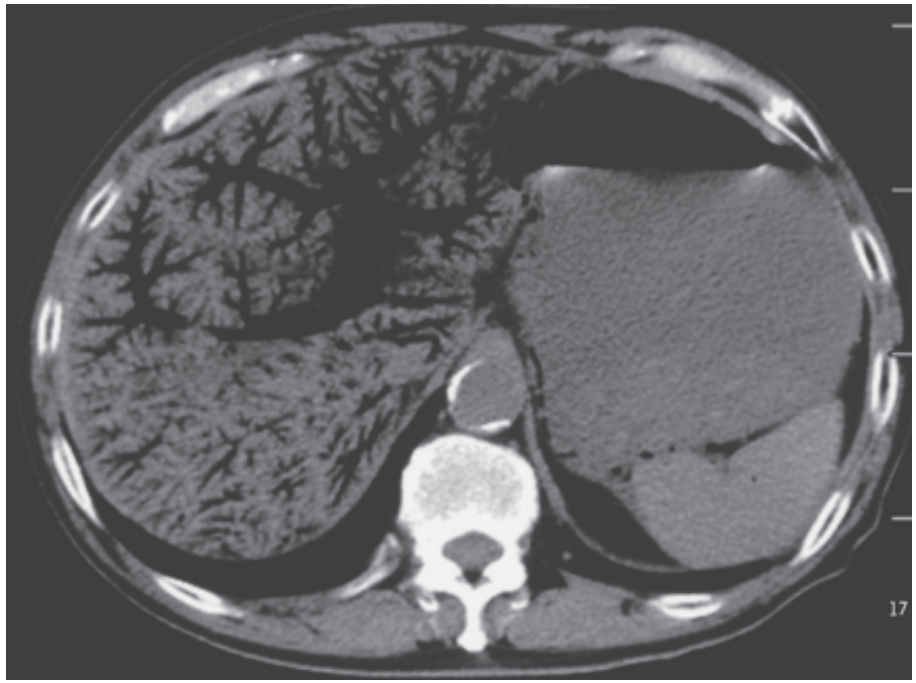
A 72-year-old man presented to the emergency department with an 11-hour history of periumbilical abdominal pain and inability to pass flatus. The pulse was 155 beats per minute, and the blood pressure 83/52 mm Hg. On physical examination, his abdomen was diffusely tender, with the most severe pain in the right upper quadrant. Computed tomography of the abdomen revealed extensive portal venous gas. What is the most common underlying cause?



Inflammatory bowel disease

Colonoscopy

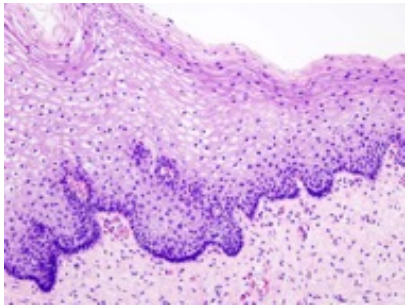
Bowel ischemia

Intra-abdominal abcess

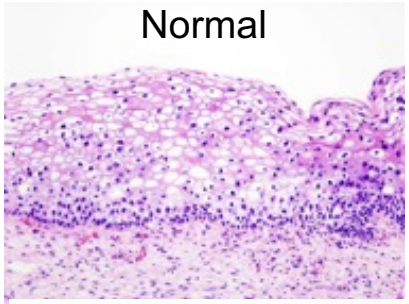
Peptic ulcer disease

The correct answer is bowel ischemia. Portal venous gas is most commonly associated with bowel ischemia and is a poor prognostic sign in patients with that condition; however, it can also develop in patients with other conditions, such as infection or inflammatory bowel disease, or as a result of an interventional procedure.

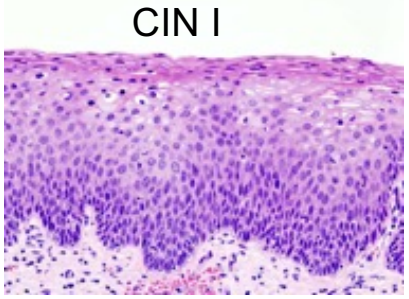
Das Zervixkarzinom (lateinisch Carcinoma cervicis uteri), auch Kollumkarzinom (von lateinisch Collum, deutsch ‚Hals ‘) oder Gebärmutterhalskrebs genannt, ist ein bösartiger (maligner) Tumor des Gebärmutterhalses (Cervix uteri). Es ist weltweit der vierthäufigste bösartige Tumor bei Frauen. Histologisch handelt es sich in der Mehrheit der Fälle um ein Plattenepithelkarzinom. Die häufigste Ursache für ein Zervixkarzinom ist eine Infektion mit bestimmten Typen des humanen Papillomvirus (HPV). Das Zervixkarzinom verursacht zunächst keine Schmerzen, nur gelegentlich treten leichte Schmierblutungen auf. Erst wenn der Tumor größer wird und mit Geschwürbildung zerfällt, kommt es zu fleischwasserfarbigem, süßlich riechendem Scheidenausfluss. Im Frühstadium ist die vollständige Entfernung der Veränderung durch eine Konisation ausreichend. Im fortgeschrittenen Stadium werden die Entfernung der ganzen Gebärmutter mit umliegendem Gewebe und manchmal auch weiterer Organe notwendig. Eine Untersuchung zur Früherkennung ist der Pap-Test. Eine Impfung mit einem HPV-Impfstoff verhindert eine Infektion durch die zwei häufigsten Hochrisiko-HPV-Typen und verringert damit das Risiko der Entstehung eines Zervixkarzinoms. Die Häufigkeit (Inzidenz) beim Gebärmutterhalskrebs unterscheidet sich weltweit erheblich. Sie liegt in Finnland bei 3,6 und in Kolumbien bei 45 pro 100.000 Frauen pro Jahr. In Deutschland lag sie 2002 bei 13,3 pro 100.000. Höhergradige Präkanzerosen der Cervix uteri sind etwa 50- bis 100-fach häufiger.



Normal

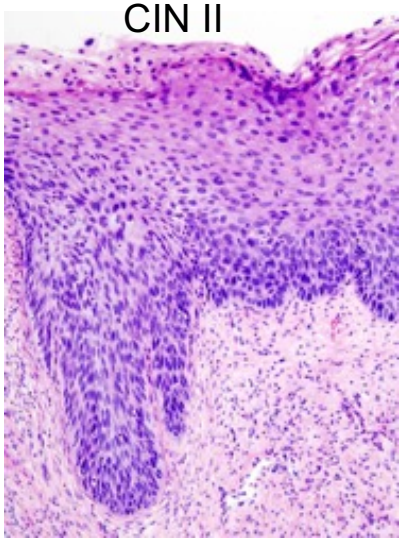


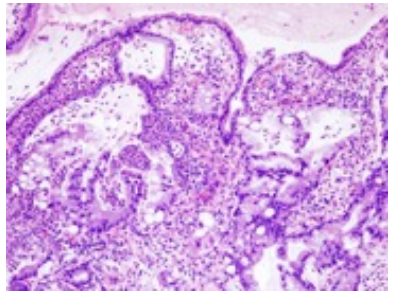
CIN I



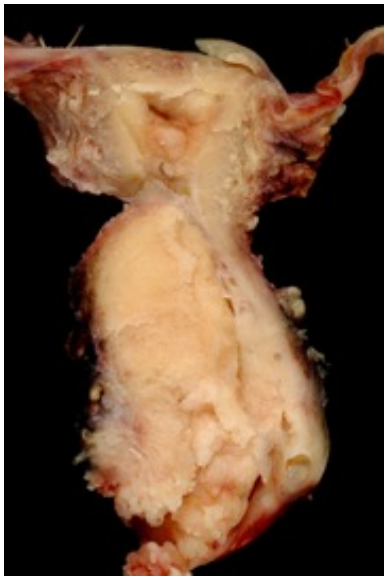
CIN II

CIN III





Adenocarcinom

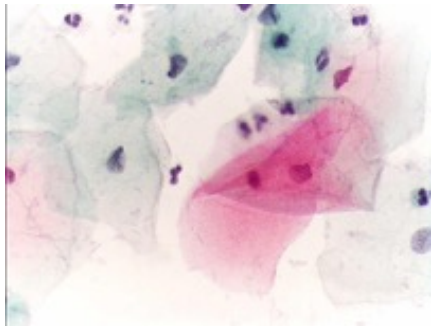


Plattenepithel-Karzinom

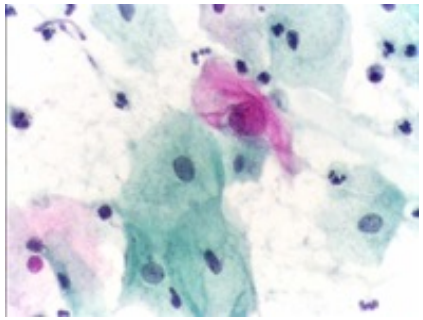
Behandlung der Krebsvorstufen

Eine Zervikale intraepitheliale Neoplasie (CIN) I kann über maximal 24 Monate im Abstand von 6 Monaten regelmäßig zytologisch und kolposkopisch beobachtet werden, wenn die Veränderungen im äußeren Bereich der Portio gut zu kontrollieren sind. Dabei können sich die Veränderungen zurückbilden oder weiterentwickeln. Voraussetzung dafür ist die sichere Diagnose durch Probeentnahme und histologische Untersuchung. CIN I im Inneren des Gebärmutterhalses (intrazervikaler Sitz, nicht gut beobachtbar) sollten bald mit einer Konisation behandelt werden. Eine Verlaufskontrolle und damit eine Verschiebung der Behandlung ist auch bei der CIN II und III in einer Schwangerschaft möglich, um die Lebensfähigkeit des Kindes abzuwarten. Außerhalb einer Schwangerschaft sollte bei einer CIN II, die über 12 Monate bestehen bleibt, und bei der CIN III eine Operation durchgeführt werden.

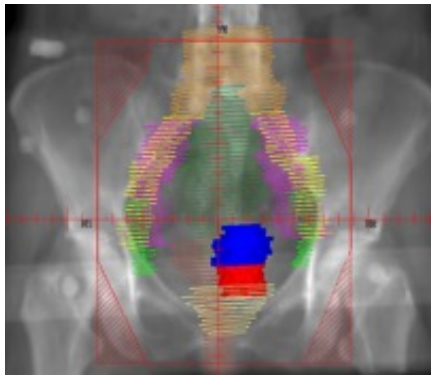
Beim Carcinoma in situ ist nach vollständiger Entfernung der Veränderung durch eine Konisation oder – im Falle einer abgeschlossenen Familienplanung – nach kompletter Gebärmutterentfernung (Hysterektomie) keine weitere Behandlung nötig. Bei unvollständiger Entfernung besteht die Möglichkeit einer erneuten Konisation. Eine Konisation kann bei strenger Indikationsstellung auch in der Schwangerschaft durchgeführt werden. Bei einem Carcinoma in situ mit vollständiger Entfernung der Veränderungen durch die Konisation kann die Schwangerschaft ausgetragen werden, das Risiko einer Frühgeburt ist dann erhöht. Eine normale Geburt ist möglich. Sechs Wochen nach der Geburt sollte dann eine erneute kolposkopische und zytologische Kontrolle erfolgen.



Normale Zellen



Atpyische Zellen (mitte)



Bestrahlungsplanung

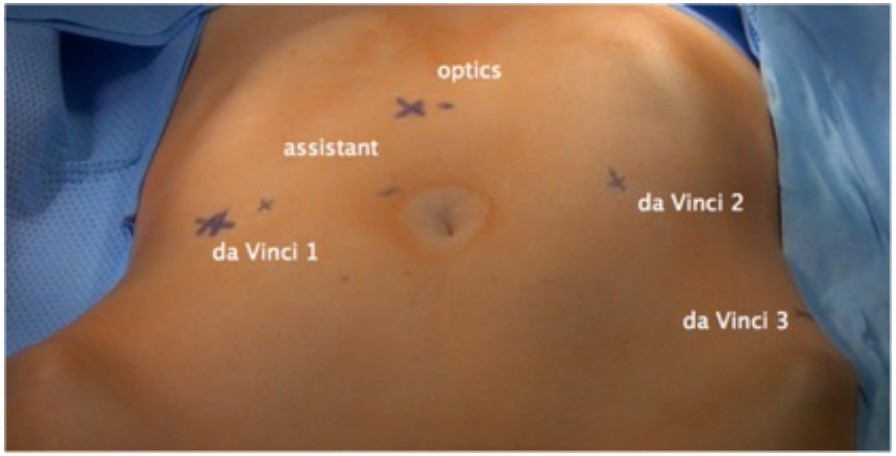
Im Stadium FIGO IA1 kann, wie bei den Krebsvorstufen, eine Konisation ausreichend sein, wenn der Tumor vollständig entfernt wurde und noch Kinderwunsch besteht, wobei dabei das Risiko für eine Zervixinsuffizienz oder auch eine Zervixstenose in der Schwangerschaft erhöht ist. Ohne Kinderwunsch sollte eine einfache Gebärmutterentfernung erfolgen. Bei Lymphgefäßeinbrüchen ist eine zusätzliche pelvine Lymphknotenentfernung angezeigt.
In den Stadien IA2, IB, IIA, IIB ist eine erweiterte Hysterektomie (radikale Hysterektomie) und systematische pelvine, stadienabhängig gegebenenfalls eine paraaortale Lymphonodektomie (Entfernung aller an der Aorta gelegenen Lymphknoten) angezeigt. Hier kommt bislang die Wertheim-Meigs-Operation als Standardtherapie zum Einsatz. Bei Plattenepithelkarzinomen können bei jungen Frauen die Eierstöcke erhalten bleiben. Liegt ein Adenokarzinom vor, wird wegen einer höheren Metastasierungswahrscheinlichkeit in die Eierstöcke eine Entfernung auch bei jungen Frauen empfohlen. Je nach histologischem Befund ist nach der Operation eine Strahlentherapie oder Radiochemotherapie nötig.
Die Klassifikation nach Piver, oder auch Rutledge-Piver, unterscheidet fünf Grade der Radikalität einer Hysterektomie beim Gebärmutterhalskrebs. Sie wurde nach den amerikanischen Gynäkologen M. Steven Piver und Felix Rutledge benannt. Als Alternativen stehen heute an Zentren die Totale mesometriale Resektion (TMMR) mit einer nervenschonenden Präparationstechnik (gezieltes Freilegen) in anatomisch-embryonalen Entwicklungsgrenzen und Verzicht auf eine anschließende Bestrahlung bei dennoch gleichen bzw. sogar besseren Überlebensdaten, die laparoskopisch assistierte vaginale radikale Hysterektomie (LAVRH) mit nervenschonender vaginalr Radikaloperation und laparoskopischer Lymphknotenentfernung sowie die laparoskopische radikale Hysterektomie (LRH) mit vollständiger laparoskopischer Präparation zur Verfügung

