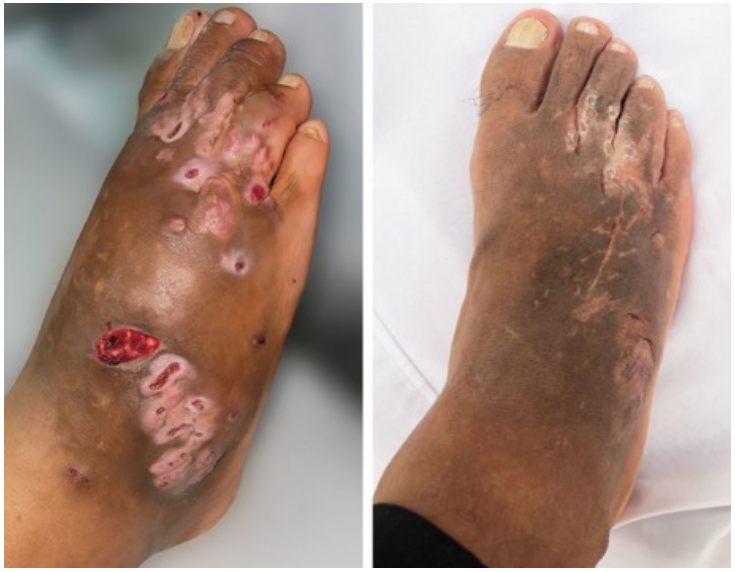
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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!



An otherwise healthy 30-year-old man presented to clinic for a 2-year history of skin lesions on his right foot. He worked as an agricultural laborer and had sustained injuries to his feet over the years, including a puncture lesion in between the fourth and fifth toes of his right foot. What is the most likely diagnosis?

Chromoblastomycosis

Cutaneous tuberculosis

Mycetoma

Mycobacterium ulcerans

Tetanus

Polymerase-chain-reaction of skin tissue identified Nocardia brasiliensis. A diagnosis of mycetoma — also known as Madura foot — was made. Mycetoma is a chronic infection of the skin that may be caused by bacteria (actinomycetoma) or fungi (eumycetoma) and commonly occurs in persons residing in tropical and subtropical climates who are frequently exposed to soil. Imaging of the foot showed concurrent osteomyelitis and septic arthritis. Surgical debridement was performed and the patient received a 6-month course of trimethoprim–sulfamethoxazole.

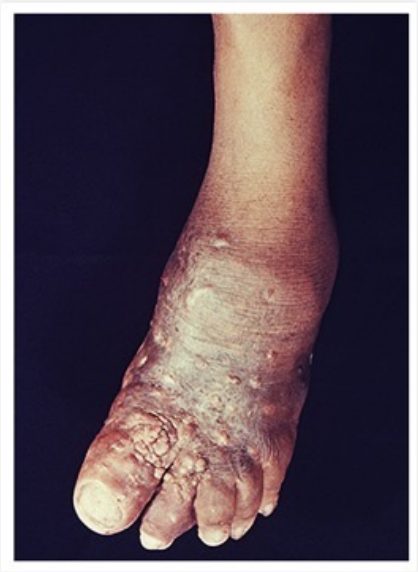
Ein **Myzetom** (auch Mycetoma oder „Madura-Fuß“) ist eine chronische, langsam fortschreitende Infektionskrankheit des Unterhautgewebes. Sie wird durch den Kontakt mit Dornen oder kleinen Hautverletzungen übertragen, über die Erreger aus dem Boden in den Körper gelangen.

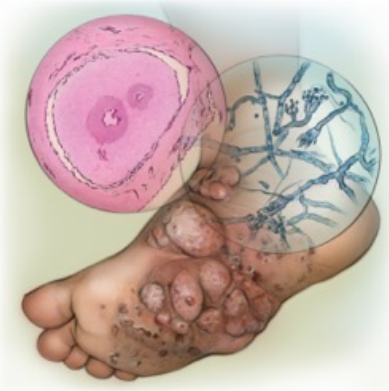
Die zwei Hauptformen

Je nach Erreger unterscheidet man zwei Typen, die völlig unterschiedliche Behandlungen erfordern:

•**Eumyzetom:** Verursacht durch **Pilze**. Diese Form ist oft schwerer zu therapieren und erfordert oft eine Amputation.

•**Aktinomyzetom:** Verursacht durch **Bakterien**. Diese Form spricht meist gut auf Antibiotika an.





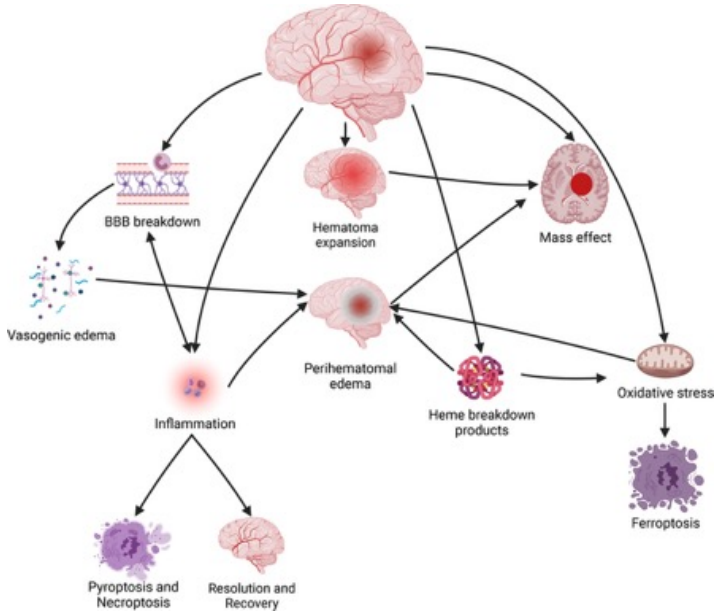
Eine intrazerebrale Blutung (ICH) ist eine Form des Schlaganfalls, bei der ein Blutgefäß im Inneren des Gehirngewebes platzt und Blut austritt. Dies führt zu einer Schädigung des Gehirns durch direkten Kontakt mit Blut sowie durch den steigenden Druck im Schädel (intrakranieller Druck).

Symptome & Warnzeichen

Suchen Sie bei folgenden Anzeichen **sofort** medizinische Hilfe auf (Notruf 112):

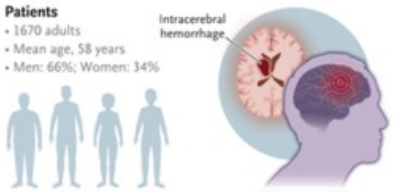
- **Plötzliche Schwäche** oder Taubheitsgefühl (oft einseitig) in Gesicht, Arm oder Bein.
- **Extreme Kopfschmerzen**, die schlagartig auftreten.
- **Verwirrung** oder Bewusstseinstrübung bis hin zum Koma.
- Übelkeit und plötzliches Erbrechen.
- Schwierigkeiten beim Sprechen oder Verstehen von Sprache.
- Sehstörungen oder Krampfanfälle.

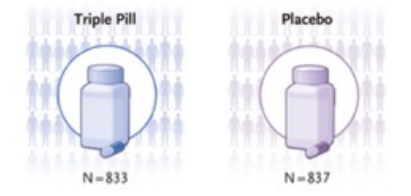
Hypertension-related intracerebral hemorrhage, more common in Asia

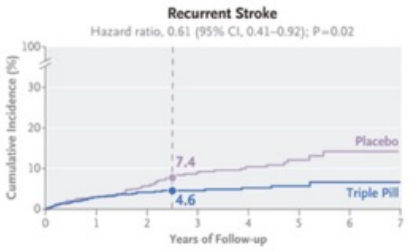


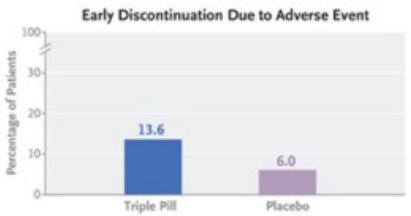
Three Low-Dose Antihypertensive Agents in a Single Pill after Intracerebral Hemorrhage

Blood-pressure reduction is the only proven treatment to prevent stroke. Whether a single pill that combines three antihypertensive drugs at low doses, in addition to standard antihypertensive treatment, can lower blood pressure more than standard care alone and reduce the risk of recurrent stroke after intracerebral hemorrhage is uncertain. We conducted a multinational, double-blind, randomized, placebo-controlled trial involving patients with a history of intracerebral hemorrhage. Patients were eligible for the trial if they had a systolic blood pressure of 130 to 160 mm Hg at baseline and were in clinically stable condition. After a 2-week active run-in phase during which all the patients received a once-daily pill containing three antihypertensive agents at low doses (telmisartan at 20 mg, amlodipine at 2.5 mg, and indapamide at 1.25 mg; the triple pill), the patients were randomly assigned to continue receiving the triple pill or to receive matching placebo. The primary outcome was the first recurrent stroke. Secondary outcomes included blood-pressure control, major cardiovascular events, death from cardiovascular causes, and safety.









Spontaneous intracerebral hemorrhage is a serious form of stroke with limited therapeutic options. The only proven treatment to prevent first and recurrent intracerebral hemorrhage is effective blood-pressure reduction. However, the benefits of intensive blood-pressure lowering and the preferred approach to treatment are uncertain. Although most survivors of stroke are discharged from the hospital with a prescription for medications to lower blood pressure, long-term blood-pressure control is generally inadequate owing to poor adherence to treatment, uncertainty surrounding the degree of benefit, varying guideline recommendations, insufficient intensification of treatment when blood pressure remains elevated, and therapeutic inertia. Combination antihypertensive therapy delivered in a single pill holds considerable promise as a strategy to improve blood-pressure control. We undertook the Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT) to evaluate the efficacy and safety of a single pill containing three antihypertensive drugs at low doses (telmisartan at 20 mg, amlodipine at 2.5 mg, and indapamide at 1.25 mg; hereafter referred to as the triple pill), in addition to standard care, in patients with a history of intracerebral hemorrhage.

Eligibility

Adult patients (≥18 years of age) with a history of spontaneous (nontraumatic) intracerebral hemorrhage were recruited from academic hospitals, either from inpatient wards or outpatient clinics. Patients were eligible for inclusion if they were in clinically stable condition, had a systolic blood pressure of 130 to 160 mm Hg while seated and at rest (with the use of any blood-pressure–lowering therapy as appropriate), and had no contraindication to any individual component of the triple pill used in the trial.

Randomization and Procedures

After the run-in period, eligible patients who had provided consent underwent centralized randomization in a 1:1 ratio, with stratification according to country, age, and systolic blood pressure at baseline, to receive the triple pill or matching placebo.

Outcomes

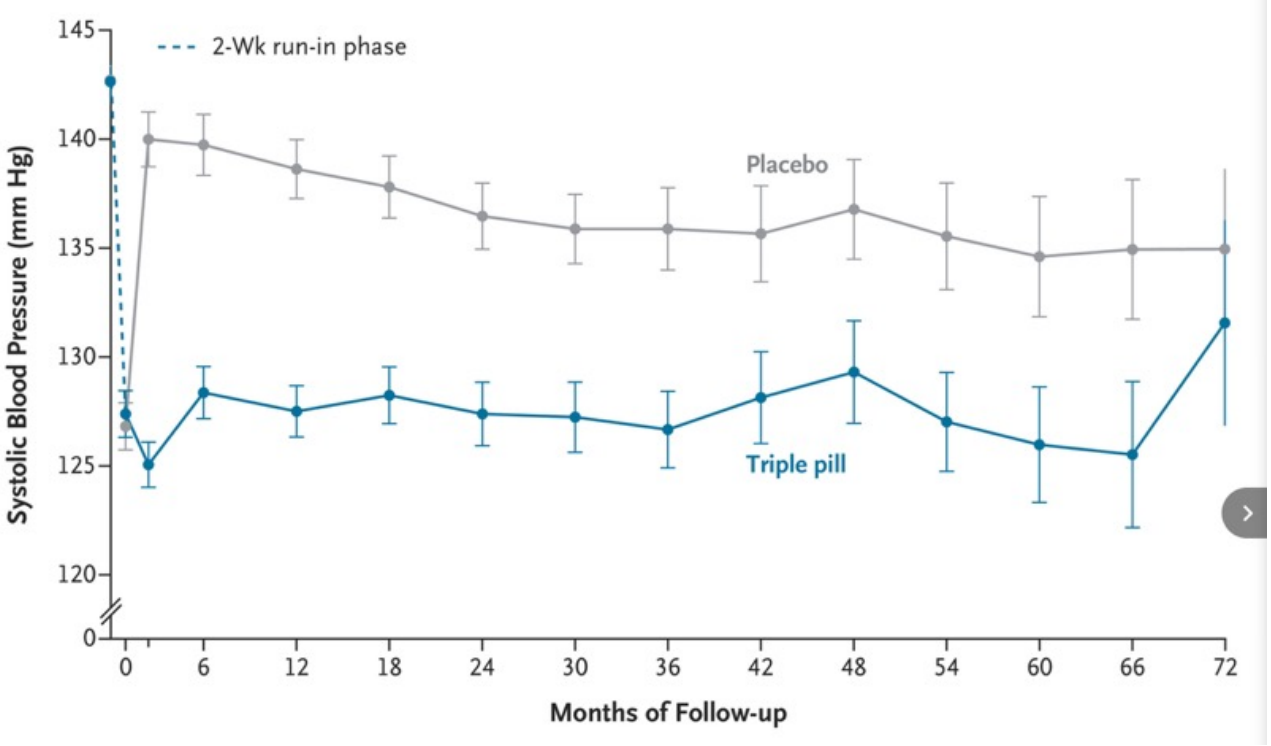
The primary outcome was the first recurrent stroke, assessed in a time-to-event analysis. The key secondary outcomes were blood-pressure control (defined as a systolic blood pressure of <130 mm Hg) at 6 months after randomization, a composite of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, whichever occurred first), and death from cardiovascular causes.

Patients

Characteristic	Triple Pill (N=833)	Placebo (N=837)
Age — yr	57.5±11.2	58.0±11.5
Female sex — no. (%)	275 (33.0)	288 (34.4)
Race — no. (%)†		
Asian	610 (73.2)	603 (72.0)
White	102 (12.2)	109 (13.0)
Black	96 (11.5)	100 (11.9)
Other	25 (3.0)	25 (3.0)
Medical history — no. (%)		
Hypertension	667 (80.1)	680 (81.2)
Previous ischemic stroke	33 (4.0)	33 (3.9)
Previous intracerebral hemorrhage before index event	56 (6.7)	56 (6.7)
Diabetes	181 (21.7)	188 (22.5)
Coronary artery disease	47 (5.6)	55 (6.6)
Current smoker	43 (5.2)	47 (5.6)
Median time from onset of symptoms (IQR) — days	52 (27–129)	54 (28–126)
Median volume of hematoma (IQR) — ml‡	12 (6–24)	11 (5–21)
Deep location of intracerebral hemorrhage — no. (%)§	653 (78.4)	635 (75.9)
BP management at baseline		
Single antihypertensive drug — no. (%)	252 (30.3)	262 (31.3)
Multiple antihypertensive drugs — no. (%)	488 (58.6)	478 (57.1)

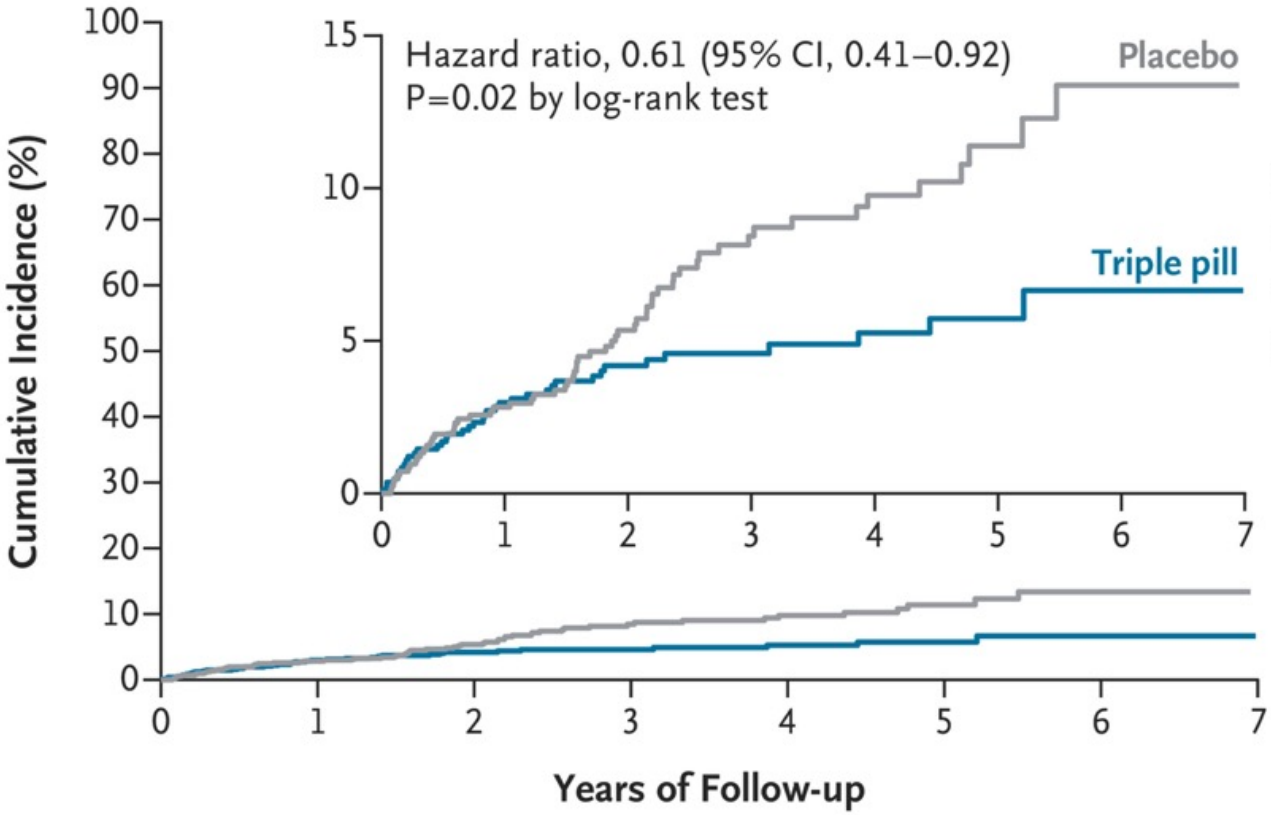
Efficacy Outcomes and Safety.

Outcome	Triple Pill (N=833)	Placebo (N=837)	Measure of Effect (95% CI)†	P Value
	no. of patients (%)			
Primary outcome				
Recurrent stroke	38 (4.6)	62 (7.4)	0.61 (0.41–0.92)‡	0.02§
Secondary outcomes¶				
BP control (SBP <130 mm Hg) at 6 mo	416 (49.9)	221 (26.4)	3.15 (2.53–3.92)‖	<0.001
Major cardiovascular event**	55 (6.6)	82 (9.8)	0.67 (0.47–0.94)	0.04
Death from cardiovascular causes	17 (2.0)	25 (3.0)	0.67 (0.36–1.25)	0.21
Other cardiovascular outcomes††				
Intracerebral hemorrhage	15 (1.8)	37 (4.4)	0.40 (0.22–0.73)	
Ischemic stroke	25 (3.0)	28 (3.3)	0.90 (0.52–1.54)	
Stroke of unknown type	0 (0.0)	2 (0.2)	NA	
Fatal stroke	3 (0.4)	12 (1.4)	0.25 (0.07–0.89)	
Nonfatal stroke	35 (4.2)	51 (6.1)	0.68 (0.44–1.05)	
Nonfatal myocardial infarction	5 (0.6)	7 (0.8)	0.69 (0.22–2.19)	
Death from any cause	54 (6.5)	72 (8.6)	0.75 (0.53–1.07)	
Safety				
Any adverse event of special interest by 6 wk‡‡	56 (6.7)	55 (6.6)		
Any serious adverse event§§	193 (23.2)	218 (26.0)	0.90 (0.74–1.09)¶¶	
Any adverse event leading to discontinuation of triple pill or placebo‖‖	113 (13.6)	50 (6.0)		



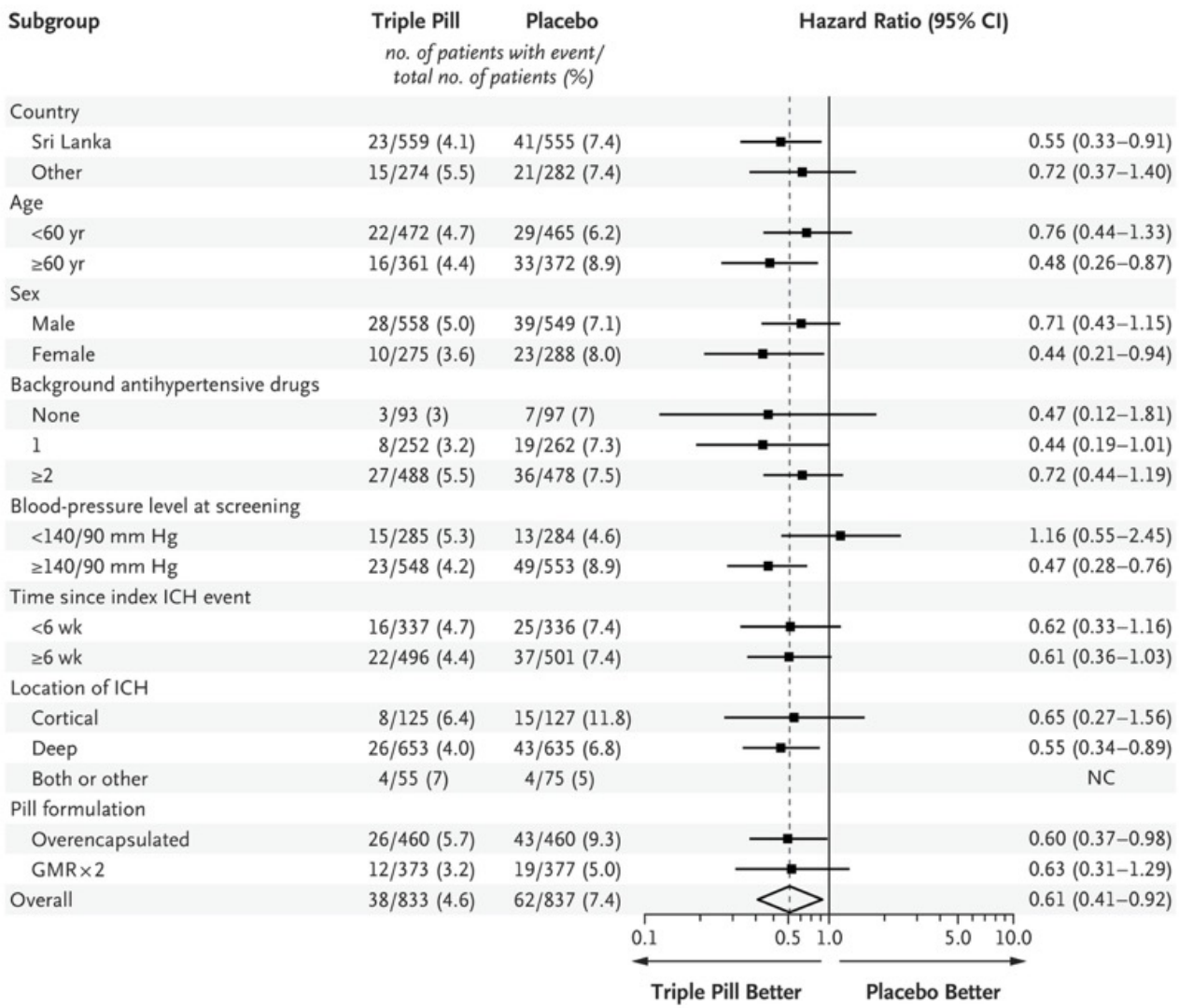
Mean Systolic Blood Pressure over Time.

I bars indicate 95% confidence intervals.



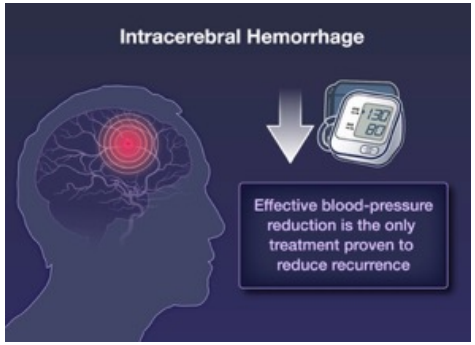
Cumulative Incidence of First Recurrent Stroke (Primary Outcome).

The inset shows the same data on an expanded y axis.

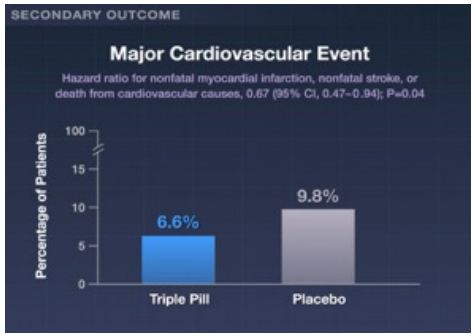


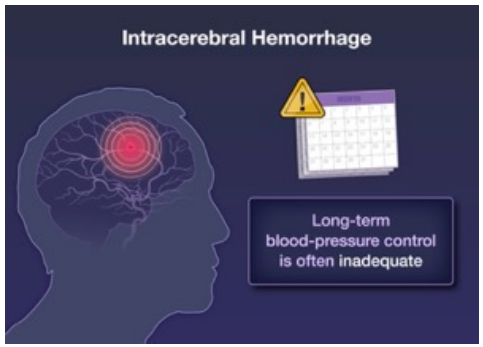
Primary Outcome According to Prespecified Subgroups.

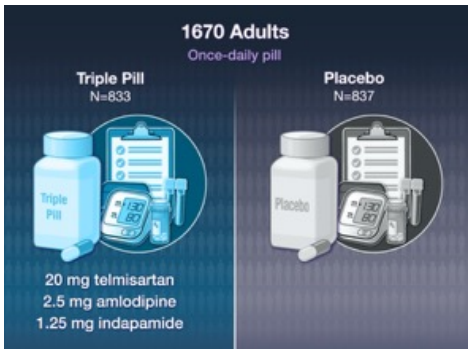
Subgroups were stratified according to characteristics recorded at the start of the active run-in phase. A hazard ratio was not calculated (NC) for the subgroup with both or other as the location of intracerebral hemorrhage because of the small numbers of patients. GMRx2 indicates a bespoke triple pill and matching placebo manufactured for the trial. ICH denotes intracerebral hemorrhage.

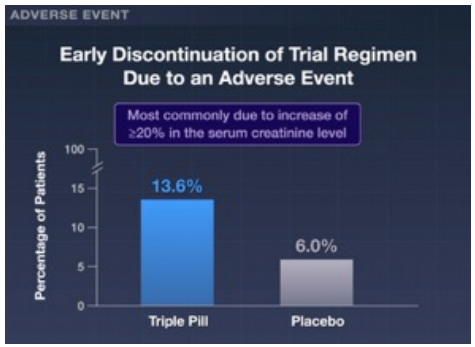

Intracerebral Hemorrhage
Effective blood-pressure reduction is the only treatment proven to reduce recurrence


New Trial
Standard Care

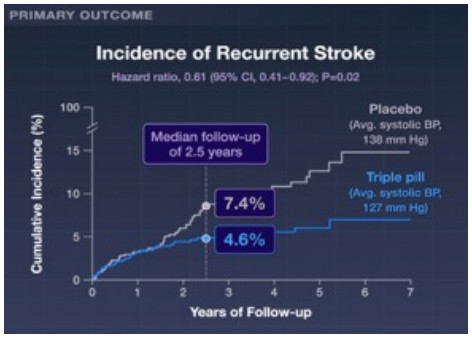

SECONDARY OUTCOME
Major Cardiovascular Event
Hazard ratio for nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, 0.67 (95% CI, 0.47–0.94); P=0.04
Percentage of Patients
100
15
10
5
0
6.6%
9.8%
Triple Pill
Placebo


Intracerebral Hemorrhage
Long-term blood-pressure control is often inadequate


1670 Adults
Once-daily pill
Triple Pill
N=833
Placebo
N=837
20 mg telmisartan
2.5 mg amlodipine
1.25 mg indapamide

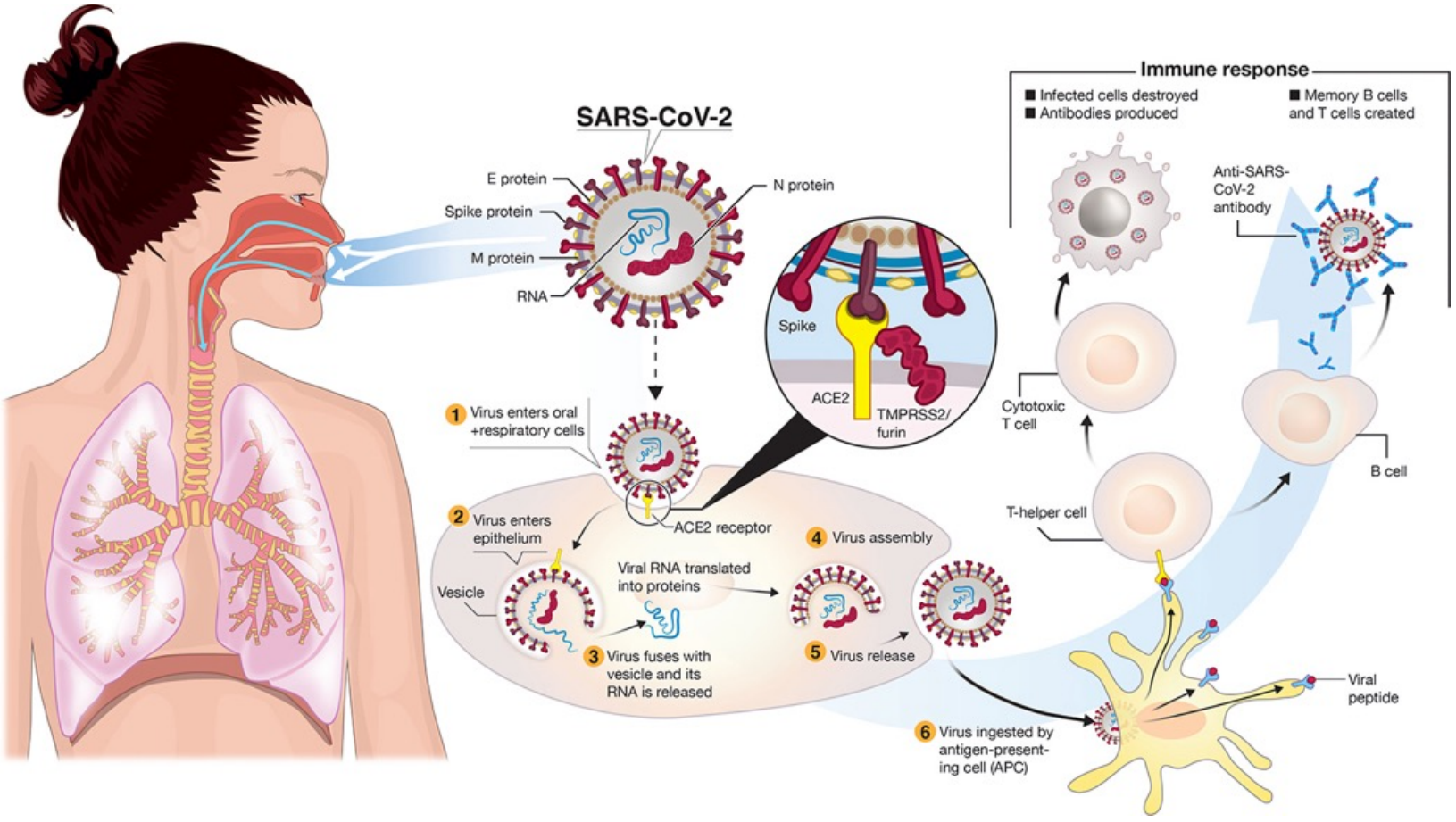

ADVERSE EVENT
Early Discontinuation of Trial Regimen Due to an Adverse Event
Most commonly due to increase of ≥20% in the serum creatinine level
Percentage of Patients
100
15
10
5
0
13.6%
6.0%
Triple Pill
Placebo


New Trial
Safety and efficacy
Single pill containing low doses of three antihypertensive agents


PRIMARY OUTCOME
Incidence of Recurrent Stroke
Hazard ratio, 0.61 (95% CI, 0.41–0.92); P=0.02
Cumulative Incidence (%)
100
15
10
5
0
Median follow-up of 2.5 years
Placebo
(Avg. systolic BP, 138 mm Hg)
Triple pill
(Avg. systolic BP, 127 mm Hg)
7.4%
4.6%
0
1
2
3
4
5
6
7
Years of Follow-up


Triple Pill
Recurrent stroke
Major cardiovascular events

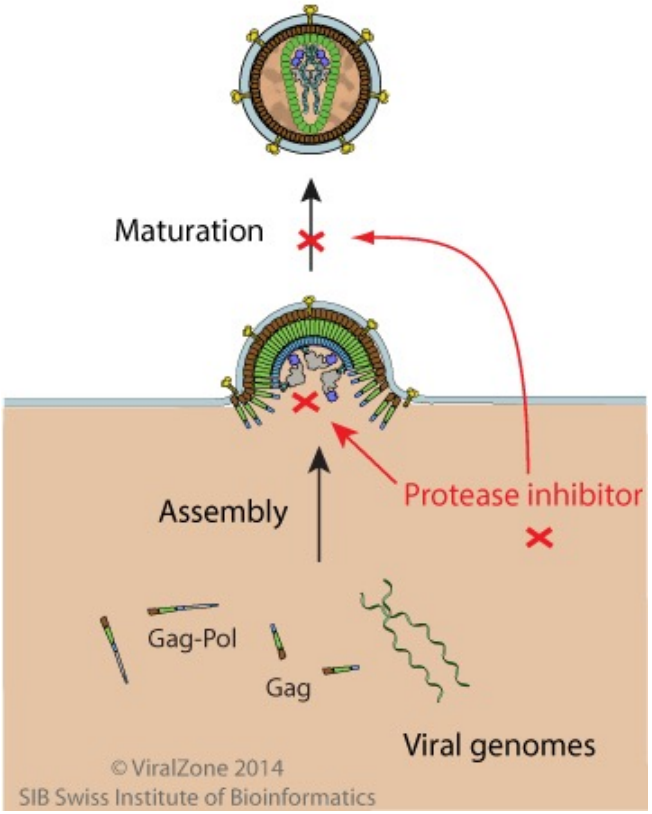
Zurück zu COVID 19



Virale Proteasen sind spezialisierte Enzyme, die von Viren kodiert werden, um lange Proteinketten (Polyproteine) in funktionelle Einheiten zu zerschneiden. Ohne diesen Schritt können Viren nicht reifen und keine neuen infektiösen Partikel bilden.

