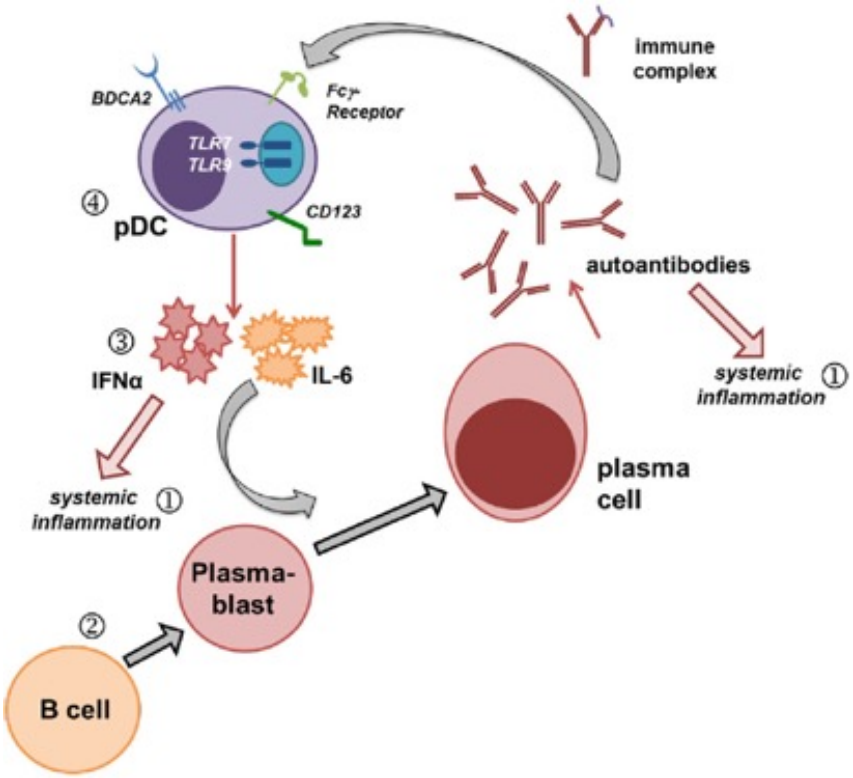

## LIMITATIONS AND REMAINING QUESTIONS

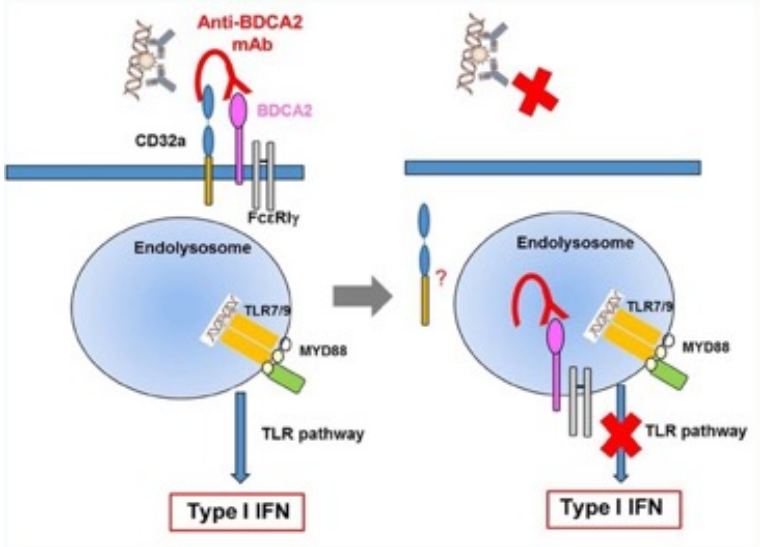
- Autoantibodies were not centrally measured at diagnosis.
- At trial entry, the closed-loop group had a higher incidence of diabetic ketoacidosis, which is associated with a more rapid decline in C-peptide secretion.
- Retention of participants was lower in the control group than in the closed-loop group.

# BDCA2 functions as a glycan-binding receptor

JEM 2001.

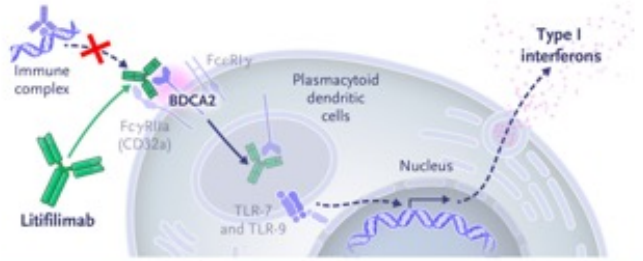
Plasmacytoid dendritic cells are present in lymphoid and nonlymphoid tissue and contribute substantially to both innate and adaptive immunity. Recently, we have described several monoclonal antibodies that recognize a plasmacytoid dendritic cell-specific antigen, which we have termed BDCA-2. Molecular cloning of BDCA-2 revealed that BDCA-2 is a novel type II C-type lectin, which shows 50.7% sequence identity at the amino acid level to its putative murine ortholog, the murine dendritic cell–associated C-type lectin 2. Anti–BDCA-2 monoclonal antibodies are rapidly internalized and efficiently presented to T cells, indicating that BDCA-2 could play a role in ligand internalization and presentation. Furthermore, ligation of BDCA-2 potently suppresses induction of interferon α/β production in plasmacytoid dendritic cells, presumably by a mechanism dependent on calcium mobilization and protein-tyrosine phosphorylation by src-family protein-tyrosine kinases. Inasmuch as production of interferon α/β by plasmacytoid dendritic cells is considered to be a major pathophysiological factor in systemic lupus erythematosus, triggering of BDCA-2 should be evaluated as therapeutic strategy for blocking production of interferon α/β in systemic lupus erythematosus patients.

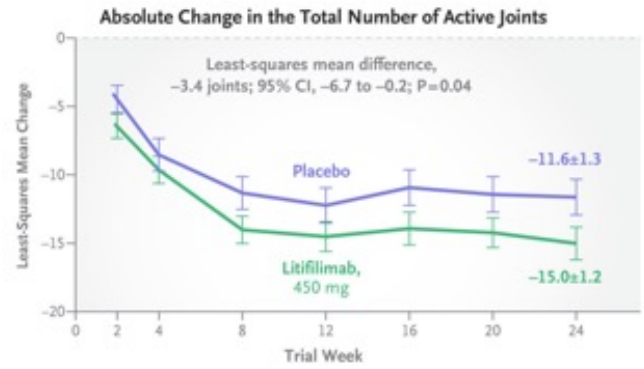


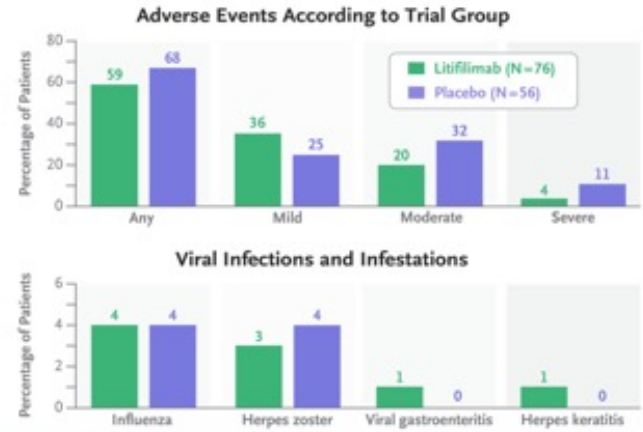



# Trial of Anti-BDCA2 Antibody Litifilimab for Systemic Lupus Erythematosus

Antibody-binding of blood dendritic cell antigen 2 (BDCA2), which is expressed exclusively on plasmacytoid dendritic cells, suppresses the production of type I interferon that is involved in the pathogenesis of systemic lupus erythematosus (SLE). The safety and efficacy of subcutaneous litifilimab, a humanized monoclonal antibody that binds to BDCA2, in patients with SLE have not been extensively studied. We conducted a phase 2 trial of litifilimab involving participants with SLE. The initial trial design called for randomly assigning participants to receive litifilimab (at a dose of 50, 150, or 450 mg) or placebo administered subcutaneously at weeks 0, 2, 4, 8, 12, 16, and 20, with the primary end point of evaluating cutaneous lupus activity. The trial design was subsequently modified; adults with SLE, arthritis, and active skin disease were randomly assigned to receive either litifilimab at a dose of 450 mg or placebo. The revised primary end point was the change from baseline in the total number of active joints (defined as the sum of the swollen joints and the tender joints) at week 24. Secondary end points were changes in cutaneous and global disease activity. Safety was also assessed.




**CONCLUSIONS**

Litifilimab administered at a dose of 450 mg was associated with a greater decrease from baseline in the number of active joints than placebo over a period of 24 weeks.

## Participants

Adults 18 to 75 years of age were eligible if they had SLE that met the 1997 classification criteria of the American College of Rheumatology at least 24 weeks before they provided written consent to participate in the trial. Eligible participants also had antinuclear antibodies at titers of 1:80 or greater, anti–double-stranded DNA (anti-dsDNA) antibody levels of 30 IU per milliliter or greater, or both. Prednisone at a dose of 20 mg or less per day (or another glucocorticoid at an equivalent dose) was allowed if the dose had been stable for at least 4 weeks before randomization.

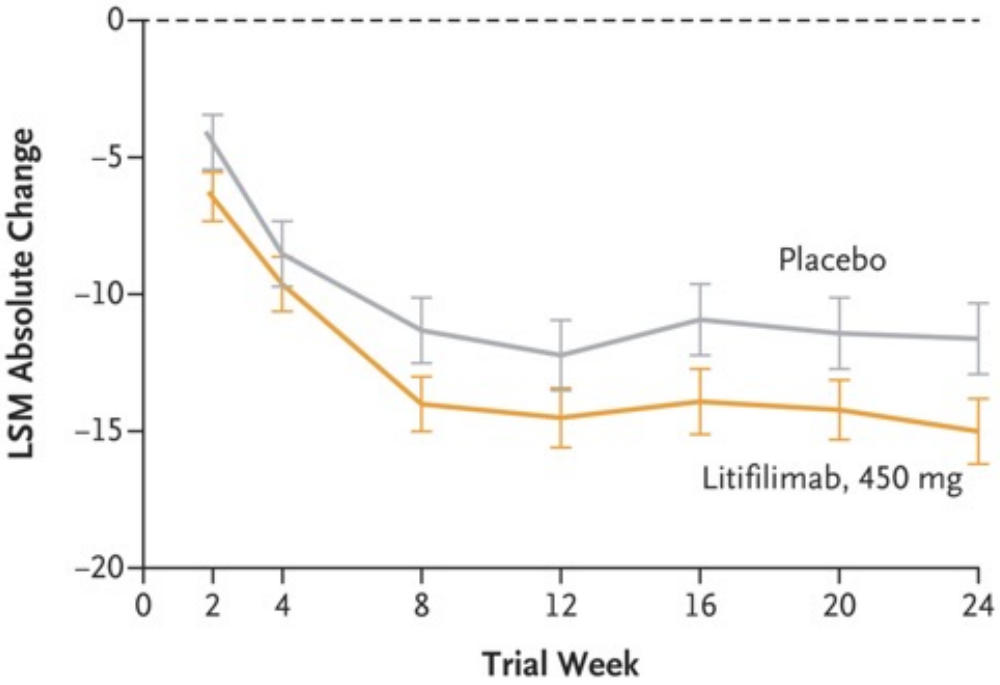
## End Points

The primary end point (originally, the percent change from baseline in the CLASI-A score at week 12) was changed in the amended protocol to the change from baseline in the total number of active joints (defined as the sum of the swollen joints and the tender joints) at week 24 according to a 28-joint assessment. A joint that was both swollen and tender could be counted twice. In a post hoc analysis, the total number of active joints was defined as the sum of the joints that were both swollen and tender.

| Characteristic | Litifilimab, 450 mg (N=64) | Placebo (N=56) |
|---|---|---|
| Age — yr | 40.3±11.4 | 41.4±12.2 |
| Female sex — no. (%) | 63 (98) | 49 (88) |
| Race or ethnic group — no. (%)† | | |
| Asian | 12 (19) | 13 (23) |
| White | 17 (27) | 16 (29) |
| American Indian or Alaska Native | 5 (8) | 8 (14) |
| Black or African American | 6 (9) | 0 |
| Not reported | 20 (31) | 15 (27) |
| Other | 4 (6) | 4 (7) |
| Cutaneous lupus erythematosus — no. (%) | 37 (58) | 38 (68) |
| Total no. of active joints | 17.4±9.1 | 18.6±10.3 |
| SLEDAI-2K score‡ | 10.5±3.2 | 9.8±3.0 |
| BILAG-2004 score§ | 20.5±6.7 | 20.2±6.5 |
| ≥1 A or ≥2 B — no. (%) | 56 (88) | 51 (91) |
| PGA score¶ | 6.1±1.8 | 6.2±1.3 |
| CLASI-A score‖ | 11.4±8.8 | 10.9±6.5 |
| Concomitant receipt of medications for SLE — no./total no. (%) | 62/64 (97) | 55/56 (98) |
| Antimalarial agent** | 55/62 (89) | 49/55 (89) |
| Glucocorticoids†††‡‡ | 56/62 (90) | 53/55 (96) |
| Antimalarial agent and glucocorticoid†† | 51/62 (82) | 47/55 (85) |
| Azathioprine | 10/62 (16) | 9/55 (16) |
| Methotrexate | 8/62 (13) | 9/55 (16) |
| Mycophenolate | 3/62 (5) | 7/55 (13) |
| Other allowed medications | 29/62 (47) | 16/55 (29) |

## Primary and Secondary Efficacy End Points Assessing Skin-Related and SLE Disease Activity at Weeks 12, 16, and 24.

**Absolute Change in the Total Number of Active Joints (Primary Efficacy End Point).**

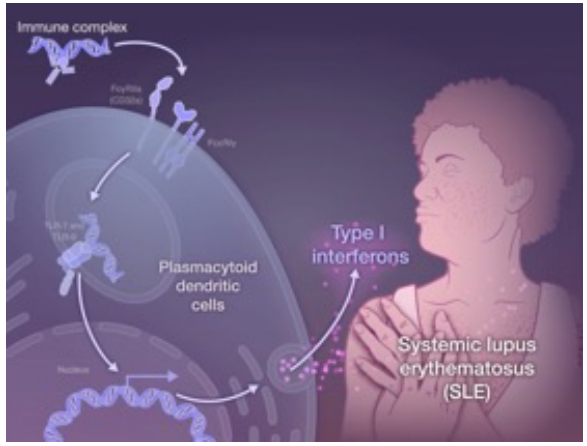


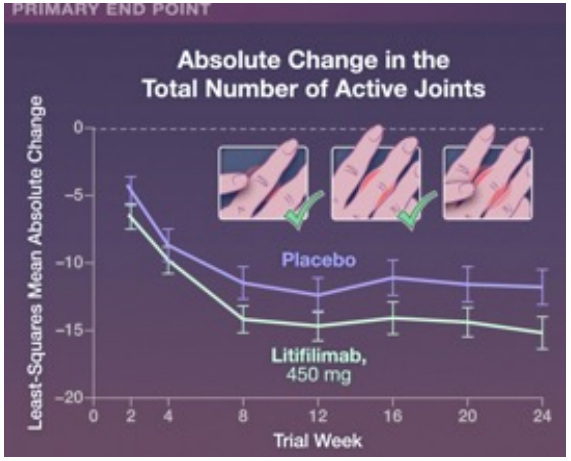

| End Point | Litifilimab, 450 mg (N=64) | Placebo (N=56) |
|---|---|---|
| **Primary** | | |
| No. of participants | 56 | 46 |
| Absolute change from baseline to wk 24 in total no. of active joints (28-joint assessment)† | | |
| LSM no. of joints | −15.0±1.2 | −11.6±1.3 |
| LSM difference vs. placebo (95% CI)‡ | −3.4 (−6.7 to −0.2) | |
| **Secondary: skin-related disease activity§** | | |
| Participants | 39 | 38 |
| CLASI-50 response: decrease of ≥50% from baseline in CLASI-A score | | |
| Participants — no./total no. (%) | 25/39 (64) | 16/38 (42) |
| LSM — % | 69.1±8.8 | 49.1±9.6 |
| LSM difference vs. placebo (95% CI) — percentage points | 20.0 (−1.3 to 41.3) | |
| Percent change from baseline in CLASI-A score | | |
| At wk 12 | | |
| LSM — % | −43.4±5.9 | −33.5±6.0 |
| LSM difference vs. placebo (95% CI) — percentage points | −9.9 (−25.9 to 6.1) | |
| At wk 16 | | |
| LSM — % | −49.1±6.2 | −40.1±6.3 |
| LSM difference vs. placebo (95% CI) — percentage points | −9.0 (−25.8 to 7.9) | |
| At wk 24 | | |
| LSM — % | −58.2±6.1 | −42.4±6.2 |
| LSM difference vs. placebo (95% CI) — percentage points | −15.7 (−32.3 to 0.8) | |
| Decrease of ≥4 points from baseline in CLASI-A score | | |
| Participants — no./total no. (%) | 28/39 (72) | 22/38 (58) |
| LSM — % | 73.9±8.7 | 58.1±9.5 |
| LSM difference vs. placebo (95% CI) — percentage points | 15.8 (−4.7 to 36.2) | |
| Decrease of ≥7 points from baseline in CLASI-A score | | |
| Participants — no./total no. (%) | 22/39 (56) | 13/38 (34) |
| LSM — % | 57.9±9.0 | 36.3±9.4 |
| LSM difference vs. placebo (95% CI) — percentage points | 21.6 (0.1 to 43.1) | |
| **Secondary: SLE disease activity¶** | | |
| SRI-4 response‖ | | |
| Participants — no./total no. (%) | 36/64 (56) | 16/56 (29) |
| LSM — % | 56.8±7.4 | 30.4±7.4 |
| LSM difference vs. placebo (95% CI) — percentage points | 26.4 (9.5 to 43.2) | |
| Absolute change in SLEDAI-2K score at wk 24 | | |
| LSM — percentage points | −4.4±0.5 | −2.6±0.5 |
| LSM difference vs. placebo (95% CI) — percentage points | −1.7 (−3.0 to −0.5) | |
| No new A score and ≤1 new B score on the BILAG-2004 index | | |
| Participants — no./total no. (%) | 55/64 (86) | 46/56 (82) |
| LSM change — % | 86.5±6.2 | 78.8±6.9 |
| LSM difference vs. placebo (95% CI) — percentage points | 7.7 (−7.6 to 23.0) | |
| Absolute change in PGA score — points | | |
| LSM | −2.2±0.3 | −2.0±0.3 |
| LSM difference vs. placebo (95% CI) | −0.2 (−0.9 to 0.6) | |

**Safety**

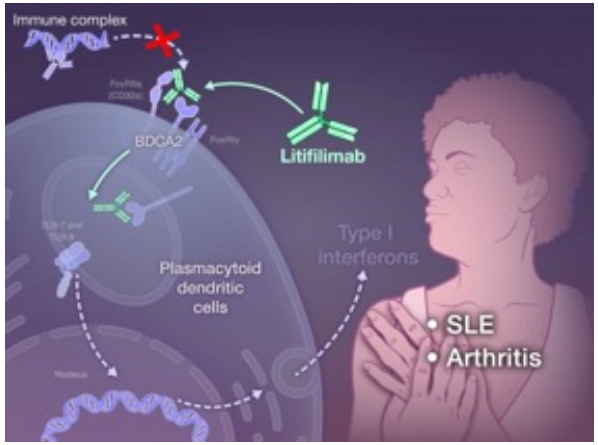
Serious adverse events were reported in four participants (5%) in the litifilimab groups and six participants (11%) in the placebo group. No serious adverse event was reported more than once in any group. Death was reported in 3 participants in the placebo group and in no participants in the litifilimab groups. No clinically significant abnormal laboratory tests or electrocardiogram results related to the receipt of litifilimab were reported.

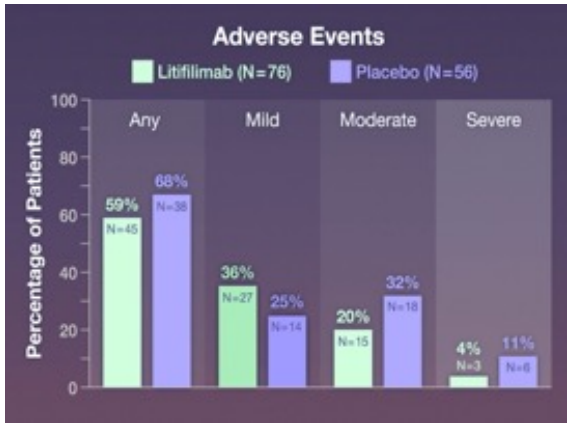
| Event | Pooled Litifilimab† (N = 76) | Placebo (N = 56) |
|---|---|---|
| | *number (percent)* | |
| Any event‡ | 45 (59) | 38 (68) |
| Severity§ | | |
| Mild | 27 (36) | 14 (25) |
| Moderate | 15 (20) | 18 (32) |
| Severe | 3 (4) | 6 (11) |
| Serious event | 4 (5) | 6 (11) |
| Serious event observed in >1 participant | 0 | 0 |
| Fatal event | 0 | 3 (5) |
| Event leading to discontinuation of litifilimab or placebo¶ | 2 (3) | 3 (5) |
| Event leading to trial withdrawal | 0 | 3 (5) |
| Viral infections and infestations | | |
| Influenza | 3 (4) | 2 (4) |
| Herpes zoster | 2 (3) | 2 (4) |
| Viral gastroenteritis | 1 (1) | 0 |
| Herpes keratitis | 1 (1) | 0 |
| Event observed in ≥5% of participants in the pooled litifilimab group | | |
| Diarrhea | 5 (7) | 3 (5) |
| Nasopharyngitis | 5 (7) | 2 (4) |
| Urinary tract infection | 5 (7) | 4 (7) |
| Fall | 4 (5) | 1 (2) |
| Headache | 4 (5) | 8 (14) |

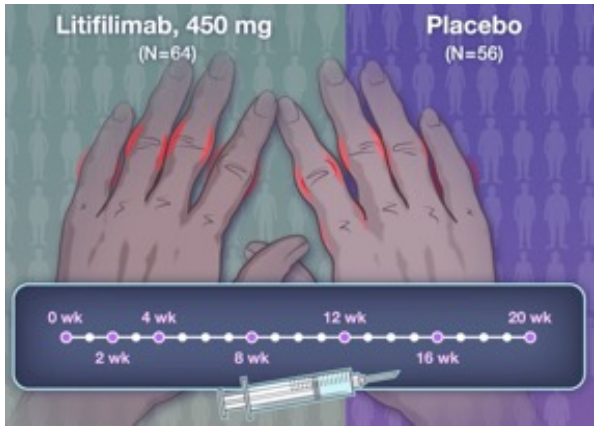


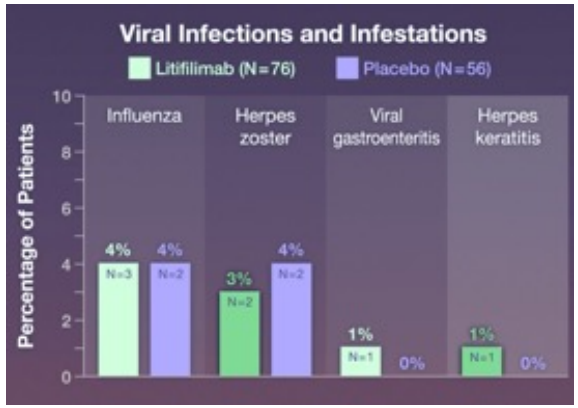







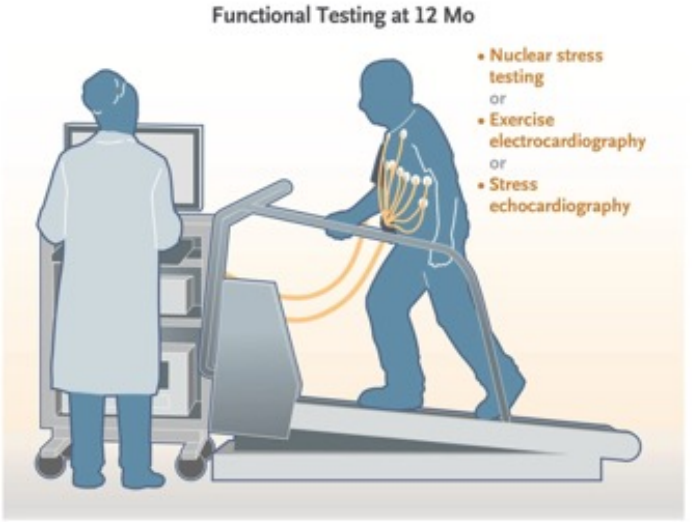



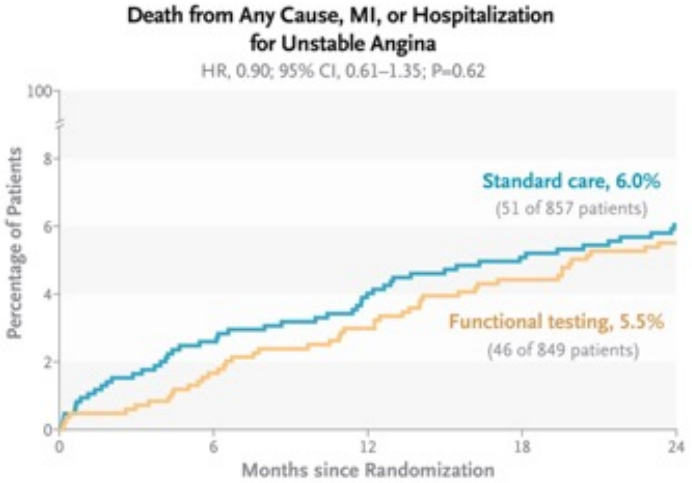




Litifilimab administered at a dose of 450 mg was associated with a greater decrease from baseline in the number of swollen and tender joints than placebo over a period of 24 weeks. Larger and longer trials are necessary to determine the effect and safety of litifilimab in patients with SLE.

