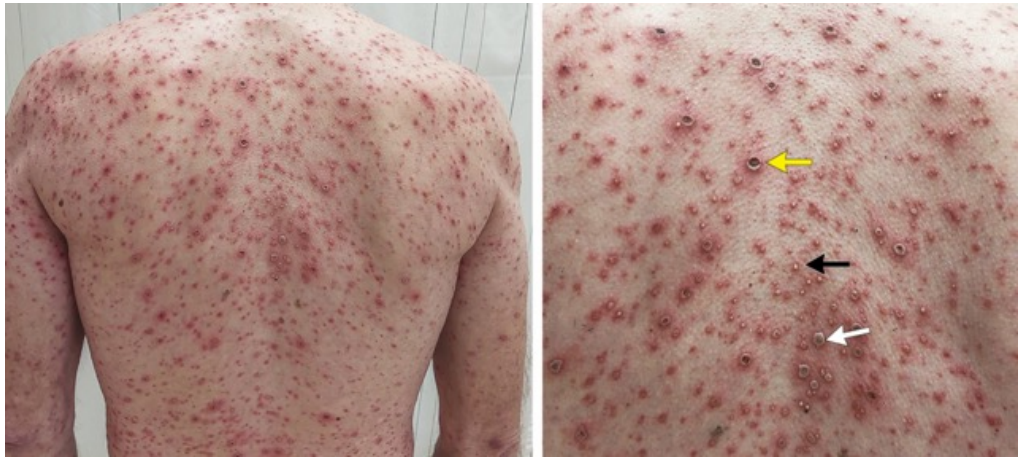
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 44-year-old man presented with a 4-day history of an itchy rash and a 2-day history of fever and malaise. The rash had first appeared on the scalp and then spread across the body within 24 hours. What is the most likely diagnosis?

A polymerase-chain-reaction assay of fluid from a vesicle was positive for varicella–zoster virus. The patient reported no history of chicken pox or varicella vaccination. Primary varicella infection, or chicken pox, in adults is often more severe than in children, which highlights the importance of childhood vaccination. Adults with varicella infection — even immunocompetent ones, such as this patient — have an increased risk of complications, such as pneumonia and encephalitis.

Cutaneous T-cell lymphoma

Dengue fever

Disseminated gonococcal infection

→ Primary varicella infection

Small pox

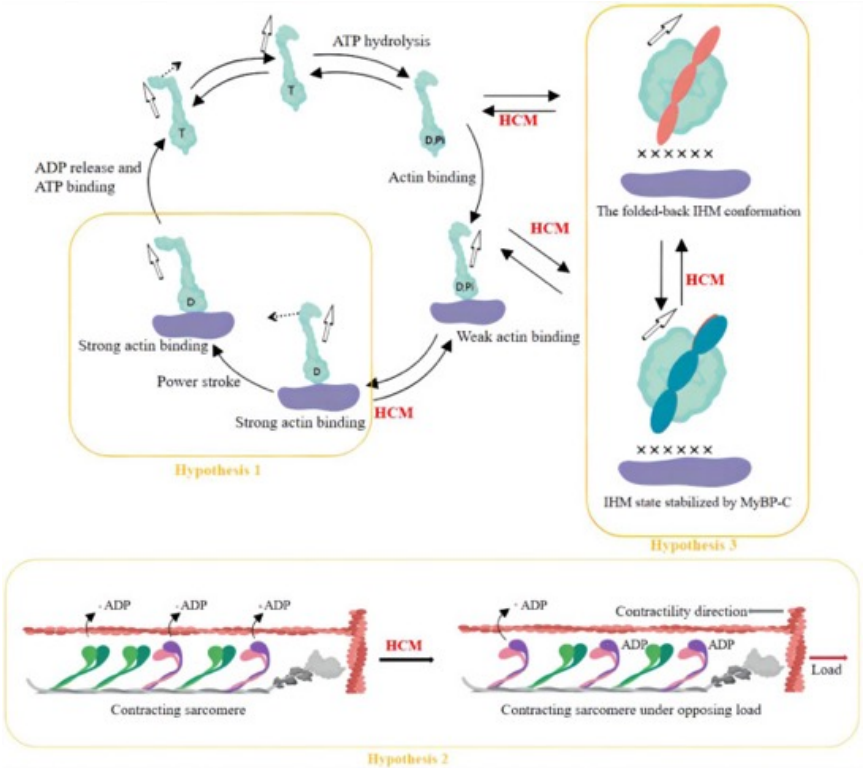
Aficamten ist ein investigationaler Medikamentenwirkstoff zur Behandlung der hypertrophen Kardiomyopathie (HCM), der die kardiale Myosinfunktion hemmt. Es ist ein kleiner, niedermolekularer Inhibitor, der die Hyperkontraktilität des Herzmuskels reduziert, was zu einer Verringerung der Symptome und einer Verbesserung der körperlichen Leistungsfähigkeit führt. Erste Studienergebnisse zeigen eine Wirksamkeit, und es wird derzeit in Phase-3-Studien für verschiedene Formen der HCM untersucht, einschließlich nicht-obstruktiver HCM.

Wirkmechanismus

• Aficamten ist ein kardialer Myosin-Inhibitor, der die Überaktivität des Herzmuskels verringert.

• Es verringert die Anzahl der aktiven Aktin-Myosin-Kreuzbrücken im Herzen, was die Kontraktionskraft reduziert.

• Aficamten reduces myocardial contractility (inotropy) by directly binding to cardiac myosin, which stabilizes the myosin pre-power stroke state and reduces the number of excessive myosin-actin cross-bridges, thus decreasing force generation in hypertrophic cardiomyopathy (HCM). This mechanism directly addresses the hypercontractility that causes left ventricular outflow tract (LVOT) obstruction in HCM.

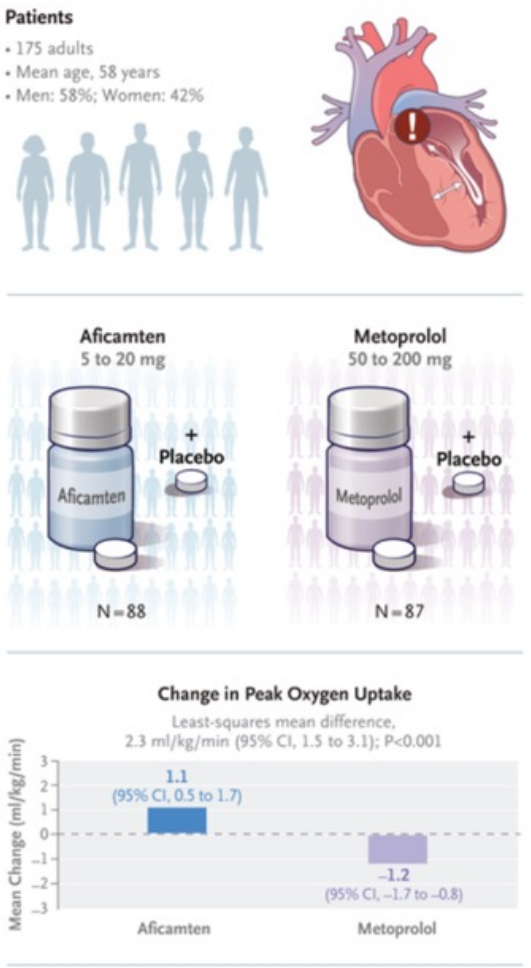


The most common German words for "ratchet" are die Ratsche and die Knarre, both referring to the tool itself.

Aficamten or Metoprolol Monotherapy for Obstructive Hypertrophic Cardiomyopathy

Beta-blockers have been the initial treatment for symptomatic obstructive hypertrophic cardiomyopathy (HCM) despite limited evidence of their efficacy. Aficamten is a cardiac myosin inhibitor that reduces left ventricular outflow tract gradients, improves exercise capacity, and decreases HCM symptoms when added to standard medications. Whether aficamten as monotherapy provides greater clinical benefit than beta-blockers as monotherapy remains unknown.

We conducted an international, double-blind, double-dummy trial in which adults with symptomatic obstructive HCM were randomly assigned in a 1:1 ratio to receive aficamten (at a daily dose of 5 mg to 20 mg) plus placebo or metoprolol (at a daily dose of 50 mg to 200 mg) plus placebo. The primary end point was the change in peak oxygen uptake at week 24; secondary end points were improvement at week 24 in New York Heart Association (NYHA) functional class and changes at week 24 in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), left ventricular outflow tract gradient after the Valsalva maneuver, N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, left atrial volume index, and left ventricular mass index.



Since the observation by Cohen and Braunwald almost 60 years ago that blocking the beta-adrenergic receptor could reduce left ventricular outflow tract obstruction, beta-blockers have been used as first-line treatment in patients with symptomatic obstructive HCM. However, this practice has been based largely on expert opinion, with only a few small, single-center, placebo-controlled studies supporting guideline recommendations.

Aficamten is a next-in-class cardiac myosin inhibitor that reduces myocardial hypercontractility by decreasing the number of active actin–myosin cross-bridges within the sarcomere. It has no clinically important drug–drug interactions and is pharmacologically designed to have a shallow dose–response relationship that facilitates individualized dose adjustments. In a recent trial, aficamten resulted in a substantial decrease in left ventricular outflow tract obstruction, a decrease in symptoms, and improvements in functional capacity, cardiac structure, and cardiac biomarkers as compared with placebo in patients with symptomatic obstructive HCM despite the receipt of conventional standard therapy, including beta-blockers in the majority of patients. Whether aficamten administered as monotherapy would be superior to beta-blockers as monotherapy is unknown. The MAPLE-HCM (Metoprolol versus Aficamten in Patients with Left Ventricular Outflow Tract Obstruction on Exercise Capacity in HCM) trial was a phase 3 trial that compared aficamten as monotherapy with beta-blockade with metoprolol as monotherapy in patients with symptomatic obstructive HCM.

Methods

Trial Design and Oversight

The MAPLE-HCM trial was a head-to-head, phase 3, international, double-blind, double-dummy, randomized trial in which patients with symptomatic obstructive HCM received aficamten plus placebo (in place of metoprolol) or metoprolol plus placebo (in place of aficamten).

Patients

Eligible patients were 18 to 85 years of age and had received a diagnosis of HCM, which was defined by a left ventricular wall thickness of at least 15 mm (or ≥13 mm in the presence of a disease-causing genetic variant or family history of HCM). At screening, patients were required to have a left ventricular ejection fraction of at least 60% and evidence of resting obstruction (left ventricular outflow tract gradient of ≥30 mm Hg at rest) or latent obstruction (left ventricular outflow tract gradient of ≥50 mm Hg after the Valsalva maneuver). Patients were required to have symptoms and impaired functional capacity, as evidenced by New York Heart Association (NYHA) functional class II or III heart failure.

End Points

The primary end point was the change from baseline to week 24 in peak oxygen uptake as assessed during cardiopulmonary exercise testing.

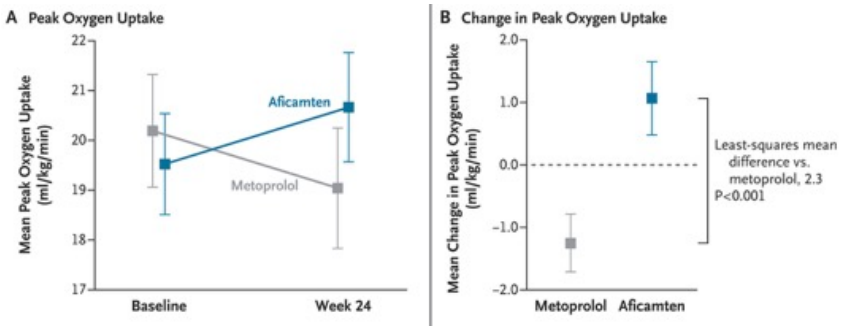
Characteristic	Aficamten (N=88)	Metoprolol (N=87)
Age — yr	58.9±13.3	56.5±13.1
Female sex — no. (%)	36 (41)	37 (43)
Race — no. (%)†		
White	70 (80)	70 (80)
Black	1 (1)	0
Asian	13 (15)	12 (14)
Other	4 (5)	5 (6)
Region — no. (%)		
China	11 (12)	11 (13)
North America	45 (51)	39 (45)
Europe, Israel, or Brazil	32 (36)	37 (43)
Medical history — no. (%)		
Family history of hypertrophic cardiomyopathy	16 (18)	18 (21)
Pathogenic sarcomeric variant‡	27 (31)	22 (25)
History of septal reduction therapy§	1 (1)	5 (6)
History of taking mavacamten¶	3 (3)	4 (5)
Hypertension	54 (61)	33 (38)
Sustained ventricular tachycardia	2 (2)	1 (1)
Implantable cardioverter–defibrillator	8 (9)	13 (15)
Background standard therapy — no. (%)‖		
Beta-blocker	64 (73)	59 (68)
Calcium-channel blocker	12 (14)	10 (11)
Not taking background therapy	19 (22)	23 (26)
Symptoms		
Kansas City Clinical Questionnaire clinical summary score**	65.5±17.0	66.0±16.0
New York Heart Association functional class — no. (%)††		
II	63 (72)	60 (69)
III	25 (28)	27 (31)
Median NT-proBNP level (IQR) — pg/ml	510 (213–993)	439 (171–907)
Peak oxygen uptake — ml/kg/min	19.5±4.8	20.2±5.3
Echocardiographic variables		
Left ventricular outflow tract gradient after Valsalva maneuver — mm Hg	75.3±34.0	71.6±31.2
Resting left ventricular outflow tract gradient — mm Hg	48.6±30.1	46.2±27.4
Left ventricular ejection fraction — %	68.3±3.8	67.3±3.9
Maximum wall thickness — mm	20.9±2.8	20.8±3.3

End Points and Vital Signs.

Variable	Aficamten (N=88)		Metoprolol (N=87)		Difference (95% CI)††	P Value
	No. of Patients Evaluated	Mean (95% CI)‡‡	No. of Patients Evaluated	Mean (95% CI)‡‡		
Primary end point						
Change in peak oxygen uptake at 24 wk assessed by cardiopulmonary exercise testing — ml/kg/min	83	1.1 (0.5 to 1.7)	82	−1.2 (−1.7 to −0.8)	2.3 (1.5 to 3.1)	<0.001
Secondary end points						
Improvement of ≥1 NYHA functional class at wk 24 — %	87	51 (40 to 62)	88	26 (18 to 37)	25 (11 to 39)	<0.001
Change in KCCQ-CSS at wk 24	87	15.8 (12.5 to 19.0)	86	8.7 (5.3 to 12.1)	6.9 (2.6 to 11.3)	0.002
Proportional change in NT-proBNP level at wk 24 — pg/ml§	87	0.3 (0.2 to 0.3)	86	1.4 (1.3 to 1.6)	0.19 (0.15 to 0.24)	<0.001
Change in left ventricular outflow tract gradient after Valsalva maneuver at wk 24 — mm Hg	83	−40.7 (−48.5 to −32.9)	85	−3.8 (−11.3 to 3.7)	−34.9 (−43.4 to −26.4)	<0.001
Change in left atrial volume index at wk 24 — ml/m²	87	−3.8 (−5.1 to −2.4)	86	2.8 (1.1 to 4.6)	−7.0 (−9.1 to −4.9)	<0.001
Change in left ventricular mass index at wk 24 — g/m²	79	−6.9 (−12.4 to −1.4)	80	−3.8 (−9.1 to 1.6)	−4.9 (−11.7 to 2.0)	0.16
Vital signs						
Change in resting heart rate at wk 24 — beats/min	87	1.4 (−0.9 to 3.7)	86	−8.3 (−10.6 to −6.0)	—	—
Change in resting systolic blood pressure at wk 24 — mm Hg	87	4.5 (1.8 to 7.3)	86	−5.8 (−8.6 to −3.1)	—	—
Change in resting diastolic blood pressure at wk 24 — mm Hg	87	2.3 (0.6 to 4.0)	86	−3.9 (−5.6 to −2.2)	—	—
Change in peak heart rate during exercise at wk 24 — beats/min	83	4.7 (2.3 to 7.1)	82	−23.4 (−27.0 to −19.8)	—	—

Safety Variables.

Adverse Event	Aficamten (N=88)	Metoprolol (N=87)
	no. of patients (%)	
Any serious adverse event — no. (%)	7 (8)	6 (7)
Any adverse event — no. (%)	65 (74)	66 (76)
Any adverse event that led to early withdrawal of treatment — no. (%)	1 (1)*	3 (3)†
Any adverse event that led to temporary interruption of treatment — no. (%)	1 (1)‡	1 (1)§
Adverse event that led to dose reduction¶	1 (1)	4 (5)



Subgroup	Metoprolol	Aficamten	Least-Squares Mean Difference in Peak Oxygen Uptake (95% CI)
	no. of patients		*ml/kg/min*
Overall	87	88	2.3 (1.5–3.1)
Sex			
Male	50	52	2.2 (1.2–3.2)
Female	37	36	2.2 (1.0–3.3)

Subgroup	Metoprolol	Aficamten	Least-Squares Mean Difference in Peak Oxygen Uptake (95% CI)
	no. of patients		*ml/kg/min*
Overall	87	88	2.3 (1.5–3.1)
Sex			
Male	50	52	2.2 (1.2–3.2)
Female	37	36	2.2 (1.0–3.3)

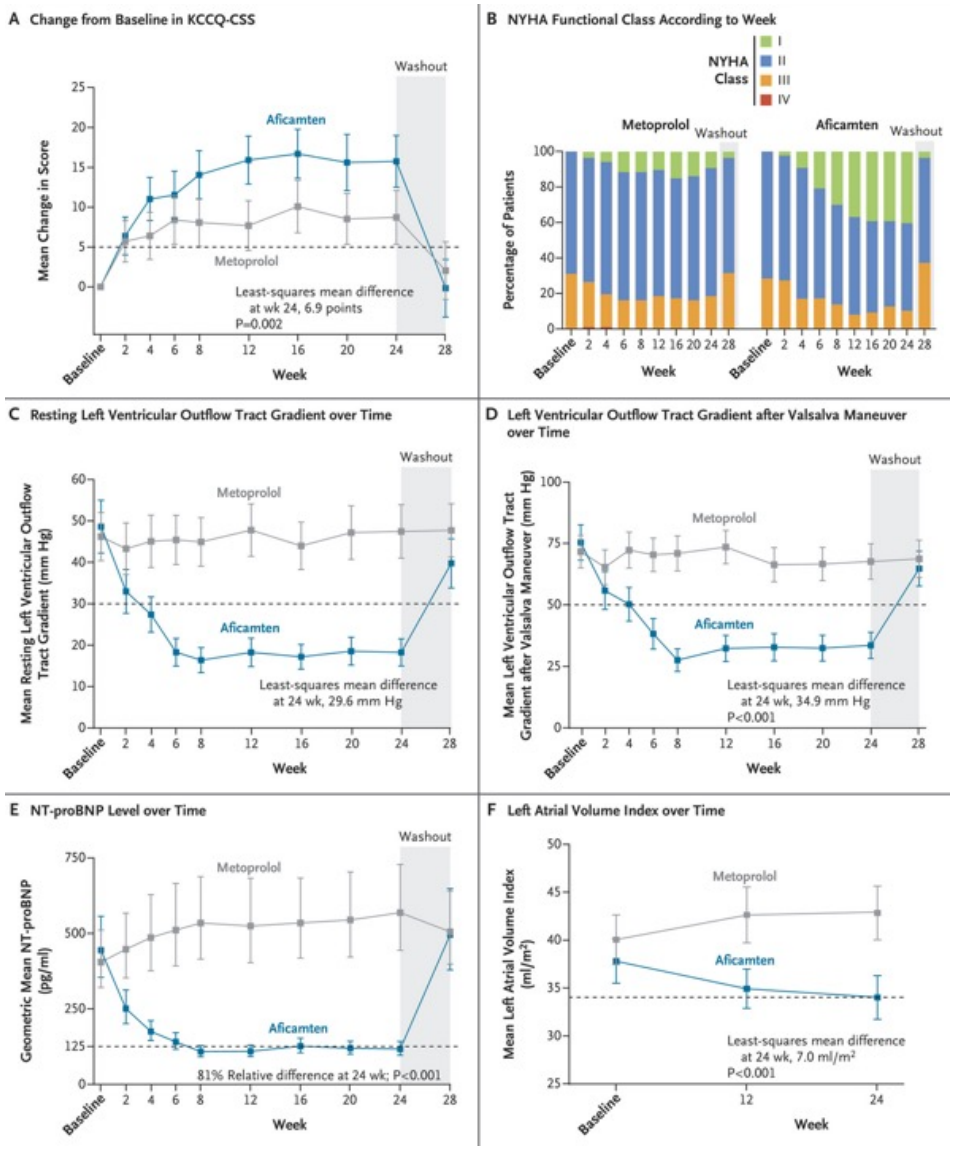
Age group			
<65 yr	61	50	2.3 (1.3–3.3)
≥65 yr	26	38	2.4 (1.1–3.8)
Baseline body-mass index			
<30	59	57	2.5 (1.6–3.5)
≥30	28	31	2.0 (0.6–3.3)
Baseline New York Heart Association functional class			
Class II	60	63	2.2 (1.3–3.2)
Class III	27	25	2.5 (1.0–3.9)
Baseline left ventricular ejection fraction			
≤Median, 68.5%	50	39	2.7 (1.6–3.8)
>Median, 68.5%	37	49	1.9 (0.8–3.1)
Baseline NT-proBNP level			
≤Median, 468.0 pg/ml	47	41	3.0 (2.0–4.1)
>Median, 468.0 pg/ml	40	47	1.6 (0.5–2.7)
Method of cardiopulmonary exercise testing			
Treadmill	52	52	2.5 (1.5–3.5)
Bicycle	35	36	2.0 (0.7–3.2)
Baseline peak oxygen uptake			
≤Median, 19.75 ml/kg/min	39	49	2.5 (1.4–3.7)
>Median, 19.75 ml/kg/min	48	39	2.0 (0.9–3.0)
Diagnosis period			
Recent diagnosis	27	26	3.2 (1.8–4.6)
Chronic obstructive HCM	60	62	1.9 (1.0–2.8)
Baseline left ventricular outflow tract gradient after Valsalva maneuver			
≤Median, 72.0 mm Hg	44	44	2.3 (1.2–3.4)
>Median, 72.0 mm Hg	42	44	2.3 (1.2–3.4)
Baseline KCCQ-CSS			
≤Median, 67.7	45	42	2.3 (1.2–3.4)
>Median, 67.7	42	46	2.3 (1.1–3.4)

Change in Peak Oxygen Uptake.

Panel A shows the mean peak oxygen uptake values at baseline and week 24. Panel B shows the least-squares mean between-group difference in the change from baseline to week 24 in the mean peak oxygen uptake. I bars denote 95% confidence intervals.

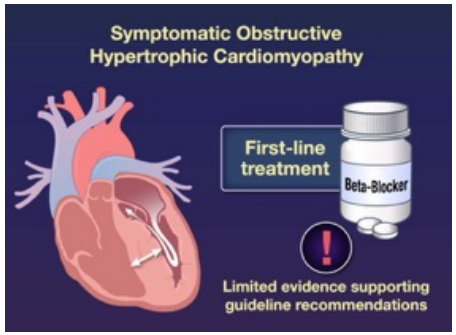
Subgroup Analysis of the Primary End Point.

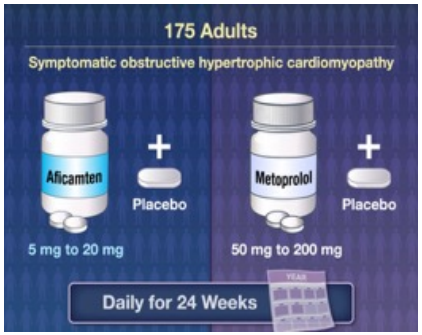
The forest plot shows the change in peak oxygen uptake (the primary end point) in prespecified subgroups. The Kansas City Clinical Questionnaire clinical summary score (KCCQ-CSS) ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. New York Heart Association functional classes range from I to IV, with higher values indicating greater disability. The body-mass index is the weight in kilograms divided by the square of the height in meters.

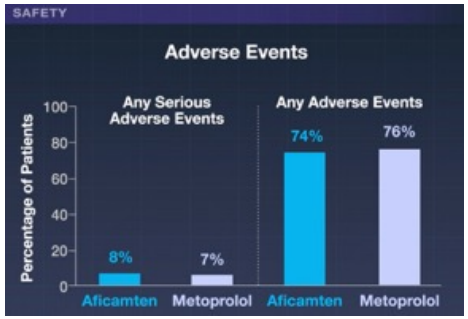


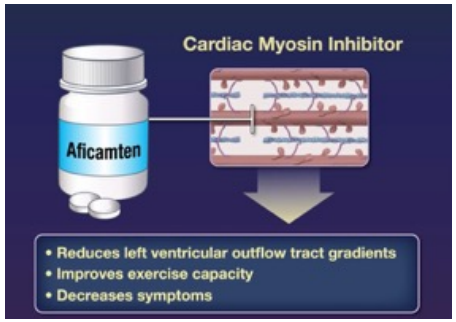
Key Secondary End Points.

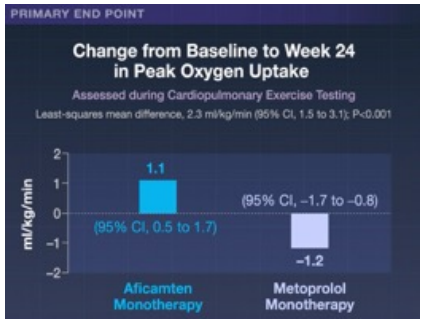
Panel A shows the change from baseline in the KCCQ-CSS. The dashed line indicates the minimum clinically important difference. Panel B shows the percentage of patients in each New York Heart Association (NYHA) functional class at baseline and at 2-week or 4-week increments. Panel C shows the mean resting left ventricular outflow tract gradient over time (exploratory end point). Panel D shows the mean left ventricular outflow tract gradient after the Valsalva maneuver over time. The dashed lines in Panels C and D denote the minimum value indicative of obstructive HCM. Panel E shows the geometric mean NT-proBNP level over time. Panel F shows the mean left atrial volume index over time. The dashed lines in Panels E and F indicate the upper limit of the normal range. All echocardiographic and biomarker values shown are based on core laboratory measurements. I bars denote 95% confidence intervals.

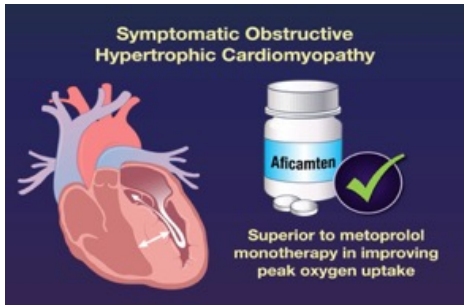

Symptomatic Obstructive Hypertrophic Cardiomyopathy
First-line treatment
Beta-Blocker
Limited evidence supporting guideline recommendations


175 Adults
Symptomatic obstructive hypertrophic cardiomyopathy
Aficamten
Placebo
5 mg to 20 mg
Metoprolol
Placebo
50 mg to 200 mg
Daily for 24 Weeks

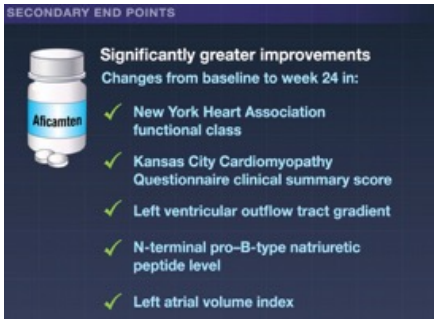

SAFETY
Adverse Events
Any Serious Adverse Events
Any Adverse Events
Percentage of Patients
100
80
60
40
20
0
8%
7%
74%
76%
Aficamten
Metoprolol
Aficamten
Metoprolol


Cardiac Myosin Inhibitor
Aficamten
• Reduces left ventricular outflow tract gradients
• Improves exercise capacity
• Decreases symptoms

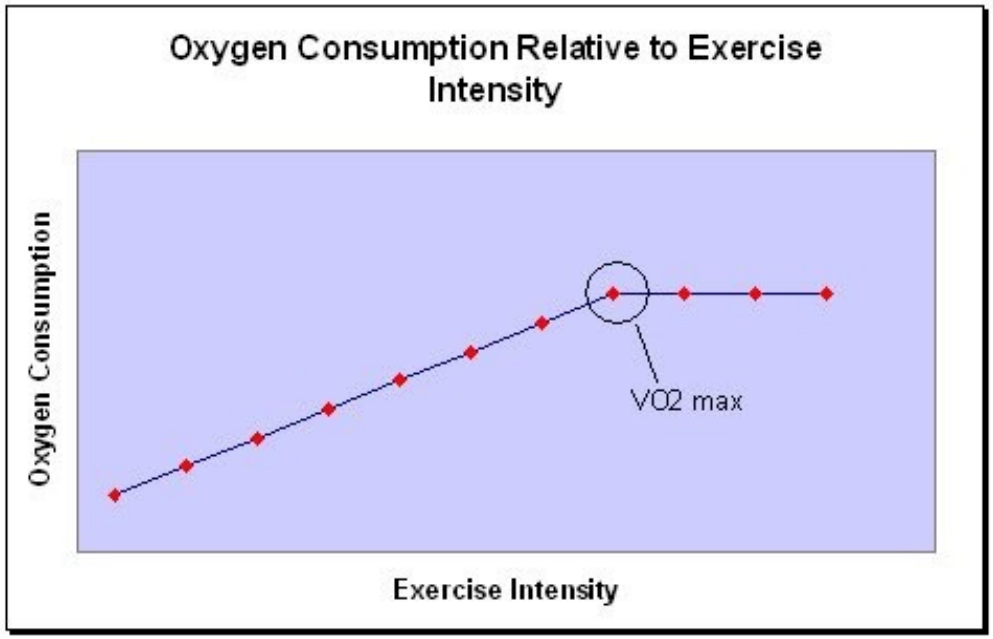

PRIMARY END POINT
Change from Baseline to Week 24 in Peak Oxygen Uptake
Assessed during Cardiopulmonary Exercise Testing
Least-squares mean difference, 2.3 ml/kg/min (95% CI, 1.5 to 3.1); P<0.001
ml/kg/min
2
1
0
−1
−2
1.1
(95% CI, 0.5 to 1.7)
(95% CI, −1.7 to −0.8)
−1.2
Aficamten Monotherapy
Metoprolol Monotherapy


Symptomatic Obstructive Hypertrophic Cardiomyopathy
Aficamten
Superior to metoprolol monotherapy in improving peak oxygen uptake


Aficamten
?
Beta-Blocker
Monotherapy
Monotherapy


SECONDARY END POINTS
Aficamten
Significantly greater improvements
Changes from baseline to week 24 in:
New York Heart Association functional class
Kansas City Cardiomyopathy Questionnaire clinical summary score
Left ventricular outflow tract gradient
N-terminal pro–B-type natriuretic peptide level
Left atrial volume index

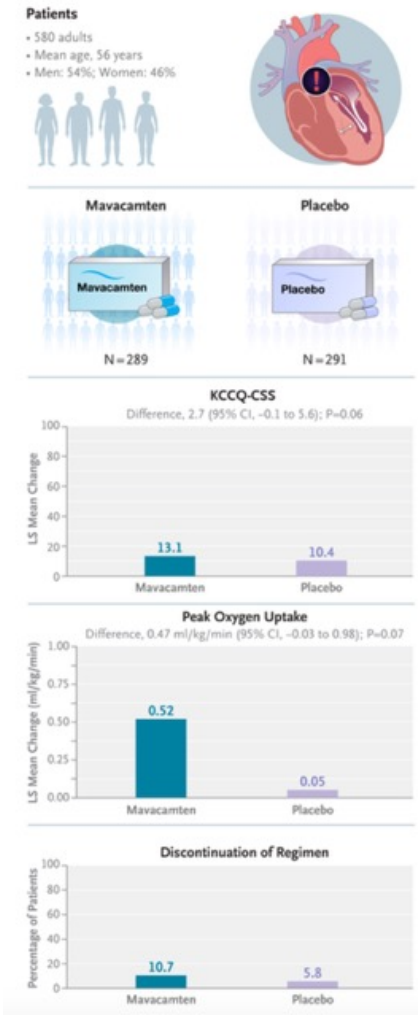
Adult peak oxygen consumption, or peak VO2, is the highest rate at which an individual's body can use oxygen during intense exercise, and it varies significantly by age, sex, and fitness level. For a healthy adult, the mean relative peak VO2 is approximately 35 mL/kg/min for males and 29 mL/kg/min for females, with values generally declining with age. This measurement is a key indicator of cardiovascular health and fitness and is assessed through cardiopulmonary exercise testing.



Mavacamten and aficamten are both cardiac myosin inhibitors used to treat obstructive hypertrophic cardiomyopathy (oHCM), but aficamten has a shorter half-life, lacks significant drug-drug interactions, has a wider therapeutic window, and shows lower rates of left ventricular ejection fraction (LVEF) reduction compared to mavacamten, which has a longer half-life and is associated with higher risks of atrial fibrillation, heart failure, and treatment interruptions due to LVEF reduction. Aficamten's distinct pharmacodynamic and pharmacokinetic properties make it a more rapidly titratable and safer, investigational option in some contexts.

Mavacamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

Mavacamten is approved to treat adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM). However, its effects in nonobstructive HCM remain uncertain.
We conducted a phase 3, international, double-blind, placebo-controlled, clinical trial to determine whether mavacamten improves functional capacity and patient-reported health status among adults with symptomatic nonobstructive HCM. Patients were randomly assigned in a 1:1 ratio to receive mavacamten (starting at 5 mg per day and adjusted up to a maximum of 15 mg per day on the basis of left ventricular ejection fraction) or placebo (with sham dose adjustment) for 48 weeks. The two primary end points were the change from baseline to week 48 in peak oxygen uptake and in the 23-item Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better health status).



Accordingly, there is an unmet medical need for safe and more-effective treatments for patients with symptomatic nonobstructive HCM that increase functional capacity, reduce symptoms, and improve quality of life.

In studies involving patients with symptomatic obstructive HCM, mavacamten decreased outflow tract obstruction, improved quality of life, reduced symptom burden, increased exercise capacity, and reduced eligibility for septal reduction therapy with favorable effects on short- and long-term cardiac remodeling. On the basis of these findings, mavacamten is approved in multiple countries to treat adult patients with obstructive HCM who remain symptomatic despite treatment with beta-blockers or calcium-channel blockers. Mavacamten also has a class I recommendation for treatment of HCM in U.S. practice guidelines and a class IIa recommendation in European practice guidelines.

A small, phase 2, placebo-controlled trial involving patients with nonobstructive HCM showed improvements in N-terminal pro–B-type natriuretic peptide (NT-proBNP) and troponin I levels with mavacamten. We conducted a phase 3 trial (ODYSSEY-HCM) to assess whether mavacamten improves functional capacity and patient-reported health status in adult patients with symptomatic nonobstructive HCM.

The trial enrolled symptomatic patients who met established diagnostic criteria for nonobstructive HCM. Full inclusion and exclusion criteria are provided. Patients were at least 18 years of age and had a peak left ventricular outflow tract gradient of less than 30 mm Hg at rest and less than 50 mm Hg during provocation, New York Heart Association (NYHA) functional class II or III heart failure, a score of 85 or lower on the 23-item Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and better physical functioning), a left ventricular ejection fraction of at least 60% as measured by transthoracic echocardiography and assessed by the core laboratory, a respiratory exchange ratio of at least 1.0 during cardiopulmonary exercise testing, and a locally assessed NT-proBNP level above the upper limits of the normal range.

Mavacamten was added to usual-care background treatments, which could be continued for the duration of the trial. Patients were required to be clinically stable and could not initiate, discontinue, or adjust the dose of new cardiac medications within 2 weeks before screening and up to the day of randomization. Eligible patients were randomly assigned in a 1:1 ratio to receive mavacamten or placebo once daily for 48 weeks.

End Points

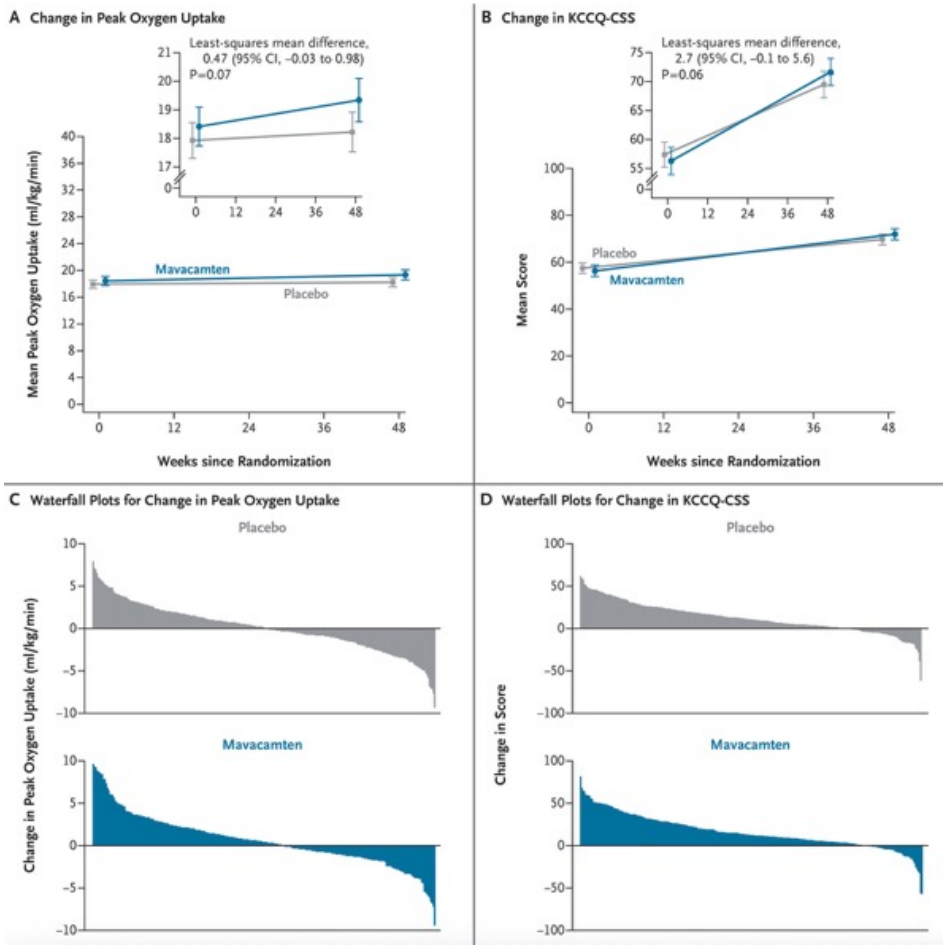
The two primary end points were the change from baseline to week 48 in peak oxygen consumption as determined by cardiopulmonary exercise testing and the change from baseline to week 48 in the KCCQ-CSS.

