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



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



A 33-year-old butcher presented with a 3-day history of painful ulcers on his left hand and several hours of worsening arm swelling. Three days before the ulcers appeared, he had slaughtered a sick cow. Ipsilateral arm edema and axillary lymphadenopathy were also noted. The lesions rapidly progressed to large hemorrhagic bullae 24 hours after presentation and subsequently ruptured 72 hours after presentation. Which of the following is the most likely diagnosis?

Cowpox

Cutaneous anthrax

Cutaneous brucellosis

Cutaneous Mycobacterium bovis infection

Ulceroglandular tularemia

A polymerase-chain-reaction assay of a skin swab was positive for Bacillus anthracis. Cutaneous anthrax results from direct inoculation of bacterial spores from infected livestock and causes a bullous lesion. The edema toxin of the bacteria increases vascular permeability and leads to progressive swelling of the affected area.

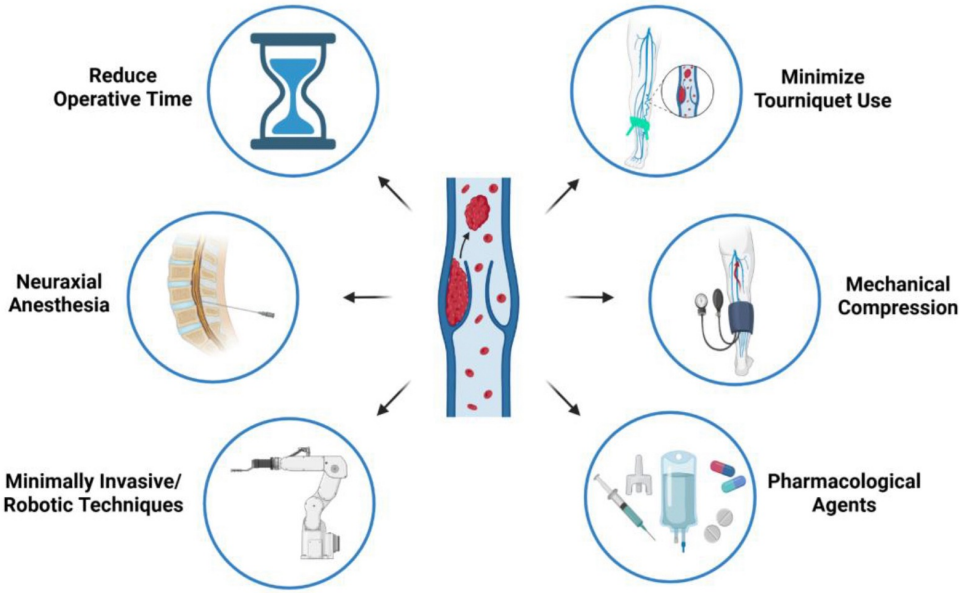
Vorbeugung (Thromboseprophylaxe)

Um das Risiko auf unter 1 Prozent zu senken, werden nach Knie- und Hüft-OPs standardmäßig kombinierte Maßnahmen eingesetzt:

- **Medikamente:** Tägliche Spritzen (z. B. niedermolekulares Heparin wie Enoxaparin) oder blutverdünnende Tabletten (z. B. NOAKs wie Rivaroxaban oder auch ASS je nach ärztlicher Vorgabe). Die Dauer richtet sich danach, wie schnell das Gelenk wieder voll belastbar ist (meist ca. 3 bis 6 Wochen).

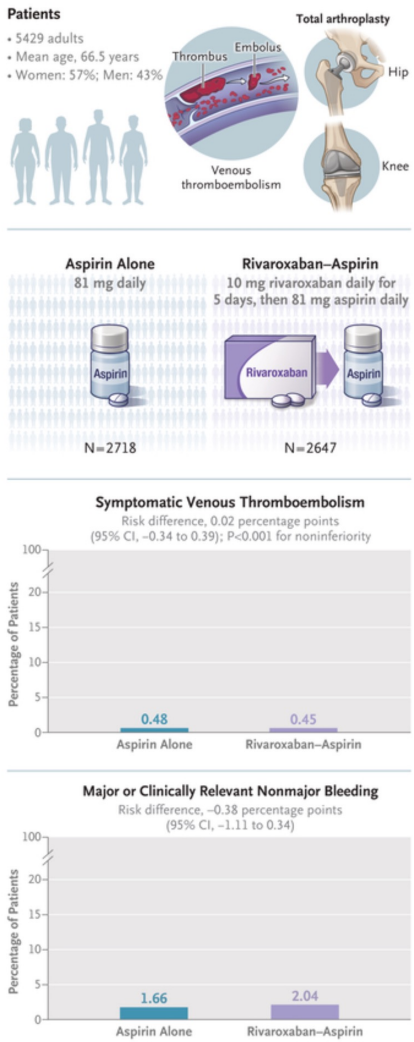
- **Frühe Mobilisation:** So früh wie möglich aufstehen und leichte Bewegungsübungen machen.

- **Mechanische Maßnahmen:** Kompressionsstrümpfe oder apparative Kompression.



Rivaroxaban Then Aspirin vs. Aspirin Alone after Total Hip or Knee Arthroplasty

Aspirin after an initial short course of rivaroxaban has been shown to be safe and effective for the prevention of venous thromboembolism after total hip or total knee arthroplasty, but uncertainty remains about the use of aspirin alone. In this multicenter, double-blind, randomized, controlled trial, we assigned patients to receive once-daily thromboprophylaxis with either 81 mg of aspirin or 10 mg of oral rivaroxaban for the first 5 days after total hip or total knee arthroplasty. All the patients then received further thromboprophylaxis with 81 mg of aspirin daily for 9 additional days after knee arthroplasty and for 30 additional days after hip arthroplasty. Patients were followed for 90 days for symptomatic venous thromboembolism, which consisted of either proximal deep-vein thrombosis or pulmonary embolism (primary effectiveness outcome), and for bleeding complications (primary safety outcome). The noninferiority margin for aspirin alone as compared with rivaroxaban–aspirin was 0.7 percentage points.



Venous thromboembolism (VTE), which includes both deep-vein thrombosis and pulmonary embolism, is a serious potential complication after lower-limb surgery. The administration of antithrombotic prophylaxis during hospitalization after total hip or total knee arthroplasty has proved to reduce the risk of death and complications from VTE and to be cost-effective. The extension of prophylaxis for up to 35 days after the standard period further reduces the rate of symptomatic VTE. Rivaroxaban, a direct oral anticoagulant, is commonly used for prophylaxis after arthroplasty because clinical trials and meta-analyses have shown that rivaroxaban is more effective than low-molecular-weight heparin for preventing VTE but is potentially associated with more clinically important bleeding complications.

We reasoned that an aspirin-alone approach to postoperative prophylaxis after arthroplasty would be as effective and safe as 5 days of rivaroxaban followed by aspirin. We designed the EPCAT III trial to study the effectiveness and safety of extended prophylaxis with aspirin alone, as compared with rivaroxaban followed by aspirin, for the prevention of VTE after total hip or total knee arthroplasty.

Methods

Patients and Trial Oversight

All the patients who were undergoing elective unilateral primary or revision hip or knee arthroplasty were potentially eligible for the trial.

Trial Procedures and Randomization

Patients who were undergoing arthroplasty were randomly assigned to receive once-daily thromboprophylaxis with either 81 mg of aspirin or 10 mg of oral rivaroxaban for the first 5 postoperative days starting on the night after surgery or postoperative day 1, according to the treating surgeon. All the patients then received further thromboprophylaxis with 81 mg of aspirin daily for 9 additional days in the patients undergoing knee arthroplasty and for 30 additional days in those undergoing hip arthroplasty.

Patients who had been taking daily low-dose aspirin before randomization (long-term aspirin subgroup) took open-label aspirin at a dose of less than 100 mg per day, as prescribed by their physician, in addition to the assigned trial regimen. Antiinflammatory drugs were permitted at the discretion of the surgeon.

Trial Outcomes

The primary effectiveness outcome was adjudicated symptomatic VTE, defined as deep-vein thrombosis involving the popliteal vein or more proximal leg veins (including the femoral, common femoral, and iliac veins and inferior vena cava) or pulmonary embolism, as confirmed by objective testing in the 90-day period after surgery.

Participants

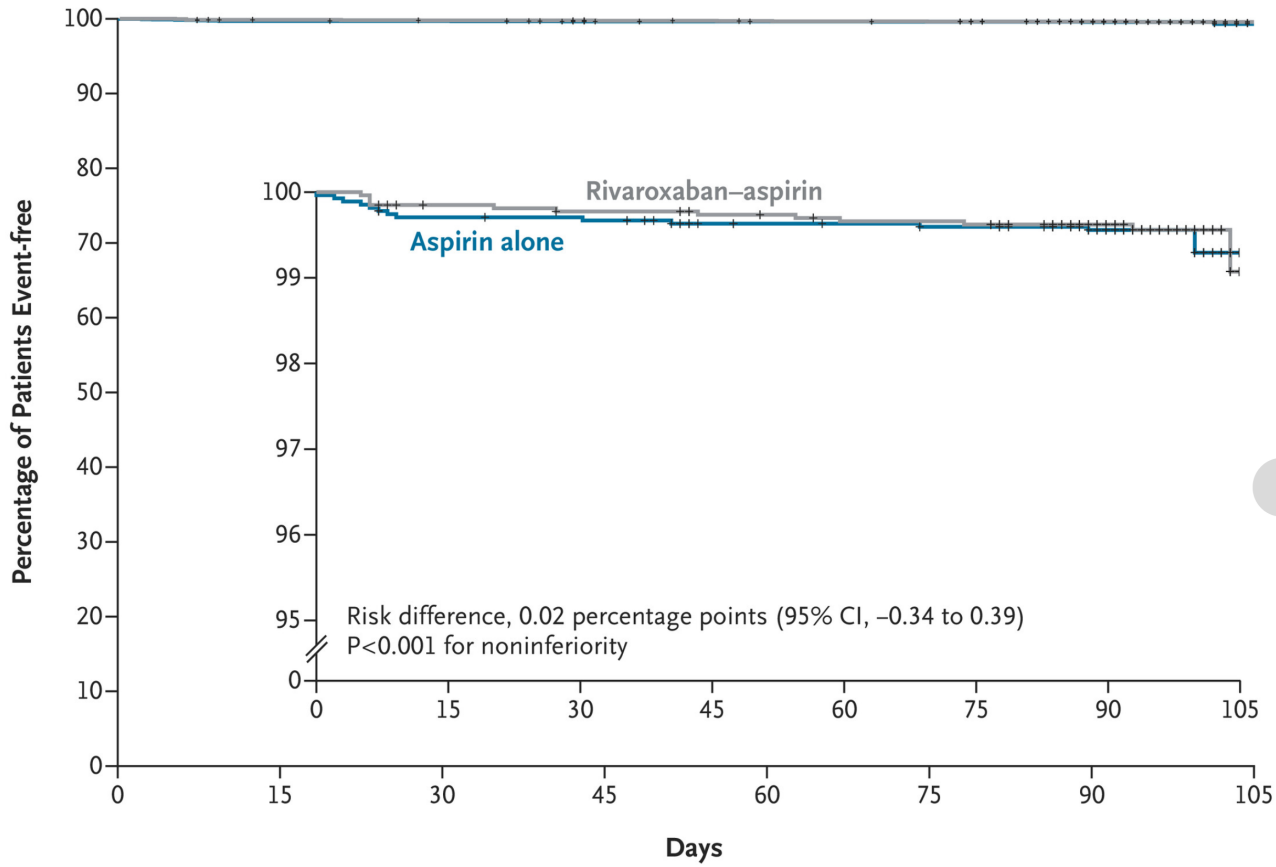
Characteristic	Rivaroxaban–Aspirin (N=2647)	Aspirin Alone (N=2718)	Total (N=5365)
Age — yr	66.3±9.8	66.7±10.0	66.5±9.9
Female sex — no./total no. (%)	1457/2636 (55.3)	1587/2714 (58.5)	3044/5350 (56.9)
Body-mass index†	30.7±6.26	30.8±6.78	30.8±6.53
Active cancer — no. (%)	9 (0.3)	16 (0.6)	25 (0.5)
Surgery group — no./total no. (%)			
Total hip arthroplasty	1247/2643 (47.2)	1269/2717 (46.7)	2516/5360 (46.9)
Total knee arthroplasty	1396/2643 (52.8)	1448/2717 (53.3)	2844/5360 (53.1)
Surgery class — no./total no. (%)			
Primary total hip or knee arthroplasty	2554/2643 (96.6)	2626/2717 (96.7)	5180/5360 (96.6)
Revision total hip or knee arthroplasty	89/2643 (3.4)	91/2717 (3.3)	180/5360 (3.4)
Length of hospital stay — days	1.1±3.7	1.1±3.7	1.1±3.7
Postoperative use of compression stockings — no. (%)	510 (19.3)	534 (19.6)	1044 (19.5)
Long-term aspirin use before surgery — no. (%)	211 (8.0)	220 (8.1)	431 (8.0)
Anesthetic type for surgery — no. (%)			
General only	213 (8.0)	225 (8.3)	438 (8.2)
Regional only	2379 (89.9)	2442 (89.8)	4821 (89.9)
Both general and regional	55 (2.1)	51 (1.9)	106 (2.0)
STOP-VTE score‡			
Mean	1.0±0.8	1.1±0.8	1.1±0.8
Risk category — no. (%)			
Standard: <3	2560 (96.7)	2621 (96.4)	5181 (96.6)
High: ≥3	87 (3.3)	97 (3.6)	184 (3.4)

Primary Effectiveness and Safety Outcomes

Outcome	Rivaroxaban–Aspirin (N=2647)	Aspirin Alone (N=2718)	Risk Difference (95% CI)
	no. of patients (%; 95% CI)		*percentage points*
Venous thromboembolism	12 (0.45; 0.20 to 0.71)	13 (0.48; 0.22 to 0.74)	0.02 (–0.34 to 0.39)*
Pulmonary embolism	7 (0.26; 0.07 to 0.46)	4 (0.15; 0 to 0.29)	–0.12 (–0.36 to 0.13)
Proximal deep-vein thrombosis	5 (0.19; 0.02 to 0.35)	6 (0.22; 0.04 to 0.40)	0.03 (–0.21 to 0.27)
Pulmonary embolism and proximal deep-vein thrombosis	0	3 (0.11; 0 to 0.24)	0.11 (–0.01 to 0.24)
Major bleeding or clinically relevant nonmajor bleeding	54 (2.04; 1.50 to 2.58)	45 (1.66; 1.18 to 2.14)	–0.38 (–1.11 to 0.34)
Major bleeding	8 (0.30; 0.09 to 0.51)	12 (0.44; 0.19 to 0.69)	0.14 (–0.19 to 0.46)
Clinically relevant nonmajor bleeding	46 (1.74; 1.24 to 2.24	33 (1.21; 0.80 to 1.63)	–0.52 (–1.17 to 0.12)
Death	3 (0.11; 0 to 0.24)	3 (0.11; 0 to 0.24)	0 (–0.18 to 0.18)

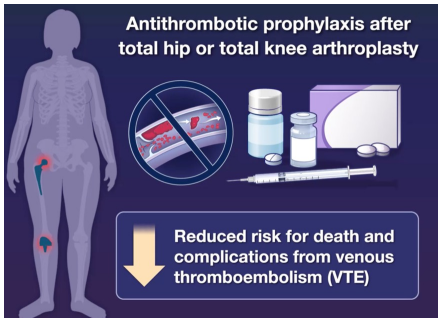
Primary Effectiveness and Safety Outcomes

Outcome	Total Hip Arthroplasty			Total Knee Arthroplasty		
	Rivaroxaban–Aspirin (N=1247)	Aspirin Alone (N=1269)	Risk Difference (95% CI)	Rivaroxaban–Aspirin (N=1396)	Aspirin Alone (N=1448)	Risk Difference (95% CI)
	no. of patients (%; 95% CI)		*percentage points*	*no. of patients (%; 95% CI)*		*percentage points*
Venous thromboembolism	6 (0.48; 0.10 to 0.87)	4 (0.32; 0.01 to 0.62)	–0.17 (–0.66 to 0.33)	6 (0.43; 0.09 to 0.77)	9 (0.62; 0.22 to 1.03)	0.19 (–0.34 to 0.72)
Pulmonary embolism	4 (0.32; 0.01 to 0.63)	1 (0.08; 0 to 0.23)	–0.24 (–0.59 to 0.11)	3 (0.21; 0 to 0.46)	3 (0.21; 0 to 0.44)	–0.01 (–0.35 to 0.33)
Proximal deep-vein thrombosis	2 (0.16; 0 to 0.38)	2 (0.16; 0 to 0.38)	0 (–0.31 to 0.31)	3 (0.21; 0 to 0.46)	4 (0.28; 0 to 0.55)	0.06 (–0.30 to 0.42)
Pulmonary embolism and proximal deep-vein thrombosis	0	1 (0.08; 0 to 0.23)	0.08 (–0.08 to 0.23)	0	2 (0.14; 0 to 0.33)	0.14 (–0.05 to 0.33)
Major bleeding or clinically relevant nonmajor bleeding	17 (1.36; 0.72 to 2.01)	16 (1.26; 0.65 to 1.87)	–0.10 (–0.99 to 0.79)	37 (2.65; 1.84 to 3.49)	29 (2.00; 1.28 to 2.72)	–0.65 (–1.76 to 0.46)
Major bleeding	3 (0.24; 0 to 0.51)	7 (0.55; 0.14 to 0.96)	0.31 (–0.18 to 0.80)	5 (0.36; 0.04 to 0.67)	5 (0.35; 0.04 to 0.65)	–0.01 (–0.45 to 0.42)
Clinically relevant nonmajor bleeding	14 (1.12; 0.54 to 1.71)	9 (0.71; 0.25 to 1.17)	–0.41 (–1.16 to 0.33)	32 (2.29; 1.51 to 3.08)	24 (1.66; 1.00 to 2.32)	–0.63 (–1.66 to 0.39)
Death	1 (0.08; 0 to 0.24)	2 (0.16; 0 to 0.38)	0.08 (–0.19 to 0.35)	2 (0.14; 0 to 0.34)	1 (0.07; 0 to 0.20)	–0.07 (–0.31 to 0.17)

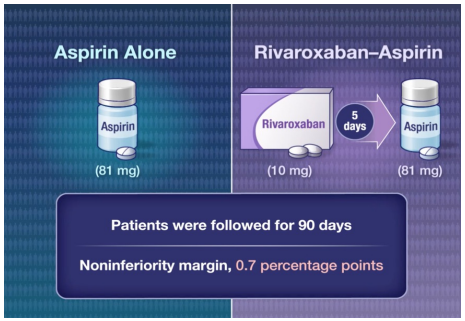


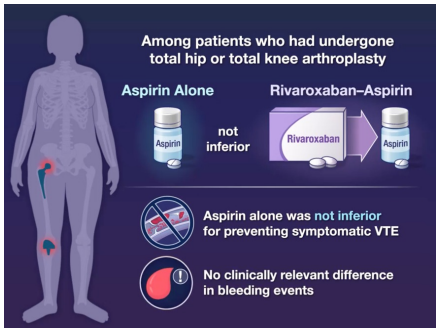
Time-to-Event Analysis of the Primary Outcome.

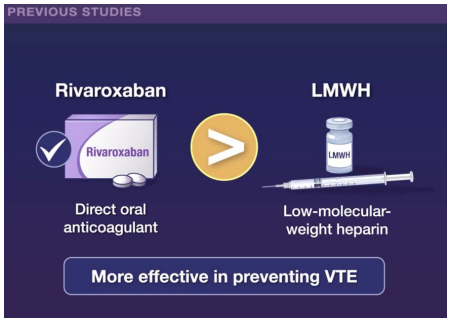
Shown is the percentage of patients without a primary-outcome event — venous thromboembolism, consisting of proximal deep-vein thrombosis or pulmonary embolism — which occurred in 13 of 2718 patients (0.48%) in the aspirin-alone group and in 12 of 2647 patients (0.45%) in the rivaroxaban–aspirin group. The inset graph shows the same data on an expanded y axis.

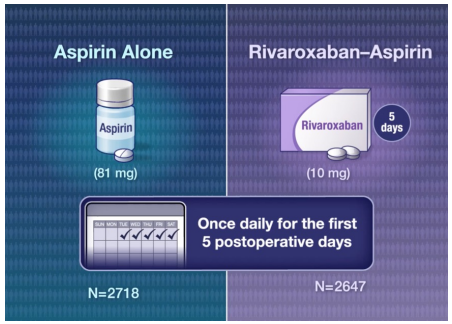


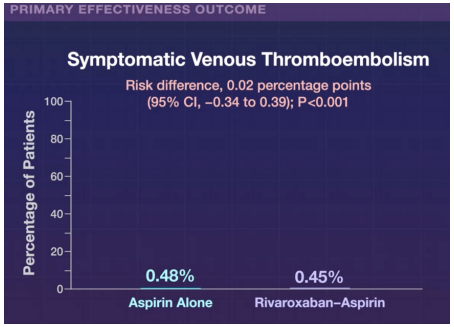


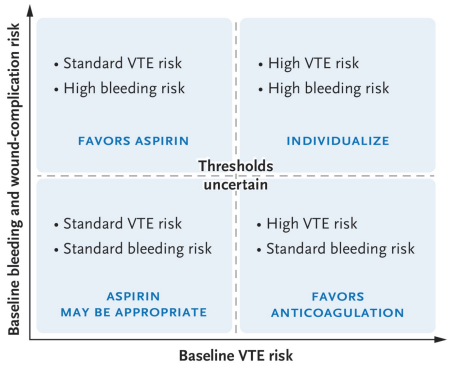


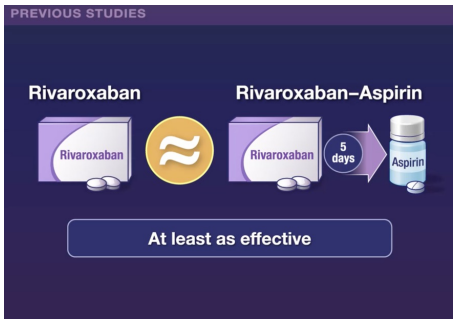


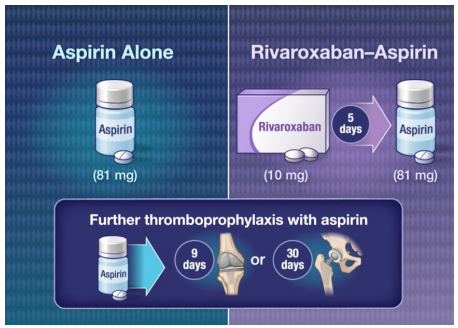


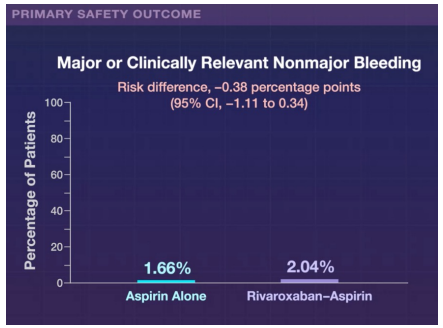




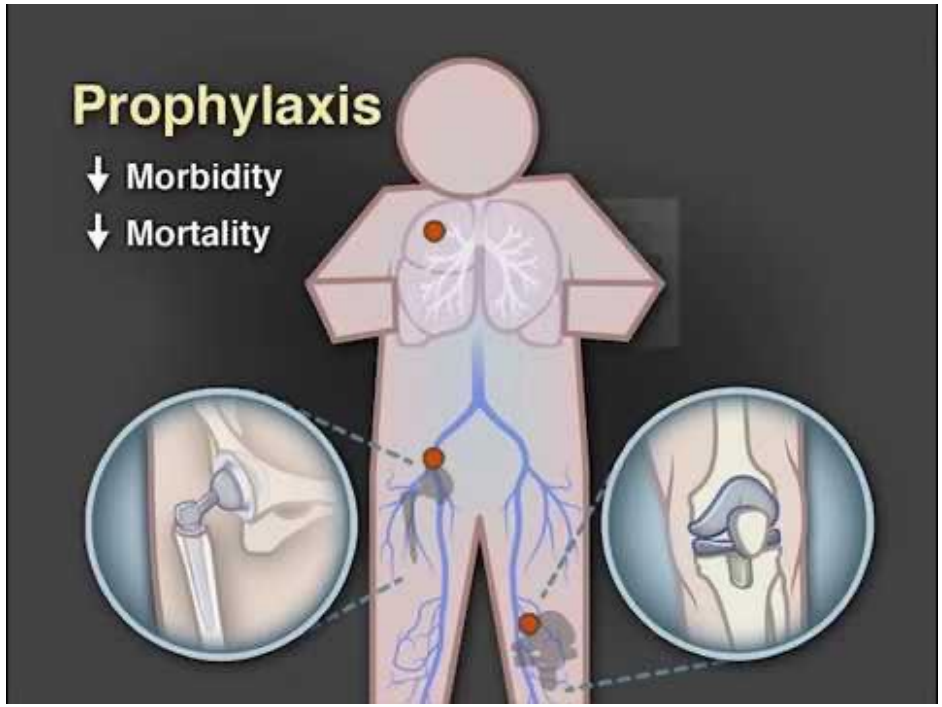


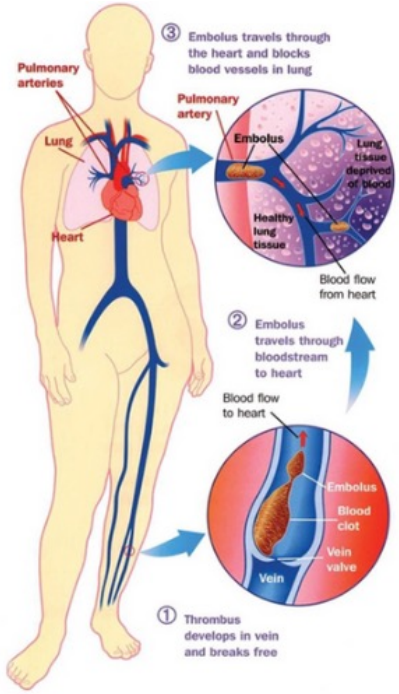






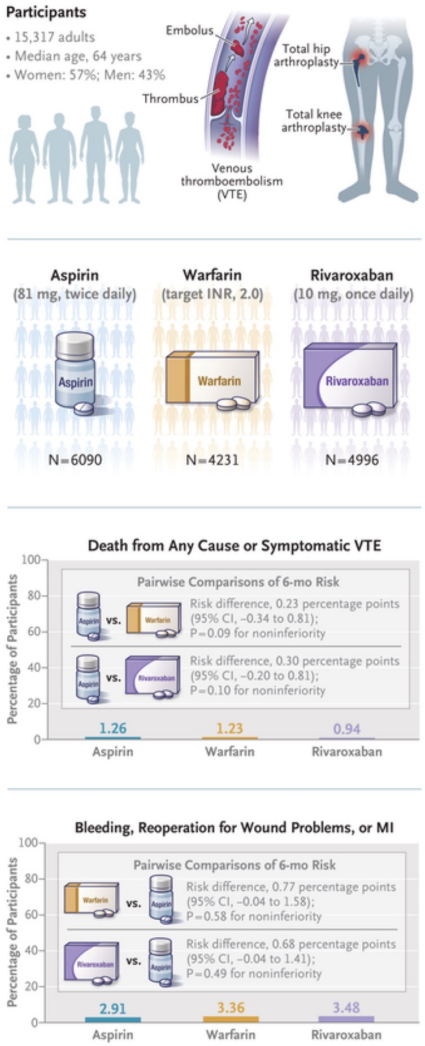
As the baseline risk of venous thromboembolism (VTE) increases, the absolute benefits of anticoagulation for the prevention of VTE may increase. As the risk of bleeding or wound complication increases, the net benefit of anticoagulation may decrease. When the bleeding risk with pharmacologic prophylaxis is deemed to be unacceptable, mechanical prophylaxis with intermittent pneumatic compression warrants consideration.


Prophylaxis
Morbidity
Mortality


③ Embolus travels through the heart and blocks blood vessels in lung
Pulmonary arteries
Pulmonary artery
Lung
Embolus
Lung tissue deprived of blood
Heart
Healthy lung tissue
Blood flow from heart
② Embolus travels through bloodstream to heart
Blood flow to heart
Embolus
Blood clot
Vein valve
Vein
① Thrombus develops in vein and breaks free

Prevention of Venous Thromboembolism after Total Hip or Knee Replacement

Studies comparing aspirin with anticoagulants for venous thromboembolism (VTE) prophylaxis after total hip or knee arthroplasty have had conflicting results. In a comparative-effectiveness noninferiority trial, we randomly assigned patients undergoing elective hip or knee arthroplasty to receive aspirin (81 mg twice daily), warfarin (to a target international normalized ratio of 2.0), or rivaroxaban (10 mg daily) for 30 days. The composite primary effectiveness outcome (death from any cause or symptomatic VTE) and primary safety outcome (bleeding, reoperation for wound problems, or myocardial infarction) were evaluated through 6 months in a blinded fashion. The noninferiority margin for the risk difference was 0.69 percentage points.



Venous thromboembolism (VTE), including pulmonary embolism and deep-vein thrombosis (DVT), is potentially life-threatening after total hip or knee arthroplasty. Evidence-based practice guidelines recommend pharmacologic prophylaxis, which can increase risks of serious bleeding and wound complications. Effective strategies for balancing the risks of thromboembolism and bleeding remain elusive owing to conflicting observational study results and the large participant numbers needed for definitive trials.

Aspirin is widely favored among orthopedic surgeons in the United States and Canada because of low cost, minimal bleeding risk, and the absence of required monitoring, in addition to concerns about anticoagulants with regard to increased risks of bleeding and associated wound complications, readmission, or reoperation. However, evidence to confirm the effectiveness of aspirin as compared with anticoagulants is scant. Accordingly, we designed a large, multicenter trial powered to concurrently evaluate whether aspirin would be noninferior to both rivaroxaban and warfarin for effectiveness of VTE prophylaxis and whether rivaroxaban and warfarin would be noninferior to aspirin with respect to minimizing bleeding risk.

Trial Population and Conduct

All patients 21 years of age or older who were undergoing elective total hip or knee arthroplasty for osteoarthritis at the clinical centers were screened. Patients receiving long-term anticoagulation therapy were excluded. Preoperatively, participants were randomly assigned to one of the treatments that they were eligible to receive; patients were included only in analyses for which they were eligible to receive either of the treatments being compared. Randomization was conducted with the use of permuted blocks with stratification according to clinical center and procedure (hip or knee arthroplasty) and with the use of an independent online platform that concealed treatment sequences until assigned. Assignment was accessed by trial coordinators only after assessing eligibility and obtaining informed consent. Participants were assigned to receive chemoprophylaxis with aspirin, warfarin, or rivaroxaban for 30 days. For aspirin, treatment started with an initial dose of 162 mg in the holding area immediately before the operation, followed by 81 mg orally twice daily starting the day after surgery; for warfarin, treatment was initiated in the holding area before the operation and given each evening thereafter to achieve a target international normalized ratio of 2.0 (targeted range, 1.7 to 2.2); and for rivaroxaban, treatment was a fixed dose of 10 mg orally once daily, with initiation delayed until 24 hours after the completion of surgery to mitigate bleeding risk.

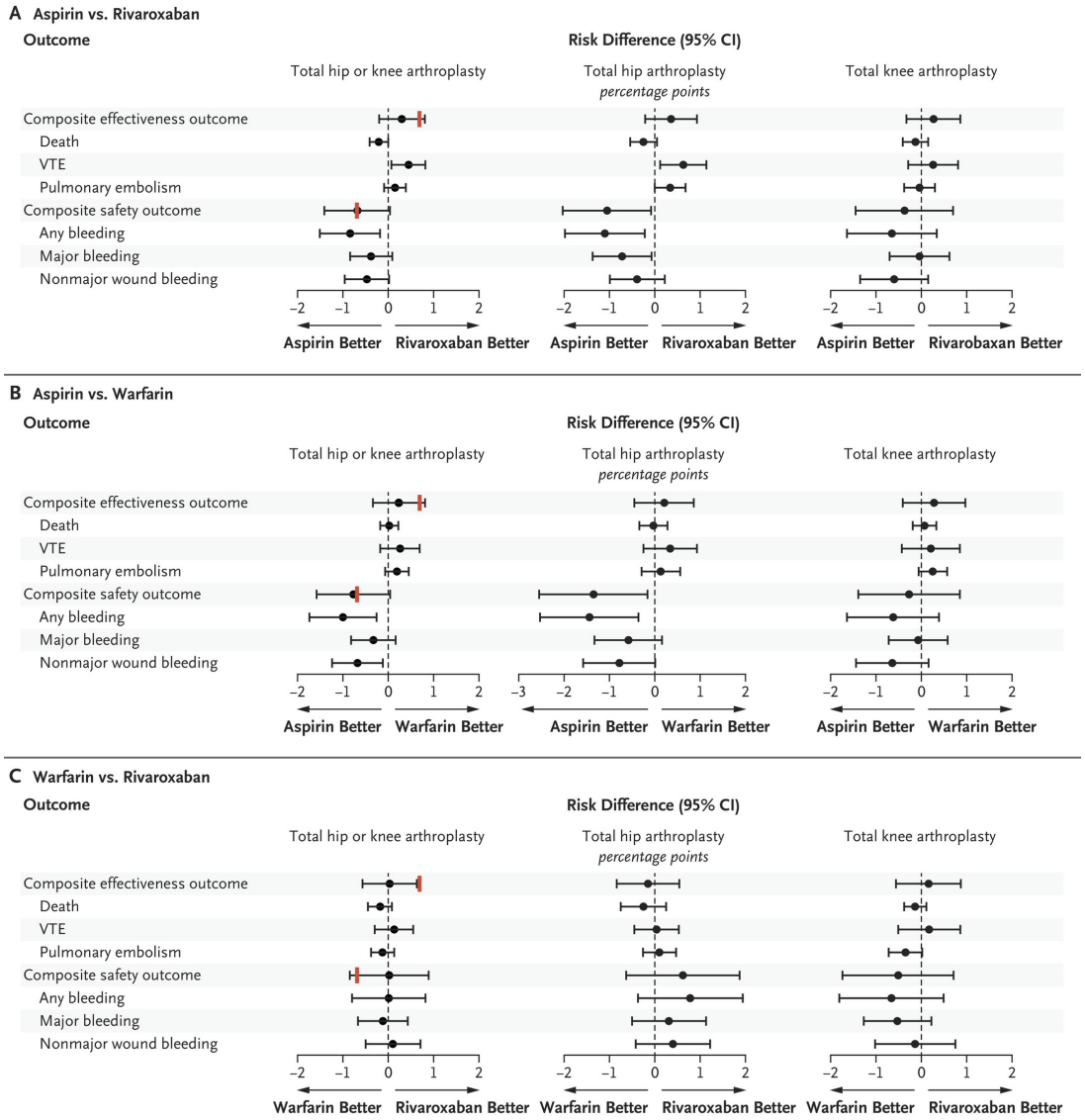
Outcomes

The primary effectiveness outcome was a composite of death from any cause or symptomatic VTE as confirmed by objective testing and resulting in readmission or therapeutic anticoagulation.