Hauptaufgaben im viralen Lebenszyklus

- **Reifung:** Sie spalten inaktive Vorläuferproteine in kleinere, aktive Proteine, die für den Aufbau neuer Viren nötig sind.
- **Zusammenbau:** Erst durch das präzise Schneiden können sich die Bausteine des Virus korrekt anordnen.
- **Wirtsmanipulation:** Einige Proteasen greifen gezielt Proteine der Wirtszelle an, um deren Abwehr zu schwächen oder den Zelltod einzuleiten.



Inhibiting viral assembly

Nirmatrelvir ist ein antiviraler Wirkstoff, der speziell zur Behandlung von **COVID-19** entwickelt wurde. Er wird fast ausschließlich in Kombination mit dem Wirkstoff Ritonavir unter dem Markennamen **Paxlovid** eingesetzt.

Wirkungsweise

Nirmatrelvir gehört zur Gruppe der **Proteaseinhibitoren**:

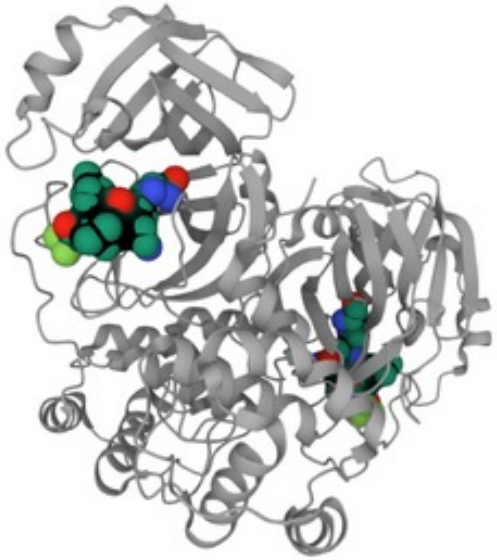
Anwendung und Zielgruppe

Das Medikament ist für Personen gedacht, die ein **erhöhtes Risiko für einen schweren Krankheitsverlauf** haben:

- **Indikation**: Behandlung von Erwachsenen (und Kindern ab 6 Jahren mit mind. 20 kg Gewicht) mit COVID-19, die keinen zusätzlichen Sauerstoff benötigen.
- **Zeitfenster**: Die Einnahme muss so früh wie möglich erfolgen, idealerweise innerhalb von **5 Tagen** nach Auftreten der ersten Symptome.
- **Dosierung**: Üblicherweise werden über 5 Tage hinweg alle 12 Stunden zwei Tabletten Nirmatrelvir und eine Tablette Ritonavir eingenommen.

Wichtige Hinweise

⚠ **Wechselwirkungen**: Da Ritonavir den Abbau vieler anderer Medikamente beeinflusst, kann es zu gefährlichen Wechselwirkungen kommen. Eine genaue Prüfung der bestehenden Medikation durch einen Arzt ist zwingend erforderlich.

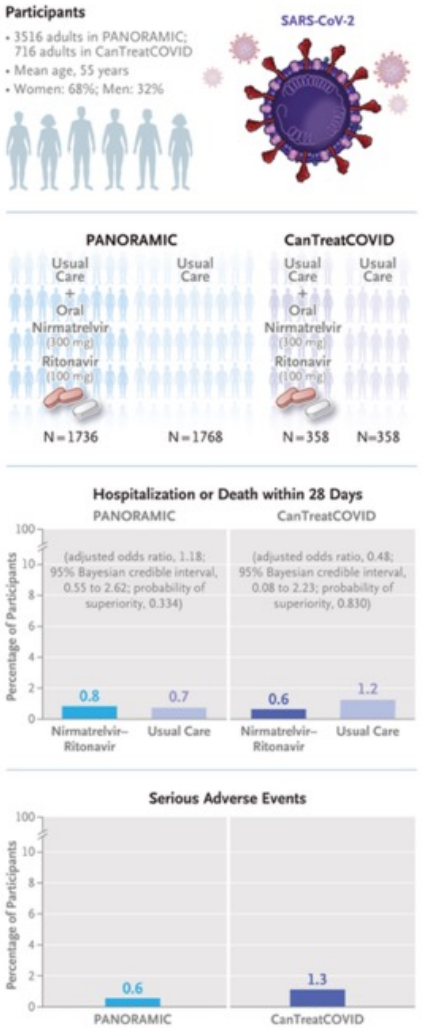


Metabolized by CYP3A4 that also metabolizes many other drugs

Oral Nirmatrelvir–Ritonavir for Covid-19 in Higher-Risk Outpatients

Nirmatrelvir–ritonavir has been shown to reduce progression to severe illness from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in unvaccinated high-risk outpatients. The effectiveness of nirmatrelvir–ritonavir in persons who have been vaccinated, infected naturally, or both is unclear. In two open-label platform trials (PANORAMIC in the United Kingdom and CanTreatCOVID in Canada), we enrolled higher-risk adults (≥50 years of age or ≥18 years of age with coexisting conditions) in the community who tested positive for SARS-CoV-2 and had been unwell for 5 days or less. The participants were randomly assigned to receive usual care plus nirmatrelvir (300 mg)–ritonavir (100 mg) twice a day for 5 days or to receive usual care alone. The primary outcome was hospitalization or death from any cause within 28 days after randomization.

Does nirmatrelvir keep „not-so-sick“ Covid patients out of the hospital?



In the EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial, nirmatrelvir–ritonavir was shown to reduce the incidence of hospitalization related to coronavirus disease 2019 (Covid-19) or death from any cause through 28 days among high-risk unvaccinated patients, a finding that led to a recommendation of this treatment as first-line therapy for outpatients with Covid-19 at the highest risk for progression to severe disease, despite a large number of drug–drug interactions.

In the time since the EPIC-HR and EPIC-SR trials were conducted, many more people have been vaccinated multiple times, have been infected naturally, or both, so whether nirmatrelvir–ritonavir still benefits those at high risk is unclear. The PANORAMIC trial, conducted in the United Kingdom, and the CanTreatCOVID trial, conducted in Canada, assessed the effectiveness of nirmatrelvir–ritonavir in reducing the incidence of hospital admissions or death among mostly vaccinated adults in the community who had risk factors for serious Covid-19.

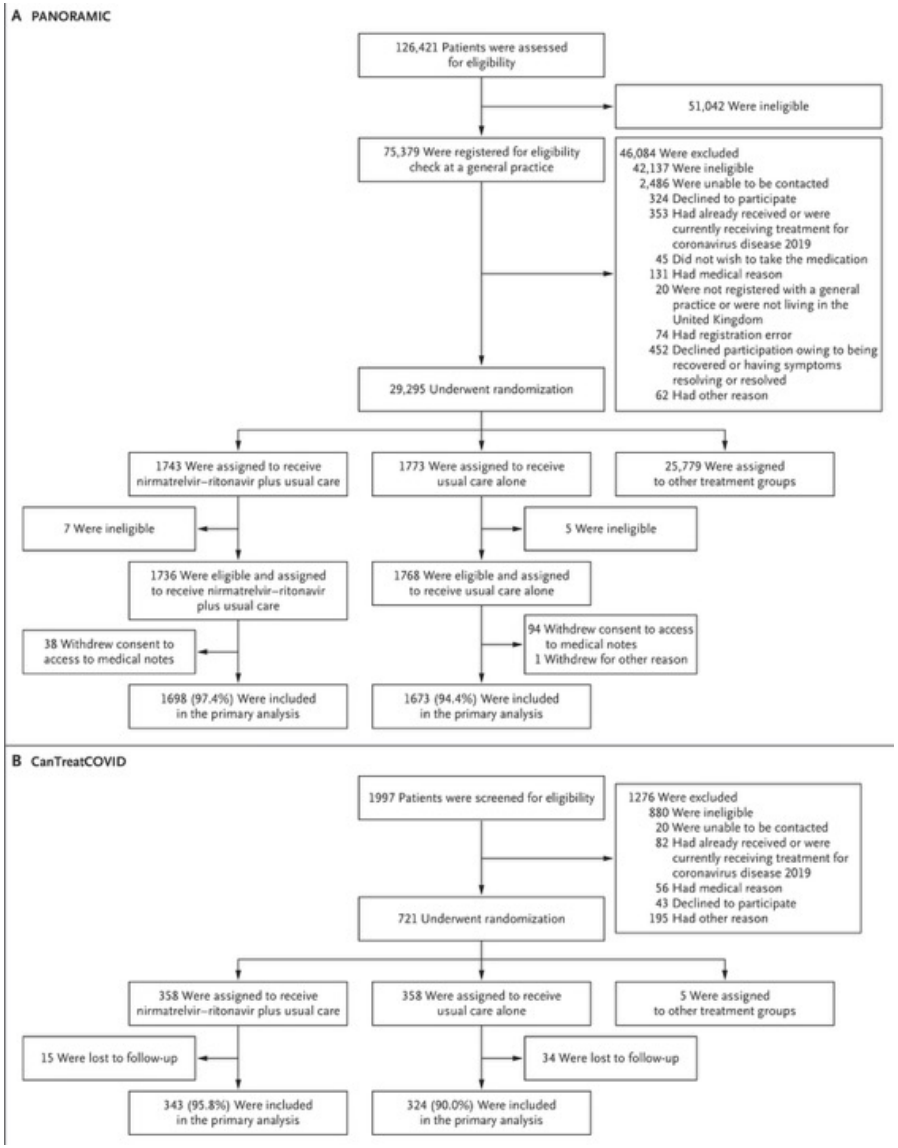
Eligible participants were higher-risk adults (≥50 years of age or ≥18 years of age with relevant coexisting conditions) in the community who had had symptoms of SARS-CoV-2 infection for 5 days or less and had a positive polymerase-chain-reaction (PCR) or rapid antigen SARS-CoV-2 test. Potential participants were excluded if they were pregnant or breast-feeding, were of childbearing potential and unwilling to use effective nonhormonal contraception, were already taking nirmatrelvir–ritonavir, or had contraindications to nirmatrelvir–ritonavir, including taking a medication with important drug–drug interactions or one requiring adjustment according to creatinine clearance or glomerular filtration rate.

Procedures

In both trials, participants in the nirmatrelvir–ritonavir group were asked to take nirmatrelvir at a dose of 300 mg (two 150-mg tablets) along with ritonavir at a dose of 100 mg (one tablet) orally twice daily for 5 days. All the participants received a trial information booklet. Packages containing nirmatrelvir–ritonavir (along with dosing and safety information) were sent by courier to participants' homes, along with a pregnancy test, if relevant.

Outcome Measures

The primary outcome was nonelective hospital admission for any cause or death from any cause within 28 days after randomization.



Characteristic	PANORAMIC		CanTreatCOVID	
	Nirmatrelvir–Ritonavir (N=1736)	Usual Care (N=1768)	Nirmatrelvir–Ritonavir (N=358)	Usual Care (N=358)
Age — yr				
Mean	54.7±12.1	54.8±11.7	54.7±13.6	55.0±13.5
Range	18–96	18–93	19–88	18–89
Sex — no. (%)†				
Female	1182 (68.1)	1223 (69.2)	237 (66.2)	231 (64.5)
Male	554 (31.9)	545 (30.8)	118 (33.0)	100 (27.9)
Other	0	0	1 (0.3)	0
Data missing or not reported	0	0	2 (0.6)	27 (7.5)
Race or ethnic group — no. (%)‡				
White	1647 (94.9)	1661 (93.9)	290 (81.0)	272 (76.0)
Asian	36 (2.1)	45 (2.5)	50 (14.0)	36 (10.1)
Mixed race	34 (2.0)	41 (2.3)	6 (1.7)	5 (1.4)
Black	8 (0.5)	9 (0.5)	2 (0.6)	3 (0.8)
Other	11 (0.6)	12 (0.7)	8 (2.2)	15 (4.2)
Data missing or not reported	0	0	2 (0.6)	27 (7.5)
Index of multiple deprivation quintile — no. (%)§				
1	154 (8.9)	167 (9.4)	—	—
2	284 (16.4)	271 (15.3)	—	—
3	334 (19.2)	388 (21.9)	—	—
4	426 (24.5)	415 (23.5)	—	—
5	525 (30.2)	510 (28.8)	—	—
Data missing or not reported	13 (0.7)	17 (1)	—	—
Household income, Canadian dollars — no. (%)				
<$40,000	—	—	38 (10.6)	46 (12.8)
≥$40,000	—	—	313 (87.4)	280 (78.2)
Data missing or not reported	—	—	7 (2.0)	32 (8.9)
Duration of symptoms — days				
Mean	2.7±1.2	2.7±1.2	2.4±1.1	2.4±1.1
Median (IQR)	3 (2–4)	3 (2–4)	2 (2–3)	2 (2–3)
Received ≥4 doses of nirmatrelvir–ritonavir — no. (%)	1504 (86.6)	—	314 (87.7)	—
Data missing	74 (4.3)	—	7 (2.0)	—
Received ≥1 vaccine dose — no. (%)	1715 (98.8)	1740 (98.4)	356 (99.4)	355 (99.2)
Data missing or not reported	0	0	0	1 (0.3)
No. of vaccine doses — no. (%)				
0	21 (1.2)	28 (1.6)	2 (0.6)	2 (0.6)
<2	16 (0.9)	7 (0.4)	6 (1.7)	5 (1.4)
≥2	1699 (97.9)	1733 (98.0)	350 (97.8)	350 (97.8)
Data missing or not reported	0	0	0	1 (0.3)
Wellness score¶				
Mean	4.7±1.7	4.7±1.7	—	—
Median (IQR)	5 (3–6)	5 (3–6)	—	—
Coexisting condition — no. (%)	1127 (64.9)	1185 (67.0)	173 (48.3)	160 (44.7)
Coexisting condition, CanTreatCOVID definition	898 (51.7)	936 (52.9)	173 (48.3)	160 (44.7)

Outcomes Trial #1

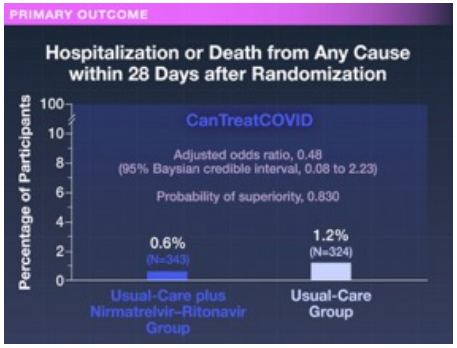
Outcome	Nirmatrelvir–Ritonavir	Usual Care	Estimated Treatment Effect (95% Bayesian Credible Interval)
Primary outcome			
Hospitalization or death — no./total no. (%)	14/1698 (0.8)	11/1673 (0.7)	1.18 (0.55–2.62)†
Secondary outcomes			
Early sustained recovery — no./total no. (%)‡	510/1546 (33.0)	330/1492 (22.1)	1.74 (1.48–2.04)†
Time to participant-reported recovery			
Recovered by day 28 — no./total no. (%)	1147/1690 (67.9)	919/1646 (55.8)	
Median days to recovery (IQR)§	14 (7 to not reached)	21 (11 to not reached)	
Time interval of recovery¶			
Day 1 or 2			0.845 (0.390–1.796)
Day 3–7			2.123 (1.792–2.511)
Day 8–11			1.599 (1.334–1.922)
Day 12–28			1.121 (0.987–1.271)
Adverse events‖			
No. of adverse events	4030	—	
No. of participants with event/total no. (%)	1551/1612 (96.2)	—	
No. of serious adverse events	10	—	
No. of participants with serious event/total no. (%)	10/1612 (0.6)	—	
Virologic testing, intensive-sampling cohort**			
Viral load below detection level at day 7 — no./total no. (%)	12/32 (38)	10/33 (30)	1.53 (0.52–4.56)††
Geometric mean viral load at day 7	759.3±10.8	3095.2±30.0	0.19 (0.06–0.63)‡‡
Virologic testing, all-sampling cohort**			
Viral load below detection level — no./total no. (%)			
Day 1	13/330 (3.9)	18/304 (5.9)	
Day 5	78/267 (29.2)	36/218 (16.5)	2.15 (1.37–3.44)††
Day 14	131/183 (71.6)	106/156 (67.9)	1.30 (0.77–2.15)††
Geometric mean viral load			
Day 1	1,988,856.5±51.2	1,713,635.8±47.5	
Day 5	3,587.0±26.6	30,267.1±52.3	0.13 (0.08–0.21)‡‡
Day 14	288.7±9.5	314.0±9.0	0.93 (0.51–1.68)‡‡

Outcomes Trial #2

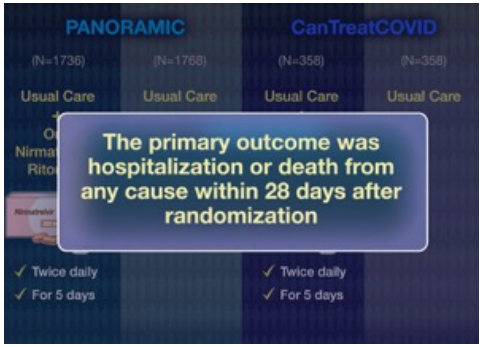
Outcome	Nirmatrelvir–Ritonavir	Usual Care	Estimated Treatment Effect (95% Bayesian Credible Interval)
Primary outcome			
Hospitalization or death — no./total no. (%)	2/343 (0.6)	4/324 (1.2)	0.48 (0.08–2.23)†
Secondary outcomes			
Early sustained recovery — no./total no. (%)‡	191/277 (69.0)	130/245 (53.1)	1.99 (1.40–2.87)†
Time to participant-reported recovery			
Recovered by day 14 — no./total no. (%)	272/345 (78.8)	194/306 (63.4)	
Median days to recovery (IQR) §	6 (4 to 11)	9 (4 to not reached)	
Time interval of recovery¶			
Day 1 or 2			0.94 (0.55–1.53)
Day 3–7			1.72 (1.35–2.23)
Day 8–11			1.54 (1.06–2.26)
Day 12–14			1.07 (0.58–1.90)
Adverse events			
No. of adverse events	190	38	
No. of participants with event/total no. (%)	112/312 (35.9)	20/358 (5.6)	
No. of serious adverse events	7	16	
No. of participants with serious event/total no. (%)	4/312 (1.3)	12/358 (3.4)	

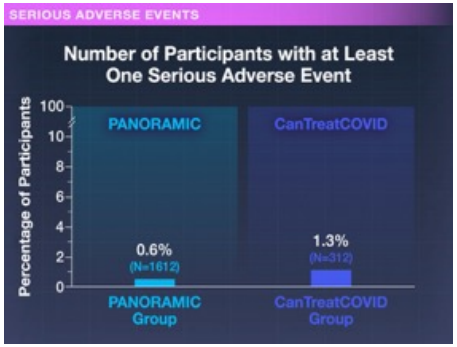

Previous Trial
Nirmatrelvir
Ritonavir
• Covid-19
• Unvaccinated
• High-risk patients


PANORAMIC
CanTreatCOVID
(N=1736)
(N=1768)
(N=358)
(N=358)
Usual Care
Usual Care
Usual Care
Usual Care
+
Oral
Nirmatrelvir–
Ritonavir
✓ Twice daily
✓ For 5 days
✓ Twice daily
✓ For 5 days

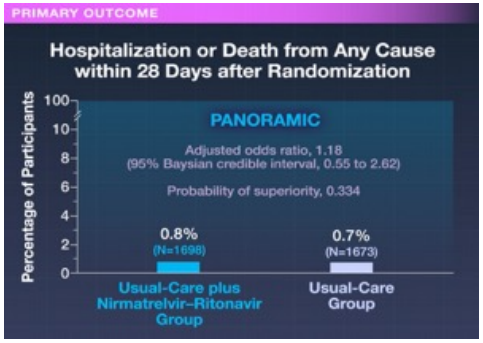

PRIMARY OUTCOME
Hospitalization or Death from Any Cause within 28 Days after Randomization
CanTreatCOVID
Adjusted odds ratio, 0.48
(95% Baysian credible interval, 0.08 to 2.23)
Probability of superiority, 0.830
Percentage of Participants
100
10
8
6
4
2
0
0.6%
(N=343)
1.2%
(N=324)
Usual-Care plus Nirmatrelvir–Ritonavir Group
Usual-Care Group

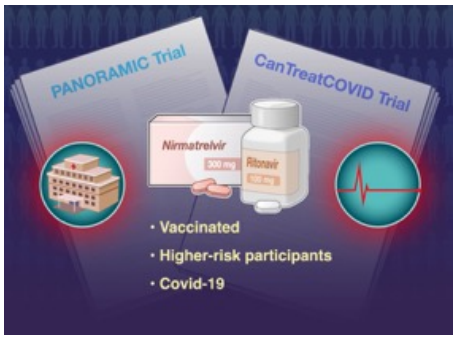

Previous Trial
Nirmatrelvir
Ritonavir
However, its effectiveness in those with immunity from previous infection, vaccination, or both is unclear


PANORAMIC
CanTreatCOVID
(N=1736)
(N=1768)
(N=358)
(N=358)
Usual Care
Usual Care
Usual Care
Usual Care
The primary outcome was hospitalization or death from any cause within 28 days after randomization
✓ Twice daily
✓ For 5 days
✓ Twice daily
✓ For 5 days


SERIOUS ADVERSE EVENTS
Number of Participants with at Least One Serious Adverse Event
PANORAMIC
CanTreatCOVID
Percentage of Participants
100
10
8
6
4
2
0
0.6%
(N=1612)
1.3%
(N=312)
PANORAMIC Group
CanTreatCOVID Group


PANORAMIC Trial
CanTreatCOVID Trial
• Two pragmatic
• Open-label
• Randomized trials


PRIMARY OUTCOME
Hospitalization or Death from Any Cause within 28 Days after Randomization
PANORAMIC
Adjusted odds ratio, 1.18
(95% Baysian credible interval, 0.55 to 2.62)
Probability of superiority, 0.334
Percentage of Participants
100
10
8
6
4
2
0
0.8%
(N=1698)
0.7%
(N=1673)
Usual-Care plus Nirmatrelvir–Ritonavir Group
Usual-Care Group

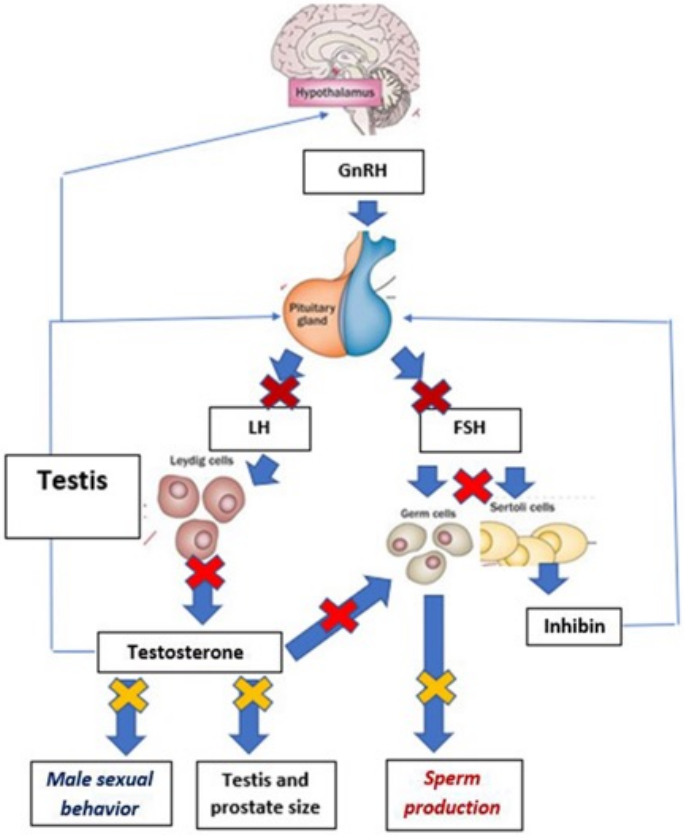

PANORAMIC Trial
CanTreatCOVID Trial
Nirmatrelvir
Ritonavir
• Vaccinated
• Higher-risk participants
• Covid-19

Gonadotropin-Releasing-Hormon-Agonisten (**GnRH-Agonisten**) sind synthetische Medikamente, die das natürliche GnRH-Hormon nachahmen. Sie werden primär eingesetzt, um die Produktion von Geschlechtshormonen (Östrogen und Testosteron) massiv zu senken.

Wirkungsweise

Der Effekt ist zeitabhängig und verläuft in zwei Phasen:

- **Flare-Up-Phase (Initial):** Kurz nach der Gabe steigen LH, FSH und die Geschlechtshormone vorübergehend stark an.
- **Down-Regulation (Dauerhaft):** Bei kontinuierlicher Gabe führen sie nach ca. 10–14 Tagen zu einer Erschöpfung (Downregulation) der Rezeptoren in der Hirnanhangdrüse.
- **Hormonsuppression:** Die Hormonproduktion sinkt auf ein extrem niedriges Niveau („medikamentöse Kastration“ beim Mann, „Pseudomenopause“ bei der Frau).



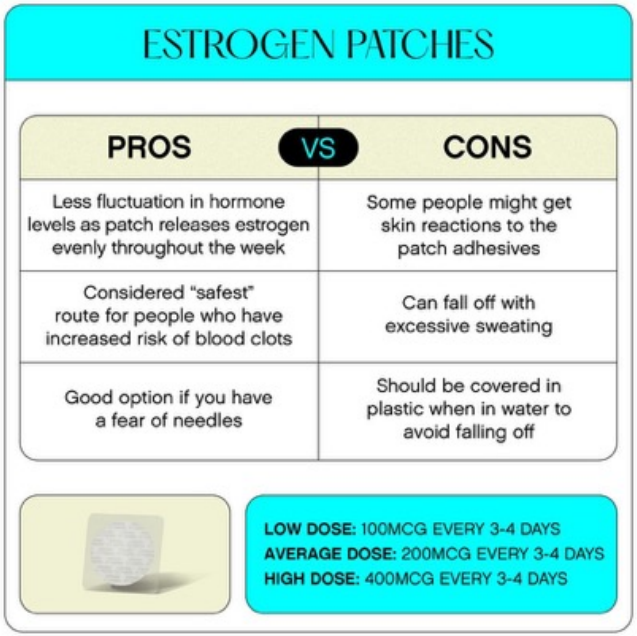
PROTACs (Proteolysis Targeting Chimeras) or Selective Androgen Receptor Degraders (SARDs) not tested here.

In men, estrogen patches act as a potent method of **androgen suppression**, effectively lowering testosterone levels to "castrate" ranges. This mechanism is primarily utilized in the treatment of advanced **prostate cancer** as a safer alternative to traditional injections.

Mechanism of Action

The release of estrogen (specifically **estradiol**) via patches affects the brain's hormonal control center:

- **Brain Feedback**: Estradiol signals the brain that there is a sufficient amount of sex hormone present.
- **LH Suppression**: The brain responds by reducing the instructions (Luteinizing Hormone or LH) sent to the testes to produce testosterone.
- **Testosterone Drop**: This results in a drop in testosterone levels just as effective as chemical castration through injections.

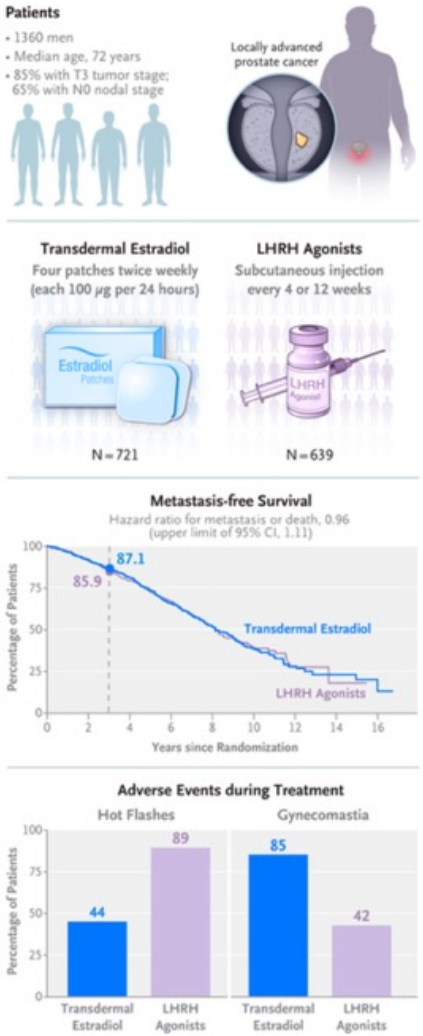


Monthly Cost Breakdown (U.S.

Medication Type	Estimated Monthly Cash Price
Estrogen Patches	$25 – $90
GnRH Agonists	$304 – $1,200+

Transdermal Estradiol Patches in Locally Advanced Prostate Cancer

Transdermal estradiol (tE2) is an alternative to luteinizing hormone–releasing hormone (LHRH) agonists as androgen-deprivation therapy in patients with prostate cancer. With tE2, testosterone is suppressed, and the side effects of estrogen depletion due to LHRH agonists and the thromboembolic side effects of oral estrogen are mitigated. In this phase 3, noninferiority, randomized trial, we assigned men with locally advanced (M0 and N0 or N+) prostate cancer to receive tE2 patches (100 µg of estradiol every 24 hours) or LHRH agonists. The primary outcome was 3-year metastasis-free survival. The noninferiority margin was 4 percentage points; this corresponded to a target hazard ratio of 1.31, as derived from the observed 3-year metastasis-free survival in the LHRH agonist group. Secondary outcomes included castrate levels of testosterone (<1.7 nmol per liter), overall survival, and safety.



Prostate cancer is the most common cancer worldwide among men. Reducing serum testosterone levels to less than 1.7 nmol per liter (<50 ng per deciliter), often referred to as castrate levels of testosterone, is the backbone of therapy for locally advanced nonmetastatic (metastasis stage M0) and metastatic (stage M1) disease. This reduction is most commonly achieved with luteinizing hormone–releasing hormone (LHRH) agonists, which also reduce serum estradiol levels given that approximately 80% of estrogens in men are derived from the aromatization of testosterone. LHRH agonists have several toxic effects, including erectile dysfunction and loss of muscle mass due to decreased testosterone levels and loss of bone mineral density (which increases the risk of osteoporosis and fracture), adverse metabolic changes (increased levels of serum lipids and glucose and increased blood pressure), and hot flashes due to decreased estradiol levels.

The administration of exogenous estrogen is an alternative approach to treatment that lowers testosterone levels by means of a negative feedback loop involving the hypothalamus and pituitary gland but mitigates the effects of estrogen depletion.

We conducted a phase 2–3 adaptive trial to assess the safety and efficacy of transdermal estradiol (tE2) patches in patients with prostate cancer who were recruited through the PATCH (Prostate Adenocarcinoma Transcutaneous Hormones) or STAMPEDE-1 (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial networks.

Patients

Patients with histologically confirmed, localized adenocarcinoma of the prostate who were scheduled to start androgen-deprivation therapy and had a World Health Organization (WHO) performance-status score of 2 or lower (range, 0 to 5, with higher scores reflecting greater disability) were eligible for the trial.

Trial Procedures

Patients were randomly assigned to receive tE2 patches or LHRH agonists according to local practice without blinding. Randomization was conducted with a computer-based minimization algorithm with a random element of 20%.

LHRH agonists were injected subcutaneously every 4 or 12 weeks; treatment with bicalutamide or flutamide for up to 8 weeks was permitted to prevent a temporary increase in the PSA level or symptoms. The tE2 patches (Progynova or FemSeven), which released 100 µg of estradiol per 24 hours, were applied by the patient.

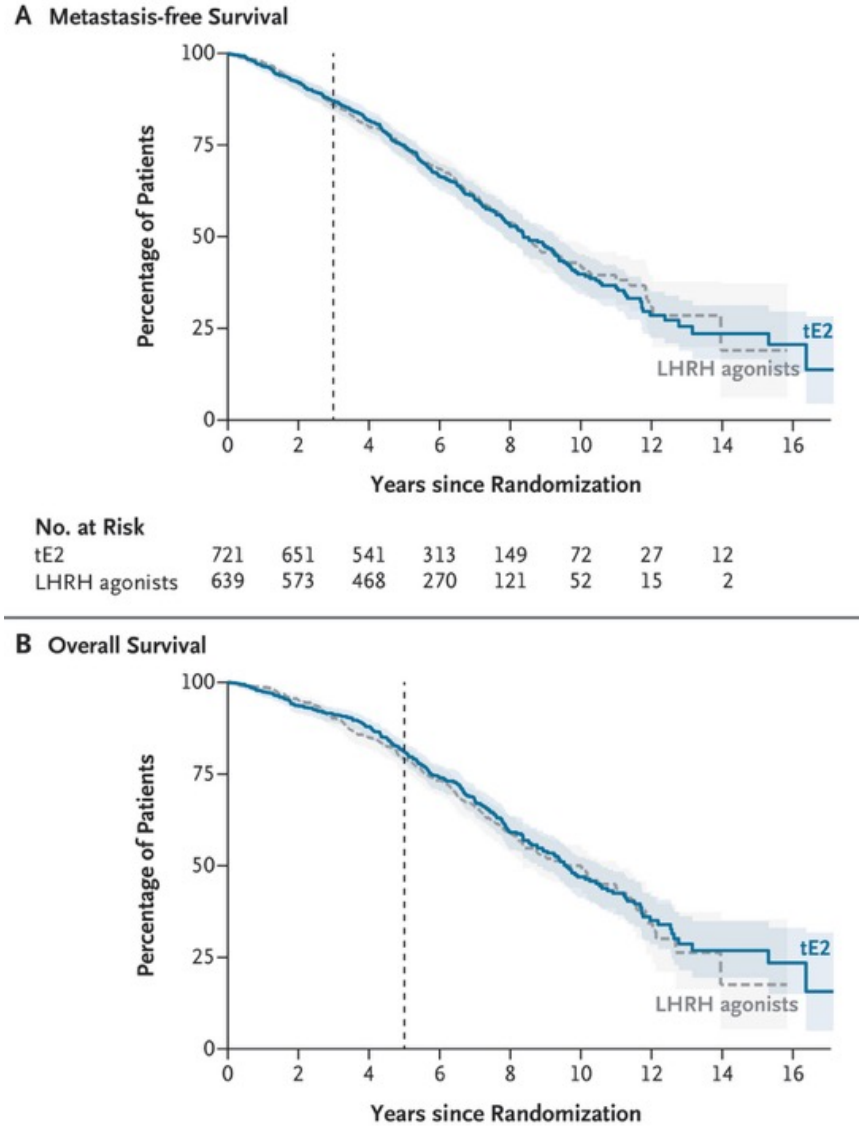
Outcomes

The primary outcome was 3-year metastasis-free survival, with survival calculated as the time from randomization to confirmation of metastasis (excluding pelvic lymph node progression) or death from any cause. Metastasis-free survival is a recognized surrogate for overall survival. Secondary outcomes included castrate levels of testosterone, overall survival, and safety.

