

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

The weekly Clinical Journal Club by Dr. Friedrich C. Luft

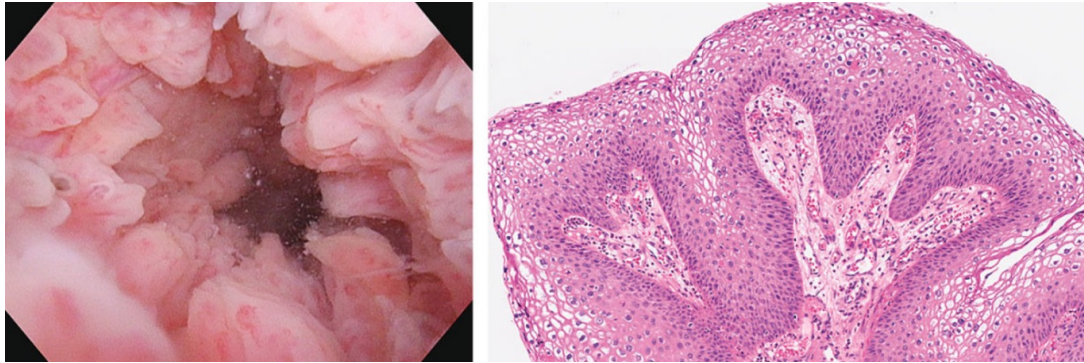
Usually every Wednesday 17:00 - 18:00



Klinische Forschung

Experimental and Clinical Research Center (ECRC) von MDC und Charité

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!](#)



The findings on urethroscopy and histopathological analysis were consistent with condyloma acuminata of the urethra. The penile papules were also excised and found to be condyloma acuminata (genital warts). Human papillomavirus infection leads to condyloma acuminata. A polymerase-chain-reaction assay of the excised penile-lesion specimen was positive for human papilloma virus type 11.

A 42-year-old man on prolonged immunosuppressive therapy for chronic graft-versus-host disease after stem-cell transplantation for acute lymphoblastic leukemia presented to clinic with a 2-week history of urinary frequency and weak stream. Physical examination was notable for several small papules on the penile shaft. Urinalysis showed 9 white cells per high-power field, and a urine culture was negative. Testing for human immunodeficiency virus was also negative. Resected urethral tissue showed papillomatous squamous proliferation with koilocytic atypia. Which of the following causes this condition?

Herpes simplex virus

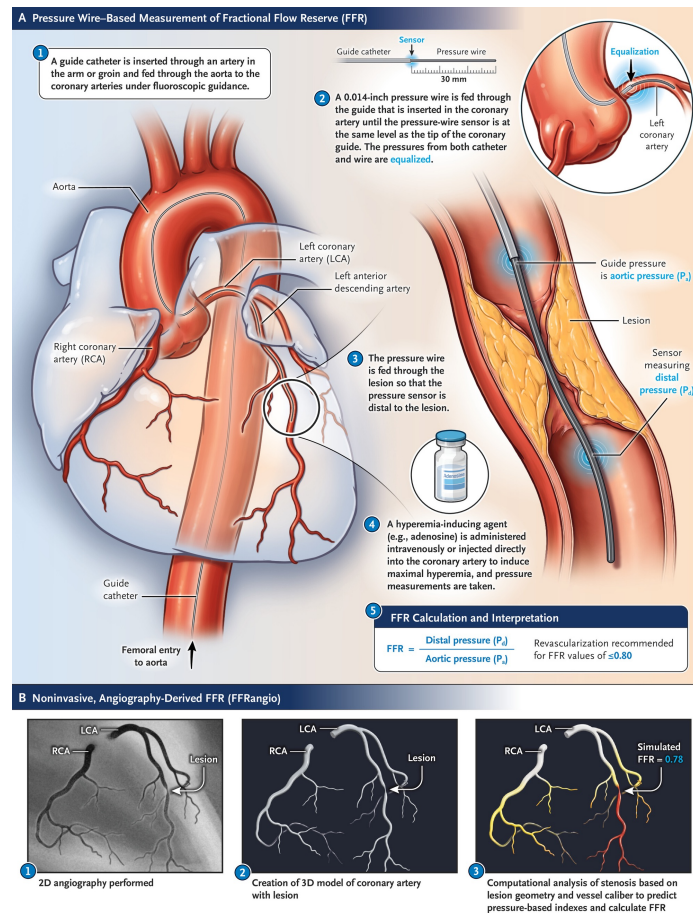
☒ Human papillomavirus

Poxvirus

Treponema pallidum

Ureaplasma urealyticum

Physiological Assessment of Coronary Artery Disease



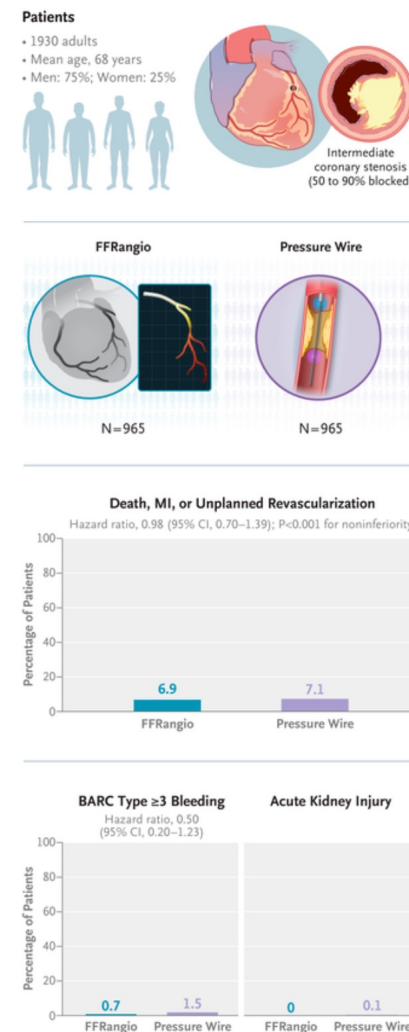
Measurement of Fractional Flow Reserve.

Invasive measurement of fractional flow reserve (FFR) is performed during coronary angiography by advancing a pressure-sensing guidewire across a coronary stenosis (Panel A). Aortic pressure (P_a) is recorded at the guiding catheter, and distal coronary pressure (P_d) is measured by the sensor on the wire positioned beyond the lesion. To minimize and stabilize resistance in the downstream microvasculature, a pharmacologic agent (e.g., adenosine) is administered to induce maximal hyperemia. Under these conditions, coronary flow is assumed to be proportional to pressure, and FFR is defined as P_d divided by P_a . FFR quantifies the fraction of maximal achievable blood flow preserved despite the presence of a stenosis. An FFR value of 0.80 or less is typically considered to be indicative of a hemodynamically significant lesion that would benefit from revascularization. Fearon et al.¹ and Daemen et al.² report in this issue of the *Journal* that FFR derived directly from coronary angiography (Panel B) is noninferior to invasive FFR with respect to a composite of death, myocardial infarction, or revascularization at 1 year.

Angiography-Derived Fractional Flow Reserve to Guide PCI

Assessing intermediate coronary lesions with an **intracoronary pressure wire** improves clinical outcomes in patients undergoing cardiac catheterization and percutaneous coronary intervention (PCI). However, clinical use of pressure-wire–based physiological assessment remains low. Measurement of **fractional flow reserve (FFR) derived from coronary angiographic images alone** correlates well with pressure-wire–based FFR measurements and may simplify procedures, but its effect on clinical outcomes is unknown.

In this international noninferiority trial, we randomly assigned patients undergoing coronary angiography who were found to have at least one intermediate coronary stenosis to physiological assessment with measurements derived from angiographic images (FFRangio) or with pressure-wire–based measurements. **The primary end point was a composite of death, myocardial infarction, or unplanned, clinically indicated coronary revascularization at 1 year.** The noninferiority margin was 3.5 percentage points.



Several randomized trials have shown the benefit of calculating fractional flow reserve (FFR; the ratio, at maximal hyperemia, of the mean arterial blood pressure measured distal to a stenosis to the mean pressure measured before the stenosis) with a coronary-artery pressure wire to evaluate the physiological importance of coronary-artery lesions and guide revascularization decisions in patients with coronary artery disease.

Computer-based software (CathWorks) has been developed to facilitate the assessment of coronary physiological features in the cardiac catheterization laboratory without the use of an intracoronary pressure wire. This computer-based software analyzes coronary angiographic images to create a three-dimensional reconstruction of the coronary-artery tree and apply a resistance model to estimate pressure gradients on the basis of vessel contours. The system (FFRangio) quantifies angiography-derived FFR, which correlates well with pressure-wire–derived FFR but does not require a pressure wire or hyperemic agent. We conducted the Advancing Cath Lab Results with FFRangio Coronary Physiology Assessment (ALL-RISE) trial to determine whether clinical outcomes after physiological assessment of coronary stenoses with FFRangio were noninferior to outcomes after pressure-wire–based assessment to guide revascularization decision making.

Methods

Trial Design

We conducted this international, randomized, noninferiority trial at 59 sites in North America, Europe, Asia, and the Middle East. Eligible participants were randomly assigned in a 1:1 ratio to receive **coronary-artery lesion assessment with the use of FFRangio (FFRangio group)** or a **coronary pressure wire (pressure-wire group)**. Before randomization, investigators identified which lesion or lesions would be the subject of physiological assessment (the study lesion) and successfully treated any nonstudy lesions that required percutaneous coronary intervention (PCI) without physiological assessment.

Trial Procedures

Diagnostic coronary angiography was performed at each site. Patients assigned to the pressure-wire group could undergo either FFR testing or nonhyperemic pressure ratio measurement with any commercially available pressure-wire system. If FFR was measured, either intracoronary or intravenous adenosine or adenosine triphosphate or intracoronary papaverine at recommended doses could be used to induce hyperemia. An FFR value of up to 0.80 or a nonhyperemic pressure ratio value of up to 0.89 was used to indicate a functionally significant lesion warranting PCI, whereas lesions with values above these cutoffs were to be treated medically.

End Points

The primary end point was a composite of death from any cause, myocardial infarction, or unplanned, clinically indicated revascularization at 1 year.

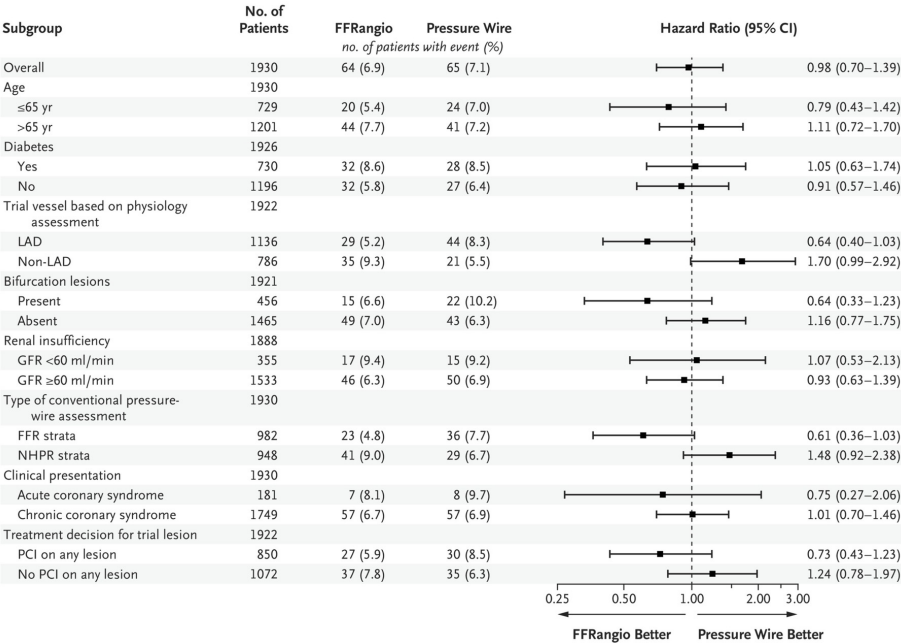
Characteristic	FFRangio (N=965)	Pressure Wire† (N=965)
Age — yr	68.4±10.1	68.4±10.3
Sex — no. (%)		
Male	729 (75.5)	719 (74.5)
Female	236 (24.5)	246 (25.5)
Race or ethnic group — no. (%)‡		
White	576 (59.7)	596 (61.8)
Asian	238 (24.7)	227 (23.5)
Black	54 (5.6)	49 (5.1)
American Indian or Alaska Native	2 (0.2)	2 (0.2)
Native Hawaiian or Pacific Islander	1 (0.1)	3 (0.3)
Other	35 (3.6)	34 (3.5)
Not reported	59 (6.1)	54 (5.6)
Body-mass index§	28.2±5.8	28.2±5.7
Diabetes — no./total no. (%)	381/964 (39.5)	349/962 (36.3)
Insulin dependent — no./total no. (%)	130/964 (13.5)	111/962 (11.5)
Hypertension — no./total no. (%)	757/964 (78.5)	769/962 (79.9)
Dyslipidemia — no./total no. (%)	759/964 (78.7)	764/962 (79.4)
Smoking status — no./total no. (%)		
Current tobacco user	150/964 (15.6)	124/962 (12.9)
Previous tobacco user	343/964 (35.6)	377/962 (39.2)
Family history of CAD — no./total no. (%)	324/964 (33.6)	371/962 (38.6)
Previous myocardial infarction — no./total no. (%)	166/964 (17.2)	158/962 (16.4)
Previous PCI — no./total no. (%)	375/964 (38.9)	375/962 (39.0)
Renal disease — no./total no. (%)	186/944 (19.7)	169/944 (17.9)
Ejection fraction ≤50% — no./total no. (%)	109/799 (13.6)	120/822 (14.6)
Hospitalized with NSTEMI/ACS — no. (%)	96 (9.9)	85 (8.8)

Procedural and Angiographic Characteristics.

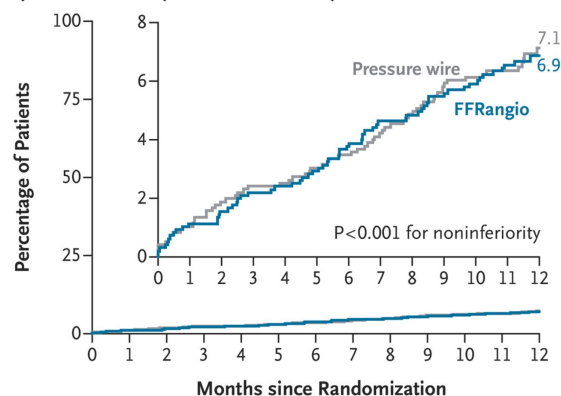
Characteristic	FFRangio (N=965)	Pressure Wire (N=965)
Patients with nonstudy lesions receiving PCI — no. (%)	166 (17.2)	138 (14.3)
Median contrast media amount used (IQR) — ml	100 (52–145)	105 (72–150)
Median fluoroscopy time (IQR) — min	9 (5–17)	12 (8–20)
Median procedure duration (IQR) — min	39 (21–62)	42 (29–60)
Median physiological assessment duration (IQR) — min	6 (4–10)	8 (5–15)
Study lesions — no.	1288	1248
Location — no./total no. (%)		
Left anterior descending	635/1288 (49.3)	624/1248 (50.0)
Left circumflex	277/1288 (21.5)	261/1248 (20.9)
Right coronary	376/1288 (29.2)	363/1248 (29.1)
Reference vessel diameter — mm	2.9±0.6	2.9±0.6
Preprocedure diameter stenosis — %	54.5±12.0	54.5±12.0
Lesion length (IQR) — mm	12.0 (8.0–19.1)	12.5 (8.0–18.8)
Successful physiological assessment — no. (%)	1269/1288 (98.5)	1230/1248 (98.6)
FFRangio-based FFR	0.81±0.12	NA
Wire-based FFR	NA	0.84±0.10
Wire-based NHRP	NA	0.89±0.11
FFRangio-based FFR ≤0.80 — no./total no. (%)	545/1268 (43.0)	NA
Wire-based FFR ≤0.80 or NHRP ≤0.89 — no. (%)	NA	454/1228 (37.0)
No. of study lesions treated with PCI — no. (%)	571/1288 (44.3)	442/1248 (35.4)
Intravascular imaging use — no./total no. (%)	280/571 (49.0)	231/442 (52.3)

End-Point Events at 1 Year.

End-Point Event	FFRangio (N = 965) no. (%)	Pressure Wire (N = 965) no. (%)	Hazard Ratio (95% CI)
Composite primary end point: death, myocardial infarction, or unplanned clinically indicated revascularization†	64 (6.9)	65 (7.1)	0.98 (0.70–1.39)
Secondary end points‡			
Death from any cause	22 (2.3)	19 (2.1)	1.16 (0.63–2.14)
Death from cardiac causes	9 (1.0)	7 (0.7)	1.29 (0.48–3.46)
Myocardial infarction	15 (1.6)	23 (2.5)	0.65 (0.34–1.25)
Spontaneous	12 (1.3)	20 (2.2)	0.60 (0.29–1.22)
Procedural	3 (0.3)	3 (0.3)	1.00 (0.20–4.94)
Unplanned clinically indicated revascularization	37 (4.1)	41 (4.6)	0.90 (0.58–1.40)
PCI	32 (3.5)	39 (4.4)	0.82 (0.51–1.30)
Coronary bypass surgery	5 (0.6)	4 (0.5)	1.26 (0.34–4.68)
Definite or probable stent thrombosis	2 (0.2)	4 (0.5)	0.50 (0.09–2.72)
Safety end points			
BARC stage 3, 4, or 5 bleeding§	7 (0.7)	14 (1.5)	0.50 (0.20–1.23)
Acute kidney injury	0	1 (0.1)	NA



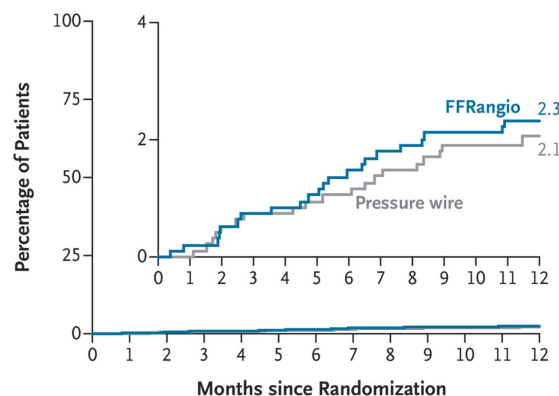
A Primary End Point: Death from Any Cause, Myocardial Infarction, or Unplanned Clinically Indicated Coronary Revascularization



No. at Risk

Pressure wire	965	940	906	859
FFRangio	965	947	907	864

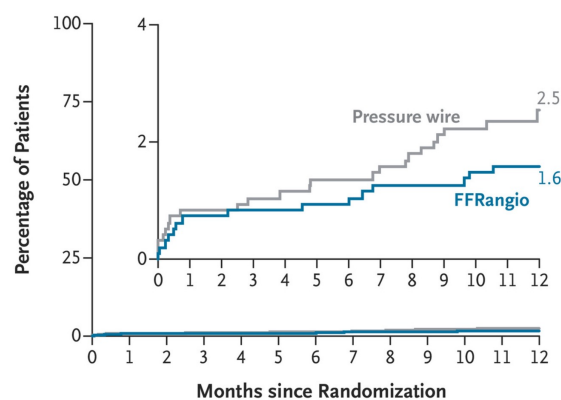
B Death from Any Cause



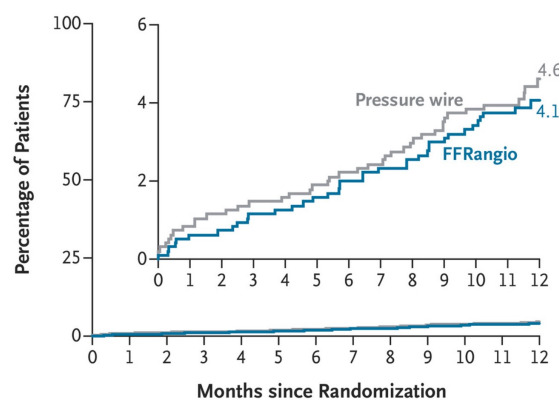
No. at Risk

Pressure wire	965	950	929	905
FFRangio	965	955	927	904

C Myocardial Infarction



D Clinically Indicated Repeat Coronary Revascularization



Composite Primary End Point and Individual Components at 12 Months (Kaplan–Meier Analysis).

Shown is the incidence, at 12 months after randomization, of the composite end point of death from any cause, myocardial infarction, or unplanned clinically indicated coronary revascularization (Panel A), and the individual components of death from any cause (Panel B), myocardial infarction (Panel C), and clinically indicated repeat coronary revascularization (Panel D). The two trial groups were patients who had angiography-derived assessment of fractional flow reserve (FFR; FFRangio group) and patients who had pressure-wire–based FFR or nonhyperemic pressure ratio measurement (pressure-wire group). The 12-month number at risk includes all patients for whom data were available at the 12-month follow-up (days 335 to 395). The insets in each panel show the same data on expanded y axes.

Fractional Flow Reserve (FFR)

Coronary-Artery Pressure Wire



✓ Improves clinical outcomes



Guide revascularization decisions

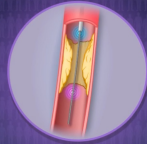
Physiological assessment

FFRangio

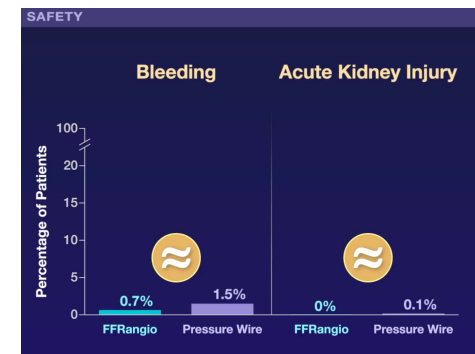


N = 965

Pressure Wire



N = 965



Fractional Flow Reserve (FFR)

Coronary Angiographic Images Alone



✓ Correlate well with pressure-wire-based FFR

✓ May simplify procedures

Coronary-Artery Pressure Wire



✓ Improves clinical outcomes

! Use remains low

PRIMARY END POINT

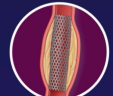
A composite of:



Death



Myocardial infarction

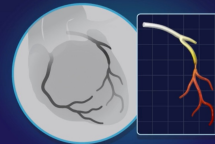


Unplanned clinically indicated coronary revascularization

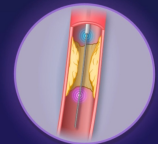
At 1 year

CONCLUSION

FFRangio



Pressure Wire



✓ **Noninferior with respect to clinical outcomes at 1 year**

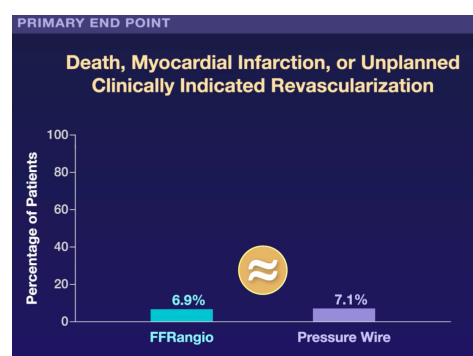
1930 Patients



Undergoing coronary angiography

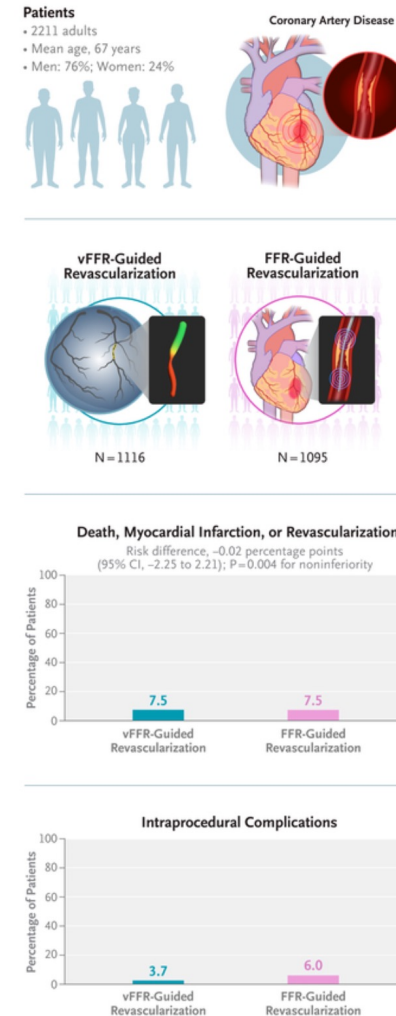


At least one intermediate coronary stenosis (50 to 90% blocked)



Angiography-Based Physiology to Guide Coronary Revascularization

Current society guidelines recommend physiological assessment of intermediate coronary lesions to guide revascularization. Data regarding revascularization guided by vessel **fractional flow reserve (vFFR)**, derived from **three-dimensional quantitative coronary angiography** without the need for a pressure wire or hyperemic agent, as compared with **pressure-wire-based fractional flow reserve (FFR)**, are lacking. We conducted an international, open-label, randomized, noninferiority trial at 37 sites in Europe. Patients with intermediate coronary-artery lesions (diameter stenosis of 30 to 80%) who presented with chronic or acute coronary syndromes were randomly assigned in a 1:1 ratio to undergo either vFFR-guided or FFR-guided revascularization of the intermediate coronary-artery lesions. The primary end point was a **composite of death from any cause, any myocardial infarction, or any revascularization at 1 year**. The noninferiority margin was 3.0 percentage points.



Guidelines for the management of coronary artery disease recommend the use of fractional flow reserve (FFR) to guide revascularization of intermediate coronary-artery lesions in the absence of noninvasive ischemia testing. With the intention to increase adoption of physiological guidance and reduce procedure time by avoiding intracoronary instrumentation and adenosine-induced hyperemia, angiography-based indexes were developed.

Vessel fractional flow reserve (vFFR) (Pie Medical Imaging) derives an FFR value from angiographic images and three-dimensional quantitative coronary angiography by using physical laws that apply to coronary flow behavior, including viscous resistance and effects of separation loss, as described by Gould et al. and Kirkeeide. In prospective, multicenter validation studies, vFFR has shown diagnostic accuracy similar to that of pressure-wire–based FFR.

The Fractional Flow Reserve or 3D-Quantitative-Coronary-Angiography–Based Vessel-FFR–Guided Revascularization (FAST III) trial was designed to assess whether vFFR-guided revascularization is noninferior to FFR-guided revascularization with respect to death from any cause, myocardial infarction, or revascularization.

Methods

Trial Design and Oversight

We conducted an investigator-initiated, international, open-label, randomized, controlled, noninferiority trial.

Patient Selection

Eligible patients were 18 years of age or older and had chronic coronary syndrome, unstable angina, or non–ST-segment elevation acute coronary syndrome and at least one intermediate coronary-artery lesion (diameter stenosis of 30 to 80%, as determined by visual estimation or quantitative coronary angiography) in a native epicardial vessel with a reference diameter of 2.5 mm or greater that was deemed to be suitable for physiological assessment with both vFFR and wire-based FFR.

Randomization, Treatment, and Follow-Up

Patients were randomly assigned in a 1:1 ratio to undergo either **vFFR-guided or FFR-guided revascularization**. Randomization was performed with the use of a concealed, Web-based system, with stratification according to participating center. Patients underwent randomization after clinical and angiographic eligibility criteria were confirmed.

Trial End Points

The primary end point was a **composite of death from any cause**, any myocardial infarction, or any revascularization within 1 year after randomization.

Characteristic	vFFR-Guided Revascularization (N = 1116)	FFR-Guided Revascularization (N = 1095)
Age — yr	67.6±9.9	67.1±9.7
Female sex — no. (%)	266 (23.8)	272 (24.8)
Clinical presentation — no. (%)		
Chronic coronary syndrome	911 (81.6)	886 (80.9)
Unstable angina	77 (6.9)	75 (6.8)
Non-STEMI†	128 (11.5)	134 (12.2)
Medical history — no. (%)		
Hypertension	808 (72.4)	794 (72.5)
Diabetes mellitus	308 (27.6)	281 (25.7)
Dyslipidemia	793 (71.1)	784 (71.6)
Current smoker	221 (19.8)	195 (17.8)
History of PCI	391 (35.0)	380 (34.7)
History of CABG	8 (0.7)	9 (0.8)
History of myocardial infarction	264 (23.7)	251 (22.9)
Peripheral vascular disease	76 (6.8)	97 (8.9)
Atrial fibrillation	147 (13.2)	152 (13.9)
Left ventricular ejection fraction — %‡	54.1±9.9	54.6±10.2
Body-mass index§	27.8±4.8	27.6±4.7
Median eGFR (IQR) — ml/min/1.73 m²¶	76 (56–97)	74 (56–94)
Anatomic SYNTAX Score		
Mean	11.8±8.2	11.5±7.7
Score of <11 — no./total no. (%)	597/1029 (58.0)	604/1031 (58.6)
Score of 11–22 — no./total no. (%)	308/1029 (29.9)	323/1031 (31.3)
Score of >22 — no./total no. (%)	124/1029 (12.1)	104/1031 (10.1)

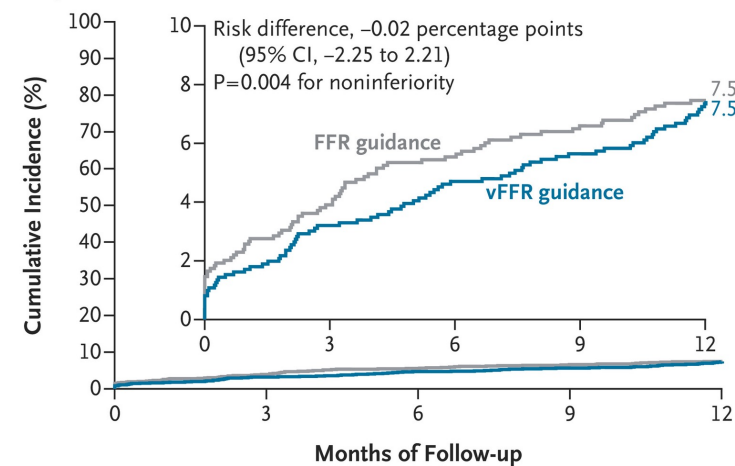
Procedural Characteristics (Full Analysis Set).