Characteristic	Aspirin (N=6090)	Warfarin (N=4231)	Rivaroxaban (N=4996)
Type of surgery			
Total hip replacement — no. (%)	2853 (46.8)	1980 (46.8)	2381 (47.7)
Revision — no./total no. (%)	1005/2853 (35.2)	735/1980 (37.1)	865/2381 (36.3)
Total knee replacement — no. (%)	3237 (53.2)	2251 (53.2)	2615 (52.3)
Revision — no./total no. (%)	1199/3237 (37.0)	928/2251 (41.2)	1049/2615 (40.1)
Median age (IQR) — yr	64 (57–70)	64 (57–70)	64 (57–71)
Sex — no. (%)			
Female	3330 (54.7)	2507 (59.3)	2950 (59.0)
Male	2760 (45.3)	1724 (40.7)	2046 (41.0)
Median body-mass index (IQR)†	30.7 (26.8–35.3)	31.1 (26.9–35.7)	31.1 (27.0–35.9)
Race or ethnic group — no. (%)‡			
White	4825 (79.2)	3389 (80.1)	3935 (78.8)
Black	905 (14.9)	644 (15.2)	771 (15.4)
Asian	66 (1.1)	30 (0.7)	54 (1.1)
Other	294 (4.8)	168 (4.0)	236 (4.7)
Smoking status — no. (%)			
Never smoked	3389 (55.6)	2345 (55.4)	2804 (56.1)
Current smoking	342 (5.6)	226 (5.3)	270 (5.4)
Former smoking	2359 (38.7)	1660 (39.2)	1922 (38.5)
Alcohol use — no./total no. (%)			
Never	1724/6066 (28.4)	1302/4220 (30.9)	1470/4985 (29.5)
1–4 times per month	2521/6066 (41.6)	1701/4220 (40.3)	2087/4985 (41.9)
>1 time per week	1821/6066 (30.0)	1217/4220 (28.8)	1428/4985 (28.6)
Educational level — no. (%)			
High school diploma or less	1553 (25.5)	1150 (27.2)	1265 (25.3)
Trade or technology school degree or some college	1809 (29.7)	1307 (30.9)	1477 (29.6)
College or graduate degree	2728 (44.8)	1774 (41.9)	2254 (45.1)
Employment status — no. (%)			
Working	2600 (42.7)	1715 (40.5)	2052 (41.1)
Retired, student, or homemaker	2057 (33.8)	1574 (37.2)	1685 (33.7)
Unemployed, disabled, or unknown	1433 (23.5)	942 (22.3)	1259 (25.2)
No. of coexisting conditions according to Charlson Comorbidity Index — no. (%)			
0	3912 (64.2)	2513 (59.4)	3057 (61.2)
1	1538 (25.3)	1181 (27.9)	1357 (27.2)
2	447 (7.3)	374 (8.8)	414 (8.3)
≥3	193 (3.2)	163 (3.9)	168 (3.4)
Recent VTE within past 6 mo — no. (%)§	89 (1.5)	208 (4.9)	193 (3.9)
Pretrial cardioprotective aspirin use — no. (%)			
No	4657 (76.5)	3169 (74.9)	3957 (79.2)
81 mg	1278 (21.0)	942 (22.3)	907 (18.2)
325 mg or other	155 (2.5)	120 (2.8)	132 (2.6)
Tranexamic acid — no. (%)	5860 (96.2)	4042 (95.5)	4790 (95.9)

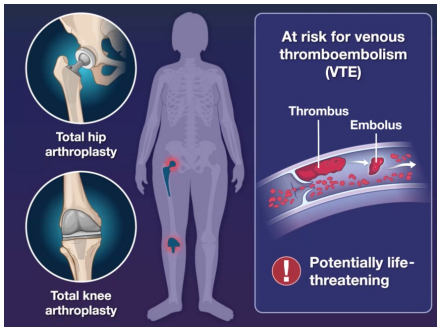
Pairwise Comparisons among Aspirin, Warfarin, and Rivaroxaban

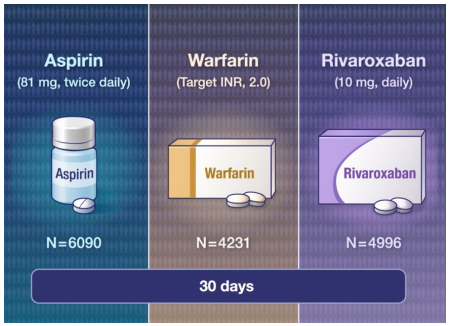
Event	Comparator 1		Comparator 2		Risk Difference (95% CI)
	No. of Events/ No. of Participants	6-Mo Risk (95% CI)†	No. of Events/ No. of Participants	6-Mo Risk (95% CI)†	
		%		%	*percentage points*
	Aspirin		**Rivaroxaban**		
Primary-outcome event	68/5609	1.24 (0.95 to 1.54)	39/4434	0.94 (0.65 to 1.23)	0.30 (–0.20 to 0.81)‡
Death§	8/5609	0.15 (0.05 to 0.25)	14/4434	0.35 (0.17 to 0.53)	–0.21 (–0.41 to 0.00)
VTE	62/5609	1.13 (0.85 to 1.41)	29/4434	0.68 (0.43 to 0.93)	0.45 (0.07 to 0.82)
Pulmonary embolism	24/5609	0.44 (0.26 to 0.61)	12/4434	0.29 (0.13 to 0.45)	0.15 (–0.09 to 0.39)
DVT	38/5609	0.69 (0.47 to 0.91)	17/4434	0.40 (0.21 to 0.59)	0.30 (0.01 to 0.59)
	Aspirin		**Warfarin**		
Primary-outcome event	54/4441	1.24 (0.91 to 1.57)	38/3655	1.01 (0.67 to 1.35)	0.23 (–0.34 to 0.81)¶
Death§	9/4441	0.21 (0.07 to 0.34)	7/3655	0.19 (0.04 to 0.34)	0.02 (–0.18 to 0.22)
VTE	47/4441	1.08 (0.77 to 1.39)	31/3655	0.82 (0.51 to 1.13)	0.26 (–0.18 to 0.69)
Pulmonary embolism	19/4441	0.44 (0.24 to 0.64)	9/3655	0.25 (0.08 to 0.42)	0.19 (–0.07 to 0.45)
DVT	28/4441	0.64 (0.40 to 0.88)	22/3655	0.57 (0.31 to 0.83)	0.07 (–0.28 to 0.42)
	Warfarin		**Rivaroxaban**		
Primary-outcome event	45/3873	1.13 (0.78 to 1.48)	38/3736	1.10 (0.75 to 1.44)	0.03 (–0.57 to 0.63)‖
Death§	9/3873	0.24 (0.08 to 0.40)	14/3736	0.42 (0.21 to 0.63)	–0.18 (–0.45 to 0.08)
VTE	36/3873	0.89 (0.58 to 1.20)	27/3736	0.77 (0.48 to 1.05)	0.13 (–0.30 to 0.55)
Pulmonary embolism	9/3873	0.24 (0.08 to 0.40)	13/3736	0.36 (0.16 to 0.56)	–0.13 (–0.38 to 0.13)
DVT	27/3873	0.66 (0.39 to 0.93)	14/3736	0.40 (0.19 to 0.61)	0.25 (–0.09 to 0.59)

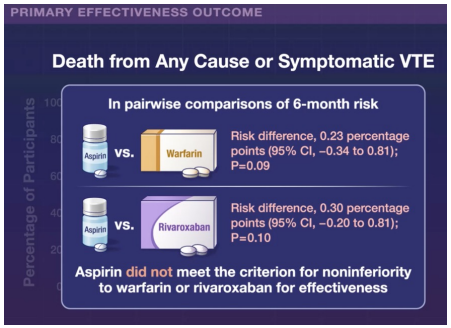


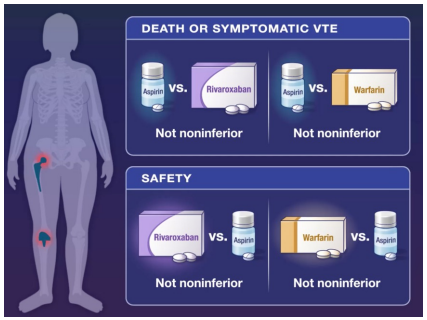
Discussion

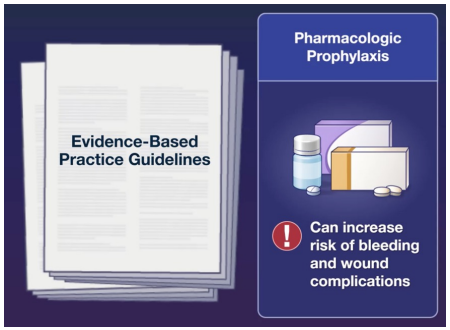
In this large, multicenter, comparative-effectiveness trial involving patients undergoing elective total hip or knee arthroplasty, we found that aspirin did not meet the prespecified criterion for noninferiority to either rivaroxaban or warfarin for the primary composite effectiveness outcome (death from any cause or VTE). Warfarin was noninferior to rivaroxaban for effectiveness. For the composite safety outcome, neither rivaroxaban nor warfarin met the criterion for noninferiority to aspirin; rivaroxaban also did not meet the criterion for noninferiority to warfarin. Composite safety outcomes were two to three times more common than composite effectiveness outcomes, each with small risk differences.

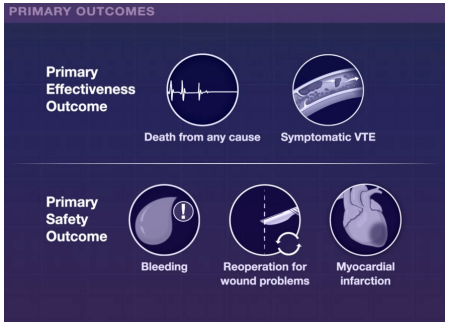


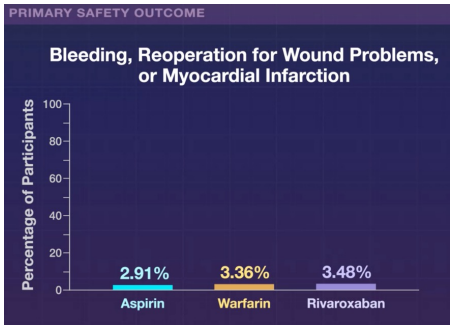


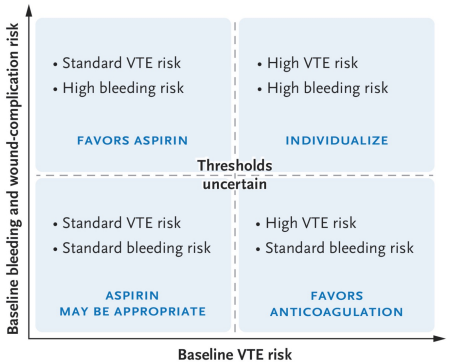


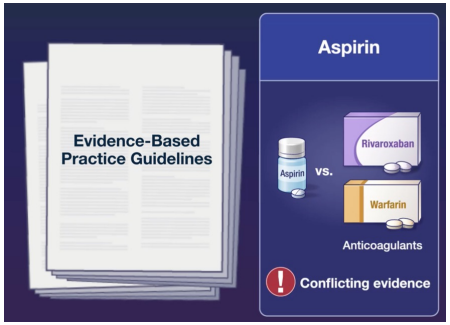


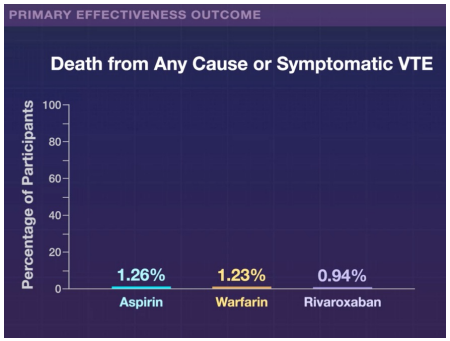


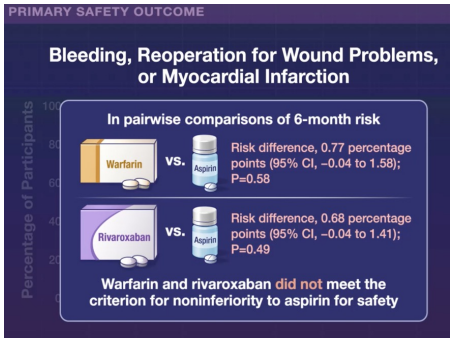








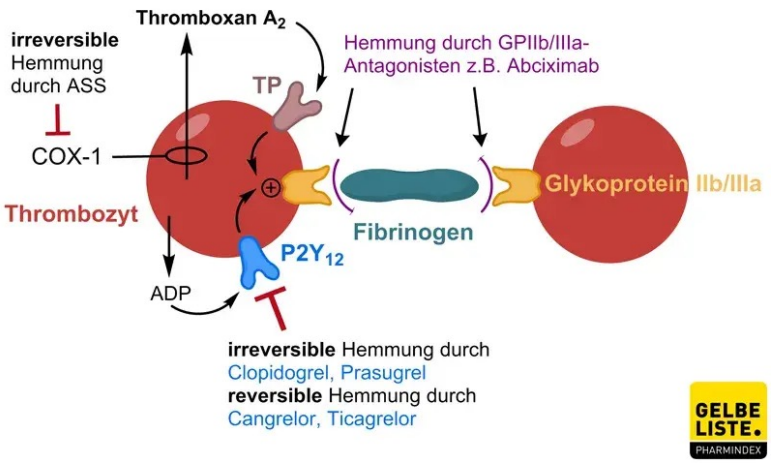




As the baseline risk of venous thromboembolism (VTE) increases, the absolute benefits of anticoagulation for the prevention of VTE may increase. As the risk of bleeding or wound complication increases, the net benefit of anticoagulation may decrease. When the bleeding risk with pharmacologic prophylaxis is deemed to be unacceptable, mechanical prophylaxis with intermittent pneumatic compression warrants consideration.

P2Y12 ist ein G-Protein-gekoppelter Purinrezeptor (ADP-Rezeptor) auf der Oberfläche von Thrombozyten (Blutplättchen), der eine Schlüsselrolle bei der Blutgerinnung und Thrombozytenaggregation spielt.

Die wichtigsten medizinischen Informationen und Wirkstoffe im Überblick:



Funktion

- **Rezeptor:** Bindet ADP (Adenosindiphosphat), welches von aktiven Plättchen ausgeschüttet wird.
- **Wirkung:** Die Aktivierung führt über intrazelluläre Signalwege (Hemmung der Adenylatcyclase) zur Aktivierung des Glykoprotein-IIb/IIIa-Rezeptors und damit zur Verklumpung (Aggregation) der Blutplättchen.

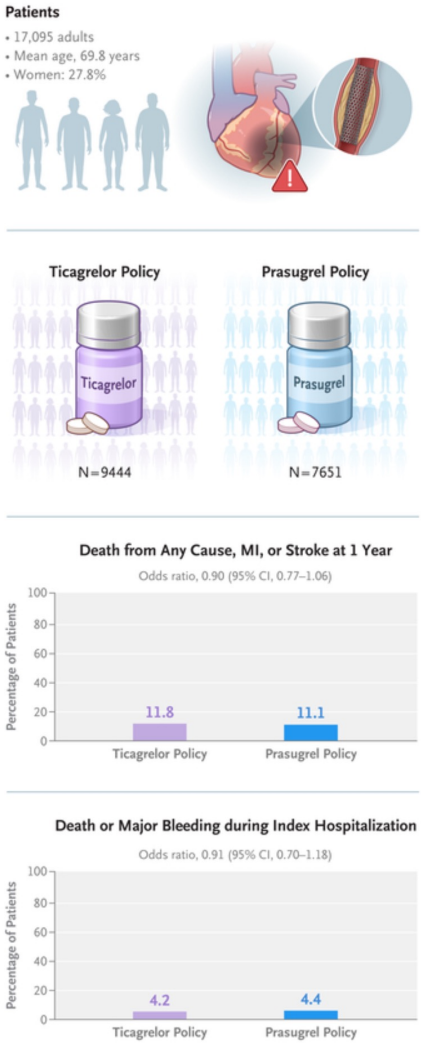
P2Y12-Hemmer (Thrombozytenaggregationshemmer)

Diese Medikamente blockieren den Rezeptor und verhindern so die Bildung von Blutgerinnseln. Sie werden oft mit Acetylsalicylsäure (ASS) als **duale Plättchenhemmung (DAPT)** kombiniert, z. B. nach einem Herzinfarkt oder einer Koronarintervention (PCI/Stent).

- **Prasugrel (Effient):**
  - **Efficacy:** Studies show prasugrel provides a stronger reduction in major adverse cardiovascular events (MACE), heart attacks, and stent thrombosis compared to both clopidogrel and ticagrelor. Current cardiology guidelines often favor prasugrel as a top choice for appropriate patients having a stent placed for an acute heart attack.
  - **Trade-off:** It carries a higher risk of serious bleeding and is generally not recommended if you have a history of stroke or transient ischemic attack (TIA), or if you are older or underweight.
- **Ticagrelor (Brilinta):**
  - **Efficacy:** It acts quickly and reduces stent clots and cardiovascular risks much better than clopidogrel. Unlike clopidogrel, its effectiveness is not weakened by your genetic makeup (such as CYP2C19 gene variations).
  - **Trade-off:** It is taken twice a day (unlike once-daily clopidogrel or prasugrel) and has a higher rate of major bleeding (including intracranial bleeding) and shortness of breath (dyspnea) as a side effect.
- **Clopidogrel (Plavix):**
  - **Efficacy:** It is a weaker and slower-acting platelet blocker, meaning it leaves a slightly higher risk of clotting in high-risk heart attack settings.
  - **Trade-off:** It has a significantly lower risk of bleeding. It is often preferred for older adults, people with a high bleeding risk, or those managing stable chronic conditions rather than an active, severe heart attack.

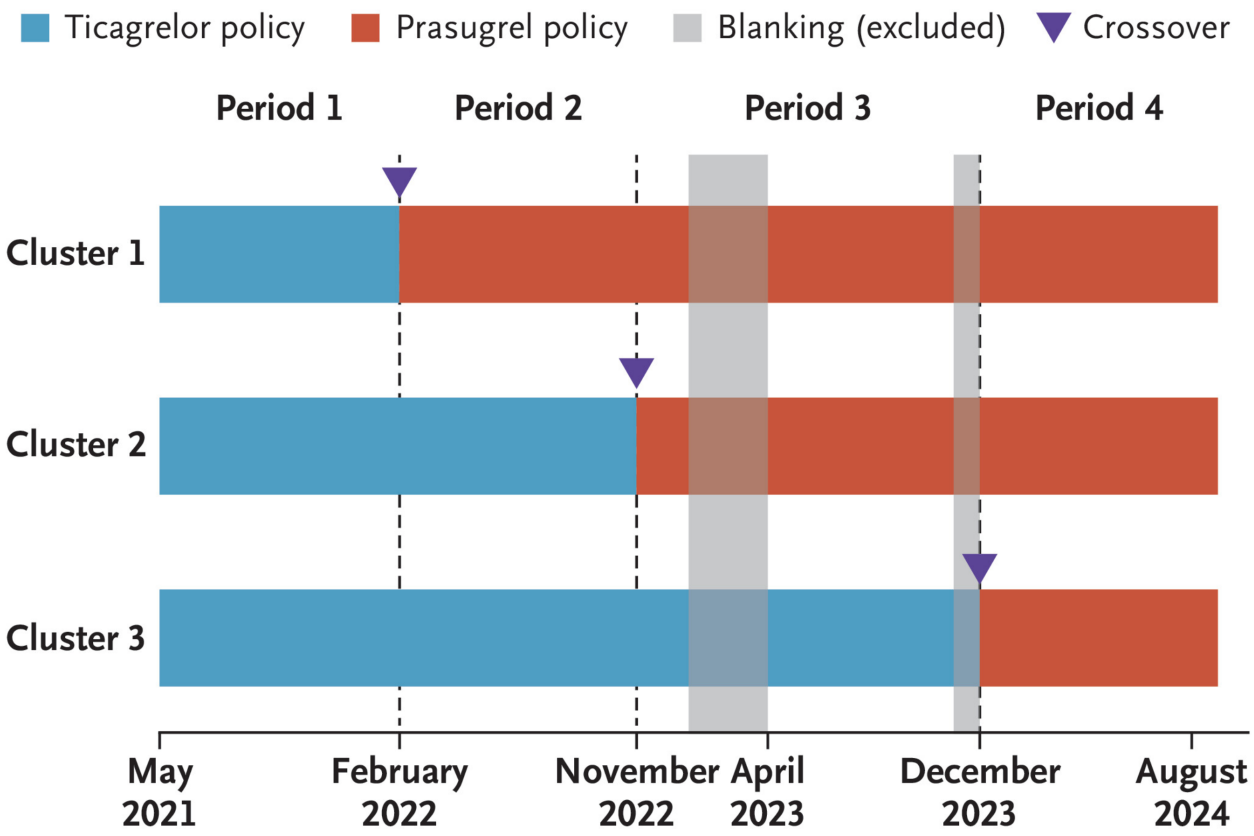
Prasugrel versus Ticagrelor in Acute Coronary Syndromes

Whether prasugrel or ticagrelor should be the preferred P2Y12 inhibitor for patients with an acute coronary syndrome is uncertain.
We conducted a registry-based, open-label, stepped-wedge, cluster-randomized trial in Sweden involving adults who had undergone percutaneous coronary intervention for an acute coronary syndrome. Seven regions, grouped into three clusters, switched from ticagrelor to prasugrel as the default P2Y12 inhibitor in a randomized sequence across four 9-month periods between 2021 and 2024. The primary end point was a composite of death from any cause, fatal or nonfatal myocardial infarction, or fatal or nonfatal stroke through 1 year, as ascertained from national registries. In the intention-to-treat analysis, a mixed model adjusted for cluster and calendar time was used to obtain a policy-level estimate.



Dual antiplatelet therapy with aspirin and a potent P2Y12 inhibitor is the standard of care for patients with an acute coronary syndrome. Both prasugrel and ticagrelor are associated with a lower incidence of ischemic events than clopidogrel and carry a class I recommendation in society guidelines. However, the relative merits of the two agents have been debated. In the investigator-initiated ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial, a prasugrel-based strategy was superior to a ticagrelor-based strategy with respect to a composite of death, myocardial infarction, or stroke at 1 year, without an increased risk of major bleeding. This result led European guidelines to express a preference for prasugrel in non–ST-segment elevation acute coronary syndromes.

Within the nationwide SWEDEHEART registry, which has previously served as the platform for large, randomized registry trials, we conducted a stepped-wedge, cluster-randomized trial to determine whether a regionwide policy with prasugrel as the default P2Y12 inhibitor, as compared with ticagrelor, improves clinical outcomes among unselected patients who had undergone percutaneous coronary intervention (PCI) for an acute coronary syndrome.



Cluster-Randomized, Stepped-Wedge Design.

Seven regions in three clusters sequentially transitioned from a ticagrelor to a prasugrel default policy across four periods (May 2021 through August 2024). Two prospectively defined blanking periods were excluded from analysis: January through March 2023 (a national prasugrel supply shortage) and November 2023 (a Swedish Medical Products Agency intervention that postponed transition in the third cluster).

Clusters, Randomization, and Treatment Strategies

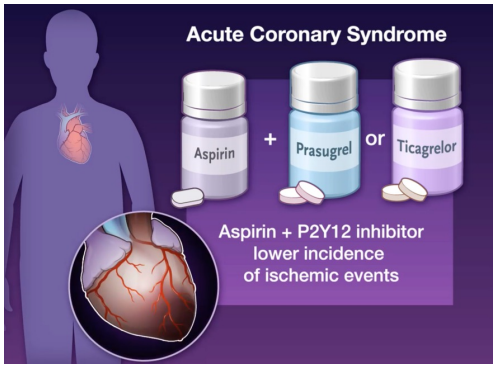
Seven regions comprising approximately half the Swedish population were grouped into three clusters of broadly similar expected size: cluster 1 (Skåne), cluster 2 (Örebro, Västerbotten, Halland, Jämtland, and Gävleborg), and cluster 3 (Västra Götaland). The order in which clusters transitioned from ticagrelor to prasugrel as the default P2Y12 inhibitor was randomly assigned with the use of a computer-generated sequence. At the start of the trial, ticagrelor was the default P2Y12 inhibitor in all the clusters; thereafter, one cluster crossed over to prasugrel as the default at the start of each successive 9-month period, until all clusters had transitioned.

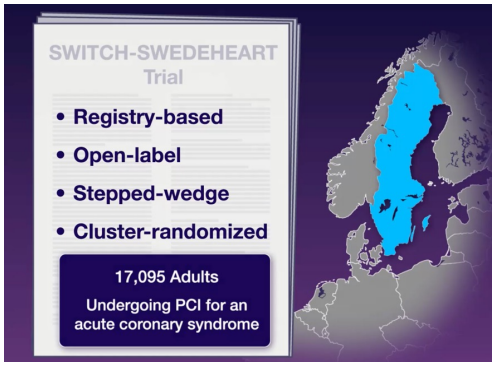
End Points

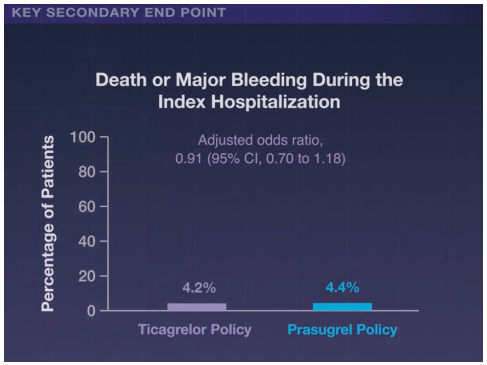
The primary end point was a major adverse cardiac event (MACE), a composite of death from any cause, fatal or nonfatal myocardial infarction, or fatal or nonfatal stroke through 1 year. The key secondary clinical end point was a composite of death or major bleeding during the index hospitalization. A prespecified key secondary health economics analysis will compare the 1-year cost-effectiveness of a default prasugrel policy with that of a default ticagrelor policy (results not reported here).

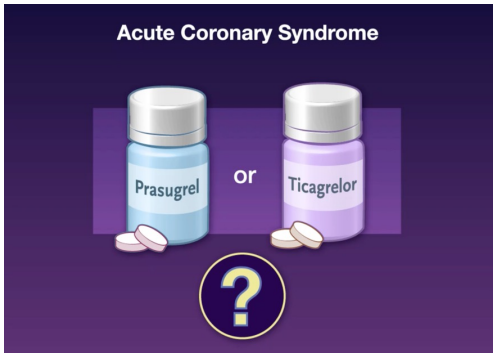
Characteristic	Total (N=17,095)	Ticagrelor-Policy Group (N=9444)	Prasugrel-Policy Group (N=7651)
Age — yr	69.8±11.5	69.9±11.5	69.6±11.6
Age ≥75 yr — no. (%)	6285 (36.8)	3495 (37.0)	2790 (36.5)
Female sex	4747 (27.8)	2655 (28.1)	2092 (27.3)
Diagnosis at admission — no. (%)			
STEMI	6742 (39.4)	3621 (38.3)	3121 (40.8)
NSTEMI	7474 (43.7)	4172 (44.2)	3302 (43.2)
Unstable angina	2879 (16.8)	1651 (17.5)	1228 (16.1)
Cardiovascular risk factors — no./total no. (%)			
Diabetes, insulin-treated	1318/16,957 (7.8)	670/9367 (7.2)	648/7590 (8.5)
Diabetes, non–insulin-treated	2340/16,957 (13.8)	1253/9367 (13.4)	1087/7590 (14.3)
Current smoking	2747/15,011 (18.3)	1429/8110 (17.6)	1318/6901 (19.1)
Arterial hypertension	10,286/16,870 (61.0)	5707/9299 (61.4)	4579/7571 (60.5)
Hypercholesterolemia	6960/16,805 (41.4)	3837/9267 (41.4)	3123/7538 (41.4)
Medical history — no./total no. (%)			
Previous myocardial infarction	3465/16,843 (20.6)	1964/9292 (21.1)	1501/7551 (19.9)
Previous PCI	3409/17,095 (19.9)	1912/9444 (20.2)	1497/7651 (19.6)
Previous CABG	983/17,088 (5.8)	525/9444 (5.6)	458/7644 (6.0)
Cardiogenic shock	272/15,402 (1.8)	158/8689 (1.8)	114/6713 (1.7)
Systolic blood pressure			
Mean — mm Hg	147.9±29.1	147.8±28.8	147.9±29.4
Patients with data — no.	14,591	8122	6469
Diastolic blood pressure			
Mean — mm Hg	86.5±17.2	86.6±16.9	86.4±17.5
Patients with data — no.	13,955	7682	6273
Heart rate			
Mean — beats/min	79.3±20.6	79.3±20.7	79.3±20.6
Patients with data — no.	14,589	8120	6469
Oral anticoagulation indication — no./total no. (%)	1696/16,710 (10.1)	944/9223 (10.2)	752/7487 (10.0)
Creatinine — μmol/liter			
Mean	90.4±53.1	89.2±53.5	91.8±52.6
Patients with data — no.	14,469	8053	6416
Medications at admission — no./total no. (%)			
Aspirin	3232/14,204 (22.8)	1841/7781 (23.7)	1391/6423 (21.7)
P2Y12 inhibitor	668/14,209 (4.7)	391/7784 (5.0)	277/6425 (4.3)
Beta-blocker	4210/14,185 (29.7)	2375/7769 (30.6)	1835/6416 (28.6)
ACE inhibitor or ARB	5809/14,123 (41.1)	3165/7737 (40.9)	2644/6386 (41.4)
Statin	4329/14,198 (30.5)	2337/7776 (30.1)	1992/6422 (31.0)

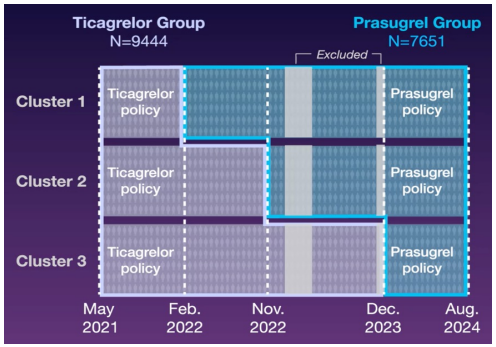
End Point	Ticagrelor-Policy Group (N=9444)	Prasugrel-Policy Group (N=7651)	Odds Ratio (95% CI)†
	no. of patients with event (%)		
Primary end point: death from any cause, fatal or nonfatal myocardial infarction, or fatal or nonfatal stroke at 1 yr	1113 (11.8)	848 (11.1)	0.90 (0.77–1.06)
Key secondary end point: death or major bleeding during the index hospitalization	400 (4.2)	335 (4.4)	0.91 (0.70–1.18)
Other secondary end points			
Death from any cause	673 (7.1)	515 (6.7)	1.01 (0.82–1.26)
Myocardial infarction	414 (4.4)	302 (3.9)	0.89 (0.71–1.12)
Stroke	83 (0.9)	67 (0.9)	1.38 (0.83–2.28)
Major bleeding at 1 yr			
With the broader ICD-10 definition	413 (4.4)	321 (4.2)	0.80 (0.64–0.99)
With the narrow ICD-10 definition	225 (2.4)	153 (2.0)	0.69 (0.50–0.93)
Stent thrombosis	30 (0.3)	25 (0.3)	1.13 (0.53–2.40)

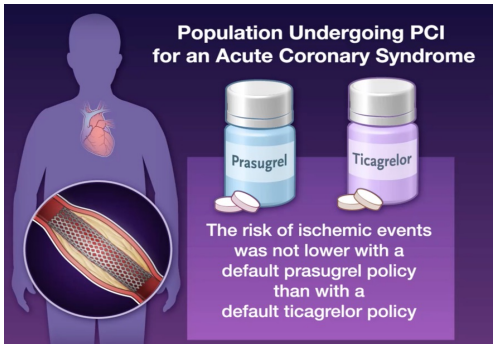

Acute Coronary Syndrome
Aspirin
+
Prasugrel
or
Ticagrelor
Aspirin + P2Y12 inhibitor
lower incidence
of ischemic events

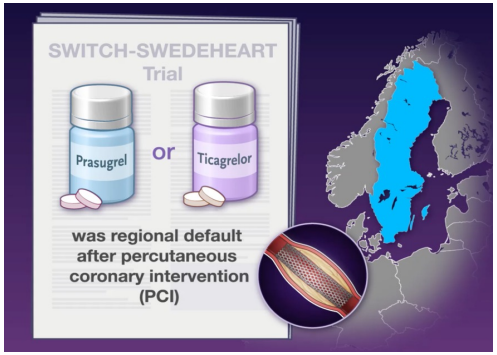

SWITCH-SWEDEHEART
Trial
• Registry-based
• Open-label
• Stepped-wedge
• Cluster-randomized
17,095 Adults
Undergoing PCI for an
acute coronary syndrome

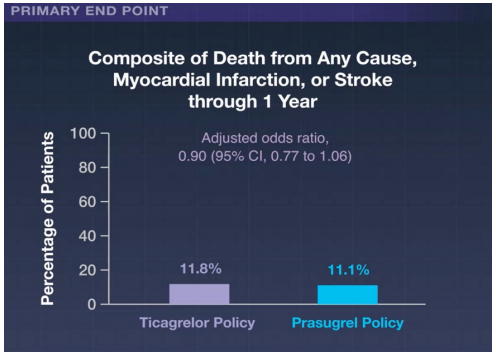

KEY SECONDARY END POINT
Death or Major Bleeding During the
Index Hospitalization
Adjusted odds ratio,
0.91 (95% CI, 0.70 to 1.18)
Percentage of Patients
100
80
60
40
20
0
4.2%
4.4%
Ticagrelor Policy
Prasugrel Policy

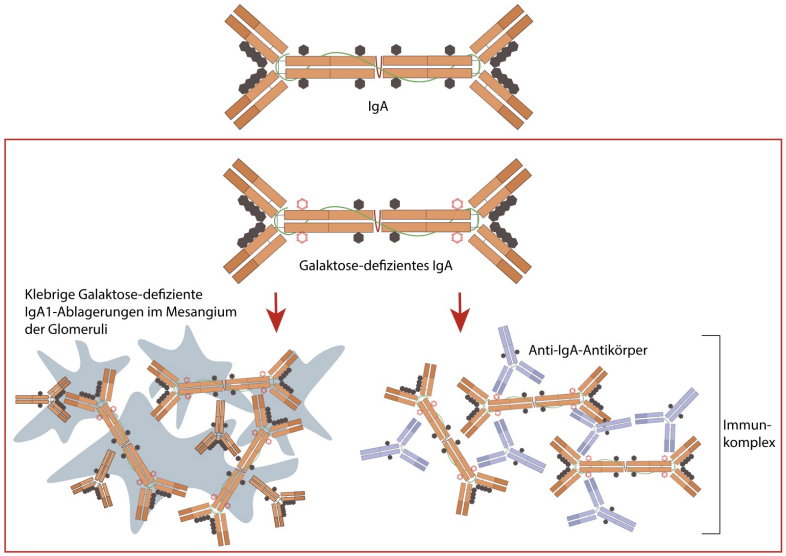

Acute Coronary Syndrome
Prasugrel
or
Ticagrelor
?