Characteristic	tE2 (N=721)	LHRH Agonists (N=639)	Total (N=1360)
Trial — no. (%)			
PATCH	583 (81)	499 (78)	1082 (80)
STAMPEDE-1	138 (19)	140 (22)	278 (20)
Age			
Median (IQR) — yr	72 (68–77)	72 (67–77)	72 (68–77)
Range — yr	46–90	50–89	46–90
Distribution — no. (%)			
<70 yr	244 (34)	219 (34)	463 (34)
≥70 yr	477 (66)	420 (66)	897 (66)
WHO performance-status score — no. (%)†			
0	544 (75)	488 (76)	1032 (76)
1	154 (21)	139 (22)	293 (22)
2	23 (3)	12 (2)	35 (3)
Tumor stage — no. (%)			
T0	0	1 (<1)	1 (<1)
T1	5 (1)	5 (1)	10 (1)
T2	25 (3)	21 (3)	46 (3)
T3	615 (85)	542 (85)	1157 (85)
T4	72 (10)	67 (10)	139 (10)
TX	4 (1)	2 (<1)	6 (<1)
Nodal stage — no. (%)			
N0	456 (63)	427 (67)	883 (65)
N+	164 (23)	150 (23)	314 (23)
NX	101 (14)	62 (10)	163 (12)
Prostate-specific antigen level			
Median (IQR) — ng/ml	25.21 (12–54.9)	23.8 (11.3–53.1)	24.4 (11.8–54.1)
Range — ng/ml	0.8–544.1	1.1–2488.0	0.8–2488.0
Distribution — no. (%)			
<50 ng/ml	519 (72)	474 (74)	993 (73)
50 to <500 ng/ml	201 (28)	161 (25)	362 (27)
≥500 ng/ml	1 (<1)	4 (1)	5 (<1)
Gleason sum, ungrouped — no. (%)‡			
4	0	1 (<1)	1 (<1)
5	3 (<1)	5 (1)	8 (1)
6	35 (5)	33 (5)	68 (5)
7	253 (35)	213 (33)	466 (34)
8	158 (22)	139 (22)	297 (22)
9	253 (35)	238 (37)	491 (36)
10	13 (2)	10 (2)	23 (2)
Gleason sum, grouped — no. (%)‡			
4, 5, or 6	39 (5)	39 (6)	77 (6)
7	253 (35)	213 (33)	466 (34)
8, 9, or 10	424 (59)	387 (61)	811 (60)
Standard care planned by treating physician — no. (%)§			
Radiotherapy to prostate			
No	241 (33)	191 (30)	432 (32)
Yes	480 (67)	448 (70)	928 (68)
Docetaxel or abiraterone			
No	683 (95)	596 (93)	1279 (94)
Docetaxel	37 (5)	43 (7)	80 (6)
Abiraterone	1 (<1)	0	1 (<1)

Adversity

Event	tE2 (N=693)				LHRH Agonists (N=612)			
	No Event	Grade 1	Grade 2	Grade 3 or 4	No Event	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Gynecomastia	105 (15)	329 (47)	226 (33)	33 (5)	357 (58)	199 (33)	47 (8)	9 (1)
Hot flashes	387 (56)	252 (36)	51 (7)	3 (<1)	70 (11)	316 (52)	195 (32)	31 (5)
Anemia	518 (75)	161 (23)	13 (2)	1 (<1)	401 (66)	182 (30)	25 (4)	4 (1)
Anxiety	519 (75)	154 (22)	20 (3)	0	424 (69)	154 (25)	32 (5)	2 (<1)
Chest pain	646 (93)	39 (6)	5 (1)	3 (<1)	550 (90)	45 (7)	10 (2)	7 (1)
Concentration impairment	559 (81)	120 (17)	12 (2)	2 (<1)	462 (75)	128 (21)	18 (3)	4 (1)
Depression	537 (77)	136 (20)	18 (3)	2 (<1)	442 (72)	137 (22)	30 (5)	3 (<1)
Dizziness	582 (84)	101 (15)	9 (1)	1 (<1)	474 (77)	124 (20)	13 (2)	1 (<1)
Erectile dysfunction	244 (35)	240 (35)	184 (27)	25 (4)	220 (36)	215 (35)	145 (24)	32 (5)
Fatigue	225 (32)	355 (51)	106 (15)	7 (1)	126 (21)	330 (54)	147 (24)	9 (1)
Insomnia	483 (70)	186 (27)	20 (3)	4 (1)	353 (58)	204 (33)	52 (8)	3 (<1)
Increased irritability	525 (76)	155 (22)	13 (2)	0	439 (72)	153 (25)	17 (3)	3 (<1)
Decreased libido	293 (42)	238 (34)	154 (22)	8 (1)	253 (41)	222 (36)	125 (20)	12 (2)
Nausea	624 (90)	64 (9)	4 (1)	1 (<1)	528 (86)	76 (12)	7 (1)	1 (<1)
Pruritus	384 (55)	268 (39)	36 (5)	5 (1)	493 (81)	106 (17)	13 (2)	0



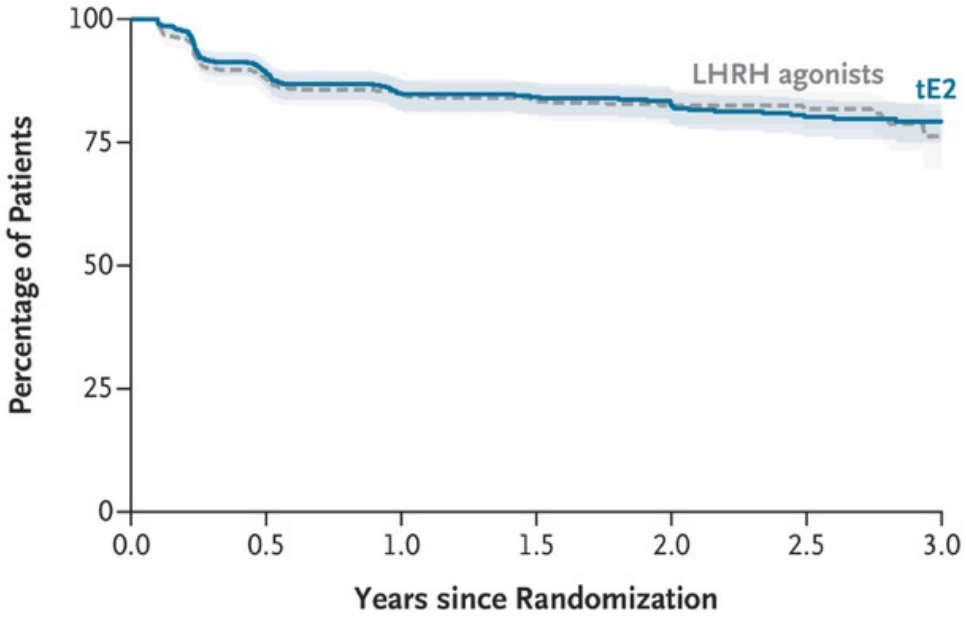
Metastasis-free Survival and Overall Survival.

The observed 3-year metastasis-free survival was 87.1% with tE2 and 85.9% with LHRH agonists, with a hazard ratio for confirmed metastasis or death from any cause of 0.96 (upper limit of one-sided 95% confidence interval [CI], 1.11) (Panel A). The upper limit of the one-sided 95% confidence interval was less than the target hazard ratio of 1.31 derived on the basis of pooled data from the LHRH agonist groups in PATCH and STAMPEDE-1, thus showing the noninferiority of tE2. The observed 5-year overall survival was 81.1% in the tE2 group and 79.2% in the LHRH agonist group, with a hazard ratio for death of 0.90 (95% CI, 0.75 to 1.07), favoring tE2 (Panel B). Shaded regions indicate 95% confidence intervals.

A Castrate Level of Testosterone

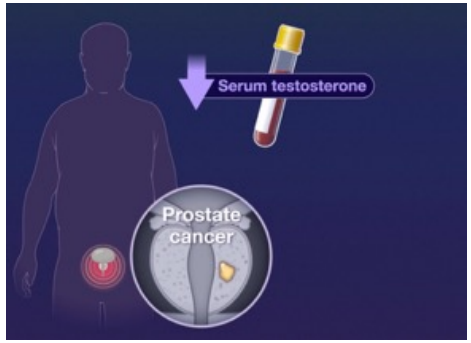
	tE2	LHRH Agonists	Overall
	no. of patients with event/no. of patients (%)		
Baseline	1/581 (<1)	0/494 (0)	1/1075 (<1)
1 Month	418/506 (83)	215/360 (60)	633/866 (73)
3 Months	441/478 (92)	343/371 (92)	784/849 (92)
6 Months	429/471 (91)	371/401 (93)	800/872 (92)
12 Months	311/331 (94)	317/327 (97)	628/658 (95)

B Sustained Castrate Level of Testosterone

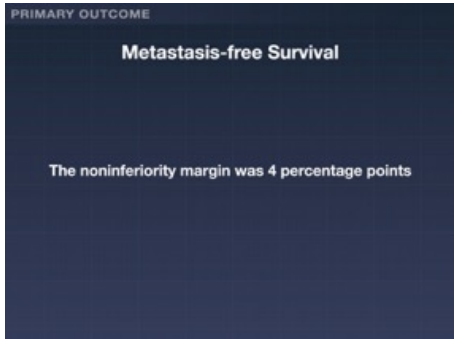


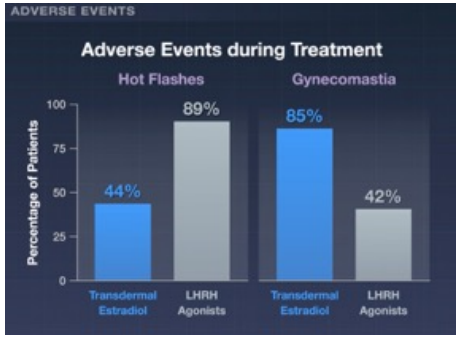
Castrate Levels of Testosterone.

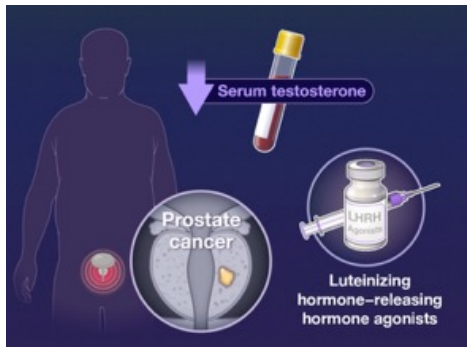
Panel A shows the prevalence of castrate levels of testosterone during the first year after randomization, overall and according to assigned treatment. Panel B shows the prevalence of sustained castrate levels of testosterone among patients who were continuing the assigned treatment. Castrate levels of testosterone were sustained during the first year after randomization in 85% of the patients in each treatment group. Patients were included in the analysis if they had at least one reported testosterone level between day 35 and year 1 after randomization. Levels that were measured within 35 days after the start of treatment were excluded from the analysis to account for the initial increase in the testosterone level that may occur with LHRH agonists.


Serum testosterone
Prostate cancer

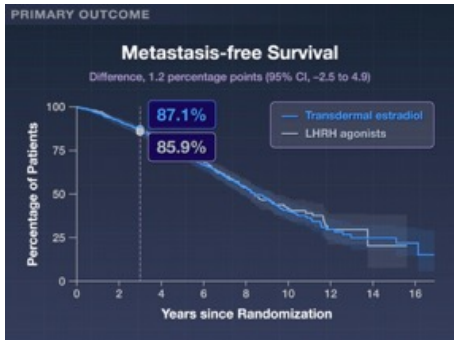

By suppressing testosterone through a negative feedback loop while maintaining estrogen levels

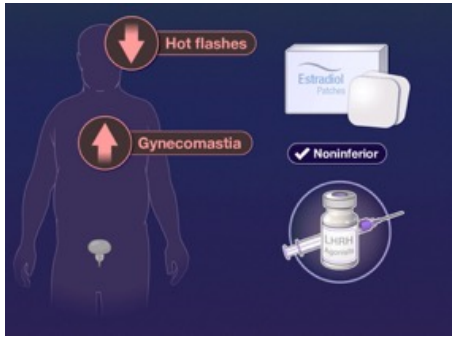

PRIMARY OUTCOME
Metastasis-free Survival
The noninferiority margin was 4 percentage points

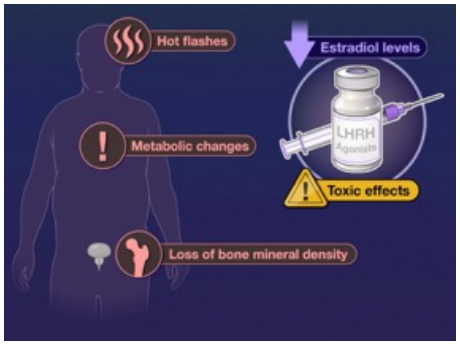

ADVERSE EVENTS
Adverse Events during Treatment
Hot Flashes
Gynecomastia
Percentage of Patients
100
75
50
25
0
44%
89%
85%
42%
Transdermal Estradiol
LHRH Agonists
Transdermal Estradiol
LHRH Agonists

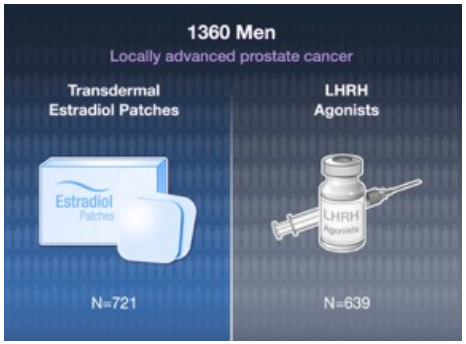

Serum testosterone
Prostate cancer
Luteinizing hormone–releasing hormone agonists


Transdermal estradiol may mitigate some of these toxic effects


PRIMARY OUTCOME
Metastasis-free Survival
Difference, 1.2 percentage points (95% CI, −2.5 to 4.9)
Percentage of Patients
100
75
50
25
0
87.1%
85.9%
Transdermal estradiol
LHRH agonists
0
2
4
6
8
10
12
14
16
Years since Randomization

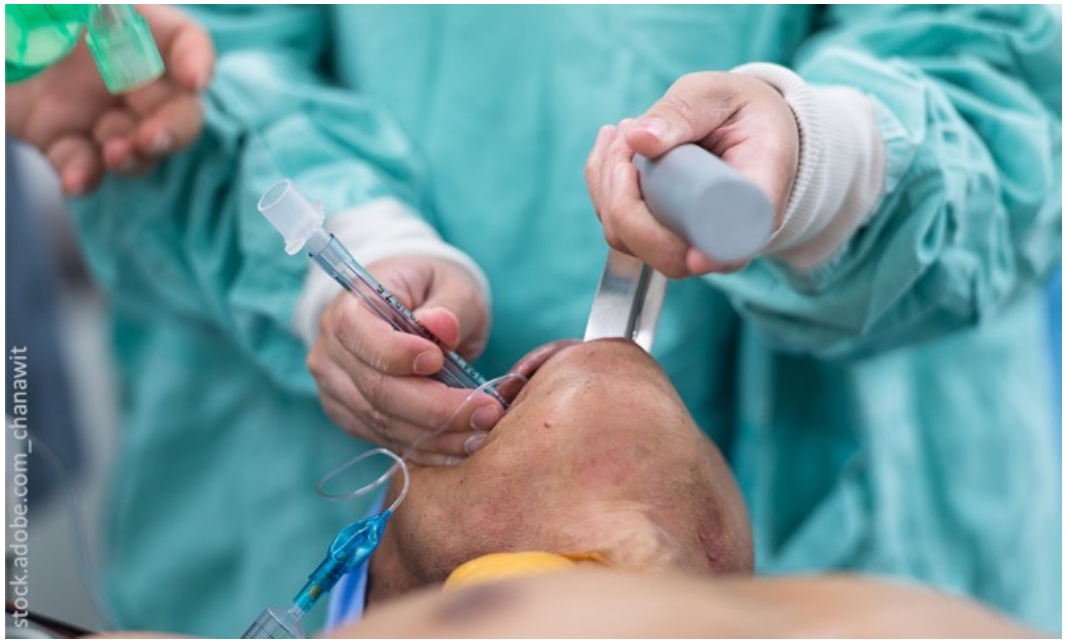

Hot flashes
Gynecomastia
Noninferior


Hot flashes
Estradiol levels
Metabolic changes
Toxic effects
Loss of bone mineral density


1360 Men
Locally advanced prostate cancer
Transdermal Estradiol Patches
LHRH Agonists
N=721
N=639


SECONDARY OUTCOME
Overall Survival
Difference, 1.8 percentage points (95% CI, −2.6 to 6.2)
Percentage of Patients
100
75
50
25
0
81.1%
79.2%
Transdermal estradiol
LHRH agonists
0
2
4
6
8
10
12
14
16
Years since Randomization

Intubation of the critically ill



Die NERDfallmedizin-Checkliste Intubation und Notfallnarkose

NERDfall medizin
Moritz Werthschulte

S SUCTION	Absaugbereitschaft herstellen - laufende Absaugpumpe!	Check!
	Großlumiger Absaugkatheter (ggf. Yankauer) montiert	Check!
	(ggf. 2. Absaugpumpe bei Erbrechen o. ä. bereit)	
O OXYGEN	Sauerstoffmaske (≥15 l/min), alternativ Beatmungsbeutel (Demandventil)	Check!
	Sauerstoffbrille zur Apnoeoxygenierung (15 l/min) über 2. Anschluss	Check!
	Guedeltubus und Wendltubus griffbereit, ggf. einliegend	Check!
	Präoxygenierung möglichst suffizient	Check!
	(ggf. NIV, falls keine ausreichende Präoxygenierung möglich)	
A AIRWAY	Laryngoskop + Spatel + Ersatzspatel (möglichst Videolaryngoskop!)	Check!
	Endotrachealtubus (♂: 8.0, ♀: 7,5) + Ersatztubus (7.0)	Check!
	Führungsstab oder Bougie (ggf. Hockeyschlägerform)	Check!
	Blockerspritze, Fixierungsmaterial, Gleitgel	Check!
	Alternativer Atemweg (SGA, Set für chirurgischen Atemweg)	Check!
P POSITIONING	Patienten lagern (Schnüffelposition/ verbesserte Jackson-Position)	Check!
	Aufgaben im Team verteilen und Positionen einnehmen	Check!
	Plan für Ablauf (10 for 10) und Alternativen (Plan B + C) kommunizieren	Check!
M MEDICATION	Frei laufende Infusion, möglichst 2 sichere i. v.-Zugänge	Check!
	Narkotikum, Analgetikum	Check!
	Muskelrelaxans	Check!
	Vasopressor (z. B. Push-Dose-Pressor/ Perfusor)	Check!
E EQUIPMENT ETCO2	Beatmungsfilter, Gänsegurgel	Check!
	Beatmungsgerät vorbereitet (angeschlossen, eingestellt)	Check!
	Kapnografie angeschlossen und laufend	Check!
	(möglichst auch während der Präoxygenierung)	
	Monitoring (RR, SpO2, EKG) - RR-Intervall ≤2 min, SpO2 laut stellen	Check!

NARKOSE MEDIKAMENTE

Beispiel-Kochrezepte - Narkose immer nach eigenem Standard!

"Quick & dirty": Midazolam 0,05 mg/kg (ca 5 mg) + Esketamin 1 mg/kg (ca 100 mg)
+ Rocuronium 1,2 mg/kg (100-150 mg) ODER Succinylcholin 1 mg/kg

Akutes kardiales Problem: Midazolam 0,15 mg/kg (ca 15 mg) + Fentanyl 2 µg/kg (ca 200 µg)
+ Rocuronium 1,2 mg/kg (100-150 mg) ODER Succinylcholin 1 mg/kg

ATEMWEG ERFOLGREICH GESICHERT	Beatmungsbeutel/ -gerät mit Kapnografie anschließen	Check!
	Kapnographische Lage-Bestätigung	Check!
	Auskultation: Atemgeräusch seitengleich, keine Mageninsufflation..	Check!
	Tubus fixieren, Doku Zahnreihe, Cuff-Druck 15-20 mmHg	Check!
	Medikamentöse Aufrechterhaltung der Narkose, ABC-Reevaluation	Check!

Intubation nicht erfolgreich: Maskenbeatmung zur Überbrückung! Ziel: Oxygenierung!

PLAN B — Supraglottischer Atemweg (SGA)
Spätestens nach dem 2. erfolglosen Intubationsversuch!
Einlage eines Larynxtubus/ Larynxmaske/ iGel (je nach Verfügbarkeit und Standards)
Bei Erfolg: Sichern des SGA und Oxygenierung/ Ventilation, Re-Evaluation

PLAN C — Emergency Front of Neck Access (EFONA) = Not-Koniotomie
Material: 10er-Skalpell, Bougie, 6.0er Endotrachealtubus
Vorbereitung: Kopf überstrecken, Laryngeal Handshake zum Finden des Lig. conicum
Quere Stichinzision - Skalpell mit Klinge nach unten drehen - Bougie - Tubus - Sichern

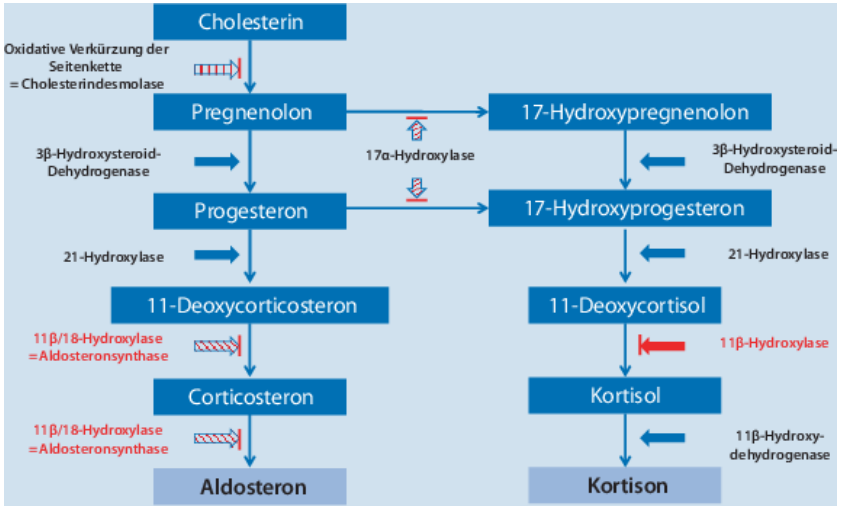
Etomidat ist ein **ultrakurzwirksames Hypnotikum**, das primär zur Einleitung einer Allgemeinanästhesie (Narkose) eingesetzt wird. Es zeichnet sich durch eine besonders hohe **kardiovaskuläre Stabilität** aus, weshalb es häufig bei Patienten mit Herz-Kreislauf-Erkrankungen oder instabilem Blutdruck bevorzugt wird.

Wichtigste Merkmale

- **Wirkung**: Wirkt rein hypnotisch (schlaferzwingend), besitzt aber **keine schmerzlindernde** (analgetische) Wirkung.
- **Wirkungseintritt**: Extrem schnell, meist innerhalb von **30 bis 60 Sekunden** nach der Injektion.
- **Wirkdauer**: Kurz, etwa **5 bis 15 Minuten** pro Einzeldosis.
- **Dosierung**: In der Regel **0,15 bis 0,3 mg pro kg** Körpergewicht.

Pharmakologie & Anwendung

Etomidat verstärkt die Wirkung des hemmenden Neurotransmitters GABA im Gehirn. Aufgrund seiner chemischen Struktur (Imidazolderivat) ist es nicht mit Barbituraten verwandt

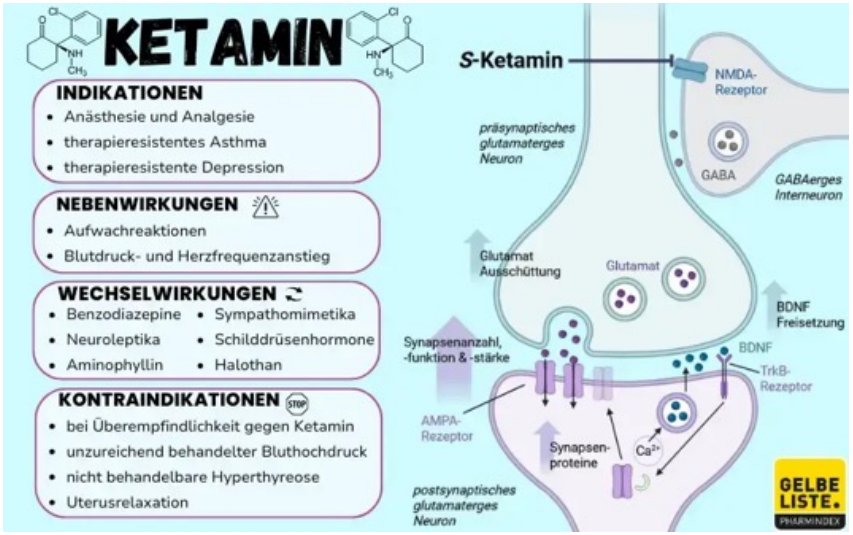


Dieses Narkosemittel blockiert gezielt das Enzym **11B-Hydroxylase** in der Nebennierenrinde. Dieses Enzym ist essenziell, um Vorstufen in aktives Cortisol umzuwandeln

Ketamin ist ein vielseitiger Wirkstoff, der primär als **Anästhetikum** (Narkosemittel) und **Schmerzmittel** in der Human- und Tiermedizin eingesetzt wird. In den letzten Jahren hat es zudem als schnell wirksames Mittel gegen **behandlungsresistente Depressionen** stark an Bedeutung gewonnen.

Medizinische Anwendung

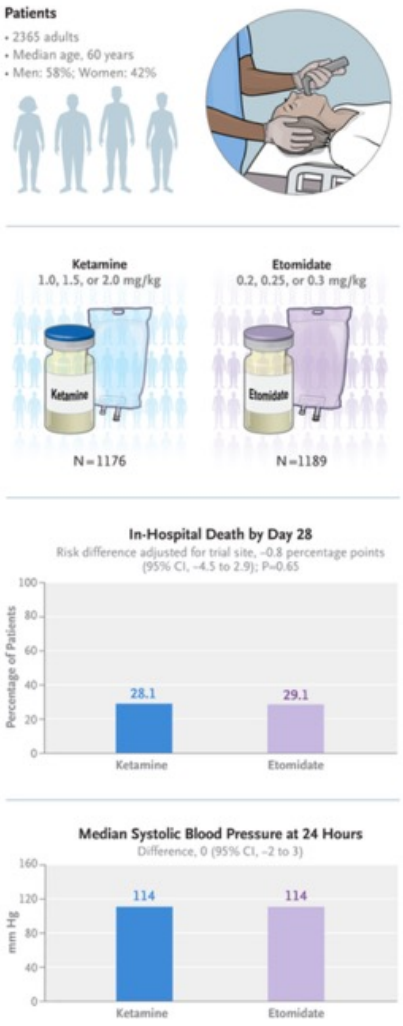
- **Anästhesie:** Es erzeugt eine „dissoziative Anästhesie“, bei der Patienten von ihrer Umwelt entkoppelt wirken, während Schutzreflexe (wie Schlucken) und die Eigenatmung meist erhalten bleiben.
- **Notfallmedizin:** Aufgrund seiner kreislaufaktivierenden Wirkung (Anstieg von Blutdruck und Herzfrequenz) ist es besonders bei Schockpatienten wertvoll.
- **Psychiatrie:** Das Enantiomer **Esketamin** ist als Nasenspray für Patienten zugelassen, bei denen herkömmliche Antidepressiva nicht wirken.



Ketamine works primarily by targeting the brain's glutamatergic system, specifically by blocking **NMDA (N-methyl-D-aspartate) receptors.**

Ketamine or Etomidate for Tracheal Intubation of Critically Ill Adults

For critically ill adults undergoing tracheal intubation, observational studies suggest that the use of etomidate to induce anesthesia may increase the risk of death. Whether the use of ketamine rather than etomidate decreases the risk of death is uncertain. In a randomized trial conducted in 14 emergency departments and intensive care units in the United States, we randomly assigned critically ill adults who were undergoing tracheal intubation to receive ketamine or etomidate for the induction of anesthesia. The primary outcome was in-hospital death from any cause by day 28. The secondary outcome was cardiovascular collapse during intubation, defined by the occurrence of a systolic blood pressure below 65 mm Hg, receipt of a new or increased dose of vasopressors, or cardiac arrest.



Etomidate is the medication most often used to induce anesthesia during emergency tracheal intubation in the United States. This imidazole-derived sedative–hypnotic agent, which acts on γ-aminobutyric acid receptors, has been described as an ideal induction medication for critically ill adults because of its rapid onset and limited effect on blood pressure and heart rate. However, etomidate inhibits 11β-hydroxylase in the adrenal glands, and a single dose decreases cortisol production for up to 72 hours. Concern that etomidate-induced corticosteroid insufficiency may cause organ dysfunction and death, particularly in patients with sepsis, has led regulators to remove etomidate from the market in multiple countries.

Ketamine, a dissociative agent that acts on *N*-methyl-d-aspartate receptors and does not impair cortisol production, is an increasingly used alternative to etomidate for induction of anesthesia in critically ill patients. Because its administration increases plasma catecholamine concentrations, ketamine has been postulated to maintain hemodynamic stability during intubation better than other induction medications. However, ketamine is also a negative inotrope and vasodilator, and observational studies have shown an association between the receipt of ketamine and hypotension, arrhythmia, and cardiac arrest during intubation.

Methods

Trial Design and Oversight

The Pragmatic Critical Care Research Group conducted this pragmatic, multicenter, unblinded, randomized, parallel-group trial in which the use of ketamine was compared with the use of etomidate for induction of anesthesia during emergency tracheal intubation of critically ill adults.

Randomization

Patients were randomly assigned in a 1:1 ratio to receive ketamine or etomidate for the induction of anesthesia during tracheal intubation. Randomization was performed with the use of permuted blocks of variable size and was stratified according to trial site.

Interventions

For patients assigned to the ketamine group, clinicians were instructed to administer ketamine intravenously to induce anesthesia for tracheal intubation. A nomogram provided a list of doses of ketamine (in milligrams) that was based on patient weight, which corresponded to a full dose (2.0 mg per kilogram of body weight), an intermediate dose (1.5 mg per kilogram), or a reduced dose (1.0 mg per kilogram).

Outcomes

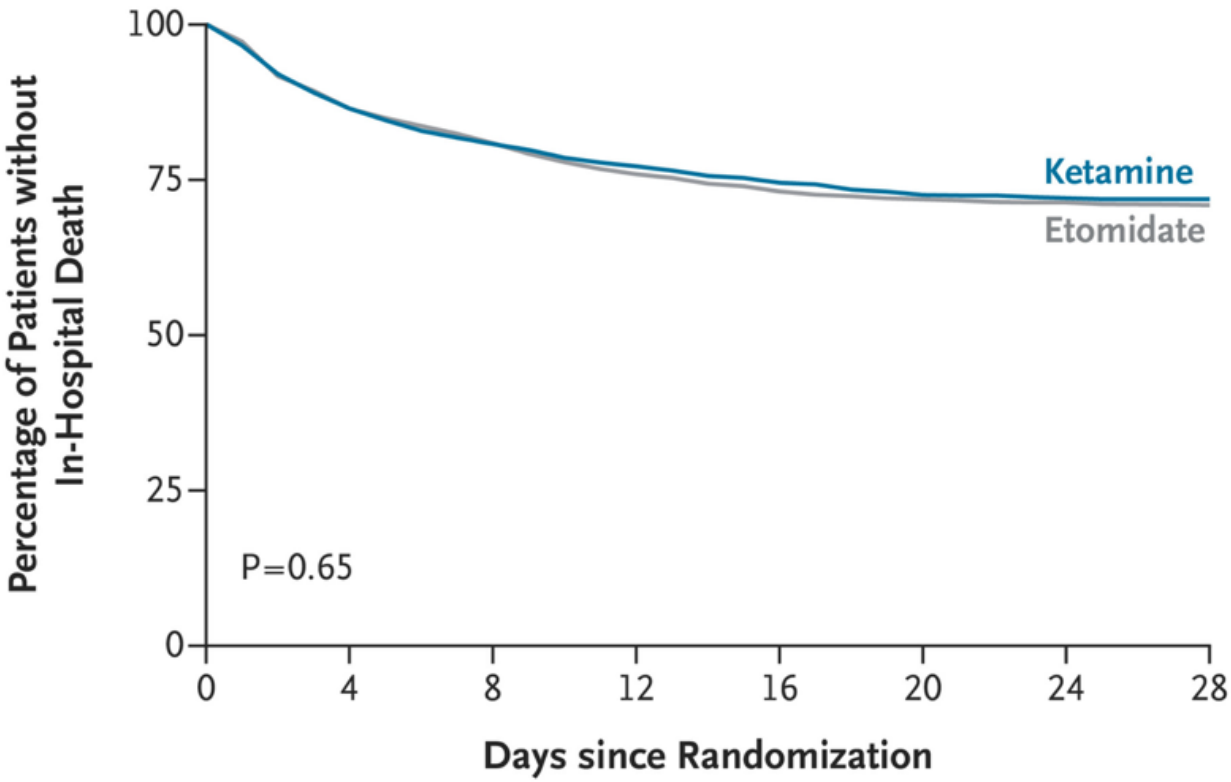
The primary outcome was in-hospital death by day 28, with outcome ascertainment ending at hospital discharge. The single prespecified secondary outcome was cardiovascular collapse during intubation, which was defined by the occurrence of any of the following events during the interval between induction of anesthesia and 2 minutes after tracheal intubation.