# Routine Functional Testing or Standard Care in High-Risk Patients after PCI

There are limited data from randomized trials to guide a specific follow-up surveillance approach after myocardial revascularization. Whether a follow-up strategy that includes routine functional testing improves clinical outcomes among high-risk patients who have undergone percutaneous coronary intervention (PCI) is uncertain.
We randomly assigned 1706 patients with high-risk anatomical or clinical characteristics who had undergone PCI to a follow-up strategy of routine functional testing (nuclear stress testing, exercise electrocardiography, or stress echocardiography) at 1 year after PCI or to standard care alone. The primary outcome was a composite of death from any cause, myocardial infarction, or hospitalization for unstable angina at 2 years. Key secondary outcomes included invasive coronary angiography and repeat revascularization.




**CONCLUSIONS**

In high-risk patients who had undergone PCI for obstructive coronary artery disease, routine surveillance with functional testing, as compared with standard care, did not improve clinical outcomes at 2 years.

## Trial Population and Randomization

Patients older than 19 years of age who had undergone successful PCI with contemporary drug-eluting stents, bioresorbable scaffolds, or drug-coated balloons (only for in-stent restenosis) were eligible to participate. Eligible patients had to have at least one high-risk coronary-artery anatomical feature or clinical characteristic associated with an increased risk of ischemic or thrombotic events during follow-up.

### Trial Procedures and Follow-up

In the functional-testing group, cardiac stress testing (exercise electrocardiography [ECG], nuclear stress testing, or stress echocardiography) was performed at 12 months (±2 months) after randomization. Given the high rate of false positive exercise ECG tests indicating ischemia, simple exercise ECG testing was discouraged; therefore, a combined noninvasive imaging approach was recommended.

### Outcomes

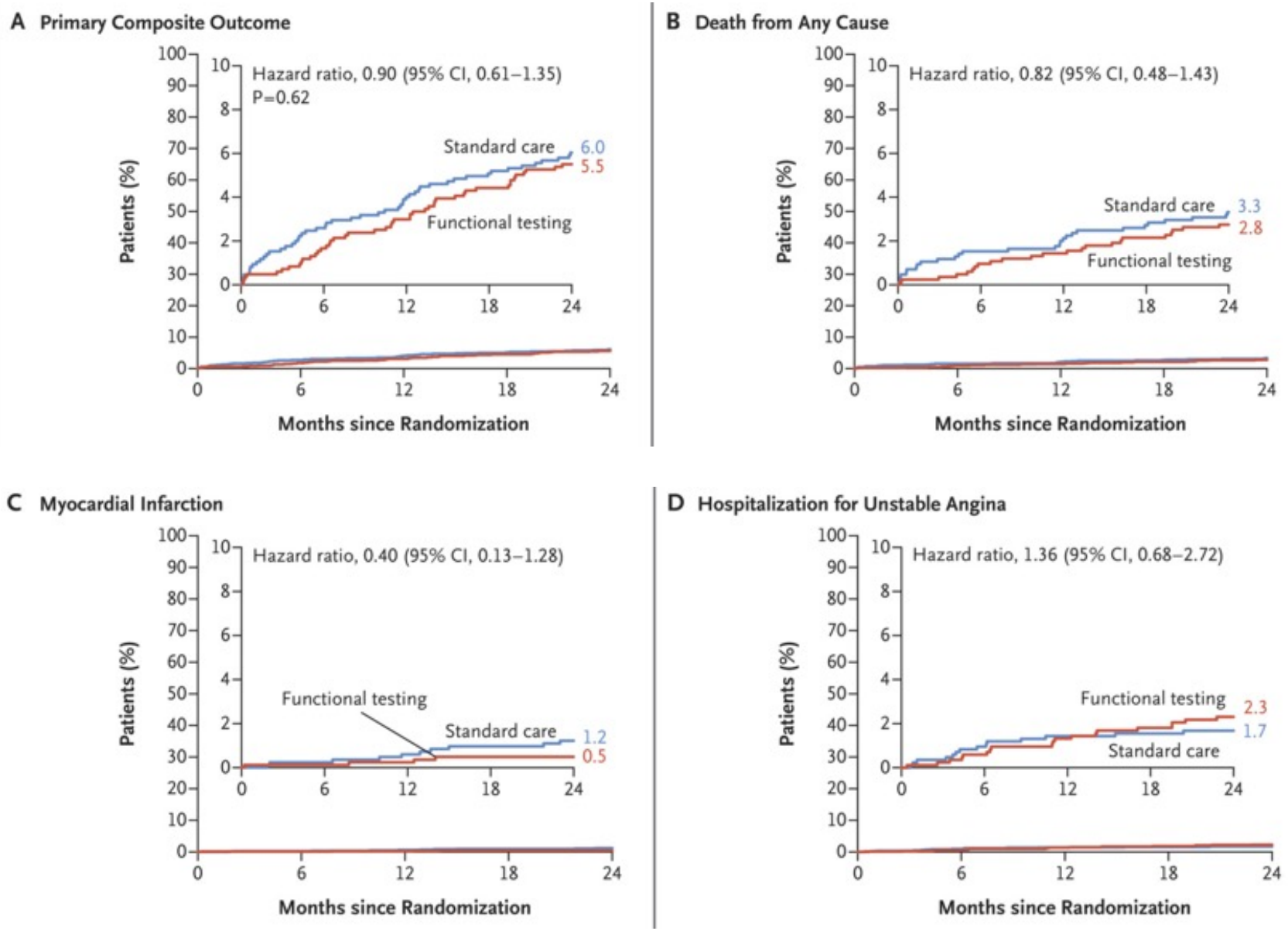
The primary outcome was a composite of major cardiovascular events (death from any cause, myocardial infarction, or hospitalization for unstable angina) at 2 years after randomization. Secondary outcomes included the following: individual components of the primary composite outcome; a composite of death or myocardial infarction; hospitalization for any reason (for either cardiac causes or noncardiac causes); invasive coronary angiography; and repeat revascularization procedures (target-lesion or nontarget-lesion revascularization).

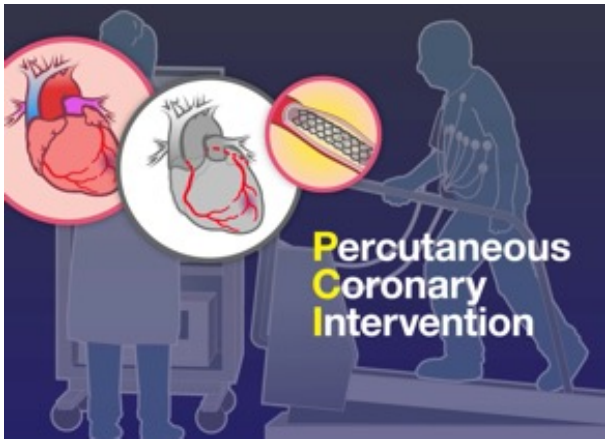
| Characteristic | Functional Testing (N=849) | Standard Care (N=857) |
|---|---|---|
| Age — yr | 64.6±10.3 | 64.8±10.3 |
| Male sex — no. (%) | 666 (78.4) | 690 (80.5) |
| Body-mass index† | 24.8±3.0 | 25.0±3.2 |
| Criteria for high risk after PCI — no. (%)‡ | | |
| High-risk anatomical characteristics | | |
| Left main disease | 181 (21.3) | 178 (20.8) |
| Bifurcation disease | 373 (43.9) | 369 (43.1) |
| Ostial lesion | 128 (15.1) | 127 (14.8) |
| Chronic total occlusion | 152 (17.9) | 190 (22.2) |
| Multivessel disease | 589 (69.4) | 602 (70.2) |
| ≥2 vessels stented | 376 (44.3) | 389 (45.4) |
| Restenotic lesion | 91 (10.7) | 103 (12.0) |
| Diffuse long lesion§ | 585 (68.9) | 611 (71.3) |
| Bypass graft disease | 4 (0.5) | 7 (0.8) |
| High-risk clinical characteristics | | |
| Diabetes mellitus | 321 (37.8) | 339 (39.6) |
| Use of insulin | 32 (3.8) | 41 (4.8) |
| Chronic renal failure¶ | 42 (4.9) | 45 (5.3) |
| Receipt of dialysis | 23 (2.7) | 26 (3.0) |
| Enzyme-positive acute coronary syndrome | 161 (19.0) | 170 (19.8) |
| Clinical indication for index PCI — no. (%) | | |
| Stable angina or silent ischemia | 598 (70.4) | 582 (67.9) |
| Unstable angina | 90 (10.6) | 105 (12.3) |
| Non-STEMI | 105 (12.4) | 98 (11.4) |
| STEMI | 56 (6.6) | 72 (8.4) |
| Left ventricular ejection fraction — %‖ | 58.8±9.1 | 58.3±10.1 |
| Procedural characteristics | | |
| Total no. of diseased lesions per patient | 2.2±1.2 | 2.3±1.1 |
| Total no. of treated lesions per patient | 1.4±0.7 | 1.5±0.7 |
| Total no. of stents per patient | 1.9±1.1 | 2.0±1.2 |
| Total stent length per patient — mm | 56.1±33.5 | 58.1±34.2 |
| Use of drug-eluting stents — no. (%) | 824 (97.1) | 821 (95.8) |
| Use of bioabsorbable scaffold — no. (%) | 6 (0.7) | 10 (1.2) |
| Use of drug-coated balloon — no. (%) | 46 (5.4) | 59 (6.9) |
| Intravascular ultrasound guidance — no. (%) | 622 (73.3) | 647 (75.5) |
| Fractional flow reserve assessed — no. (%) | 305 (35.9) | 304 (35.5) |

**Primary and Secondary Outcomes at 2 Years after Randomization.**

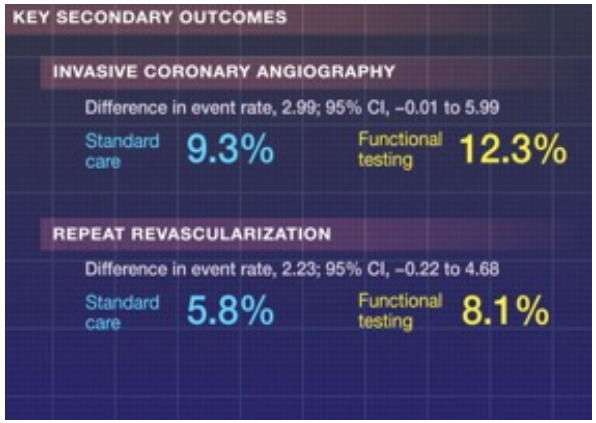
| Outcome | Functional Testing (N=849) | Standard Care (N=857) | Difference in Event Rates (95% CI) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|
| | *events (estimated percentage)* | | *percentage points* | | |
| Primary composite outcome† | 46 (5.5) | 51 (6.0) | −0.53 (−2.76 to 1.70) | 0.90 (0.61 to 1.35) | 0.62 |
| Death from any cause | 23 (2.8) | 28 (3.3) | −0.57 (−2.21 to 1.07) | 0.82 (0.48 to 1.43) | |
| Myocardial infarction | 4 (0.5) | 10 (1.2) | −0.73 (−1.61 to 0.16) | 0.40 (0.13 to 1.28) | |
| Hospitalization for unstable angina | 19 (2.3) | 14 (1.7) | 0.63 (−0.72 to 1.98) | 1.36 (0.68 to 2.72) | |
| Secondary outcomes | | | | | |
| Death or myocardial infarction | 27 (3.2) | 38 (4.5) | −1.28 (−3.12 to 0.56) | 0.71 (0.43 to 1.17) | |
| Hospitalization | | | | | |
| Any reason | 211 (25.5) | 190 (22.8) | 2.64 (−1.48 to 6.76) | 1.12 (0.92 to 1.36) | |
| Cardiac reason | 122 (14.8) | 110 (13.3) | 1.47 (−1.88 to 4.82) | 1.10 (0.85 to 1.43) | |
| Noncardiac reason | 89 (10.8) | 80 (9.6) | 1.16 (−1.75 to 4.07) | 1.13 (0.83 to 1.52) | |
| Invasive coronary angiography | 101 (12.3) | 77 (9.3) | 2.99 (−0.01 to 5.99) | | |
| Showing restenosis or obstructive CAD | 69 (68.3) | 45 (58.4) | | | |
| Showing no restenosis or obstructive CAD | 32 (31.7) | 32 (41.6) | | | |
| Repeat revascularization | 66 (8.1) | 48 (5.8) | 2.23 (−0.22 to 4.68) | | |
| Target-lesion revascularization | 34 (4.2) | 26 (3.2) | 1.00 (−0.81 to 2.81) | | |
| Nontarget-lesion revascularization | 32 (3.9) | 22 (2.7) | 1.24 (−0.48 to 2.96) | | |
| PCI | 64 (97.0) | 45 (93.8) | | | |
| CABG | 2 (3.0) | 3 (6.3) | | | |

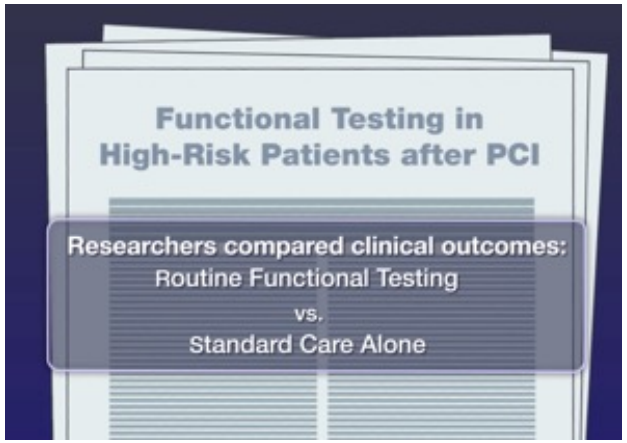
**Time-to-Event Curves for the Primary Composite Outcome and the Components of the Primary Composite Outcome.**

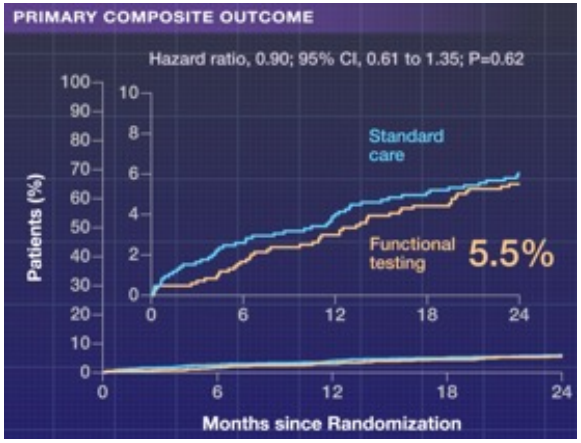


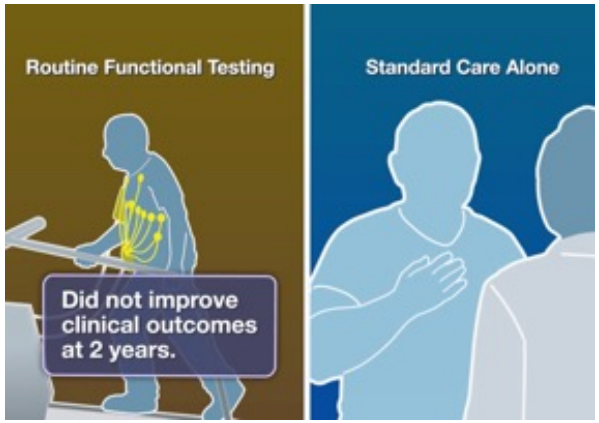


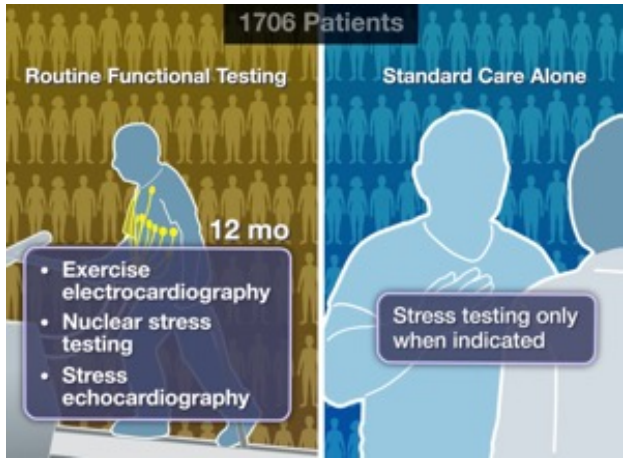






**LIMITATIONS**

- Routine stress testing included multiple methods with varying diagnostic accuracy.
- The trial did not assess quality of life, cost-effectiveness, or radiation exposure, which might be components of clinical decision making.
- Women were underrepresented.

# Personality Disorders

| Category | Features |
|---|---|
| Paranoid | Distrust and suspiciousness, with a tendency to interpret other people's motives as malevolent |
| Schizoid | Detachment from social relationships and restricted range of emotional expression |
| Schizotypal | Acute discomfort in close relationships, cognitive or perceptual distortions, and eccentricities of behavior |
| Antisocial | Disregard for, and violation of, the rights of others |
| Borderline | Instability in interpersonal relationships, self-image, and affects and marked impulsivity |
| Histrionic | Excessive emotionality and attention-seeking |
| Narcissistic | Grandiosity, need for admiration, and lack of empathy |
| Avoidant | Social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation |
| Dependent | Excessive need to be taken care of, resulting in submissive and clinging behavior |
| Obsessive–compulsive | Preoccupation with orderliness, perfectionism, and control |

**Abbreviated Diagnostic Criteria for Personality Disorder, According to the DSM-5, Section III, and the ICD-11.**

**DSM-5, Section III (Alternative Model for Personality Disorders)**

Patient has moderate or greater impairment in personality functioning (self-functioning and interpersonal functioning), rated >2 on a 5-point severity scale (ranging from 0 to 4), indicated by difficulty in at least two of the following four areas: identity, self-direction, empathy, or intimacy

Patient has maladaptive traits in one or more of the following five trait domains (or trait facets within domains): negative affectivity, detachment, antagonism, disinhibition, or psychoticism (odd, eccentric, or unusual behaviors or cognitions)

Personality dysfunction and trait expression are relatively inflexible and pervasive across multiple contexts (i.e., symptoms do not occur only at home or during certain times)

Personality dysfunction is stable across time, and onset can be traced back to adolescence or early adulthood

Dysfunction is not better explained by another mental disorder

Dysfunction is not attributable to physiological effects of a substance or another medical condition

Impairments are not better understood as normal for the person's developmental stage or sociocultural environment

**ICD-11**

Patient has impairments in aspects of self-functioning and interpersonal functioning, described as mild, moderate, or severe personality disorder

Personality disorder and personality difficulty can be further described in terms of five trait domain specifiers: negative affectivity, detachment, dissocial behavior (lack of empathy, callousness, or meanness), disinhibition, or anankastia (obsessive–compulsive behavior)

Disturbance has persisted over an extended period (e.g., ≥2 yr)

Disorder is manifested in patterns of cognition, emotional experience, emotional expression, and behavior that are maladaptive (e.g., inflexible or poorly regulated)

Disorder is manifested across a range of personal and social situations, although it may be consistently evoked by particular types of circumstances and not others

Symptoms are not due to direct effects of a medication or substance, including withdrawal effects, and are not better accounted for by another mental disorder, a disease of the nervous system, or another medical disorder

Disorder is associated with substantial distress or marked impairment in personal, family, social, educational, occupational, or other important areas of functioning

Personality disorder should not be diagnosed if the patterns of behavior characterizing the disturbance are developmentally appropriate or can be explained primarily by social or cultural factors, including sociopolitical conflict

**Categorically Defined Borderline Personality Disorder, According to the DSM-5, Section II.**

Patient has pervasive pattern of instability in interpersonal relationships, self-image, and affects and marked impulsivity, indicated by at least five of the following nine personality traits:

- Frantic efforts to avoid abandonment
- Unstable and intense interpersonal relationships
- Identity disturbance
- Impulsivity in at least two areas (e.g., spending, substance abuse, reckless driving, or binge eating)
- Recurrent suicidal or self-mutilating behavior
- Affective instability
- Chronic feelings of emptiness
- Inappropriate, intense anger or difficulty controlling anger
- Transient, stress-related paranoid ideation or severe dissociative symptoms

Symptoms are relatively inflexible and pervasive across multiple contexts (i.e., symptoms do not occur only at home or during certain times)

Symptoms result in significant distress or impairment in functioning

Symptoms or patterns of behavior are stable across time, and their onset can be traced back to adolescence or early adulthood

Symptoms are not better explained by another mental disorder

Symptoms are not attributable to physiological effects of a substance or another medical condition

## Treatment

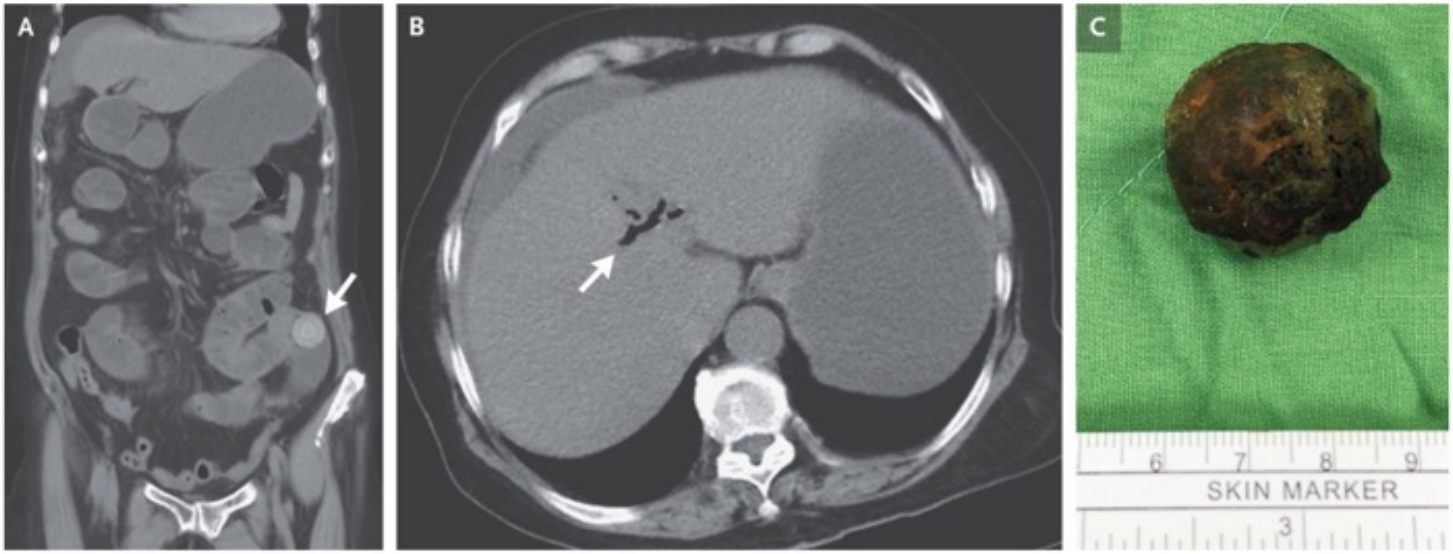
There have been few randomized disorder-specific trials of treatment for schizotypal, antisocial, narcissistic, avoidant, and obsessive–compulsive personality disorders. However, treatment protocols have been developed for BPD, and several randomized, controlled trials have been conducted to evaluate them. Although psychotropic medications such as mood stabilizers, antidepressant agents, and antipsychotic medications are routinely prescribed for persons with BPD, no medications have been approved by regulatory agencies for the treatment of BPD, and the effect of medications is uncertain. Pharmacotherapy has been used to alleviate symptoms of coexisting disorders, such as depression, anxiety, impulsivity, and psychosis, with little evidence that they address the specific symptoms of BPD.

