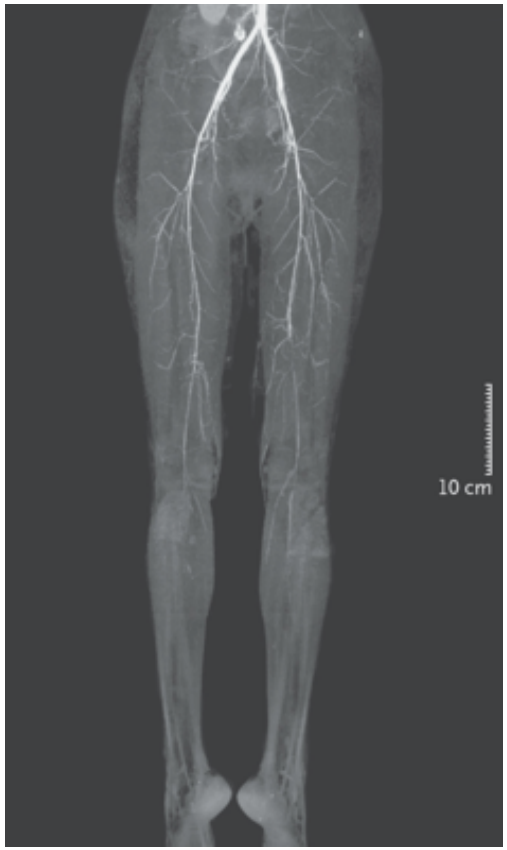
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

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



A 24-year-old woman with a history of HIV, currently on antiretroviral therapy, presented with 2 days of severe, burning leg pain. She had a migraine headache 4 days before presentation for which she was taking ergotamine twice daily. Leg pain extended from toes to midthigh. On physical examination, both legs were cold with absent popliteal and dorsalis pedis pulses. What is the diagnosis?

- Atherosclerosis
- Ergotism
- Herniated disc
- Progressive lumbosacral polyradiculopathy
- Thromboangitis obliterans

Correct!

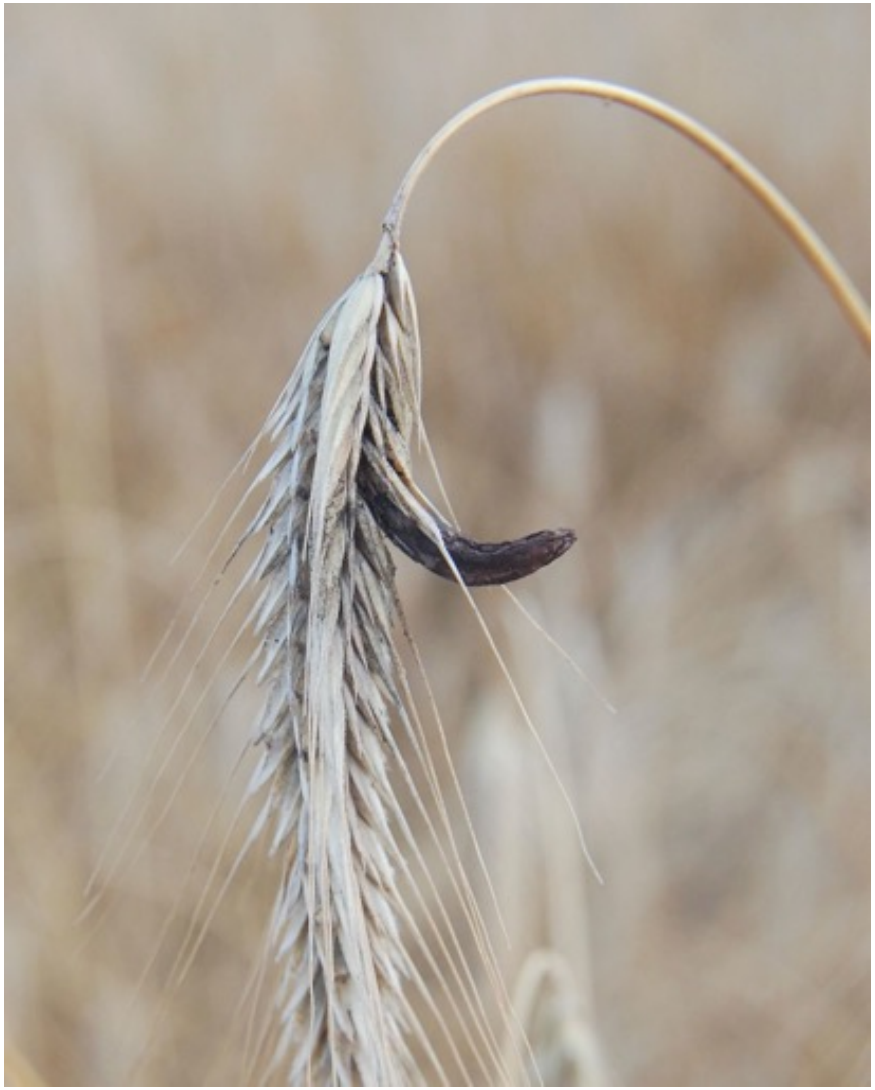
Ergotism can occur from ingestion of grains infected by fungi of the genus Claviceps or from ingestion of medications containing ergot alkaloids. This patient was taking ritonavir, a CYP3A4 enzyme inhibitor, leading to increased serum levels of ergotamine and thereby causing vasospastic limb ischemia.

Der Ergotismus ist eine Vergiftung durch Einnahme von Mutterkornalkaloiden (z.B. Ergotamin). Der Ergotismus entsteht in der heutigen Zeit am ehesten durch die Einnahme von Medikamenten, welche Mutterkornalkaloide und deren Derivate enthalten. Ergotaminhaltige Medikamente werden vor allem bei Migräne verwendet (z.B. Dihydroergotamin). Eine unkontrollierte Dossissteigerung durch den Patienten selbst kann dabei zum Ergotismus führen.
Im Mittelalter trat Ergotismus als Folge des Verzehrs mit Claviceps purpurea kontaminierten Nahrungsmitteln auf. Heutzutage tritt er nur noch selten auf, z.B. durch Verzehr von unzureichend aufbereiteten Getreideprodukten, die als Bioware angebaut wurden. Durch eine Überdosierung von Ergotamin kommt es zur massiven Vasokonstriktion der Arterien. Dadurch ist vor allem die Durchblutung von Herz, Nieren und Extremitäten kompromittiert.
Der Ergotismus imponiert meistens durch eine Ischämie der Extremitäten. Die Extremitäten sind kalt und blass. Die Pulse der unteren Extremitäten sind meist kaum nachweisbar. Mögliches Leitsymptom ist auch eine Ischämie des Myokards infolge der Konstriktion der Koronararterien.
Zusätzlich zu den vaskulären Symptomen bestehen in der Regel Allgemeinsymptome:
Wichtigstes diagnostisches Kriterium ist das Erkennen der Ergotamineinnahme. Die Anamnese und dabei insbesondere die Medikamentenanamnese ist daher meistens entscheidend.
Apparative Untersuchungen können bei Bedarf ergänzend hinzugezogen werden (z.B. Doppler-Sonographie der Extremitätengefäße).
Auslösende Medikamente sind als Erstmaßnahme sofort abzusetzen. Ist dies alleine nicht ausreichend, können die Blutgefäße durch die Gabe
von Nitraten, Calciumantagonisten und/oder Prostaglandininfusionen erweitert werden bis die Ergotaminwirkung abgeklungen ist.

Zusätzlich zu den vaskulären Symptomen bestehen in der Regel Allgemeinsymptome:
Erbrechen
Verwirrtheit
Kopfschmerzen
Diarrhö
Parästhesien

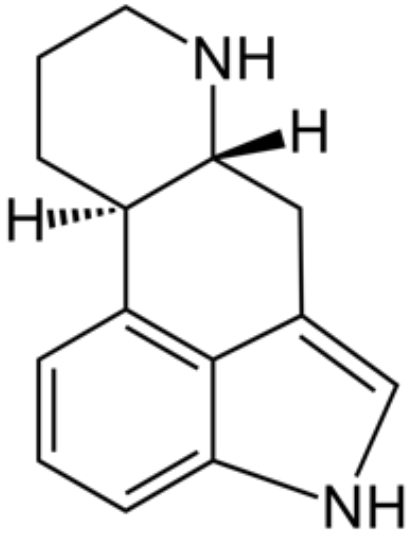
Saint Anthony‘s fire

Als Mutterkornalkaloide (Ergotalkaloide, Secalealkaloide) werden etwa 80 natürlich vorkommende organische Verbindungen aus der Gruppe der Indolalkaloide bezeichnet. Sie finden sich hauptsächlich im Mutterkorn, den Sklerotien des Mutterkornpilzes Claviceps purpurea, der auf Roggen und anderen Süßgräsern als Parasit wächst. Mutterkornalkaloide werden auch von weiteren Organismen, insbesondere Schlauchpilzen der Gattungen Claviceps, Neotyphodium, Epichloë, Balansia, Periglandula sowie Aspergillus und Penicillium, produziert. Diese zum Großteil toxischen Alkaloide waren die Ursache für die als Ergotismus bezeichneten epidemieartigen Vergiftungen, die vom Frühmittelalter bis zum Ende des 20. Jahrhunderts auftraten. Seit dem 18. Jahrhundert wurden zunächst natürlich vorkommende Mutterkornalkaloide, später teilsynthetische Abkömmlinge als Arzneistoffe eingesetzt und dienen aktuell als Bausteine für verschiedene synthetische Drogen.



Die Wirkungen der Mutterkornalkaloide sind vielfältig. Sie können die Dopamin-Rezeptoren stimulieren und die Ausschüttung von Prolaktin und Somatotropin hemmen. Sie sind partielle Agonisten an den Serotonin-Rezeptoren. Sie können die Dopamin-Rezeptoren stimulieren und die Ausschüttung von Prolaktin und Somatotropin hemmen. Sie sind partielle Agonisten an den Serotonin-Rezeptoren. Auf die Uterusmuskulatur haben sie eine kontrahierende Wirkung (v. a. Ergometrin); auf diese seit langem bekannte Wirkung geht auch der Name „Mutterkorn“ zurück. Besonders natürlichem Ergotamin ist eine vasokonstriktorische Wirkung eigen. Die hydrierten Ergotamine blockieren die (pre-synaptische) α-Adrenorezeptoren, was unter bestimmten Umständen kontrahierte Gefäße erweitern kann.

Während aus der Antike, in der vorwiegend Weizen angebaut wurde, keine Vergiftungen durch Ergotalkaloide bekannt sind, trat der erste belegte, epidemieartige Fall von Ergotismus im Jahr 857 bei Xanten auf. 922 sollen europaweit – vorwiegend in Frankreich und Spanien – etwa 40.000 Menschen einer Mutterkornepidemie zum Opfer gefallen sein. 1582 nannte Lonicerus in seinem „Kräuterbuch“ Mutterkorn (Secale cornutum) als Arznei; seit dem 17. Jahrhundert wurde die Droge in Deutschland in der gynäkologischen Praxis zur Blutstillung nach der Geburt eingesetzt. Trotz deutlicher Hinweise auf einen Zusammenhang zwischen der Verwendung von Mutterkorn-haltigem Mehl und dem Auftreten von Ergotismus wurden in Europa erst nach neuerlichen Epidemien in den Jahren 1770 und 1777 gesetzgeberische Maßnahmen ergriffen. In den USA erschien 1808 die erste Veröffentlichung über die Verwendung von Mutterkorn bei der Geburtseinleitung.



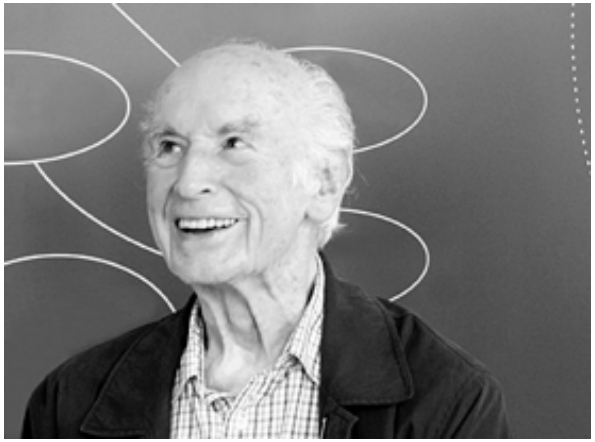
Mit dieser Entdeckung konnte die Lysergsäure als den meisten Mutterkornalkaloiden zugrundeliegende Basisstruktur identifiziert werden. Die übrigen Alkaloide des Mutterkorns wurden in den folgenden 25 Jahren entdeckt:

Ergotamin-Gruppe: Ergotamin / Ergotaminin (1918), Ergosin / Ergosinin (1936)

Ergometrin-Gruppe: Ergometrin (Ergobasin, Ergonovin) / Ergometrinin (1935)

Ergotoxin-Gruppe: Ergokristin / Ergokristinin (1935), Ergokryptin / Ergokryptinin (1937), Ergocornin / Ergocorninin (1943), Ergostin / Ergostinin (1943)

Besondere Verdienste um die Erforschung der Mutterkornalkaloide hat sich der Schweizer Chemiker Albert Hofmann erworben, dessen Forschungen 1943 auch zur zufälligen Entdeckung des psychedelisch wirksamen Halluzinogens LSD (Lysergsäurediethylamid) führte.



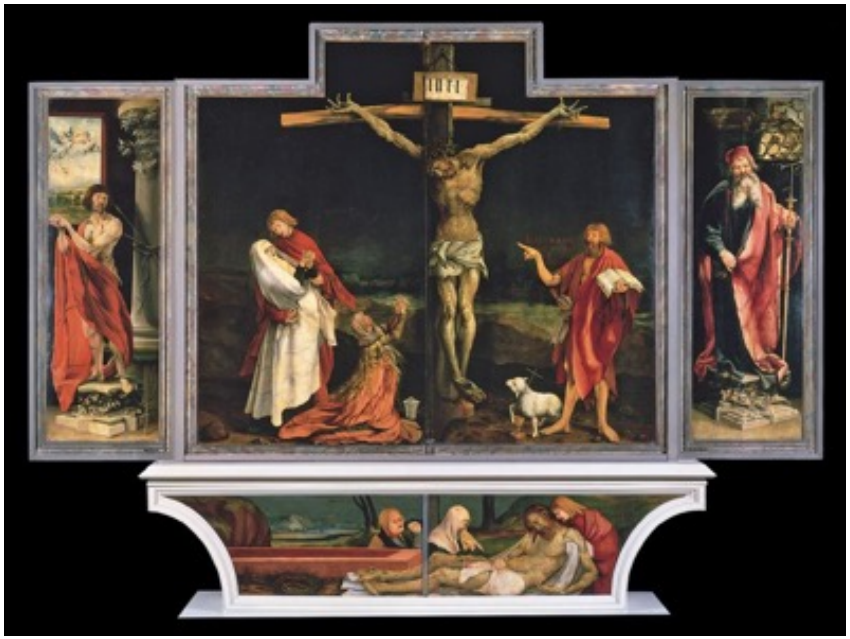
Albert Hofmann (2006)

On 15 August 1951 one in twenty of the 4000 inhabitants of another village in France called Pont Saint Esprit (Bridge of the Holy Spirit) went mad. They had hallucinations, writhed in agony in their beds, vomited, ran crazily in the streets and suffered terrible burning sensations in their limbs. The madness was quickly diagnosed. They were suffering from St Anthony's Fire, a dreaded illness that was common in the Middle Ages. The cause was poisoning from a fungus (ergot) that grows on rye grass. The fungus contaminated the rye flour used in making bread. Ergot contains a chemical that makes the sufferers go berserk and causes gangrene of the hands and feet due to constriction of blood supply to the extremities. If it is not treated (and this was not possible in the Middle Ages), victims had the sensation of being burned at the stake, before their fingers, toes, hands and feet dropped off.

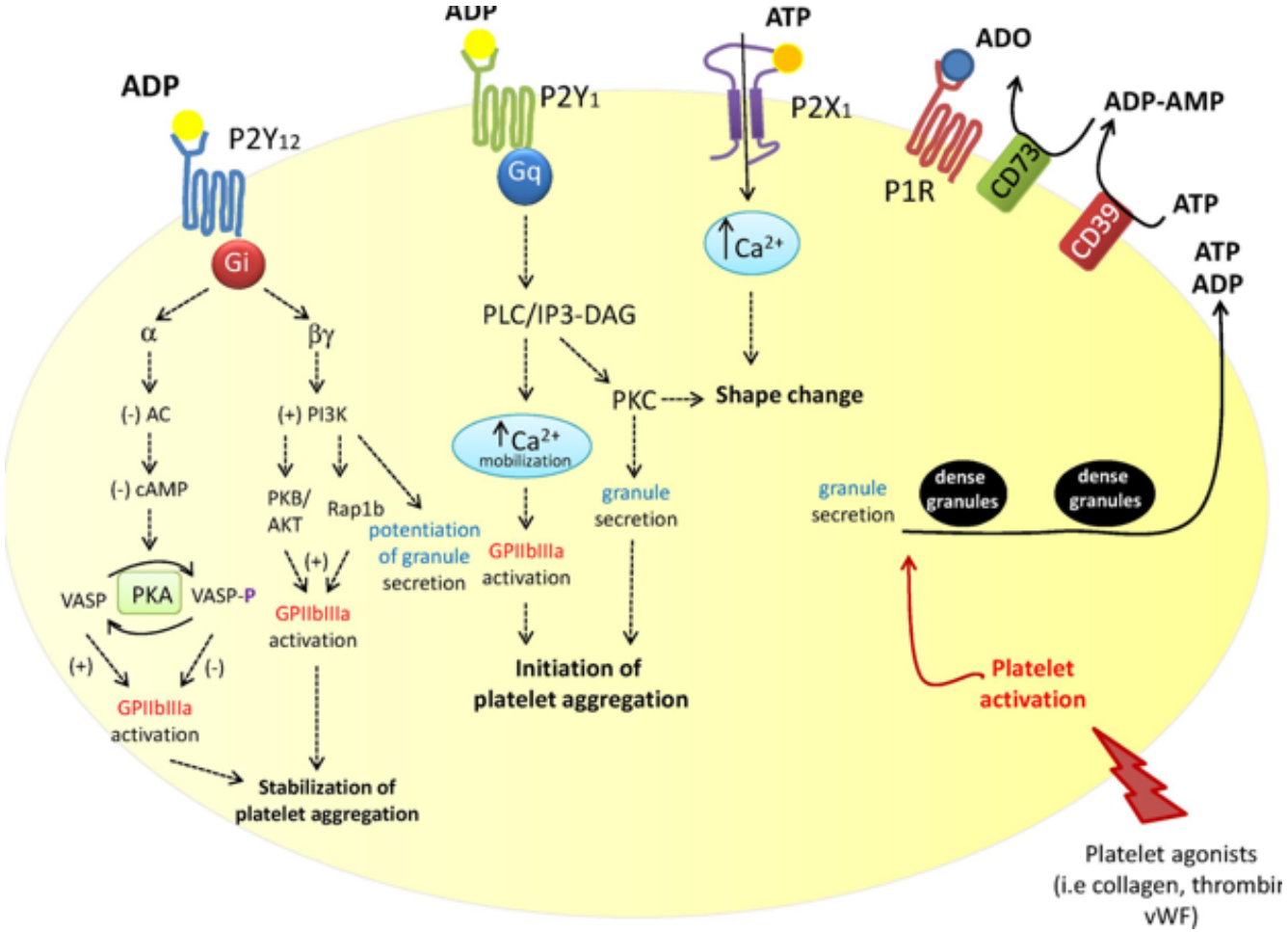
A Masterpiece Born of Saint Anthony's Fire

Matthias Grunewald's 16th-century Isenheim Altarpiece glorified suffering and offered comfort to those afflicted with a dread disease.

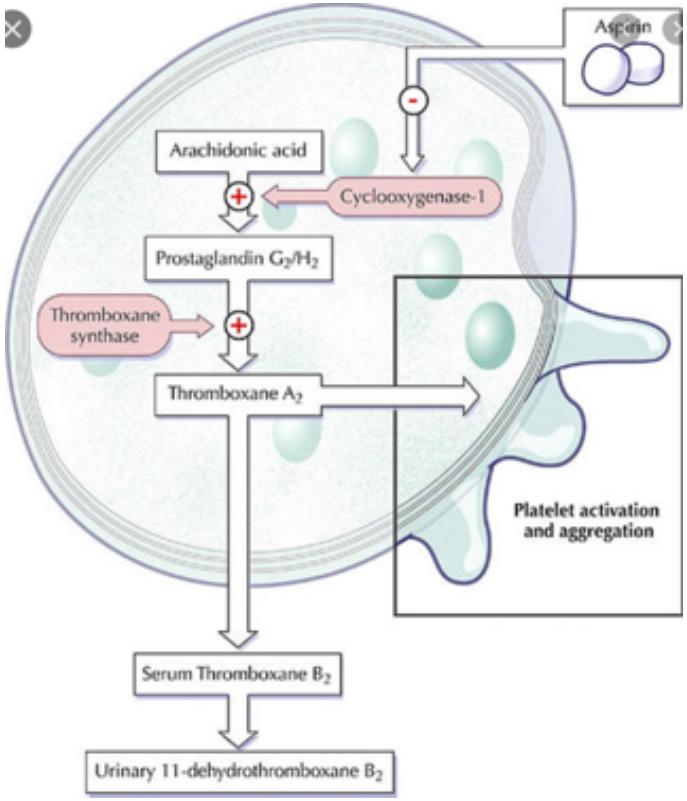
In the French town of Colmar near the German border sits one of the wonders of Western art -- a 16th-century polyptych (multipanelled altarpiece) created by an enigmatic figure for a hospital that treated victims of Saint Anthony's fire. The Isenheim Altarpiece, regarded as a "sublime artistic creation," and its creator, Matthias Grunewald, have fascinated artists and scholars since the work was first moved to Colmar some 200 years ago.



Der P2Y12-Rezeptor ist ein Oberflächenprotein der Thrombozyten, das die Thrombozytenaggregation reguliert. P2Y12 gehört zur Gruppe der G-Protein-gekoppelten purinergen Rezeptoren. Es handelt sich um einen Chemorezeptor für Adenosindiphosphat (ADP).
Die Thrombozytenaggregationshemmer Ticlopidin, Clopidogrel, Prasugrel und Ticagrelor binden an den P2Y12-Rezeptor und hemmen dadurch die Blutgerinnung. Diese Bindung ist bei Ticlopidin, Clopidogrel und Prasugrel irreversibel, wodurch die Thrombozytenfunktion für die gesamte Lebensdauer (ca. 7-10 Tage) gehemmt ist, bei Ticagrelor ist sie reversibel.



Die plättchenhemmende Wirkung der Acetylsalicylsäure beruht auf der Azetylierung der *Zyklooxygenase,* einem für die Prostaglandinbiosynthese wesentlichen Enzym. Die Hemmung der Zyklooxygenase hat zur Folge, dass in den Blutplättchen auch die Biosynthese von *Thromboxan* A_2 -- welches durch einen weiteren enzymatischen Schritt gebildet wird -- blockiert ist. Thromboxan A_2 ist ein hochaktiver Stimulator der Plättchenaggregation und zugleich ein Vasokonstriktor. Die Acetylsalicylsäure übt noch andere Wirkungen auf das Gerinnungssystem aus; die Hemmung der Thromboxan A_2-Synthese ist aber für ihre antithrombotische Wirksamkeit am wichtigsten. Im Unterschied zu den nicht-azetylierten Salizylaten und nicht-steroidalen Entzündungshemmern wie Indometacin u.a. hemmt die Acetylsalicylsäure die Zyklooxygenase irreversibel. In kernhaltigen Zellen (z.B. vaskulären Endothelien, Nieren- und Magenepithelien) wird das blockierte Enzym innerhalb von 24 bis 48 Stunden durch Neusynthese ersetzt. Die kernlosen Blutplättchen können dagegen keine Proteine synthetisieren; nach einer Einmaldosis von Acetylsalicylsäure ist die Zyklooxygenase und damit auch die Thromboxan A2-Synthese für die Lebensdauer der betroffenen Plättchenpopulation -- also für 7 bis 10 Tage -- gehemmt.



Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

Trials have evaluated the use of clopidogrel and aspirin to prevent stroke after an ischemic stroke or transient ischemic attack (TIA). In a previous trial, ticagrelor was not better than aspirin in preventing vascular events or death after stroke or TIA. The effect of the combination of ticagrelor and aspirin on prevention of stroke has not been well studied.
We conducted a randomized, placebo-controlled, double-blind trial involving patients who had had a mild-to-moderate acute noncardioembolic ischemic stroke, with a National Institutes of Health Stroke Scale (NIHSS) score of 5 or less (range, 0 to 42, with higher scores indicating more severe stroke), or TIA and who were not undergoing thrombolysis or thrombectomy. The patients were assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive a 30-day regimen of either ticagrelor (180-mg loading dose followed by 90 mg twice daily) plus aspirin (300 to 325 mg on the first day followed by 75 to 100 mg daily) or matching placebo plus aspirin. The primary outcome was a composite of stroke or death within 30 days. Secondary outcomes were first subsequent ischemic stroke and the incidence of disability within 30 days. The primary safety outcome was severe bleeding.

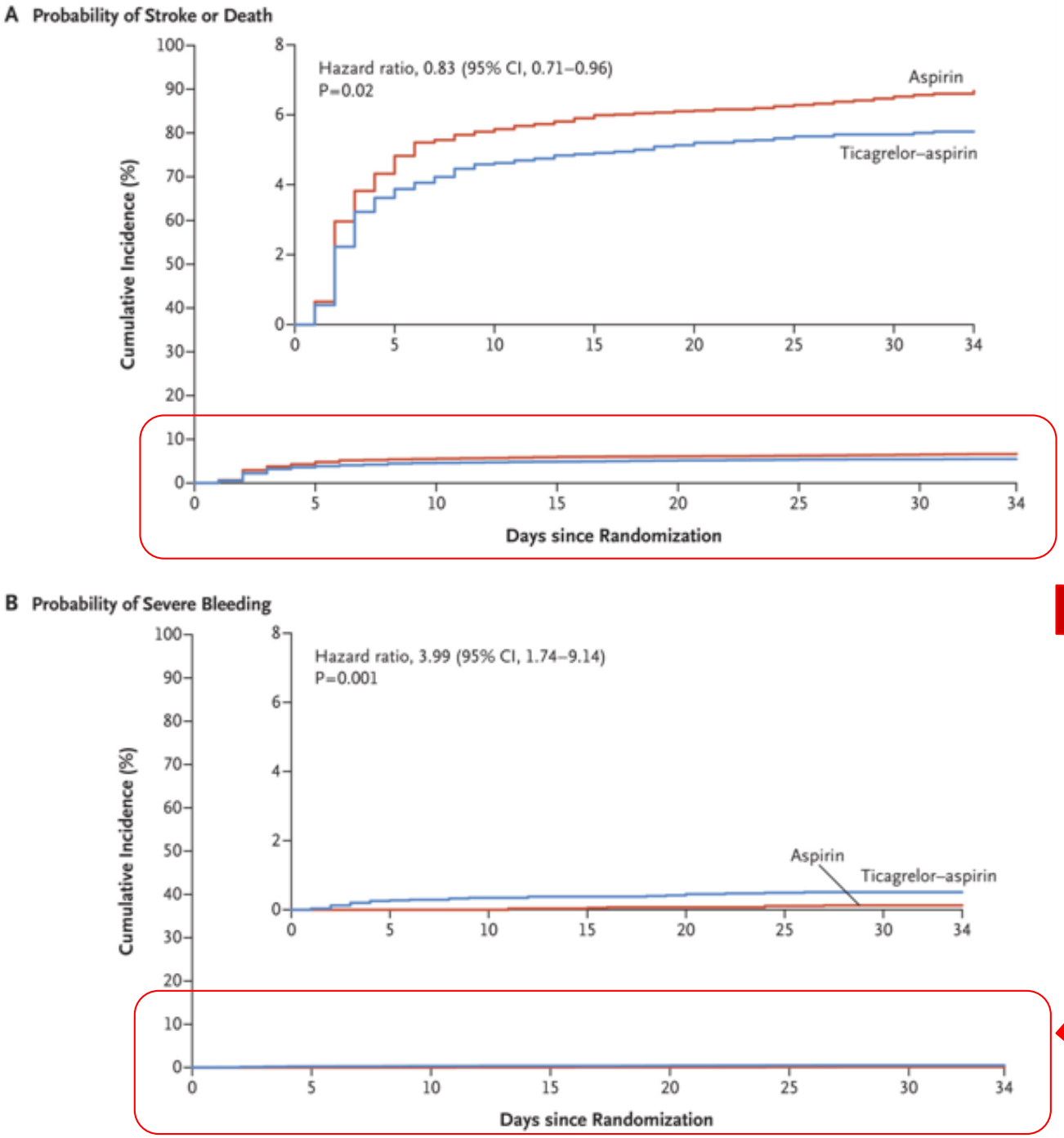
Characteristic	Ticagrelor–Aspirin Group (N=5523)	Aspirin Group (N=5493)
Age — yr	65.2±11.0	65.1±11.1
Female sex — no. (%)	2108 (38.2)	2171 (39.5)
Race — no. (%)†		
White	2973 (53.8)	2948 (53.7)
Black	21 (0.4)	32 (0.6)
Asian	2353 (42.6)	2339 (42.6)
Other	176 (3.2)	174 (3.2)
Geographic region — no. (%)		
Asia or Australia	2373 (43.0)	2356 (42.9)
Europe	2814 (51.0)	2803 (51.0)
North America	12 (0.2)	11 (0.2)
Central or South America	324 (5.9)	323 (5.9)
Median blood pressure (IQR) — mm Hg		
Systolic	150.0 (135.0–163.0)	149.0 (134.0–163.0)
Diastolic	84.0 (79.0–91.0)	84.0 (78.0–91.0)
Median BMI (IQR)‡	25.9 (23.3–29.0)	25.7 (23.2–28.9)
Current smoker — no. (%)	1504 (27.2)	1428 (26.0)
Hypertension — no. (%)	4298 (77.8)	4222 (76.9)
Type 1 or type 2 diabetes mellitus — no. (%)	1589 (28.8)	1557 (28.3)
Previous ischemic stroke — no. (%)	901 (16.3)	914 (16.6)
Previous TIA — no. (%)	275 (5.0)	240 (4.4)
Use of agent before event — no. (%)		
Aspirin	754 (13.7)	679 (12.4)
Clopidogrel	75 (1.4)	75 (1.4)
Time from symptom onset to randomization <12 hr — no. (%)	1812 (32.8)	1776 (32.3)
Qualifying event — no. (%)		
Ischemic stroke	5032 (91.1)	4953 (90.2)
TIA	491 (8.9)	540 (9.8)
ABCD^2 score in patients with qualifying TIA — no. (%)§		
≤5	60 (1.1)	71 (1.3)
6–7	431 (7.8)	469 (8.5)
NIHSS score in patients with qualifying ischemic stroke — no. (%)¶		
≤3	3359 (60.8)	3312 (60.3)
>3	1673 (30.3)	1641 (29.9)

Der ABCD2-Score ist ein prognostisches Scoring-System, das zur Abschätzung des Schlaganfallrisikos nach transitorischen ischämischen Attacken (TIA) eingesetzt werden kann. Im Score sind fünf unabhängige Risikofaktoren - Alter, Blutdruck bei der Erstuntersuchung, Clinical features (klinische Symptome), Dauer der Symptome und schließlich Diabetes mellitus - erfasst, für die jeweils Punkte vergeben werden (siehe Tabelle). Die vergebenen Punkte werden addiert, so dass sich Werte zwischen 0 und 7 Punkten ergeben.

A	Alter	< 60 Jahre	≥ 60 Jahre	
B	Blutdruck	<140 syst. und <90 diast. mm Hg	>140 syst. oder >90 diast. mmHg	
C	Clinical features (Symptome)	andere Beschwerden	Sprachstörung ohne einseitige Schwäche	einseitige Schwäche
D	Dauer der Symptome	< 10 min	10–59 min	≥ 60 min
D	Diabetes mellitus	nicht bestehend	bestehend	
	Punkte	**0**	**1**	**2**

Der **ABCD2-Score** wurde anhand von vier Kohorten in Kalifornien und in Oxford mit insgesamt 4.908 TIA-Patienten entwickelt. Das Risiko, innerhalb von zwei Tagen nach einer TIA einen erneuten Schlaganfall zu entwickeln, wurde wie folgt ermittelt:

- 6 bis 7 Punkte: Hohes Zwei-Tages-Risiko (8 %)
- 4 bis 5 Punkte: Mäßiges Zwei-Tages-Risiko (4 %)
- 0 bis 3 Punkte: Geringes Zwei-Tages-Risiko (1 %)

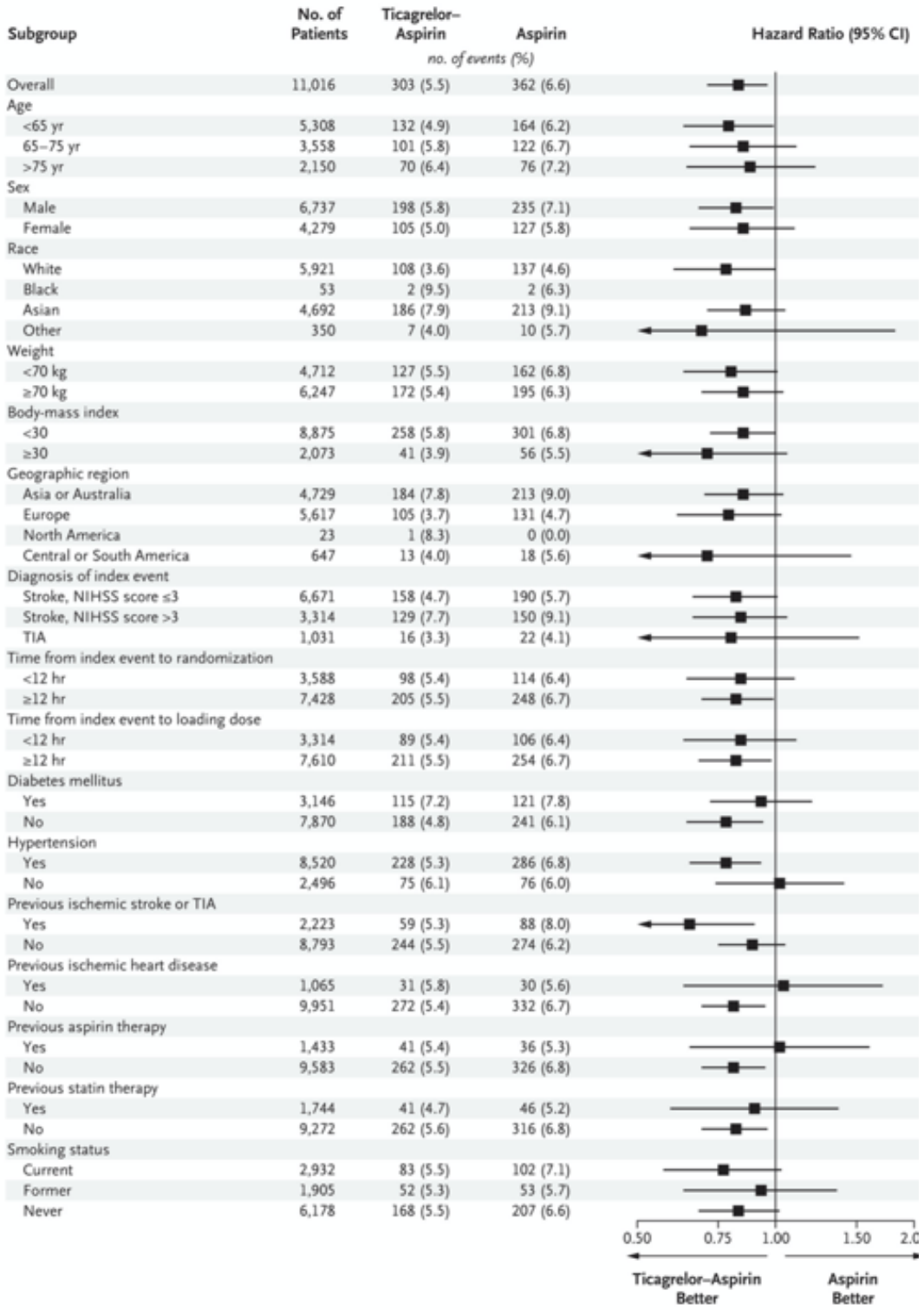


Cumulative Incidence of the Primary and Safety Outcomes.

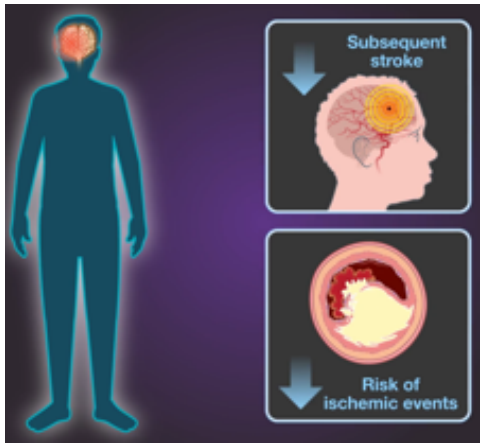
In each panel, the inset shows the same data on an enlarged y axis.

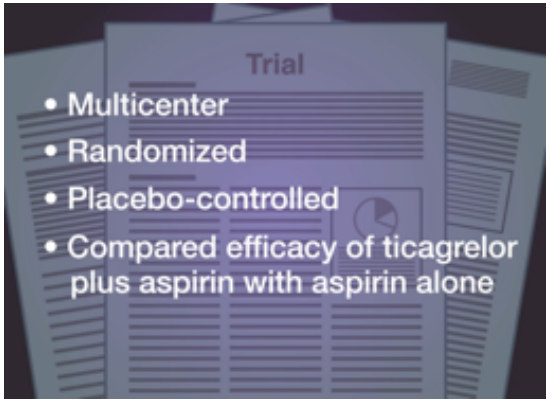
Efficacy and Safety Outcomes.