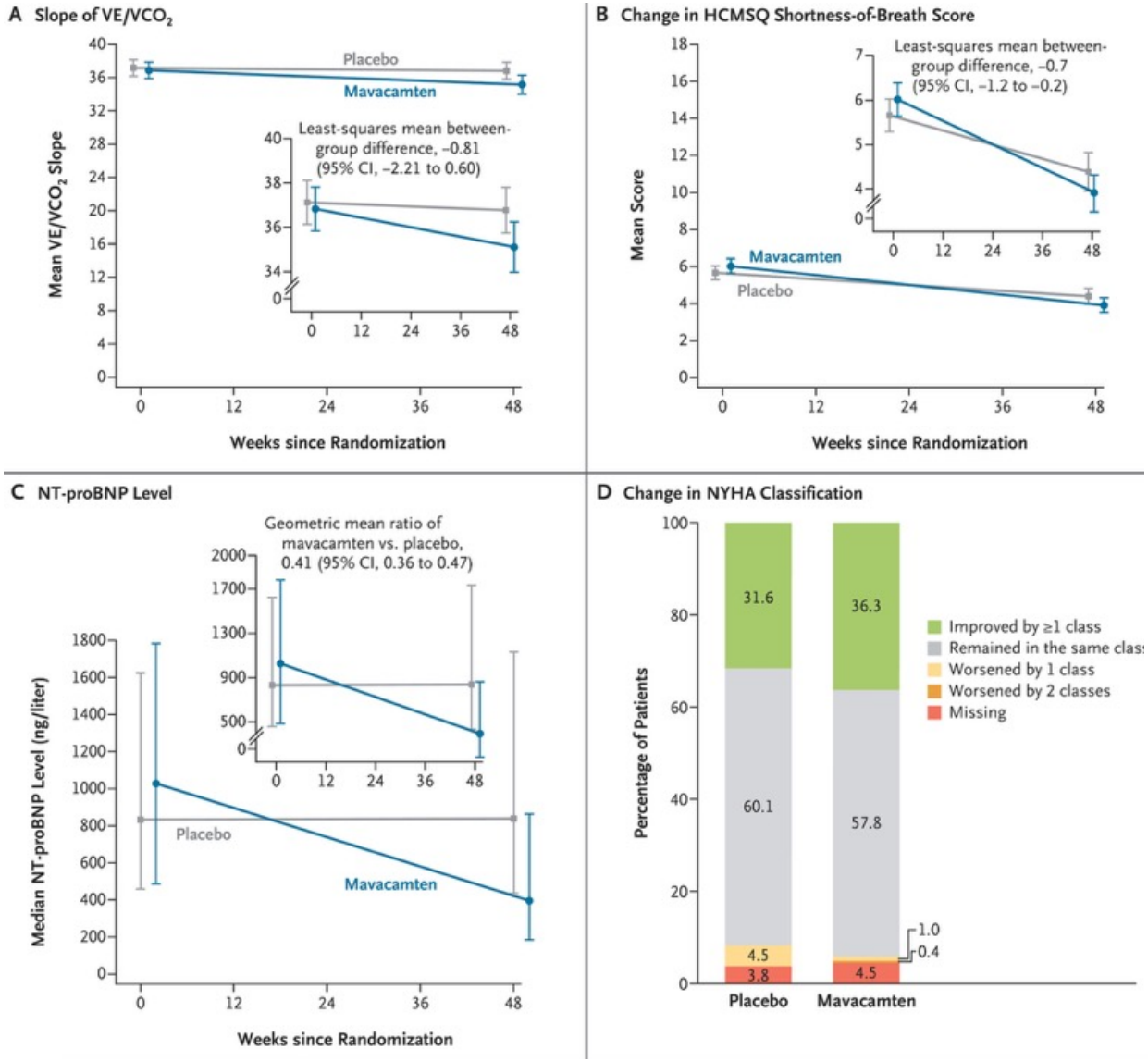
Characteristic	Mavacamten (N=289)	Placebo (N=291)
Age — yr	56.4±14.7	55.7±14.4
Male sex — no. (%)	148 (51.2)	166 (57.0)
Race or ethnic group — no. (%)†		
White	195 (67.5)	205 (70.4)
Black	11 (3.8)	14 (4.8)
Asian	51 (17.6)	39 (13.4)
Other	32 (11.1)	33 (11.3)
Hispanic	40 (13.8)	42 (14.4)
Body-mass index‡	27.9±4.9	28.6±5.2
Duration of nonobstructive HCM — yr	10.1±9.0	10.5±9.5
Family history of HCM — no. (%)	116 (40.1)	135 (46.4)
Family history of sudden cardiac death — no. (%)	46 (15.9)	38 (13.1)
New York Heart Association functional class — no. (%)		
II	203 (70.2)	202 (69.4)
III	86 (29.8)	89 (30.6)
Type of exercise testing — no. (%)		
Treadmill	139 (48.1)	129 (44.3)
Exercise bicycle	150 (51.9)	162 (55.7)
History of atrial fibrillation — no. (%)	97 (33.6)	83 (28.5)
History of hypertension — no. (%)	133 (46.0)	127 (43.6)
History of septal reduction therapy — no. (%)§	16 (5.5)	18 (6.2)
History of coronary artery disease — no. (%)	24 (8.3)	16 (5.5)
Background HCM therapy — no. (%)		
Beta-blocker	227 (78.5)	226 (77.7)
Calcium-channel blocker	34 (11.8)	36 (12.4)
Disopyramide	9 (3.1)	8 (2.7)
Echocardiographic factors		
Left ventricular ejection fraction — %	65.8±4.0	65.7±4.0
Left atrial volume index — ml/m²	43.7±16.9	43.2±14.5
Maximum left ventricular wall thickness — mm	21.0±4.3	20.7±3.9
Ratio of peak early mitral inflow velocity to peak early diastolic mitral annular velocity	13.1±5.7	13.5±5.4
Peak oxygen uptake — ml/kg/min	18.4±5.9	17.9±5.5
Predicted peak oxygen uptake — %	69.0±20.6	66.7±22.7
Slope of minute ventilation divided by carbon dioxide production	36.8±8.6	37.1±8.6
Kansas City Cardiomyopathy Questionnaire clinical summary score¶	56.3±20.7	57.5±19.1
HCMSQ shortness-of-breath score‖	6.0±3.2	5.6±3.2

Primary and Secondary Efficacy End Points at Week 48 in the Randomized Population.

End Point	Mavacamten (N=289)	Placebo (N=291)	Difference (95% CI)*
Primary efficacy end points†			
Change in peak oxygen uptake — ml/kg/min§			
Least-squares mean (95% CI)	0.52 (0.09 to 0.95)	0.05 (−0.38 to 0.47)	0.47 (−0.03 to 0.98)‡
Change in KCCQ-CSS			
Least-squares mean (95% CI)	13.1 (10.7 to 15.5)	10.4 (8.0 to 12.8)	2.7 (−0.1 to 5.6)‡
Secondary efficacy end points			
Change in the slope of minute ventilation divided by carbon dioxide production¶			
Least-squares mean (95% CI)	−0.64 (−1.84 to 0.55)	0.16 (−1.02 to 1.34)	−0.81 (−2.21 to 0.60)
Change in NT-proBNP level‖			
Geometric mean ratio of level at wk 48 to level at baseline (% coefficient of variation)	0.42 (5.84)	1.02 (5.66)	0.41 (0.36 to 0.47)
95% CI	0.37 to 0.47	0.91 to 1.13	
Improvement of at least one NYHA functional class level			
No. of patients (%)	105 (36.3)	92 (31.6)	5.0 (−2.3 to 12.2)**
Change in HCMSQ shortness-of-breath score			
Least-squares mean (95% CI)	−1.8 (−2.2 to −1.4)	−1.1 (−1.5 to −0.7)	−0.7 (−1.2 to −0.2)

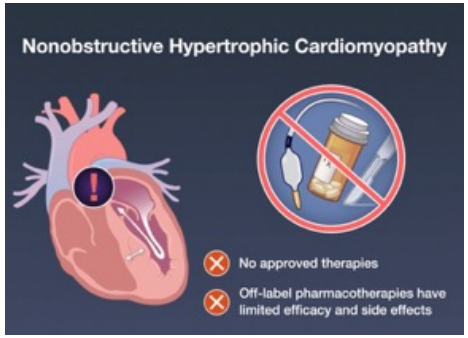
Adverse Event	Mavacamten (N=288)	Placebo (N=290)
	no. of patients (%)	
Adverse events during the treatment period		
Any adverse event	250 (86.8)	239 (82.4)
Adverse event leading to interruption of mavacamten or placebo	42 (14.6)	15 (5.2)
Adverse event leading to discontinuation of mavacamten or placebo	15 (5.2)	8 (2.8)
Adverse event leading to death	1 (0.3)	1 (0.3)
Serious adverse events		
Any serious adverse event	55 (19.1)	44 (15.2)
Cardiac disorders	31 (10.8)	21 (7.2)
Congestive heart failure	19 (6.6)	5 (1.7)
Atrial tachyarrhythmia	12 (4.2)	10 (3.4)
Ventricular tachyarrhythmia	3 (1.0)	1 (0.3)
Coronary artery disease	2 (0.7)	2 (0.7)
Cardiac conduction disorder	1 (0.3)	3 (1.0)
Cardiac arrest	1 (0.3)†	0
Cardiogenic shock	1 (0.3)†	0
Palpitations	0	2 (0.7)
Vascular disorder	1 (0.3)	3 (1.0)
Phlebitis	1 (0.3)	0
Hypertension	0	2 (0.7)
Raynaud's phenomenon	0	1 (0.3)
Nervous system disorder	9 (3.1)	6 (2.1)
Cerebral infarction	2 (0.7)	0
Stroke	2 (0.7)	1 (0.3)
Syncope	2 (0.7)	2 (0.7)
Cerebral hemorrhage	1 (0.3)	0
Seizure	1 (0.3)	1 (0.3)
Transient ischemic attack	1 (0.3)	1 (0.3)
Ischemic stroke	0	1 (0.3)
Prespecified adverse events of clinical interest		
Permanent discontinuation of mavacamten or placebo owing to left ventricular ejection fraction ≤30%	7 (2.4)	0
Left ventricular ejection fraction <50%	62 (21.5)	5 (1.7)
Major adverse cardiac events plus‡	27 (9.4)	17 (5.9)

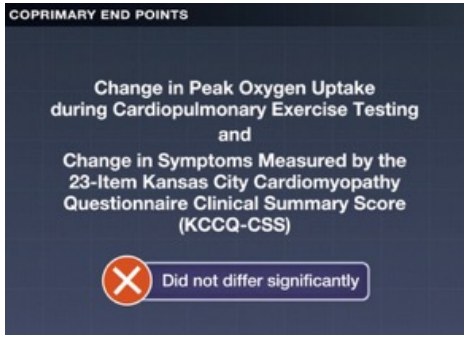


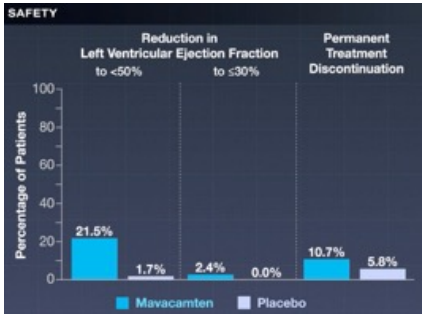


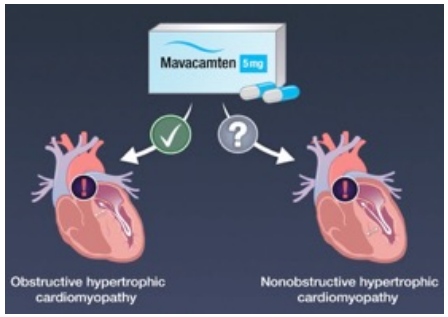
Key Secondary End Points.

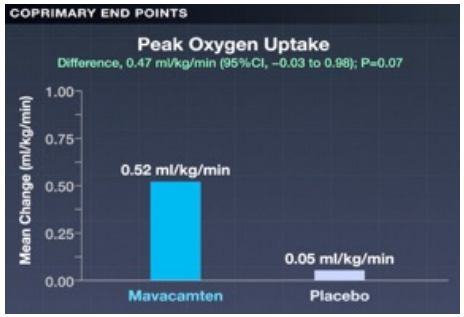
Panels A and B show the change from baseline to week 48 in the mean slope of minute ventilation (VE) divided by carbon dioxide production (VCO_2) and the mean Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) score on the shortness-of-breath domain, respectively. HCMSQ shortness-of-breath scores range from 0 to 18, with higher scores indicating more frequent shortness of breath. I bars denote 95% confidence intervals. Panel C shows the change from baseline to week 48 in the median N-terminal pro–B-type natriuretic peptide (NT-proBNP) level. I bars denote interquartile ranges. Insets in Panels A, B, and C show the same data on an expanded y axis. Panel D shows the percentage of patients with a change from baseline to week 48 in New York Heart Association (NYHA) functional class.

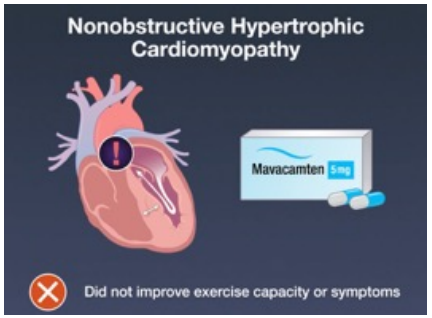

Nonobstructive Hypertrophic Cardiomyopathy
No approved therapies
Off-label pharmacotherapies have limited efficacy and side effects

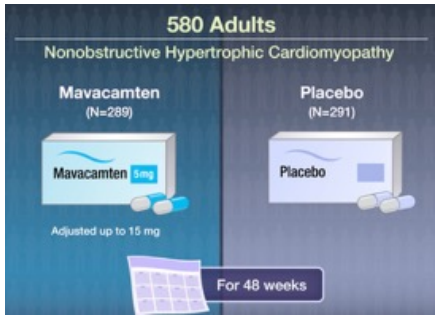

COPRIMARY END POINTS
Change in Peak Oxygen Uptake during Cardiopulmonary Exercise Testing and Change in Symptoms Measured by the 23-Item Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)
Did not differ significantly

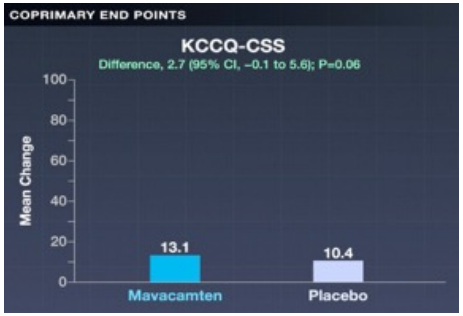

SAFETY
Reduction in Left Ventricular Ejection Fraction to <50%
to ≤30%
Permanent Treatment Discontinuation
Percentage of Patients
100
80
60
40
20
0
21.5%
1.7%
2.4%
0.0%
10.7%
5.8%
Mavacamten
Placebo


Mavacamten 5mg
Obstructive hypertrophic cardiomyopathy
Nonobstructive hypertrophic cardiomyopathy

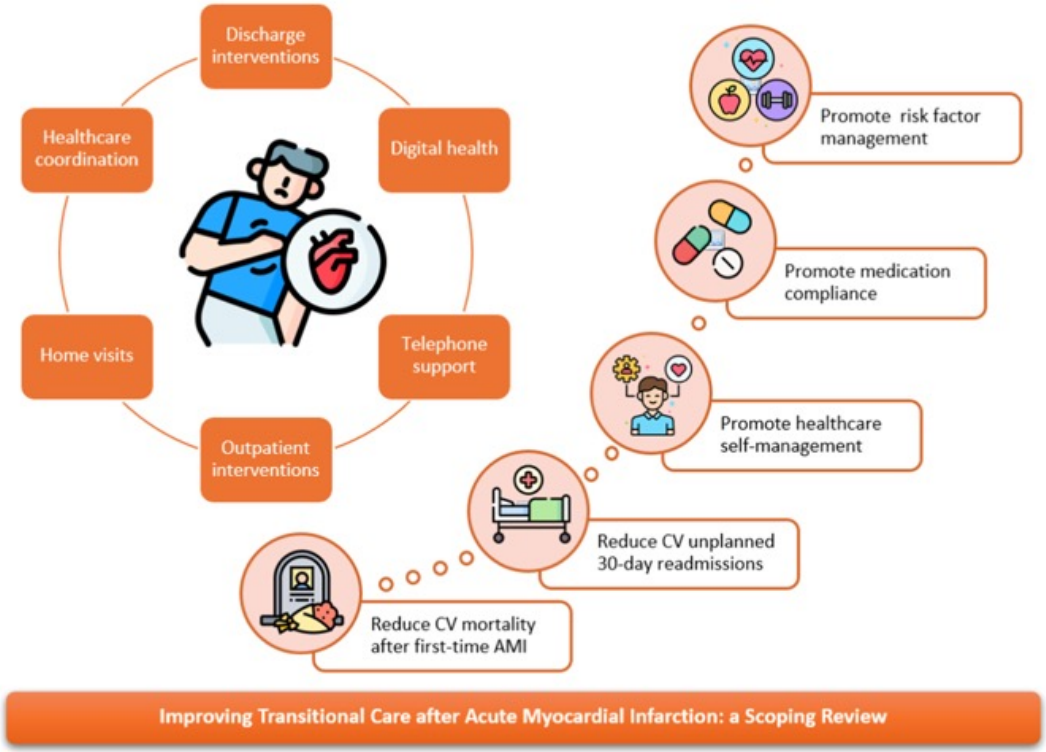

COPRIMARY END POINTS
Peak Oxygen Uptake
Difference, 0.47 ml/kg/min (95%CI, −0.03 to 0.98); P=0.07
Mean Change (ml/kg/min)
1.00
0.75
0.50
0.25
0.00
0.52 ml/kg/min
0.05 ml/kg/min
Mavacamten
Placebo


Nonobstructive Hypertrophic Cardiomyopathy
Mavacamten 5mg
Did not improve exercise capacity or symptoms


580 Adults
Nonobstructive Hypertrophic Cardiomyopathy
Mavacamten
(N=289)
Placebo
(N=291)
Mavacamten 5mg
Placebo
Adjusted up to 15 mg
For 48 weeks


COPRIMARY END POINTS
KCCQ-CSS
Difference, 2.7 (95% CI, −0.1 to 5.6); P=0.06
Mean Change
100
80
60
40
20
0
13.1
10.4
Mavacamten
Placebo

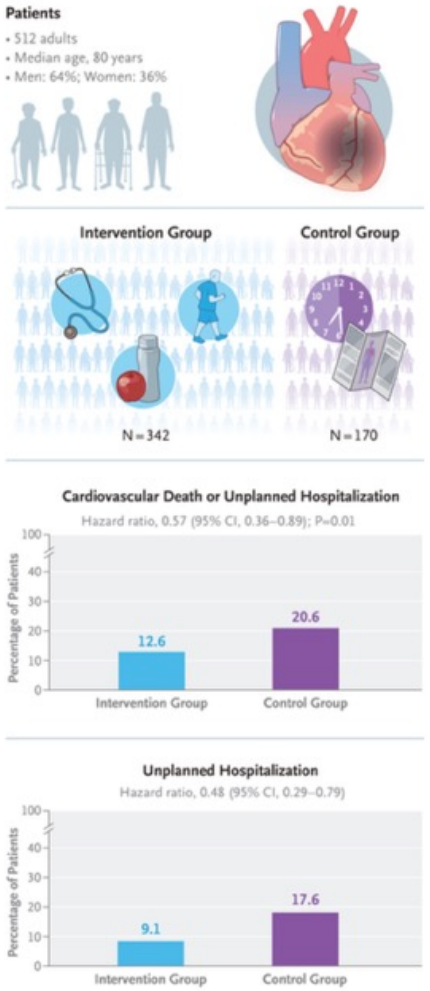
Lifestyle interventions after a heart attack (myocardial infarction, or MI) focus on secondary prevention, which includes smoking cessation, adopting a heart-healthy diet, regular physical activity, maintaining a healthy weight, and managing conditions like high blood pressure, high cholesterol, and diabetes. Psychological well-being, managing stress through relaxation techniques, and ensuring adequate sleep are also crucial components. Participation in a comprehensive cardiac rehabilitation program is highly recommended, as it integrates and supports these lifestyle changes, ultimately improving long-term health and reducing the risk of future events.



Multidomain Rehabilitation for Older Patients with Myocardial Infarction

The benefit of rehabilitation interventions in patients who are 65 years of age or older with myocardial infarction and impaired physical performance remains unclear.

In this multicenter, randomized trial conducted in Italy, we assigned older patients with impaired physical performance 1 month after myocardial infarction in a 2:1 ratio to receive either an intervention consisting of control of cardiovascular risk factors, dietary counseling, and exercise training (intervention group) or usual care (control group). The primary outcome was a composite of cardiovascular death or unplanned hospitalization for cardiovascular causes within 1 year.



Myocardial infarction remains the leading cause of death and complications in older adults. Despite advancements in acute care, this population has a higher incidence of recurrence of myocardial infarction, unplanned hospitalization, and death than younger adults. Cardiac rehabilitation is a key component of secondary cardiovascular prevention, but traditional programs have several challenges, including low participation, early withdrawal, and high costs. These limitations are even more pronounced among patients who are older or have frailty or physical impairment.

After myocardial infarction, older adults represent the least physically active group, which often results in accelerated physical decline, disability, and loss of independence. Although maintaining or improving physical function in this population is as critical as short-term treatment, a minority of older adults participate in cardiac rehabilitation programs, so the need for alternative models has been advocated.

To address these issues, we conducted a trial to evaluate whether an early, tailored, multidomain rehabilitation intervention focusing on management of cardiovascular risk factors, dietary counseling, and exercise training could improve outcomes in older patients with impaired physical performance 1 month after myocardial infarction, as compared with standard care.

Methods

Trial Design and Oversight

The Physical Activity Intervention in Elderly Patients with Myocardial Infarction (PIpELINe) trial was a randomized, investigator-initiated, multicenter superiority trial. Details of the trial design have been described previously.

Patients

Patients were eligible for screening if they were 65 years of age or older, had been admitted for either ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI), had undergone successful coronary revascularization, and had a score of 4 to 9 on the Short Physical Performance Battery.

This exercise program included a series of exercises from the Otago Program (balance and functional strength exercises for lower and upper limbs) and at least 20 minutes of moderate walking performed at least four times per week. The individualized exercise program was based on the results of the 1-km treadmill walking test. Exercise intensity and progression were individualized on the basis of the patient's performance at each session.

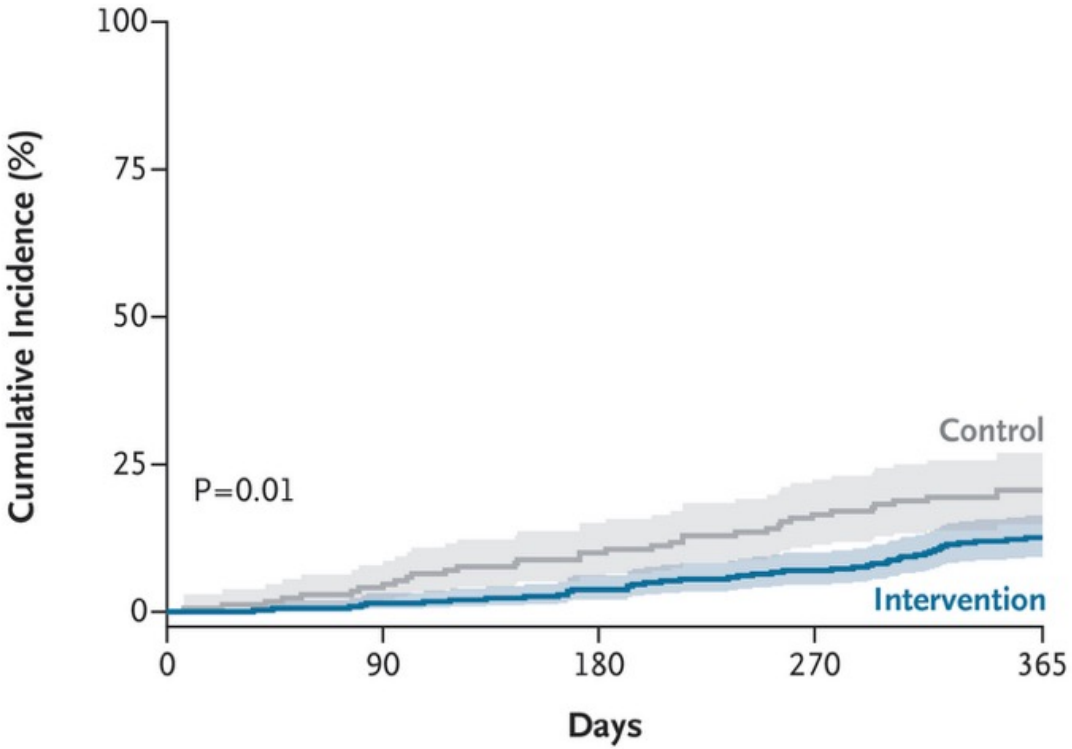
Outcomes

The primary outcome was a composite of cardiovascular death or unplanned hospitalization for cardiovascular causes within 1 year after randomization. Key secondary outcomes were individual components of the primary outcome and death from any cause.

Characteristic	Intervention (N=342)	Control (N=170)
Median age (IQR) — yr	80 (75–84)	80 (76–83)
Female sex — no. (%)	122 (35.7)	64 (37.6)
Median body-mass index (IQR)†	26.7 (24.3–29.4)	27.0 (24.3–29.3)
Medical history — no. (%)		
Hypertension	294 (86.0)	148 (87.1)
Dyslipidemia	197 (57.6)	107 (62.9)
Diabetes	87 (25.4)	50 (29.4)
Current smoker	58 (17.0)	25 (14.7)
Clinical presentation		
STEMI — no. (%)	127 (37.1)	63 (37.1)
NSTEMI — no. (%)	215 (62.9)	107 (62.9)
Median left ventricular ejection fraction (IQR) — %	49 (44–55)	50 (44–55)
Multivessel disease	220 (64.3)	107 (62.9)
Invasive procedure — no. (%)		
Coronary-artery angiography	342 (100)	170 (100)
Revascularization	342 (100)	170 (100)
Multivessel PCI	154 (45.0)	72 (42.4)
Complete revascularization‡	319 (93.3)	158 (92.9)
Mean interval from revascularization to randomization — days	35±3	35±3
Multidimensional assessment		
Short Portable Mental Status Questionnaire — no. (%)		
Intact intellectual functioning	337 (98.5)	158 (92.9)
Mild intellectual impairment	3 (0.9)	11 (6.5)
Moderate intellectual impairment	2 (0.6)	1 (0.6)
Mini-Nutritional Assessment — no. (%)		
Normal	232 (67.8)	118 (69.4)
At risk for malnutrition	96 (28.1)	47 (27.6)
Malnourished	14 (4.1)	5 (2.9)
Frailty per Fried's criteria — no. (%)§		
Prefrailty: 1 or 2 criteria	211 (61.7)	108 (63.5)
Frailty: ≥3 criteria	21 (6.1)	10 (5.9)
Median physical performance (IQR)		
SPPB score	7 (6–9)	8 (6–9)
Balance score	3 (2–4)	3 (2–4)
4-m walk score	2 (2–3)	2 (2–3)
Chair-rise score	2 (1–2)	2 (1–2)
Gait speed — m/sec	0.7 (0.5–0.8)	0.6 (0.5–0.8)
Hand-grip strength — kg		
Men	30 (25–37)	30 (22–36)
Women	20 (15–28)	21 (17–32)

Primary and Secondary Outcomes.

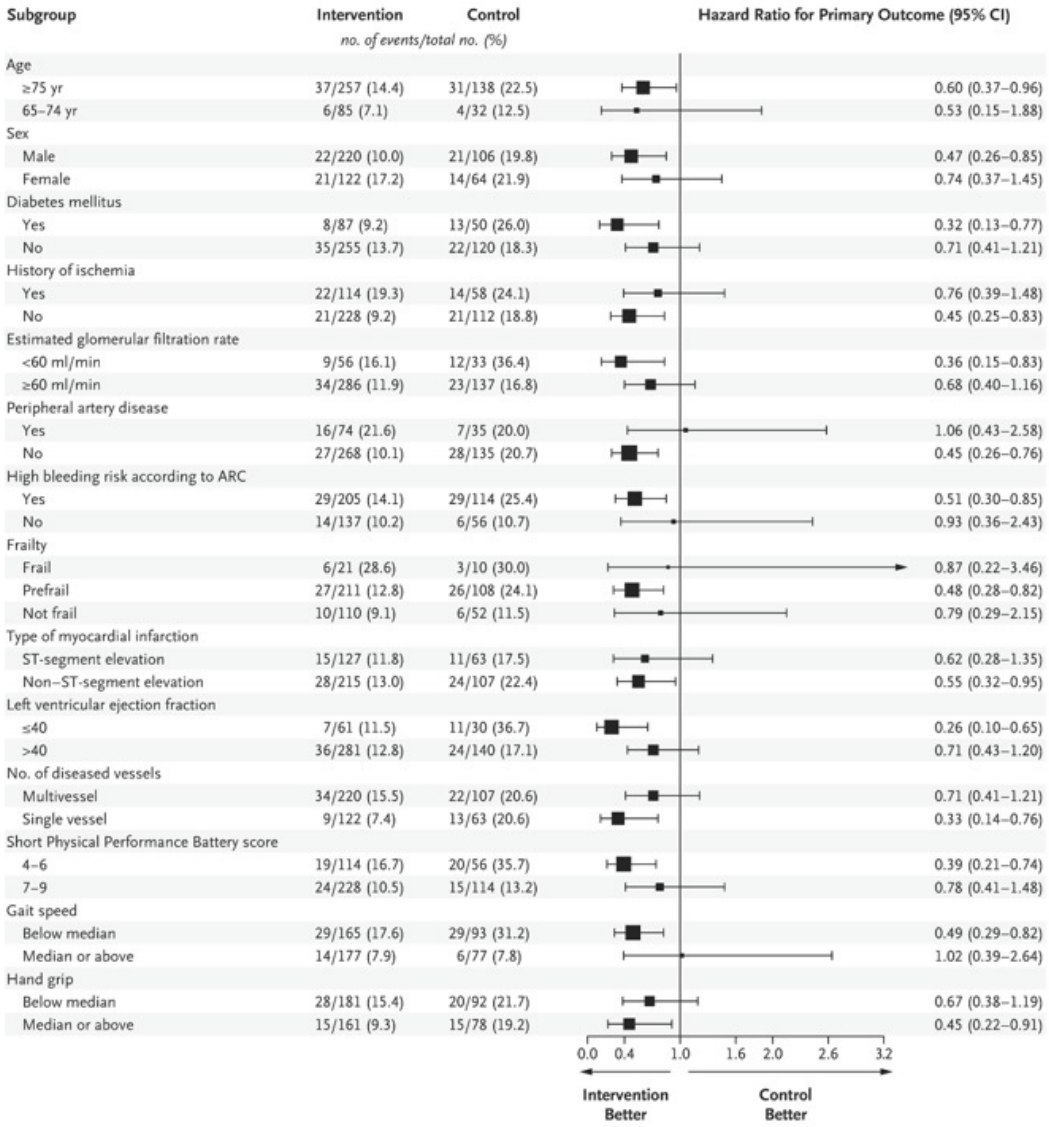
Outcome	Intervention (N=342)	Control (N=170)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary outcome				
Cardiovascular death or unplanned hospitalization for cardiovascular causes	43 (12.6)	35 (20.6)	0.57 (0.36–0.89)	0.01
Secondary outcomes*				
Death	19 (5.6)	13 (7.6)	0.72 (0.35–1.45)	
Cardiovascular death	14 (4.1)	10 (5.9)	0.69 (0.31–1.55)	
Unplanned hospitalization for cardiovascular causes	31 (9.1)	30 (17.6)	0.48 (0.29–0.79)	
Unplanned hospitalization for heart failure	5 (1.5)	12 (7.1)	0.20 (0.07–0.56)	
Myocardial infarction	13 (3.8)	10 (5.9)	0.63 (0.28–1.44)	
Coronary revascularization	13 (3.8)	8 (4.7)	0.80 (0.33–1.93)	
Cerebrovascular accident	3 (0.9)	2 (1.2)	0.74 (0.12–4.43)	
Unplanned hospitalization for any cause	56 (16.4)	39 (22.9)	0.67 (0.44–1.01)	
Unplanned hospitalization for noncardiovascular causes	28 (8.2)	13 (7.6)	1.06 (0.55–2.02)	
Infection	7 (2.0)	6 (3.5)	0.58 (0.19–1.71)	
BARC type 3 to 5 event†	18 (5.3)	9 (5.3)	0.99 (0.45–2.19)	



No. at Risk					
Control	170	163	153	141	134
Intervention	342	337	328	315	294
No. of Events					
Control	0	8	17	28	35
Intervention	0	5	13	24	43

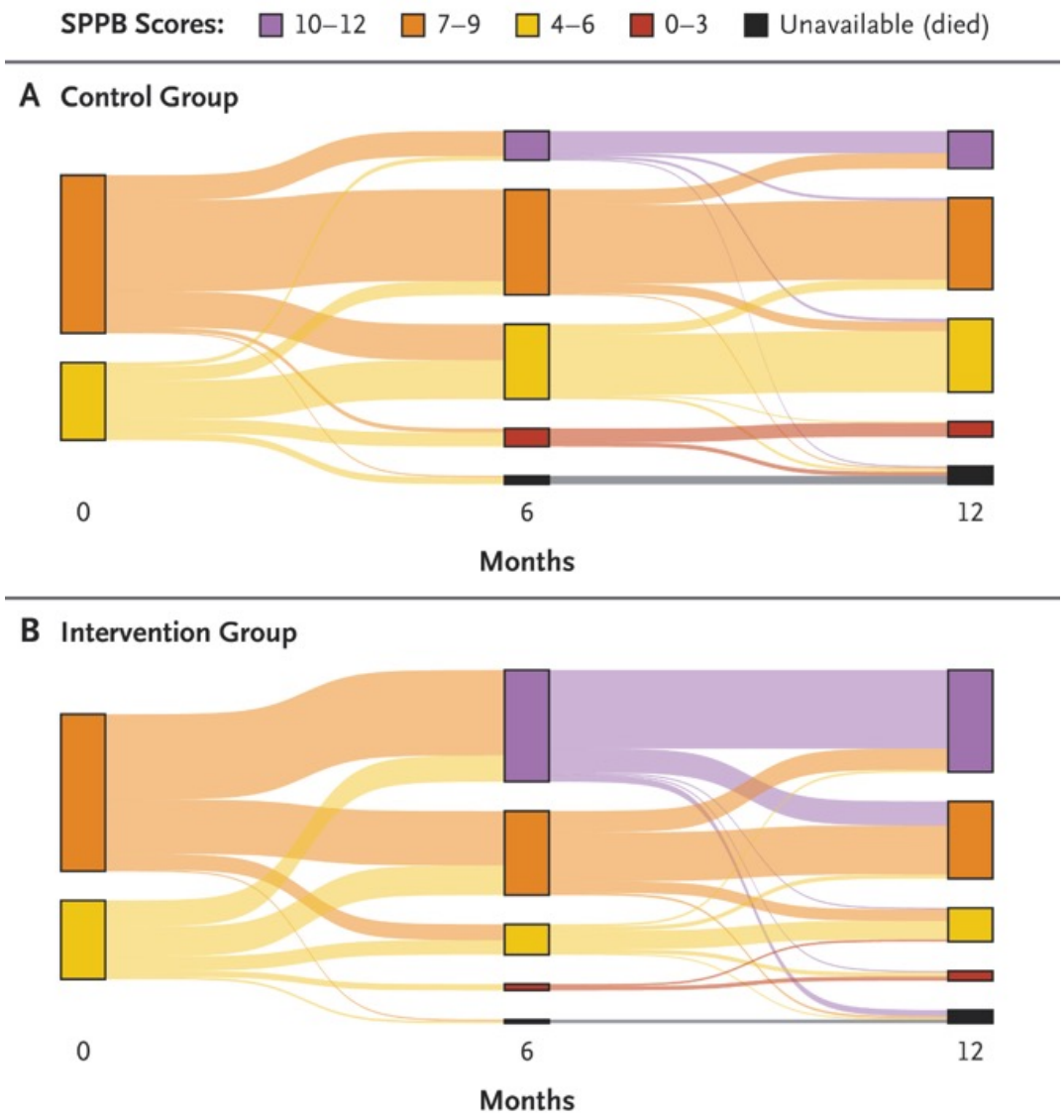
Cumulative Incidence of the Primary Outcome.

Shown is the incidence of cardiovascular death or unplanned hospitalization for cardiovascular causes at 1 year (the composite primary outcome) among patients in the intervention group (who received help with handling cardiovascular risk factors, dietary counseling, and exercise training) and the control group (who received usual care). All the patients were 65 years of age or older and had impaired physical performance 1 month after myocardial infarction. The shading indicates 95% confidence intervals.



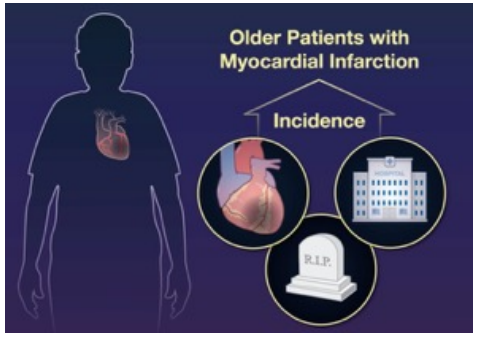
Subgroup Analysis of the Primary Outcome.

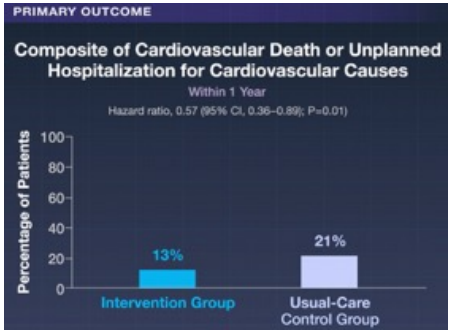
Shown is a forest plot of a subgroup analysis of the primary outcome, a composite of cardiovascular death or unplanned hospitalization for cardiovascular causes at 1 year. A hazard ratio of less than 1.00 indicates that the intervention was better. The size of the squares is proportional to the number of patients in each subgroup. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to evaluate treatment effects. The estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Scores on the Short Physical Performance Battery range from 0 to 12, with lower scores indicating more severe impairment of physical function. ARC denotes Academic Research Consortium.

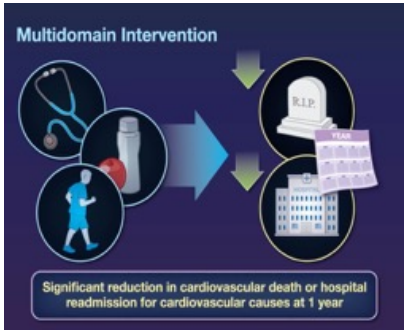


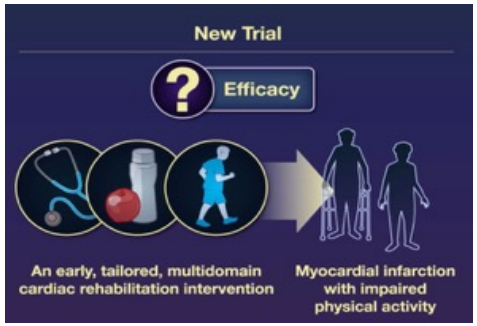
Scores on the Short Physical Performance Battery.

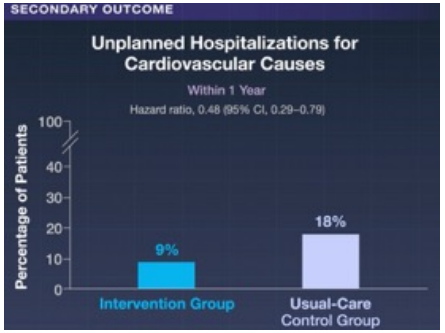
Shown is a Sankey graph of the progression in scores on the Short Physical Performance Battery (SPPB) over the 1-year trial period in the intervention group and the control group. Scores range from 0 to 12, with lower scores indicating more severe impairment. The widths of the colored bands are proportional to the number of patients. The numbers of patients who were included in each analysis are as follows: at trial inclusion, 342 patients in the intervention group and 170 in the control group; at 6 months, 337 and 164 patients, respectively; and at 12 months, 323 and 157 patients, respectively.

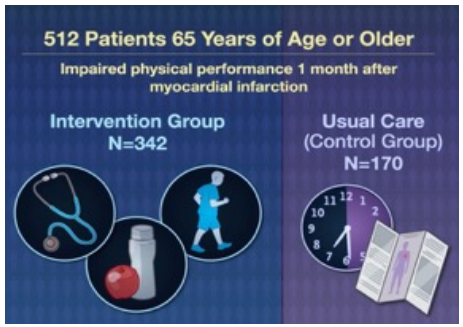

Older Patients with
Myocardial Infarction
Incidence
R.I.P.