A Cochrane review and national treatment guidelines suggest that psychotherapy may be an effective approach to treatment for BPD. The Cochrane review included randomized, controlled trials of psychotherapy that enrolled a total of 4507 patients, predominantly female patients 15 to 46 years of age in outpatient settings, with treatment lasting only up to 36 months. As compared with treatment as usual, psychotherapy had moderate but clinically relevant effects on symptom severity, self-harm, suicidality, and impaired psychosocial functioning (listed in approximately declining order of effectiveness).

## Conclusions and Future Directions

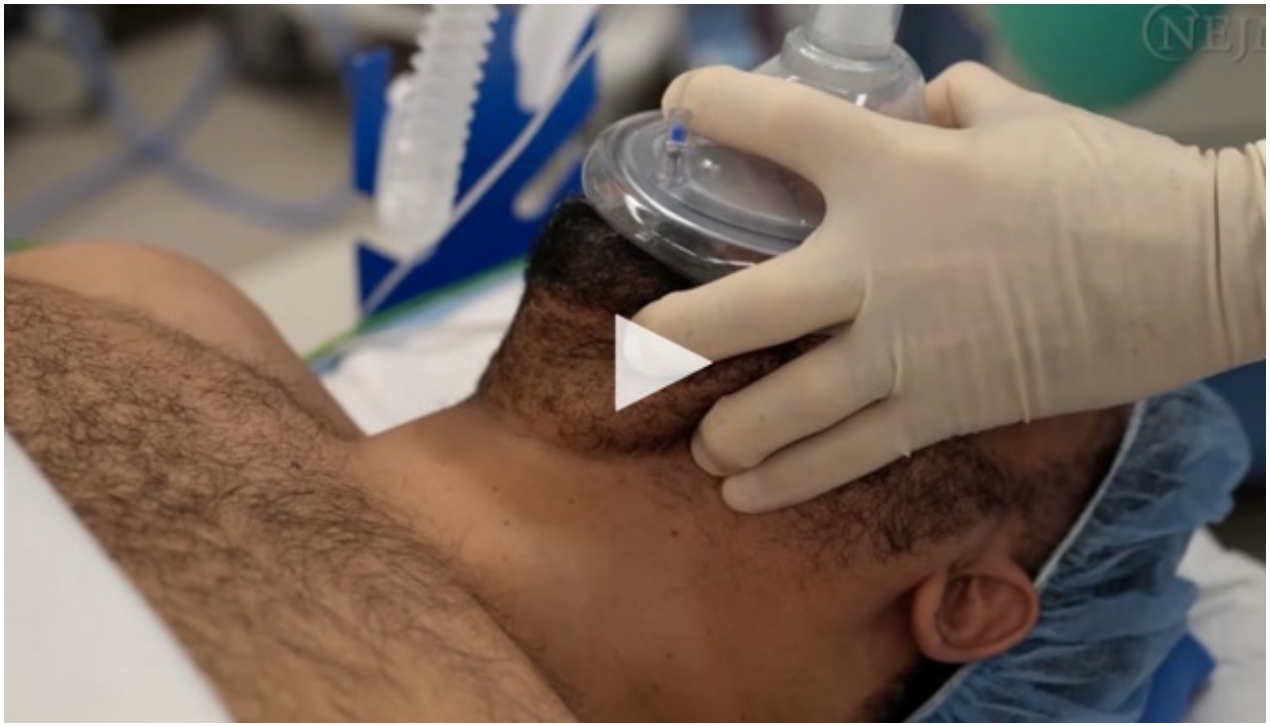
Inexpensive treatments that require fewer and shorter psychotherapy sessions delivered by less specialized mental health professionals are needed, since current approaches require considerable resources and patient involvement.

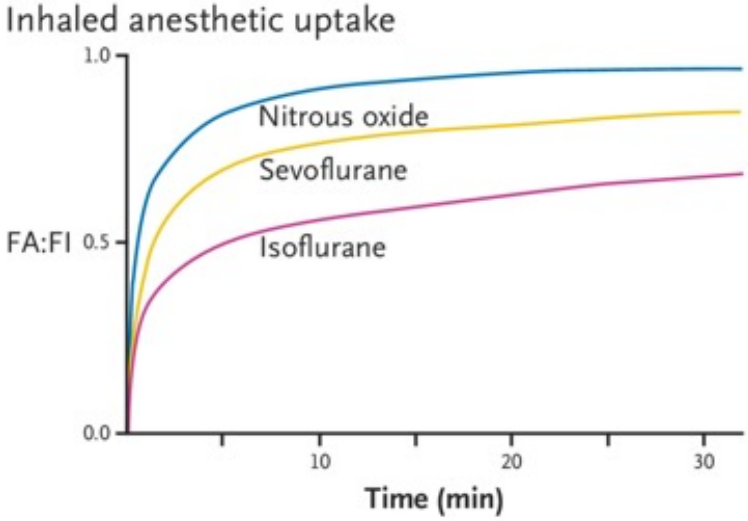
# Gallstone Ileus




A 74-year-old woman with hypertension presented to the emergency department with a 3-day history of epigastric pain, nausea, vomiting, fever, chills, weakness, and poor appetite. She also reported having had no bowel movements or flatus for the past 2 days. Her blood pressure was 150/128 mm Hg, and her heart rate 144 beats per minute. An abdominal examination revealed tenderness in the periumbilical region and in the left lower quadrant, with voluntary guarding and rebound tenderness. There was no jaundice. Computed tomography of the abdomen revealed obstruction of the ileum caused by a gallstone (Panel A, arrow) and pneumobilia (Panel B, arrow). This combination of radiologic findings — an ectopic gallstone, small-bowel obstruction, and pneumobilia — is known as Rigler's triad and aroused concern about gallstone ileus. Gallstone ileus is an uncommon cause of small-bowel obstruction, wherein a gallstone passes through a biliary–enteric fistula and becomes impacted within the intestinal lumen. The patient underwent a laparotomy, which confirmed gallstone ileus, and an enterotomy was performed to remove the gallstone (Panel C). Broad-spectrum antibacterial agents were administered after the procedure. The patient was discharged home on postoperative day 11 and was referred for an outpatient cholecystectomy.

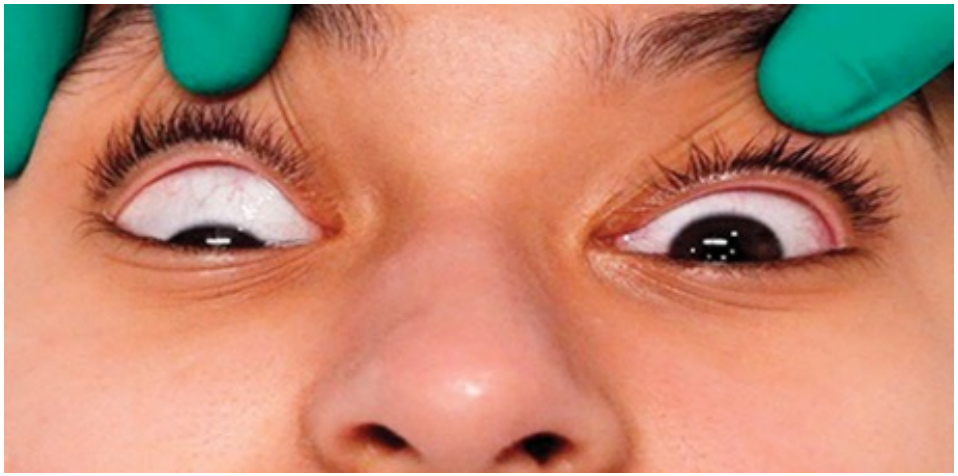
# Inhalational Induction



**Equipment.**

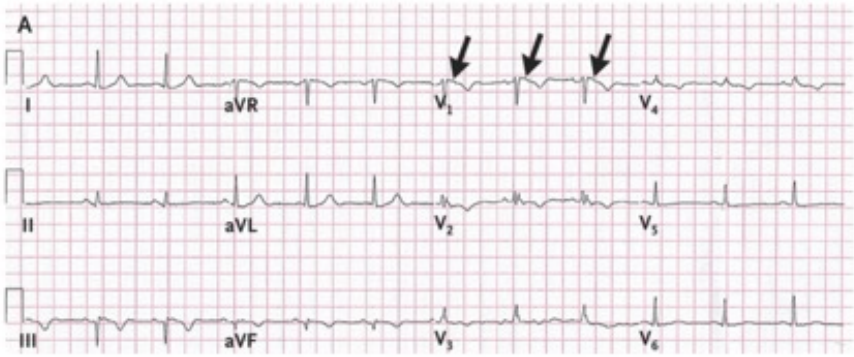
| |
|---|
| An anesthesia delivery apparatus with a circle breathing system |
| Physiological monitors, including a noninvasive device for measuring blood pressure, a pulse oximeter, and carbon dioxide and electrocardiographic monitors |
| A suction device |
| Airway-management equipment, such as a transparent mask, oral and nasal airways, a laryngoscope with appropriate handles and blades, supraglottic airway devices, and endotracheal tubes |
| Emergency medications, such as succinylcholine and atropine, for intramuscular or intravenous administration |
| Equipment needed to obtain intravenous access |
| Anesthetic medications, including induction and neuromuscular blocking agents |
| A precordial stethoscope with an ear piece, which is useful in institutions in which resources are limited. The stethoscope can provide continuous monitoring for changes in heart and breath sounds, especially in infants and young children. |

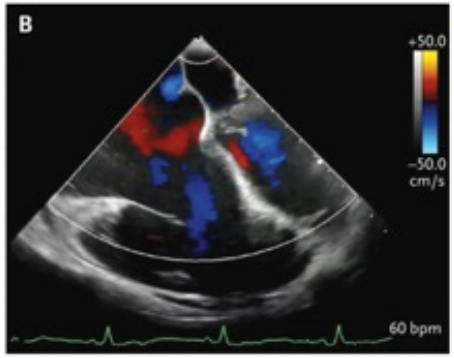


**Disconjugate Gaze.**

During the transition from the awake to the anesthetized state, the patient's gaze may become deviated or disconjugate.

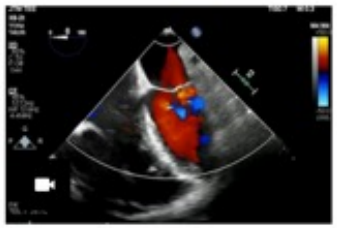
# Arrhythmogenic Right Ventricular Cardiomyopathy




A 59-year-old woman was admitted to the hospital with a subdural hematoma after an episode of unheralded syncope. She had lost a son to sudden cardiac death when he was 29 years of age. On hospital day 2, the patient began to have sustained monomorphic ventricular tachycardia with a pulse. Synchronized cardioversion was performed, and treatment with intravenous amiodarone was initiated. After the event, an electrocardiogram showed an incomplete right bundle-branch block, T-wave inversions in leads $V_1$ through $V_4$, and an epsilon wave in lead $V_1$ (Panel A, arrows). A transesophageal echocardiogram showed a severely dilated right ventricle (Panel B and video). Cardiac magnetic resonance imaging showed a right ventricular ejection fraction of 27% with regional akinesis. A diagnosis of arrhythmogenic right ventricular cardiomyopathy was made. An implantable cardioverter–defibrillator was placed, and treatment with metoprolol and antiarrhythmic medication was initiated. Genetic testing was performed, but a known pathogenic variant was not found. The patient was advised to avoid strenuous exercise, and cardiac evaluation was recommended for her first-degree relatives. On follow-up echocardiography 3 months later, the patient had a reduced left ventricular ejection fraction of 40%. Owing to the development of biventricular heart failure, she underwent evaluation for cardiac transplantation and currently awaits a heart transplant.

**Video**



Transesophageal Echocardiography (00:15)

# A 32-Year-Old Man with Confusion, Headache, and Fever

The patient had been in his usual state of health until 1 month before admission, when his wife noted that he began to have behavior suggestive of anxiety. Two weeks before admission, his wife noted that he began to have confusion; for example, he was unable to recall the ages of his children or to correctly identify the date. At that time, headache and neck stiffness developed. Two days before admission, fever developed. On the day of admission, the patient had worsening confusion and somnolence, and his wife brought him to the emergency department of this hospital for evaluation.

On presentation, the patient was not able to provide any history but was accompanied by his wife, who described his recent symptoms. His medical record showed a 10-year history of Behçet's disease, which had initially been complicated by oral and genital ulcers and intermittent fever. During the following decade, flares of Behçet's disease had been associated with various manifestations: pulmonary embolism, iliac artery aneurysm and dissection, bilateral renal vein thrombosis, erythema nodosum, deep venous thrombosis, uveitis, an inferior vena cava clot complicated by superior vena cava syndrome that led to thrombectomy, and renal infarction. The flares of Behçet's disease had usually included oral ulcers, genital ulcers, uveitis, or fever.

Past treatment for Behçet's disease had included azathioprine, cyclosporine, and prednisone. Two years before this presentation, treatment with azathioprine and cyclosporine was discontinued and adalimumab initiated. Attempts to taper the dose of prednisone resulted in flares of genital and oral ulcers. The frequency of adalimumab administration was increased to weekly, but genital and oral ulcers persisted. Thirteen months before this presentation, treatment with adalimumab was stopped and infliximab initiated. Diffuse arthralgias developed that were attributed to infliximab. Twelve months before this presentation, treatment with infliximab was stopped and golimumab initiated.

Other medical history included an episode of lymphocyte-predominant meningitis, which had been diagnosed during an evaluation for headache, fever, and neck pain 17 months before this presentation. During the episode, there was a 72-hour delay in performing lumbar puncture for cerebrospinal fluid (CSF) analysis because the patient had been taking apixaban for the treatment of venous thromboembolism. While he was awaiting lumbar puncture, broad-spectrum antibiotic agents were administered, and the headache, fever, and neck pain resolved. CSF analysis revealed normal levels of glucose and total protein, no red cells, and a nucleated-cell count of 88 per microliter (reference range, 0 to 5), with 97% lymphocytes and 3% monocytes. Nucleic acid amplification testing for herpes simplex virus type 1 and type 2 DNA was negative, and Gram's staining revealed no organisms. Antimicrobial therapy was discontinued, and the patient was discharged home.

| Variable | Reference Range, Adults* | On Admission |
|---|---|---|
| Hemoglobin (g/dl) | 13.7–17.5 | 14.5 |
| Hematocrit (%) | 41.0–53.0 | 44.2 |
| Mean corpuscular volume (fl) | 80.0–100.0 | 91.3 |
| White-cell count (per μl) | 4500–11,000 | 11,760 |
| Differential count (per μl) | | |
| Neutrophils | 1800–7700 | 9430 |
| Lymphocytes | 1000–4800 | 1100 |
| Monocytes | 200–1200 | 1080 |
| Eosinophils | 0–900 | 800 |
| Basophils | 0–300 | 300 |
| Platelet count (per μl) | 150,000–400,000 | 208,000 |
| Human immunodeficiency virus type 1 and type 2 antibody and antigen | Nonreactive | Nonreactive |
| Treponemal antibody | Nonreactive | Nonreactive |
| Cryptococcal antigen | Negative | Negative |
| Interferon-γ release assay for tuberculosis | Negative | Negative |
| C-reactive protein (mg/liter) | <8.0 | 39.1 |
| Erythrocyte sedimentation rate (mm/hr) | 0–13 | 24 |

On the fourth hospital day, a lumbar puncture was performed. The opening pressure was not obtained. CSF analysis revealed a normal total protein level, a glucose level of 40 mg per deciliter (2.2 mmol per liter; reference range, 50 to 75 mg per deciliter [2.8 to 4.2 mmol per liter]), a red-cell count of 2 per microliter (reference range, 0 to 5), and a nucleated-cell count of 284 per microliter (reference range, 0 to 5), with 72% lymphocytes, 13% neutrophils, 11% monocytes, and 4% unclassified cells. Nucleic acid amplification testing for herpes simplex virus type 1 and type 2 DNA was negative, and Gram's staining revealed no organisms. No acid-fast bacilli were observed on a mycobacterial smear, and no fungi were seen on examination of a fungal wet preparation. Testing of the CSF for cryptococcal antigen and enterovirus RNA was negative.

## Acute Confusional Encephalopathy

Patients with acute confusional encephalopathy are typically unable to engage in examination maneuvers, but simple observation of the patient can offer useful information. For example, patients with toxic metabolic encephalopathy usually have preserved eye movements and pupillary reactions. In contrast, the presence of nystagmus, impaired extraocular movements, or asymmetry in pupillary size or response to light is indicative of brain-stem distress.

## Acute Encephalitis

### *Neuro-Behçet's Disease*

The patient had had an episode of acute lymphocytic meningitis 17 months before this presentation. During the episode, no infectious causes were identified and symptoms resolved quickly. I suspect that this had been an episode of aseptic meningitis due to Behçet's disease. Patients with aseptic meningitis due to Behçet's disease are typically not as ill as patients with bacterial meningitis, and the presence of concurrent oral or genital ulcers, uveitis, or arthritis can be a clue to the diagnosis.

### *Adverse Effects of TNF-Inhibitor Therapy*

This patient had been receiving TNF-inhibitor therapy for 2 years before this presentation. Cerebral complications of TNF-inhibitor therapy are rare and characterized by demyelinating lesions with corresponding focal sensory, motor, and less often cognitive changes, which resemble features of multiple sclerosis.

### *Infectious Encephalitis*

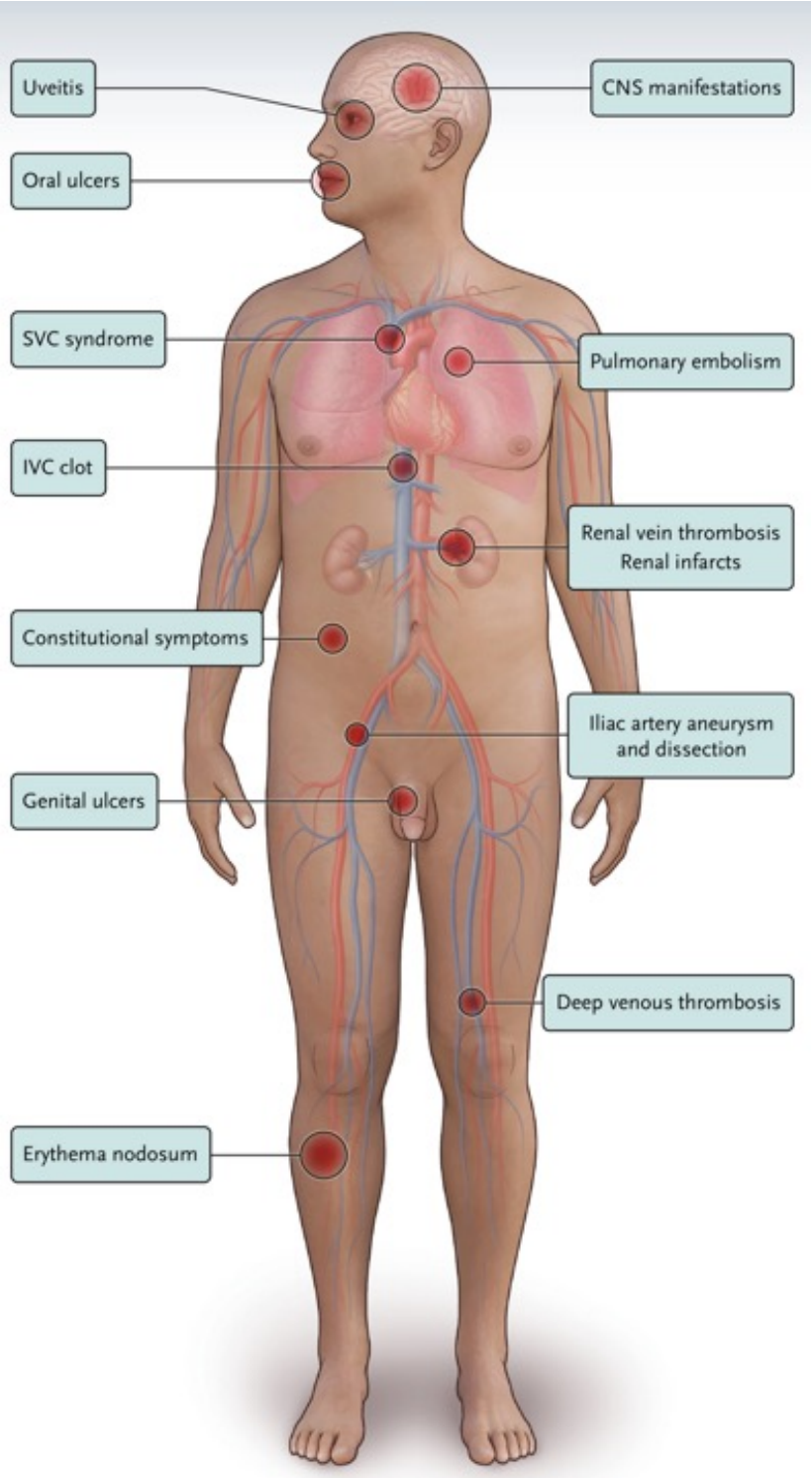
This patient's prolonged immunosuppression from treatment with prednisone and TNF-inhibitor therapy suggests the possibility of an opportunistic infection. Immunosuppression associated with TNF-inhibitor therapy confers a predisposition to reactivation of latent tuberculosis, invasive fungal infections, and bacterial infections, particularly listeriosis.

### *Autoimmune Encephalitis*

Autoimmune encephalitis is increasingly recognized as a condition that mimics infectious encephalitis. During the past 15 years, various encephalitic syndromes have been associated with specific neural antibodies, including antibodies against NMDA, LGI1, and γ-aminobutyric acid type A (GABAA) receptors, as well as anti–glutamic acid decarboxylase 65 (GAD65) antibodies and antineuronal nuclear antibodies type 1 (ANNA1).

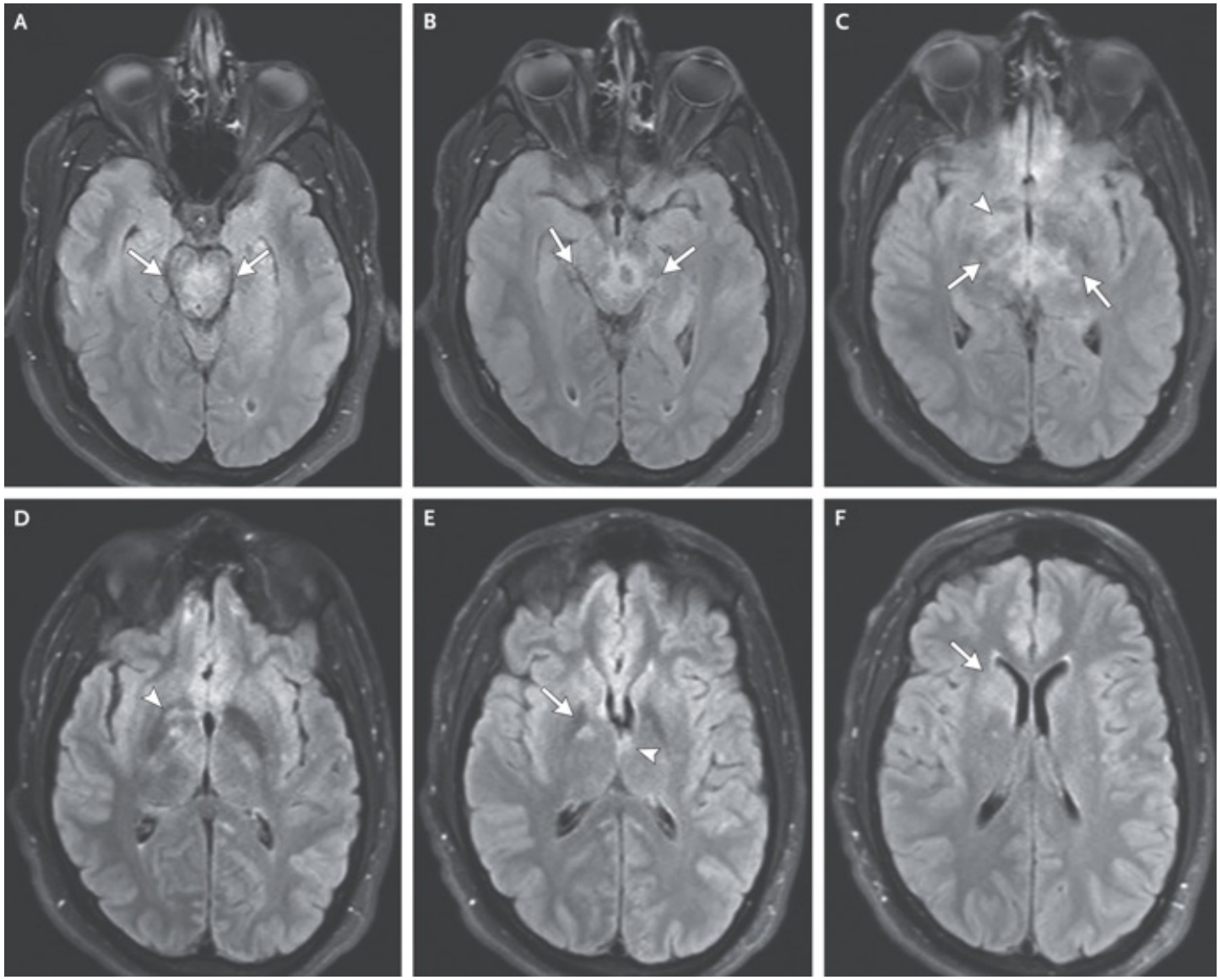
### *CNS Vasculitis*

Primary central nervous system (CNS) vasculitis is presumed to be immune-mediated, and affected patients can present with headache and acute confusional encephalopathy. However, the disease course is typically punctuated by strokes.