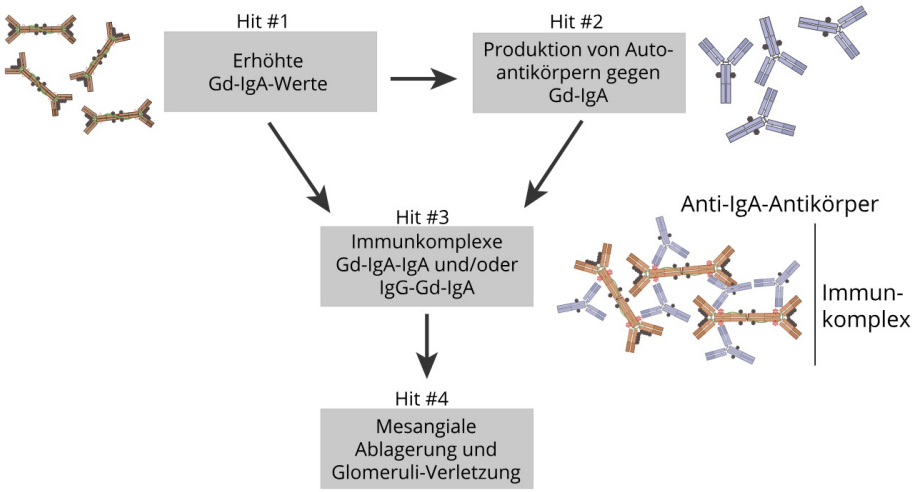

Ticagrelor Group
N=9444
Prasugrel Group
N=7651
Excluded
Cluster 1
Cluster 2
Cluster 3
Ticagrelor policy
Prasugrel policy
May
2021
Feb.
2022
Nov.
2022
Dec.
2023
Aug.
2024

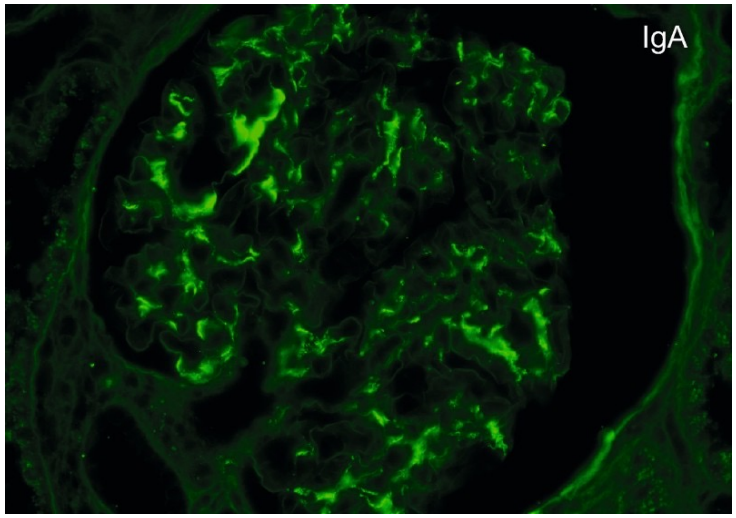

Population Undergoing PCI
for an Acute Coronary Syndrome
Prasugrel
Ticagrelor
The risk of ischemic events
was not lower with a
default prasugrel policy
than with a
default ticagrelor policy

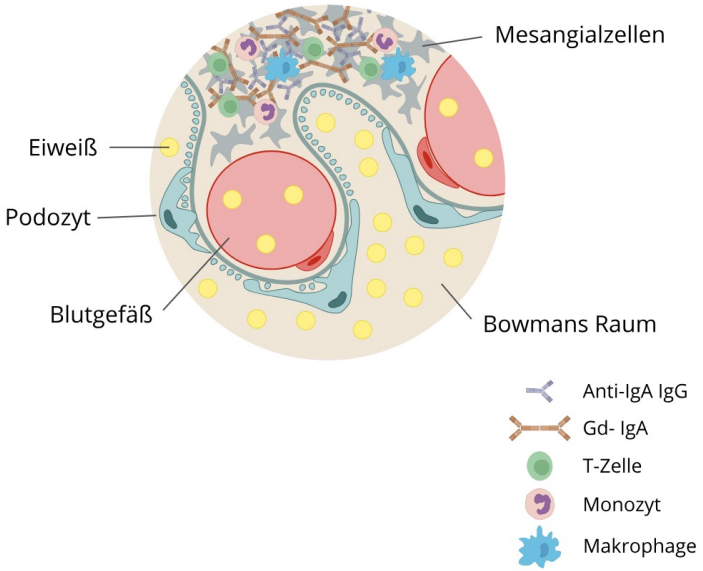

SWITCH-SWEDEHEART
Trial
Prasugrel
or
Ticagrelor
was regional default
after percutaneous
coronary intervention
(PCI)


PRIMARY END POINT
Composite of Death from Any Cause,
Myocardial Infarction, or Stroke
through 1 Year
Adjusted odds ratio,
0.90 (95% CI, 0.77 to 1.06)
Percentage of Patients
100
80
60
40
20
0
11.8%
11.1%
Ticagrelor Policy
Prasugrel Policy


IgA
Galaktose-defizientes IgA
Klebrige Galaktose-defiziente IgA1-Ablagerungen im Mesangium der Glomeruli
Anti-IgA-Antikörper
Immun-komplex


Hit #1
Erhöhte Gd-IgA-Werte
Hit #2
Produktion von Auto-antikörpern gegen Gd-IgA
Hit #3
Immunkomplexe Gd-IgA-IgA und/oder IgG-Gd-IgA
Anti-IgA-Antikörper
Immun-komplex
Hit #4
Mesangiale Ablagerung und Glomeruli-Verletzung


IgA


Mesangialzellen
Eiweiß
Podozyt
Blutgefäß
Bowmans Raum
Anti-IgA IgG
Gd- IgA
T-Zelle
Monozyt
Makrophage

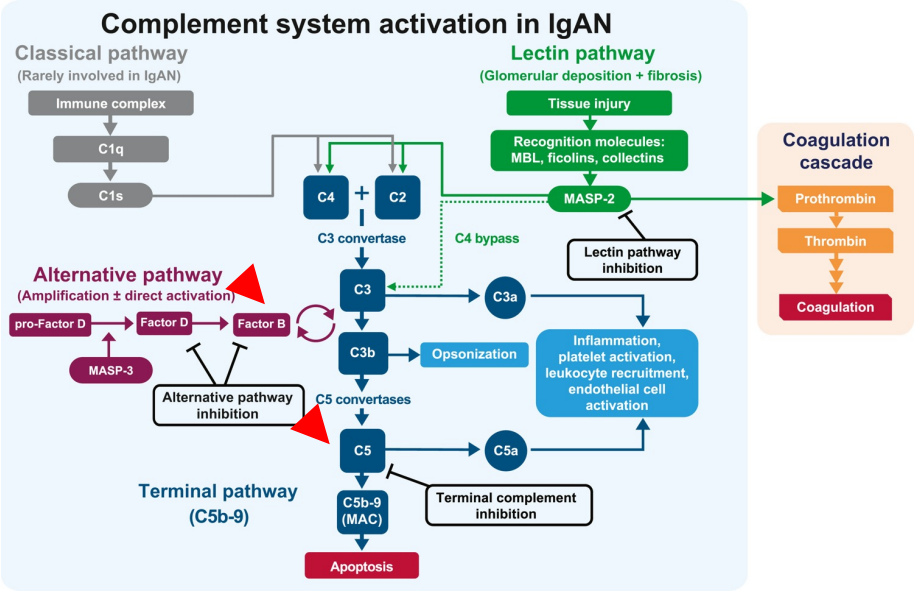
Das Komplementsystem ist ein wichtiger Teil der angeborenen Immunabwehr und besteht aus einer Kaskade von Proteinen im Blut. Bei der IgA-Nephropathie wird es vor allem über zwei spezifische Wege fehlgeleitet und dauerhaft aktiviert:

- **Alternativer Weg (Alternative Pathway).** Dieser Weg gilt als Haupttreiber der Komplementaktivierung bei der IgAN. Die im Nierengewebe (Mesangium) abgelagerten IgA-Immunkomplexe aktivieren diesen Weg direkt, was bei rund 90 % der Betroffenen zu nachweisbaren Ablagerungen des Komplementfaktors **C3** in der Nierenbiopsie führt.

- **Lektin-Weg (Lectin Pathway).** Bei einem Teil der Patienten bindet das sogenannte Mannose-bindende Lektin (MBL) an die veränderten Zuckerstrukturen der IgA1-Komplexe. Eine Aktivierung über diesen Pfad ist häufig mit einem schwereren Krankheitsverlauf und stärkeren Nierenschäden verbunden.

- **Klassischer Weg (Classical Pathway).** Dieser Weg spielt bei der IgA-Nephropathie normalerweise keine Rolle, weshalb der typische Marker **C1q** in Gewebeproben meist fehlt.

Iptacopan ist ein oraler, selektiver Komplement-Faktor-B-Inhibitor.

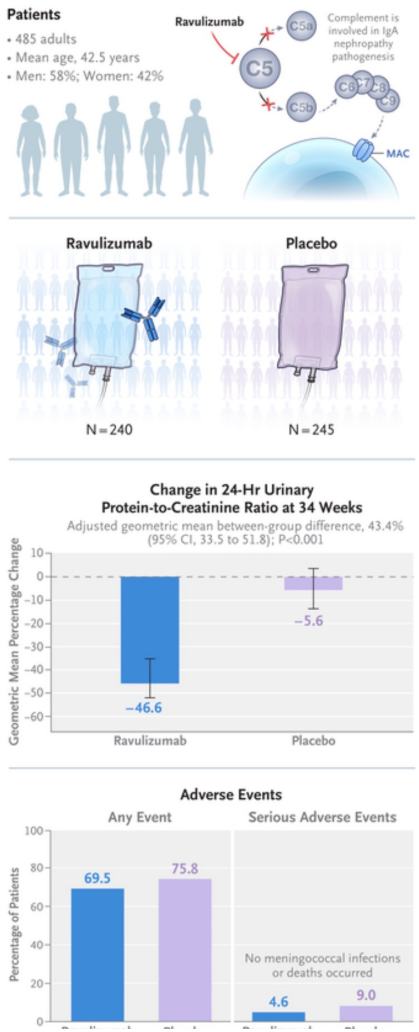


Ravulizumab ist ein humanisierter monoklonaler Antikörper und langwirksamer C5-Komplementinhibitor.

Ravulizumab in IgA Nephropathy — Interim Analysis of a Phase 3 Trial

In patients with IgA nephropathy, complement activation drives glomerular inflammation, which leads to hematuria, proteinuria, and nephron loss. Ravulizumab is a terminal complement inhibitor that prevents formation of C5a and C5b-9.

In this phase 3 trial, we enrolled adults with IgA nephropathy who had an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area and proteinuria (24-hour urinary protein-to-creatinine ratio [with protein and creatinine both measured in grams] of ≥0.75 or total urinary protein excretion of ≥1.0 g per day), despite standard therapy. Patients were randomly assigned in a 1:1 ratio to receive an intravenous infusion of either ravulizumab or placebo every 8 weeks. In the prespecified interim analysis, the primary efficacy end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 34. Safety was also assessed.



IgA nephropathy is a leading cause of kidney failure globally. At diagnosis, patients often have hematuria and may have persistent proteinuria with moderate-to-advanced kidney impairment with substantial nephron loss. Hematuria and persistent proteinuria often indicate active inflammatory disease. Timely and targeted treatment to prevent nephron loss appears to be paramount to the delay or prevention of kidney failure. Addressing the immunologic drivers of glomerular injury is integral to the recommended treatment of IgA nephropathy according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

The complement system, which plays a central role in IgA nephropathy, is activated by immune complexes of galactose-deficient IgA1 bound to anti-glycan antibodies. Glomerular deposition of complement is observed in nearly all kidney-biopsy specimens obtained from patients with IgA nephropathy. In patients with this condition, complement activation can involve several initiation pathways (e.g., alternative and lectin); however, the lectin pathway has been associated with severe disease. Either pathway can result in the activation of terminal complement, which leads to the formation of C5 convertase and the production of C5a (a proinflammatory and potent anaphylatoxin) and C5b-9 (membrane attack complex). Together, C5a and C5b-9 drive glomerular injury.

Trial Population

Eligible adults (≥18 years of age) had IgA nephropathy (confirmed on kidney biopsy any time before or during screening), an eGFR of at least 30 ml per minute per 1.73 m^2, and a 24-hour urinary protein-to-creatinine ratio of at least 0.75 or a 24-hour urinary protein excretion of at least 1.0 g per day. Patients had to have been receiving a stable and maximum tolerated dose of a renin–angiotensin–aldosterone system (RAAS) inhibitor for at least 3 months before screening, unless they had unacceptable side effects with RAAS inhibitors. Patients who were receiving an SGLT2 inhibitor, an endothelin receptor antagonist, a dual endothelin–angiotensin receptor antagonist, or a mineralocorticoid receptor antagonist had to have been taking a stable and maximum allowed or tolerated dose for at least 3 months before screening. Patients who had IgA vasculitis with nephritis were eligible for the trial unless they had received systemic immunosuppressive therapy within 12 months before screening. All the patients had to be vaccinated against *Neisseria meningitidis* at least 14 days (but no more than 3 years) before trial day 1. If day 1 occurred less than 2 weeks after the initial vaccination, patients received prophylactic antibiotic therapy for at least 2 weeks after vaccination.

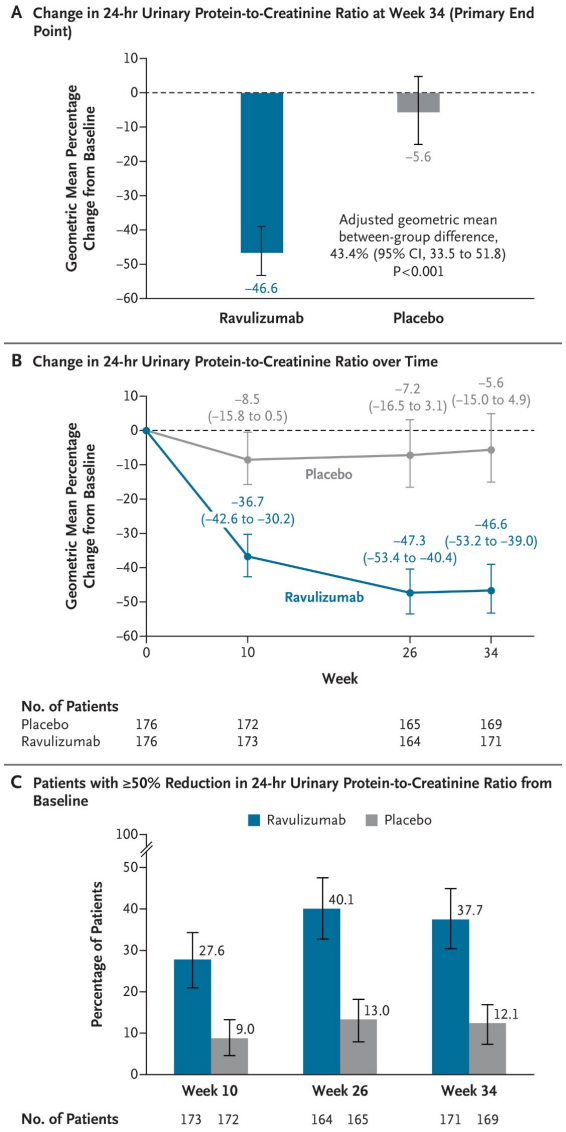
Efficacy End Points

The primary end point for the interim analysis was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 34. The baseline urinary protein-to-creatinine ratio was defined as the mean of the two results from two 24-hour urine collections obtained during screening. Predefined subgroup analyses of the primary end point were performed according to characteristics of the patients at baseline.

Characteristic	Ravulizumab (N=176)	Placebo (N=176)	Total (N=352)
Age — yr	41.8±11.5	43.2±11.9	42.5±11.7
Sex — no. (%)			
Male	99 (56.2)	105 (59.7)	204 (58.0)
Female	77 (43.8)	71 (40.3)	148 (42.0)
Race or ethnic group — no. (%)†			
Asian	99 (56.2)	104 (59.1)	203 (57.7)
White	64 (36.4)	61 (34.7)	125 (35.5)
Other, not reported, or unknown	13 (7.4)	12 (6.8)	25 (7.1)
Geographic region — no. (%)			
Asia–Pacific	105 (59.7)	112 (63.6)	217 (61.6)
Europe	39 (22.2)	47 (26.7)	86 (24.4)
Latin America	15 (8.5)	8 (4.5)	23 (6.5)
Middle East	7 (4.0)	4 (2.3)	11 (3.1)
North America	10 (5.7)	5 (2.8)	15 (4.3)
Median time since kidney biopsy (IQR) — yr	2.85 (1.00–5.90)	2.20 (0.70–5.50)	2.50 (0.80–5.85)
24-Hr urinary protein-to-creatinine ratio‡			
Median (IQR)	1.48 (1.03–2.14)	1.50 (1.04–2.43)	1.49 (1.04–2.31)
Mean — no. (%)			
<2	125 (71.0)	119 (67.6)	244 (69.3)
≥2	51 (29.0)	57 (32.4)	108 (30.7)
Median 24-hr urinary protein excretion (IQR) — g/day	2.03 (1.40–3.10)	2.06 (1.45–3.26)	2.04 (1.42–3.24)
Estimated glomerular filtration rate			
Median (IQR) — ml/min/1.73 m^2	59.0 (42.5–82.5)	59.0 (42.8–86.5)	59.0 (42.5–84.5)
Distribution — no. (%)			
<45 ml/min/1.73 m^2	49 (27.8)	49 (27.8)	98 (27.8)
≥45 ml/min/1.73 m^2	127 (72.2)	127 (72.2)	254 (72.2)
Hematuria — no. (%)§	132 (75.0)	148 (84.1)	280 (79.5)
Hypertension — no. (%)	104 (59.1)	102 (58.0)	206 (58.5)
IgA vasculitis — no. (%)	1 (0.6)	3 (1.7)	4 (1.1)
MEST-C score — %¶			
M score			
M0	30.7	23.3	27.0
M1	54.0	57.4	55.7
E score			
E0	58.0	49.4	53.7
E1	27.3	30.7	29.0
S score			
S0	15.9	13.6	14.8
S1	68.8	65.9	67.3
T score			
T0	53.4	50.0	51.7
T1	27.8	26.1	27.0
T2	4.5	5.1	4.8
C score			
C0	45.5	50.6	48.0
C1	27.3	21.6	24.4
C2	2.3	1.7	2.0
Background therapy — no. (%)			
RAAS inhibitor	169 (96.0)	170 (96.6)	339 (96.3)
SGLT2 inhibitor	123 (69.9)	121 (68.8)	244 (69.3)
Mineralocorticoid receptor antagonist	27 (15.3)	13 (7.4)	40 (11.4)
Endothelin receptor antagonist	1 (0.6)	1 (0.6)	2 (0.6)
Dual endothelin–angiotensin receptor antagonist	3 (1.7)	4 (2.3)	7 (2.0)

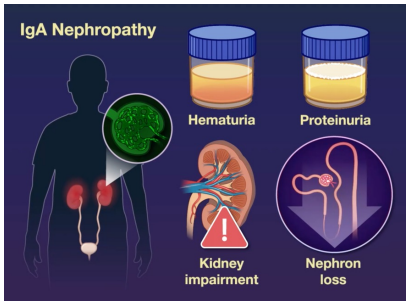
Adverse Events

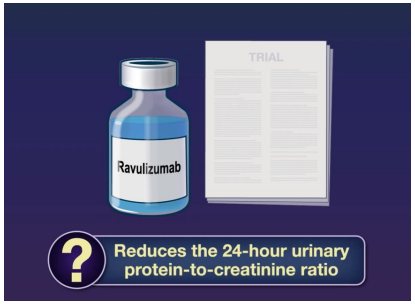
Event	Ravulizumab (N=239)	Placebo (N=244)
	no. of patients (%)	
Any adverse event	166 (69.5)	185 (75.8)
Any serious adverse event	11 (4.6)	22 (9.0)
Any adverse event leading to death	0	0
Any adverse event or serious adverse event leading to discontinuation of ravulizumab or placebo	1 (0.4)	6 (2.5)
Any adverse event related to the trial regimen	46 (19.2)	46 (18.9)
Any serious adverse event related to the trial regimen	1 (0.4)	3 (1.2)
Grade 3 or 4 adverse event	12 (5.0)	20 (8.2)
Adverse event of special interest†	0	0
Adverse events occurring in >5% of the patients in either group		
Upper respiratory tract infection	27 (11.3)	25 (10.2)
Nasopharyngitis	22 (9.2)	22 (9.0)
Infusion-related reaction	20 (8.4)	12 (4.9)
Headache	16 (6.7)	11 (4.5)
Metabolic acidosis	14 (5.9)	9 (3.7)
Hypertension	11 (4.6)	16 (6.6)
Influenza	9 (3.8)	13 (5.3)
Infections and infestations‡	92 (38.5)	87 (35.7)
Upper respiratory tract infection	27 (11.3)	25 (10.2)
Nasopharyngitis	22 (9.2)	22 (9.0)
Influenza	9 (3.8)	13 (5.3)
Urinary tract infection	9 (3.8)	7 (2.9)
Gastroenteritis	8 (3.3)	3 (1.2)
Serious adverse events§	4 (1.7)	4 (1.6)
Not related to the trial regimen	4 (1.7)	4 (1.6)
Related to the trial regimen	0	0

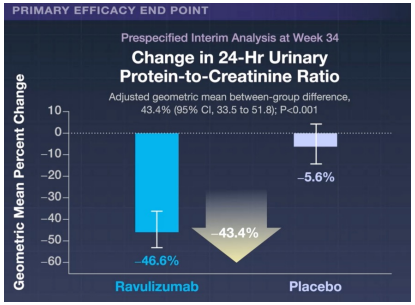


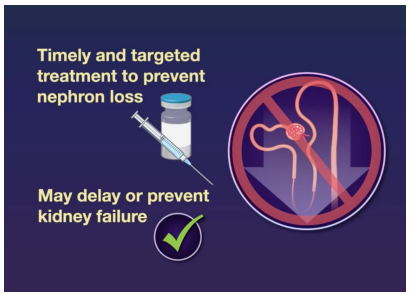
Changes from Baseline in 24-Hour Urinary Protein-to-Creatinine Ratio.

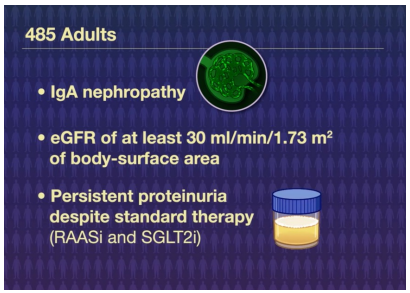
Panel A shows the change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 34 (primary end point). The log-transformed change from baseline was analyzed with the use of a mixed model for repeated measures. The results were back-transformed and are presented as percentages. I bars indicate 95% confidence intervals. Panel B shows the change from baseline in the 24-hour urinary protein-to-creatinine ratio at weeks 10, 26, and 34; from the mixed model for repeated measures. The results were back-transformed and are presented as percentages. I bars indicate 95% confidence intervals. The widths of the confidence intervals at weeks 10 and 26 have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The number of patients at each visit is the number of patients with nonmissing values and values that were not imputed according to the strategy for handling intercurrent events. Panel C shows the percentage of patients with a 50% or greater reduction from baseline in the 24-hour urinary protein-to-creatinine ratio at weeks 10, 26, and 34. The widths of the confidence intervals have not been not adjusted for multiplicity and should not be used in place of hypothesis testing. The number of patients at each visit is the number of patients with nonmissing values and values that were not imputed according to the intercurrent event handling strategy.

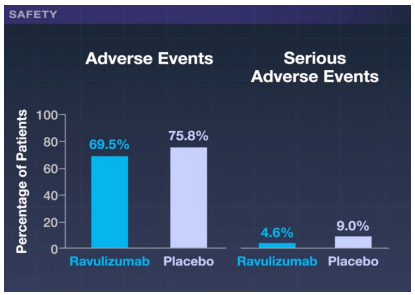


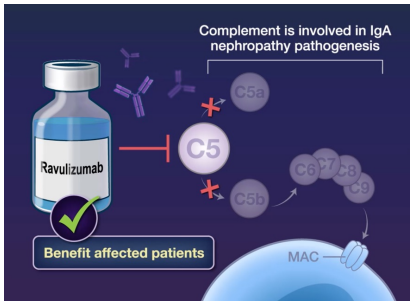




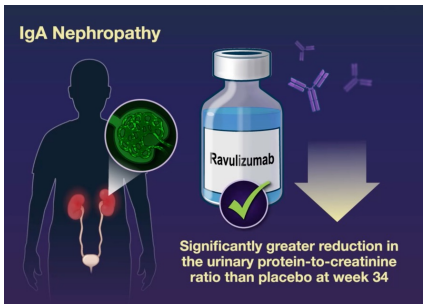












Iptacopan ist ein oraler Komplement-Faktor-B-Inhibitor, der gezielt den alternativen Komplementweg bremst. Dieser Weg spielt bei der Entstehung und dem Fortschreiten der IgA-Nephropathie (IgAN) eine entscheidende Rolle für die Entzündung in den Nierenkörperchen (Glomeruli).

Proteinurie: Die Gabe von Iptacopan (200 mg zweimal täglich) senkte die Proteinurie (Eiweißausscheidung im Urin) im Vergleich zu Placebo signifikant (um rund 38 % bis über 40 % je nach Messzeitpunkt).

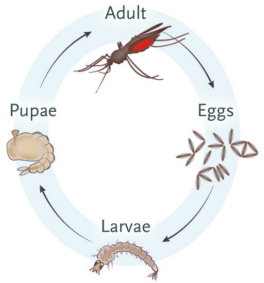
Preventing Malaria Infections and Moving toward Malaria Elimination

Summary

Malaria continues to be a major health challenge worldwide, causing an estimated 282 million cases of illness and 610,000 deaths in 2024, predominantly among African children. Despite recent stagnation in the progress of malaria prevention, the landscape is undergoing rapid transformation. This review examines current and emerging approaches to preventing malaria infection and supporting malaria elimination, including vector control, transmission-blocking interventions, chemoprevention, monoclonal antibodies, and vaccines. Next-generation insecticide-treated nets, expanded use of seasonal malaria chemoprevention, and the introduction of RTS,S/AS01 and R21/Matrix-M vaccines are already reshaping control strategies. Looking ahead, long-acting injectable chemoprevention, transmission-blocking medicines and vaccines, and improved surveillance-driven deployment may further accelerate progress. As funding becomes constrained and decision making shifts increasingly to countries where malaria is endemic, effective malaria prevention will depend on locally tailored, integrated combinations of interventions supported by strong surveillance, regulatory capacity, and national leadership.

Approaches to Malaria Prevention.

Vector control
Aim: reduce the population of insects capable of transmitting malaria parasites



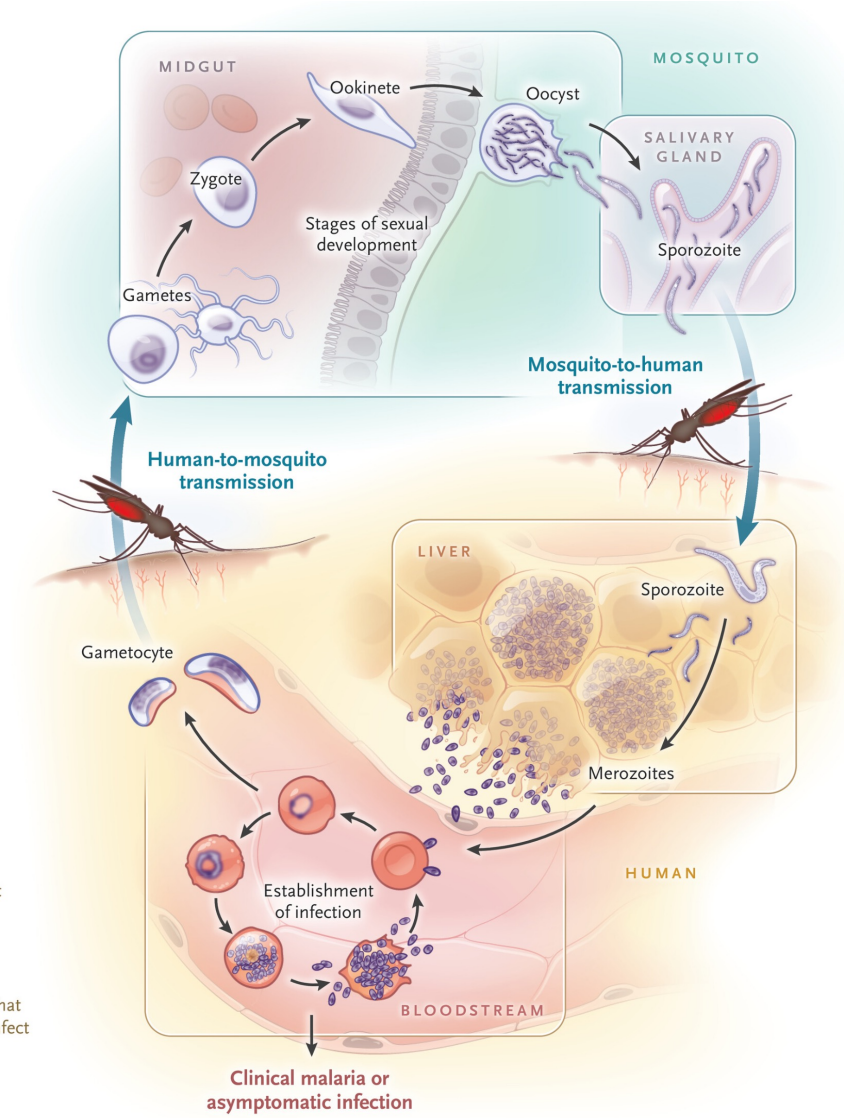
Vaccination
Aim: enhance patient's immune response to infection and prevent transmissible forms of the parasite

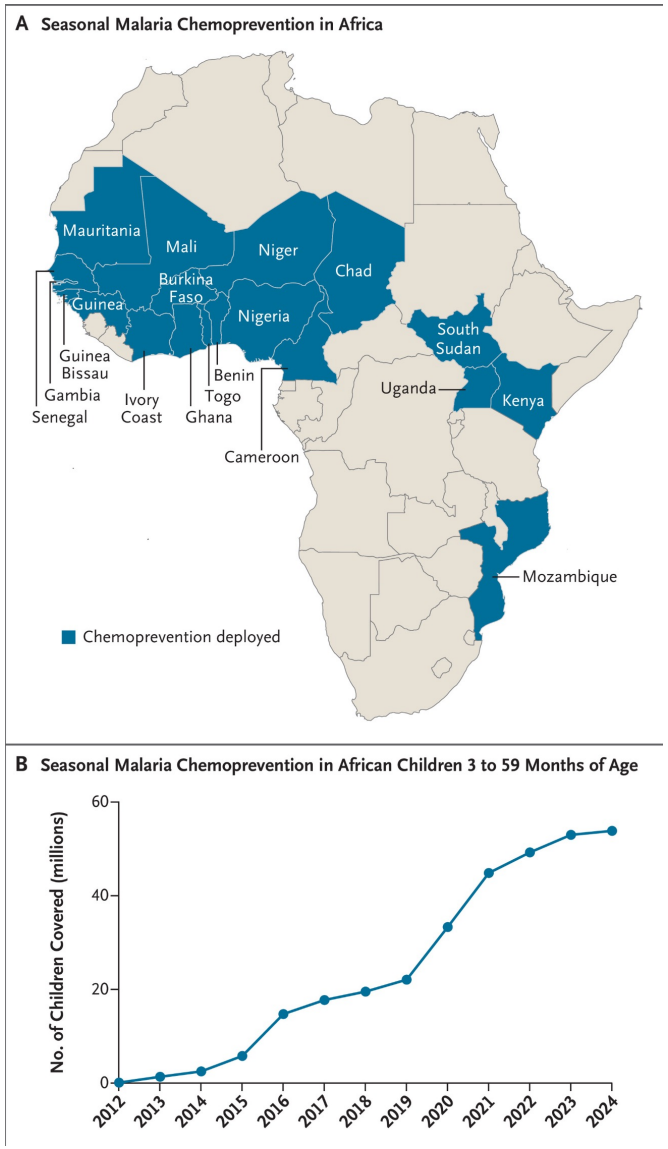
Ectocides
Aim: achieve blood concentrations that are sufficient to kill mosquitoes when feeding, preventing transmission

Transmission-blocking drugs
Aim: prevent formation of viable gametocytes to interrupt onward transmission

Chemoprevention with drugs
Aim: maintain antimalarial drug concentrations in blood that prevent infection becoming established

Passive immunization with monoclonal antibodies
Aim: provide protective antibodies that neutralize sporozoites before they infect liver cells, preventing subsequent blood-stage infection





Deployment of Seasonal Malaria Chemoprevention in Africa as of 2024.[9]

Panel A shows the countries where seasonal malaria chemoprevention was distributed in 2024, and Panel B shows the annual average number of children who received preventive coverage.

Current and Emerging Technologies for Vector Control.



KEY POINTS

Preventing Malaria Infections and Moving toward Malaria Elimination

- Malaria continues to be a major health challenge worldwide, causing an estimated 282 million cases of illness and 610,000 deaths in 2024, primarily among African children under 5 years of age. The emergence of insecticide and drug resistance threatens existing preventive tools.
- Next-generation insecticide-treated nets and new insecticidal compounds have been deployed, with innovative biologic and genetic approaches showing promise.
- Chemoprevention remains highly cost-effective; new long-acting oral and injectable drugs and monoclonal antibodies could enhance preventive coverage and adherence.
- Two preerythrocytic vaccines, RTS,S/AS01 and R21/Matrix-M, are being deployed across Africa, offering effective protection for young children.
- Strengthened surveillance, regional manufacturing, and regulatory capacity, combined with sustained African leadership, are essential to achieve durable malaria control and eventual elimination.
- Sustaining progress requires integrated strategies that combine vector control, chemoprevention, and vaccination, with efforts tailored to local transmission dynamics and resources.