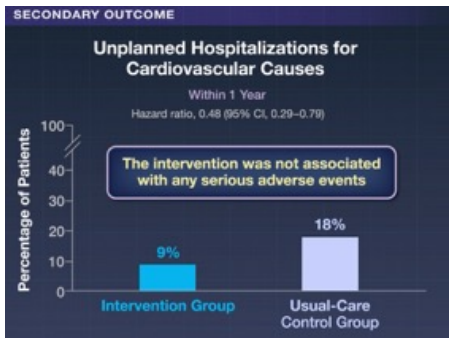

PRIMARY OUTCOME
Composite of Cardiovascular Death or Unplanned Hospitalization for Cardiovascular Causes
Within 1 Year
Hazard ratio, 0.57 (95% CI, 0.36–0.89); P=0.01)
Percentage of Patients
100
80
60
40
20
0
13%
21%
Intervention Group
Usual-Care Control Group


Multidomain Intervention
R.I.P.
YEAR
Significant reduction in cardiovascular death or hospital readmission for cardiovascular causes at 1 year


New Trial
?
Efficacy
An early, tailored, multidomain cardiac rehabilitation intervention
Myocardial infarction with impaired physical activity

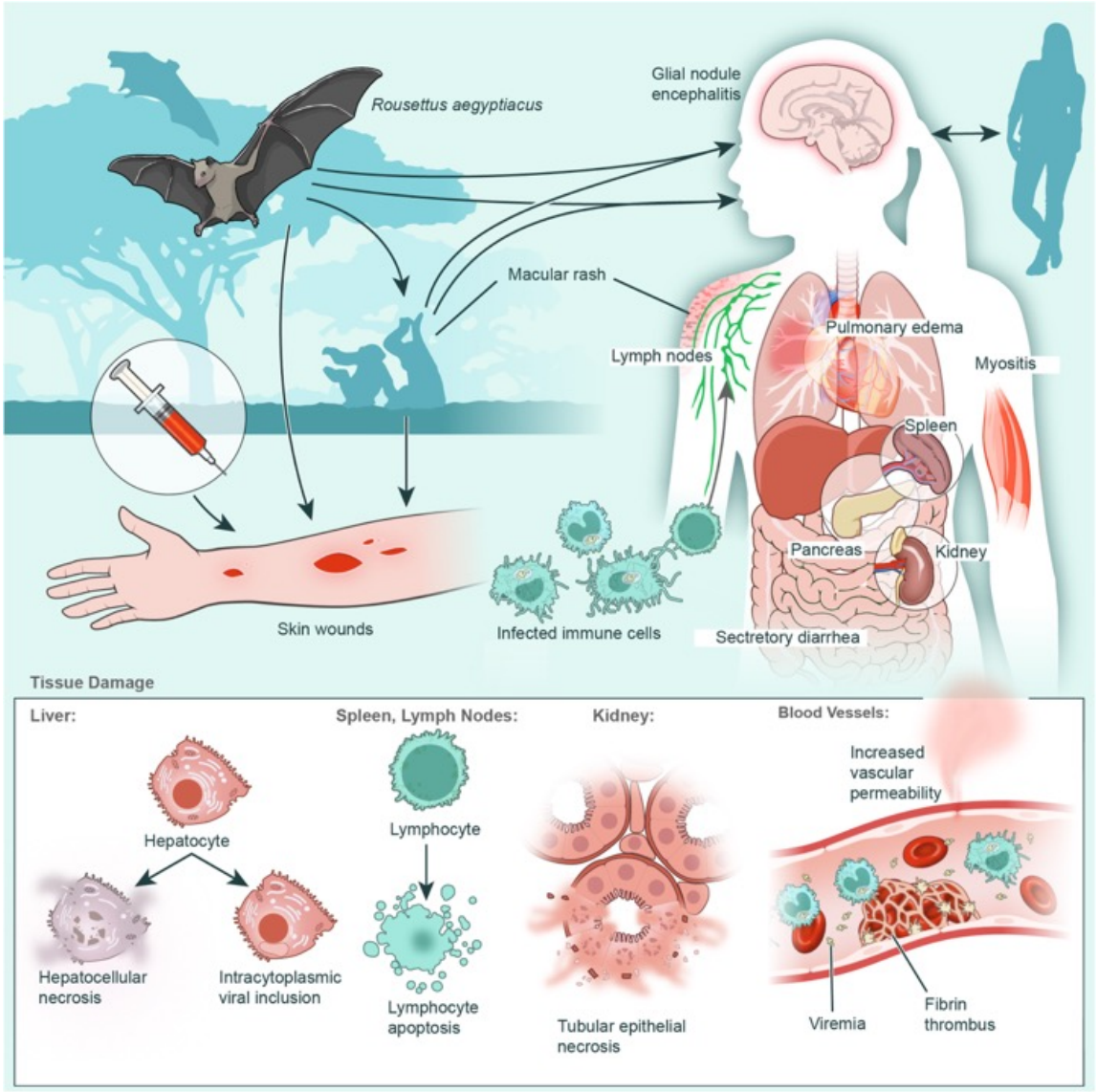

SECONDARY OUTCOME
Unplanned Hospitalizations for Cardiovascular Causes
Within 1 Year
Hazard ratio, 0.48 (95% CI, 0.29–0.79)
Percentage of Patients
100
40
30
20
10
0
9%
18%
Intervention Group
Usual-Care Control Group


512 Patients 65 Years of Age or Older
Impaired physical performance 1 month after myocardial infarction
Intervention Group
N=342
Usual Care
(Control Group)
N=170


SECONDARY OUTCOME
Unplanned Hospitalizations for Cardiovascular Causes
Within 1 Year
Hazard ratio, 0.48 (95% CI, 0.29–0.79)
The intervention was not associated with any serious adverse events
Percentage of Patients
100
40
30
20
10
0
9%
18%
Intervention Group
Usual-Care Control Group

Das Marburg-Virus ist ein Filovirus, das eine schwere, oft tödliche Krankheit, das sogenannte Marburg-Fieber, verursacht. Es gehört zur Familie der Filoviren wie auch das Ebola-Virus. Die Krankheit beginnt mit Symptomen wie Fieber, Muskelschmerzen und Kopfschmerzen, gefolgt von Erbrechen, Durchfall und Blutungen, bis hin zu Multiorganversagen. Die Übertragung von Mensch zu Mensch erfolgt durch direkten Kontakt mit Körperflüssigkeiten infizierter Personen, nicht über die Luft. Es gibt weder eine Impfung noch eine spezifische Behandlung, nur unterstützende Maßnahmen wie Flüssigkeitszufuhr.

Filoviridae oder Filoviren sind eine Virusfamilie, zu der meist fadenförmige, behüllte Einzel-Strang-RNA-Viren [ssRNA] gehören. Sie zählen zu den größten bekannten RNA-Viren.



Marburg Virus Disease in Rwanda, 2024 — Public Health and Clinical Responses

Background

On September 27, 2024, Rwanda reported an outbreak of Marburg virus disease (MVD), after a cluster of cases of viral hemorrhagic fever was detected at two urban hospitals.

Methods

We report key aspects of the epidemiology, clinical manifestations, and treatment of MVD during this outbreak, as well as the overall response to the outbreak. We performed a retrospective epidemiologic and clinical analysis of data compiled across all pillars of the outbreak response and a case-series analysis to characterize clinical features, disease progression, and outcomes among patients who received supportive care and investigational therapeutic agents.

Conclusions

Implementation of containment measures, advanced supportive care, and access to investigational countermeasures may have contributed to reduced mortality from MVD in this outbreak. Enhancing surveillance, improving infection prevention and control in health care settings, and ensuring timely deployment of medical countermeasures will be critical for mitigating the effects of future filovirus disease outbreaks.

Methods

Study Design and Data Sources

To provide a comprehensive account of the outbreak, we conducted an integrated analysis using both prospectively and retrospectively collected data. Data sources included epidemiologic surveillance, clinical case, and laboratory records. We characterized the transmission dynamics of the outbreak over time and conducted a complete clinical case review involving all patients with laboratory-confirmed MVD.

Testing and treatment data were captured in the District Health Information System 2 (DHIS2), the comprehensive public health database maintained by the Ministry of Health for collecting routine case-level data. Clinical data were documented in the electronic medical records of hospitals in which patients with MVD received care or in paper-based bedside charts at the national treatment center that had been set up in response to the outbreak. From these sources, a team of physicians systematically extracted data elements for the case-series analysis; the data were linked by patient identifiers with MVD case records in the DHIS2.

Demographics of the patients

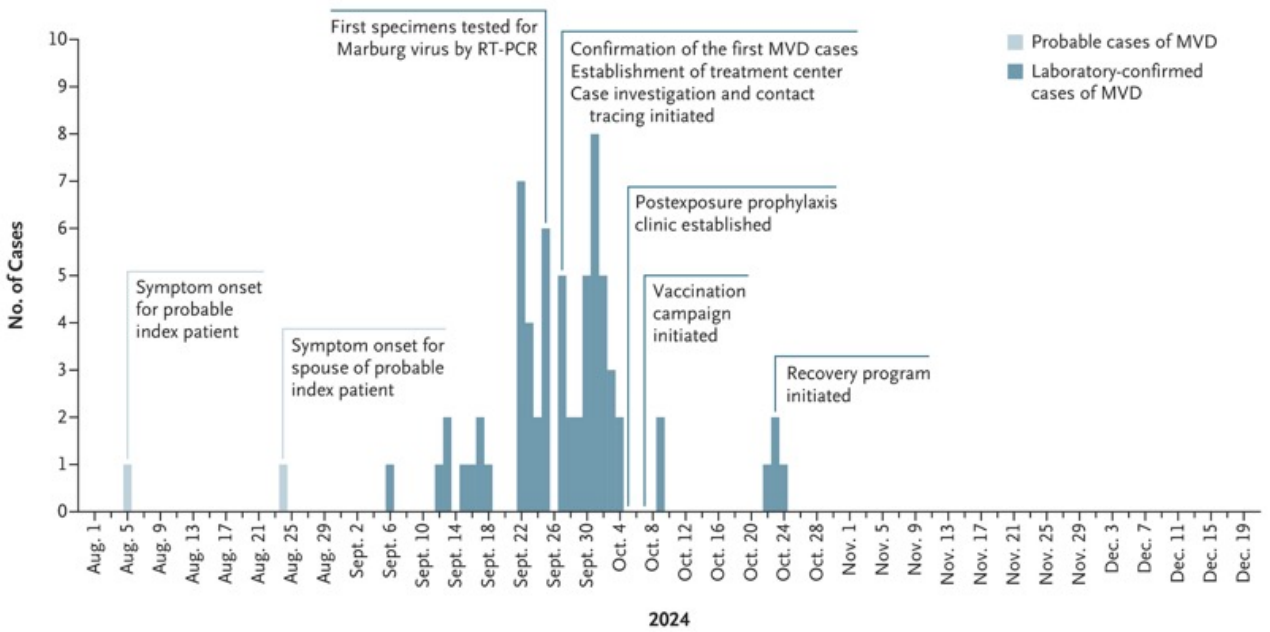
Characteristic	Patients with Suspected MVD (N = 6340)	Test Result	
		Negative	Positive
	number of patients/total number (percent)		
Age			
<10 yr	386/6159 (6)	385/386 (>99)	1/386 (<1)
10–19 yr	776/6159 (13)	775/776 (>99)	1/776 (<1)
20–29 yr	1890/6159 (31)	1870/1890 (99)	20/1890 (1)
30–39 yr	1444/6159 (23)	1414/1444 (98)	30/1444 (2)
40–49 yr	828/6159 (13)	817/828 (99)	11/828 (1)
≥50 yr	835/6159 (14)	832/835 (>99)	3/835 (<1)
Sex			
Female	2931/6235 (47)	2910/2931 (99)	21/2931 (1)
Male	3304/6235 (53)	3259/3304 (99)	45/3304 (1)
Occupation			
Health care worker	246/3480 (7)	196/246 (80)	51/246 (20)
Non–health care worker	3234/3480 (93)	3218/3234 (>99)	15/3234 (<1)
Province of residence			
City of Kigali	4018/6168 (65)	3960/4018 (99)	58/4018 (1)
Eastern Province	657/6168 (11)	656/657 (>99)	1/657 (<1)
Northern Province	545/6168 (9)	545/545 (100)	0
Southern Province	533/6168 (9)	527/533 (99)	6/533 (1)
Western Province	415/6168 (7)	414/415 (>99)	1/415 (<1)
Week of outbreak			
Week 1, September 23–29	157/6338 (2)	130/157 (83)	27/157 (17)
Week 2, September 30–October 6	1401/6338 (22)	1376/1401 (98)	25/1401 (2)
Week 3, October 7–13	988/6338 (16)	979/988 (99)	9/988 (1)
Week 4, October 14–21	949/6338 (15)	948/949 (>99)	1/949 (<1)
Week 5, October 22–29	709/6338 (11)	705/709 (99)	4/709 (1)
Week 6, October 30–November 6	1383/6338 (22)	1383/1383 (100)	0
Week 7, November 7–14	604/6338 (10)	604/604 (100)	0
Week 8, November 15–22	147/6338 (2)	147/147 (100)	0

Patient outcomes

Characteristic	Patients with Confirmed MVD (N = 66)	Outcome†	
		Recovered	Died
Age — no./total no. (%)			
<35 yr	40/66 (61)	31/40 (78)	9/40 (22)
≥35 yr	26/66 (39)	20/26 (77)	6/26 (23)
Sex — no./total no. (%)			
Female	21/66 (32)	15/21 (71)	6/21 (29)
Male	45/66 (68)	36/45 (80)	9/45 (20)
Duration of hospitalization — no./total no. (%)			
<7 days	27/66 (41)	15/27 (56)	12/27 (44)
≥7 days	39/66 (59)	36/39 (92)	3/39 (8)
Patient occupation — no./total no. (%)			
Health care worker	51/66 (77)	40/51 (78)	11/51 (22)
Non–health care worker	15/66 (23)	11/15 (73)	4/15 (27)
Province of residence — no./total no. (%)			
City of Kigali	57/66 (86)	45/57 (79)	12/57 (21)
Other provinces	9/66 (14)	6/9 (67)	3/9 (33)
Median initial Ct value on RT-PCR (IQR)	25.8 (21.5–28.8)	26.5 (21.5–28.7)	19.4 (16.3–23.0)
Initial RT-PCR Ct value — no. (%)			
<25	27/66 (41)	14/27 (52)	13/27 (48)
≥25	39/66 (59)	37/39 (95)	2/39 (5)
Median time from first known contact to symptom onset (IQR) — days	10 (8–13)	10 (7–12)	9 (7–11)
Median time from symptom onset to hospital admission (IQR) — days	2 (1–3)	1 (1–3)	3 (3–5)
Median time from MVD diagnosis to first negative RT-PCR test (IQR) — days	—	10.7 (7–13)	—
Median time from hospitalization to discharge among patients who recovered (IQR) — days	—	12 (9–15)	—
Median time from hospitalization to death among patients who died (IQR) — days	—	—	5 (3–6)

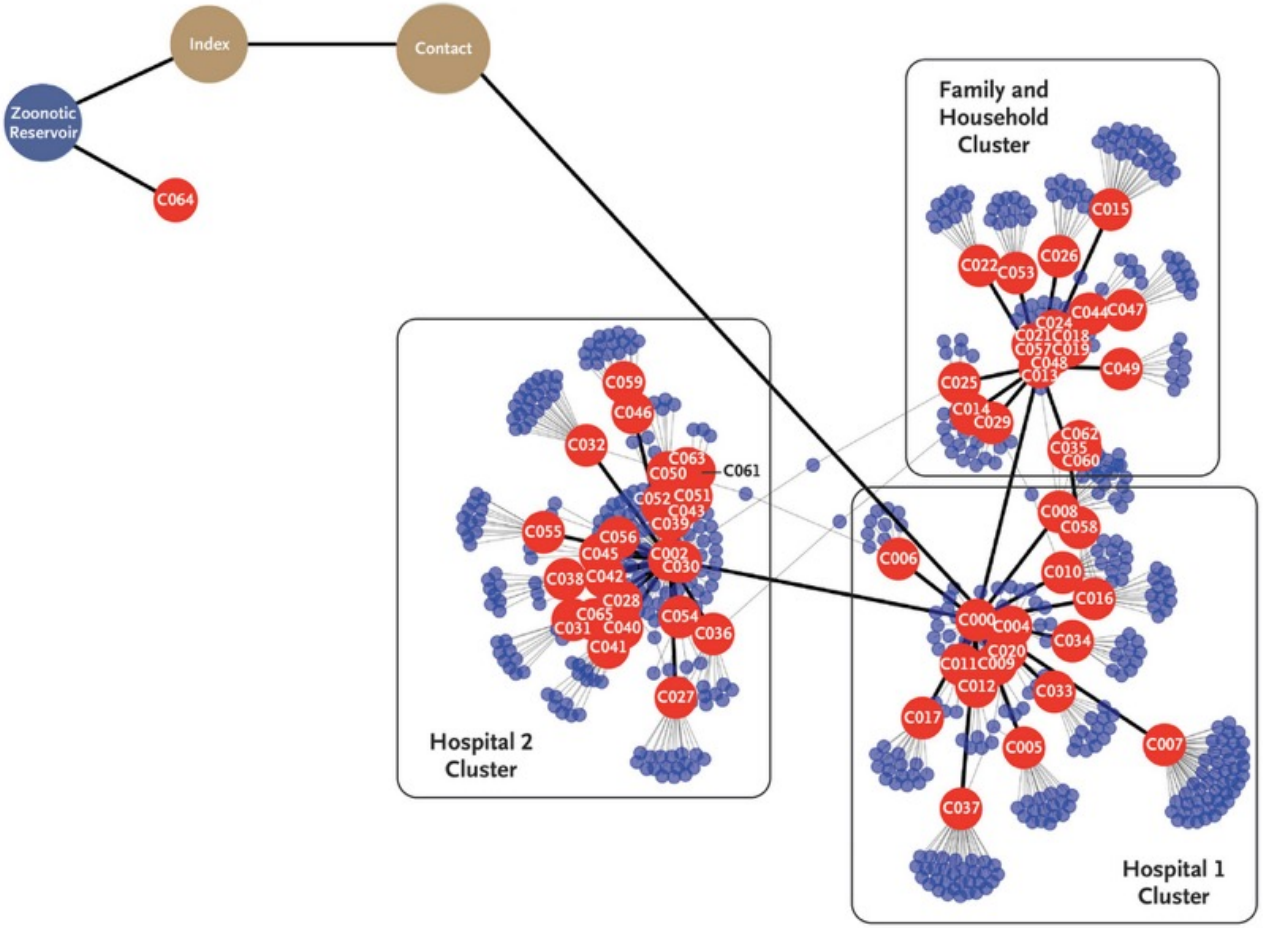
Complications

Complication or Intervention	Patients Who Recovered (N=51)	Patients Who Died (N=15)
	no. of patients (%)	
Complications		
Encephalopathy	4 (8)	11 (73)
Hypoxemia*	7 (14)	13 (87)
Hypercapnic respiratory failure	2 (4)	3 (20)
Hypotension†	6 (12)	10 (67)
Acute kidney injury‡		
KDIGO stage 1	7 (14)	7 (47)
KDIGO stage 2	2 (4)	7 (47)
KDIGO stage 3	1 (2)	8 (53)
Coinfections		
Malaria test requested	25 (49)	9 (60)
Malaria test reported positive	3 (6)	1 (7)
Bloodstream infection	12 (24)	4 (27)
Urinary tract infection	0	0
Hospital-acquired pneumonia	1 (2)	1 (7)
Radiographic findings		
Pulmonary infiltrate, lobar	1 (2)	0
Pulmonary infiltrate, multifocal	2 (4)	2 (13)
Pleural effusion	2 (4)	5 (33)
Supportive care interventions		
Supplemental oxygen	7 (14)	13 (87)
Noninvasive ventilation	0	1 (7)
Endotracheal intubation	2 (4)	7 (47)
Placement of central venous catheter	3 (6)	4 (27)
Intravenous fluid therapy	48 (94)	13 (87)
Urinary catheterization	6 (12)	12 (80)
Vasopressor therapy	1 (2)	4 (27)
Hemodialysis	0	2 (13)
Antibiotic agent	41 (80)	11 (73)
Antimalarial agent	3 (6)	1 (7)
Packed red-cell transfusion	3 (6)	3 (20)
Platelet transfusion	3 (6)	3 (20)
Fresh-frozen plasma transfusion	2 (4)	3 (20)
Cryoprecipitate transfusion	1 (2)	1 (7)
Disease-specific treatments		
Remdesivir	49 (96)	3 (20)
MBP091	8 (16)	2 (13)



Timeline of Cases and Key Response Activities.

MVD denotes Marburg virus disease, and RT-PCR reverse-transcriptase polymerase chain reaction.



Transmission Clusters Linked to Probable Index Patient.

"Index" indicates the probable index patient, who had been exposed to Egyptian fruit bats at a mining site. "Contact" indicates the spouse of the probable index patient, who was the first patient with probable MVD admitted to Hospital 1. Patients with confirmed MVD are denoted by red circles.

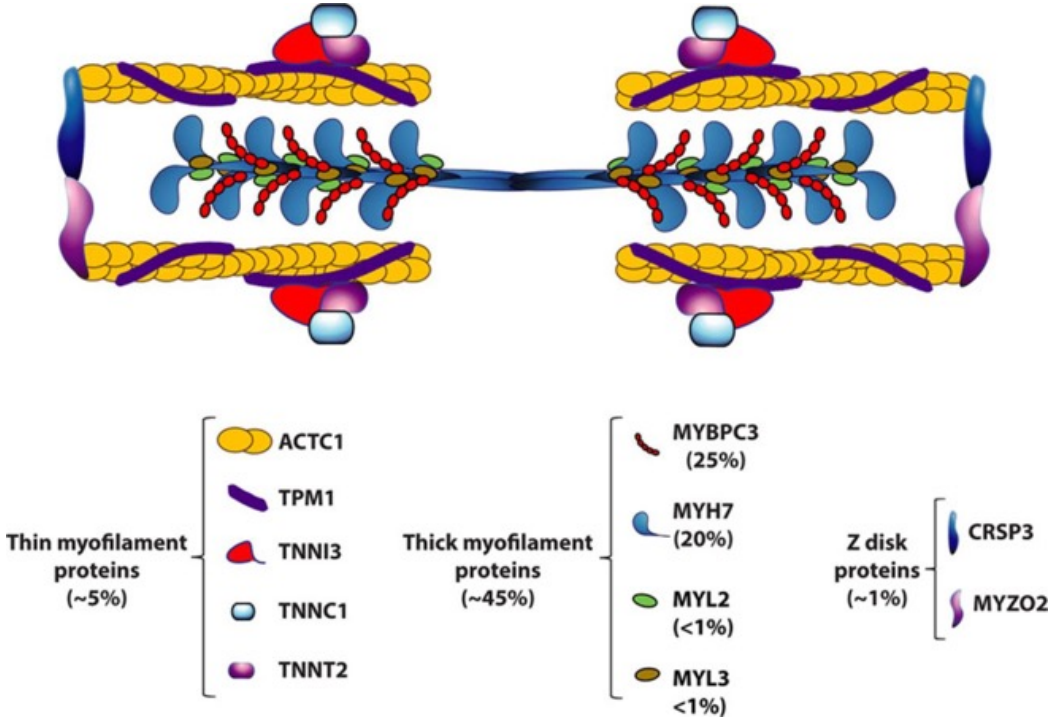
Discussion

This MVD outbreak in Rwanda represents the first documented occurrence of the virus in the country and emergence in a densely populated urban setting. Unlike past MVD outbreaks, which have been marked by high case fatality and delayed detection in remote regions, this outbreak saw the rapid initiation of a multisectoral response, which is likely to have contributed to a lower case fatality (23%). Although direct comparisons across outbreaks are limited by differences in surveillance, health care capacity, and diagnostic access, this experience underscores the potential effect of early case identification, aggressive supportive care, and access to investigational treatments in mitigating mortality from MVD.

In this outbreak, nosocomial transmission accounted for 77% of cases, which underscores the need to strengthen infection prevention and control measures in health care settings in areas where viral hemorrhagic fever is endemic, especially in the context of resuscitation of critically ill patients. An important challenge in this setting was that many of the affected health care workers were caring for critically ill colleagues, often under stressful conditions. Studies of previous filovirus disease outbreaks suggest that familiarity with infected patients, high emotional burden, and emergency clinical interventions may contribute to lapses in infection prevention and control measures. Improvements in the capacity for testing and earlier consideration of MVD in the differential diagnosis of severe febrile illness are also necessary, particularly in high-risk regions where viral hemorrhagic fever may initially be unrecognized and mimic other endemic febrile illnesses, such as malaria.

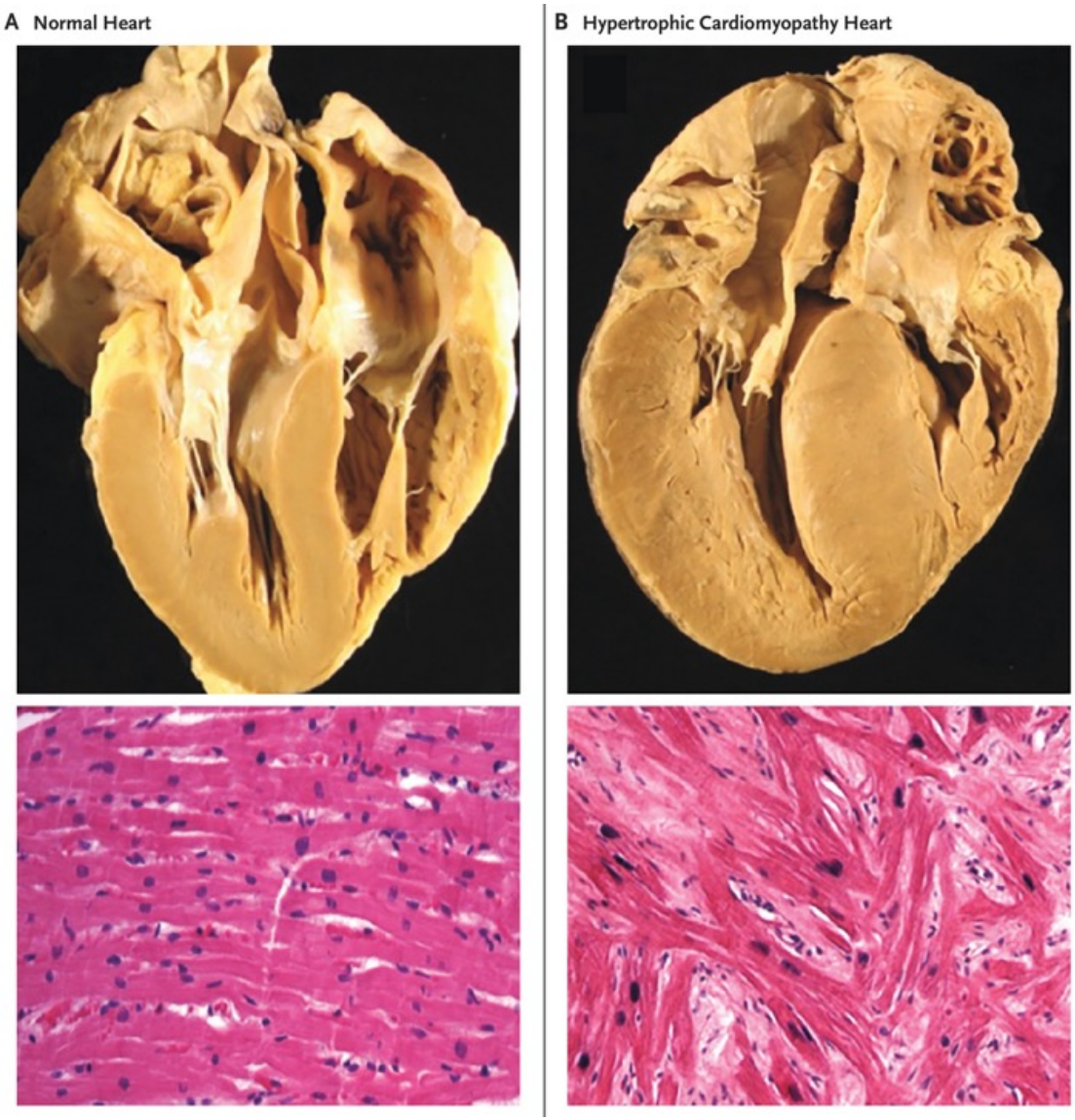
Hypertrophic cardiomyopathy genes and mutations

Genes most commonly associated with hypertrophic cardiomyopathy (HCM) are MYH7 (coding for beta-myosin heavy chain) and MYBPC3 (coding for myosin binding protein C), which account for a significant percentage of cases. Other genes involved in the sarcomere's thick and thin filaments, such as TNNT2 (troponin T), TNNI3 (troponin I), TPM1 (alpha-tropomyosin), and ACTC1 (cardiac alpha-actin 1), can also cause HCM.



Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a complex, heterogeneous disorder that directly affects only the heart. It is characterized by hypertrophy of any portion of the left ventricular wall, frequently involves the basal interventricular septum, and is not explained by abnormal loading conditions or myocardial infiltration. HCM is the most common monogenic cardiac disorder, with a prevalence of approximately 1 in every 500 adults. It occurs worldwide in both sexes, among all races, and in all age groups. The left ventricular cavity is usually small in patients with HCM, with increased contractility and abnormally elevated ejection fraction. Histologic findings include myocytes that are enlarged and in disarray and the presence of interstitial fibrosis and thick-walled intramural coronary arteries



Normal Heart and Heart with Hypertrophic Cardiomyopathy (HCM).

Panel A shows a cross-section of a normal heart (top) and an endomyocardial biopsy sample from a normal heart (bottom; with hematoxylin and eosin staining) that shows normal histologic characteristics. Panel B shows a cross-section of the heart of a patient with HCM (top), characterized by a hypertrophied free wall of the left ventricle and greatly hypertrophied interventricular septum adjacent to the anterior leaflet of the mitral valve, and an endomyocardial-biopsy sample from a heart with HCM (bottom; with hematoxylin and eosin staining) that shows enlarged myocytes in disarray. Images are reprinted from Braunwald[5] with the permission of the publisher.

Hypertrophic Cardiomyopathy

- Hypertrophic cardiomyopathy (HCM) is a complex heterogeneous disorder that is not explained by abnormal loading conditions.
- Approximately 70% of patients with HCM have subaortic muscular obstruction to left ventricular outflow that can be provoked or exacerbated by exercise or other stimulation of myocardial contractility.
- In HCM, the left ventricle, especially the interventricular septum, is thickened, and the left ventricular ejection fraction is usually supranormal. Diastolic dysfunction slows ventricular filling.
- HCM is the most common monogenic cardiac disorder. Patients may be asymptomatic or may have heart failure, angina, or sudden cardiac death.
- Cardiac imaging tests (echocardiography and cardiac magnetic resonance imaging) are of importance for the diagnosis and management of HCM.
- The prognosis is greatly improved by proven therapies, including beta-blockers, calcium-channel blockers, cardiac myosin inhibitors, implantation of a cardioverter–defibrillator, septal reduction therapy, and cardiac transplantation.

Major Applications of Imaging in HCM.

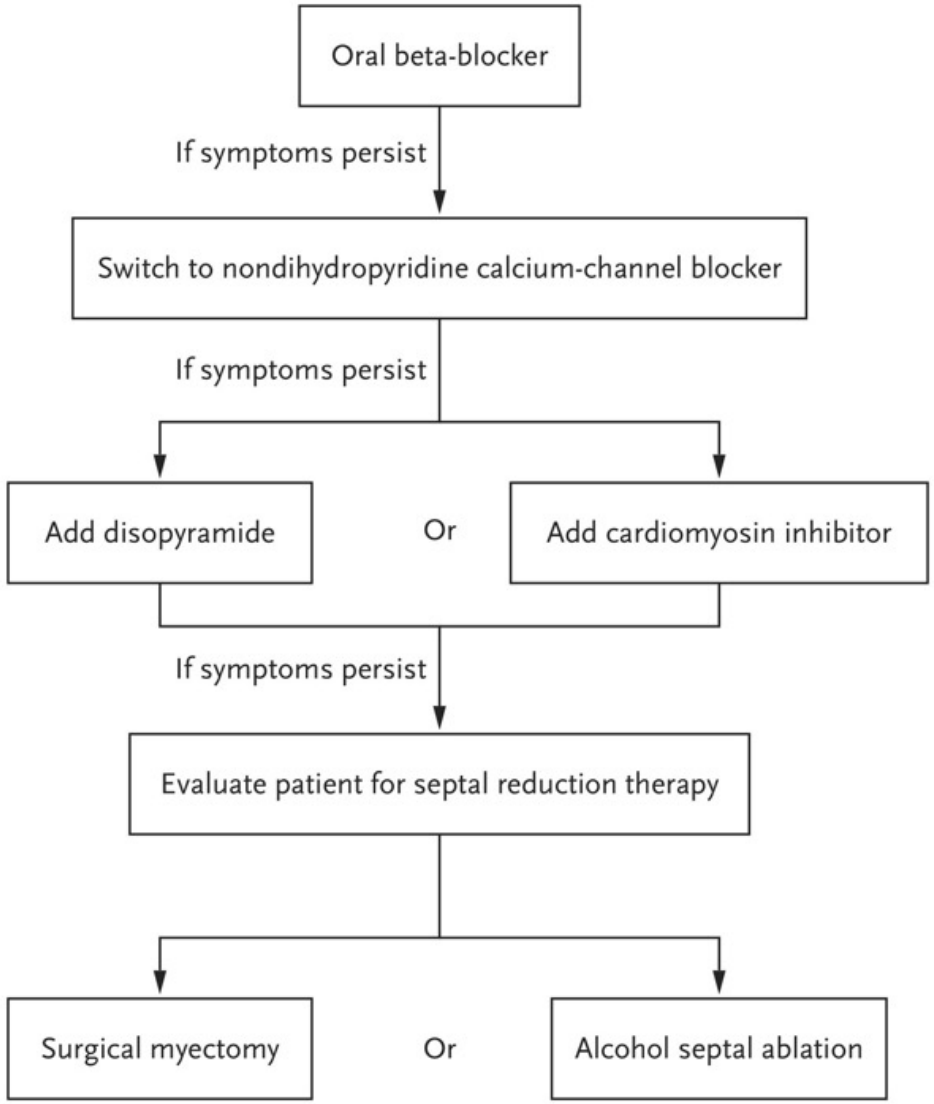
Echocardiography
Establishing diagnosis
Detection of left ventricular outflow-tract obstruction before and after provocation (e.g., as the result of the Valsalva maneuver or exercise)
Measuring thickness of left ventricular wall (asymmetric hypertrophy)
Detection of diastolic dysfunction
Detection of systolic anterior motion of the mitral valve
Determination of left atrium volume
Phenotypic conversion of phenotype negative to phenotype positive on serial studies
Detection of mitral regurgitation and assessing severity
Assessment of improving or worsening disease
Screening of family members
Cardiac MRI
Distinguishing HCM from HCM mimics and hypertensive cardiomyopathy
Determination of precise wall thickness, left atrium volume, ventricular volume, and ejection fraction
Identification of factors indicating high risk of sudden death
Identification of uncommon sites of hypertrophy (e.g., left ventricular apex and mid-left ventricle)
Detection of left ventricular abnormalities in persons who are gene positive or phenotype negative
Detection of mitral-valve and papillary-muscle abnormalities
Elucidation of appropriate technique for septal reduction therapy (myectomy or alcohol septal ablation)
Detection of myocardial perfusion abnormalities

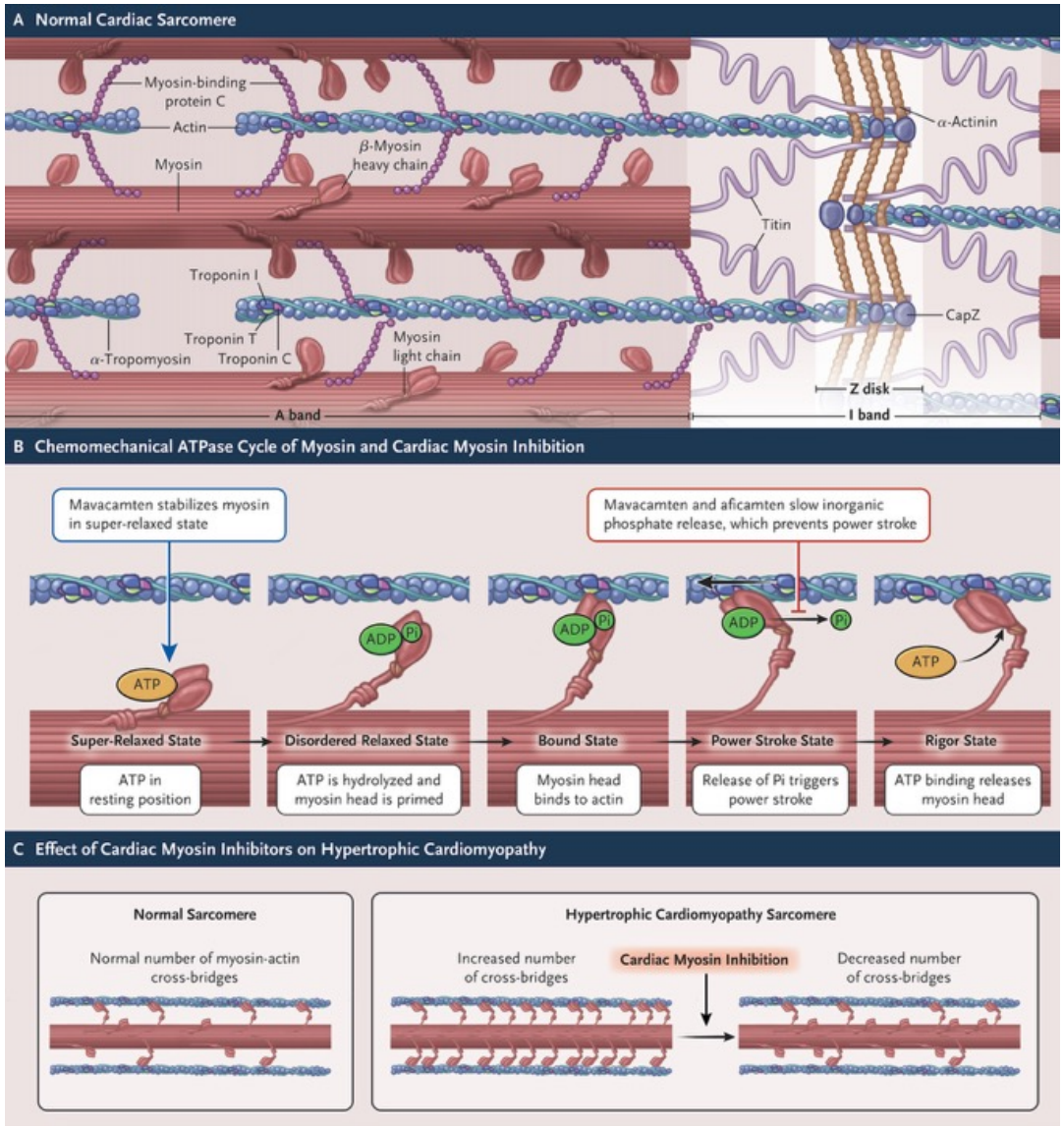
Reductions (Improvements) Induced by Cardiac Myosin Inhibitor Therapy.

Left ventricular outflow-tract gradient
Left ventricular wall thickness
Left ventricular mass
Hypercontractility
Cardiac energy requirements
Left atrial volume
Ventricular filling pressures
Ratio of early mitral inflow velocity to mitral annular diastolic velocity
New York Heart Association class

Comparison of Phase 3 Trials

Variable	Mavacamten, EXPLORER–HCM (N = 251)	Aficamten, SEQUOIA–HCM (N = 282)
Trial design and participants		
Duration — wk	30	24
Median age — yr	59	59
Female sex — %	41	41
Left ventricular outflow-tract gradient — mm Hg	≥50	≥50
New York Heart Association (NYHA) class II at baseline — %	73	76
Receiving beta-blocker	75	61
Receiving disopyramide	0	11
Primary end point	≥1.5 ml/kg/min increase in peak oxygen uptake and at least one NYHA class reduction, or ≥3.0 ml/kg/min increase in peak oxygen uptake without worsening of NYHA class	Change from baseline to week 24 in peak oxygen uptake
Findings		
Primary end point		
Results	Criteria for end-point event reached in 37% of participants with mavacamten and 17% of participants with placebo	Peak oxygen uptake 1.7 ml/kg/min higher with aficamten than with placebo
P value	P<0.001	P<0.001
Mean change in left ventricular ejection fraction — %	−4.0	−4.8
No. of participants with ejection fraction <50%	7	5





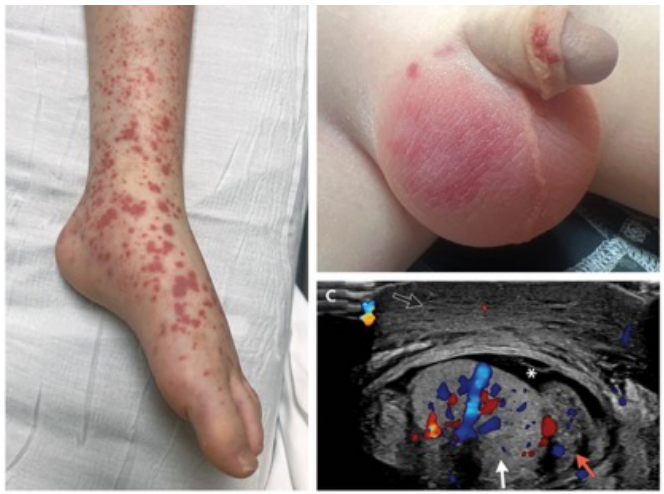
Normal, HCM, and Myosin-Inhibited Sarcomeres.