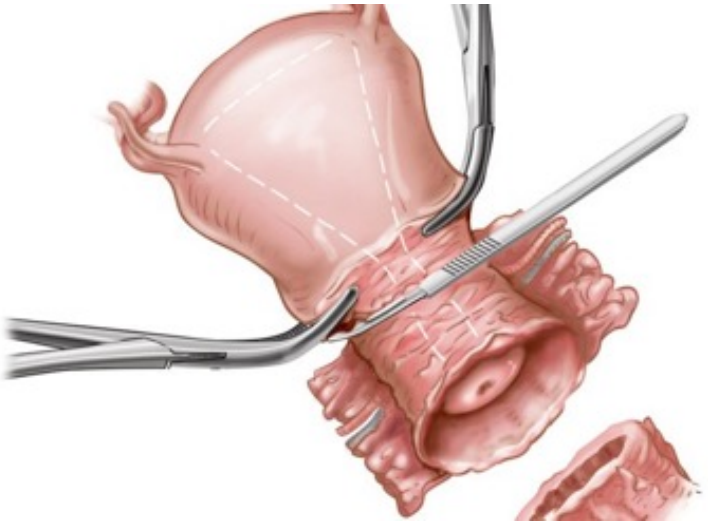
- **Stage IA**: Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
- **Stage IA1**: Stage IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.
- **Stage IA2**: Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
- **Stage IB**: Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.
- **Stage IB1**: Stage IB1: Clinical lesions no greater than 4 cm in size.
- **Stage IB2**: Stage IB2: Clinical lesions greater than 4 cm in size.

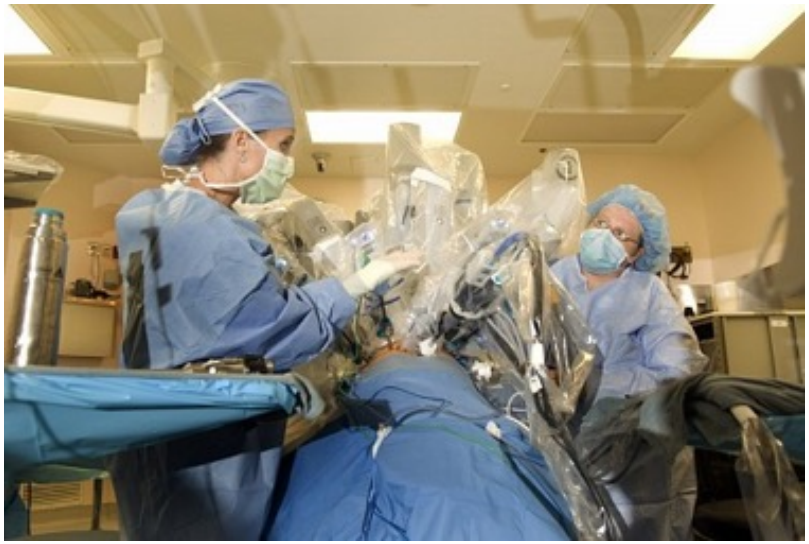
FIGO (International Federation of Gynecology and Obstetrics)

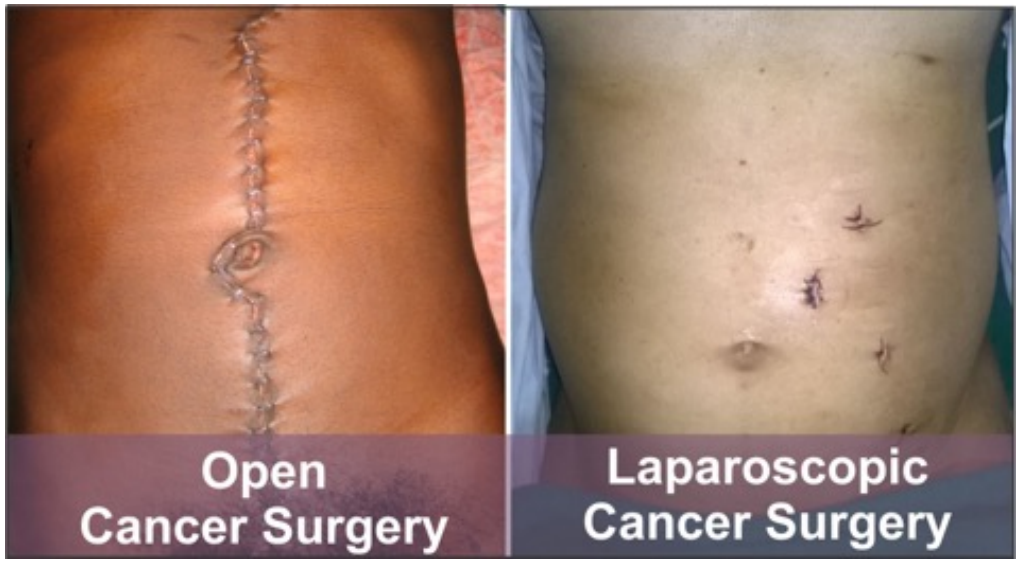
FIGO-Stadium	5-Jahres-Überlebensrate in Deutschland
IA	ca. 93 %
IB	ca. 92 %
IIA	ca. 63 %
IIB	ca. 50 %
III	ca. 40 %
IV	ca. 10 %

Laparoscopic versus open surgery for cervix cancer









Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

There are limited data from retrospective studies regarding whether survival outcomes after laparoscopic or robot-assisted radical hysterectomy (minimally invasive surgery) are equivalent to those after open abdominal radical hysterectomy (open surgery) among women with early-stage cervical cancer.

In this trial involving patients with stage IA1 (lymphovascular invasion), IA2, or IB1 cervical cancer and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma, we randomly assigned patients to undergo minimally invasive surgery or open surgery. The primary outcome was the rate of disease-free survival at 4.5 years, with noninferiority claimed if the lower boundary of the two-sided 95% confidence interval of the between-group difference (minimally invasive surgery minus open surgery) was greater than −7.2 percentage points (i.e., closer to zero).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)
Age — yr	46.0±10.6	46.1±11.0
Body-mass index†	26.2±5.3	27.2±5.6
Histologic subtype — no. (%)		
Squamous-cell carcinoma	210 (67.3)	214 (67.1)
Adenocarcinoma	80 (25.6)	87 (27.3)
Adenosquamous carcinoma	6 (1.9)	9 (2.8)
Not reported	16 (5.1)	9 (2.8)
Stage of disease — no. (%)		
IA1: lymphovascular invasion	5 (1.6)	5 (1.6)
IA2	20 (6.4)	21 (6.6)
IB1	287 (92.0)	293 (91.8)
ECOG performance-status score — no. (%)‡		
0	289 (92.6)	292 (91.5)
1	23 (7.4)	27 (8.5)
Median length of hospital stay (range) — days	5 (0–69)§	3 (0–72)
Treatment received — no. (%)		
Open surgery	274 (87.8)	2 (0.6)
Minimally invasive surgery	8 (2.6)	289 (90.6)
Patient withdrew before surgery	19 (6.1)	12 (3.8)
Surgery was aborted	11 (3.5)	16 (5.0)

* Plus–minus values are means ±SD. Minimally invasive surgery indicates laparoscopic or robot-assisted radical hysterectomy, and open surgery indicates open abdominal radical hysterectomy. There were no significant differences in baseline characteristics between the assigned groups. Percentages may not total 100 because of rounding.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

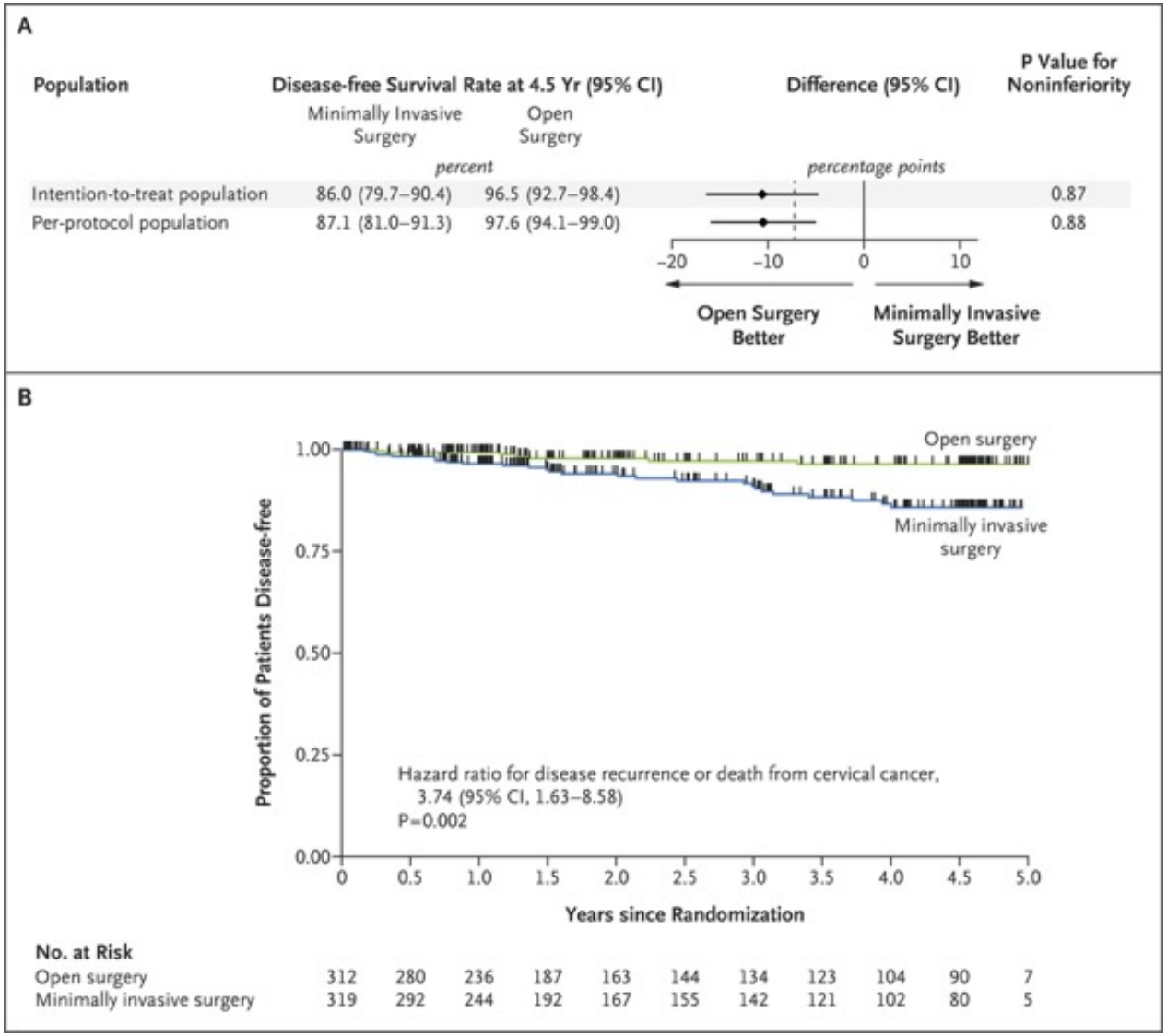
‡ Performance-status scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 to 4, with higher values indicating greater disability.

§ A zero length of stay in patients assigned to open surgery indicates patients who either withdrew before surgery or had surgery aborted and were discharged the same day.

Table 2. Adjuvant Therapy.