Targeting Human-to-Mosquito Transmission

Interrupting human-to-mosquito transmission represents an efficient malaria-control approach. In 2012, the WHO recommended adding a single low dose (0.25 mg per kilogram of body weight) of primaquine to artemisinin-based combination therapy to eliminate or sterilize mature gametocytes and interrupt transmission. Although adoption has been limited, WHO-prequalified child-friendly formulations of low-dose primaquine became available in 2025. Uptake is still limited but could be facilitated through copackaging or coformulating primaquine with artemisinin-based combination therapies, which would simplify distribution and administration.

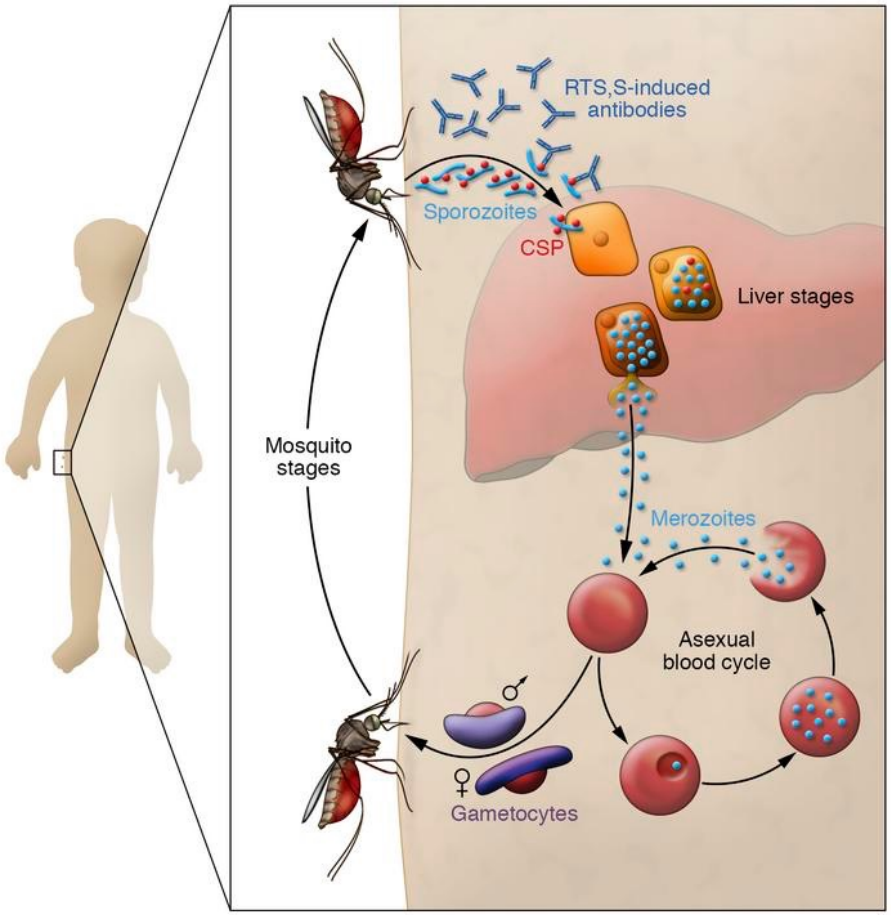
Ectocides are administered to humans at doses sufficient to achieve plasma concentrations that kill mosquitoes ingesting a blood meal. Ivermectin is the best-known example but has shown mixed results, and its short half-life may limit its usefulness. However, long-acting ectocide formulations or new compounds with longer half-lives appear promising and are entering clinical testing for insectborne infection.

Transmission-blocking vaccines induce antibodies in humans that, when ingested by mosquitoes, prevent parasite development. The most advanced candidate, Pfs230D1 M-EPA/AS01, has been clinically evaluated and has been shown to reduce the numbers of transmission events and infected mosquitoes over 2 years.

RTS,S/AS01 (known commercially as **Mosquirix**) is the world's first recommended vaccine against malaria, specifically targeting *Plasmodium falciparum*, the deadliest malaria parasite.

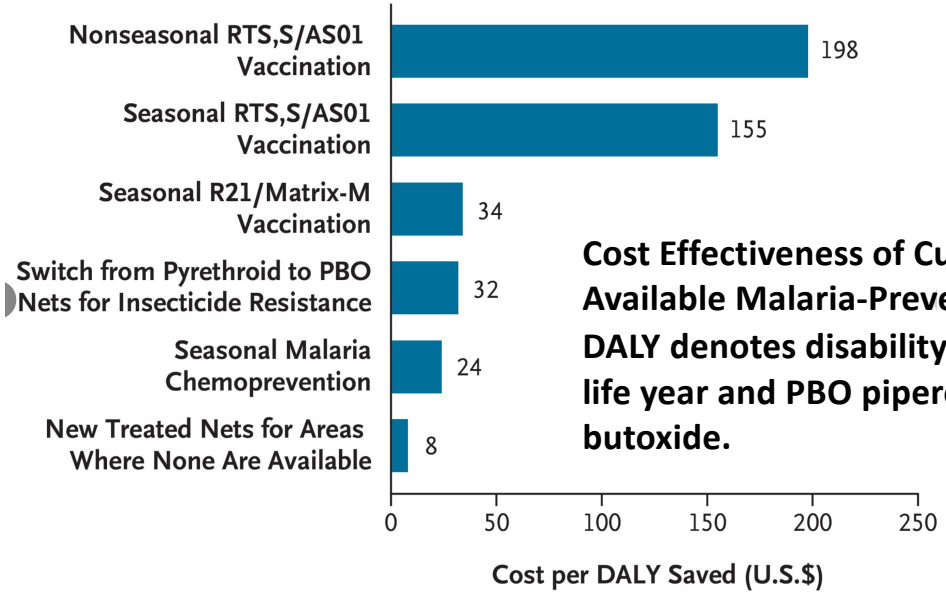
How It Works

- **Target:** It targets the circumsporozoite protein (CSP) on the surface of the parasite's sporozoite stage, which is injected into the body by mosquitoes before it reaches and infects the liver.
- **Design:** It combines parts of the parasite's CSP protein with a surface antigen from the **hepatitis B virus** to form harmless virus-like particles, paired with an AS01 adjuvant to boost the immune response.
- **Name Origin:** The name **RTS,S** comes from the specific protein structure used: **R** (repeat region) and **T** (T-cell epitope) from the parasite fused with **S** (surface antigen) of the hepatitis B virus, plus a separate free **S** antigen.



Primary Expected Attributes of Future Vaccines and Medications for Malaria Prevention.

Tool	Target Population	Frequency	Cold Chain Required	Relative Cost
Oral medicines	All ages and during pregnancy	Monthly	No	$
Long-acting injectables	All ages and during pregnancy	Every 3 to 4 mo	No	$$
Monoclonal antibodies	Up to 5 yr of age and during pregnancy	Every 3 to 4 mo	Yes	$$$
Next-generation vaccines	Children and adults	Single injection (with booster possible)	Yes	$$$



Cost Effectiveness of Currently Available Malaria-Prevention Tools. DALY denotes disability-adjusted life year and PBO piperonyl–butoxide.

Bringing It All Together

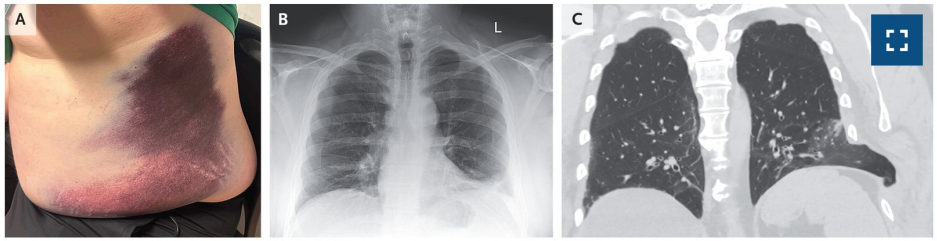
Despite an expanding malaria-prevention toolbox, funding channels are contracting, and countries face decisions on which interventions or combinations to prioritize. Consequently, surveillance-driven targeting of prevention measures and efficient integration of interventions are essential. Supported by vector control, surveillance has underpinned recent national elimination successes, such as in China, by strengthening rapid case detection and response.

Conclusions

After several years of stalled response to malaria, the development and deployment of new tools give hope that malaria control may be turning a corner. In response to insecticide resistance, new vector-control tools and innovative biologic and genetic approaches are emerging. Medicines, including long-acting and injectable options, remain the cornerstone of malaria prevention, whereas malaria vaccines offer a new protective layer for young children. New technologies could accelerate elimination, but there is no magic bullet for malaria prevention, and a flexible, multifaceted strategy is required.

Subnational tailoring of interventions, informed by local data and contextual factors, is essential for maximizing effect and ensuring cost-effectiveness. African leadership, with strengthened regulatory systems and manufacturing capacity, will support sustainable progress. Continued innovation and a strong commitment to equitable access and effective implementation are vital to achieving the goal of a malaria-free future.

Lung Hernia with a Chest-Wall Hematoma



A 54-year-old man with obesity presented to the emergency department with 5 days of cough and a painful bruise on his left side that started after he felt a “pop” during a coughing paroxysm. He had no history of thoracic surgery. On physical examination, there was a large ecchymosis on the left chest wall (Panel A) and a tender bulge within the upper bruise that became more prominent on expiration and less prominent on inspiration. A polymerase-chain-reaction assay of a nasopharyngeal sample was positive for respiratory syncytial virus. A chest radiograph showed a patchy opacity at the left lung base (Panel B). Computed tomography of the chest revealed herniation of the left lower lobe between the eighth and ninth ribs (Panel C) with ground-glass opacities at the site of the hernia. A chest-wall hematoma was also seen. A diagnosis of a lung hernia was made. Lung hernias might be missed on frontal chest radiography if they decrease in size on inspiration during the study (as probably happened in this case) or are superimposed over adjacent aerated lung. At a 2-week follow-up visit with a thoracic surgeon, no surgery was recommended owing to the abating symptoms and lack of enlargement or incarceration. The hernia was stable on imaging 5 months after diagnosis.

Lung Hernia with a Chest-Wall Bulge

VIDEO



Lung Hernia with a Chest-Wall Bulge 0m 10s

An 81-year-old man with a smoking history of approximately 60 pack-years was transferred to a tertiary-care hospital for pacemaker implantation and was incidentally noted to have a flank bulge. Twenty years earlier, the patient had undergone resection of three ribs and a segment of the lung on the left side to treat mesothelioma. A few years after surgery, he had noted a bulge on his left side, and a chronic cough had developed, for which he had received treatment for the symptoms only. Two days before being transferred to the hospital, he had had dizziness and syncope and had received a diagnosis of complete heart block. On physical examination, a soft, compressible protrusion from the lower posterolateral chest wall was observed on the left side at the site of his previous chest surgery. The protrusion moved inward during inspiration and outward during expiration (see video). Vesicular breath sounds were heard over the area. A diagnosis of a lung hernia, which most commonly occurs in patients with a history of chest-wall trauma or surgery, was made. The pacemaker was implanted without complication. Surgical repair of the lung hernia was not recommended owing to its long-term stability and the high operative risk. The patient’s pulmonary symptoms and lung hernia were stable 1 year later.





Case 32-2026: A 50-Year-Old Man with Recurrent Cardiomyopathy

A 50-year-old man was evaluhistoryated at this hospital because of recurrent systolic heart failure.

The patient had a of hypertension, hypercholesterolemia, and obstructive sleep apnea. Eleven years before the current presentation, he was admitted to this hospital because of fever, chills, and dyspnea after a trip to the Caribbean. Laboratory testing showed leukocytosis, acute kidney injury, and increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), troponin T, and N-terminal pro–B-type natriuretic peptide; laboratory test results are shown. An electrocardiogram (ECG) was normal. Transthoracic echocardiography revealed a left ventricular ejection fraction of 21% with moderately reduced right ventricular systolic function; no ventricular dilatation or myocardial wall thickening was noted. The patient had progressive cardiogenic shock in the first hours after admission, and venoarterial extracorporeal membrane oxygenation (ECMO) was initiated.

On hospital day 3, the patient was weaned from ECMO, and the ventricular function normalized. Blood cultures showed no growth, and an extensive infectious disease workup was negative, except for a mildly elevated level of anti–streptolysin O antibodies. A presumptive diagnosis of poststreptococcal myocarditis was made. The patient completed a 14-day course of amoxicillin, and treatment with an oral beta-blocker and an angiotensin-converting–enzyme inhibitor was

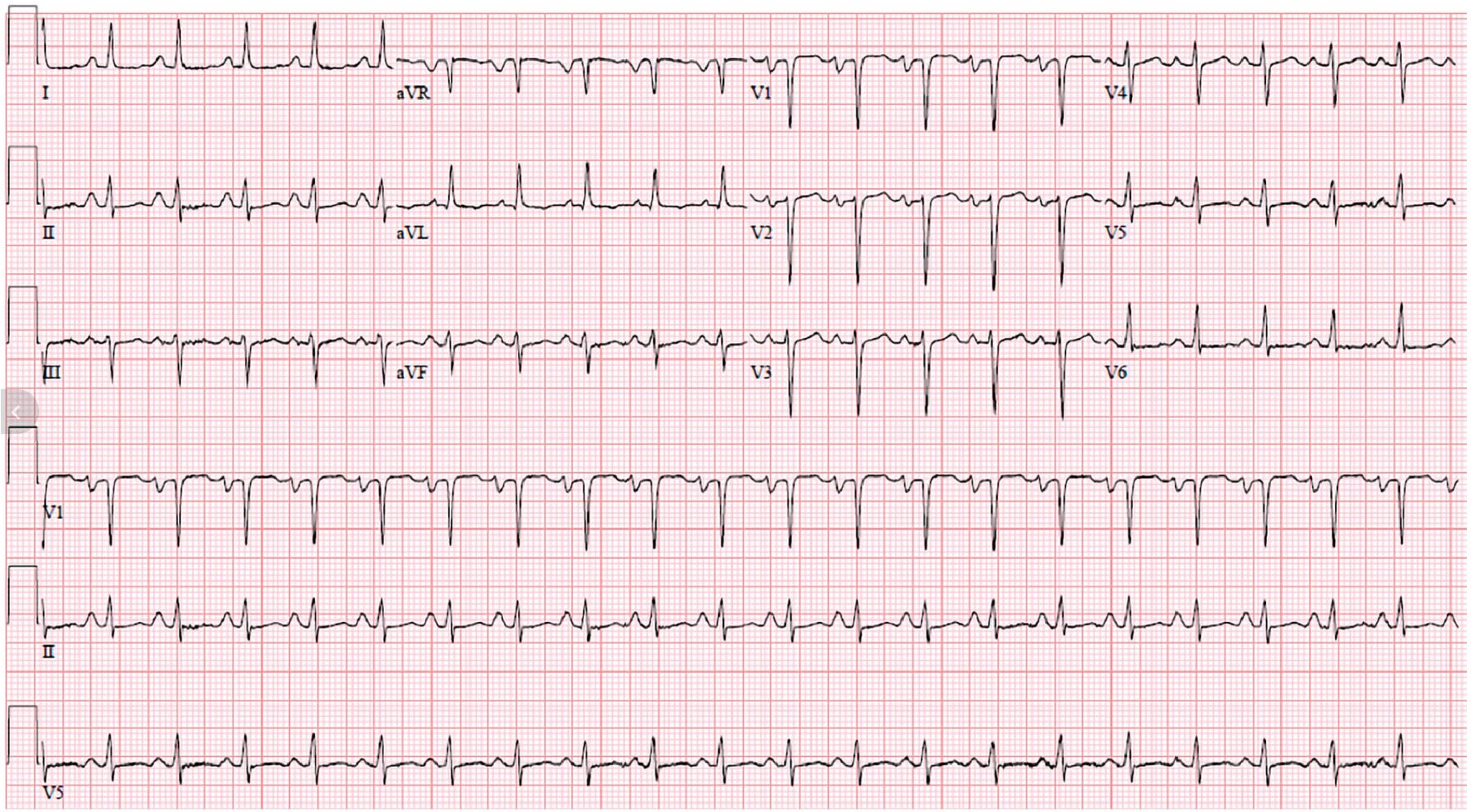
Variable	Reference Range, Adults, This Hospital†	11 Yr before Current Presentation, This Hospital	4 Yr before Current Presentation, Primary Care Clinic	4 Yr before Current Presentation, Endocrinology Clinic	3 Yr before Current Presentation, Hematology Clinic	On Current Presentation, Emergency Department	Hospital Day 2
Hemoglobin (g/dl)	13.5–17.5	17.5	18.1	—	18.8	15.3	15.5
Hematocrit (%)	41.0–53.0	50.0	53.4	—	56.7	48.5	49.3
Red-cell count (per μl)	4,500,000–5,900,000	5,430,000	5,680,000	—	6,340,000	5,380,000	5,500,000
Mean corpuscular volume (fl)	80.0–100.0	92.0	94.0	—	89.4	90.1	89.6
Mean corpuscular hemoglobin (pg)	26.0–34.0	35.0	31.9	—	29.7	28.4	28.2
White-cell count (per μl)	4500–11,000	21,500	7360	—	10,170	14,230	12,730
Platelet count (per μl)	150,000–400,000	288,000	238,000	—	310,000	400,000	369,000
Sodium (mmol/liter)	135–145	135	139	—	141	135	129
Potassium (mmol/liter)	3.4–5.0	5.1	4.7	—	4.2	4.7	4.4
Chloride (mmol/liter)	98–108	96	98	—	100	95	101
Carbon dioxide (mmol/liter)	23–32	28	28	—	27	20	20
Urea nitrogen (mg/dl)	8–25	16	18	—	14	22	19
Creatinine (mg/dl)	0.60–1.50	2.07	1.33	—	1.42	1.45	1.38
Glucose (mg/dl)	70–110	150	89	—	94	106	84
Albumin (g/dl)	3.3–5.0	3.3	4.4	—	4.7	3.9	3.6
Alanine aminotransferase (U/liter)	10–55	63	67	—	58	195	173
Aspartate aminotransferase (U/liter)	10–40	62	50	—	38	129	98
Alkaline phosphatase (U/liter)	45–115	83	66	—	73	169	176
Total bilirubin (mg/dl)	0.0–1.0	1.4	0.8	—	0.9	1.1	1.3
Direct bilirubin (mg/dl)	0.0–0.4	0.5	—	—	—	0.4	0.4
Lactate (mmol/liter)	0.5–2.2	3.1	—	—	—	1.9	—
Troponin T (ng/ml)	<0.03	0.71	—	—	—	—	—
High-sensitivity troponin T (ng/liter)	0–9	—	—	—	—	25	20
N-terminal pro–B-type natriuretic peptide	<900	3178	—	—	—	3494	—
Coxsackievirus B2 antibody (titer)	<1:8	1:8	—	—	—	1:16	—
Coxsackievirus B3 antibody (titer)	<1:8	1:8	—	—	—	1:16	—
Coxsackievirus B5 antibody (titer)	<1:8	1:8	—	—	—	1:8	—
Coxsackievirus B6 antibody (titer)	<1:8	1:8	—	—	—	1:8	—
Anti–streptolysin O antibody (U/ml)	<530	672	—	—	—	—	—
Anti–DNase B antibody (U/ml)	<300	725	—	—	—	—	—
Anti–smooth-muscle antibody (titer)	<1:20	Negative	—	—	—	—	1:40
C-reactive protein (mg/liter)	<8.0	—	—	—	—	—	67.1
Erythropoietin (mIU/ml)	2.6–18.5	—	—	—	5.9	—	—
Lactate dehydrogenase (U/liter)	110–210	—	—	—	150	—	—
D-dimer (ng/ml)	<500	—	—	—	—	718	—
Thyrotropin (μIU/ml)	0.40–5.00	2.96	1.99	—	2.25	—	0.64
Glycated hemoglobin (%)	4.3–5.6	—	5.4	—	—	—	5.8
Cholesterol (mg/dl)	0–200	—	216	—	212	—	90
Low-density lipoprotein cholesterol (mg/dl)	50–129	—	128	—	107	—	49
High-density lipoprotein cholesterol (mg/dl)	35–100	—	36	—	35	—	22
Triglycerides (mg/dl)	0–150	—	260	—	349	—	93
Iron (μg/dl)	30–160	—	131	—	—	—	30
Total iron-binding capacity (μg/dl)	230–404	—	310	—	—	—	332
Ferritin (μg/liter)	10–200	—	164	—	116	—	43
Total testosterone, morning (ng/dl)	249–836	—	95	187	130	—	—
Free testosterone (ng/dl)	6.16–19.40	—	—	3.65	2.84	—	—
Sex hormone–binding globulin (nmol/liter)	13–71	—	—	29	24	—	—
Normetanephrine (nmol/liter)	<0.90	—	—	—	—	—	0.92
Metanephrine (nmol/liter)	<0.50	—	—	—	—	—	0.33

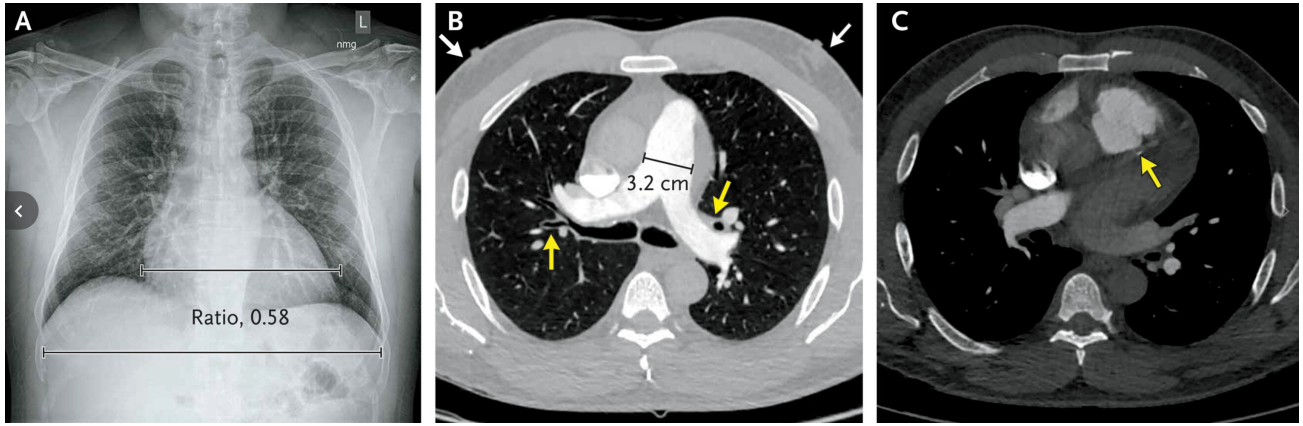
Approximately 2 years later, and 9 years before the current presentation, the patient was evaluated at another hospital because of acute abdominal and leg pain on the right side. Computed tomography (CT) of the abdomen, performed after the administration of intravenous contrast material, reportedly showed an infarct in the right kidney, along with a filling defect and possible focal dissection in the right renal artery. Ultrasonography of the right leg reportedly showed no venous thrombi. Treatment with warfarin was initiated. Transthoracic and transesophageal echocardiography reportedly showed low-normal ventricular function. No valvular vegetations, intracardiac thrombi, or intracardiac shunts were detected. Blood cultures showed no growth. Magnetic resonance imaging of the legs reportedly showed patchy perivascular inflammation of the lower legs. A diagnosis of polyarteritis nodosa was considered, and empirical treatment with a tapering course of prednisone, followed by azathioprine, was prescribed.

During the next 5 years, the patient was followed in the primary care, cardiology, nephrology, rheumatology, general medicine, sleep medicine, and psychiatry clinics of this hospital. He made the decision to stop taking azathioprine, and treatment with warfarin was discontinued after a spontaneous muscle hematoma occurred.
Four years before the current presentation, the patient was evaluated by his primary care physician for fatigue. The physical examination was reportedly normal. The blood level of thyrotropin was normal, but the total testosterone level was decreased; laboratory test results are shown.
Three months later, the patient was evaluated by an endocrinologist at this hospital. He reported poor sleep, reduced libido, and intermittent fatigue. The physical examination was normal; the testicular volume, as measured by a Prader orchidometer, was 15 ml on both sides (reference range, 15 to 25). The levels of follicle-stimulating hormone and luteinizing hormone were normal; other laboratory test results are shown. Treatment for obstructive sleep apnea, which is a risk factor for low testosterone levels, was recommended.
Three years before the current presentation, the patient was evaluated by a hematologist after routine laboratory testing showed erythrocytosis (red-cell count, 6,340,000 per microliter; reference range, 4,500,000 to 5,900,000). The blood pressure was 150/108 mm Hg; the remainder of the physical examination was normal. The carboxyhemoglobin level was normal, and testing for the V617F mutation in the gene encoding Janus kinase 2 (*JAK2*) was negative. Erythrocytosis was attributed to obstructive sleep apnea and renal-artery stenosis.
On the current presentation, the patient was evaluated in the emergency department of this hospital because of 5 days of progressive chest congestion and tightness, fatigue, leg edema, and progressive dyspnea after a trip to the Caribbean. He also noted that his pulse had been 130 beats per minute, as compared with his baseline pulse of 80 beats per minute. The patient reported several years of erectile dysfunction and decreased libido. He reported no known sick contacts, illicit drug use, exposure to animals or insects, or consumption of raw, undercooked, new, or unusual foods. He noted that he had previously used a tanning bed and applied spray tan.

The patient's medical history also included hepatic steatosis, diverticulosis, anxiety, and surgical repairs for a rotator-cuff injury and traumatic tears of the biceps tendon and a knee ligament. Medications included amlodipine and hydrochlorothiazide. The patient had been vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the 3 months before the current presentation. He had no known adverse reactions to medications. He worked as a facility manager. He lived with his wife and children in eastern Massachusetts. He drank beer occasionally and smoked marijuana several times per year; he was a lifelong nonsmoker. He drank four to six caffeinated beverages daily. The patient described himself as a workout "fanatic" and exercised most days of the week. Multiple family members had hypertension and diabetes. His father had coronary artery disease, and his maternal grandfather had died from heart failure.

On examination, the temporal temperature was 35.8°C, the heart rate 134 beats per minute, the blood pressure 148/106 mm Hg, the respiratory rate 28 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. The weight was 83.5 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 29.7. He was muscular, tanned, anxious, and in mild distress. The cardiac examination was notable for tachycardia, a systolic murmur at the base, and an S3 heart sound. The jugular venous pressure was not elevated. The lungs were clear on auscultation, without rales or wheezes. Symmetric edema was present in the legs. The remainder of the examination was normal.


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5



Chest Imaging Studies Obtained at the Current Presentation.
A posteroanterior chest radiograph (Panel A) shows a cardiothoracic ratio that exceeds 50%, which indicates enlargement of the cardiac silhouette. The lungs are clear, and no other abnormalities are seen. Representative axial images from a pulmonary CT angiogram with lung and bone window settings (Panels B and C, respectively) show enlargement of the pulmonary trunk (3.2 cm in width), which exceeds the upper limit of the normal range (2.9 cm). Subtle peribronchial cuffing is present (Panel B, yellow arrows), which is a nonspecific finding associated with conditions such as pulmonary edema or reactive airway disease. Asymmetric bilateral glandular breast tissue, which is more prominent on the left side, is present (Panel B, white arrows), a finding suggestive of gynecomastia. Coronary calcifications are seen (Panel C, arrow). There is no evidence of pulmonary embolism.

Differential Diagnosis

This 50-year-old man, who describes himself as an exercise enthusiast, initially presented with cardiac dysfunction and cardiogenic shock after returning from a trip to the Caribbean at 39 years of age. At that time, the cardiac dysfunction resolved rapidly after the patient received brief mechanical circulatory support. He now presents with biventricular dysfunction after another trip to the Caribbean.

Causes of Myocarditis

Although streptococcal pharyngitis is common, poststreptococcal myocarditis is rare. The condition is distinguished from rheumatic manifestations of streptococcal infection by the timing relative to pharyngitis, with a reported mean onset of 3.1 days after pharyngitis. ST-segment changes that are characteristic of myocarditis are usually seen on ECG, and the left ventricular ejection fraction is either normal or slightly reduced. This patient did not have pharyngitis or characteristic ST-segment changes and had a severely reduced ejection fraction, features that make poststreptococcal myocarditis an unlikely explanation for either of his presentations of heart failure. The elevated level of anti–streptolysin O antibodies that was observed during the patient's first presentation of heart failure is a nonspecific finding that can occur in the context of any immune activation.

Anabolic–Androgenic Steroids

Bioavailable testosterone levels decrease with age, particularly in patients with obesity, diabetes, or obstructive sleep apnea. Indeed, the low testosterone level that had been reported in this patient 4 years before the current presentation was attributed to obstructive sleep apnea.

Synthetic versions of testosterone have become common drugs of abuse, taken at doses far exceeding those used for medically supervised testosterone replacement or supplementation. These anabolic–androgenic steroids (AAS) are used by an estimated 2.9 to 4 million people in the United States, most of whom are male recreational athletes, to increase strength, lean mass, and performance. AAS use is estimated to account for 1.5% of cases of cardiomyopathy among persons younger than 65 years of age. Cardiac toxic effects can include severe reversible cardiomyopathy, and this patient's recurrent episodes of cardiomyopathy may have been triggered by the use of AAS before or during trips to the Caribbean.

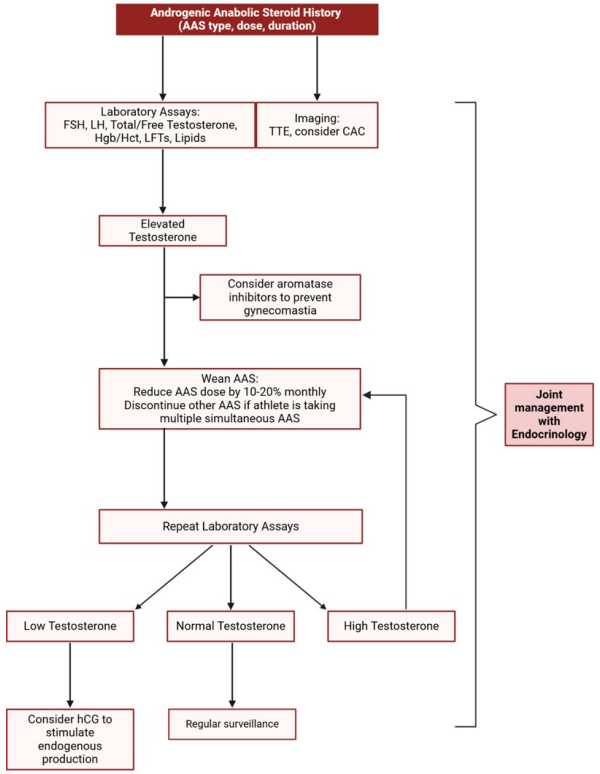
The diagnostic evaluation in this patient's case could involve a careful discussion with the patient to assess for surreptitious use of AAS. Commercially available toxin screening tests typically do not detect AAS, but special assays for measurement of the total testosterone level could be considered.

Diagnostic Testing

The diagnostic test was measurement of the total testosterone level in the blood. The testosterone level was greater than 1500 ng per deciliter, which exceeded the reportable range of the assay (reportable range, 12 to 1500; reference range, 249 to 836).

The immunoassay that was used to measure the testosterone level has cross-reactivity with multiple structurally similar compounds. Some types of AAS, such as methyltestosterone, boldenone, and 19-norclostebol, have strong-to-moderate cross-reactivity with testosterone. Other types of AAS, such as trenbolone, have only weak cross-reactivity. However, the extent of cross-reactivity has not been determined for all the possible metabolites of AAS in this assay, and the cross-reactivity may be higher or lower than that of the parent compounds.

Exogenous **anabolic-androgenic steroids (AAS)** suppress the hypothalamic-pituitary-gonadal (HPG) axis, shutting down endogenous testosterone production, lowering luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and shrinking the testes.



How AAS Affect Testosterone Assays

- **Endogenous Suppression vs. Exogenous Detection:** When someone uses exogenous testosterone or synthetic AAS, standard total testosterone assays may show high, normal, or suppressed values depending on the specific compound used (e.g., pure testosterone vs. synthetic derivatives like nandrolone or stanozolol).

- **Immunoassay Cross-Reactivity:** Many routine clinical **immunoassays** cross-react with synthetic steroids or fail to accurately quantify supraphysiological or non-endogenous variants.

Treatment with metoprolol, sacubitril–valsartan, empagliflozin, and spironolactone was initiated in this patient. Four months later, echocardiography showed a left ventricular ejection fraction of 49%, with normal chamber sizes and wall thickness. The blood levels of AST, ALT, and alkaline phosphatase had normalized with cessation of AAS use.

Six months after AAS cessation, the patient continued to have symptomatic anabolic steroid–induced hypogonadism with a low testosterone level (<100 ng per deciliter) despite normalization of the gonadotropin levels. Given the severity of his ongoing symptoms, he opted for a short course of clomiphene. No improvement in the testosterone level was observed after 1 month, and he opted to start topical testosterone-replacement therapy with a plan for a future tapering course. His testosterone level normalized, but he continued to have erectile dysfunction. This effect is consistent with reports of ongoing sexual dysfunction even after normalization of the testosterone level after cessation of AAS use.

Eight months after the current presentation, the patient had not restarted AAS use. He continued to exercise with cycling, an elliptical machine, and a jump rope, and he had no heart-failure symptoms.

Final Diagnosis

Androgen excess–related cardiomyopathy.

THE LANCET

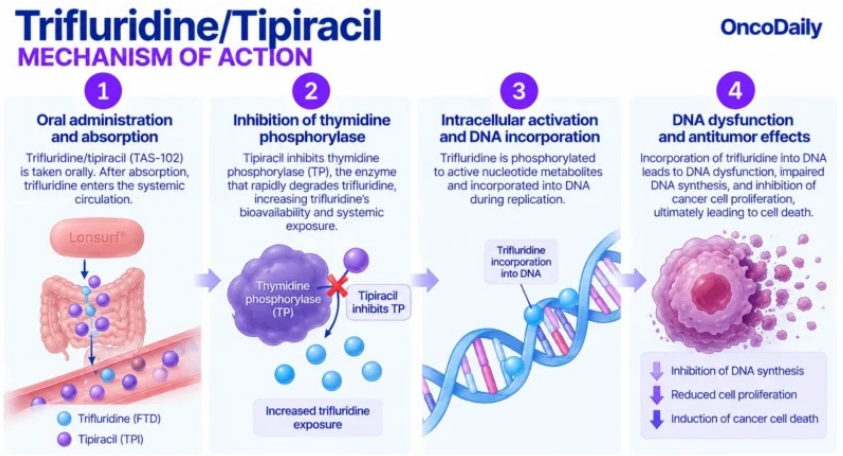
Trifluridin/Tipiracil (bekannt unter dem Handelsnamen **Lonsurf®**) ist ein orales Kombinationsmedikament aus der Gruppe der Zytostatika bzw. Nukleosidanaloga.