Patients

Characteristic	Ketamine (N=1176)	Etomidate (N=1189)
Median age (IQR) — yr	60 (45–69)	60 (44–69)
Female sex — no. (%)	498 (42.3)	492 (41.4)
Race or ethnic group — no. (%)†		
Non-Hispanic White	686 (58.3)	706 (59.4)
Non-Hispanic Black	300 (25.5)	287 (24.1)
Hispanic	130 (11.1)	132 (11.1)
Other	60 (5.1)	64 (5.4)
Median weight (IQR) — kg	78.9 (65.1–95.6)	78.5 (65.3–93.3)
Median body-mass index (IQR)‡	26.9 (23.0–32.4)	26.7 (22.5–32.1)
Location of intubation — no. (%)		
Emergency department	663 (56.4)	655 (55.1)
Intensive care unit	513 (43.6)	534 (44.9)
Chronic conditions — no. (%)		
Adrenal insufficiency or long-term receipt of glucocorticoids	136 (11.6)	129 (10.8)
Cirrhosis	165 (14.0)	166 (14.0)
Congestive heart failure	175 (14.9)	158 (13.3)
Coronary artery disease	141 (12.0)	153 (12.9)
Hypertension	536 (45.6)	533 (44.8)
Cancer	227 (19.3)	215 (18.1)
Acute conditions — no. (%)§		
Acute cardiac condition¶	216 (18.4)	223 (18.8)
Acute respiratory condition‖	678 (57.7)	683 (57.4)
Acute neurologic condition**	125 (10.6)	121 (10.2)
Sepsis or septic shock††	539 (45.8)	565 (47.5)
Median Glasgow Coma Scale score (IQR)‡‡	11 (7–15)	11 (7–15)
Median APACHE II score (IQR)§§	18 (13–24)	18 (13–24)
Median highest heart rate within 1 hr before enrollment (IQR) — beats per min	107 (90–125)	108 (92–126)
Median lowest systolic blood pressure within 1 hr before enrollment (IQR) — mm Hg¶¶	115 (96–136)	114 (94–135)
Receipt of vasopressors within 1 hr before enrollment — no. (%)	246 (20.9)	274 (23.0)

Intubation

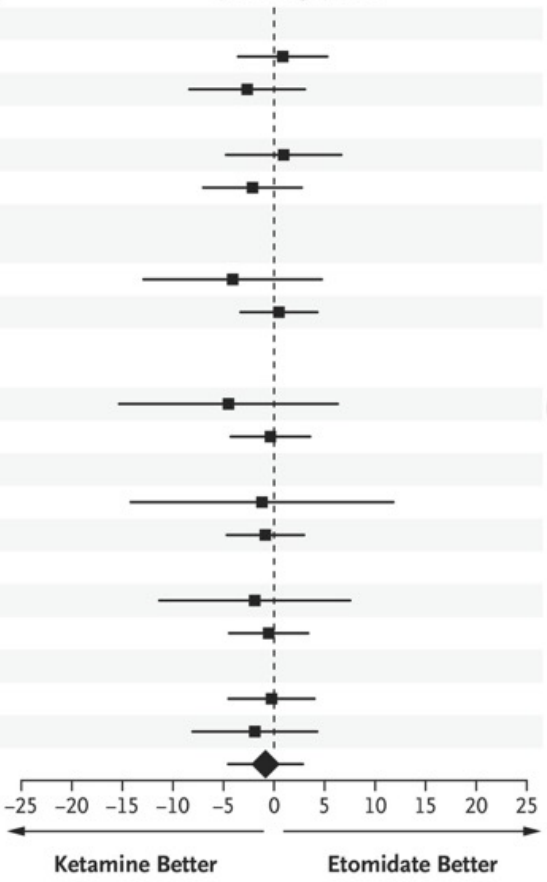
Characteristic	Ketamine (N=1176)	Etomidate (N=1189)	Difference (95% CI)*
Primary medication for induction of anesthesia — no. (%)†			
Ketamine	1167 (99.2)	3 (0.3)	99.0 (98.4 to 99.6)
Etomidate	6 (0.5)	1184 (99.6)	−99.1 (−99.6 to −98.5)
None	3 (0.3)	2 (0.2)	0.1 (−0.3 to 0.5)
Neuromuscular blocking agent — no. (%)‡			
Rocuronium	810 (69.0)	819 (69.0)	0.0 (−3.7 to 3.7)
Succinylcholine	362 (30.8)	365 (30.7)	0.1 (−3.6 to 3.8)
None	3 (0.3)	3 (0.3)	0.0 (−0.4 to 0.4)
Measurements or treatments at induction of anesthesia			
Median oxygen saturation (IQR) — %§	99 (97–100)	99 (97–100)	0 (−1 to 1)
Preoxygenation — no. (%)	1172 (99.7)	1186 (99.7)	−0.1 (−0.5 to 0.4)
Median systolic blood pressure (IQR) — mm Hg¶	127 (110–147)	127 (110–148)	0 (−3 to 3)
Vasopressor bolus or increased infusion rate — no. (%)	207 (17.6)	234 (19.7)	−2.1 (−5.2 to 1.1)
Laryngoscope used on the first attempt — no. (%)			
Video	1124 (95.6)	1127 (94.8)	0.8 (−0.9 to 2.5)
Direct	49 (4.2)	60 (5.0)	−0.9 (−2.6 to 0.8)
Other‖	3 (0.3)	2 (0.2)	0.1 (−0.3 to 0.5)
Instrument used on the first intubation attempt — no. (%)**			
Endotracheal tube with stylet	672 (57.3)	689 (58.1)	−0.8 (−4.7 to 3.2)
Bougie	455 (38.8)	446 (37.6)	1.2 (−2.7 to 5.1)
Neither endotrachal tube with stylet nor bougie	45 (3.8)	51 (4.3)	−0.5 (−2.1 to 1.1)



In-Hospital Death, According to Trial Group.

Shown is the percentage of patients without in-hospital death from enrollment through day 28. The incidence of in-hospital death by day 28 (the primary outcome) did not differ significantly between the ketamine group (28.1%) and the etomidate group (29.1%) (risk difference adjusted for trial site, −0.8 percentage points; 95% CI, −4.5 to 2.9; P=0.65 by a generalized linear mixed-effects model with a random effect for trial site).

Subgroup	Ketamine	Etomidate
	no. of patients with event/total no. of patients (%)	
Location of intubation		
Emergency department	128/661 (19.4)	121/653 (18.5)
Intensive care unit	202/512 (39.5)	224/533 (42.0)
Sepsis or septic shock		
Yes	209/538 (38.8)	215/563 (38.2)
No	121/635 (19.1)	130/623 (20.9)
Vasopressor use <1 hr before enrollment		
Yes	115/246 (46.7)	136/273 (49.8)
No	215/927 (23.2)	209/913 (22.9)
Adrenal insufficiency or long-term glucocorticoid use		
Yes	45/136 (33.1)	48/129 (37.2)
No	285/1037 (27.5)	297/1057 (28.1)
Acute neurologic condition		
Yes	44/125 (35.2)	45/120 (37.5)
No	286/1048 (27.3)	300/1066 (28.1)
Acute cardiac condition		
Yes	87/216 (40.3)	95/222 (42.8)
No	243/957 (25.4)	250/964 (25.9)
APACHE II score		
<20	118/649 (18.2)	123/658 (18.7)
≥20	212/524 (40.5)	222/528 (42.0)
Overall	**330/1173 (28.1)**	**345/1186 (29.1)**

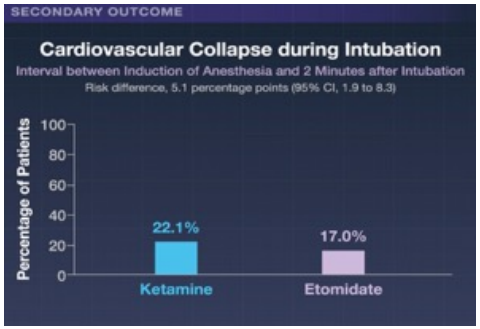


Subgroup Analyses of the Primary Outcome.

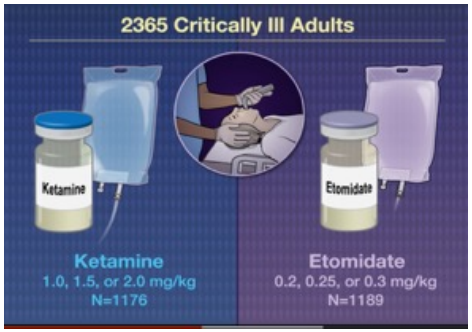
Shown are the absolute risk differences and 95% confidence intervals with adjustment for trial site for in-hospital death by day 28 (the primary outcome) in the ketamine group as compared with the etomidate group in each prespecified subgroup. Differences between the ketamine group and the etomidate group were calculated with the use of a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group, the proposed effect modifier, and the interaction between the trial group and the proposed effect modifier without adjustment for covariates. Differences of less than 0 indicate a lower likelihood of death with the use of ketamine. Sepsis or septic shock at enrollment was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Chronic glucocorticoid use was defined as receipt of glucocorticoids for at least 3 consecutive weeks before enrollment. An acute neurologic condition was defined as active intracranial bleeding, meningitis, encephalitis, or stroke. An acute cardiac condition was defined as active cardiac arrest, cardiogenic shock, congestive heart failure, cardiogenic pulmonary edema, pulmonary hypertension, or myocardial infarction. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score ranges from 0 to 71, with higher scores indicating a greater severity of illness. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two groups.

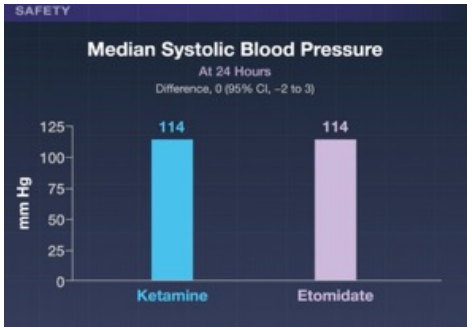

Etomidate
Commonly used to induce anesthesia


TRIAL
SAFETY
Ketamine
Etomidate


SECONDARY OUTCOME
Cardiovascular Collapse during Intubation
Interval between Induction of Anesthesia and 2 Minutes after Intubation
Risk difference, 5.1 percentage points (95% CI, 1.9 to 8.3)
Percentage of Patients
100
80
60
40
20
0
22.1%
17.0%
Ketamine
Etomidate

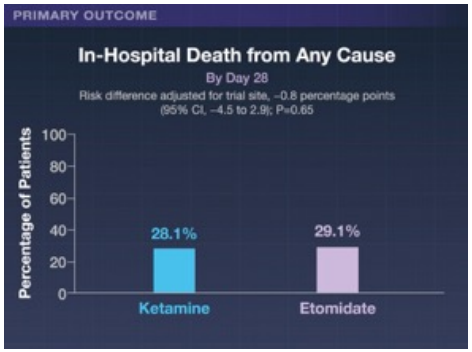

Etomidate
May increase risk of death

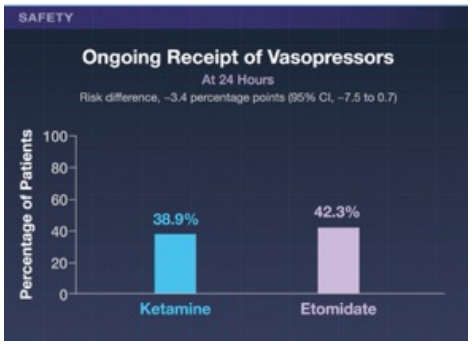

2365 Critically Ill Adults
Ketamine
Etomidate
Ketamine
1.0, 1.5, or 2.0 mg/kg
N=1176
Etomidate
0.2, 0.25, or 0.3 mg/kg
N=1189


SAFETY
Median Systolic Blood Pressure
At 24 Hours
Difference, 0 (95% CI, −2 to 3)
mm Hg
125
100
75
50
25
0
114
114
Ketamine
Etomidate


Ketamine
Incidence
Did not result in a significantly lower incidence of in-hospital death by day 28 than etomidate


Ketamine
Decrease risk of death


PRIMARY OUTCOME
In-Hospital Death from Any Cause
By Day 28
Risk difference adjusted for trial site, −0.8 percentage points
(95% CI, −4.5 to 2.9); P=0.65
Percentage of Patients
100
80
60
40
20
0
28.1%
29.1%
Ketamine
Etomidate


SAFETY
Ongoing Receipt of Vasopressors
At 24 Hours
Risk difference, −3.4 percentage points (95% CI, −7.5 to 0.7)
Percentage of Patients
100
80
60
40
20
0
38.9%
42.3%
Ketamine
Etomidate

REVIEW ARTICLE

Spinal Epidural Abscess

Summary

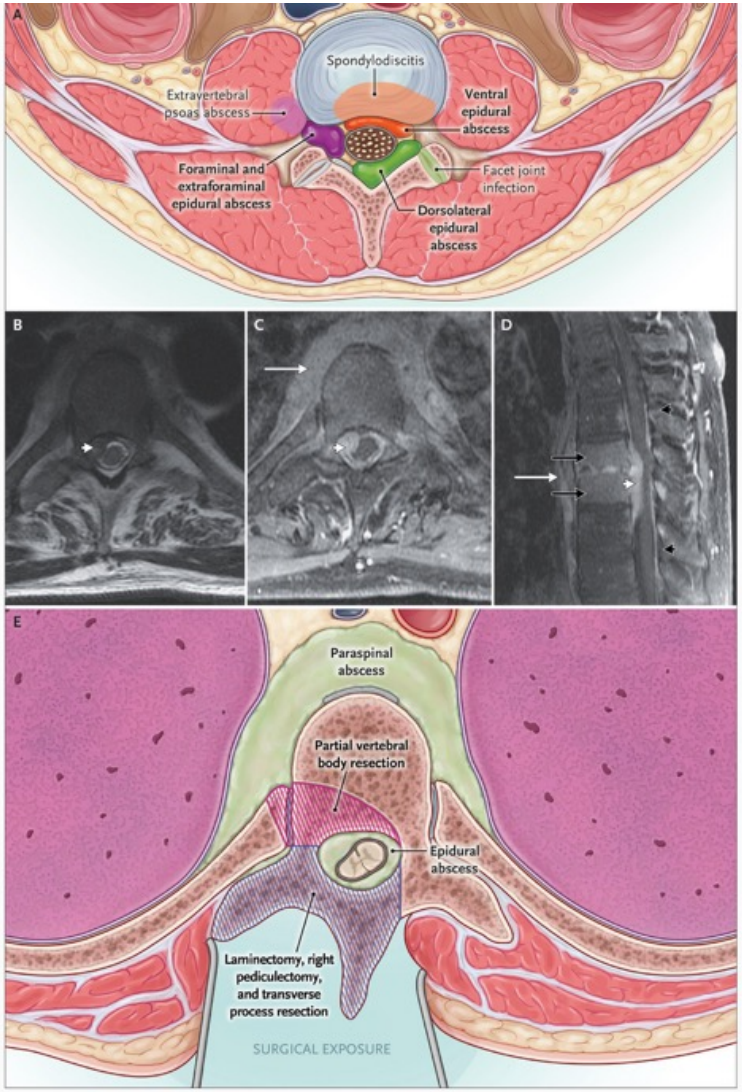
Spinal epidural abscess is an infection in the epidural space. Patients typically present with localized back or neck pain (or both) that is accompanied by fever or neurologic symptoms. Magnetic resonance imaging with contrast enhancement is the diagnostic test of choice. An accurate microbiologic diagnosis is important and can be made with blood cultures, with tissue and fluid cultures obtained by image-guided needle aspiration or biopsy, or at the time of surgery. *Staphylococcus aureus* is the most frequent pathogen, causing more than 50% of infections. All patients with spinal epidural abscess should be promptly evaluated by a spine surgeon and an infectious-disease specialist. Many patients with spinal epidural abscess undergo surgery, although antimicrobial therapy alone may be curative in carefully selected patients.

KEY POINTS

Spinal Epidural Abscess

- Spinal epidural abscess is an infection in the epidural space; patients typically present with localized back or neck pain (or both) that is accompanied by fever or neurologic symptoms.
- Concomitant infection involving intervertebral discs (discitis), vertebral bodies (vertebral osteomyelitis), or facet joints (septic arthritis) — or a combination of these — is common.
- Magnetic resonance imaging with contrast enhancement is the diagnostic test of choice.
- An accurate microbiologic diagnosis is important and can be made with blood cultures or with tissue and fluid cultures obtained by image-guided needle aspiration or biopsy or at the time of surgery. *Staphylococcus aureus* is the most frequent pathogen, causing more than 50% of infections.
- All patients with spinal epidural abscess should be promptly evaluated by a spine surgeon and an infectious-disease specialist to determine the appropriate medical and surgical treatment to achieve the best outcome.
- Although many patients with spinal epidural abscess undergo surgery, antimicrobial therapy alone may be curative in carefully selected patients.

Spinal Epidural Abscess and Contiguous Infection of Nearby Structures.
A cross-sectional image of the vertebral structures and surrounding musculature at the level of L3–L4 shows spinal epidural abscesses that are contiguous with vertebral or extravertebral structures (Panel A). In green, a facet joint infection is contiguous with a dorsolateral epidural abscess. In red, spondylodiscitis is contiguous with a ventral epidural abscess. In purple, an extravertebral psoas abscess is contiguous with a foraminal and extraforaminal epidural abscess. A 56-year-old man presented with a 2-week history of thoracic back pain and a 5-day history of progressive weakness and numbness of the legs and feet. MRI (Panel B, axial T2-weighted; Panel C, axial T1-weighted postcontrast with fat saturation at the level of T6–T7; Panel D, sagittal T1-weighted postcontrast with fat saturation) shows enhancement of the T6–T7 vertebral bodies (black arrows) and T6–T7 interspace indicating discitis osteomyelitis. Flagrant enhancing ventral paraspinal abscess (white arrow) displaces the great vessels anteriorly, and right lateral ventrolateral epidural abscess (short white arrows) causes advanced spinal canal stenosis and deformity of the cord. Enhancing ventral and dorsal (short black arrows) epidural phlgemon extends from T5 to T9. The patient underwent emergency epidural abscess evacuation by means of a laminectomy, right facetectomy, and pediculectomy to facilitate transpedicular decompression of the ventral abscess using a posterior approach. Discectomy and partial resection of the vertebral body were performed, followed by posterior fusion using allograft and segmental instrumentation from T5 to T9. Purulent fluid removed from the ventral epidural space during surgery grew *Escherichia coli* and *Bacteroides fragilis.* A posterior surgical approach was used in performance of a laminectomy, right pediculectomy, partial resection of the vertebral body for decompression, and evacuation of an epidural abscess in the thoracic spine (Panel E).

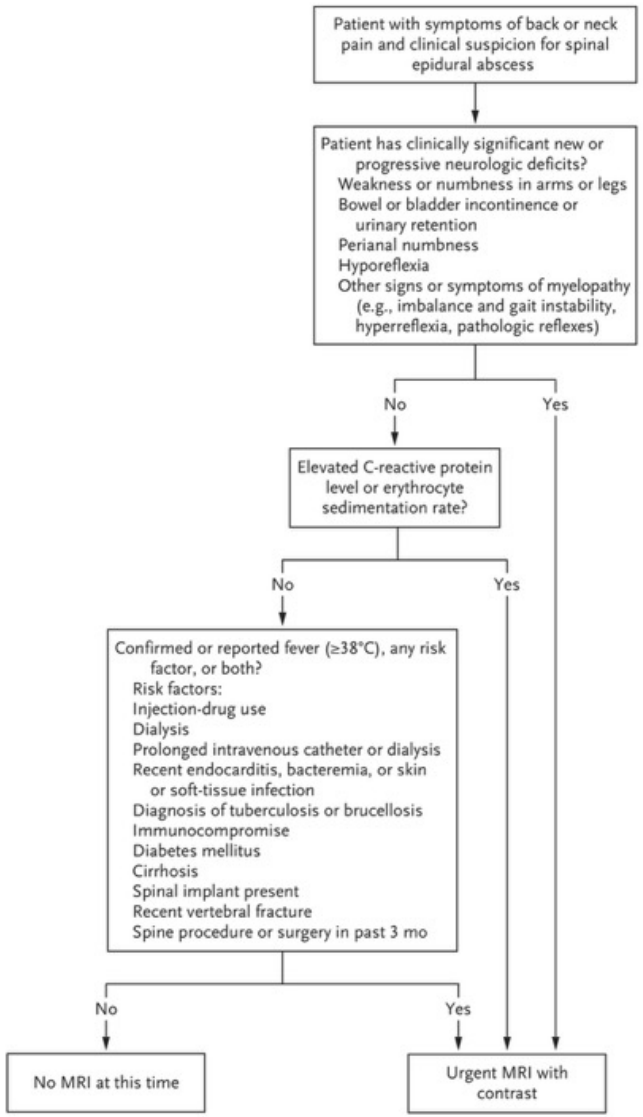


Clinical Factors Associated with Contiguous Spinal Epidural Abscess and Infection after Spinal Surgery.[*]

Factors associated with contiguous spinal epidural abscess
Injection-drug use
Diabetes mellitus
End-stage renal disease
Long-term use of indwelling vascular catheters
Immunocompromise conditions
Recent history of endocarditis, bacteremia, or skin or soft-tissue infection
Cirrhosis
Alcohol abuse
Obesity
Recent vertebral fracture
Factors associated with spinal surgical-site infection
Diabetes mellitus
Obesity
Prolonged operative time
Posterior surgical approach
Surgery on seven or more vertebral levels
Hypertension
Intraoperative blood transfusion
Elevated ASA score†
Revision surgery
Tobacco use
Osteotomy
Fusion involving pelvis or sacrum

Pathogens Associated with Spinal Epidural Abscess.

Pathogen	Infections Attributable to Pathogen or Pathogen Group
	%
Methicillin-susceptible *Staphylococcus aureus*	40
Methicillin-resistant *S. aureus*	18
Coagulase-negative staphylococcus species	5
Streptococcus or enterococcus species	10
Aerobic gram-negative bacilli	4
Other pathogens	6
Polymicrobial infections	2
No growth or unknown	14



Outcomes

There is no standard structure for reporting treatment outcomes in spinal epidural abscess. Approximately 3 to 6% of patients with the disease die during hospitalization, and 6 to 13% die within 90 days after hospitalization. Although some recent data suggest lower mortality with surgery than with nonoperative management, there are conflicting data from other high-quality studies with regard to this finding. Among the patients who survive, most are cured, and recurrence is uncommon. Neurologic outcomes are most accurately predicted by the patient's neurologic status at the time of surgery or initiation of therapy. One meta-analysis showed a good neurologic outcome in 86% of patients with early surgical intervention as compared with 69% with nonoperative treatment. However, these data may not fully reflect the experience of patients selected for nonoperative treatment, which highlights the importance of individualized treatment decisions.

Conclusions and Future Directions

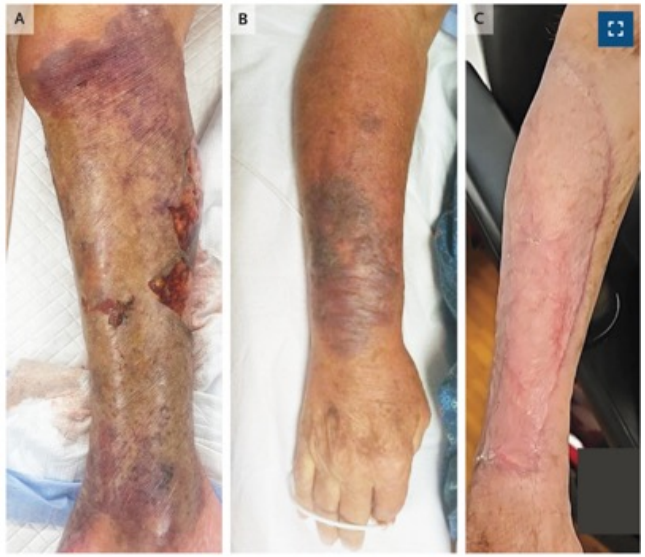
Considerable challenges remain with regard to the understanding, diagnosis, and management of spinal epidural abscess. Close cooperation between the medical team, infectious-disease specialist, and the surgeon are essential to achieving the best possible outcome. Future studies should focus on the evaluation and refinement of published diagnostic algorithms to hasten diagnosis. The explosion of knowledge about the disease and the availability of advanced statistical models have the potential to improve the identification of patients who can be successfully treated nonoperatively. Therapeutic image-guided aspiration may be a valuable adjunct to nonoperative management, but this technically challenging procedure deserves further investigation before routine implementation. Finally, establishment of standardized classification, outcome definitions, and reporting would better allow the study of this uncommon but important illness in a systematic manner, providing clear answers with regard to the appropriate management approach.

Bronchial Casts from Inhalation of Forest-Fire Smoke

The Images in Clinical Medicine featured in this issue of the Journal spotlight some of the effects of the climate crisis on clinical health.

An 87-year-old man presented to the emergency department with difficulty breathing after having inhaled thick smoke from a forest fire for several hours. His respiratory rate was 29 breaths per minute, and he had an oxygen saturation of 85% while breathing ambient air. On physical examination, diffuse rales were found on lung auscultation, but no evidence of upper-airway thermal injury or cutaneous burns was observed. A radiograph of the chest showed diffuse interstitial infiltrates. The serum carbon monoxide level was normal. The patient's respiratory status worsened, which led to endotracheal intubation and mechanical ventilation. Owing to elevated airway pressures and difficulty in providing ventilation to the patient, flexible bronchoscopy was performed to evaluate patency of the airways. Black casts were seen overlying the carina and extending into the mainstem bronchi. A diagnosis of bronchial casts from the inhalation of particulate matter from forest-fire smoke was made. The casts were removed with a cryoprobe. Extubation was performed 3 days after the casts were extracted, and the patient was treated for concurrent pneumonia (to which the infiltrates on the chest radiograph were attributed) and discharged after a 1-week hospital stay. At follow-up 2 weeks later, the patient's breathing had returned to normal.

Vibrio vulnificus Necrotizing Soft-Tissue Infection



The Images in Clinical Medicine featured in this issue of the Journal spotlight some of the effects of the climate crisis on clinical health.

A 74-year-old man presented to the emergency department with a 3-day history of a painful laceration on his right leg that he had sustained while jumping into waters off the Gulf Coast of Florida. Two days after the injury to his leg, skin changes had appeared on his right arm. He had no known history of chronic liver disease or an immunocompromising condition. On physical examination, ecchymosis, crepitus, and desquamation of the right lower leg were observed (Panel A). The right forearm had erythema, swelling, and ecchymosis with a hemorrhagic bulla (Panel B). Urgent surgical débridement of the arm and leg was performed. Blood and tissue cultures grew *Vibrio vulnificus*. A diagnosis of *V. vulnificus* necrotizing soft-tissue infection was made. *V. vulnificus* is found in warm, low-salinity coastal and estuarine waters. Transmission occurs primarily through consumption of undercooked seafood or exposure of open wounds to water containing the bacteria. The abundance and geographic range of *V. vulnificus* is projected to increase owing to factors related to climate change, including rising water temperatures, storm surges, salinity changes, and algal blooms. This patient was ultimately treated with above-the-knee amputation and meshed autografting of the forearm, and he completed a course of ceftriaxone and doxycycline. At 6 months after autografting and amputation, the forearm (Panel C) and amputation site had healed well.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

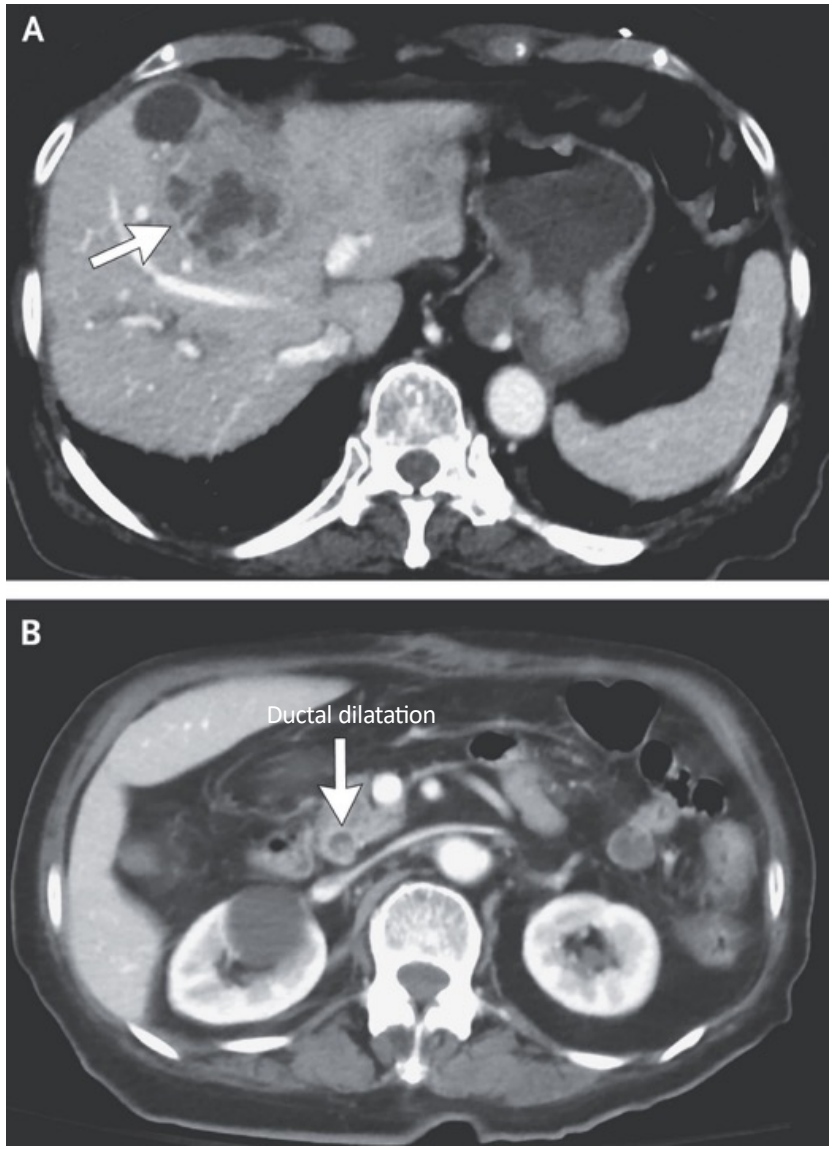
Case 12-2026: An 86-Year-Old Woman with Anorexia, Weight Loss, and Liver Lesions

An 86-year-old woman presented to the emergency department of this hospital because of anorexia, weight loss, and weakness.

The patient had been in her usual state of health until 3 weeks before the current presentation, when anorexia developed with minimal oral intake. The patient noticed generalized weakness, and she had difficulty getting out of bed and performing activities of daily living. Owing to progressively worsening symptoms, she was brought by a friend to the emergency department of this hospital.

On examination in the emergency department, the heart rate was 85 beats per minute, the oral temperature 35.9°C, the blood pressure 113/56 mm Hg, the respiratory rate 16 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. Physical examination revealed mild conjunctival icterus, fine basilar crackles in the lungs, and tenderness on deep palpation of the right upper quadrant without rebound or guarding. No organomegaly or adenopathy was detected.

Computed tomography (CT) of the abdomen and pelvis, performed after the administration of intravenous contrast material, revealed choledocholithiasis, thickening of the bile duct walls, and mild intrahepatic and extrahepatic ductal dilatation. In addition, four indeterminate hypodense hepatic lesions were identified in the left and right lobes of the liver. One lesion in liver segment 4 measured 4.5 cm in the greatest dimension. A review of systems was notable for anorexia and a weight loss of 7 kg during the previous 3 weeks. The patient reported no fever, rigors, night sweats, abdominal pain, nausea, pruritus, darkening of the urine, hematochezia, melena, acholic stools, or postprandial abdominal discomfort. Her medical history was notable for hyperlipidemia, type 2 diabetes mellitus, long-standing nonprogressive fibrotic lung disease, mild cognitive impairment, and localized estrogen receptor–positive ductal carcinoma that had been treated with mastectomy and tamoxifen therapy 30 years earlier.



Medications included metformin, donepezil, and rosuvastatin. She had no known adverse reactions to medications. She was originally from East Asia but had lived in urban Massachusetts for decades, with no recent international travel. She was widowed, lived with a friend, and had a pet cat. Her family history was notable for gallstones in her mother.

Laboratory test results were notable for a potassium level of 3.0 mmol per liter (reference range, 3.4 to 5.0), an alkaline phosphatase level of 418 U per liter (reference range, 45 to 115), and a total bilirubin level of 2.2 mg per deciliter (38 µmol per liter; reference range, 0.0 to 1.0 mg per deciliter [0 to 17 µmol per liter]). The blood levels of carcinoembryonic antigen, CA 19-9, and CA 15-3 were within normal limits. Blood specimens were obtained for culture, and no growth was observed; additional laboratory test results are shown.

Variable	Reference Range, Adults†	On Initial Evaluation
Blood		
Hemoglobin (g/dl)	12.0–16.0	13.1
Hematocrit (%)	36.0–46.0	41.3
White-cell count (per µl)	4500–11,000	12,260
Differential count (per µl)		
Neutrophils	1800–7700	10,370
Lymphocytes	1000–4800	1080
Monocytes	200–1200	680
Eosinophils	0–900	10
Basophils	0–300	10
Immature granulocytes	0–100	20
Platelet count (per µl)	150,000–400,000	311
Sodium (mmol/liter)	135–145	132
Potassium (mmol/liter)	3.4–5.0	3.0
Chloride (mmol/liter)	98–108	93
Carbon dioxide (mmol/liter)	23–32	24
Urea nitrogen (mg/dl)	8–25	20
Creatinine (mg/dl)	0.60–1.50	0.60
Glucose (mg/dl)	70–110	165
Phosphorus (mg/dl)	2.6–4.5	2.8
Calcium (mg/dl)	8.5–10.5	10.4
Total protein (g/dl)	6.0–8.3	7.4
Albumin (g/dl)	3.3–5.0	3.4
Alanine aminotransferase (U/liter)	7–33	28
Aspartate aminotransferase (U/liter)	9–32	32
Alkaline phosphatase (U/liter)	45–115	418
Total bilirubin (mg/dl)	0.0–1.0	2.2
Direct bilirubin (mg/dl)	0.0–0.4	1.5
International normalized ratio	0.91–1.16	1.10
Urine		
Color	Yellow	Yellow
Clarity	Clear	Clear
pH	5.0–9.0	6.5
Specific gravity	1.001–1.035	1.040
Glucose	Negative	1+
Ketones	Negative	3+
Leukocyte esterase	Negative	Negative
Nitrite	Negative	Negative
Blood	Negative	Negative
Protein	Negative	1+
Erythrocytes (per high-power field)	0–2	0
Leukocytes (per high-power field)	<10	0
Bacteria	None	None

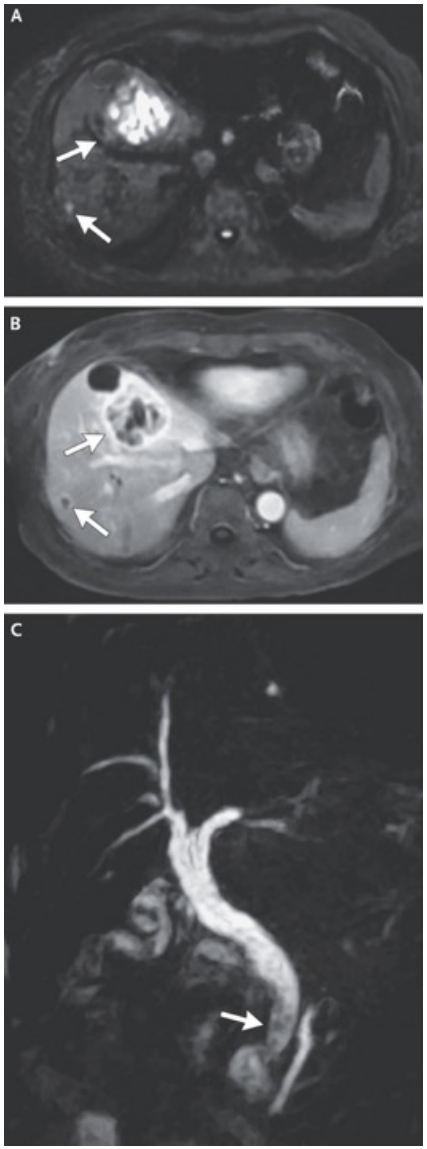
No inflammatory markers?