Adjuvant Therapy	Open Surgery (N=312)	Minimally Invasive Surgery (N=319)	P Value
	no. (%)		
Chemotherapy or radiotherapy	86 (27.6)	92 (28.8)	0.72
≥1 Cycle of chemotherapy	66 (21.2)	72 (22.6)	0.67
≥1 Dose of radiotherapy	73 (23.4)	81 (25.4)	0.56

Rates of postoperative adjuvant therapy (chemotherapy or radiotherapy) were similar in the two groups (28.8% [92 of 319 patients] in the minimally invasive surgery group and 27.6% [86 of 312 patients] in the open-surgery group). There was no significant between-group difference in the rate of the combination of adjuvant chemotherapy and radiation (18.8% in the minimally invasive surgery group and 18.1% in the open-surgery group) or in the time to initiation of any adjuvant therapy, with a median of 41 days (range, 31 to 57) in the minimally invasive surgery group and 46 days (range, 33 to 70) in the open-surgery group



Estimates of Disease-free Survival. Minimally invasive surgery indicates laparoscopic or robot-assisted radical hysterectomy, and open surgery indicates open abdominal radical hysterectomy. Panel A shows the difference in disease-free survival rates between surgical groups at 4.5 years after surgery for both the intention-to-treat and per-protocol populations. The dashed line denotes the noninferiority margin of −7.2 percentage points. Noninferiority of minimally invasive surgery would be declared if the lower boundary of the two-sided 95% confidence interval were above this margin (i.e., to the right of this line). The P value for noninferiority is two-sided. Panel B shows the Kaplan–Meier disease-free survival curves for the surgical groups. The hazard ratio, 95% confidence interval, and corresponding P value were estimated with the use of Cox proportional-hazards models. Tick marks indicate censored data. Disease recurrence or death from cervical cancer occurred in 27 of 319 patients in the minimally invasive surgery group and 7 of 312 patients in the open-surgery group.

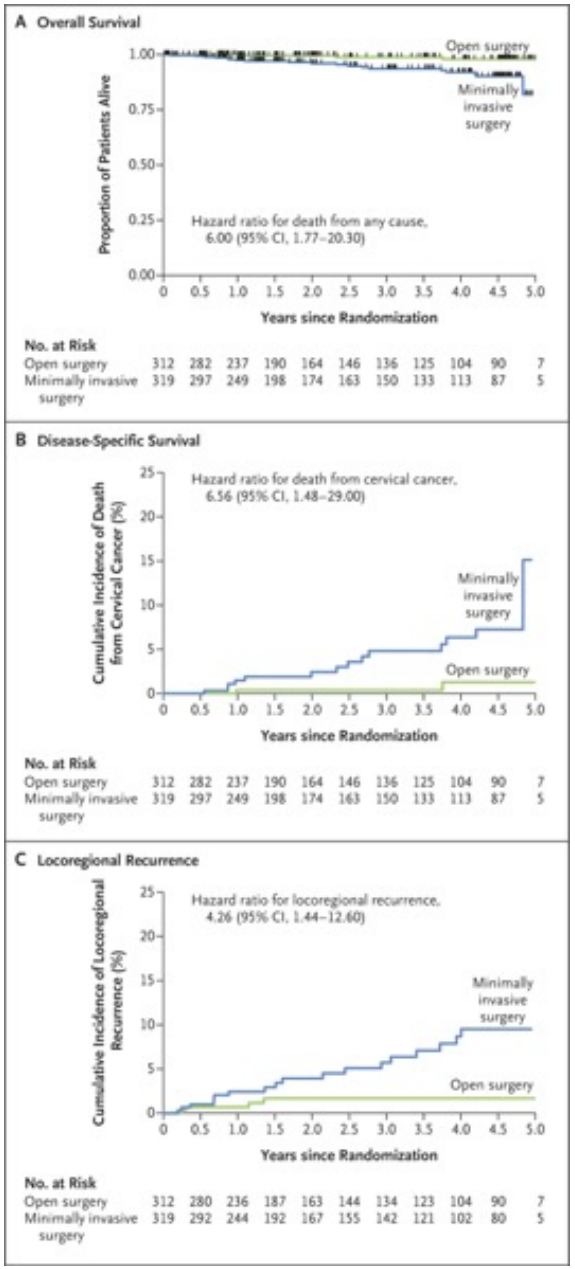
Table 3. Proportional-Hazards Models (Tests for Superiority) According to Randomized Treatment.

Outcome	Open Surgery	Minimally Invasive Surgery	Hazard Ratio vs. Open Surgery (95% CI)	P Value
	no. of events/no. of patients			
Disease recurrence or death from cervical cancer				
Unadjusted analysis	7/312	27/319	3.74 (1.63–8.58)	0.002
Adjusted analysis*	7/282	27/295	4.39 (1.88–10.20)	<0.001
Disease recurrence or death from any cause	8/312	32/319	3.88 (1.79–8.41)	
Locoregional recurrence†	4/312	18/319	4.26 (1.44–12.60)	
Death from any cause	3/312	19/319	6.00 (1.77–20.30)	
Death from cervical cancer†	2/312	14/319	6.56 (1.48–29.00)	

* The analysis was adjusted for age, body-mass index, stage of disease, lymphovascular invasion, lymph-node involvement, and ECOG performance-status score.

† The analysis was conducted on a competing-risks basis. Distant relapses and deaths from any cause were considered to be competing risks for locoregional recurrence; deaths not due to cervical cancer were considered to be competing risks for death from cervical cancer.

Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3-year rate, 91.2% vs. 97.1%; hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58), a difference that remained after adjustment for age, body-mass index, stage of disease, lymphovascular invasion, lymph-node involvement, and ECOG performance-status score. Minimally invasive surgery was also associated with a lower rate of overall survival than open surgery (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30).



Kaplan–Meier Estimates of Overall Survival, Disease-Specific Survival, and Locoregional Recurrence. Panel A shows the Kaplan–Meier plot for overall survival, measured from the date of randomization to the date of death or the date that the patient was last known to be alive.
A Cox proportional-hazards model was used to determine the hazard ratio and 95% confidence interval. Tick marks indicate censored data. Death occurred in 19 of 319 patients in the minimally invasive surgery group and 3 of 312 patients in the open-surgery group. Panel B shows the cumulative incidence curves for disease-specific survival, measured from the date of randomization to the date of death from cervical cancer. The hazard ratio and 95% confidence interval were estimated with the use of a competing-risks model (based on the method of Fine and Gray[24]) in which death from other causes was considered to be the competing risk. Death from cervical cancer occurred in 14 of 319 patients in the minimally invasive surgery group and 2 of 312 patients in the open-surgery group. Panel C shows the cumulative incidence curves for locoregional recurrence according to randomized treatment. The hazard ratio and 95% confidence interval were estimated with the use of a competing-risks model (based on the method of Fine and Gray). Adjudicated recurrences in the vaginal vault or pelvis were considered to be local recurrences, and all distant or multiple recurrences (with no sites in the vault or pelvis) and deaths from any cause were considered to be competing risks. Locoregional recurrence occurred in 18 of 319 patients in the minimally invasive surgery group and 4 of 312 patients in the open-surgery group.

In this prospective, randomized trial, patients who underwent minimally invasive radical hysterectomy for early-stage cervical cancer had lower rates of disease-free survival and overall survival and a higher rate of locoregional recurrence than patients who underwent open abdominal radical hysterectomy. Our results call into question the findings in the literature suggesting that minimally invasive radical hysterectomy is associated with no difference in oncologic outcomes as compared with the open approach.

Our trial has several limitations in that it did not reach its final intended enrollment, owing to the safety alert raised by the data and safety monitoring committee on the basis of the higher rates of recurrence and death in the minimally invasive surgery group than in the open-surgery group. The initial power was based on the assumption that there would have been a 4.5-year follow-up period for all the patients. However, at the time of analysis, 59.7% of the patients had reached the 4.5-year time point (median follow-up, 2.5 years). Even so, the trial did reach 84% power to declare noninferiority for our primary outcome. Finally, the results of this trial cannot be generalized to patients with "low-risk" cervical cancer (tumor size, <2 cm; no lymphovascular invasion; depth of invasion, <10 mm; and no lymph-node involvement), because the trial was not powered to evaluate the oncologic outcomes of the two surgical approaches in that context.

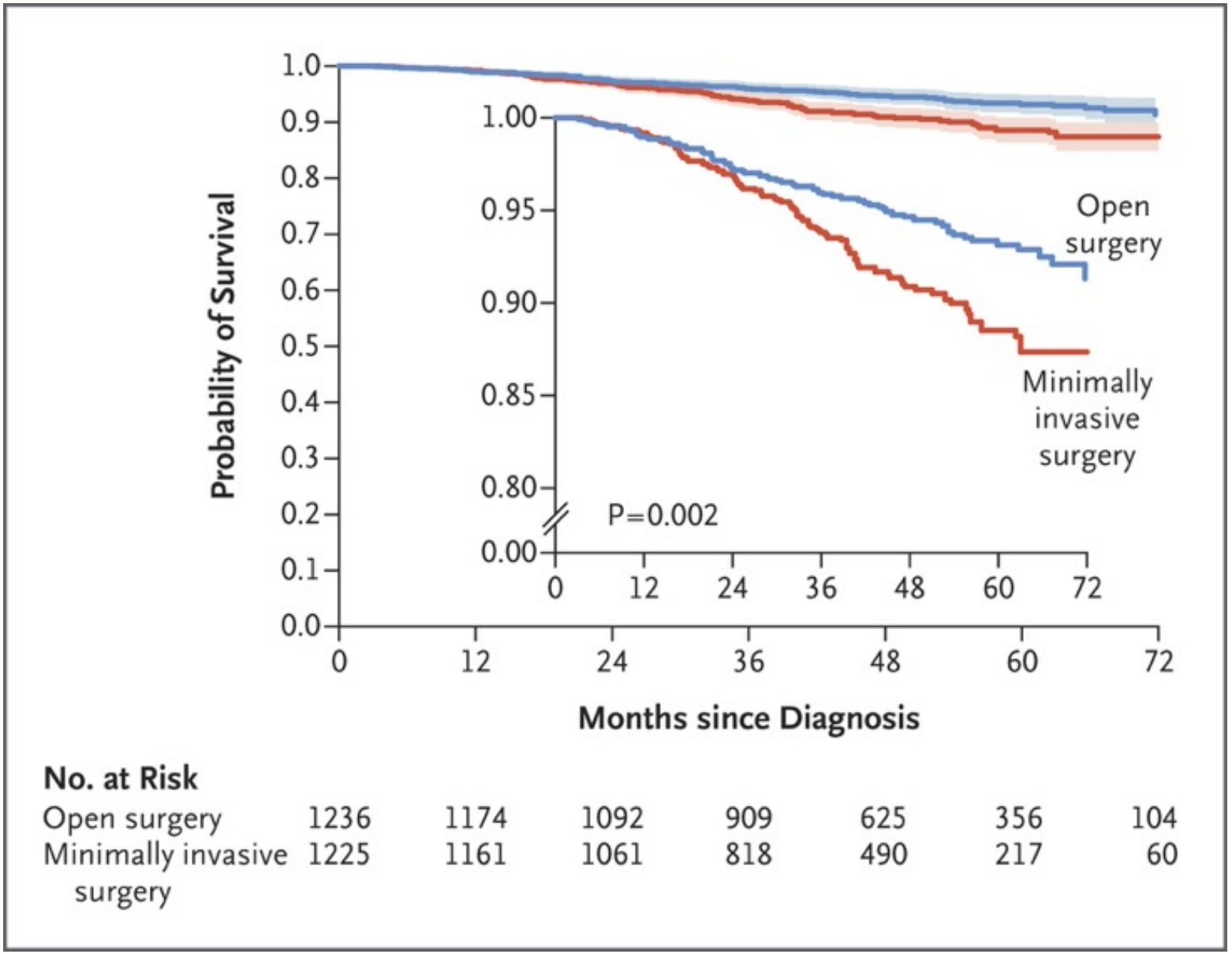
In conclusion, minimally invasive radical hysterectomy in patients with cervical cancer was associated with a higher rate of recurrence and a lower rate of disease-free survival than the open approach. In addition, the rate of overall survival was lower among patients undergoing minimally invasive surgery.

Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

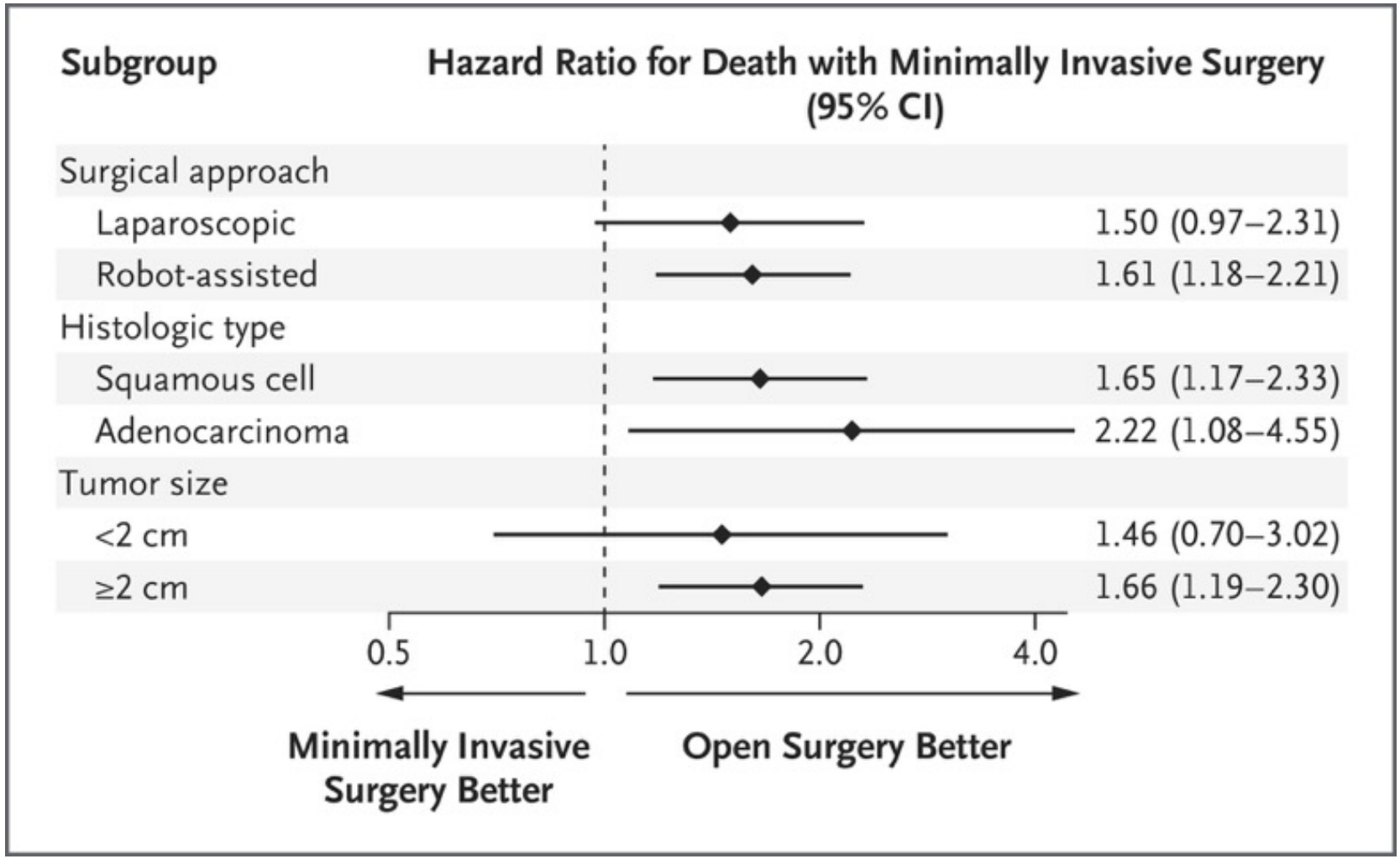
Minimally invasive surgery was adopted as an alternative to laparotomy (open surgery) for radical hysterectomy in patients with early-stage cervical cancer before high-quality evidence regarding its effect on survival was available. We sought to determine the effect of minimally invasive surgery on all-cause mortality among women undergoing radical hysterectomy for cervical cancer. We performed a cohort study involving women who underwent radical hysterectomy for stage IA2 or IB1 cervical cancer during the 2010–2013 period at Commission on Cancer–accredited hospitals in the United States. The study used inverse probability of treatment propensity-score weighting. We also conducted an interrupted time-series analysis involving women who underwent radical hysterectomy for cervical cancer during the 2000–2010 period, using the Surveillance, Epidemiology, and End Results program database. In the main patient-level analysis, we used the National Cancer Database, a cancer registry that is maintained by the American College of Surgeons and the American Cancer Society.

Characteristic	Cohort before Inverse Probability of Treatment Weighting			Cohort after Inverse Probability of Treatment Weighting		
	Open Surgery (N=1236)	Minimally Invasive Surgery (N=1225)	P Value†	Open Surgery (N=1340)	Minimally Invasive Surgery (N=1334)	P Value‡
	number (percent)			*number (percent)*		
Year of diagnosis			<0.001			1.00
2010	408 (33.0)	211 (17.2)		338 (25.2)	336 (25.2)	
2011	310 (25.1)	317 (25.9)		336 (25.1)	334 (25.1)	
2012	268 (21.7)	356 (29.1)		344 (25.7)	342 (25.6)	
2013	250 (20.2)	341 (27.8)		323 (24.1)	322 (24.1)	
Race or ethnic group§			<0.001			1.00
White	789 (63.8)	853 (69.6)		899 (67.1)	896 (67.2)	
Black	160 (12.9)	95 (7.8)		140 (10.4)	140 (10.5)	
Hispanic	196 (15.9)	169 (13.8)		196 (14.6)	191 (14.3)	
Asian	71 (5.7)	82 (6.7)		83 (6.2)	84 (6.3)	
Other or unknown	20 (1.6)	26 (2.1)		23 (1.7)	23 (1.7)	
Facility type			<0.001			0.94
Nonacademic	544 (44.0)	654 (53.4)		657 (49.0)	656 (49.2)	
Academic	692 (56.0)	571 (46.6)		683 (51.0)	678 (50.8)	
Stage of disease			0.04			0.94
IA2	127 (10.3)	159 (13.0)		157 (11.7)	155 (11.6)	
IB1	1109 (89.7)	1066 (87.0)		1183 (88.3)	1179 (88.4)	
Histologic type			0.01			1.00
Squamous cell	789 (63.8)	709 (57.9)		820 (61.2)	815 (61.1)	
Adenocarcinoma	381 (30.8)	452 (36.9)		450 (33.6)	450 (33.7)	
Adenosquamous	66 (5.3)	64 (5.2)		70 (5.2)	69 (5.2)	
Tumor size			0.005			0.99
<2 cm	459 (37.1)	534 (43.6)		543 (40.5)	541 (40.6)	
≥2 cm	615 (49.8)	543 (44.3)		626 (46.7)	624 (46.8)	
Unknown	162 (13.1)	148 (12.1)		171 (12.8)	169 (12.6)	

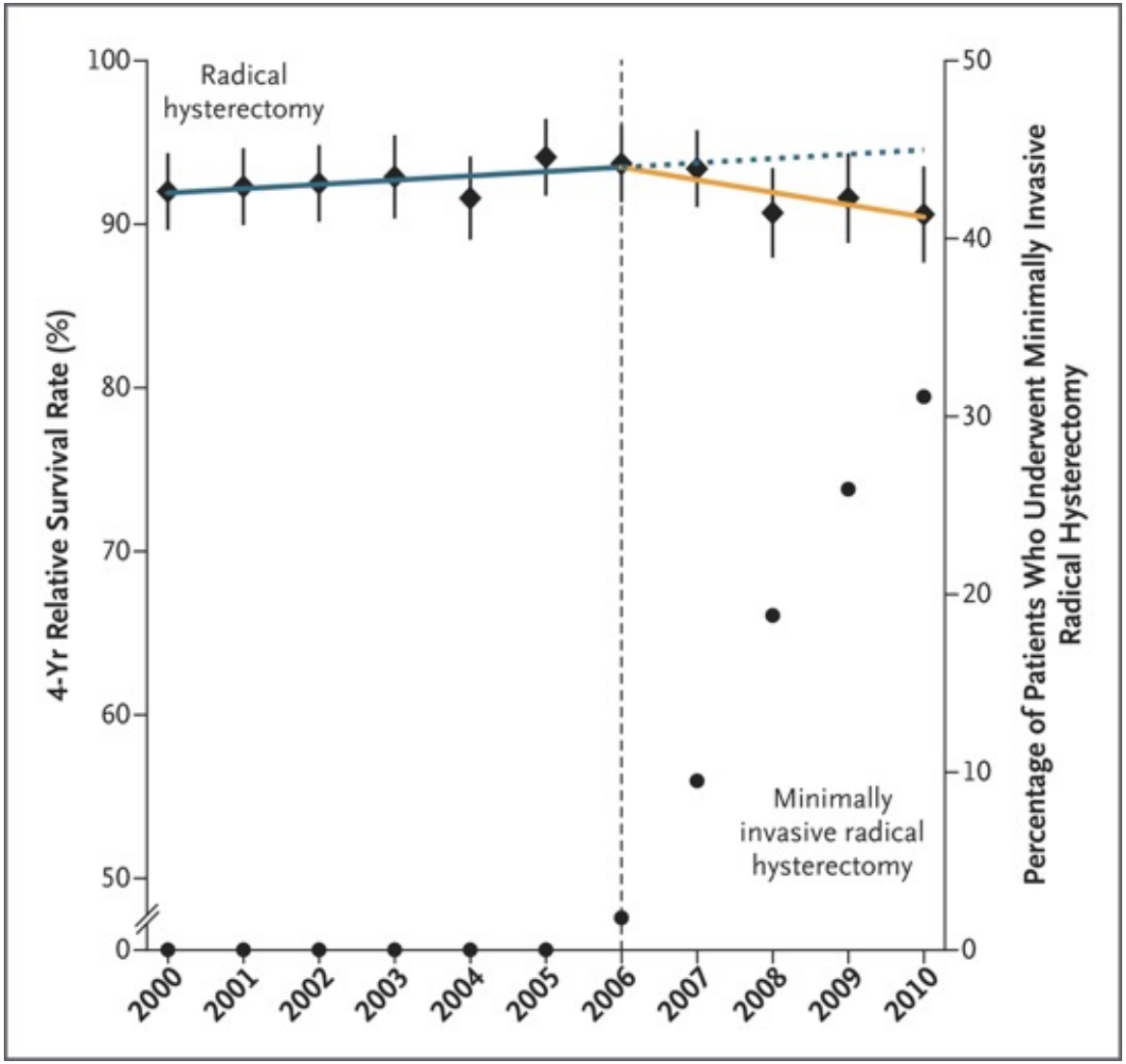
Selected Characteristics of Patients Who Underwent Radical Hysterectomy for Stage IA2 or IB1 Cervical Carcinoma, According to Surgical Approach, before and after Inverse Probability of Treatment Weighting.



Inverse Probability of Treatment–Weighted Survival Curves among Women with Stage IA2 or IB1 Cervical Cancer, According to Type of Surgery. Shaded bands represent the 95% confidence interval. Women who underwent minimally invasive surgery had shorter overall survival than those who underwent open surgery (P=0.002 by the log-rank test). The at-risk table shows the actual number of patients at risk. The inset shows the same data on an enlarged y axis.



Subgroup Analyses. Subgroup analyses show the associations between minimally invasive radical hysterectomy and all-cause mortality according to mode of minimally invasive surgery (laparoscopic approach vs. robot-assisted approach), histologic type (squamous-cell carcinoma vs. adenocarcinoma), and tumor size in the greatest dimension (<2 cm vs. ≥2 cm). Diamonds represent point estimates for the hazard ratio as compared with open surgery, and horizontal lines indicate the associated 95% confidence intervals. Separate propensity-score models were fitted to predict the probability of minimally invasive surgery for each subgroup, and hazard ratios were estimated with the use of inverse probability of treatment–weighted Cox proportional-hazards models.



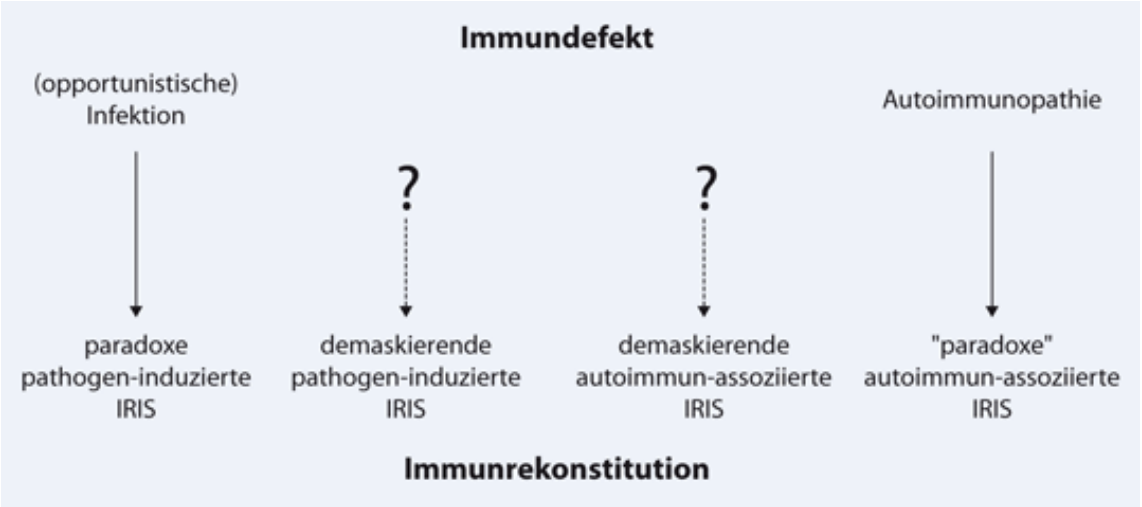
Interrupted Time-Series Evaluation of the Effect of Adoption of Minimally Invasive Radical Hysterectomy on 4-Year Relative Survival Rate. Shown are the 4-year relative survival rates among women who underwent radical hysterectomy for cervical cancer by any surgical approach (diamonds) with 95% confidence intervals (error bars) and the percentages of radical hysterectomies that were undertaken with the use of a minimally invasive approach (circles). The adoption of minimally invasive radical hysterectomy in 2006 was associated with a significant change of temporal trend (as indicated by the dotted blue line) (P=0.01) and a declining 4-year relative survival rate after 2006 (yellow line) (annual percentage change, 0.8%; 95% CI, 0.3 to 1.4).

Our findings suggest that minimally invasive surgery was associated with a higher risk of death than open surgery among women who underwent radical hysterectomy for early-stage cervical cancer. This association was apparent regardless of laparoscopic approach (robot-assisted or traditional), tumor size, or histologic type. This finding was consistent across several analytic approaches and robust to multiple sensitivity analyses. Furthermore, we observed that the adoption of minimally invasive surgery in the United States, starting in 2006, coincided with the beginning of a decline in 4-year relative survival rates among women undergoing radical hysterectomy for cervical cancer.