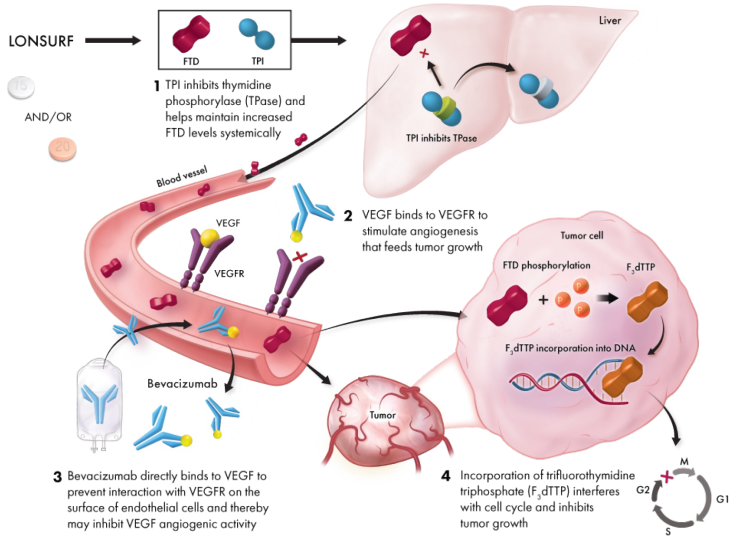
Zusammensetzung

- **Trifluridin:** Ein antineoplastisches Nukleosidanalogon, das in die DNA von Tumorzellen eingebaut wird und deren Teilung hemmt.
- **Tipiracil:** Ein Enzymhemmer (Thymidin-Phosphorylase-Inhibitor), der verhindert, dass Trifluridin im Körper zu schnell abgebaut wird, und so seine Wirksamkeit erhöht.

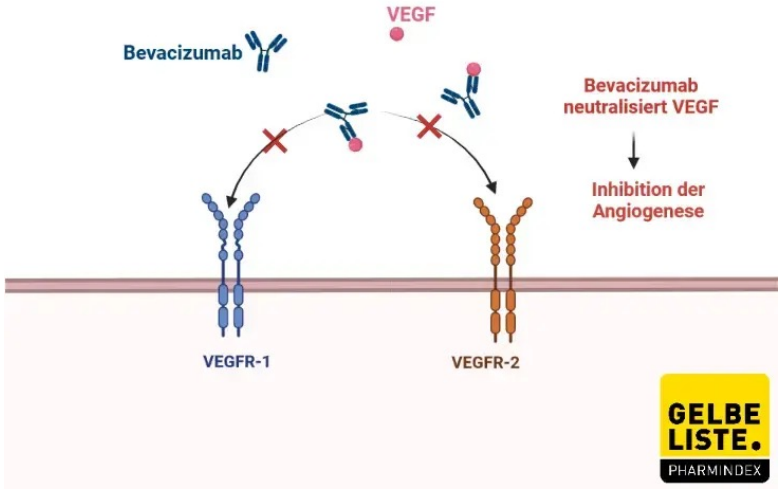
Anwendungsgebiete (Indikation)

- **Metastasiertes kolorektales Karzinom (Darmkrebs):** Für erwachsene Patienten, bei denen Vortherapien (z. B. mit Fluoropyrimidinen, Oxaliplatin, Irinotecan sowie zielgerichteten Therapien) nicht mehr wirken oder nicht geeignet sind. Es wird entweder als Monotherapie oder in Kombination mit **Bevacizumab** eingesetzt.





Bevacizumab ist ein humanisierter monoklonaler Antikörper und ein sogenannter Angiogenese-Hemmer. Bekannt geworden ist der Wirkstoff vor allem unter dem Handelsnamen **Avastin**, inzwischen sind auch verschiedene Biosimilars (Nachahmerpräparate) erhältlich.



Wirkungsweise

- **Zielmolekül:** Bevacizumab bindet gezielt an den Gefäßwachstumsfaktor **VEGF** (*Vascular Endothelial Growth Factor*).

- **Mechanismus:** Es verhindert, dass VEGF an seine Rezeptoren andockt. Dadurch wird das Wachstum neuer Blutgefäße im Tumorgewebe unterdrückt (Angiogenese-Hemmung), was die Blutversorgung des Tumors drosselt und sein Wachstum bremst.

14 or 28 days of FTD-TPI?

14-day versus 28-day trifluridine–tipiracil plus bevacizumab for refractory metastatic colorectal cancer (PRABITAS): a pragmatic, multicentre, open-label, randomised, phase 3, non-inferiority trial in Japan

Summary

Background Trifluridine–tipiracil (FTD–TPI) plus bevacizumab is the standard treatment for refractory metastatic colorectal cancer. However, the conventional schedule is frequently associated with haematological and gastrointestinal toxicity, which is clinically significant and relevant to patients. A simplified 14-day schedule has been proposed to reduce toxicity, but whether this treatment preserves survival has not been established in a randomised trial. We therefore aimed to assess whether the 14-day schedule is non-inferior to the conventional schedule for overall survival.

Methods PRABITAS was a pragmatic, multicentre, open-label, randomised, phase 3, non-inferiority trial conducted in 178 hospitals in Japan. Patients with refractory metastatic colorectal cancer were randomly assigned (1:1) using a minimisation algorithm, stratified by Eastern Cooperative Oncology Group performance status, *RAS* mutational status, and institution, to FTD–TPI (35 mg/m² orally twice daily) plus bevacizumab (5 mg/kg intravenously) on either a conventional 28-day (FTD–TPI on days 1–5 and 8–12; bevacizumab on days 1 and 15) or 14-day schedule (FTD–TPI on days 1–5; bevacizumab on day 1). Eligibility criteria were broadened compared with those of conventional explanatory trials, and trial procedures were aligned with routine clinical practice. The primary endpoint was overall survival, analysed in the intention-to-treat population, with a prespecified non-inferiority margin of 1·25. Safety was assessed in all patients who received at least one dose. Missing data were not imputed. This trial is registered with the Japan Registry of Clinical Trials, jRCTs041230120, and is closed to enrolment.

Findings Between Dec 26, 2023, and May 20, 2025, we randomly assigned 972 patients, of whom 970 (99%) constituted the intention-to-treat population after two were excluded because they were randomly assigned before site approval (486 [50%] to the 28-day treatment group, 292 [60%] men and 194 [40%] women]; and 484 [50%] to the 14-day treatment group, 264 [55%] men and 220 [45%] women). Median follow-up was 17·9 months (IQR 14·3–22·6). Median overall survival was 10·3 months (95% CI 9·5–11·6) in the 28-day group and 11·3 months (10·2–12·5) in the 14-day group (stratified hazard ratio 0·93 [95% CI 0·80–1·08]). The 12-month overall survival rates were 44·0% (95% CI 39·5–48·5) in the 28-day group and 47·5% (42·9–52·0) in the 14-day group. Neutropenia grade 3 or worse was reduced in the 14-day group (13% *vs* 39%; absolute difference 25 percentage points [95% CI 20–31]), as was anorexia grade 2 or worse (15% *vs* 26%; absolute difference 11 percentage points [6–16]). Two treatment-related deaths occurred in the 14-day group and none in the 28-day group.

Interpretation A 14-day schedule of FTD–TPI plus bevacizumab was non-inferior to the conventional 28-day schedule for overall survival, while reducing haematological and gastrointestinal toxicity. These findings support this simplified schedule as the new standard for FTD–TPI plus bevacizumab in refractory metastatic colorectal cancer.

	28-day schedule group (n=486)	14-day schedule group (n=484)
Age, years		
Median (IQR)	68·0 (59·0–74·8)	68·0 (59·8–74·0)
<65 years	197 (41%)	193 (40%)
≥65 years	289 (59%)	291 (60%)
Sex		
Male	292 (60%)	264 (55%)
Female	194 (40%)	220 (45%)
ECOG performance status		
0	269 (55%)	270 (56%)
1	202 (42%)	200 (41%)
2	15 (3%)	14 (3%)
Primary tumour location		
Right-sided colon	121 (25%)	127 (26%)
Left-sided colon	197 (41%)	193 (40%)
Rectum	168 (35%)	164 (34%)
Primary tumour resection		
Yes	357 (73%)	354 (73%)
No	129 (27%)	130 (27%)
Time from initiation of first-line chemotherapy to randomisation, months*		
Median (IQR)	21·8 (14·3–33·7)	22·4 (14·8–33·7)
<18 months	183 (38%)	165 (34%)
≥18 months	302 (62%)	318 (66%)
Metastatic sites		
Liver	318 (65%)	312 (64%)
Peritoneum	168 (35%)	152 (31%)
Lung	296 (61%)	285 (59%)
Distant lymph nodes	165 (34%)	175 (36%)
Number of metastatic organs		
0–1	146 (30%)	132 (27%)
2	176 (36%)	211 (44%)
≥3	164 (34%)	141 (29%)
***RAS* mutational status**		
Mutant	291 (60%)	285 (59%)
Wild-type	195 (40%)	199 (41%)

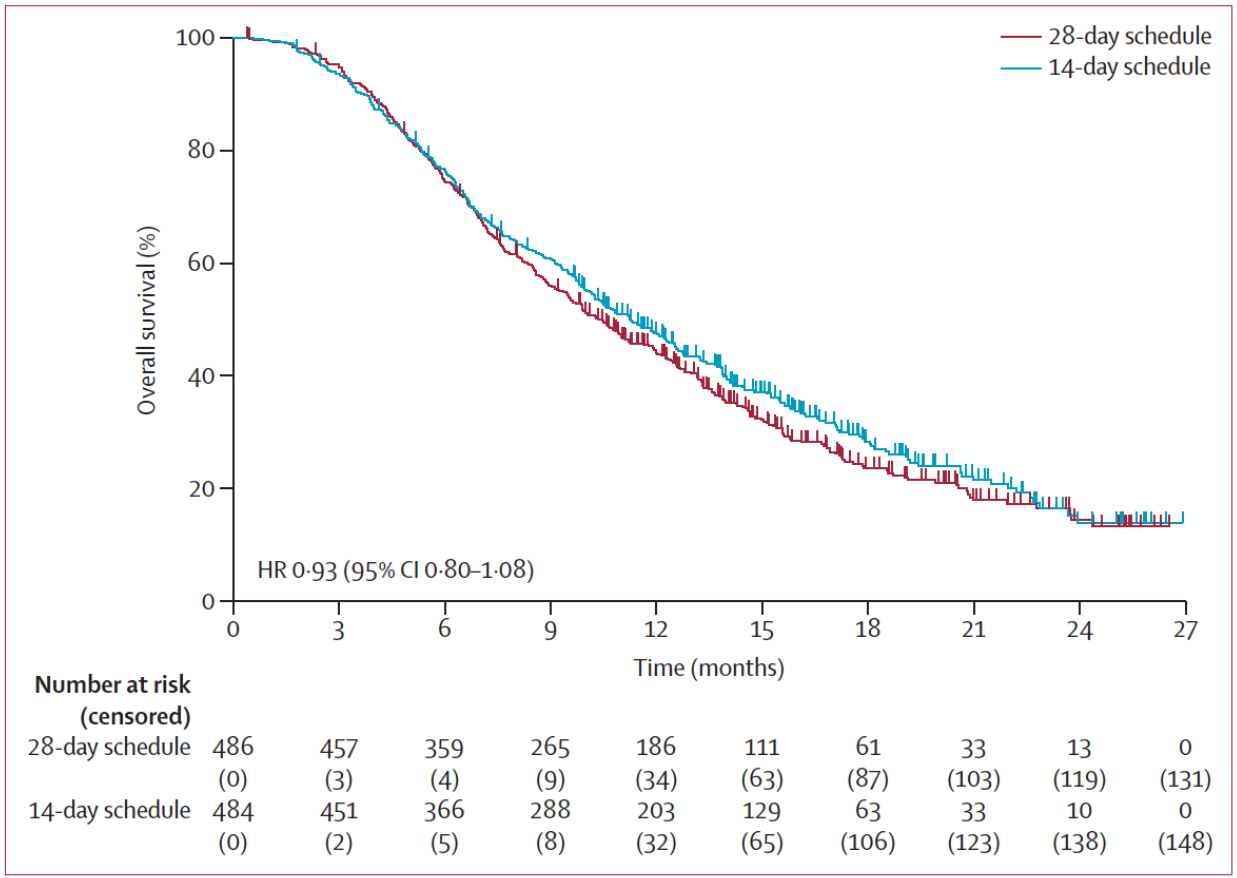
(Table 1 continues in next column)

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	28-day schedule group (n=486)	14-day schedule group (n=484)
***BRAF*^{V600E} mutation**		
Positive	22 (5%)	18 (4%)
Negative	453 (93%)	459 (95%)
Unknown or not tested	11 (2%)	7 (1%)
MSI and MMR status		
MSI high or deficient MMR	7 (1%)	7 (1%)
Non-MSI high or proficient MMR	448 (92%)	455 (94%)
Unknown or not tested	31 (6%)	22 (5%)
Previous systemic therapies		
Anti-angiogenic agents	482 (99%)	481 (99%)
Bevacizumab	419 (86%)	417 (86%)
Ramucirumab	171 (35%)	164 (34%)
Aflibercept	9 (2%)	22 (5%)
Anti-EGFR antibody	202 (42%)	201 (42%)
Regorafenib	28 (6%)	20 (4%)
Fruquintinib	0	1 (<1%)
Encorafenib-based therapy	14 (3%)	14 (3%)
Anti-HER2 therapy	10 (2%)	8 (2%)
Immune checkpoint inhibitor	6 (1%)	8 (2%)
Eligibility for explanatory trials		
Eligible	418 (86%)	407 (84%)
Ineligible†	68 (14%)	77 (16%)

Data are n (%) unless otherwise stated. Percentages might not sum to 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. MMR=mismatch repair. MSI=microsatellite instability. *Data missing for one patient in each group. †Patients with at least one feature typically used as an exclusion criterion in industry-sponsored explanatory trials (appendix p 14).

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



Number at risk (censored)										
28-day schedule	486	457	359	265	186	111	61	33	13	0
	(0)	(3)	(4)	(9)	(34)	(63)	(87)	(103)	(119)	(131)
14-day schedule	484	451	366	288	203	129	63	33	10	0
	(0)	(2)	(5)	(8)	(32)	(65)	(106)	(123)	(138)	(148)

Figure 2: **Kaplan–Meier estimates of overall survival in the intention-to-treat population**
Vertical lines indicate censored data. HRs were estimated from stratified Cox proportional-hazards models with Eastern Cooperative Oncology Group performance status (0 *vs* 1 *vs* 2) and *RAS* mutation status (wild-type *vs* mutant) as strata. Median survival times and 95% CIs were estimated by the Brookmeyer–Crowley method; 95% CIs for HRs were obtained from the stratified Cox model. The prespecified non-inferiority margin was HR 1·25. HR=hazard ratio.

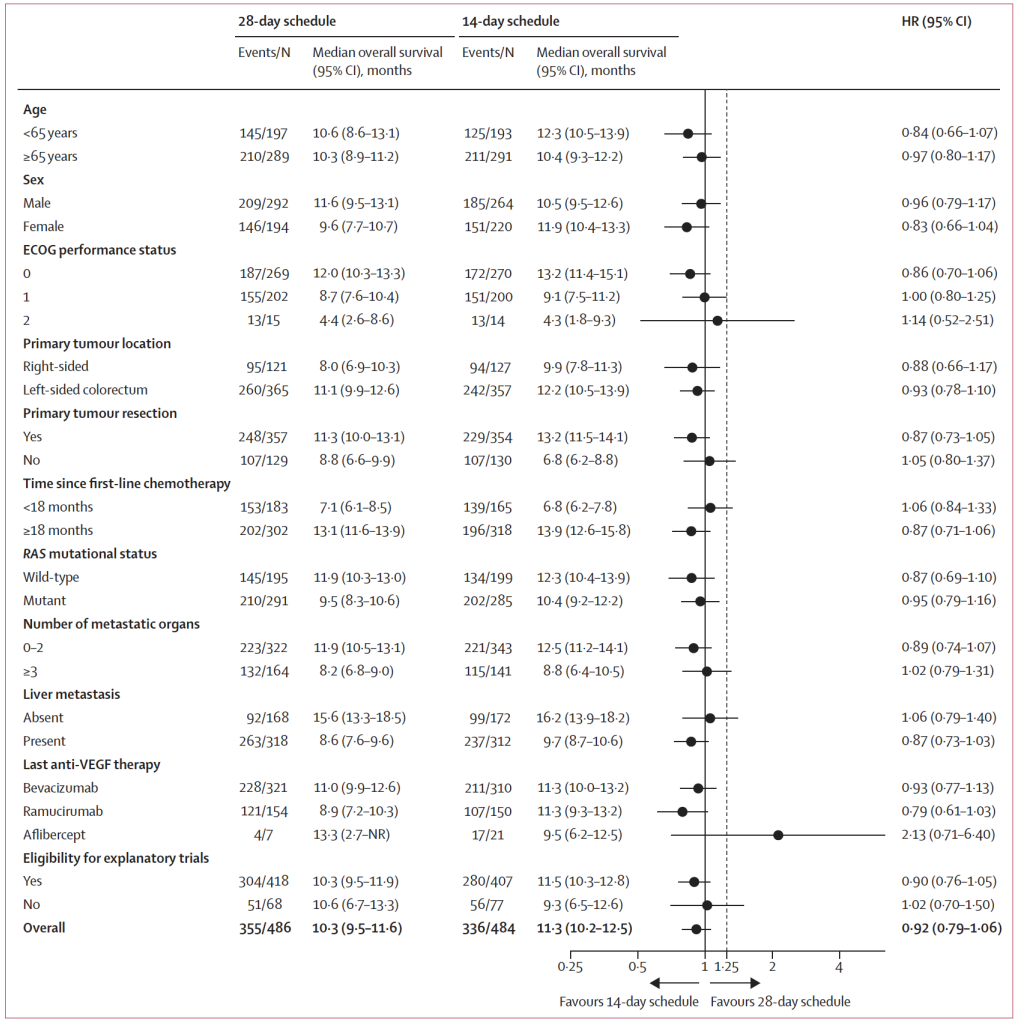
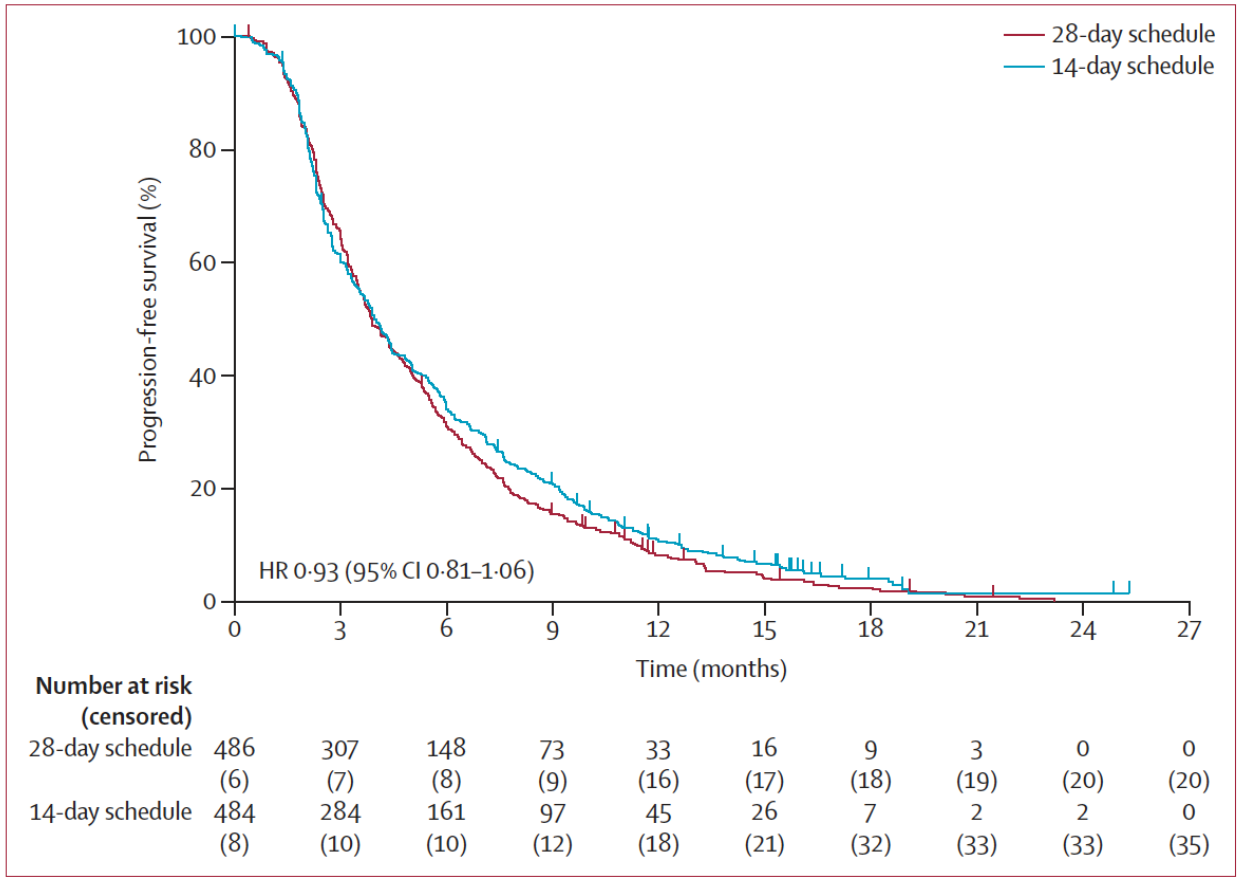


Figure 3: **Forest plot for the prespecified subgroup analyses of overall survival in the intention-to-treat population**
HRs and 95% CIs were estimated from unstratified Cox proportional-hazards models within each subgroup. Interaction p values were derived from a Cox model including a treatment-by-subgroup interaction term. The solid vertical line indicates HR 1·0 and the dotted vertical line indicates the prespecified non-inferiority margin of HR 1·25. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.



Number at risk (censored)										
28-day schedule	486 (6)	307 (7)	148 (8)	73 (9)	33 (16)	16 (17)	9 (18)	3 (19)	0 (20)	0 (20)
14-day schedule	484 (8)	284 (10)	161 (10)	97 (12)	45 (18)	26 (21)	7 (32)	2 (33)	2 (33)	0 (35)

Figure 4: **Kaplan–Meier estimates of progression-free survival in the intention-to-treat population**
Vertical lines indicate censored data. HRs were estimated from stratified Cox proportional-hazards models with Eastern Cooperative Oncology Group performance status (0 *vs* 1 *vs* 2) and *RAS* mutation status (wild-type *vs* mutant) as strata. Median progression-free survival and 95% CIs were estimated by the Brookmeyer–Crowley method; 95% CIs for HRs were obtained from the stratified Cox model. HR=hazard ratio.

	28-day schedule group (n=479)			14-day schedule group (n=478)		
	Any grade	Grade ≥2	Grade ≥3	Any grade	Grade ≥2	Grade ≥3
Gastrointestinal disorders						
Nausea	250 (52%)	85 (18%)	10 (2%)	208 (44%)	55 (12%)	4 (1%)
Diarrhoea	149 (31%)	49 (10%)	13 (3%)	120 (25%)	20 (4%)	3 (1%)
Oral mucositis	92 (19%)	25 (5%)	1 (<1%)	116 (24%)	31 (6%)	6 (1%)
Vomiting	82 (17%)	22 (5%)	3 (1%)	69 (14%)	14 (3%)	3 (1%)
Metabolism and nutrition disorders						
Anorexia	303 (63%)	126 (26%)	23 (5%)	254 (53%)	72 (15%)	17 (4%)
General disorders						
Fatigue	261 (54%)	80 (17%)	13 (3%)	258 (54%)	71 (15%)	9 (2%)
Infections						
Infection	58 (12%)	45 (9%)	12 (3%)	52 (11%)	45 (9%)	18 (4%)
Blood and lymphatic system disorders						
Neutropenia	376 (78%)	302 (63%)	185 (39%)	313 (65%)	203 (42%)	63 (13%)
Leukopenia	331 (69%)	278 (58%)	88 (18%)	251 (53%)	199 (42%)	35 (7%)
Febrile neutropenia	26 (5%)	NA	26 (5%)	7 (1%)	NA	7 (1%)
Summary						
All adverse events*	468 (98%)	402 (84%)	235 (49%)	447 (94%)	323 (68%)	116 (24%)
Gastrointestinal adverse events*	332 (69%)	136 (28%)	23 (5%)	293 (61%)	89 (19%)	14 (3%)
Haematological adverse events*	384 (80%)	331 (69%)	200 (42%)	321 (67%)	243 (51%)	80 (17%)
Treatment-related deaths†	0	..	..	2 (<1%)	..	..

Data are n (%). Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 5.0) and are grouped by system organ class. For each prespecified term, only the worst grade recorded during protocol treatment is reported. The safety-analysis population comprised all patients who received at least one dose of study treatment. One patient in the 28-day schedule group discontinued during cycle 1 before any adverse-event assessment was done and is included in the denominator with no event recorded. Leukopenia and neutropenia were assessed over cycles 1–2 in the 28-day schedule group and cycles 1–4 in the 14-day schedule group, corresponding to approximately 8 weeks of treatment in each group. NA=not applicable. *All adverse events are derived from the ten prespecified terms listed in the table: gastrointestinal adverse events comprise nausea, diarrhoea, oral mucositis, and vomiting; and haematological adverse events comprise neutropenia, leukopenia, and febrile neutropenia. †Treatment-related deaths are not derived from the ten prespecified adverse-event terms and are reported separately; both occurred in the 14-day schedule group, comprising one gastrointestinal haemorrhage and one gastrointestinal perforation attributed to bevacizumab.

Table 2: **Treatment-related adverse events in the safety-analysis population**

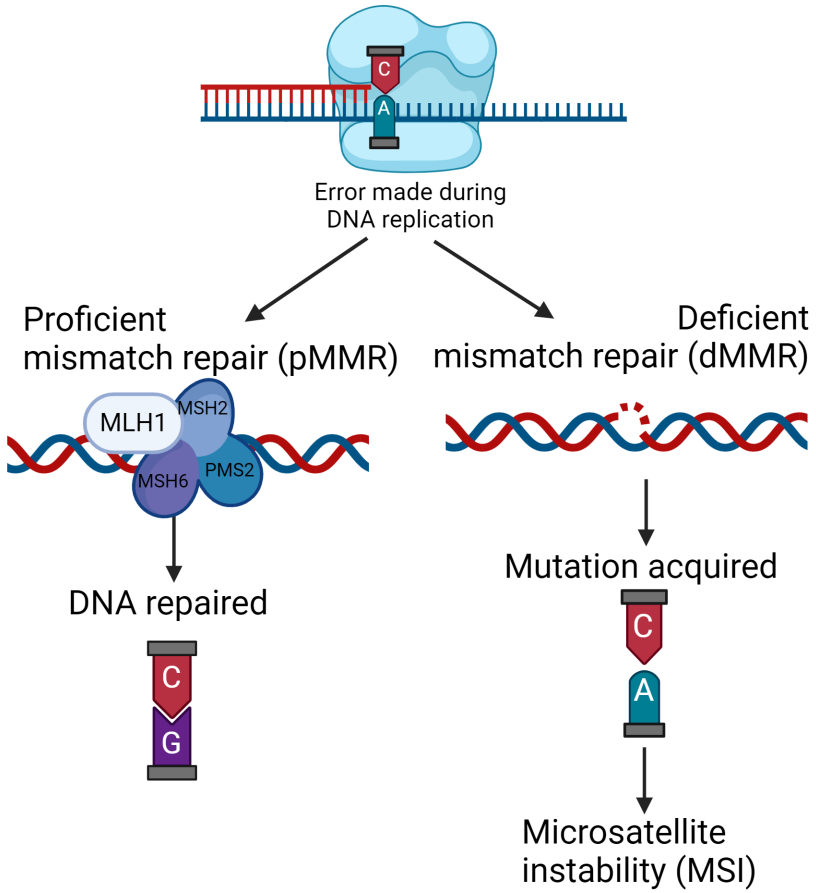
Implications of all the available evidence

Taken together with previous evidence, these findings support adoption of the 14-day FTD–TPI plus bevacizumab schedule as the preferred standard of care for refractory metastatic colorectal cancer. The ongoing French BETWEEN trial (NCT07071844) will provide complementary information regarding patient-reported outcomes associated with a similar treatment strategy. More broadly, PRABITAS highlights the potential value of pragmatic investigator-initiated trials for addressing clinically important treatment-optimisation questions that are unlikely to be prioritised through conventional drug-development pathways.

Eine **Mismatch-Reparatur-Defizienz** (kurz **dMMR**, von englisch *deficient mismatch repair*) bezeichnet eine Funktionsstörung des zelleigenen DNA-Reparatursystems.

Was dahintersteckt

- **Das DNA-Reparatursystem (MMR):** Unsere Zellen haben ein Reparaturprogramm, das Fehler korrigiert, die zufällig bei der Zellteilung (DNA-Replikation) entstehen. Die wichtigsten Proteine dafür heißen *MLH1, MSH2, MSH6* und *PMS2*.
- **Der Defekt (dMMR):** Sind eines oder mehrere dieser Proteine durch genetische Veränderungen (Mutationen) oder eine sogenannte Hypermethylierung inaktiv, spricht man von dMMR.
- **Die Folgen:** Da die DNA-Fehler nicht mehr korrigiert werden, häufen sie sich im Erbgut an. Das führt oft zu einer sogenannten **Mikrosatelliteninstabilität (MSI-H)**. Tumoren mit diesem Merkmal verhalten sich genetisch instabil, sprechen aber oft sehr gut auf eine Immuntherapie an.

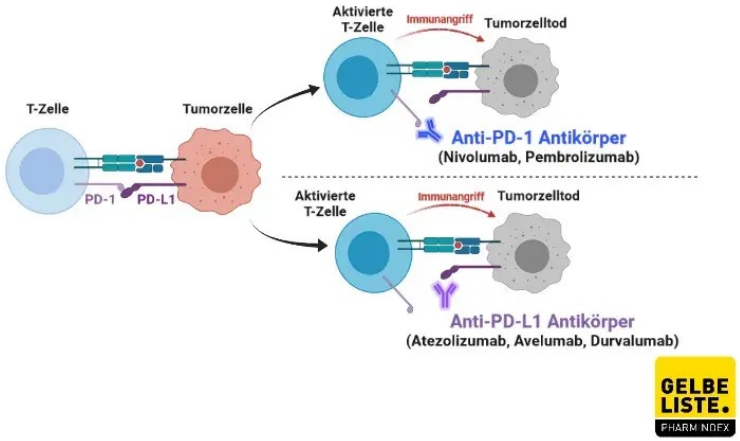


Pembrolizumab (Handelsname **Keytruda®**) ist ein immuntherapeutischer Wirkstoff aus der Gruppe der monoklonalen Antikörper, der zur Behandlung zahlreicher Krebserkrankungen eingesetzt wird. Als sogenannter Immuncheckpoint-Inhibitor unterstützt er das körpereigene Immunsystem dabei, Tumorzellen zu erkennen und gezielt zu bekämpfen.

Wirkmechanismus

Blockade der Tarnung. Viele Tumorzellen bilden an ihrer Oberfläche das Protein PD-L1, um sich vor den Abwehrzellen des Körpers zu verstecken. Bindet dieses Protein an den PD-1-Rezeptor von T-Zellen, wird die Immunantwort gebremst.

Aktivierung der T-Zellen. Pembrolizumab bindet gezielt an den PD-1-Rezeptor und blockiert diesen Signalweg. Dadurch bleiben die T-Zellen aktiv und können die Krebszellen angreifen.



GELBE LISTE. PHARM INDEX

Is pembrolizumab good against mismatch?

First-line pembrolizumab versus carboplatin plus paclitaxel in participants with mismatch repair-deficient advanced or recurrent endometrial cancer (KEYNOTE-C93/GOG-3064/ENGOT-en15): interim analysis of a multicentre, open-label, randomised, active-comparator controlled, phase 3 trial

Summary

Background A need exists for first-line chemotherapy-free options in advanced or recurrent endometrial cancer. We therefore assessed the efficacy, quality of life, and safety of first-line pembrolizumab versus carboplatin plus paclitaxel in mismatch repair-deficient (dMMR) advanced or recurrent endometrial cancer.

Methods The KEYNOTE-C93/GOG-3064/ENGOT-en15 multicentre, open-label, randomised, active-comparator controlled, phase 3 trial was conducted at 122 centres in 24 countries in the Americas, Asia, Europe, and Oceania. Adult participants (≥18 years) with inoperable, stage III or IV, persistent, advanced, or recurrent dMMR endometrial cancer were randomly assigned 1:1 to intravenous pembrolizumab 400 mg every 6 weeks for up to 18 cycles or intravenous carboplatin area under the curve 5 mg/mL or 6 mg/mL per min plus paclitaxel 175 mg/m² on day 1 of each 3-week cycle for six cycles. Randomisation was stratified by disease status, histology, and previous receipt of (neo)adjuvant chemotherapy. Primary endpoints were progression-free survival per RECIST version 1.1, by blinded independent central review, and overall survival. This trial is registered at ClinicalTrials.gov, NCT05173987, and is ongoing.

Findings Between Feb 22, 2022, and Dec 12, 2023, 299 participants were assigned to pembrolizumab (n=149) or carboplatin plus paclitaxel (n=150). At the cutoff for the prespecified interim analysis in the intention-to-treat population (April 24, 2026), median progression-free survival was 38·2 months (95% CI 17·9 months–not reached) in the pembrolizumab group versus 8·4 months (6·8–10·4) in the carboplatin plus paclitaxel group (hazard ratio [HR] 0·57, 95% CI 0·42–0·79; p=0·0002). Estimated progression-free survival was 75% (95% CI 67–81) versus 76% (68–82) at 6 months, 67% (59–74) versus 40% (32–48) at 12 months, and 53% (44–61) versus 30% (22–38) at 36 months. The prespecified statistical significance criterion for overall survival was not met at the interim analysis (medians not reached; HR 0·77, 95% CI 0·52–1·15; p=0·10). Grade 3 or higher treatment-related adverse events occurred in 27 (18%) of 149 participants in the pembrolizumab group and 73 (51%) of 144 in the carboplatin plus paclitaxel group. Treatment-related adverse events of any grade that occurred in at least 25% of participants in either group included alopecia (three [2%] of 149 in the pembrolizumab group, 72 [50%] of 144 in the carboplatin plus paclitaxel group), anaemia (seven [5%], 71 [49%]), nausea (seven [5%], 41 [28%]), decreased neutrophil count (five [3%], 40 [28%]), peripheral neuropathy (none, 38 [26%]), and fatigue (20 [13%], 37 [26%]). Treatment-related adverse events led to treatment discontinuation in 14 (9%) of 149 participants in the pembrolizumab group and 21 (15%) of 144 participants in the carboplatin plus paclitaxel group; they resulted in death in two participants in the pembrolizumab group (hepatic failure and bacterial meningitis [n=1 each]) and one participant in the carboplatin plus paclitaxel group (pulmonary embolism).