**Previous Manifestations of Behçet's Disease in This Patient.**

Behçet's disease is a vasculitis that affects arteries and veins of various sizes and multiple organ systems. Common manifestations of vasculitis — such as glomerulonephritis, diffuse alveolar hemorrhage, palpable purpura, and mononeuritis multiplex — are not usually seen in patients with Behçet's disease. Almost all patients with Behçet's disease have recurrent oral aphthous ulcers, which tend to be the first manifestation. In this patient, Behçet's disease had initially been complicated by oral and genital ulcers and intermittent fever. During the following decade, flares of Behçet's disease had been associated with various manifestations: pulmonary embolism, iliac artery aneurysm and dissection, bilateral renal vein thrombosis, erythema nodosum, deep venous thrombosis, uveitis, an inferior vena cava (IVC) clot complicated by superior vena cava (SVC) syndrome that led to thrombectomy, renal infarction, and aseptic meningitis. Of note, in patients with Behçet's disease, deep venous thrombosis and pulmonary embolism are inflammatory processes that respond primarily to immunosuppression. This patient did not have other common manifestations of Behçet's disease, such as inflammatory arthritis, colitis, or certain cutaneous findings such as pathergy, pseudofolliculitis, or acneiform lesions. CNS denotes central nervous system.




**MRI of the Head.**
Fluid-attenuated inversion recovery images show hyperintensity involving the upper central pons (Panel A, arrows), the midbrain (Panel B, arrows), the inferior thalami (Panel C, arrows), the right lentiform nucleus (Panels C and D, arrowheads), the right posterior limb of the internal capsule (Panel E, arrow), the left anterior thalamus (Panel E, arrowhead), and the right caudate head and upper anterior limb of the internal capsule (Panel F, arrow).

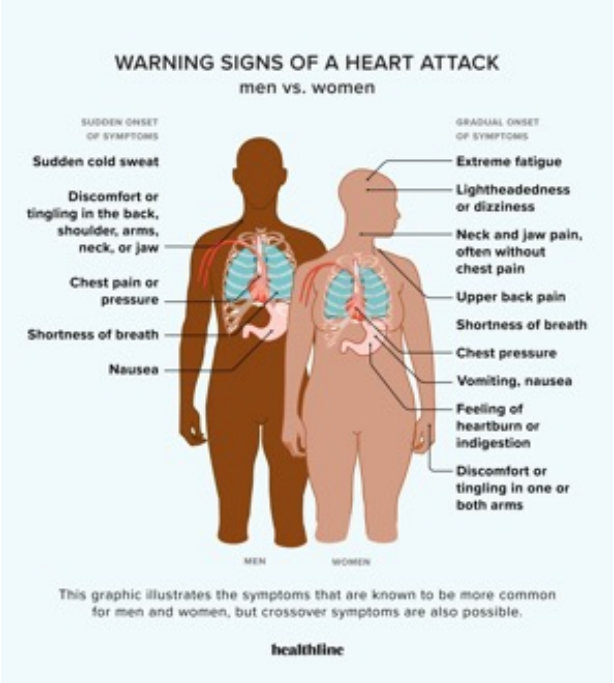
Published guidelines for treating neuro-Behçet's disease recommend combining glucocorticoid therapy with a conventional immunosuppressive agent such as azathioprine. TNF-inhibitor therapy is a viable alternative first-line therapy in combination with glucocorticoids for severe or refractory neuro-Behçet's disease, whereas cyclophosphamide has been used frequently in the past. Mycophenolate mofetil and methotrexate are considered to be alternatives to azathioprine, although published data regarding their efficacy in patients with neuro-Behçet's disease are limited.

The patient was seen in the neurology clinic 6 weeks after discharge. The prednisone dose had been decreased slowly since discharge, and the neuro-Behçet's disease remained in remission. The patient and his wife both reported steady improvement in his mental functioning. He recalled two out of three objects at 5 minutes and recalled all three objects with cueing; the remainder of the neurologic examination was normal. The patient was referred for neuropsychological evaluation and cognitive rehabilitation.

Three months after discharge, MRI of the head revealed resolution of the previous signal abnormalities in the basal ganglia, thalami, midbrain, and pons. There was no regional atrophy. Five months after discharge, the patient reported further improvement in his cognitive abilities and had returned to work; he was adapting to tasks by writing down details. He had persistent difficulty with recall.

It is remarkable that throughout the course of this patient's illness, he had no signs of brain-stem dysfunction. This represents a curious mismatch between the results of his neurologic examination and the prominent abnormalities in the brain stem and basal ganglia observed on MRI. It is possible that long-term and ongoing treatment with prednisone and TNF-inhibitor therapy, which had effectively controlled his systemic manifestations of Behçet's disease, attenuated neuroinflammation and dampened his neurologic symptoms.

# PURE Study Finds Women of All Income Levels Share Heart Disease Risks with Men




Women and men share most of the same risk factors for cardiovascular disease (CVD), a large international study has found. This was the first such study to include people from low- and middle-income countries where the burden of CVD is the greatest. Women had a lower risk of CVD than men. Also, diet was more strongly associated with CVD risk in woman than men.

"Women and men have similar CVD risk factors, which emphasizes the importance of a similar strategy for the prevention of CVD in men and women," said the paper's first author, Marjan Walli-Attaei, a research fellow at the Population Health Research Institute (PHRI) of McMaster University and Hamilton Health Sciences (HHS).

# Metabolic, behavioural, and psychosocial risk factors and cardiovascular disease in women compared with men in 21 high-income, middle-income, and low-income countries: an analysis of the PURE study


## Summary

**Background** There is a paucity of data on the prevalence of risk factors and their associations with incident cardiovascular disease in women compared with men, especially from low-income and middle-income countries.

**Methods** In the Prospective Urban Rural Epidemiological (PURE) study, we enrolled participants from the general population from 21 high-income, middle-income, and low-income countries and followed them up for approximately 10 years. We recorded information on participants' metabolic, behavioural, and psychosocial risk factors. For this analysis, we included participants aged 35–70 years at baseline without a history of cardiovascular disease, with at least one follow-up visit. The primary outcome was a composite of major cardiovascular events (cardiovascular disease deaths, myocardial infarction, stroke, and heart failure). We report the prevalence of each risk factor in women and men, their hazard ratios (HRs), and population-attributable fractions (PAFs) associated with major cardiovascular disease. The PURE study is registered with ClinicalTrials.gov, NCT03225586.

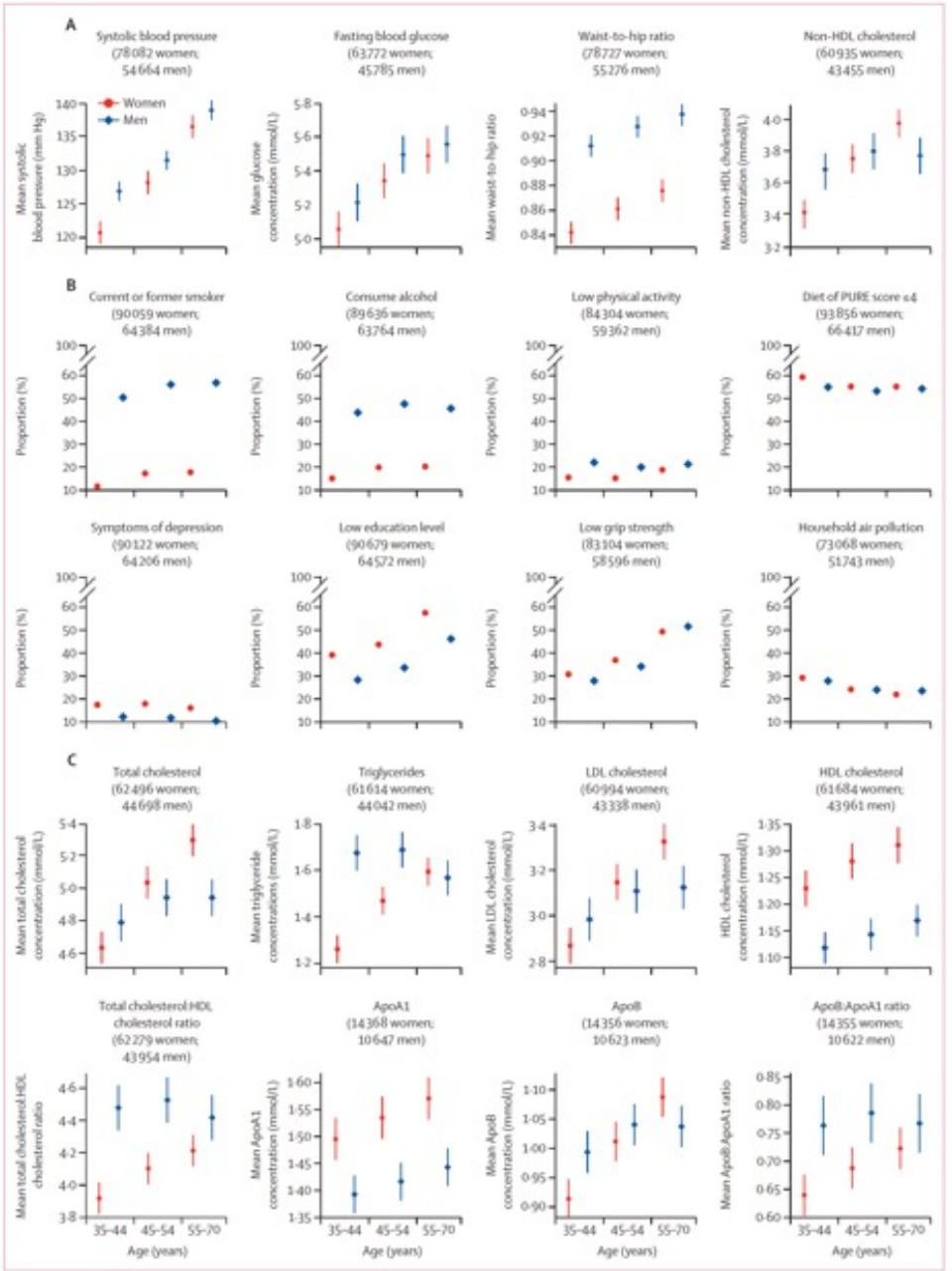
**Findings** In this analysis, we included 155 724 participants enrolled and followed-up between Jan 5, 2005, and Sept 13, 2021, (90 934 [58·4%] women and 64 790 [41·6%] men), with a median follow-up of 10·1 years (IQR 8·5–12·0). At study entry, the mean age of women was 49·8 years (SD 9·7) compared with 50·8 years (9·8) in men. As of data cutoff (Sept 13, 2021), 4280 major cardiovascular disease events had occurred in women (age-standardised incidence rate of 5·0 events [95% CI 4·9–5·2] per 1000 person-years) and 4911 in men (8·2 [8·0–8·4] per 1000 person-years). Compared with men, women presented with a more favourable cardiovascular risk profile, especially at younger ages. The HRs for metabolic risk factors were similar in women and men, except for non-HDL cholesterol, for which high non-HDL cholesterol was associated with an HR for major cardiovascular disease of 1·11 (95% CI 1·01–1·21) in women and 1·28 (1·19–1·39) in men, with a consistent pattern for higher risk among men than among women with other lipid markers. Symptoms of depression had a HR of 1·09 (0·98–1·21) in women and 1·42 (1·25–1·60) in men. By contrast, consumption of a diet with a PURE score of 4 or lower (score ranges from 0 to 8), was more strongly associated with major cardiovascular disease in women (1·17 [1·08–1·26]) than in men (1·07 [0·99–1·15]). The total PAFs associated with behavioural and psychosocial risk factors were greater in men (15·7%) than in women (8·4%) predominantly due to the larger contribution of smoking to PAFs in men (ie, 1·3% [95% CI 0·5–2·1] in women *vs* 10·7% [8·8–12·6] in men).

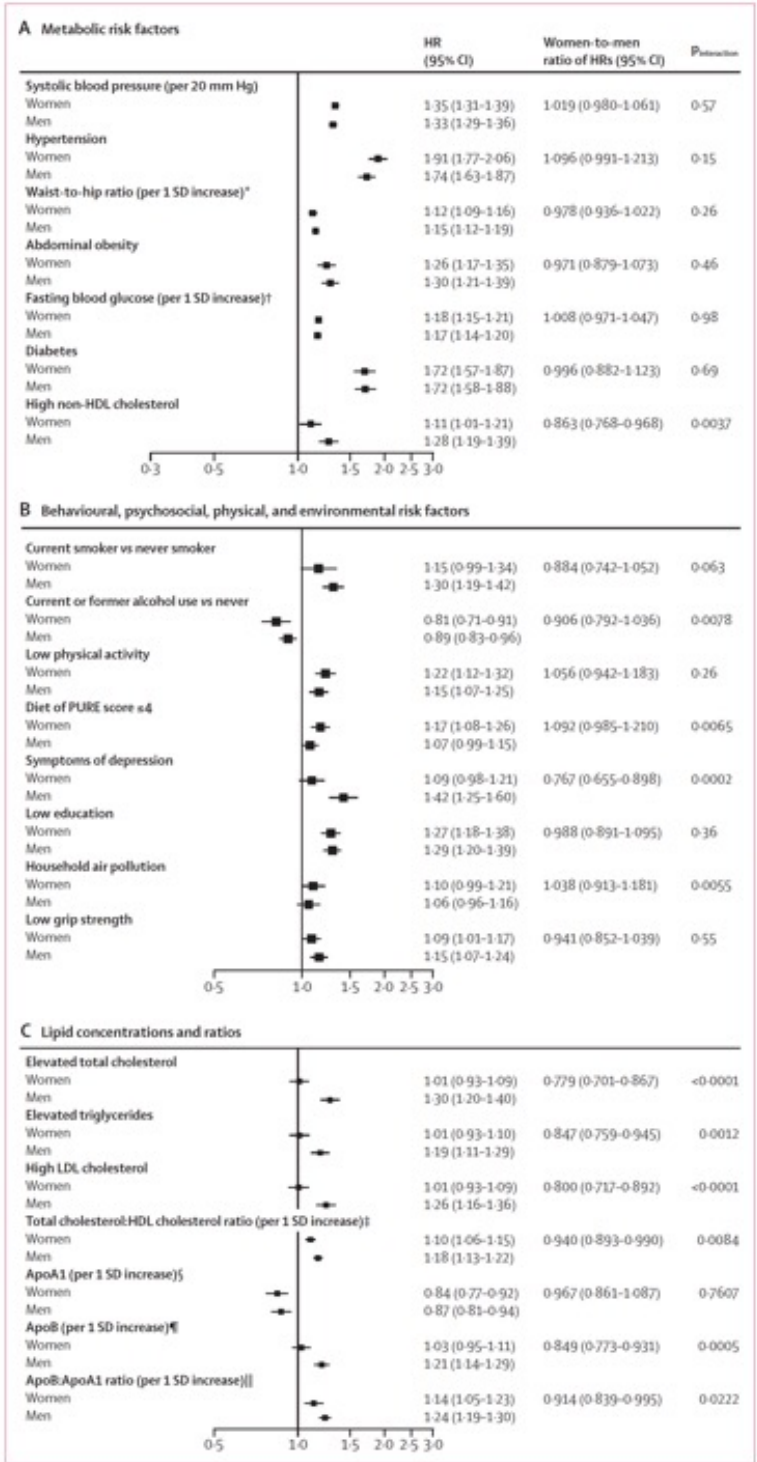
**Interpretation** Lipid markers and depression are more strongly associated with the risk of cardiovascular disease in men than in women, whereas diet is more strongly associated with the risk of cardiovascular disease in women than in men. The similar associations of other risk factors with cardiovascular disease in women and men emphasise the importance of a similar strategy for the prevention of cardiovascular disease in men and women.

| | Women (n=90 934) | Men (n=64 790) |
|---|---|---|
| **Sociodemographic characteristics** | | |
| Mean (SD) age, years | 49·8 (9·7) | 50·8 (9·8) |
| Living in high-income or upper-middle-income country* | 33 923 (37·3%) | 24 347 (37·6%) |
| Living in low-income or lower-middle-income country† | 57 011 (62·7%) | 40 443 (62·4%) |
| Living in rural community | 42 520 (46·8%) | 31 150 (48·1%) |
| **Number of events** | | |
| Major cardiovascular disease | 4280 (4·7%) | 4911 (7·6%) |
| Myocardial infarction | 1794 (2·0%) | 2490 (3·8%) |
| Stroke | 2126 (2·3%) | 2108 (3·3%) |
| Cardiovascular disease death | 1563 (1·7%) | 2072 (3·2%) |
| **Age-standardised incidence rate (95% CI) per 1000 person-years** | | |
| Major cardiovascular disease | 5·0 (4·9–5·2) | 8·2 (8·0–8·4) |
| Myocardial infarction | 2·1 (2·0–2·2) | 4·1 (4·0–4·3) |
| Stroke | 2·5 (2·4–2·6) | 3·5 (3·3–3·6) |
| Cardiovascular disease death | 1·8 (1·7–1·9) | 3·4 (3·3–3·6) |

Data are n (%), unless otherwise stated. Major cardiovascular disease is a composite of cardiovascular disease death, myocardial infarction, stroke, and heart failure. *Includes Argentina, Brazil, Canada, Chile, Malaysia, Poland, Saudi Arabia, South Africa, Sweden, Türkiye, and United Arab Emirates. †Includes Bangladesh, China, Colombia, India, Iran, Pakistan, Palestine, Philippines, Tanzania, and Zimbabwe.

***Table 1:*** **Baseline characteristics, number of events, and incidence rates during follow-up**






| | Women | Men |
|---|---|---|
| **Metabolic risk factors** | | |
| Hypertension | 23·3% (20·6 to 26·0) | 23·1% (20·1 to 26·2) |
| Abdominal obesity | 8·8% (5·5 to 12·2) | 4·0% (1·0 to 7·1) |
| Diabetes | 4·6% (3·4 to 5·9) | 4·4% (3·2 to 5·6) |
| High non-HDL cholesterol | 3·2% (–0·6 to 7·1) | 8·6% (4·4 to 12·7) |
| Total | 39·9% (36·4 to 43·4) | 40·1% (35·7 to 44·5) |
| **Behavioural, psychosocial, physical, and environmental risk factors** | | |
| Behavioural and psychosocial | | |
| Current smoker | 1·3% (0·5 to 2·1) | 10·7% (8·8 to 12·6) |
| Alcohol consumption (current or former) | –5·0% (–6·4 to –3·6) | –5·4% (–8·0 to –2·8) |
| Low physical activity | 2·1% (0·8 to 3·5) | 0·8% (–0·3 to 2·0) |
| Diet of PURE score of ≤4 | 6·5% (3·3 to 9·8) | 4·8% (2·3 to 7·3) |
| Symptoms of depression | –1·1% (–2·0 to –0·1) | 0·7% (–0·1 to 1·5) |
| Low education | 4·6% (1·7 to 7·5) | 4·1% (2·4 to 5·9) |
| Total | 8·4% (2·9 to 13·9) | 15·7% (10·4 to 21·0) |
| Low grip strength | 1·2% (–1·1 to 3·6) | 3·6% (1·3 to 5·9) |
| Household air pollution | 8·3% (6·4 to 10·3) | 5·9% (3·9 to 7·9) |
| Total | 58·0% (52·4 to 63·6) | 65·4% (61·0 to 69·7) |

Data are population-attributable fractions with 95% CIs in parentheses. Major cardiovascular disease is a composite of cardiovascular disease death, myocardial infarction, stroke, and heart failure.

***Table 2:*** **Population-attributable fractions for 12 risk factors with major cardiovascular disease in women and men**

## Research in context

### Evidence before this study

We searched MEDLINE databases, without language or publication date restrictions, on Sept 10, 2021, and again on June 8, 2022, for studies reporting on cardiovascular disease risk factors in women and men. Our key search terms included ("risk factors" OR "hypertension" OR "diabetes" OR "dyslipidaemia" OR "cholesterol" OR "smoking" OR "tobacco use" OR "diet" OR "depression" OR "alcohol" OR "physical activity" OR "waist-to-hip ratio" OR "abdominal obesity" OR "obesity") AND "cardiovascular disease" AND ("women" OR "gender" OR "sex differences"). Previous studies have emphasised that some risk factors, such as hypertension, diabetes, and smoking, are more strongly associated with cardiovascular disease in women than men. These findings would suggest that women would benefit from more intensive management of these risk factors to reduce their risk of cardiovascular disease. However, much of the existing evidence was from high-income countries (mainly North America and Europe). There is a paucity of prospective data from low-income and middle-income countries. We did not find any study that reported on differences between women and men in the levels of metabolic, behavioural, and psychosocial risk factors, and also whether the associations between these risk factors and cardiovascular disease differ between women and men using a community-based sample from high-income, middle-income, and low-income countries.

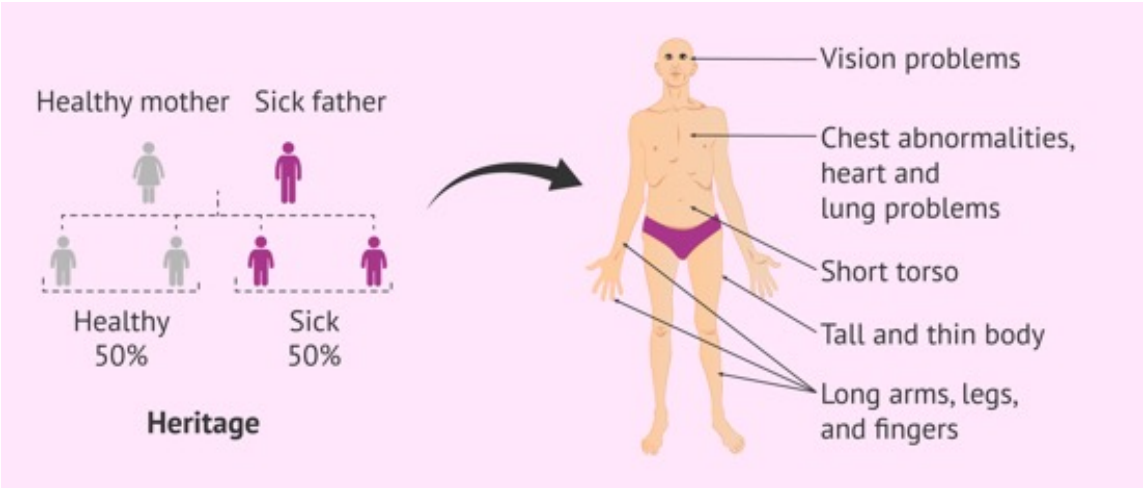
### Added value of this study

To our knowledge, this is the first comprehensive overview of the prevalence of metabolic, behavioural, and psychosocial risk factors, their hazard ratios (HRs), and population-attributable fractions for cardiovascular disease in women and men aged 35–70 years. Our results extend previous studies by reporting on a geographically diverse population from five continents, who did not have a history of cardiovascular disease and were followed up for a median of 10·1 years. Compared with men, women presented with a more favourable cardiovascular risk profile. The HRs for metabolic risk factors were similar in women and men, except for non-HDL cholesterol, for which larger HRs for cardiovascular disease were observed in men. Larger HRs for symptoms of depression were observed for men than for women. By contrast, diet was more strongly associated with cardiovascular disease in women than in men, which has not been described previously and requires independent confirmation. The total PAFs associated with behavioural and psychosocial risk factors were greater in men than in women due to the larger contribution of smoking to the overall PAFs in men.