Panel A shows the cardiac sarcomere, the repeating unit of contraction within cardiomyocytes.[37] HCM-causing variants lead to a gain-of-function effect, shown in Panel B, which increases the proportion of cross-bridges in the active state and leads to adverse structural, energetic, and clinical consequences. Cardiac myosin inhibitors bind to myosin molecules and reduce their likelihood of being in the active state, thus attenuating hyper-contractility. Panel C shows normal myosin-actin cross-bridges (left) and increased cross-bridges and the effect of cardiac myosin inhibition in the presence of HCM (right).[36] ADP denotes adenosine diphosphate, CapZ CapZ protein, and Pi phosphate.

The Future

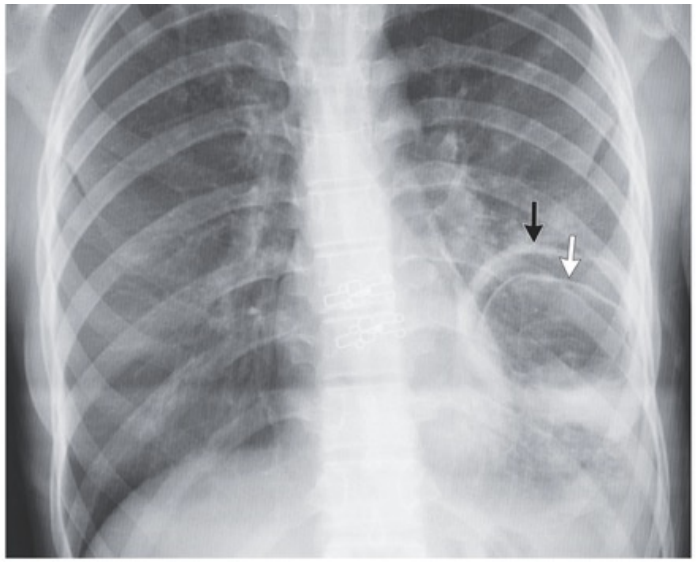
Although there has been substantial progress in the understanding, diagnosis, and management of HCM, research is active on several fronts. In the short term, there are important questions that should be addressed regarding cardiac myosin inhibitors (see above). Because the action of these agents ceases shortly after their discontinuation, will lifetime administration be necessary in patients with obstructive HCM? If so, in which subgroup? Will there be a role for cardiac myosin inhibitors in children with obstructive HCM? Can these drugs have a role in reducing the incidence of the patient profile that is gene positive and phenotype positive with left ventricular outflow-tract obstruction and has the accompanying risk of sudden cardiac death or ventricular dysfunction (or both)? Other areas of interest include deeper analyses of mitochondrial function, energetics, and inflammation.

Acute Epididymo-orchitis in IgA Vasculitis



A 5-year-old boy with recently diagnosed IgA vasculitis presented to the emergency department with a 1-day history of swelling and pain on the right side of the scrotum and worsening of a leg rash. Ten days before presentation, IgA vasculitis had been diagnosed when the patient had presented with a leg rash, abdominal pain, hematochezia, and arthritis. No treatment was initiated at the time of the initial diagnosis. At the current presentation, the physical examination was notable for purpura on the lower legs and feet (Panel A), scattered purpura on the penis and upper part of the scrotum, and swelling, erythema, and tenderness of the right side of the scrotum (Panel B). Doppler ultrasonography of the testes (Panel C) showed hyperemia of the testis (white arrow) and epididymis (red arrow), a reactive hydrocele (asterisk), and scrotal skin edema (black arrow), all on the right side. No mass or torsion was present on the right side, and the left testis was normal. A diagnosis of acute epididymo-orchitis in IgA vasculitis — a rare, genitourinary complication of IgA vasculitis that can be differentiated from other diagnoses by ultrasonography — was made. Treatment with intravenous methylprednisolone, as well as analgesia for the severe scrotal pain, was initiated. On the second hospital day, the patient was discharged with a prescription for a tapering dose of an oral glucocorticoid. At a follow-up visit 5 days later, the symptoms had abated.

Ruptured Pulmonary Hydatid Cyst



A 16-year-old girl presented to the thoracic surgery clinic with a 2-month history of cough. On physical examination, there were decreased breath sounds and dullness to percussion at the left lung base. A chest radiograph showed a well-circumscribed, cystic lesion at the base of the left lung (black arrow), within which there was another rounded structure (white arrow). The lesions resulted in a double-domed appearance that aroused concern for a ruptured pulmonary hydatid cyst, with the outer layer representing the pericyst and the inner layer representing the endocyst. On further history, the patient reported exposure to sheep, cattle, and dogs. An enzyme-linked immunosorbent assay for IgG antibodies against *Echinococcus granulosus* was negative, but computed tomography of the chest confirmed the diagnosis of a ruptured pulmonary hydatid cyst. No other cysts were found on whole-body imaging. Video-assisted utility thoracotomy that included cystotomy and capitonnage — suturing of the pericystic tissue to obliterate the cavity after removal of the cyst and its contents — was performed. Care was taken to avoid spillage of the cystic fluid. Histopathological analysis of the cyst was consistent with *E. granulosus*. Albendazole was administered. At the 9-month follow-up, there was no recurrence or secondary echinococcosis in other organs.

Case 25-2025: A 93-Year-Old Woman with Dyspnea and Fatigue

A 93-year-old woman was evaluated by her primary care physician because of dyspnea.
The patient had been in her usual state of health, which included being independent with respect to activities of daily living and participating in light exercise daily, until 1 month before the current presentation, when dyspnea developed.
Seven years before the current presentation, echocardiography was performed to assess a systolic murmur that radiated to the carotid arteries, and aortic stenosis was diagnosed. Five years before the current presentation, osteoarthritis that had been refractory to treatment resulted in total knee replacement; while the patient was hospitalized, arrhythmia was detected on telemetry and atrial fibrillation was diagnosed. During that hospitalization, repeat echocardiography was performed.
Transthoracic echocardiography showed stable aortic stenosis, with a mean aortic-valve gradient of 18 mm Hg (<20 is mild), a peak aortic velocity of 2.8 m per second (<3.0 is mild), and an aortic-valve area of 1.5 cm^2 (>1.5 is mild).

Anticoagulant therapy was not started at that time. However, 15 months before the current presentation, atrial flutter developed and treatment with apixaban and metoprolol was started. Echocardiography was performed. Transthoracic echocardiography showed progression of aortic stenosis, with a mean gradient of 23 mm Hg, a peak velocity of 3.0 m per second, and an aortic-valve area of 0.9 cm^2.

At the current presentation, the patient reported that the onset of dyspnea had been gradual and had progressed steadily during the past month. She stated that she had previously maintained a regular schedule of physical activity that had included dancing and daily walks but that the shortness of breath now prevented her from participating in these activities. She had no chest pain, palpitations, weight gain, leg swelling, or orthopnea, and she did not awaken at night with shortness of breath. She reported no melena or blood in the stool.

Additional medical history included stage 3a chronic kidney disease, type 2 diabetes mellitus, sensorineural hearing loss in both ears (for which she used hearing aids), Hashimoto's thyroiditis, vitamin B_{12} deficiency, obstructive sleep apnea, and depression. Granulomatosis with polyangiitis was diagnosed 17 years before the current presentation and had been treated with cyclophosphamide, followed by azathioprine and low-dose prednisone, which had led to remission; treatment with azathioprine was stopped 9 years before the current presentation, and low-dose prednisone therapy was continued.

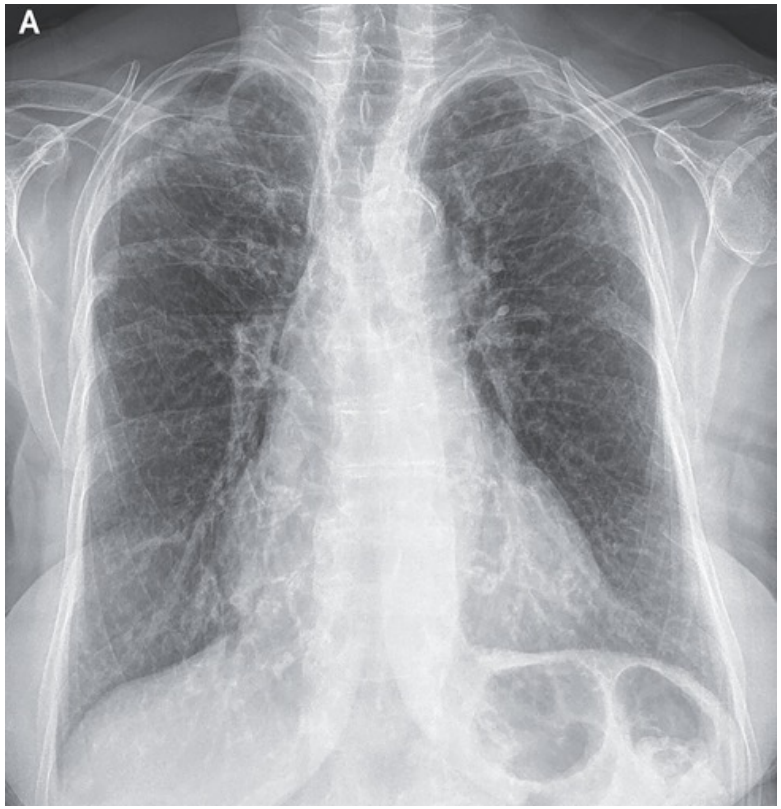
The most recent screening colonoscopy was performed when the patient was 78 years of age (15 years before the current presentation), and no polyps were seen. Other surgical history included hysterectomy and total replacement of one knee at 85 years of age and the other at 88 years of age.

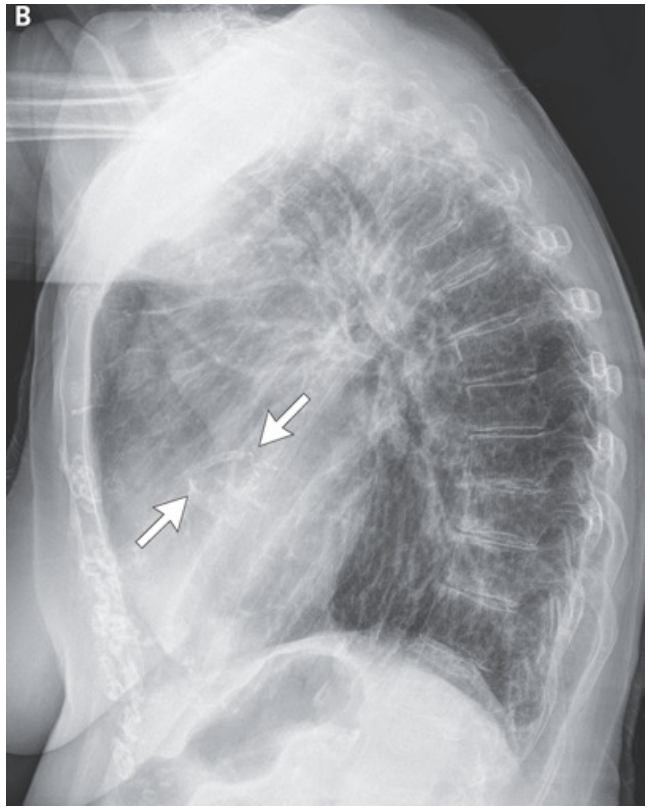
Other medications included aspirin, calcium carbonate, vitamin D, vitamin B_{12}, citalopram, glipizide, and levothyroxine. The patient had no known adverse reactions to medications. Approximately 2.5 years before the current presentation, she had moved to an assisted-living facility after the death of her husband. She was a lifelong nonsmoker and did not drink alcohol or use illicit drugs.

On examination, the temporal temperature was 36.2°C, the blood pressure 123/62 mm Hg, the pulse 61 beats per minute, the respiratory rate 12 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 23.2. She appeared mildly fatigued but was in good spirits. The jugular venous pressure was estimated at 5 cm of water. The heart rhythm was regular, with normal heart sounds, and S2 was normal. A grade 4/6 systolic murmur that did not obscure the second heart sound was noted. The lungs were clear on auscultation. The skin was not pale. She had no leg edema. An electrocardiogram (ECG) showed sinus rhythm. Imaging studies were obtained.

Chest Radiographs.

A frontal radiograph of the chest (Panel A) shows a normal cardiac silhouette without pulmonary edema. Stable pleuroparenchymal scarring is present in the lung apexes. Coronary and aortic-valve calcifications are seen on a lateral radiograph (Panel B, arrows).





Diagnostic Testing

A complete blood count was performed, and the level of hemoglobin was 7.7 g per deciliter (reference range, 12.0 to 16.0), which had decreased from a level of 10.6 g per deciliter obtained 2 months earlier. The remainder of the complete blood count was normal. The blood levels of iron and ferritin were normal, and the reticulocyte count was 1.1% (reference range, 0.5 to 2.0); the corrected reticulocyte count was 0.8% (reference range, 0.5 to 2.0), and the reticulocyte production index was 0.4 (reference value, >3.0). When the patient was asked again about stool color, she reported that her stools had occasionally been dark. Treatment with apixaban and aspirin was stopped. One unit of packed red cells was transfused. After transfusion, the blood level of hemoglobin increased to 9.0 g per deciliter and dyspnea resolved.

A diagnosis of slow gastrointestinal bleeding due to Heyde's syndrome (the triad of aortic stenosis, gastrointestinal bleeding, and acquired von Willebrand's disease) was considered. Further evaluation by means of esophagogastroduodenoscopy and colonoscopy was discussed, but the patient's preference was to avoid these procedures unless absolutely necessary. Treatment with apixaban was resumed, but aspirin was not restarted. Echocardiography was repeated.

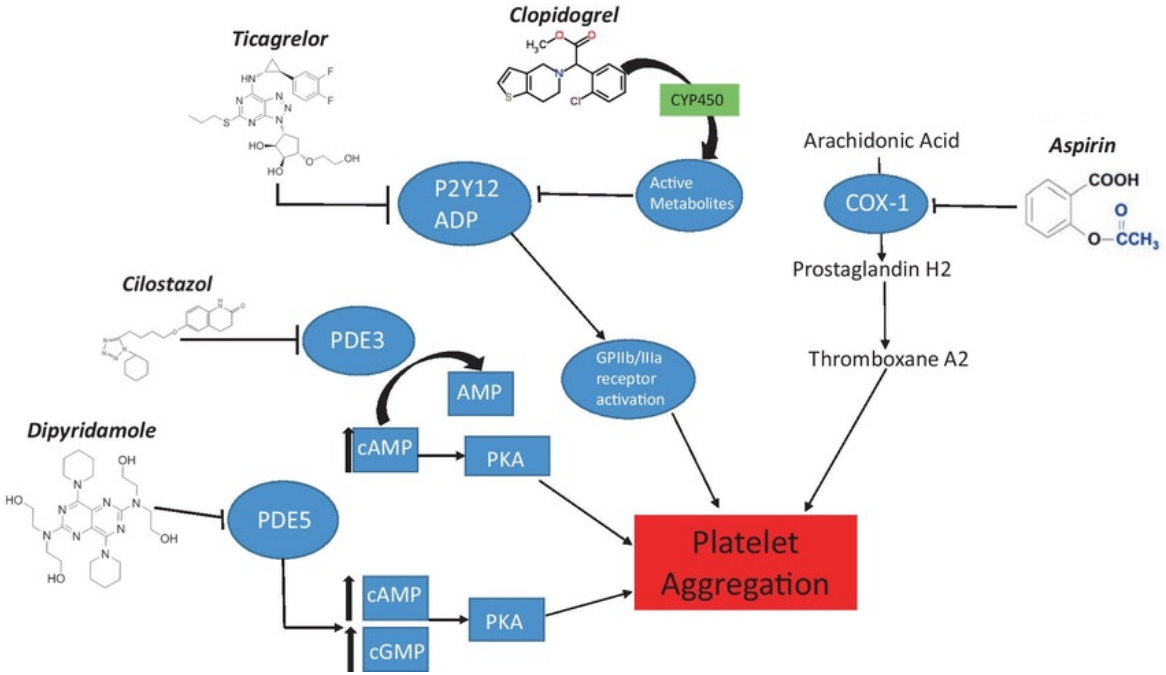
Transthoracic echocardiography revealed moderate-to-severe aortic stenosis; the mean gradient had increased to 32 mm Hg, the peak velocity was 3.6 m per second, and the aortic-valve area was 0.6 cm^2.

Follow-up

I referred the patient to a cardiologist, and I counseled her that she would be discussing management options for aortic stenosis. I assumed that she would be offered TAVR and expected that she would choose to proceed with that option. The patient met with the cardiologist three times over the course of a year and carefully discussed her options. The patient ultimately decided that she did not wish to undergo the extensive testing that would be required to be considered for aortic-valve replacement. She indicated that when she becomes more symptomatic with aortic stenosis, she would like to enroll in hospice care and cited her husband's positive experience with hospice as one of the reasons she was choosing this path. She has chosen to have no further monitoring of her aortic stenosis.

Approximately 1.5 years after the current presentation, the patient continues to feel well and engages in her usual activities, including dancing, without dyspnea or substantial fatigue. She continues to receive apixaban therapy for stroke prevention. The complete blood count has been checked every 2 to 3 months, and anemia has not recurred.

Clopidogrel und Aspirin (ASS) sind beides Thrombozytenaggregationshemmer, die zur Vorbeugung von Blutgerinnseln nach einem Herzinfarkt, Schlaganfall oder einer Stentimplantation eingesetzt werden. Studien deuten darauf hin, dass Clopidogrel in bestimmten Situationen, wie nach einer perkutanen Koronarintervention (PCI), eine bessere Wirksamkeit als Aspirin bei gleichzeitigem Beibehalten eines ähnlichen oder geringeren Blutungsrisikos zeigen kann. Die Wahl zwischen den Medikamenten hängt jedoch von der individuellen Patientensituation und den spezifischen Risiken ab, die von einem Arzt sorgfältig abgewogen werden müssen.



Clopidogrel versus aspirin for secondary prevention of coronary artery disease: a systematic review and individual patient data meta-analysis

Summary

Background Aspirin monotherapy is recommended indefinitely for patients with established coronary artery disease (CAD). The aim of this individual patient level meta-analysis was to provide a comprehensive evaluation of the comparative efficacy and safety of clopidogrel versus aspirin monotherapy in patients with established CAD, most of whom had undergone percutaneous coronary intervention or had acute coronary syndrome.

Methods We conducted a systematic search in PubMed, Scopus, Web of Science, and Embase to identify randomised trials published from database inception to April 12, 2025, comparing clopidogrel monotherapy with aspirin monotherapy in patients with established CAD who had discontinued or never started dual antiplatelet therapy. Randomised trials featuring an initial phase of dual antiplatelet therapy were eligible for inclusion in this individual patient data meta-analysis. In the main analysis, we used semi-parametric shared log-normal frailty models (one-stage analysis), including a random intercept to account for differences in the baseline hazard across trials, and a random slope to account for between-trial differences in treatment effects. The primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, or stroke (major adverse cardiovascular or cerebrovascular events [MACCE]); the primary safety endpoint was major bleeding. This study is registered with PROSPERO (CRD42025645594).

Findings Seven randomised trials including 28 982 patients (14 507 assigned to clopidogrel; 14 475 assigned to aspirin) with a median follow-up of 2·3 years (IQR 1·1–4·0) were eligible and included. At 5·5 years, MACCE was less common in patients assigned to clopidogrel than in patients assigned to aspirin (929 events [2·61 per 100 patient-years] *vs* 1062 events [2·99 per 100 patient-years]; hazard ratio 0·86 [95% CI 0·77–0·96]; p=0·0082). Mortality and major bleeding (256 events [0·71 per 100 patient-years] with clopidogrel *vs* 279 events [0·77 per 100 patient-years] with aspirin; 0·94 [0·74–1·21]; p=0·64) did not differ.

Interpretation These findings add to the evidence that clopidogrel monotherapy is superior to aspirin monotherapy for MACCE prevention with no increase in the risk of bleeding, and support the preferential use of clopidogrel over aspirin for secondary prevention in patients with established CAD.

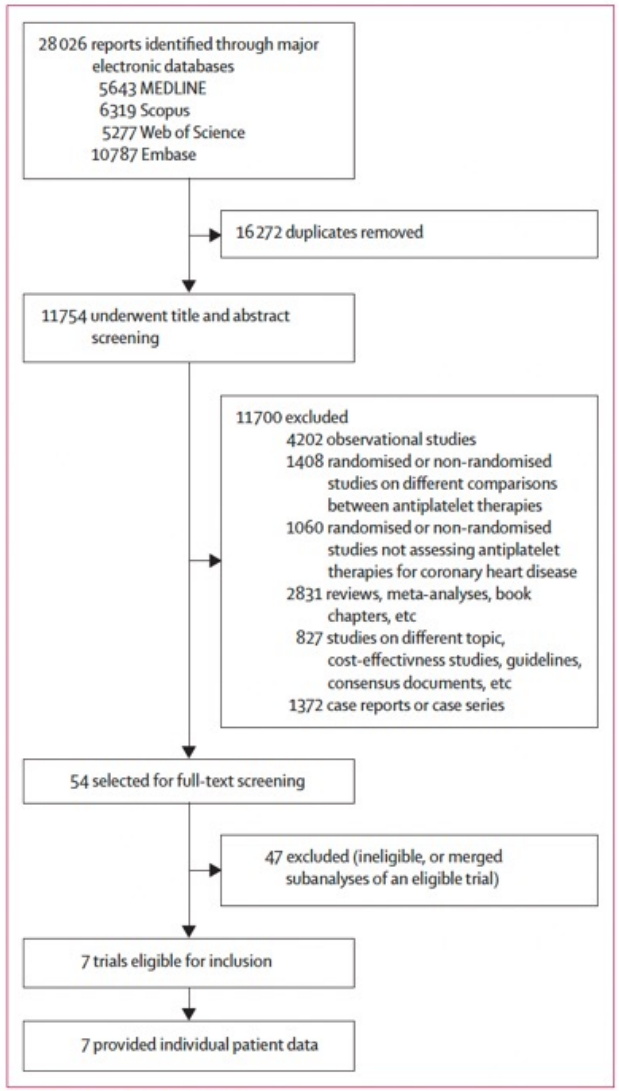


Figure 1: **PRISMA flow diagram**

	Clopidogrel (n=14 507)	Aspirin (n=14 475)	p value
Age, years	65·5 (58·0–74·9)	65·5 (57·0–74·5)	0·42
Sex	..	..	0·40
Male	11 430 (78·8%)	11 346 (78·4%)	..
Female	3077 (21·2%)	3129 (21·6%)	..
BMI, kg/m²	24·5 (22·5–26·8)	24·5 (22·5–26·7)	0·70
Region	..	..	0·92
Asia	9672 (66·7%)	9679 (66·9%)	..
Europe	2530 (17·4%)	2520 (17·4%)	..
North America	2305 (15·9%)	2276 (15·7%)	..
Diabetes*	4689 (32·5%)	4691 (32·6%)	0·89
Hypertension	8834 (60·9%)	8630 (59·6%)	0·027
Hypercholesterolaemia†	8291 (59·6%)	8244 (59·4%)	0·78
Current smoker	3346 (23·1%)	3393 (23·4%)	0·45
Previous myocardial infarction	7384 (50·9%)	7299 (50·4%)	0·42
Previous stroke*	1079 (7·5%)	1060 (7·4%)	0·70
Clinical presentation	..	..	0·48
Acute coronary syndrome	9896 (68·2%)	9930 (68·6%)	..
Chronic coronary syndrome	4611 (31·8%)	4545 (31·4%)	..
Myocardial ischaemia treatment‡	..	..	0·020
Percutaneous coronary intervention	10 229/14 413 (71·0%)	10 207/14 385 (71·0%)	..
Medical therapy alone	3687/14 413 (25·6%)	3607/14 385 (25·1%)	..
Coronary artery bypass grafting	356/14 413 (2·5%)	377/14 385 (2·6%)	..
Percutaneous coronary intervention and coronary artery bypass grafting	141/14 413 (1·0%)	194/14 385 (1·3%)	..
Type of device used in percutaneous coronary intervention†	..	..	0·35
Second-generation drug-eluting stent	9407/10 016 (93·9%)	9404/10 024 (93·8%)	..
First-generation drug-eluting stent	90/10 016 (0·9%)	115/10 024 (1·1%)	..
Bioresorbable vascular scaffold, bare-metal stent, plain balloon angioplasty, or other	491/10 016 (4·9%)	479/10 024 (4·8%)	..
Drug-eluting stent of unknown generation	28/10 016 (0·3%)	26/10 024 (0·3%)	..
Peripheral artery disease§	1058 (7·3%)	1094 (7·6%)	0·39
Chronic kidney disease¶	2046 (20·3%)	2028 (20·1%)	0·74
Estimated glomerular filtration rate (mL/min per 1·73 m²)	80·2 (63·5–99·4)	80·6 (63·6–99·5)	0·57
Previous bleeding events‖	127 (1·2%)	113 (1·1%)	0·37
Haemoglobin (g/dL)	13·9 (12·6–15·0)	13·9 (12·6–14·9)	0·69
Aspirin dose	..	..	0·76
Low (≤100 mg per day)	Not applicable	9769 (67·5%)	..
High (>100 mg per day)	Not applicable	4706 (32·5%)	..
Proton pump inhibitor	4517/14 169 (31·9%)	4920/14 143 (34·8%)	<0·0001

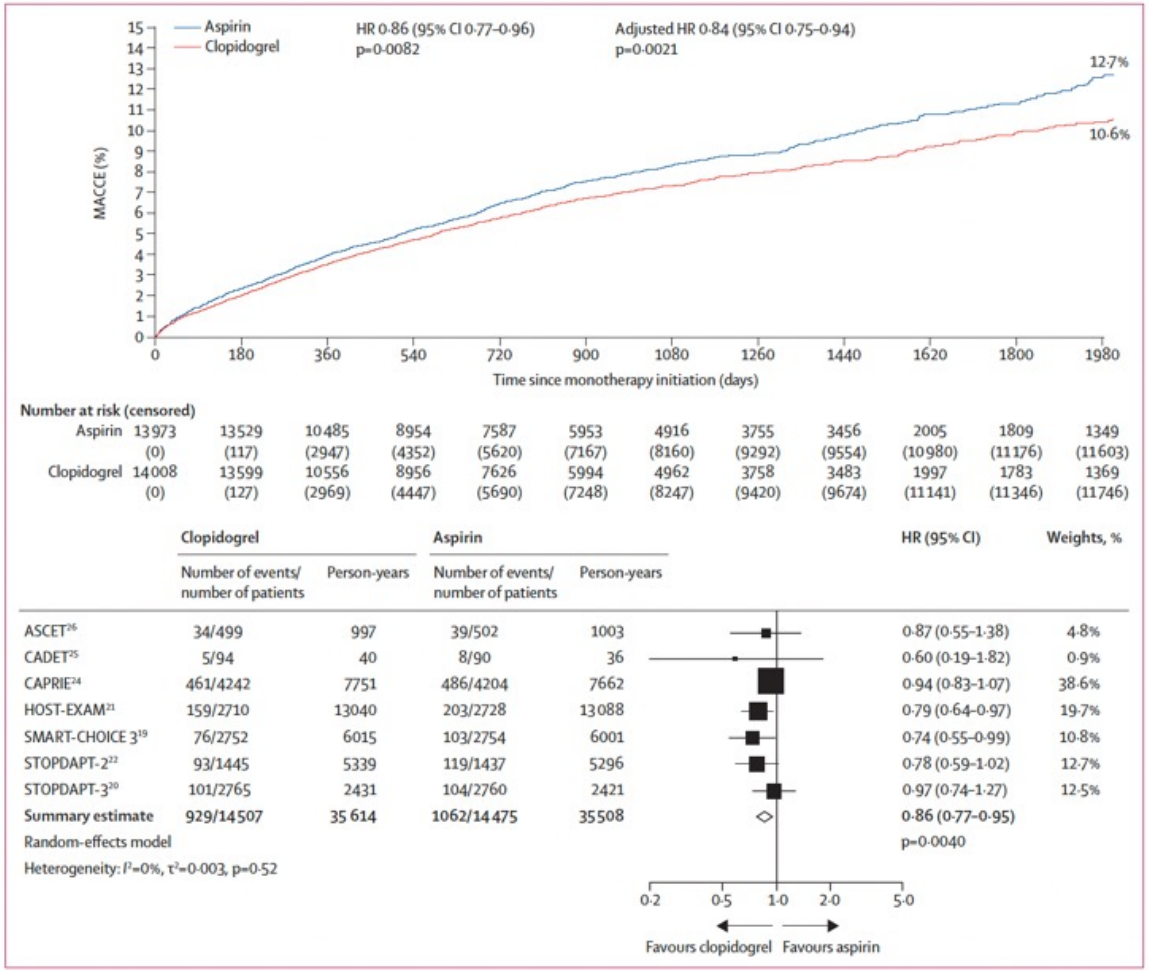
Data shown are median (IQR) or n (%), unless otherwise stated. Observed imbalances might in part reflect the exclusion of patients who had early trial termination, died, or had myocardial infarction, stroke, stent thrombosis, or major bleeding during the initial dual antiplatelet therapy phase in the STOPDAPT-2I9 and STOPDAPT-3I7 trials. *94 missing values in the clopidogrel group, 90 missing values in the aspirin group. †593 missing values in the clopidogrel group, 592 missing values in the aspirin group. ‡Data were not available for 94 patients in the clopidogrel group and 90 patients in the aspirin group. †Of 10 370 patients in the clopidogrel group who underwent percutaneous coronary intervention alone or with coronary artery bypass grafting, data were unavailable for 354 patients, and of 10 401 patients in the aspirin group who underwent percutaneous coronary intervention alone or with coronary artery bypass grafting, data were unavailable for 377 patients. §100 missing values in the clopidogrel group, 95 missing values in the aspirin group. ¶4425 missing values in the clopidogrel group, 4387 missing values in the aspirin group. ‖4336 missing values in the clopidogrel group, 4294 missing values in the aspirin group.

Table 1: **Baseline characteristics across all included trials**

	Clopidogrel		Aspirin		HR (95% CI)	p value	Adjusted HR (95% CI)	Adjusted p value
	Number of events/number of patients (Kaplan–Meier estimate)	Events per 100 person-years	Number of events/number of patients (Kaplan–Meier estimate)	Events per 100 person-years				
MACCE	929/14 507 (10·7%)	2·61	1062/14 475 (12·9%)	2·99	0·86 (0·77–0·96)	0·0082	0·84 (0·75–0·94)	0·0021
Major bleeding	256/14 507 (3·4%)	0·71	279/14 475 (3·9%)	0·77	0·94 (0·74–1·21)	0·64	1·00 (0·76–1·32)	0·99
NACCE	1116/14 507 (12·9%)	3·16	1247/14 475 (15·3%)	3·54	0·89 (0·81–0·98)	0·023	0·87 (0·79–0·96)	0·0051
Death	713/14 507 (9·4%)	1·96	723/14 475 (10·1%)	1·98	0·99 (0·89–1·09)	0·79	0·99 (0·89–1·10)	0·82
Cardiovascular death	430/14 507 (5·1%)	1·18	435/14 475 (5·8%)	1·19	0·98 (0·84–1·13)	0·74	0·96 (0·83–1·11)	0·58
Myocardial infarction	356/14 507 (3·9%)	0·99	457/14 475 (5·1%)	1·27	0·76 (0·66–0·89)	0·0004	0·75 (0·65–0·88)	0·0003
Stroke	264/14 507 (3·4%)	0·73	316/14 475 (4·0%)	0·88	0·79 (0·66–0·96)	0·018	0·84 (0·71–0·98)	0·032
Ischaemic stroke	218/14 008 (2·7%)	0·62	253/13 973 (3·1%)	0·72	0·80 (0·65–0·98)	0·032	0·86 (0·71–1·03)	0·092
Haemorrhagic stroke	35/14 008 (0·7%)	0·10	46/13 973 (0·8%)	0·13	0·77 (0·49–1·19)	0·23	0·78 (0·50–1·21)	0·27
Definite or probable stent thrombosis	22/9672 (0·3%)	0·08	33/9679 (0·5%)	0·12	0·63 (0·36–1·11)	0·11	0·63 (0·35–1·14)	0·13
Definite stent thrombosis	17/9672 (0·2%)	0·06	22/9679 (0·3%)	0·08	0·77 (0·39–1·50)	0·44	0·78 (0·41–1·50)	0·46
Probable stent thrombosis	5/9672 (0·1%)	0·02	11/9679 (0·2%)	0·04	0·39 (0·13–1·16)	0·090	0·41 (0·14–1·21)	0·11
Any bleeding	780/14 507 (8·8%)	2·21	760/14 475 (8·8%)	2·14	1·04 (0·86–1·26)	0·69	1·07 (0·87–1·31)	0·54
Major gastrointestinal bleeding	110/14 008 (1·5%)	0·31	111/13 973 (1·7%)	0·31	0·98 (0·58–1·64)	0·93	1·03 (0·60–1·77)	0·91
Any gastrointestinal bleeding	220/14 008 (2·8%)	0·63	242/13 973 (3·1%)	0·69	0·93 (0·71–1·22)	0·60	0·97 (0·73–1·27)	0·80

Percentages are Kaplan–Meier estimates of cumulative incidence at 2000 days (longest available follow-up). For patients in the ASCET trial, event timing was unavailable and was assumed to occur at the end of follow-up, as prespecified in the protocol. ASCET patients are included in the table estimates but excluded from the graphical representation in figures, as stated in the figure legends. One-stage analyses were performed by Cox models with a random intercept (accounting for differences in the baseline hazard across trials) and a random slope (accounting for between-trial differences in treatment effects). HR=hazard ratio. MACCE=major adverse cardiovascular or cerebrovascular events. NACCE=net adverse cardiovascular or cerebrovascular events.

Table 2: **Clinical outcomes by one-stage analyses**



	Clopidogrel		Aspirin		HR (95% CI)	Weights, %
	Number of events/ number of patients	Person-years	Number of events/ number of patients	Person-years		
ASCET[26]	34/499	997	39/502	1003	0·87 (0·55–1·38)	4·8%
CADET[25]	5/94	40	8/90	36	0·60 (0·19–1·82)	0·9%
CAPRIE[24]	461/4242	7751	486/4204	7662	0·94 (0·83–1·07)	38·6%
HOST-EXAM[21]	159/2710	13040	203/2728	13088	0·79 (0·64–0·97)	19·7%
SMART-CHOICE 3[19]	76/2752	6015	103/2754	6001	0·74 (0·55–0·99)	10·8%
STOPDAPT-2[22]	93/1445	5339	119/1437	5296	0·78 (0·59–1·02)	12·7%
STOPDAPT-3[20]	101/2765	2431	104/2760	2421	0·97 (0·74–1·27)	12·5%
Summary estimate	**929/14507**	**35 614**	**1062/14475**	**35508**	**0·86 (0·77–0·95)**	
Random-effects model					p=0·0040	
Heterogeneity: I^2=0%, τ^2=0·003, p=0·52						

0·2 0·5 1·0 2·0 5·0

Figure 2: **Analysis of the primary efficacy outcome of MACCE**

The upper panel illustrates the cumulative distribution of the primary efficacy outcome of MACCE, defined as a composite of cardiovascular death, myocardial infarction, or stroke. The rates are computed by the Kaplan-Meier method. Patients enrolled in the ASCET trial[26] were excluded from the graphical representation as the timing of events was unavailable; in the analyses, these events were assumed to occur at the end of follow-up. HR and 95% CI were computed by mixed-effects models (one-stage analysis). Adjusted HRs and 95% CIs were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting. HR=hazard ratio. MACCE=major adverse cardiovascular or cerebrovascular events.

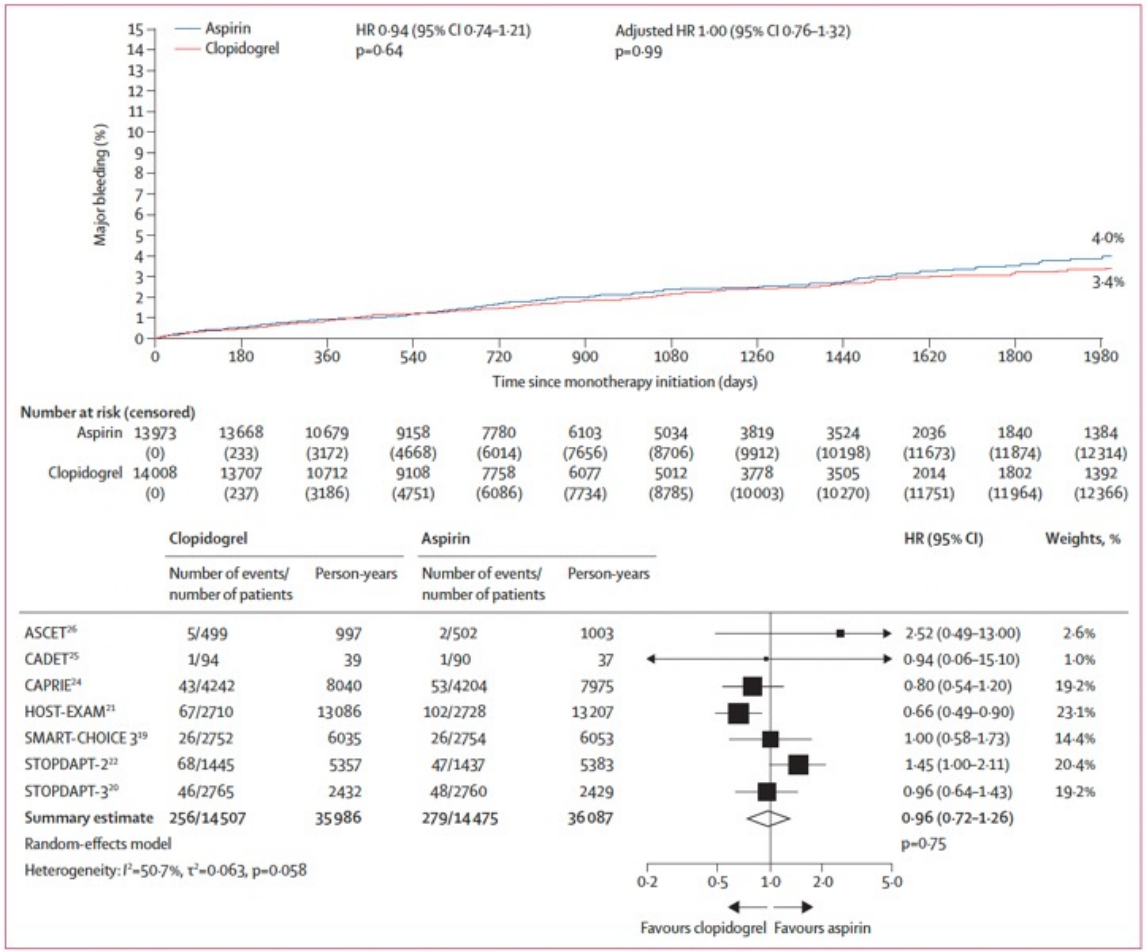


Figure 3: **Analysis of the primary safety outcome of major bleeding**

The upper panel illustrates the cumulative distribution of the primary safety outcome of major bleeding. The rates are computed by the Kaplan–Meier method. Patients enrolled in the ASCET trial[26] were excluded from the graphical representation as the timing of events was unavailable; in the analyses, these events were assumed to occur at the end of follow-up. HR and 95% CIs were computed by mixed-effects models (one-stage analysis). Adjusted HRs and 95% CIs were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting. HR=hazard ratio.