Magnetic resonance imaging (MRI) of the abdomen and magnetic resonance cholangiopancreatography (MRCP) were performed on hospital day 1. MRCP confirmed the presence of choledocholithiasis and showed biliary ductal dilatation with wall thickening and hyperenhancement. The four hepatic lesions previously identified in segments 2, 4, 7, and 8 showed heterogeneous signal intensity on T2-weighted images, irregular enhancement, and restricted diffusion.

A diagnostic test was performed.

Naming the Clinical Syndrome

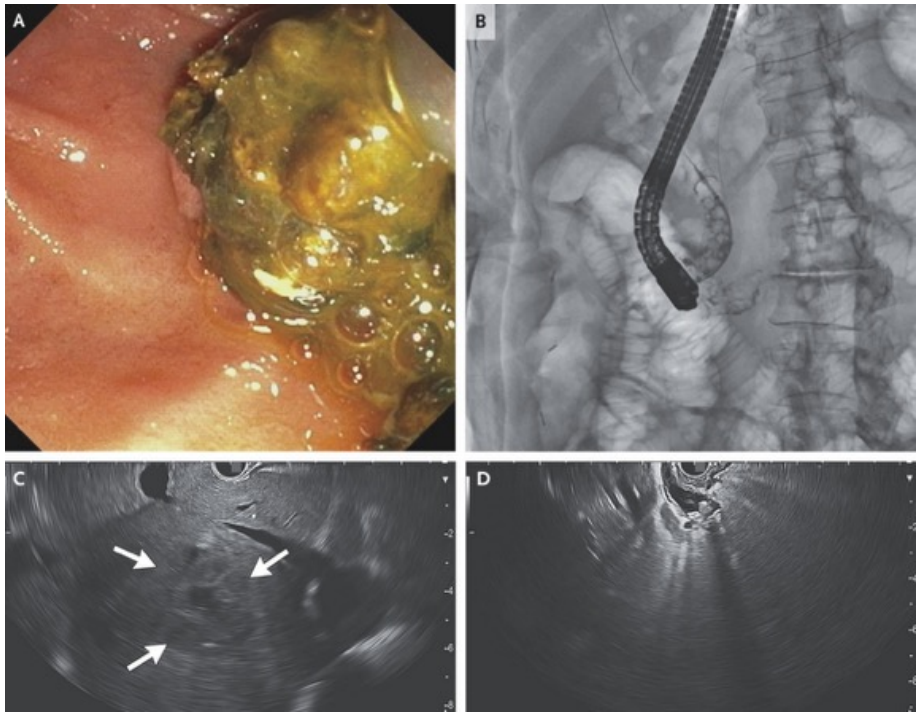
The final component of the problem representation is to name the clinical syndrome. In addition to the multifocal liver lesions, the patient's clinical course is also characterized by wasting, with a 7-kg weight loss, and cholestatic liver injury, each of which suggests an inflammatory process leading to liver injury and tissue catabolism.



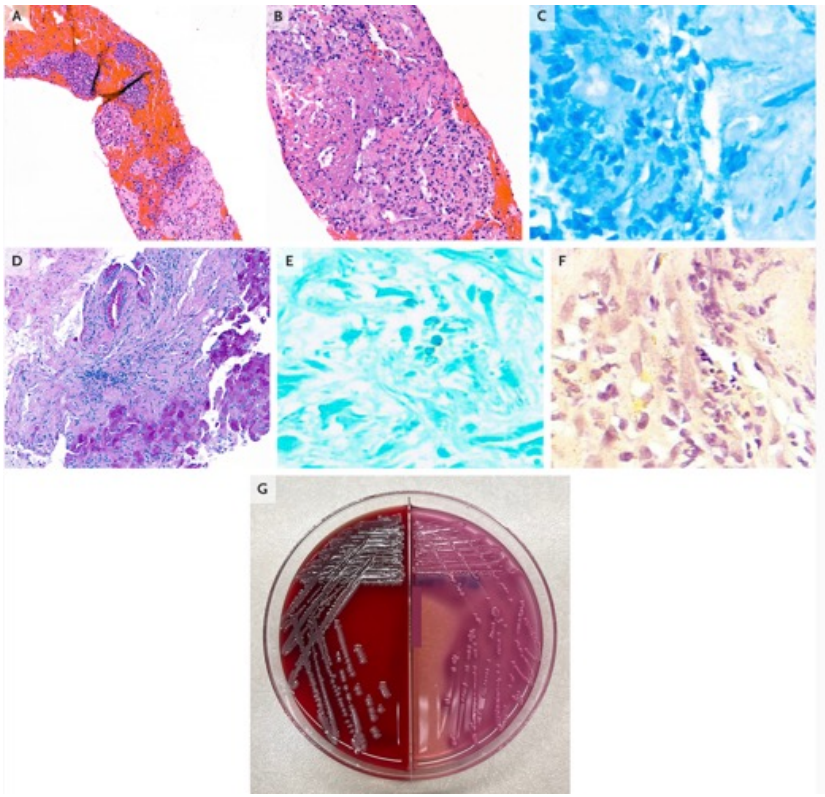
Diagnostic Studies and Discussion of Management

Given the detection of choledocholithiasis on MRCP, endoscopic retrograde cholangiopancreatography (ERCP) was planned. In addition, the presence of multiple liver masses on imaging was suggestive of metastases and warranted further evaluation with endoscopic ultrasonography and guided fine-needle biopsy for pathological confirmation.

An initial upper endoscopy was performed. After no abnormal findings were noted in the esophagus, stomach, or duodenum, the therapeutic linear echoendoscope was advanced to the stomach. From the gastric cardia, a round mass was identified in the left lobe of the liver. The mass was lobulated, appeared multicystic, and measured 30 mm in the maximal cross-sectional diameter. Fine-needle biopsy of the mass was performed with the use of a 22-gauge core-biopsy needle.



Next, ERCP was performed. After cannulation of the bile duct, endoscopic ultrasound images showed a heterogeneous, well-circumscribed mass in the left lobe of the liver and a moderately dilated common bile duct with numerous filling defects that were consistent with gallstones. A complete biliary sphincterotomy was performed. Extensive sludge and stone fragments were removed with the use of an extraction balloon.



Pathological Discussion

A core-biopsy specimen of the liver mass was submitted for pathological evaluation. The specimen contained an abscess characterized by necrotic tissue and a mixed inflammatory infiltrate. Hematoxylin and eosin staining revealed areas of necrosis with an infiltrate composed of neutrophils, lymphocytes, and macrophages that was consistent with acute inflammation. These findings strongly suggested an infection, although the specific causative microorganism remained undetermined.

Additional Pathological Discussion

The aspirate obtained from the liver was cultured on both blood agar and MacConkey agar. Blood agar provides a rich medium that supports the growth of a broad range of microorganisms, including common gram-positive and gram-negative organisms. In contrast, MacConkey agar is selective for gram-negative bacteria, particularly enteric organisms. The use of both media enhances the likelihood of detecting the spectrum of possible pathogens.

Bacterial growth was observed on a biplate of blood agar and MacConkey agar, a finding that suggested the presence of a mixed microbial population. Matrix-assisted laser desorption ionization–time-of-flight (MALDI-TOF) mass spectrometry was subsequently used for precise microbial identification; this technique enabled the accurate detection of *E. coli* as the causative organism. The identification of *E. coli* in this case suggested either a gastrointestinal or hepatobiliary source of infection or hematogenous or portal venous spread from distant viscera, since this bacterium is a common pathogen in intraabdominal infections.

Pathological Diagnosis

Pyogenic liver abscess due to *Escherichia coli* infection.

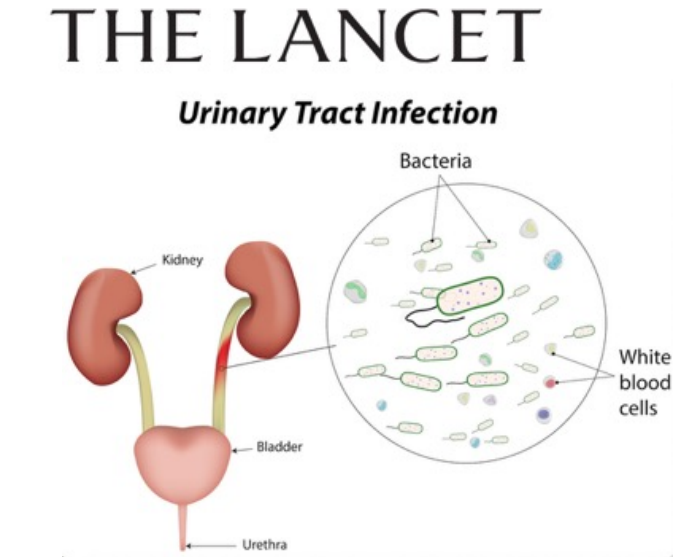
Follow-up

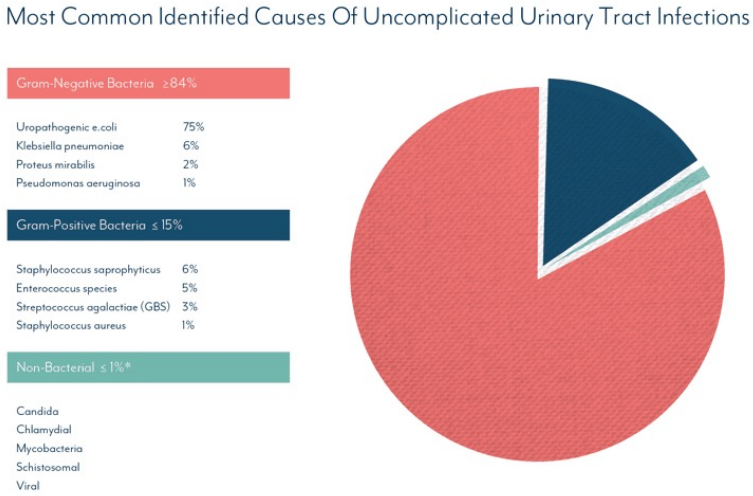
After the diagnostic procedure, the patient initially received treatment with piperacillin–tazobactam, which was later changed to ceftriaxone and metronidazole on the basis of results of antimicrobial susceptibility testing.

Unkomplizierte Harnwegsinfektionen (HWI), insbesondere die **akute, unkomplizierte Zystitis** (Blasenentzündung), sind sehr häufige bakterielle Infektionen, die vor allem Frauen im geschlechtsreifen Alter betreffen. Als „unkompliziert“ gilt eine Blasenentzündung, wenn sie bei einer nicht schwangeren Frau ohne relevante anatomische oder funktionelle Anomalien des Harntrakts sowie ohne Begleiterkrankungen auftritt.

Symptome:

- Brennen oder Schmerzen beim Wasserlassen (Dysurie).
- Häufiger Harndrang (Pollakisurie) mit Entleerung kleiner Mengen.
- Schmerzen oberhalb des Schambeins.
- Trüber oder stark riechender Urin, manchmal Blutbeimengung.
- *Fehlen* von Fieber oder Flankenschmerzen.

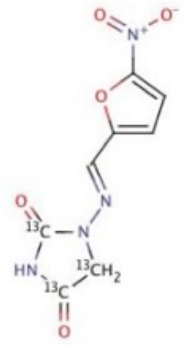




Nitrofurantoin ist ein **Antibiotikum**, das fast ausschließlich zur Behandlung und Vorbeugung von unkomplizierten **Harnwegsinfektionen** (z. B. Blasenentzündungen) eingesetzt wird. Es gehört zur Gruppe der Nitrofurane und zeichnet sich dadurch aus, dass es im Blut schnell abgebaut wird, sich aber in hohen Konzentrationen im Urin ansammelt.

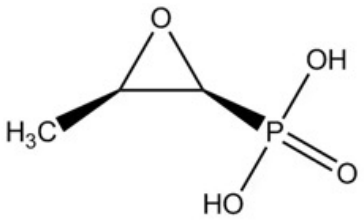
Wichtige Fakten zur Anwendung

- **Wirkungsweise**: Es tötet Bakterien ab (bakterizid), indem es deren Stoffwechsel und Erbgut schädigt.
- **Einnahme**: In der Regel mit oder nach den Mahlzeiten einnehmen, um die Aufnahme zu verbessern und Magenbeschwerden zu lindern.
- **Dauer**: Bei akuten Infektionen meist 5 bis 7 Tage.
- **Besonderheit**: Der Urin kann sich dunkelgelb oder bräunlich verfärben. Das ist harmlos und kein Grund zur Sorge.



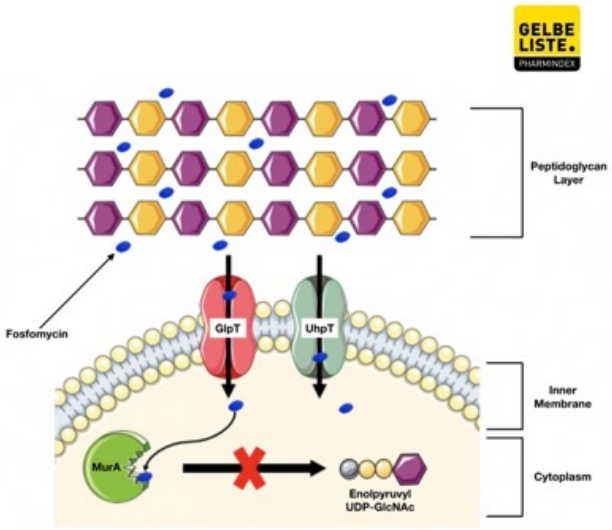
Nitrofurantoin is **not** derived from a microorganism.
It is a **fully synthetic** chemical compound.

Fosfomycin ist ein Breitbandantibiotikum und gehört zu den Epoxyd-Verbindungen. Es zeigt eine gute Wirksamkeit gegen grampositive und gramnegative Bakterien. Aufgrund seiner besonderen Wirkweise ist es vor allem bei akuten Harnwegsinfektionen von besonderer Bedeutung.



Wirkmechanismus

Fosfomycin wirkt bakterizid auf wachsende Krankheitserreger, indem es die Synthese der Bakterienzellwand hemmt. Es blockiert die erste Stufe der intrazellulären Zellwandsynthese durch die Hemmung der Peptidoglykansynthese. Der Wirkstoff wird über zwei verschiedene Transportsysteme, das sn-Glycerin-3-phosphat- und das Hexose-6-Transportsystem, aktiv in die Bakterienzelle transportiert.



Fosfomycin was first isolated in 1969 from soil samples containing cultures of *Streptomyces fradiae*, *Streptomyces viridochromogenes*, and *Streptomyces wedmorensis*.

Pharmakokinetik

Resorption

Nach oraler Einnahme von Fosfomycin beträgt die Bioverfügbarkeit etwa 33–53%.
Nahrung verzögert den Zeitpunkt der maximalen Harnkonzentrationen um vier Stunden.
Fosfomycin wird auch über die enterohepatische Rezirkulation wieder aufgenommen.

Clinical and bacteriological effectiveness of three different short-course antibiotic regimens and single-dose fosfomycin for uncomplicated lower urinary tract infections in women (SCOUT): a pragmatic, multicentre, open-label, randomised clinical trial

Summary

Background Most guidelines recommend nitrofurantoin, fosfomycin, and sometimes pivmecillinam for uncomplicated urinary tract infections (UTIs), but direct comparisons between these antibiotics are needed. This study evaluated the effectiveness and safety of a single dose of fosfomycin compared with two doses of fosfomycin and short-course regimens of nitrofurantoin and pivmecillinam in women with UTI symptoms.

Methods This phase 4, pragmatic, multicentre, parallel-group, open-label, randomised clinical trial was conducted in Spanish primary care centres from 2022 to 2024. Women aged 18 years or older with at least one UTI-specific symptom (dysuria, urinary urgency, urinary frequency, or suprapubic tenderness) and a positive urine dipstick test for either nitrites or leukocyte esterase were randomly assigned (1:1:1:1) to one of four treatments: a single 3 g dose of fosfomycin, two 3 g doses of fosfomycin, nitrofurantoin (100 mg three times per day for 5 days), or pivmecillinam (400 mg three times per day for 3 days). Doctors and patients were not masked to group assignment. The primary outcome was the proportion of patients with clinical resolution (defined as the disappearance of all infection symptoms) at day 7. This trial is registered with ClinicalTrials.gov (NCT04959331) and EudraCT (2021-001332-26) and is completed.

Findings Of the 804 patients assessed for eligibility between April 4, 2022 and Nov 14, 2024, 768 patients were randomly allocated (191 to the single-dose fosfomycin group, 194 to the two-dose fosfomycin group, 190 to the nitrofurantoin group, and 193 to the pivmecillinam group). Patients had a median age of 48 years (IQR 34–63). Race and ethnicity data were not collected. Among the 720 women with available data included in the primary analysis, single-dose fosfomycin had the lowest proportion of clinical resolution (109 [59%] of 185 patients), while nitrofurantoin had the highest (128 [74%] of 172 patients; difference 15·5 percentage points [95% CI 5·9 to 25·1] *vs* single-dose fosfomycin; p=0·0168), followed by pivmecillinam (127 [70%] of 182; difference 10·9 percentage points [1·1 to 20·6]; p=0·2352) and the two-dose fosfomycin group (122 [67%] of 181; difference 8·5 percentage points [–1·4 to 18·3]; p=0·6935). Adverse events occurred in 38 (19·9% [95% CI 14·9 to 26·1) of 191 patients who received single-dose fosfomycin, 51 (26·3% [20·6 to 32·9]) of 194 who received two-dose fosfomycin, 51 (26·8% [21·0 to 33·6]) of 190 who received nitrofurantoin, and 41 (21·2% [16·1 to 27·5]) of 193 who received pivmecillinam. Most adverse events were mild and self-limiting, primarily gastrointestinal. Four serious adverse events occurred, of which one was related to the study treatment (one case of pyelonephritis in the pivmecillinam group).

Interpretation Nitrofurantoin was the most effective treatment and single-dose fosfomycin the least effective treatment for UTIs. Adverse events were mild. The role of fosfomycin as a first-line antibiotic for uncomplicated UTI should be re-evaluated.

The patients

	Single-dose fosfomycin group (n=191)	Two-dose fosfomycin group (n=194)	Nitrofurantoin group (n=190)	Pivmecillinam group (n=193)
Median age, years	50 (35·5–64·5)	47·5 (34–62)	47 (33–62)	49 (34–64)
Previous UTI				
At any time	164 (86%)	161 (83%)	152 (80%)	154 (80%)
In the year preceding inclusion in the trial	83/164 (51%)	75/161 (47%)	71/152 (47%)	76/154 (49%)
General health condition, median visual analogue scale*	70 (50–90)	70 (50–90)	70 (50–90)	70 (57·5–80)
Median days since onset of symptoms	2 (1–3)	2 (1–4)	2 (1–4)	2 (1–3)
UTI-specific symptoms				
Dysuria	163 (85%)	174 (90%)	154 (81%)	162 (84%)
Urinary urgency	161 (84%)	167 (86%)	153 (81%)	166 (86%)
Urinary frequency	165 (86%)	172 (89%)	166 (87%)	178 (92%)
Suprapubic pain	141 (74%)	137 (71%)	127 (67%)	146 (76%)
Median number of UTI-specific symptoms†	4 (3–4)	4 (3–4)	3 (3–4)	4 (3–4)
Other symptoms				
Feverish sensation	27 (14%)	19 (10%)	21 (11%)	27 (14%)
General discomfort	91 (48%)	95 (49%)	85 (45%)	89 (46%)
Restriction of daily activities	57 (30%)	44 (23%)	44 (23%)	48 (25%)
Haematuria	67 (35%)	77 (40%)	69 (36%)	79 (41%)
Cloudy urine	89 (47%)	99 (51%)	91 (48%)	103 (53%)
Foul-smelling urine	55 (29%)	60 (31%)	45 (24%)	41 (21%)
Urinalysis				
Urine dipstick positive for leukocytes	189/191 (99%)	189/193 (98%)	184/190 (97%)	186/193 (96%)
Urine dipstick positive for nitrites	57/191 (30%)	48/193 (25%)	49/190 (26%)	46/192 (24%)
Baseline urine culture obtained	187 (98%)	185 (95%)	183 (96%)	183 (95%)
Confirmed UTI‡	109/187 (58%)	102/185 (55%)	91/183 (50%)	119/183 (65%)
Contaminated	24/187 (13%)	20/185 (11%)	22/183 (12%)	19/183 (10%)
Negative	54/187 (29%)	63/185 (34%)	70/183 (38%)	45/183 (25%)
Number of uropathogens isolated‡	107	104	95	120
Escherichia coli	74/107 (69%)	78/104 (75%)	67/95 (71%)	88/120 (73%)
Staphylococcus saprophyticus	9/107 (8%)	5/104 (5%)	6/95 (6%)	10/120 (8%)
Proteus mirabilis	9/107 (8%)	5/104 (5%)	6/95 (6%)	4/120 (3%)
Klebsiella pneumoniae	7/107 (7%)	4/104 (4%)	4/95 (4%)	8/120 (7%)
Others§	8/107 (7%)	12/104 (12%)	12/95 (13%)	10/120 (8%)
Proportion of strains resistant to the allocated antibiotic¶	10/100 (10%)	10/96 (10%)	9/87 (10%)	12/76 (16%)
Proportion of *E coli* strains resistant to the allocated antibiotic‖	1/74 (1%)	2/78 (3%)	0/65	5/60 (8%)

Additional information regarding patient characteristics is provided in the appendix (p 2). UTI=urinary tract infection. *Visual analogue scale ranged from 0 (worst health status) to 100 (best health status). †UTI-specific symptoms included are dysuria, urinary urgency, urinary frequency, and suprapubic pain. ‡Positive culture was defined as the growth of at least 10^5 colony-forming units per mL of at least one uropathogen; some cultures had polymicrobial growth; there were two patients with missing details on the uropathogen identified in the single-dose fosfomycin group. §*Citrobacter koseri, Enterococcus faecalis, Streptococcus agalactie, Klebsiella aerogenes, Morganella morganii, Lactobacillus crispatus, Staphylococcus saccharolyticus, Citrobacter freundii, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhimurium, Enterobacter cloacae,* or *Klebsiella varilcola*. ¶Antibiograms for study treatments were done in cultures positives for any uropathogen; a pivmecillinam antibiogram was an additional determination compared with usual practice (this extra determination was not done on 43 occasions); a nitrofurantoin antibiogram was not done on four occasions; a fosfomycin antibiogram was not done on nine occasions in the single-dose fosfomycin group and on six occasions in the two-dose fosfomycin group; all these cases were treated as missing values. ‖Antibiograms for study treatments were done in cultures positive for *E coli*; a pivmecillinam antibiogram was not done on 28 occasions; a nitrofurantoin antibiogram was not done on two occasions; all these cases were treated as missing values.

Table 1: **Baseline characteristics in the intention-to-treat population (n=768)**

	Clinical resolution on day 7	Clinical resolution on day 7 in patients with a positive baseline urine culture	Clinical resolution on day 14	Clinical resolution on day 28	Bacterial eradication on day 14	Bacterial eradication on day 28
Two-dose fosfomycin *vs* single-dose fosfomycin	8·5 (−1·4 to 18·3)	13·7 (0·3 to 27·2)	5·4 (−3·9 to 18·3)	5·3 (−4·1 to 14·8)	4·0 (−10·5 to 18·4)	4·6 (−10·7 to 19·8)
Nitrofurantoin *vs* single-dose fosfomycin	15·5 (5·9 to 25·1)*	34·9 (22·9 to 46·8)*	12·7 (3·8 to 21·6)*	12·6 (3·5 to 21·7)*	−3·0 (−18·4 to 12·4)	8·3 (−6·7 to 23·3)
Pivmecillinam *vs* single-dose fosfomycin	10·9 (1·1 to 20·6)	22·0 (9·6 to 34·5)*	8·8 (−0·3 to 17·9)	8·8 (−0·5 to 18·0)	−0·1 (−14·5 to 14·3)	−0·2 (−15·5 to 15·1)

Values are percentage points difference (95% CI). Numbers and percentages of participants with each outcome per group are provided in the appendix (p 5). *Significant difference at the 5% level after adjustment using the Bonferroni method.

Table 2: **Pairwise comparisons of efficacy outcomes**

Nitrofurantoin beats fosfomycin

	All patients in ITT population	Population with a positive baseline urine culture
Best-case scenario*		
Two-dose fosfomycin *vs* single-dose fosfomycin	9·4 (−0·1 to 18·9)	14·4 (1·4 to 27·5)
Nitrofurantoin *vs* single-dose fosfomycin	16·6 (7·5 to 25·8)†	34·7 (23·2 to 46·2)†
Pivmecillinam *vs* single-dose fosfomycin	11·3 (1·9 to 20·7)	21·6 (9·4 to 33·8)†
Worst-case scenario‡		
Two-dose fosfomycin *vs* single-dose fosfomycin	5·8 (−4·0 to 15·6)	11·3 (−2·0 to 24·6)
Nitrofurantoin *vs* single-dose fosfomycin	10·3 (0·6 to 20·0)	28·7 (16·1 to 41·2)†
Pivmecillinam *vs* single-dose fosfomycin	8·7 (−1·0 to 18·4)	21·0 (8·6 to 33·4)†
Extreme superiority§		
Two-dose fosfomycin *vs* single-dose fosfomycin	12·5 (3·0 to 22·1)†	17·2 (4·1 to 30·2)
Nitrofurantoin *vs* single-dose fosfomycin	19·8 (10·5 to 29·0)†	37·5 (25·9 to 49·0)†
Pivmecillinam *vs* single-dose fosfomycin	14·4 (5·0 to 23·9)†	24·3 (12·1 to 36·5)†
Counterintuitive outcomes¶		
Two-dose fosfomycin *vs* single-dose fosfomycin	2·7 (−7·0 to 12·4)	8·6 (−4·7 to 21·8)
Nitrofurantoin *vs* single-dose fosfomycin	7·2 (−2·5 to 16·8)	25·9 (13·4 to 38·5)†
Pivmecillinam *vs* single-dose fosfomycin	5·6 (−4·0 to 15·2)	18·2 (5·8 to 30·6)†

Data are percentage points difference (95% CI) in proportion of patients with clinical resolution at day 7. ITT=intention-to-treat. *All missing values for the primary outcome are imputed as recovered. †Significant difference at the 5% level after adjustment using the Bonferroni method. ‡All missing values for the primary outcome are imputed as treatment failures. §For the primary outcome, missing values in the single-dose fosfomycin group are imputed as treatment failures, whereas in the two-dose fosfomycin, nitrofurantoin, and pivmecillinam groups, they are imputed as recovered. ¶For the primary outcome, missing values in the single-dose fosfomycin group are imputed as recovered, whereas in the two-dose fosfomycin, nitrofurantoin, and pivmecillinam groups, they are imputed as treatment failures.

Table 3: **Pairwise main outcome comparisons with missing data imputation**

Adverse events?

Coin flip

	Single-dose fosfomycin group (n=191)	Two-dose fosfomycin group (n=194)	Nitrofurantoin group (n=190)	Pivmecillinam group (n=193)
Patients with one or more adverse events	38/191 (19·9% [14·9–26·1])	51/194 (26·3% [20·6–32·9])	51/190 (26·8% [21·0–33·6])	41/193 (21·2% [16·1–27·5])
Discontinuation due to adverse event	0/191 (0·0% [0·0–2·0])	1/194 (0·5% [0·1–2·9])	5/190 (2·6% [1·1–6·0])	3/193 (1·6% [0·5–4·5])
Patients with at least one serious adverse event*	0/191 (0·0% [0·0–2·0])	1/194 (0·5% [0·1–2·9])	1/190 (0·5% [0·1–2·9])	2/193 (1·0% [0·3–3·7])
Related to trial drug†	0/191 (0·0% [0·0–2·0])	0/194 (0·0% [0·0–1·9])	0/190 (0·0% [0·0–2·0])	1/193 (0·5% [0·1–2·9])
Total number of adverse events reported	41	73	77	57
Expected adverse events‡	33/41 (80·5% [66·0–89·8])	55/73 (75·3% [64·4–83·8])	54/77 (70·1% [59·2–79·2])	38/57 (66·7% [53·7–77·5])
Adverse event of special interest: pyelonephritis	0/191 (0·0% [0·0–2·0])	0/194 (0·0% [0·0–1·9])	2/190 (1·1% [0·3–3·8])	1/193 (0·5% [0·1–2·9])
Adverse event severity§				
Mild	30/40 (75·0% [59·8–85·8])	60/72 (83·3% [73·1–90·2])	55/77 (71·4% [60·5–80·3])	40/54 (74·1% [61·1–83·9])
Moderate	9/40 (22·5% [12·3–37·5])	11/72 (15·3% [8·8–25·3])	21/77 (27·3% [18·6–38·1])	10/54 (18·5% [10·4–30·8])
Severe	1/40 (2·5% [0·4–12·9])	1/72 (1·4% [0·2–7·5])	1/77 (1·3% [0·2–7·0])	4/54 (7·4% [2·9–17·6])
Most common adverse events¶				
Diarrhoea	17/191 (8·9% [5·6–13·8])	27/194 (13·9% [9·7–19·5])	7/190 (3·7% [1·8–7·4])	7/193 (3·6% [1·8–7·3])
Abdominal pain	3/191 (1·6% [0·5–4·5])	6/194 (3·1% [1·4–6·6])	7/190 (3·7% [1·8–7·4])	5/193 (2·6% [1·1–5·9])
Vulvovaginal candidiasis	6/191 (3·1% [1·4–6·7])	3/194 (1·5% [0·5–4·4])	3/190 (1·6% [0·5–4·5])	5/193 (2·6% [1·1–5·9])
Nausea	2/191 (1·0% [0·3–3·7])	1/194 (0·5% [0·1–2·9])	6/190 (3·2% [1·5–6·7])	6/193 (3·1% [1·4–6·6])
Headache	0/191 (0·0% [0·0–2·0])	2/194 (1·0% [0·3–3·7])	5/190 (2·6% [1·1–6·0])	7/193 (3·6% [1·8–7·3])
Fatigue	0/191 (0·0% [0·0–2·0])	2/194 (1·0% [0·3–3·7])	9/190 (4·7% [2·5–8·8])	2/193 (1·0% [0·3–3·7])
Vaginitis	2/191 (1·0% [0·3–3·7])	3/194 (1·5% [0·5–4·4])	2/190 (1·1% [0·3–3·8])	1/193 (0·5% [0·1–2·9])
Pruritus	0/191 (0·0% [0·0–2·0])	3/194 (1·5% [0·5–4·4])	2/190 (1·1% [0·3–3·8])	2/193 (1·0% [0·3–3·7])
Dizziness	1/191 (0·5% [0·1–2·9])	0/194 (0·0% [0·0–1·9])	4/190 (2·1% [0·8–5·3])	1/193 (0·5% [0·1–2·9])
Somnolence	0/191 (0·0% [0·0–2·0])	0/194 (0·0% [0·0–1·9])	5/190 (2·6% [1·1–6·0])	0/193 (0·0% [0·0–2·0])

Data are n/N (% [95% CI]); values represent the number of affected patients, except where otherwise noted. The safety population included all the patients who had received any dose of a trial drug. Events were coded according to the terms used in the Medical Dictionary for Regulatory Activities (version 27.1). *Serious adverse events recorded were acute myocardial infarction (pivmecillinam group), mesenteric panniculitis (two-dose fosfomycin group), and pyelonephritis (nitrofurantoin and pivmecillinam groups), all of which resolved with recovery. †The relationship of the severe adverse event to a trial drug was assessed by the pharmacovigilance department; one case of pyelonephritis in the pivmecillinam group was judged to be related to the study drug. ‡Expected adverse events were those described in the technical data sheet for each study treatment; values represent the number of expected adverse events out of all adverse events reported. §Values represent the number of adverse events of each severity level out of all adverse events reported for which severity data were available; severity data were missing for five adverse events. ¶Adverse events reported during treatment are listed in the order of descending overall frequency; events that occurred in fewer than five cases are not included in the table; the maximum number of adverse events reported per patient was four (occurring in four patients).

Table 4: **Summary of adverse events (safety population)**

There is no single "best" drug; your doctor will choose based on local antibiotic resistance patterns, your health history, and cost.

Added value of this study

In an open-label, pragmatic, randomised controlled trial involving 768 women presenting to primary care with symptoms of uncomplicated lower UTI, clinical effectiveness at day 7 was lower in those treated with a single 3 g dose of fosfomycin than in those who received other short-course antibiotic regimens (two 3 g doses of fosfomycin, nitrofurantoin at 100 mg three times daily for 5 days, or pivmecillinam at 400 mg three times daily for 3 days).

Implications of all the available evidence

Current guidelines recommend a single 3 g dose of fosfomycin tromethamine or short courses of pivmecillinam or nitrofurantoin as the first-line treatment for uncomplicated UTIs. The results of the current study support findings from a previous randomised clinical trial indicating the lower efficacy of single-dose fosfomycin compared with nitrofurantoin. In light of this new evidence, the use of short-course antibiotic regimens should be encouraged over single-dose fosfomycin.