Variable	vFFR-Guided Revascularization (N = 1116)	FFR-Guided Revascularization (N = 1095)
Physiological assessment — no. (%)†		
Complete assessment	1079 (96.7)	1085 (99.1)
Assessment completed with the non–randomly assigned strategy	30 (2.7)	4 (0.4)
Incomplete assessment	7 (0.6)	6 (0.5)
Outcome of physiological assessment — no. (%)		
vFFR or FFR value of ≤0.80 in ≥1 study lesion‡§	510 (45.7)	401 (36.6)
vFFR or FFR value of >0.80 in all study lesions‡§	601 (53.9)	688 (62.8)
Assessment could not be performed because of missing vFFR or FFR measurements	5 (0.4)	6 (0.5)
Revascularization		
Revascularization of ≥1 study lesion performed — no. (%)	502 (45.0)	394 (36.0)
PCI — no./total no. (%)¶	481/502 (95.8)	373/394 (94.7)
CABG — no./total no. (%)¶	21/502 (4.2)	21/394 (5.3)
Revascularization of all study lesions performed in accordance with outcome of physiological assessment — no./total no. (%)‡	482/502 (96.0)	379/394 (96.2)
Revascularization of ≥1 study lesion not performed in accordance with outcome of physiological assessment — no./total no. (%)‡§	20/502 (4.0)	15/394 (3.8)
Deferral of revascularization of all study lesions — no. (%)	614 (55.0)	701 (64.0)
Deferral of revascularization of all study lesions in accordance with outcome of physiological assessment — no./total no. (%)‡	592/614 (96.4)	682/701 (97.3)
Deferral of revascularization of ≥1 study lesion not in accordance with outcome of physiological assessment — no./total no. (%)‡§	22/614 (3.6)	19/701 (2.7)
Any revascularization performed — no. (%)¶	659 (59.1)	568 (51.9)
PCI — no./total no. (%)	637/659 (96.7)	547/568 (96.3)
CABG — no./total no. (%)	22/659 (3.3)	21/568 (3.7)
No. of stents placed per patient	0.92±1.13	0.80±1.06
No. among patients who underwent PCI	1.60±1.07	1.60±0.99
Stent length per patient — mm	23.1±30.6	20.7±30.0
Use of intravascular imaging — no. (%)	120 (10.8)	99 (9.0)
Physiological assessment — no. of lesions/total no. (%)		
Assessment successful according to random assignment	1383/1417 (97.6)	1391/1403 (99.1)
Assessment successful with non–randomly assigned strategy	27/1417 (1.9)	6/1403 (0.4)
Assessment not performed successfully	7/1417 (0.5)	6/1403 (0.4)
Outcome of physiological assessment		
Mean vFFR or FFR value	0.80±0.12	0.84±0.09
Median vFFR or FFR value (IQR)	0.83 (0.74–0.89)	0.85 (0.79–0.91)
vFFR or FFR value ≤0.80 — no. of lesions/total no. (%)‡	580/1417 (40.9)	439/1403 (31.3)
vFFR or FFR value >0.80 — no. of lesions/total no. (%)‡	830/1417 (58.6)	958/1403 (68.3)
vFFR or FFR value not available — no. of lesions/total no. (%)‡	7/1417 (0.5)	6/1403 (0.4)

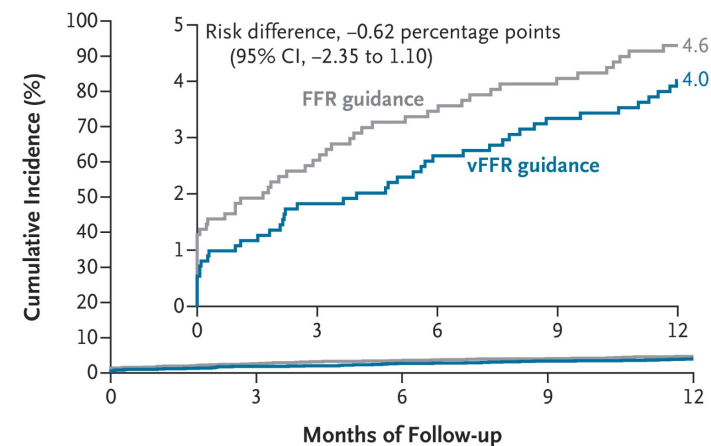
Primary and Secondary End Points.

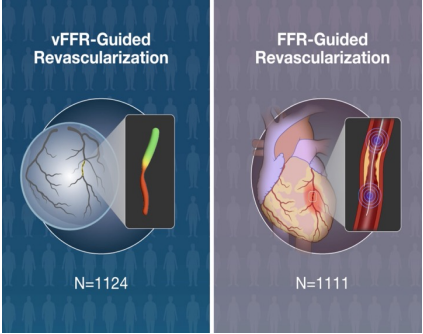
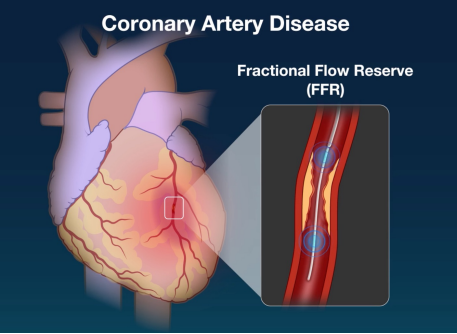
End Point	Full Analysis Set			Per-Protocol Population		
	vFFR-Guided Revascularization (N=1116)	FFR-Guided Revascularization (N=1095)	Risk Difference (95% CI)†	vFFR-Guided Revascularization (N=1047)	FFR-Guided Revascularization (N=1057)	Risk Difference (95% CI)†
	no. (%)			no. (%)		
Primary end point						
Death from any cause, any myocardial infarction, or any revascularization	80 (7.5)	79 (7.5)	-0.02 (-2.25 to 2.21)‡	71 (7.0)	76 (7.4)	-0.40 (-2.65 to 1.86)
Secondary end points						
Study-vessel failure: death from cardiac causes, study-vessel myocardial infarction, or clinically indicated study-vessel revascularization	43 (4.0)	49 (4.6)	-0.62 (-2.35 to 1.10)	38 (3.8)	47 (4.6)	-0.83 (-2.57 to 0.91)
Patient-oriented composite end point§	85 (7.9)	82 (7.8)	0.16 (-2.12 to 2.44)	76 (7.5)	79 (7.7)	-0.20 (-2.51 to 2.11)
Device-oriented composite end point¶	40 (3.7)	41 (3.9)	-0.14 (-1.76 to 1.47)	35 (3.4)	41 (4.0)	-0.54 (-2.18 to 1.10)
Study-oriented composite end point	60 (5.6)	60 (5.7)	-0.08 (-2.04 to 1.87)	52 (5.1)	58 (5.7)	-0.52 (-2.49 to 1.44)
Target-vessel failure**	40 (3.7)	41 (3.9)	-0.14 (-1.76 to 1.48)	36 (3.6)	41 (4.0)	-0.43 (-2.09 to 1.22)
Target-lesion failure**	37 (3.4)	40 (3.8)	-0.33 (-1.90 to 1.25)	33 (3.3)	40 (3.9)	-0.63 (-2.25 to 0.98)
Death from any cause	23 (2.2)	24 (2.3)	-0.11 (-1.37 to 1.14)	19 (1.9)	23 (2.3)	-0.36 (-1.60 to 0.89)
Death from cardiac causes	11 (1.0)	16 (1.5)	-0.47 (-1.43 to 0.48)	9 (0.9)	16 (1.6)	-0.66 (-1.63 to 0.30)
Any myocardial infarction††	31 (2.9)	26 (2.4)	0.44 (-0.92 to 1.80)	28 (2.8)	26 (2.5)	0.24 (-1.15 to 1.64)
Periprocedural myocardial infarction	11 (1.0)	13 (1.2)	-0.20 (-1.08 to 0.68)	10 (1.0)	13 (1.2)	-0.27 (-1.17 to 0.62)
Study-vessel myocardial infarction	19 (1.8)	19 (1.8)	-0.02 (-1.13 to 1.10)	16 (1.6)	19 (1.8)	-0.26 (-1.38 to 0.86)
Any revascularization‡‡	45 (4.2)	44 (4.2)	0.03 (-1.69 to 1.75)	40 (4.0)	42 (4.2)	-0.16 (-1.89 to 1.57)
Clinically indicated revascularization	38 (3.6)	37 (3.5)	0.04 (-1.52 to 1.62)	34 (3.4)	35 (3.5)	-0.06 (-1.66 to 1.53)
Clinically indicated study-vessel revascularization	22 (2.1)	24 (2.3)	-0.23 (-1.48 to 1.02)	19 (1.9)	22 (2.2)	-0.28 (-1.52 to 0.96)
Any stroke	7 (0.6)	4 (0.4)	0.27 (-0.33 to 0.87)	7 (0.7)	4 (0.4)	0.30 (-0.33 to 0.93)
Definite or probable stent thrombosis§§	2 (0.2)	3 (0.3)	-0.09 (-0.49 to 0.32)	2 (0.2)	3 (0.3)	-0.09 (-0.51 to 0.34)

A Death, Myocardial Infarction, or Revascularization

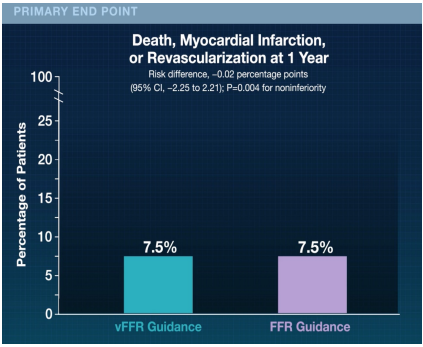
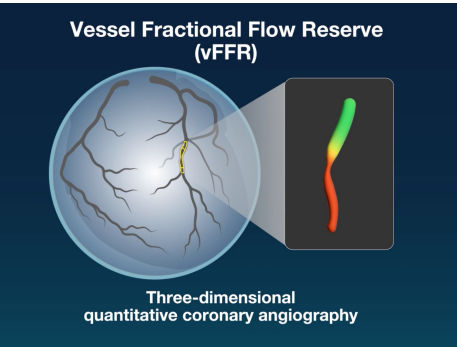


B Study-Vessel Failure





vFFR-guided revascularization was noninferior to an FFR-guided approach in the composite outcome of death, myocardial infarction, or revascularization at 1 year

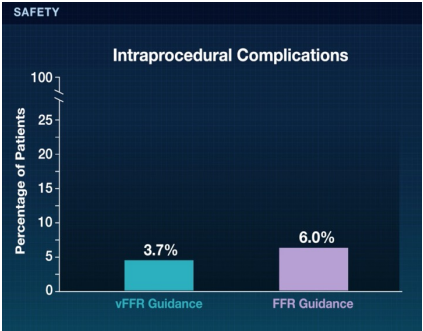


FAST III Trial

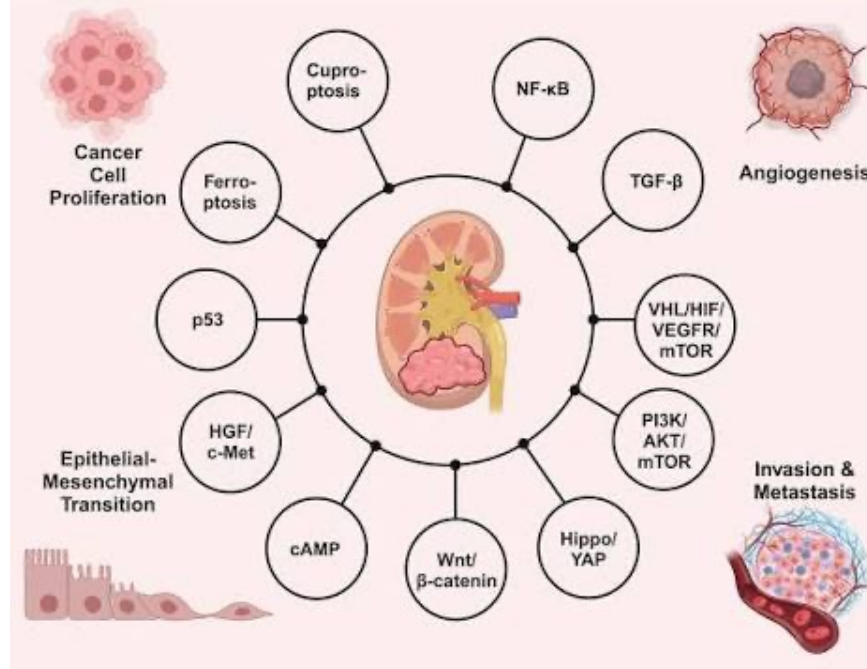
- International
- Open-label
- Randomized
- Controlled
- Noninferiority

• 2235 Patients

- With chronic or acute coronary syndromes
- At least 1 intermediate coronary-artery lesion

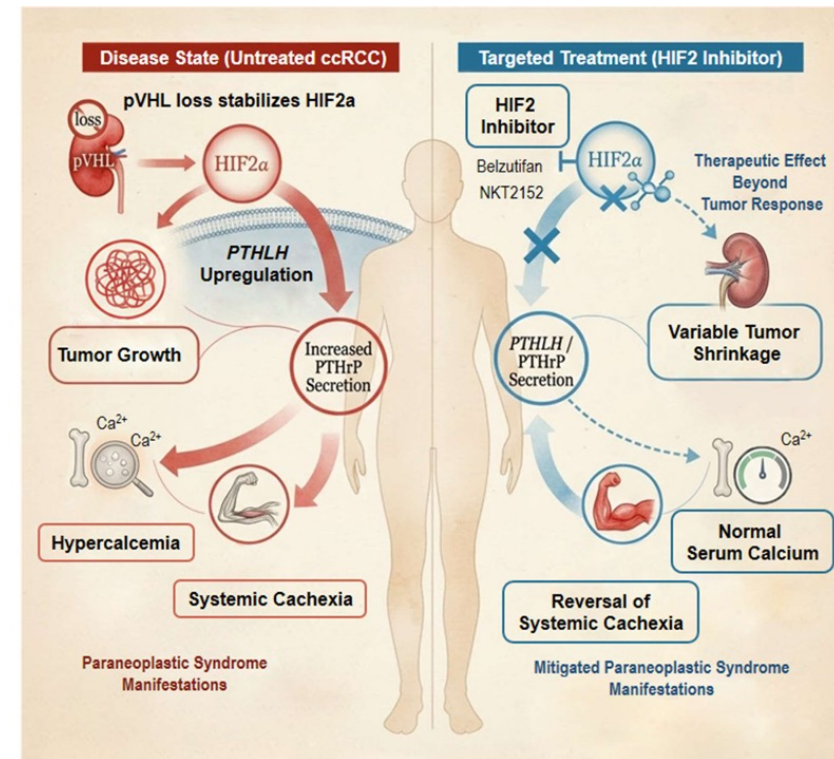


Renal Cancer: Signaling Pathways



The HIF2-PTHrP axis in untreated clear cell renal cell carcinoma (ccRCC) and after targeted HIF2 Inhibitor treatment.

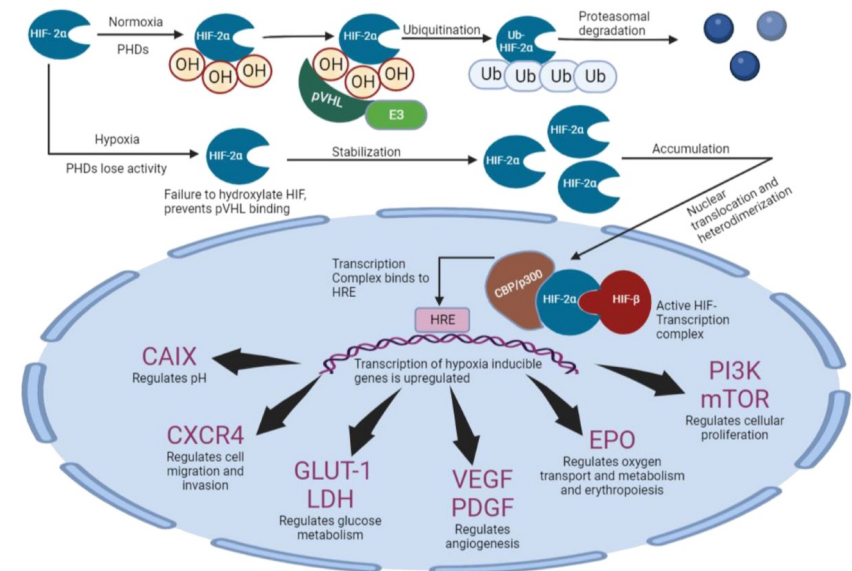
Abbreviations: ccRCC, clear cell renal cell carcinoma; HIF2α, Hypoxia-Inducible Factor-2 alpha; PTHrP, parathyroid hormone-related protein; pVHL, von Hippel-Lindau protein



HIF-2 α (Hypoxie-induzierbarer Faktor-2 α) ist ein zentraler Treiber des klarzelligen Nierenzellkarzinoms (ccRCC) . Bei über 90 % dieser Tumoren führt der Verlust des *VHL* (von-Hippel-Lindau)-Gens dazu, dass HIF-2 α nicht mehr abgebaut wird . Es sammelt sich an und kurbelt massiv das Tumorwachstum und die Gefäßneubildung an.

Mechanismus und Wirkung

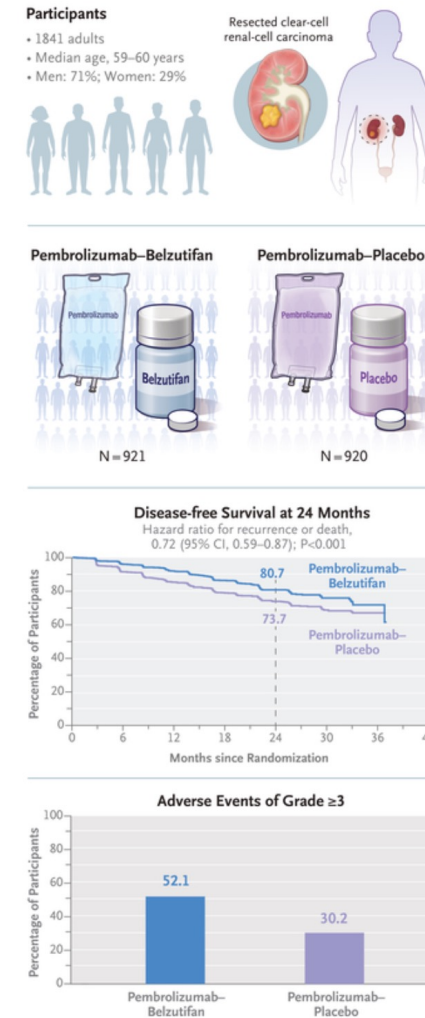
- Pseudo-Hypoxie:** Obwohl ausreichend Sauerstoff vorhanden ist, signalisiert HIF-2 α dem Körper einen Sauerstoffmangel .
- Folge:** Der Tumor bildet neue Blutgefäße, um sich selbst zu versorgen, und der zelluläre Stoffwechsel wird aggressiv auf Wachstum umprogrammiert.



Adjuvant Pembrolizumab plus Belzutifan for Renal-Cell Carcinoma

Adjuvant pembrolizumab improves disease-free and overall survival among patients with resected clear-cell renal-cell carcinoma. The hypoxia-inducible factor 2 α inhibitor belzutifan has activity in advanced disease. Adjuvant pembrolizumab with belzutifan may further improve outcomes in patients with clear-cell renal-cell carcinoma at increased risk for recurrence.

In this phase 3, double-blind trial, we randomly assigned participants in a 1:1 ratio to receive intravenous pembrolizumab at a dose of 400 mg every 6 weeks (≤ 9 doses) and either daily oral belzutifan at a dose of 120 mg (pembrolizumab–belzutifan) or placebo (pembrolizumab–placebo) for up to 1 year. The primary end point was disease-free survival as assessed by the investigator; secondary end points included overall survival and safety.



Adjuvant pembrolizumab is the standard of care for patients with clear-cell renal-cell carcinoma at intermediate-to-high risk for recurrence (tumor stage T2 with nuclear grade 4 or sarcomatoid features or tumor stage T3 of any grade; no regional lymph node or distant metastases) or at high risk for recurrence (tumor stage T4 of any grade with no regional lymph node or distant metastases or any tumor stage with lymph node involvement but no distant metastases) after nephrectomy or nephrectomy and resection of metastatic lesions on the basis of the results from the phase 3 KEYNOTE-564 trial.

Despite this improvement, death or disease recurrence occurs within 5 years or less after nephrectomy in approximately 40% of patients with an increased risk of recurrence. Belzutifan is a potent, selective hypoxia-inducible factor 2 α (HIF-2 α) inhibitor with clinical activity and mainly low-grade toxic effects in patients with localized von Hippel–Lindau disease–associated neoplasms and advanced heavily pretreated clear-cell renal-cell carcinoma.

Trial Design and Treatment

In this phase 3, double-blind, multinational trial, participants were randomly assigned in a 1:1 ratio to receive intravenous pembrolizumab at a dose of 400 mg every 6 weeks with either oral belzutifan at a dose of 120 mg daily (pembrolizumab–belzutifan) or placebo administered daily (pembrolizumab–placebo) as adjuvant therapy after nephrectomy or nephrectomy and metastasectomy. Treatment continued for no more than nine doses of pembrolizumab (approximately 1 year); belzutifan was continued concurrently with pembrolizumab or for 54 weeks or less in the event of pembrolizumab discontinuation.

End Points

The primary end point was disease-free survival, which was defined as the time from randomization to first documented local or distant recurrence as assessed by the investigator or death from any cause, whichever occurred first. Overall survival (defined as the time from randomization to death from any cause) was a key secondary end point; safety was a secondary end point. An exploratory sensitivity analysis of disease-free survival as assessed by central review was conducted.

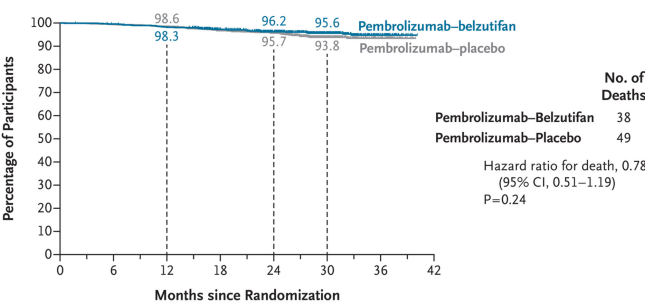
Characteristic	Pembrolizumab– Belzutifan (N = 921)	Pembrolizumab– Placebo (N = 920)
Age		
Median (range) — yr	59.0 (20–91)	60.0 (24–86)
≥65 yr — no. (%)	283 (30.7)	298 (32.4)
Male sex — no. (%)	673 (73.1)	642 (69.8)
Race or ethnic group — no. (%) [†]		
American Indian or Alaska Native	15 (1.6)	17 (1.8)
Asian	267 (29.0)	272 (29.6)
Black	6 (0.7)	7 (0.8)
Multiple	15 (1.6)	19 (2.1)
White	576 (62.5)	581 (63.2)
Missing	42 (4.6)	24 (2.6)
Geographic location — no. (%)		
North America	152 (16.5)	134 (14.6)
Western Europe	310 (33.7)	292 (31.7)
Rest of the world	459 (49.8)	494 (53.7)
PD-L1 status — no. (%) [‡]		
CPS <1	222 (24.1)	217 (23.6)
CPS ≥1	547 (59.4)	502 (54.6)
Not available [§]	152 (16.5)	201 (21.8)
Baseline ECOG performance-status score — no. (%) [¶]		
0	788 (85.6)	777 (84.5)
1	133 (14.4)	143 (15.5)
Risk category — no. (%)		
Intermediate-to-high risk	779 (84.6)	782 (85.0)
High risk	58 (6.3)	53 (5.8)
Tumor stage M1 with no evidence of disease	84 (9.1)	84 (9.1)
Tumor grade — no. (%)		
1	23 (2.5)	36 (3.9)
2	299 (32.5)	292 (31.7)
3	344 (37.4)	336 (36.5)
4	255 (27.7)	256 (27.8)
Primary tumor stage — no. (%)		
T1	22 (2.4)	24 (2.6)
T2	42 (4.6)	55 (6.0)
T3	826 (89.7)	817 (88.8)
T4	31 (3.4)	24 (2.6)
Lymph node stage — no. (%)		
N0 [⌘]	883 (95.9)	879 (95.5)
N1	38 (4.1)	41 (4.5)
Type of nephrectomy — no. (%)		
Partial	101 (11.0)	90 (9.8)
Radical	820 (89.0)	830 (90.2)

Adverse Events (As-Treated Population).

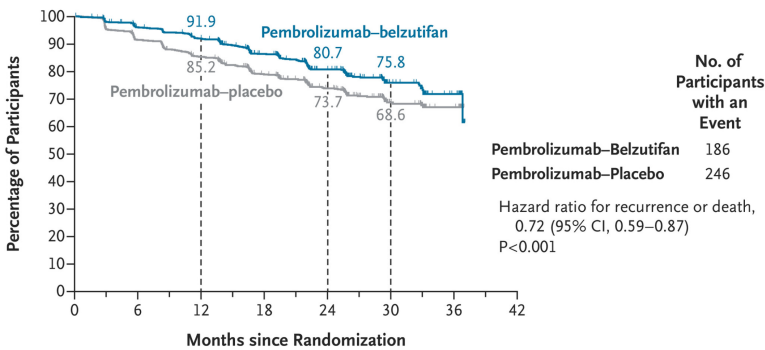
Adverse Event	Pembrolizumab– Belzutifan (N=915)	Pembrolizumab– Placebo (N=913)
	number of participants (percent)	
Adverse events of any cause		
Adverse event of any grade	905 (98.9)	863 (94.5)
Adverse event of grade ≥3	477 (52.1)	276 (30.2)
Death due to an adverse event	10 (1.1)	11 (1.2)
Serious adverse event†	270 (29.5)	182 (19.9)
Discontinuation of any trial regimen because of an adverse event	314 (34.3)	178 (19.5)
Discontinuation of any trial regimen because of a serious adverse event	119 (13.0)	82 (9.0)
Treatment-related adverse events‡		
Adverse event of any grade	884 (96.6)	737 (80.7)
Adverse event of grade ≥3	386 (42.2)	163 (17.9)
Death due to an adverse event	3 (0.3)	3 (0.3)
Serious adverse event†	174 (19.0)	96 (10.5)
Discontinuation of any trial regimen because of an adverse event	293 (32.0)	156 (17.1)
Discontinuation of any trial regimen because of a serious adverse event	104 (11.4)	63 (6.9)

Adverse Events

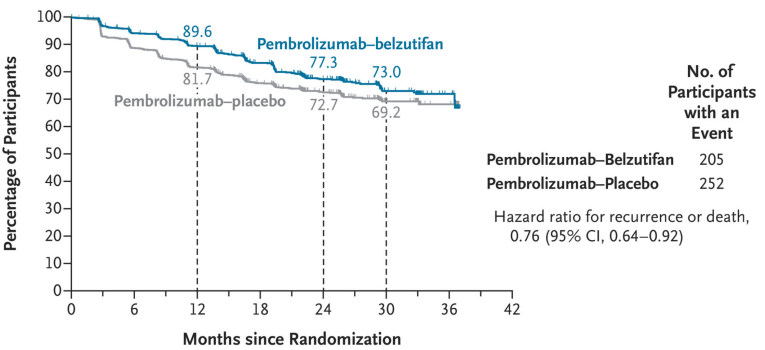
Adverse Event	Pembrolizumab–Belzutifan (N=915)		Pembrolizumab–Placebo (N=913)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	number of participants (percent)			
Any adverse event	905 (98.9)	477 (52.1)	863 (94.5)	276 (30.2)
Anemia	769 (84.0)	111 (12.1)	104 (11.4)	4 (0.4)
Fatigue	333 (36.4)	19 (2.1)	240 (26.3)	6 (0.7)
ALT level increased	264 (28.9)	59 (6.4)	129 (14.1)	18 (2.0)
AST level increased	201 (22.0)	31 (3.4)	109 (11.9)	13 (1.4)
Diarrhea	191 (20.9)	22 (2.4)	148 (16.2)	18 (2.0)
Pruritus	186 (20.3)	1 (0.1)	215 (23.5)	2 (0.2)
Dizziness	177 (19.3)	2 (0.2)	75 (8.2)	0
Headache	155 (16.9)	6 (0.7)	99 (10.8)	1 (0.1)
Nausea	149 (16.3)	3 (0.3)	111 (12.2)	2 (0.2)
Arthralgia	138 (15.1)	5 (0.5)	154 (16.9)	3 (0.3)
Hypothyroidism	136 (14.9)	1 (0.1)	172 (18.8)	1 (0.1)
Asthenia	118 (12.9)	9 (1.0)	68 (7.4)	0
Rash	113 (12.3)	6 (0.7)	141 (15.4)	4 (0.4)
Blood creatinine level increased	110 (12.0)	2 (0.2)	112 (12.3)	2 (0.2)
Dyspnea	98 (10.7)	7 (0.8)	40 (4.4)	1 (0.1)
Hyperthyroidism	70 (7.7)	0	104 (11.4)	0
Cough	69 (7.5)	0	93 (10.2)	0

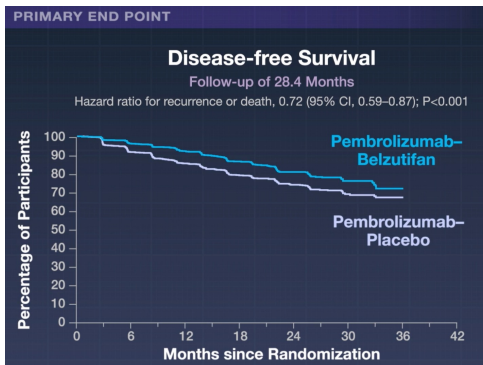
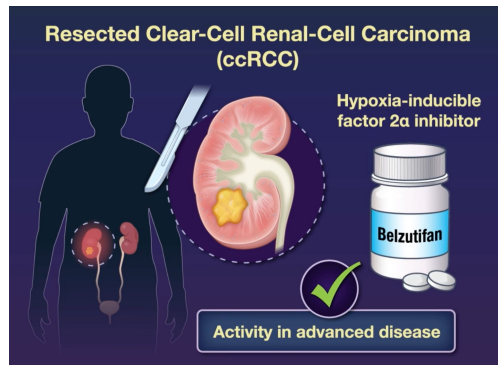
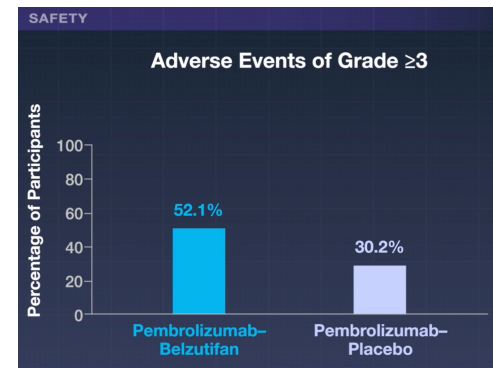
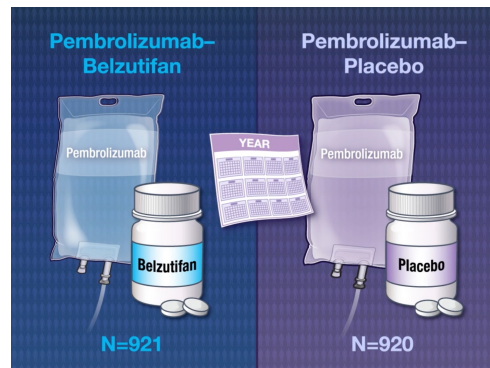
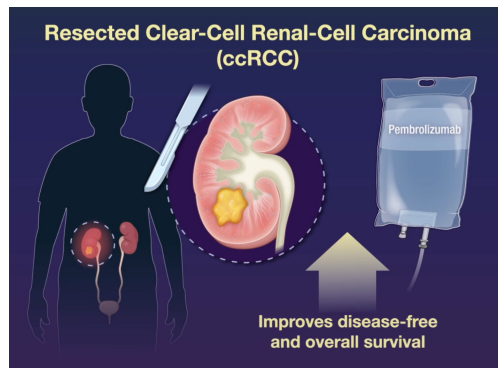


A Disease-free Survival as Assessed by the Investigator in the Primary Analysis

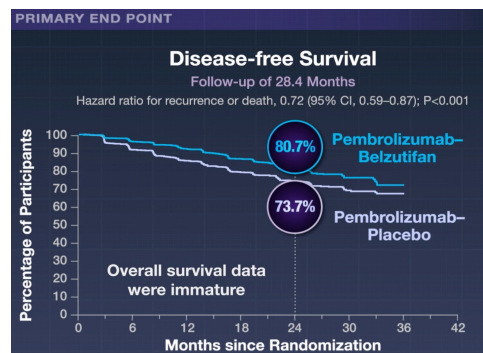


B Disease-free Survival as Assessed by Central Review in the Sensitivity Analysis

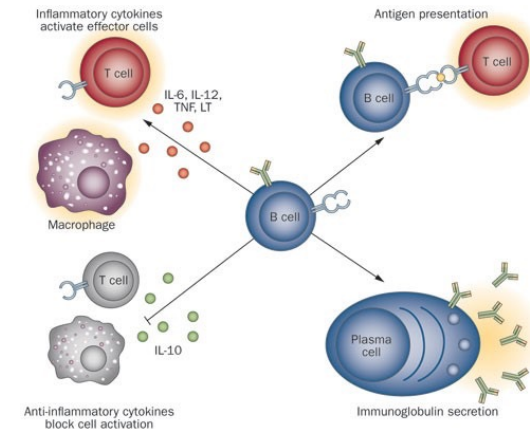




Increased alanine aminotransferase levels (in 5.2% vs. 1.8%), anemia (in 4.0% vs. 0.1%), and increased aspartate aminotransferase levels (in 3.3% vs. 1.6%).