The first analysis, which used propensity-score weighting, showed that women with early-stage cervical cancer who had been treated at Commission on Cancer–accredited hospitals with minimally invasive radical hysterectomy had a lower rate of overall survival within 4 years after diagnosis than those who had been treated with open radical hysterectomy (90.9% vs. 94.7%, P=0.002). The second analysis, a time-interrupted study of a similar population that used data from the Surveillance, Epidemiology, and End Results program database, showed a progressive decrease in the 4-year relative survival rate by 0.8% per year that coincided with the initial period of adoption of robot-assisted surgery in the United States (2007–2010) (P=0.01 for change of trend). Taken together, the LACC Trial and the epidemiologic study call into question the equivalency of cancer outcomes with open as compared with minimally invasive radical hysterectomy for cervical cancer.

Do these studies signal the death knell for minimally invasive radical hysterectomy in cervical-cancer treatment? Not necessarily, but this approach has been dealt a great blow. Although the data are alarming, select patient subgroups may still benefit from a less invasive approach. No patients with stage IA2 disease and only one with stage IB1, grade 1, disease had a recurrence in the LACC Trial. In addition, patients with a tumor size of less than 2 cm did not have worse outcomes with minimally invasive surgery than with open surgery in either study. Until further details are known, however, surgeons should proceed cautiously, counsel their patients regarding these collective study results, and assess each woman's individual risks and benefits with respect to minimally invasive as compared with open radical hysterectomy.

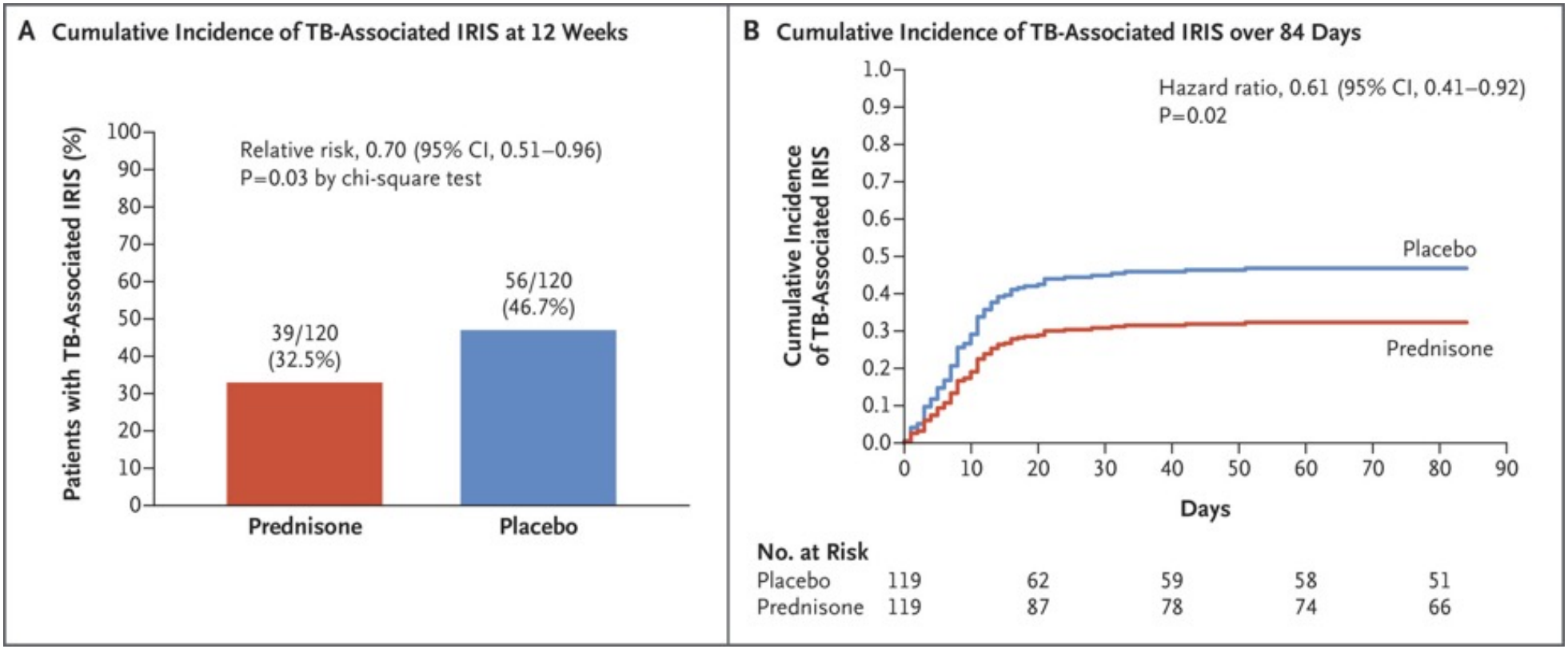
Das “Immunrekonstitutionssyndrom“ (die Abkürzung IRIS steht für „Immune Reconstitution Inflammatory Syndrome“) ist einem kürzlich gefundenen Konsens zufolge definiert ist als eine Verschlechterung eines infektiösen oder inflammatorischen Geschehens, dass in zeitlichem Zusammenhang mit einem ART-Beginn steht (http://www.inshi.umn.edu/). Als Response-Kriterium wird ein Viruslastabfall von mindestens einer Logstufe gefordert, und die Symptome dürfen nicht durch einen erwarteten Verlauf einer bestehenden Infektion, durch Nebenwirkungen, Therapieversagen oder Non-Adhärenz erklärbar sein.
Zu unterscheiden sind subklinische Infektionen, die unter ART demaskiert werden („unmasking IRIS“), von bereits zu ART-Beginn klinisch evidenten Infektionen, die sich unter Therapie paradoxerweise verschlechtern („paradoxical IRIS“). Darüber hinaus muss ein IRIS nicht unbedingt durch eine opportunistische Infektion bedingt sein – das Spektrum umfasst neben unspezifischen Symptomen auch autoimmune Erkrankungen und Malignome. **Mykobakterielle IRIS:** Für MAC übersteigt die Zahl publizierter Fälle mit fistelnden Lymphadenitiden, kutanen oder muskulären Abszessen, Osteomyelitiden, Nephritiden oder Meningitiden den zitierbaren Rahmen. Wir selber sahen bei insgesamt 83 Patienten, die bei weniger als 200 CD4-Zellen/µl mit ART begannen, in den ersten Wochen nach Therapiebeginn 6 Mykobakteriosen, darunter 4 MAC-Infektionen (Hoffmann 1999). Die Lymphknoten-Abszesse treten meist in den ersten Wochen auf. Es muss nicht immer avium sein: Auch IRIS-Fälle mit *Mycobacterium xenopi* oder *kansasii* wurden beschrieben.



Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

Early initiation of antiretroviral therapy (ART) in human immunodeficiency virus (HIV)–infected patients who have tuberculosis reduces mortality among patients with low CD4 counts, but it increases the risk of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS). We conducted this randomized, double-blind, placebo-controlled trial to assess whether prophylactic prednisone can safely reduce the incidence of paradoxical tuberculosis-associated IRIS in patients at high risk for the syndrome. We enrolled HIV-infected patients who were initiating ART (and had not previously received ART), had started tuberculosis treatment within 30 days before initiating ART, and had a CD4 count of 100 cells or fewer per microliter. Patients received either prednisone (at a dose of 40 mg per day for 14 days, then 20 mg per day for 14 days) or placebo. The primary end point was the development of tuberculosis-associated IRIS within 12 weeks after initiating ART, as adjudicated by an independent committee. Paradoxical tuberculosis-associated IRIS — an immunopathologic reaction characterized by recurrent or new inflammatory features of tuberculosis that manifest shortly after the initiation of antiretroviral therapy (ART) in patients receiving antituberculosis treatment — occurs in 18% of patients (range, 4 to 54), according to a pooled estimate derived from 40 observational cohort studies.

Characteristic	Prednisone Group (N=120)	Placebo Group (N=120)
Median age (IQR) — yr	36 (31–42)	36 (29–42)
Male sex — no. (%)	71 (59.2)	73 (60.8)
Median body-mass index (IQR)†	21 (19–24)	21 (19–24)
Median CD4 count (IQR) — no. of cells/μl	51 (27–84)	49 (23–88)
Median HIV-1 RNA viral load (IQR) — $\log_{10}$ copies/ml	5.5 (5.2–5.9)	5.6 (5.2–5.9)
Microbiologically confirmed TB — no. (%)‡	86 (71.7)	89 (74.2)
Median hemoglobin level (IQR) — g/dl	9.7 (8.8–11.1)	9.8 (8.5–10.9)
Median white-cell count (IQR) — $\times 10^{-9}$/liter	3.7 (2.9–5.1)	3.4 (2.6–5.0)
Median neutrophil count (IQR) — $\times 10^{-9}$/liter	2.3 (1.5–3.1)	2.0 (1.4–2.9)
Median platelet count (IQR) — $\times 10^{-9}$/liter	311 (259–413)	300 (226–396)
Median sodium level (IQR) — mmol/liter	136 (134–139)	137 (135–139)
Median creatinine level (IQR) — μmol/liter	57 (50–66)	59 (50–70)
Median total bilirubin level (IQR) — μmol/liter	6 (4–7)	6 (4–8)
Median alanine aminotransferase level (IQR) — IU/liter	26 (18–38)	28 (20–40)
Median alkaline phosphatase level (IQR) — IU/liter	113 (87–149)	115 (91–163)
Median C-reactive protein level (IQR) — mg/liter	10.9 (4.0–30.1)	10.7 (4.6–29.9)
Median Karnofsky performance score (IQR)§	90 (80–90)	90 (80–90)
Median duration of TB treatment before initiation of ART (IQR) — days	16 (15–22)	17 (15–21)



Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS). Panel A shows the cumulative incidence of the primary end point of paradoxical TB-associated IRIS at 12 weeks. If paradoxical TB-associated IRIS had not developed before a patient died, withdrew, or was lost to follow-up, the patient was considered not to have had the syndrome. Panel B shows the cumulative incidence of TB-associated IRIS over 84 days. Diagnosis of TB-associated IRIS was determined according to the International Network for the Study of HIV-associated IRIS criteria. Day 0 is the day ART was initiated.

Table 2. Analysis of the Primary End Point in Prespecified Subgroups.*

Subgroup	Prednisone Group (N=120)	Placebo Group (N=120)	Relative Risk (95% CI)
	no./total no. (%)		
CD4 count at screening			
≤50 cells/μl	28/60 (46.7)	37/62 (59.7)	0.78 (0.56–1.10)
>50 cells/μl	11/60 (18.3)	19/58 (32.8)	0.56 (0.29–1.07)
HIV-1 RNA viral load at screening			
>100,000 copies/ml	36/102 (35.3)	50/99 (50.5)	0.70 (0.50–0.97)
≤100,000 copies/ml	3/17 (17.6)	5/20 (25.0)	0.71 (0.20–2.53)
Microbiologically confirmed TB†	33/86 (38.4)	43/89 (48.3)	0.79 (0.56–1.12)
No rifampin-resistant TB diagnosed after enrollment‡	39/118 (33.1)	55/119 (46.2)	0.72 (0.52–0.99)

* The primary end point was the development of paradoxical TB-associated IRIS within 12 weeks after enrollment according to the International Network for the Study of HIV-associated IRIS (INSHI) criteria.[14]
† Microbiologically confirmed TB was defined as *Mycobacterium tuberculosis* detected on culture or with the use of the Xpert MTB/RIF assay (Cepheid) or as positive acid-fast bacilli on smear microscopy.
‡ In three patients (two in the prednisone group and one in the placebo group), rifampin-resistant TB was diagnosed after enrollment, and these patients are excluded from the denominator in this analysis.

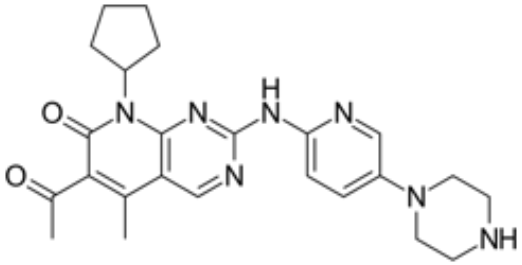
Primary and Secondary End Points.