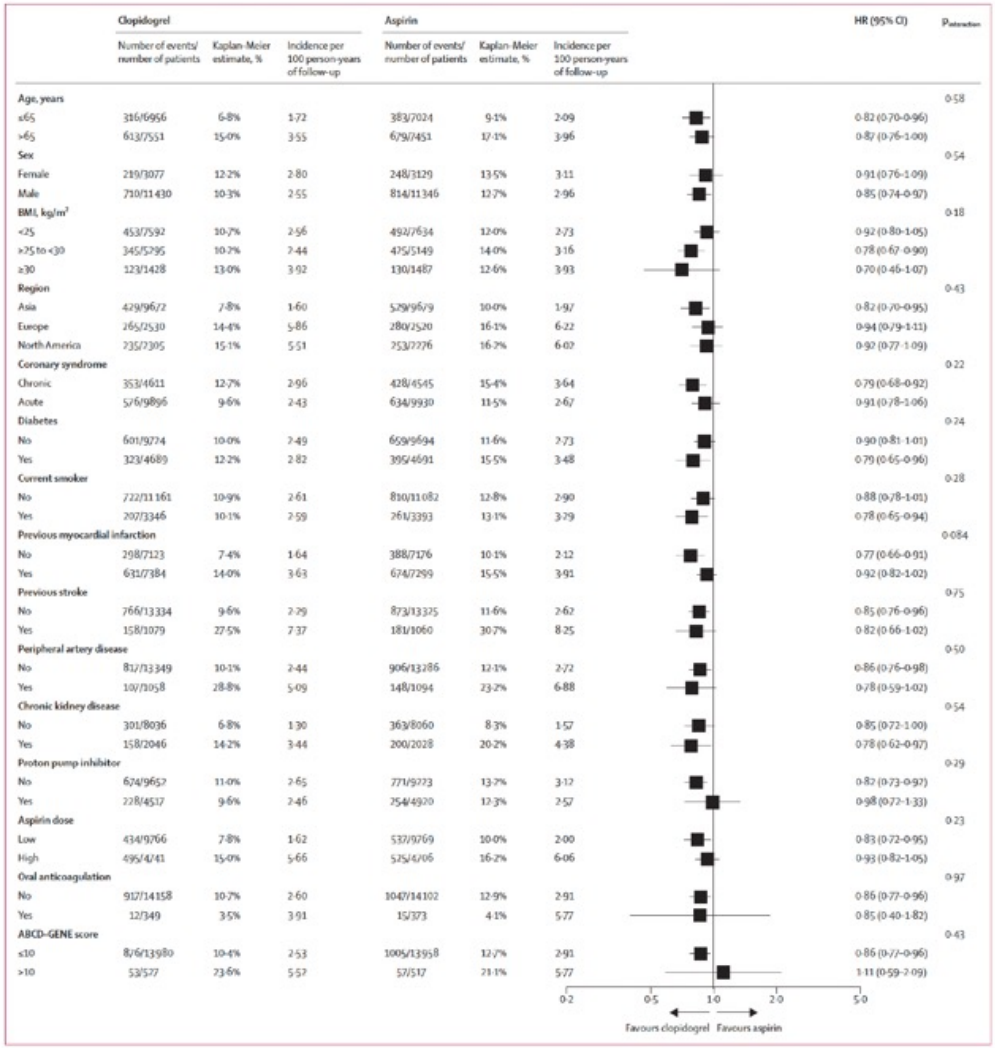


Figure 4: Subgroup analysis for MACCE

The Kaplan-Meier estimates refers to the maximum available follow-up of 2000 days. HRs and 95% CIs were computed by mixed-effects models (one-stage analysis). Unadjusted $p_{interaction}$ values formally describe the heterogeneity of treatment effects between or across subgroups. Low-dose aspirin was defined as ≤100 mg per day, high-dose aspirin as >100 mg per day. HR=hazard ratio. MACCE=major adverse cardiovascular or cerebrovascular events.

Research in context

Evidence before this study

We searched MEDLINE (via PubMed), Scopus, Web of Science, Embase (via Ovid), and five websites (www.tctmd.com, www.pcronline.org, www.crtonline.org, www.escardio.org, and www.heart.org), without language restrictions, from database inception to April 12, 2025, for randomised trials that compared clopidogrel versus aspirin monotherapy in patients with coronary artery disease (CAD) who discontinued or never started dual antiplatelet therapy. The following search terms were used: "aspirin", "acetylsalicylic acid", "$P2Y_{12}$ inhibitor", "clopidogrel", "prasugrel", "ticagrelor", "atherosclerosis", "coronary artery disease", "percutaneous coronary intervention", "coronary artery bypass grafting", "myocardial infarction", "stroke", and "peripheral artery disease". Previous evidence on the comparative efficacy and safety of the two antiplatelet strategies has been inconsistent and limited by insufficient statistical power of individual trials and heterogeneity across trial designs and objectives. Earlier meta-analyses suggested a potential advantage of $P2Y_{12}$ inhibitors over aspirin for cardiovascular event prevention; however, their findings were limited by the pooled evaluation of different $P2Y_{12}$ inhibitors (eg, clopidogrel and ticagrelor) and the inclusion of mixed atherosclerotic disease populations or selected cohorts of patients treated with percutaneous coronary intervention. In addition, previous analyses did not incorporate extended follow-up data from earlier studies or recent evidence from the STOPDAPT-3 trial and the SMART-CHOICE 3 trial, which together compared clopidogrel and aspirin in a total of 11 339 patients with CAD. Moreover, although clinical factors associated with poor response to clopidogrel have been identified, their influence on the comparative outcomes of long-term monotherapy with clopidogrel versus aspirin in stable CAD remains unexamined.

Added value of this study

We analysed patient-level data from all available randomised trials comparing clopidogrel and aspirin monotherapy for secondary prevention in patients with established CAD, irrespective of the initial clinical presentation (acute or chronic coronary syndrome) and treatment strategy (percutaneous coronary intervention, coronary artery bypass grafting, or medical therapy alone). Clopidogrel monotherapy was associated with a reduced risk of major adverse cardiovascular and cerebrovascular events, driven primarily by lower rates of myocardial infarction and stroke. There were no differences between the two strategies in the risk of major bleeding, any bleeding, or gastrointestinal bleeding. Treatment effects were consistent across all prespecified subgroups, including individuals with clinical features associated with poor responsiveness to clopidogrel, as defined by the ABCD-GENE score, evaluated both individually and in combination.

Implications of all the available evidence

This comprehensive synthesis of available evidence indicates that, in patients with CAD, long-term clopidogrel monotherapy offers superior protection against major cardiovascular and cerebrovascular events compared with aspirin, without an excess risk of bleeding. The superior efficacy of clopidogrel versus aspirin was consistent across multiple key subgroups, including individuals with clinical features predictive of poor clopidogrel responsiveness, supporting the generalisability of these findings to the broad spectrum of patients with CAD. These results support a preference for clopidogrel over aspirin for chronic antiplatelet monotherapy for patients with stable CAD. The widespread availability, generic formulation, and affordability of clopidogrel further supports its potential for extensive adoption in clinical practice.

SWEDEPAD: No Mortality Signal With Paclitaxel in PAD

The finding, from a study with a mean follow-up of 2-and-a-half years, bolsters support for trials and device use to continue.

Paclitaxel-coated versus uncoated devices for infrainguinal endovascular revascularisation in chronic limb-threatening ischaemia (SWEDEPAD 1): a multicentre, participant-

Summary

Background Drug-coated devices are frequently used in coronary and peripheral interventions, but their effect on amputation risk in peripheral artery disease is unclear. We assessed whether drug-coated devices affect the rate of above-ankle amputation in patients with chronic limb-threatening ischaemia undergoing infrainguinal endovascular revascularisation.

Methods The Swedish Drug-Elution Trial in Peripheral Arterial Disease 1 (SWEDEPAD 1) was a pragmatic, nationwide, multicentre, participant-masked, registry-based, randomised controlled trial at 22 Swedish centres. Adult patients with Rutherford category 4–6 peripheral artery disease scheduled for infrainguinal endovascular treatment were eligible for inclusion. Participants were randomly allocated in a 1:1 ratio after successful guidewire crossing to receive either paclitaxel-coated or uncoated balloons or stents. Randomisation was stratified by centre and performed using a computer-generated sequence with allocation concealment via a secure, registry-embedded web system. The primary efficacy endpoint was ipsilateral major amputation (above the ankle) during follow-up. All analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov (NCT02051088) and the primary analysis is complete; further analyses are ongoing.

Findings From Nov 5, 2014, to Sept 29, 2023, 2400 patients were randomly assigned to treatment with paclitaxel-coated devices (n=1206) or with uncoated devices (n=1194). 2355 patients were included in the intention-to-treat analysis (1180 in the paclitaxel-coated group and 1175 in the uncoated group). The median age was 77 years (IQR 71–83), 1317 (55·9%) of 2355 patients were male and 1038 (44·1%) were female, and 1237 (52·6%) patients had preoperative diabetes. Median follow-up was 2·67 years (IQR 1·08–4·78). Most patients (1761 [74·9%] of 2351) had wounds or tissue loss (Rutherford stage 5 or 6). Treated lesions were located in the femoropopliteal vascular segment in 1241 (52·7%) of 2355 patients, in the infrapopliteal segment in 537 (22·8%) patients, and in both segments in 561 (23·8%) patients. Nearly all paclitaxel-coated devices (>99%) used paclitaxel as the coating agent (>99%). There was no significant difference in the rate of ipsilateral major amputation between using paclitaxel-coated or uncoated devices (hazard ratio [HR] 1·05 [95% CI 0·87–1·27]; p=0·61) with maximum of 5 years of follow-up. There was no difference in all-cause mortality (HR 1·04 [95% CI 0·92–1·17]; p=0·54).

Interpretation In patients with chronic limb-threatening ischaemia undergoing infrainguinal endovascular revascularisation, paclitaxel-coated devices did not reduce major ipsilateral amputations.

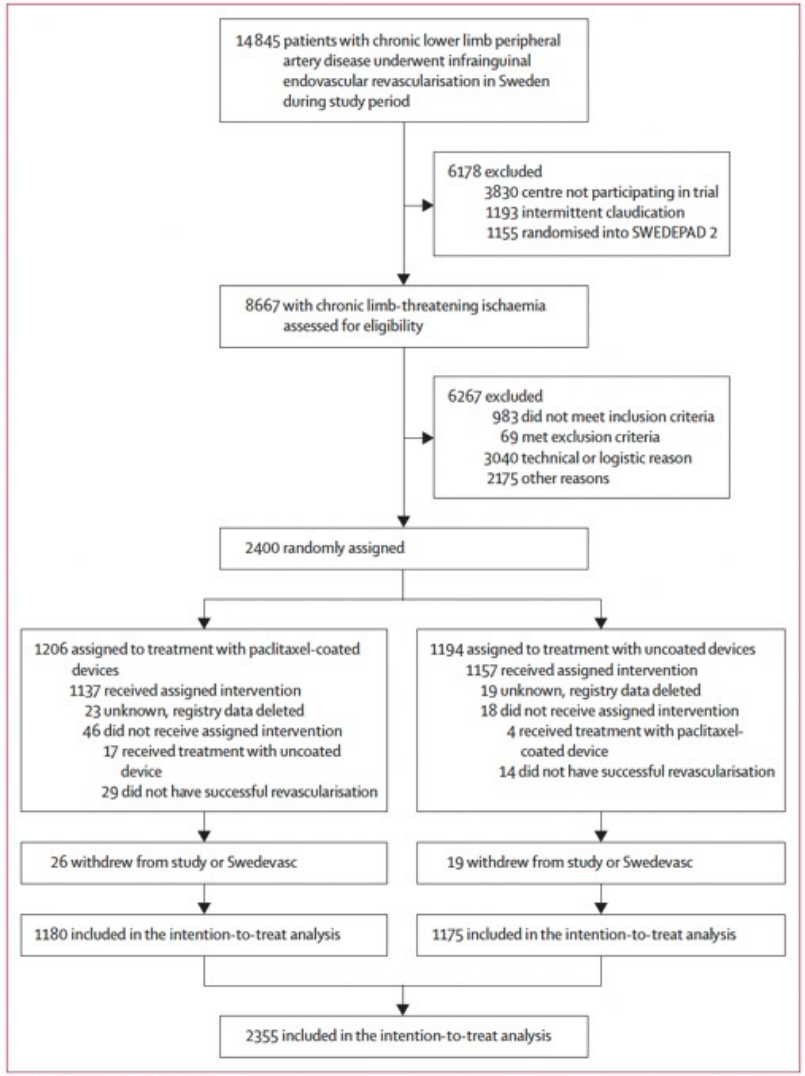


Figure 1: **Trial profile**

	Treatment with paclitaxel-coated devices (n=1180)	Treatment with uncoated devices (n=1175)
Age, years	77·0 (72·0–83·0)	77·0 (71·0–83·0)
Sex		
Male	666 (56·4%)	651 (55·4%)
Female	514 (43·6%)	524 (44·6%)
Smoking status		
Never	330/1176 (28·1%)	331 (28·2%)
Previous	496 (42·2%)	505 (43·0%)
Current	167 (14·2%)	161 (13·7%)
Unknown	183 (15·6%)	178 (15·1%)
Hypertension	988/1176 (84·0%)	967 (82·3%)
Preoperative diabetes	632/1176 (53·7%)	605 (51·5%)
Previous cardiovascular disease	615/1176 (52·3%)	574 (48·9%)
Pulmonary disease	218/1176 (18·5%)	191 (16·3%)
Cerebrovascular disease	175/1176 (14·9%)	157 (13·4%)
Medication		
Statins	915/1176 (77·8%)	887 (75·5%)
Anticoagulant treatment	335/1176 (28·5%)	380 (32·3%)
Platelet inhibitor	860/1176 (73·1%)	799 (68·0%)
Paclitaxel-coated device before index procedure	21 (1·8%)	21 (1·8%)
Ankle–brachial index	0·6 (0·4–0·8), n=955	0·6 (0·4–0·8), n=948
Renal insufficiency	284/1119 (25·4%)	263/1118 (23·5%)
Dialysis	55/1176 (4·7%)	56 (4·8%)
Vascular segment to be treated		
Femoropopliteal	610 (51·7%)	631 (53·7%)
Infrapopliteal	283 (24·0%)	254 (21·6%)
Femoropopliteal and infrapopliteal	275 (23·3%)	286 (24·3%)
Neither	12 (1·0%)	4 (0·3%)
Planned primary stenting*	161 (13·6%)	150 (12·8%)
Rutherford classification		
Asymptomatic (category 0)	0/1176	0
Mild claudication (category 1)	0	0
Moderate claudication (category 2)	0	1 (0·1%)
Severe claudication (category 3)	1 (0·1%)	2 (0·2%)
Ischaemic rest pain (category 4)	298 (25·3%)	288 (24·5%)
Minor tissue loss (category 5)	780 (66·3%)	792 (67·4%)
Major tissue loss (category 6)	97 (8·2%)	92 (7·8%)
TASC II class		
TASC A lesion	175/1020 (17·2%)	181/1031 (17·6%)
TASC B lesion	334/1020 (32·7%)	342/1031 (33·2%)
TASC C lesion	315/1020 (30·9%)	306/1031 (29·7%)
TASC D lesion	196/1020 (19·2%)	202/1031 (19·6%)
VascuQol-6	10·0 (8·0–12·5), n=1175	10·0 (8·0–13·0)

Data are median (IQR) or n (%). Percentages computed by group. *As stated by the operator ahead of randomisation.

Table 1: **Baseline characteristics of SWEDEPAD 1 trial participants**

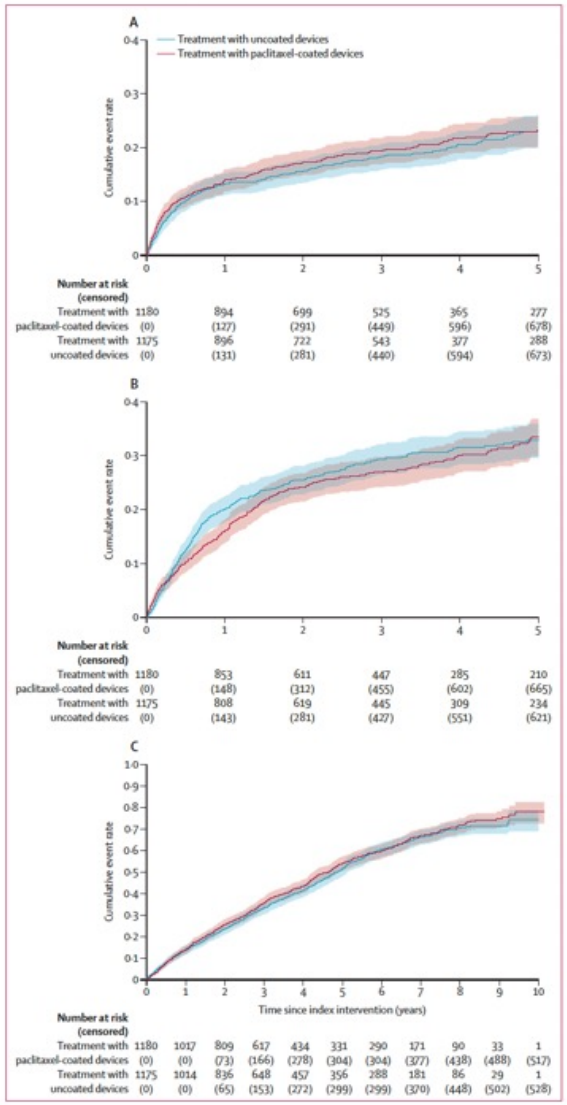


Figure 2: Kaplan–Meier estimates of major ipsilateral amputation (A), target vessel reinterventions with a follow-up of a maximum of 5 years (B), and all-cause mortality during the full follow-up period (C)

	Treatment with paclitaxel-coated devices (n=1180)		Treatment with uncoated devices (n=1175)		Hazard ratio (95% CI)*	p value
	Number of events	Event rate per 100 person-years	Number of events	Event rate per 100 person-years		
Ipsilateral amputation						
Up to 1 year	159	15·87	148	14·77	1·07 (0·86–1·35)	0·53
Up to 5 years	225	7·09	214	6·62	1·05 (0·87–1·27)	0·61
Complete follow-up	235	6·17	229	5·96	1·02 (0·85–1·22)	0·85
Death						
Up to 1 year	163	14·86	161	14·77	0·97 (0·78–1·20)	0·75
Up to 5 years	545	15·01	520	13·99	1·04 (0·92–1·17)	0·54
Complete follow-up	662	15·11	646	14·44	1·01 (0·91–1·13)	0·86
Ipsilateral amputation or death						
Up to 1 year	286	28·54	279	27·85	1·00 (0·85–1·18)	0·98
Up to 5 years	646	20·34	628	19·43	1·01 (0·90–1·12)	0·90
Complete follow-up	744	19·52	740	19·25	0·97 (0·88–1·08)	0·59
Target vessel revascularisation						
Up to 1 year	179	18·08	224	23·23	0·81 (0·66–0·98)	0·031
Up to 5 years	305	10·68	320	11·22	0·97 (0·83–1·14)	0·71
Complete follow-up	319	9·70	324	9·79	1·01 (0·86–1·18)	0·94
Ipsilateral reintervention						
Up to 1 year	198	20·25	242	25·40	0·82 (0·68–0·99)	0·042
Up to 5 years	330	11·81	344	12·41	0·97 (0·83–1·13)	0·69
Complete follow-up	346	10·76	353	11·04	0·99 (0·86–1·15)	0·93

*All models are adjusted for age, sex, vascular segment to be treated, planned revascularisation technique, and centre.

Table 2: Time-to-event outcomes

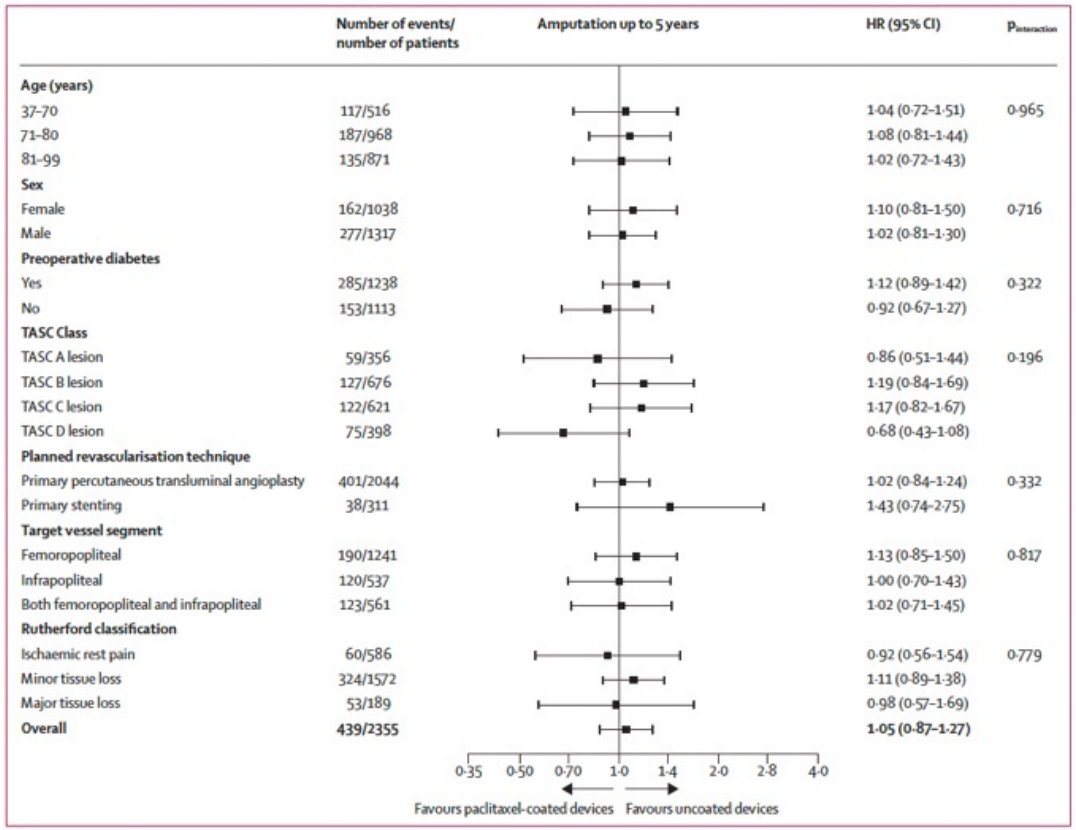


Figure 3: Forest plot of intergroup differences in the primary endpoint of ipsilateral major amputation across relevant subgroups

	Treatment with paclitaxel-coated devices (n=1180)	Treatment with uncoated devices (n=1175)	Mean difference or odds ratio* (95% CI)	p value
VascuQoL-6				
30 days	14 (10–18), n=915	14 (10–18), n=949	MD 0·04 (–0·38 to 0·46)	0·85
1 year	13 (8–18), n=1027	13 (8–18), n=1053	MD –0·05 (–0·54 to 0·44)	0·84
Ankle–brachial index				
30 days	1·0 (0·8–1·1), n=854	1·0 (0·8–1·1), n=889	MD –0·03 (–0·06 to 0·01)	0·19
1 year	0·9 (0·6–1·1), n=625	0·9 (0·6–1·0), n=644	MD –0·01 (–0·05 to 0·04)	0·67
Rutherford category 0–III†				
30 days	499/1081 (46%)	505/1111 (46%)	OR 0·92 (0·79 to 1·08)	0·33
1 year	508/854 (60%)	517/878 (59%)	OR 0·88 (0·74 to 1·05)	0·15
Binary restenosis ≥50%				
30 days	36/131 (28%)	28/120 (23%)	OR 1·25 (0·71 to 2·23)	0·44
1 year	51/204 (25%)	40/187 (21%)	OR 1·23 (0·77 to 1·98)	0·39

Data are median (IQR) or n/N (%), unless stated otherwise. MD=mean difference. OR=odds ratio. * All models are adjusted for age, sex, vascular segment to be treated, planned revascularisation technique, and centre and the baseline value of the corresponding outcome. †Rutherford category was treated as an ordinal outcome and was analysed with a proportional odds logistic regression.

Table 3: Follow-up outcomes

Research in context

Evidence before this study

Drug-coated balloons and stents have been shown to reduce restenosis and the need for reintervention in patients undergoing endovascular treatment for peripheral artery disease. However, whether these devices reduce the risk of amputation in patients with chronic limb-threatening ischaemia remains uncertain. Concerns have also been raised about possible small-particle distal embolisation and increased late mortality associated with the most commonly used coating drug used for peripheral artery disease indications, paclitaxel, which has led to uncertainty regarding the long-term effectiveness and safety of drug-eluting devices for this patient population. This study was initiated in response to a Health Technology Assessment report, which concluded that drug-eluting stents or balloons did not demonstrate effectiveness in reducing the risk of amputation in patients with severe limb ischaemia.

Added value of this study

This pragmatic, registry-based, randomised trial assessed the effect of drug-coated devices (nearly all of which used paclitaxel as the coating agent) versus uncoated devices in patients with chronic limb-threatening ischaemia (Rutherford categories 4–6) undergoing infrainguinal endovascular revascularisation. The trial found no difference in the rate of ipsilateral major amputations between the two groups. Although treatment with paclitaxel-coated devices was associated with a significant reduction in target vessel reinterventions during the first year, this benefit was not sustained over longer follow-up. All-cause mortality, improvement in disease stage, or disease-specific quality of life did not differ between the two groups.

Implications of all the available evidence

The findings from SWEDEPAD 1 implicate that paclitaxel-coated devices do not reduce the risk of major amputation in patients with peripheral artery disease and chronic limb-threatening ischaemia. This trial is simultaneously published with its parallel study, SWEDEPAD 2, which investigated the effect of paclitaxel-coated devices in patients with intermittent claudication, a less severe form of chronic lower-limb peripheral artery disease. Taken together, the absence of benefit in preventing amputation in chronic limb-threatening ischaemia, the lack of improvement in quality of life in patients with intermittent claudication, and a signal of increased late mortality in patients with intermittent claudication suggest that paclitaxel-coated devices should be used with caution in the management of peripheral artery disease. Given that restenosis prevention remains a key research priority to improve the effectiveness of interventions for patients with peripheral artery disease, further investigation of drug-coated balloons and stents incorporating antiproliferative agents other than paclitaxel is warranted.

Safety of Paclitaxel Devices in PAD: SWEDEPAD

What to make of the registry findings is debatable, but a mortality signal in PAD patients with claudication raised eyebrows.

Paclitaxel-coated versus uncoated devices for infrainguinal endovascular revascularisation in patients with intermittent claudication (SWEDEPAD 2): a multicentre, participant-masked, registry-based, randomised controlled trial

Summary

Background Drug-coated devices are widely used to reduce restenosis after lower limb revascularisation in patients with peripheral artery disease, but their effect on patient-centred outcomes remains unclear. We assessed the effect of paclitaxel-coated devices on clinically important outcomes in patients with intermittent claudication undergoing infrainguinal endovascular revascularisation.

Methods The Swedish Drug-Elution Trial in Peripheral Arterial Disease 2 (SWEDEPAD 2) was a pragmatic, nationwide, multicentre, participant-masked, registry-based, randomised controlled trial conducted at 22 Swedish vascular centres. Adults 18 years or older with intermittent claudication (Rutherford categories 1–3) undergoing infrainguinal endovascular treatment and with no acute thromboembolic disease of the lower limb or infrainguinal aneurysmal disease were eligible for inclusion. Participants were randomly assigned in a 1:1 ratio after successful guidewire crossing to receive either paclitaxel-coated devices or uncoated balloons or stents. Randomisation was stratified by centre and performed using a computer-generated sequence with allocation concealment via a secure, registry-embedded web system. The primary efficacy endpoint was the between-group difference in quality of life at 1 year, assessed with the six-item Vascular Quality of Life Questionnaire (VascuQoL-6), a peripheral artery disease-specific quality of life instrument. The trial is registered at ClinicalTrials.gov (NCT02051088) and the primary analysis is complete; further analyses are ongoing.

Findings Between Nov 5, 2014, and Sept 27, 2023, a total of 1155 patients were enrolled and randomly assigned across 22 vascular centres in Sweden, of whom 1136 (98·3%) had follow-up data available for analysis. 577 patients were randomly assigned to paclitaxel-coated devices and 578 to uncoated devices, of whom 565 (97·9%) and 571 (98·7%) were included in the intention-to-treat population, respectively. The median age in the analysed cohort was 73·0 years (IQR 68·0–78·0). Of the 1136 patients, 612 (53·9%) were male and 524 (46·1%) were female; and 382 (33·7%) of 1135 had preoperative diabetes (one participant in the paclitaxel-coated device group was missing data). Most patients (677 [59·6%] of 1135) presented with severe claudication (Rutherford category 3). Femoropopliteal interventions were performed in 1092 patients (96·1%). At 1 year, VascuQoL-6 scores did not differ between groups (mean difference –0·02 [95% CI –0·66 to 0·62]; p=0·96). All-cause mortality did not differ over a median 7·1 years (IQR 3·9–8·2); hazard ratio (HR) 1·18 (95% CI 0·94–1·48); p=0·16, although 5-year mortality incidence was higher in patients randomly assigned to the paclitaxel-coated devices group (4·57 *vs* 3·28 per 100 person-years; HR 1·47 [95% CI 1·09–1·98]; p=0·010).

Interpretation In patients with Rutherford stage 1–3 peripheral artery disease undergoing infrainguinal endovascular revascularisation, paclitaxel-coated devices did not improve disease-specific quality of life at 1 year compared with uncoated devices. All-cause mortality was not different over the total follow-up time, but significantly higher over 5 years. These findings do not support routine use of paclitaxel-coated devices in this patient population.

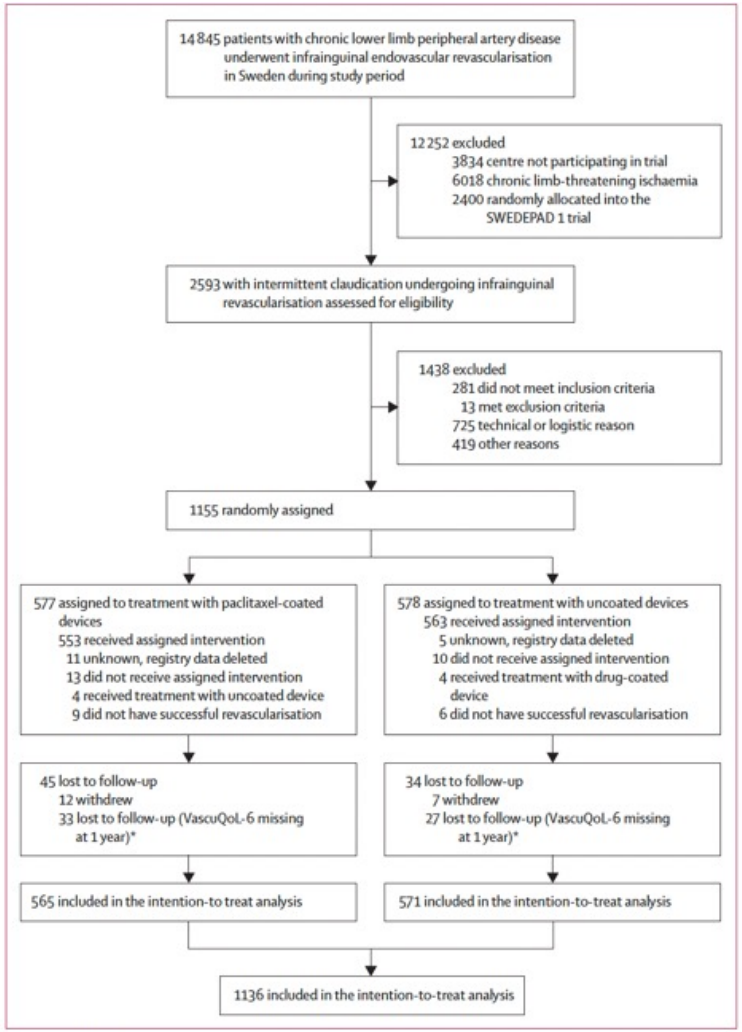


Figure 1: **Trial profile**
Flow of patients, starting from all national infrainguinal endovascular revascularisation procedures for chronic peripheral arterial disease recorded in Swedvasc during the study period to those included in the final trial analysis. Swedvasc captures more than 95% of all vascular procedures performed in Sweden. VascuQoL-6=six-item Vascular Quality of Life Questionnaire. *Lost to follow-up but included in intention-to-treat analysis.

	Treatment with uncoated devices (n=571)	Treatment with paclitaxel-coated devices (n=565)
Age, years	73·0 (68·0–77·0)	73·0 (68·0–78·0)
Sex		
Male	309 (54·1%)	303 (53·6%)
Female	262 (45·9%)	262 (46·4%)
Smoking status		
Never	90 (15·8%)	88/564 (15·6%)
Previous	406 (71·1%)	404/564 (71·6%)
Current	41 (7·2%)	38/564 (6·7%)
Unknown	34 (6·0%)	34/564 (6·0%)
Hypertension	468 (82·0%)	464/564 (82·3%)
Preoperative diabetes, any type	187 (32·7%)	195/564 (34·6%)
Previous cardiovascular disease	214 (37·5%)	211/564 (37·4%)
Pulmonary disease	81 (14·2%)	65/564 (11·5%)
Cerebrovascular disease	60 (10·5%)	58/564 (10·3%)
Medication		
Statins	504 (88·3%)	499/564 (88·5%)
Anticoagulant treatment	95 (16·6%)	87/564 (15·4%)
Platelet inhibitor	487 (85·3%)	481/564 (85·3%)
Paclitaxel-coated device before index procedure	10 (1·8%)	17 (3·0%)
Ankle-brachial index‡	0·6 (0·5–0·7)	0·6 (0·5–0·7)
Renal insufficiency	78/568 (13·7%)	65/560 (11·6%)
Dialysis	3 (0·5%)	4/564 (0·7%)
Vascular segment to be treated		
Femoropopliteal	521 (91·2%)	516 (91·3%)
Infrapopliteal	18 (3·2%)	14 (2·5%)
Femoropopliteal and infrapopliteal	28 (4·9%)	27 (4·8%)
Neither	4 (0·7%)	8 (1·4%)
Planned primary stenting†	117 (20·5%)	96 (17·0%)
Rutherford classification		
Asymptomatic (category 0)	0	0/564
Mild claudication (category 1)	43 (7·5%)	37/564 (6·6%)
Moderate claudication (category 2)	183 (32·0%)	195/564 (34·6%)
Severe claudication (category 3)	345 (60·4%)	332/564 (58·9%)
Ischaemic rest pain (category 4)	0	0
Minor tissue loss (category 5)	0	0
Major tissue loss (category 6)	0	0
TASC II class		
TASC A lesion	116/486 (23·9%)	118/489 (24·1%)
TASC B lesion	189/486 (38·9%)	200/489 (40·9%)
TASC C lesion	122/486 (25·1%)	114/489 (23·3%)
TASC D lesion	59/486 (12·1%)	57/489 (11·7%)
VascuQol-6‡	10·0 (9·0–13·0)	10·0 (9·0–13·0)

Data are median (IQR), n (%), or n/N (%) when there were missing observations. Percentages computed by group. For an expanded baseline characteristics table including patients from the Swedvasc who underwent infrainguinal endovascular revascularisation for Rutherford 1–3 peripheral artery disease during the trial period but were not included in the trial, see appendix (pp 13–14). Swedvasc=National Registry of Vascular Surgery. TASC II=Trans-Atlantic Inter-Society Consensus II. VascuQoL-6=six-item Vascular Quality of Life Questionnaire. *52 and 68 participants for uncoated and paclitaxel-coated groups, respectively, were missing data for their ankle-brachial index score. †As stated by the operator ahead of randomisation. ‡One participant each in the paclitaxel-coated and uncoated device groups were missing VascuQoL-6 data.

Table 1: **Baseline characteristics of SWEDEPAD 2 trial participants**

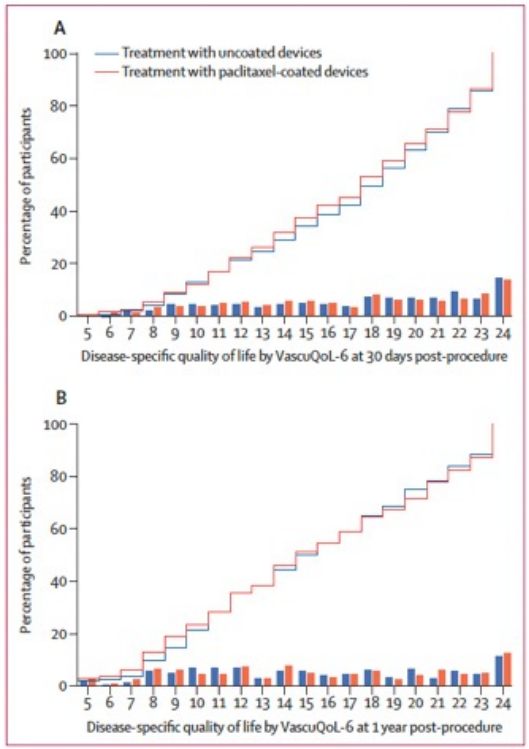


Figure 2: **Distribution of VascuQoL-6 sum scores by treatment group at 30 days (A) and 1 year (B) follow-up in SWEDEPAD 2**
The VascuQoL-6 score ranges from 6 to 24, with higher scores indicating better quality of life. VascuQoL-6=six-item Vascular Quality of Life Questionnaire.

	Treatment with paclitaxel-coated devices (n=565)		Treatment with uncoated devices (n=571)		Mean difference* (95% CI)	p value
	Patients, n (%)	Median (IQR)	Patients, n (%)	Median (IQR)		
1 year	532 (94·2%)	15·0 (11·0 to 21·0)	544 (95·3%)	15·0 (11·0 to 20·2)	−0·02 (−0·66 to 0·62)	0·96
30 days	500 (88·5%)	18·0 (13·0 to 22·0)	505 (88·4%)	19·0 (14·0 to 22·0)	−0·26 (−0·86 to 0·35)	0·41

VascuQoL-6=six-item Vascular Quality of Life Questionnaire. *All models are adjusted for age, sex, vascular segment to be treated, planned revascularisation technique, centre, and baseline score.

Table 2: **Changes in the primary outcome by group at 30 days and 1 year of follow-up**

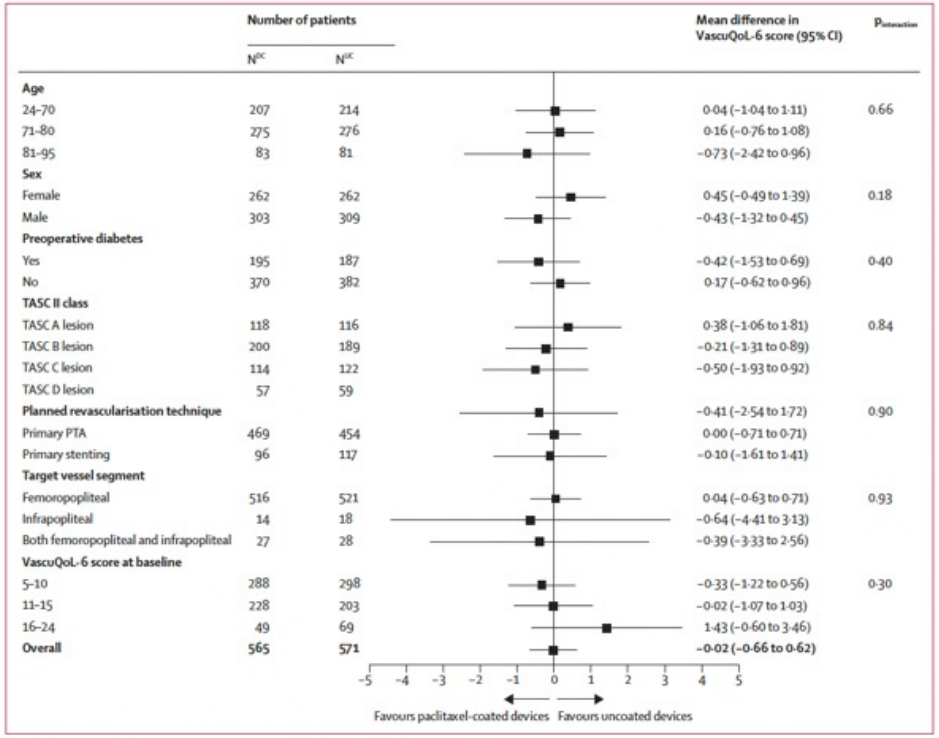


Figure 3: **Forest plot of mean difference in VascuQoL-6 score at 1 year by subgroup**
PTA=percutaneous transluminal angioplasty. TASC II=Trans-Atlantic Inter-Society Consensus II. VascuQoL-6=six-item Vascular Quality of Life Questionnaire. DC=paclitaxel-coated devices. UC=uncoated devices.

	Treatment with paclitaxel-coated devices (n=565)		Treatment with uncoated devices (n=571)		Hazard ratio* (95% CI)	p value
	Events, n	Event rate, percentage per 100 person-years	Events, n	Event rate, percentage per 100 person-years		
Ipsilateral amputation						
Up to 5 years	16	0·71 (0·41–1·16)	11	0·47 (0·24–0·85)	1·58 (0·73–3·45)	0·24
Up to 1 year	8	1·44 (0·62–2·83)	3	0·53 (0·11–1·55)	3·46 (0·86–13·9)	0·062
Complete follow-up	20	0·66 (0·41–1·02)	17	0·54 (0·32–0·87)	1·28 (0·66–2·47)	0·46
Death						
Up to 5 years	104	4·57 (3·73–5·54)	77	3·28 (2·59–4·10)	1·47 (1·09–1·98)	0·010
Up to 1 year	15	2·68 (1·50–4·42)	12	2·11 (1·09–3·69)	1·27 (0·57–2·81)	0·56
Complete follow-up	154	5·01 (4·25–5·87)	146	4·61 (3·89–5·42)	1·18 (0·94–1·48)	0·16
Ipsilateral amputation or death						
Up to 5 years	112	4·99 (4·11–6·00)	85	3·66 (2·93–4·53)	1·44 (1·08–1·92)	0·011
Up to 1 year	21	3·77 (2·34–5·77)	14	2·47 (1·35–4·15)	1·58 (0·79–3·17)	0·19
Complete follow-up	163	5·41 (4·61–6·30)	152	4·87 (4·12–5·70)	1·19 (0·95–1·48)	0·13
Target vessel reintervention						
Up to 5 years	145	7·83 (6·60–9·21)	151	8·06 (6·83–9·45)	0·96 (0·76–1·20)	0·71
Up to 1 year	68	12·98 (10·08–16·45)	79	15·09 (11·95–18·80)	0·86 (0·62–1·19)	0·37
Complete follow-up	166	7·00 (5·97–8·15)	165	6·80 (5·80–7·92)	1·01 (0·81–1·25)	0·93
Ipsilateral reintervention						
Up to 5 years	149	8·12 (6·87–9·53)	155	8·36 (7·09–9·78)	0·96 (0·77–1·21)	0·74
Up to 1 year	73	14·01 (10·98–17·61)	82	15·72 (12·50–19·51)	0·90 (0·66–1·24)	0·53
Complete follow-up	171	7·27 (6·22–8·44)	170	7·08 (6·06–8·23)	1·01 (0·82–1·25)	0·90

*All models are adjusted for age, sex, vascular segment to be treated, planned revascularisation technique, and centre.