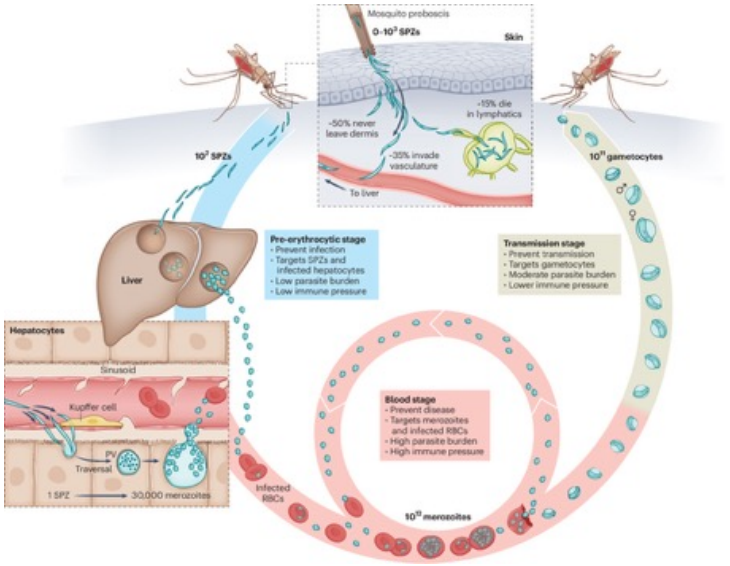
Das **Circumsporozoiten-Protein (CSP)** ist das Hauptoberflächenprotein der Sporozoiten, dem infektiösen Stadium des Malaria-Parasiten (*Plasmodium*), das von Anopheles-Mücken auf den Menschen übertragen wird. Es ist entscheidend für den Lebenszyklus des Parasiten, da es das Eindringen in die Speicheldrüsen der Mücke sowie die Interaktion mit und das Eindringen in die Leberzellen des menschlichen Wirtes vermittelt.

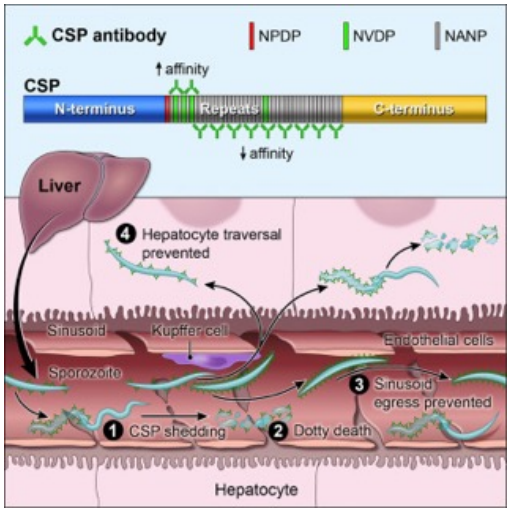
Struktur und Funktion:

•**Aufbau:** Das hochkonservierte, ca. 58 kDa große Protein besteht aus drei Bereichen: Einem N-Terminus mit einer Bindungsregion (Region I) für Heparansulfat-Proteoglykane, einer zentralen Wiederholungsregion (NANP-Wiederholungen) und einem C-terminalen Bereich mit einer Thrombospondin-ähnlichen Domäne (TSP-Region II) sowie einem GPI-Anker.

•**Funktion:** Die zentrale Region enthält humane B-Zell-Epitope, während der C-Terminus T-Zell-Epitope aufweist.

•**Struktur:** In der Bildgebung erscheint CSP als flexible, stäbchenförmige Struktur.





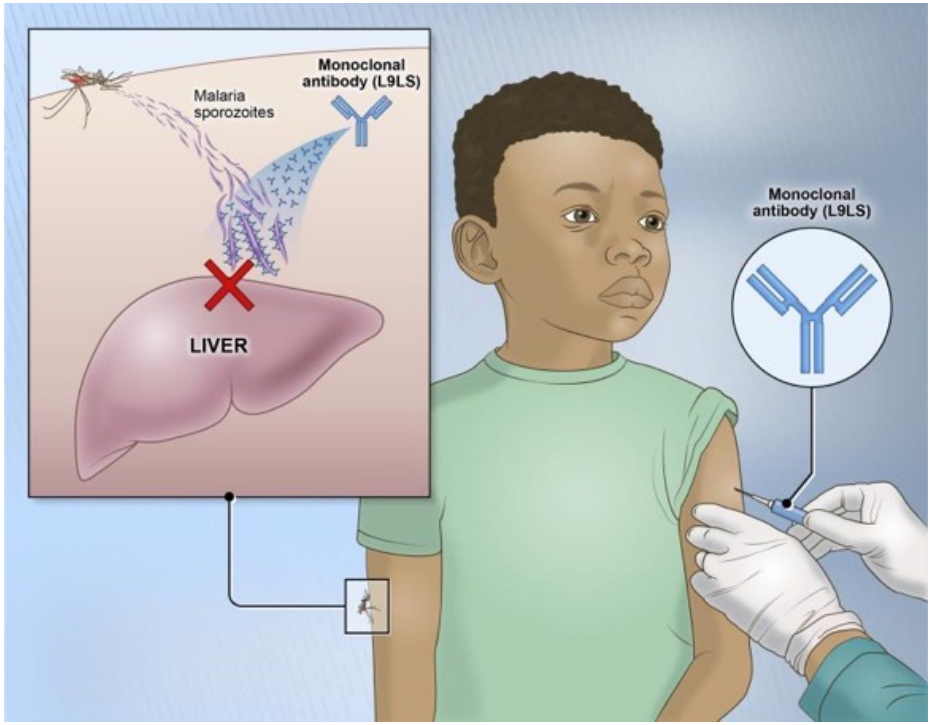
L9LS ist ein hochwirksamer **monoklonaler Antikörper**, der zur Vorbeugung von Malaria entwickelt wurde. Er wird als passive Immunisierung eingesetzt, um den Malariaparasiten *Plasmodium falciparum* abzuwehren, bevor dieser die Leber infizieren kann.

Wichtige Erkenntnisse zur Wirksamkeit

Aktuelle Studien belegen die hohe Schutzwirkung von L9LS:

- **Kinder in Mali (Phase 2):** Eine Einzeldosis schützte Kinder im Alter von 6 bis 10 Jahren über eine sechsmonatige Malariasaison.
  - **77 % Wirksamkeit** gegen klinische Malaria (bei einer 300-mg-Dosis).
  - **70 % Wirksamkeit** gegen Infektionen insgesamt.
- **Kleinkinder in Kenia:** In Gebieten mit ganzjähriger Übertragung zeigte L9LS bei Kindern (5–59 Monate) eine Schutzwirkung von etwa **43 % bis 48 %**.
- **Erwachsene (Phase 1):** In kontrollierten Studien verhinderte L9LS bei **88 %** der Teilnehmer eine Infektion nach Mückenstichen.

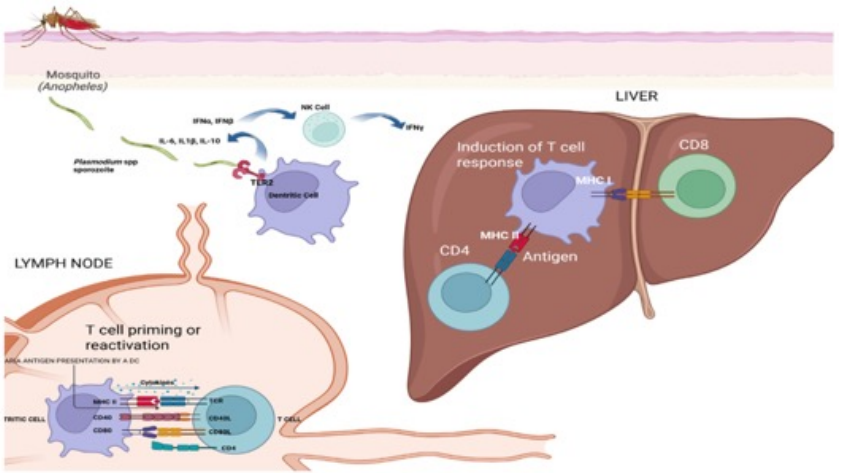
Passive Immunität



Es gibt auch einen aktiven Impfstoff aber hier nicht getestet

Hauptmerkmale von L9LS

- **Anwendung:** Wird meist als einfache **subkutane Injektion** (unter die Haut) verabreicht, was den Einsatz in ländlichen Regionen erleichtert.
- **Wirkungsweise:** Er bindet an das Circumsporozoit-Protein (PfCSP) auf der Oberfläche der Parasiten und neutralisiert diese sofort nach dem Mückenstich.
- **Vorteil gegenüber Impfstoffen:** Bietet **sofortigen Schutz** nach einer einzigen Dosis, während herkömmliche Impfstoffe oft mehrere Dosen über Monate benötigen.
- **Sicherheit:** In klinischen Studien wurden bisher keine schwerwiegenden Sicherheitsbedenken festgestellt; häufigste Nebenwirkung sind leichte Schwellungen an der Einstichstelle.



Safety and efficacy of the monoclonal antibody L9LS for malaria prevention in children exposed to perennial malaria transmission in Kenya: a randomised, double-blind, placebo-controlled, phase 2 trial

Summary

Background Malaria remains a major cause of mortality globally, especially among young children in sub-Saharan Africa. The long-acting monoclonal antibody L9LS has shown high efficacy in preventing malaria in children aged 6–10 years exposed to seasonal transmission but remains untested in perennial transmission settings and younger children. We assessed the safety, tolerability, and efficacy of L9LS in infants and children in a high perennial malaria transmission setting.

Methods This double-blind, two-part, randomised, placebo-controlled, phase 2 trial was done in Siaya county in western Kenya. In parts 1a and 1b, we tested the safety and tolerability of L9LS using an age de-escalation and dose escalation approach and randomly assigned (3:1) cohorts of healthy children (three cohorts aged 5–10 years, three cohorts aged 5–59 months, and two cohorts aged 5–71 months) to L9LS at doses of 5, 10, 20, 30, or 40 mg/kg subcutaneously or to placebo (normal saline). In part 2, healthy children aged 5–59 months were randomly assigned (1:1:1) by use of centralised computer-generated lists to receive two doses of L9LS at 10–20 mg/kg at baseline and month 6, one dose of L9LS at baseline and placebo at month 6, or placebo at both timepoints. Children were followed up for 12 months with monthly clinic visits and blood smear collections. Primary safety outcomes were incidence and severity of local and systemic solicited adverse events within 7 days of dosing and serious adverse events throughout follow-up. The primary efficacy endpoint was *Plasmodium falciparum* infection detected by blood smear over 12 months. Primary analyses were done in the modified intention-to-treat population, consisting of all randomly assigned participants who received the study intervention. This trial is registered with ClinicalTrials.gov (NCT05400655) and is complete.

Findings In parts 1a and 1b, 96 children were enrolled and randomly assigned between Oct 1, 2022, and Jan 16, 2024; 72 participants were assigned to L9LS and 24 were assigned to placebo. In part 2, 324 children aged 5–59 months were enrolled and randomly assigned between Jan 26 and June 2, 2023; 108 children were assigned to one-dose L9LS, 106 to two-dose L9LS, and 110 to placebo. Across all study parts, grade 3 or worse treatment-related adverse events occurred after four (1%) of 384 L9LS injections and two (1%) of 338 placebo injections; these events all resolved by study end. The proportion of solicited and unsolicited adverse events was similar across all L9LS dose groups. There were no serious adverse events related to the trial. In part 2, 70 (66%) of 106 children in the two-dose L9LS group had at least one *P falciparum* infection during the 12-month follow-up versus 91 (83%) of 110 children in the placebo group (protective efficacy 42·7%, 95% CI 22·5–57·7; p=0·0003).

Interpretation L9LS was protective against malaria in young children in western Kenya without evident safety concerns over 6–12 months. A higher dose of L9LS might be needed to achieve high-level efficacy against malaria in young children exposed to intense perennial *P falciparum* transmission.

	18–59 months of age*			5–17 months of age*		
	One-dose L9LS (n=54)	Two-dose L9LS (n=52)	Placebo (n=56)	One-dose L9LS (n=54)	Two-dose L9LS (n=54)	Placebo (n=54)
Sex						
Female	29 (54%)	27 (52%)	27 (48%)	28 (52%)	34 (63%)	27 (50%)
Male	25 (46%)	25 (48%)	29 (52%)	26 (48%)	20 (37%)	27 (50%)
Age, months	37 (25–45)	34 (27–49)	31 (24–41)	13 (9–15)	10 (6–14)	13 (7–15)
Study site						
Kogelo	22 (41%)	21 (40%)	24 (43%)	19 (35%)	19 (35%)	20 (37%)
Siaya	32 (59%)	31 (60%)	32 (57%)	35 (65%)	35 (65%)	34 (63%)
Weight at first dose, kg	13·6 (2·4)	14·1 (2·4)	13·2 (2·2)	9·3 (1·3)	8·9 (1·3)	9·2 (1·4)
L9LS dose, mg/kg	12·4 (1·5)	12·3 (1·5)	12·6 (1·5)	15·4 (2·4)	15·6 (2·8)	14·9 (2·5)
Positive blood smear at baseline†	11 (20%)	14 (27%)	12 (21%)	5 (10%)	9 (17%)	2 (4%)
Positive qRT-PCR at baseline†‡	26 (49%)	31 (61%)	32 (58%)	23 (45%)	19 (37%)	14 (26%)

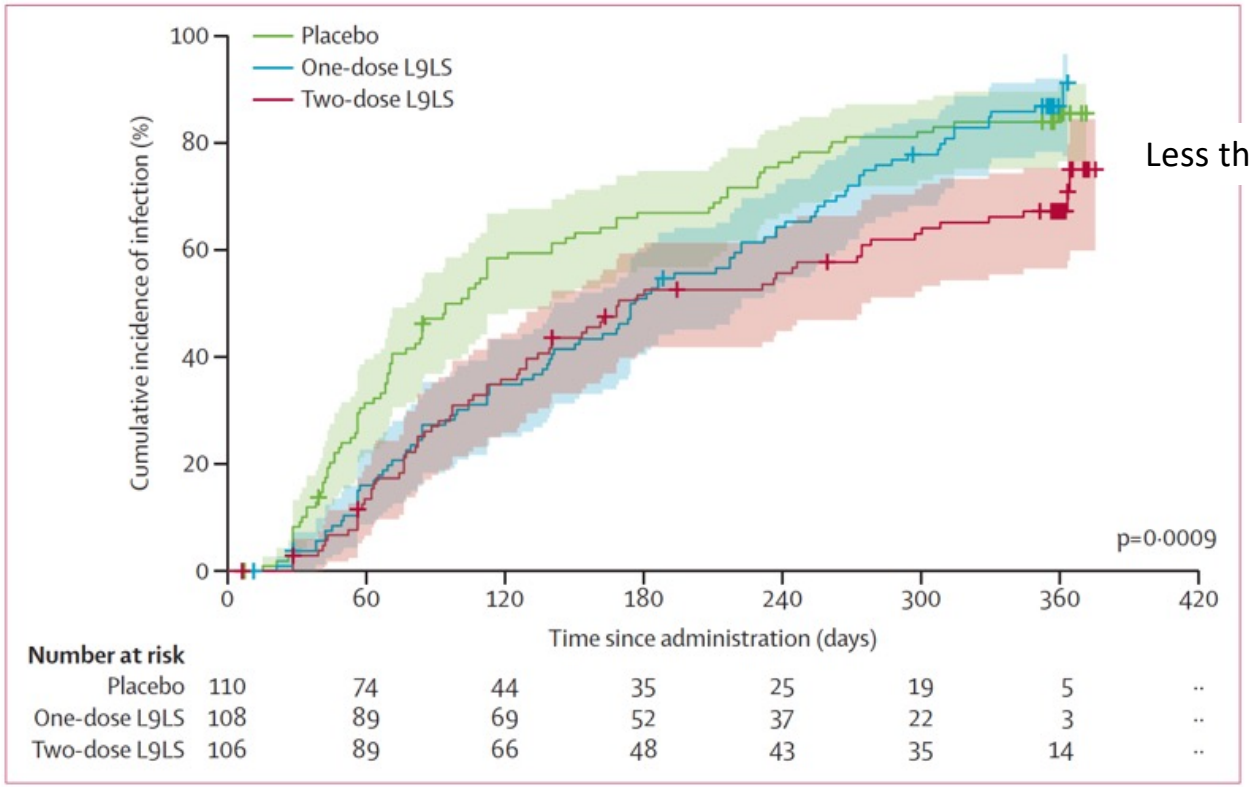
Data are n (%), median (IQR), or mean (SD). qRT-PCR=quantitative RT-PCR. *Age at time of dosing. †Baseline refers to the pre-enrolment visit for giving dihydroartemisinin–piperaquine for parasite clearance, 2–3 weeks before antibody administration. Positivity is only for *Plasmodium falciparum*. ‡qRT-PCR unable to be run on nine baseline samples: four in the one-dose L9LS group, three in the two-dose L9LS group, and two in the placebo group. Other variables have no missing data.

Table 1: **Characteristics of participants enrolled in efficacy cohort**

	One-dose L9LS		Two-dose L9LS		Placebo	
	After dose 1 (n=108)	After dose 2 (n=103)	After dose 1 (n=106)	After dose 2 (n=98)	After dose 1 (n=110)	After dose 2 (n=101)
Solicited adverse events						
Participants with at least one solicited local adverse event within 7 days of dosing	1 (1%)	0	3 (3%)	3 (3%)	0	1 (1%)
Participants with at least one solicited systemic adverse event within 7 days of dosing	12 (11%)	10 (10%)	8 (8%)	14 (14%)	6 (5%)	12 (12%)
Local reactogenicity adverse events						
Injection site induration*						
Severe	0	0	0	1 (1%)	0	0
Injection site pain						
Mild	0	0	1 (1%)	0	0	0
Injection site reaction†						
Mild	0	0	1 (1%)	0	0	0
Injection site swelling						
Mild	1 (1%)	0	1 (1%)	2 (2%)	0	1 (1%)
Systemic solicited adverse events						
Nausea						
Moderate	2 (2%)	2 (2%)	3 (3%)	3 (3%)	2 (2%)	2 (2%)
Mild	3 (3%)	1 (1%)	2 (2%)	4 (4%)	1 (1%)	4 (4%)
Malaise						
Mild	0	1 (1%)	0	0	0	0
Pyrexia						
Severe‡	0	0	0	2 (2%)	0	0
Moderate	1 (1%)	2 (2%)	1 (1%)	2 (2%)	0	3 (3%)
Mild	7 (6%)	5 (5%)	3 (3%)	5 (5%)	3 (3%)	5 (5%)
Headache						
Mild	1 (1%)	0	1 (1%)	0	0	1 (1%)
Unsolicited adverse events						
Participants with at least one unsolicited adverse event within 28 days of dosing	83 (77%)	84 (82%)	83 (78%)	81 (83%)	86 (78%)	81 (80%)
Participants with at least one related unsolicited adverse event within 28 days of dosing	6 (6%)	9 (9%)	1 (1%)	6 (6%)	5 (5%)	7 (7%)
All adverse events						
Participants with a grade 3 related adverse event (solicited or unsolicited)	0	0	0	3 (3%)	0	1 (1%)
Participants with a serious adverse event§	3 (3%)	4 (4%)	3 (3%)	1 (1%)	6 (5%)	10 (10%)

No participants had local reactions of injection site tenderness, redness, pruritus, or bruising. No participants had systemic solicited events of muscle aches, chills, or joint pain. All local events were deemed related to the study. All systemic events were deemed related to the study, apart from one case of nausea in a participant in the placebo group after dose 2, who had concomitant malaria and bacterial infection. *Injection site induration began 1 day after dosing (maximum swelling of 30 mm) and resolved by day 3. †Injection site reaction was a muscle tension under the injection site that appeared within 1 h of dosing and resolved by day 3. ‡Severe pyrexia defined as axillary temperature from 39·5°C to 41·9°C. §No deaths occurred in part 2, and none of the serious adverse events were deemed related to the study.

Table 2: **Summary of adverse events in efficacy cohort**



Less than bombastic

Figure 2: **Kaplan–Meier curve of time to first *Plasmodium falciparum* infection as detected by blood smear, by treatment group**

Data for all participants (ie, 5–17-month and 18–59-month age groups combined). Surveillance for infection by blood smear began 7 days after the first dose of L9LS or placebo and continued until the close-out visit. Shaded areas represent 95% CIs. Log-rank test p=0·0009 for all participants comparing the two-dose L9LS group with the placebo group. Median time to first infection for all participants was 176 days (95% CI 141–222) in the one-dose L9LS group, 169 days (139–274) in the two-dose L9LS group, and 101 days (77–140) in the placebo group.

	Events/participants (%)		Protective efficacy (95% CI)	p value
	L9LS	Placebo		
6 months				
Blood smear	99/214 (46%)	71/110 (65%)	45·9 (26·5 to 60·1)	0·0001
Clinical malaria definition 2	84/214 (39%)	64/110 (58%)	47·5 (26·5 to 62·5)	0·0002
Clinical malaria definition 1	61/214 (29%)	47/110 (43%)	43·8 (16·5 to 62·1)	0·0043
12 months				
Blood smear, one dose	92/108 (85%)	91/110 (83%)	20·0 (−9·8 to 41·7)	0·17
Clinical malaria definition 2, one dose	84/108 (78%)	90/110 (82%)	28·4 (3·1 to 47·1)	0·030
Clinical malaria definition 1, one dose	70/108 (65%)	74/110 (67%)	20·6 (−10·5 to 43·0)	0·17
Blood smear, two doses	70/106 (66%)	91/110 (83%)	42·7 (22·5 to 57·7)	0·0003
Clinical malaria definition 2, two doses	64/106 (60%)	90/110 (82%)	48·3 (27·4 to 63·1)	0·0001
Clinical malaria definition 1, two doses	57/106 (54%)	74/110 (67%)	36·7 (11·1 to 54·9)	0·0083

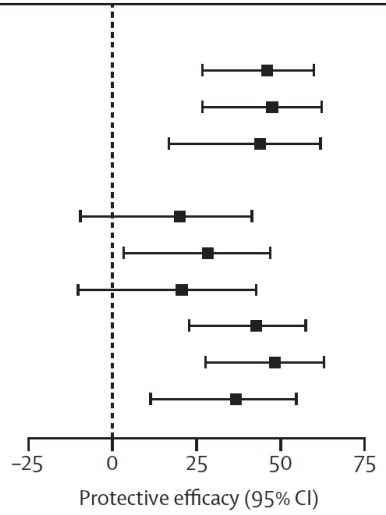
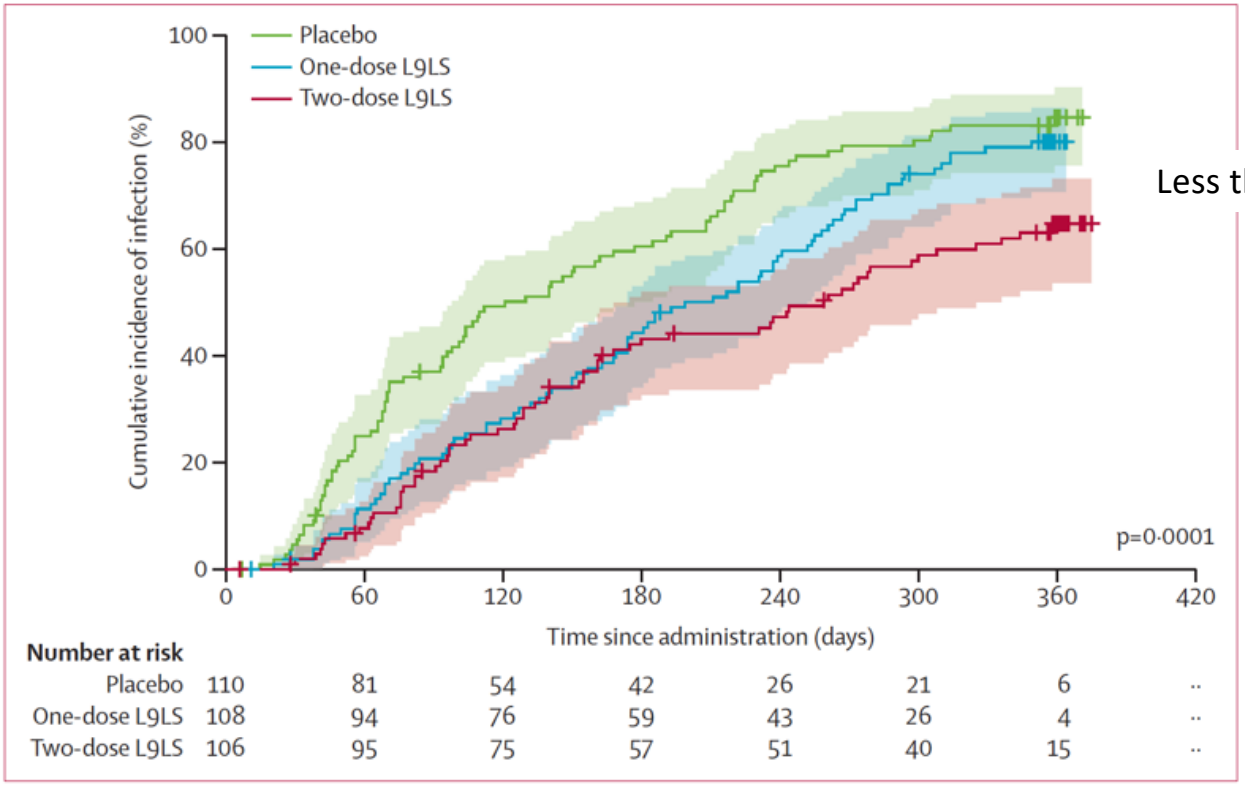


Figure 3: **Protective efficacy of one or two doses of L9LS against *Plasmodium falciparum* infection and clinical malaria at 6 months and 12 months compared with placebo, by time-to-event analysis**

Protective efficacy calculated using Cox proportional hazards model ([1–hazard ratio] × 100%) accounting for interval censoring. Lines around protective efficacy point estimates represent 95% CIs. Clinical malaria defined as either: (1) parasitaemia of more than 5000 parasites per µL with axillary temperature at least 37·5°C; or (2) any parasitaemia with either temperature at least 37·5°C or history of fever within the past 24 h.



Less than bombastic

Figure 4: **Kaplan–Meier curve of time to first clinical malaria, by treatment group**
Data for all participants (ie, 5–17-month and 18–59-month age groups combined). Clinical malaria defined as blood smear-detected *Plasmodium falciparum* infection plus high measured temperature (≥37·5°C) or history of fever in past 24 h. Surveillance for clinical malaria began 7 days after the first dose of L9LS or placebo and continued until the close-out visit. Shaded areas represent 95% CIs. Log-rank test p=0·0001 comparing the two-dose L9LS group with the placebo group. Median time to first clinical malaria for all participants was 199 days (95% CI 174–252) in the one-dose L9LS group, 259 days (175–336) in the two-dose L9LS group, and 121 days (98–177) in the placebo group.

Implications of all the available evidence

Building on evidence from phase 1 and 2 studies in the USA and Mali, findings from this trial suggest that L9LS is safe and efficacious in infants and young children, paving the way for future implementation in this age group that is particularly vulnerable to malaria. Although protection against infection was significant (for both one dose at 6 months and two doses at 12 months), efficacy was approximately 35% lower than that seen in older children in Mali (aged 6–10 years) who received L9LS subcutaneously at a similar dose range. Age-dependent differences in L9LS pharmacokinetics, potential differences in malaria transmission between Mali and Kenya, and population-specific immunological profiles, along with other factors, might explain the lower efficacy in young children in western Kenya.

Because the previous studies have shown dose-dependent protection by CIS43LS and L9LS, higher dosing might contribute to achieving optimal efficacy, especially in young children and infants in perennial transmission sites. On the basis of these findings, planned and continuing studies (NCT06461026) will evaluate a dose of about 30 mg/kg of L9LS across different clinical use cases, which include an ongoing study in vulnerable children discharged from hospital with severe malaria or severe anaemia in Kenya (NCT07082205). Additional studies are needed to understand potential differences in pharmacokinetics of L9LS in infants and young children and to elucidate other possible factors affecting protective efficacy of antimalarial monoclonal antibodies in sites of intense, perennial transmission.

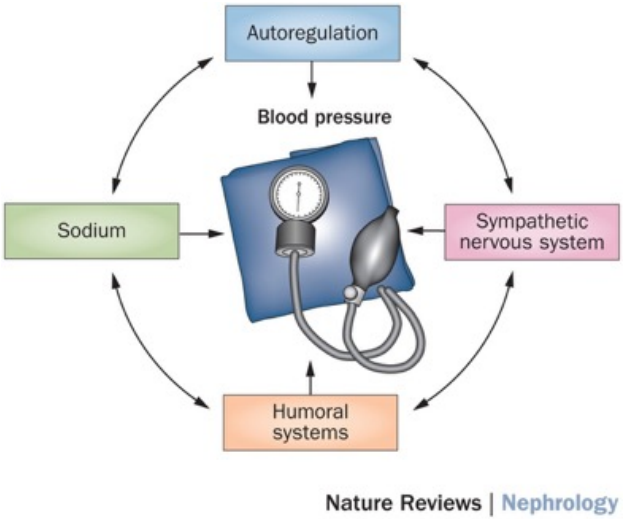
Senkung des Blutdrucks ist der wichtigste veränderbare Faktor, um das Fortschreiten einer chronischen Nierenerkrankung (CKD) zu verlangsamen und das Risiko für Herz-Kreislauf-Erkrankungen zu senken.

Zielwerte für den Blutdruck

Die Empfehlungen variieren je nach Leitlinie und dem Vorliegen von Eiweiß im Urin (Albuminurie):

- **Allgemeiner Zielwert:** Meist wird ein Ziel von **< 130/80 mmHg** empfohlen.
- **Intensivierte Senkung:** Die KDIGO-Leitlinien 2021 schlagen bei guter Verträglichkeit sogar einen systolischen Wert von **< 120 mmHg** vor, basierend auf standardisierten Messungen.
- **Bei Proteinurie:** Wenn vermehrt Eiweiß ausgeschieden wird (> 300 mg/Tag), ist eine strikte Kontrolle besonders wichtig, um die Nieren zu schützen.
- **Individuelle Anpassung:** Bei älteren oder gebrechlichen Menschen können höhere Zielwerte (z. B. < 140/90 mmHg) sinnvoll sein, um Stürze oder Schwindel durch zu niedrigen Blutdruck zu vermeiden.

Man hat „angst“ BD bei CKD zu reduzieren



CKD will be the 4th commonest cause of death by 2040

Pharmacological blood-pressure lowering for the prevention of cardiovascular disease and death across the full spectrum of chronic kidney disease severity: an individual-participant data meta-analysis

Summary

Background Individuals with chronic kidney disease (CKD), particularly those at more advanced stages, have been systematically under-represented in randomised controlled trials (RCTs) of blood-pressure-lowering treatment due to safety concerns, leading to a persistent paucity of evidence for cardiovascular risk management in this high-risk group. We investigated the effect of blood-pressure-lowering treatment on the risk of major cardiovascular disease and death across the full spectrum of CKD stages and by key clinical subgroups.

Methods We conducted a one-stage meta-analysis of individual-participant data from RCTs in which participants were randomly assigned to a blood-pressure-lowering therapy versus a comparator. We used RCTs collated in the Blood Pressure Lowering Treatment Trialists' Collaboration dataset, published at any time in any language, which were eligible for inclusion if they had at least 1000 person-years of follow-up per arm, baseline blood-pressure and creatinine measurements, and time-to-event outcomes; those with unclear randomisation procedures or restricted to heart failure or acute care settings were excluded. Participants with a documented history of heart failure or extreme creatinine values were excluded. No age criteria were applied. The primary outcome was major cardiovascular events, defined as a composite of fatal or non-fatal stroke, ischaemic heart disease, or hospitalisation for, or death from, heart failure. Relative treatment effects were estimated with a stratified Cox proportional hazards model. Heterogeneity of treatment effects was evaluated across prespecified subgroups defined by CKD status, CKD stage (1–5), diabetes, proteinuria, and baseline blood pressure. A stratified network meta-analysis was performed to examine whether treatment effects differed by defined subgroups within each of five principal antihypertensive drug classes. The systematic review was registered in PROSPERO (CRD42018099283).

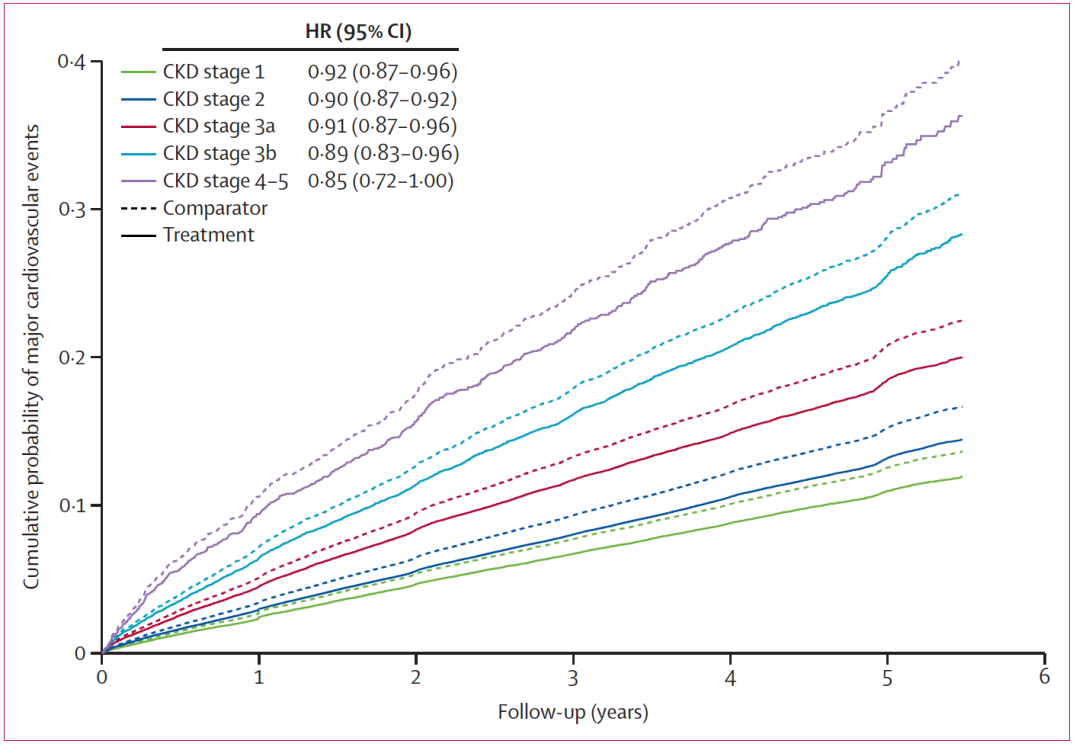
Findings From 52 RCTs (363 684 participants), a total of 285 124 participants from 46 randomised trials met the eligibility criteria; 116 145 (40·7%) were women, 168 979 (59·3%) were men, 59 185 (20·7%) had CKD at baseline, and 86 067 (30·2%) had type 2 diabetes. During a median follow-up of 4·4 years (IQR 3·2–5·1), a 5 mm Hg reduction in systolic blood pressure reduced the risk of major cardiovascular disease in individuals with CKD (hazard ratio [HR] 0·91 [95% CI 0·87–0·94]) and without CKD (0·90 [0·88–0·93]; $p_{interaction}$>0·99). Furthermore, these observed relative risk reductions were consistent across all CKD stages, including severe stages 4–5 ($p_{interaction}$>0·99). Similar treatment effects were observed by proteinuria status and across blood-pressure categories, down to <120/70 mm Hg. However, the relative treatment effect in individuals with CKD was notably attenuated among those with coexisting diabetes (HR 0·96 [95% CI 0·90–1·02]) compared with those without (0·88 [0·84–0·93]; $p_{interaction}$=0·044). The stratified analysis within each drug class showed that the class-specific effects of antihypertensive agents versus placebo on cardiovascular disease risk remained unchanged across the investigated subgroups.