End Point	Prednisone Group (N=120)	Placebo Group (N=120)	Relative Risk (95% CI)	P Value
Primary end point				
TB-associated IRIS meeting INSHI criteria — no. (%)	39 (32.5)	56 (46.7)	0.70 (0.51–0.96)	0.03
Secondary efficacy end points				
TB-associated IRIS meeting at least 1 major INSHI criterion — no. (%)	25 (20.8)	44 (36.7)	0.57 (0.37–0.87)	
Sustained TB-associated IRIS — no. (%)†	35 (29.2)	50 (41.7)	0.70 (0.49–0.99)	
Median duration of TB-associated IRIS (IQR) — days†	49 (31–97)	35 (19–82)		
Open-label glucocorticoid treatment of TB-associated IRIS — no. (%)	16 (13.3)	34 (28.3)	0.47 (0.27–0.81)	
Hospitalization for TB-associated IRIS — no. (%)	5 (4.2)	9 (7.5)	0.56 (0.19–1.61)	
Hospitalization for any cause — no. (%)	17 (14.2)	27 (22.5)	0.63 (0.36–1.09)	
Death from any cause — no. (%)	5 (4.2)	4 (3.3)	1.25 (0.34–4.54)	1.00
Death attributed to TB-associated IRIS — no. (%)	0	1 (0.8)	Could not be calculated	1.00
Composite end point of death, hospitalization, and hepatotoxicity — no. (%)	22 (18.3)	32 (26.7)	0.69 (0.43–1.11)	
Interruption of ART, TB treatment, or both owing to adverse event — no. (%)	10 (8.3)	19 (15.8)	0.53 (0.26–1.08)	
Interruption of ART, TB treatment, or both owing to drug-induced liver injury or rash — no. (%)	6 (5.0)	8 (6.7)	0.75 (0.27–2.10)	
Secondary safety end points‡				
Severe infection — no./total no. (%)§	11/119 (9.2)	18/119 (15.1)	0.61 (0.30–1.24)	0.23
Grade 3 clinical adverse event — no./total no. (%)¶	33/119 (27.7)	53/119 (44.5)	0.62 (0.44–0.89)	0.01
Grade 4 clinical adverse event — no./total no. (%)¶	8/119 (6.7)	10/119 (8.4)	0.80 (0.33–1.96)	0.81
Serious adverse event — no./total no. (%)‖	24/119 (20.2)	30/119 (25.2)	0.80 (0.50–1.28)	0.44
Adverse drug reaction — no./total no.**	22/119	21/119	1.05 (0.61–1.80)	1.00
Definitely related to trial regimen	0/22	0/21		
Probably related to trial regimen	1/22	2/21		
Possibly related to trial regimen	21/22	19/21		
CD4 count at week 12				
No. of patients in analysis	106	106		
Median (IQR) — no. of cells/μl	164 (97–226)	150 (100–226)		0.73
Decrease in HIV-1 RNA viral load of <2 $\log_{10}$ copies/ml at week 12 — no./total no. (%)	6/105 (5.7)	9/105 (8.6)	0.67 (0.25–1.81)	0.59

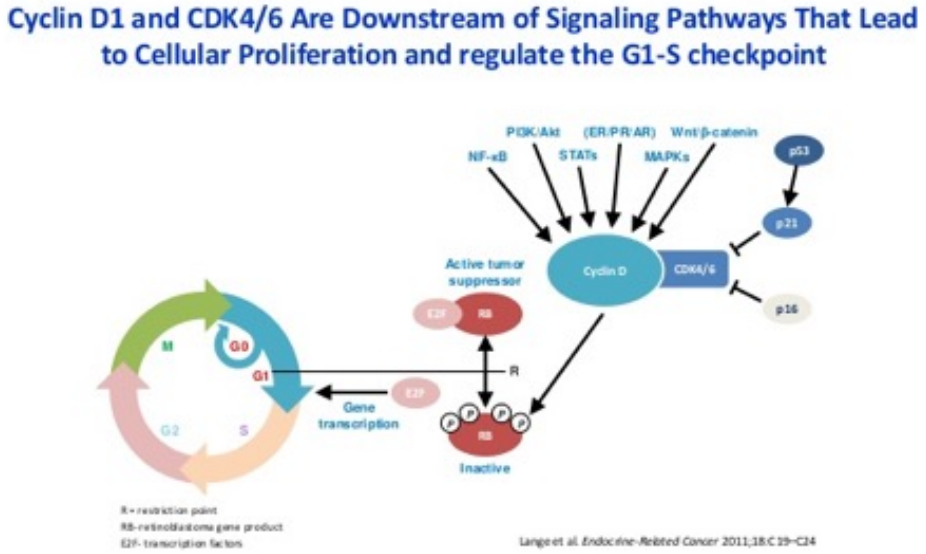
Prophylactic prednisone during the first 4 weeks after the initiation of ART in adult patients at high risk for tuberculosis-associated IRIS resulted in a 30% lower incidence of tuberculosis-associated IRIS than placebo. Prednisone use was not associated with an excess risk of severe infections, cancers, or adverse events. Prednisone might exert its effect by suppressing the symptoms of only mild cases of tuberculosis-associated IRIS, but our findings suggest that this was not the case. We found that prescription of open-label glucocorticoids, which are generally prescribed to treat patients with more severe tuberculosis-associated IRIS, was 53% less in the prednisone group than in the placebo group, and a significantly smaller proportion of patients in the prednisone group than in the placebo group met at least one major INSHI criterion.

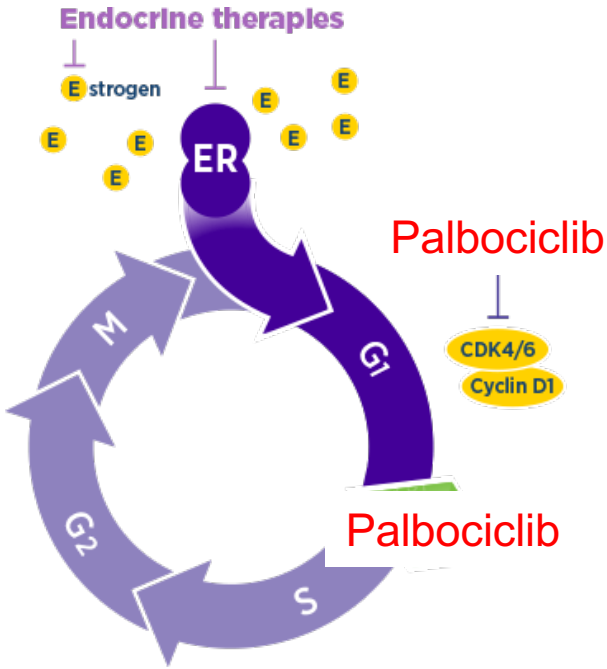
The development of tuberculosis-associated IRIS in 47% of the patients in the placebo group in our trial is higher than the pooled estimate of 18% from a meta-analysis of 40 cohort studies; our finding reflects our enrollment of patients at high risk for tuberculosis-associated IRIS who had low CD4 counts and short intervals between starting antituberculosis treatment and starting ART. A study in India involving patients with a similar high-risk profile showed an incidence of tuberculosis-associated IRIS of 54%. In one previous trial of a prophylactic strategy for IRIS, the CCR5 antagonist maraviroc was evaluated for prevention of all causes of IRIS, but the trial did not show a lower incidence of IRIS in the group that received maraviroc than in the group that received placebo.

Palbociclib ist der erste Vertreter der neuen Wirkstoffklasse der Cyclin-abhängige Kinase-Inhibitoren und ist bei peroraler Gabe wirksam. Palbociclib bewirkt durch die Hemmung der cyclin-abhängigen Kinasen CDK4 und CDK6 eine verringerte Zellproliferation während des Übergangs von Phase G1 zu S des Zellzyklus. Als häufigste Nebenwirkungen wurden Infektionen, Verringerung der Anzahl weißer und roter Blutkörperchen sowie der Blutplättchen, Müdigkeit, Appetitverlust, Entzündungen im Mund und an den Lippen, Übelkeit, Erbrechen, Durchfall, Hautausschlag und Haarausfall beobachtet.



Die Wirkung von Fulvestrant basiert darauf, dass es zum Einen als Antiöstrogen die Bindung des weiblichen Sexualhormons an den Östrogenrezeptor (ER) hemmt, und zum Anderen als ER-Downregulator die Dichte zellulärer Östrogenrezeptoren senkt. Dadurch wir eine Hemmung des hormonell bedingten Krebswachstums erreicht.

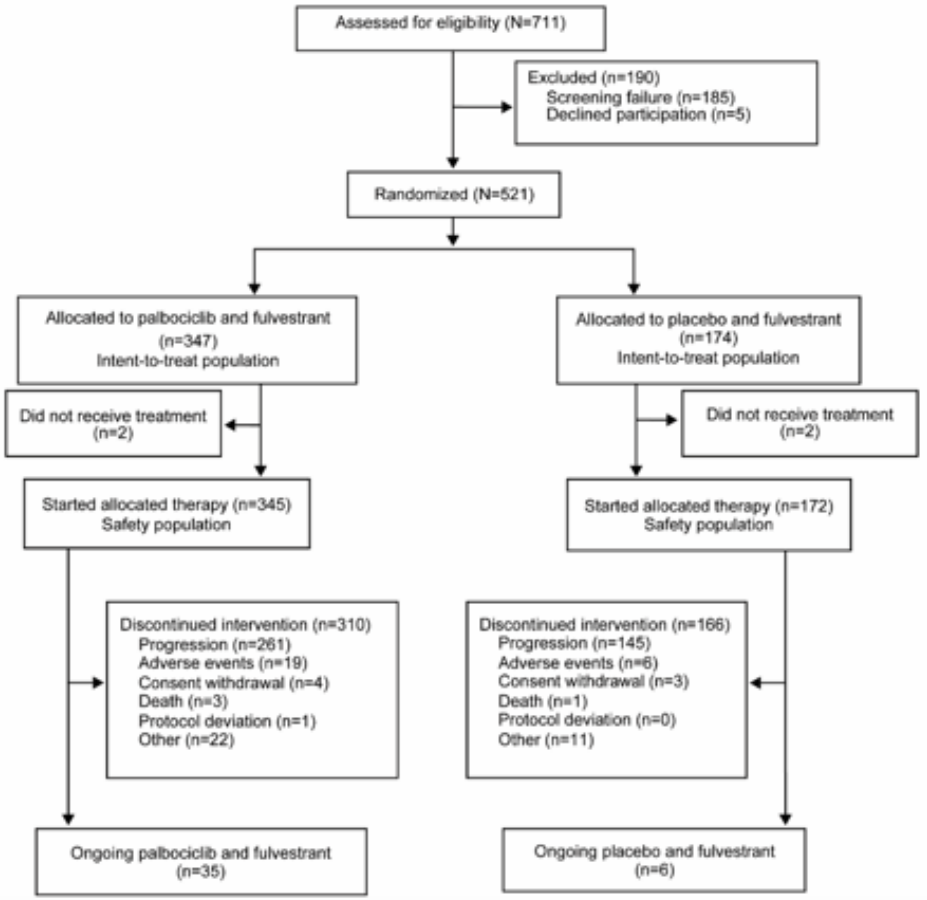


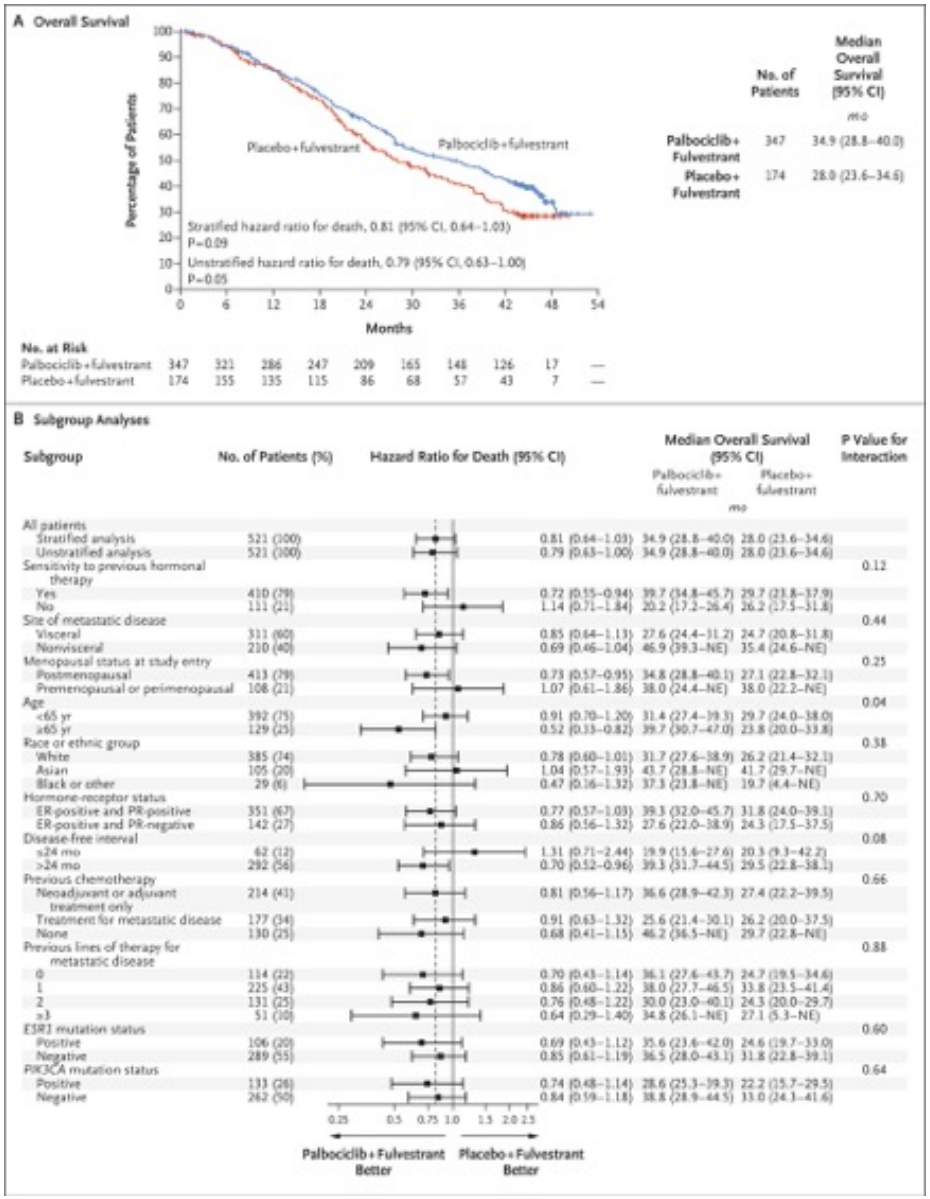


Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer

The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor palbociclib, in combination with fulvestrant therapy, prolongs progression-free survival among patients with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. We report the results of a prespecified analysis of overall survival. We randomly assigned patients with hormone-receptor–positive, HER2-negative advanced breast cancer who had progression or relapse during previous endocrine therapy to receive palbociclib plus fulvestrant or placebo plus fulvestrant. We analyzed overall survival; the effect of palbociclib according to the prespecified stratification factors of presence or absence of sensitivity to endocrine therapy, presence or absence of visceral metastatic disease, and menopausal status; the efficacy of subsequent therapies after disease progression; and safety.