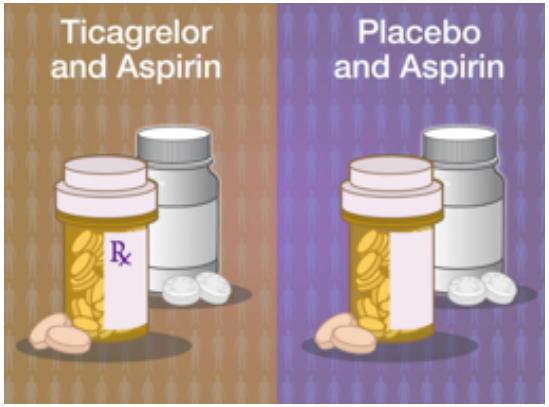
Outcome	Ticagrelor–Aspirin Group (N=5523)		Aspirin Group (N=5493)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate†	Patients with Event	Event Rate†		
	no. (%)	%	no. (%)	%		
Primary outcome						
Stroke or death	303 (5.5)	5.4	362 (6.6)	6.5	0.83 (0.71–0.96)	0.02
Stroke	284 (5.1)	5.1	347 (6.3)	6.3	0.81 (0.69–0.95)	
Death	36 (0.7)	0.6	27 (0.5)	0.5	1.33 (0.81–2.19)	
Secondary outcomes						
Ischemic stroke	276 (5.0)	5.0	345 (6.3)	6.2	0.79 (0.68–0.93)	0.004
Overall disability‡	1282 (23.8)	NA	1284 (24.1)	NA	0.98 (0.89–1.07)	0.61
Safety outcomes						
Severe bleeding	28 (0.5)	0.5	7 (0.1)	0.1	3.99 (1.74–9.14)	0.001
Intracranial hemorrhage or fatal bleeding	22 (0.4)	0.4	6 (0.1)	0.1	3.66 (1.48–9.02)	0.005
Fatal bleeding	11 (0.2)		2 (<0.1)			
Intracranial hemorrhage	20 (0.4)	0.4	6 (0.1)	0.1	3.33 (1.34–8.28)	0.01
Hemorrhagic stroke	10 (0.2)		2 (<0.1)			
Moderate or severe bleeding	36 (0.7)	0.6	11 (0.2)	0.2	3.27 (1.67–6.43)	<0.001
Premature permanent discontinuation of trial treatment owing to bleeding	152 (2.8)	2.9	32 (0.6)	0.6	4.80 (3.28–7.02)	<0.001

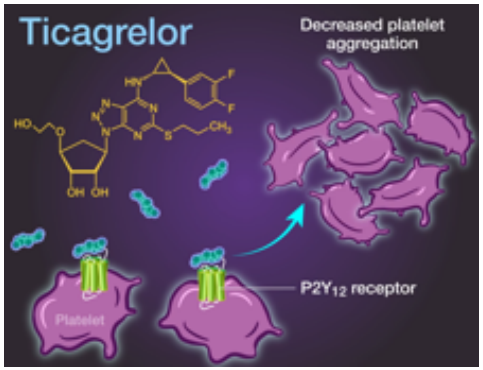


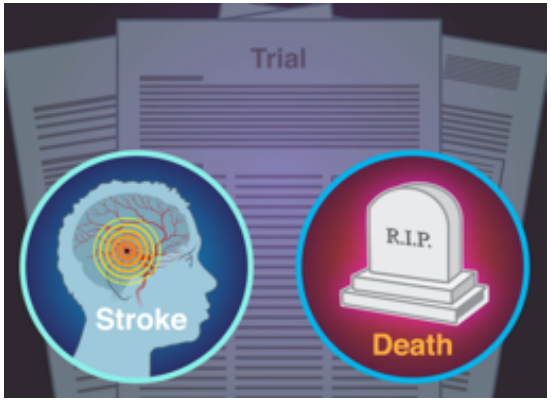
Permanent discontinuation of the trial treatment owing to bleeding occurred in 152 patients in the ticagrelor–aspirin group (2.8%) and in 32 patients in the aspirin group (0.6%). Discontinuation of the trial treatment because of dyspnea occurred in 1.0% and 0.2% of the patients in the ticagrelor–aspirin group and the aspirin group, respectively.Bleeding events and dyspnea accounted for the entire between-group difference in discontinuations from the trial treatment. Serious adverse events and adverse events leading to discontinuation of a trial treatment are presented in Tables S1 and S2. The results of an on-treatment analysis of safety were consistent with those of the primary intention-to-treat analysis.

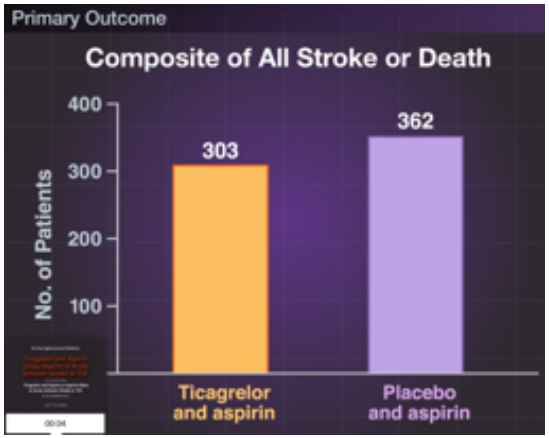

Subsequent stroke
Risk of ischemic events


Trial
• Multicenter
• Randomized
• Placebo-controlled
• Compared efficacy of ticagrelor plus aspirin with aspirin alone


Ticagrelor and Aspirin
Placebo and Aspirin
Rx

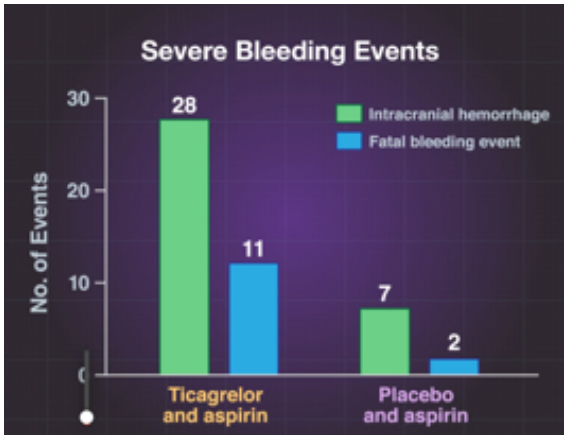

Ticagrelor
Decreased platelet aggregation
P2Y12 receptor
Platelet

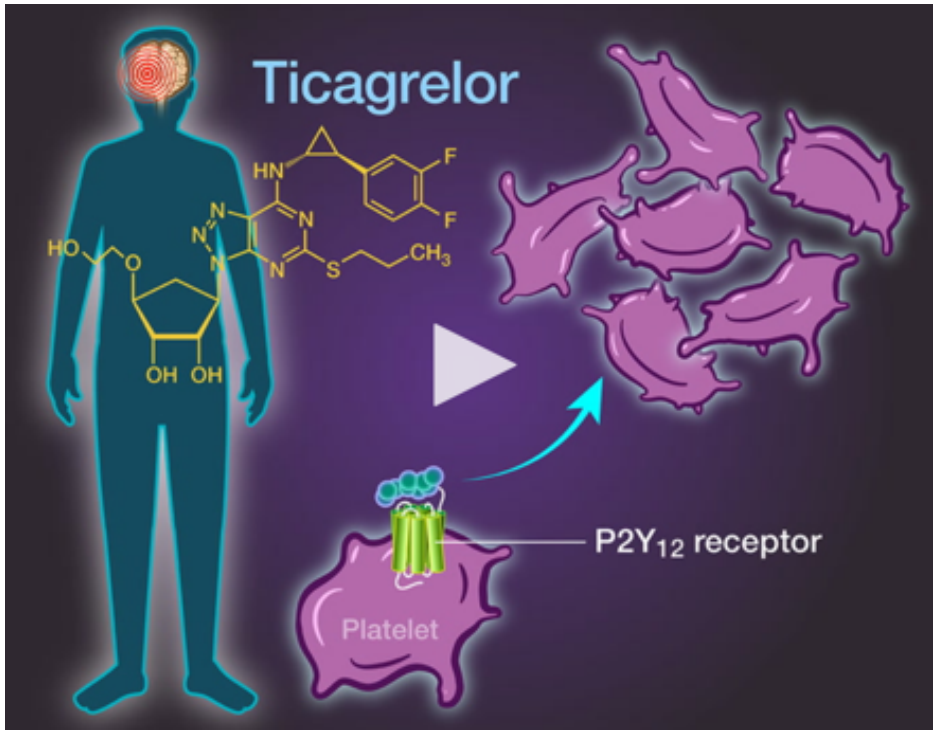

Trial
Stroke
R.I.P.
Death

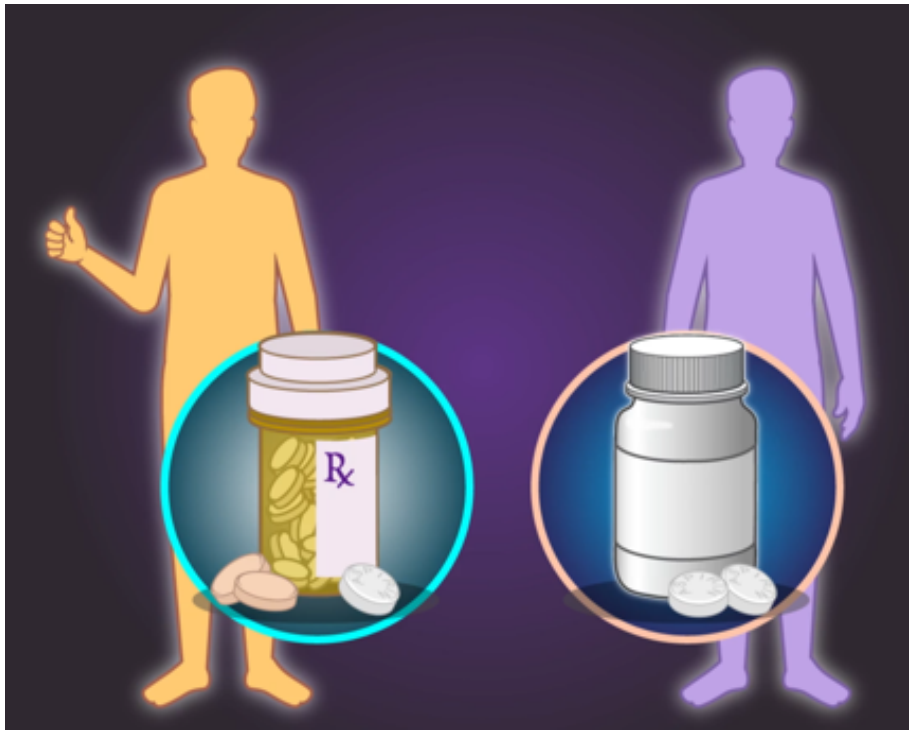

Primary Outcome
Composite of All Stroke or Death
No. of Patients
400
300
200
100
303
362
Ticagrelor and aspirin
Placebo and aspirin


Rx
Ticagrelor wit
Aspirin
Aspirin

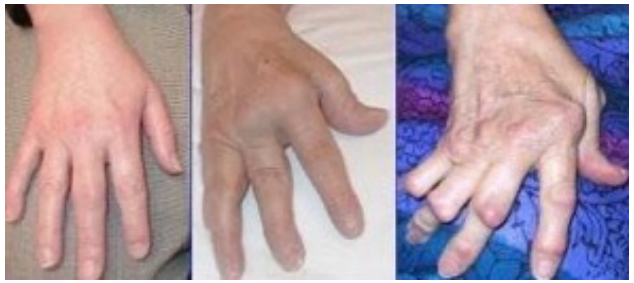

11,016 Patients
Randomized 1:1

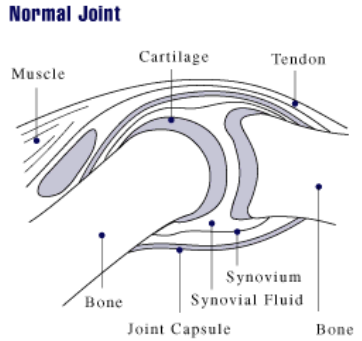

Severe Bleeding Events
No. of Events
30
20
10
0
28
11
7
2
Intracranial hemorrhage
Fatal bleeding event
Ticagrelor and aspirin
Placebo and aspirin

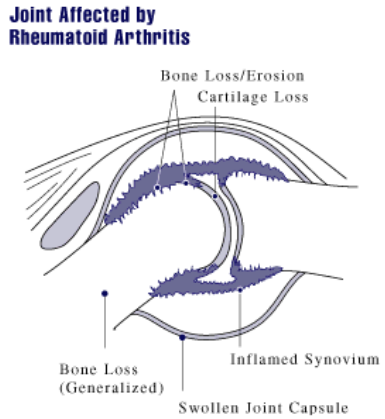

Ticagrelor
HO
O
OH OH
HN
F
F
N
N
N
N
S
CH3
Platelet
P2Y12 receptor

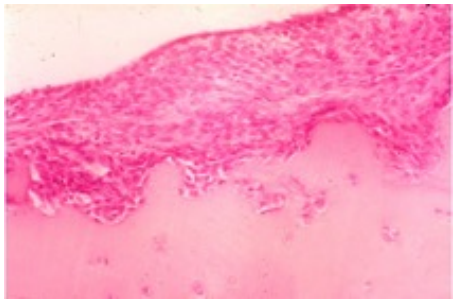

Rx

Die rheumatoide Arthritis (auch chronische Polyarthritis oder (veraltet) primär chronische Polyarthritis und chronischer Gelenkrheumatismus) ist eine langwierige andauernde rheumatische Erkrankung und die häufigste entzündliche Erkrankung der Gelenke. Der Krankheitsbeginn ist oft schleichend, kann aber auch plötzlich eintreten, mit Schmerzen in den kleinen Finger- oder Zehengelenken. Es können auch andere Gelenke betroffen sein, insbesondere Hand-, Knie-, Schulter, Fuß-, Hüftgelenke. Typischerweise werden bevorzugt die Handwurzelknochen, die Fingergrundgelenke (Metacarpophalangealgelenke) und die Fingermittelgelenke (proximale Interphalangealgelenke, PIP) befallen. Die Fingerend- und Zehenendgelenke (distale Interphalangealgelenke, DIP) sind im Gegensatz zur Psoriasisarthritis nicht betroffen. Die betroffenen Gelenke schwellen an und sind überwärmt. Eine Rötung der betroffenen Gelenke kann hinzukommen. Eine symmetrische (= beidseits auftretende) Synovitis der stammfernen Gelenke ist typisch, aber nicht zwingend. Morgens sind diese Symptome zumeist am stärksten ausgeprägt; es handelt sich dabei um die symptomatische Morgensteife. Im Krankheitsverlauf werden immer mehr Gelenke befallen. Die Ursachen der Erkrankung sind bislang weitgehend ungeklärt. Es wird eine autoimmune Ursache angenommen, bei der körpereigene Substanzen, z. B. der Gelenkknorpel, von Zellen des Immunsystems angegriffen werden. Dabei muss zwischen dem Auslöser der störenden Immunreaktion und weiteren Faktoren unterschieden werden, die diese Reaktion im Immunsystem etablieren und aufrechterhalten. Früher wurden auch psychosomatische Einflüsse angenommen.



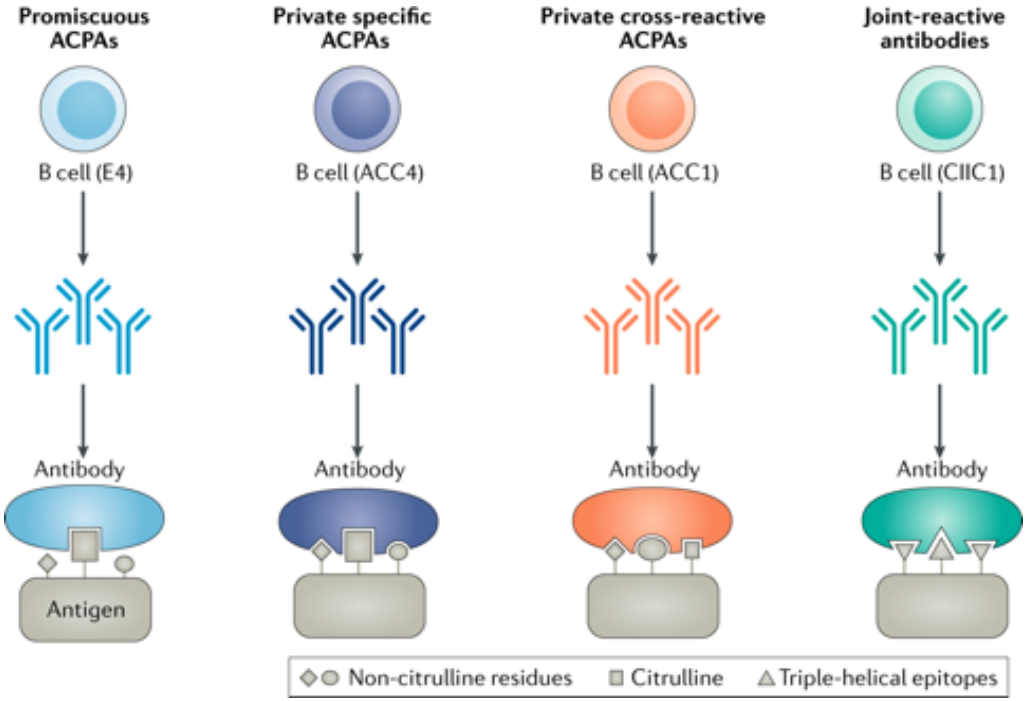






Eindringende Zellverbände

Antikörper gegen citrullinierte Proteine (engl. anti citrullinated protein antibodies, daher kurz: ACPAs) sind Autoantikörper (Antikörper gegen Bestandteile des eigenen Körpers), die bei Patienten mit rheumatoider Arthritis (RA) auftreten. In neuerer Zeit haben die Testsysteme zum serologischen Nachweis der ACPAs die klassische Serodiagnostik über die Rheumafaktoren entscheidend verbessert. Prominenteste Vertreter der ACPA-Testsysteme sind der Nachweis von Autoantikörpern gegen mutiertes citrulliniertes Vimentin (Anti-MCV-ELISA) und der CCP-Assay. Beide erreichen Sensitivitäten von nahezu 80 % und Spezifitäten von nahezu 98 %. Für bestimmte ACPAs ist ein Zusammenhang zwischen dem Antikörper-Titer (die „Konzentration“ der Autoantikörper im Blutserum) und der Krankheitsaktivität belegt, was sie für den behandelnden Rheumatologen zu einem guten Werkzeug für die Prognose der Erkrankung und zu einer guten Basis für die individuelle Therapieentscheidung macht.
ACPA sind neben ihrer Bedeutung für die frühe Diagnose auch wichtig für die Prognose von Gelenkschädigungen bei rheumatoider Arthritis. Bei Patienten mit dieser Erkrankung und positivem ACPA-Befund schreitet im Allgemeinen die Zerstörung der Gelenke schneller voran als bei Patienten mit rheumatoider Arthritis ohne ACPA.



RNA Identification of PRIME Cells Predicting Rheumatoid Arthritis Flares

Rheumatoid arthritis, like many inflammatory diseases, is characterized by episodes of quiescence and exacerbation (flares). The molecular events leading to flares are unknown. We established a clinical and technical protocol for repeated home collection of blood in patients with rheumatoid arthritis to allow for longitudinal RNA sequencing (RNA-seq). Specimens were obtained from 364 time points during eight flares over a period of 4 years in our index patient, as well as from 235 time points during flares in three additional patients. We identified transcripts that were differentially expressed before flares and compared these with data from synovial single-cell RNA-seq. Flow cytometry and sorted-blood-cell RNA-seq in additional patients were used to validate the findings.

Patients

We enrolled patients who met American College of Rheumatology–European League Against Rheumatism 2010 criteria for having rheumatoid arthritis and who were seropositive for cyclized citrullinated protein antibody (CCP). Disease activity was assessed from home each week, or up to four times daily during escalation of flares, with the Routine Assessment of Patient Index Data 3 (RAPID3) questionnaire.

RNA Preparation from Fingerstick Blood Specimens

Patients performed fingerstick collection of three drops of blood at home; the blood was placed into a microtainer tube prefilled with fixative, and the specimens were mailed overnight each week to Rockefeller University.

Comparison of Disease-Activity Measures

To describe the bivariate relationship between clinical assessments of disease activity and disease activity as assessed with RAPID3, we used the locally weighted scatterplot smoothing (LOWESS) technique. R^2 values were calculated to assess correlations of complete blood counts inferred from CIBERSORTx and counts measured by clinical laboratories.

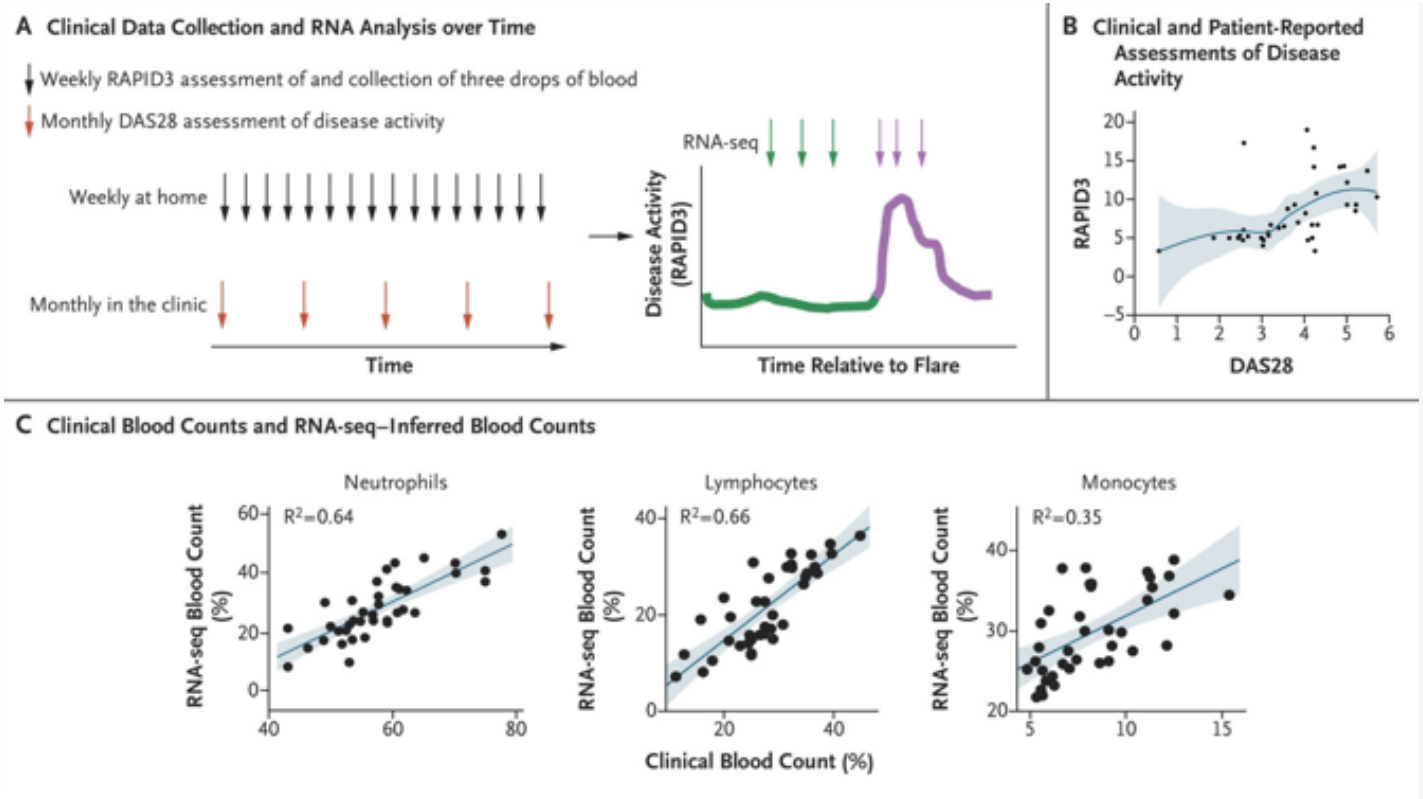
Analyses of Differential Expression among Patients

Before gene-expression analysis, specimens were labeled as baseline (i.e., obtained during a period of stable RAPID3 scores), flare (obtained during a period in which the RAPID3 score was >2 SD above the baseline mean), or glucocorticoid (obtained during a period when the patient was taking glucocorticoids).

Identification and Characterization of Coexpressed Gene Clusters

We hierarchically clustered the mean expression of significantly differentially expressed genes that were identified in the ImpulseDE2 analysis according to week relative to flare initiation (batch-corrected expression values [expressed as $\log_2$ reads per kilobase million] were calculated with edgeR) and identified five coexpressed gene clusters (clusters 1 through 5).

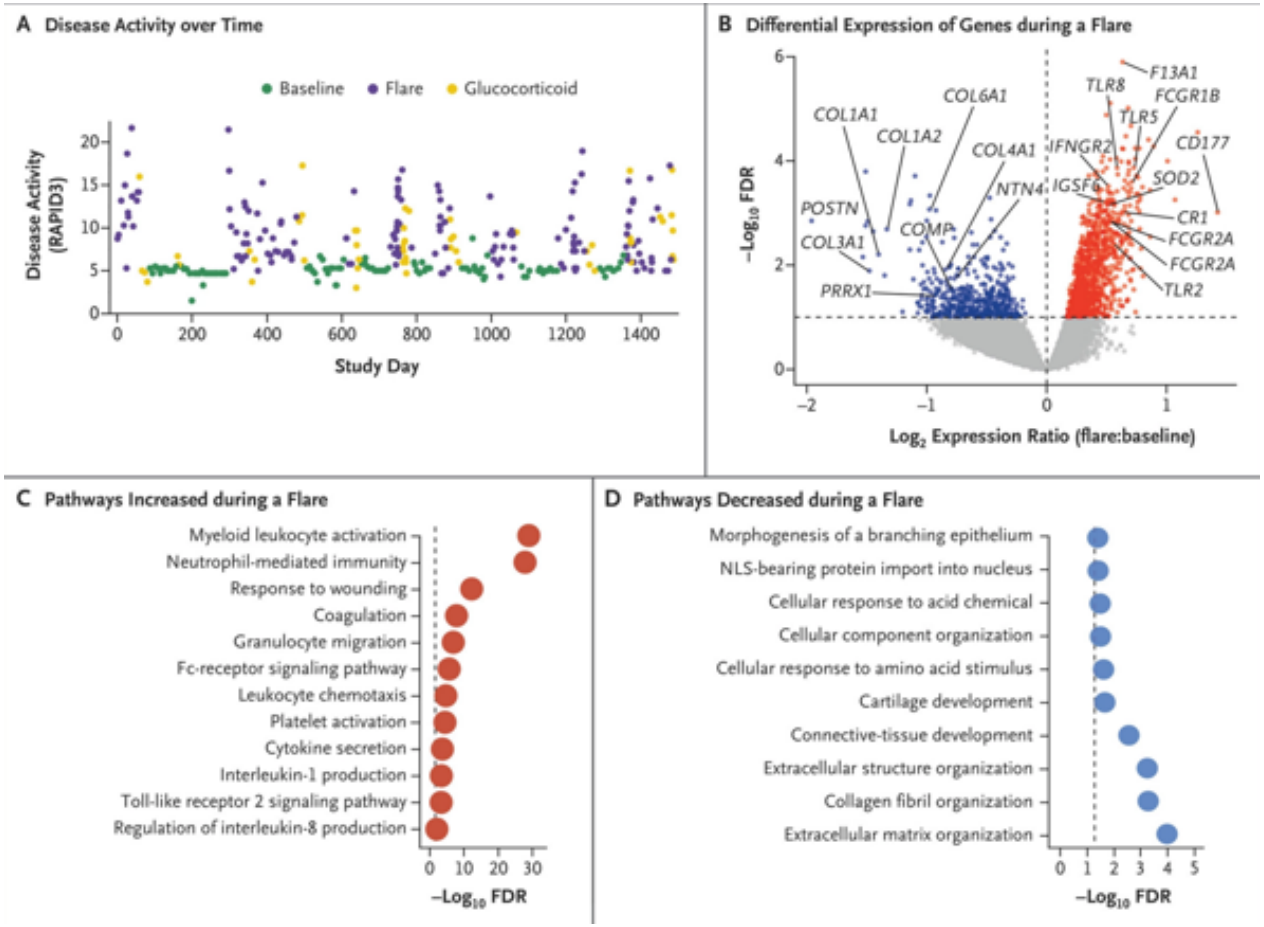
Study Overview and Validation of In-Home Assessments of Disease Activity and Gene Expression.



Panel A shows an overview of the collection of clinical data and specimens over time. The Routine Assessment of Patient Index Data 3 (RAPID3) questionnaire and the Disease Activity Score 28 (DAS28) were used to assess disease activity weekly at home and monthly in the clinic, respectively. Green indicates the time leading up to a flare, and purple the time during a flare. Panel B shows a scatterplot (with locally weighted smoothing) of the relationship between the change in scores on the RAPID3 questionnaire and the DAS28 in the index patient. DAS28 scores range from 2 to 10, with higher scores indicating more disease activity. RAPID3 scores range from 0 to 30, with higher scores indicating more severe disease. The blue line represents the point estimates, and the shaded area represents the 95% confidence interval. Panel C shows neutrophil, lymphocyte, and monocyte counts in paired clinical complete blood counts conducted with blood drawn by venipuncture as compared with the CIBERSORTx-inferred blood counts from RNA sequencing (RNA-seq) data obtained with the use of fingerstick blood specimens (38 paired specimens). The shaded areas represent the 95% confidence intervals.

RNA was sequenced from a total of 189 fingerstick blood specimens from the four patients; 162 (87%) of the specimens passed quality-control filtering. In the index patient, we assessed 364 time points by RAPID3 during eight flares over a period of 4 years and analyzed specimens from 84 time points by RNA-seq. We collected data on disease activity from 43 clinic visits from the index patient and from 25, 14, and 12 clinic visits for the other three patients who were included in the longitudinal study.

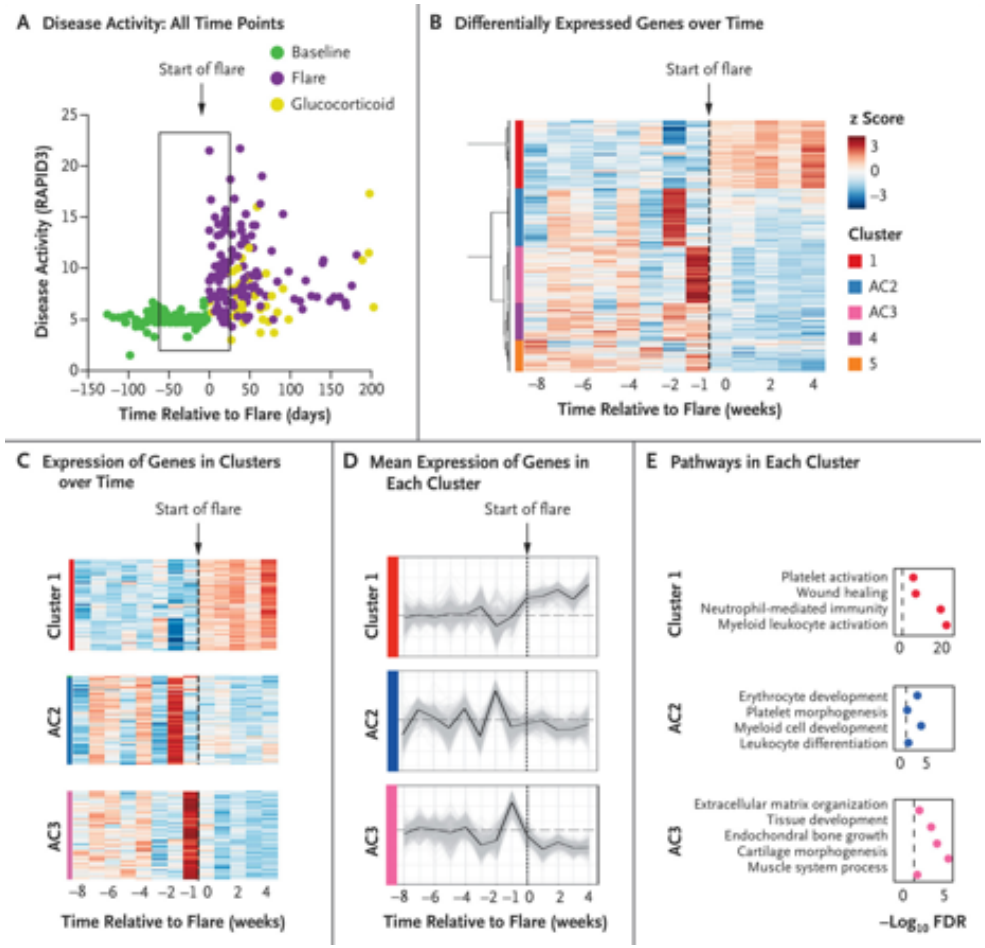
Clinical and Transcriptional Characteristics of Rheumatoid Arthritis Flares in the Index Patient.



Panel A shows disease activity (measured with the RAPID3 questionnaire; 356 scores included in the analysis) over the course of 4 years in the index patient. Panel B shows a volcano plot of differential gene expression during flares (46 specimens) and during baseline (33 specimens), with significance ($-\log_{10}$ false discovery rate [FDR]) plotted against the $\log_2$ relative expression (flare:baseline ratio). Gray points indicate genes with no significant difference in expression between flares and baseline (with FDR >0.1), red indicates genes with significantly increased expression during a flare (FDR <0.1 and $\log_2$ expression ratio >0), and blue indicates genes with significantly decreased expression during a flare (FDR <0.1 and $\log_2$ expression ratio <0). Panels C and D show pathways enriched among genes with significantly increased (Panel C) or decreased (Panel D) expression during a flare relative to baseline. The dashed line represents the threshold for significance (FDR <0.05, or $-\log_{10}$ FDR >1.3). NLS denotes nuclear localization signal.

RNA-seq analysis of fingerstick blood specimens identified 2613 genes that were differentially expressed at the time of a flare as compared with baseline (false discovery rate, <0.1); the expression of 1437 of these genes was increased during a flare. Pathway analysis identified enrichment in myeloid, neutrophil, Fc receptor–signaling, and platelet-activation genes. The expression of 1176 genes was significantly decreased during flares, and pathway analysis of these genes indicated enrichment for extracellular matrix, collagen, and connective-tissue development.

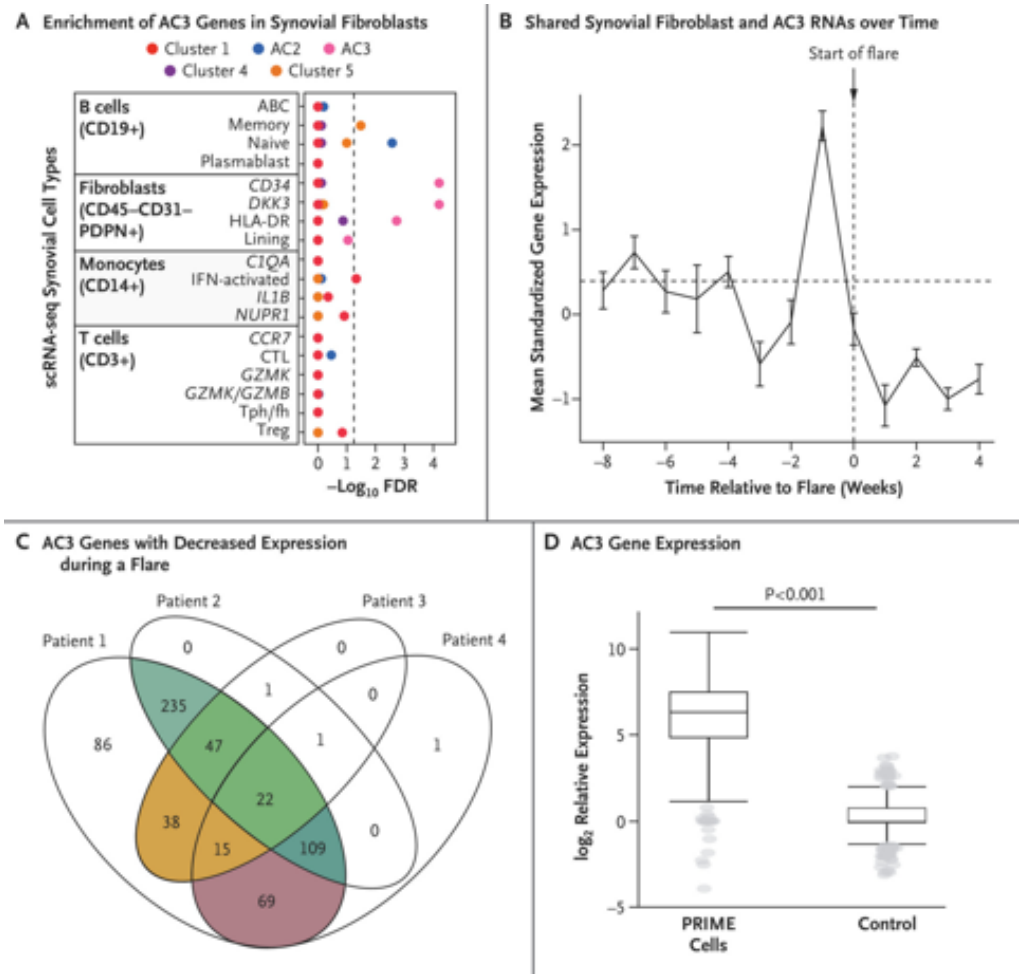
Transcriptional Characteristics of Immune Activation before Symptom Onset in Rheumatoid Arthritis Flares.