Interpretation In the context of cardiovascular risk reduction, the relative benefit of blood-pressure lowering in patients with CKD is similar to that in individuals without CKD, with consistent efficacy across all CKD stages, blood-pressure thresholds, and proteinuria status. However, notably, this relative benefit is attenuated in patients with CKD and concomitant diabetes, underscoring the requirement for adapted therapeutic strategies in this high-risk subgroup. Moreover, the class-specific effects of principal antihypertensives in CKD mirror those observed in the broader population, independent of CKD stage or proteinuria status.

	Individuals with CKD at baseline (n=59 185)			Individuals without CKD at baseline (n=225 939)		
	Intervention	Comparator	Total	Intervention	Comparator	Total
Sex						
Female	14 340/27 804 (51·6%)	16 201/31 381 (51·6%)	30 541/59 185 (51·6%)	40 474/106 149 (38·1%)	45 130/119 790 (37·7%)	85 604/225 939 (37·9%)
Male	13 464/27 804 (48·4%)	15 180/31 381 (48·4%)	28 644/59 185 (48·4%)	65 675/106 149 (61·9%)	74 660/119 790 (62·3%)	140 335/225 939 (62·1%)
Age, years	69·5 (9·4)	70·0 (9·2)	69·8 (9·3)	63·6 (9·6)	64·1 (9·3)	63·9 (9·5)
Systolic blood pressure, mm Hg	156 (23)	155 (23)	156 (23)	153 (21)	152 (21)	152 (21)
Diastolic blood pressure, mm Hg	86 (13)	86 (13)	86 (13)	88 (13)	88 (12)	88 (13)
BMI, kg/m²	28·1 (5·2)	28·1 (5·6)	28·1 (5·4)	27·8 (5·0)	28·0 (9·9)	27·9 (8·0)
Smoking status						
Never	10 082/20 001 (50·4%)	11 366/23 019 (49·4%)	21 448/43 020 (49·9%)	33 991/74 382 (45·7%)	37 972/86 375 (44·0%)	71 963/160 757 (44·8%)
Past	7108/20 001 (35·5%)	8416/23 019 (36·6%)	15 524/43 020 (36·1%)	25 526/74 382 (34·3%)	31 463/86 375 (36·4%)	56 989/160 757 (35·5%)
Current	2811/20 001 (14·1%)	3237/23 019 (14·1%)	6048/43 020 (14·1%)	14 865/74 382 (20·0%)	16 940/86 375 (19·6%)	31 805/160 757 (19·8%)
Ethnicity						
White, Caucasian, or European	13 837/21 202 (65·3%)	15 472/24 590 (62·9%)	29 309/45 792 (64·0%)	52 596/80 312 (65·5%)	60 554/92 425 (65·5%)	113 150/172 737 (65·5%)
Black	2893/21 202 (13·6%)	3856/24 590 (15·7%)	6749/45 792 (14·7%)	4852/80 312 (6·0%)	7241/92 425 (7·8%)	12 093/17 737 (68·2%)
Hispanic	965/21 202 (4·6%)	1386/24 590 (5·6%)	2351/45 792 (5·1%)	3751/80 312 (4·7%)	5644/92 425 (6·1%)	9395/17 737 (53·0%)
Asian	2484/21 202 (11·7%)	2792/24 590 (11·4%)	5276/45 792 (11·5%)	16 670/80 312 (20·8%)	16 452/92 425 (17·8%)	33 122/17 737 (186·7%)
Other	1023/21 202 (4·8%)	1084/24 590 (4·4%)	2107/45 792 (4·6%)	2443/80 312 (3·0%)	2534/92 425 (2·7%)	4977/17 737 (28·1%)
Comorbidity						
Peripheral vascular disease	1510/11 314 (13·3%)	1451/11 038 (13·1%)	2961/22 352 (13·2%)	3415/41 368 (8·3%)	3540/39 850 (8·9%)	6955/81 218 (8·6%)
Atrial fibrillation	1300/14 345 (9·1%)	1404/16 519 (8·5%)	2704/30 864 (8·8%)	3124/55 179 (5·7%)	3373/63 051 (5·3%)	6497/118 230 (5·5%)
Cerebrovascular disease	4466/22 080 (20·2%)	4879/23 813 (20·5%)	9345/45 893 (20·4%)	15 702/85 469 (18·4%)	17 132/91 583 (18·7%)	32 834/177 052 (18·5%)
Ischaemic heart disease	8191/25 157 (32·6%)	9333/26 788 (34·8%)	17 524/51 945 (33·7%)	27 243/94 999 (28·7%)	31 934/101 237 (31·5%)	59 177/196 236 (30·2%)
Type 2 diabetes	8474/27 801 (30·5%)	9582/31 377 (30·5%)	18 056/59 178 (30·5%)	31 824/106 109 (30·0%)	36 187/119 741 (30·2%)	68 011/225 850 (30·1%)
Previous use of non-trial medications						
Diuretics	5210/15 556 (33·5%)	5967/16 673 (35·8%)	11 177/32 229 (34·7%)	9492/56 753 (16·7%)	11 054/61 340 (18·0%)	20 546/118 093 (17·4%)
α blockers	833/12 126 (6·9%)	898/13 323 (6·7%)	1731/25 449 (6·8%)	1379/40 945 (3·4%)	1633/46 040 (3·5%)	3012/86 985 (3·5%)
β blockers	5734/16 365 (35·0%)	6637/17 461 (38·0%)	12 371/33 826 (36·6%)	18 464/60 339 (30·6%)	21 748/64 936 (33·5%)	40 212/125 275 (32·1%)
Angiotensin-converting enzyme inhibitors	5780/14 954 (38·7%)	6699/16 105 (41·6%)	12 479/31 059 (40·2%)	14 827/53 623 (27·7%)	18 617/58 153 (32·0%)	33 444/111 776 (29·9%)
Angiotensin-receptor blockers	748/9193 (8·1%)	746/8726 (8·5%)	1494/17 919 (8·3%)	3198/39 354 (8·1%)	3195/37 053 (8·6%)	6393/76 407 (8·4%)
Calcium-channel blockers	5977/16 377 (36·5%)	6360/17 475 (36·4%)	12 337/33 852 (36·4%)	18 634/60 342 (30·9%)	19 961/64 936 (30·7%)	38 595/125 278 (30·8%)
Antiplatelets	4825/12 353 (39·1%)	6088/13 556 (44·9%)	10 913/25 909 (42·1%)	16 138/41 257 (39·1%)	21 601/46 943 (46·0%)	37 739/88 200 (42·8%)
Anticoagulants	765/8027 (9·5%)	878/9188 (9·6%)	1643/17 215 (9·5%)	1804/26 857 (6·7%)	2221/32 457 (6·8%)	4025/59 314 (6·8%)
Lipid-lowering treatments	4159/12 528 (33·2%)	5065/12 991 (39·0%)	9224/25 519 (36·1%)	16 540/50 834 (32·5%)	20 677/53 476 (38·7%)	37 217/104 310 (35·7%)
eGFR, mL/min per 1·73m²	49·8 (8·6)	49·9 (8·6)	49·9 (8·6)	81·8 (13·5)	81·6 (13·3)	81·7 (13·4)
Proteinuria	2975/14 036 (21·2%)	3023/15 152 (20·0%)	5998/29 188 (20·5%)	5434/46 821 (11·6%)	6146/52 076 (11·8%)	11 580/98 897 (11·7%)
Follow-up, years	4·3 (3·0–5·0)	4·4 (3·0–5·0)	4·4 (3·0–5·0)	4·4 (3·2–5·1)	4·4 (3·3–5·1)	4·4 (3·3–5·1)

Data are n/N (%), mean (SD), or median (IQR). Sex refers to biological sex as recorded by trial investigators at enrolment and harmonised across trials. Data on gender identity and psychosocial or cultural gender constructs were not available in the Blood Pressure Lowering Treatment Trialists' Collaboration database and therefore could not be analysed. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate.

Table: **Baseline characteristics of participants by CKD status and study arm**



All treatments lie below comparators

Figure 1: **Kaplan–Meier curves for major cardiovascular disease, by treatment allocation and CKD stage**
Cumulative incidence curves for major cardiovascular events stratified by CKD stage, with solid lines representing the treatment arm and dashed lines representing the comparator arm. Number-at-risk data are given in the appendix (p 25). HRs with 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. CKD stages were defined with the CKD Epidemiology Collaboration 2021 race-free equations:[18] stage 1 (eGFR ≥90 mL/min per 1·73 m²), stage 2 (60–89 mL/min per 1·73 m²), stage 3a (45–59 mL/min per 1·73 m²), stage 3b (30–44 mL/min per 1·73 m²), and stages 4–5 (<30 mL/min per 1·73 m²). Major cardiovascular events were defined as fatal or non-fatal stroke or other cerebrovascular disease, fatal or non-fatal ischaemic heart disease, or heart failure leading to death or hospitalisation. The increasing cumulative incidence with advancing CKD stage reflects the higher baseline cardiovascular risk among patients with more severe CKD. Relative treatment benefit was consistent across all CKD stages ($p_{interaction}$>0·99). CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. HR=hazard ratio.

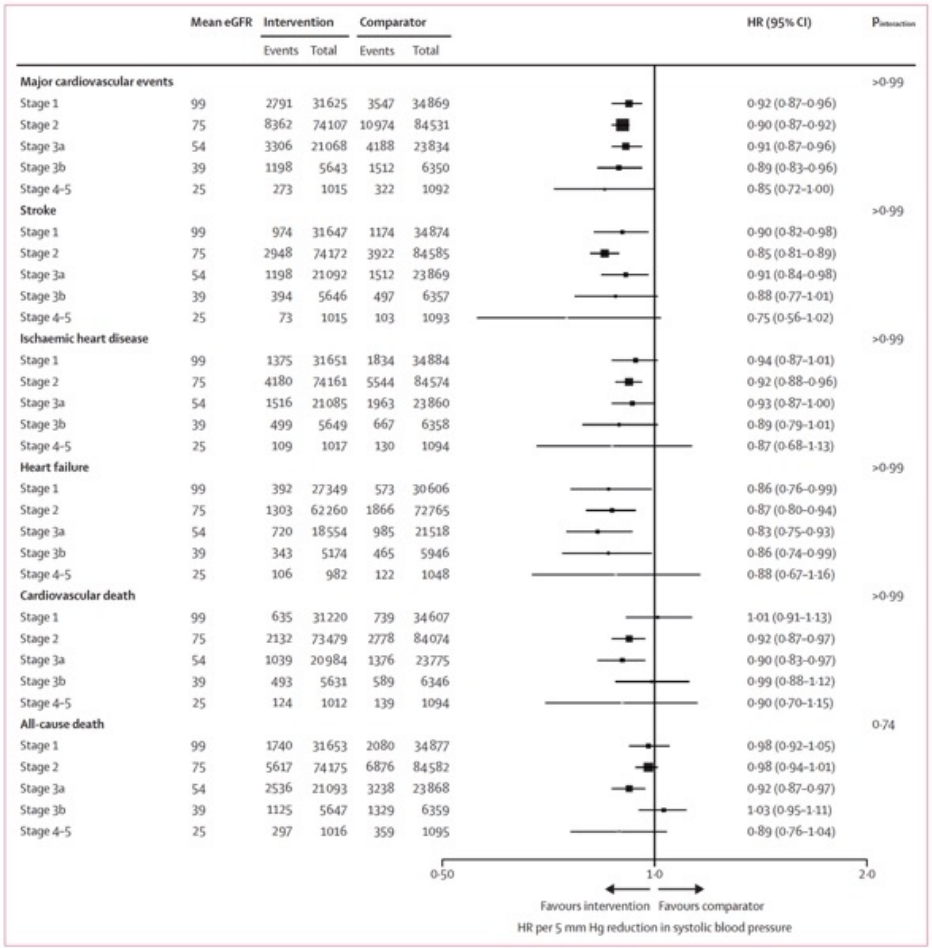


Figure 2: **Effects of blood-pressure-lowering treatment on primary and secondary outcomes by CKD stage**

The forest plot shows HRs and 95% CIs per 5 mm Hg reduction in systolic blood pressure, separately for each outcome. HRs and 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. CKD stages were defined with the CKD Epidemiology Collaboration 2021 race-free equations:[18] stage 1 (eGFR ≥90 mL/min per 1·73 m^2), stage 2 (60–89 mL/min per 1·73 m^2), stage 3a (45–59 mL/min per 1·73 m^2), stage 3b (30–44 mL/min per 1·73 m^2), and stages 4–5 (<30 mL/min per 1·73 m^2). Mean eGFR values within each stage represent the baseline eGFR of participants classified in that subgroup. p values for interaction were derived from likelihood ratio tests comparing models with and without treatment-by-CKD stage interaction terms, assessing heterogeneity of treatment effect across the five CKD stages, and were adjusted for multiple testing with Hommel's method. Events denotes the number of participants who had the outcome; total denotes the total number at risk. The size of each square is proportional to the inverse variance of the log HR. The vertical line indicates an HR of 1·0 (ie, no effect). CKD=chronic kidney disease. HR=hazard ratio.

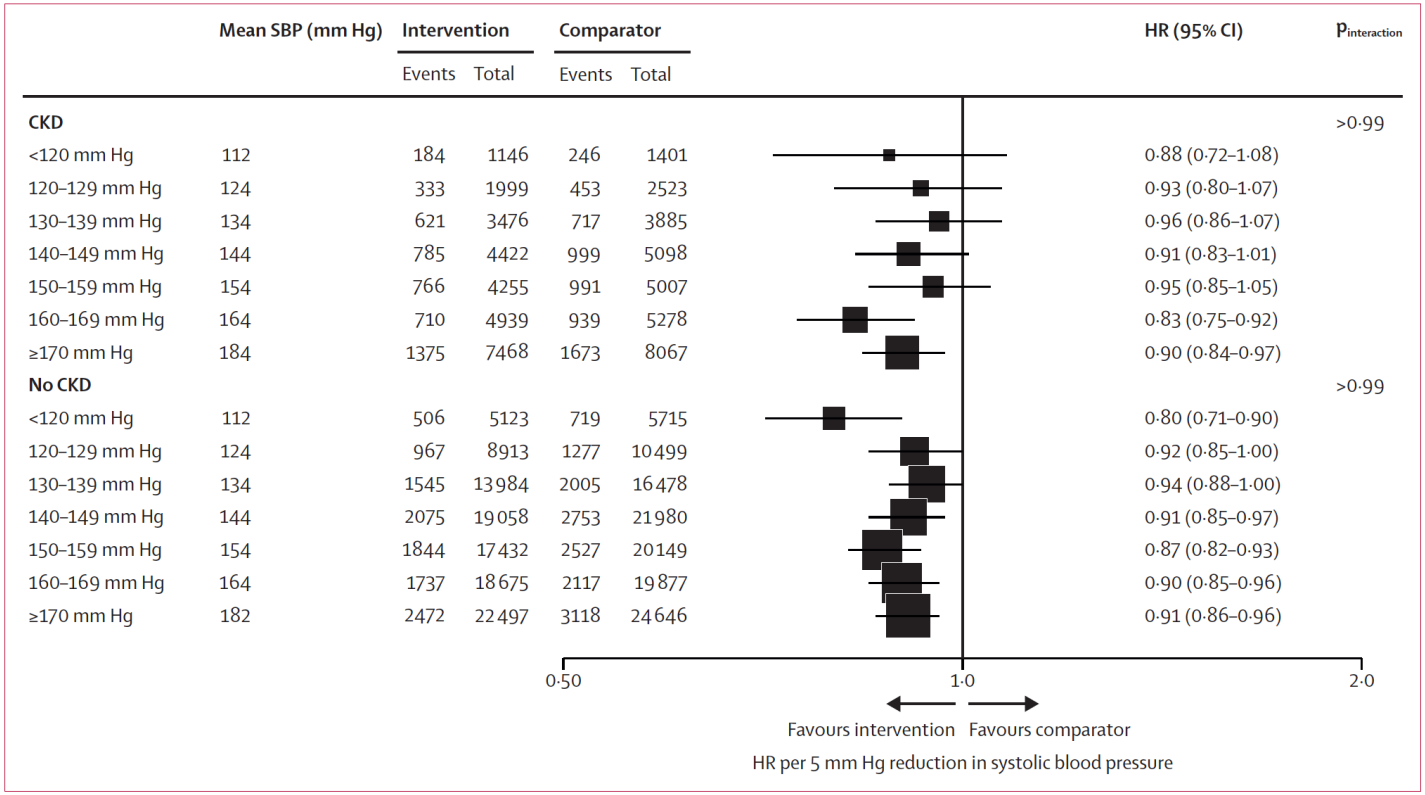


Figure 3: **Effects of blood-pressure-lowering treatment on major cardiovascular events by baseline CKD status and SBP**

The forest plot shows HRs and 95% CIs for major cardiovascular events by baseline SBP categories, separately for participants with and without CKD. HRs and 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. Mean SBP values within each category represent the baseline SBP of participants classified in that subgroup. p values for interaction were derived from likelihood ratio tests comparing models with and without treatment-by-baseline SBP category interaction terms, assessing heterogeneity of treatment effect across the seven SBP categories within each CKD stratum, and were adjusted for multiple testing with Hommel's method. Events denotes the number of participants who had the outcome; total denotes the total number at risk. The size of each square is proportional to the inverse variance of the log HR. The vertical line indicates an HR of 1·0 (ie, no effect). CKD=chronic kidney disease. HR=hazard ratio. SBP=systolic blood pressure.

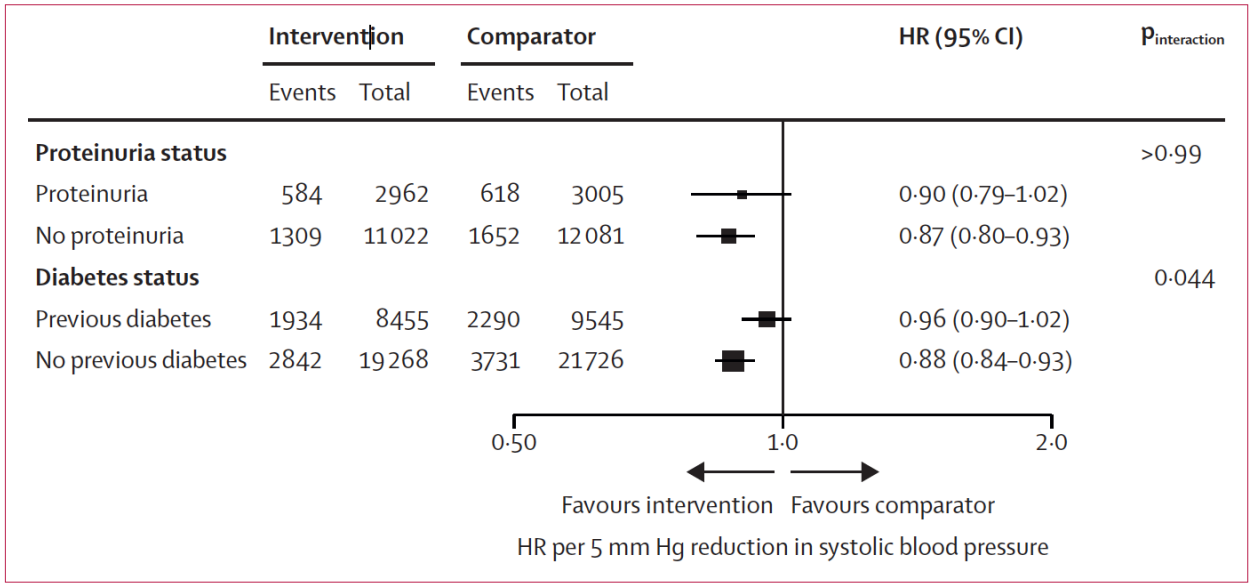


Figure 4: **Effects of blood-pressure-lowering treatment on major cardiovascular disease in people with CKD, stratified by baseline diabetes and proteinuria status**

The forest plot shows HRs and 95% CIs for major cardiovascular events within participants with CKD, stratified by proteinuria and diabetes status. HRs and 95% CIs were standardised to a 5 mm Hg reduction in systolic blood pressure, estimated from one-stage stratified Cox proportional hazards models. Proteinuria was defined as urine albumin-to-creatinine ratio of ≥30 mg/g or urine protein-to-creatinine ratio of ≥0·22 or dipstick ≥1. Previous diabetes was defined as a history of diabetes at baseline. p values for interaction were derived from likelihood ratio tests comparing models with and without treatment-by-subgroup interaction terms, assessing heterogeneity of treatment effect, and were adjusted for multiple testing with Hommel's method. Sample sizes for proteinuria analysis are smaller because proteinuria data were available only in a subset of trials. Events denotes the number of participants who had the outcome; total denotes the total number at risk. The size of each square is proportional to the inverse variance of the log HR. The vertical line indicates an HR of 1·0 (ie, no effect). CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. HR=hazard ratio.

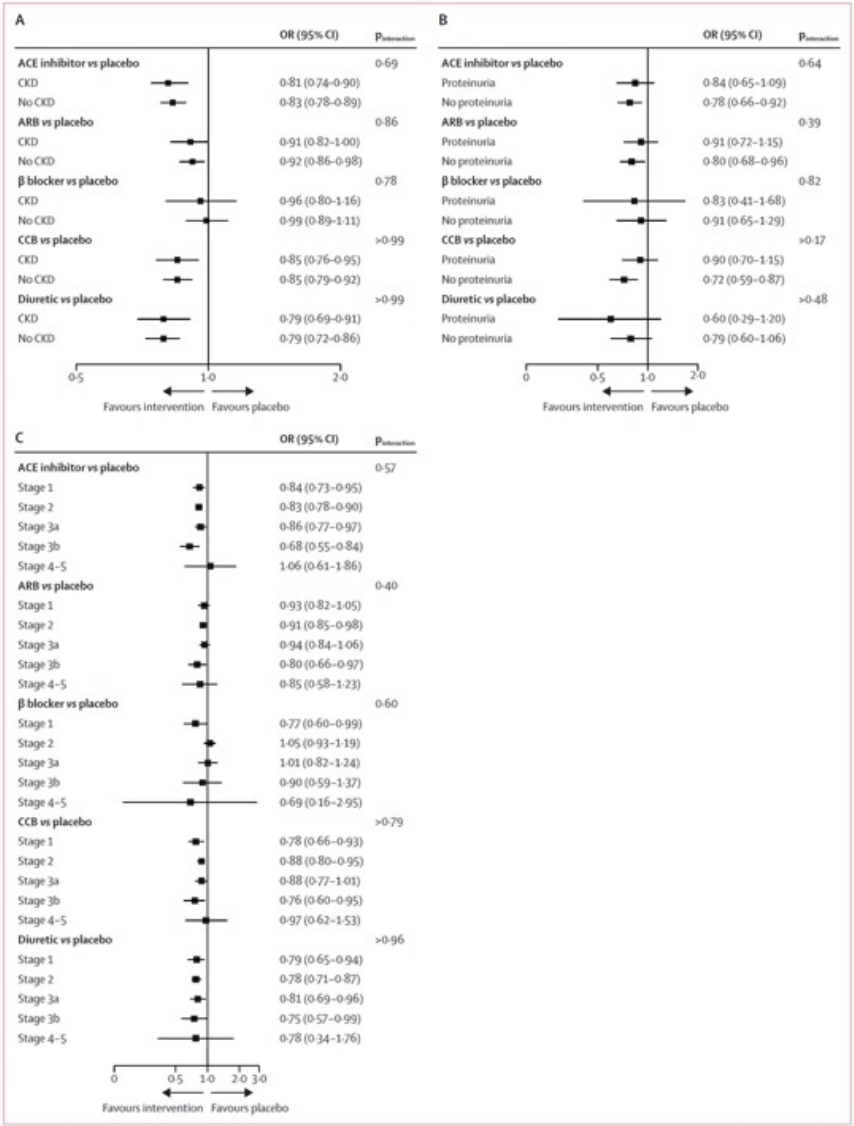


Figure 5: **Class-specific effects of antihypertensive drugs on the risk of major cardiovascular disease, stratified by CKD status, stage, and proteinuria**

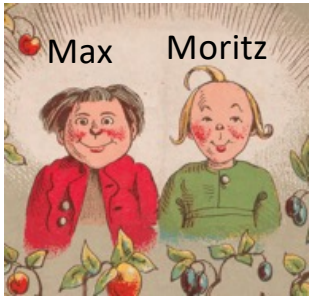
The forest plots show ORs as the relative treatment effect and their corresponding 95% CIs for major cardiovascular events stratified by CKD status (A), proteinuria existence (B), and CKD stage (C), comparing each antihypertensive drug class with placebo, estimated from a Bayesian network meta-analysis with fixed-effects models. p values for interaction were derived from meta-regression comparing treatment effects across subgroups. The size of each square is proportional to the inverse variance of the log OR. The vertical line indicates an OR of 1·0 (ie, no effect). CKD stages were defined with the CKD Epidemiology Collaboration 2021 race-free equations:[18] stage 1 (eGFR ≥90 mL/min per 1·73 m^2), stage 2 (60–89 mL/min per 1·73 m^2), stage 3a (45–59 mL/min per 1·73 m^2), stage 3b (30–44 mL/min per 1·73 m^2), and stages 4–5 (<30 mL/min per 1·73 m^2). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. OR=odds ratio.

Implications of all the available evidence

When the main therapeutic goal is cardiovascular risk management, clinicians can recommend blood-pressure-lowering treatment to individuals at all stages of CKD progression, regardless of blood-pressure values, provided the balance of benefits and harms is favourable and patient preferences are considered. This recommendation can be done with the expectation that the class-specific effects of different antihypertensive drugs mirror those observed in the broader population. In individuals with CKD and coexisting diabetes, blood-pressure-lowering treatment is essential due to their notably elevated absolute risk and the well documented beneficial effects of treatment in patients with diabetes. However, the attenuated relative risk reduction associated with diabetes highlights the need for adapted strategies to enhance cardiovascular risk management in this population at high risk.

What‘s with MEK?!?

Die Wendung „mecke, mecke, meck“ stammt aus Wilhelm Buschs berühmtem Werk „Max und Moritz“ (1865), spezifisch aus dem 3. Streich. Die Buben verspotten Schneider Böck, nachdem sie dessen Brücke angesägt haben, mit diesem Ziegenlaut, was ihn in die Brücke stürzen lässt. Der Ausruf steht symbolisch für ihren Spott und das Leiden der Opfer.



Bad boys

Taylor Böck suffers from gastric ulcers

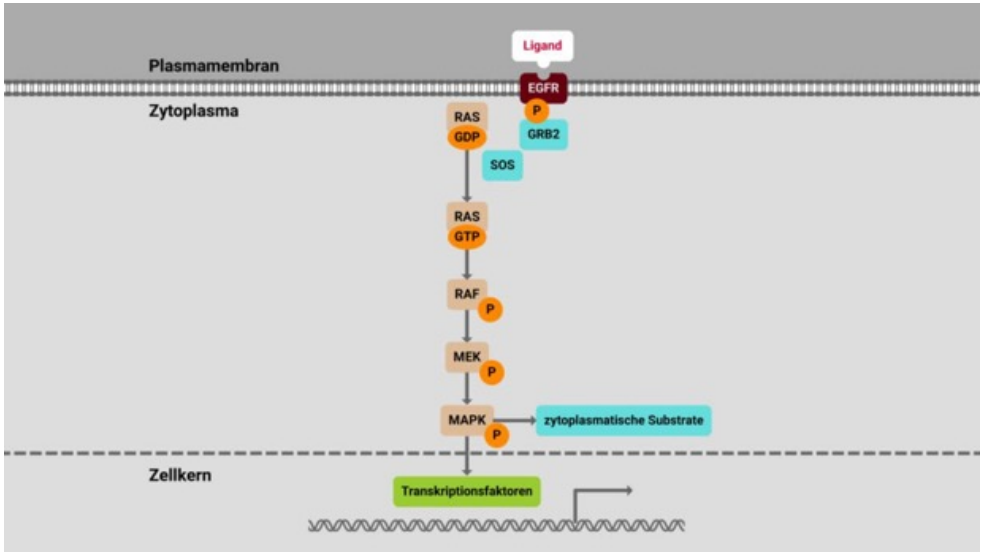
Bad boys sabotage bridge by sawing it in half

Bad boys, Max and Moritz, celebrate as taylor Böck falls in creek

In der Zellbiologie ist **MEK** (Mitogen-activated protein kinase kinase) ein zentrales Protein im sogenannten MAP-Kinase-Weg.

- **Funktion**: MEK leitet Signale von der Zelloberfläche in den Zellkern weiter.
- **Wirkungskette**: Es wird meist durch **Raf** aktiviert und aktiviert seinerseits **ERK**.
- **Bedeutung**: Dieser Weg steuert Zellwachstum und Teilung. Fehler in diesem Signalsystem können zu Krebs führen.

RAF (Rapidly Accelerated Fibrosarcoma) ist eine Familie von Serin/Threonin-Proteinkinasen (A-Raf, B-Raf, C-Raf/Raf-1), die im MAPK-Signalweg (Ras-Raf-MEK-ERK) als zentrale Schnittstelle fungieren. Sie werden durch aktiviertes RAS-GTP gebunden, aktiviert und phosphorylieren anschließend MEK, um Signale für Zellwachstum, Proliferation und Differenzierung weiterzuleiten.



In der MAP-Kinase-Signaltransduktion steht das Akronym **MEK** für **MAPK/ERK-Kinase**.

Die **ERK-Kinase** (Extracellular-signal-Regulated Kinase) ist ein zentrales Enzym in der intrazellulären Signalübertragung, das extrazelluläre Signale (z. B. Wachstumsfaktoren) in den Zellkern leitet, um Prozesse wie Proliferation, Differenzierung und Überleben zu regulieren.

Targeting MEK in cancer and beyond: mechanistic insights and therapeutic opportunities

MEK inhibitors are established therapies in *BRAF*-driven cancers, yet their broader clinical effect is limited by toxicity, resistance, and modest durability as a monotherapy, particularly in *RAS*-mutant tumours. Dose intensity is often restricted by severe adverse effects, particularly dermatological, gastrointestinal, ocular, and cardiopulmonary toxic effects. Predictive biomarkers, such as tumour mutational burden, interferon signatures, and MAPK pathway activity, are emerging as crucial tools for refining patient selection and monitoring therapeutic response. Advances in drug design, including dual-targeting strategies, aim to expand the therapeutic window and overcome resistance mechanisms. Combination regimens, particularly those incorporating immune checkpoint inhibitors or PI3K–mTOR pathway inhibition, show promise for enhancing efficacy and treatment durability. Beyond oncology, MEK pathway modulation is under investigation in fibrotic, inflammatory, and developmental disorders, although clinical validation remains at an early stage. Building on more than a decade of use in *BRAF*^{V600} (ie, Val600)-mutant melanoma, MEK inhibitors continue to be refined through biomarker-guided combination strategies and exploration in additional cancers and non-oncological diseases.

Introduction

The mitogen-activated protein kinase (MAPK) pathway—also known as the RAS–RAF–MEK–ERK cascade—is a highly conserved signalling axis that governs fundamental processes in cellular and organismal development and tissue homoeostasis, including organogenesis, proliferation, survival, and migration.[1,2] Dysregulated MAPK activity is a hallmark of cancer, with activating mutations in core components such as *RAS* (eg, *KRAS* and *NRAS*) and *BRAF*, or loss-of-function mutations in negative regulators, such as *NF1* (which encodes neurofibromin 1), identified in approximately one-third of all human malignancies (figure 1).[3–6] Beyond cancer, germline mutations that affect more than 20 MAPK-related genes, including *PTPN11, SOS1, SOS2, RAF1, KRAS, BRAF, MAP2K1* (which encodes MEK1), and *NF1*, underpin a spectrum of developmental disorders collectively termed RASopathies. These disorders, which include Noonan syndrome, neurofibromatosis type 1, LEOPARD syndrome, and cardiofaciocutaneous syndrome, share phenotypes such as congenital cardiac defects, facial dysmorphism, impaired growth, learning disabilities, and skeletal and ectodermal anomalies.[7]

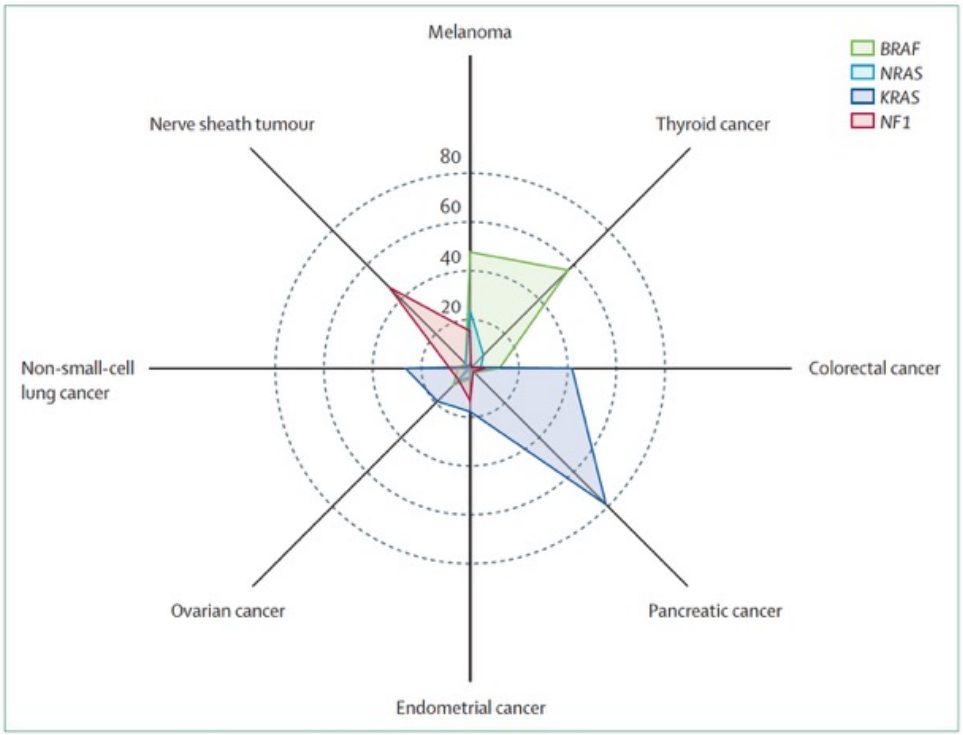


Figure 1: **Comparative frequencies of *BRAF, KRAS, NRAS,* and *NF1* alterations across tumour subsets**
Radar plot showing the frequency of alterations in *BRAF, KRAS, NRAS,* and *NF1* across 95 474 tumour samples from the curated The Cancer Genome Atlas Program dataset. Overall, 24% of tumours harboured alterations in these genes, whereas alterations in *MAP2K1* or *MAP2K2* were observed in fewer than 2% of cases. Each axis represents one cancer type, with values indicating the frequency of alterations. Data were obtained from cBioPortal and visualised using Flourish.