Table 3: **Overview of secondary time-to-event and prespecified timepoint outcomes at 30 days and 1 year in the SWEDEPAD 2 trial**

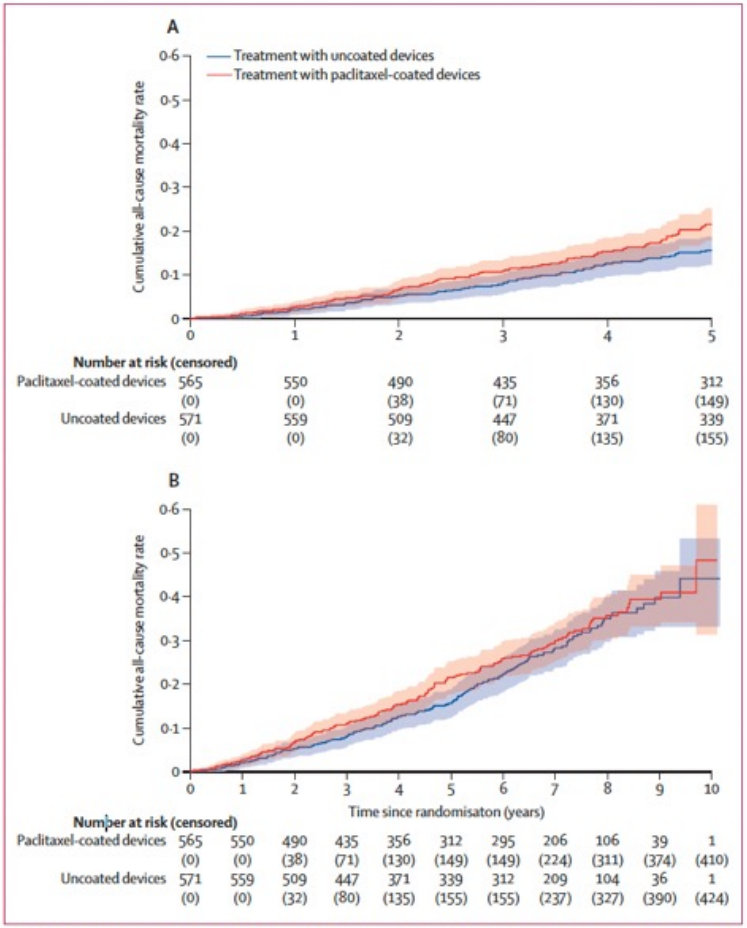


Figure 4: **All-cause mortality in the SWEDEPAD 2 trial over 5 years (A) and over the entire available follow-up period (B)**

Research in context

Evidence before this study

Drug-coated balloons and stents, particularly those coated with paclitaxel, are widely used in the endovascular treatment of peripheral artery disease to reduce restenosis and target lesion revascularisation, with the aim of decreasing the need for repeated procedures due to limb symptom recurrence. However, most previous trials have focused on non-complex vascular lesions and have used surrogate angiographic or anatomical endpoints—such as vessel patency, late lumen loss, and binary restenosis—rather than patient-centred outcomes. To support the conduct and reporting of this trial, we conducted systematic literature searches in PubMed, Embase, the Cochrane Library, and several Health Technology Assessment databases. Systematic reviews, controlled studies, and case-series on adverse events published in English, Swedish, Norwegian, and Danish were considered for inclusion. Searches were restricted to publications between Jan 1, 2000, and May 14, 2013, with two updated searches on April 8, 2014, and Nov 19, 2014. The search resulted in 34 records included in our trial synthesis. This study was initiated in response to a Health Technology Assessment report, which included data from nearly 3000 patients, and concluded that drug-eluting stents or balloons did not demonstrate a consistent benefit over uncoated devices in improving patient-related outcomes for the treatment of lower limb atherosclerotic disease. Additionally, concerns have been raised regarding a potential late mortality signal associated with paclitaxel-coated devices when used during lower limb revascularisation for peripheral artery disease. This signal was initially observed in patients with Rutherford categories 1–3 peripheral artery disease (intermittent claudication), but, as the evidence base has expanded, subsequent findings have been mixed, and the association remains inconclusive.

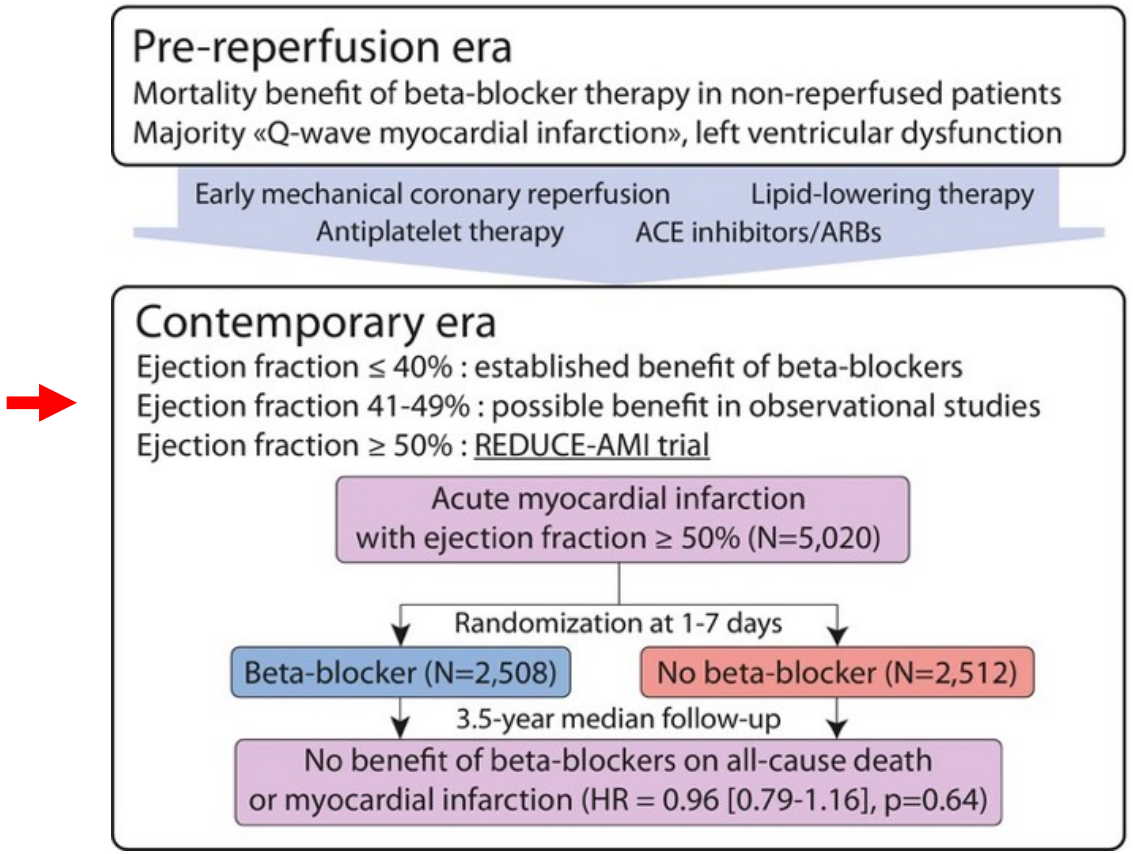
Added value of this study

To our knowledge, the Swedish Drug-Elution Trial in Peripheral Arterial Disease (SWEDEPAD 2) is the largest randomised trial to date assessing the effect of drug-coated devices on disease-specific quality of life in patients with Rutherford categories 1–3 peripheral artery disease (ie, those with symptoms of intermittent claudication) undergoing infrainguinal endovascular revascularisation. Using a pragmatic, registry-based, randomised design across 22 vascular centres in Sweden, the trial found no difference in peripheral artery disease-specific quality of life at 12 months between patients treated with paclitaxel-coated devices versus uncoated devices. Furthermore, no significant differences were observed in reintervention or major amputation rates, but a significantly higher incidence of all-cause mortality was observed in the paclitaxel-coated group up to 5 years, although not over the total follow-up period.

Implications of all the available evidence

These findings suggest that paclitaxel-coated devices offer no additional benefit in improving quality of life for patients with peripheral artery disease and symptoms of intermittent claudication, and were associated with increased mortality at 5 years, though not at 10 years. Although paclitaxel-coated devices might still be indicated for carefully selected patients with Rutherford stage 1–3 peripheral artery disease, the contributions of this trial to totality of evidence do not support their routine use. Taken together with the results of the parallel SWEDEPAD 1 trial, published simultaneously in *The Lancet*, which show that paclitaxel-coated devices do not improve limb salvage rates, clinicians should carefully weigh the potential risks and benefits when considering these devices for endovascular revascularisation in patients with peripheral artery disease. Future peripheral artery disease research should prioritise patient-centred outcomes when testing new revascularisation strategies and devices used during lower limb revascularisation procedures. Furthermore, given that restenosis prevention remains a key research priority to improve the durability of interventions in this patient population, drug-coated balloons and drug-eluting stents incorporating antiproliferative agents other than paclitaxel warrant investigation in future trials.

Beta-blockers are recommended after a myocardial infarction (MI) with reduced ejection fraction (EF), as they improve outcomes like death, new MI, and heart failure, though the benefit in mildly reduced EF patients is more recently confirmed by meta-analysis of trials. Guidelines for patients with preserved EF without heart failure are less certain and are being re-evaluated by new research that questions their long-term necessity.



An ejection fraction (EF) of 41% to 49% is generally considered mildly reduced. While a normal EF is typically 50% or higher, this range of 41% to 49% can indicate potential heart damage or an early risk of developing heart failure, though not always the presence of full-blown heart failure.

β blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data meta-analysis of randomised controlled trials

Summary

Background The effects of β-blocker therapy on clinical outcomes in patients with myocardial infarction and mildly reduced (40–49%) left ventricular ejection fraction (LVEF) are largely unknown. Four recently conducted randomised trials tested the efficacy of β blockers after a recent myocardial infarction in patients without reduced LVEF (LVEF ≥40%). However, none were individually powered to assess these effects in the subgroup of patients with mildly reduced LVEF. We aimed to assess the efficacy of β blockers in patients with myocardial infarction and mildly reduced LVEF during the index hospitalisation.

Methods We conducted an individual patient-level meta-analysis of patients with mildly reduced LVEF and no history or signs of heart failure from four recent clinical trials. These studies were included because they were randomised controlled trials testing long-term effects (median follow-up >1 year) of oral β-blocker therapy in patients who recently had a myocardial infarction (randomisation within 14 days) and had mildly reduced LVEF. No further studies were found in a systematic review (Jan 1, 2020 to June 26, 2025). A one-stage, fixed-effects, Cox proportional hazards regression model was used to assess the treatment effect of β blockers on the predefined primary composite endpoint of all-cause death, new myocardial infarction, or heart failure. All endpoints were independently adjudicated. This meta-analysis was registered with PROSPERO (CRD420251023480).

Findings 1885 patients with myocardial infarction and mildly reduced LVEF were included in the meta-analysis: 979 from the REBOOT trial, 422 from the BETAMI trial, 430 from the DANBLOCK trial, and 54 from the CAPITAL-RCT trial. Overall, 991 patients were assigned to β blockers and 894 to control (no β blockers). The primary composite endpoint occurred in 106 patients (32·6 events per 1000 patient-years) in the β-blocker group and 129 patients (43·0 per 1000 patient-years) in the no β-blocker group (hazard ratio 0·75 [95% CI 0·58–0·97]; p=0·031). No heterogeneity between the trials (trial-by-treatment $p_{interaction}$=0·95) or between countries of enrolment was observed ($p_{interaction}$=0·98).

Interpretation In patients with acute myocardial infarction with mildly reduced LVEF without history or clinical signs of heart failure, β-blocker therapy was associated with a reduction in the composite of all-cause death, new myocardial infarction, or heart failure. These results extend the known benefits of these agents in patients with myocardial infarction with reduced LVEF to the subgroup with mildly reduced LVEF.

Demographics		
Median age, years	63 (55–71)	62 (55–71)
Sex		
Male	791/991 (80%)	735/894 (82%)
Female	200/991 (20%)	159/894 (18%)
Country		
Spain	327/991 (33%)	285/894 (32%)
Italy	188/991 (19%)	179/894 (20%)
Denmark	226/991 (23%)	204/894 (23%)
Norway	220/991 (22%)	202/894 (23%)
Japan	30/991 (3%)	24/894 (3%)
Medical history		
Current smoker	360/887 (41%)	336/812 (41%)
Hypertension	467/990 (47%)	430/892 (48%)
Diabetes	191/989 (19%)	178/891 (20%)
Dyslipidaemia	380/991 (38%)	346/892 (39%)
Previous myocardial infarction*†	80/740 (11%)	69/666 (10%)
Stroke*	31/961 (3%)	26/868 (3%)
Atrial fibrillation*	29/961 (3%)	25/868 (3%)
Chronic obstructive pulmonary disease*	62/961 (6%)	39/869 (4%)
Index myocardial infarction		
STEMI	674/991 (68%)	605/894 (68%)
Median LVEF†	45·0 (45·0–47·5)	45·0 (45·0–47·5)
In-hospital treatment		
Percutaneous coronary intervention	935/988 (95%)	858/892 (96%)
Coronary artery bypass grafting	8/931 (1%)	6/852 (1%)
No revascularisation	53/991 (5%)	29/894 (3%)
Blood samples		
Mean creatinine concentration, µmol/L	0·9 (0·3)	1·0 (0·6)
Medication at discharge		
Aspirin	952/982 (97%)	869/889 (98%)
$P2Y_{12}$ receptor blocker	968/988 (98%)	861/893 (96%)
Anticoagulants	65/987 (7%)	56/892 (6%)
ACE inhibitors and ARB	668/987 (68%)	606/892 (68%)
Statins	959/987 (97%)	869/892 (97%)
β blocker therapy		
Previous β blocker therapy	105/988 (11%)	100/889 (11%)
Type of β blocker at randomisation		
Metoprolol	485/984 (49%)	..
Bisoprolol	430/984 (44%)	..
Carvedilol	46/984 (5%)	..
Other	23/984 (2%)	..

Data are median (IQR), n/N (%), or mean (SD). ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. LVEF=left ventricular ejection fraction. STEMI=ST-segment elevation myocardial infarction. *Not available in the CAPITAL-RCT trial. †Not available in the BETAMI trial.

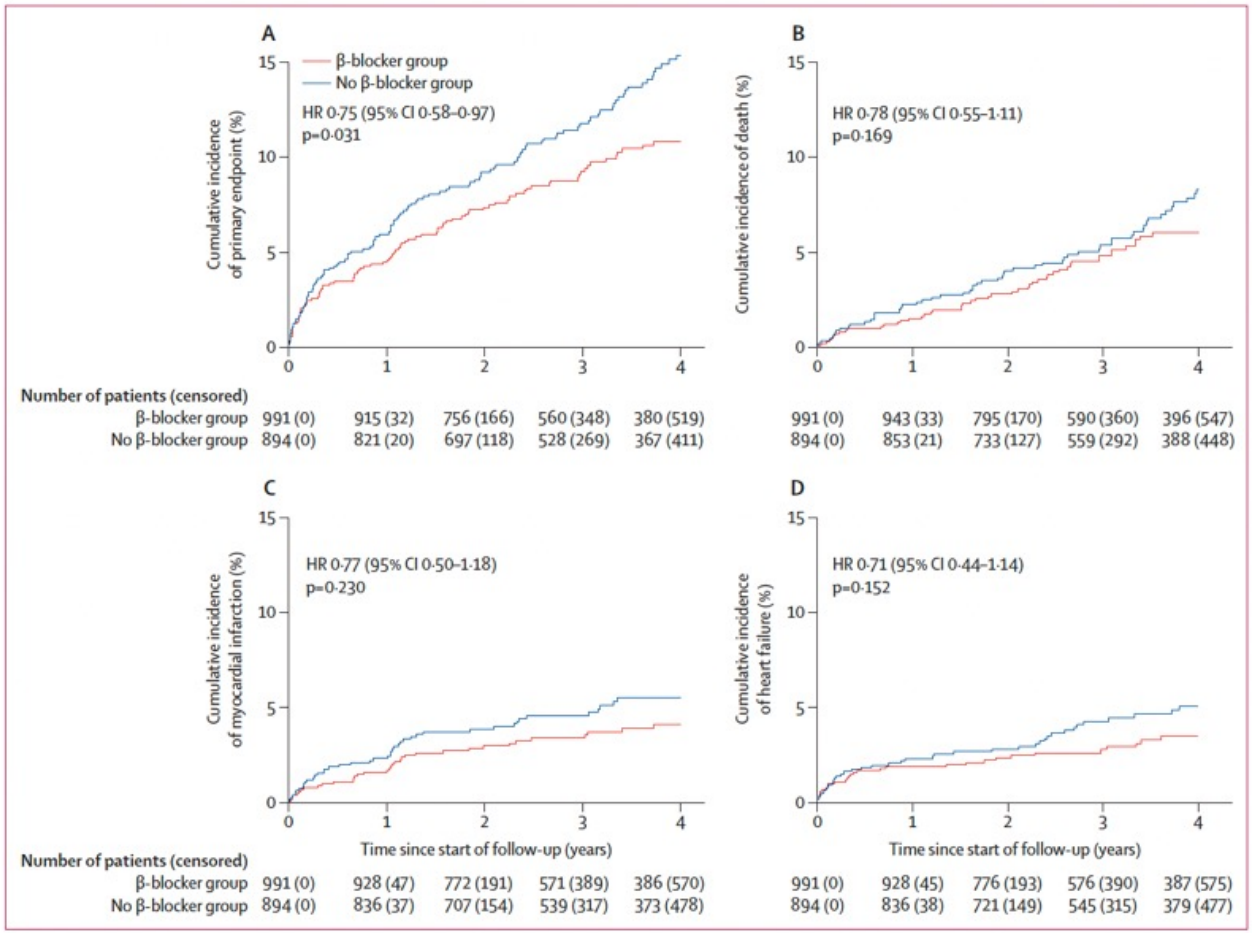


Figure 1: **Cumulative incidence of the primary endpoint and its individual components**
(A) Primary endpoint (a composite of all-cause death, new myocardial infarction, or heart failure). (B) All-cause death. (C) New myocardial infarction. (D) Heart failure. HR=hazard ratio.

	Patients with event, n (%)		Hazard ratio (95% CI)	p value
	β-blocker group (n=991)	No β-blocker group (n=991)		
Primary endpoint*	106 (11%)	129 (14%)	0·75 (0·58–0·97)	0·031
All-cause death	58 (6%)	69 (8%)	0·78 (0·55–1·11)	0·169
Cardiac death†	14 (2%)	23 (3%)	0·55 (0·28–1·06)	0·076
Myocardial infarction	39 (4%)	46 (5%)	0·77 (0·50- 1·18)	0·230
Heart failure	30 (3%)	39 (4%)	0·71 (0·44–1·14)	0·152
Unplanned coronary revascularisation	35 (4%)	38 (4%)	0·83 (0·52–1·31)	0·420
Malignant ventricular arrhythmia‡	9 (1%)	5 (1%)	1·64 (0·55–4·89)	0·375
Hospital admission for stroke	13 (1%)	7 (1%)	1·70 (0·68–4·25)	0·260
Second-degree or third-degree atrioventricular block§	12 (1%)	11 (1%)	1·00 (0·44–2·27)	0·984

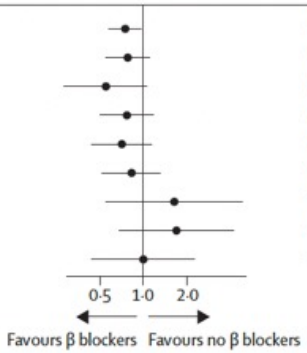


Figure 3: **Effect estimates for key secondary and safety endpoints**

*Composite of all-cause death, new myocardial infarction, or heart failure. †Data were available for 1463 patients (771 in the β-blocker group, and 692 in the no β-blocker group; missing for the 422 patients from Norway). ‡Composite of ventricular tachycardia, ventricular fibrillation, or resuscitated cardiac arrest. §Data were available for 1831 patients (961 in the β-blocker group, and 870 in the no β-blocker group); all data were missing for the 54 patients from Japan.

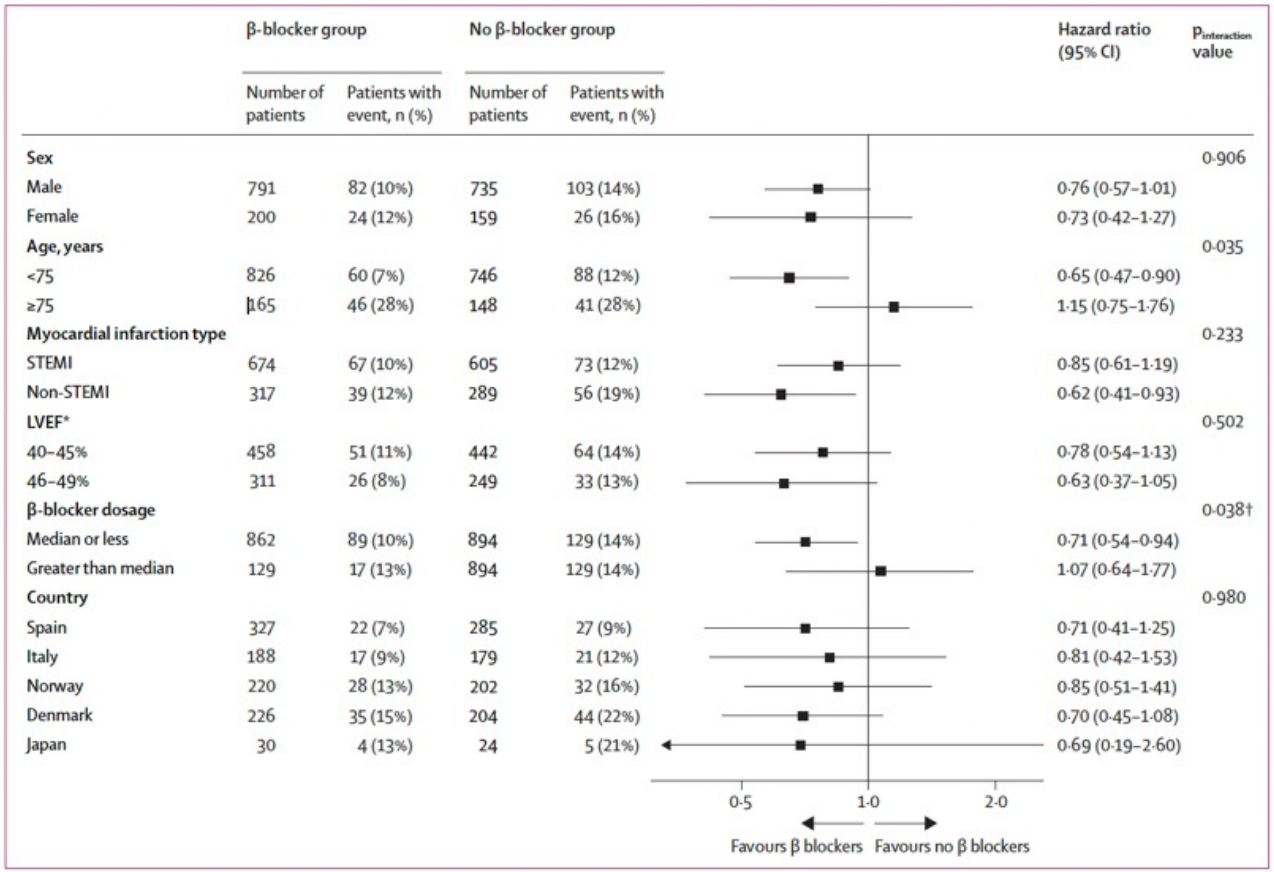


Figure 4: **Prespecified subgroup analyses of the primary endpoint**

LVEF=left ventricular ejection fraction. STEMI=ST-segment elevation myocardial infarction. *Data were missing for the 422 patients from Norway and three from Denmark. †As the control group could not be subgrouped by dosage, the p value is from a Wald test of equality of three groups (no β-blocker group *vs* β-blocker subgroup with median dose or less *vs* β-blocker subgroup with higher than median dose); for direct comparison of median dose or less versus above median dose, p=0·21.

Research in context

Evidence before this study

While evidence strongly supports β-blocker therapy after myocardial infarction in patients with reduced left ventricular ejection fraction (LVEF; ≤40%), the benefit in those with LVEF greater than 40% and no heart failure remains uncertain. Current recommendations for this group—class IIa from the European Society of Cardiology and class I from the American College of Cardiology and American Heart Association—are based on older trials conducted before the widespread adoption of contemporary management. Four recent randomised trials in patients with LVEF above 40% yielded different results (three showed no benefits of β-blockers and one did). These studies included a proportion of patients with mildly reduced LVEF (40–49%), although they were not individually powered to detect differences in treatment effect. We conducted a systematic review of MEDLINE via PubMed to identify randomised controlled trials published since Jan 1, 2000, with a median follow-up of more than 1 year in patients with a recent ST-segment elevation myocardial infarction (STEMI) or non-STEMI (randomisation within 14 days) and treated with β blockers, and including patients with mildly reduced LVEF. The search strategy yielded four trials: REBOOT, BETAMI, DANBLOCK, and CAPITAL-RCT. There were no previous meta-analysis using randomised data on this topic.

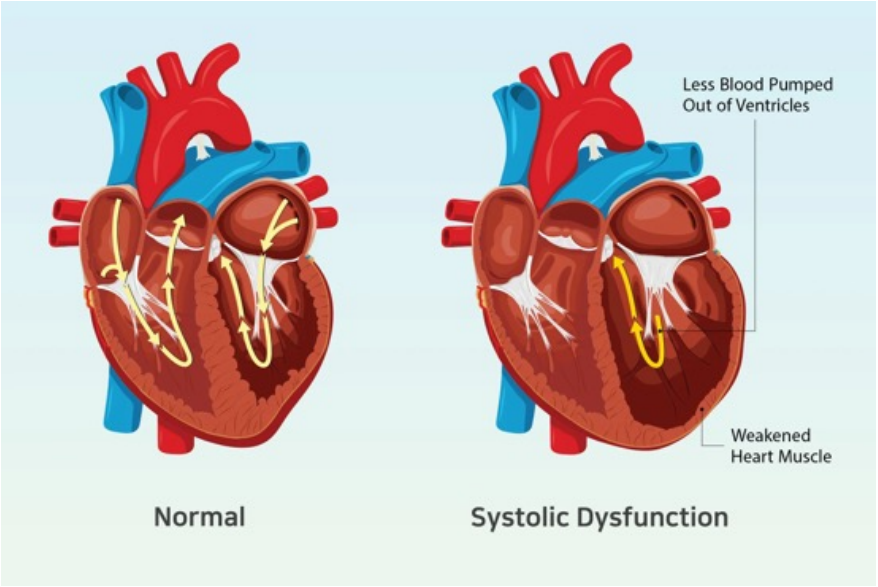
Added value of this study

This collaborative individual patient data meta-analysis is the only study based entirely on randomised trials specifically addressing the effect of β blockers in patients with myocardial infarction and mildly reduced LVEF (40–49%). The results of this analysis of 1885 patients indicate that this subgroup benefits from a routine use of β blockers, with use of β blockers associated with a significant 25% reduction in the incidence of the primary endpoint, a composite of all-cause death, new myocardial infarction, or heart failure. The three individual components of the primary endpoint, as well as cardiac death, showed a similar pattern of reduced incidence, although without reaching statistical significance. No heterogeneity of treatment effect was observed across the four trials nor across the five countries that enrolled patients (Spain, Italy, Norway, Denmark, and Japan).

Implications of all the available evidence

This individual patient data meta-analysis expands the current evidence on the benefits of initiating β blockers in patients with recent myocardial infarction with reduced LVEF (≤40%) by showing that those with mildly reduced LVEF (40–49%) also derive clinical benefit. Further research should focus on patients with preserved LVEF (≥50%).

Die Herzinsuffizienz oder Herzschwäche ist die krankhafte Unfähigkeit des Herzens, das vom Körper benötigte Herzzeitvolumen ohne Anstieg des enddiastolischen Drucks zu fördern. Die „Pumpschwäche“ äußert sich in reduzierter körperlicher und geistiger Leistungsfähigkeit, man spricht auch von Vorwärtsversagen.



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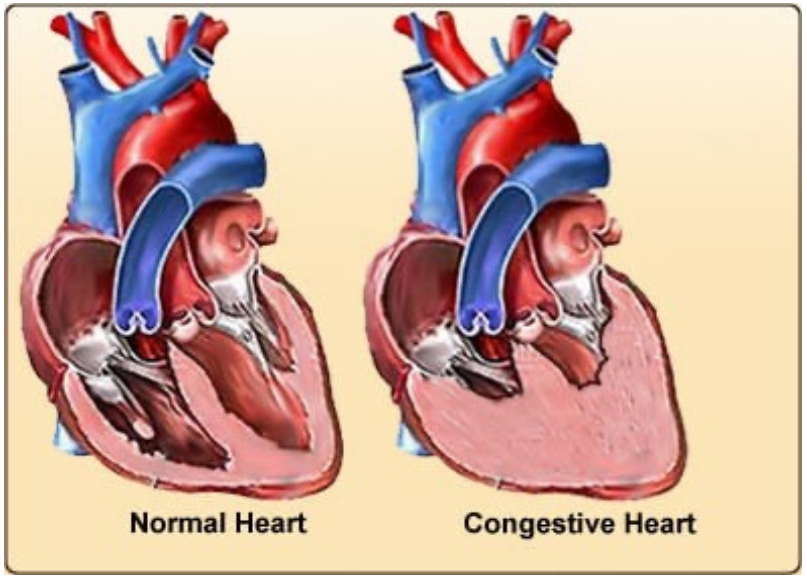

HFpEF

Heart Failure Prevention 1

Prioritising the primary prevention of heart failure

Heart failure remains one of the 21st century's greatest unmet clinical and public health challenges. Heart failure is a highly prevalent chronic condition that affects approximately 55 million people worldwide. Although heart failure can be prevented, the global burden of this condition continues to grow, fuelled by an ageing population, improved survival after myocardial infarction, and increasing prevalence of metabolic and kidney disease. Public health efforts for cardiovascular disease prevention to date have primarily targeted coronary heart disease. Despite overlapping prevention targets for coronary heart disease and heart failure, prevention of the latter requires tailored approaches to target its unique pathophysiology and heterogeneous subtypes. This *Lancet* Series serves as a call to action for clinicians, health systems, and governments to prioritise the primary prevention of heart failure. Herein, we review the epidemiology, pathophysiology, and risk factors of heart failure and propose a comprehensive framework for prevention of this condition that includes screening to assess risk of this condition (eg, multivariable risk equations) and detection of pre-heart failure (eg, biomarkers). Successfully reducing the burden of heart failure will require concerted efforts to define clinical workflows across the life course, scalable implementation strategies, and increased public awareness of this pressing crisis.

Panel 1: **Cardiovascular-kidney-metabolic syndrome (CKM): summary of a novel staging construct introduced by the American Heart Association**

Stage 0

- No metabolic risk factors, chronic kidney disease (CKD), or evidence of subclinical or clinical cardiovascular disease (CVD)

Stage 1—excess or dysfunctional adiposity*

- Identified by either an elevated BMI (≥25 kg/m^2), abdominal obesity (waist circumference ≥88 cm in women or ≥102 cm in men), or dysglycaemia (impaired glucose tolerance or prediabetes or gestational diabetes), without other CKM risk factors

Stage 2—Metabolic risk factors and CKD

- Stage defined as the presence of metabolic risk factors (ie, diabetes or hypertension), moderate-to-high-risk CKD, or both
  - Includes non-metabolic causes of hypertension, such as primary aldosteronism, metabolic syndrome, hypertriglyceridemia (serum triglyceride concentrations ≥135 mg/dL)
  - Moderate-to-high-risk CKD defined according to Kidney Disease: Improving Global Outcomes risk criteria as: eGFR ≥60 mL/min/1·73 m^2 and urine albumin-to-creatinine ratio (UACR) ≥30 mg/g OR eGFR ≥45 to <60 mL/min/1·73 m^2 and UACR <300 mg/g OR eGFR ≥30 and <45 mL/min/1·73 m^2 and UACR <30 mg/g
  - Includes non-metabolic causes of CKD, such as primary glomerulopathies

Stage 3—subclinical CVD

- Defined as either: the presence of subclinical CVD among individuals with stage 1 or 2 criteria; or the presence of CVD risk equivalents
  - Subclinical atherosclerotic cardiovascular disease (ASCVD) indicated by imaging evidence of coronary artery calcification or non-obstructive atherosclerosis by coronary angiography
  - Subclinical heart failure indicated by elevated cardiac biomarkers: N-terminal prohormone of B-type natriuretic peptide ≥125 pg/mL, high-sensitivity cardiac troponin (hs-cTnT) ≥14 ng/L for women and ≥22 ng/L for men; hs-cTnI ≥10 ng/L for women and ≥12 ng/L for men, imaging (eg, echocardiography) evidence of abnormal cardiac structure or function
- CVD risk equivalents (ie, high absolute risk of CVD)
  - Very high risk CKD: eGFR <60 mL/min/1·73 m^2 and UACR ≥300 mg/g OR eGFR ≥30 to <45 mL/min/1·73 m^2 and UACR ≥30 mg/g OR eGFR <30 mL/min/1·73 m^2
  - High predicted 10-year CVD risk (with the use of CKM risk algorithm: PREVENT†)

Stage 4—clinical CVD

- Defined as established CVD among individuals with stage 1 or 2 criteria
  - Clinical CVD includes health failure and other subtypes: coronary heart disease, stroke, peripheral artery disease, or atrial fibrillation
- Further subdivided into stage 4a (without kidney failure) and stage 4b (with kidney failure)

*Might consider lower thresholds in Asian populations for stage 1 to define excess or dysfunctional adiposity (ie, ≥23 kg/m^2 or waist circumference ≥80 cm in women or ≥90 cm in men). †Validated Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) risk model introduced by American Heart Association for prediction of 10-year and 30-year risk of ASCVD, heart failure, and total CVD (ASCVD and health failure). Base model includes sex, age, total cholesterol, HDL cholesterol, systolic blood pressure, BMI, eGFR, diabetes status, current smoking, use of blood pressure-lowering medications, and use of lipid-lowering medications. The expanded model includes UACR, HbA_{1c}, and zip code.

COR	LOE	Recommendations
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure		
I	A	Treatment of hypertension is recommended to prevent or delay the onset of heart failure, and to prevent heart failure hospitalisations
I	A	Treatment with statins is recommended in patients at high risk of CVD or with CVD to prevent or delay the onset of heart failure, and to prevent heart failure hospitalisations
I	A	SGLT2 inhibitors (ie, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, or sotagliflozin) are recommended in patients with diabetes who are at high risk of CVD or with CVD to prevent heart failure hospitalisations
I	C	Counselling against sedentary habits, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of heart failure
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure		
I	A	In patients with type 2 diabetes and CKD, SGLT2 inhibitors are recommended to reduce the risk of heart failure hospitalisation or CV disease death
I	A	In patients with type 2 diabetes and CKD, fineronone is recommended to reduce the risk of heart failure hospitalisation
2022 AHA/ACC/HFSA guideline for the management of heart failure		
1	A	In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic heart failure
1	A	In patients with type 2 diabetes and either established cardiovascular disease or at high cardiovascular risk, SGLT2i should be used to prevent hospitalisations for heart failure
1	B - NR	In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of heart failure
2a	B - R	For patients at risk of developing heart failure, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimising GDMT, can be useful to prevent the development of left ventricle dysfunction (systolic or diastolic) or new-onset heart failure
2a	B - NR	In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident heart failure

ACC=American College of Cardiology. AHA=American Heart Association. CKD=chronic kidney disease. CVD=cardiovascular disease. ESC=European Society of Cardiology. GDMT=guideline-directed medical therapy. COR=class of recommendation. HFSA=Heart Failure Society of America. LOE=level of evidence.

Table 1: **Summary of ESC and US guideline recommendations for the primary prevention of heart failure**

	At-risk for heart failure (stage A)	Pre-heart failure (stage B heart failure or subclinical disease defined as either structural, functional, or elevated biomarkers)
Signs and symptoms	Absence of signs or symptoms of heart failure	Absence of signs or symptoms of heart failure
Risk factors	Hypertension, diabetes, obesity, atherosclerotic cardiovascular disease, known exposure to cardiotoxins, a positive family history of cardiomyopathy, or genetic cardiomyopathy	Hypertension, diabetes, obesity, atherosclerotic cardiovascular disease known exposure to cardiotoxins, a positive family history of cardiomyopathy, or genetic cardiomyopathy
Structural or functional abnormalities	No	Structural heart disease, which includes: LAVI ≥29 mL/m^2, LVMI >116 per 95 g/m^2, RWT >0·42, and LV wall thickness ≥12 mm Ventricular systolic dysfunction, which includes suggested thresholds of: LVEF <50%, and GLS <16%. Ventricular diastolic dysfunction, which includes suggested thresholds of: septal e' <7 cm/s, lateral e' <10 cm/s, and TR velocity >2·8 m/s
Evidence of increased filling pressures	No	Evidence of increased filling pressures on non-invasive imaging, which includes: estimated PA systolic pressure >35 mm Hg, average E/e' ≥15
Cardiac biomarkers*	No	Elevated natriuretic peptides: BNP ≥ 35 pg/mL, NT-proBNP: ≥ 125 pg/mL; and cardiac troponins: persistently elevated >99th percentile in a normal reference population

Table adapted from: Bozkurt B and colleagues.[21] BNP=B-type natriuretic peptide. LV=left ventricle. NT-proBNP=N-terminal proBNP. GLS=global longitudinal strain. LAVI=left atrial volume index. LVEF=left ventricular ejection fraction. LVMI=left ventricular mass index. PA=pulmonary artery. RWT=relative wall thickness. TR=tricuspid regurgitation. *Risk factors with elevated concentrations of cardiac biomarkers in the absence of a competing diagnosis resulting in biomarker elevations such as acute coronary syndrome, pulmonary embolus, or myopericarditis defines stage B heart failure. The specificity of these cardiac biomarker thresholds might be lower in those who are older or have chronic kidney disease.