Panel A shows RAPID3 disease-activity scores over time (measured in days). The box represents disease activity from day −56 to day 28 relative to the start of a flare (day 0). Panel B shows hierarchical clustering of z scores of 2791 significantly differentially expressed genes over time. Significant clusters are labeled by color. Antecedent cluster 2 (AC2) and AC3 refer to clusters of genes with expression that changed before flares. Panel C shows a detailed representation of the cluster 1, AC2, and AC3 genes depicted in Panel B over the time to a flare. Panel D shows the mean standardized cluster gene expression over the time to a flare. Light gray lines represent expression of individual genes in the cluster. The dashed horizontal line represents the mean baseline gene expression (weeks −8 to −4). Panel E shows pathways enriched in cluster 1, AC2, and AC3. The dashed vertical line represents the threshold for significance (FDR <0.05, or $-\log_{10}$ FDR >1.3).

We focused the analysis on 65 specimens that were acquired 8 weeks before a flare and 4 weeks after flare initiation, binning samples according to the week in which they were drawn. With this method, we identified 2791 genes with significant differential expression over the time leading up to and during a flare (false discovery rate, <0.05), and with hierarchical clustering of gene expression we identified five clusters.

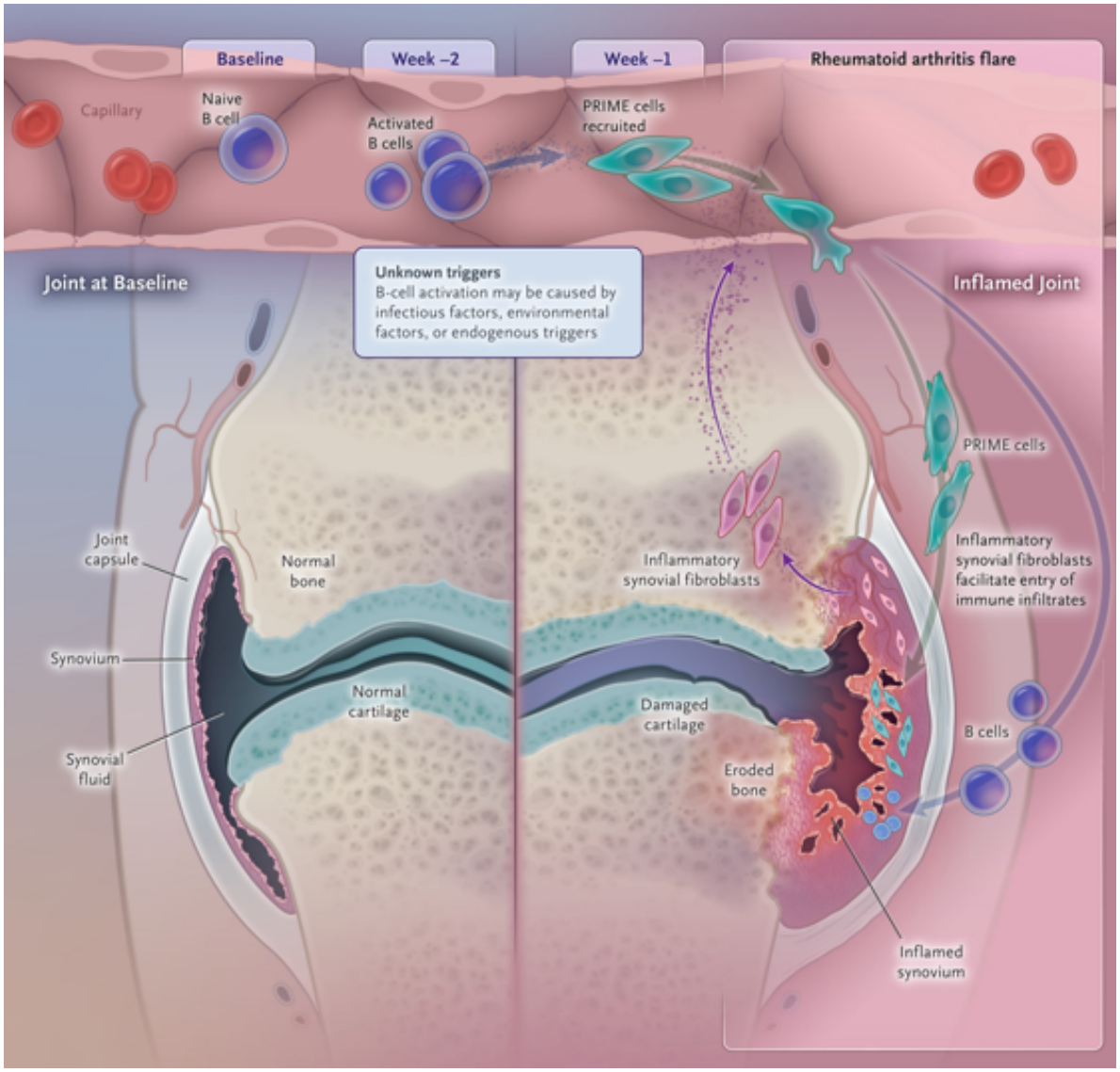
Expression of AC3 Genes in PRIME Cells.



Antecedent (vorausgegangen) cluster 3 (AC3) transcripts increased during the week before a flare and then decreased for the duration of the flare.

Panel A shows synovial cell subtype marker genes in clusters identified in blood. Enrichment scores of 200 single-cell RNA-seq (scRNA-seq) marker genes from 18 synovial subset cell types are shown. The dashed vertical line represents the threshold for significance (FDR <0.05, or $-\log_{10}$ FDR >1.3). ABC denotes age-associated B cell, CTL cytotoxic T lymphocyte, IFN interferon, Tph/fh T peripheral helper/follicular helper, Treg T regulatory. Panel B shows the means of the standardized expression of genes that are common to synovial sublining fibroblasts (CD34+DKK+HLA−DRA+ fibroblasts) and AC3 in blood over the time to a flare (the dashed vertical line represents the start of a flare); I bars represent 95% confidence intervals. For standardization, the mean expression level for each gene was calculated across flares per week and then normalized across weeks. Panel C shows a Venn diagram of the numbers of AC3 genes that decreased during flares in the index patient (Patient 1) and the three additional patients (Patients 2, 3, and 4). Shading is used to highlight overlap between the index patient and the other patients. Panel D shows the $\log_2$ relative expression ratio for AC3 genes in PRIME cells (flow-sorted CD45−CD31−PDPN+ cells) as compared with hematopoietic cells (flow-sorted CD45+) and in stained peripheral blood mononuclear cells (not flow sorted) as compared with hematopoietic cells (flow-sorted CD45+) as a technical control for the stress of flow sorting. The box-and-whisker plots indicate the median, interquartile range, and 1.5 times the interquartile range; the P value is from a Mann–Whitney U test.

Model of Blood and Synovial Gene-Expression Changes before and during Rheumatoid Arthritis Flares.



Inflammatory signals activate naive B cells (AC2), which in turn activate PRIME cells (AC3); these cells harbor the signature of synovial sublining fibroblast genes. According to this model, PRIME cells demarginate and are increased in blood before a flare and then decrease just after symptom onset; these cells or their progeny are increased in inflammatory synovium in patients with rheumatoid arthritis, where they contribute to and may be sufficient to cause joint inflammation.

Discussion

We present longitudinal genomics as a strategy to study the antecedents to rheumatoid arthritis flares that may be generalizable to autoimmune diseases associated with waxing and waning clinical courses. We developed tools for patients to acquire both data on clinical symptoms and molecular data at home over the course of many years. This allowed us to capture data before the onset of flares and identify different RNA signatures (AC2 and AC3) evident in peripheral blood 1 to 2 weeks before a flare.

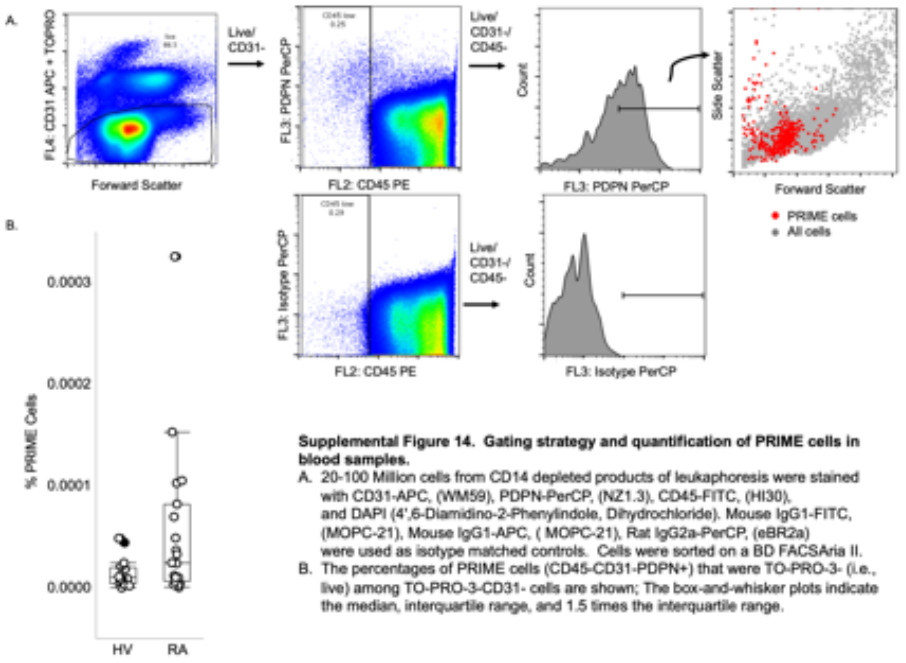
The RNA signature of AC3 and sorted CD45−CD31−PDPN+ circulating cells revealed enrichment for pathways including cartilage morphogenesis, endochondral bone growth, and extracellular matrix organization and strongly overlapped with the RNA signatures of synovial sublining fibroblasts. We therefore propose that antecedent PRIME cells are the precursors to inflammatory sublining fibroblasts that have previously been found adjacent to blood vessels in inflamed synovium in patients with rheumatoid arthritis.

We developed methods for collecting frequent (weekly) longitudinal clinical and gene-expression data that can be used to identify changes in transcriptional profiles in blood weeks before the onset of symptoms in patients with rheumatoid arthritis. This approach led to the identification of PRIME cells, which bear hallmarks of synovial fibroblasts, are more common in patients with rheumatoid arthritis than in healthy controls, and increase in blood just before flares. We suggest that before a clinical flare, B-cell immune activation (detected as AC2) acts on PRIME cells, which traffic to the blood (detected as AC3) and subsequently to the synovial sublining during flares of disease activity. More generally, this study of rheumatoid arthritis provides an example of an approach to the study of waxing and waning inflammatory diseases.

AC = antecedent (vorausgegangen) cluster

Rheumatoid arthritis, like many autoimmune diseases, has a course characterized by intermittent flares, yet our understanding of the mechanisms underlying flares remains limited. Orange and colleagues describe a study in which serial fingerstick collection of blood was combined with weekly monitoring of patient-reported disease activity with the use of a questionnaire. They applied a dense longitudinal transcriptional monitoring approach, which revealed transcriptional signatures in blood that were associated with disease flares. By anchoring their informatics analysis on the point in time at which clinical flares occurred, they were able to obtain an unprecedented level of granularity that sheds light on the kinetics of immune activation leading to flares. Anchoring the analysis on disease flares enabled the authors to identify molecular markers that were predictive of imminent flares and to identify transcriptional modules representing activation of naive B cells, which increased in blood approximately 2 weeks before a flare.

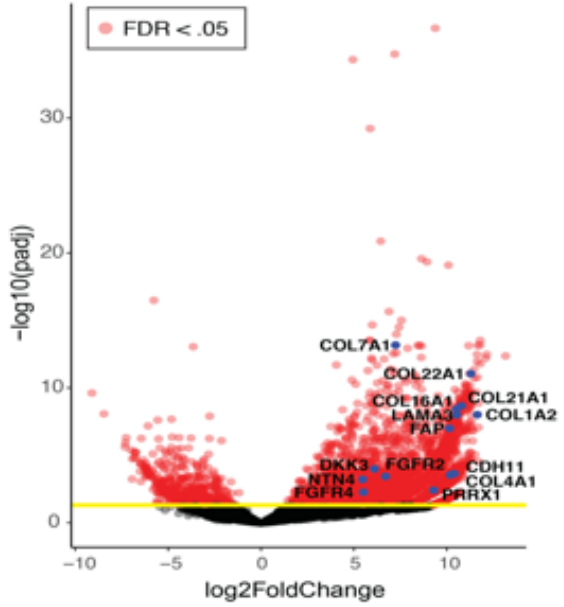
It further allowed for the identification of a new cell type — termed preinflammatory mesenchymal, or PRIME, cells — that appeared in blood just before disease flares. In contrast to CD45+ “fibrocytes,” these fibroblast-like PRIME cells are CD45−.



Supplemental Figure 14. Gating strategy and quantification of PRIME cells in blood samples.

A. 20-100 Million cells from CD14 depleted products of leukaphoresis were stained with CD31-APC, (WM59), PDPN-PerCP, (NZ1.3), CD45-FITC, (HI30), and DAPI (4',6-Diamidino-2-Phenylindole, Dihydrochloride). Mouse IgG1-FITC, (MOPC-21), Mouse IgG1-APC, (MOPC-21), Rat IgG2a-PerCP, (eBR2a) were used as isotype matched controls. Cells were sorted on a BD FACSAria II.

B. The percentages of PRIME cells (CD45-CD31-PDPN+) that were TO-PRO-3- (i.e., live) among TO-PRO-3-CD31- cells are shown; The box-and-whisker plots indicate the median, interquartile range, and 1.5 times the interquartile range.

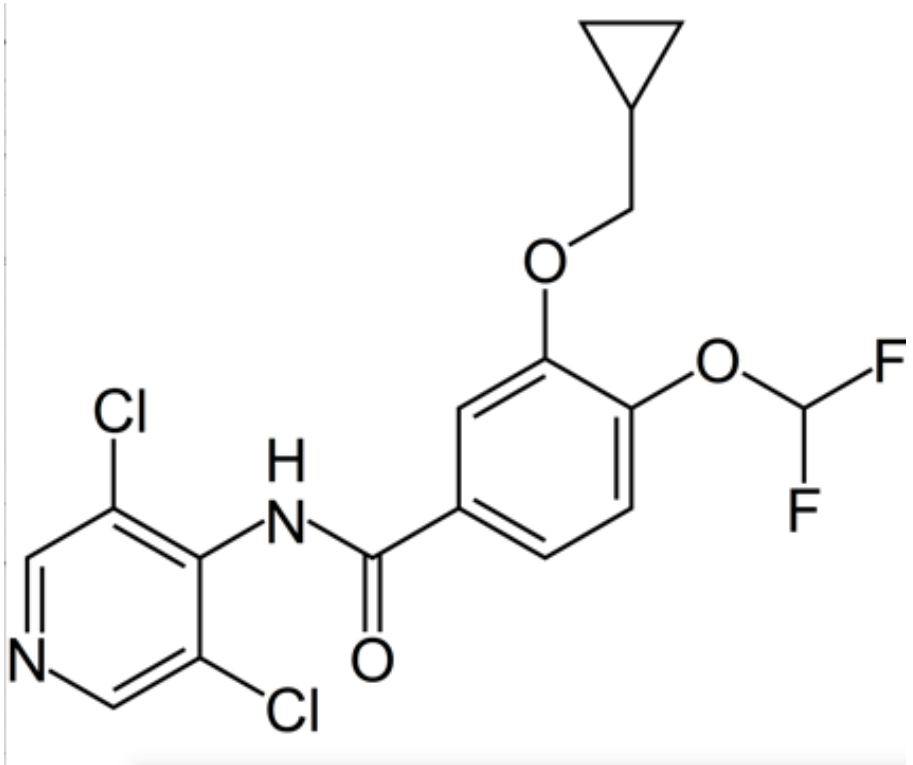


Supplemental Figure 18. Sorted PRIME cells express classic synovial fibroblast genes.
Volcano plot of log10(-padj) vs Log2 fold change of PRIME cells (flow sorted DAPI-/CD45-/CD31-/PDPN+ cells) versus hematopoietic cells (flow sorted DAPI-/CD45+). Classic fibroblast genes are significantly increased in PRIME cells relative to hematopoietic cells.

Phosphodiesterasen (PDE), genauer 3',5'-Cyclonukleotid-Phosphodiesterasen, sind eine Gruppe von Enzymen in Wirbeltieren, die die second Messenger cAMP und cGMP zu AMP und GMP abbauen. Es werden elf Isoenzyme unterschieden, die im menschlichen Organismus unterschiedlich in den Geweben lokalisiert sind. Phosphodiesterasen können durch verschiedene Arzneistoffe, sogenannte Phosphodiesterase-Hemmer unspezifisch oder spezifisch (ein bestimmtes Enzym) gehemmt werden. Ein weit verbreiteter nicht-selektiver Phosphodiesterase-Hemmer ist zum Beispiel das Koffein.

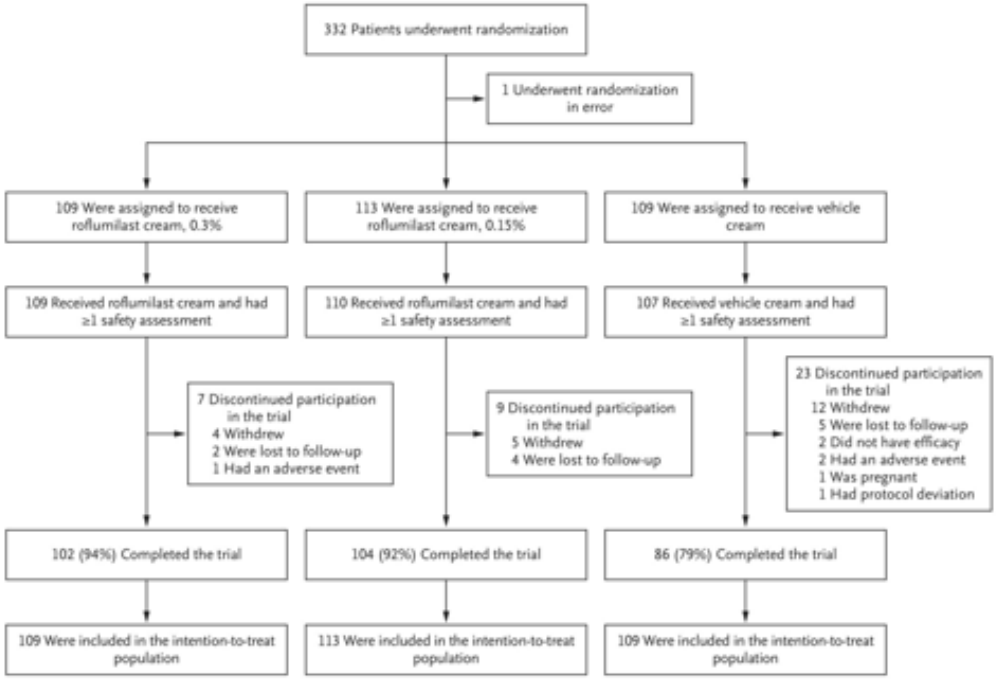
Isoenzyme	Zahl der Isoformen	Substrat	Gewebe	Spezifische Hemmstoffe
Typ 1	8	Calcium- und Calmodulin-stimuliert	Herz, Hirn, Lunge, glatte Muskulatur	KS-505a
Typ 2	–	cGMP-stimuliert	Nebenniere, Herz, Lunge, Leber, Thrombozyten; beteiligt an Lern- und Gedächtnisprozessen	Erythro-9-(2-hydroxy-3-nonyl)adenin
Typ 3	4	cGMP-gehemmt, cAMP-selektiv	Herz, glatte Muskulatur der Blutgefäße, Lunge, Leber, Thrombozyten, Fettgewebe, Leukozyten	Cilostamid, Enoximon, Milrinon, Siguazodan
Typ 4	20	cAMP-spezifisch	Lunge, Hoden, Niere, Hirn, Leber, Leukozyten	Rolipram, Roflumilast, Daxalipram
Typ 5	3	cGMP-spezifisch	glatte Muskulatur der Blutgefäße des Penisschwellkörpers, Lunge, Thrombozyten	Sildenafil, Tadalafil, Vardenafil
Typ 6	–	cGMP-spezifisch	Fotorezeptor des Auges	Dipyridamol
Typ 7	3	cAMP-spezifisch, hochaffin	Skelettmuskulatur, Herz, Niere, Hirn, Pankreas, Lymphozyten	BRL-50481
Typ 8	–	cAMP-spezifisch	Hoden, Auge, Leber, Skelettmuskulatur, Herz, Niere, Ovarien, Hirn, Lymphozyten	kein spezifischer Hemmstoff bekannt
Typ 9	4	cGMP-spezifisch	Niere, Leber, Lunge, Hirn	BAY 73-6691
Typ 10	2	cGMP-sensitiv, cAMP-selektiv	Hoden, Hirn	kein spezifischer Hemmstoff bekannt
Typ 11	4	cGMP-sensitiv, duale Spezifität	Skelettmuskulatur, Prostata, Niere, Leber, Hypophyse, Speicheldrüsen, Hoden	kein spezifischer Hemmstoff bekannt

PDE-4-Hemmer sind Arzneistoffe, die das Enzym Phosphodiesterase IV (PDE-4) hemmen. Die Phosphodiesterase vom Typ 4 ist ein Enzym, das den Second Messenger cAMP abbaut. PDE-4-Hemmer erhöhen daher die Konzentration von intrazellulärem cAMP. PDE-4 kommt in der Lunge und anderen Geweben (u.a. Gehirn, Leber, Niere) vor.
Bislang (Stand 2017) als Arzneimittel zugelassene PDE-4-Hemmer sind Roflumilast (Daxas®) und Apremilast (Otezla®). Weitere Vertreter (z.B. Cilomilast) befinden sich in klinischer Entwicklung.
PDE-4-Hemmer finden zum Beispiel Anwendung bei der Behandlung einer COPD.
Roflumilast ist der erste zugelassene Arzneistoff aus der Gruppe der Phosphodiesterase-4-Hemmer (PDE-4-Hemmer), der zur Behandlung der chronisch obstruktiven Lungenerkrankung (COPD) eingesetzt wird. Roflumilast kann zur Dauertherapie bei erwachsenen Patienten mit schwerer COPD und chronischer Bronchitis sowie häufigen Verschlechterungen des Krankheitsbildes (sog. Exazerbationen) in der Vergangenheit zusätzlich zu einer Behandlung mit einem bronchodilatativen Arzneimittel eingesetzt werden. Eine schwere COPD im Sinne der Zulassung von Roflumilast weist eine verminderte Einsekundenkapazität (FEV1) nach Anwendung eines bronchodilatativen Arzneimittels von weniger als 50 % des Sollwerts auf.



Trial of Roflumilast Cream for Chronic Plaque Psoriasis

Systemic oral phosphodiesterase type 4 (PDE-4) inhibitors have been effective in the treatment of psoriasis. Roflumilast cream contains a PDE-4 inhibitor that is being investigated for the topical treatment of psoriasis. In this phase 2b, double-blind trial, we randomly assigned adults with plaque psoriasis in a 1:1:1 ratio to use roflumilast 0.3% cream, roflumilast 0.15% cream, or vehicle (placebo) cream once daily for 12 weeks. The primary efficacy outcome was the investigator's global assessment (IGA) of a status of clear or almost clear at week 6 (assessed on a 5-point scale of plaque thickening, scaling, and erythema; a score of 0 indicates clear, 1 almost clear, and 4 severe). Secondary outcomes included an IGA score indicating clear or almost clear plus a 2-grade improvement in the IGA score for the intertriginous area and the change in the Psoriasis Area and Severity Index (PASI) score (range, 0 to 72, with higher scores indicating worse disease). Safety was also assessed.



Patients

Eligible patients were 18 years of age or older and, at the time of their initial trial visit, had had plaque psoriasis for at least 6 months. Patients had to have a score indicating a psoriasis status of at least mild severity (score, ≥2) on a 5-point investigator's global assessment (IGA; a 5-point scale assessing plaque thickening, scaling, and erythema, ranging from 0 [clear] and 1 [almost clear] to 4 [severe]). Patients with an IGA score indicating mild psoriasis (score of 2) were limited to 20% of the total enrollment, patients with an IGA score indicating severe psoriasis (score of 4) were limited to 15% of the total enrollment, and all the enrolled patients must have had at least 2% and no more than 20% involvement of the body-surface area with plaque psoriasis.

Characteristic	Roflumilast Cream, 0.3% (N=109)	Roflumilast Cream, 0.15% (N=113)	Vehicle Cream (N=109)
Age — yr	51.7±14.1	54.4±14.2	55.5±13.5
Male sex — no. (%)	56 (51)	62 (55)	67 (61)
Race — no. (%)†			
White	82 (75)	95 (84)	92 (84)
Black	12 (11)	10 (9)	7 (6)
Asian	8 (7)	7 (6)	5 (5)
American Indian or Alaska Native	0	0	1 (1)
Multiple or other	7 (6)	1 (1)	4 (4)
Percent of body-surface area affected by psoriasis	6.3±4.0	6.4±3.9	6.4±3.6
IGA score — no. (%)‡			
2: Mild	17 (16)	18 (16)	11 (10)
3: Moderate	84 (77)	83 (73)	89 (82)
4: Severe	8 (7)	12 (11)	9 (8)
Intertriginous area involvement — no. (%)	16 (15)	18 (16)	17 (16)
Intertriginous-area IGA score — no./total no. (%)‡			
1: Almost clear	1/16 (6)	2/18 (11)	0/17
2: Mild	6/16 (38)	12/18 (67)	7/17 (41)
3: Moderate	8/16 (50)	3/18 (17)	8/17 (47)
4: Severe	1/16 (6)	1/18 (6)	2/17 (12)
PASI score§	7.7±3.6	8.0±3.9	7.6±3.1
WI-NRS score¶			
Mean	6.1±2.7	5.6±3.1	5.9±2.9
Score ≥6 — no. (%)	71 (65)	62 (55)	64 (59)
Psoriasis Symptom Diary total score‖	68.9±41.2	69.6±46.2	75.1±42.6

Efficacy Outcomes (Intention-to-Treat Population).

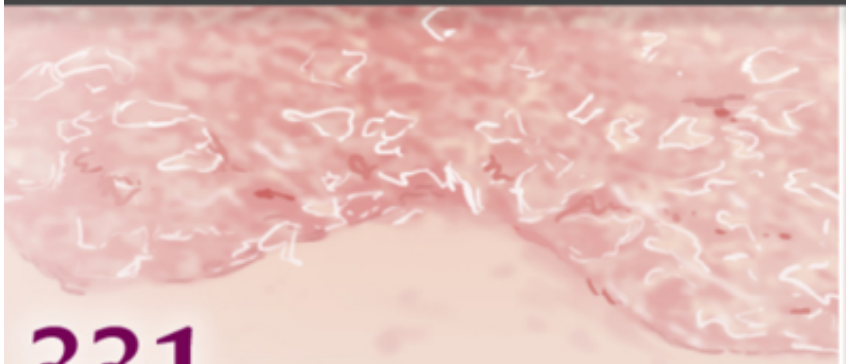
Outcome	Roflumilast Cream, 0.3% (N=109)	Roflumilast Cream, 0.15% (N=113)	Vehicle Cream (N=109)
Primary outcome			
IGA score of 0 or 1 at wk 6 — % of patients (95% CI)	28 (20 to 37)†	23 (16 to 31)‡	8 (4 to 15)
Secondary outcomes§			
IGA score of 0 or 1 plus 2-grade improvement at wk 12 — % of patients (95% CI)	31 (23 to 41)	27 (20 to 36)	14 (8 to 21)
IGA score of 0 or 1 at wk 12 — % of patients (95% CI)	38 (29 to 47)	32 (24 to 41)	16 (10 to 24)
IGA score of 0 or 1 plus 2-grade improvement at wk 12 among patients with baseline intertriginous-area IGA score ≥2 — % of patients (95% CI)¶	94 (67 to 99)	32 (14 to 60)	24 (9 to 50)
IGA score of 0 or 1 at wk 12 among patients with baseline intertriginous-area IGA score ≥2 — % of patients (95% CI)¶	95 (69 to 99)	49 (24 to 74)	24 (9 to 50)
Least-squares mean change in PASI score at wk 12 — % (95% CI)	−53.2 (−61.1 to −45.2)	−55.0 (−62.8 to −47.2)	−17.0 (−25.0 to −9.1)
PASI response at wk 12 — % of patients (95% CI)‖			
PASI 50	62 (53 to 71)	64 (55 to 73)	24 (17 to 33)
PASI 75	34 (26 to 43)	31 (23 to 40)	16 (10 to 24)
PASI 90	20 (14 to 29)	13 (8 to 21)	7 (4 to 14)
WI-NRS response at wk 12 among patients with baseline WI-NRS score ≥6 — % of patients (95% CI)**	63 (51 to 73)	70 (58 to 80)	33 (22 to 45)
Least-squares mean change in PSD score at wk 12 (95% CI)	−42.0 (−48.5 to −35.6)	−44.2 (−50.5 to −37.9)	−20.9 (−27.3 to −14.5)

97% of the adverse events were rated as being mild or moderate in severity. Four serious adverse events were reported: worsening of chest pain in a patient with history of myocardial infarction (in the roflumilast 0.3% group), melanoma (not in the area where roflumilast cream was applied; in the roflumilast 0.15% group), acute infarction of the left basal ganglia (in the vehicle group), and spontaneous miscarriage (in the vehicle group). The most common adverse events (those occurring in >3% of the patients in any trial group) were upper respiratory tract infection, nasopharyngitis, and viral upper respiratory tract infection.

Event	Roflumilast Cream, 0.3% (N=109)	Roflumilast Cream, 0.15% (N=110)	Vehicle Cream (N=107)
	no. of patients with event (%)		
Any adverse event	42 (39)	30 (27)	32 (30)
Serious adverse event	1 (1)	1 (1)	2 (2)
Adverse event leading to discontinuation of trial regimen	1 (1)	0	3 (3)
Adverse events in >1% of patients in any group			
Upper respiratory tract infection	8 (7)	7 (6)	0
Nasopharyngitis	4 (4)	3 (3)	4 (4)
Sinusitis	3 (3)	0	0
Application-site pain	2 (2)	1 (1)	3 (3)
Limb abscess	2 (2)	0	0
Weight increased	2 (2)	0	0
Pain in arm or leg	2 (2)	0	0
Insomnia	2 (2)	1 (1)	0
Cough	2 (2)	0	0
Hypertension	2 (2)	2 (2)	1 (1)
Viral upper respiratory tract infection	1 (1)	1 (1)	4 (4)
Bronchitis	1 (1)	2 (2)	0
Arthralgia	1 (1)	2 (2)	1 (1)
Influenza-like illness	1 (1)	0	2 (2)
Headache	1 (1)	2 (2)	0
Upper abdominal pain	0	0	2 (2)
Urinary tract infection	0	3 (3)	1 (1)
Contact dermatitis	0	0	2 (2)
Adverse event considered to be related to the trial regimen	7 (6)	3 (3)	7 (7)
Adverse event considered to be related to the trial regimen and reported in >1% of the patients in any group			
Application-site pain	2 (2)	0	3 (3)
Insomnia	2 (2)	0	0

Roflumilast Cream, a PDE-4 Inhibitor, for Chronic Plaque Psoriasis

PHASE 2B, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL



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Adults with chronic plaque psoriasis

	Roflumilast cream (0.3%)	Roflumilast cream (0.15%)	Vehicle cream (placebo)
			
	(N=109)	(N=113)	(N=109)
IGA status of clear or almost clear (on 5-point scale of plaque thickening, scaling, and erythema)	28%	23%	8%
	P<0.001 vs. placebo	P=0.004 vs. placebo	
Application-site reactions	4 patients	1 patient	5 patients

AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology. Many patients with AKI have a mixed aetiology where the presence of sepsis, ischaemia and nephrotoxicity often co-exist and complicate recognition and treatment. Furthermore the syndrome is quite common among patients without critical illness and it is essential that health care professionals, particularly those without specialisation in renal disorders, detect it easily.

RIFLE criteria for classification and staging AKI and the modifications proposed by the AKIN network - modified from references ([6] and [7])

RIFLE criteria for classification/staging AKI			**AKIN criteria for classification/staging AKI**		
Stage	**GFR criteria**	**Urine output criteria**	**Stage**	**Serum Creatinine criteria**	**Urine output criteria**
Risk	1.5fold increase in sCr or >25% decrease in GFR	UO < 0.5mL/kg/h for 6h	Stage 1	Absolute increase in sCr ≥ 0.3 mg/dL (≥26.5 **µmol**/L) or ≥ 1.5 to 2.0 fold from baseline	UO < 0.5mL/kg/h for 6h
Injury	2.0fold increase in sCr or >50% decrease in GFR	UO < 0.5mL/kg/h for 12h	Stage 2	Increase in sCR> 2.0 to 3.0 fold from baseline	UO < 0.5mL/kg/h for 12h
Failure	3.0fold increase in sCr or >75% decrease in GFR or sCr>4.0 mg/dL with an acute increase of 0.5 mg/dL	UO < 0.3mL/kg/h for 24h or anuria for 12 h	Stage 3	Increase in sCr > 3fold from baseline or increase of sCr to ≥4.0 mg/dL (≥ 354 **µmol**/L) with an acute increase of at least 0.5 mg/dL (44 **µmol**/L)	UO < 0.3mL/kg/h for 24h or anuria for 12h
Loss	Complete loss of kidney function for > 4 weeks				
ESKD	End stage kidney disease for > 3 months				

ESKD=end stage kidney disease, AKI=acute kidney injury, GFR=glomerular filtration rate, sCr= serum creatinine, UO=urinary output

Timing of initiation of renal replacement therapy

The question of when to initiate RRT in patients with AKI has been debated nearly as long as hemodialysis has been part of the armamentarium of clinical medicine. In 1960, in their seminal article on prophylactic dialysis in acute kidney injury, Paul Teschan and colleagues wrote:

"*While there is increasing recognition of the value of earlier dialysis, the published consensus, and the practice in many centers at present, is still to apply dialysis to relatively ill rather than to relatively healthy patients.*"

A, E, I, O, U

Acidosis, Electrolyte disturbances, Intoxications, Overload, Uremia

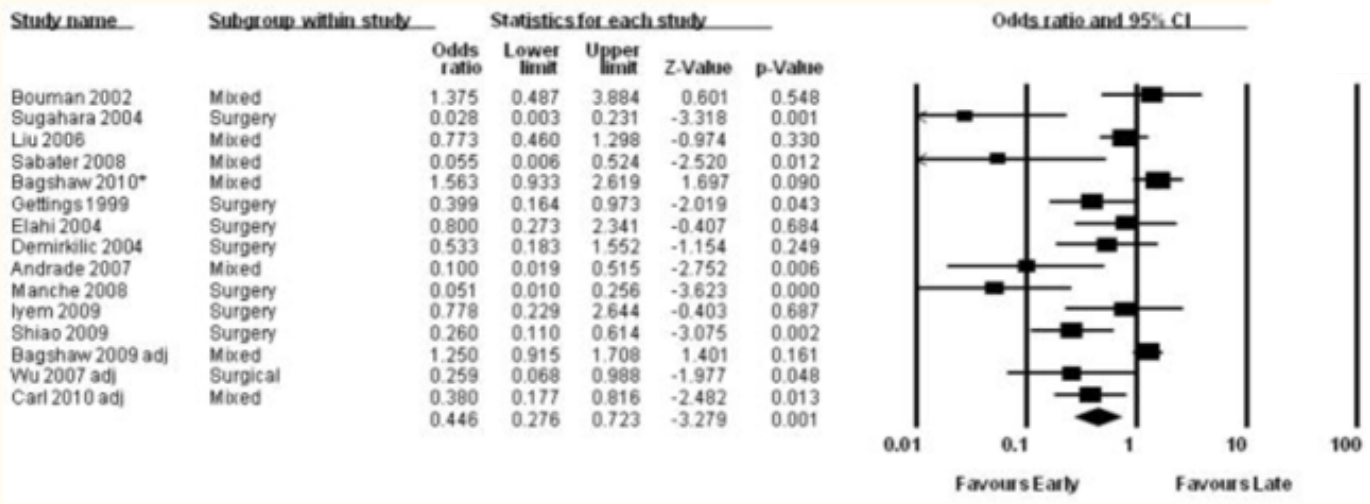


Figure 1

Forest plot of pooled odds ratios for mortality of studies comparing early to late initiation of renal replacement therapy published between 1985 and July 2010. Using a random effects model the calculated pooled odds ratio is 0.45 (95% confidence interval [CI]: 0.28 – 0.72). Reproduced from: Karvellas CJ, Farhat MR, Sajjad I, et al.: A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 15: R72, 2011, with permission.

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney

Acute kidney injury is common in critically ill patients, many of whom receive renal-replacement therapy. However, the most effective timing for the initiation of such therapy remains uncertain. We conducted a multinational, randomized, controlled trial involving critically ill patients with severe acute kidney injury. Patients were randomly assigned to receive an accelerated strategy of renal-replacement therapy (in which therapy was initiated within 12 hours after the patient had met eligibility criteria) or a standard strategy (in which renal-replacement therapy was discouraged unless conventional indications developed or acute kidney injury persisted for >72 hours). The primary outcome was death from any cause at 90 days.

When acute kidney injury is complicated by major metabolic disorders (e.g., acidosis, hyperkalemia, and uremia) and fluid disturbances that can be treated with renal-replacement therapy, there is general consensus that such therapy should be initiated. However, when severe acute kidney injury is not accompanied by one of these complications, the benefits of renal-replacement therapy are unclear.