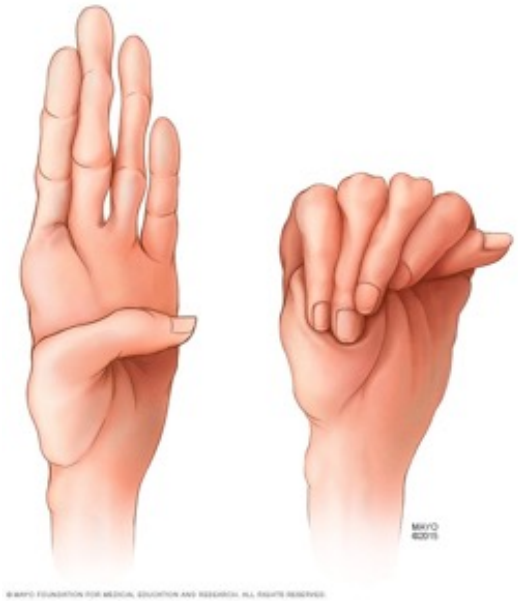
### Implications of all the available evidence

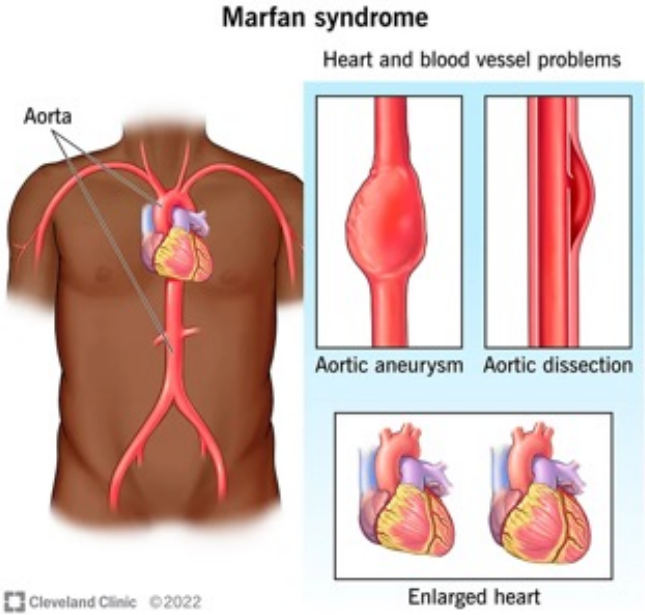
Our results emphasise the importance of a similar strategy for the prevention of cardiovascular disease in both sexes. However, the increased risk of cardiovascular disease in men might be substantially attenuated with better reductions in tobacco use and lipid concentrations.

# Marfan‘s syndrome









# Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of randomised trials


## Summary

**Background** Angiotensin receptor blockers (ARBs) and β blockers are widely used in the treatment of Marfan syndrome to try to reduce the rate of progressive aortic root enlargement characteristic of this condition, but their separate and joint effects are uncertain. We aimed to determine these effects in a collaborative individual patient data meta-analysis of randomised trials of these treatments.

**Methods** In this meta-analysis, we identified relevant trials of patients with Marfan syndrome by systematically searching MEDLINE, Embase, and CENTRAL from database inception to Nov 2, 2021. Trials were eligible if they involved a randomised comparison of an ARB versus control or an ARB versus β blocker. We used individual patient data from patients with no prior aortic surgery to estimate the effects of: ARB versus control (placebo or open control); ARB versus β blocker; and indirectly, β blocker versus control. The primary endpoint was the annual rate of change of body surface area-adjusted aortic root dimension Z score, measured at the sinuses of Valsalva.

**Findings** We identified ten potentially eligible trials including 1836 patients from our search, from which seven trials and 1442 patients were eligible for inclusion in our main analyses. Four trials involving 676 eligible participants compared ARB with control. During a median follow-up of 3 years, allocation to ARB approximately halved the annual rate of change in the aortic root Z score (mean annual increase 0·07 [SE 0·02] ARB *vs* 0·13 [SE 0·02] control; absolute difference –0·07 [95% CI –0·12 to –0·01]; p=0·012). Prespecified secondary subgroup analyses showed that the effects of ARB were particularly large in those with pathogenic variants in fibrillin-1, compared with those without such variants (heterogeneity p=0·0050), and there was no evidence to suggest that the effect of ARB varied with β-blocker use (heterogeneity p=0·54). Three trials involving 766 eligible participants compared ARBs with β blockers. During a median follow-up of 3 years, the annual change in the aortic root Z score was similar in the two groups (annual increase –0·08 [SE 0·03] in ARB groups *vs* –0·11 [SE 0·02] in β-blocker groups; absolute difference 0·03 [95% CI –0·05 to 0·10]; p=0·48). Thus, indirectly, the difference in the annual change in the aortic root Z score between β blockers and control was –0·09 (95% CI –0·18 to 0·00; p=0·042).

**Interpretation** In people with Marfan syndrome and no previous aortic surgery, ARBs reduced the rate of increase of the aortic root Z score by about one half, including among those taking a β blocker. The effects of β blockers were similar to those of ARBs. Assuming additivity, combination therapy with both ARBs and β blockers from the time of diagnosis would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery.

| | Treatment comparison (daily doses) | Number of randomly assigned patients | Median age, years | Median follow-up, months | Measures collected, months | Data provided to MTT secretariat | Main outcome measures | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Body surface area | | Aortic dimension at the sinuses of Valsalva (mm) | | Z score at the sinuses of Valsalva | |
| | | | | | | | Method | Baseline, mean (SD) | Methods | Baseline, mean (SD) | Method | Baseline, mean (SD) |
| **ARB *vs* control (placebo or open control)** | | | | | | | | | | | | |
| Marfan Sartan[18] | Losartan (50–100 mg) *vs* placebo | 299 | 26 | 42 | 0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 | Yes | * | 1·83 (0·27) | Echo, end diastole, and leading edge to leading edge | 38·8 (5·8) | Roman and colleagues[33] | 3·60 (2·15) |
| COMPARE[20] | Losartan (50–100 mg) *vs* open control | 233 | 35 | 36 | 0, 36 | Yes | Haycock and colleagues[34] | 2·02 (0·24) | MRI, end diastole, and inner edge to outer edge | 44·3 (5·2) | † | 4·42 (1·75) |
| AIMS[19] | Irbesartan (150–300 mg) *vs* placebo | 192 | 18 | 46 | 0, 12, 24, 36, 48, 60 | Yes | DuBois and Du Bois[35] | 1·71 (0·40) | Echo, peak systole, and inner edge to inner edge | 34·4 (5·6) | Devereux and colleagues[36] | 3·24 (2·04) |
| Ghent Marfan[15] | Losartan (25–100 mg) *vs* placebo | 22 | 36 | 36 | 0, 6, 12, 24, 36 | Yes | DuBois and Du Bois[35] | 1·98 (0·24) | Echo and leading edge to leading edge | 41·2 (3·5) | † | 3·55 (1·04) |
| Taiwanese trial[32] | Losartan plus β blocker *vs* β blocker‡ | 28 | 13 | 35 | 0, 6, 12, 18, 24, 30, 35 | Yes (but only included in sensitivity analyses) | Unknown | 1·39 (0·38) | Echo and inner edge to inner edge | 32·9 (6·1) | † | 2·07 (1·89) |
| Italian trial[19] | Losartan (100 mg adults or ≤1·4 mg/kg children) plus nebivolol (10 mg adults or ≤0·16 mg/kg children) *vs* nebivolol (10 mg adults or ≤0·16 mg/kg children) | 160§ | Unknown | 48 | 0, 12, 24, 36, 48 | No (trial yet to publish its full results) | Unknown | .. | .. | .. | .. | .. |
| **ARB *vs* β blocker** | | | | | | | | | | | | |
| PHN[24] | Losartan (0·4–1·4 mg/kg) *vs* atenolol (0·5–4·0 mg/kg) | 608 | 11 | 36 | 0, 6, 12, 24, 36 | Yes | Haycock and colleagues[34] | 1·28 (0·48) | Echo, systole, and inner edge to inner edge | 33·6 (7·1) | Sluysmans and Colan[37] | 4·32 (1·35) |
| LOAT[21] | Losartan (12·5–100 mg) *vs* atenolol (12·5–100 mg) | 140 | 26 | 36 | 0, 36 | Yes | DuBois and Du Bois[35] | 1·75 (0·36) | MRI and end diastolic frame | 36·1 (6·2) | Devereux and colleagues[36] | 3·17 (2·21) |
| Canadian trial[17] | Losartan (25 mg) *vs* atenolol (25–50 mg) | 18 | 17 | 12 | 0, 3, 6, 9, 12 | Yes | DuBois and Du Bois[35] | 1·77 (0·22) | Echo and trailing edge to leading edge | 39·0 (5·8) | † | 3·55 (1·93) |
| Italian trial[19] | Losartan (100 mg adults or ≤1·4 mg/kg children) *vs* nebivolol (10 mg adults or ≤0·16 mg/kg children) | 155§ | Unknown | 48 | 0, 12, 24, 36, 48 | No (trial yet to publish its full results) | Unknown | .. | .. | .. | .. | .. |
| Boston, USA trial[16] | Losartan (100 mg) *vs* atenolol (50 mg) | 34 | 35 | 6 | 0, 6 | No (trialist unable to provide data) | Unknown | .. | .. | .. | .. | .. |

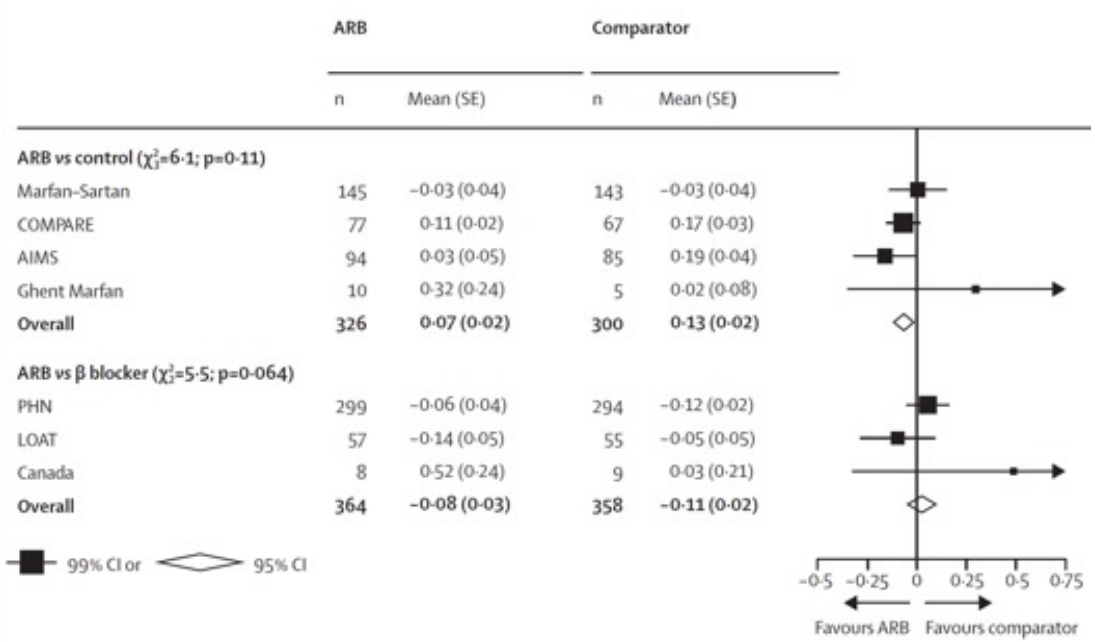
For each trial, the imaging method used to estimate aortic root dimension was the method used in that trial's primary analysis. ARB=angiotensin receptor blocker. MTT=Marfan Treatment Trialists. *Data not provided by the trialist so estimated using the DuBois and Du Bois[34] method. †Data not provided by the trialist so estimated using the Devereux and colleagues[36] method). ‡Adults were randomly assigned to losartan (25–100 mg per day) plus β blocker (at a low maintenance dose [50 mg atenolol once daily or 20 mg propranolol twice daily]) *vs* β blocker (atenolol or propranolol, maximum 150 mg per day), and children were randomly assigned to losartan (0·7 mg/kg per day, to a maximum of 50 mg per day) plus β blocker (low maintenance dose, 1 mg/kg per day atenolol or propranolol) *vs* β blocker (atenolol or propranolol, maximum 2 mg/kg per day). §Number reported in trialists' abstract was number analysed (the total number of patients randomly assigned across all three groups of the Italian trial was 262).

***Table 1:*** **Characteristics of ten trials of angiotensin receptor blockers in patients with Marfan syndrome**

| | ARB *vs* control | | ARB *vs* β blocker | |
|---|---|---|---|---|
| | ARB (n=353) | Control (n=323) | ARB (n=384) | β blocker (n=382) |
| Median follow-up, years | 3·0 (2·9–4·0) | 3·0 (3·0–4·0) | 3·0 (3·0–3·0) | 3·0 (3·0–3·0) |
| Mean age, years | 28·8 (14·7) | 28·3 (13·8) | 13·9 (9·9) | 13·9 (9·7) |
| Age, years | | | | |
| <16 | 75 (21%) | 67 (21%) | 258 (67%) | 254 (66%) |
| ≥16 to <25 | 80 (23%) | 78 (24%) | 82 (21%) | 88 (23%) |
| ≥25 to <40 | 114 (32%) | 119 (37%) | 37 (10%) | 31 (8%) |
| ≥40 | 84 (24%) | 59 (18%) | 7 (2%) | 9 (2%) |
| Gender | | | | |
| Male | 164 (46%) | 145 (45%) | 218 (57%) | 212 (55%) |
| Female | 189 (54%) | 178 (55%) | 166 (43%) | 170 (45%) |
| Family history of Marfan syndrome | | | | |
| Yes | 100 (28%) | 82 (25%) | 187 (49%) | 188 (49%) |
| No | 164 (46%) | 158 (49%) | 111 (29%) | 116 (30%) |
| Unknown | 89 (25%) | 83 (26%) | 86 (22%) | 78 (20%) |
| Family history of aortic dissection | | | | |
| Yes | 6 (2%) | 1 (<1%) | 55 (14%) | 58 (15%) |
| No | 4 (1%) | 4 (1%) | 258 (67%) | 254 (66%) |
| Unknown | 343 (97%) | 318 (98%) | 71 (18%) | 70 (18%) |
| Presence of *FBN1* | | | | |
| Yes | 270 (76%) | 256 (79%) | 135 (35%) | 145 (38%) |
| No | 59 (17%) | 45 (14%) | 27 (7%) | 20 (5%) |
| Unknown | 24 (7%) | 22 (7%) | 222 (58%) | 217 (57%) |
| Ectopia lentis | | | | |
| Yes | 84 (24%) | 67 (21%) | 129 (34%) | 133 (35%) |
| No | 116 (33%) | 108 (33%) | 150 (39%) | 134 (35%) |
| Unknown | 153 (43%) | 148 (46%) | 105 (27%) | 115 (30%) |
| Current β-blocker use | 265 (75%) | 242 (75%) | 0 | 0 |
| Aorta at the sinuses of Valsalva | | | | |
| Mean dimension, mm | 39·0 (6·8) | 38·9 (6·5) | 34·2 (7·0) | 34·2 (7·1) |
| Mean Z score | 3·76 (2·14) | 3·64 (1·94) | 4·18 (1·71) | 4·03 (1·50) |
| Other baseline measures | | | | |
| Mean weight, kg | 67·6 (19·7) | 69·6 (21·3) | 45·0 (23·7) | 46·5 (23·7) |
| Mean height, cm | 178 (15) | 179 (15) | 155 (31) | 156 (32) |
| Mean systolic blood pressure, mm Hg | 117 (16) | 117 (15) | 102 (16) | 102 (16) |
| Mean diastolic blood pressure, mm Hg | 70 (11) | 70 (10) | 62 (11) | 62 (11) |
| Mean heart rate, beats per min | 64 (14) | 65 (14) | 78 (18) | 77 (17) |
| Mean body surface area, $m^2$ | 1·83 (0·32) | 1·86 (0·33) | 1·36 (0·49) | 1·40 (0·50) |
| Mean BMI, $kg/m^2$ | 20·9 (4·6) | 21·3 (5·3) | 17·3 (4·0) | 17·5 (4·0) |

Data are n (%), median (IQR), or mean (SD). 70 patients with previous aortic root surgery at enrolment were excluded: two in the ARB group and five in the placebo group from Ghent Marfan and 27 in the ARB group and 36 in the control group from COMPARE. ARB=angiotensin receptor blocker. *FBN1*=fibrillin-1.

***Table 2:*** **Baseline characteristics by randomised allocation**



| | ARB | | Control | |
|---|---|---|---|---|
| | n | Mean (SE) | n | Mean (SE) |
| **Age, years ($\chi^2_1$=0·6; p=0·43)** | | | | |
| <16 | 72 | −0·02 (0·06) | 65 | 0·13 (0·06) |
| ≥16 | 254 | 0·08 (0·02) | 235 | 0·13 (0·02) |
| **Gender ($\chi^2_1$=0·5; p=0·47)** | | | | |
| Female | 174 | 0·08 (0·02) | 162 | 0·14 (0·02) |
| Male | 152 | 0·04 (0·02) | 138 | 0·12 (0·02) |
| **Family history of Marfan syndrome ($\chi^2_1$=1·2; p=0·28)** | | | | |
| Yes | 92 | 0·07 (0·02) | 80 | 0·08 (0·04) |
| No | 156 | −0·02 (0·03) | 152 | 0·08 (0·03) |
| Unknown | 78 | 0·11 (0·02) | 68 | 0·17 (0·03) |
| **Presence of *FBN1* ($\chi^2_1$=7·9; p=0·0050)** | | | | |
| Yes | 252 | 0·06 (0·02) | 238 | 0·14 (0·02) |
| No | 52 | 0·14 (0·04) | 43 | 0·05 (0·03) |
| Unknown | 22 | 0·04 (0·10) | 19 | 0·29 (0·13) |
| **Ectopia lentis ($\chi^2_1$=0·1; p=0·71)** | | | | |
| Yes | 76 | 0·10 (0·03) | 60 | 0·12 (0·02) |
| No | 104 | 0·09 (0·02) | 97 | 0·19 (0·03) |
| Unknown | 146 | −0·03 (0·04) | 143 | −0·03 (0·04) |
| **β blocker ($\chi^2_1$=0·4; p=0·54)** | | | | |
| Yes | 247 | 0·06 (0·02) | 225 | 0·13 (0·02) |
| No | 79 | 0·10 (0·03) | 75 | 0·13 (0·03) |
| **BSA-adjusted Z score ($\chi^2_1$=0·2; p=0·63)** | | | | |
| <4·5 | 220 | 0·07 (0·02) | 207 | 0·09 (0·02) |
| ≥4·5 | 106 | 0·07 (0·03) | 93 | 0·14 (0·04) |
| **Systolic blood pressure, mm Hg ($\chi^2_1$=0·1; p=0·80)** | | | | |
| <130 | 235 | 0·04 (0·02) | 224 | 0·09 (0·02) |
| ≥130 | 63 | 0·12 (0·02) | 52 | 0·15 (0·03) |
| **Diastolic blood pressure, mm Hg ($\chi^2_1$=0·3; p=0·57)** | | | | |
| <80 | 240 | 0·05 (0·02) | 228 | 0·12 (0·02) |
| ≥80 | 58 | 0·10 (0·03) | 47 | 0·13 (0·04) |
| **Overall** | **326** | **0·07 (0·02)** | **300** | **0·13 (0·02)** |

99% CI or 95% CI

−0·5 −0·25 0 0·25 0·5

Favours ARB Favours control

| | ARB | | β blocker | |
|---|---|---|---|---|
| | n | Mean (SE) | n | Mean (SE) |
| **Age, years ($\chi^2_1$=3·2; p=0·075)** | | | | |
| < 16 | 250 | −0·02 (0·04) | 244 | −0·14 (0·02) |
| ≥16 | 114 | −0·09 (0·03) | 114 | −0·04 (0·03) |
| **Gender ($\chi^2_1$=1·5; p=0·22)** | | | | |
| Female | 155 | −0·14 (0·05) | 159 | −0·12 (0·03) |
| Male | 209 | −0·05 (0·02) | 199 | −0·11 (0·02) |
| **Family history of Marfan syndrome ($\chi^2_1$=0·5; p=0·48)** | | | | |
| Yes | 182 | −0·03 (0·06) | 183 | −0·14 (0·02) |
| No | 109 | −0·06 (0·04) | 112 | −0·10 (0·03) |
| Unknown | 73 | −0·15 (0·04) | 63 | −0·06 (0·04) |
| **Family history of aortic dissection ($\chi^2_1$=6·6; p=0·010)** | | | | |
| Yes | 54 | −0·22 (0·05) | 56 | −0·09 (0·04) |
| No | 252 | 0·00 (0·04) | 247 | −0·12 (0·02) |
| Unknown | 58 | −0·14 (0·05) | 55 | −0·05 (0·05) |
| **Presence of *FBN1* ($\chi^2_1$=1·0; p=0·31)** | | | | |
| Yes | 128 | −0·16 (0·05) | 136 | −0·16 (0·03) |
| No | 20 | −0·10 (0·07) | 17 | 0·15 (0·09) |
| Unknown | 216 | −0·09 (0·02) | 205 | −0·10 (0·02) |
| **Ectopia lentis ($\chi^2_1$=1·1; p=0·30)** | | | | |
| Yes | 125 | −0·12 (0·03) | 131 | −0·13 (0·03) |
| No | 148 | 0·03 (0·07) | 127 | −0·09 (0·03) |
| Unknown | 91 | −0·14 (0·03) | 100 | −0·10 (0·04) |
| **BSA-adjusted Z score ($\chi^2_1$=2·8; p=0·10)** | | | | |
| <4·5 | 237 | −0·10 (0·02) | 242 | −0·10 (0·02) |
| ≥4·5 | 127 | 0·28 (0·06) | 116 | −0·14 (0·04) |
| **Systolic blood pressure, mm Hg ($\chi^2_1$=0·0; p=0·83)** | | | | |
| <130 | 341 | −0·07 (0·03) | 337 | −0·10 (0·02) |
| ≥130 | 19 | −0·07 (0·05) | 19 | −0·17 (0·09) |
| **Diastolic blood pressure, mm Hg ($\chi^2_1$=1·5; p=0·22)** | | | | |
| <80 | 333 | −0·07 (0·03) | 331 | −0·12 (0·02) |
| ≥80 | 27 | 0·58 (0·02) | 25 | −0·03 (0·08) |
| **Overall** | **364** | **−0·08 (0·03)** | **358** | **−0·11 (0·02)** |

99% CI or 95% CI

−0·5 −0·25 0 0·25 0·5

Favours ARB Favours β blocker

## Research in context

### Evidence before this study

We searched Embase, MEDLINE, and CENTRAL from inception until Nov 2, 2021, for randomised trials that assessed the effects of angiotensin receptor blocker (ARB) versus control or ARB versus β blockers in patients with Marfan syndrome. Cochrane search filters were used in Embase and Medline to identify randomised trials, and the terms "Marfan" or "Marfan syndrome" were used in all three databases (appendix p 2). The searches were not restricted to English language publications. We identified a number of randomised trials of ARB versus placebo (or open control) in which the aim was to estimate the effects of treatment with ARBs on aortic root size in patients with Marfan syndrome. Several meta-analyses of published data from these trials were also identified, but none were able to define the effects of ARBs in different circumstances, including according to age, sex, or blood pressure, but also according to whether or not a β blocker was part of existing treatment, and whether or not a diagnosis of Marfan syndrome had been confirmed by genotyping. There were no large, randomised trials assessing the efficacy of a β blocker for Marfan syndrome, despite the fact that such treatment is used widely for this condition.