Table 2: **Defining asymptomatic heart failure stages according to the universal definition of heart failure**

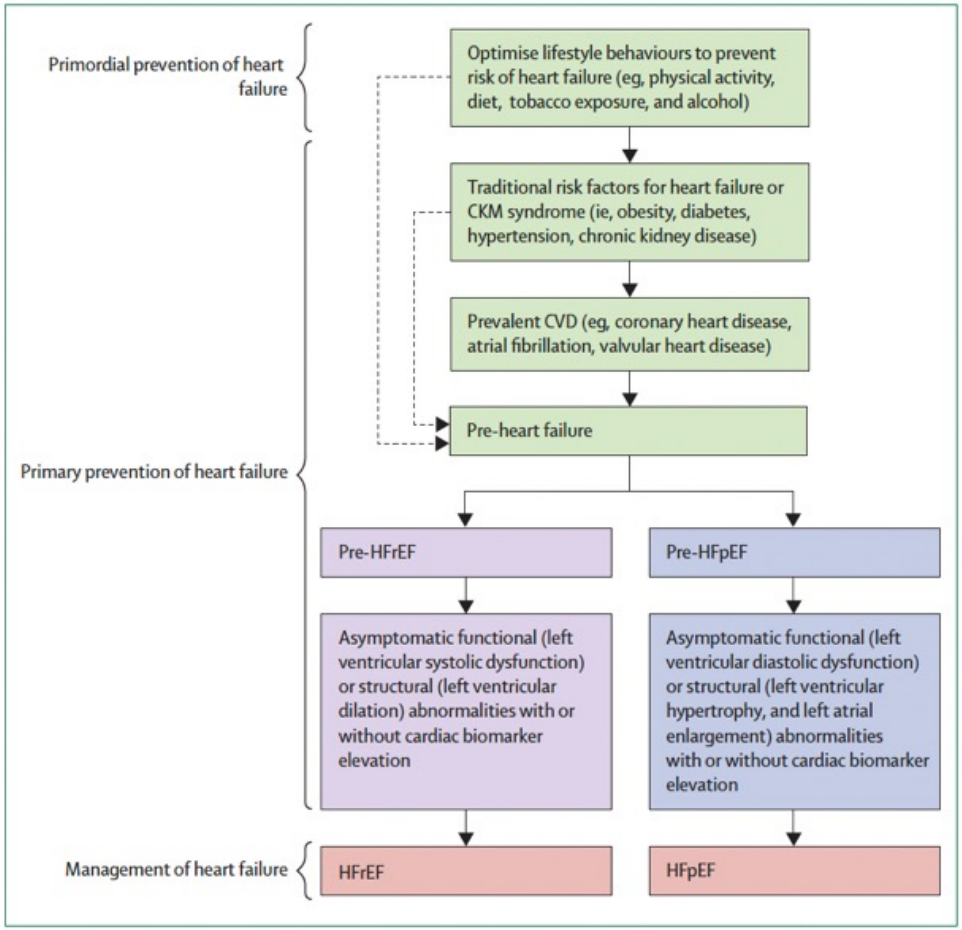

Figure 1: **Direct and indirect pathways to incident heart failure and its subtypes: opportunities for tailored prevention strategies**

CKM=cardiovascular-kidney-metabolic. CVD=cardiovascular disease.

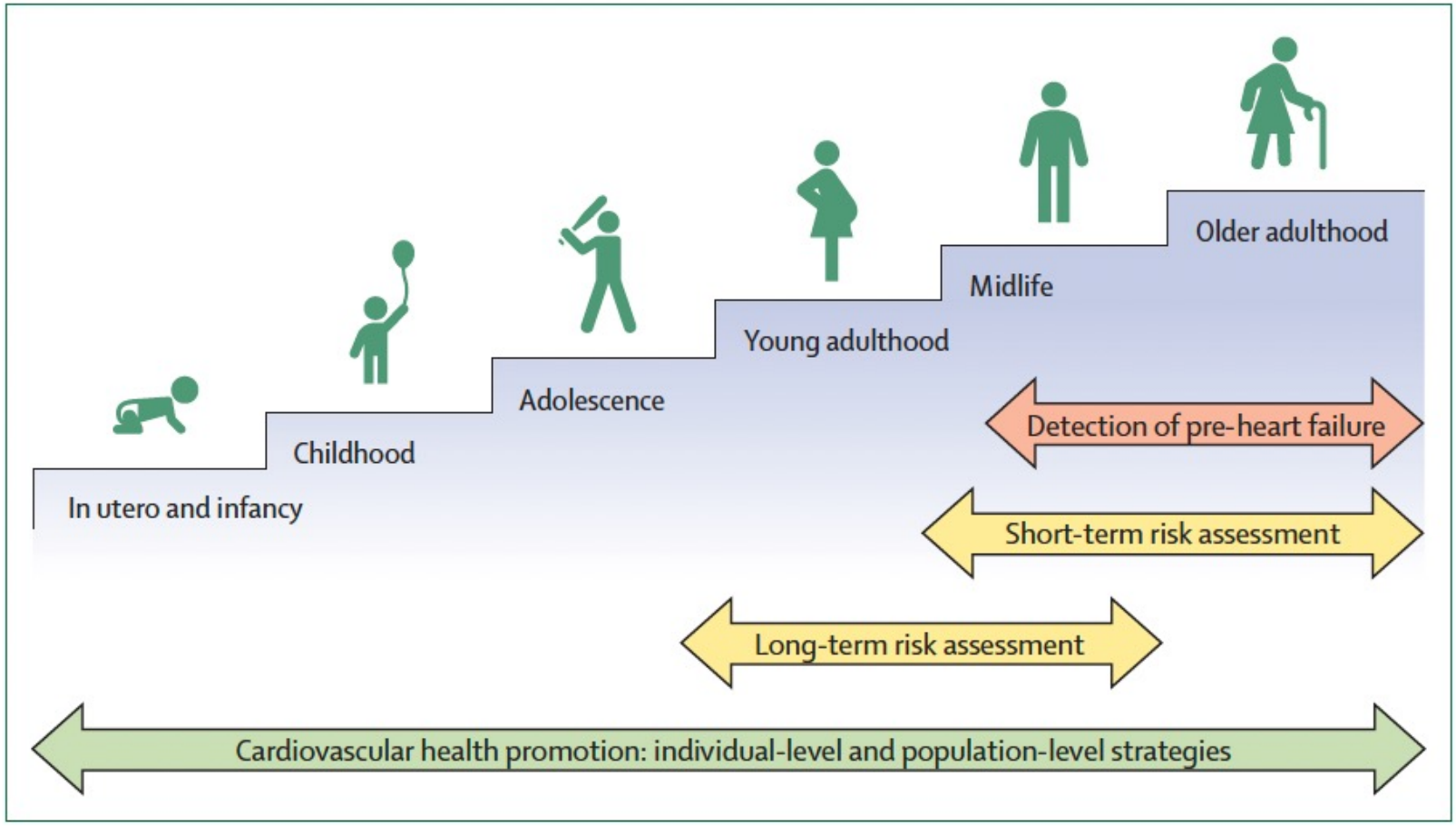

Figure 2: **Life-course perspective to heart failure prevention**

Panel 2: **Current controversies and future directions to operationalise screening and detection for at-risk and pre-heart failure**

Who to screen for prevention of heart failure

- There is no current consensus by national societies or in guidelines on whether universal or population-wide screening with biomarkers or echocardiography is warranted for prevention of heart failure
- Evidence is still evolving for a risk-based or targeted approaches that use sequential screening, such as biomarker testing followed by imaging with echocardiography or both in individuals at increased risk based on predicted risk scores, age, or comorbidities
- Country-specific or region-specific policy frameworks are needed to evaluate and support value-based screening and equitable delivery of preventive care

What to screen for prevention of heart failure

- The role of routine or targeted blood-based biomarker testing and which biomarkers to test for (eg, natriuretic peptides or high sensitivity cardiac troponin or both or other) remains uncertain
- What is the role of screening for impaired kidney function in heart failure prevention with urinary albumin-to-creatinine ratio as a potent risk marker of kidney and heart failure?
- The applicability and cost-effectiveness of point-of-care or standard echocardiography requires further study with consideration for cardiac magnetic resonance imaging when quality of echocardiography is poor
- Whether the use of artificial intelligence for the acquisition of echocardiography by non-trained sonographers or for the interpretation of echocardiography images might be useful, especially in resource-limited settings, is uncertain
- Genomic screening for rare variants or polygenic risk scores might have future application in precision-based approaches to identify inherited risk or predisposition for heart failure who might represent a risk-enriched subset for further screening
- Pragmatic trials are needed to assess the effectiveness of sequential or multimodal screening strategies to reduce incident heart failure
- Partnerships with key stakeholders from primary care and community organisations are essential to design and implement scalable screening and prevention strategies within real-world health-care delivery systems

How to define at-risk or pre-heart failure for prevention

- There is no standardised threshold to define at-risk individuals, which might include predicted risk scores, age, and comorbidities
- The risk of overdiagnosis and medicalisation must be carefully weighted when applying the universal definition of heart failure framework to define at-risk or pre-heart failure to asymptomatic individuals
- Sex-specific definitions for abnormal cardiac biomarkers or cardiac structure and function should be considered
- The classification of pre-heart failure or subclinical disease based on echocardiography requires refinement to avoid mislabelling changes of physiological ageing as pathology

Heart Failure Prevention 2

Prevention of heart failure after acute myocardial infarction

This Series paper highlights the substantial progress made in understanding and preventing heart failure after acute myocardial infarction. Improving global standards of care for management of acute myocardial infarction with timelier reperfusion has led to stepwise reductions in risk of incident heart failure. Landmark clinical trials have established the role of renin–angiotensin–aldosterone system inhibitors, β blockers, and mineralocorticoid receptor antagonists to specifically reduce the risk of incident heart failure after acute myocardial infarction. However, residual risk of heart failure persists in many individuals, even after revascularisation and standard medical therapies. We review recent epidemiological trends from the past four decades, evolving understanding of the pathological mechanisms underlying incident heart failure, and modern risk stratification tools. We then propose a treatment pathway tailored to individual patient risk and discuss potential future strategies to incrementally improve the risk of development of heart failure after acute myocardial infarction.

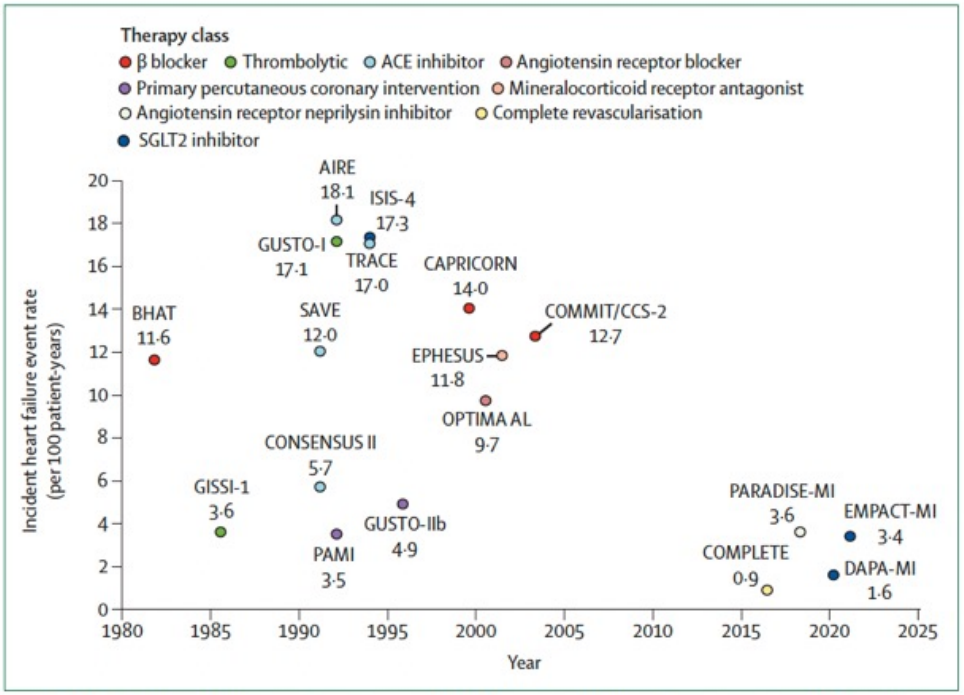

Figure 1: **Incident heart failure event rates across trials of patients with recent acute myocardial infarction**
Markers represent the incident control group event rates within a trial and therapy class unless otherwise stated. Incidence rates were reported from the approximate 1-year event rates, derived from Kaplan–Meier curves, or events per 100 patient-years of follow-up, except for BHAT (~2 years of follow-up), GISSI-1 (6 months), CONSENSUS II (6 months), PAMI (1 month), GUSTO-I (1 month), ISIS-4 (~1 month), GUSTO-IIb (1 month), OPTIMAAL (~2 years), and COMMIT/CCS-2 (1 month).

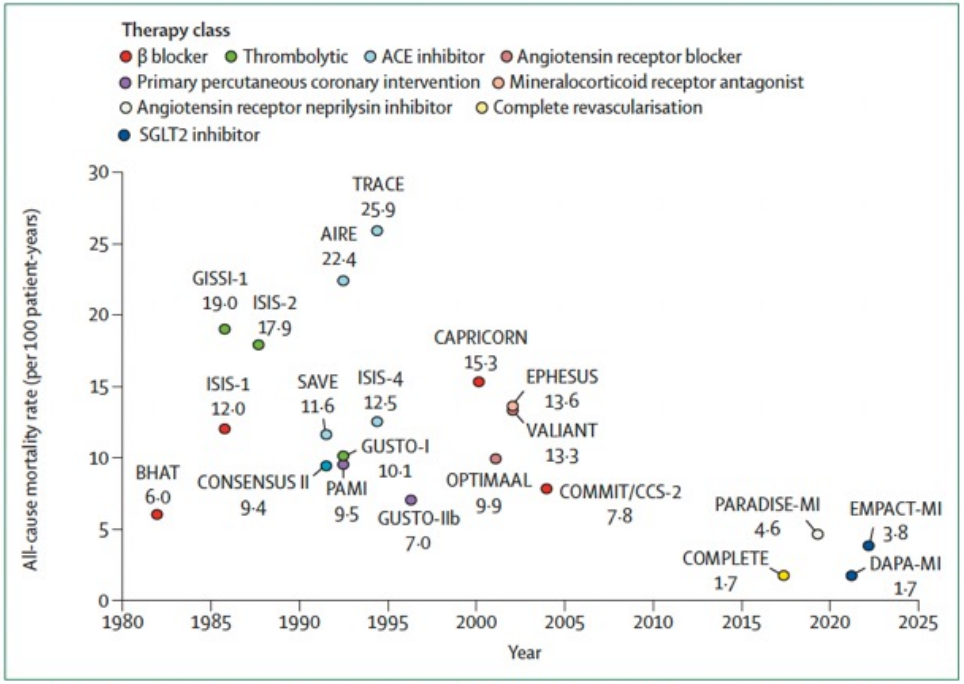

Figure 2: **All-cause mortality event rates across trials of patients with recent acute myocardial infarction**
Markers represent the incident control group event rates within a trial and therapy class unless otherwise stated. Incidence rates were reported from approximate one year event rates, derived from Kaplan–Meier curves, or events per 100 patient-years of follow-up except for CONSENSUS II (6 months of follow-up), GUSTO-IIb (1 month), and COMMIT/CCS-2 (1 month).

	Therapy	Comparator	N	Population	Duration	Primary outcome	Heart failure outcome
Thrombolytic therapy							
GISSI-1 (1986)[106]	Streptokinase	Usual care	11 806	People with STEMI within 12 h of symptom onset	3 weeks	All-cause mortality: 19% RRR (p=0·0002)	Left ventricular failure: −14% RRR
ISIS-2 (1988)[107]	Streptokinase	Usual care	17 187	People with STEMI within 12 h of symptom onset	5 weeks	Vascular mortality: 25% RRR (p<0·00001)	Not recorded
GUSTO-1 (1993)[108]	Alteplase	Streptokinase	41 021	People with STEMI within 6 h of symptom onset	1 month	All-cause mortality: 14% RRR (p=0·001)	Congestive heart failure: −13% RRR (p<0·001)
Primary percutaneous coronary intervention							
PAMI (1993)[109]	Primary percutaneous coronary intervention	Tissue plasminogen activator	395	People with STEMI within 12 h of symptom onset	Duration of hospital stay	All-cause mortality or non-fatal myocardial infarction: −57% RRR (p=0·02)	Not recorded
GUSTO-IIb (1997)[110]	Primary percutaneous coronary intervention	Tissue plasminogen activator	1138	People with STEMI within 12 h of symptom onset	1 month	All-cause mortality, non-fatal myocardial infarction, or non-fatal stroke: 23% RRR (p=0·03)	Congestive heart failure: −12% RRR
Transfer for percutaneous coronary intervention							
DANAMI-2 (2002)[111]	Transfer for percutaneous coronary intervention	Immediate tissue plasminogen activator	1572	People with STEMI within 12 h of symptom onset	1 month	All-cause mortality, non-fatal myocardial infarction, or non-fatal stroke: 40% RRR (p=0·002)	Not recorded
Early ACE inhibitors							
CONSENSUS II (1992)[112]	Intravenous and oral enalapril*	Placebo	6090	People with myocardial infarction within 24 h of symptom onset	6 months	No difference in all-cause mortality	No difference in total heart failure hospitalisation: 25% RRR (not significant)
GISSI-3 (1994)[113]	Lisinopril	Usual care	19 394	People with myocardial infarction within 24 h of symptom onset	6 weeks	All-cause mortality: 12% RRR (p=0·03)	No difference in clinical heart failure
ISIS-4 (1995)[114]	Captopril	Placebo	58 050	People with myocardial infarction within 24 h of symptom onset	5 weeks	All-cause mortality: 7% RRR (p=0·02)	No difference in heart failure
CCS-1 (1997)[115]	Captopril	Placebo	14 962	People with myocardial infarction within 36 h of symptom onset	4 weeks	No difference in all-cause mortality	Heart failure: −9% RRR (p=0·01)
Long-term ACE inhibitors							
SAVE (1992)[116]	Captopril	Placebo	2231	People who are day 3–16 post-myocardial infarction with LVEF≤40%	Mean duration of 3·5 years	All-cause mortality: 19% RRR (p=0·02)	Heart failure hospitalisation: 22% RRR (p=0·02)
AIRE (1993)[116]	Ramipril	Placebo	2006	People who are day 3–10 post-myocardial infarction with clinical heart failure	Mean duration of 15 months	All-cause mortality: 27% RRR (p=0·002)	Total severe or resistant heart failure: 21% RRR
TRACE (1995)[117]	Trandolapril	Placebo	1749	People who are day 3–7 post-myocardial infarction with LVEF≤35%	Mean duration of 36 months	All-cause mortality: 22% RRR (p=0·001)	Severe heart failure: 29% RRR (p=0·003)
Early β blockers							
ISIS-1 (1986)[118]	Intravenous and oral atenolol*	Placebo	16 027	People with myocardial infarction within 12 h of symptom onset	1 week	Vascular mortality: 15% RRR (p=0·04)	Not recorded
COMMIT/CCS-2 (2005)[119]	Intravenous and oral metoprolol*	Placebo	45 852	People with myocardial infarction within 24 h of symptom onset	1 month	No difference in all-cause mortality, non-fatal myocardial infarction, cardiac arrest, or all-cause mortality	Heart failure: 12% RR increase (p<0·0001)
Long-term β blockers							
BHAT (1982)[120,121]	Propranolol	Placebo	3837	People who are day 5–21 post-myocardial infarction	Mean duration of 2 years	All-cause mortality: −27% RRR (p<0·005)	No difference in congestive heart failure
CAPRICORN (2001)[122]	Carvedilol	Placebo	1959	People who are day 3–21 post-myocardial infarction with LVEF≤40%	Mean duration of 1·3 years	No difference in all-cause mortality or cardiovascular hospitalisation; all-cause mortality 23% RRR (p=0·03)	No difference in heart failure hospitalisation: 14% RRR (p=0·21)

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	Therapy	Comparator	N	Population	Duration	Primary outcome	Heart failure outcome
Long-term angiotensin receptor blocker							
OPTIMAAL (2002)[123]	Losartan	Captopril	5477	People who are day 0–10 post-myocardial infarction with LVEF<35% and heart failure	Mean duration of 2·7 years	No difference in all-cause mortality	No difference in heart failure hospitalisation
VALIANT (2003)[124]	Valsartan	Captopril	14 703	People who are day 0–10 post-myocardial infarction with LVEF≤35% on echocardiogram or LVEF≤40% radionuclide ventriculography or clinical heart failure	Median duration of 2 years	No difference in all-cause mortality	No difference in heart failure hospitalisation
MRAs							
EPHESUS (2003)[125]	Eplerenone	Placebo	6632	People who are day 3–14 post-myocardial infarction with LVEF≤40% and clinical heart failure or diabetes	Mean duration of 1·3 years	All-cause mortality: 15% RRR (p=0·008)	Heart failure hospitalisation: 15% RRR (p=0·03)
Angiotensin receptor neprilysin inhibitors							
PARADISE-MI (2021)[126]	Sacubitril–valsartan combination therapy	Ramipril	5661	People who are between 12 h and 7 days post-myocardial infarction with LVEF≤40% or clinical heart failure	Median duration of 2 years	No difference in cardiovascular mortality or incident heart failure (outpatient heart failure or heart failure hospitalisation)	No difference in heart failure hospitalisation or outpatient heart failure: 16% RRR (not significant)
Sodium/glucose co-transporter 2 inhibitors							
EMPACT-MI (2024)[127,128]	Empagliflozin	Placebo	6522	People who are within 14 days post-myocardial infarction with LVEF<45% or clinical heart failure	Median duration of 1·5 years	No difference in all-cause mortality or heart failure hospitalisation	23% RRR for first heart failure hospitalisation; 33% RRR for total heart failure hospitalisations (recurrent events)

p values reported in the table where available. ACE=angiotensin-converting enzyme. LVEF=left ventricular ejection fraction. MRA=mineralocorticoid receptor antagonists. RR=relative risk. RRR=relative risk reduction. STEMI=ST-elevation myocardial infarction. *First dose was given intravenously, then the protocol transitioned people to the oral version of the therapy.

Table: Key outcome trials of therapies for patients with acute myocardial infarction who are at high risk of heart failure

***Panel*: Potential reasons why post-myocardial infarction trials from the past 5 years have not been successful**

Population at low clinical risk of heart failure

- High background rates of reperfusion or revascularisation
- Absence of pathological process (eg, adverse remodelling) underlying heart failure onset
- Inclusion of patients at low risk with more myocardial stunning than persistent left ventricular dysfunction

High standard of care

- Comparative efficacy of comparator therapy
- Chronology of studying layered interventions on effective standard care

Issues with therapy under investigation

- Therapy not being relevant to myocardial infarction population studied (eg, non-modifiable substrate)
- Modest or minimal effect size of therapy

Competing risks

- High burden of non-modifiable comorbidities and frailty
- Heightened competing risks of non-cardiovascular events

Targeting atherosclerotic or coronary risk	Timely reperfusion or revascularisation	Antiplatelet therapy	Intensive lipid-lowering therapy
Targeting adverse cardiac remodeling	ACE inhibitors (ARBs if intolerant to ACE inhibitors)	β-blockers (shared decision making to omit if preserved LVEF)	Steroidal MRAs (if reduced LVEF and clinical congestion)
Promoting cardiovascular and systemic health	In-hospital optimisation of cardiovascular–kidney–metabolic risk factors (especially SGLT2 inhibitors if comorbid type 2 diabetes or chronic kidney disease)		
	Diet and lifestyle management	Tobacco cessation	Cardiac rehabilitation
Ongoing surveillance for incident heart failure	Early post-discharge follow-up		
	Implementation of guideline-directed medical therapy if newly diagnosed heart failure		

***Figure 3*: Evidence-based approach to prevention of heart failure after acute myocardial infarction**
ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. LVEF=left ventricular ejection fraction. MRA=mineralocorticoid receptor antagonist. SGLT2=sodium/glucose cotransporter 2.

Heart Failure Prevention 3

Cardiovascular, kidney, and metabolic health: an actionable vision for heart failure prevention

The substantial and growing prevalence of heart failure, which remains the leading cause of preventable hospitalisation worldwide, has brought heart failure prevention into sharp focus. Although this condition has historically been characterised by impaired cardiac function, mounting evidence has underscored its complex and multisystem pathobiology. Epidemiological studies have indicated that other forms of cardiovascular disease, along with kidney and metabolic dysfunction, frequently and increasingly contribute to heart failure onset. Clinical trials have additionally demonstrated the power of several new pharmacotherapies to simultaneously modify cardiovascular, kidney, and metabolic (CKM) health. This convergence of epidemiology and therapy highlights deeply interconnected mechanisms of disease, identifying CKM diseases—and their pathophysiological and sociostructural antecedents—as important but often under-recognised targets for heart failure prevention. Herein, we illustrate that positioning heart failure prevention within the broader context of CKM health provides an actionable framework for patients, health-care professionals, health systems, communities, and policy makers.

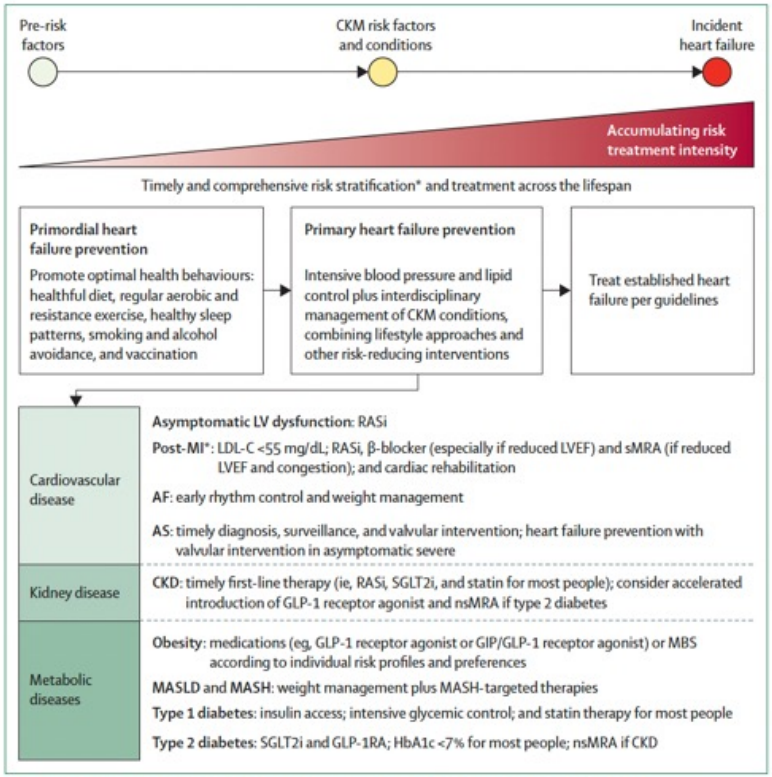

***Figure 1*: CKM health and heart failure prevention—a conceptual vision for implementation**
The figure provides a conceptual, life course-oriented framework for heart failure prevention through longitudinal maintenance of CKM health. Selected guidance for treatment of CKM risk factors and conditions is also highlighted. People at increased risk with obesity might include individuals with established complications or other risk-enhancing features, such as subclinical heart failure, systemic inflammation, or genetic risks. AF=atrial fibrillation. AS=aortic stenosis. CKD=chronic kidney disease. CKM=cardiovascular-kidney-metabolic. GIP=glucose-dependent insulinotropic polypeptide. GLP-1=glucagon-like peptide-1. MASLD and MASH=metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis. MBS=metabolic-bariatric surgery. MI=myocardial infarction. nsMRA=non-steroidal mineralocorticoid receptor antagonist. RASi=renin-angiotensin system inhibitor. SGLT2i=sodium-glucose co-transporter 2 inhibitor. sMRA=steroidal mineralocorticoid receptor antagonist. *For more details refer to papers 1 and 2 of the Series. Comprehensive risk stratification includes medical history, screening for social determinants of health and environmental risks, physical examination, vital signs, BMI plus additional anthropometrics, laboratory studies, use of validated heart failure risk algorithms, and natriuretic peptides and imaging (eg, echocardiography, coronary artery calcium scoring, and transient liver elastography) in selected cases.

***Panel 1*: Health behaviours and heart failure prevention**

Primordial heart failure prevention

- Rigorous attention to optimal eating and physical activity patterns throughout the lifespan, even among apparently healthy children, adolescents, and adults
  - In the STRIP study,[15-18] infancy-onset dietary counselling longitudinally improved diet quality and cardiometabolic risk factors after 26 years of follow-up
  - In the CALERIE trial,[19] 2 years of moderate (~12%) caloric restriction significantly reduced bodyweight and improved cardiovascular, kidney, and metabolic risk factors among healthy adults without obesity

Dietary considerations

- Optimal dietary approaches for heart failure prevention are uncertain; tailor recommendations to individual preferences and goals
- Minimise preprepared and highly processed foods, which might enhance risk of incident heart failure;[20] saturated fats and excessive sodium intake should be avoided[21]
- Caloric restriction with optimal protein intake (to enhance satiety and preserve lean mass) should be prioritised for people targeting bodyweight reduction
- Plant-based diets rich in vegetables, fruits, whole-grains, and nuts and legumes (or lean proteins, such as poultry and seafood) are generally preferred
- Mediterranean diets might also be preferred in some individuals, but have not been clearly shown to reduce incident heart failure[22]
- Salt substitution (reduced sodium and increased potassium concentrations) might reduce hypertension and cardiovascular events[23,24]
- Collaborative management with registered dietician nutritionists, when available, can be considered

Physical activity considerations

- ≥150 min per week of moderate-intensity aerobic exercise is recommended for all adults
  - Moderate-intensity aerobic exercise is associated with reductions in incident heart failure even when restricted to one to two days per week[25]
  - Among less active individuals, efforts to minimise sedentary time can afford important benefits on heart failure risk[26]
- Resistance exercise training (eg, two sessions per week, 30 min each) is recommended
  - This type of activity can provide additive benefits on insulin sensitivity, resting metabolic rate, body composition, weight management, and quality of life when combined with aerobic exercise[27]

Selected guidance for other health behaviours

- Smoking and tobacco use
  - Combustible cigarette smoking is associated with a two-times increase in the risk of new-onset heart failure[28]
  - Routine screening, prevention of incident use, and sustained cessation of smoking is recommended
- Electronic nicotine-delivery systems (ie, e-cigarettes) are increasingly used[29] but cardiovascular safety is uncertain; shared decisions are recommended
- Cannabis
  - Insufficient evidence on cardiovascular safety; shared decision making on cannabis use is recommended given potential harms[30,31]
- Alcohol use
  - Alcohol consumption at any level appears to be associated with incident heart failure[32]
  - Abstinence from alcohol intake might be optimal for heart failure prevention
- Sleep
  - Healthful sleep patterns have been incrementally associated with a lower risk of incident heart failure;[33] target consistent and optimal sleep duration (eg, 7–8 h nightly)
- Management of stress and mental health conditions
  - Cumulative stress burden (ie, allostatic load) is associated with incident heart failure[34]
- Routine age-appropriate vaccination
  - Influenza, COVID-19, and zoster vaccinations have each been associated with reductions in heart failure and other cardiovascular events[35-38]
- Heart failure-promoting medications
  - Several medications, such as hydroxychloroquine, ergot-based migraine medications, cancer therapies, and dopamine agonists, have been shown to enhance heart failure risk[39]
  - Other medications might promote heart failure risk factors, such as substances used for treatment of hypertension (eg, non-steroidal anti-inflammatory drugs), kidney disease (eg, proton pump inhibitors), and obesity (eg, β-blockers, sulfonylureas, gabapentin and pregabalin, and some selective serotonin reuptake inhibitors)
  - Routine screening and either avoidance or close monitoring (when heart failure risk-enhancing medications are required) is appropriate to mitigate cardiovascular risk

	Trial name	Enrolment period	Key eligibility criteria	Key results	Effect on incident heart failure
Renin-angiotensin system inhibitors					
Losartan	RENAAL	1996–98	Type 2 diabetes and CKD with albuminuria	28% reduction in ESKD 25% reduction in doubling of serum creatinine concentration 35% reduction in UACR	32% reduction in incident heart failure hospitalisation
Irbesartan	IDNT	1996–99	Type 2 diabetes and CKD with hypertension and proteinuria	20% reduction in doubling of the serum creatinine concentration, ESKD, or all-cause death with irbesartan *vs* placebo; 23% reduction with irbesartan *vs* amlodipine	28% reduction in incident heart failure with irbesartan *vs* placebo (HR=0·72; 95% CI 0·52–1·00). 35% reduction in incident heart failure with irbesartan *vs* amlodipine (HR=0·65; 95% CI 0·48–0·87)
Sodium-glucose co-transporter 2 inhibitors					
Empagliflozin	EMPA-REG OUTCOME	2010–13	Type 2 diabetes and CVD	14% reduction in cardiovascular death, myocardial infarction, or stroke	41% reduction in incident heart failure hospitalisation (HR=0·59; 95% CI 0·43–0·82)
Empagliflozin	EMPA-KIDNEY	2019–21	CKD with or without type 2 diabetes, with or without albuminuria	28% reduction in CKD progression or cardiovascular death	20% reduction in first heart failure hospitalisations (HR=0·80; 95% CI 0·60–1·06)
Canagliflozin	CANVAS Program	CANVAS: 2009–11; CANVAS-R: 2014–15	Type 2 diabetes with or at risk of CVD	14% reduction in cardiovascular death, myocardial infarction, or stroke	33% reduction in heart failure hospitalisation, without evidence of heterogeneity according to baseline heart failure status ($p_{interaction}$=0·47)
Canagliflozin	CREDENCE	2014–17	Type 2 diabetes and CKD with albuminuria	30% reduction in ESKD, doubling of serum creatinine, or death from kidney-related or cardiovascular causes	39% reduction in heart failure hospitalisation, without evidence of heterogeneity according to baseline heart failure status ($p_{interaction}$=0·25)
Dapagliflozin	DECLARE-TIMI 58	2013–19	Type 2 diabetes with or at risk of CVD	17% reduction in cardiovascular death or heart failure hospitalisation; no significant reduction in MACE (cardiovascular death, myocardial infarction, or stroke)	23% reduction in incident heart failure hospitalisation
Dapagliflozin	DAPA-CKD	2017–18	CKD with or without type 2 diabetes, with albuminuria	39% reduction in sustained eGFR decline ≥50%, ESKD, or death from kidney-related or cardiovascular causes	49% reduction in heart failure hospitalisation, without evidence of heterogeneity according to baseline heart failure status ($p_{interaction}$=0·28)
Ertugliflozin	VERTIS CV	2013–15; 2016–17	Type 2 diabetes and CVD	Sotagliflozin non-inferior to placebo on MACE (cardiovascular death, myocardial infarction, or stroke)	30% reduction in heart failure hospitalisation, without evidence of heterogeneity according to baseline heart failure status ($p_{interaction}$=0·40)
Sotagliflozin (dual SGLT2 and SGLT1 inhibitor)	SCORED	2017–20	Type 2 diabetes and CKD, with or without albuminuria	26% reduction in cardiovascular death and total heart failure events	28% reduction in cardiovascular death and total heart failure events among participants without heart failure-related criteria at baseline (HR=0·72; 95% CI 0·57–0·91)
GLP-1 receptor agonists (oral or subcutaneous, non-continuous infusion)					
Lixisenatide	ELIXA	2010–13	Type 2 diabetes and acute coronary syndrome within 180 days of screening	No reduction in cardiovascular death, myocardial infarction, stroke, or unstable angina (p for non-inferiority<0·001; p for superiority=0·81)	No significant reduction in heart failure hospitalisation (HR=0·96; 95% CI 0·75–1·23); no evidence of heterogeneity in treatment effects by baseline heart failure status ($p_{interaction}$=0·87)
Liraglutide (1·8 mg)	LEADER	2010–12	Type 2 diabetes with or at risk of CVD	13% reduction in cardiovascular death, myocardial infarction, or stroke (p for non-inferiority<0·001; p for superiority=0·01)	13% reduction in heart failure hospitalisation, without evidence of heterogeneity in treatment effects by baseline heart failure status ($p_{interaction}$=0·22)
Semaglutide (0·5 or 1·0 mg)	SUSTAIN-6	2013	Type 2 diabetes with or at risk of CVD	26% reduction in cardiovascular death, myocardial infarction, or stroke (p for non-inferiority<0·001; p for superiority=0·02)	No reduction in heart failure hospitalisation (HR=1·11; 95% CI 0·77–1·61); treatment effects on incident heart failure not reported
Exenatide	EXSCEL	2010–15	Type 2 diabetes with or without previous CVD events	9% reduction in cardiovascular death, myocardial infarction, or stroke (p for non-inferiority<0·001; p for superiority=0·06)	No significant reduction in heart failure hospitalisation (HR=0·94; 95% CI 0·78–1·13); no evidence of heterogeneity in treatment effects by baseline heart failure status ($p_{interaction}$=0·33)
Dulaglutide (1·5 mg)	REWIND	2011–13	Type 2 diabetes with or at risk of CVD	12% reduction in cardiovascular death, myocardial infarction, or stroke (p for superiority=0·026)	No significant reduction in heart failure events (HR=0·93; 95% CI 0·77–1·12); no evidence of heterogeneity in treatment effects by baseline heart failure status ($p_{interaction}$=0·19)
Albiglutide (30–50 mg)	HARMONY-OUTCOMES	2015–16	Type 2 diabetes and CVD	22% reduction in cardiovascular death, myocardial infarction, or stroke (p for non-inferiority<0·001; p for superiority<0·001)	51% reduction in incident heart failure hospitalisation
Semaglutide (oral)	PIONEER 6	2017	Type 2 diabetes with or at risk of CVD	21% reduction in cardiovascular death, myocardial infarction, or stroke (p for non-inferiority<0·001; p for superiority=0·17)	No significant reduction in heart failure hospitalisation (HR=0·86; 95% CI 0·48–1·55); treatment effects on incident heart failure not reported

(Table 1 continues on next page)

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	Trial name	Enrolment period	Key eligibility criteria	Key results	Effect on incident heart failure
Efpeglenatide (4 or 6 mg)	AMPLITUDE-O	2018–19	Type 2 diabetes with or at risk of CVD	27% reduction in cardiovascular death, myocardial infarction, or stroke (p for non-inferiority<0·001; p for superiority=0·007)	39% reduction in heart failure hospitalisation (HR=0·61; 95% CI 0·38–0·98); 82% without heart failure at baseline
Semaglutide (2·4 mg)	SELECT	2018–21	BMI ≥27 kg/m², CVD, and without diabetes	20% reduction in cardiovascular death, myocardial infarction, or stroke (p for superiority<0·001)	18% reduction in the heart failure composite endpoint of cardiovascular death or heart failure events, without evidence of heterogeneity in treatment effects by baseline heart failure status ($P_{interaction}$=0·64)
Semaglutide (1·0 mg)	FLOW	2019–21	Type 2 diabetes and CKD with proteinuria	24% reduction in the composite of kidney failure, sustained ≥50% reduction in eGFR, or death from kidney-related or cardiovascular causes (p for superiority<0·001)	32% reduction in incident heart failure events (HR=0·68; 95% CI 0·50–0·91)
Semaglutide (oral)	SOUL	2019–21	Type 2 diabetes and atherosclerotic CVD, CKD, or both	14% reduction in the composite of cardiovascular death, myocardial infarction, or stroke (p for superiority=0·006)	No significant reduction in cardiovascular death, heart failure hospitalisation, or urgent heart failure visit (HR=0·90; 95% CI 0·79–1·03); treatment effects on incident heart failure not reported
Non-steroidal mineralocorticoid receptor antagonists					
Finerenone	FIDELIO-DKD	2015–18	Type 2 diabetes and CKD with albuminuria, treated with maximally tolerated RASi, and serum potassium ≤4·8 mmol/L	18% reduction in reduction in the composite of kidney failure, sustained ≥40% reduction in eGFR, or death from kidney-related causes	14% reduction in heart failure hospitalisation (HR=0·86; 95% CI 0·68–1·08); 92% without heart failure at baseline
Finerenone	FIGARO-DKD	2015–18	Type 2 diabetes and CKD with albuminuria, treated with maximally tolerated RASi, and serum potassium ≤4·8 mmol/L	13% reduction in the composite of cardiovascular death, myocardial infarction, stroke, or heart failure hospitalisation	39% reduction in heart failure hospitalisation, without evidence of heterogeneity according to baseline heart failure status ($p_{interaction}$=0·77)

CKD=chronic kidney disease. CVD=cardiovascular disease. eGFR=estimated glomerular filtration rate. ESKD=end-stage kidney disease. HR=hazard ratio. MACE=major adverse cardiovascular events. RASi=renin-angiotensin system inhibitor. UACR=urine albumin-to-creatinine ratio.