B-Zellen spielen eine entscheidende Rolle bei der Entstehung und dem Verlauf von Multipler Sklerose (MS). Früher wurde MS hauptsächlich als eine Erkrankung angesehen, die durch T-Zellen verursacht wird. Heute weiß man jedoch, dass B-Zellen (eine Untergruppe der weißen Blutkörperchen) maßgeblich an den Entzündungsprozessen beteiligt sind, die die schützende Myelinschicht der Nervenfasern im zentralen Nervensystem (ZNS) zerstören.



Aktivierung anderer Immunzellen: B-Zellen dienen als hocheffiziente Antigenpräsentierende Zellen (APCs). Sie fangen Antigene ein und "zeigen" diese den T-Zellen, was eine aggressive Kettenreaktion des Immunsystems auslöst.

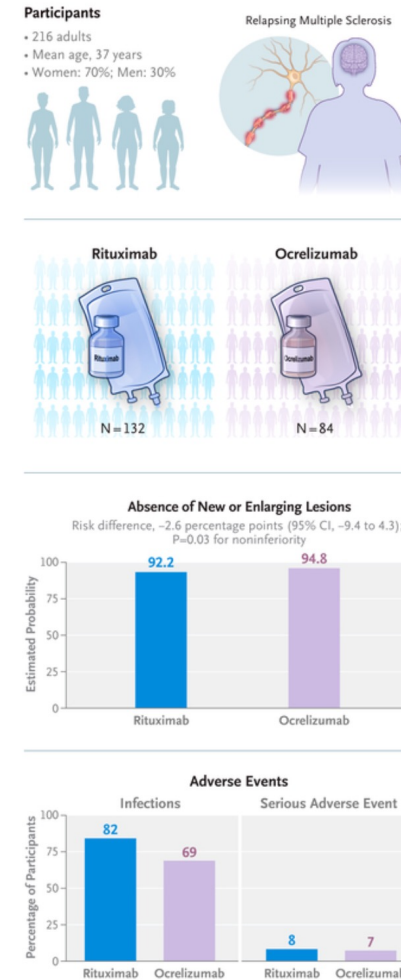
Ausschüttung von Entzündungsstoffen: Sie sondern entzündungsfördernde Botenstoffe (Zytokine) wie IL-6 und GM-CSF ab. Diese Stoffe stacheln das Immunsystem weiter an, das Gehirn und das Rückenmark zu attackieren.

Antikörper-Produktion: B-Zellen reifen zu Plasmazellen heran und produzieren Antikörper. Diese Antikörper lassen sich im Nervenwasser (Liquor) von über 90 % der MS-Betroffenen als sogenannte **oligoklonale Bande** nachweisen.

Bildung von Entzündungsnestern: Bei fortschreitender (progressiver) MS können sich B-Zellen in den Hirnhäuten (Meningen) ansammeln und dort nestartige Gewebestrukturen bilden. Diese halten die Entzündung direkt im Gehirn dauerhaft aufrecht

Rituximab versus Ocrelizumab in Newly Diagnosed Relapsing Multiple Sclerosis

Anti-CD20 monoclonal antibodies are effective for relapsing multiple sclerosis. However, data from head-to-head trials are lacking. In this phase 3, multicenter, double-blind, noninferiority trial, we randomly assigned adults with newly diagnosed relapsing multiple sclerosis and recent disease activity in a 3:2 ratio to receive rituximab or ocrelizumab every 6 months for 24 months. The primary end point was the absence of new or enlarging lesions on T2-weighted magnetic resonance imaging (MRI) from month 6 to month 24. Noninferiority was defined as a lower limit of the 95% confidence interval for the risk difference (rituximab minus ocrelizumab) of greater than or equal to –10 percentage points. Secondary end points included efficacy and safety.



Imaging evidence of inflammatory activity in relapsing multiple sclerosis has been associated with subsequent disability, and observational studies suggest that early use of high-efficacy therapy may improve long-term outcomes. Anti-CD20 monoclonal antibodies are among the most effective therapies for relapsing multiple sclerosis. Rituximab showed efficacy in the phase 2 HERMES trial, with results similar to those in early studies of ocrelizumab. In phase 3 trials, ocrelizumab showed superiority over interferon beta-1a, which led to regulatory approval for its use in relapsing multiple sclerosis. After patent expiration, biosimilar versions of rituximab have facilitated widespread off-label use owing to lower costs. However, comparative evidence between rituximab and ocrelizumab is limited to observational studies subject to residual confounding and heterogeneity in doses and monitoring. We therefore conducted OVERLORD-MS, a randomized, double-blind, head-to-head, noninferiority trial comparing rituximab with ocrelizumab in persons with newly diagnosed relapsing multiple sclerosis.

Methods

Trial Design and Oversight

OVERLORD-MS was a phase 3, randomized, double-blind, multicenter, noninferiority trial conducted at 12 neurology departments in Norway and Sweden. Participants were randomly assigned in a 3:2 ratio to receive rituximab or ocrelizumab and were treated for 24 months, with an additional prespecified blinded follow-up visit at month 30.

Participants

Eligible participants were between 18 and 60 years of age, had received a diagnosis of relapsing multiple sclerosis within the previous 12 months, showed evidence of recent inflammatory disease activity, and had an EDSS score of 0 to 4.0 (on a scale from 0 to 10, with higher scores indicating greater disability).

Interventions

Participants received intravenous rituximab (Rixathon, Sandoz) at a dose of 1000 mg at baseline, followed by 500 mg every 6 months, or intravenous ocrelizumab (Ocrevus, Roche) at a dose of 600 mg at baseline and every 6 months. Premedication included intravenous methylprednisolone (100 mg), oral antihistamine, and antipyretic agents.

Assessments

MRI scans were obtained at baseline and at months 6, 12, and 24. MRI acquisition followed protocol-defined sequences; scanner platforms varied across centers. MRI outcomes, including lesion counts on T2-weighted MRI, contrast-enhancing lesions, and brain volumes, were assessed at a blinded central reading center.

Characteristic	Rituximab (N = 132)	Ocrelizumab (N = 84)	Overall (N = 216)
Age — yr	37.4±9.4	36.6±10.1	37.1±9.7
Female sex — no. (%)	95 (72)	57 (68)	152 (70)
Months since first clinical event	20.8±42.0	24.1±38.3	22.1±40.6
Months since diagnosis	0.6±2.0	0.4±0.5	0.5±1.6
EDSS score†	1.6±1.1	1.7±1.0	1.6±1.1
No. of relapses in past year	1.2±0.4	1.1±0.6	1.2±0.5
Total no. of relapses	1.5±0.7	1.8±1.0	1.6±0.8
Days since last relapse	120±218	131±310	124±257
Current smoker — no. (%)	13 (10)	7 (8)	20 (9)
Body-mass index‡	26.3±5.2	25.9±4.8	26.2±5.0
No. of lesions on T2-weighted MRI — no. (%)			
1–9	12 (9)	13 (15)	25 (12)
10–19	32 (24)	19 (23)	51 (24)
≥20	84 (64)	51 (61)	135 (62)
Missing	4 (3)	1 (1)	5 (2)
No. of contrast-enhancing lesions on T1-weighted MRI before inclusion — no. (%)			
0	70 (53)	48 (57)	118 (55)
1	21 (16)	9 (11)	30 (14)
≥2	35 (27)	25 (30)	60 (28)
Missing	6 (5)	2 (2)	8 (4)
Oligoclonal bands — no. (%)			
Yes	109 (83)	77 (92)	186 (86)
No	3 (2)	2 (2)	5 (2)
Not analyzed or missing	20 (15)	5 (6)	25 (12)

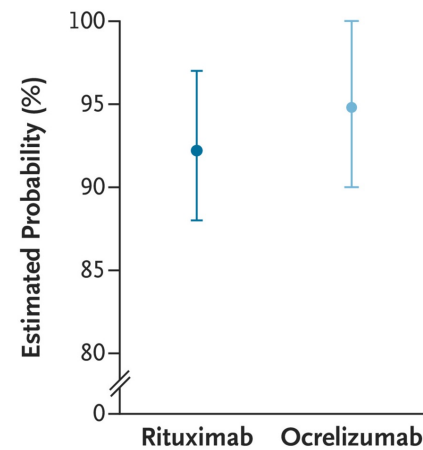
Primary and Secondary End Points during the 2-Year Trial.

End Point	Rituximab (N = 132)	Ocrelizumab (N = 84)
Primary end point		
No new or enlarging lesions on T2-weighted MRI from month 6 to month 24 — no. (%)	117 (89)	78 (93)
Estimated probability of no new or enlarging lesions on T2-weighted MRI (95% CI)	0.92 (0.88 to 0.97)	0.95 (0.90 to 1.00)
Risk difference: rituximab minus ocrelizumab (95% CI)	–0.03 (–0.09 to 0.04)	—
Secondary MRI end points		
No new or enlarging lesions on T2-weighted MRI from baseline to month 6 — no. (%)	98 (74)	65 (77)
Estimated probability of no new or enlarging lesions on T2-weighted MRI (95% CI)	0.78 (0.70 to 0.85)	0.79 (0.71 to 0.88)
No new or enlarging lesions on T2-weighted MRI from baseline to month 24 — no. (%)	94 (71)	61 (73)
Estimated probability of no new or enlarging lesions on T2-weighted MRI (95% CI)	0.80 (0.66 to 0.93)	0.79 (0.66 to 0.91)
Change in brain volume on MRI from baseline to month 24 — %†	–0.70±2.20	–1.75±2.12
Change in brain volume on MRI from month 6 to month 24 — %†	–0.42±1.77	–1.47±1.79
Secondary clinical end points		
Estimated annualized relapse rate over 24 months (95% CI)	0.09 (0.00 to 0.18)	0.04 (0.00 to 0.09)
Mean treatment difference: rituximab minus ocrelizumab (95% CI)	0.05 (–0.02 to 0.12)	—
Freedom from relapse over 24 months — no. (%)	121 (92)	79 (94)
Estimated probability of freedom from relapse (95% CI)	0.92 (0.85 to 0.99)	0.95 (0.89 to 1.00)
Disability progression at month 24, confirmed at month 30 — no. (%)‡	4 (3)	6 (7)
Estimated probability of confirmed disability progression (95% CI)	0.03 (0.00 to 0.07)	0.08 (0.02 to 0.14)
Disability improvement at month 24, confirmed at month 30 — no. (%)‡	38 (29)	20 (24)
Estimated probability of confirmed disability improvement (95% CI)	0.28 (0.16 to 0.40)	0.22 (0.11 to 0.33)
Worsening of SDMT score from baseline to month 24 — no. (%)§	3 (2)	3 (4)
Estimated probability of worsening of SDMT score (95% CI)	0.02 (0.00 to 0.06)	0.03 (0.00 to 0.09)

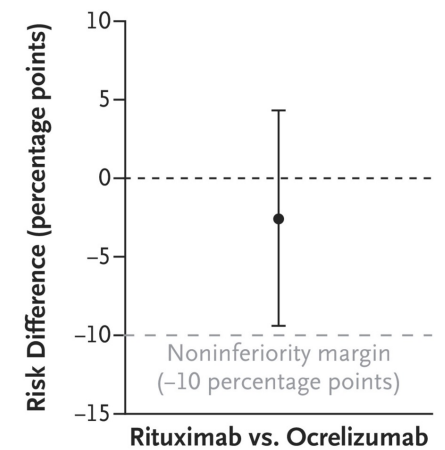
Adverse Events and Serious Adverse Events.

Event	Rituximab (N = 132)	Ocrelizumab (N = 84)
	<i>no. of participants (%)</i>	
Any adverse event	113 (86)	67 (80)
Adverse event leading to treatment discontinuation†	2 (2)	1 (1)
Serious adverse event	10 (8)	6 (7)
Infections‡	108 (82)	58 (69)
Covid-19	63 (48)	43 (51)
Nasopharyngitis	59 (45)	28 (33)
Influenza	24 (18)	10 (12)
Upper respiratory tract infection	10 (8)	7 (8)
Urinary tract infection	11 (8)	6 (7)
Viral gastroenteritis	8 (6)	4 (5)
Pneumonia	3 (2)	3 (4)
Serious infection§	4 (3)	4 (5)
Infusion-related reaction¶	31 (23)	21 (25)
Hypogammaglobulinemia	0	2 (2)
Neoplasm**	0	1 (1)
Death	0	0

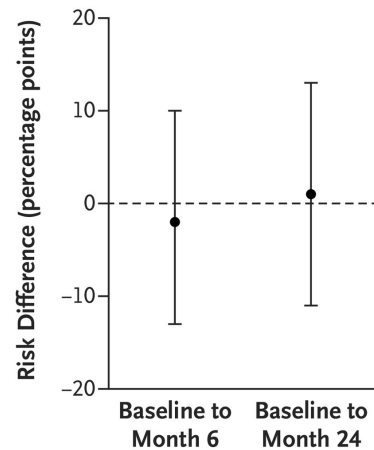
A No New or Enlarging Lesions on T2-Weighted MRI



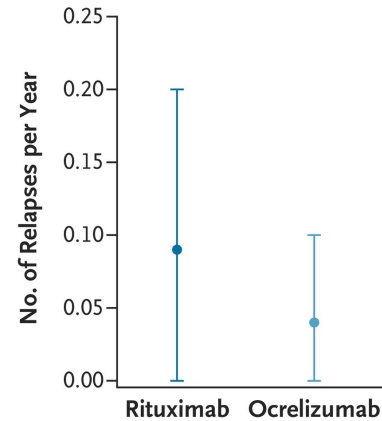
B Noninferiority Test



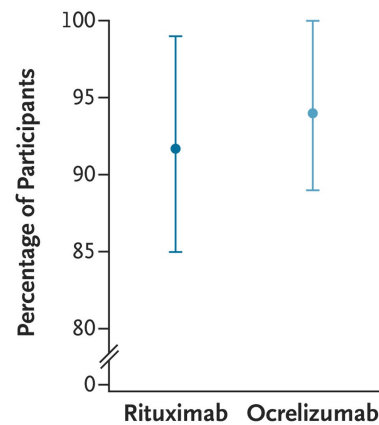
A Risk Differences for No New or Enlarging Lesions on T2-Weighted MRI



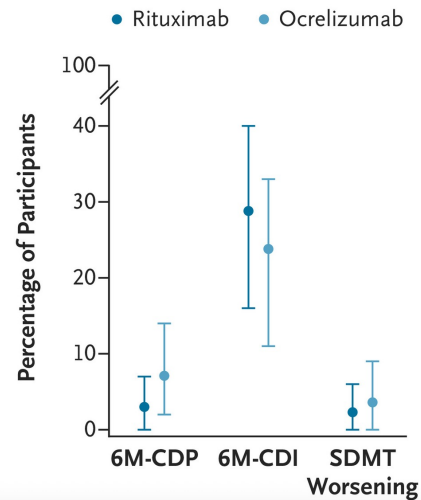
B Annualized Relapse Rate



C Freedom from Relapse

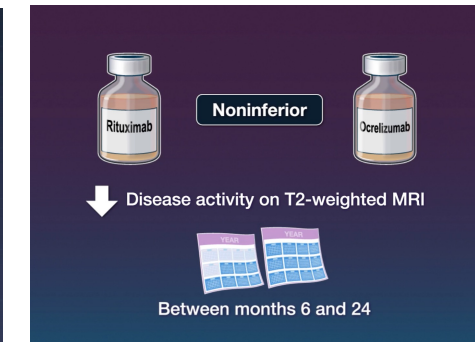
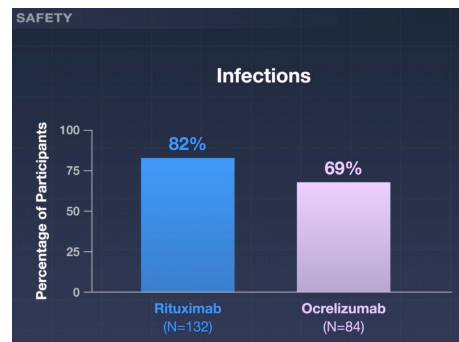
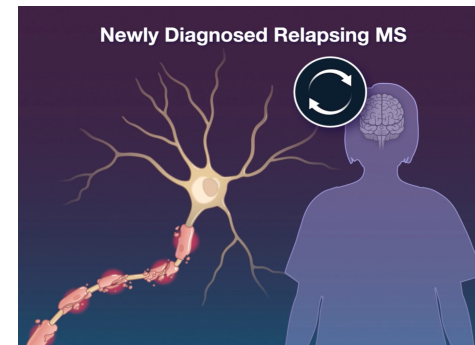
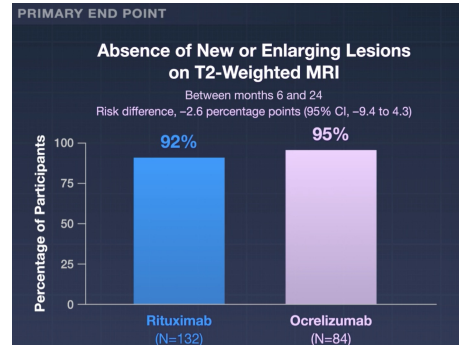
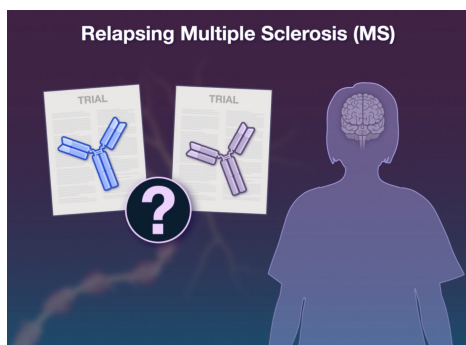
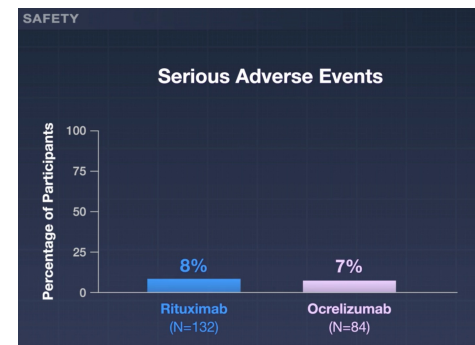
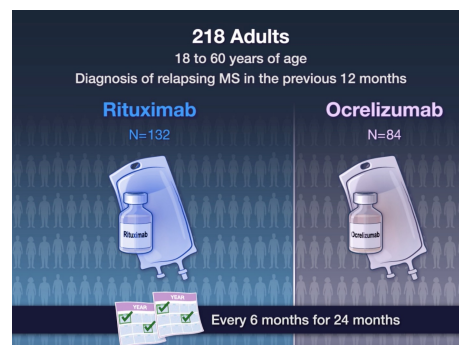
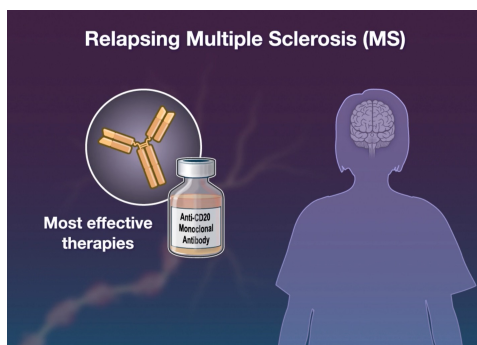


D Disability and Cognitive End Points



Secondary End Points.

Panel A shows the risk differences between treatment groups in the percentage of participants without new or enlarging lesions on T2-weighted MRI from baseline to month 6 and from baseline to month 24; risk differences are calculated as rituximab minus ocrelizumab, and the dashed horizontal line at 0 indicates no difference between groups. Panel B shows the estimated annualized relapse rate over 24 months in the modified intention-to-treat population. Panel C shows the estimated probability of remaining relapse-free from baseline to month 24. Panel D shows the estimated probabilities of confirmed disability progression that was sustained for at least 6 months (6M-CDP), disability improvement that was sustained for at least 6 months (6M-CDI), and worsening of the Symbol Digit Modalities Test (SDMT) score regarding cognitive performance from baseline to month 24, with confirmation at month 30 for disability outcomes. I bars indicate two-sided 95% confidence intervals.

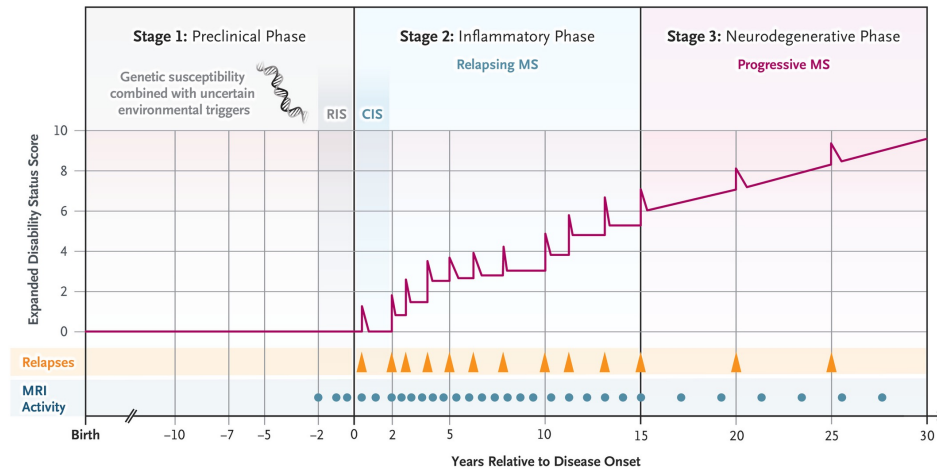


Advances in Multiple Sclerosis

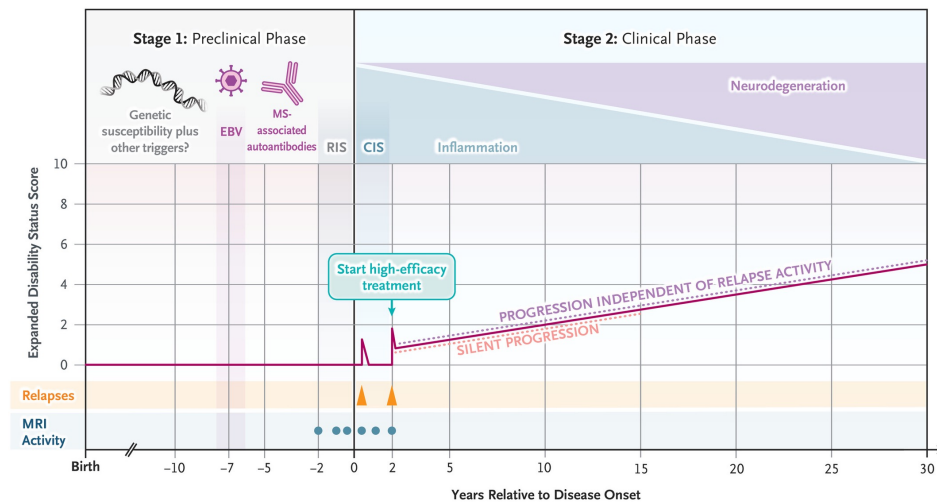
Summary

Multiple sclerosis is a chronic autoimmune disorder that affects the central nervous system, causing episodes of neurologic dysfunction and often gradual disease progression. The immune system primarily targets myelin, the protective covering of nerve fibers, leading to inflammation and damage, and secondary neurodegeneration is a major cause of long-term disability. Common symptoms include vision problems, sensory disturbances, muscle weakness, balance difficulties, and bladder dysfunction. Important advances in treatment have improved outcomes in patients with relapsing forms of multiple sclerosis, particularly through highly effective immune-modifying therapies such as CD20-targeting monoclonal antibodies. However, treatment options for progressive forms remain limited, which highlights the need for therapies that can prevent progression and promote myelin repair. Comprehensive symptom management and lifestyle support are also essential to maintaining quality of life and reducing disability.

A The Traditional Model



B New Concepts in the Current Treatment Era



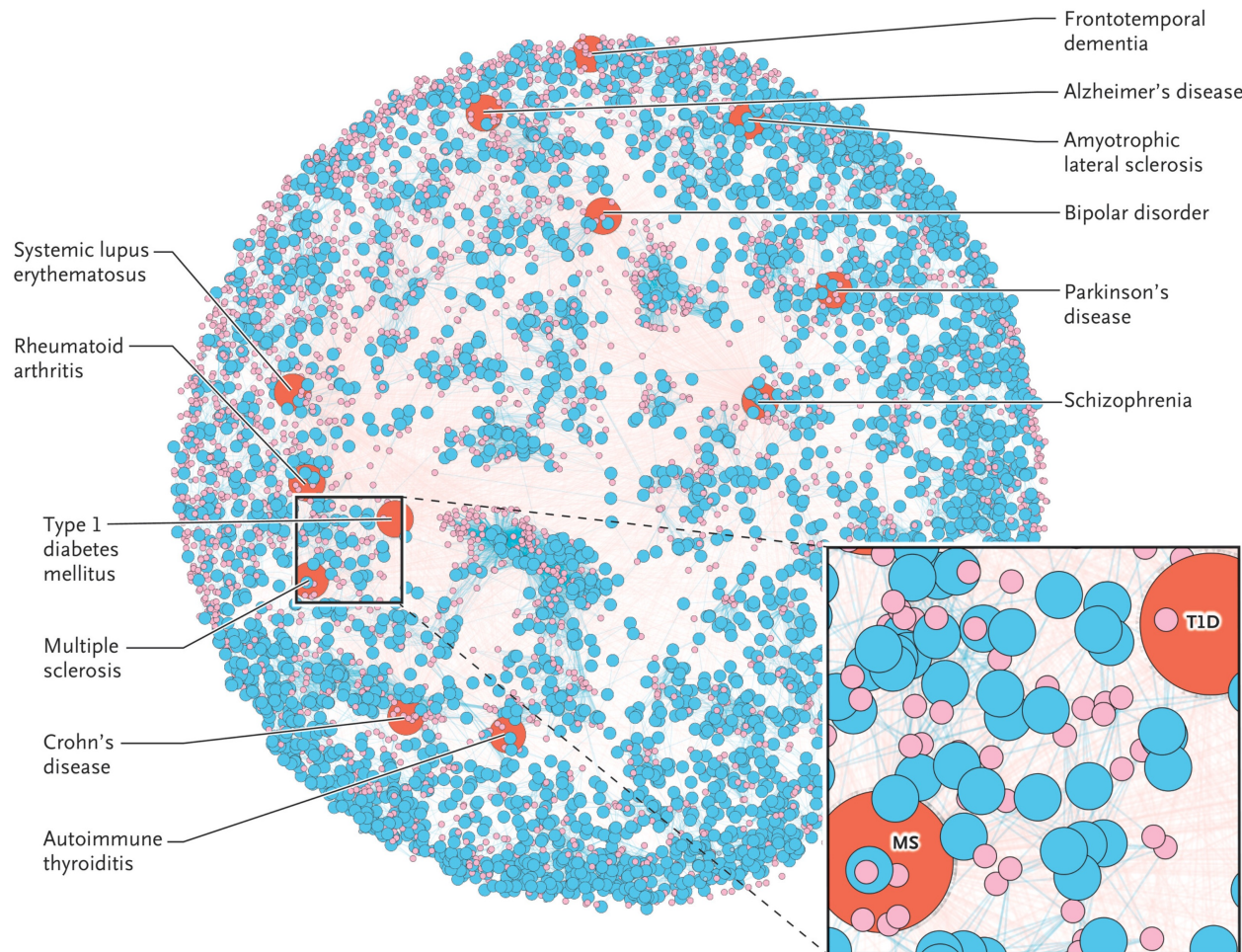
Evolving Understanding of Multiple Sclerosis.

Panel A shows traditional concepts of the natural history of relapsing multiple sclerosis (MS) before the era of highly effective treatment. The purple line indicates disease progression. Disease onset begins after a preclinical phase, with environmental risk factors acting on a genetically susceptible person. Magnetic resonance imaging (MRI) evidence of preclinical MS is occasionally identified in asymptomatic persons (radiologically isolated syndrome [RIS]). The initial attack is designated as a clinically isolated syndrome (CIS). In the traditional model, during the relapsing phase, disability accumulation was thought to result entirely from incomplete recovery from relapses, until clinically significant relapse-independent disability (secondary progressive multiple sclerosis) supervened, on average 15 to 16 years after clinical onset. Less commonly, progressive MS developed without earlier relapses (primary progressive multiple sclerosis; not shown). Panel B summarizes more recent concepts regarding the natural history of MS in the current treatment era. A key role of Epstein-Barr virus (EBV) infection has been established during the preclinical phase, and specific serum autoantibodies cross-reactive to EBV and other proteins are present in some patients. With early treatment, attacks are prevented in most patients, but insidious progression independent of relapse activity, known as silent progression (or progression independent of disease activity), is now evident during the relapsing phase, which reveal that both inflammation and neurodegeneration are present throughout the disease course. In addition, the time to reach permanent disability milestones and secondary progressive multiple sclerosis is substantially lengthened. Scores on the Expanded Disability Status Scale range from 0 to 10, with higher scores indicating worse disability.

KEY POINTS

Advances in Multiple Sclerosis

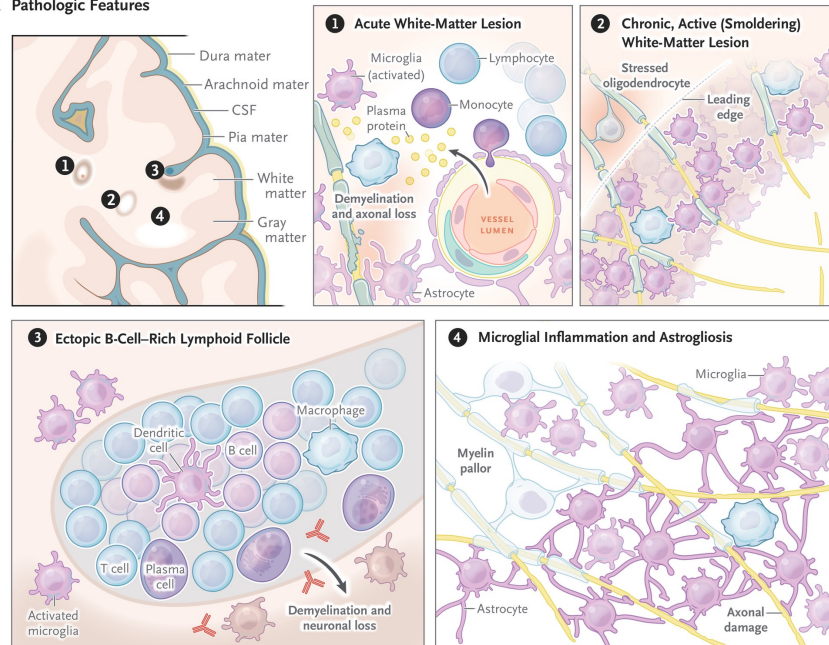
- Multiple sclerosis is a chronic autoimmune disease of the central nervous system that is characterized clinically by acute attacks and gradual progression.
- Myelin is a key target of the autoimmune process, and secondary neurodegeneration is the main contributor to disability.
- Symptoms can include monocular vision loss or double vision, sensory changes, weakness, imbalance, and bladder dysfunction.
- Highly effective disease-modifying treatments now exist for relapsing forms of multiple sclerosis, including monoclonal antibodies that deplete CD20-expressing B cells; these agents have dramatically improved the long-term outlook for patients.
- For pure progressive forms of multiple sclerosis, current disease-modifying therapies have limited efficacy, and more effective treatments to prevent progression and rebuild myelin are needed.
- All patients with multiple sclerosis benefit greatly from effective management of symptoms, including fatigue, spasticity, pain, and bladder dysfunction, as well as avoiding risks of deconditioning, sleep deprivation, and social isolation.