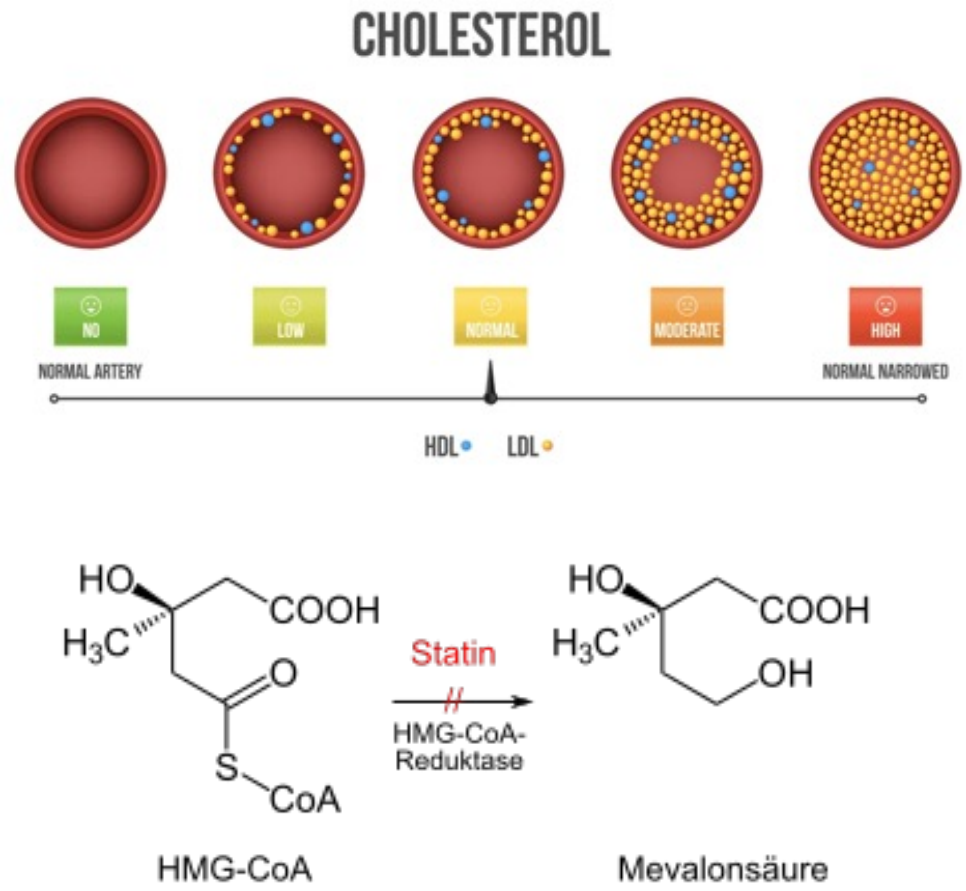
### Added value of this study

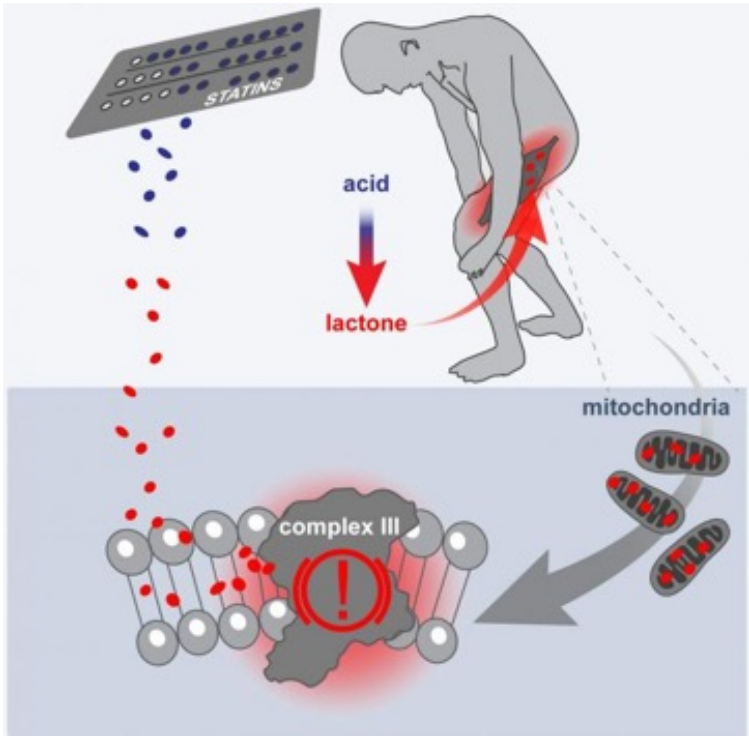
This meta-analysis of individual patient data from randomised trials, which followed a protocol that was agreed and published before any analyses, showed that ARBs reduced the rate of aortic root enlargement by about one half, and that this effect was generalisable to different types of patients. In particular, ARBs were effective even among those already taking a β blocker. The estimated effect of ARBs was significantly greater among those with a pathogenic variant in fibrillin-1, than those without such a fibrillin-1 variant, providing biological support for the effect. β blockers were estimated to have a similar beneficial effect as ARBs.

### Implications of all the available evidence

If tolerated, the combination of a β blocker and an ARB could reduce the rate of enlargement of the aortic root by at least one half, and potentially by much more than this. Although this meta-analysis of trials did not have sufficient power to assess effects on the need for surgery (and it is unlikely that any randomised study will ever be done to study this question directly), as elective surgery is almost always driven by aortic root size and rate of expansion, our results suggest that long-term combination therapy could eventually reduce such outcomes.

# Statins and muscle pain



# Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials


## Summary

**Background** Statin therapy is effective for the prevention of atherosclerotic cardiovascular disease and is widely prescribed, but there are persisting concerns that statin therapy might frequently cause muscle pain or weakness. We aimed to address these through an individual participant data meta-analysis of all recorded adverse muscle events in large, long-term, randomised, double-blind trials of statin therapy.

**Methods** Randomised trials of statin therapy were eligible if they aimed to recruit at least 1000 participants with a scheduled treatment duration of at least 2 years, and involved a double-blind comparison of statin versus placebo or of a more intensive versus a less intensive statin regimen. We analysed individual participant data from 19 double-blind trials of statin versus placebo (n=123 940) and four double-blind trials of a more intensive versus a less intensive statin regimen (n=30 724). Standard inverse-variance-weighted meta-analyses of the effects on muscle outcomes were conducted according to a prespecified protocol.

**Findings** Among 19 placebo-controlled trials (mean age 63 years [SD 8], with 34 533 [27·9%] women, 59 610 [48·1%] participants with previous vascular disease, and 22 925 [18·5%] participants with diabetes), during a weighted average median follow-up of 4·3 years, 16 835 (27·1%) allocated statin versus 16 446 (26·6%) allocated placebo reported muscle pain or weakness (rate ratio [RR] 1·03; 95% CI 1·01–1·06). During year 1, statin therapy produced a 7% relative increase in muscle pain or weakness (1·07; 1·04–1·10), corresponding to an absolute excess rate of 11 (6–16) events per 1000 person-years, which indicates that only one in 15 ([1·07–1·00]/1·07) of these muscle-related reports by participants allocated to statin therapy were actually due to the statin. After year 1, there was no significant excess in first reports of muscle pain or weakness (0·99; 0·96–1·02). For all years combined, more intensive statin regimens (ie, 40–80 mg atorvastatin or 20–40 mg rosuvastatin once per day) yielded a higher RR than less intensive or moderate-intensity regimens (1·08 [1·04–1·13] *vs* 1·03 [1·00–1·05]) compared with placebo, and a small excess was present (1·05 [0·99–1·12]) for more intensive regimens after year 1. There was no clear evidence that the RR differed for different statins, or in different clinical circumstances. Statin therapy yielded a small, clinically insignificant increase in median creatine kinase values of approximately 0·02 times the upper limit of normal.

**Interpretation** Statin therapy caused a small excess of mostly mild muscle pain. Most (>90%) of all reports of muscle symptoms by participants allocated statin therapy were not due to the statin. The small risks of muscle symptoms are much lower than the known cardiovascular benefits. There is a need to review the clinical management of muscle symptoms in patients taking a statin.

| | Year of publication of primary results | Number of patients | Treatment comparison, mg per day | Median follow-up, years | Baseline LDL cholesterol, mmol/L (mean [SD]) | Baseline age, years (mean [SD]) | Number of women (%) | Number of White participants (%) | Number of participants with a history of vascular disease (%) | Number of participants with a history of diabetes (%) | Baseline BMI, kg/m$^2$ (mean [SD]) | Baseline estimated GFR, mL per min per 1·73 m$^2$ (mean [SD]) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Statin versus placebo** | | | | | | | | | | | | |
| 4S[20] | 1994 | 4444 | Simvastatin (20–40 mg) *vs* placebo | 5·4 | 4·9 (0·7) | 59 (7) | 827 (19%) | NA | 4444 (100%) | 202 (5%) | 26·0 (3·3) | NA |
| WOSCOPS[21] | 1995 | 6595 | Pravastatin (40 mg) *vs* placebo | 4·8 | 5·0 (0·5) | 55 (6) | 0 | NA | 1066 (16%) | 77 (1%) | 26·0 (3·2) | 77·8 (12·4) |
| CARE[22] | 1996 | 4159 | Pravastatin (40 mg) *vs* placebo | 4·9 | 3·6 (0·4) | 59 (9) | 576 (14%) | 3851 (93%) | 4159 (100%) | 586 (14%) | 27·6 (4·4) | 67·2 (15·7) |
| AFCAPS/TexCAPS[23] | 1998 | 6605 | Lovastatin (20–40 mg) *vs* placebo | 5·0 | 3·9 (0·4) | 58 (7) | 997 (15%) | 5860 (89%) | 0 | 155 (2%) | 26·9 (3·1) | 65·4 (11·6) |
| LIPID[24] | 1998 | 9014 | Pravastatin (40 mg) *vs* placebo | 5·9 | 3·9 (0·8) | 61 (8) | 1516 (17%) | NA | 9014 (100%) | 782 (9%) | 26·8 (3·8) | 70·6 (16·3) |
| LIPS[25] | 2002 | 1677 | Fluvastatin (80 mg) *vs* placebo | 4·0 | 3·4 (0·8) | 60 (10) | 271 (16%) | 1650 (98%) | 1677 (100%) | 202 (12%) | 26·5 (3·3) | 67·6 (15·5) |
| HPS[26] | 2002 | 20536 | Simvastatin (40 mg) *vs* placebo | 5·2 | 3·4 (0·8) | 64 (8) | 5082 (25%) | 19901 (97%) | 17386 (85%) | 5963 (29%) | 27·6 (4·4) | 72·2 (16·5) |
| PROSPER[27] | 2002 | 5804 | Pravastatin (40 mg) *vs* placebo | 3·3 | 3·8 (0·8) | 75 (3) | 3000 (52%) | NA | 2565 (44%) | 623 (11%) | 26·8 (4·2) | 56·7 (13·6) |
| ASCOT-LLA[28] | 2003 | 10240 | Atorvastatin (10 mg) *vs* placebo | 3·3 | 3·4 (0·7) | 63 (9) | 1919 (19%) | 9687 (95%) | 1684 (16%) | 2540 (25%) | 28·6 (4·6) | 68·4 (12·9) |
| ALERT[29] | 2003 | 2102 | Fluvastatin (40–80 mg) *vs* placebo | 5·5 | 4·1 (1·0) | 50 (11) | 715 (34%) | 2039 (97%) | 409 (19%) | 396 (19%) | 25·8 (4·5) | 49·6 (17·0) |
| CARDS[30] | 2004 | 2838 | Atorvastatin (10 mg) *vs* placebo | 4·2 | 2·9 (0·8) | 61 (8) | 909 (32%) | 2676 (94%) | 106 (4%) | 2838 (100%) | 28·8 (3·6) | 64·2 (11·3) |
| 4D[31] | 2005 | 1255 | Atorvastatin (20 mg) *vs* placebo | 2·7 | 3·3 (0·8) | 66 (8) | 578 (46%) | 924 (74%) | 1041 (83%) | 1255 (100%) | 27·6 (4·8) | NA |
| ASPEN[32] | 2006 | 2410 | Atorvastatin (10 mg) *vs* placebo | 4·0 | 2·9 (0·7) | 60 (8) | 811 (34%) | 2029 (84%) | 747 (31%) | 2410 (100%) | 28·9 (3·8) | 65·9 (12·8) |
| SPARCL[33] | 2006 | 4731 | Atorvastatin (80 mg) *vs* placebo | 4·9 | 3·5 (0·6) | 63 (11) | 1908 (40%) | 4415 (93%) | 4731 (100%) | 794 (17%) | 27·9 (5·2) | 65·2 (13·8) |
| CORONA[34] | 2007 | 4982 | Rosuvastatin (10 mg) *vs* placebo | 2·7 | 3·6 (0·9) | 72 (7) | 1175 (24%) | NA | 4982 (100%) | 1473 (30%) | 26·4 (3·6) | 55·4 (15·1) |
| GISSI-HF[35] | 2008 | 4574 | Rosuvastatin (10 mg) *vs* placebo | 3·9 | 3·1 (0·9) | 68 (11) | 1032 (23%) | 4574 (100%) | 4574 (100%) | 1196 (26%) | 27·1 (4·5) | 66·3 (20·4) |
| JUPITER[36] | 2008 | 16714 | Rosuvastatin (20 mg) *vs* placebo | 1·9 | 2·7 (0·5) | 65 (8) | 6374 (38%) | NA | 0 | 44 (<1%) | 27·5 (3·6) | 72·3 (14·8) |
| AURORA[37] | 2009 | 2555 | Rosuvastatin (10 mg) *vs* placebo | 3·9 | 2·6 (0·9) | 64 (9) | 969 (38%) | NA | 1025 (40%) | 658 (26%) | 24·8 (3·9) | NA |
| HOPE-3[38] | 2016 | 12705 | Rosuvastatin (10 mg) *vs* placebo | 5·5 | 3·3 (0·9) | 66 (6) | 5874 (46%) | 2546 (20%) | 0 | 731 (6%) | 27·1 (4·7) | 79·6 (16·1) |
| Subtotal of the 19 statin versus placebo trials | NA | 123940 | NA | 4·3 | 3·5 (0·7) | 63 (8) | 34533 (28%) | 60152 (81%)* | 59610 (48%) | 22925 (18%) | 27·2 (4·1) | 69·5 (15·0) |

(Table 1 continues on next page)

| | Year of publication of primary results | Number of patients | Treatment comparison, mg per day | Median follow-up, years | Baseline LDL cholesterol, mmol/L (mean [SD]) | Baseline age, years (mean [SD]) | Number of women (%) | Number of White participants (%) | Number of participants with a history of vascular disease (%) | Number of participants with a history of diabetes (%) | Baseline BMI, kg/m$^2$ (mean [SD]) | Baseline estimated GFR, mL per min per 1·73 m$^2$ (mean [SD]) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | | | | | |
| **More intensive versus less intensive statin regimen (double blind)** | | | | | | | | | | | | |
| PROVE-IT[39] | 2004 | 4162 | Atorvastatin (80 mg) *vs* pravastatin (40 mg) | 2·1 | 2·6 (0·7)† | 58 (11) | 911 (22%) | 3776 (91%) | 4162 (100%) | 762 (18%) | 29·5 (5·7) | 78·8 (18·7) |
| A to Z[40] | 2004 | 4497 | Simvastatin (40 mg) then simvastatin (80 mg) *vs* placebo then simvastatin (20 mg) | 2·0 | 2·1 (0·7)† | 60 (11) | 1100 (24%) | 3825 (85%) | 4497 (100%) | 1059 (24%) | 27·6 (4·8) | 68·4 (16·0) |
| TNT[41] | 2005 | 10 001 | Atorvastatin (80 mg) *vs* atorvastatin (10 mg) | 5·0 | 2·5 (0·5) | 61 (9) | 1902 (19%) | 9410 (94%) | 10001 (100%) | 1501 (15%) | 28·8 (6·1) | 65·0 (12·4) |
| SEARCH[42] | 2010 | 12 064 | Simvastatin (80 mg) *vs* simvastatin (20 mg) | 7·0 | 2·5 (0·6) | 64 (9) | 2052 (17%) | 11 854 (98%) | 12 064 (100%) | 1267 (11%) | 28·1 (4·1) | 77·2 (17·1) |
| Subtotal of the four more intensive versus less intensive trials | NA | 30 724 | NA | 4·9 | 2·5 (0·6) | 62 (9) | 5965 (19%) | 28 865 (94%) | 30 724 (100%) | 4589 (15%) | 28·4 (5·1) | 72·2 (15·6) |
| Total of all trials | NA | 154 664 | NA | 4·4 | 3·1 (0·7) | 63 (8) | 40 498 (26%) | 89 017 (85%)* | 90 334 (58%) | 27 514 (18%) | 27·5 (4·3) | 70·1 (15·1) |

Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation except for CORONA and JUPITER, where the estimated GFR was supplied by trialists (and the absence of data meant that the estimated GFR could not be derived by the Cholesterol Treatment Trialists' Collaboration); estimated GFR statistics were not presented for 4D and AURORA because these were trials done in participants who were on regular maintenance dialysis. AURORA, CORONA, and JUPITER supplied age in categorical bands, and so the midpoint of each categorical band was used as a surrogate for baseline age in all analyses. A small number of participants in the AURORA (n=218), CORONA (n=27), and JUPITER (n=1088) trials withdrew consent for use of their data post-trial, and hence data from these participants is excluded. The ASCOT-LLA trial excludes 65 patients for whom data were not available due to protocol violations. Note that some baseline characteristics might differ from previous publications because of the receipt of updated data and a broader definition of baseline vascular disease being applied in these analyses. 4D=ie Deutsche Diabetes Dialyse Studie. 4S=Scandinavian Simvastatin Survival Study. AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study. ALERT=Assessment of Lescol in Renal Transplantation. ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm. ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus. A to Z=Aggrastat to Zocor. AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events. CARDS=Collaborative Atorvastatin Diabetes Study. CARE=Cholesterol And Recurrent Events. CORONA=Controlled Rosuvastatin Multinational Trial in Heart Failure. GFR=glomerular filtration rate. GISSI-HF=Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca. HOPE-3=Heart Outcomes Prevention Evaluation-3 trial. HPS=Heart Protection Study. JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study group. LDL=low density lipoprotein. LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease. LIPS=Lescol Intervention Prevention Study. NA=not available. PROSPER=PROspective Study of Pravastatin in the Elderly at Risk. PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy. SEARCH=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels. TNT=Treating to New Targets. WOSCOPS=West of Scotland Coronary Prevention Study. *Percentages were calculated after excluding the seven trials where information on race and ethnicity was not provided (the relevant denominators are therefore 73 832 for the 12 trials of statin *vs* placebo and 104 556 for all 16 trials with information on race and ethnicity). †These two trials did not have active run-in periods; the values shown are the estimated on-treatment LDL cholesterol concentrations in the standard statin group.

***Table 1:*** **Characteristics of the trials included in the meta-analysis**

| | Events (%) | | O–E | Var(O–E) | Rate ratio (95% CI or 99% CI) |
|---|---|---|---|---|---|
| | Statin or more intensive statin group | Placebo or less intensive statin group | | | |
| **(A) Statin *vs* placebo** | **(n=62028)** | **(n=61912)** | | | |
| Myalgia | 7446 (12·0%) | 7269 (11·7%) | 120·1 | 3657·4 | 1·03 (0·99–1·08) |
| Limb pain | 1850 (3·0%) | 1836 (3·0%) | 3·6 | 921·3 | 1·00 (0·92–1·09) |
| Other musculoskeletal pain | 8245 (13·3%) | 8037 (13·0%) | 131·3 | 4066·1 | 1·03 (0·99–1·08) |
| Muscle cramp or spasm | 1697 (2·7%) | 1553 (2·5%) | 71·2 | 812·4 | 1·09 (1·00–1·19) |
| **Any muscle pain** | **16656 (26·9%)** | **16281 (26·3%)** | **274·8** | **8206·8** | **1·03 (1·01–1·06)** |
| Muscle fatigue or weakness | 445 (0·7%) | 406 (0·7%) | 19·4 | 212·7 | 1·10 (0·92–1·31) |
| **Any muscle pain or weakness** | **16835 (27·1%)** | **16446 (26·6%)** | **283·1** | **8292·7** | **1·03 (1·01–1·06)** |
| **(B) More *vs* less intensive statin** | **(n=15390)** | **(n=15334)** | | | |
| Myalgia | 3485 (22·6%) | 3380 (22·0%) | 70·2 | 1712·7 | 1·04 (0·98–1·11) |
| Limb pain | 619 (4·0%) | 603 (3·9%) | 7·3 | 305·5 | 1·02 (0·88–1·19) |
| Other musculoskeletal pain | 1721 (11·2%) | 1628 (10·6%) | 47·8 | 836·9 | 1·06 (0·97–1·16) |
| Muscle cramp or spasm | 515 (3·3%) | 495 (3·2%) | 10·3 | 252·5 | 1·04 (0·89–1·22) |
| **Any muscle pain** | **5490 (35·7%)** | **5274 (34·4%)** | **132·0** | **2686·6** | **1·05 (1·01–1·09)** |
| Muscle fatigue or weakness | 158 (1·0%) | 148 (1·0%) | 4·9 | 76·5 | 1·07 (0·79–1·43) |
| **Any muscle pain or weakness** | **5558 (36·1%)** | **5342 (34·8%)** | **132·8** | **2720·5** | **1·05 (1·01–1·09)** |

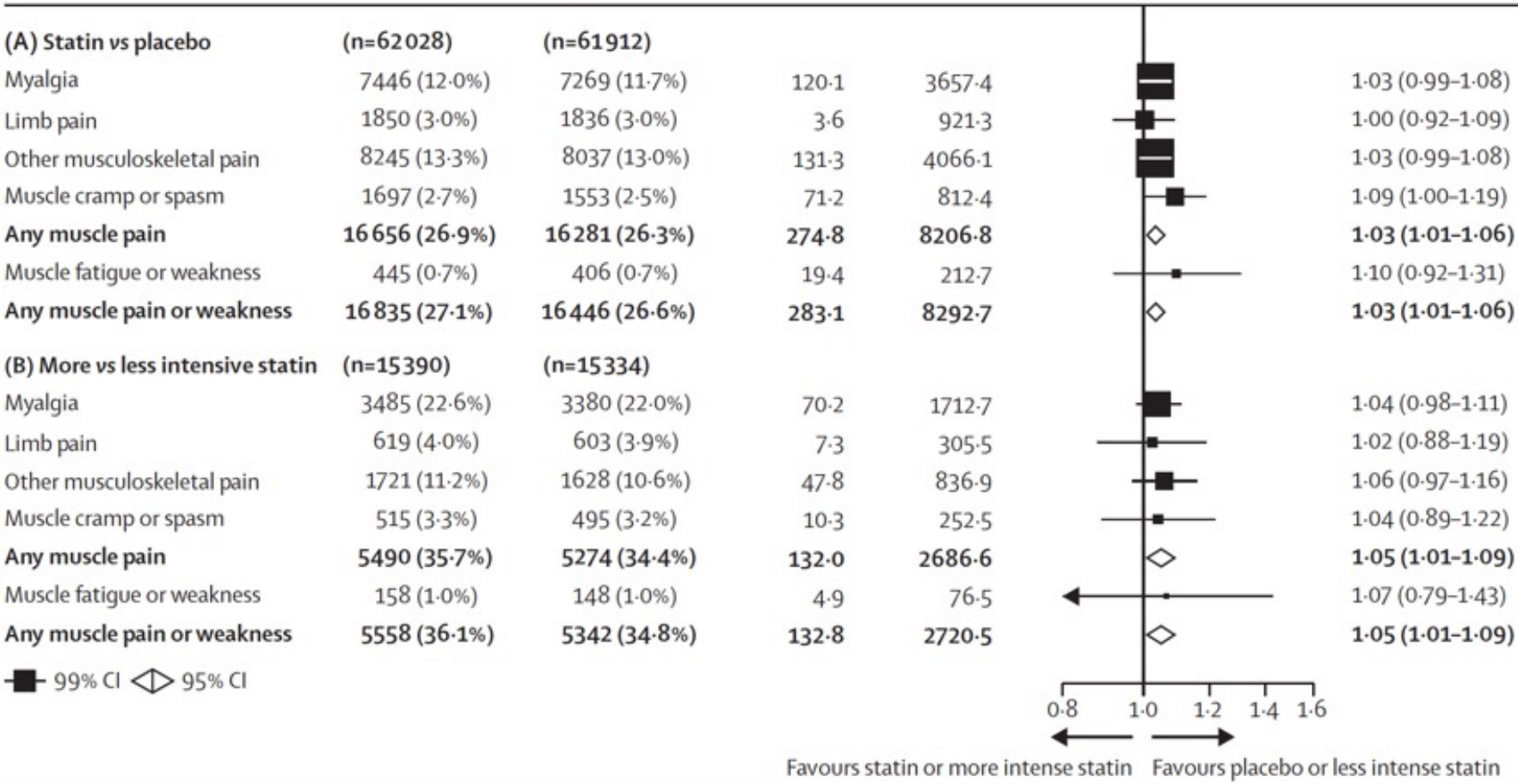



***Figure 1:*** **Effect on muscle adverse events in trials of any statin regimen versus placebo (A) and more versus less intensive statin regimens (B)**
Bold data are the totals or subtotals. O–E=observed minus expected. Var=variance.