Table 1: **Placebo-controlled outcomes trials reporting treatment effects on incident heart failure in populations with kidney and metabolic conditions**

	Goals of screening	Whom to screen or consider screening	Components of screening	Frequency of screening	Selected evidence gaps and comments
Cardiovascular disease					
Subclinical heart failure	Risk stratification, inform preventive treatment targets, and heart failure prevention	Consider if diabetes or other risk factors (eg, hypertension, obesity, elevated LDL-C, and ASCVD)	BNP or NT-proBNP; and transthoracic echocardiography if BNP or NT-proBNP elevated	Not established	Uncertain whether targeted screening with BNP or NT-proBNP is cost-effective or reduces incident heart failure.* Need for scalable heart failure prevention pathways after preclinical heart failure diagnosis. Optimal natriuretic peptide screening thresholds uncertain in obesity
Subclinical ASCVD	Risk stratification and inform need for (and intensity of) lipid-lowering therapy and aspirin for ASCVD prevention	Signs (eg, carotid bruits). Consider CAC scoring if intermediate 10-year ASCVD risk. Increased risk for PAD: age ≥65 years, age 50–64 years if risk factors (eg, type 2 diabetes, hypertension, CKD, previous smoking), or age <50 if diabetes and at least one additional risk factor for atherosclerosis	In selected cases: carotid duplex ultrasound, CAC scoring, and ABI	Carotid duplex ultrasound: not well established. CAC: if 0, consider about every 5 years. BI: not well established	Routine screening for ASCVD not recommended. Uncertain whether CAC scoring improves outcomes. Optimal ABI, CAC, and carotid duplex ultrasonography re-assessment interval uncertain. Targeted ASCVD screening likely not applicable to all global settings
Atrial fibrillation	Diagnosis, treatment, and thromboprophylaxis, and establishing mechanism for cryptogenic thromboembolic events	After thromboembolic event (eg, cryptogenic stroke); individuals with signs of AF (eg, irregular pulse); and groups at high risk (eg, age ≥75 years or ≥65 years plus other risk factors for thromboembolism, such as diabetes)	Prolonged invasive or non-invasive ECG (if recent cryptogenic thromboembolic event); pulse assessment and ECG (opportunistic); and consider prolonged non-invasive ECG in older adults at high risk	Annual (if opportunistic screening)	Clinical AF prediction models have been developed, but whether targeted community-based screening for AF is cost-effective and improves outcomes remains uncertain. Value of digital wearable devices and AI-based algorithms uncertain. Uncertain value of population-based screening approaches. Consider OSA screening in AF
Aortic stenosis	Early diagnosis, risk factor modification, and establishing monitoring interval to optimise timing of referral and valvular intervention	Signs (eg, systolic murmur) or first-degree relative with bicuspid aortic valve	Transthoracic echocardiography; BNP or ETT to optimise timing of valvular intervention in asymptomatic severe AS	Repeat echocardiography: every 3–5 years for mild AS, 1–2 years for moderate AS, and 6–12 months for severe AS. BNP/NT-proBNP can be assessed annually	Targeting screening echocardiography (eg, if risk factors for valvular calcification) of uncertain value in the absence of other indications. Value of point-of-care echocardiography, AI-based ECG analysis, other serum biomarkers, and imaging for risk stratification uncertain
Chronic kidney disease	Early diagnosis, CKD staging, treatment, and establishing monitoring interval and need for referral	Individuals with metabolic risk factors (diabetes,† obesity, and hypertension); cardiovascular disease; family history of CKD or other genetic risks (eg, *APOL1* variants); previous acute kidney injury; and people with other conditions such as chronic inflammatory conditions, HIV, nephrotoxin exposures, pregnancy-related risks (eg, pre-eclampsia), genitourinary disorders, and occupational exposures (eg, pesticides)	eGFR and UACR‡	If no CKD or diabetes: annually. Other risk factors or high 5-year risk of CKD§ consider annual screening. If CKD detected: every 3–6 months, guided by CKD risk category	Utility and cost-effectiveness of population screening. Optimal frequency of screening in people at risk of CKD. Uncertain whether targeted CKD detection and treatment improves outcomes in community settings. Pathogenic gene variants might be common and actionable, but testing not broadly available and cost-effectiveness uncertain
Metabolic diseases					
Obesity	Early diagnosis, risk stratification, prevention, and treatment	All people (using sex-specific and age-specific growth charts for children and adolescents)	BMI and waist circumference (or WHtR or WHR)¶ or direct fat mass measurement (eg, DEXA or BIA)	At least annually (more frequent monitoring might be considered for people at high risk or those receiving obesity treatments)	Once excess adiposity is confirmed, further assessment is needed to identify complications of obesity. Optimal screening intervals uncertain
Type 2 diabetes and prediabetes	Early diagnosis, prevention, and treatment	Aged ≥18 years with BMI-defined overweight or obesity combined with other risk factors (eg, hypertension, cardiovascular disease, physical inactivity, and MASLD); individuals in other groups at high risk: HIV, high-risk medication exposures, periodontal disease, and previous pancreatitis; and individuals aged ≥35 years	Fasting plasma glucose or HbA_{1c} or 2 h plasma glucose after 75 g OGTT	If no type 2 diabetes: annually for prediabetes; every 1–3 years for previous gestational diabetes; and otherwise every 3 years. More frequent intervals based on risk and initial testing in all other cases. 3–6 months if type 2 diabetes (or type 1 diabetes) diagnosed	Screening programmes applicable in all global settings have not been established. Optimal screening interval uncertain. Screening tests for diabetes reflect different aspects of glucose metabolism. OGTT might classify more individuals as having dysglycaemia

(Table 2 continues on next page)

	Goals of screening	Whom to screen or consider screening	Components of screening	Frequency of screening	Selected evidence gaps and comments
(Continued from previous page)					
Type 1 diabetes	Early diagnosis, predict disease progression, prevent DKA, establish need for referral, and disease modification	Presymptomatic people with family history of type 1 diabetes or other genetic risk factors; individuals with diabetes and phenotypic features of type 1 diabetes, such as younger age or ketosis	Islet autoantibodies (anti-GAD, anti-insulin,|| anti-IA-2, anti-ZnT8) and C-peptide (in select antibody-negative cases if type 2 diabetes suspected)	If one persistent islet Ab: metabolic monitoring annually if risk factors; otherwise per type 2 diabetes guidelines. If at least two persistent islet Ab: HbA_{1c} annually (every 2 years if stable for 5 years) at stage 1; HbA_{1c} every 6 months plus blinded CGM, increased SMBG, or OGTT at stage 2**	Genetic and clinical data from non-European populations are insufficient. Need for further evidence to inform monitoring strategies and timing and use of insulin and disease-modifying therapies in early-stage type 1 diabetes. Population-based type 1 diabetes screening deployed in some countries, but cost-effectiveness in all settings uncertain
MASLD (without cirrhosis)	Diagnosis, determine risk of advanced fibrosis and liver complications, establish need for referral, and treatment	Individuals with: type 2 diabetes; BMI-defined obesity and at least one risk factors (eg, hypertension, prediabetes, dyslipidaemia, or central obesity); or persistently elevated liver enzymes	FIB-4 measurement; sequential non-invasive testing (eg, VCTE or ELF) if high-risk for advanced fibrosis	If FIB-4 <1·3:†† repeat every 1–3 years. If FIB-4 1·3–2·67: repeat within 1 year and pursue VCTE or ELF if persistently ≥1·3.‡‡ If FIB-4 >2·67 or high-risk findings on non-invasive testing: hepatology referral	Role of genetic testing uncertain. Knowledge of comparative performance of different non-invasive tests is insufficient. Need for personalised MASH screening and treatment pathways. Uncertain whether MASH-targeted therapies improve clinical outcomes

AI=artificial intelligence. ASCVD=atherosclerotic cardiovascular disease. BIA=bioimpedance analysis. BNP=B-type natriuretic peptide. CAC=coronary artery calcium. CGM=continuous glucose monitor. CKD=chronic kidney disease. DEXA=dual-energy x-ray absorptiometry. DKA=diabetic ketoacidosis. eGF=estimated glomerular filtration rate. ELF=enhanced liver fibrosis. ETT=exercise tolerance testing. FIB-4=fibrosis-4 index. GAD=glutamic acid decarboxylase. HbA_{1c}=glycated haemoglobinIA-2. MASLD=metabolic dysfunction-associated steatotic liver disease. MASH=metabolic dysfunction-associated steatohepatitis. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. OGTT=oral glucose tolerance test. SMBG=self-monitored blood glucose. UACR=urine albumin-to-creatinine ratio. VCTE=vibration-controlled transient elastography. WHR=waist-hip ratio. WHtR=waist-to-height ratio. ZnT8=zinc transporter 8. *In the STOP-HF trial, BNP screening in people at high risk combined with echocardiography and team-based care (if BNP ≥50 pg/mL) reduced incident left ventricular dysfunction and emergency hospitalisation for major adverse cardiovascular events, but was underpowered for assessment of incident heart failure events. †Comprehensive kidney screening recommended annually in people with type 2 diabetes and after 5 years from diagnosis of type 1 diabetes. ‡eGFR should be estimated with the use of serum creatinine or the combination of serum creatinine and cystatin C if available and indicated (eg, extremes of muscle mass, smoking, high or low protein diets, and chronic diseases including obesity, cirrhosis, and heart failure). A urine dipstick examination for proteinuria detection recommended if UACR testing is unavailable. §Might be estimated according to validated equations. ¶Appropriate age, gender, and ethnicity-specific thresholds should be employed. Measurement of additional anthropometrics can be deferred if BMI ≥40 kg/m² as excess adiposity is likely present in these settings. ||Not informative in people treated with insulin. **Referral to clinical centres with expertise in early-stage type 1 diabetes treatment (or ongoing clinical trials or other research studies) should be considered. Disease-modifying therapies should be considered based on local approval, availability, and expertise. ††The lower FIB-4 threshold for adults aged ≥65 years is 2·0. ‡‡VCTE or alternative non-invasive tests can be considered initially (ie, without further monitoring) based on clinical risk and local resources and expertise.

Table 2: **Guideline-based screening approaches for cardiovascular, kidney, and metabolic conditions in asymptomatic adults**

	Blood pressure	Glycaemia*	Blood cholesterol	Selected health behaviours	Bodyweight and adiposity
ASCVD	<130/80 mm Hg (<120/80 mm Hg might be preferred to reduce heart failure)	ADA: less stringent goals (eg, HbA_{1c} <8%) recommended if established ASCVD; consider stricter control if acceptable risk-benefit balance. ESC: HbA_{1c} <7% for most	ACC and AHA: high-intensity statin therapy and LDL-C goal <70 mg/dL (lower if very high-risk†). ESC: high-intensity statin therapy and LDL-C goal <55 mg/dL. Statins appear to reduce incident heart failure	Smoking avoidance; avoiding excess alcohol (eg, ≥100 g/week) intake; mediterranean diet; saturated fat <10% total daily caloric intake; limit sodium intake to <2·3 g/day; minimise sedentary time; 150–300 min/week of at least moderate-intensity physical activity; and resistance training at least two days per week	≥5% bodyweight reduction in 3–6 months recommended if elevated BMI. ≥10% bodyweight reduction associated with 20% lower risk of cardiovascular events in Look AHEAD
Calcific AS	120–140/70–90 mm Hg; elevated blood pressure associated with higher rate of AS progression and worse cardiovascular outcomes in people with mild or moderate AS	HbA_{1c} ≥7% associated with AS progression	Treat according to local guidelines; statins do not reduce aortic event rates, but reduce ischaemic events in people with AS	Smoking avoidance; maintaining optimal dental hygiene; minimising sedentary time; regular physical activity might improve health and enhance detection of exercise intolerance	Maintain healthy bodyweight; BMI ≥25 kg/m² associated with increased risk of heart failure and mortality in people with AS; higher visceral adiposity associated with worse outcomes after TAVR
AF	Blood pressure control according to local guidelines to reduce cardiovascular events	HbA_{1c} <7% pre-ablation and improved glycaemic control post-ablation associated with lower AF recurrence	Treatment and management goals guided by cardiovascular risk‡	Smoking avoidance; minimising or eliminating alcohol intake; and 210 min/week of moderate-to-vigorous physical activity	≥10% bodyweight reduction if BMI ≥27 kg/m²; ≥10% bodyweight reduction provides greater reductions in AF burden *vs* ≥3–9%
CKD	<120/80 mm Hg preferred for most people (KDIGO)	Individualise HbA_{1c} goals between 6·5% and <8%; stricter control favoured in earlier disease stages or low risk of hypoglycaemia	Primary prevention: statin if age ≥50 years and no chronic KRT; consider statin if age 18–49 and diabetes or 10-year ASCVD risk >10%‡	Smoking avoidance; avoiding ultra processed foods; encouraging consumption of plant-based foods; limiting sodium intake to <2 g/day; maintaining protein intake of 0·8 g/kg/day if G3–5 CKD; avoiding sedentary behaviour; and >150 min/week of moderate intensity physical activity	Bodyweight reduction advised if concomitant obesity; about 7–8% bodyweight reduction in Look AHEAD reduced UACR and CKD onset and progression
Type 2 diabetes	<130/80 mm Hg (<120/80 mm Hg might be preferred to reduce heart failure)	HbA_{1c} <7% for most people (>70% time in range when using CGM)	Primary prevention by ADA and EASD: statin if age >40 years or age 20–39 years if cardiovascular risk factors or 10-year ASCVD risk >10%‡ and target LDL-C <70 mg/dL if increased cardiovascular risk	Smoking avoidance; avoid excess alcohol intake; minimise ultra processed foods, sugar-sweetened beverages, saturated fat, and overall carbohydrate intake; prioritise vegetables, fruits, plant-based and lean proteins, and whole grains; limit sodium intake to <2·3 g/day; minimise sedentary time; >150 min/week of at least moderate-intensity physical activity; and two to three sessions per week of resistance training	Primary management goal; about 5% bodyweight reduction improves glycaemia; >10% bodyweight reduction is disease-modifying in most people (10% reduction in BMI associated with 31% lower risk of heart failure in Look AHEAD)
Type 1 diabetes	<130/80 mm Hg (<120/80 mm Hg might be preferred to reduce heart failure)	HbA_{1c} <7% for most people (>70% time in range when using CGM); early use of CGM and automated insulin delivery systems to improve or maintain glycaemic control and reduce hypoglycaemia	Primary prevention by ADA and EASD: statin if age >40 years or age 20–39 years if cardiovascular risk factors or 10-year ASCVD risk >10%;‡ target LDL-C <70 mg/dL if increased cardiovascular risk. Primary prevention by ADA and ISPAD: statin if age >10 years and LDL-C >160 mg/dL or >130 mg/dL with cardiovascular risk factors; goal LDL-C <100 mg/dL	Smoking and cannabis avoidance; avoid excess alcohol intake; minimise ultra processed foods, sugar-sweetened beverages, saturated fat, and overall carbohydrate intake; prioritise vegetables, fruits, plant-based and lean proteins, and whole grains; limit sodium intake to <2·3 g/day; minimise sedentary time; >150 min/week of at least moderate-intensity physical activity; 2–3 sessions per week of resistance training	5–10% bodyweight reduction for most individuals if concomitant obesity
MASLD and MASH	Optimal blood pressure control according to local guidelines and cardiovascular risk	Optimal glycaemic control according to local guidelines and cardiovascular risk	Statin therapy recommended if hypercholesterolemia; treatment and management goals otherwise guided by cardiovascular risk‡	Smoking avoidance; discourage alcohol use or avoid if advanced fibrosis; avoid processed foods and sugar-sweetened beverages; consider Mediterranean diet; minimise sedentary time; >150 min/week of at least moderate intensity physical activity	Normal BMI: 3–5% bodyweight reduction. Elevated BMI: ≥5% bodyweight reduction to improve steatosis; ≥10% reduction to improve inflammation and fibrosis; consider MBS if BMI ≥35 kg/m²

ACC=American College of Cardiology. ADA=American Diabetes Association. AF=atrial fibrillation. AHA=American Heart Association. AS=aortic stenosis. ASCVD=atherosclerotic cardiovascular disease. CKD=chronic kidney disease. CGM=continuous glucose monitoring. EASD=European Association for the Study of Diabetes. ESC=European Society of Cardiology. HbA_{1c}=glycated haemoglobin. ISPAD=International Society for Pediatric and Adolescent Diabetes. KDIGO = Kidney Disease: Improving Global Outcomes. KRT=kidney replacement therapy. LDL-C=LDL cholesterol. MASLD and MASH=metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis. MBS=metabolic-bariatric surgery. *Glycaemic goals if comorbid diabetes. †Some guidelines recommend further intensification of lipid-lowering therapy if LDL-C ≥70 mg/dL if very high cardiovascular risk (eg, history of multiple ASCVD events or previous ASCVD event combined with age ≥65 years, diabetes, hypertension, CKD, current tobacco smoking, history of heart failure, or familial hypercholesterolemia). Use of a validated cardiovascular risk score inclusive of kidney metrics (eg, SCORE and PREVENT) recommended.

Table 3: **Goals for modifiable risk factor management and control in people with selected cardiovascular, kidney, or metabolic conditions**

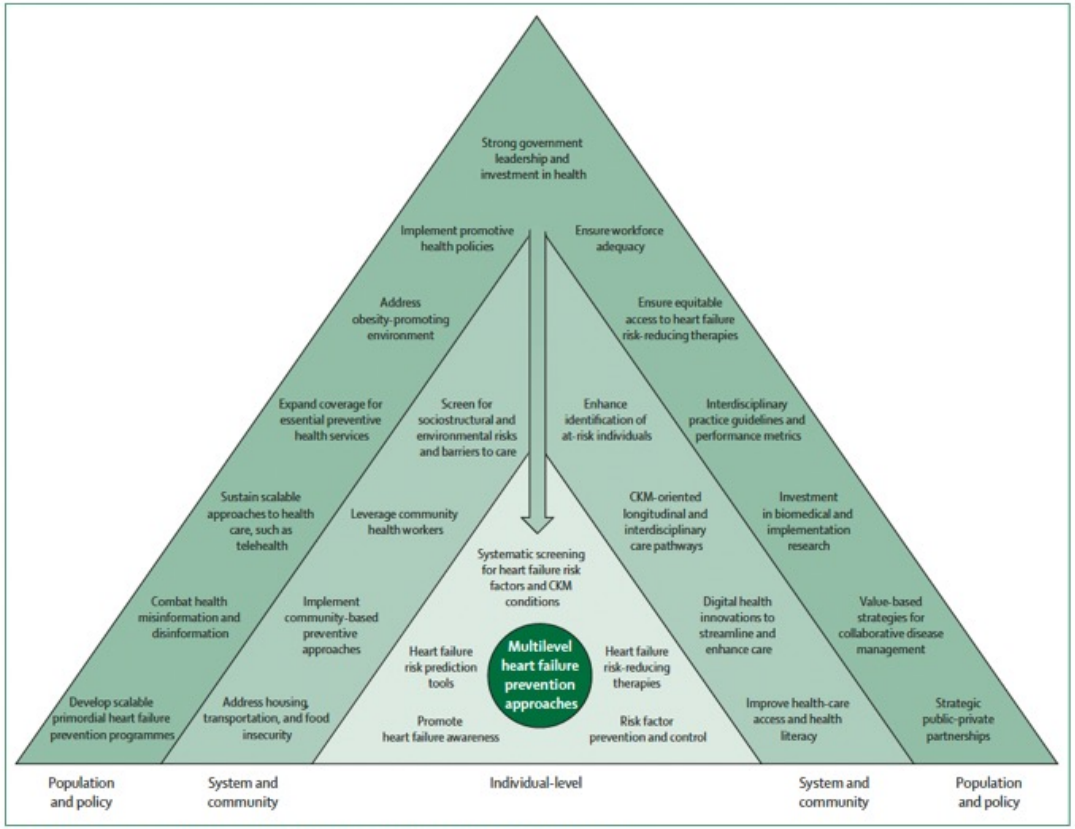


Figure 2: **Multilevel opportunities for heart failure prevention through CKM health promotion**
Graphic highlights selected opportunities for promotion of CKM health and prevention of heart failure at the individual, health-care system and community, and population and policy levels. CKM=cardiovascular-kidney-metabolic.

Panel 2: **Key knowledge gaps and priorities in heart failure prevention**

Research gaps

Epidemiology and disease mechanisms

- Improve understanding of global CKM health and its temporal trajectory
- Ascertain multi-omic drivers of CKM health impairments and the role of genetic testing to inform risk-based interventions in diverse populations
- Enhance understanding of key mechanisms by which CKM risk factors contribute to incident heart failure, and the mechanisms by which heart failure contributes to CKM conditions
- Improve understanding of the interplay between social, structural, and environmental factors and CKM health impairments

Primordial heart failure prevention

- Develop, evaluate, and scale high-value multisectoral approaches that prevent or delay the onset of CKM risk factors (eg, dietary and lifestyle risks)

Primary heart failure prevention

- Establish evidence-based, cost-effective, and scalable approaches to detection and treatment of subclinical heart failure, especially in high-risk persons with other CKM conditions
- Develop and validate heart failure risk estimation algorithms inclusive of CKM health metrics (eg, UACR) in all global settings
- Improve understanding of risk factor treatment goals for heart failure prevention
- Design and conduct randomised outcomes trials explicitly targeting heart failure prevention in people with heart failure risk factors, including CKM conditions

Implementation of CKM-oriented care models

- Determine the value of the CKM syndrome framework (and CKM-oriented performance metrics) in global clinical care settings
- Develop sustainable and affordable health-care infrastructure for CKM risk factors and conditions, including scalable, flexible, and interdisciplinary approaches to support early detection, prevention, and timely management of CKM risk factors and conditions across the lifespan
- Establish the role of artificial intelligence-based strategies in the identification, risk stratification, and treatment of persons at increased risk of heart failure, ensuring safety, effectiveness, transparency, and equity

Gaps in medical education, health-care delivery, and health policy

Supply and access to care

Ensure adequate supply of, and access to, primary and specialty care services throughout the lifespan

- Foster collaboration and coordinated care between historically siloed, organ-centric specialty providers
- Empower non-physician health-care professionals (eg, community health workers)
- Leverage telehealth and other digital approaches

Integrative, actionable, and living clinical practice guidelines

- Promote the development of actionable and continuously updated guidelines applicable across the spectrum of CKM health
- Tailor guidance to different policy and health-care ecosystems

Awareness and education

- Improved patient awareness and clinician education to support prevention, identification, and treatment of CKM conditions and their risk factors
- Enhance focus on primordial and primary prevention of CKM conditions in medical education, including historically neglected topics of substantial importance to public health (eg, evaluation and management of obesity and malnutrition)
- Develop and support intersectional training pathways

Access to key therapeutic interventions

- Support sustained implementation and access to multicomponent lifestyle interventions
- Promote multistakeholder engagement to expand sustained access to, and affordability of, key risk-reducing medications

Explicit goal setting and accountability

- Set meaningful but attainable goals for CKM health promotion and prevention
- Ensure regular accountability cycles to: monitor local, national, and international progress; and foster innovation

Intersectoral engagement

- Support multisectoral engagement and alignment on CKM health priorities (eg, rapidly rising rates of childhood and adolescent obesity)
- Encourage collaboration between sectors to foster innovative, community-based, and cross-cutting solutions to structural and environmental drivers of CKM health impairments

Panel 3: *Lancet* 2025 Series on heart failure prevention—top ten key messages

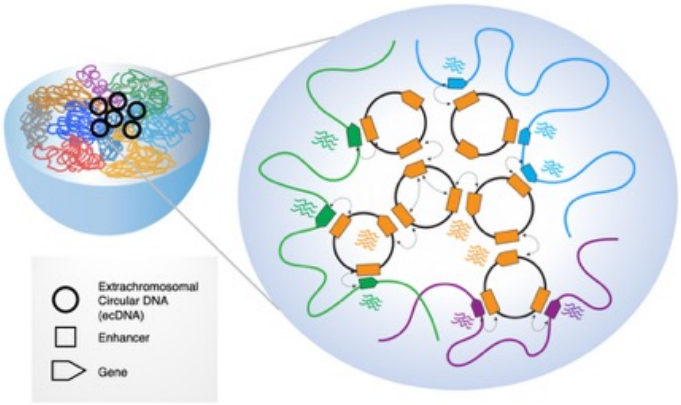
- This *Lancet* Series serves as a call to action for clinicians, health systems, and governments and underscores the urgent need to prioritise the primary prevention of heart failure
- Heart failure prevalence is growing worldwide, and its onset is linked with a steep increment in morbidity, mortality, and health-care resource utilisation
- Despite substantial progress in the development of disease-modifying therapies for the treatment of people with established heart failure, less attention has been given to heart failure prevention
- Modern staging systems identify a specific group of individuals with pre-heart failure (stage B) who may be at particular risk for development of clinical heart failure (stage C)
- Sensitive biomarkers (such as a natriuretic peptides), point-of-care imaging tools, and powerful risk scores can robustly and accurately predict risk of heart failure
- Longitudinal improvements in timely revascularisation, systems of care, and pharmacotherapies have led to stepwise reductions in risk of heart failure after acute myocardial infarction
- Despite improvements in care after myocardial infarction, care disparities persist globally, and ischemic heart disease remains an important pathway to heart failure onset
- Heart failure is a frequent but under-recognised complication of other cardiovascular (eg, atherosclerotic cardiovascular disease, atrial fibrillation, and aortic stenosis), kidney (eg, chronic kidney disease), and metabolic (eg, obesity, hypertension, and diabetes) diseases
- Cardiovascular, kidney, and metabolic conditions have shared root causes, overlapping and interdependent pathobiology, syndemic and sequential epidemiology, and converging therapy; treatment of other forms of cardiovascular disease, chronic kidney disease, obesity, and diabetes have been shown to prevent or delay incident heart failure
- Early detection and treatment of cardiovascular, kidney, and metabolic conditions, combined with systematic prevention and management of upstream risk factors, should be considered primary targets of heart failure prevention efforts across the lifespan

Conclusion

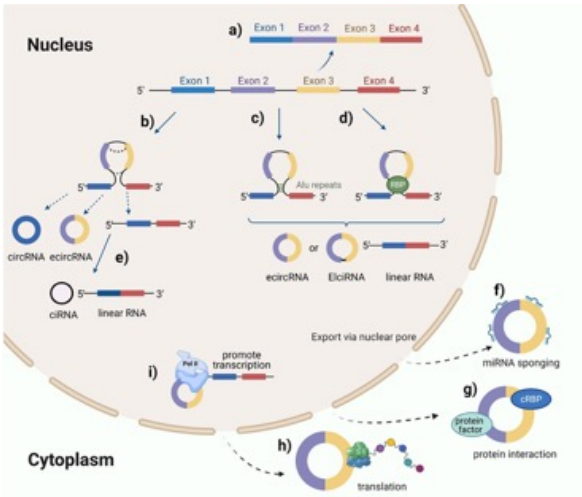
Although heart failure prevention efforts in global settings have historically targeted prevention and treatment of IHD, the rapidly escalating global burden of heart failure despite important progress in IHD has challenged this approach. Indeed, heart failure is increasingly identified as part of a broader network of CKM conditions with shared root causes, syndemic and sequential epidemiology, overlapping and interdependent pathobiology, and converging therapy. This contemporary understanding of heart failure as a modifiable outcome (and driver) of CKM conditions underscores the need for patients, clinicians, health-care systems, policy makers, and other stakeholders to look beyond IHD and embrace CKM health as a primary target of heart failure prevention efforts at-scale.

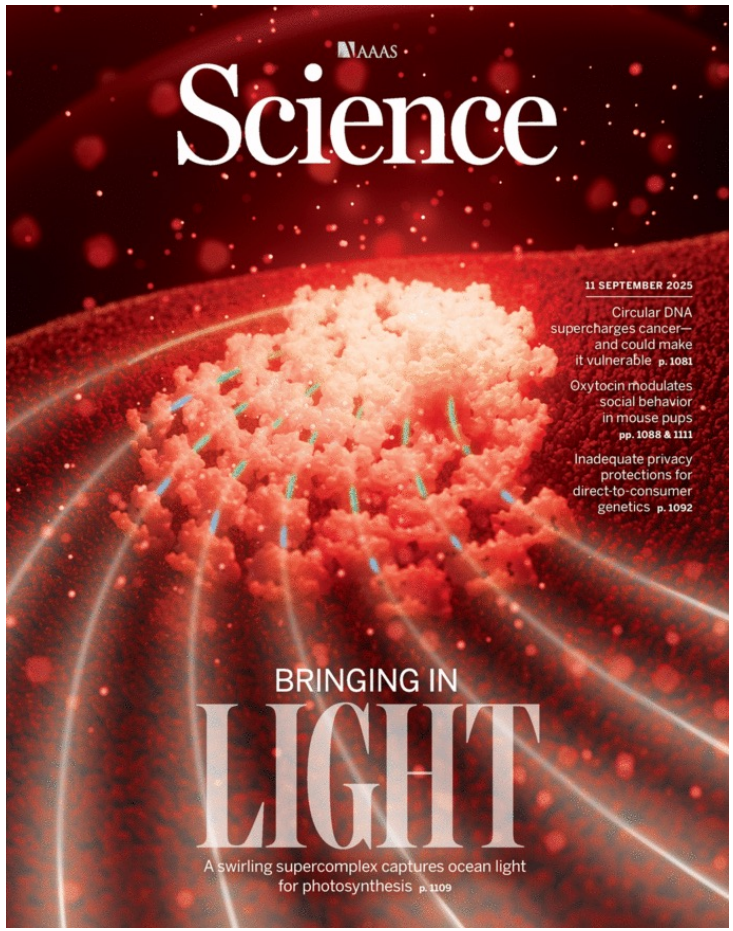
Although important knowledge gaps (panel 2) remain, the individual and societal burden of heart failure can be mitigated through multilevel promotive and preventive strategies to: ameliorate behavioural, environmental, and sociostructural determinants of heart failure; curtail widespread gaps in the screening and control of modifiable CKM risk factors; develop and implement cost-effective screening programmes targeting subclinical heart failure; secure broad access, affordability, and timely introduction of established therapies that reduce new-onset heart failure (and target-organ disease progression); and foster collaborative and accountable care pathways to ensure attainment and maintenance of key care goals across the lifespan (panel 3).

Circular (zirkuläre) extrachromosomal DNA (eccDNA) refers to small, closed-loop DNA molecules that are distinct from the main chromosomal DNA and are found in various eukaryotic organisms. These molecules often originate from chromosome segments, are common in cancer, and can carry oncogenes that drive tumor development, heterogeneity, and resistance to therapy. Their unique circular structure allows for an open chromatin configuration and non-Mendelian inheritance during cell division, contributing to the dynamic nature of the cancer genome.



Circular (zirkuläre) RNA (circRNA) is a type of non-coding RNA that forms a closed, continuous loop instead of a linear structure with distinct 5’ and 3’ ends, like typical messenger RNAs. These stable molecules are generated from pre-mRNA through a process called back-splicing and are thought to be functional, not just byproducts of splicing, playing roles in gene regulation, acting as miRNA sponges, and even serving as templates for protein translation. CircRNAs are increasingly recognized for their involvement in various diseases and their potential as biomarkers and therapeutic targets.





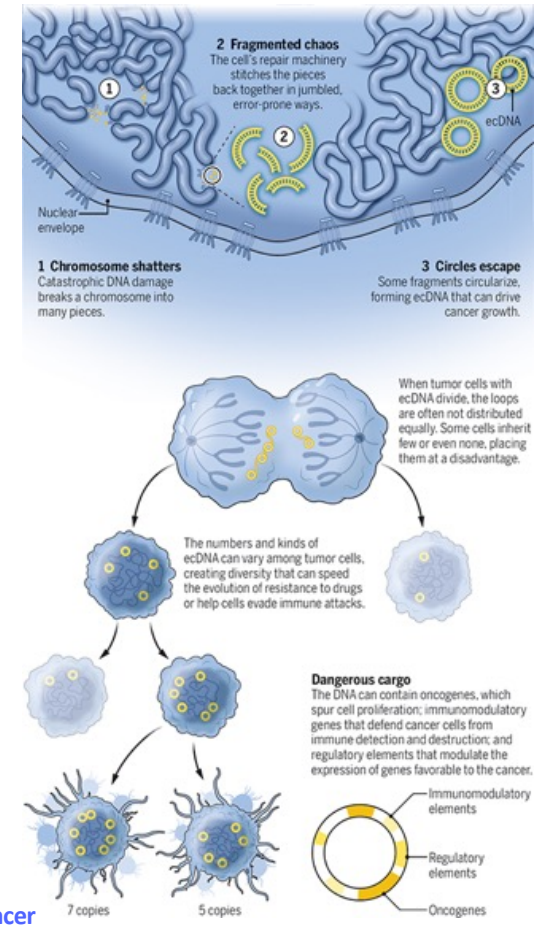
In the loop

Paul Mischel is championing the importance of odd genetic loops in tumors—and their promise as targets for cancer therapy. When Paul Mischel started his lab in the late 1990s, the rules of cancer biology seemed straightforward and solutions finally within reach. A wave of targeted therapies was taking shape. For the first time, it seemed possible to design drugs that didn't just carpet-bomb tumors—with healthy tissue as collateral damage—but struck only malignant cells, taking aim at the precise mutations fueling their growth. In glioblastoma, the lethal brain cancer Mischel had set out to understand and subdue, the target appeared obvious: a gene, encoding a cell surface protein called epidermal growth factor receptor (EGFR), that was amped up to unusually high levels in nearly half of all cases by extra copies found within tumor cells.

Mischel's first curious observation had to do with how quickly glioblastomas adapted to treatment. Within a week or two, tumors that had once bristled with extra copies of the receptor gene, EGFR, shed most of them. That kind of genomic shift should have unfolded gradually, over successive rounds of cell division. Instead, it happened with unsettling speed. Stranger still, cells that had seemingly rid themselves of EGFR retained the uncanny ability to bring it roaring back, spawning new tumors with high gene expression as soon as the drug pressure lifted. It was like watching a doused fire suddenly reignite from cold ash.

The mystery deepened when David Nathanson, a trainee in Mischel's lab, began to examine glioblastoma cells under the microscope. He stained chromosomes blue; *EGFR* was tagged in red. He expected the red signals— the extra copies of *EGFR*—to align neatly along the blue chromosomes. What appeared instead was chaos: scattered red dots drifting across the nucleus, unmoored from any chromosomal structure. "It was really crazy to see," says Nathanson, now a brain cancer biologist at the University of California (UC), Los Angeles.

The receptor gene, it turned out, was traveling on rogue loops of circular DNA.



Circling in on cancer
Cancer cells harbor loops of DNA, separate from the chromosomes, that fuel tumor growth and evolution. First noticed in the 1960s, extrachromosomal DNA (ecDNA) can form in several ways, including when chromosomes shatter during cell division, and is found in greater amounts in more aggressive tumors. Now, scientists are testing drugs to eliminate the loops, hoping for a new type of cancer treatment.

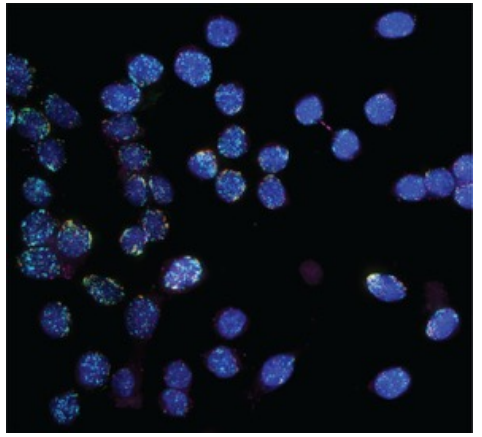
UNBEKNOWNST TO MISCHEL, other groups were converging on these same cancer circles—and detailing how such extrachromosomal elements rewire tumor genomes at breakneck speed. In 2018, cancer biologist Roel Verhaak, now at the Yale School of Medicine, independently spotted ecDNA loops in glioblastoma and showed that they foster genetic diversity; the next year, pediatric oncologist Anton Henssen of the Charité University Hospital of Berlin and computational biologist Richard Koche of Memorial Sloan Kettering Cancer Center tied similar circles to wholesale remodeling of the genome in neuroblastoma, a childhood cancer that develops from immature nerve cells outside the brain.

Howard Chang, a molecular geneticist then at Stanford (and now chief scientific officer of the biotech company Amgen), was closing in on ecDNA as well, though he didn't realize it initially. His lab was focused on the architecture of chromatin—the tightly packed skeins of DNA and proteins in the nucleus that regulate which genes are turned on or off. In cancer cells, Chang and his colleagues noticed unusually large swaths of unpacked DNA, regions where the genome seemed to be bent and rewired to drive massive bursts of oncogene expression. After hearing Mischel present his work on ecDNA, Chang realized that his hot spots were powered not by chromosomes, but by runaway circles, and he joined forces with Mischel.

Rings revealed

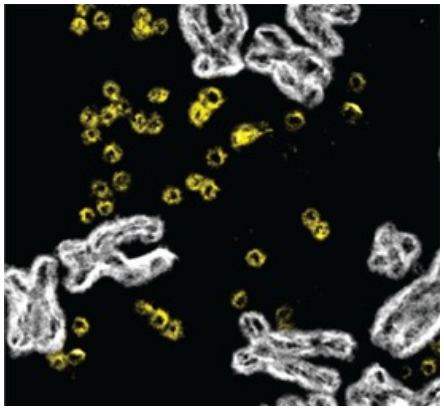
A large study found extrachromosomal DNA in 17% of tumor samples, but some cancer types had it more often.

Glioblastoma **49%**
Stomach **33**
Bladder **25**
Sarcoma **23**
Breast **23**
Colorectal **22**
Ovarian **20**
Liver **17**
Skin **14**
Lung **13**
Pancreatic **2**
Prostate **1**



Gastric cancer cells sparkle with extrachromosomal DNA harboring two oncogenes, one stained red and one green. The genetic circles can cooperate and often travel together as cells divide.

What's more, as tumors grow and cells divide, these hubs often stay intact from one generation to the next, riding into one daughter cell while skipping the other. The result is a patchwork tumor, with some cells brimming with extra cancer-driving genes on the loops while others have far fewer. The whole mass is then primed for rapid evolution. "It's a bet on diversity," says Vincenzo Corbo, a cancer biologist at the University of Verona. "It makes these cells ready to respond to any fluctuation in the environment."



A scanning electron micrograph of extrachromosomal DNA shows the discrete genetic rings (yellow) alongside standard chromosomes (white).

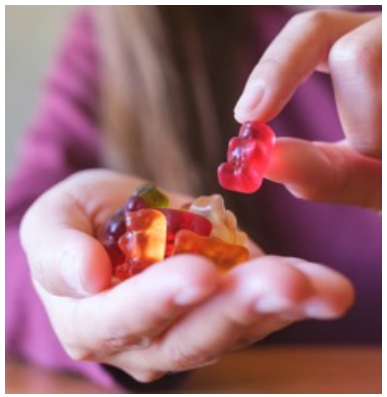
That capacity helps explain the failure of targeted treatments. Traditionally, scientists have pictured tumors developing drug resistance gradually, with a single cell picking up a helpful mutation, growing faster, and gradually pushing out its neighbors. But with ecDNA, the whole population can reshuffle its genetic deck at once.

"This is a totally different way that cancer cells are evolving through more of a bet-hedging approach," says Elizabeth Brunk, a systems biologist at the University of North Carolina at Chapel Hill. The result: Resistance doesn't trickle in from a lone survivor—it erupts from many cells at once, making even the most precisely targeted agent easy for the tumor to dodge.

Mischel hears the caution, yet he is unshaken. He keeps in mind the scattered red dots that first astonished Nathanson, the thrill Holmes felt spotting them in one tumor after another, and the sense of urgency that comes from his belief these circles could finally be turned against cancer. "I'm not letting anything stop this," he says. "At the end of the day, the science is compelling, the clinical need is obvious and real—and, collectively, we'll figure this out."

If he's right, the very circles that let tumors bend the rules of biology may soon be the loophole that brings them down.

Avoid these 5 food additives that may harm your health



1. Carboxymethyl cellulose

Carboxymethyl cellulose is a synthetic emulsifier that improves the texture of ultra-processed food, in part because it prevents oil and water from separating. It's commonly found in such food as ice cream, candy, cookies, salad dressing, sauces and some peanut butters.

2. Polysorbates

Polysorbates are a group of emulsifiers in such things as ice cream, salad dressing, icing, baking mix and frozen dessert. They serve a lot of functions in ultra-processed food. They keep ice cream from melting, they make flavored yogurt smoother and creamier, and they extend the shelf life of other processed food by preventing ingredients from separating.

3. Butylated hydroxyanisole (BHA)

BHA is a synthetic preservative widely found in food such as breakfast cereal, potato chips, frozen pizza, canned soup and cured meat. It's added to animal feed and fried food. It's even used to make tires because it helps to prevent rubber from breaking down.

4. Propyl paraben

One reason tortillas, pastries, jams and baked desserts can stay on store shelves for weeks or months without going rancid is because of preservatives such as propyl paraben. This preservative is widely used to prevent mold and bacteria in a variety of packaged foods. It's also used in drugs, lotions, sunscreens, cosmetics and antiperspirants.

5. Erythritol and xylitol

Erythritol and xylitol belong to a group of low-calorie sweeteners called sugar alcohols. Food manufacturers like using them for a few reasons: They have fewer calories than sugar, they add sweetness to foods without the intensity of artificial sweeteners, and unlike real sugar, they don't cause spikes in your blood sugar levels.

If you want to avoid sugar alcohols, here are a few things you can do:

- Look for sweet foods marketed as keto, low-carb, sugar-free or zero sugar. They're often made with sugar substitutes.
- Look at the nutrition facts label. Food manufacturers sometimes list the amount of sugar alcohols in their products under the section for total carbohydrates.
- Look at the ingredients list. Sugar alcohols typically end in "-ol," such as xylitol, erythritol, maltitol and sorbitol.