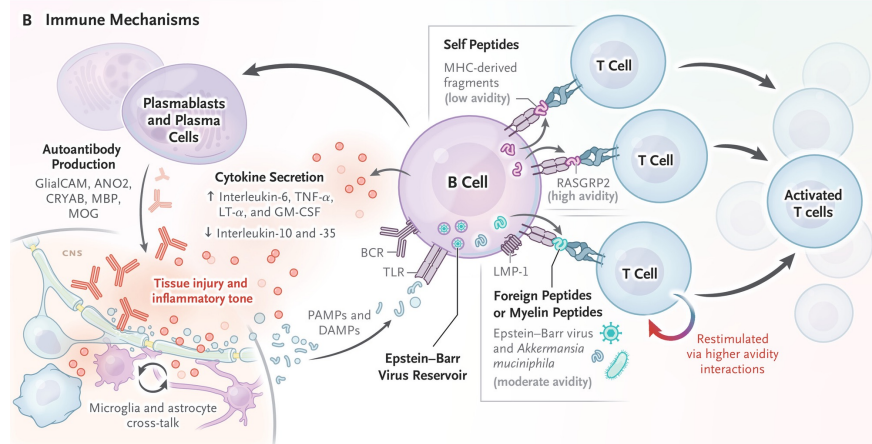
Multiple Sclerosis Genetics Landscape.

Genetic susceptibility for multiple sclerosis clusters with other autoimmune diseases, but not with neurodegenerative diseases. Genetic associations for 12 diseases (6 neurodegenerative and 6 autoimmune) were extracted from the SPOKE (Scalable Precision Medicine Open Knowledge Engine) knowledge graph (which obtains genetic information from the Genome-Wide Association Study Catalog).⁵ Each disease (large red circles) is connected to its associated single-nucleotide polymorphisms (SNPs; small pink circles) by pink lines (shown in expanded view, inset), overall representing the genetic architecture of all 12 diseases. Diseases and SNPs were clustered with the use of the Cytoscape software spring-embedded layout algorithm, which positions diseases next to one another on the basis of shared SNP associations. In a subsequent step, genes (blue circles) were arranged with the same layout algorithm on the basis of the SNPs they contain within their extended boundaries (connected by blue lines, inset). The strongest genomewide locus for multiple sclerosis lies within the major histocompatibility complex on chromosome 6. T1D denotes type 1 diabetes mellitus. Data visualization courtesy of Sergio Baranzini.

A Pathologic Features



B Immune Mechanisms



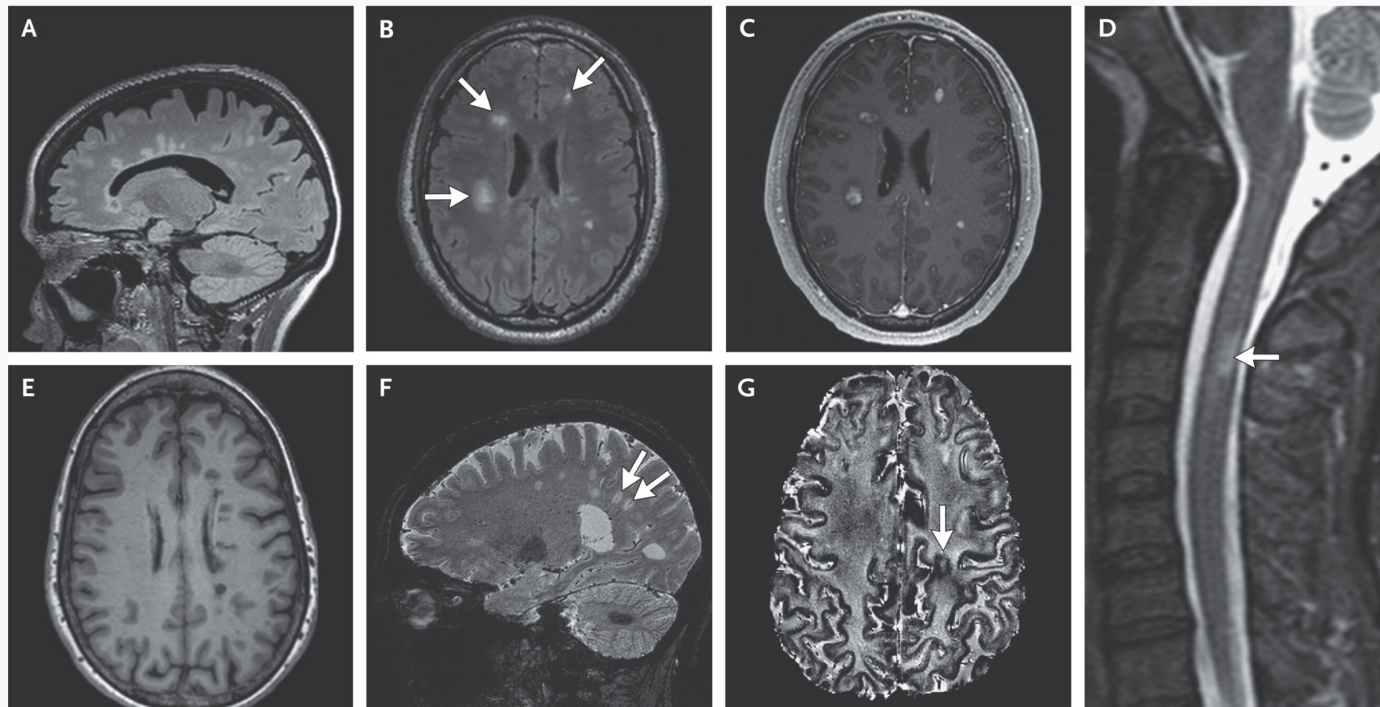
Immunopathogenesis of Multiple Sclerosis.

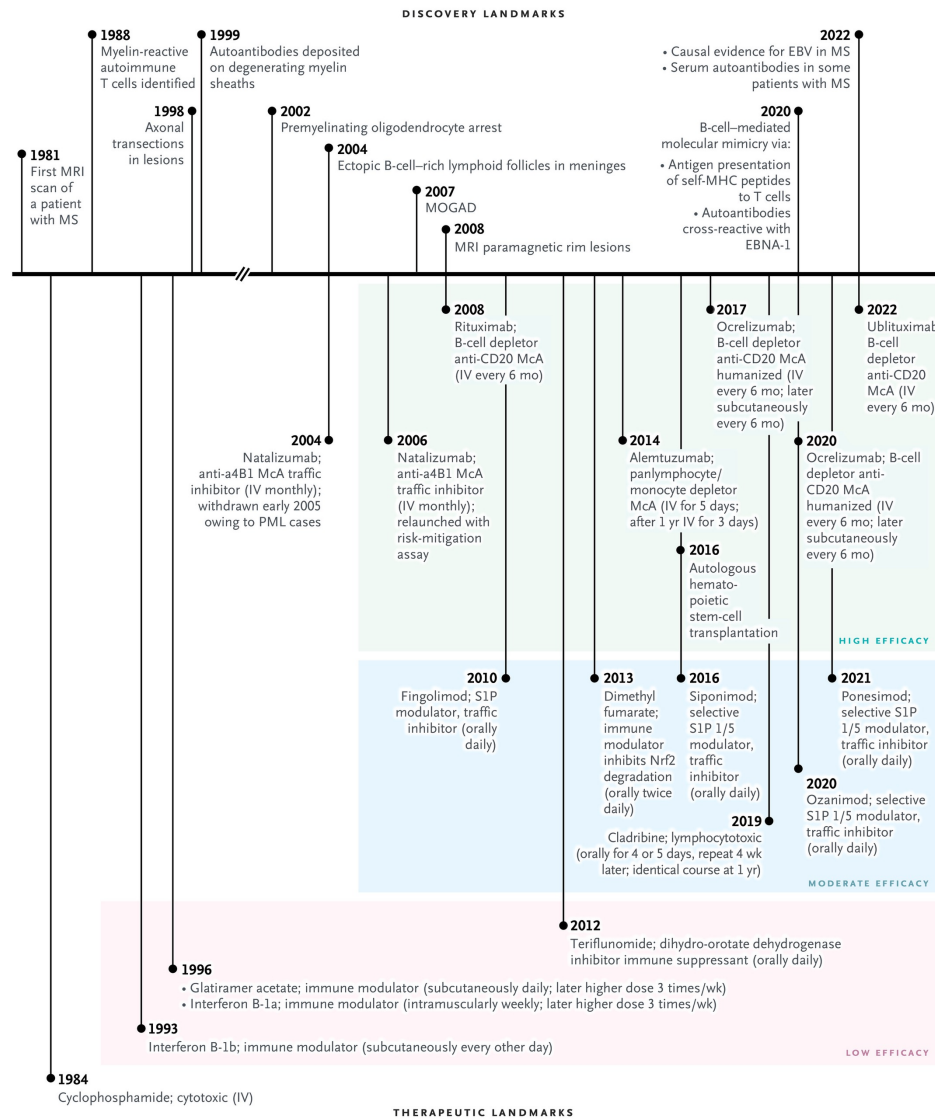
Multiple pathologic features acting over the life span of the illness contribute to relapses, progression, and disability (Panel A). Acute focal inflammatory white-matter lesions are responsible for relapses but are more often asymptomatic; hallmarks are perivenous inflammation with lymphocytes and monocytes, disruption of the blood–brain barrier with leakage of plasma proteins, demyelination associated with activated microglia, astrocyte proliferation (gliosis), and axonal loss with secondary retrograde and anterograde degeneration. Acute lesions can evolve to become slowly enlarging (“smoldering”) chronic active lesions, some with a rim of activated microglia at the leading edge (paramagnetic rim lesions), stressed oligodendrocytes, and progressive axonal injury; other acute lesions become inactive, and in some, partial remyelination can occur. B-cell-rich lymphoid aggregates form in the deep sulci of the meninges, producing underlying cortical demyelination and neuronal loss. In long-standing cases, widespread microglial inflammation and astrogliosis throughout the nervous system is present, associated with myelin pallor and ongoing axonal damage; these changes can be superimposed on age-related neurodegeneration. B cells can contribute to tissue damage in multiple sclerosis through varied mechanisms (Panel B). Antigen presentation of self-peptide fragments derived from major histocompatibility complex (MHC) molecules and other proteins expressed in B cells trigger low avidity activation of a pool of responding T cells, which can be restimulated through higher avidity interactions with

bacterial components as well as cross-reactive myelin antigens.¹⁰⁻¹² Polarized B cells expressing higher than normal levels of disease-associated cytokines (interleukin 6, tumor necrosis factor- α [TNF- α], and lymphotoxin- α [LT- α]) and lower levels of regulatory molecules (interleukin-10 and interleukin-35) promote inflammation.¹³ Autoantibodies targeted to myelin and other components of the central nervous system, produced by B-cell-derived plasmablasts and plasma cells, may also contribute to tissue injury. B cells receive feedback from T cells, in particular T follicular helper cells, which are prominent in the nervous system of persons with multiple sclerosis.¹⁴ Toll-like receptors expressed on B cells can recognize damage-associated signals (pathogen-associated molecular pattern molecules [PAMPs] and damage-associated molecular pattern molecules [DAMPs]), further stimulating inflammation. There is extensive cross-talk between microglia and astrocytes,¹⁵ as well as between B and T lymphocytes.¹⁶ Many cell–cell interactions amplify damage, while others promote resilience and repair.¹⁷ B cells are also the long-term reservoir of Epstein–Barr virus persistence, and B cells infected with Epstein–Barr virus are thought to play a catalytic role in these processes. ANO2 denotes anoctamin-2, CRYAB $\alpha\beta$ crystallin, CSF cerebrospinal fluid, GlialCAM glial-cell adhesion molecule, MBP myelin basic protein, MOG myelin oligodendrocyte glycoprotein, and RASGRP2 RAS guanyl-releasing protein 2.

Features of Multiple Sclerosis on MRI.

In Panel A, sagittal T2 FLAIR (fluid-attenuated inversion recovery) shows multiple lesions involving the corpus callosum with their major axis oriented toward the ependymal surface of the ventricle (Dawson's fingers). In Panel B, postcontrast axial T2 FLAIR shows multiple white-matter lesions within the corona radiata bilaterally, consistent with demyelination. Circumferential halos surround the T2 bright cores (arrows); these changes are related to vasogenic edema often associated with blood-brain barrier disruption in acute inflammatory lesions. In Panel C, a T1 postcontrast MPRAGE (magnetization-prepared rapid gradient echo) image from the patient in Panel B shows heterogeneous enhancement within five of the white-matter lesions in the section, indicating active inflammation and demyelination. In Panel D, a sagittal T2 TIRM (turbo inversion recovery magnitude) sequence of the cervical spine shows a short segment with focally increased T2 signal at the dorsal C2–C3 level (arrow). In Panel E, an axial T1 MPRAGE image of a patient with long-standing disease shows lesions that reveal T1 signal intensity that is lower than that of the gray matter; these lesions are defined as “black holes,” radiologic correlates of lesions that are characterized by greater tissue disruption. In Panel F, a sagittal magnitude image from 3D Echo Planar Imaging (3D-EPI) acquisition reveals multiple lesions with a classic perivenular distribution and a positive central vessel sign (arrows). In Panel G, an axial phase image from 3D-EPI acquisition highlights a paramagnetic rim surrounding a nonenhancing lesion within the left centrum semiovale (arrow); paramagnetic rim lesions can represent a radiologic correlate of chronically active plaques. Images courtesy of Simone Sacco.





Timeline of Selected Advances in Multiple Sclerosis.

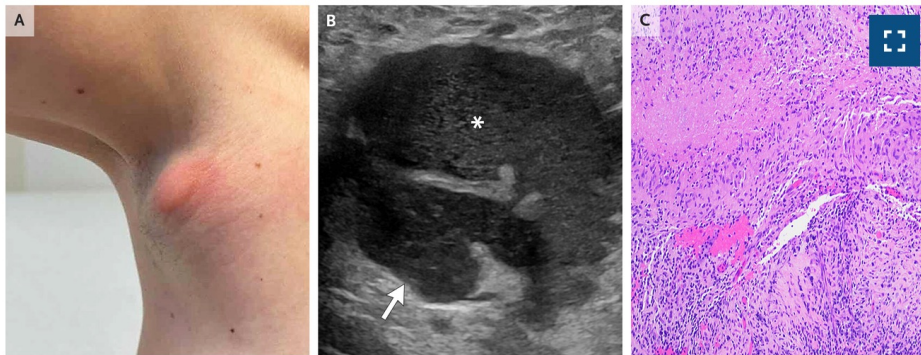
Discovery landmarks are shown above the timeline, and therapeutic landmarks are shown below. Therapies are also grouped according to efficacy tiers, with high efficacy treatments shown in green shading, moderate efficacy treatments in blue shading, and low efficacy in pink shading. IM denotes intramuscular, IV intravenous, McA monoclonal antibody, MHC major histocompatibility complex, MOGAD myelin oligodendrocyte glycoprotein antibody-associated disease, and PML progressive multifocal leukoencephalopathy.

Conclusions and Future Directions

Beyond B-cell therapies, efforts to reduce inflammation include targeting the proinflammatory epitope of fibrin, which is deposited in the subendothelia of multiple sclerosis lesions and triggers microglial activation, as well as approaches that are directed against cytotoxic T cells. Another area of experimental therapeutics is focused on enhancing myelin repair within lesions by promotion of the differentiation of oligodendroglial precursor cells to remyelinate denuded but still-viable axons. A particularly promising target is the M1 muscarinic receptor, and a preliminary clinical trial with the over-the-counter drug clemastine improved visual evoked-potential latencies in patients with relapsing multiple sclerosis, a finding that suggests that remyelination of the visual pathways had occurred.

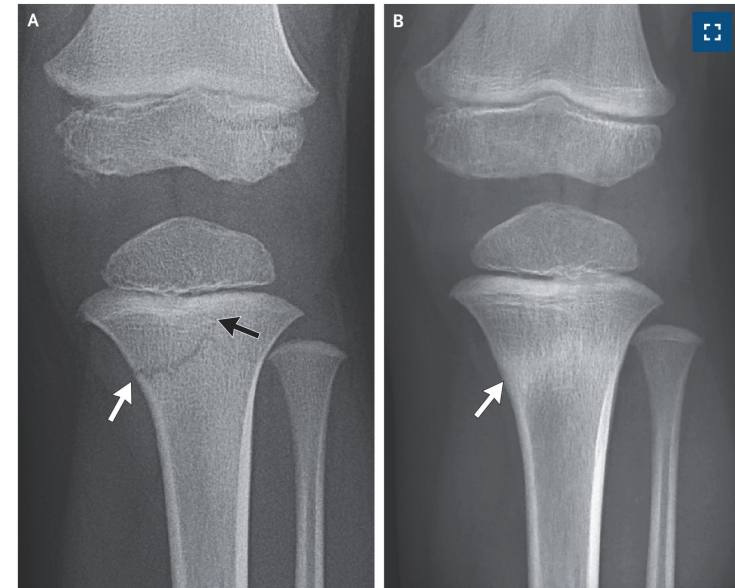
Considerable interest exists around testing the concept that eradication of Epstein–Barr virus would prevent or ameliorate multiple sclerosis. A theoretical challenge to any vaccination approach is the possibility that the vaccine might trigger or worsen multiple sclerosis if the epitopes used for immunization cross-react with critical host proteins. Antiviral drugs, or virus-directed T-cell therapy, would presumably be free of this risk.

Cat Scratch Disease



A previously healthy 40-year-old woman presented to the primary care clinic with a 1-month history of fevers and a 3-week history of swelling in her right armpit that had not abated with a course of trimethoprim–sulfamethoxazole. On physical examination, there was tender lymphadenopathy with overlying erythema in the right axilla (Panel A, anterior view). A cluster of papules and a scar were noted on the distal right index finger, where the patient recalled being bitten by a stray kitten 2.5 months before presentation. Owing to concern for cat scratch disease, azithromycin was prescribed. The fevers abated but the lymphadenopathy persisted; therefore, further evaluation was performed. Ultrasonography showed enlarged lymph nodes (Panel B, arrow) with an adjacent fluid collection (Panel B, asterisk). Histopathological analysis of a core-needle biopsy specimen obtained from a lymph node showed palisading histiocytes surrounding caseous necrosis and granulomatous inflammation (Panel C). Polymerase-chain-reaction testing of a tissue specimen was positive for *Bartonella henselae*. IgG serologic testing for bartonella was also positive. A diagnosis of cat scratch disease was confirmed. Treatment with doxycycline and rifampin was given. Three weeks after initiation of treatment, the lymphadenopathy had worsened and the lymph nodes were leaking pus, so débridement was performed. Three months after initiation of treatment, the symptoms resolved.

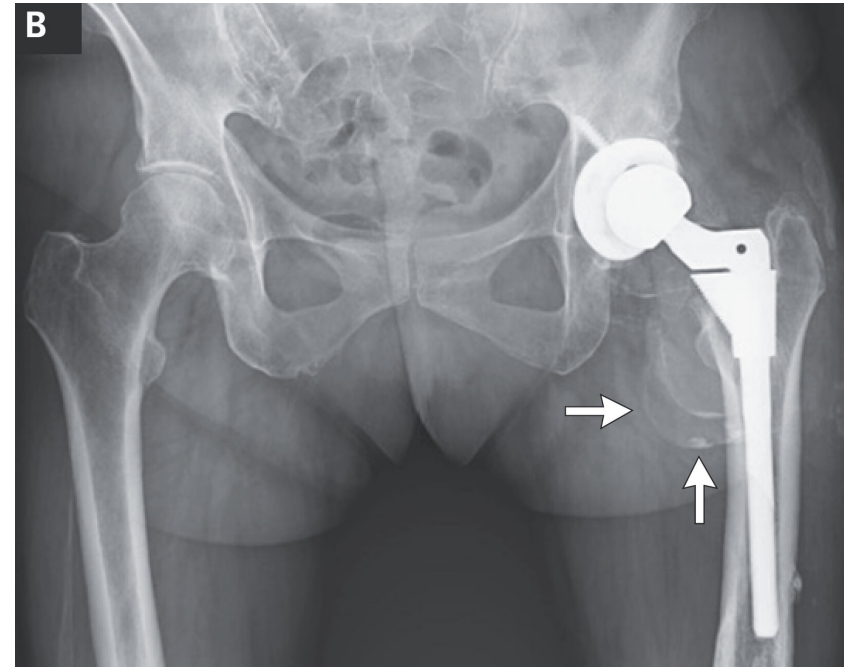
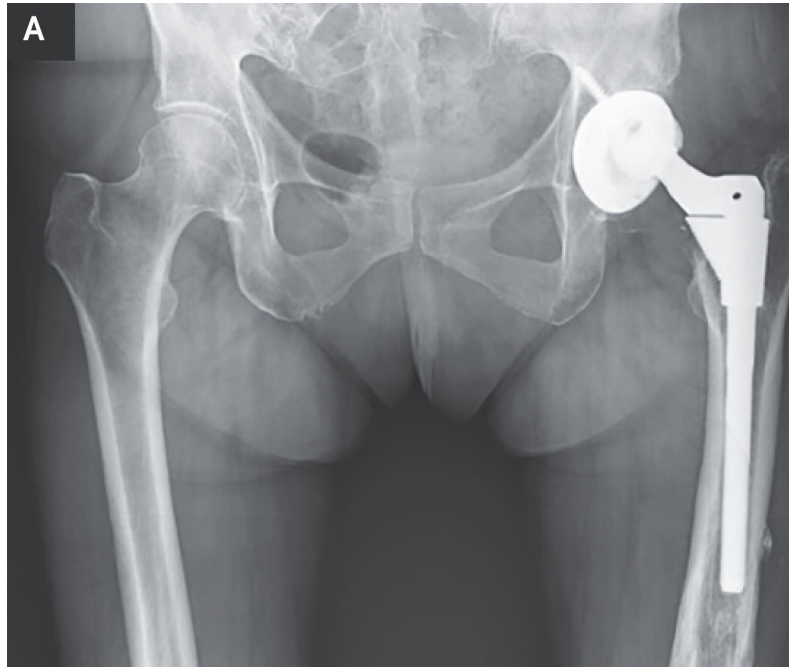
Trampoline Fracture



A previously healthy 4-year-old boy presented to the emergency department with a 1-hour history of leg pain and an inability to bear weight on his left side. While jumping on a trampoline with his father at home, he had leaped higher than usual, landed on his feet, and then felt the leg pain. Physical examination was notable for knee swelling and tenderness to palpation on the left side. Radiographs of the left tibia and fibula showed a nondisplaced fracture of the proximal tibial metaphysis (Panel A, frontal view, white arrow) extending up to the growth plate (black arrow). A diagnosis of a trampoline fracture was made. Trampoline fractures in children typically manifest as transverse, proximal tibial fractures owing to compressive axial forces on the bone while bouncing. The risk of these injuries increases when a heavier person is also jumping and generating increased recoil of the trampoline. Growth-plate involvement in these fractures may result in altered limb growth. After 4 weeks in a cast with no weight bearing, the child started to resume normal activities. Six months after the injury, a repeat radiograph showed interval healing with mild residual sclerosis and no complications of growth-plate involvement (Panel B, arrow).

The Daily Grind

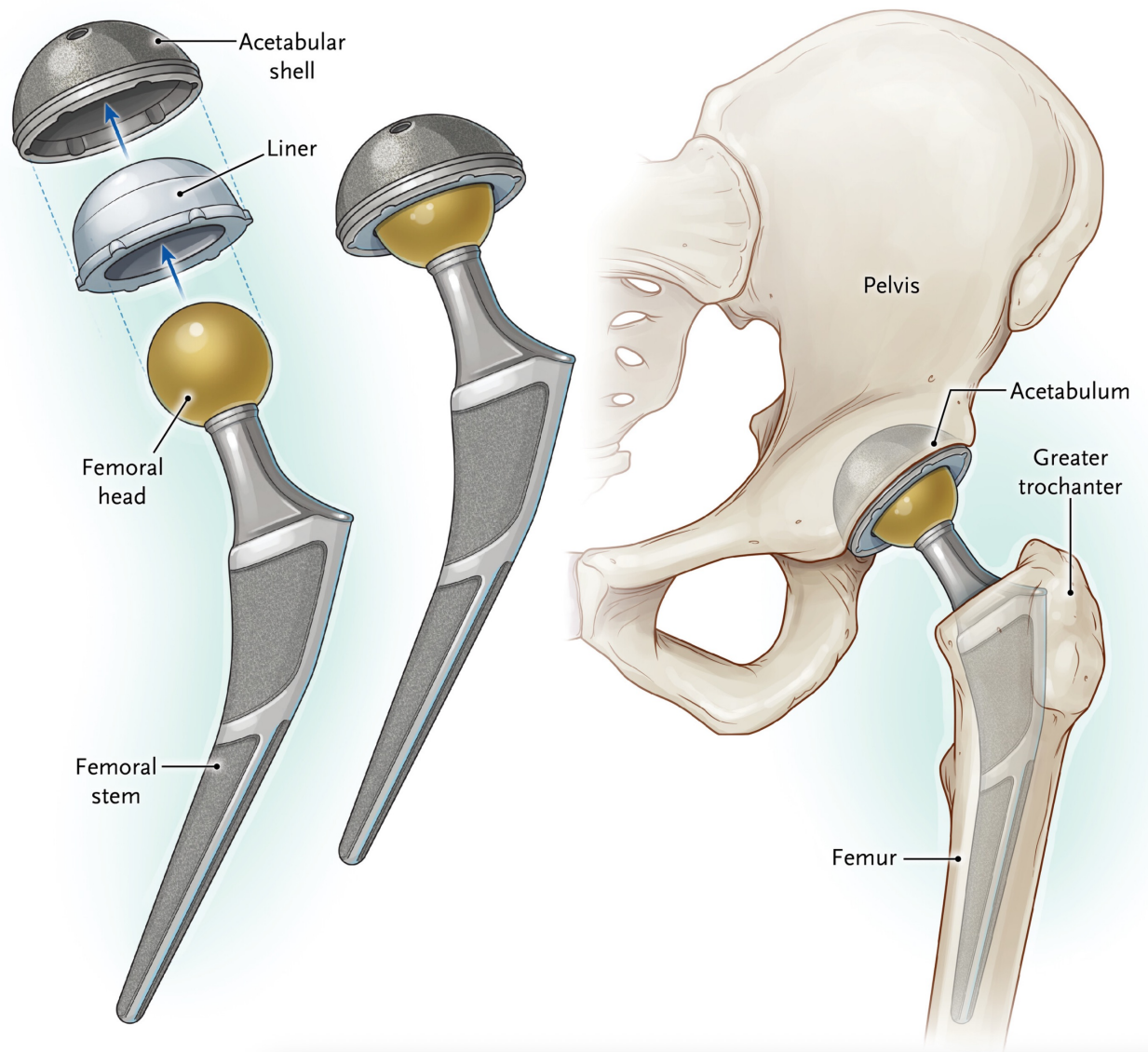
A 56-year-old woman was admitted to the hospital for gait instability. Eight weeks before presentation, she had noticed a gradual onset of **ascending symmetric sensations of painful “pins and needles”** that had begun in her feet. Two weeks before presentation, she began to have short-term memory impairment, difficulty concentrating, irritability, anorexia, and palpitations, along with paresthesias in her hands that were similar to those that had begun in her feet. She was unable to feel her feet on the ground when she walked, which led to frequent stumbling, and she braced herself against walls for stability. She reported no headaches, weakness, or weight loss. Her medical history included **hypertension, hypothyroidism, depression, and anxiety**. Hypothyroidism had been present for more than a decade and had been treated with a stable dose of levothyroxine. Thirty years before presentation, she had been in a vehicle collision that resulted in splenectomy and the development of post-traumatic arthritis of the left hip. **Ten years after the accident** (20 years before the current presentation), **she underwent a left total hip arthroplasty**. Her medications were amlodipine, levothyroxine, and fluoxetine. Four weeks before presentation, her primary care physician increased the levothyroxine dose in response to a newly elevated thyrotropin level of 8.8 μIU per milliliter (normal range, 0.3 to 4.2); the free thyroxine level was 1.5 ng per deciliter (normal range, 0.9 to 1.8). She had consumed approximately **three glasses of wine daily** for the past two decades and had smoked one pack of cigarettes per day for the past 30 years.



Anteroposterior Radiographs of the Pelvis.

A radiograph of the pelvis obtained 12 weeks before presentation (Panel A) shows that the prosthetic femoral head is positioned eccentrically within the acetabular shell, a finding that indicates degradation of the acetabular liner with resultant contact between the femoral head and the acetabular shell. This finding led to revision hip arthroplasty, with exchange to a cobalt–chromium femoral head and a polyethylene liner. A radiograph of the pelvis obtained 12 weeks after implantation of the cobalt–chromium femoral head (Panel B) shows amorphous, cloudlike periarticular opacities that are indicative of a large seroma, along with dispersed radiopaque deposits that are consistent with metallosis.

The patient was afebrile. The blood pressure was 128/90 mm Hg, the heart rate 105 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 24. She was oriented to person, place, and time, but she had some **impairment in memory** (e.g., she was unable to remember what she had eaten for dinner the night before). Aside from tachycardia, her cardiac examination was normal, as were her lung, skin, and abdominal examinations. Her strength was normal in all four limbs. **Sensation to light touch was reduced** in all four limbs, with distal sensory loss in the hands and feet. She had **decreased proprioception and vibratory sensation at the feet and ankles**. Patellar deep-tendon reflexes were normal; ankle reflexes were not assessed. **She had a wide-based gait and had difficulty walking with a tandem gait. The Romberg test was positive.**



Components of Prosthesis in Total Hip Arthroplasty.

The main prosthetic components in total hip arthroplasty are shown separately, assembled, and in position within the native hip joint.

The white-cell count was 12,700 per microliter (of which 81% were neutrophils, 10% were lymphocytes, 7% were monocytes, 1% were eosinophils, and 1% were basophils); the white-cell count was 11,500 per microliter 7 weeks before presentation. The hemoglobin level was 18.8 g per deciliter with a mean corpuscular volume of 86 fl; previous hemoglobin measurements included a level of 12.5 g per deciliter 1 year before presentation, 17.8 g per deciliter 8 weeks before presentation, and 19.0 g per deciliter 1 week before presentation. The platelet count was 209,000 per microliter. The ferritin level was 355 ng per milliliter (normal range, 30 to 336).

The potassium level was 2.4 mmol per liter (normal range, 3.5 to 5.1), the magnesium level 1.6 mg per deciliter (0.7 mmol per liter; normal range, 1.7 to 2.2 mg per deciliter [0.7 to 0.9 mmol per liter]), and the glucose level 250 mg per deciliter (14 millimoles per liter). The glycated hemoglobin level was 7.5%, and the vitamin B₁₂ level 1100 pg per milliliter (812 pmol per liter; normal range, 232 to 1245 pg per milliliter [171 to 919 pmol per liter]). Both the potassium level and the magnesium level normalized after repletion.



Intraoperative Findings of Metallosis in the Left Hip.

During the second revision surgery, a gray fluid collection is present. The gluteus maximus, gluteus medius, and vastus lateralis show diffuse silver-gray discoloration consistent with cobalt-related metallosis. The involved tissue is noncontractile to stimulation and easily débrided, findings that are indicative of metallosis-associated soft-tissue necrosis.

On hospital day 3, the patient underwent a second revision left hip arthroplasty with extensive débridement of the soft tissues, which had been infiltrated by cobalt–chromium. The previous acetabular polyethylene liner was replaced with a new polyethylene liner. The cobalt–chromium femoral head was replaced with a ceramic femoral head.

The same day, chelation therapy with *N*-acetylcysteine and calcium EDTA was initiated. On hospital day 6, the serum cobalt and chromium levels that had been measured preoperatively became available. The cobalt level before surgery was 592 ng per milliliter (normal value, <10), and the chromium level before surgery was 62.4 ng per milliliter (normal value, <0.2).

After surgery, the hemoglobin level had decreased to 14.4 mg per deciliter and remained at that level throughout the hospitalization. Intraoperative blood loss was estimated to be 400 ml. An erythropoietin level was not obtained, and Janus kinase 2 mutation analysis was not performed. Additional chelation therapy with oral succimer (2,3-dimercaptosuccinic acid, at a dose of 650 mg every 8 hours for 2 weeks) and *N*-acetylcysteine (at a dose of 1800 mg twice daily) was prescribed by a medical toxicologist. Metformin was also prescribed; it was discontinued 3 months after discharge because the patient's glycated hemoglobin level had decreased to 5.8%. Six months after discharge, her encephalopathy and ataxic gait had resolved, and the glycated hemoglobin level was 5.5%. The thyrotropin level was 1.12 μ IU per milliliter, and her levothyroxine dose was reduced to her previous dose of 150 μ g daily. The serum cobalt level was less than 10 ng per milliliter.