Interpretation First-line pembrolizumab showed a statistically significant and clinically meaningful improvement in progression-free survival, with lower frequency of overall and grade 3 or above treatment-related adverse events. The study did not compare pembrolizumab monotherapy with the current standard of care (immunotherapy plus chemotherapy).

	Pembrolizumab group (n=149)	Carboplatin plus paclitaxel group (n=150)
Age, years		
Median (IQR)	62 (56–69)	61 (55–67)
≥65	60 (40%)	52 (35%)
Race		
Asian	43 (29%)	47 (31%)
Black or African American	1 (<1%)	5 (3%)
Multiple	1 (<1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	2 (1%)
White	103 (69%)	93 (62%)
Missing*	0	2 (1%)
Ethnicity		
Hispanic or Latino	6 (4%)	6 (4%)
Not Hispanic or Latino	142 (95%)	137 (91%)
Not reported	1 (<1%)	7 (5%)
Region		
North America	26 (17%)	34 (23%)
Western Europe	63 (42%)	55 (37%)
Rest of the World	60 (40%)	61 (41%)
ECOG performance status		
0	78 (52%)	83 (55%)
1	71 (48%)	67 (45%)
Diagnosis at randomisation		
Newly diagnosed advanced endometrial cancer	66 (44%)	70 (47%)
Recurrent endometrial cancer	83 (56%)	80 (53%)
FIGO stage at diagnosis		
I	56 (38%)	59 (39%)
II	14 (9%)	9 (6%)
III	34 (23%)	37 (25%)
IV	45 (30%)	44 (29%)
Missing	0	1 (<1%)

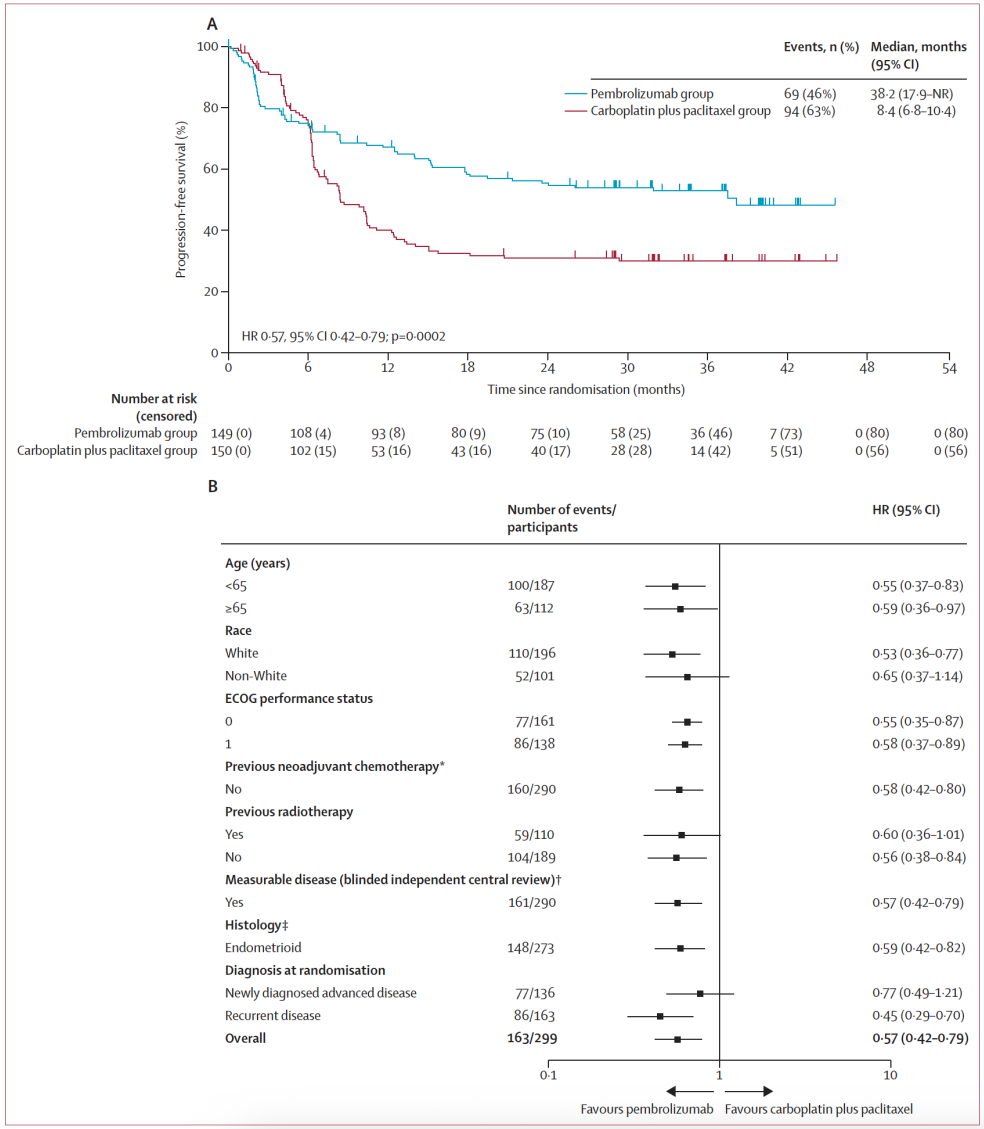
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	Pembrolizumab group (n=149)	Carboplatin plus paclitaxel group (n=150)
Histology per central laboratory data		
Endometrioid	136 (91%)	137 (91%)
Grade 1	15 (10%)	25 (17%)
Grade 2	59 (40%)	57 (38%)
Grade 3	62 (42%)	55 (37%)
Undifferentiated	6 (4%)	5 (3%)
Clear cell	3 (2%)	5 (3%)
Serous	0	3 (2%)
Carcinosarcoma	2 (1%)	0
Other	2 (1%)	0
Measurable disease by blinded independent central review		
Yes	145 (97%)	145 (97%)
No	4 (3%)	5 (3%)
Received previous (neo) adjuvant therapy	4 (3%)	5 (3%)
Received previous surgery	128 (86%)	128 (85%)
Received previous radiotherapy	57 (38%)	53 (35%)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. *Country regulations did not allow collection of data.

Table 1: **Baseline demographics and disease characteristics in the intention-to-treat population**


A
Events, n (%)
Median, months (95% CI)
Pembrolizumab group 69 (46%) 38·2 (17·9–NR)
Carboplatin plus paclitaxel group 94 (63%) 8·4 (6·8–10·4)
Progression-free survival (%)
HR 0·57, 95% CI 0·42–0·79; p=0·0002
Time since randomisation (months)
Number at risk (censored)
Pembrolizumab group 149 (0) 108 (4) 93 (8) 80 (9) 75 (10) 58 (25) 36 (46) 7 (73) 0 (80) 0 (80)
Carboplatin plus paclitaxel group 150 (0) 102 (15) 53 (16) 43 (16) 40 (17) 28 (28) 14 (42) 5 (51) 0 (56) 0 (56)
B
Number of events/ participants
HR (95% CI)
Age (years)
<65 100/187 0·55 (0·37–0·83)
≥65 63/112 0·59 (0·36–0·97)
Race
White 110/196 0·53 (0·36–0·77)
Non-White 52/101 0·65 (0·37–1·14)
ECOG performance status
0 77/161 0·55 (0·35–0·87)
1 86/138 0·58 (0·37–0·89)
Previous neoadjuvant chemotherapy*
No 160/290 0·58 (0·42–0·80)
Previous radiotherapy
Yes 59/110 0·60 (0·36–1·01)
No 104/189 0·56 (0·38–0·84)
Measurable disease (blinded independent central review)†
Yes 161/290 0·57 (0·42–0·79)
Histology‡
Endometrioid 148/273 0·59 (0·42–0·82)
Diagnosis at randomisation
Newly diagnosed advanced disease 77/136 0·77 (0·49–1·21)
Recurrent disease 86/163 0·45 (0·29–0·70)
Overall 163/299 0·57 (0·42–0·79)
0·1
1
10
Favours pembrolizumab
Favours carboplatin plus paclitaxel

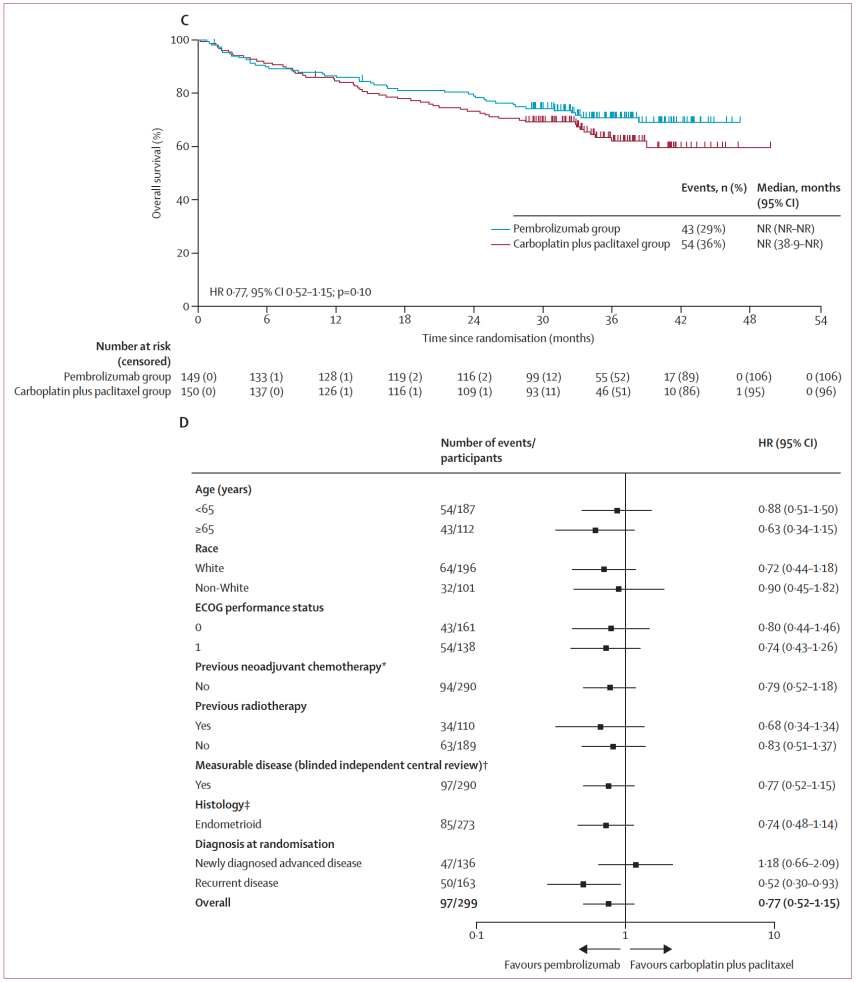
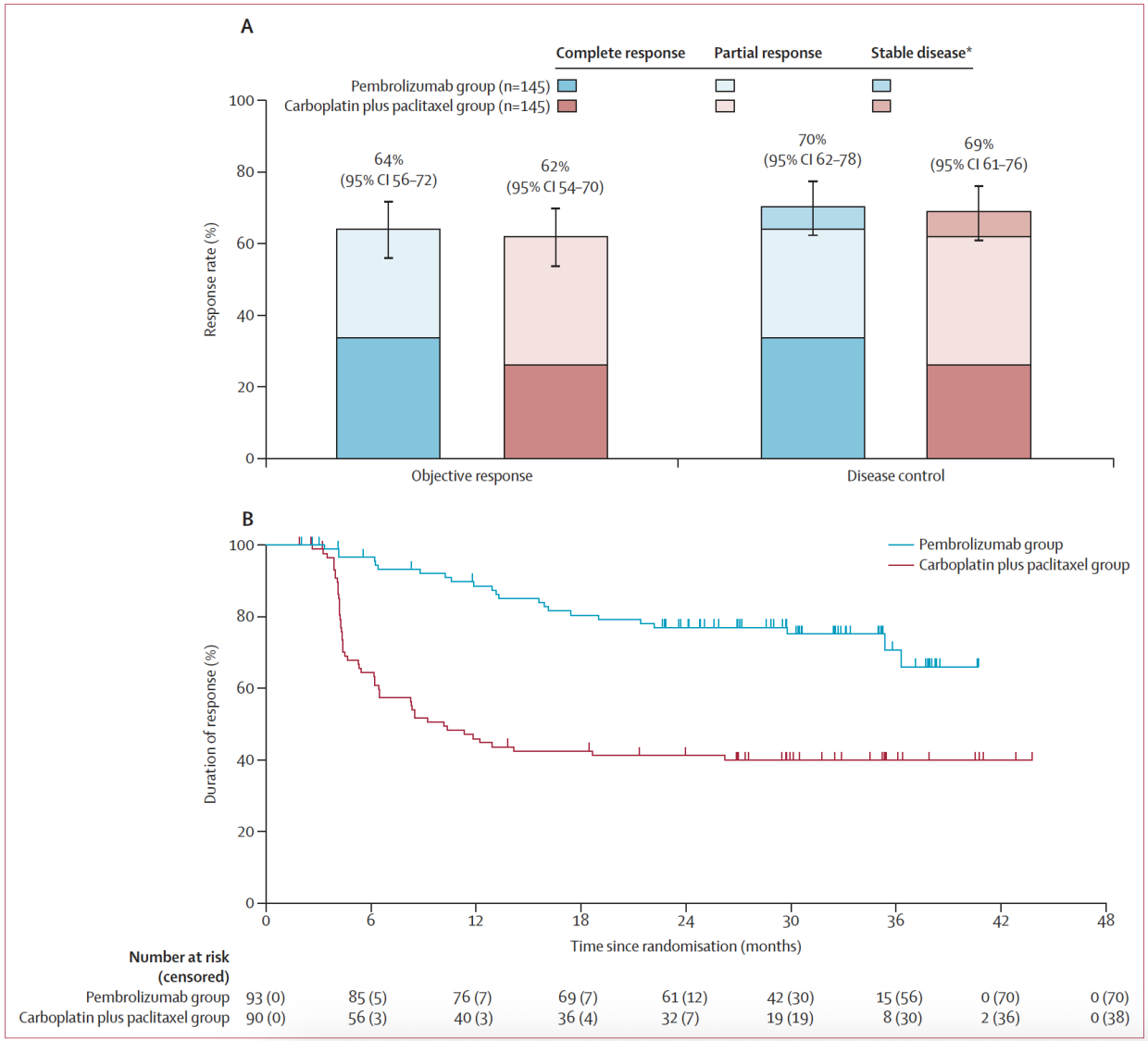


Figure 2: **Progression-free survival per RECIST version 1.1 by blinded independent central review and overall survival in the intention-to-treat population**
(A) Kaplan-Meier estimates of progression-free survival. (B) Prespecified subgroup analyses of progression-free survival. (C) Kaplan-Meier estimates of overall survival. (D) Prespecified subgroup analyses of overall survival. Participants in the pembrolizumab and carboplatin plus paclitaxel groups were censored at randomisation (n=1; n=6) or at the last disease assessment before either two or more missed assessments preceding an event (n=0; n=1), initiation of new anticancer treatment without documented progression (n=6; n=9), or their final assessment showing no progression (n=73; n=40). ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NR=not reached. RECIST=Response Evaluation Criteria in Solid Tumors. *Subgroup analysis of previous exposure to (neo)adjuvant therapy was not assessed because of a small number of participants. †Subgroup analysis in non-measurable disease per blinded independent central review at baseline was not assessed because of a small number of participants. ‡Subgroup analysis in non-endometrioid histology was not assessed because of a small number of participants.


A
Complete response
Partial response
Stable disease*
Pembrolizumab group (n=145)
Carboplatin plus paclitaxel group (n=145)
Response rate (%)
100
80
60
40
20
0
64%
(95% CI 56–72)
62%
(95% CI 54–70)
70%
(95% CI 62–78)
69%
(95% CI 61–76)
Objective response
Disease control
B
Pembrolizumab group
Carboplatin plus paclitaxel group
Duration of response (%)
100
80
60
40
20
0
0
6
12
18
24
30
36
42
48
Time since randomisation (months)
Number at risk (censored)
Pembrolizumab group 93 (0) 85 (5) 76 (7) 69 (7) 61 (12) 42 (30) 15 (56) 0 (70) 0 (70)
Carboplatin plus paclitaxel group 90 (0) 56 (3) 40 (3) 36 (4) 32 (7) 19 (19) 8 (30) 2 (36) 0 (38)

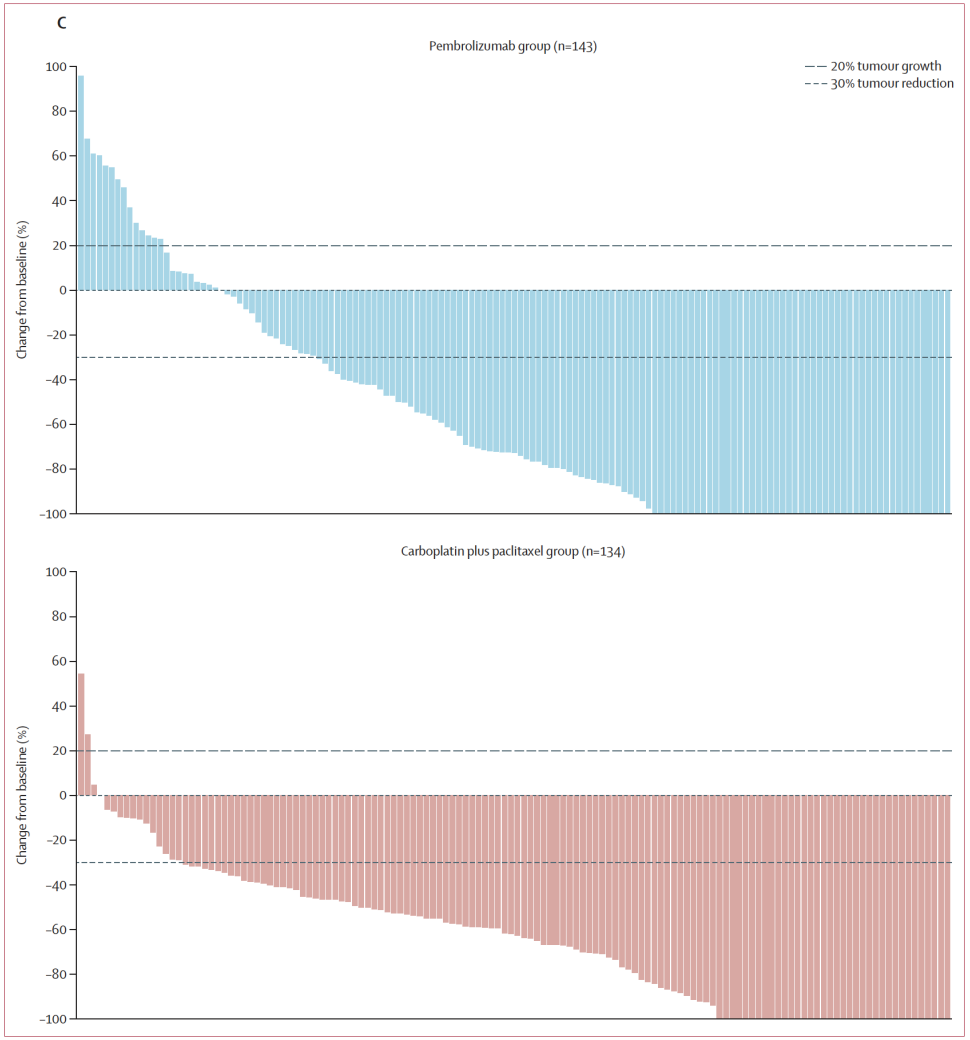


Figure 3: **Antitumour activity**

(A) Objective response rate and disease control rate in participants with measurable disease at baseline. Error bars represent 95% CIs. (B) Duration of response in participants with measurable disease at baseline. (C) Best percentage change from baseline in target lesion size in participants with measurable disease per blinded independent central review at baseline. *Included participants with stable disease for at least 24 weeks.

	Pembrolizumab group (n=149)						Carboplatin plus paclitaxel group (n=144)					
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Meeting serious criteria	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Meeting serious criteria
Any adverse event	145 (97%)	70 (47%)	60 (40%)	9 (6%)	6 (4%)	61 (41%)	142 (99%)	55 (38%)	58 (40%)	24 (17%)	5 (3%)	46 (32%)
Treatment-related adverse events	106 (71%)	79 (53%)	23 (15%)	2 (1%)	2 (1%)*	21 (14%)	141 (98%)	68 (47%)	49 (34%)	23 (16%)	1 (<1%)†	23 (16%)
Anaemia	7 (5%)	4 (3%)	3 (2%)	0	0	1 (<1%)	71 (49%)	45 (31%)	26 (18%)	0	0	4 (3%)
Alopecia	3 (2%)	3 (2%)	0	0	0	0	72 (50%)	72 (50%)	0	0	0	0
Fatigue	20 (13%)	17 (11%)	3 (2%)	0	0	0	37 (26%)	34 (24%)	3 (2%)	0	0	0
Nausea	7 (5%)	6 (4%)	1 (<1%)	0	0	2 (1%)	41 (28%)	40 (28%)	1 (<1%)	0	0	1 (<1%)
Decreased neutrophil count	5 (3%)	5 (3%)	0	0	0	0	40 (28%)	15 (10%)	12 (8%)	13 (9%)	0	2 (1%)
Arthralgia	19 (13%)	19 (13%)	0	0	0	0	24 (17%)	24 (17%)	0	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	38 (26%)	38 (26%)	0	0	0	0
Diarrhoea	16 (11%)	14 (9%)	2 (1%)	0	0	1 (<1%)	21 (15%)	21 (15%)	0	0	0	0
Hypothyroidism	35 (23%)	35 (23%)	0	0	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0	35 (24%)	30 (21%)	5 (3%)	0	0	0
Decreased white blood cell count	2 (1%)	2 (1%)	0	0	0	0	32 (22%)	19 (13%)	9 (6%)	4 (3%)	0	3 (2%)
Decreased platelet count	2 (1%)	2 (1%)	0	0	0	0	29 (20%)	20 (14%)	4 (3%)	5 (3%)	0	5 (3%)
Constipation	4 (3%)	4 (3%)	0	0	0	0	24 (17%)	23 (16%)	1 (<1%)	0	0	1 (<1%)
Myalgia	7 (5%)	7 (5%)	0	0	0	0	21 (15%)	21 (15%)	0	0	0	0
Rash	15 (10%)	15 (10%)	0	0	0	0	11 (8%)	11 (8%)	0	0	0	0
Vomiting	1 (<1%)	1 (<1%)	0	0	0	0	25 (17%)	25 (17%)	0	0	0	0
Decreased appetite	3 (2%)	3 (2%)	0	0	0	0	22 (15%)	22 (15%)	0	0	0	1 (<1%)
Asthenia	7 (5%)	7 (5%)	0	0	0	0	15 (10%)	14 (10%)	1 (<1%)	0	0	0
Neutropenia	0	0	0	0	0	0	21 (15%)	7 (5%)	10 (7%)	4 (3%)	0	0
Hypomagnesaemia	2 (1%)	2 (1%)	0	0	0	0	16 (11%)	13 (9%)	3 (2%)	0	0	0
Infusion-related reaction	3 (2%)	3 (2%)	0	0	0	0	15 (10%)	14 (10%)	1 (<1%)	0	0	0
Hyperthyroidism	17 (11%)	16 (11%)	0	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0
Thrombocytopenia	2 (1%)	2 (1%)	0	0	0	0	14 (10%)	11 (8%)	2 (1%)	1 (<1%)	0	0
Decreased lymphocyte count	2 (1%)	2 (1%)	0	0	0	0	11 (8%)	8 (6%)	3 (2%)	0	0	0
Decreased weight	4 (3%)	3 (2%)	1 (<1%)	0	0	0	4 (3%)	4 (3%)	0	0	0	0
Dyspepsia	2 (1%)	2 (1%)	0	0	0	0	6 (4%)	5 (3%)	1 (<1%)	0	0	1 (<1%)
Leukopenia	1 (<1%)	1 (<1%)	0	0	0	0	7 (5%)	3 (2%)	4 (3%)	0	0	0
Increased gamma-glutamyltransferase	2 (1%)	1 (<1%)	1 (<1%)	0	0	0	5 (3%)	4 (3%)	0	1 (<1%)	0	0
Drug hypersensitivity	0	0	0	0	0	0	6 (4%)	4 (3%)	2 (1%)	0	0	1 (<1%)
Hyperglycaemia	3 (2%)	3 (2%)	0	0	0	0	3 (2%)	2 (1%)	1 (<1%)	0	0	0
Hyponatraemia	2 (1%)	2 (1%)	0	0	0	0	3 (2%)	1 (<1%)	2 (1%)	0	0	1 (<1%)
Febrile neutropenia	0	0	0	0	0	0	4 (3%)	0	2 (1%)	2 (1%)	0	4 (3%)
Hypokalaemia	1 (<1%)	1 (<1%)	0	0	0	0	3 (2%)	2 (1%)	1 (<1%)	0	0	0
Urinary tract infection	0	0	0	0	0	0	4 (3%)	3 (2%)	1 (<1%)	0	0	1 (<1%)
Adrenal insufficiency	3 (2%)	2 (1%)	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Colitis	3 (2%)	1 (<1%)	2 (1%)	0	0	2 (1%)	0	0	0	0	0	0
Gastritis	2 (1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0
Increased transaminases	2 (1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0
Mucosal inflammation	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	2 (1%)	2 (1%)	0	0	0	0
Syncope	0	0	0	0	0	0	3 (2%)	0	3 (2%)	0	0	1 (<1%)
Hypercalcaemia	1 (<1%)	1 (<1%)	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Pancytopenia	0	0	0	0	0	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	2 (1%)
Vertigo	2 (1%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Acute kidney injury	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0

(Table 2 continues on next
Karten

	Pembrolizumab group (n=149)						Carboplatin plus paclitaxel group (n=144)					
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Meeting serious criteria	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Meeting serious criteria
(Continued from previous page)												
Acute pancreatitis	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Anaphylactic reaction	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	0
Atrial fibrillation	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	0	0
Bacterial meningitis	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Colonic fistula	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
COVID-19	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Dehydration	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Diabetes mellitus	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0
Diabetic ketoacidosis	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Drug-induced liver injury	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Hepatic failure	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Hepatotoxicity	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Hypopituitarism	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Increased blood pressure	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	0	0
Increased lipase	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	0	0
Infectious enterocolitis	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Lymphopenia	0	0	0	0	0	0	1 (<1%)	0	0	1 (<1%)	0	0
Myelosuppression	0	0	0	0	0	0	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)
Nephritis	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)
Pancreatic failure	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	0
Pulmonary embolism	0	0	0	0	0	0	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)
Radiculopathy	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0

Data are n (%). Shown are grade 1–2 adverse events occurring in 10% or more of patients and any grade 3–5 adverse event. Treatment-emergent adverse events are shown in the appendix (pp 21–31). *Due to hepatic failure and bacterial meningitis (n=1 each). †Due to pulmonary embolism (n=1).

Table 2: **Adverse events in the all-participants-as-treated population by maximum grade**

Added value of this study

To our knowledge, this is the first phase 3 study to assess monotherapy with a PD-1 or PD-L1 inhibitor compared with carboplatin plus paclitaxel in the first-line setting for dMMR advanced or recurrent endometrial cancer. The results from the randomised, open-label KEYNOTE-C93/GOG-3064/ENGOT-en15 study, which evaluated efficacy, quality of life, and safety, therefore provide valuable evidence comparing two potential treatment approaches for this patient population. The study did not compare pembrolizumab monotherapy with the current standard of care (immunotherapy plus chemotherapy).

Implications of all the available evidence

Pembrolizumab monotherapy demonstrated a statistically significant progression-free survival benefit over carboplatin plus paclitaxel in the first-line setting for dMMR advanced or recurrent endometrial cancer. The findings suggest that pembrolizumab monotherapy may serve as a potential chemotherapy-sparing first-line treatment approach in this setting.

Bei Säuglingen mit einer unbehandelten HIV-Infektion ist die Pneumocystis-jirovecii-Pneumonie (PjP) die häufigste und gefährlichste Form der Lungenentzündung. Sie tritt besonders oft im Alter von **3 bis 6 Monaten** auf und erfordert sofortiges medizinisches Handeln.

Wichtige Formen der Lungenentzündung bei HIV-positiven Säuglingen

- **Pneumocystis-jirovecii-Pneumonie (PjP).** Diese schwere, durch einen Schlauchpilz ausgelöste Lungenentzündung gilt als Haupttodesursache bei unbehandelten Säuglingen mit HIV. Sie kann sich bereits ab der 4. Lebenswoche entwickeln und verläuft oft sehr schnell.
- **Lymphozytäre interstitielle Pneumonie (LIP).** Diese chronische Lungenerkrankung tritt ebenfalls bei unbehandelten Kindern auf, entwickelt sich aber meist langsamer als die PjP.
- **Bakterielle Lungenentzündungen.** Aufgrund der Immunschwäche sind Säuglinge anfälliger für schwere Infektionen durch Bakterien wie Pneumokokken oder *Haemophilus influenzae*.
- **Virale und andere Erreger.** Auch Infektionen durch das Zytomegalievirus (CMV) oder Tuberkulose-Erreger können die Lunge befallen



Pneumonia in HIV children: routine antibiotics, +anti-pneumocystis plus anti-CMV?

Empirical treatment with valganciclovir in infants living with HIV and hospitalised with severe pneumonia in Africa: a multicentre, open-label, factorial, randomised, controlled, superiority trial

Summary

Background Mortality among infants with severe HIV-associated pneumonia remains high. This trial (EMPIRICAL) tested whether empirical valganciclovir treatment for cytomegalovirus improves survival in infants in Africa.

Methods This multicentre, open-label, group-sequential designed, 2×2 factorial, randomised, controlled, superiority trial was conducted in 19 hospitals across Côte d'Ivoire, Malawi, Mozambique, Uganda, Zambia, and Zimbabwe. Infants aged 28–365 days admitted with severe HIV-associated pneumonia were centrally and individually randomly assigned (1:1:1:1) using a secure web-based system stratified by site and severity to receive standard of care (SOC) comprising treatment for bacterial (WHO-recommended antibiotics) and *Pneumocystis jirovecii* (cotrimoxazole and steroids) pneumonia, SOC plus 15 days of oral valganciclovir (16 mg/kg per 12 h), or SOC plus 6 months of tuberculosis treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, plus isoniazid and rifampicin for 4 subsequent months), or both interventions combined. The primary endpoint was all-cause mortality, assessed at day 15 and over 1-year follow-up in the intention-to-treat population. In this Article, we report results for the valganciclovir comparison groups. The trial is registered with ClinicalTrials.gov, NCT03915366 and is complete.

Findings From March 15, 2020, to Jan 31, 2024, 563 participants were enrolled; 558 were included in the analyses, with 276 allocated to valganciclovir groups (140 valganciclovir; 136 valganciclovir plus tuberculosis treatment) and 282 to groups without valganciclovir (142 SOC; 140 tuberculosis treatment). The median patient age was 4·4 months (IQR 3·2–7·4), and 274 (49%) were female. There was no evidence of interaction between valganciclovir and tuberculosis treatment (adjusted hazard ratio 1·19 [95% CI 0·73–1·95], heterogeneity p=0·48). At day 15, 64 (23%) of 276 participants in the valganciclovir group and 76 (27%) of 282 in groups without valganciclovir died (rate ratio 0·81 [95% CI 0·61–1·08], p=0·15). 24 (9%) of 276 participants and 13 (5%) of 282, respectively, were lost to follow-up. After 12 months, 119 (43%) of 276 participants in the valganciclovir groups and 134 (48%) of 282 in the groups without valganciclovir died (0·88 [95% CI 0·74–1·05] p=0·15). In a time-varying effects model, at day 15, the adjusted hazard ratio of death was 0·60 (95% CI 0·41–0·87, p=0·0063), and their hazard of death over 1 year was 0·79 (0·62–1·01; p=0·068), or 0·76 (0·58–1·00; p=0·0500) when excluding deaths within 48 h of treatment. Severe adverse events during follow-up were not more common in the valganciclovir treatment groups (odds ratio 0·64 [95% CI 0·35–1·16]).

Interpretation Empirical valganciclovir treatment appeared to be associated with a lower hazard of death in infants with severe HIV-associated pneumonia than SOC alone or SOC plus empirical tuberculosis treatment, and there was little evidence of associated harms.