Characteristic	Accelerated Strategy (N=1465)	Standard Strategy (N=1462)
Age — yr	64.6±14.3	64.7±13.4
Female sex — no. (%)	470 (32.1)	467 (31.9)
Weight — kg	88.0±27.4	88.0±25.1
Serum creatinine — mg/dl†	1.4±1.0	1.3±1.0
Estimated glomerular filtration rate — ml/min/1.73 m^2‡	66.0±29.8	67.3±29.8
Preexisting conditions — no./total no. (%)		
Chronic kidney disease	658/1465 (44.9)	626/1462 (42.8)
Hypertension	814/1465 (55.6)	823/1462 (56.3)
Diabetes mellitus	439/1465 (30.0)	459/1461 (31.4)
Heart failure	204/1465 (13.9)	204/1461 (14.0)
Coronary artery disease	320/1465 (21.8)	328/1461 (22.5)§
Liver disease	172/1465 (11.7)	165/1461 (11.3)
Metastatic cancer	77/1465 (5.3)	84/1462 (5.7)
Hematologic cancer	87/1465 (5.9)	83/1462 (5.7)
HIV infection or AIDS	13/1465 (0.9)	13/1462 (0.9)
Admission category — no. (%)		
Scheduled surgery	207 (14.1)	184 (12.6)
Unscheduled surgery	285 (19.5)	289 (19.8)
Medical	973 (66.4)	989 (67.6)
Hospital-acquired risk factor for AKI in previous wk — no./total no. (%)		
Cardiopulmonary bypass	112/1465 (7.6)	118/1462 (8.1)
Aortic aneurysm repair	71/1465 (4.8)	74/1461 (5.1)
Other vascular surgery	76/1465 (5.2)	77/1462 (5.3)
Major trauma	62/1465 (4.2)	55/1462 (3.8)
Obstetric complication	5/1465 (0.3)	5/1462 (0.3)
Exposure to radiocontrast material	382/1463 (26.1)	375/1460 (25.7)
Receipt of aminoglycoside	154/1463 (10.5)	148/1458 (10.2)
Receipt of amphotericin B	9/1464 (0.6)	12/1460 (0.8)
Clinical condition at randomization		
Sepsis — no. (%)	855 (58.4)	834 (57.0)
Septic shock — no. (%)	640 (43.7)	643 (44.0)
SAPS II value¶	58.1±17.4	59.4±17.4
SOFA score‖	11.6±3.6	11.8±3.6
Mechanical ventilation — no. (%)	1103 (75.3)	1148 (78.5)
Vasoactive support — no. (%)	1008 (68.8)	1052 (72.0)
Serum creatinine — mg/dl	3.6±1.7	3.4±1.6
Serum potassium — mmol/liter	4.5±0.8	4.5±0.8
Serum bicarbonate — mmol/liter	19.7±4.7	19.5±4.5
Median urinary output (IQR) — ml/24 hr**	450 (190–945)	478 (187–975)
Oliguria or anuria — no./total no. (%)††	647/1415 (45.7)	618/1420 (43.5)
Median cumulative fluid balance (IQR) — ml‡‡	2581 (820–5362)	2819 (836–5603)

Patient selection

The determination of kidney injury was defined by a doubling of the serum creatinine level from baseline, a serum creatinine level of 4 mg per deciliter (354 μmol per liter) or more with an increase of 0.3 mg per deciliter (27 μmol per liter) from baseline, or a urine output of less than 6 ml per kilogram of body weight during the preceding 12 hours.

In the accelerated-strategy group, clinicians were to start renal-replacement therapy as soon as possible and within 12 hours after patients had met full eligibility criteria. In the standard-strategy group, clinicians were discouraged from initiating renal-replacement therapy until the development of one or more of the following criteria: a serum potassium level of 6.0 mmol or more per liter, a pH of 7.20 or less or a serum bicarbonate level of 12 mmol per liter or less, evidence of severe respiratory failure based on a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 or less and clinical perception of volume overload, or persistent acute kidney injury for at least 72 hours after randomization. For patients in the standard-strategy group, clinicians were not obligated to initiate renal-replacement therapy. Similarly, clinicians had discretion to initiate such therapy at any time if they perceived that deferral was no longer in the patient's best interest.

Outcomes

The primary outcome was death from any cause at 90 days after randomization. Key secondary outcomes at 90 days were dependence on renal-replacement therapy; a composite of death or dependence on renal-replacement therapy; and a major adverse kidney event, which was defined as death, dependence on renal-replacement therapy, or a sustained reduction in kidney function (i.e., an estimated glomerular filtration rate [eGFR] of <75% of the baseline value).

Similarly sick

Table S5: Expanded baseline characteristics by allocated treatment-strategy.

Characteristic	Accelerated-strategy	Data available	Standard-strategy	Data available
Age – yr	64.6 ± 14.3	1465	64.7 ± 13.4	1462
Female sex – no. (%)	470 (32.1)	1465	467 (31.9)	1462
Weight – kg	88.0 ± 27.4	1461	88.0 ± 25.1	1459
Baseline serum creatinine[a] – mg/dl	1.4 ± 1.0	1465	1.3 ± 1.0	1462
Baseline eGFR[b] – mL/min/1.73m^2	66.0 ± 29.8	1465	67.3 ± 29.8	1462
Clinical Frailty Scale score	3 (2 to 5)	1163	3 (2 to 5)	1142
Clinical Frailty Scale score > 4 – no. (%)	308 (26.5)	1163	308 (27.0)	1142
EQ-VAS	59.0 ± 26.7	756	60.4 ± 26.1	738
Pre-existing conditions – no. (%)				
Chronic kidney disease – (eGFR <60 mL/min/1.73m^2)	658 (44.9)	1465	626 (42.8)	1462
eGFR – mL/min/1.73m^2		1465		1462
≥ 60	807 (55.1)		836 (57.2)	
45-59	257 (17.5)		260 (17.8)	
30-44	230 (15.7)		183 (12.5)	
< 30	171 (11.7)		183 (12.5)	
Hypertension	814 (55.6)	1465	823 (56.3)	1461
Diabetes mellitus	439 (30.0)	1465	459 (31.4)	1462
Heart failure	204 (13.9)	1465	204 (14.0)	1461
Coronary artery disease	320 (21.8)	1465	328 (22.5)	1461
Liver disease	172 (11.7)	1465	165 (11.3)	1461
Metastatic cancer	77 (5.3)	1465	84 (5.7)	1462
Hematologic malignancy	87 (5.9)	1465	83 (5.7)	1462
HIV/AIDS	13 (0.9)	1465	13 (0.9)	1462
Admission category – no. (%)		1465		1462
Scheduled surgery	207 (14.1)		184 (12.6)	
Unscheduled surgery	285 (19.5)		289 (19.8)	
Medical	973 (66.4)		989 (67.6)	
Hospital-acquired risk factors for AKI in preceding 7 days – no. (%)				
Cardiopulmonary bypass	112 (7.6)	1465	118 (8.1)	1462
Aortic aneurysm repair	71 (4.8)	1465	74 (5.1)	1461
Other vascular surgery	76 (5.2)	1465	77 (5.3)	1462
Major trauma	62 (4.2)	1465	55 (3.8)	1462
Obstetric complications	5 (0.3)	1465	5 (0.3)	1462
Radiocontrast exposure	382 (26.1)	1463	375 (25.7)	1460
Receipt of an aminoglycoside	154 (10.5)	1463	148 (10.2)	1458
Receipt of amphotericin B	9 (0.6)	1464	12 (0.8)	1460
Characteristics at enrollment				
Sepsis – no. (%)	855 (58.4)	1465	834 (57.0)	1462
Septic Shock – no. (%)	640 (43.7)	1465	643 (44.0)	1462
SAPS II score[c]	58.1 ± 17.4	1465	59.4 ± 17.4	1462
SOFA score[d]	11.6 ± 3.6	1465	11.8 ± 3.6	1462
Physiological support and interventions – no. (%)				
Mechanical ventilation	1103 (75.3)	1465	1148 (78.5)	1462
Vasoactive support	1008 (68.8)	1465	1052 (72.0)	1462
Diuretic therapy	502 (34.3)	1465	508 (34.8)	1461
Enteral nutrition	525 (35.8)	1465	559 (38.2)	1462
Total parenteral nutrition	182 (12.4)	1465	167 (11.4)	1462
Physiological parameters				
Heart rate – beats/min	107 ± 27	1463	108 ± 26	1459
Systolic blood pressure – mmHg	102 ± 28	1462	101 ± 28	1457
Temperature – degrees Celsius	37.4 ± 1.3	1458	37.5 ± 1.4	1458
Glasgow coma scale	9.2 ± 4.9	1432	8.8 ± 5.0	1417
Urine output – mL/24hr	450 (190 to 945)	1415	478 (187 to 975)	1420
Oliguria or anuria[e]– no. (%)	647 (45.7)	1415	618 (43.5)	1420
Cumulative fluid balance[f] – mL	2581 (820 to 5362)	1378	2819 (836 to 5603)	1360
Percent Fluid overload[g] – no. (%)	3.1 (1.0 to 6.6)	1374	3.2 (0.9 to 6.8)	1357
Laboratory parameters				
Hemoglobin – g/dL	10.0 ± 2.3	1457	10.0 ± 3.0	1451
White blood cell count – cells x 10^3/L	18.4 ± 20.6	1455	17.8 ± 17.4	1444
Platelets – cells x 10^3/L	175 ± 122	1455	168 ± 115	1450
Serum bilirubin – mg/dL	2.6 ± 5.2	1269	2.4 ± 4.3	1277
Arterial pH	7.3 ± 0.1	1367	7.3 ± 0.1	1350
Serum sodium – mmol/L	138 ± 7	1465	138 ± 7	1460
Serum creatinine – mg/dL	3.6 ± 1.7	1464	3.4 ± 1.6	1461
Serum potassium – mmol/L	4.5 ± 0.8	1464	4.5 ± 0.8	1461
Serum bicarbonate – mmol/L	19.7 ± 4.7	1437	19.5 ± 4.5	1423
Blood urea nitrogen – mg/dL	60.8 ± 34.3	1382	61.0 ± 33.9	1380

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: eGFR = estimated glomerular filtration rate; EQ-VAS = EuroQoL visual analogue scale; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; AKI = acute kidney injury; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; TPN = total parenteral nutrition.

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

[a] Baseline serum creatinine was defined as the most recent outpatient serum creatinine obtained during the year preceding the current hospitalization. If this value was not available, the lowest serum creatinine during the current hospitalization was used to establish the baseline serum creatinine.
[b] Baseline eGFR was derived using the Chronic Kidney Disease - Epidemiology equation which incorporates the baseline serum creatinine, age, sex and whether the patient was of African background.
[c] Scores on the SAPS II score range from 0 to 163, with higher scores indicating more severe disease and a higher risk of death.
[d] Scores on the SOFA score range from 0-24, with higher scores indicating more severe disease and a higher risk of death.
[e] Oliguria was defined as urine output <400 mL/24hr. Data expressed as a proportion of patients with urine output available.
[f] Cumulative fluid balance from ICU admission.
[g] Fluid overload defined as cumulative fluid balance from ICU admission divided by earliest recorded weight during the hospitalization times 100 and expressed as a percentage.

Randomization functioned

Table S6: Characteristics at renal-replacement therapy initiation.

	Accelerated-strategy (N=1418)	Patients with available data	Standard-strategy (N=903)	Patients with available data
Time from eligibility to RRT initiation – hours	6.1 (3.9 to 8.8)	1417	31.1 (19.0 to 71.8)	903
Time from randomization to RRT initiation – hours	4.4 (2.7 to 6.6)	1417	29.1 (17.3 to 68.4)	903
Physiological parameters at RRT initiation				
Heart rate – beats/min	94 ± 21	1415	93 ± 20	898
Systolic blood pressure - mmHg	118 ± 23	1414	119 ± 23	897
Respiratory rate – breaths/min	21 ± 7	1410	22 ± 7	894
PaO_2/FiO_2 ratio	243 ± 110	1375	232 ± 113	873
Urine output in the preceding 24 hours – mL	453 (190 to 973)	1384	350 (100 to 1000)	889
Fluid balance – mL	2714 (872 to 5659)	1328	5893 (2265 to 11068)	829
Laboratory parameters at RRT initiation				
Serum creatinine – mg/dL	3.7 ± 1.7	1414	4.9 ± 2.1	900
Blood urea nitrogen – mg/dL	63.7 ± 49.8	1356	85.3 ± 51.3	869
Serum potassium – mmol/L	4.4 ± 0.7	1409	4.6 ± 0.8	903
Serum bicarbonate – mmol/L	20.6 ± 4.4	1388	19.5 ± 4.7	888
Arterial pH	7.3 ± 0.1	1335	7.3 ± 0.1	843
Hemoglobin – g/dL	9.9 ± 2.2	1399	9.3 ± 1.8	899
SOFA score at RRT initiation	10.9 ± 3.6	1417	12.1 ± 3.6	903
Presence of ≥ 1 Indication for RRT at time of RRT initiation in the standard arm – no. (%)	-		597 (66.1)	
Serum potassium ≥ 6 mmol/L – no. (%)			48 (5.3)	
pH ≤ 7.2 or Bicarbonate ≤ 12 mmol/L – no. (%)	-		150 (16.6)	
$PaO_2/FiO_2 \leq 200$ and clinical perception of volume overload – no. (%)	-		394 (43.6)	
Time from randomization to RRT ≥ 72hrs – no. (%)	-		214 (23.7)	

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: RRT = renal replacement therapy; AKI = acute kidney injury; SOFA = sequential organ failure assessment.

Treatment modalities no different

Table S7: Characteristics of the initial renal-replacement therapy prescription.

Characteristic	Accelerated-strategy (N=1418)	Patients with available data	Standard-strategy (N=903)	Patients with available data
RRT modality – no. (%)		1417		880
CRRT	969 (68.4)		621 (70.6)	
IHD	383 (27.0)		223 (25.3)	
SLED	65 (4.6)		36 (4.1)	
Dialysis catheter insertion site – no. (%)		1365		841
Jugular	805 (59.0)		488 (58.0)	
Femoral	519 (38.0)		332 (39.5)	
Subclavian	41 (3.0)		21 (2.5)	
Intermittent RRT duration prescribed				
IHD – hours	4.0 (3.0 to 4.0)	382	4.0 (2.6 to 4.0)	222
SLED – hours	8.0 (6.0 to 8.0)	65	8.0 (7.3 to 8.0)	36
CRRT dose prescribed – mL/kg/hr	28.3 (23.0 to 33.0)	963	28.6 (23.0 to 33.1)	619
Anticoagulation – no. (%)		1417		880
Citrate	639 (45.1)		383 (43.5)	
Heparin	407 (28.7)		260 (29.5)	
None	338 (23.9)		213 (24.2)	
Other	33 (2.3)		24 (2.7)	
Ultrafiltration achieved during first RRT session – mL	360 (0 to 1290)	1389	860 (50 to 2000)	867

Data are presented as mean ± standard deviation, median (interquartile range) or number (%).

Abbreviations: RRT = renal replacement therapy; IHD = intermittent hemodialysis; SLED = slow low efficiency dialysis; CRRT = continuous renal replacement therapy

Died at the same rate

Table S9: Causes of death[a].

Cause	Accelerated-strategy (N=640)	Standard-strategy (N=630)
Neurological – no. (%)		
Brain death	6 (0.9)	8 (1.3)
Hypoxic encephalopathy	12 (1.9)	16 (2.5)
Intracranial hemorrhage	6 (0.9)	3 (0.5)
Ischemic stroke	8 (1.3)	4 (0.6)
Other	9 (1.4)	8 (1.3)
Cardiovascular – no. (%)		
Primary arrhythmia	30 (4.7)	28 (4.5)
Refractory cardiogenic shock	34 (5.3)	36 (5.7)
Cardiac tamponade	3 (0.5)	3 (0.5)
Hypovolemia (bleeding)	17 (2.7)	13 (2.1)
Septic shock	195 (30.5)	176 (28.0)
Massive pulmonary embolism	5 (0.8)	1 (0.2)
Anaphylaxis	1 (0.2)	1 (0.2)
Other	114 (17.8)	110 (17.5)
Respiratory – no. (%)		
Refractory hypoxia due to ARDS	40 (6.3)	46 (7.3)
COPD	6 (0.9)	9 (1.4)
Asthma	0	2 (0.3)
Pulmonary hemorrhage	0	2 (0.3)
Pneumothorax	2 (0.3)	0
Other	86 (13.4)	82 (13.0)
Metabolic – no. (%)		
Hypoglycemia	0	0
Hyperkalemia	0	4 (0.6)
Hypothermia	0	0
Liver failure	22 (3.4)	24 (3.8)
Other	44 (6.9)	54 (8.6)

Abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease.

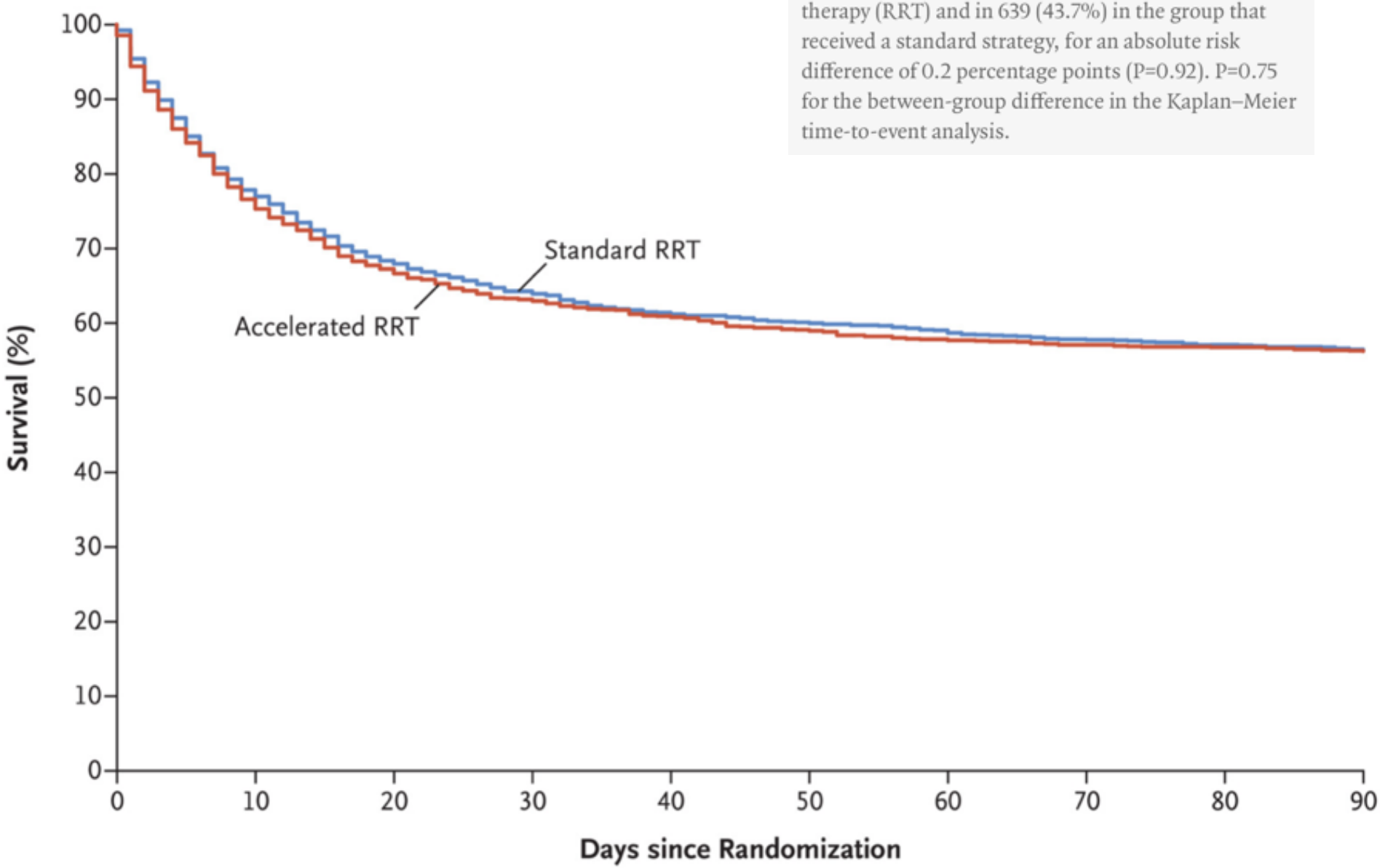
[a] Cause of death not available for 12 patients, 3 patients in the accelerated-strategy and 9 patients in the standard-strategy.

Data were available on withdrawal of life-sustaining therapy for 1270/1282 patients (99.1%) who died: 412 (64.4%) in the accelerated-strategy and 391 (61.2%) in the standard-strategy.

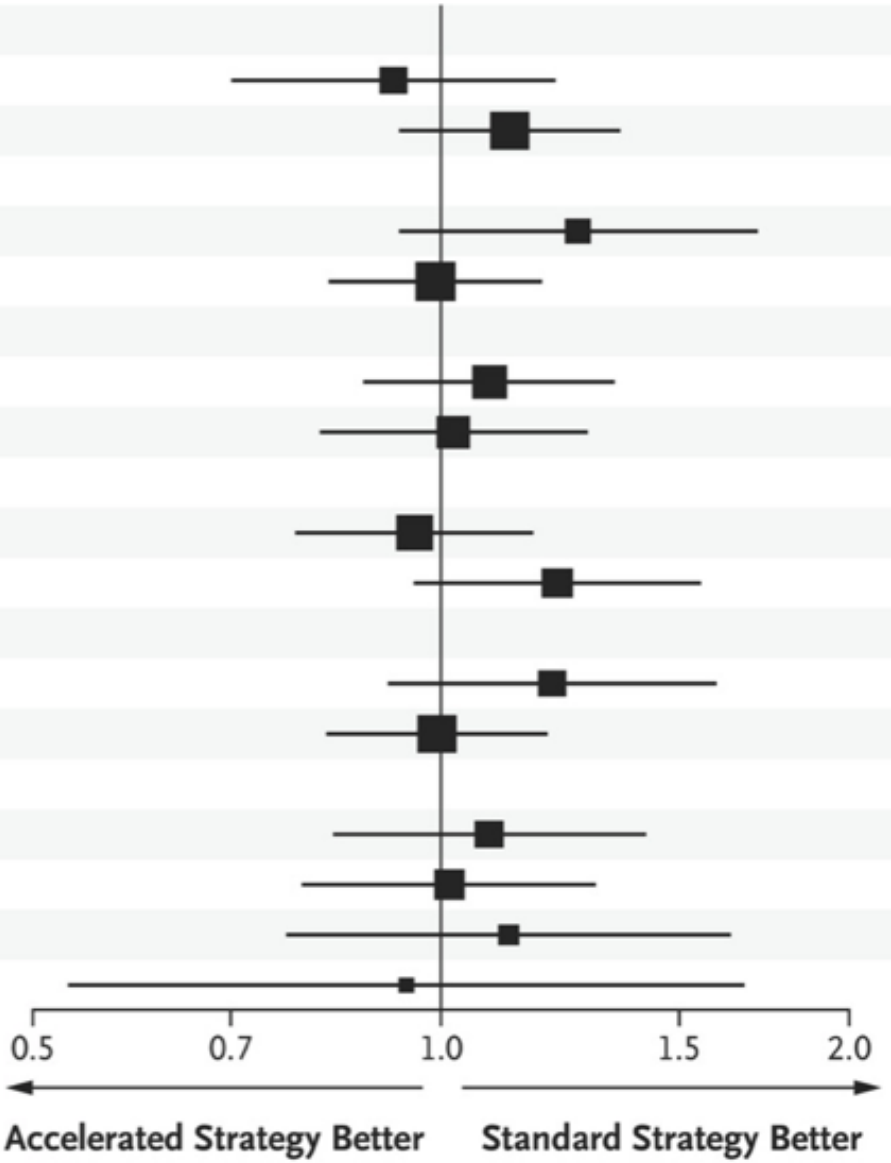
No difference in outcomes anywhere

	Accelerated Strategy (N=1465)	Standard Strategy (N=1462)	Relative Risk or Difference (95% CI)
Primary outcome			
Death from any cause at 90 days — no. (%)†	643 (43.9)	639 (43.7)	1.00 (0.93 to 1.09)‡
Secondary outcomes			
RRT dependence among survivors at 90 days — no./total no. (%)	85/814 (10.4)	49/815 (6.0)	1.74 (1.24 to 2.43)‡
Death or RRT dependence at 90 days — no./total no. (%)	728/1457 (50.0)	688/1454 (47.3)	1.06 (0.98 to 1.14)‡
Major adverse kidney events at 90 days — no./total no. (%)	867/1131 (76.7)	860/1115 (77.1)	0.99 (0.95 to 1.04)‡
Serum creatinine at 90 days — mg/dl§	1.20±1.00	1.23±1.00	−0.03 (−0.11 to 0.06)¶
Estimated glomerular filtration rate‖			
At 90 days — ml/min/1.73 m^2	65±30	64±31	0.31 (−3.88 to 4.49)¶
Reduction of >25% from baseline at 90 days — no./total no. (%)	139/403 (34.5)	172/427 (40.3)	0.86 (0.72 to 1.02)‡
Death from any cause — no./total no. (%)			
At any time in the ICU	461/1464 (31.5)	468/1462 (32.0)	0.98 (0.88 to 1.09)‡
At 28 days	538/1465 (36.7)	523/1462 (35.8)	1.03 (0.93 to 1.13)‡
During hospitalization	552/1458 (37.9)	546/1459 (37.4)	1.01 (0.92 to 1.11)‡
Use of health services			
Median no. of days of use (IQR)			
RRT-free days at 90 days**	50 (0 to 87)	64 (0 to 90)	−2.62 (−5.66 to 0.42)¶
RRT††	4 (2 to 8)	5 (3 to 9)	−0.48 (−0.82 to −0.14)¶
Continuous RRT††	4 (3 to 8)	5 (3 to 8)	−0.40 (−0.78 to −0.02)¶
Sustained low-efficiency dialysis††	2 (1 to 4)	2 (1 to 4)	0.15 (−0.65 to 0.96)¶
Intermittent hemodialysis††	2 (1 to 4)	3 (2 to 5)	−0.45 (−0.80 to −0.09)¶
Median length of stay in ICU (IQR) — days			
Survivors	9 (5 to 16)	10 (5 to 19)	−1.58 (−2.90 to −0.26)¶
Nonsurvivors	7 (3 to 13)	7 (4 to 15)	−1.33 (−2.56 to −0.09)¶
Median length of hospital stay (IQR) – days			
Survivors	28 (16 to 50)	29 (17 to 54)	−1.23 (−3.87 to 1.41)¶
Nonsurvivors	8 (3 to 18)	9 (4 to 19)	−0.99 (−2.66 to 0.67)¶
Median no. of ventilator-free days at 28 days (IQR)	13 (0 to 24)	12 (0 to 24)	0.50 (−0.34 to 1.35)¶
Median no. of days free of vasoactive agents at 28 days (IQR)	21 (0 to 26)	20 (0 to 26)	0.31 (−0.57 to 1.18)¶
Median no. of days out of ICU at 28 days (IQR)	8 (0 to 21)	4 (0 to 20)	0.69 (−0.06 to 1.43)¶
Median no. of days out of hospital at 90 days (IQR)	10 (0 to 65)	9 (0 to 64)	0.55 (−1.82 to 2.91)¶
Rehospitalization at 90 days — no./total no. (%)	191/913 (20.9)	156/916 (17.0)	1.23 (1.02 to 1.49)‡
Health-related quality of life			
Median score on EQ-5D-5L at 90 days (IQR)			
Descriptive system‡‡			
Mobility	2 (1 to 3)	2 (1 to 3)	−0.07 (−0.23 to 0.08)¶
Self care	1 (1 to 3)	1 (1 to 3)	−0.10 (−0.25 to 0.05)¶
Usual activities	2 (1 to 3)	2 (1 to 4)	−0.15 (−0.31 to 0.01)¶
Pain or discomfort	2 (1 to 3)	2 (1 to 3)	−0.04 (−0.17 to 0.08)¶
Anxiety or depression	1 (1 to 3)	2 (1 to 3)	−0.06 (−0.19 to 0.07)¶
EQ-VAS§§	70 (50 to 80)	70 (50 to 80)	0.11 (−2.55 to 2.76)¶
Score of >4 on Clinical Frailty Scale at 90 days — no. (%)¶¶	213/655 (32.5)	227/647 (35.1)	0.93 (0.80 to 1.08)‡

In the modified intention-to-treat analysis, death at 90 days occurred in 643 patients (43.9%) in the group that received an accelerated strategy for renal-replacement therapy (RRT) and in 639 (43.7%) in the group that received a standard strategy, for an absolute risk difference of 0.2 percentage points (P=0.92). P=0.75 for the between-group difference in the Kaplan–Meier time-to-event analysis.



Subgroup	Accelerated Strategy	Standard Strategy
	no. of events/total no.	
Sex		
Female	191/470	207/467
Male	452/995	432/995
Estimated GFR		
<45	184/401	150/365
≥45	459/1064	488/1097
SAPS II		
>58	387/701	403/751
≤58	256/764	236/711
Sepsis		
Yes	392/855	402/834
No	251/610	237/628
Type of ICU admission		
Surgical	185/492	156/473
Medical	458/973	483/989
Geographic region		
North America	231/497	225/497
Europe	254/574	260/572
Australia or New Zealand	91/275	86/278
Asia or South America	67/119	68/115



Adverse Events	Accelerated Strategy (N=1503)		Standard Strategy (N=1489)		P Value†
	Patients	Events	Patients	Events	
	no. (%)	*no. (per 1000 patient-mo)*	*no. (%)*	*no. (per 1000 patient-mo)*	
Any adverse event	346 (23.0)	556 (195.7)	245 (16.5)	364 (128.1)	<0.001
Associated with renal-replacement therapy					
Hypotension	131 (8.7)	188 (66.2)	83 (5.6)	112 (39.4)	0.001
Arrhythmia	37 (2.5)	45 (15.8)	23 (1.5)	29 (10.2)	0.07
Seizure	1 (0.1)	1 (0.4)	0	0	1.00
Bleeding	4 (0.3)	4 (1.4)	1 (0.1)	1 (0.4)	0.37
Allergic reaction	1 (0.1)	1 (0.4)	1 (0.1)	1 (0.4)	1.00
Decreased phosphate (<0.5 mmol/liter)	112 (7.5)	124 (43.7)	62 (4.2)	68 (23.9)	<0.001
Decreased potassium (<3.0 mmol/liter)	34 (2.3)	43 (15.1)	34 (2.3)	40 (14.1)	0.97
Decreased ionized calcium (<0.90 mmol/liter)	80 (5.3)	102 (35.9)	66 (4.4)	80 (28.1)	0.26
Associated with use of a dialysis catheter					
Pneumothorax or hemothorax	4 (0.3)	5 (1.8)	2 (0.1)	2 (0.7)	0.69
Bleeding	6 (0.4)	6 (2.1)	4 (0.3)	4 (1.4)	0.75
Thrombus (as confirmed on ultrasonography)	3 (0.2)	3 (1.1)	5 (0.3)	5 (1.8)	0.51
Arterial puncture	3 (0.2)	3 (1.1)	2 (0.1)	2 (0.7)	1.00
Bloodstream infection	7 (0.5)	7 (2.5)	1 (0.1)	1 (0.4)	0.07
Other	21 (1.4)	24 (8.4)	20 (1.3)	19 (6.7)	0.90
Serious adverse events — no. (%)	15 (1.0)	17 (6.0)	8 (0.5)	8 (2.8)	0.15

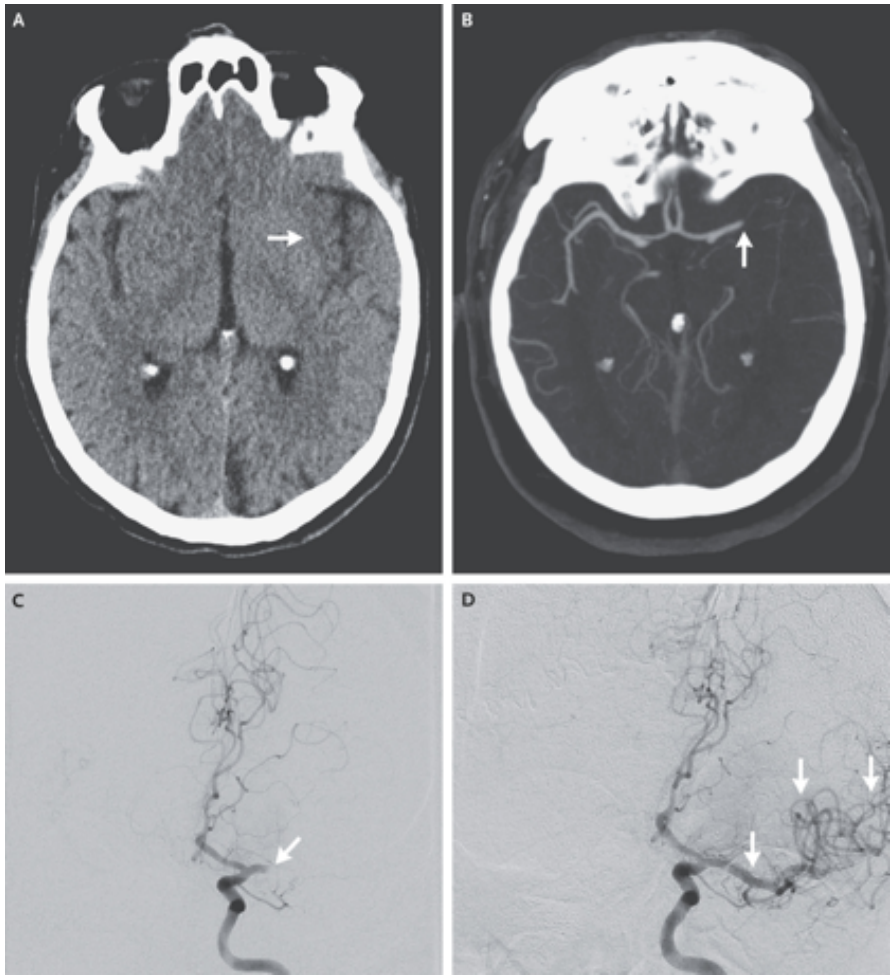
Discussion

In this large, multinational, randomized trial, critically ill patients with severe acute kidney injury who received an accelerated strategy for the initiation of renal-replacement therapy did not have a lower risk of death at 90 days than those who received a standard strategy. This finding clarifies a long-standing clinical dilemma regarding the treatment strategy for critically ill patients with acute kidney injury who have no overt complications that would mandate the immediate initiation of renal-replacement therapy. Observational studies using various biochemical thresholds as surrogates for the timing of initiation and a single-center randomized trial that enrolled primarily surgical patients suggested that earlier renal-replacement therapy resulted in a lower mortality than delayed therapy. Conversely, two multicenter, randomized trials, including one that exclusively involved patients with septic shock, did not show a lower risk of death with an early strategy than with a delayed strategy for the initiation of renal-replacement therapy. In these two trials, eligibility was tied to fulfilling consensus-defined serum creatinine levels and urine-output thresholds for severe acute kidney injury, with renal-replacement therapy initiated promptly after this determination in the early-therapy group. In the delayed-therapy group, the initiation of renal-replacement therapy was mandated for patients in whom acute kidney injury persisted for 48 to 72 hours or in whom metabolic or fluid complications developed. In the two trials, a sizable percentage of patients in the delayed-therapy group did not receive renal-replacement therapy because they either recovered kidney function or died.

A greater percentage of survivors who received the accelerated strategy were dependent on renal-replacement therapy at 90 days and had adverse events. This finding suggests that greater exposure to renal-replacement therapy, possibly modified according to baseline risk (e.g., the presence of chronic kidney disease) or mediated by iatrogenic factors (e.g., hypotension), may compromise kidney repair and the return of endogenous kidney function.

Acute Ischemic Stroke

A 62-year-old, right-handed, independently functioning man presents 1 hour after a sudden, witnessed onset of speech difficulty and right-sided numbness and weakness. He is alert with moderate aphasia, facial weakness on the right side, and weakness in the right arm and leg with decreased sensation to light touch. His blood pressure is 160/95 mm Hg, plasma glucose level 79 mg per deciliter (4.4 mmol per liter), and body temperature 37.2° C. His medical history is unremarkable, and he is taking no medications. Noncontrast computed tomography (CT) of the head shows slight hypodensity in the left insular cortex. What would you do?



Panel A shows a noncontrast computed tomographic (CT) scan of the head (transverse section) revealing slight hypodensity in the left insular cortex (arrow). Panel B shows a CT angiogram (transverse section) revealing an occlusion of the first segment of the left middle cerebral artery (arrow). Panel C shows a cerebral arteriogram (anterior projection) revealing an occlusion of the first segment of the middle cerebral artery before mechanical thrombectomy (arrow). Panel D shows a cerebral arteriogram (anterior projection) revealing recanalization of the left middle cerebral artery after thrombectomy (arrows).

KEY CLINICAL POINTS

Acute Ischemic Stroke

- Treatment for patients with acute ischemic stroke is guided by the time from the onset of stroke, the severity of neurologic deficit, and findings on neuroimaging. By convention, the time of stroke onset is established as the time that the patient was last known to be well (i.e., in a normal or baseline state, as confirmed by medical history).
- Intravenous thrombolysis with alteplase (a recombinant tissue plasminogen activator) improves outcomes in selected patients with acute ischemic stroke when administered within 4.5 hours after onset. Later treatment may improve outcomes in selected patients, with the treatment window extended to 9 hours from onset.
- Intraarterial catheter-based mechanical thrombectomy of occluded large intracranial arteries improves outcomes in selected patients with acute ischemic stroke when performed up to 24 hours after onset.
- The benefit of alteplase and mechanical thrombectomy is time-dependent, so assessment and treatment should be instituted rapidly.
- In selected patients with mild acute ischemic stroke who do not qualify for intravenous thrombolysis or mechanical thrombectomy, dual antiplatelet therapy with clopidogrel and aspirin when administered within 24 hours after onset and continuedfor 21 days lowers the risk of recurrent stroke.

Alteplase within 4.5 Hours after Stroke Onset

Randomized, controlled trials have shown that intravenous administration of alteplase (at a dose of 0.9 mg per kilogram of body weight over 60 minutes [maximum total dose, 90 mg], with the first 10% of the dose given as a single bolus over 1 minute) within 4.5 hours after the onset of stroke reduces disability from acute ischemic stroke.