Commentary

This patient presented with gait instability and cognitive and distal sensory abnormalities. Although a local complication of her recent hip arthroplasty was considered to be a possible cause of her gait difficulties, the concomitant cognitive and sensory dysfunction and the subsequent recognition of new-onset polycythemia and endocrinopathy suggested a systemic disorder. Ultimately, cobalt toxicity from the prosthesis was recognized to be the cause of her multisystem illness.

Cobalt–chromium alloy is used in orthopedic implants because of its hardness, corrosion resistance, and favorable wear properties. Although the use of cobalt–chromium in hip arthroplasty has declined substantially over the past 15 years owing to improvements in ceramics and polyethylene and heightened awareness of metal-related complications, cobalt–chromium components remain in use in selected contexts (such as revision hip arthroplasty and fracture-related hip arthroplasty).

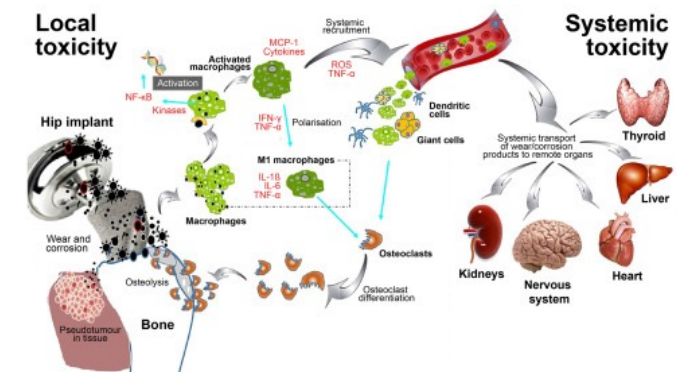
Cobalt toxicity results from mechanical stress on a cobalt component; the resulting metal debris causes a local inflammatory reaction (metallosis), and cobalt enters the bloodstream. In this patient's case, residual ceramic debris formed a “third body,” which refers to the interposition of abrasive particles between the two primary bearing surfaces (the cobalt–chromium femoral head and the polyethylene liner). This mechanism leads to accelerated metal release as compared with the gradual wear that occurs in metal-on-metal articulations.

Eine **Kobaltvergiftung (Cobalt Toxicity)** ist eine seltene, aber ernste Erkrankung, die durch die Aufnahme zu großer Mengen des Schwermetalls Kobalt in den Körper entsteht. Während winzige Mengen Kobalt als Bestandteil von Vitamin B12 lebenswichtig sind, schädigt ein Überschuss lebenswichtige Organe wie das **Herz, die Schilddrüse und das Nervensystem**. **Hauptursachen für eine Vergiftung**

Medizinische Implantate: Die häufigste Ursache im Alltag ist der Verschleiß von fehlerhaften oder abgenutzten **Metall-auf-Metall-Hüftprothesen**. Durch die Reibung gelangen mikroskopische Kobaltpartikel direkt in das umliegende Gewebe und die Blutbahn.

Berufliche Belastung: Arbeiter in der Metallverarbeitung (besonders bei der Herstellung von Wolframkarbid-Hartmetallen), beim Diamantschleifen oder in der Keramikindustrie können feine Kobaltstäube einatmen.

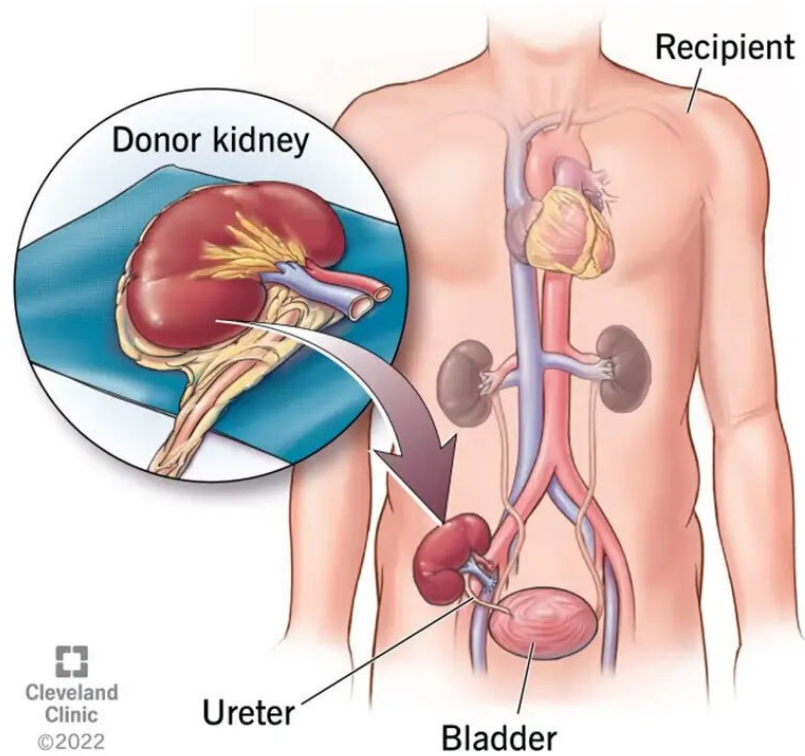
Historische / Nahrungsmittel-Ursachen: In den 1960er Jahren wurde Kobaltsulfat Bier als Schaumstabilisator zugesetzt, was zu schweren Herzschäden bei Konsumenten führte (sogenannte „Biertrinker-Kardiomyopathie“).



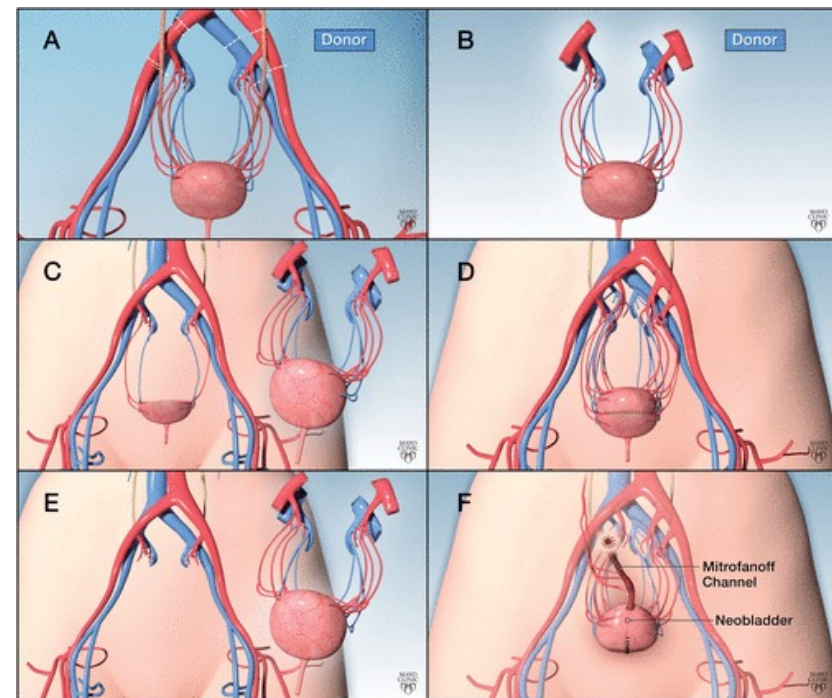
Wenn zu viel Kobalt in den Körper gelangt, stimuliert dies das Protein HIF-1 α (Hypoxia-inducible factor 1-alpha). Dies signalisiert dem Körper fälschlicherweise, dass ein Sauerstoffmangel vorliegt, was die Produktion von Erythropoietin (EPO) in den Nieren anregt und in der Folge zu einer vermehrten Bildung roter Blutkörperchen führt.

THE LANCET

Kidney Transplant



Bladder Transplant



Combined bladder–kidney transplantation: first-in-human feasibility trial

Summary

Background Current surgical treatments for terminal bladder dysfunction include intestinal-based reconstructive approaches that carry substantial morbidity, particularly in immunosuppressed patients. These limitations prompted investigation into vascularised composite bladder allograft transplantation as a novel reconstructive alternative.

Methods This is an ongoing phase 0 feasibility trial of decreased-donor bladder or combined bladder–kidney transplantation at two academic medical centres in the USA. Eligible bladder transplant recipients are adults aged 18–70 years with non-functional, poorly compliant bladders. Ideal candidates for this trial include patients with pre-existing or concurrent immunosuppression requirements. The primary endpoints are technical feasibility, defined as completion of the operation with restoration of urinary continuity with graft perfusion, and patient safety, reported through adverse events. Here, we report on the safety, feasibility, and immunological and functional outcomes from the first-in-human kidney and bladder transplant as part of the study. This study was registered with ClinicalTrials.gov, NCT06337942 and NCT05462561, and is ongoing.

Findings The surgery was carried out in May, 2025. The patient was a 41-year-old anephric male with a terminal bladder and end-stage kidney disease from hypertension who had been on peritoneal dialysis for 7 years. Kidney and bladder were recovered from an ABO compatible 35-year-old female donor with terminal anoxic brain injury. The 8 h surgery was successful, with both organs having excellent perfusion and no intraoperative complications. On postoperative day 25, the patient developed a urine leak from the suprapubic tube tract and wound breakdown (Clavien–Dindo 4), which was managed surgically with good recovery. More than 6 months post-transplantation, the patient maintained appropriate renal (estimated glomerular filtration rate 52–55 mL/min per 1.73 m²) and bladder allograft function, with intact sensation and appropriate urge, bladder capacity of 600 mL, complete continence, spontaneous voiding with maximum flow rate 17 mL/s, and complete emptying with negligible post-void residual urine. The patient is maintained on triple therapy immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone. Serial bladder biopsies have remained negative for cell-mediated or antibody-mediated rejection.

Interpretation The first-in-human combined bladder–kidney transplantation demonstrates the technical feasibility of vascularised composite bladder allograft transplantation, with sustained bladder allograft function, sensation, continence, and voiding parameters, and no evidence of rejection beyond 6 months. These findings suggest bladder transplantation might represent a viable option for select patients with terminal bladder dysfunction, particularly those already requiring immunosuppression.

Introduction

Failure of the bladder to adequately store and empty is an anatomical cause of recurrent urinary tract infections, nephrolithiasis, and renal dysfunction.^{1,2} The current standard for patients with terminal bladder pathology uses a vascularised segment of bowel to either augment or replace the bladder. Availability of an intestinal segment might be limited by previous abdominal surgery, poor bowel quality, or inadequate length. Although broadly used, reconstructive techniques utilising intestine are often associated with various infectious, functional, and biochemical morbidities that

substantially affect patient outcomes.³⁻⁵ In patients with pre-existing or impending organ transplants who are already or imminently immunosuppressed, the risk and effect of such complications is amplified.⁶

We previously reported on the first preclinical studies demonstrating the technical feasibility of human bladder transplantation,^{7,8} which laid the foundations for this first-in-human attempt at vascularised composite bladder allograft (VCBA) transplantation. Herein, we describe the technique, safety profile, and initial functional outcomes of the first successful combined kidney–bladder transplantation.

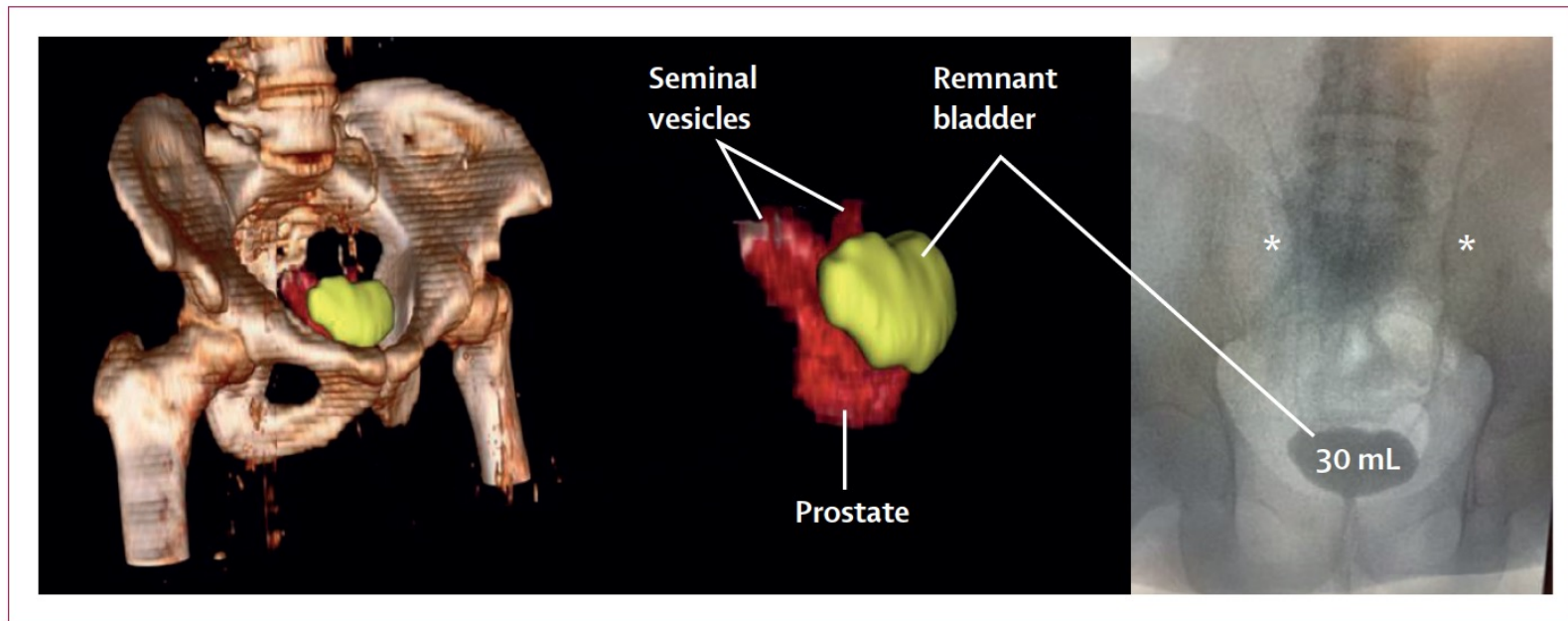


Figure 1: Three-dimensional reconstruction of pre-operative CT imaging showing a severely contracted remnant bladder

The small size of the bladder is no larger than the size of the prostate and seminal vesicles. Fluoroscopic urodynamic evaluation confirmed a small remnant bladder with a capacity of 30 mL and bilateral vesicoureteral reflux. *Bilateral vesicoureteral reflux.

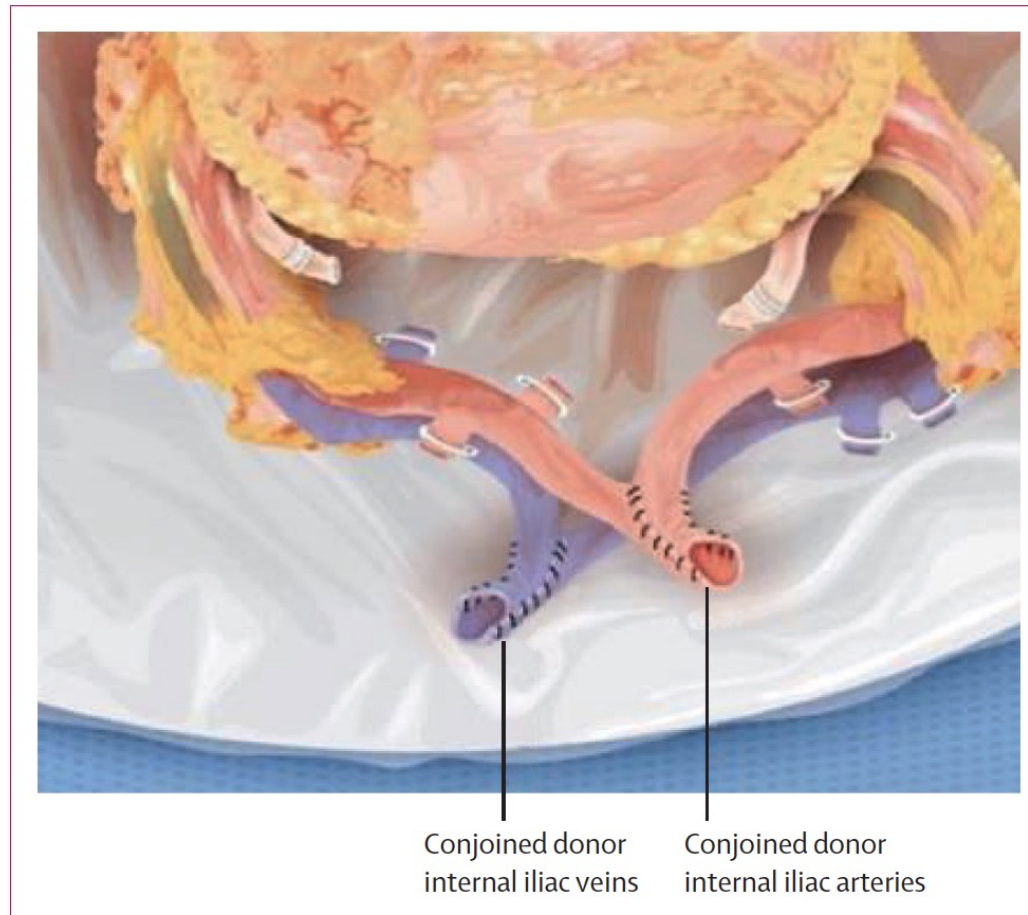
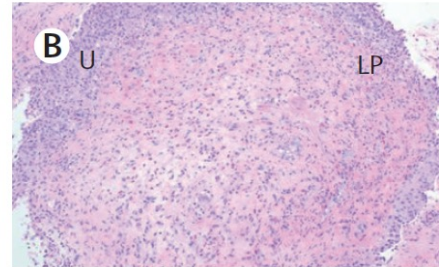
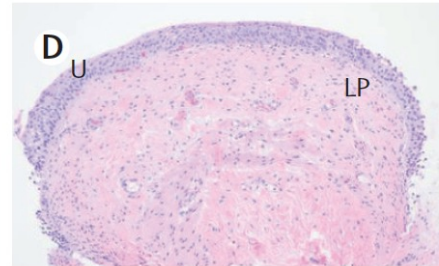


Figure 2: Back-table preparation of the vascularised composite bladder allograft, creating a single arterial inflow and a single venous outflow supplying the entire bladder

1 month



3 months



6 months

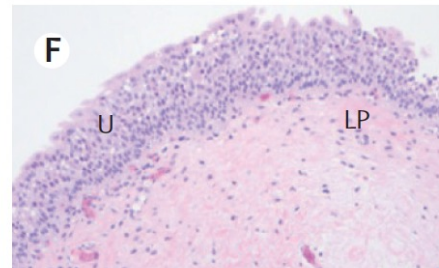


Figure 3: Cytoscopic and histopathological examination of the transplanted bladder

(A) 1 month after bladder transplantation, cystoscopic evaluation showed viable, healthy appearing bladder mucosa without any concerning findings, lesions, or areas of necrosis. (B) 1 month after bladder transplantation, bladder biopsy specimens showed viable mucosa with mixed inflammation, without evidence of perivascular lymphocytic inflammation or necrosis (100 $\times$; haematoxylin and eosin stain). (C) 3 months after transplantation, cystoscopy showed viable bladder mucosa. (D) 3 months after transplantation, biopsy showed resolution of the inflammation identified in the first biopsy (100 $\times$; haematoxylin and eosin stain). (E) 6 months after transplantation, bladder mucosa remained healthy on cystoscopic evaluation. (F) 6 months after transplantation, on biopsy there are no substantial interstitial, perivascular, or intraepithelial inflammatory infiltrates to suggest allograft rejection (200 $\times$; haematoxylin and eosin stain). U=urothelium. LP=lamina propria.

Findings	
1 month after surgery	
Filling	
First sensation	190 mL
Capacity	270 mL
P _{detr} volume <200 mL	<18 cmH ₂ O
P _{detr} capacity	47 cmH ₂ O
Compliance, volume <200 mL	>18 mL/cmH ₂ O
Compliance, capacity	5.7 mL/cmH ₂ O
Vesicoureteral reflux	Absent
Stress urinary incontinence	Absent
Detrusor overactivity	Absent
Emptying	
Voided volume	180 mL
Q _{max}	11 mL/s
PVR	87 mL
Curve	Flattened bell
Percentage emptying	68%
3 months after surgery	
Filling	
First sensation	270 mL
Capacity	410 mL
P _{detr} volume <300 mL	<9.7 cmH ₂ O
P _{detr} capacity	34 cmH ₂ O
Compliance, volume <300 mL	>30.9 mL/cmH ₂ O
Compliance, capacity	12 mL/cmH ₂ O
Vesicoureteral reflux	Absent
Stress urinary incontinence	Absent
Detrusor overactivity	Absent
Emptying	
Voided volume	380 mL
Q _{max}	18 mL/s
PVR	30 mL
Curve	Bell
Percentage emptying	93%

(Table continues in next column)

Findings	
(Continued from previous column)	
6 months after surgery	
Filling	
First sensation	300 mL
Capacity	600 mL
P _{detr} volume <500 mL	<18 cmH ₂ O
P _{detr} capacity	35 cmH ₂ O
Compliance, volume <500 mL	>27.8 mL/cmH ₂ O
Compliance, capacity	17.1 mL/cmH ₂ O
Vesicoureteral reflux	Absent
Stress urinary incontinence	Absent
Detrusor overactivity	Absent
Emptying	
Voided volume	590 mL
Q _{max}	17 mL/s
PVR	Minimal
Curve	Staccato bell
Percentage emptying	>95%

During the filling phase, serial improvements in bladder capacity, compliance, and filling pressures were noted. Across all timepoints, there was no vesicoureteral reflux, stress urinary incontinence, or detrusor overactivity. During emptying, the patient generated a normal maximum flow rate and emptied the bladder to completion. The patient has a bladder capacity of 600 mL with safe bladder pressures throughout all stages of filling and empties to completion with a normal maximum flow rate. P_{detr}=detrusor pressure. PVR=post-void residual. Q_{max}=maximum flow rate.

Table: Urodynamic findings at 1 month, 3 months, and 6 months after bladder transplantation

Research in context

Evidence before this study

Previous work in vascularised composite bladder allograft transplantation has been limited to preclinical and experimental models exploring the feasibility of such a procedure, including a series of translational cadaveric, animal, and preclinical human studies performed by our group evaluating donor recovery, vascular reconstruction, transplantation technique, and graft perfusion. The clinical management of terminal bladder pathologies, particularly in the setting of pre-existing end-stage renal disease, has relied on bowel-based urinary reconstruction, which is associated with metabolic, infectious, and functional complications.

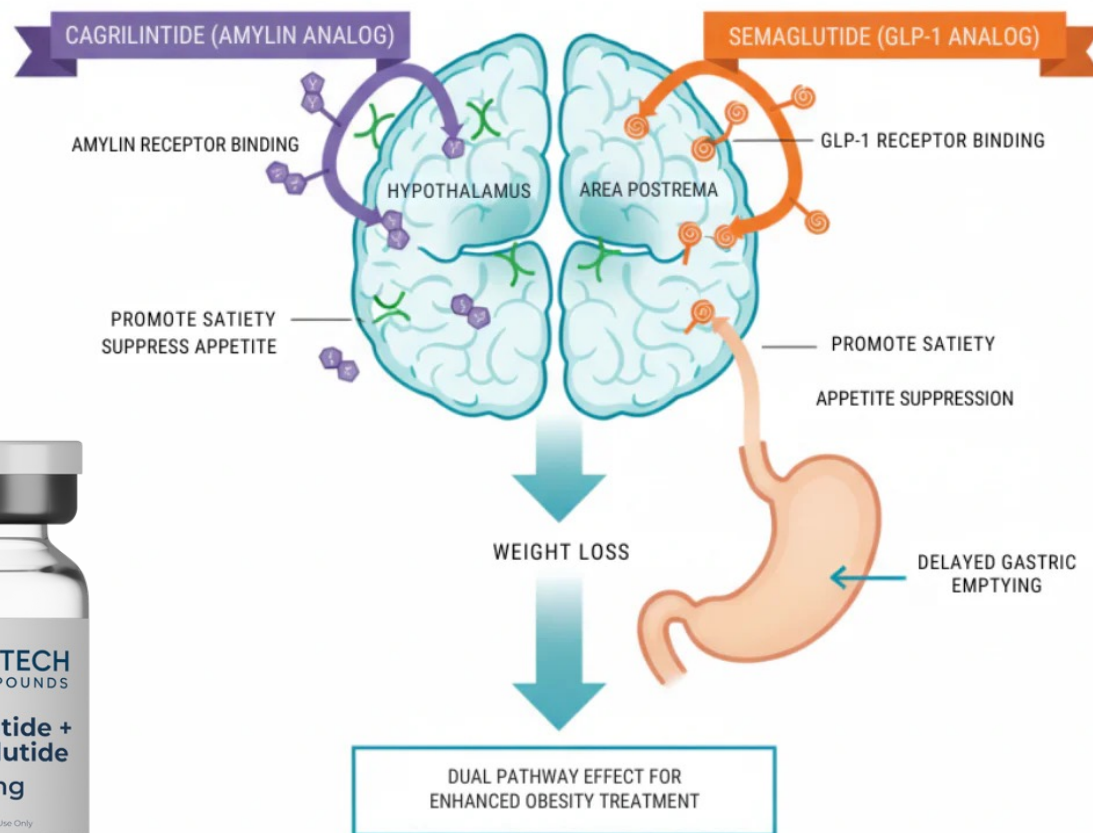
Added value of this study

To our knowledge, this study reports the first successful human vascularised composite bladder allograft transplantation. In this

study, we show the feasibility of combined kidney–bladder transplantation with encouraging early outcomes, including stable renal function, a viable bladder allograft without evidence of rejection, and restoration of functional bladder storage and emptying.

Implications of all the available evidence

Our findings suggest that bladder transplantation might provide a physiological urothelial alternative to bowel reconstruction for carefully selected patients, particularly those already requiring immunosuppression, and support further evaluation in prospective clinical trials.



Cagrilintide–semaglutide (CagriSema) as an add-on to basal insulin in adults with type 2 diabetes (REIMAGINE 3): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study

Summary

Background Basal insulin treatment for type 2 diabetes often results in inadequate glycaemic control and is associated with weight gain and increased risk of hypoglycaemia. We aimed to compare the efficacy and safety of a once per week combination of cagrilintide with semaglutide (CagriSema) versus placebo as an add-on to basal insulin in individuals with type 2 diabetes.

Methods This double-blind, parallel-group, randomised, controlled, phase 3a study (REIMAGINE 3) was done at 46 centres (university hospitals, health-care centres, research centres, and other clinical trial sites) in six countries (the USA, China, Japan, Serbia, Slovakia, and South Africa). Adults with type 2 diabetes (glycated haemoglobin [HbA_{1c}] 7·0–10·5%) receiving stable once per day basal insulin with or without metformin were randomly assigned (2:2:1:1) to once per week subcutaneous cagrilintide 2·4 mg plus semaglutide 2·4 mg (hereafter cagrilintide–semaglutide [2·4 mg each]) or cagrilintide 1·0 mg plus semaglutide 1·0 mg (hereafter cagrilintide–semaglutide [1·0 mg each]) or dose-matched placebo (2·4 mg plus 2·4 mg or 1·0 mg plus 1·0 mg) for 40 weeks. Randomisation was stratified by HbA_{1c} of less than 8·5% at screening (yes or no) and country (Japan; yes or no). Participants, care providers, investigators, and outcome assessors were masked within each dose level to treatment allocation, with active treatments visually identical to placebo. The primary endpoint was mean HbA_{1c} change (percentage points) from baseline to week 40 in all participants randomly assigned to treatment; secondary endpoints included change in bodyweight and safety, including hypoglycaemia. This trial was registered with ClinicalTrials.gov (NCT06323161) and is complete.

Findings Between March 26 and Nov 29, 2024, we screened 340 individuals and 274 were included and randomly assigned to cagrilintide–semaglutide (2·4 mg each; n=90), cagrilintide–semaglutide (1·0 mg each; n=93), or placebo (pooled; n=91). Mean baseline HbA_{1c} was 8·8% (SD 1·0), 159 (58%) participants were male, and 115 (42%) were female. Mean HbA_{1c} reductions were significantly greater with cagrilintide–semaglutide (2·4 mg each –2·33% [SE 0·08] and 1·0 mg each –2·10% [0·08]) versus placebo (–0·66% [0·11]) at week 40, using the efficacy estimand (estimated treatment difference for cagrilintide–semaglutide [2·4 mg each] vs placebo –1·68 percentage points [95% CI –1·95 to –1·41], p<0·0001; for cagrilintide–semaglutide [1·0 mg each] vs placebo –1·44 percentage points [95% CI –1·71 to –1·17], p<0·0001). Cagrilintide–semaglutide provided bodyweight reductions of 10–12%. Adverse events were reported by 72 (80%) of 90 participants receiving cagrilintide–semaglutide (2·4 mg each), 66 (71%) of 93 receiving cagrilintide–semaglutide (1·0 mg each), and 65 (71%) of 91 receiving placebo, and were mostly mild or moderate gastrointestinal disorders. No severe hypoglycaemia was reported. There was one death in the cagrilintide–semaglutide (1·0 mg each) group not related to treatment (due to malignancy).

Interpretation Cagrilintide–semaglutide at doses of 2·4 mg each and 1·0 mg each met the primary endpoint, with statistically significant and clinically relevant HbA_{1c} reductions versus placebo when added to basal insulin-treated type 2 diabetes. These reductions were accompanied by robust bodyweight reduction and no additional risk of hypoglycaemia. The safety profile was consistent with that of the GLP-1 receptor agonist class and previous safety data for cagrilintide. Findings support the use of cagrilintide–semaglutide as an add-on to once per day basal insulin to significantly improve glycaemic control.

Funding Novo Nordisk.