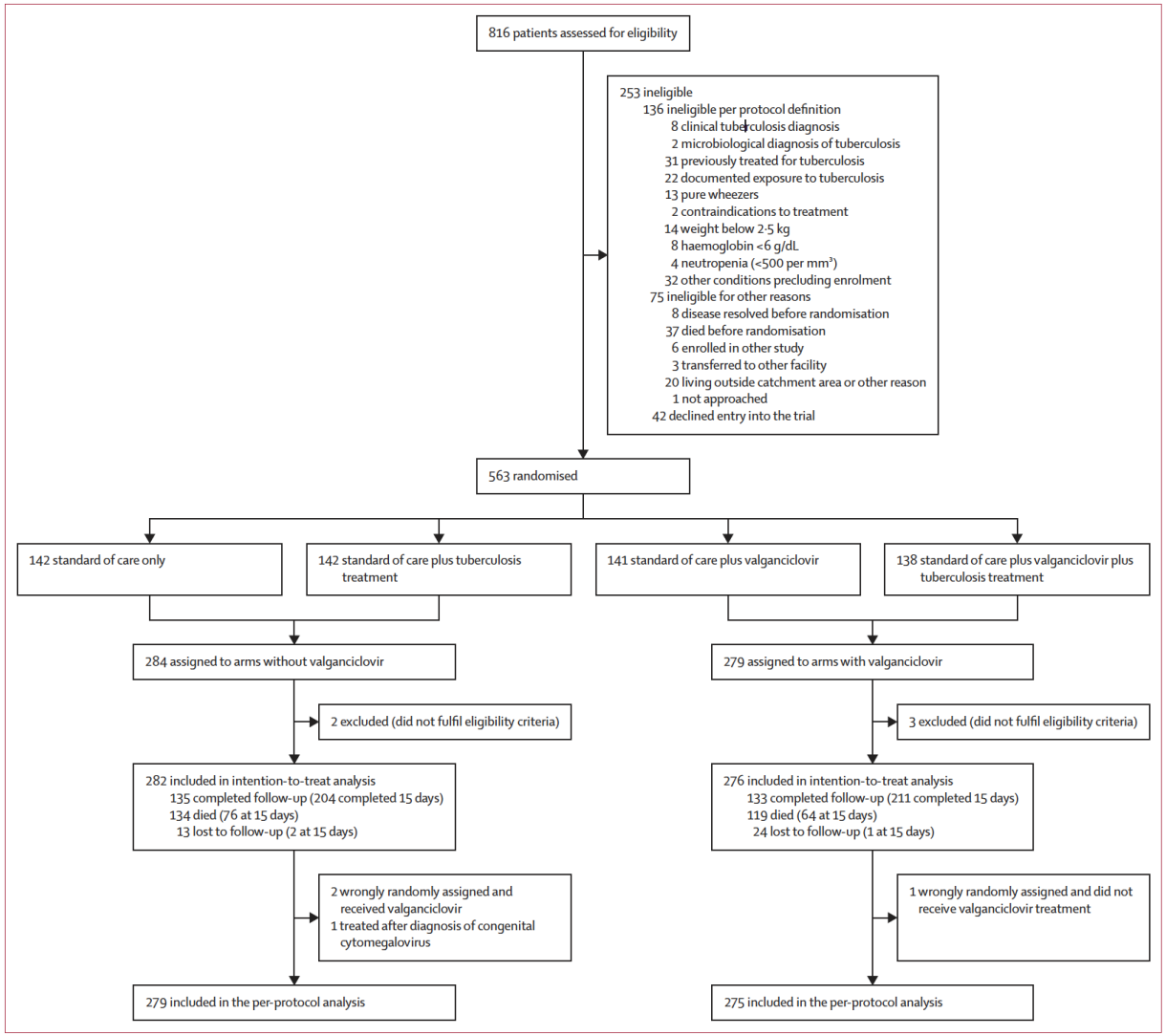


Figure 1: **Trial flowchart**

	Valganciclovir arms (n=276)	Non-valganciclovir arms (n=282)
Demographic characteristics		
Enrolling country		
Mozambique: institution 1*	99 (36%)	101 (36%)
Uganda	68 (25%)	69 (25%)
Zimbabwe	36 (13%)	36 (13%)
Zambia	34 (12%)	37 (13%)
Malawi: institution 2†	18 (7%)	17 (6%)
Malawi: institution 1‡	16 (6%)	16 (6%)
Mozambique: institution 2§	4 (2%)	6 (2%)
Côte d'Ivoire	1 (<1%)	0
Median age (IQR), months	4·6 (3·1–7·3)	4·3 (3·2–7·5)
Female	135 (49%)	139 (49%)
Male	141 (51%)	143 (51%)
Family situation		
Both parents alive	215 (78%)	220 (78%)
Orphaned or mother absent	4 (1·5%)	1 (<1%)
Orphaned or father absent	48 (17%)	55 (20%)
Caregivers other than parents	7 (3%)	4 (1%)
Unknown	2 (<1%)	2 (<1%)
Clinical characteristics		
Oxygen saturation <90% at arrival	172 (63%)	162 (58%)
Respiratory support		
None	41 (15%)	40 (14%)
Nasal cannula	169 (61%)	151 (54%)
CPAP or mechanical ventilation	66 (24%)	90 (32%)
New HIV diagnosis		
No	83 (30%)	77 (27%)
Yes	190 (69%)	205 (73%)
Unknown	3 (1%)	0
ART naive	211 (76%)	221 (78%)
Median HIV RNA logs (IQR), copies per mL	6·2 (5·5–6·9)	6·4 (5·7–7·0)
HIV RNA >5 $\log_{10}$ copies per mL	218 (82%)	228 (84%)
Median CD4 % (IQR), cells per mm^3	15·0 (9·0–23·0)	16·0 (9·7–24·0)
Severe immunosuppression (CD4 <25%)	176 (78%)	180 (75%)
Median baseline weight for length Z score (IQR)¶	−1·6 (−3·2 to 0·4)	−1·3 (−2·8 to −0·0)
Baseline severe malnutrition (≤−3 SD or oedematous malnutrition)	83 (31%)	69 (25%)
Baseline moderate malnutrition (≤−2 SD to >−3 SD)	33 (12·1%)	44 (15·7%)
Median cytomegalovirus viral load in plasma, $\log_{10}$ copies per mL (IQR)	4·3 (3·0–5·4)	4·0 (3·0–5·2)

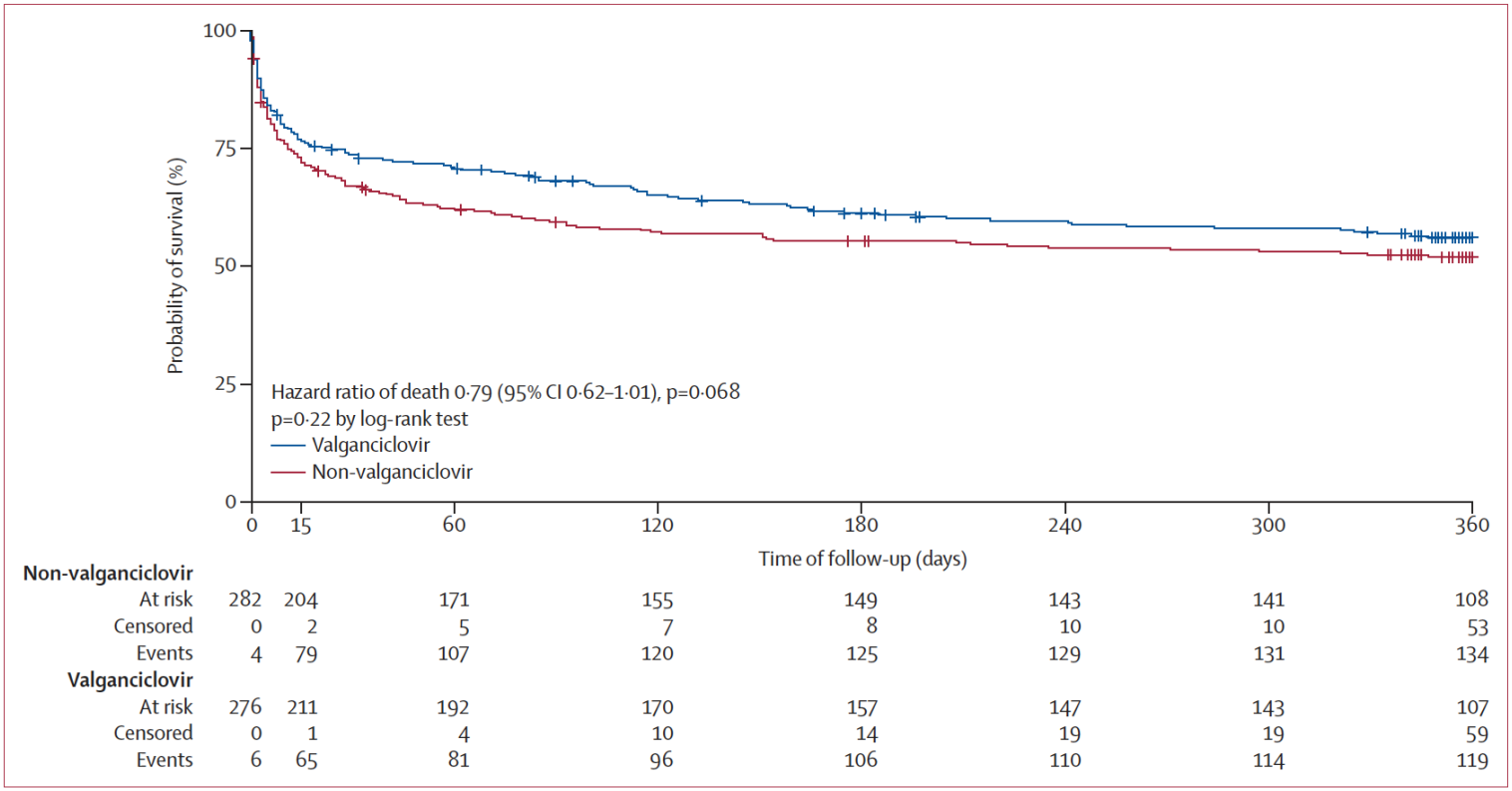
(Table 1 continues on next page)

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	Valganciclovir arms (n=276)	Non-valganciclovir arms (n=282)
Medical history		
Median days from hospitalisation to randomisation (IQR)	2·0 (1·0–4·0)	2·0 (1·0–4·0)
Immunisation schedule complete for age	213 (77%)	209 (74%)
Breastfeeding		
Never	6 (2%)	5 (2%)
Exclusive	125 (45%)	140 (50%)
Mixed	116 (42%)	104 (37%)
Weaned	29 (11%)	33 (12%)
Prophylaxis with cotrimoxazole		
Yes but stopped	8 (3%)	28 (10%)
Ongoing	82 (30%)	68 (24%)
Never	183 (67%)	181 (64%)
Unknown	2 (<1%)	4 (1%)
Baseline antiretroviral regimen		
None	211 (77%)	221 (78%)
2 NRTIs plus lopinavir and ritonavir	17 (6%)	22 (8%)
3 NRTIs	4 (2%)	8 (3%)
2 NRTIs plus nevirapine	2 (<1%)	1 (<1%)
2 NRTIs plus dolutegravir	33 (12%)	27 (10%)
Unknown	9 (3%)	3 (1%)

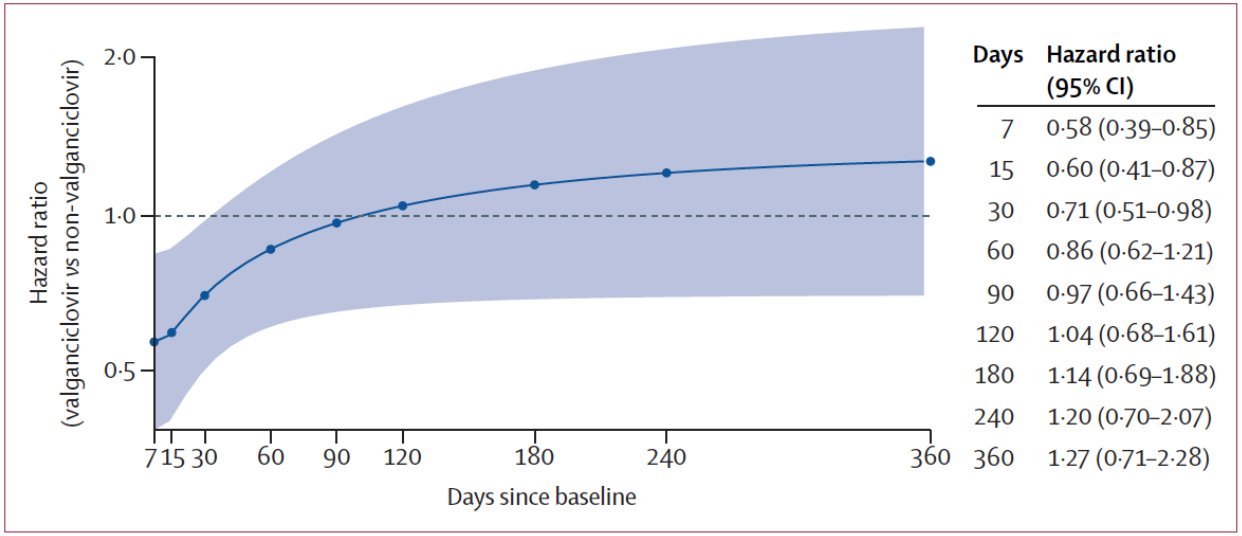
Data are n (%) unless otherwise stated. Percentages might not total 100 due to rounding. ART=antiretroviral therapy. CPAP=continuous positive airway pressure. NRTI=nucleoside reverse-transcriptase inhibitors. *Mozambique institution 1: Universidade Eduardo Mondlane-Maputo and linked hospitals (in Maputo City, Maputo Province, Sofala, and Nampula provinces). †Malawi institution 2: Lilongwe Medical Relief Fund Trust (Lilongwe). ‡Malawi institution 1: Malawi-Liverpool Wellcome Trust (Blantyre). §Mozambique institution 2: CISM-Manhiça and linked hospitals (Maputo Province [Manhiça] and Gaza [Xai-Xai] province). ¶Z scores were calculated using the WHO Child Growth Standards.

Table 1: **Baseline characteristics**



Non-valganciclovir								
At risk	282	204	171	155	149	143	141	108
Censored	0	2	5	7	8	10	10	53
Events	4	79	107	120	125	129	131	134
Valganciclovir								
At risk	276	211	192	170	157	147	143	107
Censored	0	1	4	10	14	19	19	59
Events	6	65	81	96	106	110	114	119

Figure 2: **Kaplan–Meier event curves for death**
Figure created using R.



Days	Hazard ratio (95% CI)
7	0·58 (0·39–0·85)
15	0·60 (0·41–0·87)
30	0·71 (0·51–0·98)
60	0·86 (0·62–1·21)
90	0·97 (0·66–1·43)
120	1·04 (0·68–1·61)
180	1·14 (0·69–1·88)
240	1·20 (0·70–2·07)
360	1·27 (0·71–2·28)

Figure 3: **Time-varying effects model estimates at study timepoints**

Time-varying hazard ratio for valganciclovir versus no valganciclovir. Shaded areas indicate 95% CIs. Adjusted estimates from an stpm2 model with a time-varying effect. Hazard ratios shown represent the estimated hazard ratio at each specific timepoint; they should not be interpreted as average treatment effects over the preceding interval. The estimate at day 360 represents the modelled hazard ratio at day 360 and should not be interpreted as the overall treatment effect over 1 year. These estimates differ from the overall hazard ratio reported in the primary analysis, which assumes a constant treatment effect over follow-up. Figure created using R.

	Valganciclovir arms (n=276)	Non-valganciclovir arms (n=282)	Number of repeated events	Odds ratio (95% CI), p value	Incidence rate ratio (95% CI), p value
Serious adverse events	231 (84%)	220 (78%)	2·0 (1·5)	0·64 (0·35–1·16), p=0·14	0·71 (0·62–0·81), p<0·0001
Adverse events	271 (98%)	273 (97%)	3·8 (2·9)	0·91 (0·21–3·89), p=0·90	1·15 (1·06–1·26), p=0·0020
Neutropenia events	86 (31%)	57 (20%)	1·2 (0·3)	0·77 (0·44–1·37), p=0·38	1·48 (1·07–2·06), p=0·0187
Anaemia events	173 (63%)	159 (56%)	1·2 (0·5)	1·49 (0·77–2·86), p=0·23	1·34 (1·10–1·64), p=0·0041
Thrombocytopenia events	52 (19%)	45 (16%)	1·1 (0·4)	0·54 (0·28–1·03), p=0·062	0·55 (0·35–0·86), p=0·0099
Any infectious disease requiring antimicrobial treatment	215 (78%)	212 (75%)	1·8 (1·1)	0·77 (0·43–1·38), p=0·38	0·80 (0·69–0·93), p=0·0042
Any renal alteration*	10 (4%)	5 (2%)	1·0 (0)	..	..

Data are n (%) or mean (SD) unless otherwise stated. Number of participants with at least one event and mean number of repeated events are included. The median time from enrolment to adverse event occurrences was 5·0 days (IQR 1·0–15·0) in the valganciclovir arms and 5·0 days (2·0–15·0) in the non-valganciclovir arms. Estimates were calculated using a zero-inflated Poisson model. *Low number of events precluded reliable model-based estimation of odds ratio and incidence rate ratio.

Table 2: **Adverse events during follow-up (up to day 360)**

Research in context

Evidence before this study

Data for this review were identified by searches of PubMed and OpenEvidence and references from relevant articles using the search terms "pneumonia" AND "HIV" AND "children" AND "cytomegalovirus (CMV)" (107 results). We searched in registries of trials, including ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and the European Union Drug Regulating Authorities Clinical Trials Database. Searches were done on Oct 1, 2025, and again on Dec 1, 2025. Articles not referring to children living with HIV were excluded. Most papers were case series or reviews, with one prospective cohort; therefore, the risk of bias is high. No trials were found. Abstracts and reports from meetings were included only when they were related directly to previously published work. Only articles published in English between Jan 1, 1985 and Dec 31, 2025 were included. Necropsy studies have previously identified cytomegalovirus (CMV) as a relevant cause of HIV-associated pneumonia in infants, and CMV disease has been recognised frequently as the causal pathway to death in minimally invasive autopsies. However, in the absence of efficacy or effectiveness data of empirical treatment for possible CMV pneumonitis or targeted treatment for confirmed CMV pneumonitis in children living with HIV, WHO does not recommend the use of empirical treatment for children living with HIV with pneumonia. Antivirals are recommended for disseminated CMV infection and retinitis. CMV end-organ disease diagnosis is difficult because it is invasive and requires laboratory capacities that are not available in low-resource settings. There are a few case series from South Africa suggesting a potential benefit of valganciclovir for children living with HIV and severe pneumonia. High CMV viral loads ($\geq$4·1 $\log_{10}$ copies per mL) seem to be associated with CMV disease and mortality.

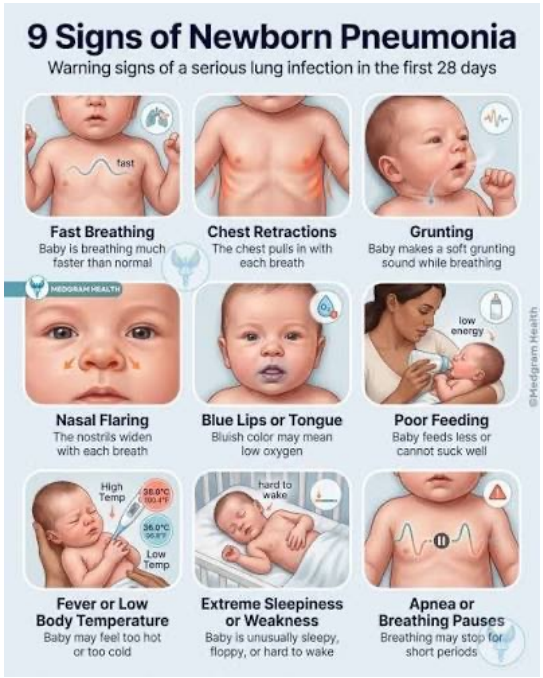
Added value of this study

To our knowledge, this trial shows for the first time that an empirical 15-day course of oral valganciclovir given to infants hospitalised with severe HIV-associated pneumonia reduces mortality, compared with infants who did not receive valganciclovir. The effect was more notable during the first 30 days after treatment commenced, and treatment effect diminished over time and was neutral at the end of the follow-up period. The risk of neutropenia was higher during the first 2 weeks of treatment, but by the end of 1 year it was similar to infants without valganciclovir.

Implications of all the available evidence

CMV is a neglected but potentially life-threatening pathogen in infants with severe HIV-associated pneumonia. This is, to our knowledge, the first trial showing that empirical valganciclovir treatment can reduce mortality in this population. Guidelines should consider the addition of empirical valganciclovir to the current standard of care for infants with severe HIV-associated pneumonia.

Bei Säuglingen mit einer unbehandelten HIV-Infektion stellen schwere Lungenentzündungen (Pneumonien) und Tuberkulose (TBC) lebensbedrohliche Komplikationen dar, da ihr Immunsystem noch unreif ist und zusätzlich geschwächt wird**.** Eine frühzeitige Diagnose und Therapie dieser Infektionen ist entscheidend, da opportunistische Erkrankungen bei Kindern oft rasch und schwer verlaufen.



1. Fachbegriffe im Überblick

- **Infants (Säuglinge).** Kinder im ersten Lebensjahr, die sich meist vor, während oder nach der Geburt (perinatal) über die Mutter mit HIV infiziert haben.
- **HIV (Humanes Immundefizienz-Virus).** Ein Virus, das gezielt Abwehrzellen des Körpers (CD4-Zellen) zerstört und ohne Behandlung zu einer schweren Immunschwäche führt.
- **Pneumonia (Lungenentzündung).** Eine akute oder chronische Entzündung des Lungengewebes, die bei HIV-infizierten Säuglingen durch Bakterien, Viren oder spezielle Pilze ausgelöst wird.
- **TBC (Tuberkulose).** Eine durch Bakterien (*Mycobacterium tuberculosis*

Empirical tuberculosis treatment in infants living with HIV hospitalised with severe pneumonia in Africa (EMPIRICAL): a multicentre, randomised, open-label, 2 × 2 factorial, controlled superiority trial

Pneumonia in HIV children: routine antibiotics, +anti-pneumocystis plus anti-TBC?

Summary

Background Mortality among infants with severe HIV-associated pneumonia remains high globally. The EMPIRICAL trial evaluated whether empirical tuberculosis treatment (eTB-T) improves survival compared with the currently recommended microbiologically and clinically guided strategy.

Methods This multicentre, open-label, group-sequential designed, 2×2 factorial, randomised, controlled, superiority trial was conducted in 19 hospitals across Côte d'Ivoire, Malawi, Mozambique, Uganda, Zambia, and Zimbabwe. Infants aged 28–365 days admitted with severe HIV-associated pneumonia, without a current tuberculosis diagnosis or contact, were centrally and individually randomly assigned (1:1:1:1) using a secure web-based system stratified by site and severity. A computer-generated block randomisation schedule was used, with fixed blocks of eight allocations (two allocations to each factorial treatment group) within each stratum. Participants received standard of care (SoC) comprising treatment for bacterial (WHO-recommended antibiotics) and *Pneumocystis jirovecii* (cotrimoxazole and steroids) pneumonia, SoC plus 15 days of oral valganciclovir (16 mg/kg per 12 h), or SoC plus 6 months of tuberculosis treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, plus isoniazid and rifampicin for 4 subsequent months), or both interventions combined. Here, we report the comparison between the eTB-T (ie, SoC plus tuberculosis treatment and SoC plus oral valganciclovir plus tuberculosis treatment) and non-eTB-T (ie, SoC or SoC plus 15 days of oral valganciclovir) groups. Nasopharyngeal aspirates, stools for Xpert MTB/RIF Ultra testing, and urine for tuberculosis lipoarabinomannan assay were collected at recruitment. In the non-eTB-T groups, tuberculosis treatment was initiated if microbiological results collected at recruitment yielded positive results or if, during follow-up, the treating clinician suspected tuberculosis on clinical grounds, including radiological findings, in accordance with routine clinical practice and guidelines. The primary endpoint was all-cause mortality (at 15 days and 360 days). Survival was estimated using flexible parametric models with covariate-adjusted conditional estimates; missing data were imputed by chained equations. The trial is registered with ClinicalTrials.gov (NCT03915366) and is now complete.

Findings Between March 15, 2020, and Jan 31, 2024, 563 participants were enrolled; 558 were analysed after excluding five patients who did not meet eligibility criteria. 276 participants were allocated to the eTB-T groups (n=140 eTB-T and n=136 valganciclovir plus eTB-T) and 282 to the non-eTB-T groups (n=142 SoC and n=140 valganciclovir). 17 (6%) of 276 in the eTB-T groups and 20 (7%) of 282 in the non-eTB-T groups were lost to follow-up. Median age was 4·4 months (IQR 3·2–7·4) and 274 (49%) of participants were female and 284 (51%) were male. In the non-eTB-T groups, 130 (46%) of 282 participants eventually initiated tuberculosis treatment at a median of 4·0 days (IQR 3·0–15·0) after recruitment due to positive microbiological findings in 55 (20%) cases (53 confirmed by tuberculosis lipoarabinomannan assay and two by nasopharyngeal aspirates Xpert MTB/RIF) or clinical decision in 75 (27%) cases. There was no evidence of interaction between valganciclovir and eTB-T (adjusted hazard ratio 1·19, 95% CI 0·73–1·95; $p_{heterogeneity}$=0·4836). At 12 months, 132 (48%) of 276 participants in eTB-T groups and 121 (43%) of 282 participants in non-eTB-T groups died. In the eTB-T groups, the adjusted hazard ratio for death was 1·12 (95% CI 0·87–1·43; p=0·3868). At 15 days, the odds ratio was 1·24 (95% CI 0·83–1·84; p=0·2950). Serious adverse events did not differ between groups (1·19, 0·82–1·73; p=0·3523). There were no treatment-related deaths. The most common adverse events were elevation of transaminases (72 [26%] cases in the eTB-T groups and 74 [26%] in the non-eTB-T group), anaemia (163 [59%] cases in the eTB-T groups and 169 [60%] in the non-eTB-T groups), and infectious disease requiring antimicrobial treatment (161 [58%] cases in the eTB-T groups and 176 [62%] in the non-eTB-T groups).

Interpretation In contrast to empirical treatment with valganciclovir, there was no evidence that eTB-T was superior to a clinically and microbiologically guided strategy in reducing all-cause mortality among infants with HIV-associated pneumonia. However, the high proportion of infants who eventually initiated tuberculosis treatment during follow-up in the non-eTB-T groups might have reduced the contrast between strategies and attenuated the ability to detect differences in outcomes.

	eTB-T groups (n=276)	Non-eTB-T groups (n=282)	Total (N=558)
Demographic characteristics			
Enrolling country			
Mozambique: institution 1*	99 (36%)	101 (36%)	200 (36%)
Uganda	69 (25%)	68 (24%)	137 (25%)
Zimbabwe	35 (13%)	37 (13%)	72 (13%)
Zambia	35 (13%)	36 (13%)	71 (13%)
Malawi: institution 2†	18 (7%)	17 (6%)	35 (6%)
Malawi: institution 1‡	15 (5%)	17 (6%)	32 (6%)
Mozambique: institution 2§	5 (2%)	5 (2%)	10 (2%)
Côte d'Ivoire	0	1 (<1%)	1 (<1%)
Median age (IQR), months	4·5 (3·2–7·8)	4·2 (3·1–7·1)	4·4 (3·2–7·4)
Sex			
Female	136 (49%)	138 (49%)	274 (49%)
Male	140 (51%)	144 (51%)	284 (51%)
Family situation			
Both parents alive	216 (78%)	219 (78%)	435 (78%)
Orphaned or mother absent	2 (1%)	3 (1%)	5 (1%)
Orphaned or father absent	47 (17%)	56 (20%)	103 (18%)
Caregivers other than parents	9 (3%)	2 (1%)	11 (2%)
Unknown	2 (1%)	2 (1%)	4 (1%)
Clinical characteristics			
Oxygen saturation <90% at arrival	167 (61%)	168 (60%)	335 (60%)
Respiratory support			
No	39 (14%)	42 (15%)	81 (15%)
Nasal cannula	161 (58%)	159 (56%)	320 (57%)
CPAP or mechanical ventilation	76 (28%)	80 (28%)	156 (28%)
New HIV diagnosis¶			
No	75 (27%)	85 (30%)	160 (29%)
Yes	201 (73%)	194 (69%)	395 (71%)
Unknown	0	3 (1%)	3 (1%)
ART naive	217 (79%)	215 (76%)	432 (77%)
HIV RNA logs (IQR), copies per mL	6·3 (5·6–7·0)	6·28 (5·6–7·0)	6·3 (5·6–7·0)
HIV RNA >5 $\log_{10}$ copies per mL	228 (85%)	218 (81%)	446 (83%)
CD4 T-cell percentage (IQR)	15·9% (10·0–25·0)	15·0% (9·0–21·9)	15·3% (9·6–23·2)
Severe immunosuppression (CD4 <25%)	176/266 (78%)	180/240 (75%)	356/466 (76%)
Median baseline weight for length Z score (IQR)‖	−1·5 (−3·2 to −0·3)	−1·36 (−2·8 to −0·1)	−1·5 (−3·0 to −0·2)
Baseline severe malnutrition (≤−3 SD weight-for-length)	76 (28%)	64 (23%)	140 (25%)
Baseline moderate malnutrition (≤−2 to ≥−3 SD weight-for-length)	36 (13%)	41 (15%)	77 (14%)
Tuberculosis microbiologically confirmed**	68 (25%)	73 (26%)	141 (25%)
Urinary TB-LAM positive	62/238 (26%)	65/252 (26%)	127/490 (26%)
NPA Xpert MTB/RIF Ultra positive††	4/193 (2%)	6/282 (2%)	10/479 (2%)
Stool Xpert MTB/RIF Ultra positive	9/257 (4%)	10/263 (4%)	19/520 (4%)
Mycobacterium tuberculosis-positive culture	0	1/33 (3%)	1/65 (2%)

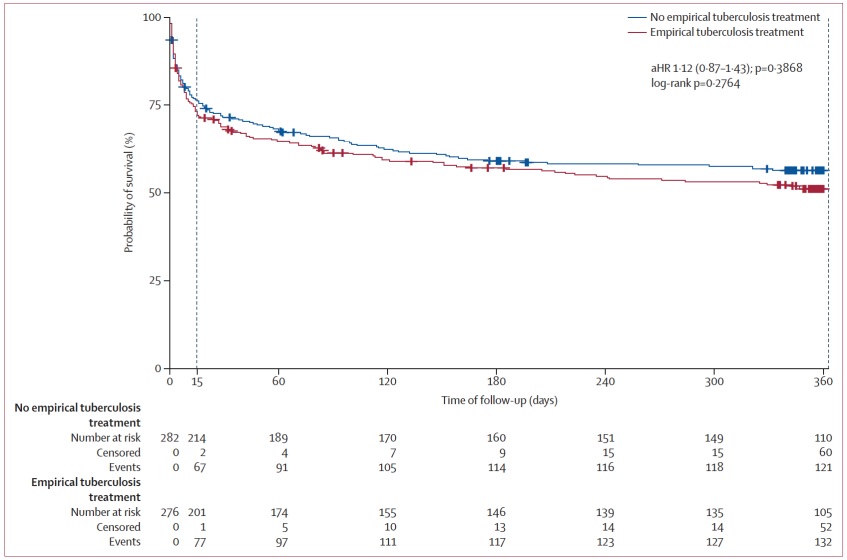
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	eTB-T groups (n=276)	Non-eTB-T groups (n=282)	Total (N=558)
Medical history			
Median days from hospitalisation to randomisation (IQR)	2·00 (1·00–4·00)	2·00 (1·00–4·00)	2·00 (1·00–4·00)
Immunisation schedule complete for age	212 (77%)	210 (74%)	422 (76%)
BCG immunisation	258 (93%)	253 (90%)	511 (92%)
Breastfeeding			
Never	6 (2%)	5 (2%)	11 (2%)
Exclusive	116 (42%)	149 (53%)	265 (47%)
Mixed	113 (41%)	107 (38%)	220 (39%)
Weaned	41 (15%)	21 (7%)	62 (11%)
Prophylaxis with cotrimoxazole			
Yes, but stopped	19 (7%)	17 (6%)	36 (6%)
Ongoing	81 (29%)	69 (25%)	150 (27%)
Never	174 (63%)	190 (68%)	364 (65%)
Unknown	1 (<1%)	5 (2%)	6 (1%)
Baseline antiretroviral therapy regimen			
None	217 (79%)	215 (76%)	432 (77%)
2 NRTIs plus lopinavir and ritonavir	11 (4%)	28 (10%)	39 (7%)
3 NRTIs	12 (4%)	0	12 (2%)
2 NRTIs plus nevirapine	0	3 (1%)	3 (1%)
2 NRTIs plus dolutegravir	30 (11%)	30 (11%)	60 (11%)
Unknown	6 (2%)	6 (2%)	12 (2%)
Tuberculosis treatment eventually initiated on clinical and microbiological grounds‡‡	NA	130 (46%)	130 (23%)
Following clinical decision	NA	75 (27%)	75 (13%)
Due to positive TB-LAM	NA	53 (19%)	53 (9%)
Due to positive NPA Xpert MTB/RIF Ultra	NA	2 (1%)	2 (<1%)
Median time from randomisation to tuberculosis treatment, days (IQR)	NA	4·0 (3·0–15·0)	4·0 (3·0–15·0)
Tuberculosis treatment initiated due to randomisation error	NA	2 (1%)	2 (<1%)

Data are n (%), median (IQR), or n/N (%). Percentages might not total 100% due to rounding. CPAP=continuous positive airway pressure. eTB-T=empirical tuberculosis treatment. NA=not applicable. NPA=nasopharyngeal aspirate. NRTI=nucleoside reverse-transcriptase inhibitor. TB-LAM=tuberculosis lipoarabinomannan. *Universidade Eduardo Mondlane-Maputo and linked hospitals (in Maputo City, Maputo Province, Sofala, and Nampula provinces). †Lilongwe Medical Relief Fund Trust (Lilongwe). ‡Malawi Liverpool Wellcome Trust (Blantyre). §Centro de Investigação em Saúde de Manhiça–Manhiça and linked hospitals (in Maputo Province [Manhiça] and Gaza [Xai-Xai] provinces). ¶New HIV diagnosis means that the HIV status was unknown before admission, and positive HIV status was discovered at admission. ‖Z scores were calculated using the WHO Child Growth Standards. **The total number of positive confirmatory tests does not equal 141 because individual participants could have multiple positive tests. ††The data of rifampicin resistance was recorded in nine participants and one was detected to be resistant; this patient was treated with a tuberculosis regimen without rifampicin following national guidelines. ‡‡No tuberculosis treatment was initiated due to positive stool Xpert MTB/RIF Ultra or positive *Mycobacterium tuberculosis* culture.