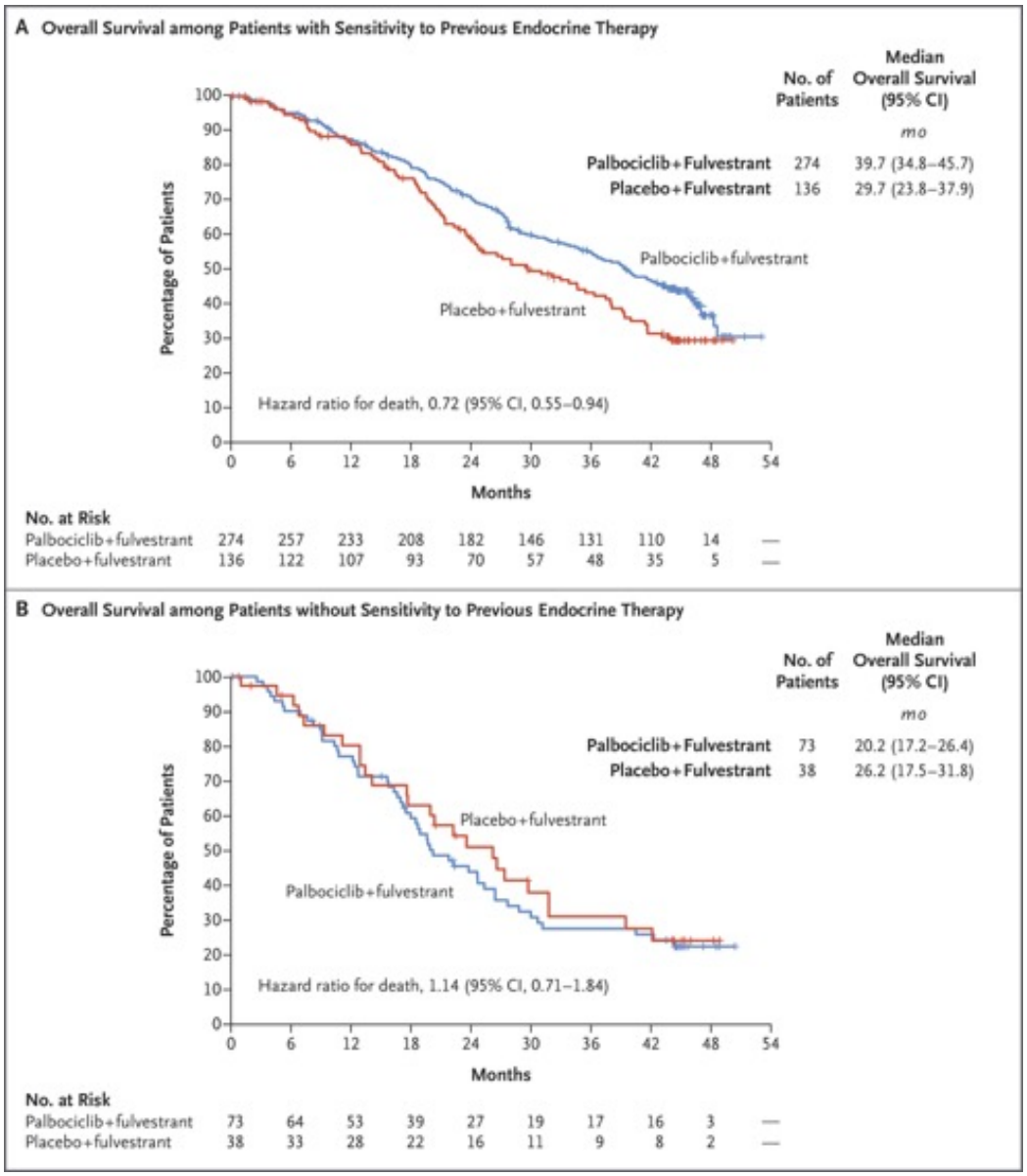
We conducted this prospective, international, randomized, double-blind, placebo-controlled, phase 3 trial to compare treatment with palbociclib–fulvestrant with placebo–fulvestrant in women with hormone-receptor–positive, HER2-negative advanced breast cancer who had disease progression after previous endocrine therapy. Women were enrolled regardless of menopausal status; postmenopausal women were at least 60 years of age, had undergone bilateral oophorectomy, or were younger than 60 years of age and had had a cessation of regular menses for at least 12 consecutive months.





Overall Survival in the Overall Population and According to Subgroup.

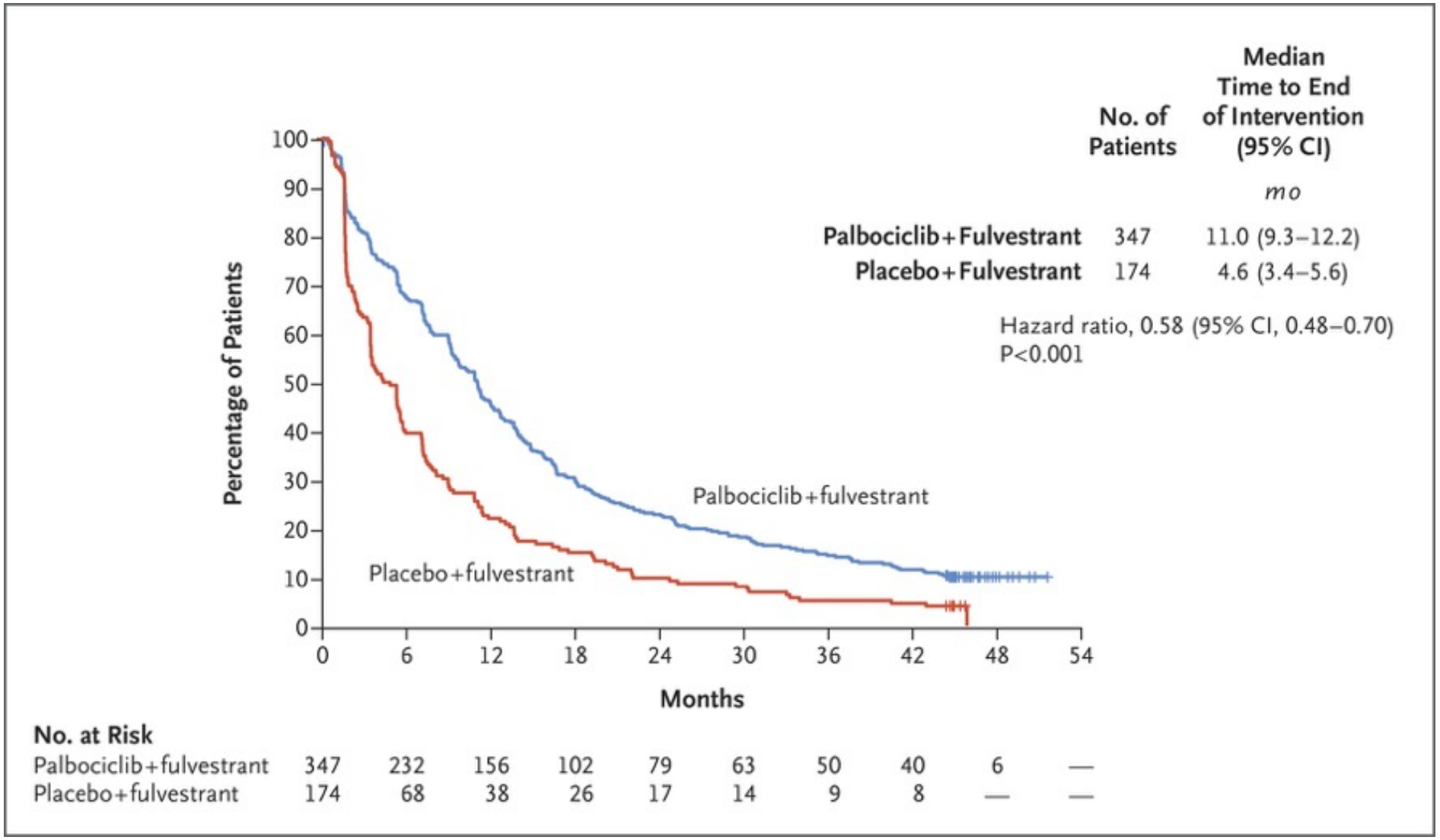
Panel A shows overall survival in the intention-to-treat population (all the patients who underwent randomization). Tick marks indicate censored data. Panel B shows a subgroup analysis of overall survival. Boxes represent hazard ratios for death, with error bars indicating 95% confidence intervals, in various subgroups according to characteristics of the patients at baseline. The prespecified stratification factors were the presence or absence of sensitivity to previous endocrine therapy, presence or absence of visceral metastatic disease, and menopausal status at trial entry. Race was reported by the patient; 2 patients (<1%) did not report their race on the case-report form. A total of 6% of the patients had estrogen receptor (ER)–negative, progesterone receptor (PR)–positive tumors. A total of 32% of the patients had received an initial diagnosis of metastatic disease or did not have data regarding a date of the initial diagnosis of early-stage disease, so they were not included in the estimation of values for the disease-free interval. Data regarding *ESR1* (encoding estrogen receptor 1) and *PIK3CA* (encoding phosphatidylinositol 3-kinase catalytic alpha polypeptide) were from a subgroup of patients who had samples of circulating tumor DNA that were tested for the mutations; 25% of the patients did not have adequate circulating tumor DNA for testing. NE indicates that the value could not be estimated.



Overall Survival According to Patients' Sensitivity to Previous Endocrine Therapy. Tick marks indicate censored data.

Among 410 patients with documented sensitivity to previous endocrine therapy, the median overall survival was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib–fulvestrant group and 29.7 months (95% CI, 23.8 to 37.9) in the placebo–fulvestrant group (hazard ratio for death, 0.72; 95% CI, 0.55 to 0.94)

Among 111 patients without documented sensitivity to previous endocrine therapy (also referred to as intrinsic endocrine resistance), the median overall survival was 20.2 months (95% CI, 17.2 to 26.4) in the palbociclib–fulvestrant group and 26.2 months (95% CI, 17.5 to 31.8) in the placebo–fulvestrant group (hazard ratio, 1.14; 95% CI, 0.71 to 1.84; P=0.12 for interaction)



Time from Randomization to the End of the Trial Intervention. Tick marks indicate censored data.

Table 1. Systemic Anticancer Therapies Received as First, Second, and Third or Greater Lines of Subsequent Treatment by More Than 10% of the Patients in Either Trial Group Who Discontinued the Intervention.*

Treatment	Palbociclib–Fulvestrant Group (N=347)			Placebo–Fulvestrant Group (N=174)		
	First Line	Second Line	Third Line or Greater	First Line	Second Line	Third Line or Greater
	number of patients (percent)					
Any†	248 (71)	182 (52)	131 (38)	140 (80)	113 (65)	85 (49)
Chemotherapy						
Any	138 (56)	133 (73)	121 (92)	87 (62)	76 (67)	76 (89)
Eribulin	7 (3)	13 (7)	42 (32)	3 (2)	11 (10)	29 (34)
Paclitaxel	31 (12)	39 (21)	42 (32)	31 (22)	18 (16)	28 (33)
Capecitabine	66 (27)	43 (24)	36 (27)	36 (26)	20 (18)	24 (28)
Doxorubicin	12 (5)	7 (4)	35 (27)	1 (1)	10 (9)	12 (14)
Vinorelbine	6 (2)	8 (4)	23 (18)	7 (5)	5 (4)	21 (25)
Gemcitabine	7 (3)	6 (3)	26 (20)	5 (4)	9 (8)	15 (18)
Cyclophosphamide	13 (5)	9 (5)	23 (18)	8 (6)	4 (4)	8 (9)
Carboplatin	5 (2)	6 (3)	19 (15)	1 (1)	5 (4)	7 (8)
Antihormonal agent						
Any	100 (40)	40 (22)	38 (29)	52 (37)	29 (26)	31 (36)
Exemestane	57 (23)	20 (11)	21 (16)	25 (18)	15 (13)	13 (15)
mTOR kinase inhibitor						
Any	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
Everolimus	40 (16)	17 (9)	20 (15)	21 (15)	12 (11)	13 (15)
CDK4/6 inhibitor‡						
Any	6 (2)	2 (1)	6 (5)	9 (6)	6 (5)	15 (18)
Palbociclib	4 (2)	2 (1)	5 (4)	7 (5)	6 (5)	13 (15)
Ribociclib	1 (<1)	0	1 (1)	2 (1)	0	1 (1)
Abemaciclib	1 (<1)	0	0	0	0	2 (2)

* Percentages in the first row were calculated on the basis of the number of patients in the intention-to-treat population. Percentages in the remaining rows were calculated on the basis of the number of patients who received any treatment after the discontinuation of the trial intervention (i.e., the values in the first row). The term mTOR denotes mammalian target of rapamycin.