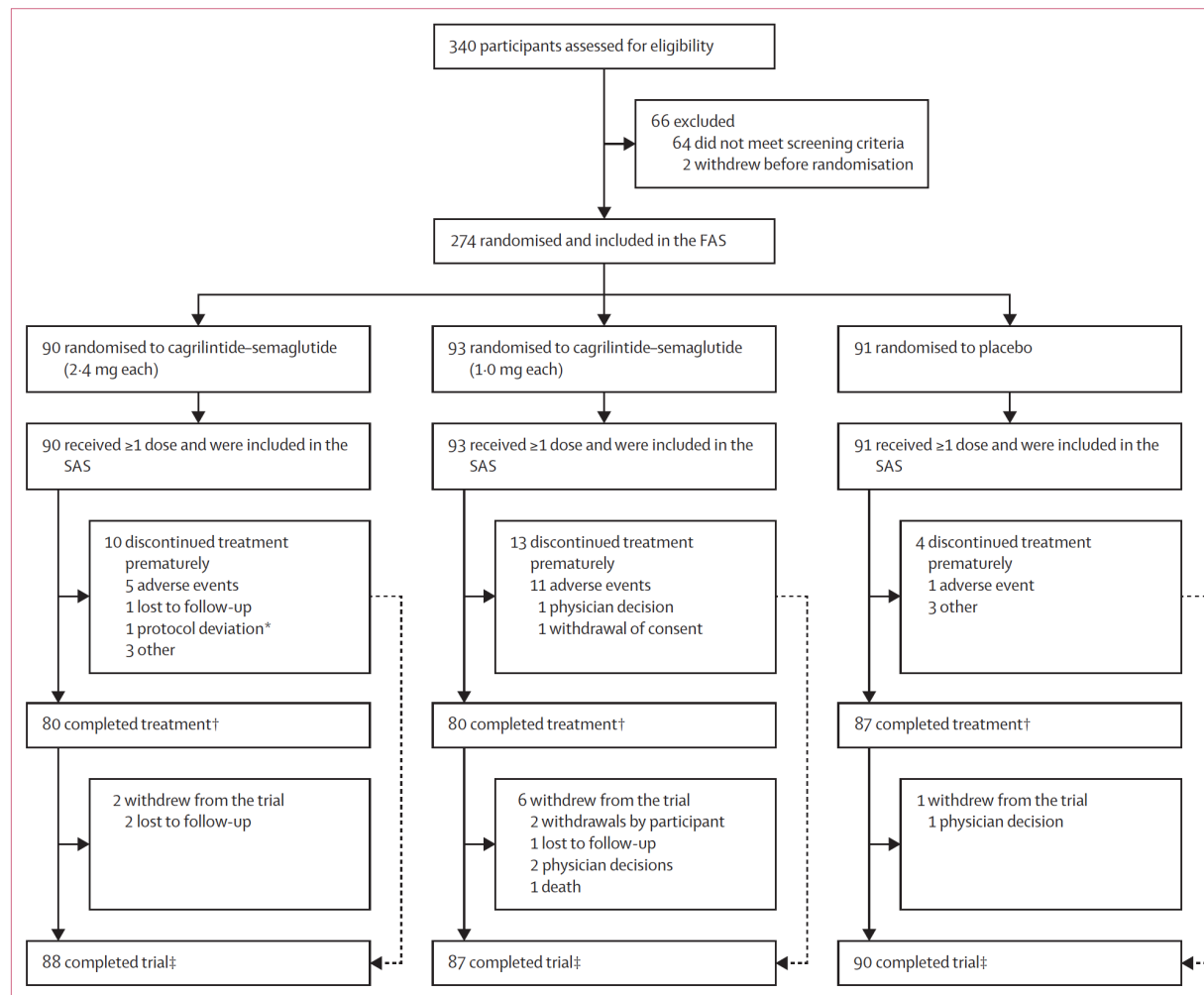


Figure 1: Study profile

SAS=safety analysis set. *Included in the study in violation of the inclusion and/or exclusion criteria. †Participants were considered to have completed treatment if they were on treatment at week 40. ‡Participants were considered to have completed the study if they attended the end-of-study visit at week 47, regardless of whether they completed treatment.

	Cagrilintide– semaglutide (2.4 mg each; n=90)	Cagrilintide– semaglutide (1.0 mg each; n=93)	Placebo (n=91)	Total (N=274)
Sex				
Female	38 (42%)	41 (44%)	36 (40%)	115 (42%)
Male	52 (58%)	52 (56%)	55 (60%)	159 (58%)
Age, years	59.2 (9.3)	58.8 (10.8)	59.0 (10.4)	59.0 (10.2)
Race				
Asian	43 (48%)	44 (47%)	38 (42%)	125 (46%)
Black or African American	3 (3%)	3 (3%)	8 (9%)	14 (5%)
White	41 (46%)	43 (46%)	45 (49%)	129 (47%)
Other*	3 (3%)	3 (3%)	0	6 (2%)
Hispanic or Latino ethnicity	11 (12%)	12 (13%)	16 (18%)	39 (14%)
Bodyweight, kg	88.9 (18.5)	86.7 (15.8)	88.9 (19.4)	88.2 (17.9)
BMI, kg/m ²	32.0 (6.0)	31.4 (5.5)	31.5 (6.2)	31.6 (5.9)
Waist circumference, cm	106.8 (16.0)	104.9 (13.5)	104.9 (14.1)	105.5 (14.6)
HbA _{1c} , %	8.8 (0.9)	8.8 (1.0)	8.8 (1.0)	8.8 (1.0)
HbA _{1c} , mmol/mol	72.7 (10.1)	72.4 (10.5)	72.4 (11.4)	72.5 (10.7)
Duration of diabetes, years	15.1 (7.9)	14.6 (7.4)	14.9 (7.7)	14.9 (7.6)
FPG, mmol/L				
Mean (SD)	8.4 (2.3)†	8.2 (3.0)‡	8.8 (2.7)‡	8.5 (2.7)§
Median (IQR)	8.4 (6.8–9.7)†	7.7 (6.1–9.5)‡	8.1 (7.1–10.3)‡	8.1 (6.7–9.8)§
FPG, mg/dL				
Mean (SD)	151.9 (41.7)†	147.3 (53.3)‡	158.3 (48.0)‡	152.5 (48.0)§
Median (IQR)	151.2 (122.0–174.3)†	139.3 (109.0–170.6)‡	146.2 (127.2–185.1)‡	145.1 (120.0–176.8)§
Systolic blood pressure, mm Hg	128.1 (14.4)	131.6 (14.4)	133.4 (13.2)	131.1 (14.2)
Diastolic blood pressure, mm Hg	78.1 (9.6)	80.5 (9.7)	80.4 (8.0)	79.7 (9.2)
eGFR, mL/min per 1.73 m ²	98.6 (16.3)	92.7 (20.8)	97.4 (16.9)	96.2 (18.2)
Once per day basal insulin dose at baseline, U				
Mean (SD)	31.6 (14.9)	35.8 (22.8)	34.7 (17.6)	34.0 (18.8)
Median (IQR)	26 (20–36)	28 (22–40)	28 (22–42)	28 (22–40)
Metformin at screening	81 (90%)	76 (82%)	77 (85%)	234 (85%)
Data are mean (SD) or n (%), unless otherwise specified. Percentages might not sum to 100 as a result of rounding. eGFR=estimated glomerular filtration rate. FPG=fasting plasma glucose. HbA _{1c} =glycated haemoglobin. * American Indian, Alaska Native, or not reported. †n=89. ‡n=90. §n=269.				
Table 1: Baseline demographics and clinical characteristics				

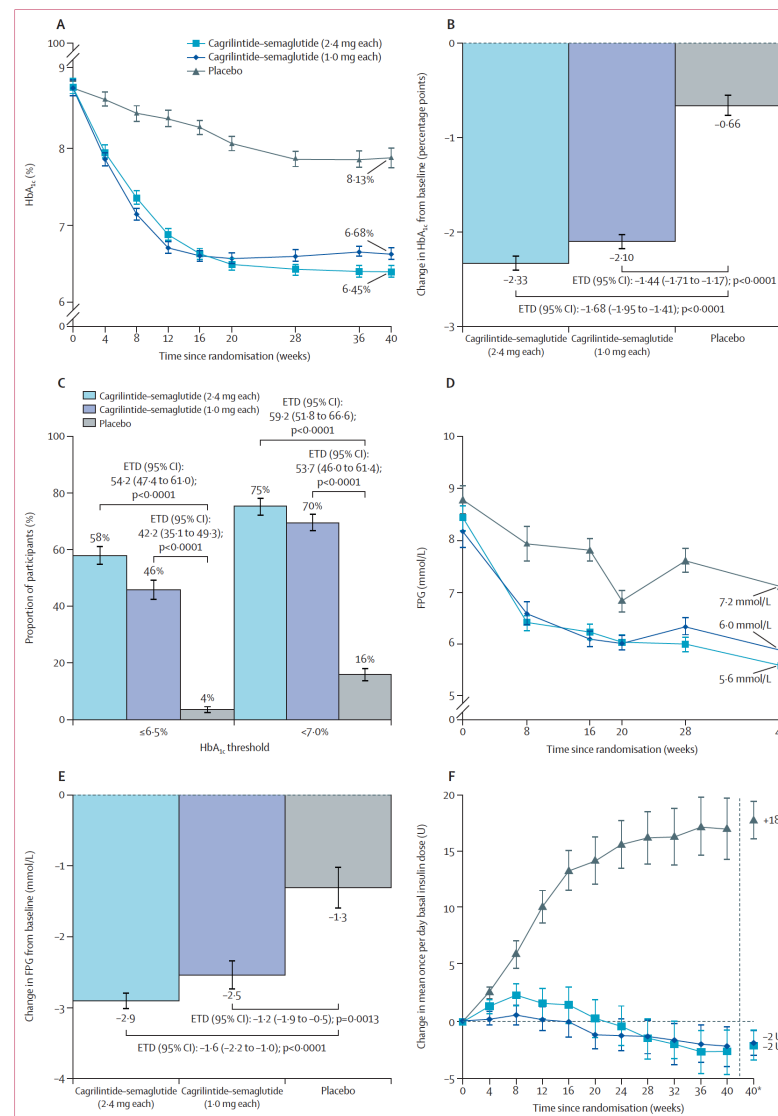


Figure 2: Change from baseline in glycaemic endpoints (efficacy estimand)

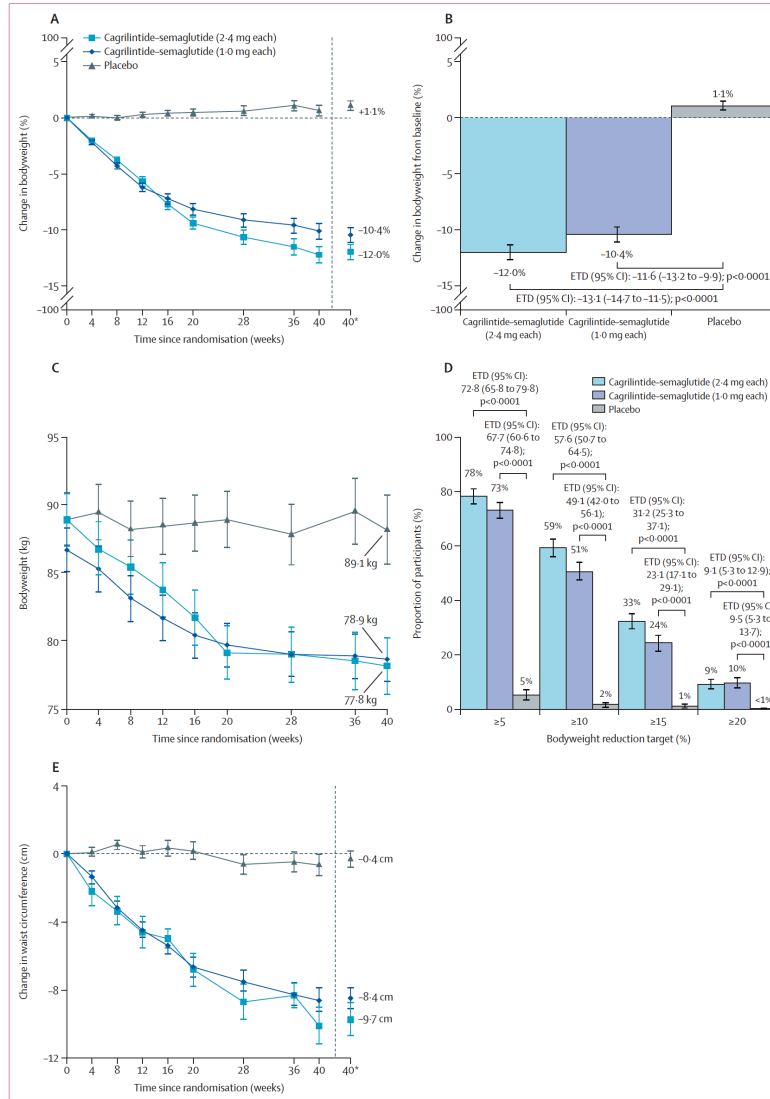
(A) Mean HbA_{1c} (%) over time (overall mean HbA_{1c} at baseline was 8.8% [SD 1.0] or 72.5 mmol/mol [SD 10.7]).

(B) Mean change in HbA_{1c} (percentage points) from baseline to week 40.

(C) Proportions of participants meeting HbA_{1c} targets of 6.5% or less and less than 7.0% at week 40. (D) Mean FPG (mmol/L) over time (overall mean FPG at baseline was 8.5 mmol/L [SD 2.7]; median 8.1 mmol/L [IQR 6.7–9.8]).

(E) Mean change in FPG (mmol/L) from baseline to week 40. (F) Mean change in once per day basal insulin dose (U) over time (overall mean once per day basal insulin dose at baseline was 34 U [SD 19]; median 28 U [IQR 22–40]). Data are for the full analysis set and efficacy estimand. Error bars in panels A, D, and F indicate SE of the mean. Error bars in panels B, C, and E indicate SE. ETD=estimated treatment difference. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin. *Estimated mean at week 40.

Figure 3: Change from baseline in bodyweight-related endpoints (efficacy estimand)
 (A) Mean relative change in bodyweight (%) over time (overall mean bodyweight at baseline was 88.2 kg [SD 17.9]). (B) Mean relative change in bodyweight (%) from baseline to week 40. (C) Mean absolute bodyweight (kg) over time. (D) Proportions of participants who had bodyweight reductions of 5% or more, 10% or more, 15% or more, and 20% or more at week 40; proportions of participants with 5% or more and 20% or more bodyweight reduction were not adjusted for multiplicity. (E) Mean change in waist circumference (cm) over time; this endpoint was not adjusted for multiplicity (overall mean waist circumference at baseline was 105.5 cm [SD 14.6]). Data are for the full analysis set and efficacy estimand. Error bars in panels A, C, and E indicate SE of the mean. Error bars in panels B and D indicate SE. ETD=estimated treatment difference. *Estimated mean at week 40.



	Cagrilintide-semaglutide (2.4 mg each; n=90)			Cagrilintide-semaglutide (1.0 mg each; n=93)			Placebo (n=91)		
	n (%)	Number of events	Event rate per 100 years	n (%)	Number of events	Event rate per 100 years	n (%)	Number of events	Event rate per 100 years
Adverse events and serious adverse events									
Any adverse event*	72 (80%)	396	492.7	66 (71%)	280	340.2	65 (71%)	224	273.9
Serious adverse event*	5 (6%)	10	12.4	7 (8%)	7	8.5	8 (9%)	9	11.0
Adverse event leading to trial product discontinuation*	6 (7%)	8	10.0	11 (12%)	13	15.8	1 (1%)	1	1.2
Gastrointestinal-related adverse events leading to trial product discontinuation	2 (2%)	3	4.0	8 (9%)	9	12.0	0	0	0
Fatal events*	0	0	0	1 (1%)†	1	1.2	0	0	0
Hypoglycaemic episodes‡									
Level 1 (alert value)	40 (44%)	163	216.2	35 (38%)	137	183.0	41 (45%)	205	260.8
Level 2 (clinically significant)	13 (14%)	23	30.5	8 (9%)	10	13.4	13 (14%)	32	40.7
Level 3 (severe)	0	0	0	0	0	0	0	0	0
Level 2 or 3	13 (14%)	23	30.5	8 (9%)	10	13.4	13 (14%)	32	40.7
Nocturnal level 2 or 3	5 (6%)	8	10.6	1 (1%)	1	1.3	3 (3%)	5	6.4
Selected safety focus areas									
Gastrointestinal disorders§	51 (57%)	148	196.3	42 (45%)	117	156.3	21 (23%)	32	40.7
Retinal disorders*§	13 (14%)	16	19.9	5 (5%)	6	7.3	10 (11%)	12	14.7
Neoplasms*§	7 (8%)	8	10.0	6 (6%)	10	12.1	2 (2%)	3	3.7
Hypersensitivity reactions§	4 (4%)	4	5.3	3 (3%)	3	4.0	3 (3%)	3	3.8
Gallbladder-related disorders§	4 (4%)	6	8.0	0	0	0	0	0	0
Injection site reactions§	1 (1%)	1	1.3	0	0	0	0	0	0
Malignant neoplasms*¶	1 (1%)	1	1.2	2 (2%)	2	2.4	1 (1%)	1	1.2
Most frequent adverse events by system order class and preferred term									
Gastrointestinal disorders									
Nausea	28 (31%)	42	55.7	25 (27%)	39	52.1	3 (3%)	3	3.8
Diarrhoea	14 (16%)	22	29.2	10 (11%)	16	21.4	3 (3%)	3	3.8
Vomiting	13 (14%)	31	41.1	9 (10%)	16	21.4	1 (1%)	1	1.3
Constipation	10 (11%)	11	14.6	11 (12%)	13	17.4	5 (5%)	5	6.4
Abdominal discomfort	5 (6%)	5	6.6	2 (2%)	2	2.7	3 (3%)	3	3.8
Metabolism and nutrition disorders									
Decreased appetite	18 (20%)	23	30.5	14 (15%)	17	22.7	1 (1%)	2	2.5
Hypoglycaemia	6 (7%)	6	8.0	2 (2%)	2	2.7	3 (3%)	3	3.8
Eye disorders									
Diabetic retinopathy	8 (9%)	8	10.6	4 (4%)	4	5.3	8 (9%)	9	11.5
General disorders and administration site conditions									
Fatigue	7 (8%)	9	11.9	3 (3%)	5	6.7	3 (3%)	3	3.8
Infections and infestations									
Nasopharyngitis	7 (8%)	8	10.6	10 (11%)	14	18.7	12 (13%)	16	20.4
Nervous system disorders									
Headache	6 (7%)	10	13.3	5 (5%)	6	8.0	3 (3%)	4	5.1
Investigations									
Blood glucose increased	0	0	0	0	0	0	5 (5%)	8	10.2
Data are from the safety analysis set from the on-treatment period, unless otherwise stated. *In-study period. †One death was reported in the cagrilintide-semaglutide (1.0 mg each) group; the event adjudication committee established the cause of death as malignancy (exocrine and endocrine pancreatic cancer). ‡Episodes with onset date within the on-treatment period; hypoglycaemic episodes were defined according to the American Diabetes Association 2018 classification: level 1 (blood glucose <3.9 mmol/L and ≥3.0 mmol/L); level 2 (blood glucose <3.0 mmol/L); level 3 (requiring assistance from another person for recovery). §Based on a pre-defined Medical Dictionary for Regulatory Activities (version 28.1) search. ¶The malignant neoplasms recorded here are those that were confirmed by the event adjudication committee. Adverse events occurring in 5% or more of participants in any treatment group.									
Table 2: Selected adverse events in the safety analysis set									

Added value of this study

REIMAGINE 3 extends the evaluation of cagrilintide–semaglutide to individuals receiving basal insulin, a clinically complex population in whom late-stage disease is common, thereby addressing a key evidence gap regarding the role of dual amylin and GLP-1 receptor agonism in this treatment setting. Whereas REIMAGINE 1 investigated efficacy across less intensive treatment settings and REIMAGINE 2 assessed efficacy versus active comparators, REIMAGINE 3 provides evidence in individuals for whom treatment intensification with insulin is often associated with weight gain, hypoglycaemia risk, and therapeutic inertia. Collectively, the REIMAGINE trials provide a comprehensive assessment of cagrilintide–semaglutide across the type 2 diabetes treatment continuum, supporting its potential to address unmet needs related to glycaemic regulation, weight management, metabolic control, and treatment burden across diverse patient populations and lines of therapy.

Implications of all the available evidence

Treatment intensification in type 2 diabetes in those receiving basal insulin therapy is often accompanied by risk of weight gain and hypoglycaemia, and glycaemic targets are often not achieved. The results of REIMAGINE 3 support cagrilintide–semaglutide as an effective option for advancing therapy in inadequately controlled, basal insulin-treated type 2 diabetes to achieve meaningful near-normoglycaemia. In addition, cagrilintide–semaglutide was associated with robust bodyweight reduction, with no increase in the risk of hypoglycaemia observed in this study.

Beim **Patella-Resurfacing** (auch Kniescheiben-Oberflächenersatz genannt) handelt es sich um einen chirurgischen Eingriff, bei dem die **Unterseite der Kniescheibe (Patella) während einer totalen Knieendoprothese (Knie-TEP) durch ein Kunststoffimplantat ersetzt wird**. Der Chirurg trägt dabei wenige Millimeter des abgenutzten Knorpels ab und setzt stattdessen einen glatten „Knopf“ aus Polyethylen ein. Dies verhindert nach der Operation das schmerzhafte Reiben von Knochen auf den neuen Metallkomponenten des künstlichen Kniegelenks.

Freilegung: Der Chirurg klappt die Kniescheibe während der Knie-TEP vorsichtig zur Seite.

Knorpelentfernung: Die beschädigte Knorpelschicht auf der Rückseite wird präzise abgeschabt.

Höhenmessung: Die ursprüngliche Dicke der Kniescheibe wird genau gemessen, um eine Über- oder Unterdimensionierung zu vermeiden.

Fixierung: Der kuppelförmige Kunststoffknopf wird meist mit Knochenzement fest auf der Rückseite verankert



Patellar resurfacing in total knee replacement: 20-year clinical and economic results of a large multicentre, randomised controlled trial in the UK

Summary

Background There is conflicting evidence regarding the merits of patellar resurfacing during total knee replacement (TKR), as previous randomised controlled trials (RCTs) have been under-powered and with follow-up of ten years or less.

Methods A pragmatic, multicentre, open-label RCT was initiated in 1999 in the UK. Within a partial-factorial design, participants were randomly allocated to receive or not receive patellar resurfacing during primary TKR and were followed up for 20 years. Adult (aged ≥ 18 years) patients due to have a primary TKR under the care of a collaborating surgeon were eligible. Participants were allocated (1:1) using an automated telephone service stratified by surgeon, with minimisation according to the patients' age (<60 years, 60–79 years, ≥ 80 years), sex, and location of disease. The primary outcome measure was the Oxford Knee Score (OKS), analysed using repeated measures mixed-effects linear regression analysis with marginal differences reported. Secondary measures included the 12-Item Short Form Health Survey (SF-12), the European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L), costs, cost-effectiveness, and subsequent knee surgery. This trial is registered with ISRCTN Registry, ISRCTN45837371.

Findings Between April 8, 1999, and Jan 13, 2003, 1715 participants (955 female and 760 male; mean age 70 years [SD 8], mean BMI 29.7 kg/m²) were randomly assigned: 861 to patellar resurfacing and 854 to no resurfacing. At the 20-year follow-up, 132 participants in the patellar resurfacing group and 110 participants in the non-resurfacing group provided outcome data, although marginal differences included earlier data for participants who died or had missing 20-year data. The marginal difference in OKS over the whole 20-year follow-up was 0.76 (95% CI –0.08 to 1.59; $p=0.076$) in favour of patellar resurfacing. During the 20-year follow-up period, although not significant, differences in OKS, SF-12, and EQ-5D-3L, readmissions, minor or intermediate operations, patella-related operations, major operations, and complications all favoured patellar resurfacing. At 20 years, the resurfaced group accrued significantly more quality-adjusted life-years (QALYs) than the non-resurfaced group (7.295 vs 6.884; difference 0.380, 95% CI 0.061 to 0.700; $p=0.020$). However, QALY differences were smaller in a sensitivity analysis assuming no difference in mortality (7.209 vs 6.964; difference 0.183, 95% CI –0.034 to 0.400; $p=0.10$). The cost of readmissions was non-significantly lower in the resurfaced group and offset the higher cost of primary TKR; therefore, overall 20-year health-care costs per participant were similar (£10 825 vs £10 889; difference –£6, 95% CI –£721 to £708; $p=0.99$).

Interpretation There was no significant difference in primary outcome (OKS) or other clinical endpoints. However, as clinical differences tend to support patellar resurfacing, the resurfacing group had significantly higher QALYs. There was no difference in costs over the 20-year period, and patellar resurfacing had a 99% probability of being cost-effective at any threshold above £10 000 per QALY gained. The evidence is therefore weighted towards resurfacing being the approach of first choice.

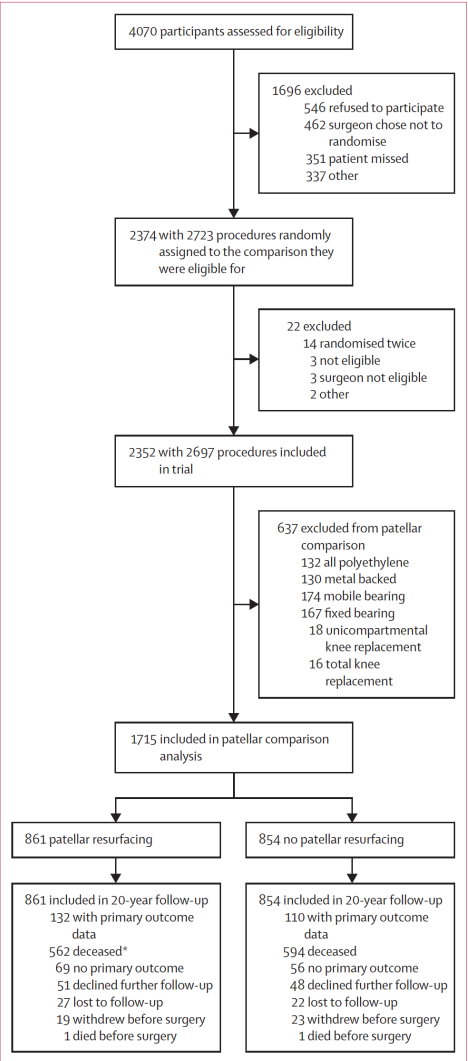


Figure 1: Trial profile

*Additional participant died within follow-up after completing the 20-year questionnaire.

	Patellar resurfacing (n=861)	No patellar resurfacing (n=854)
Age, years	70 (8)	70 (8)
Sex		
Female	474 (55%)	481 (56%)
Male	387 (45%)	373 (44%)
BMI, kg/m ²	29.5 (5.5)	29.8 (5.2)
ASA classification		
Completely fit and healthy	153 (18%)	143 (17%)
Some illness but has no effect on normal activity	500 (58%)	497 (58%)
Symptomatic illness present but minimal restriction	144 (17%)	136 (16%)
Symptomatic illness causing severe restriction	5 (1%)	5 (1%)
Missing	59 (7%)	73 (9%)
Primary type of knee arthritis		
Osteoarthritis	800 (93%)	789 (92%)
Rheumatoid	29 (3%)	37 (4%)
Both	2 (<1%)	1 (<1%)
Missing	30 (3%)	27 (3%)
Extent of knee arthritis affecting mobility		
One knee	225 (26%)	229 (27%)
Both knees	366 (43%)	342 (40%)
General	270 (31%)	283 (33%)
Other conditions affecting mobility*		
Total	101 (12%)	127 (15%)
Medical	61 (7%)	66 (8%)
Locomotor or musculoskeletal	55 (7%)	78 (10%)
Previous knee surgery†		
Total	281 (34%)	268 (33%)
Ipsilateral osteotomy	11 (1%)	13 (2%)
Contralateral previous knee replacement	112 (14%)	94 (11%)
Other previous knee surgery	167 (20%)	172 (21%)
Arthroscopy†	146 (18%)	150 (18%)
Other related surgery†	26 (3%)	23 (3%)

Table 1: Baseline characteristics

Data are n (%) or mean (SD). Race and ethnicity were not collected on trial participants. ASA=American Society of Anesthesiologists. *There were 831 participants with available data in the patellar resurfacing group and 820 in the no patellar resurfacing group; participants could have multiple other conditions. †There were 829 participants with available data in the patellar resurfacing group and 824 in the no patellar resurfacing group; participants could have multiple other conditions.

	Patellar resurfacing (n=861)	No patellar resurfacing (n=854)	Effect estimate (95% CI)*	p value
OKS (primary outcome)				
Baseline	18.5 (7.4; n=793)	18.1 (7.7; n=798)	..	..
20 years	32.7 (11.4; n=132)	30.8 (11.2; n=110)	1.48 (-0.18 to 3.15)	0.081
Marginal estimate	..	..	0.76 (-0.08 to 1.59)	0.076
EQ-5D-3L score				
Baseline	0.404 (0.301; n=791)	0.389 (0.309; n=807)	..	..
20 years	0.604 (0.296; n=142)	0.558 (0.311; n=119)	0.022 (-0.028 to 0.072)	0.38
Marginal estimate	..	..	0.016 (-0.004 to 0.036)	0.13
SF-12 physical component score				
Baseline	31.1 (8.0; n=780)	31.3 (8.5; n=792)	..	..
20 years	35.4 (10.7; n=141)	34.2 (10.4; n=111)	1.04 (-0.83 to 2.91)	0.27
Marginal estimate	..	..	0.47 (-0.31 to 1.28)	0.23
SF-12 mental component score				
Baseline	50.7 (11.4; n=780)	49.7 (11.2; n=792)	..	..
20 years	46.5 (11.4; n=141)	46.0 (12.1; n=111)	-0.40 (-2.41 to 1.60)	0.69
Marginal estimate	..	..	0.48 (-0.24 to 1.21)	0.19
Re-operations				
Time to readmission, months	137 (16.3)	145 (17.5)	0.93 (0.73 to 1.17)	0.53
Time to any operation, months	99 (11.8)	109 (13.1)	0.88 (0.67 to 1.16)	0.37
Time to minor operation, months	64 (7.6)	74 (8.9)	0.85 (0.58 to 1.23)	0.38
Time to patella-related operation, months	16 (1.9)	17 (2.0)	0.93 (0.45 to 1.95)	0.86
Time to major operation, months	42 (5.0)	54 (6.5)	0.75 (0.51 to 1.11)	0.15
Time to patellar or major operation, months	56 (6.7)	66 (8.0)	0.82 (0.57 to 1.20)	0.31
Time to patellar resurfacing, months	9 (1.1)	17 (2.0)	0.52 (0.21 to 1.32)	0.17
Time to any operation or OKS dropping below baseline levels beyond 1 year, months	234 (27.8)	238 (28.7)	0.95 (0.77 to 1.16)	0.61
Data are mean (SD; n) or n (%) for re-operations, unless otherwise indicated. EQ-5D-3L=the European Quality of Life 5-Dimensions 3-Levels. OKS=Oxford Knee Score. SF-12=12-Item Short Form Health Survey. *Hazard ratios for re-operations and mean differences for all other outcomes.				
Table 2: Primary and secondary outcomes at baseline and 20 years				

	Patellar resurfacing (n=841)	No patellar resurfacing (n=830)
Number of participants requiring at least one readmission	137 (16%)	145 (17%)
Total number of readmissions	216	243
Multiple readmissions	47 (6%)	51 (6%)
Number of participants requiring a non-operation readmission	54 (6%)	51 (6%)
Total number of non-operation readmissions	65	60
Multiple non-operation readmissions	7 (1%)	7 (1%)
Number of participants requiring a procedural readmission	99 (12%)	109 (13%)
Total number of procedural readmissions	151	183
Multiple procedural readmission	35 (4%)	41 (5%)
Minor or intermediate operations		
Number of participants requiring a minor operation	64 (8%)	74 (9%)
Total number of operations	87	98
Multiple minor operations	15 (2%)	18 (2%)
Number requiring at least one		
Wound closure	..	1 (<1%)
Debridement, exploration, or washout	17 (2%)	18 (2%)
Debridement, washout, and plastic exchange	..	1 (<1%)
Manipulation under anaesthetic	18 (2%)	24 (3%)
Arthrolysis and quadriceplasty	1 (<1%)	..
Arthroscopy, examination under anaesthetic, or biopsy	6 (1%)	13 (2%)
Aspiration	25 (3%)	25 (3%)
Bone removal	2 (<1%)	1 (<1%)
Drain abscess	1 (<1%)	..
Cement block exchange	..	1 (<1%)
Exchange of polyethylene insert	5 (1%)	5 (1%)
Removal of screws and plates	..	1 (<1%)
Patella-related operations		
Number of participants requiring patella-related operation	16 (2%)	17 (2%)
Total number of patella-related operations	16	17
Number requiring at least one		
Late patellar resurfacing	9 (1%)	17 (2%)
Patella fracture	2 (<1%)	..
Patella revision	3 (<1%)	..
Patella realignment	1 (<1%)	..
Removal of patella button	1 (<1%)	..
Major operations		
Number of participants requiring a major operation	42 (5%)	54 (7%)
Total number of operations	48	68
Multiple major operations	6 (1%)	9 (1%)
Number requiring at least one		
Above-knee amputation	1 (<1%)	3 (<1%)
Two-stage revision	11 (1%)	16 (2%)
One-stage revision	34 (4%)	41 (5%)

Data are n (%). Participants could be readmitted multiple times.