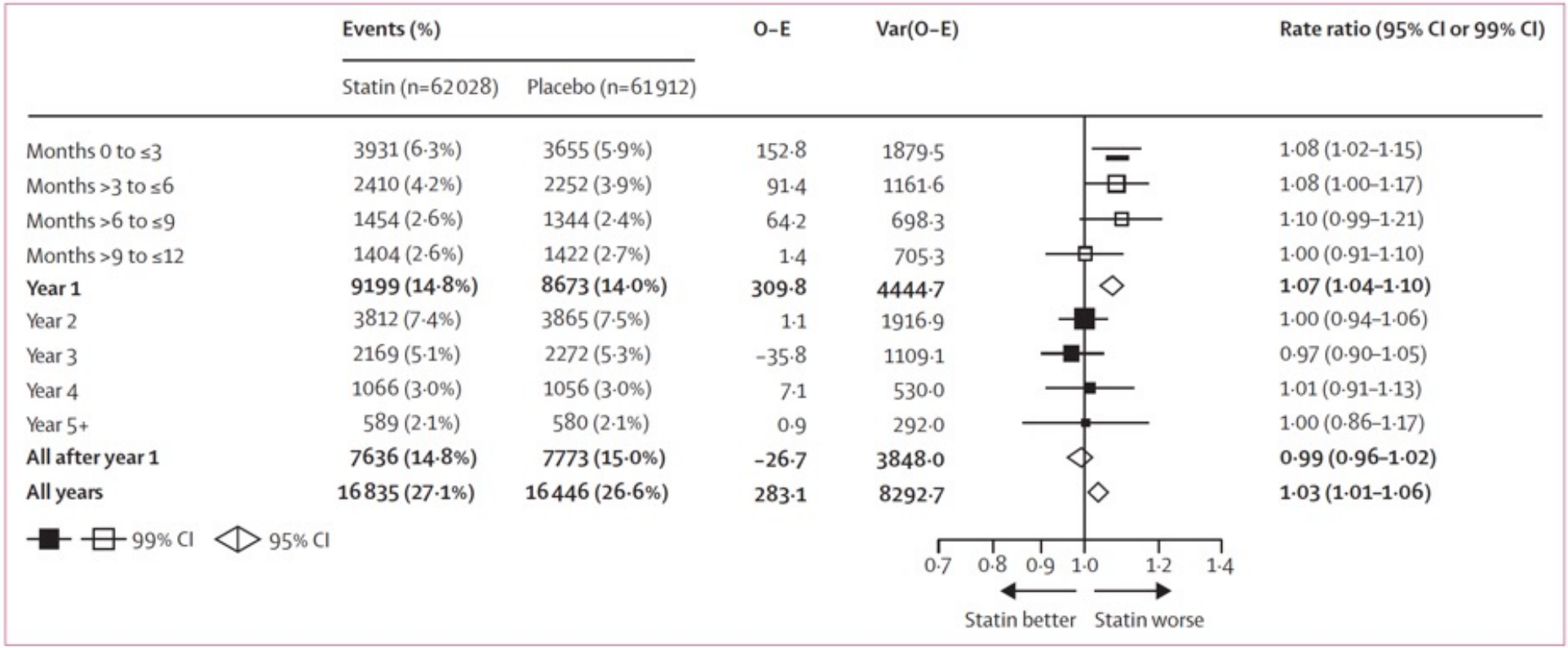
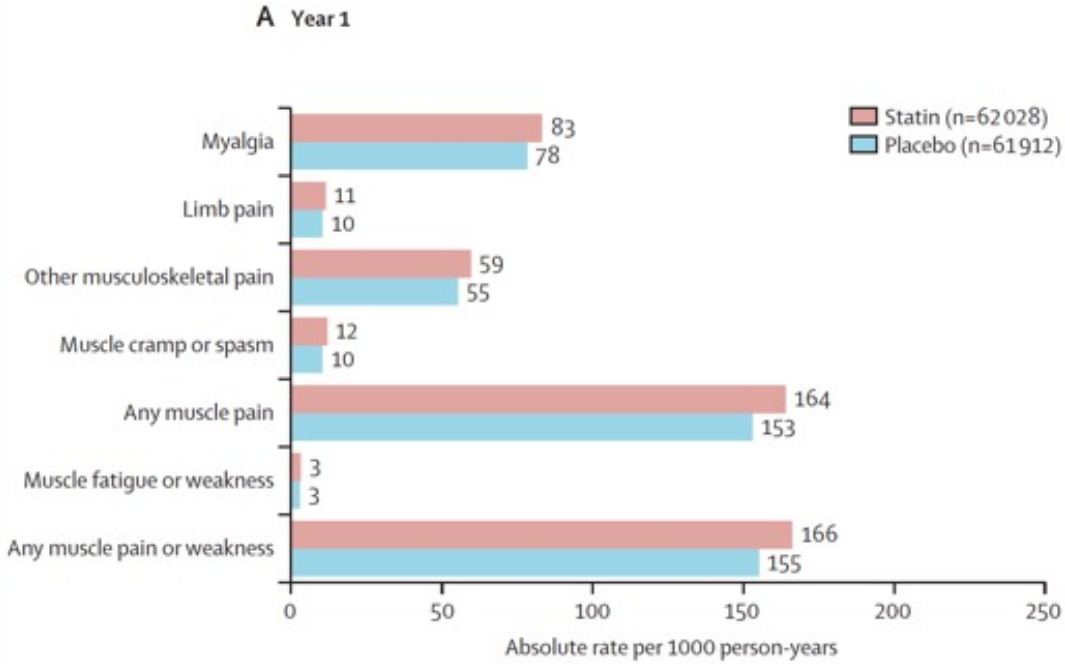
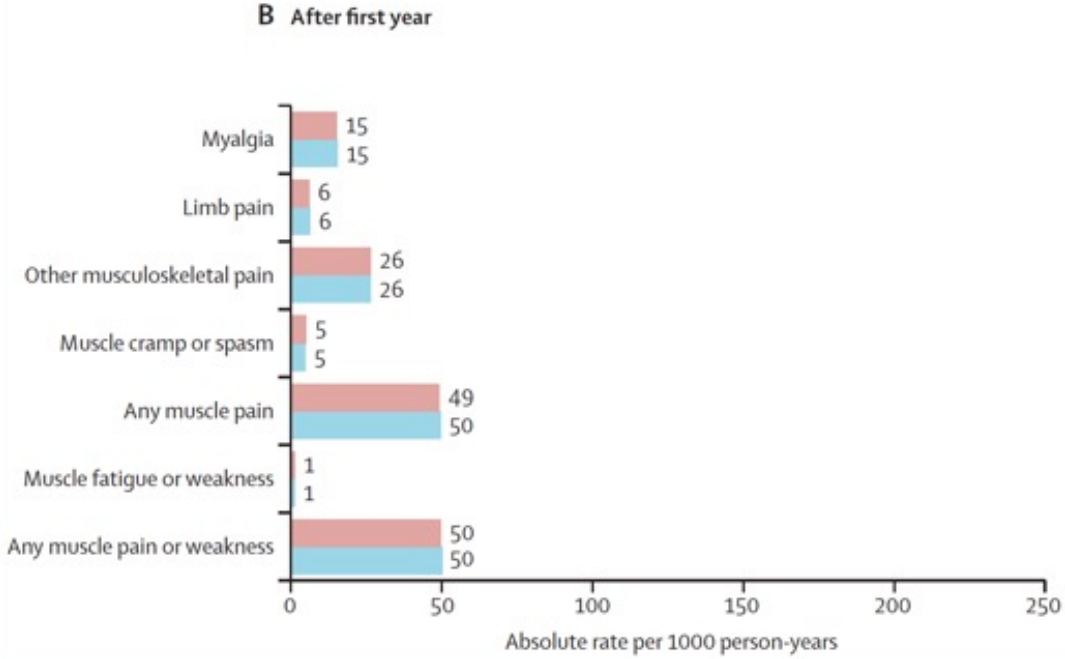



***Figure 2:*** **Effect on any muscle pain or weakness, by duration of treatment, in trials of any statin regimen versus placebo**

Bold data are the totals or subtotals. White squares indicate months, black squares indicate years. The test for heterogeneity in the log rate ratio between the first year and all subsequent years combined: $\chi^2$ =12·1, p=0·0005. For each risk period, percentages shown are of those alive and still at risk of a first report of muscle pain or weakness at the start of the risk period. O–E=observed minus expected. Var=variance.




| Rate ratio (95% CI) | Absolute excess rate per 1000 person-years (95% CI) |
|---|---|
| 1·06 (1·02 to 1·11) | 5 (1 to 8) |
| 1·08 (0·97 to 1·21) | 1 (0 to 2) |
| 1·08 (1·03 to 1·13) | 4 (1 to 7) |
| 1·14 (1·02 to 1·27) | 1 (0 to 3) |
| 1·07 (1·04 to 1·10) | 11 (6 to 16) |
| 1·14 (0·92 to 1·40) | 0 (0 to 1) |
| 1·07 (1·04 to 1·10) | 11 (6 to 16) |




| Rate ratio (95% CI) | Absolute excess rate per 1000 person-years (95% CI) |
|---|---|
| 0·99 (0·93 to 1·04) | 0 (−1 to 1) |
| 0·96 (0·89 to 1·04) | 0 (−1 to 0) |
| 1·00 (0·96 to 1·04) | 0 (−1 to 1) |
| 1·06 (0·97 to 1·16) | 0 (0 to 1) |
| 0·99 (0·96 to 1·03) | 0 (−2 to 1) |
| 1·07 (0·89 to 1·27) | 0 (0 to 0) |
| 0·99 (0·96 to 1·02) | 0 (−2 to 1) |

*Figure 3*: Rate ratio and absolute rate difference for muscle adverse events by duration of treatment, in trials of any statin regimen versus placebo

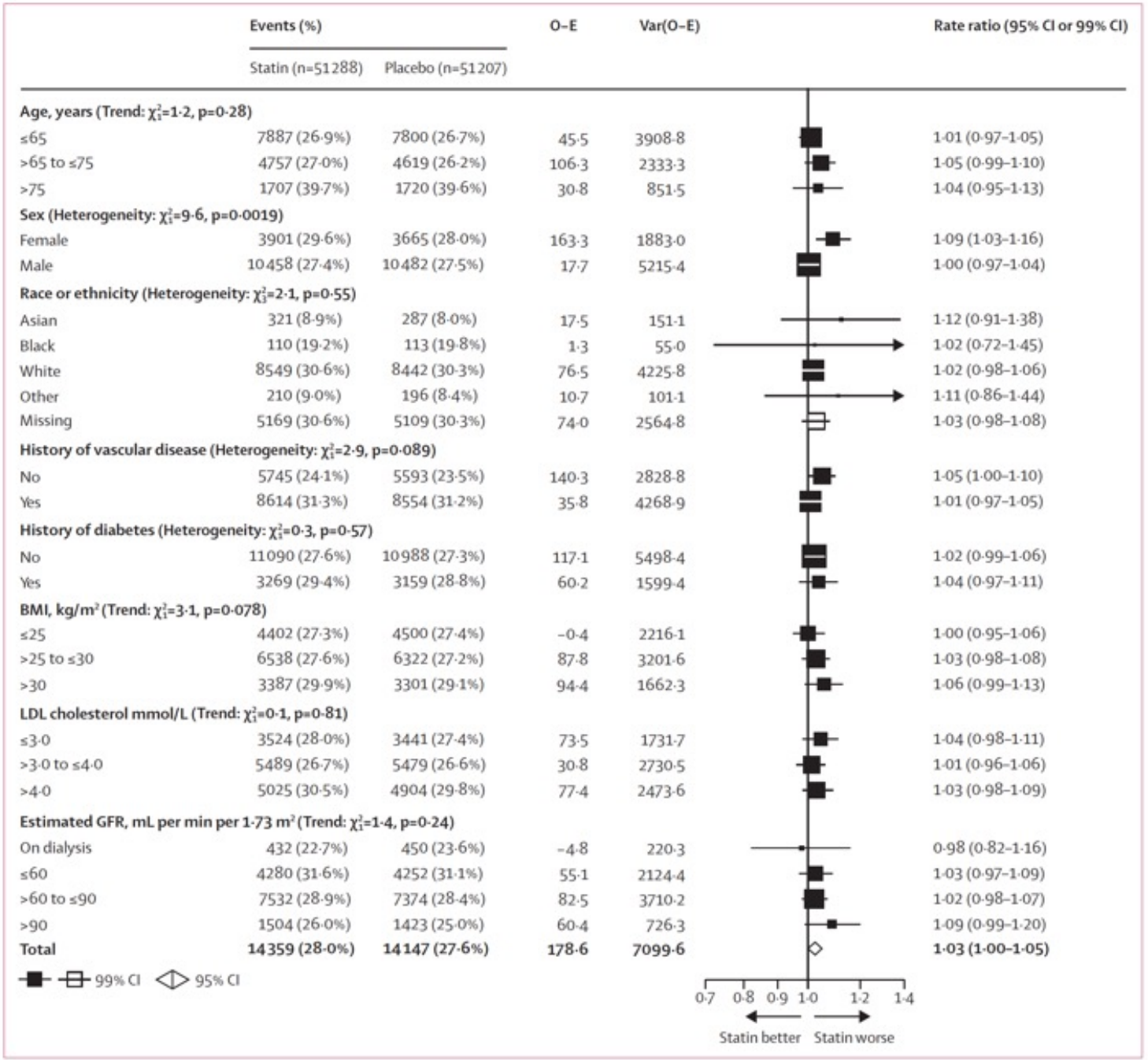



*Figure 4:* **Effect of less intensive or moderate-intensity statin regimens on any muscle pain or weakness, by participant characteristics**
Bold indicates the overall summary result. White squares indicate missing data. Tests of heterogeneity (or trend) listed after each prognostic characteristic are of the log rate ratio for each of the subgroups of that characteristic, and are uncorrected for multiple comparisons. GFR=glomerular filtration rate. LDL=low-density lipoprotein. O–E=observed minus expected. Var=variance.

| | Events (% py) | | Rate ratio (95% CI) |
|---|---|---|---|
| | Statin or more intensive statin group | Placebo or less intensive statin group | |
| **Direct assessments, 0–1 year** | | | |
| High-intensity statin *vs* placebo (2 trials) | 1495 (15·4% py) | 1351 (13·8% py) | 1·11 (1·03–1·20) |
| Moderate-intensity statin *vs* placebo (16 trials) | 7668 (18·0% py) | 7282 (17·0% py) | 1·07 (1·03–1·10) |
| High-intensity *vs* moderate-intensity (2 trials) | 1259 (20·4% py) | 1218 (19·6% py) | 1·04 (0·96–1·12) |
| **Indirect assessments, 0–1 year** | | | |
| High-intensity statin *vs* placebo | NA | NA | 1·10 (1·01–1·20) |
| **Overall (direct and indirect) assessments, 0–1 year** | | | |
| High-intensity statin *vs* placebo | NA | NA | 1·11 (1·05–1·17) |
| **Direct assessments, after 1 year** | | | |
| High-intensity statin *vs* placebo (2 trials) | 981 (6·8% py) | 948 (6·4% py) | 1·06 (0·97–1·16) |
| Moderate-intensity statin *vs* placebo (16 trials) | 6616 (5·2% py) | 6802 (5·4% py) | 0·98 (0·95–1·02) |
| High-intensity *vs* moderate-intensity (2 trials) | 1308 (8·5% py) | 1248 (8·0% py) | 1·06 (0·98–1·14) |
| **Indirect assessments, after 1 year** | | | |
| High-intensity statin *vs* placebo | NA | NA | 1·04 (0·95–1·13) |
| **Overall (direct and indirect) assessments, after 1 year** | | | |
| High-intensity statin *vs* placebo | NA | NA | 1·05 (0·99–1·12) |
| **Direct assessments, all years** | | | |
| High-intensity statin *vs* placebo (2 trials) | 2476 (10·3% py) | 2299 (9·4% py) | 1·09 (1·03–1·16) |
| Moderate-intensity statin *vs* placebo (16 trials) | 14 284 (8·4% py) | 14 084 (8·3% py) | 1·02 (1·00–1·05) |
| High-intensity *vs* moderate-intensity (2 trials) | 2567 (11·9% py) | 2466 (11·3% py) | 1·05 (0·99–1·11) |
| **Indirect assessments, all years** | | | |
| High-intensity statin *vs* placebo | NA | NA | 1·07 (1·01–1·14) |
| **Overall (direct and indirect) assessments, all years** | | | |
| High-intensity statin *vs* placebo | NA | NA | 1·08 (1·04–1·13) |

The table excludes one trial of a low intensity statin versus placebo (AFCAPS/TexCAPS) and two trials that compared two moderate-intensity statin regimens (SEARCH and A to Z). High intensity statin versus placebo trials: JUPITER and SPARCL. Moderate-intensity statin versus placebo trials: ALERT, ASCOT-LLA, ASPEN, AURORA, CARDS, CARE, CORONA, 4D, GISSI-HF, HOPE-3, HPS, LIPID, LIPS, PROSPER, WOSCOPS, and 4S. High intensity versus moderate-intensity, double blind trials: PROVE-IT and TNT. py=per year.

***Table 2:*** **Effects of moderate-intensity and more intensive statin regimens on any muscle pain or weakness by period of follow-up**

## Research in context

### Evidence before this study

We searched Medline and the Cochrane Central Register of Controlled Trials for randomised trials, meta-analyses, or review articles published in any language between Jan 1, 1990, and June 1, 2021, that had specifically assessed the effects of statin regimens on muscle symptoms. These previous randomised trials, and several meta-analyses of published data from such trials, indicated that statins cause a small excess risk of muscle pain, but these studies might be affected by biases due to missing data. Observational studies, and meta-analyses including such studies, have also estimated the prevalence of statin-associated muscle symptoms, but such studies are subject to reporting biases and other biases, and cannot reliably establish the causal contribution of statins to such symptoms. There is a need, therefore, for a reliable assessment of the effects of various statin regimens on muscle symptoms in different clinical circumstances.

### Added value of this study

We were able to minimise biases by restricting our analyses to large-scale, randomised, double-blind trials of statin therapy versus placebo in which there was systematic and unbiased event reporting. To overcome the potential bias arising from the selected publication of results, we obtained details of all adverse events related to muscle recorded in each individual trial participant, and coded them using the common nosological standard (from the Medical Dictionary for Regulatory Activities). The availability of individual participant data permitted more detailed analyses of risk for each statin than have previously been possible, including analyses examining the effects on particular symptoms, the timing of any excess risk, and the variation in treatment effects in different types of patients. Statin regimens caused a small relative increase (3%) in the number of first reports of muscle symptoms, but the excess of reports due to statin therapy was largely confined to the first year of treatment, during which there was an absolute excess rate of 11 (95% CI 6–16) events per 1000 person-years. Statins had similar effects on a range of reported muscle symptoms, including myalgia, muscle cramps or spasm, limb pain, and other musculoskeletal pain. There was no evidence for variation in the relative effects of different statins. The relative increase in the rate of muscle symptoms was similar in a wide range of trial participants, and was irrespective of the variation in the methods used to ascertain symptoms, suggesting that the observed relative effects of statins on muscle symptoms are likely to be generalisable. Overall, for the regimens studied in these trials, the increase in symptoms was greater for more intensive statin regimens, and a small excess risk was likely to persist for longer, than for less intensive or moderate-intensity regimens. Based on previous analyses of these trials, this excess risk of muscle symptoms is greatly outweighed by the known cardiovascular benefits of statin therapy.

### Implications of all the available evidence

These results from randomised double-blind trials suggest that when a patient reports muscle symptoms when taking a statin, the probability that it is actually caused by the statin is low (<10%). Consequently, current recommendations on the management of such muscle symptoms should be reviewed.

# Human monkeypox virus infection in an immunocompromised man: trial with tecovirimat

*Loren E Hernandez, Arvin Jadoo, Robert S Kirsner*

A 37-year-old man attended our hospital with a 1-week history of fever, chills, headaches, sore throat, generalised malaise, and a rash on his arms, legs, trunk, and in his groin. The patient also reported significant pain and discomfort in his rectum when defecating. He had a history of HIV and metastatic Kaposi sarcoma; secondary syphilis, which had been treated; and hypertension. He was prescribed the following medications: emtricitabine-tenofovir, doravarine, darunavir-cobicistat, and hydrochlorothiazide.

The patient reported no recent travel or contact with human or animal with a similar rash or illnesses. He reported no history of varicella zoster virus infection as a child and said he had received all childhood vaccinations. The patient reported no sexual activity for the past 6 months.

On examination, the patient was afebrile: temperature 37·3°C. He appeared uncomfortable and had several scattered, pink, umbilicated papules, vesicles, and pustules on the trunk, upper and lower extremities, groin, and peri-anal region (figure).

Laboratory investigations showed a haemoglobin concentration of 12·7 g/dL (normal 13·3–16·3), CD4+ T-helper cell count of 262 cells per mcL (normal 490–1740), HIV-1 RNA PCR less than 20 copies per mL, and an absolute lymphocyte count of 3·01 per uL (normal 1·1–2·7). Serology was negative for *Bartonella henselae*, *Aspergillus* spp, hepatitis A, B, and C, cryptococcal antigen, herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and (1→3)-β-D-glucan.

Immunohistochemical analysis of a biopsy sample of one of the truncal papules was negative for HSV-1, HSV-2, and *Treponema pallidum*. Warthin-Starry staining was negative for spirochetes and periodic-acid-Schiff staining was negative for fungal organisms. Histopathological analysis of the biopsy sample showed focal epidermal necrosis with underlying acute inflammation in the superficial dermis and individually necrotic keratinocytes at the periphery. A Dacron swab of one of the truncal lesions was positive for human monkeypox virus.

Considering our patient's history of immunosuppression, we prescribed doxycycline, ceftriaxone, and valacyclovir; we subsequently gave him a 2-week course of 600 mg of tecovirimat twice a day. He reported no significant adverse effects and the skin lesions healed rapidly. At follow-up one month later, the patient reported areas of hyperpigmentation at the sites of the healed lesions and said he was doing well.

Monkeypox is caused by the monkeypox virus, a member of the *Poxviridae* family and *Orthopoxvirus* genus. The virus is transmitted via large respiratory droplets, direct or indirect contact with bodily fluids or lesion material, or contact with fomites—including bedding or towels. Malaise, lymphadenopathy, headache, myalgia, and cutaneous symptoms can occur within 1–3 days of the onset of fever. Lesions may initially appear as macules progressing to papules, vesicles, and pustules that dry up and fall off. The development of skin lesions, in addition to viral prodromal symptoms, in immunocompromised patients should raise the possibility of other diagnosis, such as primary or secondary infection with varicella zoster virus or other organisms such as *Cryptococcus neoformans*, *Histoplasma capsulatum*, or *Bartonella henselae*; we considered this unlikely in our patient given his presentation. Molluscum contagiosum also presents with umbilicated papules, but usually without systemic symptoms. Notably, proctitis has recently been recognised as being associated with a human monkeypox infection. Tecovirimat is approved for treating human smallpox disease. Treatment in cases of human monkeypox should be considered in severe cases, immunocompromised patients, paediatric populations, pregnant or breastfeeding women, and people with concurrent disease or other comorbidities.

**Contributors**
We were all involved in the patient's care. AJ and LEH wrote the manuscript under RSK's supervision. Written consent for publication was obtained from the patient.

**Declaration of interests**
We declare no competing interests.



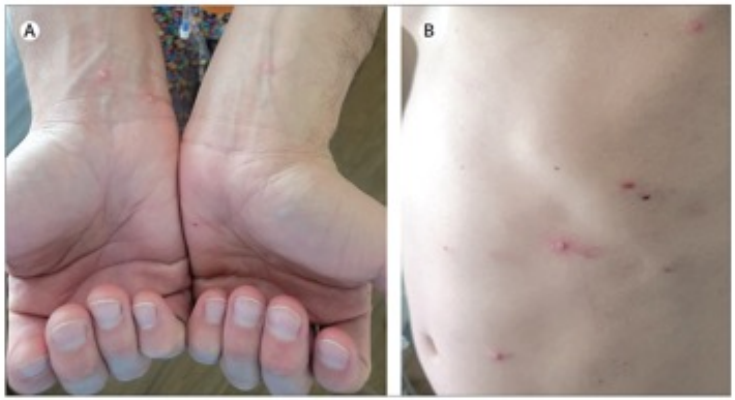



**Figure: Monkeypox infection in HIV-positive person**
(A) Photograph shows pustules on volar wrists. (B) Photograph shows pustules at left hypochondriac and lumbar regions.