Alteplase at More Than 4.5 Hours after Stroke Onset

In the WAKE-UP (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) trial, 503 patients with a time of onset of disabling acute ischemic stroke that was unclear, but greater than 4.5 hours from the time last known to be well (94% of whom awoke with stroke), were randomly assigned to receive intravenous alteplase at a standard dose or placebo administered within 4.5 hours after the recognition of stroke symptoms. More participants in the alteplase group than in the placebo group attained the primary end point of a modified Rankin scale score of 0 or 1 at 90 days (53% vs. 42%; adjusted odds ratio, 1.61; 95% CI, 1.09 to 2.36).

Mechanical Thrombectomy within 6 hours after Stoke Onset

Mechanical thrombectomy entails passing an intraarterial catheter from a peripheral puncture into an intracranial artery and removing an occluding thrombus by ensnaring it or by suction.

Mechanical Thrombectomy at More Than 6 Hours after Stroke Onset

Two randomized, controlled trials have shown a benefit of mechanical thrombectomy performed at more than 6 hours after the onset of stroke in patients with an occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery. The percentage of patients with a score of 0 to 2 on the modified Rankin scale at 90 days was significantly higher among those who underwent mechanical thrombectomy than among those who did not (49% vs. 13%; adjusted difference, 33%; 95% CI, 21 to 44).

Tenecteplase

Tenecteplase is a tissue plasminogen activator that is modified to be more fibrin-specific and more resistant to plasminogen activator inhibitor and to have a longer plasma half-life than alteplase so that it can be given as a single intravenous bolus.

Antithrombotic Agents

In patients who receive intravenous alteplase, administration of an antiplatelet agent is generally delayed for 24 hours to minimize the risk of bleeding. Pooled data from two large, randomized, placebo-controlled trials showed that the risk of recurrent stroke or death in the hospital was lower with aspirin (at a dose of 160 to 300 mg administered within 48 hours after acute ischemic stroke) than with placebo (8.2% vs. 9.1%, P=0.001).

General Medical and Supportive Care for Patients with Acute Ischemic Stroke.

Patients should be admitted to a specialized stroke unit.

Cardiac monitoring should be performed for at least the first 24 hours.

Supplemental oxygen should be provided to maintain oxygen saturation of higher than 94%, if necessary.

Sources of fever (temperature >38°C) should be identified and treated. Antipyretic medications should be administered to lower temperature in patients with hyperthermia.

Hyperglycemia should be treated to attain blood glucose levels in a range of 140 to 180 mg per deciliter, and treatment should be monitored closely to prevent hypoglycemia.

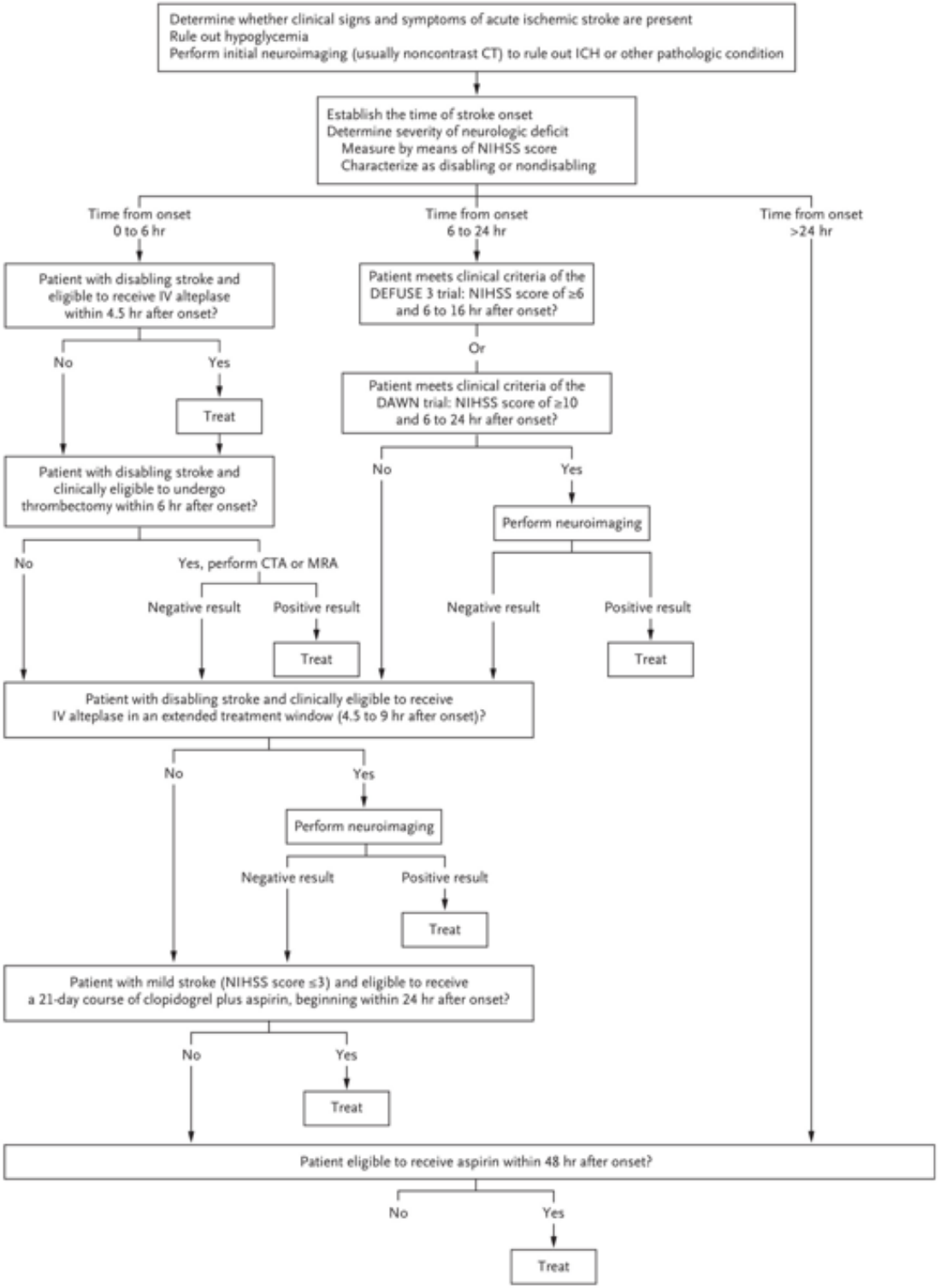
For patients with a blood pressure of lower than 220/120 mm Hg who did not receive intravenous alteplase or undergo mechanical thrombectomy and who do not have a coexisting medical complication that requires urgent antihypertensive treatment, treatment of hypertension within the first 48 to 72 hours after the onset of stroke does not reduce the risk of death or disability.

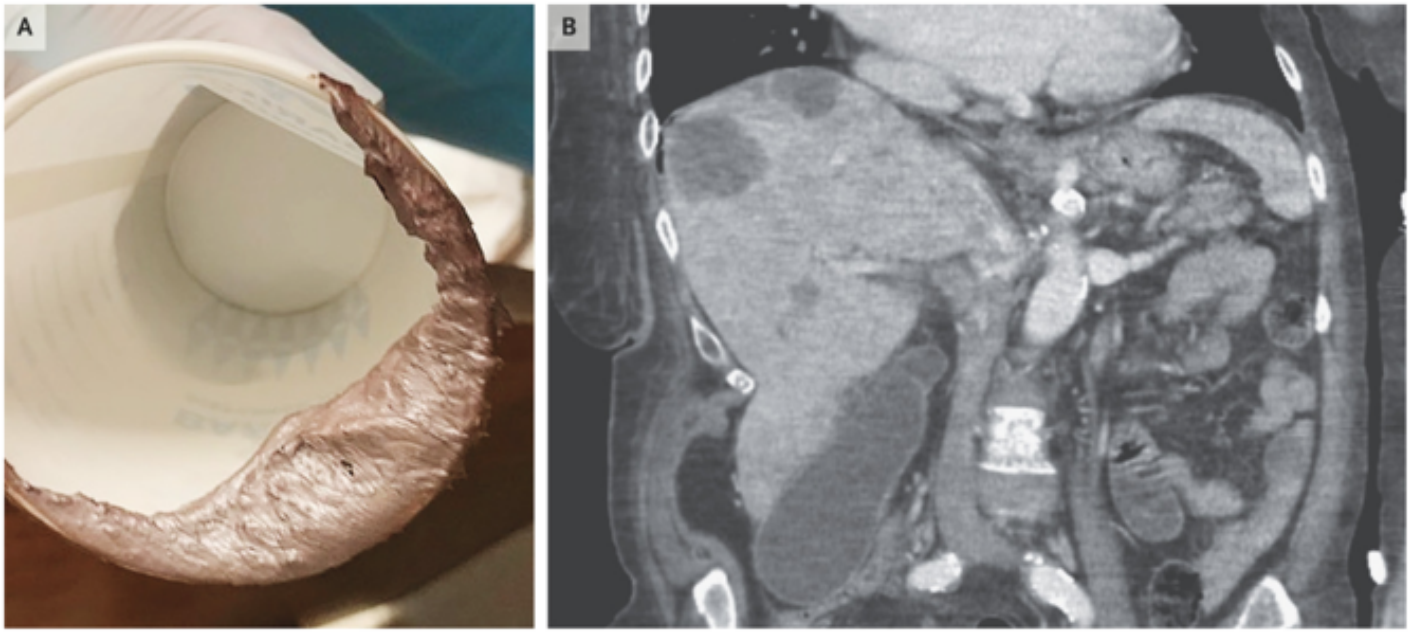
For patients with a blood pressure of 220/120 mm Hg or higher who did not receive intravenous alteplase or undergo mechanical thrombectomy and who do not have a coexisting medical complication that requires urgent antihypertensive treatment, the benefit of treating hypertension within the first 48 to 72 hours after the onset of stroke is uncertain. It may be reasonable to lower the blood pressure by 15% during the first 24 hours after the onset.

In immobile patients without contraindications, intermittent pneumatic compression stockings are recommended to reduce the risk of deep-vein thrombosis.

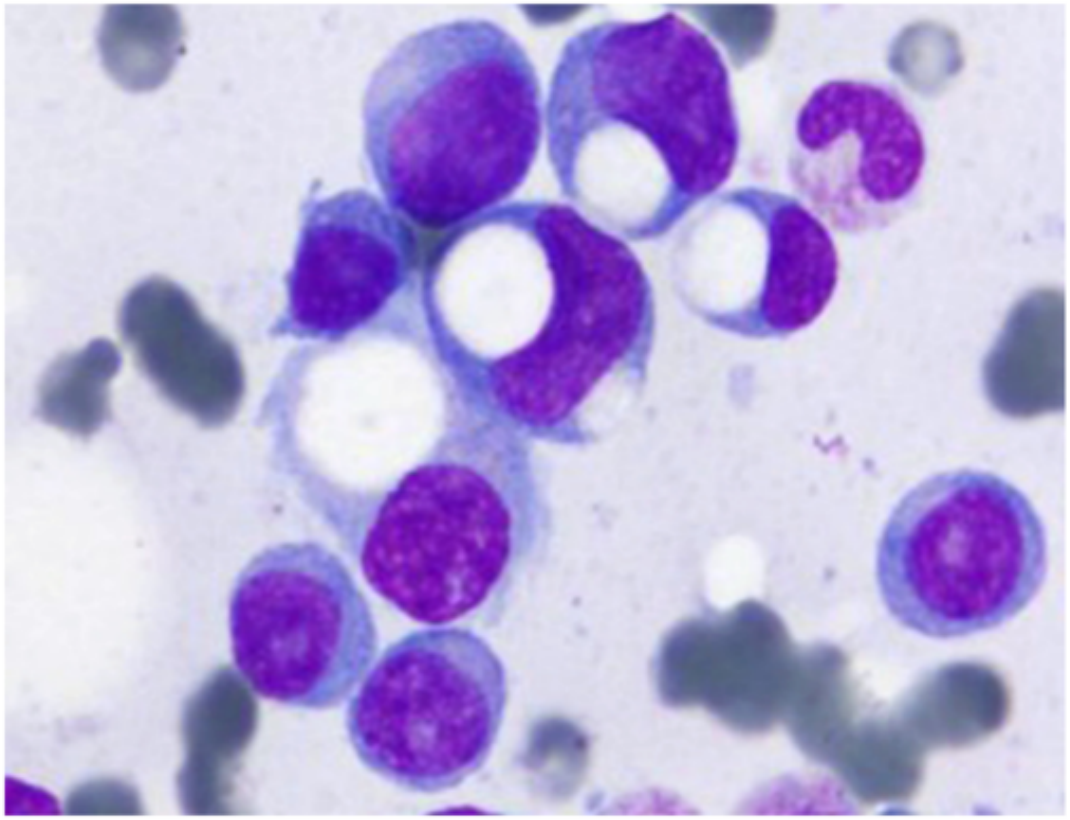
Screening for dysphagia can identify patients at increased risk for aspiration.

Patients with large cerebral and cerebellar infarctions are at high risk for brain swelling and herniation during the first days. These patients should be monitored closely. Neurosurgical intervention can be lifesaving in those with early decreased consciousness. If management of malignant brain swelling is unavailable locally, patients at risk for this condition should be transferred to an institution with expertise in such management.


Determine whether clinical signs and symptoms of acute ischemic stroke are present
Rule out hypoglycemia
Perform initial neuroimaging (usually noncontrast CT) to rule out ICH or other pathologic condition
Establish the time of stroke onset
Determine severity of neurologic deficit
Measure by means of NIHSS score
Characterize as disabling or nondisabling
Time from onset 0 to 6 hr
Time from onset 6 to 24 hr
Time from onset >24 hr
Patient with disabling stroke and eligible to receive IV alteplase within 4.5 hr after onset?
No
Yes
Treat
Patient with disabling stroke and clinically eligible to undergo thrombectomy within 6 hr after onset?
No
Yes, perform CTA or MRA
Negative result
Positive result
Treat
Patient meets clinical criteria of the DEFUSE 3 trial: NIHSS score of ≥6 and 6 to 16 hr after onset?
Or
Patient meets clinical criteria of the DAWN trial: NIHSS score of ≥10 and 6 to 24 hr after onset?
No
Yes
Perform neuroimaging
Negative result
Positive result
Treat
Patient with disabling stroke and clinically eligible to receive IV alteplase in an extended treatment window (4.5 to 9 hr after onset)?
No
Yes
Perform neuroimaging
Negative result
Positive result
Treat
Patient with mild stroke (NIHSS score ≤3) and eligible to receive a 21-day course of clopidogrel plus aspirin, beginning within 24 hr after onset?
No
Yes
Treat
Patient eligible to receive aspirin within 48 hr after onset?
No
Yes
Treat



A 69-year-old woman with metastatic colon cancer presented to the emergency department with a 2-week history of dizziness and unusually colored stool. She had no associated itching or darkening of the urine. The physical examination was notable for jaundice, hepatomegaly, and a diffusely tender abdomen. The rectal examination showed silver-colored stool (Panel A). Laboratory studies were notable for a hemoglobin level of 7.5 g per deciliter (reference range, 11.0 to 14.5), a total bilirubin level of 4.0 mg per deciliter (68 μmol per liter) (reference range, 0.2 to 1.3 mg per deciliter [3 to 22 μmol per liter]), and an alkaline phosphatase level of 369 U per liter (reference range, 45 to 117). Testing of the stool was positive for occult blood. Findings on computed tomography of the abdomen and pelvis included a cecal mass and multiple liver metastases (Panel B). The appearance of silver stool results from a combination of white stool associated with obstructive jaundice and black stool of melena. After a discussion of treatment options with the patient, a decision was made to focus on her comfort. She was discharged home with hospice care.

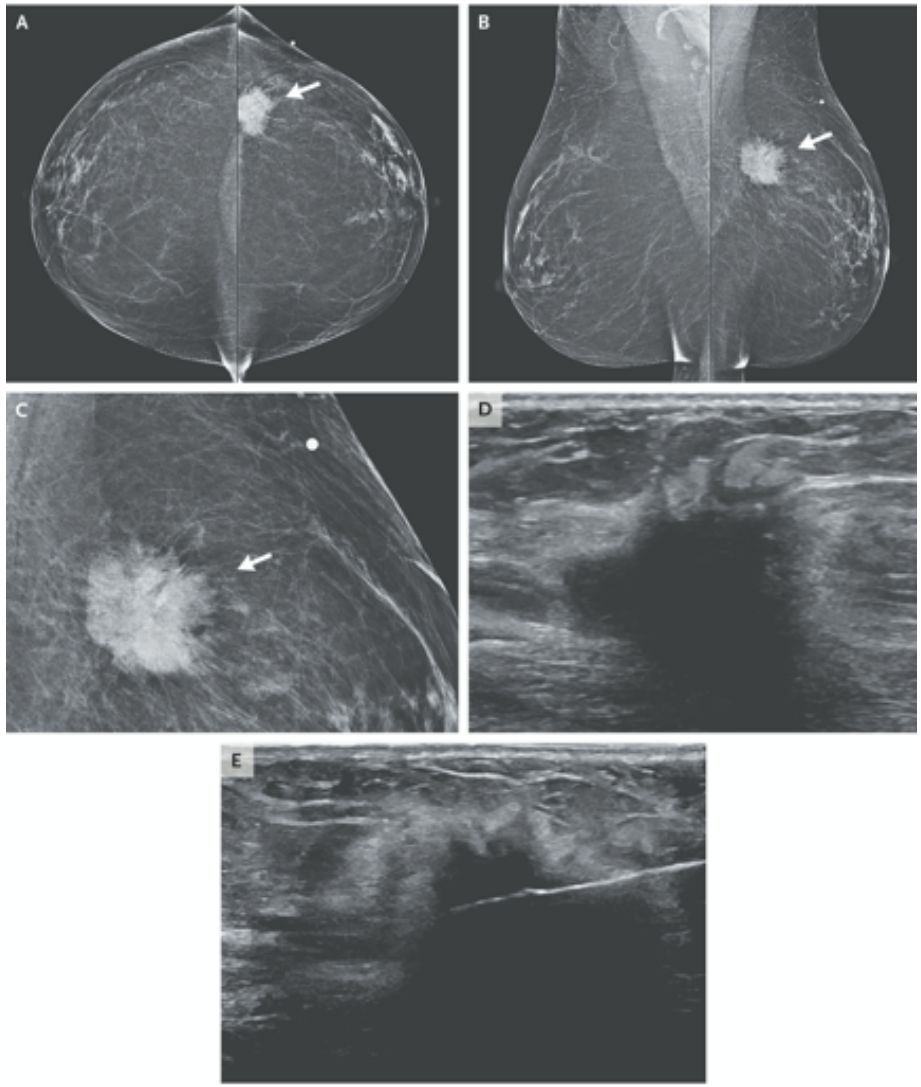


A 72-year-old man was referred to the hematology service after an evaluation for a 1-month history of fatigue and pain in the right hip revealed abnormal results on serum protein electrophoresis. Relevant laboratory test results included a creatinine level of 0.8 mg per deciliter (71 mmol per liter) (normal range, 0.7 to 1.2 mg per deciliter [62 to 106 mmol per liter]), a calcium level of 9.4 mg per deciliter (2.4 mmol per liter) (normal range, 8.8 to 10.6 mg per deciliter [2.2 to 2.6 mmol per liter]), and a total protein level of 9.4 g per deciliter (normal range, 6.6 to 8.3). Serum protein electrophoresis with immunofixation confirmed the presence of an IgG kappa monoclonal spike of 5.5 g per deciliter. A skeletal survey showed lytic lesions in the ilium, pubis, and calvaria, and a bone marrow biopsy confirmed 70% involvement of plasma cells with kappa light-chain restriction. A diagnosis of multiple myeloma was made. Examination of the plasma cells revealed the presence of cells with morphologic features characteristic of signet-ring cells. This type of cell is common in mucin-producing adenocarcinomas; however, in myeloma, the cause of its appearance is incompletely understood. It has been proposed that the presence of such cells is a result of large cytoplasmic inclusions of defective immunoglobulins that displace the nucleus to the periphery. Treatment with an induction regimen of bortezomib, cyclophosphamide, and dexamethasone was initiated, and maintenance therapy was planned.

A 62-Year-Old Woman with Early Breast Cancer during the Covid-19 Pandemic

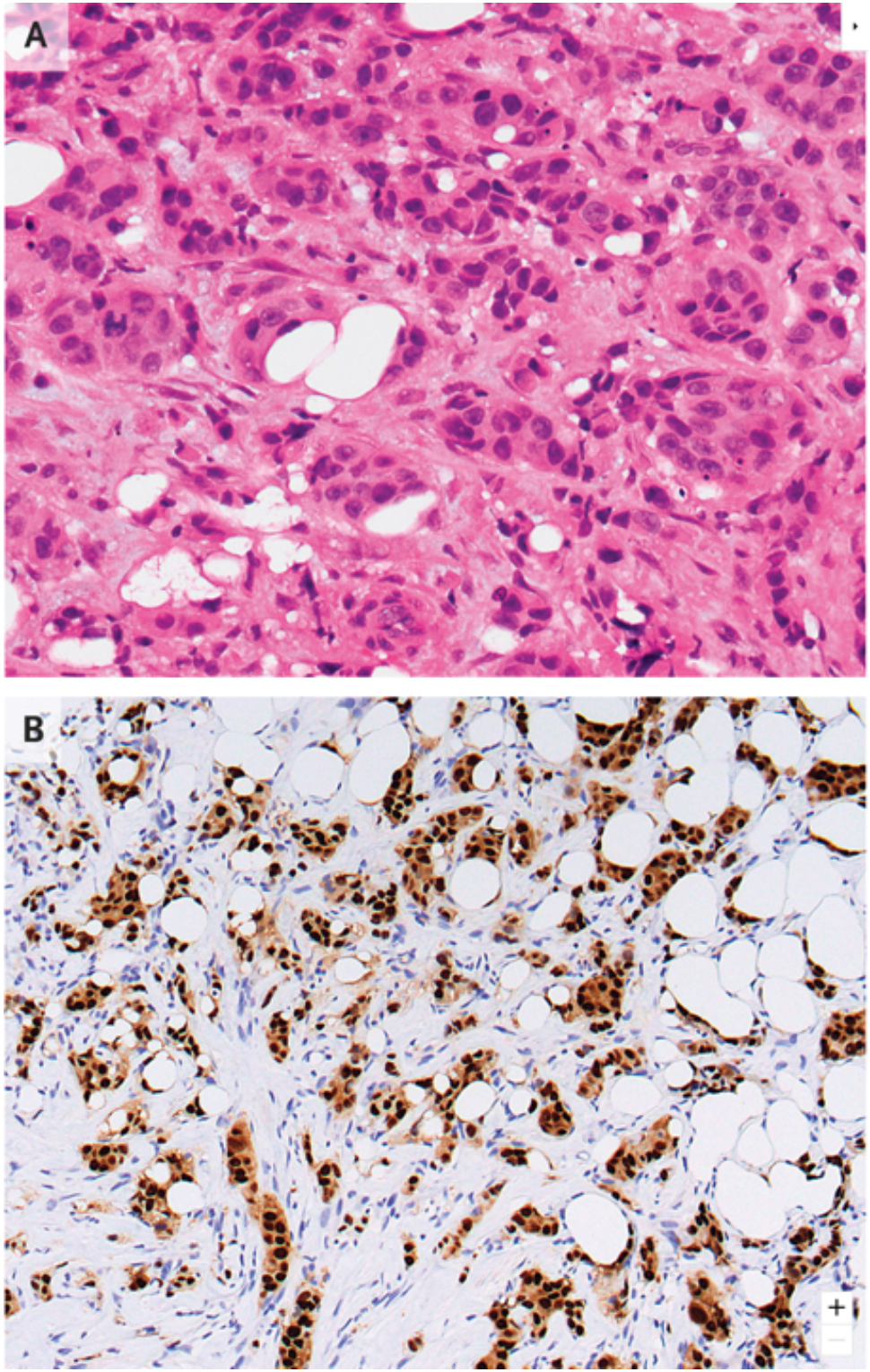
The patient, who was of Ashkenazi Jewish ancestry, had no known family history of breast or ovarian cancer. Medical history included asthma and a fibroadenoma in the left breast, for which she had undergone excisional biopsy 30 years earlier. Menarche had occurred at 12 years of age and menopause at 54 years of age; she had not received hormone-replacement therapy.

Physical examination revealed a mass, measuring 3 cm in greatest dimension, in the left breast. No other masses or axillary lymph nodes were palpable. The patient underwent imaging studies in accordance with the American College of Radiology guidelines. Both breasts were imaged, since the patient's last mammogram had been obtained 7 years earlier.



Bilateral mammograms obtained from the craniocaudal and mediolateral oblique views (Panels A and B, respectively) show a mass in the left breast underlying the skin marker (arrows). At higher magnification (Panel C), the mass appears irregular and spiculated (arrow). An ultrasound image (Panel D) shows a solid, irregular mass, measuring 3.1 cm by 1.5 cm by 1.2 cm. An image obtained during core-needle biopsy under ultrasonographic guidance (Panel E) shows the needle positioned within the mass.

Histologic evaluation of the biopsy specimen revealed invasive ductal carcinoma, grade 2, spanning at least 1.6 cm in greatest dimension. No definitive lymphovascular invasion or carcinoma in situ was identified. Immunohistochemical staining showed tumor cells that were strongly and diffusely positive for estrogen receptor (ER) and progesterone receptor (PR). Human epidermal growth factor receptor 2 (HER2) overexpression was equivocal on immunohistochemical staining. Subsequent fluorescence in situ hybridization for HER2 did not reveal amplification.



Hematoxylin and eosin staining of a tissue core (Panel A) shows invasive ductal carcinoma. Immunohistochemical staining (Panel B) shows invasive carcinoma cells that are strongly and diffusely positive for estrogen receptor and progesterone receptor.

Final Diagnosis

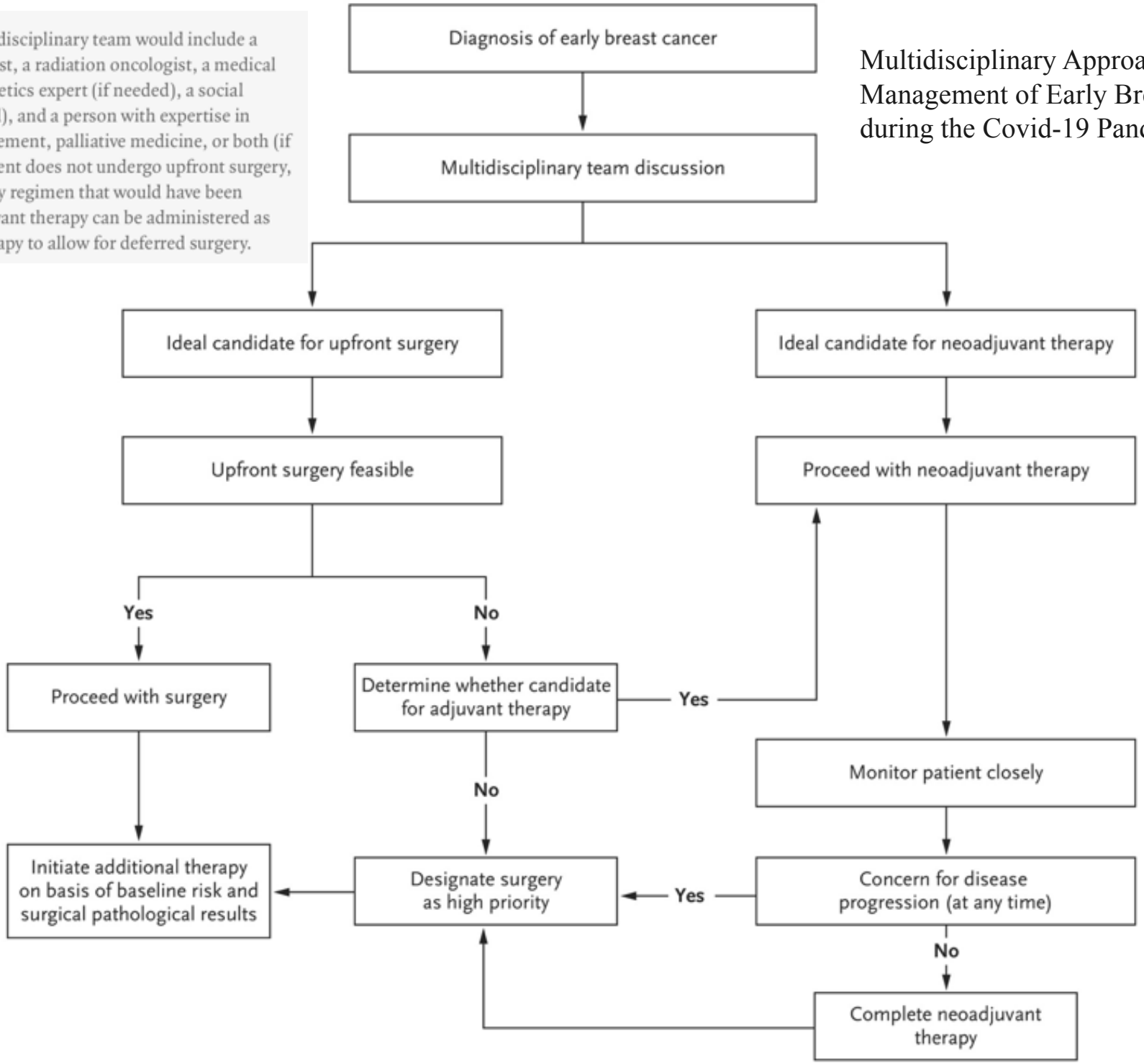
Invasive ductal carcinoma of the left breast, clinical prognostic stage IB (T2N0), estrogen receptor–positive, progesterone receptor–positive, human epidermal growth factor receptor 2–negative, grade 2, with an intermediate recurrence score on the 21-gene assay.

General Management of Select Early Breast Cancer Scenarios before and during the Covid-19 Pandemic.

Clinical Scenario	Typical Management, before Covid-19 Pandemic	Modified Management, during Covid-19 Pandemic†
Newly diagnosed postmenopausal early HR-positive, HER2-negative breast cancer	Stage I–II: Upfront surgery, followed by adjuvant endocrine therapy (with or without adjuvant chemotherapy, radiation therapy, or both). Stage III: Neoadjuvant therapy, followed by surgery, radiation therapy, and adjuvant therapy.	Stage I–II: Neoadjuvant therapy (endocrine therapy preferred), followed by surgery (with or without adjuvant chemotherapy, radiation therapy, or both). Stage III: Neoadjuvant therapy (endocrine therapy preferred), followed by surgery and radiation therapy (with or without adjuvant chemotherapy).
Newly diagnosed premenopausal early HR-positive, HER2-negative breast cancer	Stage I–II: Upfront surgery, followed by adjuvant endocrine therapy (with or without adjuvant chemotherapy, radiation therapy, or both). Stage III: Neoadjuvant chemotherapy, followed by surgery, radiation therapy, and adjuvant endocrine therapy with ovarian suppression.	Stage I: Neoadjuvant therapy (endocrine therapy preferred), followed by surgery (with or without adjuvant chemotherapy, radiation therapy, or both). Stage II–III: Neoadjuvant therapy (endocrine therapy preferred), followed by surgery, adjuvant chemotherapy, and radiation therapy.
Newly diagnosed localized HER2-amplified breast cancer	Stage I: Upfront surgery, followed by adjuvant HER2-targeted therapy (with or without radiation therapy). Stage II–III: Neoadjuvant HER2-targeted therapy, followed by surgery and adjuvant HER2-targeted therapy (with or without radiation therapy).	Stage I: Modified neoadjuvant HER2-targeted therapy, followed by surgery and adjuvant HER2-targeted therapy (with or without radiation therapy). Stage II–III: Neoadjuvant HER2-targeted therapy, followed by surgery and adjuvant HER2-targeted therapy (with or without radiation therapy).
Newly diagnosed localized triple-negative breast cancer	Stage I: Upfront surgery, followed by adjuvant chemotherapy (with or without radiation therapy). Stage II–III: Neoadjuvant chemotherapy, followed by surgery (with or without radiation therapy).	Stage I: Neoadjuvant chemotherapy, followed by surgery (with or without radiation therapy). Stage II–III: Neoadjuvant chemotherapy, followed by surgery (with or without radiation therapy).

Ideally, the multidisciplinary team would include a surgical oncologist, a radiation oncologist, a medical oncologist, a genetics expert (if needed), a social worker (if needed), and a person with expertise in symptom management, palliative medicine, or both (if needed). If a patient does not undergo upfront surgery, the chemotherapy regimen that would have been selected for adjuvant therapy can be administered as neoadjuvant therapy to allow for deferred surgery.

Multidisciplinary Approach for Management of Early Breast Cancer during the Covid-19 Pandemic.



APPROACHES TO RADIATION THERAPY

Dr. Jimenez: During the Covid-19 pandemic, a few treatment options can be considered regarding the administration of radiation therapy after surgery. First, the initiation of radiation therapy after breast-conserving surgery can be delayed in order to limit a patient's exposure to health care facilities. Several retrospective studies showed that, among patients who were not receiving chemotherapy, the efficacy of radiation therapy was not affected by delaying the start of radiation up to 20 weeks after breast-conserving surgery.

OPTIONS FOR NEOADJUVANT ENDOCRINE THERAPY IN LIEU OF SURGERY

Dr. Spring: In lieu of upfront surgery, an alternative treatment option for this patient would be preoperative (neoadjuvant) therapy. Neoadjuvant endocrine therapy has been shown to improve surgical outcomes by increasing rates of eligibility to undergo breast-conserving therapy and by increasing response rates.

PATIENTS WITH HER2-AMPLIFIED BREAST CANCER

A widely accepted evidence-based treatment approach used in patients with early HER2-positive breast cancer is surgery, followed by adjuvant therapy, for patients with clinical stage T1N0 disease and neoadjuvant systemic therapy, followed by surgery, for patients with clinical stage T2–4N0 or node-positive disease.

PATIENTS WITH TRIPLE-NEGATIVE BREAST CANCER

Dr. Steven J. Isakoff: Chemotherapy remains the cornerstone of systemic treatment for early ER-negative, PR-negative, HER2-negative (triple-negative) breast cancer. For this patient with clinical stage T2N0 cancer, the standard approach for triple-negative breast cancer before the Covid-19 pandemic would have involved neoadjuvant chemotherapy with deferred surgery, and this remains the preferred approach during the pandemic.

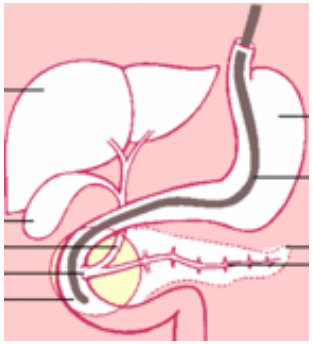
PATIENTS WHO HAVE COMPLETED NEOADJUVANT THERAPY AND NEED SURGERY

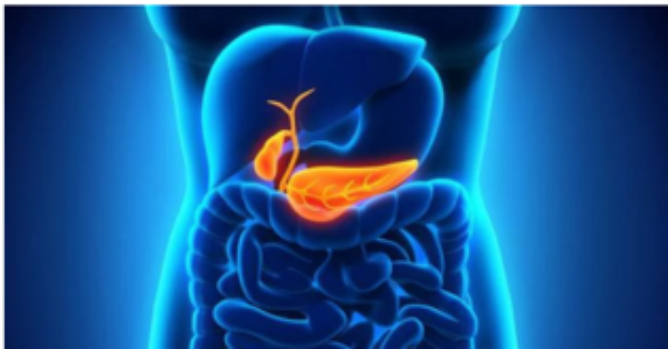
Dr. Isakoff: Patients completing neoadjuvant chemotherapy regimens during the Covid-19 pandemic who are unable to proceed to surgery because of limitations in hospital resources require special attention to ensure that long-term outcomes are not compromised.

FOLLOW-UP

Dr. Bardia: After discussing the care of this patient during a virtual multidisciplinary tumor board conference, we determined that upfront surgery was not an option because of Covid-19 restrictions; consequently, neoadjuvant endocrine therapy with an aromatase inhibitor was initiated. The patient is currently doing well and has a 2-month follow-up visit scheduled with the multidisciplinary team.

Mit einer **ERCP** (endoskopisch retrograde Cholangio-Pankreatikografie) werden die Gallengänge, die Gallenblase und die Gänge der Bauchspeicheldrüse mit Hilfe von Röntgenkontrastmittel und einem speziellen Endoskop dargestellt.
Die ERCP ist eine radiologische Untersuchung, bei der der Arzt die Hohlräume der Gallenwege, die Gallenblase (griech. cholé = Galle) und die Gänge der Bauchspeicheldrüse (griech. pán = alles, kréas = Fleisch) entgegen der normalen Flussrichtung (retrograd) bis zu ihrem Ursprung zurückverfolgen und beurteilen kann. Dafür werden die Hohlräume mit Hilfe eines Endoskops – ein schlauchförmiges, mit einer Lichtquelle und einem optischen System versehenes Instrument – von der Mündung des Gallengangs im Magen aus mit Röntgenkontrastmittel gefüllt und durchleuchtet. Außerdem sind im Rahmen der ERCP kleine Eingriffe möglich.
Die ERCP ist ein ambulanter Eingriff nach dem Sie in der Regel rasch wieder nach Hause gehen können. Vor der ERCP bespricht der Arzt mit Ihnen, ob Sie unter Gerinnungsstörungen leiden oder gerinnungshemmende Medikamente nehmen. Besteht eine Entzündung, wird vorher ein Antibiotikum gegeben.
Vor Beginn der Untersuchung werden dem Patienten Medikamente für eine Kurznarkose (Dämmerschlaf) über einen venösen Zugang zugeführt. Während der gesamten ERCP werden Blutdruck, Puls und Sauerstoffgehalt des Blutes kontrolliert. Der Arzt schiebt das Endoskop über Mund, Speiseröhre und Magen bis in den Zwölffingerdarm vor. Das Instrument ist mit einer Spül- und Absaugvorrichtung, einer Lichtquelle und einer kleinen Kamera ausgestattet. Außerdem können darüber zusätzliche Instrumente eingeführt werden. Sobald der Arzt die Endposition erreicht hat, füllt er die Gangsysteme mit Röntgenkontrastmittel. Anschließend wird die Körperregion geröntgt.
Auf dem Röntgenbild kann der Arzt Veränderungen feststellen. Bei Verdacht auf Tumore kann bei der ERCP eine Gewebeprobe (Biopsie) entnommen werden. Außerdem lassen sich Verengungen mit Hilfe von Röhrchen – sogenannten Stents – aufweiten. In manchen Fällen ist eine Spaltung der Papilla vateri, einer Schleimhautfalte im Zwölffingerdarm nötig (Papillotomie), wodurch der gemeinsame Ausgang der Gänge vergrößert wird. Auch Gallensteine lassen sich entfernen.





Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial

Summary

Background It remains unclear whether urgent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy improves the outcome of patients with gallstone pancreatitis without concomitant cholangitis. We did a randomised trial to compare urgent ERCP with sphincterotomy versus conservative treatment in patients with predicted severe acute gallstone pancreatitis.

Methods In this multicentre, parallel-group, assessor-masked, randomised controlled superiority trial, patients with predicted severe (Acute Physiology and Chronic Health Evaluation II score ≥8, Imrie score ≥3, or C-reactive protein concentration >150 mg/L) gallstone pancreatitis without cholangitis were assessed for eligibility in 26 hospitals in the Netherlands. Patients were randomly assigned (1:1) by a web-based randomisation module with randomly varying block sizes to urgent ERCP with sphincterotomy (within 24 h after hospital presentation) or conservative treatment. The primary endpoint was a composite of mortality or major complications (new-onset persistent organ failure, cholangitis, bacteraemia, pneumonia, pancreatic necrosis, or pancreatic insufficiency) within 6 months of randomisation. Analysis was by intention to treat. This trial is registered with the ISRCTN registry, ISRCTN97372133.

Findings Between Feb 28, 2013, and March 1, 2017, 232 patients were randomly assigned to urgent ERCP with sphincterotomy (n=118) or conservative treatment (n=114). One patient from each group was excluded from the final analysis because of cholangitis (urgent ERCP group) and chronic pancreatitis (conservative treatment group) at admission. The primary endpoint occurred in 45 (38%) of 117 patients in the urgent ERCP group and in 50 (44%) of 113 patients in the conservative treatment group (risk ratio [RR] 0·87, 95% CI 0·64–1·18; p=0·37). No relevant differences in the individual components of the primary endpoint were recorded between groups, apart from the occurrence of cholangitis (two [2%] of 117 in the urgent ERCP group *vs* 11 [10%] of 113 in the conservative treatment group; RR 0·18, 95% CI 0·04–0·78; p=0·010). Adverse events were reported in 87 (74%) of 118 patients in the urgent ERCP group versus 91 (80%) of 114 patients in the conservative treatment group.

Interpretation In patients with predicted severe gallstone pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment. Our findings support a conservative strategy in patients with predicted severe acute gallstone pancreatitis with an ERCP indicated only in patients with cholangitis or persistent cholestasis.

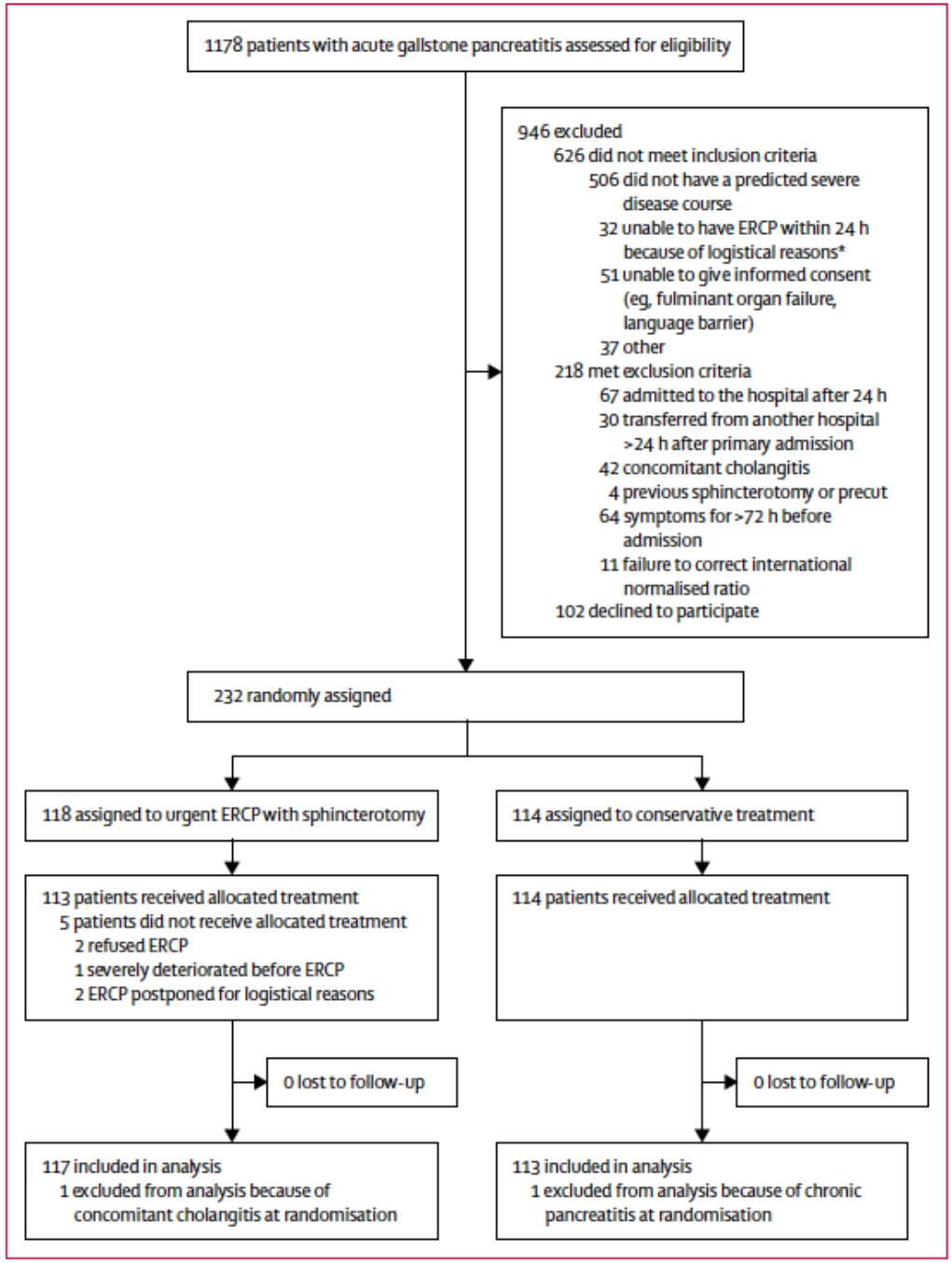


Figure: **Trial profile**
ERCP=endoscopic retrograde cholangiopancreatography. *Logistical reasons included insufficient staff capacity (nurses, endoscopists, or anaesthetists), full (emergency) endoscopy schedule, inability to arrange ERCP within the remaining hours of the first 24 h after presentation, and failure or maintenance of devices.

	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)
Sex		
Men	66 (56%)	60 (53%)
Women	51 (44%)	53 (47%)
Age (years)	69 (13)	71 (12)
Basis of gallstone aetiology		
Gallstones or sludge on imaging	88 (75%)	88 (78%)
Dilated common bile duct on imaging	24 (21%)	32 (28%)
More than twice the upper limit of normal ALT	103 (88%)	93 (82%)
More than twice the upper limit of normal ALT in the absence of meeting other gallstone criteria	24 (21%)	18 (16%)
Cholestasis	63 (54%)	67 (59%)
Bilirubin >2·3 mg/dL (>40 µmol/L)	50 (43%)	51 (45%)
Dilated common bile duct*	23 (20%)	31 (27%)
ASA class on admission		
Healthy status	21 (18%)	16 (14%)
Mild systemic disease	55 (47%)	57 (50%)
Severe systemic disease	40 (34%)	40 (35%)
Severe systemic disease with constant threat to life	1 (1%)	0
Body-mass index (kg/m²)	28 (6)	29 (6)
Disease severity		
APACHE-II score†	11 (9–15)	10 (8–13)
Imrie score‡	2 (1–3)	2 (1–3)
C-reactive protein (mg/L)	60 (13–166)	38 (11–104)
SIRS§	76 (65%)	61 (54%)
Organ failure¶	29 (25%)	25 (22%)
Time from onset of symptoms to presentation at emergency department (h)	10 (5–22)	9 (5–18)
Time from presentation at emergency department to randomisation (h)	15 (7–20)	15 (8–20)

Data are n (%), mean (SD), or median (IQR). ERCP=endoscopic retrograde cholangiopancreatography. ALT=alanine aminotransferase. ASA=American Society of Anesthesiologists. APACHE-II=Acute Physiology and Chronic Health Evaluation. SIRS=systemic inflammatory response syndrome. *A dilated common bile duct was defined as more than 8 mm in patients 75 years or younger, or more than 10 mm in patients older than 75 years on imaging. †APACHE-II score ranges from 0 to 71, with higher scores indicating more severe disease. ‡Imrie (or modified Glasgow) score ranges from 0 to 8, with higher scores indicating more severe disease. §SIRS was defined according to the consensus conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine. ¶Organ failure was defined as a modified Marshall score of two or more (on a scale of 0 to 12, with higher scores indicating more severe disease), as proposed in the revised Atlanta classification.[7]

Table 1: **Baseline characteristics**

	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)	Risk ratio (95% CI)	p value
Primary composite endpoint				
Mortality or major complication*	45 (38%)	50 (44%)	0·87 (0·64–1·18)	0·37
Secondary endpoints				
Mortality	8 (7%)	10 (9%)	0·77 (0·32–1·89)	0·57
Major complication				
New-onset organ failure†	22 (19%)	17 (15%)	1·25 (0·70–2·23)	0·45
Single organ failure	17 (15%)	18 (16%)	0·91 (0·50–1·68)	0·77
Persistent single organ failure	14 (12%)	9 (8%)	1·50 (0·68–3·33)	0·31
Multiple organ failure	13 (11%)	13 (12%)	0·97 (0·47–1·99)	0·93
Persistent multiple organ failure	10 (9%)	8 (7%)	1·21 (0·49–2·95)	0·68
Cholangitis	2 (2%)	11 (10%)	0·18 (0·04–0·78)	0·010
Bacteraemia	17 (15%)	25 (22%)	0·66 (0·38–1·15)	0·14
Pneumonia	9 (8%)	10 (9%)	0·87 (0·37–2·06)	0·75
Pancreatic parenchymal necrosis‡	17 (15%)	18 (16%)	0·91 (0·50–1·68)	0·77
Pancreatic endocrine or exocrine insufficiency§	9 (8%)	3 (3%)	2·90 (0·81–0·43)	0·086
Other outcomes				
CT severity index score‡¶	3 (2–5)	3 (2–5)	NA	0·64
Hospital stay (days)	13 (9–24)	14 (10–26)	NA	0·67
Intensive care admission	24 (21%)	13 (12%)	1·78 (0·96–3·33)	0·063
Intensive care stay (days)	6 (4–17)	8 (4–35)	NA	0·67
Readmission for gallstone-related complication	14 (12%)	24 (21%)	0·56 (0·31–1·03)	0·058
Recurrent gallstone pancreatitis	0	10 (9%)	NA	0·0010
Cholangitis	1 (1%)	3 (3%)	0·32 (0·03–3·05)	0·36
Cholecystitis	10 (9%)	7 (6%)	1·38 (0·54–3·50)	0·50
Gallstone colic	4 (3%)	7 (6%)	0·55 (0·17–1·83)	0·37
Choledocholithiasis	1 (1%)	7 (6%)	0·14 (0·02–1·10)	0·033

Data are n (%) or median (IQR), unless otherwise stated. Risk ratios are for urgent ERCP with sphincterotomy compared with conservative treatment. ERCP=endoscopic retrograde cholangiopancreatography. NA=not applicable. *The same patient may have had multiple events; this was considered as one endpoint. †New-onset organ failure was defined as organ failure that was not present at randomisation. Persistent organ failure was defined as organ failure that lasted more than 48 h. Multiple organ failure was defined as failure of two or more organs at the same time. ‡A contrast-enhanced CT scan was done 5–7 days after hospital admission for assessment of pancreatic necrosis. 11 (9%) of 117 patients in the urgent ERCP group and ten (9%) of 113 patients in the conservative treatment group did not have a CT scan. §Pancreatic insufficiency (endocrine and exocrine) was assessed 6 months after randomisation. ¶CT severity index scores range from 0 to 10, with higher scores indicating more extensive pancreatic parenchymal or extrapancreatic necrosis.

Table 2: **Primary and secondary endpoints**

	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)
Patients who had ERCP	112 (96%)	35 (31%)
Total number of ERCPs performed	128	44
ERCPs per patient	1 (1–1)	0 (0–1)
Time from onset of symptoms to first ERCP (h)	29 (22–44)	216 (99–832)
Time from presentation to first ERCP (h)	20 (12–23)	211 (75–815)
Time from randomisation to first ERCP (h)	3 (1–5)	187 (67–807)
Duration of first ERCP procedure (min)*	25 (15–40)	25 (17–50)
Indication for first ERCP		
Trial-related	112	0
Persistent cholestasis	0	21
Cholangitis according to treating physician	0	5
Cholangitis according to trial criteria	0	8
Endoprosthesis placement	0	1
Main bile duct stones or sludge†	48 (43%)	23 (66%)
Common bile duct cannulation†	91 (81%)	32 (91%)
Pancreatic duct cannulation (unintentional)†	40 (36%)	12 (34%)
Precut sphincterotomy†	24 (21%)	6 (17%)
Sphincterotomy†	91 (81%)	30 (86%)
Stone extraction†	54 (48%)	25 (71%)
Incomplete†	0	1 (3%)
ERCP-related complications †‡	3 (3%)	1 (3%)

Data are n (%) or median (IQR), unless otherwise stated. ERCP=endoscopic retrograde cholangiopancreatography. *Data on the duration of the ERCP procedure was missing in one patient in the urgent ERCP group and in 13 patients in the conservative treatment group. †Denominators are the number of patients who had ERCP (ie, 112 in the urgent ERCP group and 35 in the conservative treatment group). ‡ERCP-related complications included bleeding, perforation, respiratory insufficiency, and cardiovascular complications. Definitions are provided in the appendix p 8.

Table 3: **ERCP characteristics**

	Patients with cholestasis (n=130)				Patients without cholestasis (n=100)			
	Urgent ERCP with sphincterotomy (n=63)	Conservative treatment (n=67)	Risk ratio (95% CI)	p value	Urgent ERCP with sphincterotomy (n=54)	Conservative treatment (n=46)	Risk ratio (95% CI)	p value
Primary endpoint: mortality or major complication	20 (32%)	29 (43%)	0·73 (0·47–1·16)	0·18	25 (46%)	21 (46%)	1·01 (0·66–1·55)	0·95
Mortality	2 (3%)	7 (10%)	0·30 (0·07–1·41)	0·17	6 (11%)	3 (7%)	1·70 (0·45–6·44)	0·50
New-onset organ failure	9 (14%)	9 (13%)	1·06 (0·45–2·51)	0·89	13 (24%)	8 (17%)	1·38 (0·63–3·04)	0·41
Pancreatic parenchymal necrosis	7 (11%)	14 (21%)	0·53 (0·23–1·23)	0·13	10 (19%)	4 (9%)	2·13 (0·72–6·34)	0·16
Bacteraemia	8 (13%)	14 (21%)	0·61 (0·27–1·35)	0·21	9 (17%)	11 (24%)	0·70 (0·32–1·53)	0·37
Cholangitis	1 (2%)	6 (9%)	0·18 (0·02–1·43)	0·12	1 (2%)	5 (11%)	0·17 (0·02–1·41)	0·092
Pneumonia	4 (6%)	6 (9%)	0·71 (0·21–2·40)	0·75	5 (9%)	4 (9%)	1·07 (0·30–3·73)	1·00
Pancreatic endocrine or exocrine insufficiency	2 (3%)	1 (2%)	2·13 (0·20–22·88)	0·61	7 (13%)	2 (4%)	2·98 (0·65–13·65)	0·17

Data are n (%), unless otherwise stated. ERCP=endoscopic retrograde cholangiopancreatography.

Table 4: **Outcome according to cholestasis subgroup**

Research in context

Evidence before this study

Patients with gallstone pancreatitis frequently undergo endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy to remove obstructing gallstones with the intention to ameliorate the disease course. Before initiation of this trial, we searched PubMed, Embase, the Cochrane Library, and the NHS Economic Evaluation Database for studies published in English up to May 22, 2012, with the terms "ERCP" and "gallstone" and "pancreatitis". Six trials fulfilled the inclusion criteria. Findings from this systematic review suggested that ERCP did not reduce mortality but did reduce complications in patients with gallstone pancreatitis at high risk for developing complications. However, these trials had substantial shortcomings, such as heterogeneous patient populations, ERCPs performed late after hospital admission, no routine sphincterotomy, no separate assessment of patients with cholestasis, and use of various endpoint definitions. More importantly, the pooled sample size of patients with predicted severe gallstone pancreatitis without cholangitis was too small to detect differences in endpoints such as major complications or mortality between urgent ERCP and conservative treatment. As widely agreed, it therefore remains unclear whether ERCP truly improves outcome in these patients.

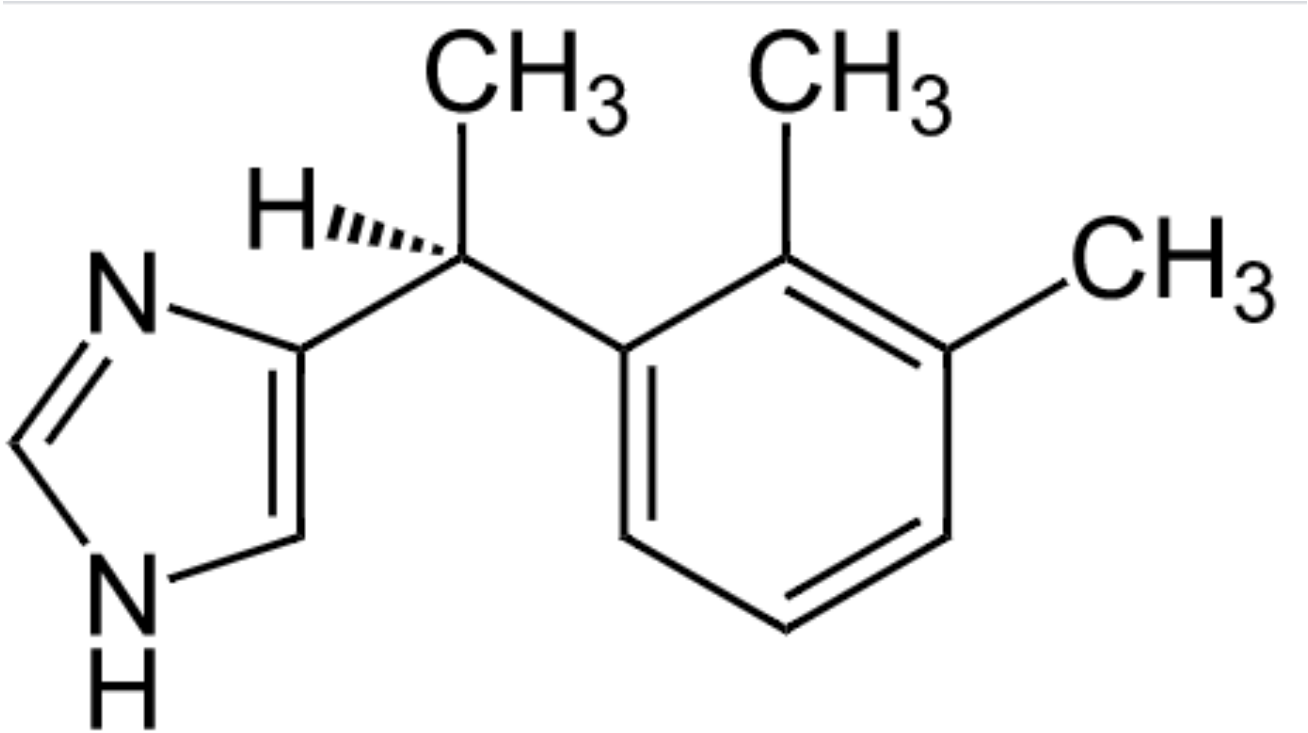
Added value of this study

This trial answers the question of whether urgent ERCP with biliary sphincterotomy should be done in patients with predicted severe acute gallstone pancreatitis, with or without cholestasis, but without cholangitis. Our findings suggest that urgent ERCP with biliary sphincterotomy did not reduce the composite endpoint of major complications or mortality compared with conservative treatment. Although cholangitis occurred more often in patients treated conservatively, this had no negative impact on overall outcome.

Implications of all the available evidence

Urgent ERCP with biliary sphincterotomy should not be done routinely in patients with predicted severe acute gallstone pancreatitis and is indicated only in patients with concomitant cholangitis. With this strategy, around two-thirds of patients are spared an invasive procedure from which they gain no benefit but could have procedure-associated complications.

Dexmedetomidin ist das wirksame Isomer (Eutomer) von Medetomidin, welches als Beruhigungsmittel eingesetzt wird. Dexmedetomidin aktiviert ähnlich wie Clonidin dosisabhängig α2-Adrenozeptoren und vermindert so die Freisetzung von Noradrenalin. Dies geschieht insbesondere im Locus caeruleus im Hirnstamm, der an der Steuerung von Aufmerksamkeit und Wachheit beteiligt ist. Angeblich führt dieser spezifische Wirkmechanismus zu einem schlafähnlichen Zustand, aus dem die Patienten auf Ansprache sofort wieder erwachen können und in der Lage sind, zu kommunizieren oder Anweisungen zu befolgen. Weiterhin werden auch α2-Adrenozeptoren des sympathischen Nervensystems aktiviert, was zu dessen Hemmung führt (Sympathikolyse). Neben seiner sedierenden Eigenschaft wirkt Dexmedetomidin vermutlich über eine veränderte Schmerzverarbeitung auch schmerzlindernd (analgetisch), angstlösend und muskelrelaxierend.
Als Nebenwirkung kommt es bei den üblichen geringen Dosen im Rahmen der Hemmung des sympathischen Nervensystems Sympathikolyse zu Herzfrequenzabnahme und Blutdrucksenkung. Bei hohen Konzentrationen, wie sie kurzzeitig beim schnellen intravenösen Spritzen entstehen können, überwiegt die periphere gefäßverengende Wirkung von Dexmedetomidin, so dass es zu einem Blutdruckanstieg kommt.



Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial

Summary

Background Atrial fibrillation and delirium are common consequences of cardiac surgery. Dexmedetomidine has unique properties as sedative agent and might reduce the risk of each complication. This study coprimarily aimed to establish whether dexmedetomidine reduces the incidence of new-onset atrial fibrillation and the incidence of delirium.

Methods A randomised, placebo-controlled trial was done at six academic hospitals in the USA. Patients who had had cardiac surgery with cardiopulmonary bypass were enrolled. Patients were randomly assigned 1:1, stratified by site, to dexmedetomidine or normal saline placebo. Randomisation was computer generated with random permuted block size 2 and 4, and allocation was concealed by a web-based system. Patients, caregivers, and evaluators were all masked to treatment. The study drug was prepared by the pharmacy or an otherwise uninvolved research associate so that investigators and clinicians were fully masked to allocation. Participants were given either dexmedetomidine infusion or saline placebo started before the surgical incision at a rate of 0·1 μg/kg per h then increased to 0·2 μg/kg per h at the end of bypass, and postoperatively increased to 0·4 μg/kg per h, which was maintained until 24 h. The coprimary outcomes were atrial fibrillation and delirium occurring between intensive care unit admission and the earlier of postoperative day 5 or hospital discharge. All analyses were intention-to-treat. The trial is registered with ClinicalTrials.gov, NCT02004613 and is closed.

Findings 798 patients of 3357 screened were enrolled from April 17, 2013, to Dec 6, 2018. The trial was stopped per protocol after the last designated interim analysis. Among 798 patients randomly assigned, 794 were analysed, with 400 assigned to dexmedetomidine and 398 assigned to placebo. The incidence of atrial fibrillation was 121 (30%) in 397 patients given dexmedetomidine and 134 (34%) in 395 patients given placebo, a difference that was not significant: relative risk 0·90 (97·8% CI 0·72, 1·15; p=0·34). The incidence of delirium was non-significantly increased from 12% in patients given placebo to 17% in those given dexmedetomidine: 1·48 (97·8% CI 0·99–2·23). Safety outcomes were clinically important bradycardia (requiring treatment) and hypotension, myocardial infarction, stroke, surgical site infection, pulmonary embolism, deep venous thrombosis, and death. 21 (5%) of 394 patients given dexmedetomidine and 8 (2%) of 396 patients given placebo, had a serious adverse event as determined by clinicians. 1 (<1%) of 391 patients given dexmedetomidine and 1 (<1%) of 387 patients given placebo died.

Interpretation Dexmedetomidine infusion, initiated at anaesthetic induction and continued for 24 h, did not decrease postoperative atrial arrhythmias or delirium in patients recovering from cardiac surgery. Dexmedetomidine should not be infused to reduce atrial fibrillation or delirium in patients having cardiac surgery.

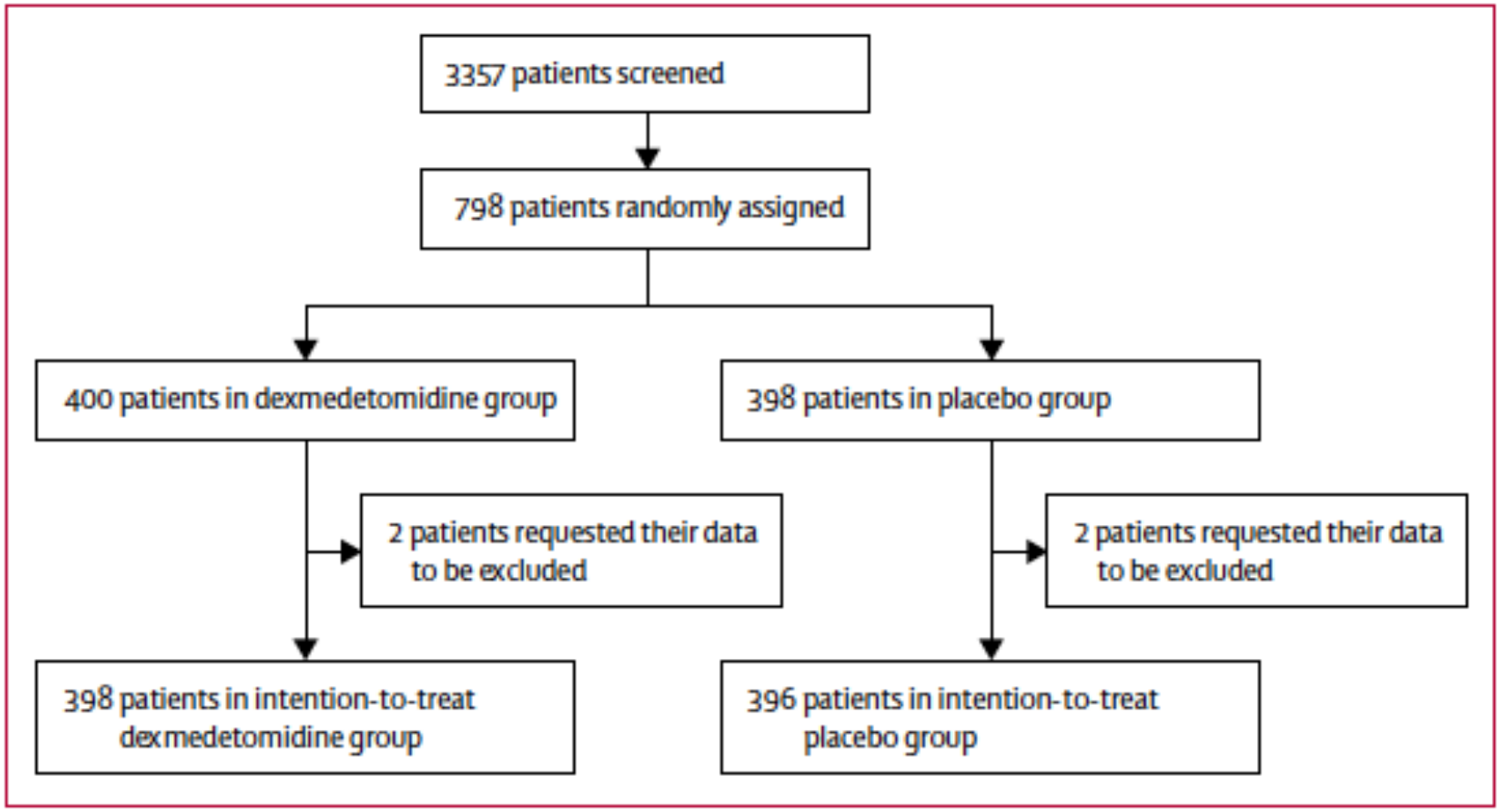


Figure 1: **Trial profile**

	Missing	Dexmedetomidine (n=398)	Missing	Placebo (n=396)
Demographics				
Age, years	2	63 (11)	2	62 (12)
Sex	2	..	2	..
Female	..	130 (33%)	..	107 (27%)
Male	..	266 (67%)	..	287 (73%)
White (versus not white)	3	365 (92%)	2	363 (92%)
American Society of Anesthesiologists	3	..	3	..
1–2	..	8 (2%)	..	5 (1)
3	..	105 (27%)	..	96 (24%)
4–5	..	282 (71%)	..	292 (74%)
Body-mass index, kg/m²	3	29 (15)	2	29 (8)
Short Form 12 Health Survey				
Physical health score	30	44 (38–53)	23	46 (38–53)
Mental health score	30	56 (48–60)	23	55 (48–60)
Modified Brief Pain Inventory				
Overall severity (any)	24	95 (24%)	20	89 (23%)
Pain interference	23	85 (21%)	20	83 (21%)
Pain Catastrophizing Scale				
Rumination	37	5 (4–8)	45	5 (4–8)
Magnification	37	3 (3–5)	45	3 (3–5)
Helplessness	38	7 (6–9)	45	6 (6–9)
Social history				
Current smoker	3	33 (8%)	3	34 (9%)
Uses illegal drugs	3	13 (3%)	3	7 (2%)

(Table 1 continues on next page)

	Missing	Dexmedetomidine (n=398)	Missing	Placebo (n=396)
(Continued from previous page)				
Medical history				
Pulmonary disease	3	46 (12%)	3	56 (14%)
Diabetes	3	91 (23%)	3	74 (19%)
Kidney disease	3	40 (10%)	3	35 (9%)
Stroke	3	21 (5%)	3	17 (4%)
Hypertension	3	264 (67%)	3	269 (68%)
Dyslipidaemia	3	246 (62%)	3	232 (59%)
Peptic ulcer disease	3	22 (6%)	3	26 (7%)
Previous gastrointestinal bleed	3	6 (2%)	3	5 (1%)
Peripheral artery disease	3	21 (5%)	3	15 (4%)
Chronic renal failure	3	18 (5%)	3	11 (3%)
Any coagulopathies	3	9 (2%)	3	10 (3%)
Chronic obstructive pulmonary disease	3	23 (6%)	3	13 (33%)
Neurological disease	3	25 (6%)	3	27 (7%)
Chronic pain condition	3	41 (10%)	3	34 (9%)
Cardiac disease history				
Angina	3	111 (28%)	3	87 (22%)
Congestive heart failure	3	30 (8%)	3	28 (7%)
Previous myocardial infarction	3	47 (12%)	3	39 (10%)
Stent placement	3	51 (13%)	3	42 (11%)
Previous cardiac surgery	3	40 (10%)	3	58 (15%)
Left ventricular ejection fraction	16	60% (55–65)	15	60% (56–65)
Medications				
Angiotensin-converting enzyme inhibitor	5	99 (25%)	3	119 (30%)
Angiotensin receptor blocker agent	5	71 (18%)	3	63 (16%)
β blocker	5	204 (52%)	3	186 (47%)
Calcium channel blocker	5	76 (19%)	3	66 (17%)
Diuretic	5	87 (22%)	3	97 (25%)
Antiarrhythmic	5	5 (1%)	3	7 (2%)
Digoxin	5	2 (1%)	3	1 (<1%)
Nitroglycerine	5	60 (15%)	3	52 (13%)
Statin	5	229 (58%)	3	208 (53%)
Insulin	5	40 (10%)	3	32 (8%)
Sulfonylurea	5	21 (5%)	3	17 (4%)
Non-statin lipid-lowering agent	5	25 (6%)	3	17 (4%)
Other oral hypoglycaemic	5	44 (11%)	3	45 (12%)
H2 antagonist	5	15 (4%)	3	16 (4%)
Proton pump inhibitor	5	89 (23%)	3	93 (24%)
Aspirin	5	226 (58%)	3	207 (53%)
Thienopyridine	5	16 (4%)	3	11 (3%)
Glycoprotein IIb-IIIa inhibitor	5	6 (2%)	3	3 (1%)
Ticagrelor	5	1 (<1%)	3	3 (1%)
Vitamin K antagonist	5	8 (2%)	3	10 (3%)
Thrombolytic therapy	5	4 (1%)	3	5 (1%)
Dabigatran	5	0	4	1 (<1%)
Unfractionated heparin	5	10 (3%)	3	4 (1%)
Low molecular weight heparin	5	4 (1%)	3	3 (1%)

(Table 1 continues on next page)

	Missing	Dexmedetomidine (n=398)	Missing	Placebo (n=396)
(Continued from previous page)				
Baseline laboratory tests				
Baseline creatinine, mg/L	9	1 (0·8–1·2)	7	1 (0·9–1·1)
Baseline blood urea nitrogen, mg/L	65	17 (14–22)	56	17 (14–21)
Surgical information				
Surgical type	5	–	7	–
Valve-aorta only	–	212 (54%)	–	230 (59%)
Coronary artery bypass grafting only	–	8 (2%)	–	3 (1%)
Coronary artery bypass grafting + valve or aorta	–	173 (44%)	–	156 (40%)
Preoperative inotropes or vasopressor infusion	5	39 (10%)	7	32 (8%)
Preoperative intra-aortic balloon pump or ventricular assist device	5	5 (1%)	7	5 (1%)
Anaesthesia maintained with	5	–	7	–
Propofol infusion	–	16 (4%)	–	17 (4%)
Volatile gas	–	377 (96%)	–	372 (96%)
Antifibrinolytic use	8	180 (46%)	10	177 (46%)
Cardiopulmonary bypass use	5	388 (99%)	7	387 (100%)
Site				
Main campus	–	219 (55%)	–	220 (56)
Fairview	–	48 (12%)	–	45 (11)
Hillcrest	–	44 (11%)	–	43 (11)
Maryland	–	1 (<1%)	–	1 (<1%)
Northwestern	–	37 (9%)	–	37 (9%)
Ohio State University	–	14 (4%)	–	14 (4%)
University of California Los Angeles	–	35 (9%)	–	36 (9%)

Data are mean (SD), median (IQR), or n (%).

Table 1: **Baseline characteristics**

	Dexmedetomidine (n=398)		Placebo (n=396)		Relative risk*†	p value†
	Missing	Incidence	Missing	Incidence		
Primary						
Atrial arrhythmia	1	121 (30%)	1	134 (34%)	0·91 (0·72–1·15)	0·34
Delirium	9	67 (17%)	9	46 (12%)	1·48 (0·99–2·23)	0·026
Secondary						
Kidney function‡						
Acute Kidney Injury Network classification	9	–	7	–	1·40 (0·84–2·34)	0·14
No risk	–	348 (89%)	–	359 (92%)	–	–
Stage 1	–	33 (8%)	–	29 (7%)	–	–
Stage 2	–	4 (1%)	–	0	–	–
Stage 3	–	4 (1%)	–	1 (<1%)	–	–
90-day pain						
Any pain (Modified Brief Pain Inventory)	109	79 (27%)	96	93 (31%)	0·87 (0·65–1·16)	0·29
Modified Brief Pain Inventory average pain§	–	2 (1–4)	–	1 (1–2)	–	–

Data are n (%) and median (Q1–Q3), as appropriate. *Relative risk (dexmedetomidine *vs* placebo) was estimated from a logistic regression model with a log link, adjusted for previous cardiac history; data are 97·8% CI for primary outcomes; 97·5% CI for secondary outcomes. There was no heterogeneity of the treatment effect across sites for all outcomes. The p values of interaction between treatment and site were 0·53 for atrial arrhythmia and 0·48 for delirium. †The overall α was maintained at 0·05. For the primary outcomes, the significant level is p<0·022 after adjusting for two outcomes (ie, 0·05/2, Bonferroni correction) and further for α spending in interim analyses. For secondary outcomes, the significance level is p<0·025 adjusted for two outcomes (ie, 0·05/2, Bonferroni correction). ‡The effect on kidney function is compared as the risk of risk or injury or failure. §Among patients who reported any 90-day pain.