Table 3: Readmissions postoperatively for patella comparison by allocation

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	No patellar resurfacing	Patellar resurfacing	Patellar resurfacing vs no patellar resurfacing difference (95% CI, p value)
Base case analysis			
Total cost of inpatient stay for primary total knee replacement, £	7998	8250	266 (39 to 492; 0.021)
Total cost over 20 years, £	10 889	10 825	–6 (–721 to 708; 0.99)
Total QALYs	6.884	7.295	0.380 (0.061 to 0.700; 0.020)
Discounted life-years over 20 years	10.596	10.862	0.296 (–0.045 to 0.636; 0.089)
Undiscounted life-years over 20 years	0.154	0.175	0.023 (0.003 to 0.043; 0.023)
Sensitivity and subgroup analyses			
QALYs if groups had equal survival*	6.964	7.209	0.183 (–0.034 to 0.400; 0.10)
Cost if groups had equal survival*, £	10 876	10 778	–11.60 (–733.66 to 710.46; 0.99)
Cost: patients aged <70 years, £	11 620	11 282	–135.16 (–1343.26 to 1072.93; 0.83)
Cost: patients aged ≥70 years, £	10 259	10 447	205.89 (–618.30 to 1030.08; 0.62)
Cost: anatomic patellofemoral joint on femur, £	12 548	11 406	–970.78 (–2634.63 to 693.07; 0.25)
Cost: domed patellofemoral joint on femur, £	10 047	10 686	631.57 (–106.86 to 1370.00; 0.094)
QALYs: patients aged <70 years	7.903	8.529	0.501 (–0.002 to 1.004; 0.051)
QALYs: patients aged ≥70 years	6.006	6.272	0.223 (–0.177 to 0.622; 0.27)
QALYs: anatomic patellofemoral joint on femur	6.720	7.286	0.396 (–0.236 to 1.028; 0.22)
QALYs: domed patellofemoral joint on femur	6.962	7.324	0.402 (0.024 to 0.779; 0.037)

Data are mean (95% CI). EQ-5D-3L=the European Quality of Life 5-Dimensions 3-Levels. QALY=quality-adjusted life-year. Costs are in pound sterling 2021–22 values. Group means are unadjusted; between-group differences were adjusted for age, gender, baseline EQ-5D-3L, date of primary knee arthroplasty, and whether patients were American Society of Anesthesiologists grade 3 or greater at baseline. All costs and QALYs are discounted to allow for time preference at 3.5% per annum. *Post-hoc sensitivity analysis using a common survival curve for both groups. See appendix (pp 15–18) for more details.

Table 4: Results of the economic evaluation

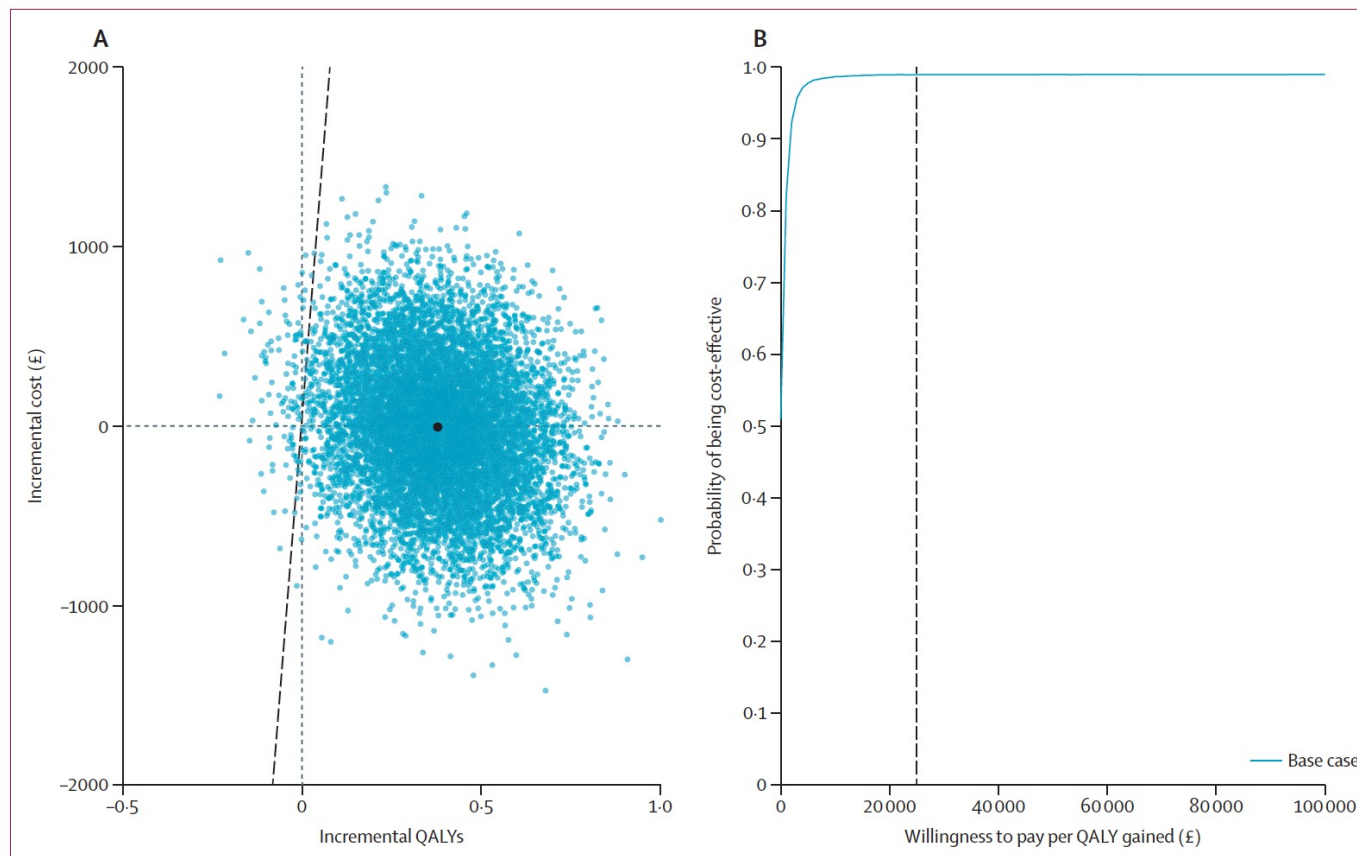


Figure 2: Base case cost-effectiveness results

(A) Scatter graph showing base case cost-effectiveness results on the cost-effectiveness plane. (B) Cost-effectiveness acceptability curve plotting the probability that patellar resurfacing is cost-effective compared with no resurfacing against the ceiling ratio showing different values for the amount the National Health Service is assumed to be willing or able to pay per QALY gained. Estimated using bootstrapping, adjusted for age, gender, the European Quality of Life 5-Dimensions 3-Levels score at baseline, date of primary knee arthroplasty, and whether patients were American Society of Anesthesiologists grade 3 or greater at baseline. Costs are in pound sterling. QALY=quality-adjusted life-year.

Research in context

Evidence before this study

Total knee replacement (TKR) is a common and successful surgical procedure. However, up to 20% of patients have poor functional outcomes and pain. Many of these poor results are attributed to problems with the patellofemoral joint. There remains considerable debate as to whether the patella should be resurfaced or not at the time of the primary knee replacement. It has been proposed that patellar resurfacing should decrease the incidence of poor outcomes; however, the resurfacing can fail, requiring further surgery. Literature searches were done before and during the study. Previous randomised controlled trials (RCTs), non-randomised cohort studies, and systematic reviews have not resolved the uncertainty regarding the benefits of patellar resurfacing. These RCTs have tended to have insufficient sample sizes to detect clinically meaningful differences and have been followed up for 10 years or less, which is short compared with the length of time many TKRs have to last. As a result, there is great variability in the use of patellar resurfacing, with hardly any patellae being resurfaced in some countries (eg, Sweden), and almost all in others (eg, the USA).

Added value of this study

The Knee Arthroplasty Trial is appropriately powered, with 1715 participants randomly assigned and 20 years of follow-up. It has multiple clinical outcome measures and a health economic analysis. There was no significant difference in the primary outcome of the Oxford Knee Score or other clinical endpoints; therefore, both procedures are clinically effective. However, as clinical differences tend to support patellar resurfacing, the resurfacing group accrued significantly more quality-adjusted life-years (QALYs). There was no difference in costs over the 20-year period, and as a result there is strong evidence that patellar resurfacing is cost-effective, which was the primary economic outcome.

Implications of all the available evidence

The long-term evidence is therefore weighted towards patellar resurfacing being the approach of first choice. Although there was no difference in the primary clinical outcome, there was a significant difference in the primary economic outcome measure due to significant increases in QALYs.

Unter einer **postpartalen Hämorrhagie (PPH)** versteht man eine starke, potenziell lebensbedrohliche Blutung nach der Geburt. Sie tritt typischerweise innerhalb der ersten 24 Stunden auf, kann sich aber auch bis zu 12 Wochen nach der Entbindung entwickeln. Eine schnelle medizinische Intervention ist entscheidend

Klassisch: Ein Blutverlust von ≥ 500 ml nach einer vaginalen Geburt oder ≥ 1.000 ml nach einem Kaiserschnitt.

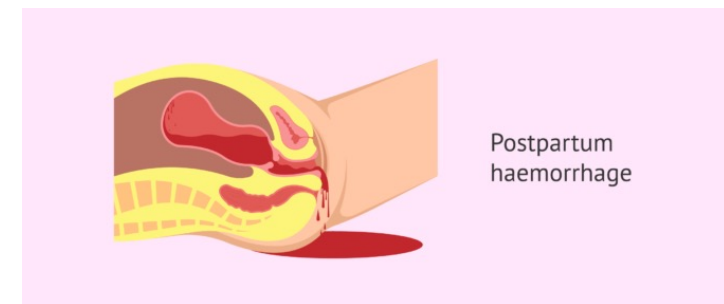
Schwere PPH: Verlust von mehr als 1.000 ml Blut innerhalb von 24 Stunden oder Anzeichen eines kritischen Blutdruckabfalls.

Tone (Tonusverlust / Uterusatonie): Die Gebärmutter zieht sich nach der Geburt nicht ausreichend zusammen. Dies ist die häufigste Ursache.

Trauma: Verletzungen, Risse oder Schnitte im Gebärmutterhals, in der Scheide oder im Dammbereich.

Tissue (Gewebe): Verbleibende Reste der Plazenta oder der Eihäute in der Gebärmutter, die das Zusammenziehen verhindern.

Thrombin (Gerinnungsstörungen): Probleme mit der Blutgerinnung (z.B. durch angeborene Gerinnungsstörungen oder starke Komplikationen während der Geburt).



4 T's

Postpartum Haemorrhage 1

Postpartum haemorrhage: epidemiology, consequences, and missed opportunities

Excessive bleeding after childbirth, known as postpartum haemorrhage (PPH), can turn an uncomplicated birth into a catastrophe. Each year, PPH occurs in an estimated 27 million women worldwide—17 million after vaginal birth and 10 million during or after caesarean birth. An estimated 43 000 women die from PPH annually, translating to a death every 12 min. The pooled prevalence of PPH at vaginal birth is 12·6% (95% CI 10·1–15·2) and at caesarean birth 30·9% (95% credible interval 24·9–37·6), based on the conventional definition of PPH. Common causes of PPH are uterine atony, genital tract trauma, retained placenta, abnormal placentation, and coagulopathy. Risk factors include caesarean birth, multiple pregnancy, anaemia, high maternal BMI, previous PPH, female genital mutilation, sepsis, pre-eclampsia, macrosomia, and inadequate antenatal care. In addition to being the leading cause of maternal mortality worldwide, the consequences of PPH include serious morbidities such as severe anaemia, hysterectomy, organ failure, and long-term psychological trauma. The global economic burden of PPH is estimated at US\$10·4 billion (95% credible interval \$9·8–13·2 billion) annually, consisting of \$3·6 billion (\$3·2–6·2 billion) for health systems and \$6·8 billion (\$6·2–7·5 billion) for societies. Based on a rigorous review of the evidence, WHO has recently redefined PPH as objectively measured blood loss of at least 300 mL plus an abnormal haemodynamic sign, or objectively measured blood loss of at least 500 mL, whichever occurs first. This new definition prioritises early PPH diagnosis and treatment to avert life-threatening maternal outcomes. Comprehensive efforts to address missed opportunities in the prevention, diagnosis, and treatment of PPH are needed to improve outcomes. These efforts include addressing the unmet need for contraception, mitigating modifiable risks such as anaemia, avoiding caesarean sections that are not medically indicated, using effective single uterotonic prophylaxis for all births and combination prophylaxis for women at high risk of PPH, ensuring accurate and objective measurement of blood loss for early PPH diagnosis, and promptly implementing treatment with an evidence-based bundle. The PPH Roadmap (2023–30) provides a global framework for action.

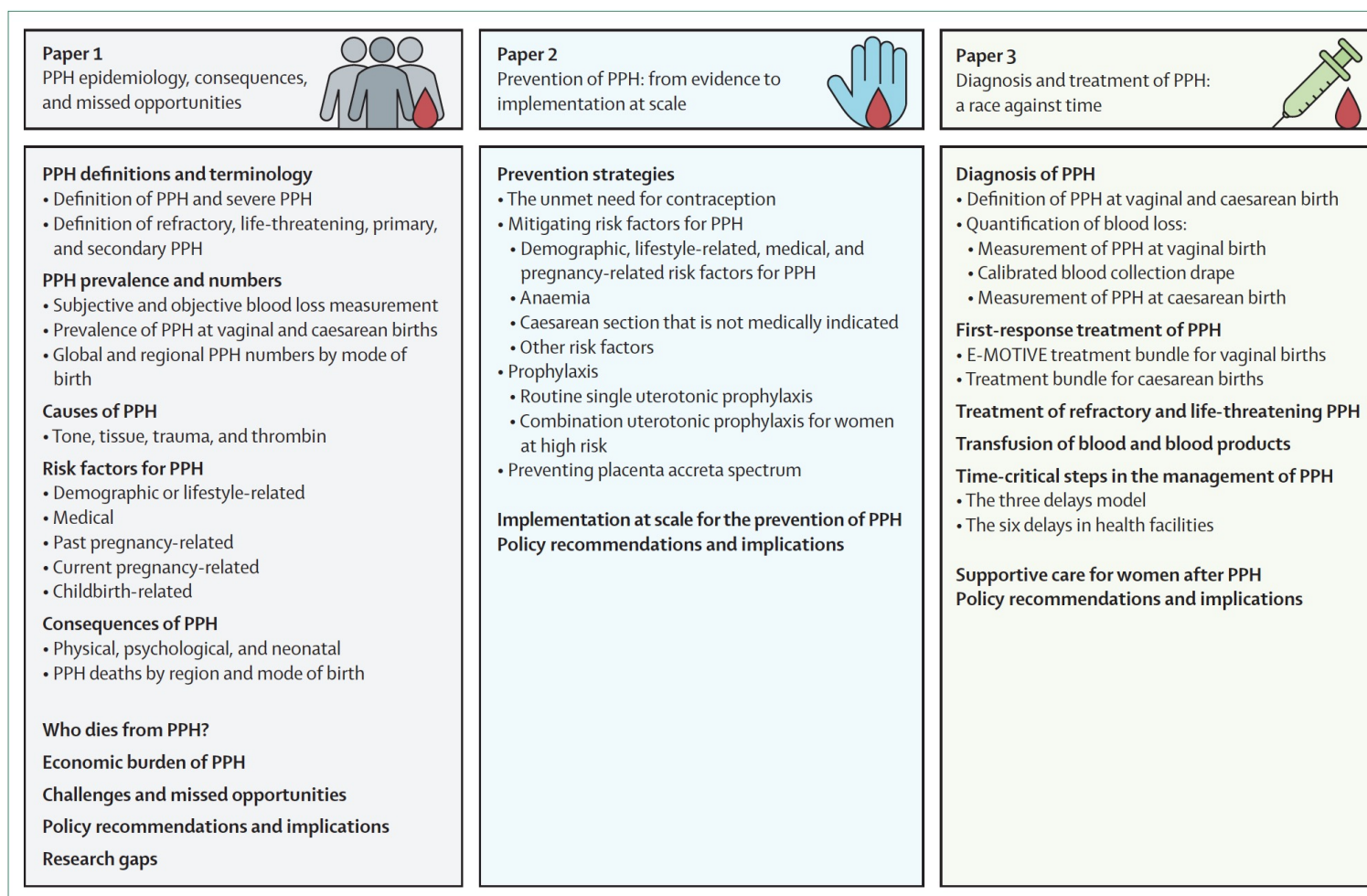


Figure 1: Outline of the 2026 Lancet Series on postpartum haemorrhage
PPH=postpartum haemorrhage.

Panel 1: Search strategy and consensus-building consultations

We published systematic reviews of postpartum haemorrhage (PPH) prevalence⁶ (last search: Aug 11, 2025), and causes and risk factors⁷ (last search: Nov 30, 2024) in the lead-up to this Series. For our systematic review on the consequences of PPH, we conducted a comprehensive literature search on MEDLINE, Web of Science, Embase, Google Scholar, Cochrane Library, and ClinicalTrials.gov, using relevant free text search terms and Medical Subject Headings (last search: July 13, 2025). We also reviewed the latest international guidelines on the diagnosis, prevention, and treatment of PPH, and updated several systematic reviews on diagnosis, prevention, and treatment of PPH.^{6–12}

An international consensus meeting on PPH was held in March, 2023, with a group of 27 key stakeholders from Argentina, Brazil, Kenya, Malawi, Nigeria, Norway, Pakistan, South Africa, Sri Lanka, Tanzania, the UK, and the USA. The conference was funded by the Gates Foundation, with no involvement or sponsorship from commercial organisations. Key questions and evidence on policies and recommendations for PPH diagnosis, prevention, treatment, and organisation of care were presented for discussion, and the scope of work for this Series was defined.

In March, 2023, WHO convened 136 stakeholders at the Global Summit on Postpartum Haemorrhage to identify persistent challenges in reducing the global burden of PPH and chart a course of action. Stakeholders included researchers, policy makers, guideline developers, programme implementers, women's advocates, funders, UN agencies, industry representatives, and innovators from more than 50 countries.¹³ Key challenges identified included guideline variations, difficulties in implementing evidence-based recommendations in the field, insufficient clarity on research priorities, and fragmented advocacy efforts resulting in diluted messages and slower-than-desired progress. The PPH Roadmap (2023–30) was developed to outline steps for addressing these challenges.¹⁴ As a key step in advancing the Roadmap, WHO, in collaboration with the International Federation of Gynecology and Obstetrics and the International Confederation of Midwives, developed the *Consolidated Guidelines for the Prevention, Diagnosis and Treatment of Postpartum Haemorrhage*.¹⁵ This comprehensive set of guidelines provides an up-to-date repository of clinical practice guidance.

Panel 2: Postpartum haemorrhage terminology

By severity of bleeding

- PPH: objectively measured blood loss of at least 300 mL with any abnormal haemodynamic sign, or objectively measured blood loss of at least 500 mL, whichever happens first.
- Severe PPH: objectively measured blood loss of at least 1000 mL.
- Life-threatening PPH: bleeding that has compromised a woman's condition through haemodynamic shock, collapse, or acute organ failure, necessitating immediate life-saving interventions from health-care professionals. Life-threatening PPH is likely to occur when objectively measured blood loss is at least 1500 mL but can also occur at lower volumes of blood loss; for example, in a woman with severe anaemia.

By response to treatment

- Refractory PPH: PPH that has not responded to the first-line treatment bundle.

By timing of onset

- Primary PPH: PPH that occurs within the first 24 h of childbirth.
- Secondary PPH: PPH that occurs after the first 24 h of childbirth.

PPH=postpartum haemorrhage.

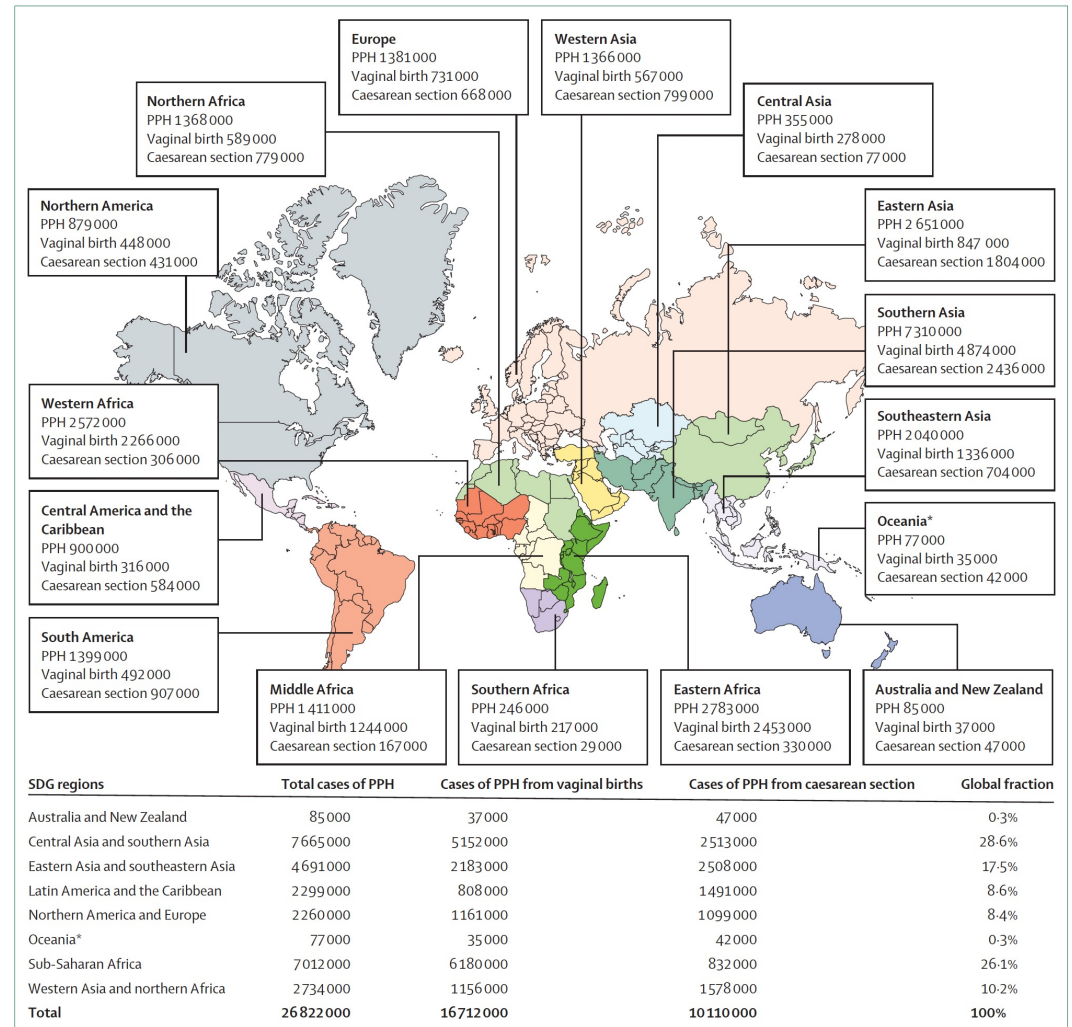


Figure 2: Estimated annual postpartum haemorrhage (≥500 mL) numbers by SDG regions and subregions, and mode of birth

Estimates from modelled data for 2023 (total PPH cases in the figure vary slightly from the modelled estimates due to rounding of numbers for representation in the map). Data derived from Bayesian hierarchical modelling (appendix pp 3–50). Global fraction represents the proportion of the global total in a specific region or subregion. PPH=postpartum haemorrhage. SDG=Sustainable Development Goal. *Oceania excludes Australia and New Zealand.

	Risk factor	OR (95% CI)
Sociodemographic		
Weak association (OR >1-1.5)	Black vs white ethnicity	1.44 (1.03-2.01)
Weak association (OR >1-1.5)	Asian vs white ethnicity	1.15 (1.04-1.27)
Medical		
Strong association (OR >2)	Anaemia	2.36 (1.29-4.32)
Strong association (OR >2)	Female genital mutilation	2.14 (1.43-3.20)
Strong association (OR >2)	Sepsis	2.31 (1.55-3.46)
Moderate association (OR >1.5-2)	BMI 30-34.9 vs 18.5-24.9 kg/m ²	1.51 (1.32-1.72)
Moderate association (OR >1.5-2)	Liver disease	1.64 (1.12-2.42)
Moderate association (OR >1.5-2)	COVID-19	1.85 (1.56-2.18)
Weak association (OR >1-1.5)	BMI 25-29.9 vs 18.5-24.9 kg/m ²	1.21 (1.13-1.30)
Weak association (OR >1-1.5)	Uterine fibroids	1.20 (1.06-1.35)
Weak association (OR >1-1.5)	Antidepressant use	1.47 (1.28-1.70)
Weak association (OR >1-1.5)	Asthma	1.24 (1.13-1.36)
Weak association (OR >1-1.5)	Epilepsy [¶]	1.21 (1.17-1.25)
Past pregnancy-related		
Strong association (OR >2)	Previous PPH	3.17 (2.42-4.16)
Strong association (OR >2)	Grand multiparity vs nulliparity	2.62 (1.24-5.52)
Moderate association (OR >1.5-2)	Family history of PPH [§]	1.63 (1.24-2.14)
Weak association (OR >1-1.5)	Grand multiparity vs multiparity	1.48 (1.14-1.91)
Current pregnancy-related		
Strong association (OR >2)	Multiple pregnancy	2.62 (2.14-3.21)
Strong association (OR >2)	Placenta praevia	3.10 (1.61-5.97)
Strong association (OR >2)	No antenatal care vs antenatal care	2.78 (1.78-4.36)
Strong association (OR >2)	Resolved placenta praevia	3.35 (2.43-4.62)
Strong association (OR >2)	Stillbirth	5.39 (3.32-8.75)
Strong association (OR >2)	Assisted conception vs natural conception	2.40 (2.08-2.76)
Moderate association (OR >1.5-2)	Pre-eclampsia	1.54 (1.48-1.60)
Moderate association (OR >1.5-2)	Gestational diabetes	1.88 (1.16-3.03)
Moderate association (OR >1.5-2)	Polyhydramnios	1.73 (1.32-2.28)
Labour and childbirth		
Strong association (OR >2)	Caesarean birth	5.18 (3.42-7.85)
Strong association (OR >2)	General anaesthesia [¶]	2.90 (1.90-4.50)
Strong association (OR >2)	Magnesium infusion [‡]	2.02 (1.15-3.56)
Strong association (OR >2)	Prolonged second stage of labour [¶]	3.40 (2.40-4.70)
Strong association (OR >2)	Shoulder dystocia	2.06 (1.67-2.54)
Strong association (OR >2)	Birthweight 4500-5000 g vs <4000 g	2.08 (1.70-2.54)
Moderate association (OR >1.5-2)	Birthweight 4000-4500 g vs <4000 g	1.67 (1.54-1.80)
Moderate association (OR >1.5-2)	Episiotomy [‡]	1.81 (1.56-2.11)
Weak association (OR >1-1.5)	PROM vs no PROM	1.39 (1.28-1.51)
Weak association (OR >1-1.5)	Induction of labour	1.37 (1.22-1.54)
Weak association (OR >1-1.5)	Augmentation of labour	1.28 (0.85-1.94)
Weak association (OR >1-1.5)	Instrumental birth	1.44 (1.03-2.00)
Information sourced from Yunas et al, ⁷ or from other referenced sources. Adjusted pooled ORs are reported, where available; otherwise, pooled crude ORs are reported. Nulliparity=no previous births. Multiparity=one or more previous births. Grand multiparity=five or more previous births. PPH=postpartum haemorrhage. PROM=premature rupture of membranes. OR=odds ratio.		
Table 1: Risk factors for postpartum haemorrhage, grouped by category		

	Percentage risk of the complication or consequence (95% CI)	Risk of the consequence in women with PPH vs no PPH (95% CI)
Immediate physical consequences		
Acute renal complications*	1.0 (0.5-1.7)	..
Acute respiratory complications†	2.2 (0.7-4.7)	..
Blood transfusion	12.3 (9.9-15.0)	..
Cardiac complications‡	1.7 (0.4-3.8)	aHR 1.02 (0.97-1.07); ²⁹ aHR 1.96 (1.51-2.53) [¶]
Coagulopathy	3.4 (1.4-6.3)	..
Hepatic failure	0.3 (0.2-0.4)	..
Hysterectomy	2.1 (1.3-3.1)	..
ICU admission	3.3 (1.0-6.7)	..
Maternal death	1.6 (0.8-2.6)	cOR 5.6 (3.75-8.37) [¶]
Near-miss§	18.0 (6.6-33.3)	..
Pulmonary embolism	0.3 (0.1-0.6)	..
Prolonged hospitalisation¶	13.1 (0.0-51.0)	..
Seizure	0.4 (0.3-0.6)	..
Shock	2.9 (0.3-7.5)	..
Cerebral complications	0.5 (0.0-2.0)	..
Delayed physical consequences		
Postnatal anaemia	46.3 (30.8-62.1)	..
Postnatal sepsis	0.6 (0.1-1.6)	..
Psychological consequences		
Anxiety	28.5 (0.0-88.3)	aHR 0.99 (0.90-1.09) [¶]
Postnatal depression	15.5 (8.5-24.2)	aHR 1.08 (0.99-1.17); ³³ aOR 1.68 (1.16-2.42); ³⁴ aOR 1.68 (1.16-2.42) [¶]
Post-traumatic stress disorder	10.7 (3.1-21.7)	aHR 1.17 (0.73-1.89) [¶]
Consequences on the newborn		
Inability to exclusively breastfeed	27.8 (19.3-37.2)	aOR 0.88 (0.86-0.90)**
Need for NICU admission	16.1 (11.9-20.8)	..
Information from a systematic review conducted by the Series authors (appendix pp 67-83), or from other identified sources. aHR=adjusted hazard ratio. cOR=crude odds ratio. ICU=intensive care unit. NICU=neonatal intensive care unit. PPH=postpartum haemorrhage. *Four of the eight studies specified the complication as renal failure. †Three of the seven studies specified the complication as respiratory failure. ‡Four of the ten studies specified the complication as heart failure, and two studies as cardiac arrest. §A woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy. ¶Includes one study from a low-income country, where it was estimated that ≥1 additional day in hospital was expected in 51.9% of women with PPH; and two studies from high-income countries, where it was estimated that ≥4 additional days in hospital were expected in 2.4% of women with PPH. Two of the three studies specifically reported this as stroke. **Women with PPH were less likely to be exclusively breastfeeding their babies compared with those without PPH.		
Table 2: Consequences of postpartum haemorrhage		

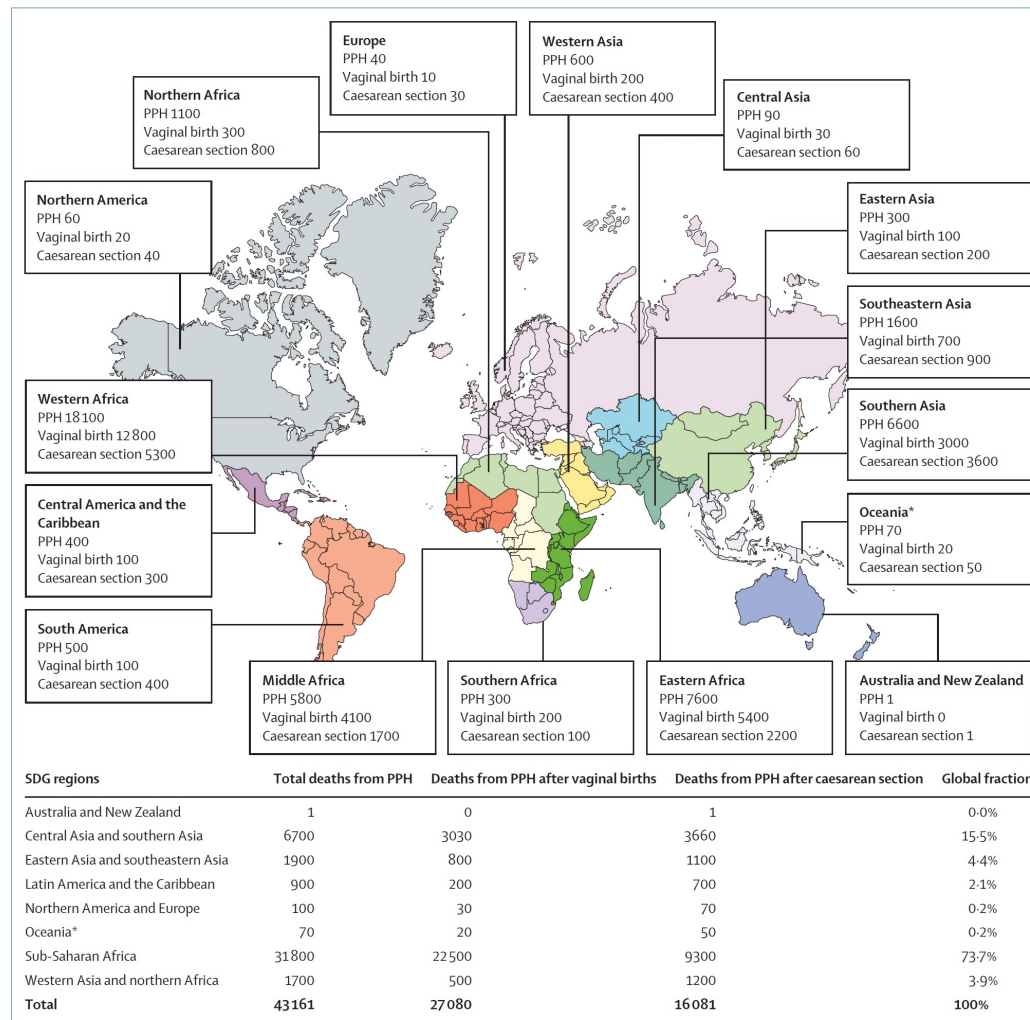


Figure 3: Estimated annual postpartum haemorrhage deaths by Sustainable Development Goal regions and mode of birth
 Estimates from modelled data for 2023 (total PPH deaths in the figure vary slightly from the modelled estimates due to rounding of numbers for representation in the map). Data derived from Bayesian hierarchical modelling (appendix pp 3–50). Global fraction represents the proportion of the global total in a specific region or subregion. PPH=postpartum haemorrhage. SDG=Sustainable Development Goal. *Oceania excludes Australia and New Zealand.