Table 1: **Baseline characteristics**



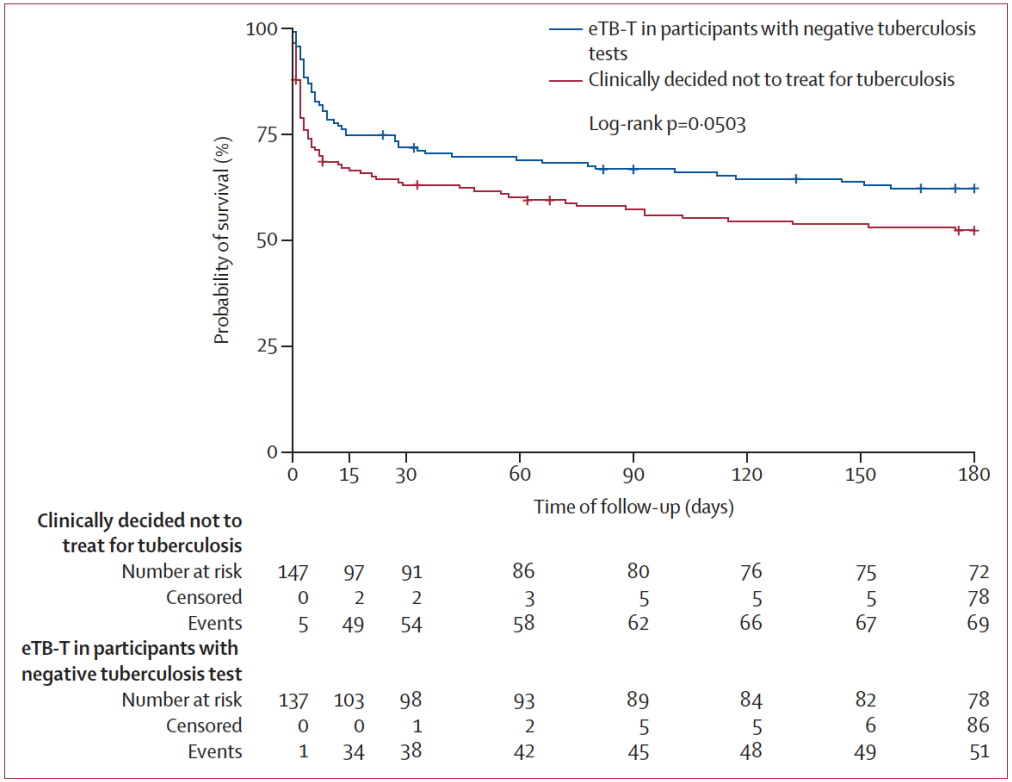
No empirical tuberculosis treatment								
Number at risk	282	214	189	170	160	151	149	110
Censored	0	2	4	7	9	15	15	60
Events	0	67	91	105	114	116	118	121
Empirical tuberculosis treatment								
Number at risk	276	201	174	155	146	139	135	105
Censored	0	1	5	10	13	14	14	52
Events	0	77	97	111	117	123	127	132

Figure 2: **Kaplan–Meier event curves for death**
Dashed vertical lines indicate the 15-day and 1-year assessment timepoints. aHR=adjusted hazard ratio.

	eTB-T groups (n=276)	Non-eTB-T groups (n=282)	Number of repeated events	Odds ratio (95% CI), p value	Incidence rate ratio (95% CI),* p value
All adverse events (other than tuberculosis)	262 (95%)	267 (95%)	3·5 (2·8)	0·91 (0·41–2·03); p=0·8127	1·26 (1·11–1·69); p<0·0001
Serious adverse events (other than tuberculosis)	194 (70%)	189 (67%)	1·9 (1·3)	1·19 (0·82–1·73); p=0·3523	1·07 (0·91–1·25); p=0·4313
Elevation of transaminases	72 (26%)	74 (26%)	1·2 (0·4)	0·93 (0·54–1·37); p=0·7434	0·97 (0·62–1·53); p=0·9090
Anaemia	163 (59%)	169 (60%)	1·3 (0·5)	0·93 (0·65–1·32); p=0·6879	1·05 (0·86–1·28); p=0·6450
Thrombocytopenia	52 (19%)	45 (16%)	1·1 (0·3)	1·29 (0·82–2·04); p=0·2611	0·97 (0·63–1·48); p=0·8802
Tuberculosis diagnosis†	76 (28%)	138 (49%)	1 (0·1)	0·38 (0·27–0·55); p<0·0001	0·85 (0·59–1·25); p=0·4135
IRIS‡	13 (5%)	11 (4%)	0	1·32 (0·57–3·08); p=0·5140	NA§
Any infectious disease requiring antimicrobial treatment (other than tuberculosis)	161 (58%)	176 (62%)	1·6 (1·0)	0·85 (0·60–1·21); p=0·1369	1·12 (0·92–1·36); p=0·2548

Data are n (%) or mean (SD) unless otherwise stated. Number of participants with at least one event and the mean number of repeated events are shown. eTB-T=empirical tuberculosis treatment. IRIS=immune reconstitution inflammatory syndrome. NA=not applicable. *Estimates were calculated using a zero-inflated Poisson model. †214 tuberculosis events in 558 participants, with 29 participants presenting tuberculosis as a unique event. ‡Among the 24 participants who developed IRIS, three died during follow-up (two in the eTB-T groups and one in the non-eTB-T groups). IRIS was not considered part of the causal chain of death in any of these participants following death adjudication. §No repeated incidents were observed.

Table 2: **Adverse events to end of follow-up (up to day 360)**



Clinically decided not to treat for tuberculosis								
Number at risk	147	97	91	86	80	76	75	72
Censored	0	2	2	3	5	5	5	78
Events	5	49	54	58	62	66	67	69
eTB-T in participants with negative tuberculosis test								
Number at risk	137	103	98	93	89	84	82	78
Censored	0	0	1	2	5	5	6	86
Events	1	34	38	42	45	48	49	51

Figure 3: **Post-hoc survival analysis comparing mortality in participants in the eTB-T group with negative baseline tuberculosis tests compared with participants in the non-eTB-T group who were not treated for tuberculosis based on clinical decision**
Survival probabilities are shown over 180 days of follow-up. eTB-T=empirical tuberculosis treatment.

Implications of all the available evidence

In people with advanced HIV disease, including adults and children with severe immunosuppression, sepsis, or severe pneumonia, available evidence, including the present trial, indicates that empirical treatment against tuberculosis does not confer a survival benefit over strategies that prioritise early and concurrent microbiological diagnosis. Tuberculosis seems to be part of the chain of events leading to death even in infants treated for tuberculosis, which might be related to low levels of tuberculosis treatment, resistance, or co-infections. Uncertainty remains about the role of empirical treatment in settings where concurrent diagnostic tools are unavailable or cannot be implemented promptly. Current evidence supports prioritising investment in improved tuberculosis diagnostics in high-burden settings. Our findings suggest that eTB-T might be beneficial in settings where access to skilled clinicians, chest radiography, or tuberculosis diagnostic tests are restricted, or in some infants with negative tests; however, this requires confirmation in prospective studies.

A *Lancet* Commission on the Health and Poverty Alleviation Initiative in China

Executive summary

Poverty alleviation is a pressing global challenge that is intricately linked with health, as emphasised by the Sustainable Development Goals (SDGs). In 2019, out-of-pocket health expenditure—health-care costs paid directly by individuals or households rather than covered by insurance or other third-party payers—pushed an additional 344 million people into poverty globally. In 2020, 724 million people were living in extreme poverty, defined as living on less than US$2·15 per person per day at 2017 purchasing power parity, 90 million more than the pre-COVID-19 pandemic UN projection. When prioritising economic development and growth, governments often overlook the intrinsic link between ill health and poverty, an oversight that is reflected in the poor integration of health into poverty-reduction strategies of low-income and middle-income countries.

Over the past few decades, China has made progress in poverty alleviation due not only to rapid socioeconomic growth, but also to its campaign to eliminate poverty-related illness. Launched in 2015, China's Health and Poverty Alleviation Initiative was a pioneering effort to integrate health into its national poverty reduction strategy, and contributed to China achieving its ambitious goal of eradicating extreme poverty by 2020. The campaign was underpinned by values of equity and inclusivity and has evolved from fragmented medical and welfare programmes into universal coverage and so-called last mile efforts, which target the most vulnerable people.

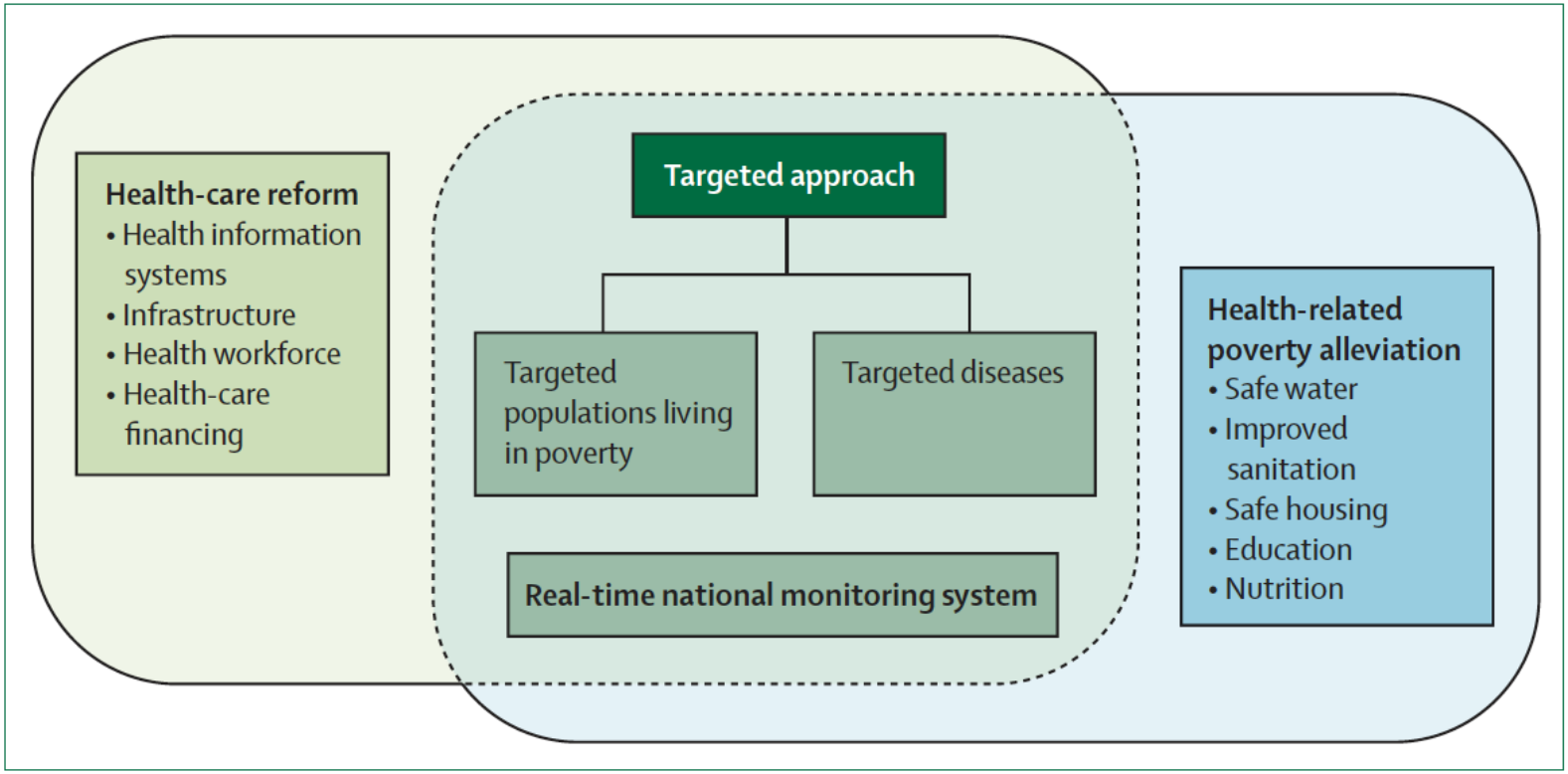


Figure 1: **Health and poverty alleviation**

Key messages

- Despite the strong link between ill health and poverty, health considerations are often inadequately integrated into poverty alleviation strategies around the world.
- Between 2015 and 2020, China lifted approximately 55·8 million people (around 4% of its population) out of poverty, ending absolute poverty in all counties.
- Between 2015 and 2020, China's central government invested a total of CN¥1·4 trillion (approximately US$215·6 billion) into the Health and Poverty Alleviation Initiative, representing an average annual growth rate of 11·6% in funding.
- China's Health and Poverty Alleviation Initiative integrates efforts across health, water, sanitation, housing, nutrition, and education to address the root causes of poverty and health disparities and emphasise the need for a coordinated, multisectoral framework for poverty reduction.
- In this initiative, a targeted approach using verified sociodemographic data and real-time national monitoring enabled precise identification of households at high risk of poverty, ensuring that assistance reached those most in need.
- The initiative built upon previous health-care reforms and prioritised the enhancement of both health-care delivery and financing to better serve people living below the poverty line.
- Financial protection and service coverage for people living below the poverty line improved substantially: their share of out-of-pocket inpatient expenditure among total inpatient expenditure declined from 41·0% in 2013 to 31·0% in 2018, treatment rates for 30 curable severe diseases reached 99·6%, and hypertension control increased from 33·0% in 2019 to 45·4% in 2022. These improvements were accompanied by accelerated gains in access to safe water, sanitation, and housing among people living below the poverty line, narrowing equity gaps.
- Despite progress, China's Health and Poverty Alleviation Initiative faces challenges, including financial sustainability, continued urban–rural health disparities, rising incidence of non-communicable diseases, evaluation difficulties, and threats such as population ageing, climate change, pandemics, technological shifts, and the digital divide.
- China's health-related poverty alleviation efforts need to evolve from campaign-based action into a long-term, institutionalised model, addressing structural weaknesses, adapting to changing socioeconomic and environmental conditions, and strengthening the resilience of social support and health-care systems.
- For other low-income and middle-income countries, integrating health as a core pillar of poverty alleviation could transform health investment into a powerful driver of sustainable poverty reduction. Strong multisectoral coordination and data-driven precision targeting, in alignment with health system reforms, are essential to ensure resources reach people who are most in need and achieve equitable impact.

Ambient Scribes (übersetzt etwa **„mithörende Schreiber“** oder **KI-basierte Hintergrunddokumentation**) sind KI-gestützte Softwarelösungen für das Gesundheitswesen, die Arzt-Patienten-Gespräche im Hintergrund mithören und automatisch in strukturierte medizinische Notizen umwandeln. Im Gegensatz zu klassischer Spracherkennung muss das medizinische Personal dabei nicht mehr aktiv diktieren oder tippen.



Funktionsweise in drei Schritten

Laut dem Ratgeber von basebox läuft die Software auf einem Computer, Tablet oder Smartphone während der Sprechstunde mit und verarbeitet das Gesprochene automatisch:

- **Transkription.** Eine Spracherkennung wandelt das gesprochene Wort in Text um und unterscheidet dabei zwischen verschiedenen sprechenden Personen.
- **Strukturierung.** Ein KI-Modell filtert die relevanten medizinischen Inhalte heraus und ordnet sie nach Praxisvorlagen (z. B. Anlass, Anamnese, Befund, Beurteilung und Plan).
- **Übernahme.** Ärztinnen oder Ärzte prüfen den fertigen Entwurf, nehmen bei Bedarf Korrekturen vor und übertragen ihn in die Patientenakte oder das Praxisverwaltungssystem.

Vorteile im Praxisalltag

- **Weniger Bürokratie.** Die Technologie reduziert den administrativen Schreibaufwand und spart Zeit nach der Sprechstunde.
- **Mehr Fokus auf Patientinnen und Patienten.** Da der Blick nicht mehr ständig auf den Bildschirm gerichtet sein muss, verbessert sich die direkte Interaktion während der Behandlung.
- **Zusatzfunktionen.** Viele moderne Systeme wie smartSCRIBE oder vergleichbare Lösungen schlagen zusätzlich Diagnose- und Abrechnungscodes vor oder erstellen direkt Entwürfe für Überweisungs- und Arztbriefe.

Ambient scribes as narrative technologies

Ambient scribes, also known as artificial intelligence-powered voice-to-text technology, are widely cited as time-saving tools that reduce administrative burden for clinicians. Yet, in their current use, these tools pose substantial, often unacknowledged risks that threaten to undermine patient-centred care. We argue that ambient scribes are inherently narrative technologies whose risks—and potential benefits—cannot be fully understood without careful attention to the ways that patients tell their stories and the broader context in which those stories are told. Drawing on medical humanities scholarship, we show that current approaches to ambient scribes take a superficial approach to narrative interpretation that omits the clinically relevant aspects of patient experience. We propose three ways to integrate more robust narrative analysis that can increase the value of ambient scribes: centring patient perspectives, accounting for material and social structures that shape narrative, and reframing the clinical encounter as a node in a broader narrative system. We conclude by outlining five priorities for commissioners, administrators, clinical leaders, and practice managers to ensure that the roll-out of ambient scribes does not deepen existing harms, and could instead contribute to more humane and trustworthy care.

Ambient scribes are now among the most heavily promoted artificial intelligence (AI) tools in health care.[1] The UK National Health Service (NHS) approved 19 suppliers for use across the NHS in early 2026,[2] and ambient voice technologies sit at the heart of the NHS 10-year plan for England.[3] In the USA, adoption is also rapid, but unaccompanied by a specific regulatory framework: ambient scribes fall outside the definition of a medical device and so are not subject to review by the US Food and Drug Administration.[4] In both settings, adoption has run ahead of the evidence and of any serious regulatory oversight.[5]

We write from the medical humanities, where the clinical encounter has long been understood as a site of meaning–making and interpretation rather than simply a transactional exchange of information.[6,7] From this perspective, current debates about ambient scribes seem oddly narrow. Ambient scribes are most commonly described as documentation aids optimised for speed and accuracy: AI stenographers. Recognising these tools as narrative technologies is essential to understanding what they do, and what should be asked of them, both in and beyond the clinical setting.

Ambient scribes use automatic speech recognition and large language models (LLMs) to generate clinical notes from a recorded consultation.[8] Ambient scribes are being introduced into a remarkably diverse set of systems: primary and secondary care; different national regulatory environments and digital infrastructures; and patient populations with different relationships to medical institutions. This diversity is rarely acknowledged in the dominant framing of ambient scribes, which tends to present this tool as a universal solution to physician burnout, documentation burden, and the depersonalisation of care.[9]

The evidence base is mixed on whether or not ambient scribes save time or increase efficiency and accuracy,[10,11] particularly when the time and attention required for the careful review of AI scribe notes is taken into account.[12] For these reasons, it could be premature to embrace AI scribes so confidently and invest so heavily in them.[13] Two recent randomised controlled trials report low rates of fabrications and omissions,[14,15] which is reassuring but not yet conclusive, given the small number of trials, insufficient settings examined, and broader literature dominated by perspectives, editorials, and early-stage pilot studies. Almost all of this work approaches the question of time saved and increased efficiency from the clinician's vantage point. Patient experience is rarely the primary outcome, and, where included, it is typically captured through narrow instruments such as likelihood to recommend scores rather than through patients' own accounts.[16]

	Who needs to act*	How to operationalise
Patient narratives are flattened		
Patient's emotional tone, hesitancy or certainty, and specific concerns could be omitted by transcript, thereby losing important information	Developers	Co-produce scribe technology with clinicians and patients; enable patients to address the ambient scribe directly; empower patient review panels to review transcripts for quality control; and use fidelity to the patient narrative as a procurement criterion alongside speed and cost
Patients might withhold information		
Discomfort with surveillance, particularly for members of vulnerable groups, could lead to patients withholding their full lived experience	Clinicians and clinical leads	Enact a robust process of ensuring patients consent to the use of ambient scribes, with mechanisms for tailoring the tool to patient preferences in real time; routinely explain how clinical notes are generated, stored, reviewed, and used; and ensure that robust and sustained patient and public involvement shapes decisions about whether and how ambient scribes are introduced
Bias and inequity are entrenched		
Ambient scribes could automate and minimise the inequities that are known to exist within health-care and generative AI systems	Regulators and policy makers	Ensure that scribes are validated with diverse populations; require transparency of training data and validation; and make representativeness a condition of procurement and regulatory approval
Generic institutional narratives are reproduced		
AI models rely on statistical probability and reproduce the most common storylines about patients, according to values of efficiency, risk management, and compliance; shared decision-making about patient priorities, values, and goals of care are limited by the model's programmed parameters for what counts as a good outcome	Regulators and policy makers	Push for technology that is optimised for the delivery of better health outcomes, rather than only efficiency, cost savings, or increased revenue; limit design choices that are primarily intended to capture the greatest complexity of the patient for billing purposes, where this applies; and define outcome measures that are concordant with patient priorities, including trust, recognition, and the experience of being heard, rather than relying on standardised satisfaction scores designed for other purposes
Narrative is distorted across the record over time		
Ambient scribe outputs are not transcriptions of discrete encounters but summaries that shape a patient's story over time, affecting interactions across visits, clinicians, and institutional contexts	Researchers	Commission longitudinal evaluation of how patients' narratives are subtly compressed or transformed over repeated encounters in ways that shape subsequent interpretation and care; support clinicians to occupy their new role as editors rather than authors of patient records; and educate clinicians to recognise when an AI-generated clinical note misrepresents an event
Accountability is unclear and AI literacy is low		
Clinicians are not trained in ambient scribe use, and are not given time during clinical encounters to explore the opportunities and constraints of these tools with their patients; neither clinicians nor patients have a real say in the design or governance of these systems	Educators and professional bodies	Embed critical AI literacy in clinical training, continuing professional development, and patient information; form patient AI advisory committees to provide a holistic safety assessment of ambient scribes against cultural and ethical safety guidelines; and ensure clinician and patient involvement in governance setting limits on data storage, use, and re-use

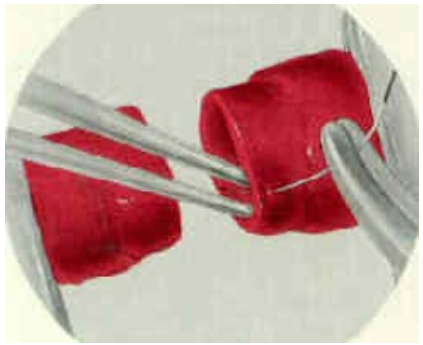
AI=artificial intelligence. *In practice, the health–AI system requires involvement at varying levels from all stakeholders listed in this table and patients.

Table: **Risks and responsibilities**

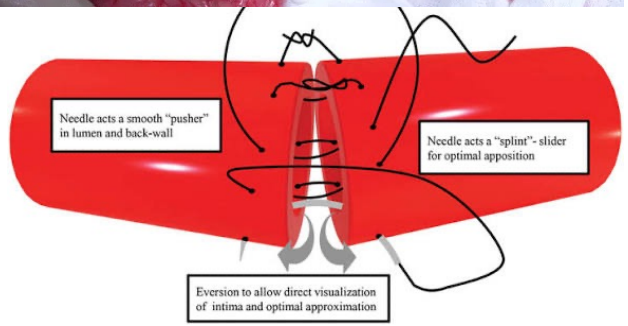
Suturing small blood vessels together is called microvascular anastomosis, a delicate surgical technique used to reconnect tiny vessels like arteries and veins during procedures like reattaching a severed finger, performing free flap tissue reconstruction, or bypassing blocked channels.

Key Aspects of the Process

- **Microscope and Special Tools:** Surgeons work under an operating microscope using ultra-fine instruments, jeweler's forceps, and tiny needle holders.
- **Micro-Sutures:** The procedure typically uses **9–0 or 10–0 monofilament nylon** sutures attached to tapered, non-cutting needles that are thinner than a human hair.
- **Vessel Preparation:**
  - The damaged or severed ends are cleanly trimmed and flushed with heparinized saline to clear out blood.
  - The outer layer of tissue (the **adventitia**) is carefully trimmed back from the edge so it doesn't get pulled into the stitch line and cause a dangerous clot.
  - A micro-dilator is gently inserted to slightly widen the opening







The **integrated microneedle-interlocking adhesive system (iMAS)** is a bioinspired, sutureless surgical bioadhesive platform designed to connect small-caliber blood vessels (microvascular anastomosis) and continuously monitor tissue health.

Structural Design & Adhesion Mechanism
Inspired by how underwater plant roots anchor into wet soil, iMAS overcomes the limitations of traditional surgical sutures and conventional glues in dynamic, fluid-rich surgical environments.

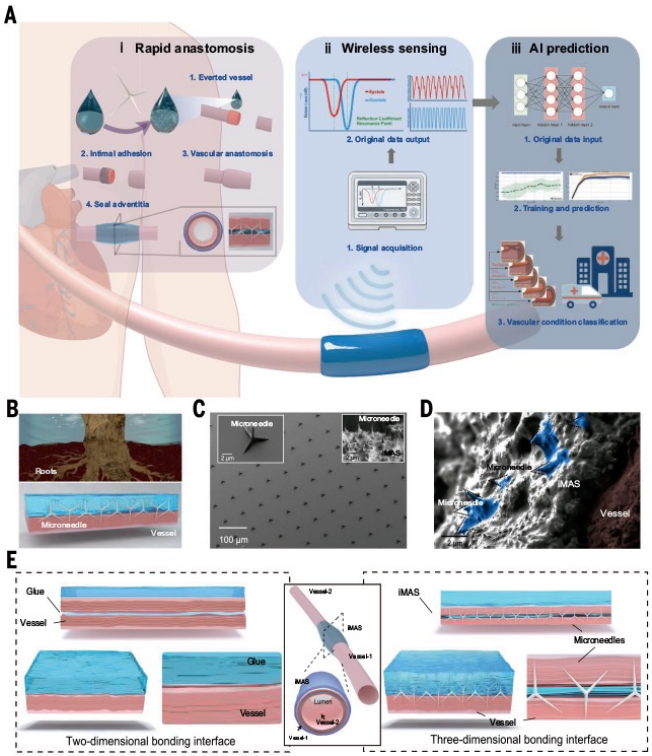
3D-Printed Microneedle "Roots". The system features a three-dimensional, four-armed, radially symmetric microneedle framework. Its tetrahedral skeleton penetrates and physically interlocks with the blood vessel wall to provide immediate mechanical stability.

Hydrophobic Polymer Matrix. A silicone-based dissipative adhesive matrix surrounds the microneedles. This hydrophobic polymer repels blood and moisture at the tissue interface, creating a rapid, 3D watertight seal across the vessel cross-section.

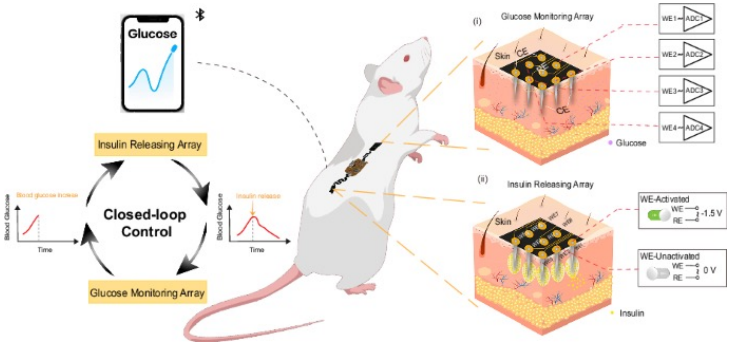
AI-monitored bioadhesive for sutureless microvascular anastomosis

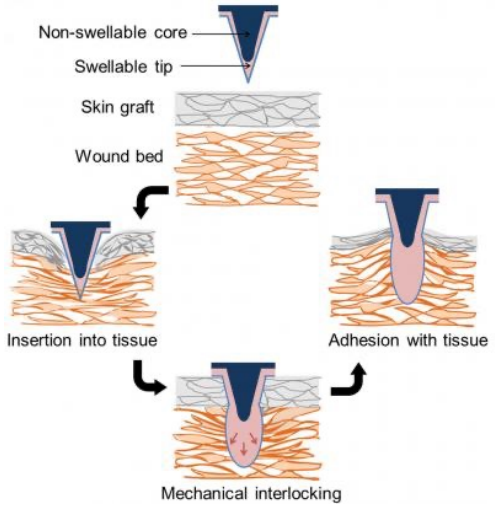


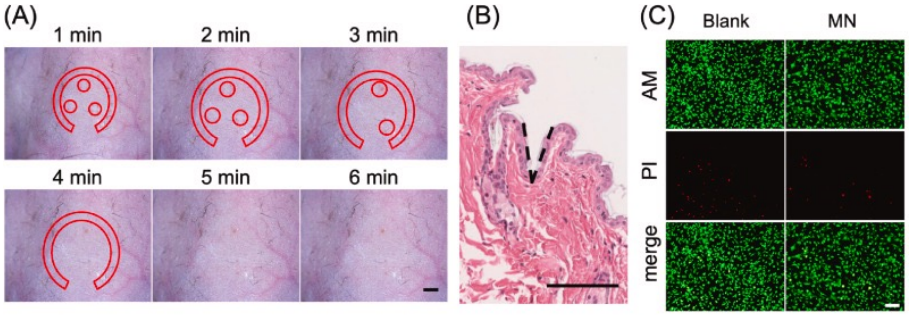
Microvascular anastomosis, the surgical suturing of small-caliber blood vessels, is technically demanding, time-consuming, and prone to failure from complications such as thrombosis. existing adhesives are ineffective in the dynamic, wet surgical field, particularly for the limited cross-sectional interface of blood vessels. We present an integrated microneedle-interlocking adhesive system (iMAS) bioinspired by plant root anchoring. This platform combines a hydrophobic polymeric matrix with tetrahedral microneedles, creating robust, three-dimensional bonding for rapid, secure anastomosis. An embedded artificial intelligence (AI)–assisted wireless sensor enables continuous, real-time monitoring of vascular hemodynamics and cardiac graft health, facilitating predictive identification of complications such as stenosis and transplant rejection. In rat models, iMAS reduced procedural time by 78% and suppressed neointimal hyperplasia. iMAS streamlines microvascular anastomosis and enables proactive graft monitoring in transplantation.

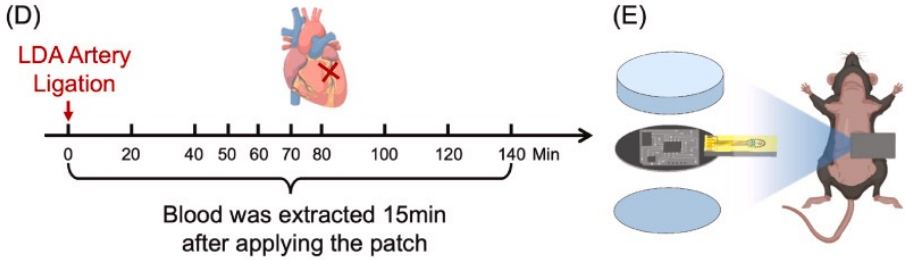


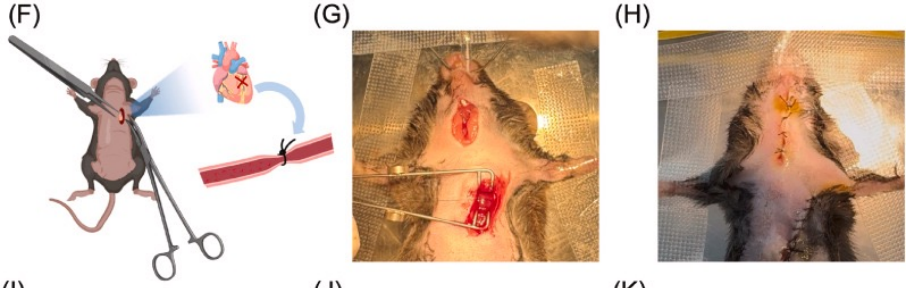
Design and operational principle of the bioadhesive system for microvascular anastomosis. (**A**) Schematic illustrating the workflow for sutureless anastomosis and wireless monitoring. (i) The vessel end is everted to expose the intimal surface, onto which the iMAS, integrated with a wireless sensor, is applied. (ii) The device continuously acquires hemodynamic data, such as pulsatile flow waveforms corresponding to systolic (red) and diastolic (blue) phases. (iii) Data are wirelessly transmitted to an external receiver and processed by an AI-based algorithm trained to predict vascular outcomes such as stenosis or occlusion. (**B**) Conceptual design of the bioinspired adhesive interface.

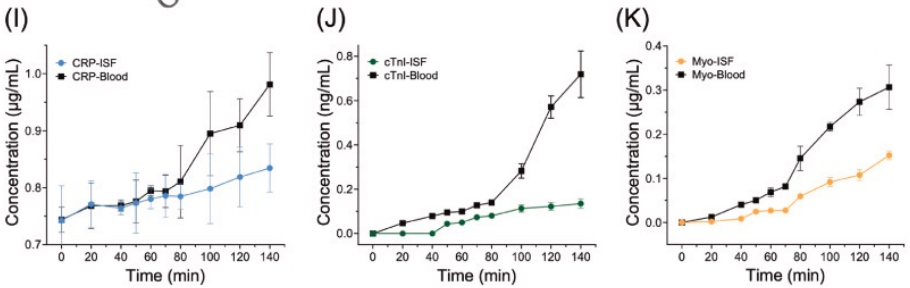

Glucose
Insulin Releasing Array
Closed-loop Control
Glucose Monitoring Array
Glucose Monitoring Array
Insulin Releasing Array
WE-Activated
WE-Unactivated
Glucose
Insulin


Non-swellable core
Swellable tip
Skin graft
Wound bed
Insertion into tissue
Adhesion with tissue
Mechanical interlocking


(A)
1 min
2 min
3 min
4 min
5 min
6 min
(B)
(C)
Blank
MN
AM
PI
merge


(D)
LDA Artery Ligation
0
20
40
50
60
70
80
100
120
140 Min
Blood was extracted 15min after applying the patch
(E)


(F)
(G)
(H)


(I)
CRP-ISF
CRP-Blood
Concentration (μg/mL)
Time (min)
(J)
cTnI-ISF
cTnI-Blood
Concentration (ng/mL)
Time (min)
(K)
Myo-ISF
Myo-Blood
Concentration (μg/mL)
Time (min)

Integrated microneedle-interlocking adhesive system

The iMAS design principles, encompassing hydrophobic, waterdisplacing adhesion combined with mechanical interlocking, are applicable not only to microvascular anastomosis but also to a range of other challenging wet tissue–bonding scenarios. These include nerve coaptation, dural repair for cerebrospinal fluid leak sealing, tendon reattachment, and hemostatic wound closure. Furthermore, the integrated wireless sensing capability is highly adaptable for monitoring the healing and function of any tubular structure, such as bile ducts, ureters, and intestinal anastomoses.

4 reasons to eat dark chocolate every day, according to science



A potential boost for heart health

The flavonoids in chocolate and other plant foods may have beneficial effects on the heart and blood vessels. Dive deeper

A lower risk of diabetes

Many studies have indicated that the flavonoids in cocoa can improve how our bodies respond to insulin and regulate blood sugar. Lab studies suggest they may also help protect the beta cells that produce and release insulin from the pancreas. This may explain why researchers have found that people who consume dark chocolate have lower rates of Type 2 diabetes.

A better mood

Chocolate's benefits go beyond its effects on metabolic health. If you've ever bitten into a square and felt your spirits lift, there's a reason for that. Scientists have found that dark chocolate may indeed make you feel better.

Changes in gut microbiome

When the South Korean researchers dug a little deeper, they found that dark chocolate might improve mood in part because it influences the "gut-brain axis," the communication network between our central nervous system and our gut microbes.

Dark chocolate is healthy mainly because of flavanols (a type of antioxidant polyphenol found in cocoa), along with a mix of essential minerals and healthy fats.

Here is what is inside that gives it those perks:

- **Flavanols & Polyphenols:** These plant compounds fight oxidative stress, lower blood pressure, and help your body produce nitric oxide, which relaxes and widens your blood vessels to improve blood flow.
- **Minerals:** A good dark chocolate (70% cocoa or higher) packs solid amounts of **iron**, **magnesium**, **copper**, **manganese**, **zinc**, and **potassium**.
- **Soluble Fiber:** It contains a decent amount of fiber that helps feed the good bacteria in your gut microbiome.
- **Stimulants:** Small amounts of **caffeine and theobromine** can give you a mild boost in alertness and focus.
- **Healthy Fats:** Most of the fat comes from cocoa butter, which includes oleic acid (a heart-healthy monounsaturated fat also found in olive oil)



Biochemical constituents of dark chocolate

Constituent Class	Specific Compounds	Primary Health Effects
Flavanols	Epicatechin, catechin, procyanidins	Boosts nitric oxide, lowers blood pressure, improves insulin sensitivity
Methylxanthines	Theobromine, caffeine	Enhances focus, supports vascular health, correlates with slower cellular aging
Minerals	Magnesium, iron, copper, zinc	Supports nerve function, oxygen transport, and immune health
Neuroactives	Tryptophan, PEA, anandamide	Supports serotonin production, reduces stress, and elevates mood

*(Note: Processing methods like heavy roasting and alkalization—often called "Dutch processing"—significantly reduce flavanol content. Choosing minimally processed dark chocolate with **70% or higher cacao** ensures the highest concentration of these compounds.)*