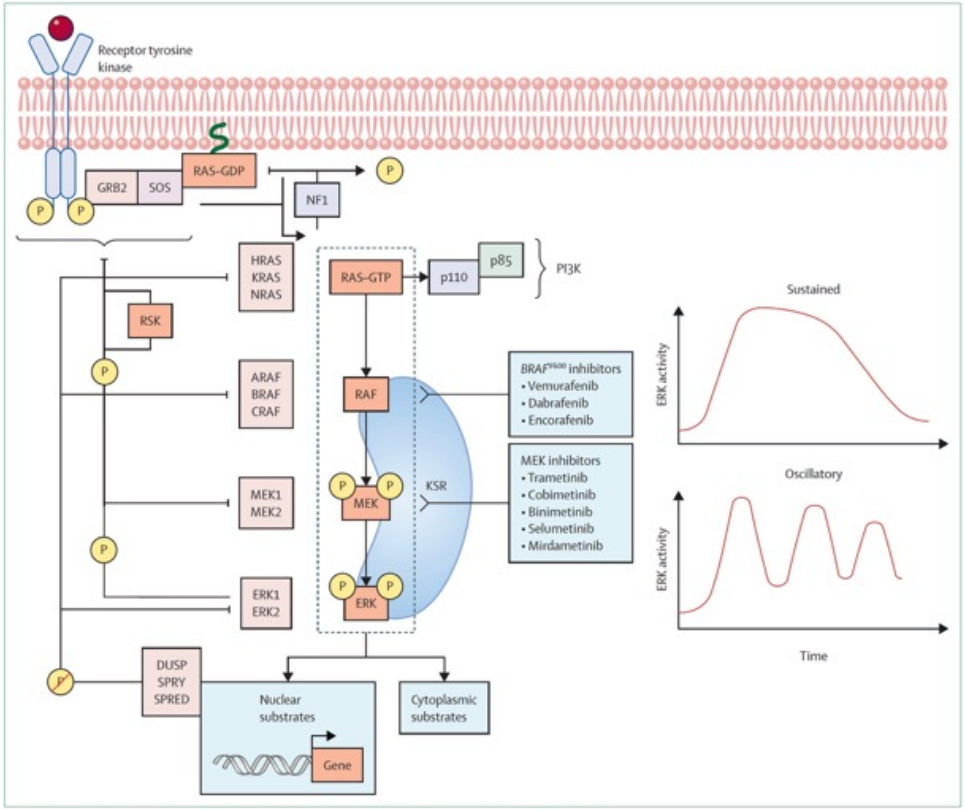


Figure 2: **Overview of canonical MAPK–ERK signalling cascade and regulatory feedback mechanisms**

The dotted boxed region denotes the core MAPK module, highlighting the sequential phosphorylation cascade from RAF to MEK to ERK. Activation of receptor tyrosine kinases at the plasma membrane triggers recruitment of adaptor proteins GRB2 and the guanine nucleotide exchange factor SOS, facilitating the conversion of RAS from its inactive GDP-bound form to the active GTP-bound state. Active RAS interacts with and activates RAF kinases (ARAF, BRAF, and CRAF), which subsequently phosphorylate and activate the dual-specificity kinases MEK1 and MEK2. Activated MEK1 and MEK2 then phosphorylate the extracellular signal-regulated kinases ERK1 and ERK2, which translocate to the nucleus to regulate nuclear substrates, including transcription factors, while also phosphorylating cytoplasmic targets to modulate diverse cellular responses. In parallel, RAS–GTP can also interact with the p110 catalytic subunit of PI3K, activating the PI3K signalling pathway. Feedback regulation is mediated by phosphorylation-dependent inhibitory loops: ERK phosphorylates multiple upstream RTKs, adaptor proteins, BRAF, CRAF, and MEK1, to dampen MAPK signalling, and RSK, a downstream effector of ERK, phosphorylates upstream components, including SOS and CRAF, to attenuate pathway output. Additional negative regulators, including phosphatases DUSPs and the inhibitory SPRY and SPRED proteins, modulate RAS and ERK activity to fine-tune signal intensity and duration. The RAS GTPase-activating protein NF1 promotes RAS inactivation by stimulating hydrolysis of GTP to GDP. The scaffold protein KSR facilitates the spatial organisation of the pathway components to enhance signalling efficiency. Clinically approved BRAF inhibitors and MEK inhibitors are indicated. Temporal dynamics of MAPK are shaped by the interplay of feedback loops, scaffold proteins, and phosphatases. Oscillatory ERK signalling, often driven by pulsatile upstream inputs and rapid feedback, is associated with transient gene expression, whereas sustained ERK activation typically results from persistent upstream stimulation or impaired feedback. Phosphorylation events are indicated by circled P symbols; arrows denote activation, and T-shaped lines represent inhibition. Figure created with BioRender.com. DUSPs=dual-specificity phosphatases.

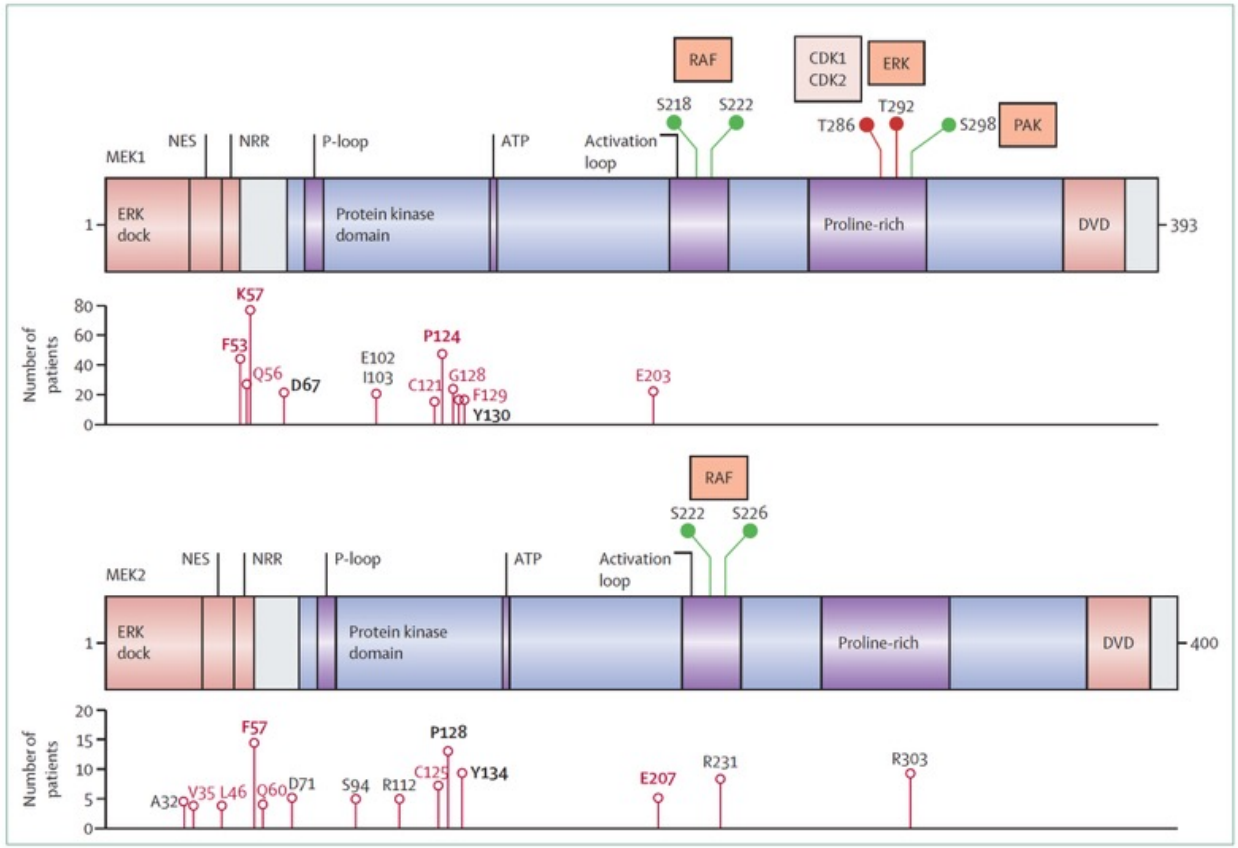


Figure 3: **Human MEK1 and MEK2 protein domains, key regulatory sites, and frequent cancer-associated mutations**

The multifunctional N-terminal region contains the ERK-binding domain (ERK dock), the NES and the NRR. The central kinase domain includes the glycine rich P-loop, the ATP-binding pocket, the activation loop with the RAF (MAP3K)-targeted serine phosphorylation sites, and the proline-rich domain. Key phosphorylation sites are annotated: activating sites are shown in green and inhibitory sites in red, along with the kinases responsible for their modifications. The C-terminal region features an unstructured DVD motif for binding with upstream MAP3Ks.[19] In MEK1, Thr292 is an ERK1-mediated and ERK2-mediated feedback phosphorylation site (absent in MEK2), whereas Ser298 is an activating site phosphorylated by PAK. Below each MEK schema, the frequency and distribution of common cancer-associated mutation sites are shown, and mutation sites linked with BRAF or MEK inhibitor resistance (or both) are in red text.[20–22] Cancer-associated mutation frequency was derived from a curated set of non-redundant studies in cBioPortal (95 474 samples).[23,24] RASopathy MEK1 and MEK2 variants also cluster near the NRR and amino-terminal region of the kinase domain, and common RASopathy variants are in bold text (data were obtained from the Clinical Genome Resource).[25] The schematic design and annotation were informed by literature.[8,26,27] Figure created with BioRender.com. CDK=cyclin-dependent kinase. DVD=domain for versatile docking. NES=nuclear export sequence. NRR=negative regulatory region.

	Trametinib	Cobimetinib	Binimetinib	Selumetinib	Mirdametinib
Biopharmaceutics classification system class	Class II	Class I	Class IV	Class IV	Class I
In vitro enzyme[55,56]	MEK1 IC_{50}=0·7 nM; MEK2 IC_{50}=0·9 nM	MEK1 IC_{50}=0·95 nM; MEK2 IC_{50}=199 nM	MEK1 IC_{50}=12 nM; MEK2 IC_{50}=46 nM	MEK1 IC_{50}=10–14 nM	MEK1 IC_{50}=1 nM; MEK2 IC_{50}=1 nM
Recommended dosage	2 mg once a day	60 mg once a day, for 21 days of a 28-day cycle followed by 7 days of no treatment	45 mg twice a day	25 mg/m² twice a day	2 mg/m² twice a day, for 21 days of a 28-day cycle followed by 7 days of no treatment
Elimination half-life	4–5 days	43·6 h	3·5 h	6·2 h	28 h
Peak time	1·5 h	2·4 h	1·5 h	1 h	0·8 h
Plasma clearance	5·4 L/h	13·8 L/h	20·2 L/h	8·8 L/h	6·3 L/h
Approved indications	Monotherapy: unresectable or metastatic *BRAF*^{V600E} and *BRAF*^{V600K} melanoma (2013); combination (with dabrafenib): unresectable or metastatic *BRAF*^{V600E} and *BRAF*^{V600K} melanoma (2014), *BRAF*^{V600E} NSCLC (2017), adjuvant *BRAF*^{V600E} and *BRAF*^{V600K}-mutant melanoma (2018), *BRAF*^{V600E} anaplastic thyroid cancer (2018), and *BRAF*^{V600E} solid tumours (2022)	Monotherapy: histiocytic neoplasms (eg, Erdheim–Chester disease and Langerhans cell histiocytosis; 2022); combination (with vemurafenib): unresectable or metastatic *BRAF*^{V600E} and *BRAF*^{V600K} melanoma (2015); triplet therapy (cobimetinib + vemurafenib + atezolizumab): metastatic *BRAF*^{V600E} and *BRAF*^{V600K} melanoma (2020)	Combination (with encorafenib): unresectable or metastatic *BRAF*^{V600E} and *BRAF*^{V600K} melanoma (2018), and *BRAF*^{V600E} metastatic NSCLC (2023)	Monotherapy: paediatric, symptomatic, inoperable neurofibromatosis type 1-related plexiform neurofibromas (2020)	Monotherapy: adult and paediatric patients (≥2 years) with neurofibromatosis type 1 who have symptomatic plexiform neurofibromas not amenable to complete resection (2025)
Common adverse reactions	Fatigue, nausea, rash, diarrhoea, myalgia, peripheral oedema, and acneiform dermatitis	Fatigue, nausea, rash, diarrhoea, photosensitivity, peripheral oedema, and acneiform dermatitis	Fatigue, nausea, rash, diarrhoea, and peripheral oedema	Fatigue, nausea, diarrhoea, oedema, acneiform dermatitis, and asymptomatic creatine kinase elevation	Fatigue, nausea, vomiting, rash, diarrhoea, and creatine kinase elevation

Class I refers to high solubility and high permeability, class II refers to low solubility and high permeability, class III refers to high solubility and low permeability, and class IV refers to low solubility and low permeability. Dabrafenib, vemurafenib, and encorafenib are selective inhibitors of *BRAF*^{V600}-mutant kinases; atezolizumab is an anti-PD-L1 immune checkpoint inhibitor. Approved indications accessed from the US FDA. FDA=Food and Drug Administration. IC_{50}=half maximal inhibitory concentration. NSCLC=non-small-cell lung cancer.

Table 1: **MEK inhibitors approved by the US FDA for clinical use**

	n	Study focus	ORR, % (95% CI)	Median progression-free survival, months (95% CI)	Median overall survival, months (95% CI)
METRIC, Flaherty et al (2012)[62,68]					
Trametinib	214	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant metastatic melanoma	40% (33·6–47·1)	4·9 (NR)	15·6 (NR)
Dacarbazine or paclitaxel	108	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant metastatic melanoma	14% (8·0–21·9)	1·5 (NR)	11·3 (NR)
Combi-d, Long et al (2014)[77,78]					
Trametinib + dabrafenib	211	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant metastatic melanoma	69% (62–75)	11·0 (8·0–13·9)	25·1 (19·2 to not reached)
Placebo + dabrafenib	212	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant metastatic melanoma	53% (46–60)	8·8 (5·9–9·3)	18·7 (15·2–23·7)
coBRIM, Ascierto et al (2015)[79,80]					
Cobimetinib + vemurafenib	247	Untreated locally advanced or metastatic	70% (63·5–75·3)	12·3 (9·5–13·4)	22·3 (20·3 to not estimable)
Placebo + vemurafenib	248	$BRAF^{V600}$-mutant melanoma	50% (43·6–56·4)	7·2 (5·6–7·5)	17·4 (15·0–19·8)
NEMO, Dummer et al (2017)[66]					
Binimetinib	269	$NRAS^{mut}$ unresectable or metastatic melanoma	41% (11–20)	3·0 (2·8–4·1)	11·0* (8·9–13·6)
Dacarbazine	133	$NRAS^{mut}$ unresectable or metastatic melanoma	9% (3–13)	1·8 (1·5–2·8)	10·1* (7·0–16·5)
SUMIT, Carvajal et al (2018)[81]					
Selumetinib + dacarbazine	97	Metastatic uveal melanoma	3% (NR)	2·8* (NR)	NR
Placebo + dacarbazine	32	Metastatic uveal melanoma	0% (NR)	1·8* (NR)	NR
BEACON, Kopetz et al (2019)[82]					
Binimetinib + encorafenib + cetuximab	222	$BRAF^{V600K}$-mutant colorectal cancer	26% (18–35)	4·3 (4·1–5·2)	9·0 (8·0–11·4)
Encorafenib + cetuximab	216	$BRAF^{V600K}$-mutant colorectal cancer	20% (13–29)	4·2 (3·7–5·4)	8·4 (7·5–11·0)
Investigator choice	193	$BRAF^{V600K}$-mutant colorectal cancer	2% (0–7)	1·5 (1·5–1·7)	5·4 (4·8–6·6)
Combi-v, Robert et al (2019)[83]					
Trametinib + dabrafenib	352	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant metastatic melanoma	64% (59–61)	11·4 (NR)	NR
Vemurafenib	352	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant metastatic melanoma	51% (46–57)	7·3 (NR)	17·2 (NR)
IMblaze370, Eng et al (2019)[84]					
Cobimetinib + atezolizumab	183	Microsatellite-stable metastatic colorectal cancer	3% (0·9–6·3)	1·91* (1·87–1·97)	8·87* (7·00–10·61)
Atezolizumab	90	Microsatellite-stable metastatic colorectal cancer	2% (0·3–7·8)	1·94* (1·91–2·10)	7·10* (6·05–10·05)
Regorafenib	90	Multikinase inhibitor microsatellite-stable metastatic colorectal cancer	2% (0·3–7·8)	2·00 (1·87–3·61)	8·51 (6·41–10·71)
COLUMBUS, Dummer et al (2020)[85,86]					
Binimetinib + encorafenib	192	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant melanoma	64·1% (56·8–70·8)	14·9 (11·0–20·2)	33·6 (24·4–39·2)
Encorafenib	194	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant melanoma	51·5% (44·3–58·8)	9·6 (7·4–14·8)	23·5 (19·6–33·6)
Vemurafenib	191	$BRAF^{V600K}$-mutant or $BRAF^{V600K}$-mutant melanoma	40·8% (33·8–48·2)	7·3 (5·6–7·9)	16·9 (14·0–24·5)
IMspire170, Gogas et al (2021)[87]					
Cobimetinib + atezolizumab	222	$BRAF^{V600}$-negative melanoma	26·0% (20·1–32·6)	5·5* (3·8–7·2)	NR
Pembrolizumab	224	$BRAF^{V600}$-negative melanoma	31·6% (25·3–38·4)	5·7* (3·7–9·6)	NR
IMspire150, Ascierto et al (2023)[88]					
Cobimetinib + vemurafenib + atezolizumab	160	$BRAF^{V600K}$-mutant melanoma	67% (61–72)	15·1 (11·4–18·4)	39·0 (29·9 to not estimable)
Cobimetinib + vemurafenib + placebo	170	$BRAF^{V600K}$-mutant melanoma	65% (59–71)	10·6 (9·3–12·7)	25·8 (22·0–34·6)

NR=not reported. ORR=objective response rate. *Did not meet statistical significance.

Table 2: **Selected phase 3 clinical trials evaluating MEK inhibitors (monotherapy and combination)**

	Drug action	Study focus
Sullivan et al (2015),[130] phase 1/2, completed		
Trametinib	MEK inhibition	Advanced solid tumours
Palbociclib	CDK4 and CDK6 inhibition	Advanced solid tumours
Carter et al (2016),[147] phase 2, completed		
Selumetinib	MEK inhibition	Metastatic pancreatic adenocarcinoma
Erlotinib	EGFR inhibition	Metastatic pancreatic adenocarcinoma
Lee et al (2016),[128] phase 1, completed		
Binimetinib	MEK inhibition	$KRAS^{mut}$ and $NRAS^{mut}$ colorectal cancer
Palbociclib	CDK4 and CDK6 inhibition	$KRAS^{mut}$ and $NRAS^{mut}$ colorectal cancer
Ascierto et al (2017),[131] phase 1, completed		
Binimetinib	MEK inhibition	Advanced solid tumours
Encorafenib	BRAF inhibition	Advanced solid tumours
Ribociclib	CDK4 and CDK6 inhibition	Advanced solid tumours
Algazi et al (2018),[148] phase 2, completed		
Trametinib	MEK inhibition	$BRAF^{WT}$ and $NRAS^{WT}$ wild-type melanoma
GSK2141795	AKT inhibition	$BRAF^{WT}$ and $NRAS^{WT}$ wild-type melanoma
Bendell et al (2020),[149] phase 1/2, completed		
Cobimetinib	MEK inhibition	$EGFR^{mut}$ NSCLC
Osimertinib	EGFR inhibition	$EGFR^{mut}$ NSCLC
RMC-4630	SHP2 inhibition	$EGFR^{mut}$ NSCLC
Gaudreau et al (2020),[150] phase 1/2, completed		
Selumetinib	MEK inhibition	NSCLC
Durvalumab	Anti-PD-L1 immune checkpoint inhibition	NSCLC
Tremelimumab	Anti-CTLA-4 immune checkpoint inhibition	NSCLC
LoRusso et al (2020),[132] phase 1, terminated per sponsor decision		
Trametinib	MEK inhibition	Advanced solid tumours
Ribociclib	CDK4 and CDK6 inhibition	Advanced solid tumours
Schuler et al (2022),[133] phase 1/2, completed		
Binimetinib	MEK inhibition	$NRAS^{mut}$ melanoma
Ribociclib	CDK4 and CDK6 inhibition	$NRAS^{mut}$ melanoma
Buchbinder et al (2023),[151] phase 1/2, completed		
Dabrafenib	BRAF inhibition	Melanoma post-BRAF– MEK inhibitor progression
Trametinib	MEK inhibition	Melanoma post-BRAF– MEK inhibitor progression
MCS110	CSF-1 inhibition	Melanoma post-BRAF– MEK inhibitor progression
Manji et al (2023),[152] phase 1/2, terminated due to toxicity and lack of efficacy		
Cobimetinib	MEK inhibition	$KRAS^{mut}$ malignancies
Atezolizumab	Anti-PD-L1 immune checkpoint inhibition	$KRAS^{mut}$ malignancies
Hydroxychloroquine	Autophagy inhibition	$KRAS^{mut}$ malignancies
Schjesvold et al (2023),[153] phase 1/2, completed		
Cobimetinib	MEK inhibition	Multiple myeloma
Atezolizumab	Anti-PD-L1 immune checkpoint inhibition	Multiple myeloma
Venetoclax	BCL-2 inhibition	Multiple myeloma

(Table 3 continues on next page)

	Drug action	Study focus
(Continued from previous page)		
Tian et al (2023),[154] phase 2, completed		
Dabrafenib	BRAF inhibition	$BRAF^{V600E}$-mutant colorectal cancer
Trametinib	MEK inhibition	$BRAF^{V600E}$-mutant colorectal cancer
Spartalizumab	Anti-PD-1 immune checkpoint inhibition	$BRAF^{V600E}$-mutant colorectal cancer
Van Cutsem et al (2023),[155] phase 2, completed		
Binimetinib	MEK inhibition	$BRAF^{V600E}$-mutant colorectal cancer
Encorafenib	BRAF inhibition	$BRAF^{V600E}$-mutant colorectal cancer
Cetuximab	EGFR inhibition	$BRAF^{V600E}$-mutant colorectal cancer
Manoharan et al (2024),[156] phase 2, completed		
Cobimetinib	MEK inhibition	Platinum-resistant high-grade serous ovarian cancer
Atezolizumab	Anti-PD-L1 immune checkpoint inhibition	Platinum-resistant high-grade serous ovarian cancer
Bevacizumab	VEGF inhibition	Platinum-resistant high-grade serous ovarian cancer
Mutch et al (2024),[157] phase 1, completed		
Cobimetinib	MEK inhibition	$BRCA^{WT}$ ovarian cancer
Atezolizumab	Anti-PD-L1 immune checkpoint inhibition	$BRCA^{WT}$ ovarian cancer
Niraparib	PARP inhibition	$BRCA^{WT}$ ovarian cancer
Somaiah et al (2024),[158] phase 2, completed		
Selumetinib	MEK inhibition	Malignant peripheral nerve sheath tumours
Sirolimus	mTOR inhibition	Malignant peripheral nerve sheath tumours
Dagogo-Jack et al (2025),[159] phase 1/2, active, not recruiting		
Cobimetinib	MEK inhibition	ALK-rearranged NSCLC
Alectinib	ALK inhibition	ALK-rearranged NSCLC
Prasath et al (2025),[160] phase 2, completed		
Trametinib	MEK inhibition	Triple negative breast cancer
GSK2141795	AKT inhibition	Triple negative breast cancer
NCT03272464, phase 1, terminated due to slow accrual		
Dabrafenib	BRAF inhibition	$BRAF^{V600E}$-mutant or $BRAF^{V600K}$-mutant melanoma and solid tumours
Trametinib	MEK inhibition	$BRAF^{V600E}$-mutant or $BRAF^{V600K}$-mutant melanoma and solid tumours
Itacitinib	JAK1 inhibition	$BRAF^{V600E}$-mutant or $BRAF^{V600K}$-mutant melanoma and solid tumours
NCT03631953, phase 1, recruiting		
Trametinib	MEK inhibition	Refractory meningiomas
Alpelisib	PIK3CA inhibition	Refractory meningiomas
NCT03947385, phase 1/2, recruiting		
Binimetinib	MEK inhibition	GNAQ, GNA11, or PRKC fusion solid tumours
Darovasertib	PKC inhibition	GNAQ, GNA11, or PRKC fusion solid tumours
NCT03979651, phase 1/2, completed		
Trametinib	MEK inhibition	$NRAS^{mut}$ melanoma
Hydroxychloroquine	Autophagy inhibition	$NRAS^{mut}$ melanoma

(Table 3 continues on next page)

	Drug action	Study focus
(Continued from previous page)		
NCT04109456, phase 1, active, not recruiting		
Cobimetinib	MEK inhibition	Metastatic melanoma
IN10018 (FAK)	FAK inhibition	Metastatic melanoma
NCT04201457, phase 1/2, active, not recruiting		
Dabrafenib	BRAF inhibition	Recurrent low-grade or high-grade glioma with BRAF alteration
Trametinib	MEK inhibition	Recurrent low-grade or high-grade glioma with BRAF alteration
Hydroxychloroquine	Autophagy inhibition	Recurrent low-grade or high-grade glioma with BRAF alteration
NCT05585320, phase 1/2, active, not recruiting		
Atebimetinib (IMM-1-104)	MEK inhibition	Metastatic pancreatic ductal adenocarcinoma
Modified gemcitabine and nab-paclitaxel	Inhibition of DNA synthesis and microtubule function	Metastatic pancreatic ductal adenocarcinoma
Dabrafenib	BRAF inhibition	$BRAF^{mut}$ melanoma post anti-PD-(L)1 monoclonal antibody progression

NSCLC=non-small-cell lung cancer.

Table 3: Interventions in clinical trials involving MEK inhibitor combination therapies

The future of MEK inhibitors lies not in monotherapy, but in the integration of MEK inhibitors into biomarker-driven, combination-based, and precision-guided strategies. With ongoing innovations in drug design and a deepening understanding of resistance biology, MEK inhibition is poised to remain a foundational element of targeted therapy and potentially extend its relevance beyond oncology.

The heart puts pressure on cancer growth

Heart cancer is very rare in mammals. Moreover, the healthy adult heart does not regenerate. Human heart cells (cardiomyocytes) renew at an ~1% rate per year. The high mechanical load placed on cardiac tissue, which must overcome strong resistance to pump blood to all body organs, has been proposed to inhibit cardiomyocyte proliferation. Indeed, reducing the mechanical load on the heart promotes the expression of cell cycle markers in cardiomyocytes of patients whose hearts were unloaded by a ventricular assist device. Ciucci *et al*. report that the constant mechanical load to which cardiac tissue is subjected also inhibits the proliferation of cancer cells in the heart.

Primary cardiac tumors are exceptionally rare, whereas secondary cardiac metastases originating elsewhere are more prevalent. Notably, even cardiac metastases are frequently clinically silent, with many cases identified only incidentally or at autopsy. Although this observation is well accepted, mechanistic understanding was lacking.

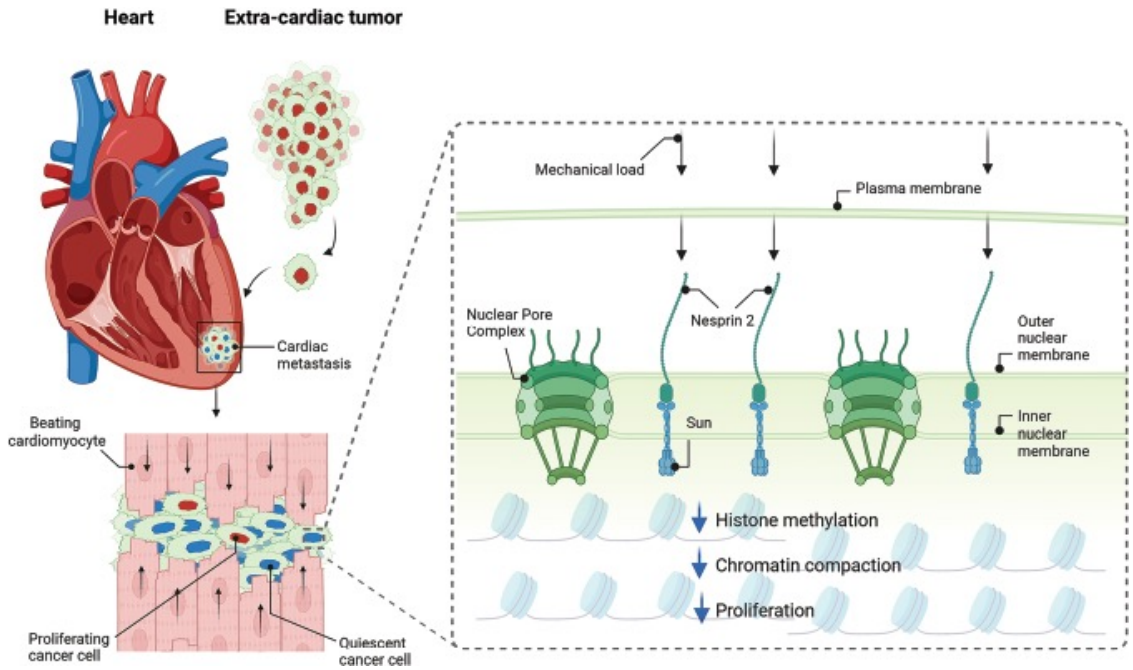
Mechanical load inhibits cancer growth in mouse and human hearts

INTRODUCTION: The heart is rarely affected by cancer; both primary cardiac tumors and metastases are uncommon despite the high vascularization of the myocardium. The mechanisms underlying this resistance remain unclear.

RATIONALE: Mechanical load has been proposed as a major mechanism halting cardiomyocyte proliferation early after birth, thus limiting the regenerative potential of the adult mammalian heart. We hypothesized that it could similarly hamper the proliferation of cancer cells in the heart.

RESULTS: We first used an in vivo genetic model of cancer in mice, in which Cre-mediated recombination results in the overexpression of mutated K-Ras and deletion of p53, to confirm that the heart resists oncogenic events. Despite a comparable extent of recombination in liver, heart, and skeletal muscle, multiple cancers arose at different anatomical sites but never in the heart. In addition, we set up a mouse model of heterotopic heart transplantation to mechanically unload the heart in vivo. In this model, the aorta and pulmonary artery of the transplanted heart are surgically connected with the carotid artery and external jugular vein of the recipient animal, respectively, thereby restoring perfusion in the absence of mechanical load within the left ventricle.

In parallel, we used engineered heart tissues in which mechanical load can be controlled at will. In these models, mechanical load inhibited, whereas tissue unloading promoted the proliferation of lung adenocarcinoma, colon carcinoma, and melanoma cells within the myocardium. To investigate the mechanisms underlying these effects, we used spatial transcriptomics to analyze samples of human cancers that gave rise to both cardiac and extracardiac metastases. We found that cardiac metastases shared a common transcriptional profile, independent from the origin of the primary tumor. Among the most up-regulated genes in cardiac metastases were histone demethylases. Consistently, cardiac metastases showed reduced histone 3 lysine 9 trimethylation and reduced chromatin compaction. Similar findings were observed in our experimental models of cardiac load modulation in which chromatin accessibility and histone methylation were altered at sites controlling cancer cell proliferation, as determined by single-nuclei assay for transposaseaccessible chromatin with sequencing and chromatin immunoprecipitation sequencing. Nesprin-2, a protein known to mediate mechanotransduction from the cytoplasm to the nucleus, emerged as a key molecule sensing mechanical forces operating in beating hearts and translating them into reduced cell proliferation. Silencing of Nesprin-2 in lung cancer cells prior to their implantation in the heart in vivo restored the capacity of the cells to proliferate in the presence of physiological mechanical load, resulting in the formation of large tumors.



Key mechanisms inhibiting cancer cell proliferation in the heart. Cancer cells that engraft into the myocardium are exposed to mechanical forces generated by both cardiomyocyte contraction and pressurevolume load. Nesprin-2 is a key molecule in sensing these forces, resulting in reduced histone methylation and chromatin compaction in cancer cells, overall halting their proliferation.

CONCLUSION: Collectively, these results shed light on the role of mechanical forces in protecting the heart from cancer and may pave the way to cancer therapies based on mechanical stimulation.

Scientists just discovered a 60-foot-long, kraken-like octopus

It's the stuff of science fiction.

A kraken-like octopus that could grow to 60 feet long, prowl the oceans as a fierce predator, seize prey with long, agile arms and crush its catches with massive jaws.

But it turns out that such fantastical creatures actually did roam the depths of the ancient world, according to research published Thursday in the journal Science.

Scientists have long focused on sharks and large aquatic reptiles as the top ocean predators during the Cretaceous period, which spanned roughly 145 million to 66 million years ago. But the novel discovery details how colossal octopuses also hunted the Late Cretaceous seas, competing with — and perhaps even preying upon — apex predators such as mosasaurs.

The findings begin to lift the veil on that largely overlooked aspect of how ancient marine ecosystems functioned.

“Some of the earliest octopuses were much larger than we had imagined,” Yasuhiro Iba, a professor at Hokkaido University and co-author of the study, said in an email to The Washington Post. “Invertebrates — especially soft-bodied animals like octopuses — have remained largely invisible in the fossil record, and their ecological roles have been poorly understood.”

A lateral view of the lower jaw of an adult Nanaimoteuthis haggarti, with the weathered parts reconstructed. (Hokkaido University)

Because soft-bodied animals rarely fossilize, paleontology has historically focused on organisms with hard skeletons or shells. But new technologies have allowed researchers new insights into key animals that left fewer traces behind.