Table 2: **Comparisons of dexmedetomidine versus placebo on primary outcomes**

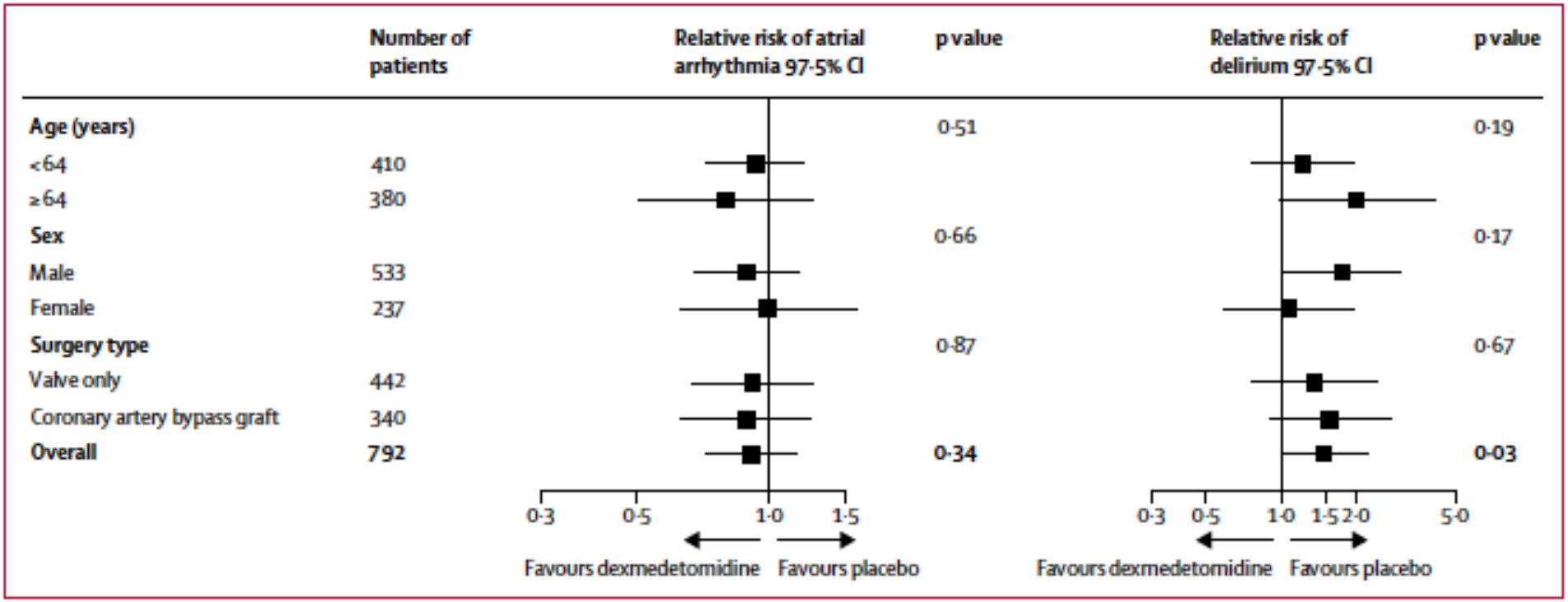


Figure 2: Forest plot of relative risk for subgroups of age, sex, and surgery type

	Dexmedetomidine (n=398)		Placebo (n=396)	
	Missing	Summary statistics	Missing	Summary statistics
Length of intensive care unit stay, h	5	51 (29–93)	7	47 (26–78)
Length of postoperative hospital stay, days	6	6 (5–8)	6	6 (5–7)
Kidney function outcomes				
Maximum blood urea nitrogen (mg/dL)	63	20 (15–26)	65	19 (15–25)
Maximum creatinine, mg/dL	3	1·02 (0·85–1·30)	3	1·03 (0·86–1·20)
90-day outcomes				
SF-12—physical health	117	51 (43–55)	104	50 (43–55)
SF-12—mental health	117	57 (49–60)	104	57 (51–60)
Neuropathic pain	109	85 (29%)	97	96 (32%)
Major complications				
Clinically important bradycardia	4	36 (9%)	6	45 (11%)
Clinically important hypotension	4	224 (57%)	6	140 (36%)
Postoperative myocardial infarction	4	3 (1%)	6	3 (1%)
Postoperative stroke	4	7 (2%)	6	4 (1%)
Surgical site infection	4	1 (<1%)	6	0
Documented pulmonary embolism or deep vein thrombosis	4	1 (<1%)	6	0
Serious adverse event	4	21 (5%)	6	8 (2%)
Death	7	1 (<1%)	9	1 (<1%)

Data are n (%), mean (SD), or median (IQR). SF-12=12-item short form health survey.

Table 3: **Descriptive summary of exploratory outcomes**

Research in context

Evidence before this study

Atrial fibrillation and delirium are among the most common complications after cardiac surgery. Cardiac surgery and cardiopulmonary bypass activate the sympathetic system, and the consequent systemic inflammation contributes to atrial fibrillation and delirium. Dexmedetomidine is a unique sedative that has sympatholytic and anti-inflammatory properties that can reduce atrial fibrillation and delirium. Before starting the trial, we searched the National Library of Medicine for randomized trials, systematic reviews, and meta-analyses, published in English, between Jan 1, 2000, and March 31, 2013, with the terms of "dexmedetomidine and delirium", and "dexmedetomidine and atrial fibrillation". We identified only a few small studies of dexmedetomidine for delirium in critical care patients, and two others in cardiac surgical patients. There were similarly only a few small studies for atrial fibrillation. The studies individually and combined did not provide a clear consensus on the effect of dexmedetomidine on delirium or atrial fibrillation.

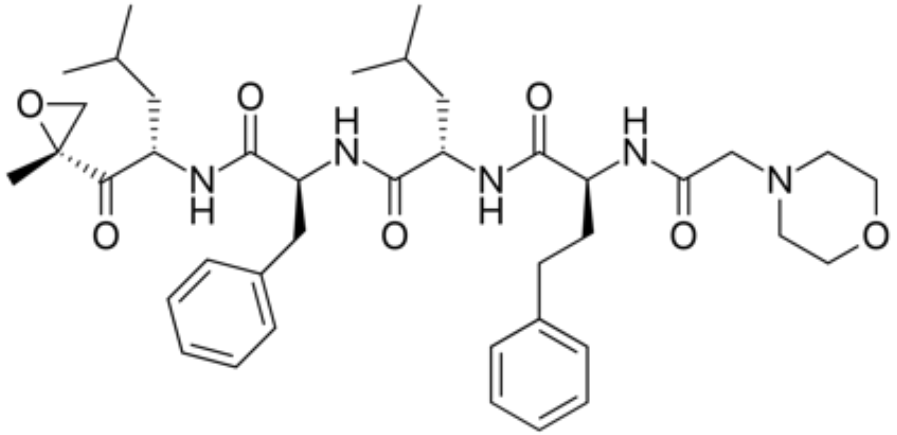
Added value of this study

We conducted a randomised and blinded trial in patients having cardiac surgery with cardiopulmonary bypass. Specifically, we tested the hypothesis that a continuous infusion of dexmedetomidine started at induction of anaesthesia and continuing for 24 h reduces atrial fibrillation and delirium in patients recovering from cardiac surgery.

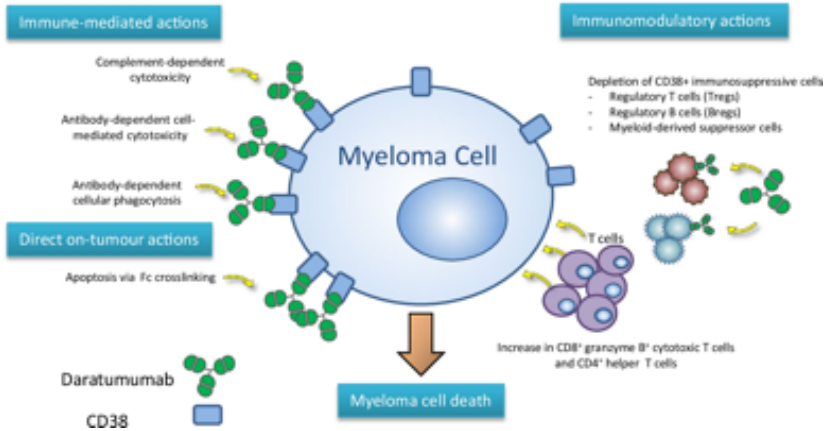
Implications of all the available evidence

Dexmedetomidine infusion did not decrease postoperative atrial fibrillation in patients recovering from cardiac surgery. Furthermore, dexmedetomidine non-significantly worsened delirium, possibly by provoking hypotension. Dexmedetomidine should be used cautiously in cardiac surgical patients because it provokes hypotension, and should not be given in the expectation that the drug will reduce atrial fibrillation or delirium.

Carfilzomib ist ein Krebsmedikament, das als selektiver Proteasom-Inhibitor wirkt. Chemisch ist es ein Tetrapeptid-Epoxyketon und ein Analogon von Epoxomicin.



Daratumumab ist ein humaner monoklonaler Antikörper und wird als Arzneistoff zur Behandlung maligner hämatologischer Erkrankungen eingesetzt. Die Produktion des rekombinanten Proteins erfolgt durch CHO-Zellen.



Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study

Summary

Background Lenalidomide and bortezomib frontline exposure has raised a growing need for novel treatments for patients with relapsed or refractory multiple myeloma. Carfilzomib in combination with daratumumab has shown substantial efficacy with tolerable safety in relapsed or refractory multiple myeloma in a phase 1 study. In this study, we aimed to compare the efficacy and safety of carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma.

Methods In this randomised, multicentre, open-label, phase 3 study, 466 patients recruited from 102 sites across North America, Europe, Australia, and Asia with relapsed or refractory multiple myeloma were randomly assigned 2:1 to carfilzomib, dexamethasone, and daratumumab (KdD) or carfilzomib and dexamethasone (Kd). All patients received twice per week carfilzomib at 56 mg/m² (20 mg/m²; days 1 and 2 during cycle 1). Daratumumab (8 mg/kg) was administered intravenously on days 1 and 2 of cycle 1 and at 16 mg/kg weekly for the remaining doses of the first two cycles, then every 2 weeks for four cycles (cycles 3–6), and every 4 weeks thereafter. Patients received 40 mg dexamethasone weekly (20 mg for patients ≥75 years old starting on the second week). The primary endpoint was progression-free survival assessed by intention to treat. Adverse events were assessed in the safety population. This trial (NCT03158688) is registered with ClinicalTrials.gov, and is active but not recruiting.

Findings Between June 13, 2017, and June 25, 2018, 466 patients of 569 assessed for eligibility were enrolled. After median follow-up of approximately 17 months, median progression-free survival was not reached in the KdD group versus 15·8 months in the Kd group (hazard ratio 0·63; 95% CI 0·46–0·85; p=0·0027). Median treatment duration was longer in the KdD versus the Kd group (70·1 *vs* 40·3 weeks). Grade 3 or higher adverse events were reported in 253 (82%) patients in the KdD group and 113 (74%) patients in the Kd group. The frequency of adverse events leading to treatment discontinuation was similar in both groups (KdD, 69 [22%]; Kd, 38 [25%]).

Interpretation KdD significantly prolonged progression-free survival versus Kd in patients with relapsed or refractory multiple myeloma and was associated with a favourable benefit–risk profile.

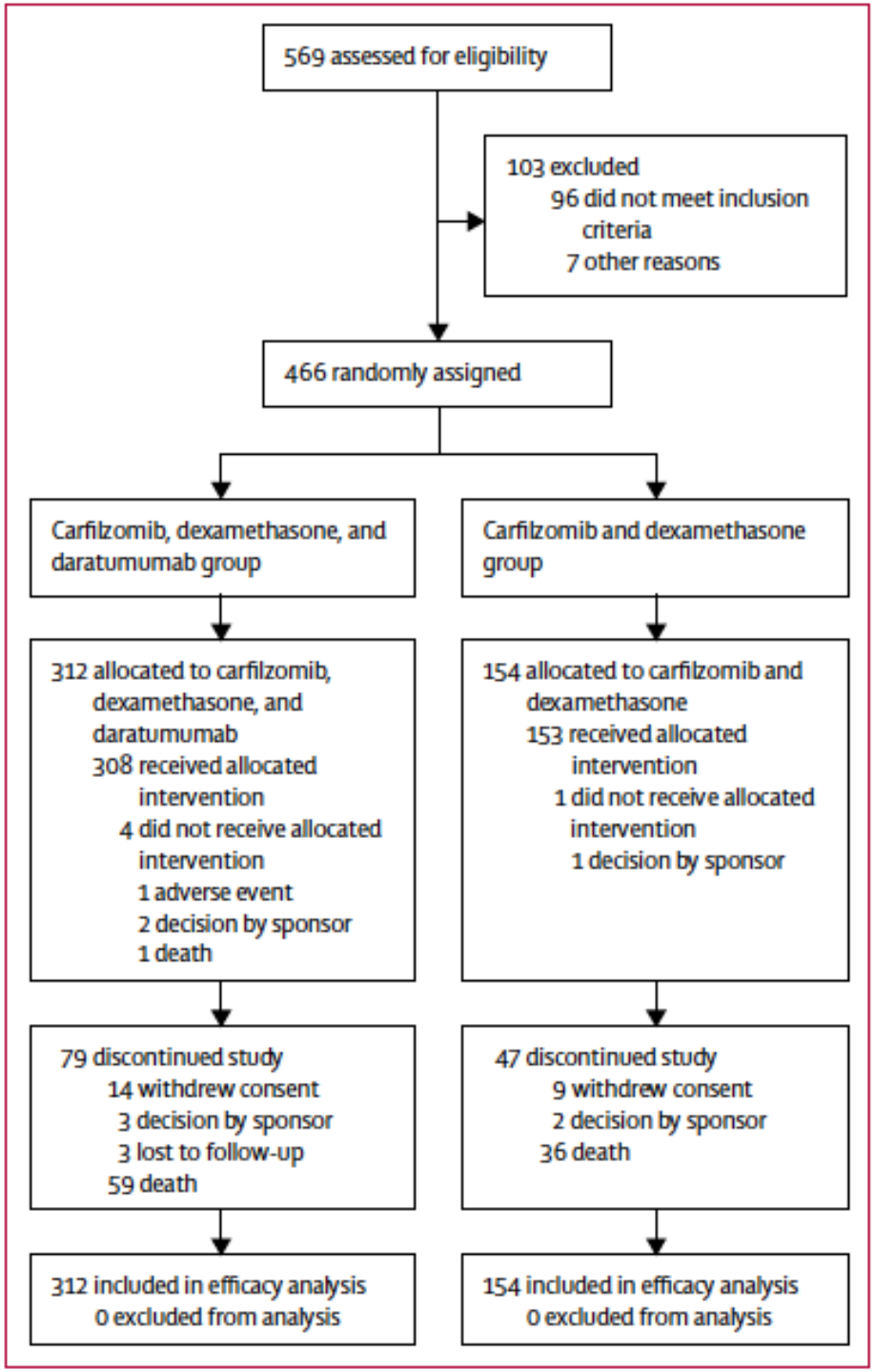


Figure 1: **Trial profile**

	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)
Age		
Median, years	64·0 (57–70)	64·5 (59–71)
Distribution		
18–64	163 (52%)	77 (50%)
65–74	121 (39%)	55 (36%)
≥75	28 (9%)	22 (14%)
Sex		
Female	135 (43%)	63 (41%)
Male	177 (57%)	91 (59%)
Geographical region		
Europe	207 (66%)	103 (67%)
Asia Pacific	84 (27%)	39 (25%)
North America	21 (7%)	12 (8%)
Eastern Cooperative Oncology Group performance status		
0 or 1	295 (95%)	147 (95%)
2	15 (5%)	7 (5%)
Missing	2 (<1%)	0
International Staging System disease stage at baseline		
I	147 (47%)	79 (51%)
II	103 (33%)	48 (31%)
III	61 (20%)	27 (18%)
Unknown	1 (<1%)	0
Cytogenetic risk group established by fluorescence in-situ hybridisation (%)*		
High risk	48 (15%)	26 (17%)
Standard risk	104 (33%)	52 (34%)
Unknown	160 (51%)	76 (49%)
Creatinine clearance		
Mean, mL/min	85·8 (32·5)	81·9 (32·7)
Distribution		
≥15 to <30 mL/min	5 (2%)	3 (2%)
≥30 to <50 mL/min	33 (11%)	24 (16%)
≥50 to <80 mL/min	97 (31%)	50 (32%)
≥80 mL/min	176 (56%)	77 (50%)
Missing	1 (<1)	0
Beta-2 microglobulin		
<3·5 mg/L	158 (51%)	83 (54%)
≥3·5 and <5·5 mg/L	92 (29%)	44 (29%)
≥5·5 mg/L	61 (20%)	27 (18%)
Unknown	1 (<1%)	0
Time since initial diagnosis to randomisation, months	37·5 (24·7–62·1)	34·6 (21·0–55·2)
Previous lines of therapy		
Median	2·0 (1–2)	2·0 (1–2)
Distribution		
One line of therapy	144 (46%)	70 (45%)
≥Two lines of therapy	168 (54%)	83 (54%)

(Table 1 continues on next page)

	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)
(Continued from previous page)		
Previous therapies		
Transplant	195 (63%)	75 (49%)
CD38 antibody therapy†	1 (<1%)	0
Proteasome inhibitor	290 (93%)	139 (90%)
Immunomodulatory drug	206 (66%)	110 (71%)
Bortezomib	287 (92%)	134 (87%)
Refractory to any previous bortezomib-including regimen‡	88 (28%)	47 (31%)
Lenalidomide	123 (39%)	74 (48%)
Refractory to any previous lenalidomide-including regimen‡	99 (32%)	55 (36%)

Data are median (IQR), n (%), or mean (SD). *Fluorescence in-situ hybridisation analysis was conducted by the central laboratory. The high-risk group consisted of patients with the genetic subtypes t(4;14), t(14;16), or deletion 17p. The standard-risk group consisted of patients without t(4; 14), t(14; 16), and deletion 17p. The unknown risk group consisted of patients with fluorescence in-situ hybridisation results that failed or were cancelled. †Based on the Interactive Voice and Web Response System at the time of randomisation. ‡Patients were considered refractory to a drug received in previous regimens if any of the following criteria were met: best response to any regimen containing the drug was stable disease or progressive disease; reason the drug was stopped was progression in any regimen; date of relapse or progression was after start date and within 60 days after stop date of the drug in any regimen.

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

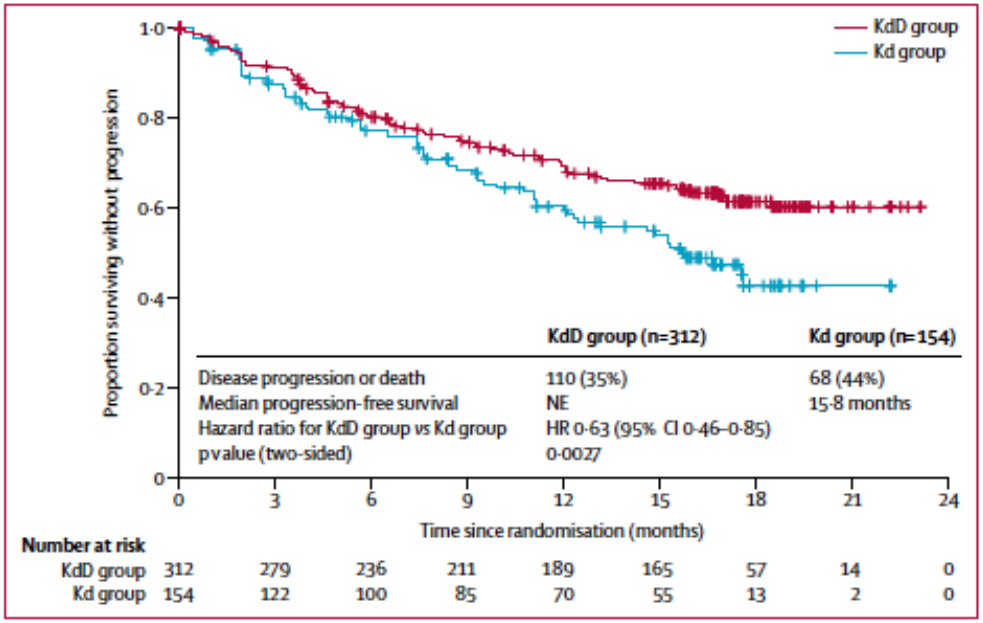


Figure 2: **Progression-free survival**
KdD=carfilzomib, dexamethasone, and daratumumab. Kd=carfilzomib and dexamethasone. NE=not estimable. HR=Hazard ratio.

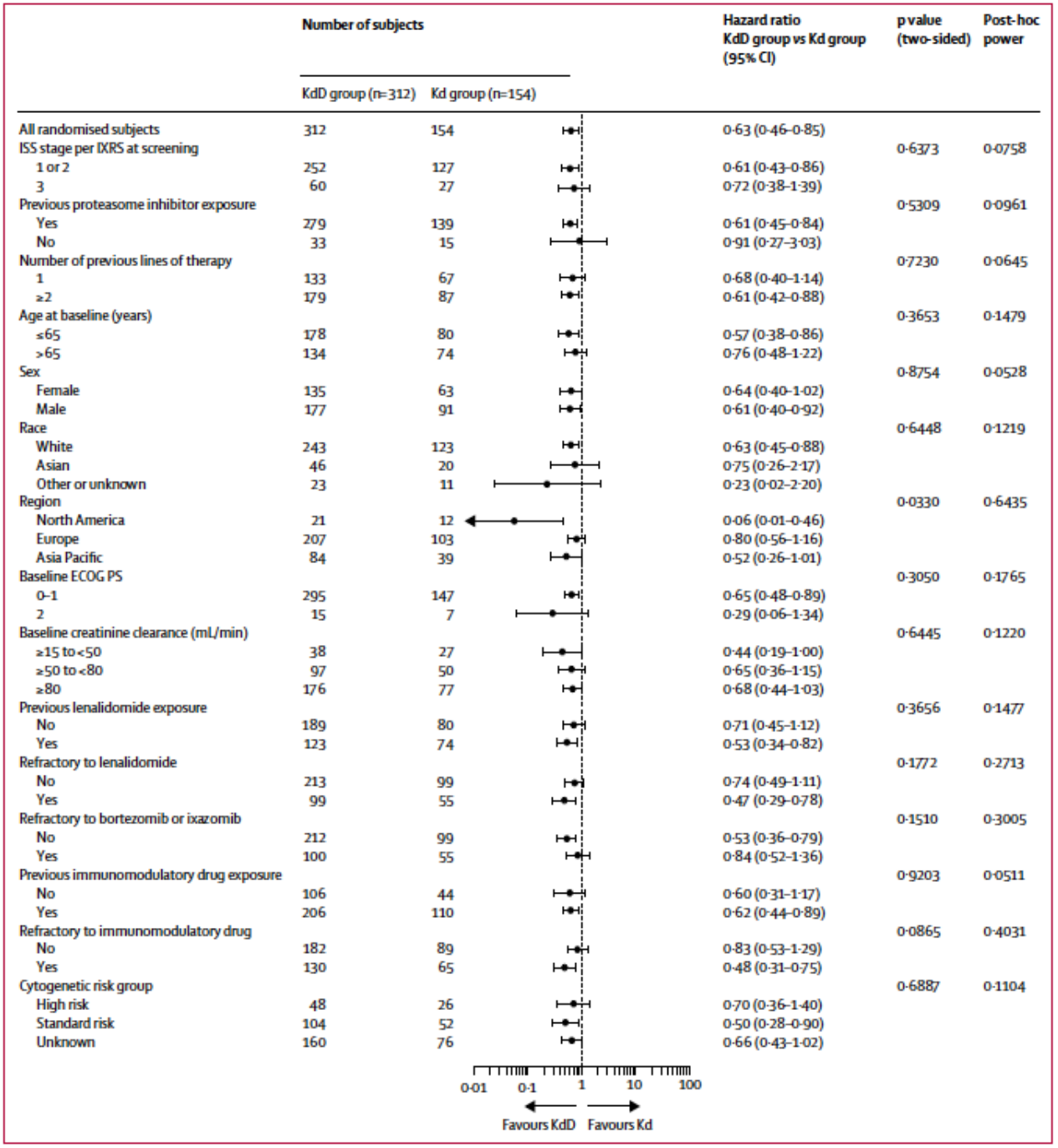


Figure 3: **Hazard ratios and 95% CIs for progression-free survival in subgroups (stratified)**

Hazard ratios were calculated based on stratified Cox proportional hazards model. p values and post-hoc powerwere calculated by means of Gail and Simon quantitative and qualitative interaction tests and a post-hoc power test based on stratified Cox proportional hazards model. KdD=carfilzomib, dexamethasone, and daratumumab. Kd=carfilzomib and dexamethasone. ISS=International Staging System. IXRS=interactive voice-web response system. ECOG PS=Eastern Cooperative Oncology Group performance status.

	KdD group (n=308)	Kd group (n=153)	Risk ratio
Grade 3 or higher	195·8 (173·1–221·5)	172·5 (143·4–207·4)	1·1 (0·9–1·4)
Serious	75·9 (65·4–88·1)	73·4 (58·0–92·7)	1·0 (0·8–1·4)
Fatal	9·1 (6·4–13·0)	6·2 (3·1–12·4)	1·5 (0·7–3·2)

Data are exposure-adjusted risk estimates per 100 patient-years (95% CI) or risk ratio (95% CI). KdD=carfilzomib, dexamethasone, and daratumumab. Kd=carfilzomib and dexamethasone. *The safety population included all patients who received at least one dose of trial treatment.

Table 4: **Exposure-adjusted treatment-emergent adverse events in the safety population***

	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)	Odds ratio (95% CI)	p value (two-sided)
Best response†				
Complete response	89 (29%)	16 (10%)	..	..
Minimum residual disease-negative complete response‡	43 (14%)	5 (3%)	..	..
Very good partial response or better	216 (69%)	75 (49%)	..	..
Stable or progressive disease	23 (7%)	22 (14%)	..	..
Minimum residual disease-negative rate, 12 months§	55 (18%; 13·6–22·3)	6 (4%; 1·4–8·3)	5·8 (2·4–14·0)	<0·0001
Minimum residual disease-negative complete response rate, 12 months¶	39 (13%; 9·0–16·7)	2 (1%; 0·2–4·6)	11·3 (2·7–47·5)	<0·0001
Overall response rate‖	263 (84%; 79·8–88·1)	115 (75%; 67·0–81·3)	1·9 (1·2–3·1)	0·0080
Time to overall response, months**				
Mean	1·4 (1·4)	1·5 (1·1)	..	..
Median	1·0 (0·99–1·09)	1·0 (0·99–1·94)	..	..
Time to complete response, months**				
Mean	8·7 (3·1)	7·5 (3·4)	..	..
Median (IQR)	8·4 (6·2–11·9)	7·0 (5·5–9·8)	..	..
Duration of overall response, months††				
Median	Not estimable	16·6	..	..
95% CI	Not estimable–not estimable	13·9–not estimable	..	..

Data are n (%), n (%; 95% CI), mean (SD), or median (IQR). *Best overall responses and duration of response were assessed by an independent review committee. †Best responses were established per International Myeloma Working Group Uniform Response Criteria. These criteria are listed in the protocol in the appendix (p 7). ‡Minimum residual disease-negative complete response was defined by achievement of a complete response and minimum residual disease-negativity by next-generation sequencing at any time during the study. §Minimum residual disease-negative rate at 12 months was defined as achievement of minimum residual disease-negative status as assessed by next-generation sequencing at the 12-month landmark (from 8 months to 13 months window). ¶Minimum residual disease-negative complete response at 12 months was defined by achievement of a complete response and minimum residual disease-negativity by next-generation sequencing at the 12-month landmark. ‖Overall response rate was defined as the proportion of patients with a partial response or better. **Time to overall response was defined as the time from randomisation to the earliest of stringent complete response, complete response, very good partial response, or partial response. ††Duration of overall response was calculated for patients who achieved a partial response or better.

Table 2: **Treatment responses in the intention-to-treat population***

	Carfilzomib, dexamethasone, and daratumumab group (n=308)					Carfilzomib and dexamethasone group (n=153)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological adverse events										
Thrombocytopenia	115 (37%)	40 (13%)	49 (16%)	26 (8%)	0	45 (29%)	20 (13%)	19 (12%)	6 (4%)	0
Anaemia	101 (33%)	50 (16%)	48 (16%)	3 (1%)	0	48 (31%)	26 (17%)	21 (14%)	1 (1%)	0
Neutropenia	43 (14%)	17 (6%)	24 (8%)	2 (1%)	0	15 (10%)	6 (4%)	7 (5%)	2 (1%)	0
Lymphopenia	27 (9%)	6 (2%)	9 (3%)	12 (4%)	0	12 (8%)	1 (1%)	9 (6%)	2 (1%)	0
Non-haematological adverse events										
Hypertension	94 (31%)	40 (13%)	54 (18%)	0	0	42 (27%)	22 (14%)	20 (13%)	0	0
Upper respiratory tract infection	90 (29%)	82 (27%)	7 (2%)	1 (<1%)	0	35 (23%)	33 (22%)	2 (1%)	0	0
Diarrhoea	97 (31%)	85 (28%)	12 (4%)	0	0	22 (14%)	21 (14%)	1 (1%)	0	0
Fatigue	75 (24%)	51 (17%)	23 (7%)	1 (<1%)	0	28 (18%)	21 (14%)	7 (5%)	0	0
Dyspnoea	61 (20%)	49 (16%)	12 (4%)	0	0	34 (22%)	30 (20%)	4 (3%)	0	0
Pneumonia	55 (18%)	14 (5%)	32 (10%)	5 (2%)	4 (1%)	19 (12%)	6 (4%)	12 (8%)	1 (1%)	0
Adverse events of interest										
Respiratory tract infections (HLGT)	225 (73%)	136 (44%)	77 (25%)	7 (2%)	5 (2%)	84 (55%)	60 (39%)	22 (14%)	1 (1%)	1 (1%)
Viral infection (JMQ)	63 (20%)	44 (14%)	19 (6%)	0	0	22 (14%)	19 (12%)	2 (1%)	0	1 (1%)
Peripheral neuropathy (SMQN)	53 (17%)	50 (16%)	3 (1%)	0	0	13 (8%)	13 (8%)	0	0	0
Daratumumab-related infusion reaction (AMQN)†	56 (18%)	49 (16%)	7 (2%)	0	0	0	0	0	0	0
Cardiac failure (SMQN)	23 (7%)	11 (4%)	9 (3%)	1 (<1%)	2 (1%)	16 (10%)	3 (2%)	10 (7%)	3 (2%)	0
Acute renal failure (SMQN)	18 (6%)	9 (3%)	5 (2%)	4 (1%)	0	12 (8%)	2 (1%)	6 (4%)	4 (3%)	0
Ischaemic heart disease (SMQN)	13 (4%)	4 (1%)	7 (2%)	2 (1%)	0	5 (3%)	1 (1%)	4 (3%)	0	0

Data are n (%). Haematological and non-haematological all-grade adverse events (preferred terms) occurring in ≥20% of patients and grade ≥3 adverse events (preferred terms) occurring in >5% of patients in either treatment group are shown; no percentage cutoff was applied to adverse events of interest. AMQN=Amgen MedDRA query—narrow. HLGT=high level group terms. JMQ=Janssen MedDRA query. MedDRA=Medical Dictionary of Regulatory Activities. SMQN=Standardised MedDRA query—narrow. *The safety population included all patients who received at least 1 dose of trial treatment. †Event on same date or next date of any daratumumab dosing.

Table 3: **Adverse events in the safety population***

Research in context

Evidence before this study

The increased use of lenalidomide and bortezomib has improved survival for newly diagnosed patients with multiple myeloma. Despite therapeutic advances, many patients either progress on or discontinue these agents owing to toxicity. There is a growing need for active and tolerable therapeutic options for managing relapsed or refractory multiple myeloma. We searched PubMed for clinical trial studies published between Sept 1, 2011, and Sept 1, 2019, using the search terms "multiple myeloma", "carfilzomib", "daratumumab", "relapsed", "refractory", "bortezomib", and "lenalidomide". In the phase 3 CASTOR study, the anti-CD38 monoclonal antibody daratumumab in combination with the first-in-class proteasome inhibitor bortezomib plus dexamethasone improved clinical outcomes compared with bortezomib and dexamethasone alone in patients with relapsed or refractory multiple myeloma. The randomised phase 3 ENDEAVOR study showed superiority of the second-generation irreversible proteasome inhibitor carfilzomib over bortezomib. The clinical benefit of combining carfilzomib with daratumumab was initially communicated in the publication of the non-randomised phase 1b study MMY1001, which showed tolerability and activity of the carfilzomib–dexamethasone–daratumumab triplet combination in patients with multiple myeloma who were nearly entirely pre-exposed to lenalidomide and 60% lenalidomide refractory. At a time when many patients are progressing on lenalidomide treatment, encouraging results from the MMY1001 study show that the carfilzomib–dexamethasone–daratumumab combination is a relevant and efficacious lenalidomide-free regimen and set a precedent for the randomised, multicentre phase 3 CANDOR study.

Added value of this study

CANDOR is the first randomised phase 3 study that compared the efficacy and safety of carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. In this study, patients treated with carfilzomib, dexamethasone, and daratumumab had significantly longer progression-free survival and achieved deeper responses, with a nearly 10-times higher minimal residual disease negative–complete response rate compared with patients treated with carfilzomib and dexamethasone alone. The observed benefit for the carfilzomib–dexamethasone–daratumumab combination was generally consistent across prespecified subgroups of clinical relevance, including patients exposed to lenalidomide or who are lenalidomide refractory.

Implications of all the available evidence

Overall, our results show a favourable benefit–risk profile for carfilzomib, dexamethasone, and daratumumab compared with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma with one to three previous lines of treatment. The triplet combination of carfilzomib, dexamethasone, and daratumumab should be considered as an efficacious and tolerable novel treatment option for relapsed or refractory multiple myeloma, including for patients exposed to lenalidomide or who are lenalidomide refractory.

Temporary circulatory support for cardiogenic shock

Alain Combes, Susanna Price, Arthur S Slutsky, Daniel Brodie

Cardiogenic shock can occur due to acute ischaemic or non-ischaemic cardiac events, or from progression of long-standing underlying heart disease. When addressing the cause of underlying disease, the management of cardiogenic shock consists of vasopressors and inotropes; however, these agents can increase myocardial oxygen consumption, impair tissue perfusion, and are frequently ineffective. An alternative approach is to temporarily augment cardiac output using mechanical devices. The use of these devices—known as temporary circulatory support systems—has increased substantially in recent years, despite being expensive, resource intensive, associated with major complications, and lacking high-quality evidence to support their use. This Review summarises the physiological basis underlying the use of temporary circulatory support for cardiogenic shock, reviews the evidence informing indications and contraindications, addresses ethical considerations, and highlights the need for further research.

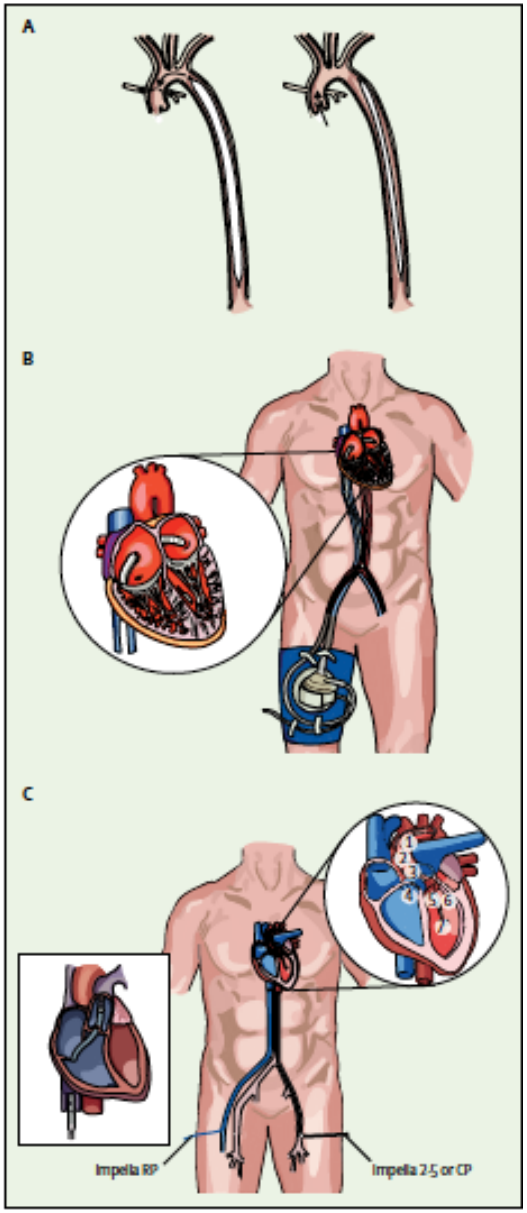


Figure 1: Temporary circulatory support systems

(A) An intra-aortic balloon pump. A balloon in the descending aorta is inflated with helium during diastole (counter pulsation), and actively deflated in systole. The inflated balloon helps direct blood flow to the coronary arteries during diastole (black arrows) and into the aorta during systole. (B) TandemHeart. (C) Impella. Impella CP, 2·5, and 5·0 are catheter-based, continuous axial flow pumps with propellers at the tips, which are positioned in a retrograde way across the aortic valve to support the left ventricle. Impella 2·5 and Impella CP are inserted percutaneously through the femoral artery. Top right: (1) catheter; (2) motor; (3) pump exit; (4) differential pressure sensor; (5) pump; (6) pump entry; and (7) pigtail. Bottom left: Impella RP designed to support the right ventricle, is inserted percutaneously through the inferior vena cava into the pulmonary artery.