Panel 3: Who dies from postpartum haemorrhage?

Maternal death reviews, of which the most comprehensive are confidential enquiries into maternal deaths, provide detailed information on maternal deaths, including causes, contributory factors, context, and the quality of care received.⁴² Several countries periodically publish their maternal death review reports, often identifying elements of substandard care and providing recommendations for improvements.⁴³ A systematic evidence synthesis of maternal death review reports from countries where maternal death rates are high showed several common themes on causes, contributory factors, quality of care provided, and outcomes of PPH.^{44,45} Women who are most likely to die from PPH are those who have home births; those with anaemia or pre-existing medical problems; those who have a caesarean birth, particularly an emergency caesarean at full cervical dilation; and those delivering in health-care settings with staffing challenges.^{7,46-48} Delayed identification of PPH and delayed initiation of treatment were particular problems for women who died from PPH. Substandard care was reported in 50–75% of women who died from PPH.^{45,49} Lessons from South Africa, which has robust triennial Confidential Enquiries into Maternal Deaths, show that 86% of obstetric haemorrhage deaths are possibly or probably avoidable.⁵⁰ Patient-related avoidable factors, mostly delays in seeking care, were present for 35% of women who died. Avoidable health service factors were observed in 70% of deaths, including inadequate blood

supplies for transfusion (8.5%), delays in inter-institutional transport (11.4%), delays in initiating clinical care due to overburdened services (12.2%), staff shortages (13.4%), and shortages of staff with appropriate skill (18.5%). Important problems were identified with initial assessment and recognition of PPH at community health-care centres and district hospitals. Many women were discharged from labour wards to postnatal wards with abnormal vital signs and unrecognised PPH. At all levels of care, substandard care was the most frequent problem.

Key recommendations from maternal death reviews target women, communities, health-care providers, and policy makers.^{43,44} Recommendations targeting women and communities include promotion of facility births assisted by skilled birth attendants; those targeting health-care providers include improving timely decision making in managing obstetric complications, such as PPH; and those targeting policy makers include greater interventions at the health-system level to ensure adequate numbers of competent staff, quality-assured essential medicines, effective clinical governance and risk management systems, and sustained funding.^{44,51} These recommendations are further explored in the second and third papers in this Series.

Figure 4: Challenges and opportunities to reduce postpartum haemorrhage morbidity and mortality
PPH=postpartum haemorrhage.

	Challenges	Opportunities for intervention
Menstrual health	Heavy menstrual bleeding	Treat heavy menstrual bleeding Test and treat for anaemia Dietary improvements
Sexual and reproductive health	Unmet need for contraception	Routine and emergency contraception
	Female genital mutilation	Policy interventions for prevention Expert assessment and care
Pre-pregnancy	Anaemia Risk factors (eg, high BMI and hypertension)	Test and treat anaemia Optimise risk factors
Pregnancy	No antenatal care Anaemia Placenta praevia and accreta spectrum Multiple pregnancy Pre-eclampsia Macrosomia Polyhydramnios	Optimise regular antenatal care Test and treat for anaemia Antenatal ultrasound Robust risk assessment, diagnosis, and forward planning
Labour and childbirth	Childbirth without skilled attendance	Promote childbirth in health facilities
	Risk factors (eg, induction, augmentation, prolonged second stage, and macrosomia)	Robust risk assessment, diagnosis, and forward planning Consider assisted vaginal birth Avoid routine episiotomy
	Caesarean birth (too much, too soon; too little, too late)	Avoid caesarean sections that are not medically indicated Conduct medically indicated caesarean sections on time Avoid general anaesthesia if possible
Postpartum	Poor preventive care	Routine use of oxytocin or carbocin for all births Combination uterotonic prophylaxis for women at high risk Controlled cord traction
	Delayed or missed diagnosis of PPH	Objective blood loss assessment Early treatment trigger if vital signs are abnormal
	Delayed or incomplete first-response treatment of PPH	MOTIVE bundle for vaginal birth Consider adapted MOTIVE bundle for caesarean birth
	Refractory PPH	Refractory PPH action package Temporising measures Operative management Prompt referral if necessary
	Life-threatening PPH	Resuscitation Deploy massive transfusion protocol Operative management Intensive care unit management
	Anaemia	Test and treat for anaemia
Post discharge	Weak referral systems	Strengthen referral systems, protocols, and transportation
	Anaemia	Test and treat for anaemia
	Unmet contraception need	Regular and emergency contraception

Postpartum Haemorrhage 2

Prevention of postpartum haemorrhage: from evidence to implementation at scale

Postpartum haemorrhage (PPH) is a leading cause of maternal death. Preventing PPH can spare women from experiencing the trauma and risks of PPH, reduce the strain on overstretched health systems, and probably produce better outcomes than a strategy solely focused on PPH treatment. Prevention of PPH is often interpreted as provision of uterotonic drugs to contract the uterus at the time of childbirth. Although uterotonics are a central strategy for PPH prevention, several other approaches can prevent PPH or ameliorate its severity. These approaches include addressing the unmet need for contraception, remedying anaemia and other modifiable risk factors for PPH, optimising medical conditions that predispose to PPH, and tackling the rise in caesarean births in many countries. Effective delivery of preventive care requires early and regular antenatal care and planned birth at appropriately resourced health facilities. Social and behavioural change interventions for improving contraceptive provision and uptake, targeting adolescents, postpartum women, geographically remote communities, and families on low income, are a priority. Effective interventions to tackle anaemia include the management of heavy menstrual bleeding, pre-pregnancy or antenatal haemoglobin testing and oral or intravenous iron treatment, dietary improvements, and—on rare occasions—blood transfusion. Risk factors for PPH that need attention include high BMI, multiple pregnancy, gestational diabetes, pre-eclampsia, macrosomia, and several medical conditions. Caesarean births are associated with a substantial increase in PPH risk and should therefore only be done when medically indicated. A Cochrane network meta-analysis of 122 trials, with 121931 women, found that the combinations of oxytocin plus misoprostol, or oxytocin plus ergometrine, were the most effective prophylaxis for PPH when given at the time of childbirth; however, these combinations had a higher risk of side-effects compared with single-drug prophylaxis. Oxytocin and carbetocin were the most effective single drugs for PPH prophylaxis, with minimal side-effects. Single uterotonic prophylaxis with either oxytocin or carbetocin is, therefore, recommended for routine prophylaxis. However, if oxytocin or carbetocin is not accessible, misoprostol is an alternative. Combination prophylaxis with oxytocin plus misoprostol can be considered for women at high risk of PPH. Ergometrine alone and oxytocin plus ergometrine combination are no longer recommended due to hypertension-related safety concerns. A robust implementation approach that engages various stakeholders to promote change, ensures the supply of quality-assured medicines and devices, provides training and support, and secures ongoing political and financial commitment is necessary to translate evidence into global impact.

Panel 1: Search strategy and consensus-building consultations

The recommendations are based on published systematic reviews of the current literature, appraisal of professional body guidelines, and expert group discussions. For the systematic review on causes and risk factors of postpartum haemorrhage, we searched MEDLINE, Web of Science, Embase, Cochrane Library, and Google Scholar (last search Nov 30, 2024).² We also refer to the latest updated Cochrane network meta-analysis on uterotonic agents for preventing postpartum haemorrhage.³ For the review of professional body guidelines, we reviewed the latest WHO–International Federation of Gynecology and Obstetrics–International Confederation of Midwives consolidated guidelines for the prevention, diagnosis, and treatment of postpartum haemorrhage,⁴ WHO’s comprehensive framework for action in accelerating anaemia reduction,⁵ and the Royal College of Obstetricians and Gynaecologists guideline for the diagnosis and management of placenta praevia and placenta accreta.⁶ For expert group meetings, recommendations were formulated based on an international consensus meeting on postpartum haemorrhage held in March, 2023, with a group of 27 key stakeholders from Argentina, Brazil, Kenya, Malawi, Nigeria, Norway, Pakistan, South Africa, Sri Lanka, Tanzania, the UK, and the USA. Agreements were reached through consensus.

Panel 2: Risk factors for postpartum haemorrhage

Risk factors with strong association (OR >2)

- Anaemia
- Female genital mutilation
- Sepsis
- Previous PPH
- Grand multiparity
- No antenatal care
- Placenta praevia
- Resolved placenta praevia
- Stillbirth
- Multiple pregnancy
- Assisted conception
- Caesarean birth
- General anaesthesia¹²
- Magnesium infusion¹³
- Prolonged second stage of labour¹⁴
- Shoulder dystocia
- Birthweight ≥ 4500 g

Risk factors with moderate association (OR >1.5 to 2)

- BMI ≥ 30 kg/m²
- Liver disease
- Family history of PPH
- Hypertensive disorders of pregnancy¹³
- Pre-eclampsia
- Gestational diabetes
- Polyhydramnios
- Birthweight 4000 g to <4500 g
- Episiotomy¹³
- COVID-19

Risk factors with weak association (OR >1 to 1.5)

- BMI 25–29.9 kg/m²
- Black ethnicity
- Asian ethnicity
- Uterine fibroids
- Antidepressant use
- Asthma
- Epilepsy¹⁵
- Premature rupture of membranes
- Induction of labour
- Augmentation of labour
- Instrumental birth

Information sourced from Yunas et al.² or from other cited sources. PPH=postpartum haemorrhage. OR=pooled odds ratio (adjusted pooled ORs are reported, where available; otherwise, pooled crude ORs are reported).

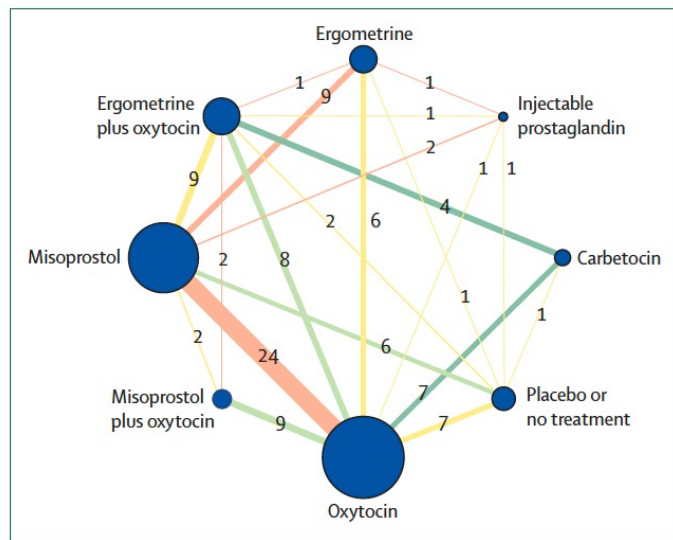


Figure 1: Network diagram of uterotonic drugs for the prevention of postpartum haemorrhage (blood loss ≥ 500 mL)

Figure adapted from Gallos et al.³ The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other in the network. The lines connecting each pair of interventions represent a direct comparison; their width is proportional to the number of trials contributing to each direct comparison. Numbers on the lines represent the number of trials for each comparison. Dark green lines represent high-certainty evidence, light green lines are for moderate-certainty evidence, yellow lines are for low-certainty evidence, and red lines are for very low-certainty evidence.

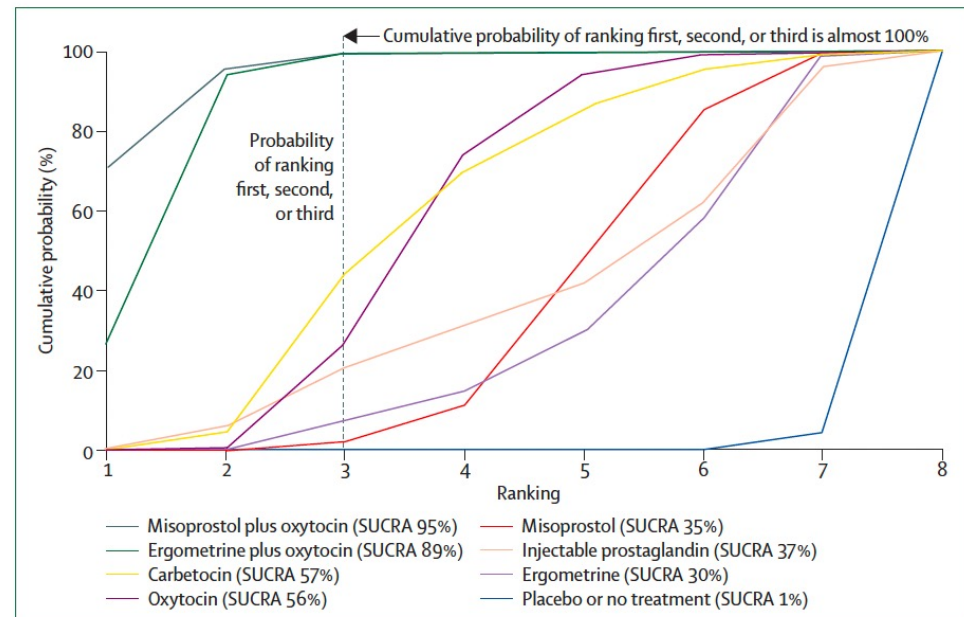


Figure 2: Cumulative rankograms comparing each of the uterotonic agents for prevention of postpartum haemorrhage (blood loss ≥ 500 mL)

Figure adapted from Gallos et al.³ Ranking indicates the cumulative probability of being the best agent, the second best, the third best (and so on). The x-axis shows the relative ranking and the y-axis the cumulative probability of each ranking. We estimate the surface underneath this cumulative ranking line (SUCRA); the larger the SUCRA, the higher its rank among all available agents.

Panel 3: Priority interventions at scale for postpartum haemorrhage prevention

- Address the unmet need for contraception
- Improve antenatal care coverage
- Mitigate modifiable risk factors for PPH (eg, high BMI and hypertensive disorders)
- Diagnose and address anaemia
- Ensure women at high risk of PPH give birth at appropriate facilities
- Reduce caesarean sections that are not medically indicated
- Take steps to reduce the prevalence of placenta accreta
- Offer single uterotonic prophylaxis for all births
- Consider combination uterotonic prophylaxis for women at high risk of PPH

PPH=postpartum haemorrhage.

Postpartum Haemorrhage 3

Diagnosis and treatment of postpartum haemorrhage: a race against time

Postpartum haemorrhage (PPH) is common, affecting an estimated 13% of women having vaginal birth and 31% of women having caesarean birth. Successful management of PPH requires early and accurate diagnosis and effective treatment. A systematic review found that subjective visual estimation of blood loss misses 52% of PPH diagnoses at vaginal birth (pooled sensitivity 48%, 95% CI 44–53), and probably more at caesarean birth. The WHO–International Federation of Gynecology and Obstetrics–International Confederation of Midwives consolidated guidelines on PPH therefore recommend objective quantification of blood loss with products such as a calibrated blood collection drape. When supported by a robust implementation strategy and a first-response treatment bundle, objective measurement of blood loss and monitoring of vital signs has been shown to diagnose PPH accurately and early, and improve clinical outcomes. Refractory PPH can progress to life-threatening PPH, which should be managed by a multidisciplinary team providing aggressive resuscitation and targeted treatment. Saving the life of a woman with excessive postpartum bleeding is a race against time. The six delays to avoid are: (1) in the diagnosis (by use of objective cumulative blood loss measurement and early trigger criteria), (2) in the first-response treatment (by authorising midwives to administer all components of a standardised bundle of interventions), (3) in the escalation (by use of explicit escalation criteria and red flags), (4) in the use of temporising measures (eg, non-pneumatic anti-shock garment), (5) in the identification and targeted management of any specific causes of bleeding, and (6) in the provision of blood and blood products. Quick actions to avoid these delays can mean the difference between life and death for a woman with PPH.

Key messages

- Address modifiable risk factors for PPH, particularly anaemia and caesarean sections that are not medically indicated
- Provide routine prophylaxis for PPH with cold-chain maintained oxytocin or heat-stable carbetocin
- Consider dual prophylaxis with oxytocin and misoprostol for women at high risk of PPH
- Apply the reappraised definition of PPH to avoid missed cases
- Use objective methods of blood loss assessment, such as calibrated drapes, to accurately diagnose PPH
- Use first-response treatment bundles to avoid the delays of sequential treatments, and treat multiple concurrent causes of PPH
- Use red flags to identify women diagnosed with PPH who could deteriorate beyond first-response treatment
- Maintain urgency across the spectrum of prevention, diagnosis, and treatment of PPH to avoid missed opportunities

PPH=postpartum haemorrhage.

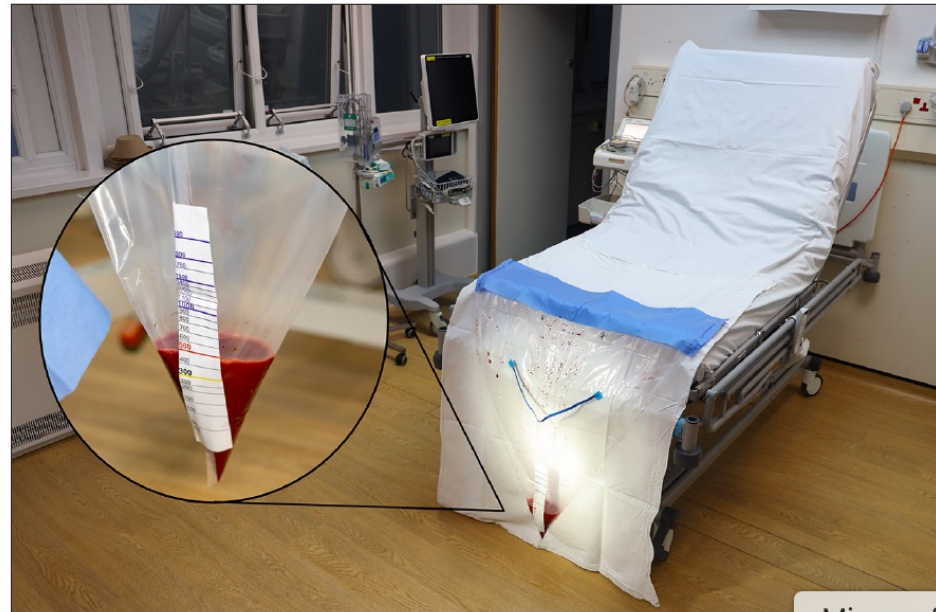


Figure 1: Ammalife calibrated blood collection drape
Courtesy of Kimal, UK.²¹

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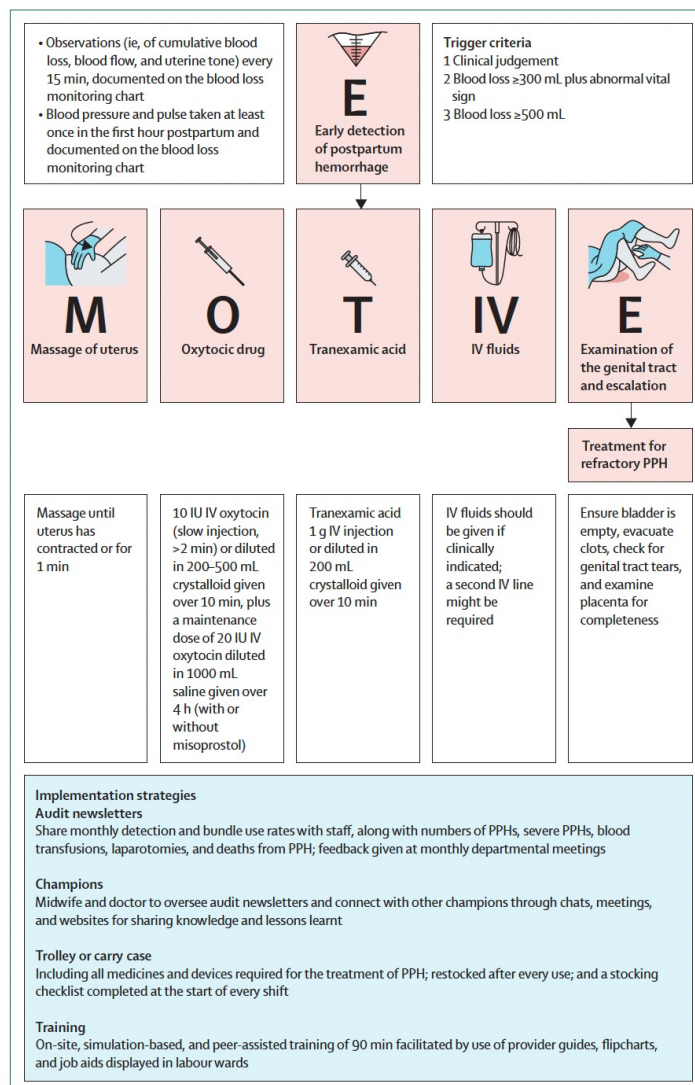


Figure 2: E-MOTIVE treatment bundle for vaginal births
Reproduced from Gallos et al.⁷ PPH=postpartum haemorrhage. IU=international units. IV=intravenous.

PPH carry case item	Number of items
Large bore IV cannula	×2
Tourniquet	×2
Alcohol swabs	×6
10 mL sterile water for injection	×4
Medical tape/plaster	×2
TXA 500 mg/5 mL vials or 1 mg/10 mL vials	×10
21G needles (green)	×6
23G needles (blue)	×6
5 mL syringes	×6
10 mL syringes	×8
Additive stickers for IV fluids	×3
1000 mL IV fluids (NaCl or Ringer's Lactate)	×1
500 mL IV fluids (NaCl or Ringer's Lactate)	×2
Giving set	×2
Small packet sterile swabs	×2
Medium packet sterile swabs	×2
Catheter bag	×1
Foley's catheter	×1
Size small sterile gloves	×2
Size medium sterile gloves	×2
Size large sterile gloves	×2
Lignocaine 1% 10 mL	×1
Plastic apron	×1
Cradle device, fully charged	×1



Figure 3: An example PPH carry case with a checklist of contents
Oxytocin ampoules are stored in the fridge until required. IV=intravenous.
NaCl=sodium chloride. PPH=postpartum haemorrhage. TXA=tranexamic acid.

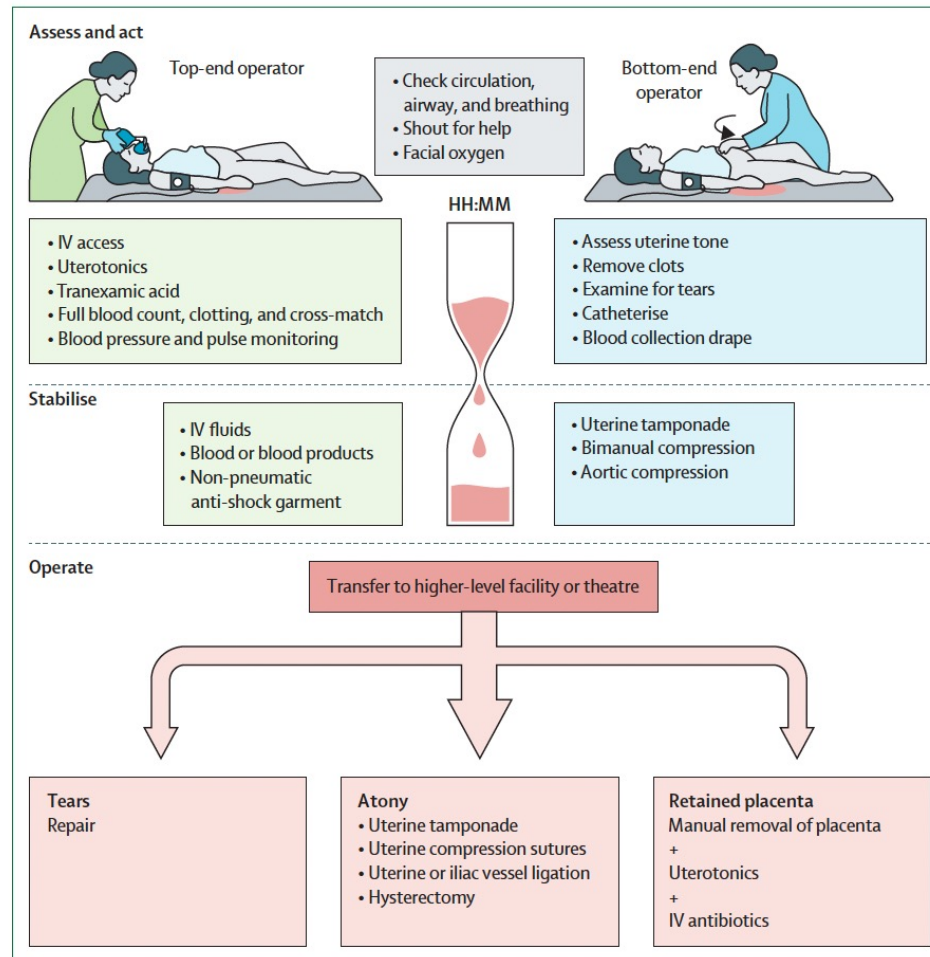


Figure 4: A structured approach for managing refractory postpartum haemorrhage
IV=intravenous.

The principles outlined in this Series represent achievable goals that could transform PPH outcomes globally. The essential knowledge and tools to substantially reduce PPH-related morbidity and mortality now exist; the primary challenge lies in translating this evidence into consistent clinical practice across diverse health-care settings. The required transformation extends beyond merely enhancing individual clinical skills to encompass systemic and systematic changes in health-care delivery and organisational culture. Success will demand sustained commitment from policy makers and health-care leaders, adequate resource allocation, and continuous quality improvement efforts. The ultimate goal—the elimination of preventable maternal deaths from PPH through the consistent application of evidence-based practices worldwide—is within our collective grasp.

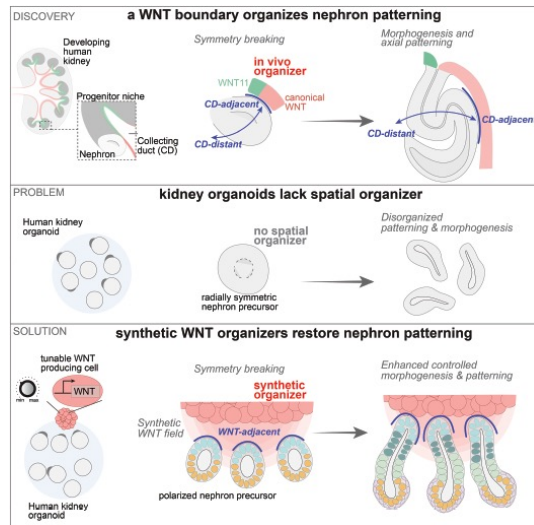


Patterning human kidney organoids with synthetic Wnt-secreting organizers

INTRODUCTION: Organoids—miniature tissues grown from stem cells—can reproduce aspects of organ development, but their architecture often emerges through self-organization and is therefore difficult to control. Understanding how to impose spatial patterning in organoid systems is therefore an important challenge. Kidney organoids illustrate this limitation. Unlike in vivo nephrons, which form long segmented tubules oriented so that filtered fluid drains into a common collecting system, organoid nephrons exhibit variable patterning and orientation. This lack of spatial organization limits the ability of kidney organoids to form coherent nephron architectures and to model normal nephron physiologies.

RATIONALE: In embryos, spatial patterning is often organized by localized signaling centers known as developmental organizers. In the kidney, nephrons form next to the developing and branching collecting duct, and work in model organisms suggests that this epithelium provides localized signals that guide nephron polarity and segmentation. How this organizing geometry is arranged in human development and which cues are sufficient to recreate it have remained unclear. We mapped this organizing geometry in developing human kidneys and tested whether a minimal cue of localized WNT signaling could restore spatial control of nephron patterning in organoids.

RESULTS: Spatial transcriptomics revealed that nascent human nephrons form adjacent to a boundary in the collecting duct where two WNT signaling proteins, WNT11 and WNT9B, mark neighboring tip and stalk domains. Forming nephrons displayed asymmetric gene expression relative to the WNT9B-expressing collecting duct. This finding allowed us to define an adjacent-to-distant axial nephron polarity that emerges early and persists as nephrons elongate and simultaneously form their proximal-distal axes. WNT response genes were enriched near the WNT9B domain, consistent with localized WNT signaling at the nephron-to-collecting duct interface. We tested whether this signaling geometry is sufficient to guide organoid architecture and engineered self-assembling WNT-secreting “synthetic organizers.” When placed next to kidney organoids, nephrons adjacent to organizers showed restored localized WNT responses, acquired axial polarity, and oriented tubule growth and segment patterning toward the signal source. Tuning of organizer output controlled nephron architecture and revealed conditions in which nephrons generate multiple segments while remaining coherently oriented.



WNT organizers control nephron patterning. Spatial transcriptomics of the developing human kidney reveals a *WNT11-WNT9B* boundary at the collecting duct that establishes an adjacent-distant polarity guiding nephron morphogenesis. Kidney organoids lack this spatial organizer and show disorganized patterning. Introducing tunable synthetic WNT-secreting organizers restores localized signaling, inducing symmetry breaking, orienting nephron growth and enabling controlled nephron patterning in organoids. CD, collecting duct.

CONCLUSION: Our findings link a spatial organizing geometry in the developing human kidney to controllable engineering in vitro. Synthetic organizers provide a modular way to restore missing spatial interactions without reconstructing the entire collecting duct lineage, complementing approaches that rebuild collecting duct-to-nephron cellular interactions. More broadly, combining in vivo spatial mapping with synthetic reconstruction provides a general pipeline to identify organizer geometries in developing tissues and recreate them to guide organ morphogenesis.

What a gastroenterologist wants you to know about bidets



Could dirty water splash back at me? How does it know where to spray?

Bidet owners are so obnoxious. They need the world to know they have one — whether anyone asked or not — and they ensure all the creatures of lesser plumbing know precisely how much they're missing out.

I know because I am one of them.

As a gastroenterologist, I think about bidets the way others might think about their retirement accounts or the rain forecast. I get worked up more quickly than I intended, and I usually carry the conviction that everyone else around me is wrong.