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# Spontaneous subarachnoid haemorrhage

*Jan Claassen, Soojin Park*

Subarachnoid haemorrhage (SAH) is the third most common subtype of stroke. Incidence has decreased over past decades, possibly in part related to lifestyle changes such as smoking cessation and management of hypertension. Approximately a quarter of patients with SAH die before hospital admission; overall outcomes are improved in those admitted to hospital, but with elevated risk of long-term neuropsychiatric sequelae such as depression. The disease continues to have a major public health impact as the mean age of onset is in the mid-fifties, leading to many years of reduced quality of life. The clinical presentation varies, but severe, sudden onset of headache is the most common symptom, variably associated with meningismus, transient or prolonged unconsciousness, and focal neurological deficits including cranial nerve palsies and paresis. Diagnosis is made by CT scan of the head possibly followed by lumbar puncture. Aneurysms are commonly the underlying vascular cause of spontaneous SAH and are diagnosed by angiography. Emergent therapeutic interventions are focused on decreasing the risk of rebleeding (ie, preventing hypertension and correcting coagulopathies) and, most crucially, early aneurysm treatment using coil embolisation or clipping. Management of the disease is best delivered in specialised intensive care units and high-volume centres by a multidisciplinary team. Increasingly, early brain injury presenting as global cerebral oedema is recognised as a potential treatment target but, currently, disease management is largely focused on addressing secondary complications such as hydrocephalus, delayed cerebral ischaemia related to microvascular dysfunction and large vessel vasospasm, and medical complications such as stunned myocardium and hospital acquired infections.

| | Clinical grading scale | | Imaging grading scale | |
|---|---|---|---|---|
| | WFNS scale | Hunt Hess scale | Modified Fisher scale | SEBES |
| Prediction purpose | Outcome | Outcome | Delayed cerebral ischaemia | Quantify oedema |
| Range | 1–5 | 1–5 | 0–4 | 0–4 |
| Criteria | .. | .. | Quantify location and extent of SAH and IVH | At two levels in each hemisphere: (1) effacement of sulci or (2) disruption of grey-white matter |
| Grade | | | | |
| 0 | .. | .. | No SAH | .. |
| 1 | GCS 15 | Mild headache | Thin SAH, no IVH | .. |
| 2 | GCS 13–14, no motor deficit | Moderate to severe headache, cranial nerve palsy, nuchal rigidity | Thin SAH, with IVH | .. |
| 3 | GCS 13–14, with motor deficit | Lethargy or confusion, mild focal deficit | Thick SAH, no IVH | .. |
| 4 | GCS 7–12 | Stupor, hemiparesis | Thick SAH, with IVH | .. |
| 5 | GCS 3–6 | Coma, decerebrate posturing | .. | .. |

WFNS=World Federation of Neurological Surgeons. SEBES=subarachnoid hemorrhage early brain oedema score. GCS=Glasgow coma scale. SAH=subarachnoid haemorrhage. IVH=intraventricular haemorrhage.

***Table:*** **Clinical and imaging scales**

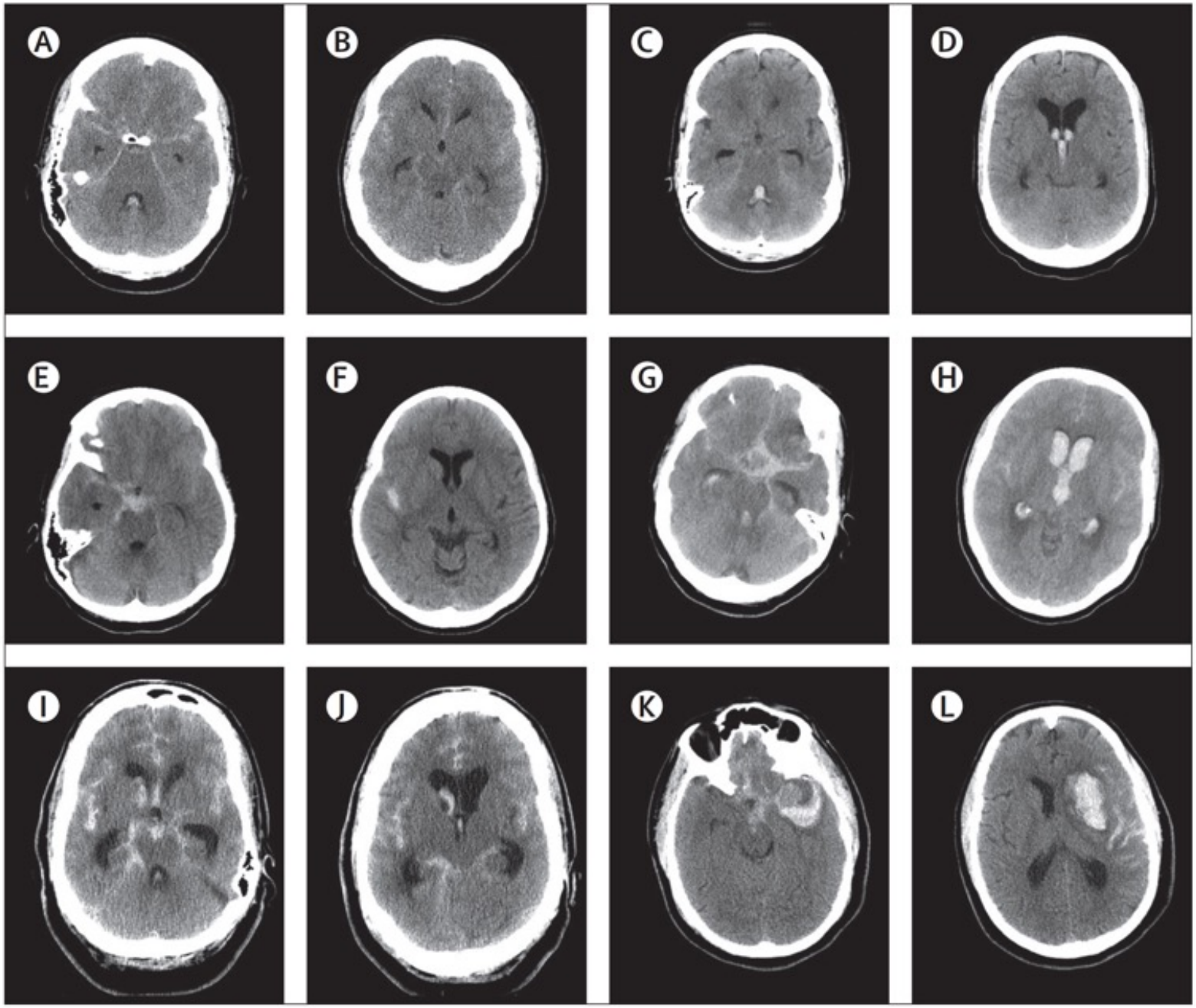


***Figure 1:*** **Neuroimaging of patients with aneurysmal subarachnoid haemorrhage**
Head CT demonstrating modified Fisher scores 1 (A, B), 2 (C, D), 3 (E, F), 4 (G, H), hydrocephalus (I, J), and intracerebral haemorrhage (K, L).

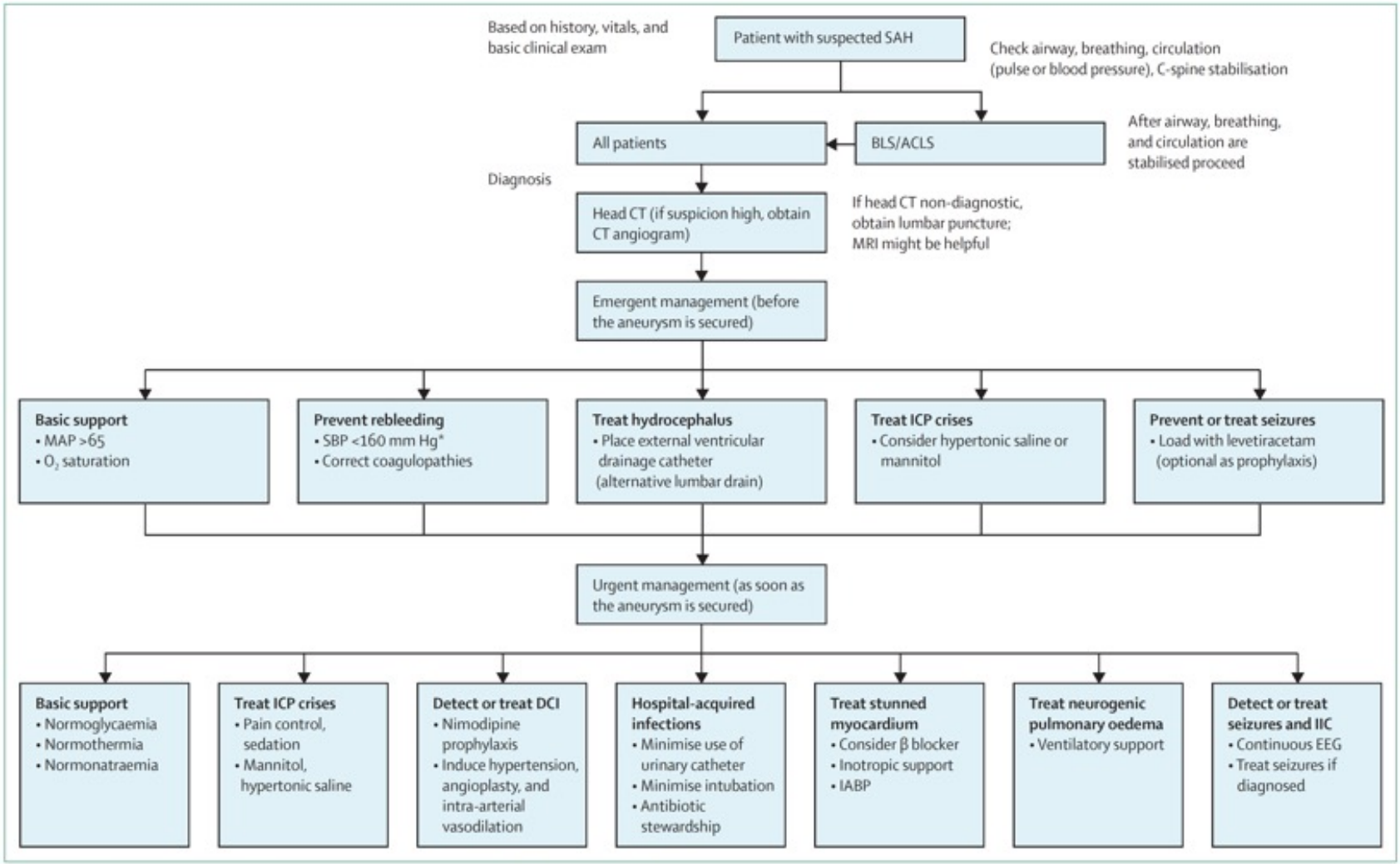


***Figure 2:*** **Management approach for patients with aneurysmal subarachnoid haemorrhage**

SAH=subarachnoid haemorrhage. BLS=basic life support. ACLS=advanced cardiac life support. ICP=intracranial pressure. MAP=mean arterial pressure. SBP=systolic blood pressure. DCI=delayed cerebral ischaemia. IIC=ictal-interictal continuum. IABP=intra-aortic balloon pump. EEG=electroencephalogram. *As per US guidelines (European guidelines recommend <180 mm Hg).

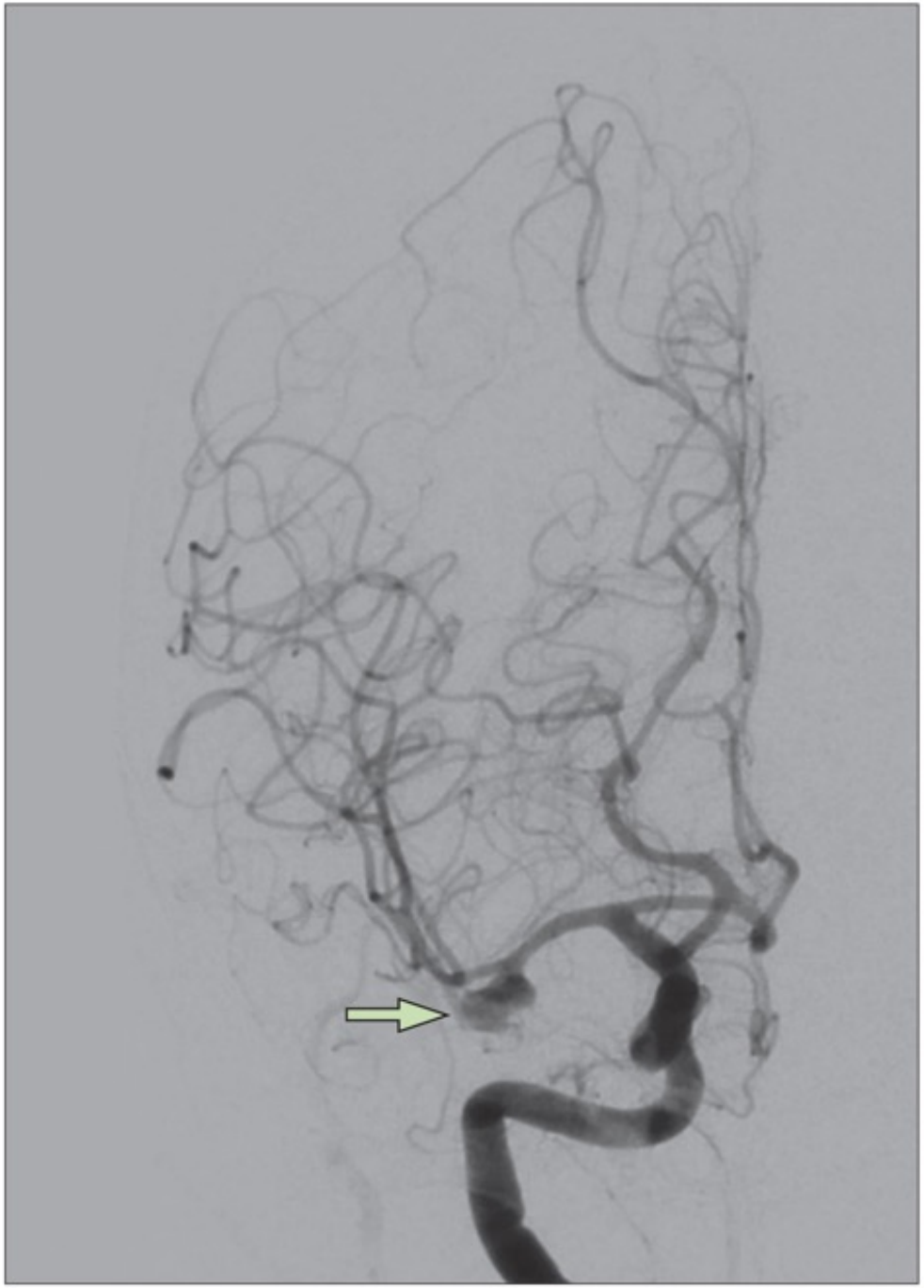

*Figure 3:* Digital subtraction angiography of patient demonstrating right, multilobulated middle cerebral artery bifurcation aneurysm

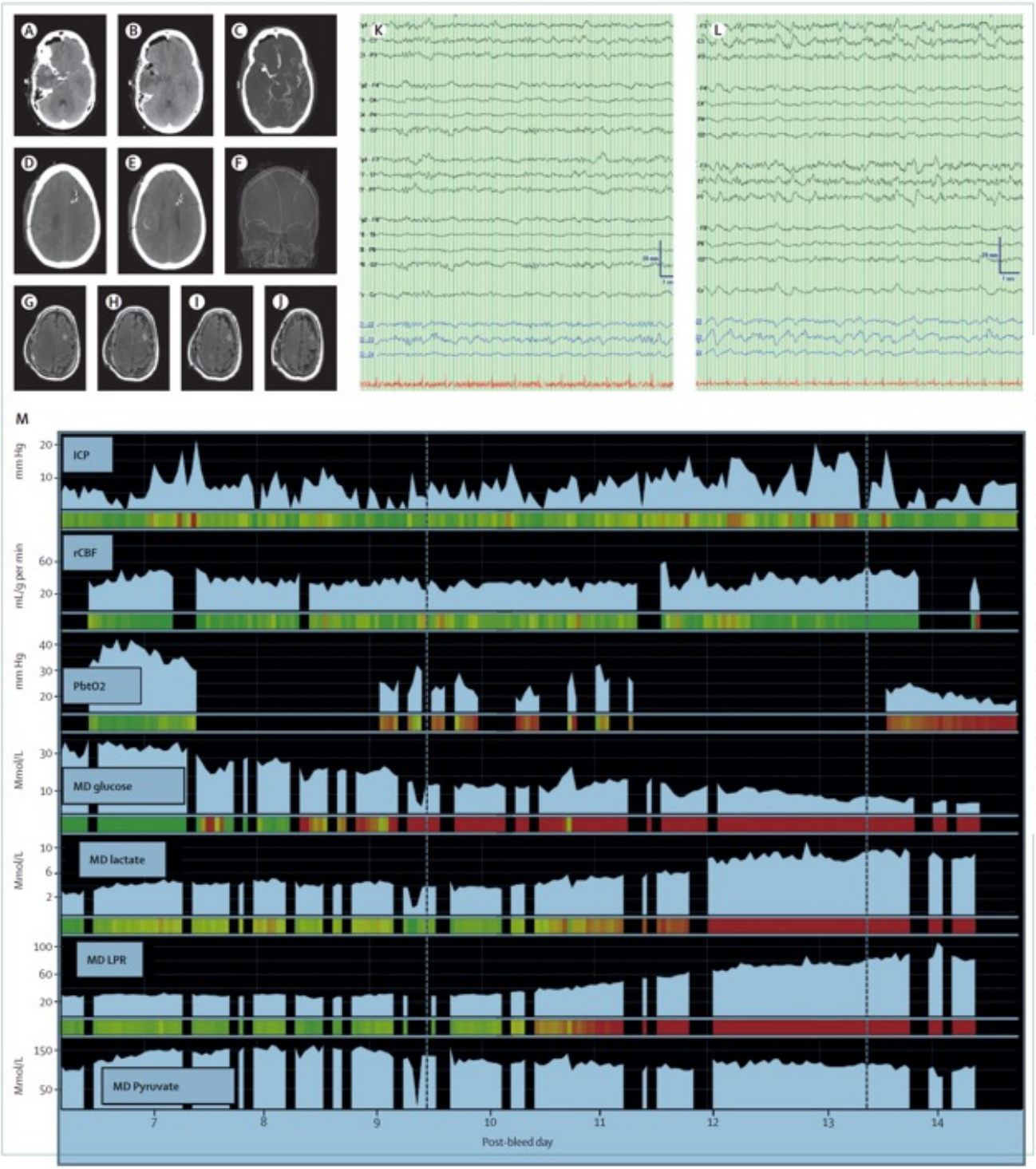


***Figure 4:*** **Patient with aneurysmal SAH and DCI diagnosed with multimodality monitoring and cognitive-motor dissociation**

A 73-year-old woman who presented with severe headache and loss of consciousness. She was diagnosed with aneurysmal subarachnoid haemorrhage (SAH) (A, B; Hunt Hess 4, mFS 4) from an aneurysm at the right middle cerebral artery (CT angiography; C). Operative treatment failed at an outside hospital before she was transferred to a tertiary care centre. She arrived in deep coma with a coma recovery scale-revised score of 9 out of 23 that quickly deteriorated to 7. To support detection of delayed cerebral ischaemia (DCI), on post-bleed day 5 the decision was made to place a multimodality monitoring bundle into the left frontal lobe (placement on the right was impossible due to the previous craniotomy) including measurements for intracranial pressure (ICP), brain oxygenation (PbtO2), brain temperature, regional cerebral blood flow (rCBF), cerebral microdialysis (MD), and surface and intracortical electroencephalogram (EEG). Baseline EEG demonstrated a minor breach over the right hemisphere but otherwise symmetric EEG (K). On post-bleed day 10 she was diagnosed with DCI triggered by focal changes on surface EEG (L) and PbtO2, rCBF, cerebral glucose, pyruvate and rising lactate and lactate-pyruvate ratio (LPR) (M, first dotted line). On post-bleed day 13 she was diagnosed with cognitive motor dissociation using the motor command protocol while the coma recovery scale-revised remained unchanged at 7 (M, second dotted line). She was severely disabled at 3 months (Glasgow outcome scale-extended of 3) post-injury.

## Future directions

Common data elements aimed at standardisation of research efforts for patients with SAH will facilitate future studies.[12]

### Aneurysm treatment

Worldwide, most aneurysms are treated with coil embolisation and ongoing trials are addressing the benefits of clipping versus coiling in patients eligible for clipping who were underrepresented or excluded from previous trials such as ISAT.[185] Numerous ongoing trials are exploring the benefits of newly developed neurosurgical and neuroradiological technology to allow for treatment of the most challenging aneurysms.

## Conclusion

Despite overall improvements in outcome, aneurysmal SAH continues to have a major public health impact with a mean age of onset in the mid-fifties, leading to many years of reduced quality of life. Active areas of investigation are in the categories of optimising early management approaches, goal-directed haemodynamic and perfusion-guided management, personalised medicine for prognostication, and cerebroprotection.

NEJM Knowledge+

## Question of the Week

**Which one of the following treatments is most appropriate for a 40-year-old woman with an acute, hemodynamically unstable narrow-complex tachycardia?**

- ○ Intravenous metoprolol followed by intravenous amiodarone
- ● Synchronized direct-current cardioversion
- ○ Intravenous propafenone
- ○ Intravenous ibutilide
- ○ Intravenous adenosine

SUBMIT

### Your answer is correct.

Intravenous metoprolol followed by intravenous amiodarone
✓ **Synchronized direct-current cardioversion**
Intravenous propafenone
Intravenous ibutilide
Intravenous adenosine

**Key Learning Point**

View Case Presentation ›

The most appropriate first-line therapy for a patient with an acute, hemodynamically unstable narrow-complex tachycardia is direct-current cardioversion.

### Detailed Feedback

In a patient with a hemodynamically unstable tachyarrhythmia, the treatment of choice is direct-current cardioversion.

Although intravenous metoprolol can reduce the ventricular rate in an otherwise stable patient, it is not the best choice for someone who is hemodynamically unstable (i.e., hypotensive), because it can further lower the blood pressure.

Ibutilide is indicated for conversion of atrial fibrillation, but it is not indicated for other supraventricular tachycardias.

Adenosine is indicated for patients with narrow-complex tachycardia due to atrioventricular nodal tachycardia reentry or atrioventricular reentry. Because it may worsen hypotension, it is not indicated in a patient with hemodynamically unstable tachycardia.

Propafenone is indicated for treating ventricular arrhythmias and paroxysmal atrial fibrillation but is not appropriate for a patient with an unstable narrow-complex tachycardia.

Mülltonnenproblem

# Kakadus gegen Menschen – »Innovationswettrüsten« in Australien

Anwohner entwickeln neue Abwehrmechanismen – und Kakadus im Gegenzug neue Techniken, um Reste aus Mülltonnen zu klauen. Das beschäftigt nun auch die Forschung.

Gezielt greift ein Vogel mit seinem Schnabel unter den Deckel einer Mülltonne, drückt ihn auf – bis er senkrecht steht und ganz aufklappt. Ein Video zeigt, was Australierinnen und Australier gerade vielfach live erleben: Mülltonnen sind in Sydney zum Streitobjekt zwischen Kakadus und Anwohnern geworden.

Die Gelbhaubenkakadus haben eine ausgefeilte Technik entwickelt, um die Deckel von Plastikmülltonnen mit Schnabel und Füßen zu öffnen, wie ein Forschungsteam um Barbara Klump vom Max-Planck-Institut für Verhaltensbiologie in Konstanz in der Fachzeitschrift »Current Biology« berichtet. Weil sie beim Stöbern in den Tonnen Abfall in den Wohngebieten verteilen, versuchen die Anwohner die Vögel mit immer neuen Tricks davon abzuhalten.

Cockatoos – no garbage can is safe