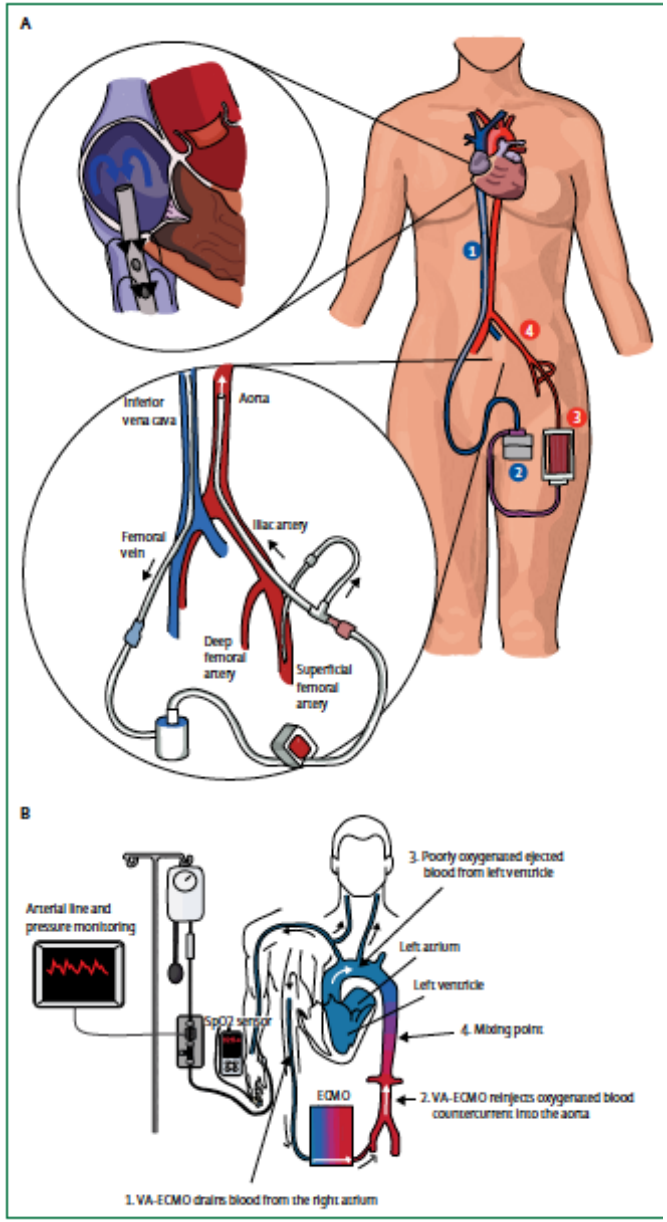


Figure 2: Peripheral VA-ECMO and VA-ECMO differential oxygenation

(A) Peripheral VA-ECMO; (1) venous drainage through a percutaneous cannula into right atrium; (2) venous blood is removed by the centrifugal pump and expelled under positive pressure; (3) blood is oxygenated by the membrane lung; and (4) percutaneous cannulation of the common femoral artery for blood return to the aorta and distal leg perfusion through the superficial femoral artery. (B) VA-ECMO differential oxygenation; (1) blood drained from the right atrium decreases right ventricular preload; (2) oxygenated blood reinjected countercurrent into the lower aorta which increases mean arterial pressure and left ventricular afterload; (3) in patients with impaired gas exchange, poorly oxygenated blood can be ejected by the native heart creating a mixing point where well oxygenated blood from the ECMO circuit is mixed with poorly oxygenated blood from the left ventricle (differential oxygenation); (4) the mixing point between the heart and ECMO flows is dynamic, depending on competitive flow between the ECMO blood flow, and blood flow from the left ventricle. Patients who receive peripheral femoro-femoral VA-ECMO need to have their arterial line and oxygen saturation probe on the right arm to detect this differential oxygenation. ECMO=extracorporeal membrane oxygenation. SpO_2=peripheral capillary oxygen saturation. VA-ECMO=venoarterial extracorporeal membrane oxygenation. Reproduced from Rao et al,* by permission of Wolters Kluwer Health.

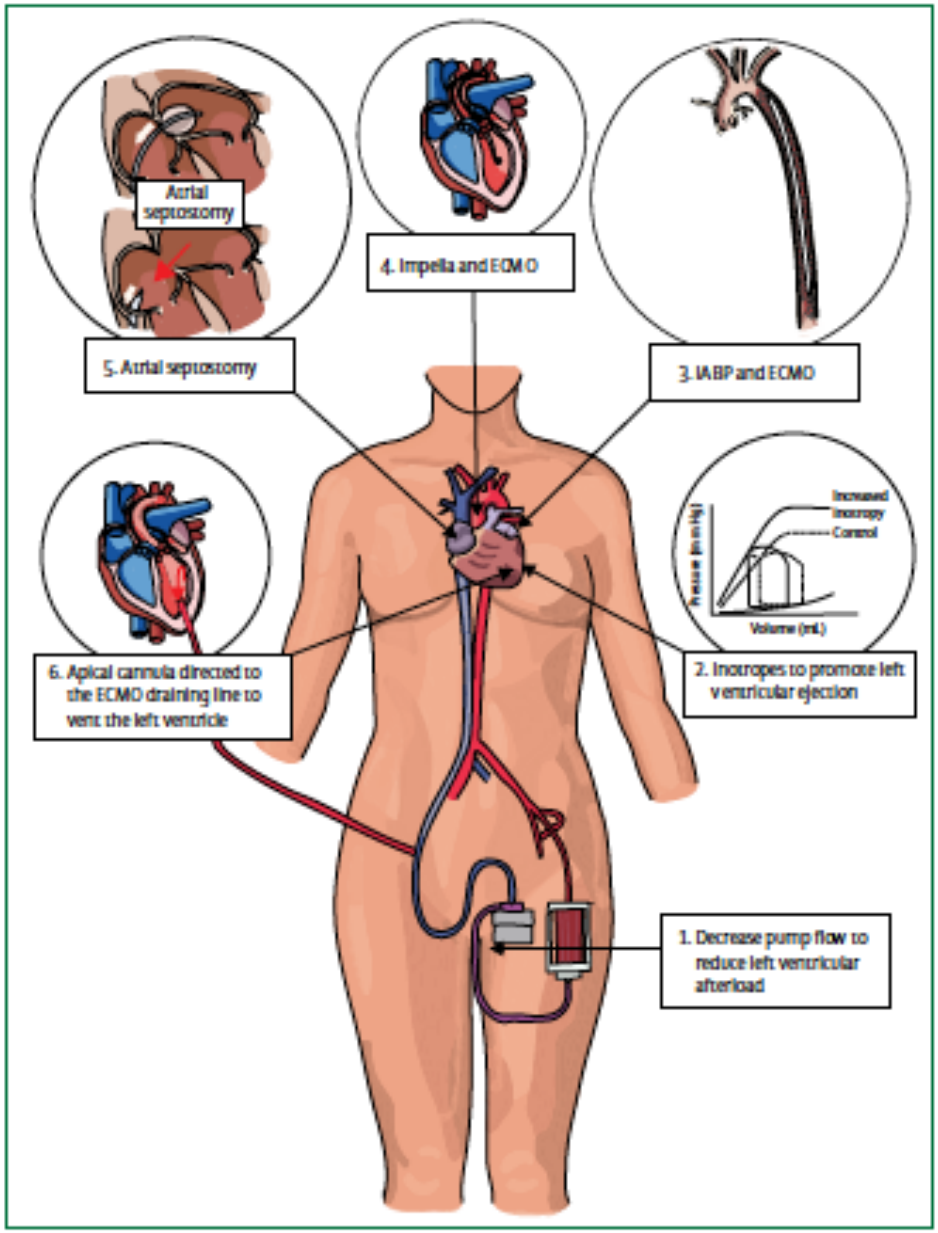


Figure 3: Strategies for left ventricular venting
Commonly used strategies to decrease left ventricular afterload and vent the left ventricle in patients receiving venoarterial extracorporeal membrane oxygenation. ECMO=extracorporeal membrane oxygenation. IABP=intra-aortic balloon pump. Reproduced from Rao et al[20] by permission of Wolters Kluwer Health.

Panel: Nomenclature and definitions

TCS: mechanical assist device used as a first-line strategy in the setting of acute cardiogenic shock; current TCS devices include the IABP, Impella, TandemHeart, and VA-ECMO systems

IABP: mechanical device that uses helium to inflate a balloon in the descending aorta during diastole (counter pulsation) and actively deflates the balloon during systole; an IABP increases coronary artery blood flow and reduces left ventricular afterload with a small increase in cardiac output

TandemHeart: percutaneous VAD consisting of an extracorporeal centrifugal continuous flow pump that drains blood from the left atrium via a cannula introduced through the femoral vein and extended trans-septally from the right atrium to the left atrium; blood is pumped back to the femoral artery at a flow rate of up to 4 L/min

Impella: catheter-based percutaneous VAD with a continuous axial flow pump with a propeller at the tip of the catheter, positioned in a retrograde way across the aortic valve to directly vent the left ventricle (Impella CP, 2.5, and 5.0), or inserted percutaneously through the inferior vena cava into the pulmonary artery to support the right ventricle (Impella RP)

Extracorporeal life support: overarching term for support with gas exchange, intended to support the failing heart or lungs, for short-term or medium-term use; encompasses VA-ECMO, VV-ECMO, and extracorporeal carbon dioxide removal

VA-ECMO: a form of extracorporeal life support where blood is withdrawn from the venous system and then infused into the arterial system to provide partial or complete circulatory or cardiac support; respiratory support by VA-ECMO can be adequate or suboptimal depending on the circumstances

Long-term VAD: an electromechanical device for assisting cardiac circulation, used to partly or completely replace the function of a failing heart; long-term VADs are used as a bridge to heart transplantation or as a destination therapy; most long-term VADs are mechanical pumps that only support the left ventricle (LVADs); in case of severe biventricular failure, a total artificial heart can be inserted

Shock team: a multidisciplinary team involving cardiologists, cardiothoracic surgeons, critical care physicians, specialised nurses, and other health-care professionals to provide comprehensive management of cardiogenic shock across the spectrum of care in tertiary high-volume cardiovascular centres capable of deploying a range of temporary and long-term cardiac assist devices

IABP=intra-aortic balloon pump. LVAD=left ventricular assist device. TCS=temporary circulatory support. VAD=ventricular assist device. VA-ECMO=venoarterial extracorporeal membrane oxygenation. VV-ECMO=venovenous extracorporeal membrane oxygenation.

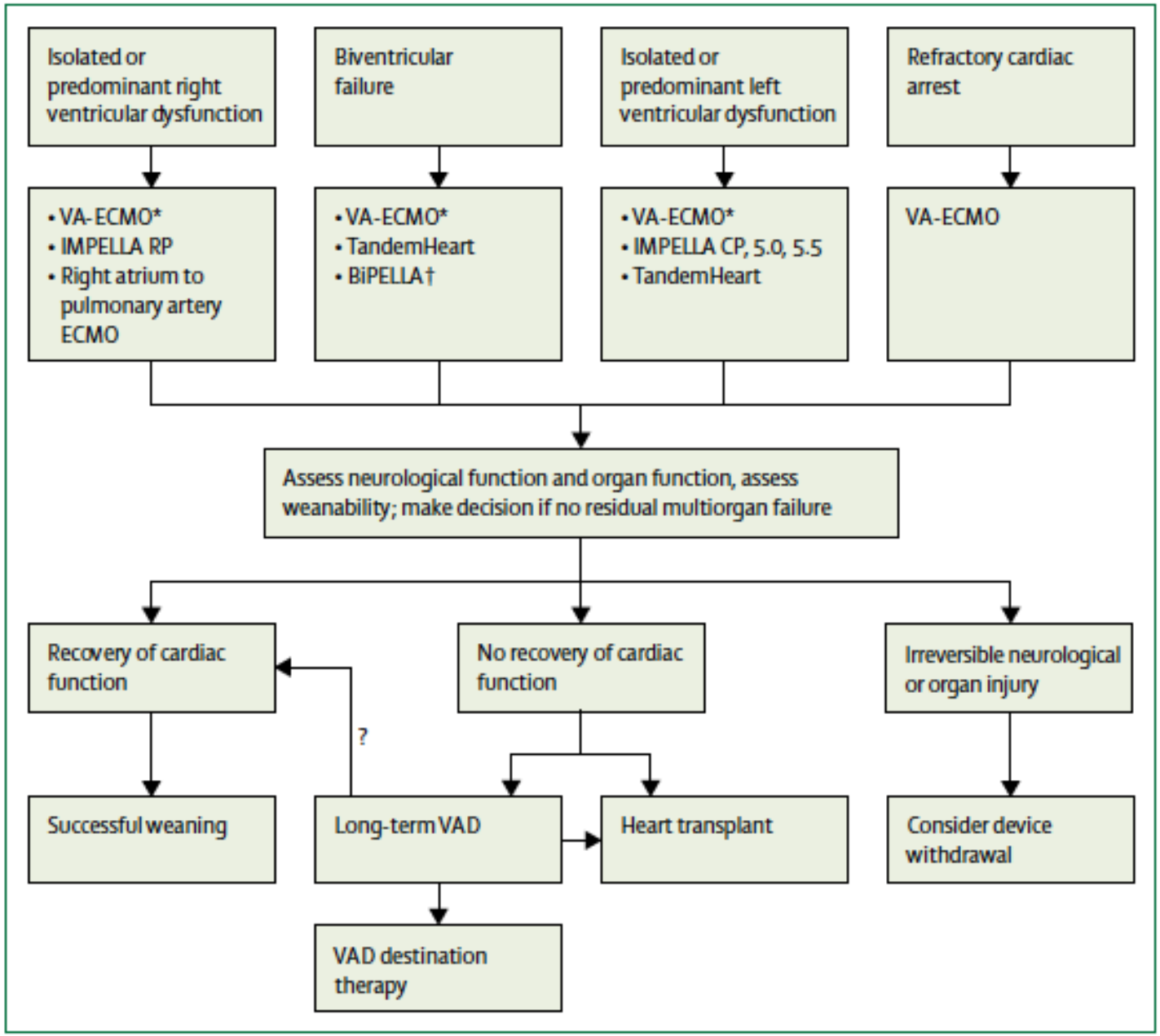


Figure 4: **Uses of TCS in patients with cardiogenic shock**

ECMO=extracorporeal membrane oxygenation. TCS=temporary circulatory support. VAD=ventricular assist device. VA-ECMO=venoarterial extracorporeal membrane oxygenation. *VA-ECMO is chosen for concomitant gas exchange failure. †BiPELLA combines left ventricular support with an Impella CP, 5.0, or 2.5, and right ventricular support with an Impella RP.

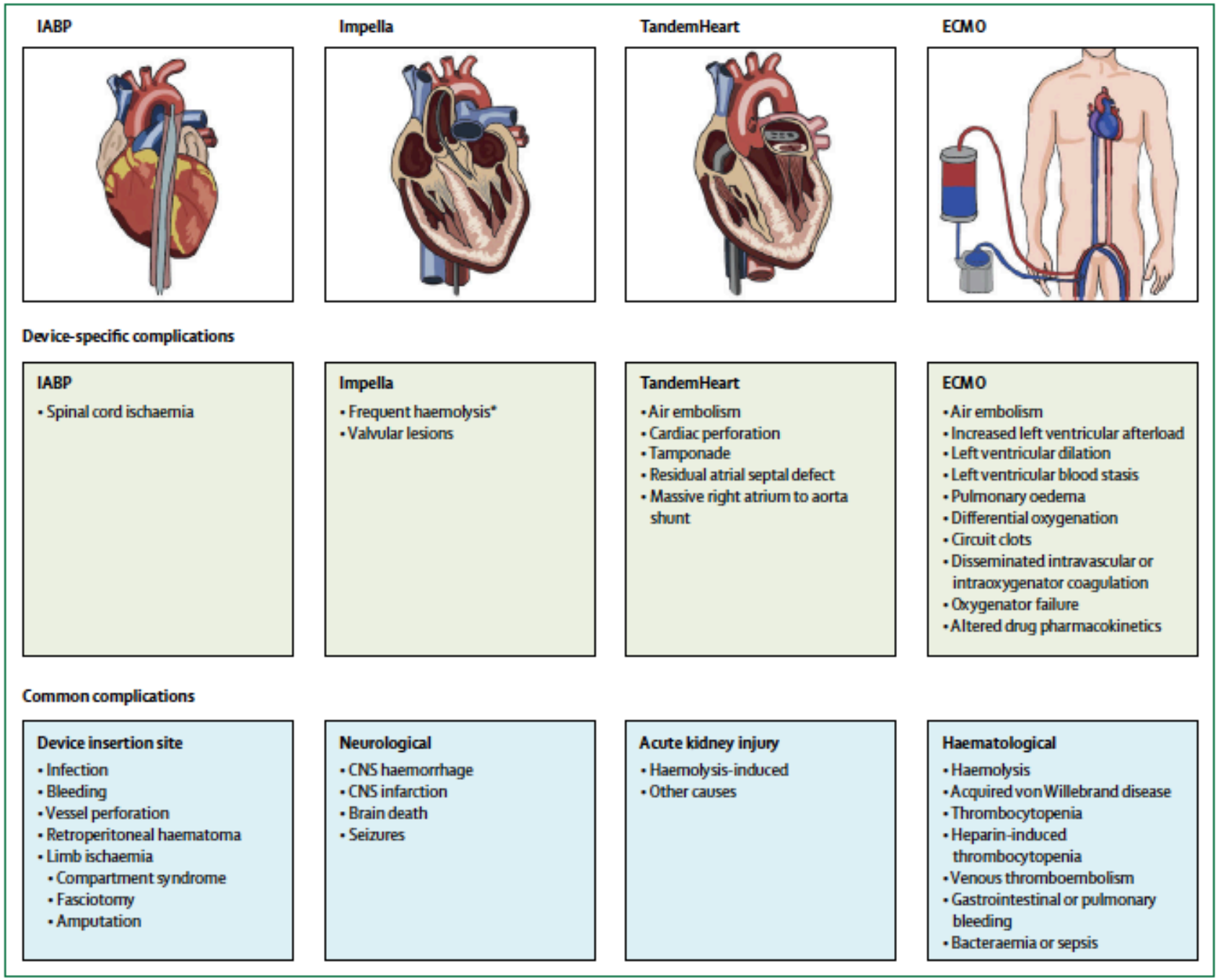


Figure 5: **Complications associated with TCS use**

ECMO=extracorporeal membrane oxygenation. IABP=intra-aortic balloon pump. TCS=temporary circulatory support. *Severe haemolysis might occur in the case of Impella pump malposition. Daily Doppler echocardiography is needed to ensure correct positioning of the pump.

Key messages

- The most common cause of cardiogenic shock is acute myocardial infarction, representing up to 70% of cases and occurring in 5–10% of patients with acute myocardial infarction.
- Temporary circulatory support systems can be used to temporarily augment cardiac output in patients with cardiogenic shock.
- The IABP does not increase cardiac output but might increase coronary artery blood flow and reduce left ventricular ventricle afterload. However, it was not associated with reduced 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction and its routine use is no longer recommended in these patients.
- The Impella 2.5, 5.0, 5.5, and Impella CP are continuous axial flow pumps, which are positioned in a retrograde way across the aortic valve and actively deliver blood to the aorta to decrease left ventricular size, pressure, and wall tension. However, registry data suggested that Impella use was associated with more adverse events and higher costs.
- In peripheral femoro-femoral VA-ECMO, blood is drained from the right atrium, pumped through a membrane oxygenator for oxygenation and decarboxylation, and returned retrograde up the aorta. VA-ECMO increases left ventricular afterload, and might result in increased left ventricular end-diastolic pressure, aortic and mitral regurgitation, a decrease in coronary artery blood flow, and pulmonary oedema. Directly removing blood from the left ventricle (known as venting) might be needed in some patients. Although the use of VA-ECMO is rapidly increasing, it has also been associated with greater morbidity that might compromise patient outcomes.
- Adequately powered randomised controlled trials are urgently needed to better define the roles of various temporary circulatory support devices in patients with cardiogenic shock.

IABP=intra-aortic balloon pump. VA-ECMO=venoarterial extracorporeal membrane oxygenation.

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

METHODS

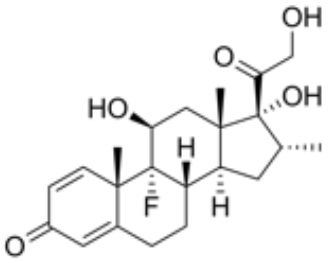
In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)



Drug	Equivalent
Hydrocortisone (Solu-Cortef®)	20
Cortisone	25
Prednisone (Deltasone®)	5
Methylprednisolone (Solu-Medrol®)	4
Dexamethasone (Decadron®)	0.75

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

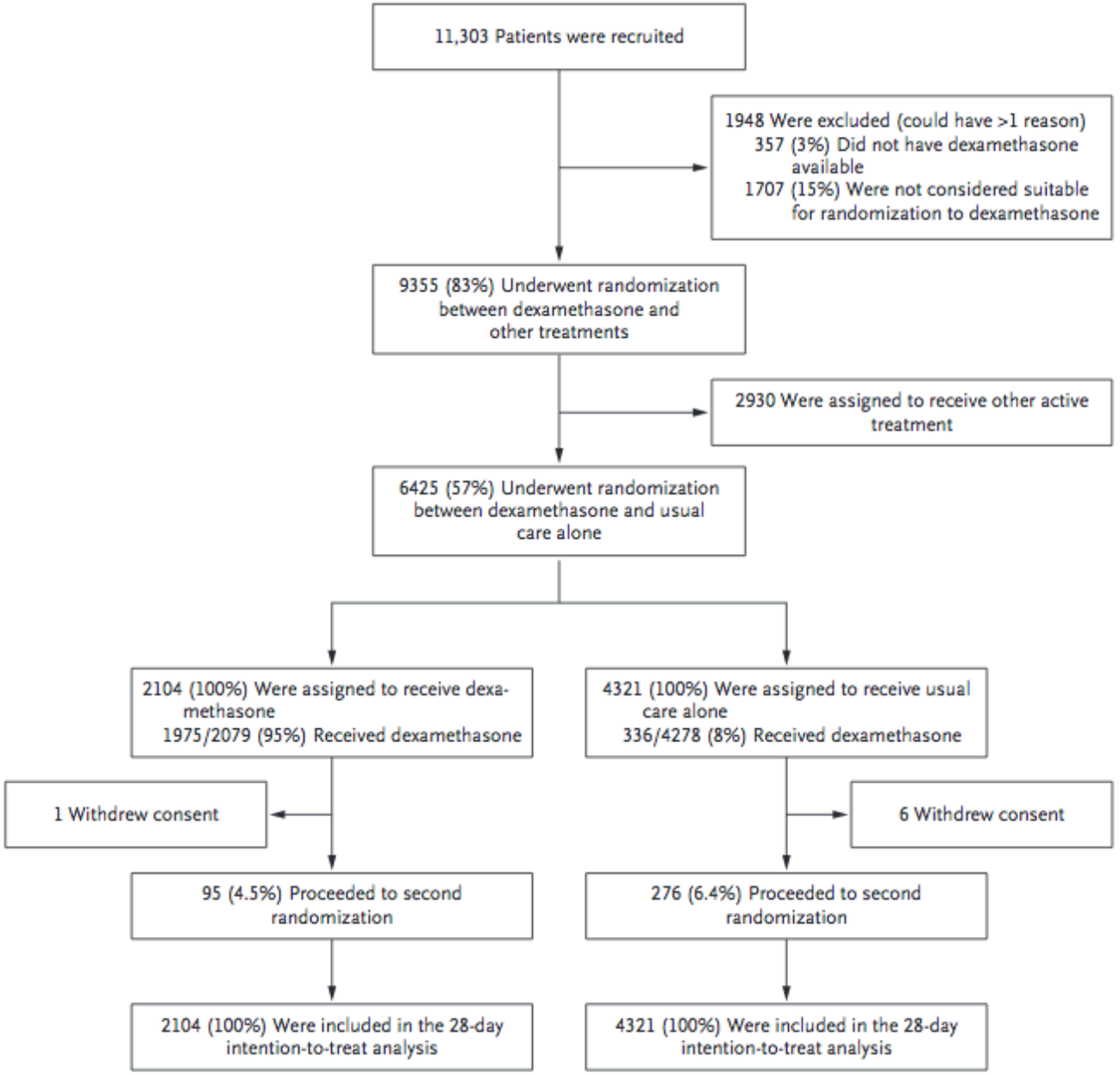


Figure 1. Enrollment, Randomization, and Inclusion in the Primary Analysis.

At the time of this analysis, completed follow-up forms were available for 2079 of 2104 patients (98.8%) in the dexamethasone group and 4278 of 4321 patients (99.0%) in the usual care group. The subgroup of patients who later underwent a second randomization to tocilizumab versus usual care in the RECOVERY trial included 95 of 2104 patients (4.5%) in the dexamethasone group and 276 of 4321 patients (6.4%) in the usual care group. In addition, 13 patients were randomly assigned to receive either convalescent plasma or usual care alone.

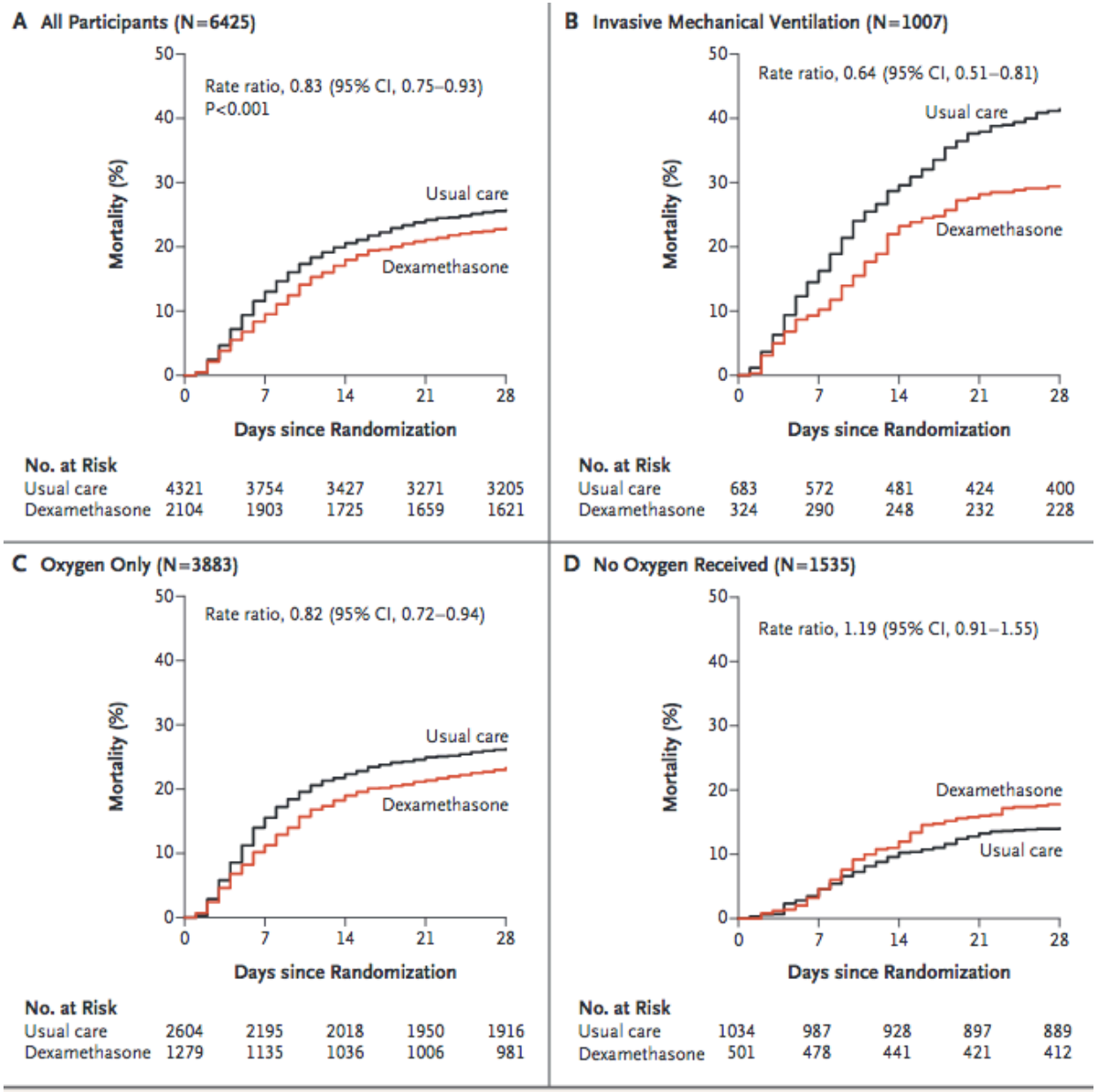


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

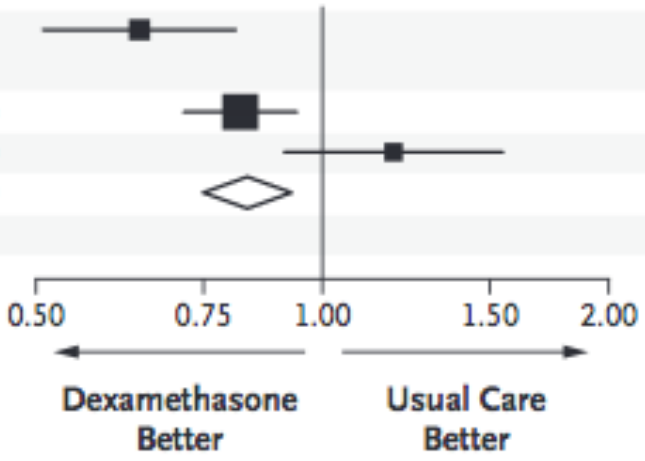
Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
		no./total no. of patients (%)	
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5



The RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with Covid-19 who are receiving respiratory support. We found no benefit (and the possibility of harm) among patients who did not require oxygen. Before the completion of the trial, many Covid-19 treatment guidelines stated that the use of glucocorticoids was either contraindicated or not recommended.[18] Dexamethasone is on the list of essential medicines of the World Health Organization and is readily available worldwide at low cost. Guidelines issued by the U.K. chief medical officers and by the National Institutes of Health in the United States have already been updated to recommend the use of glucocorticoids in patients hospitalized with Covid-19.[27,39]

Our preliminary results show that among hospitalized patients with Covid-19, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality than usual care in patients who were receiving invasive mechanical ventilation at randomization (by 12.3 age-adjusted percentage points, a proportional reduction of approximately one third) and those who were receiving oxygen without invasive mechanical ventilation (by 4.1 age-adjusted percentage points, a proportional reduction of approximately one fifth). However, there was no evidence that dexamethasone provided any benefit among patients who were not receiving respiratory support at randomization, and the results were consistent with possible harm in this subgroup. The benefit was also clear in patients who were being treated more than 7 days after symptom onset, when inflammatory lung damage is likely to have been more common. In a recent trial involving patients with acute respiratory distress syndrome who were undergoing mechanical ventilation, mortality at 60 days was 15 percentage points lower among those receiving dexamethasone than among those receiving usual care, a finding that was consistent with our results.[22]

Androgen-receptor-positive hepatocellular carcinoma in a transgender teenager taking exogenous testosterone

A 17-year-old transgender man attended our hospital with a 2-month history of intermittent right-sided abdominal pain, nausea, early satiety, profuse night sweats, and 14 kg weight loss.

For the past 14 months, he had been undergoing hormonal gender reassignment—female to male—with weekly intramuscular injections of 32 mg of testosterone cypionate.

On examination he showed secondary male sexual characteristics: he had a deep voice and he had facial hair and acne. He was thin with a body-mass index of 18·5 kg/m². On deep palpation he had increased mild tenderness of the right upper abdominal quadrant, compared to the left side.

MRI of the patient's abdomen showed a 17·5 cm× 7·2 cm×8·0 cm enhancing mass in the left hemiliver with numerous small surrounding satellite lesions and tumour thrombi in the main, right, and left portal veins (figure). Core needle biopsy of the liver mass showed hepatocellular carcinoma (HCC) with clear cell change (figure); androgen receptor (AR) nuclear staining was seen in 40% of the cells (figure). Liver tissue outside the tumour was normal—confirmed on staining with trichrome, reticulin, periodic acid-Schiff, and iron.

The patient's serum alpha-fetoprotein concentration was 4320 ng/mL (normal less than 8·3) with a non-reactive hepatitis serology panel—including hepatitis A virus IgM, HBsAg, HBcAg IgM, and hepatitis C virus antibody.

We treated him initially with yttrium-90 (^{90}Y)-loaded glass microspheres (TheraSphere, Boston Scientific, Marlborough, MA, USA) at a dose of 160 Gray (Gy), delivered by intra-arterial injection to the involved segments of his liver, 1·48 gigabecquerel (GBq) to segment 4 and 1·87 GBq to segments 2 and 3.

MRI of the patient's abdomen 2 months after the treatment showed new lesions in the right hemiliver (figure) and his alpha-fetoprotein concentration had increased to 10933 ng/mL. The patient stopped taking the exogenous testosterone after we discussed with him the possible effects it might be having upon the tumour. He was then started on intramuscular injections of leuprolide—a synthetic gonadotropin-releasing hormone—at a dose of 30 mg every 30 days to prevent the development of secondary female sexual characteristics.

He returned for a second treatment of ^{90}Y-loaded glass microspheres to the right hemiliver at a dose of 151 Gy: 4·42 GBq to segments 5–8. He was found to have partial radiographic response in both the right and left hemiliver lesions and subsequently received additional ^{90}Y-loaded glass microsphere treatment. The patient continues to be monitored for progression of the disease. Future treatment—if necessary—may include systemic targeted therapy or immunotherapy in a clinical trial.

HCC is mostly found in men and studies have linked the AR to development of the disease. AR expression and its role in HCC remains unclear. AR is overexpressed in the nuclei of approximately 74% of HCCs in men and 38% in women; it is associated with advanced disease and poor survival. Preclinical work suggests AR may play a role in the early development of HCC, but knocking out AR signalling in the later stages of the disease does not attenuate tumour growth. AR staining is not routinely obtained in patients with HCC and antiandrogen therapy is not indicated.

The relationship between exogenous testosterone and development and progression of HCC in peripubertal transgender patients is unknown. Further, it is unknown whether continuation of testosterone in patients positive for AR nuclear staining affects the outcome of the disease (video).

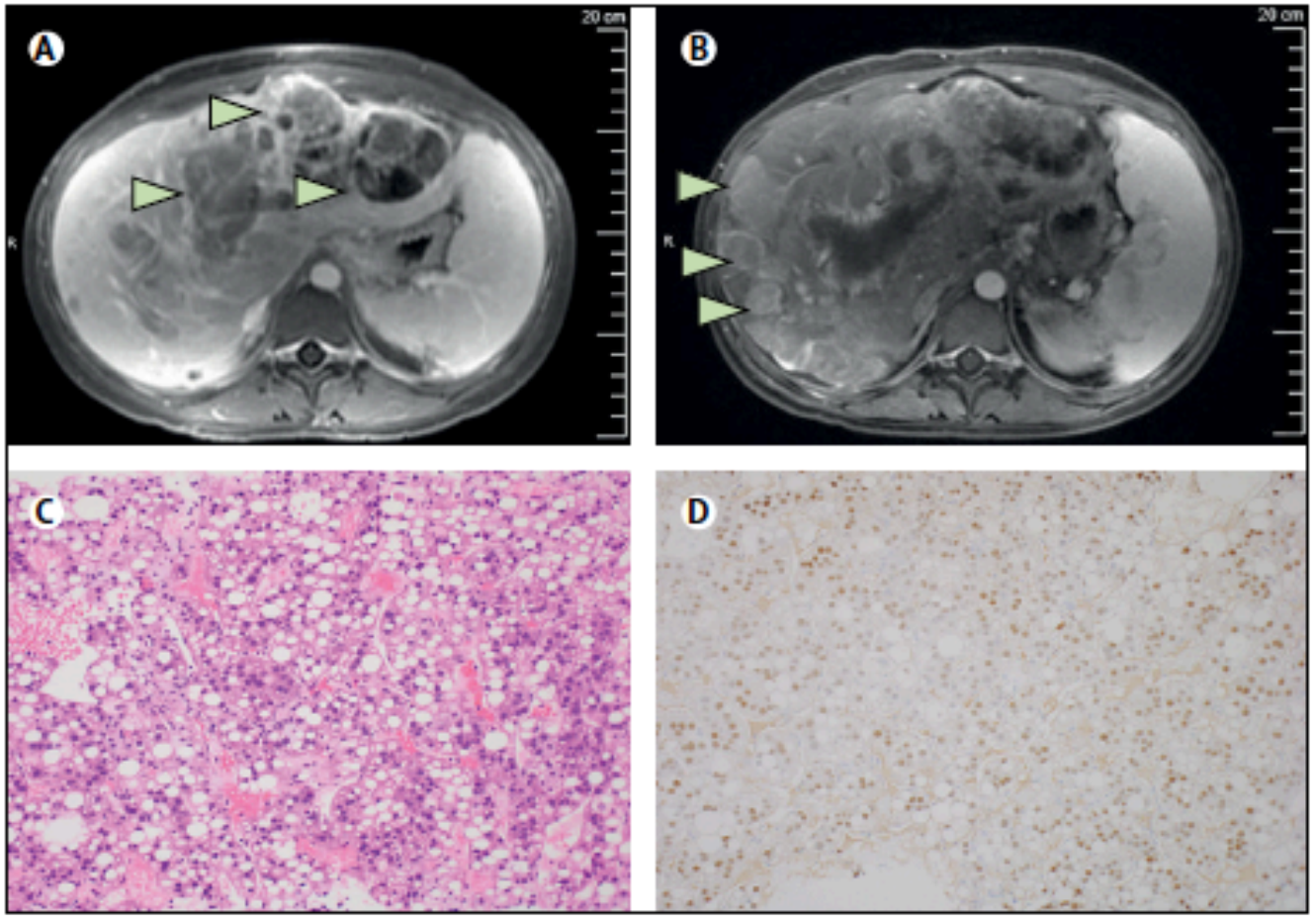


Figure: **Androgen-receptor positive hepatocellular carcinoma in a transgender man taking exogenous testosterone**

(A) MRI shows a 17·5 cm x 7·2 cm x 8 cm enhancing mass in the left hemiliver with numerous small surrounding satellite lesions and tumour thrombi in the main, right, and left portal veins (arrowheads). (B) MRI 2 months after the treatment shows additional, new lesions in the right liver (arrowheads). (C) Core needle biopsy of the liver mass shows hepatocellular carcinoma with clear cell change (original magnification x 20). (D) Androgen-receptor nuclear staining in 40% of the cells (original magnification x 20).

Anthony Fauci (170 cm) mit 17 Jahren