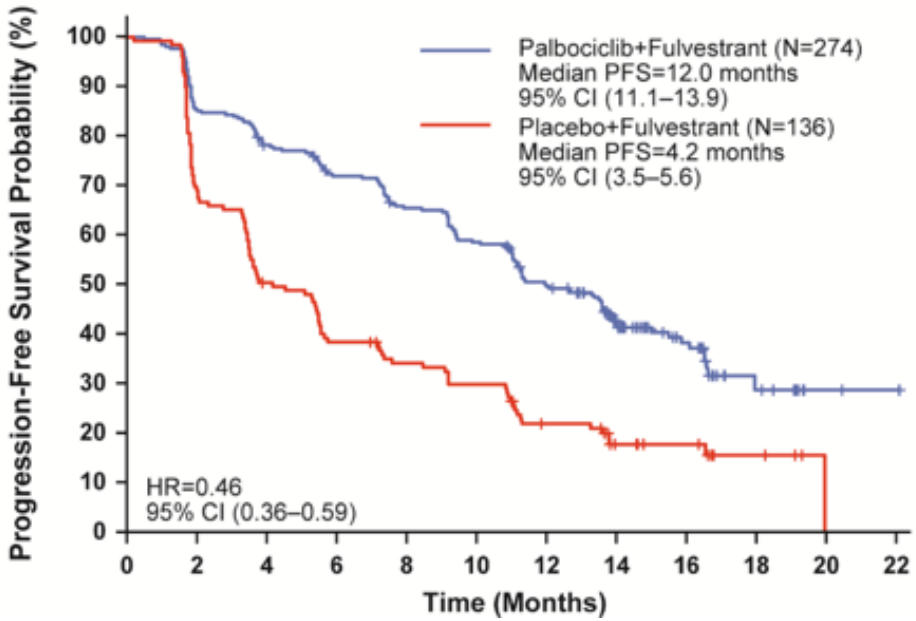
† One patient with missing data or partial information about start and stop dates for all reported follow-up therapies was not included in this analysis.

‡ In the placebo–fulvestrant group, 27 patients received inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) after disease progression: 3 patients received ribociclib only; 22 patients received palbociclib only, 2 of whom received palbociclib twice in combination with different endocrine therapies (24 counts in the table); and 2 patients received both palbociclib and subsequent abemaciclib (4 counts in the table).

Systemic Anticancer Therapies Received as First, Second, and Third or Greater Lines of Subsequent Treatment by More Than 10% of the Patients in Either Trial Group Who Discontinued the Intervention.

Neutropenia of grade 3 or 4 occurred in 70% of the patients receiving palbociclib–fulvestrant and in none of the patients receiving placebo–fulvestrant, anemia of grade 3 or 4 occurred in 4% and 2% of the patients, respectively, and thrombocytopenia of grade 3 or 4 occurred in 3% and none of the patients, respectively. Febrile neutropenia remained uncommon, occurring in 1% of the patients (3 of 345 patients) who received palbociclib–fulvestrant and in none of those who received placebo–fulvestrant. Nonhematologic adverse events of grade 3 or 4 were also uncommon.

Although the results of the analysis of overall survival did not meet the prespecified threshold for statistical significance, the addition of palbociclib to fulvestrant resulted in an absolute prolongation of overall survival of 6.9 months among patients with hormone-receptor–positive, HER2-negative advanced breast cancer who had disease progression after previous endocrine therapy. This result is consistent with the significant prolongation in progression-free survival that was observed with the addition of palbociclib to fulvestrant. Among patients with previous sensitivity to endocrine therapy, one of the largest subpopulations enrolled in the trial, overall survival was prolonged by 10.0 months. Taken together, the data from the PALOMA-3 trial showed that palbociclib in combination with fulvestrant led to a 6.9-month prolongation of overall survival, although the finding did not reach significance in the intention-to-treat population. In the subgroup of patients with sensitivity to previous endocrine therapy, overall survival was 10 months longer with palbociclib–fulvestrant than with placebo–fulvestrant.



Lymphedema after Breast Cancer Treatment

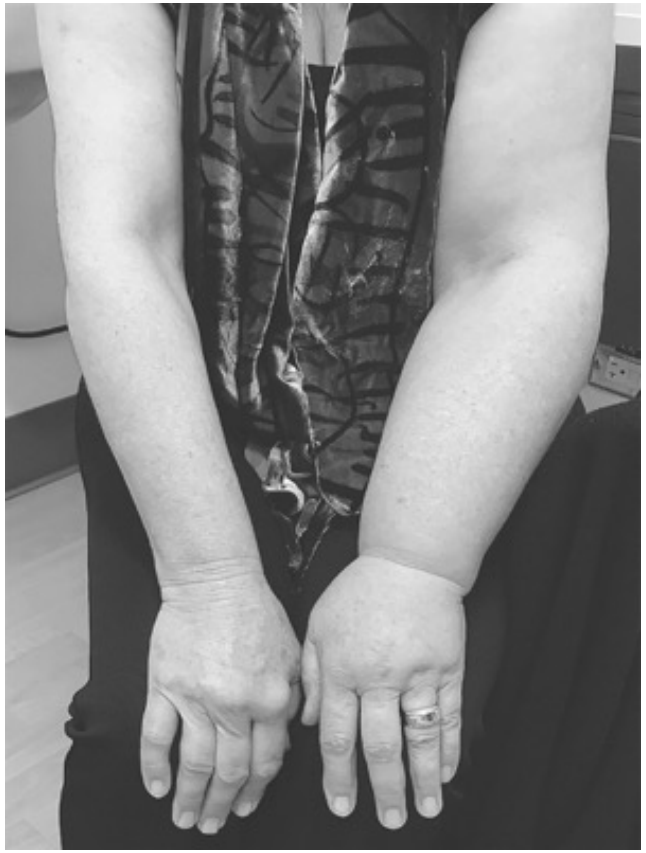
A 43-year-old perimenopausal woman who recently received a diagnosis of breast cancer visited her physician for follow-up after lumpectomy and axillary-node dissection, in which specimens of 12 lymph nodes were obtained. There was a positive finding only in the sentinel node. She is undergoing adjuvant radiotherapy. The patient is concerned about the development of lymphedema. She wonders what she can do to minimize the risk of this complication and how it would be managed if it were to develop. She has no coexisting conditions and no symptoms related to the arms. Her body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is 29. There is no detectable swelling on physical examination. How would you advise this patient?

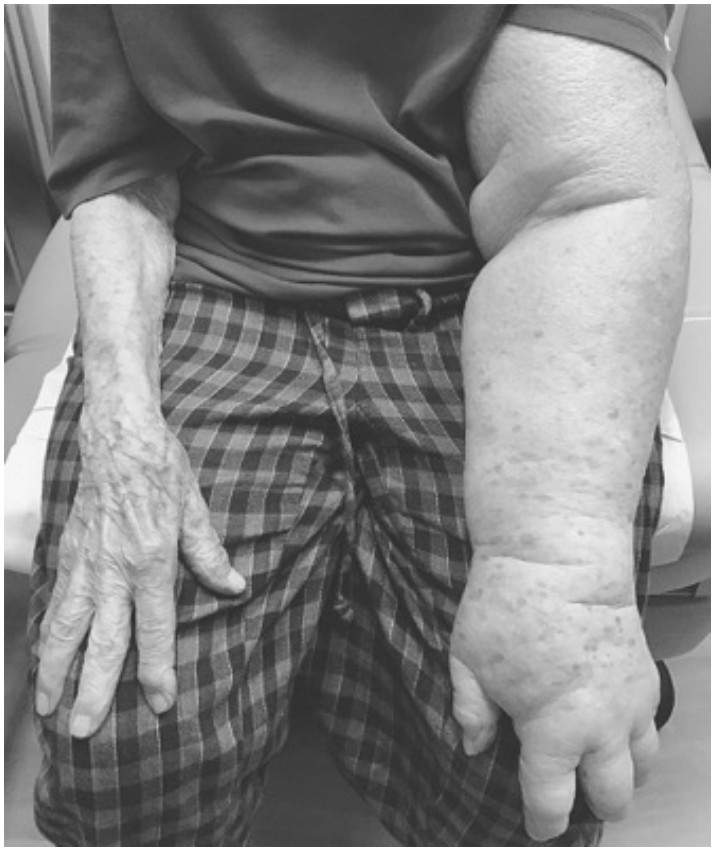
Lymphedema is the clinical expression of an impaired lymphatic circulation. Acquired lymphedema is most often the consequence of regionalized injury to a previously normal vasculature and is usually a consequence of trauma, infection, neoplasia, radiation damage, or surgical interventions, especially those that include lymphadenectomy. Estimates of the risk of lymphedema after breast cancer treatment vary widely, from 14 to 40%. Increasingly conservative approaches to surgery and radiotherapy have driven the estimated incidence closer to the lower limits of this range; sentinel-node sampling techniques reduce the estimated risk of breast cancer–associated lymphedema to 6 to 10%. Approximately 90% of the expected cases occur during the first 24 months after treatment,[8] but the remainder occur years to decades later.

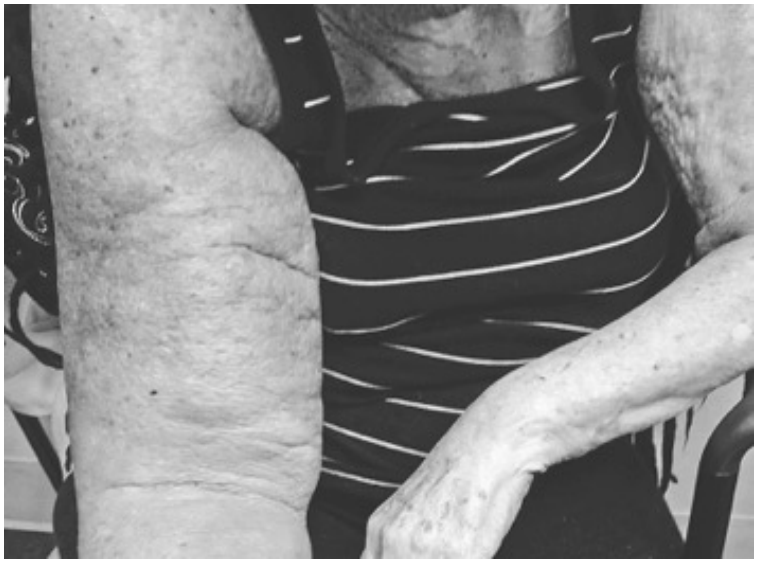
KEY CLINICAL POINTS

Lymphedema after Breast Cancer Treatment

- Breast cancer–related lymphedema is the most common form of lymphedema in the United States and other developed nations.
- Axillary lymph-node dissection and adjuvant radiation therapy are major risk factors.
- The diagnosis of lymphedema is generally based on the patient's risk status and physical findings.
- Early or subclinical lymphedema can be objectively detected and serially assessed, and surveillance is associated with earlier diagnosis and better outcomes.
- Treatment generally involves manual lymphatic drainage (a massage technique that stimulates lymphatic contractility), skin care, serial application of multilayer bandaging, and exercise.
- Exercise does not exacerbate and may ameliorate symptoms in patients with established lymphedema. For patients with an elevated body-mass index, weight reduction and maintenance strategies are indicated.
- Debulking surgeries appear to be helpful in the later, advanced stages of disease; there is also some evidence for benefit from microsurgery, but more data are needed regarding its effectiveness.







Magnetic resonance imaging is increasingly used in diagnosis and is reported to have greater specificity (85.7%) for the detection of delayed lymphatic drainage and greater sensitivity (100%) for the delineation of lymph vessels than radionuclide lymphoscintigraphy (which has rates of detection of 66.7% and 83.3%, respectively) when a reference standard based on clinical presentation and combined imaging results is used.

Strategies for Risk Reduction

The clinical appearance of breast cancer–associated lymphedema is thought to require both a causal lymphatic injury and one or more initiating factors that convert the latent injury into overt edema.[2] Clinical experience suggests that infection, inflammation, skin injury, or any state that increases capillary filtration are initiating factors.

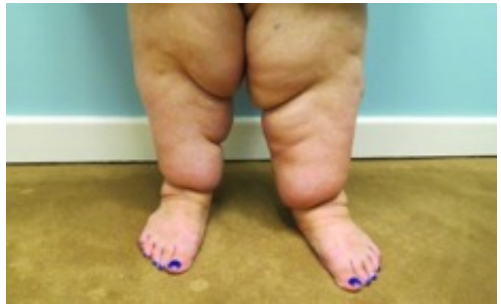
There is controversy regarding what interventions are appropriate for the reduction of risk. Common recommendations include the avoidance of high environmental temperatures as well as venipuncture, injection, and measurement of blood pressure on the side of the body on which breast surgery was performed. However, RCTs are needed to assess the efficacy of these approaches, and a recent observational study showed no significant associations between lymphedema and change in arm volume in women who had been treated for breast cancer and had a history of blood draws or injections. Moreover, prospective studies have not consistently supported any relationship between phlebotomy, venipuncture, blood pressure assessment, or air travel and risk of lymphedema. Given the association between BMI and the risk of lymphedema, weight loss is commonly recommended in patients who are overweight or obese, but the effect of weight loss on risk in such patients has not been formally studied.

Treatment

Historically, no medications have been shown to alleviate lymphedema. Instead, treatment involves various physiotherapeutic interventions. Decongestive lymphatic therapy relies heavily on manual lymphatic drainage, a massage technique that stimulates lymphatic contractility through gentle, directed stretching of the skin. In addition, decongestive lymphatic therapy includes skin care, serial application of multilayer bandaging, and exercise (gentle, repetitive contraction of the musculature beneath the bandages). Typically, the patient participates in 15 to 30 sessions over 4 to 6 weeks. Once a nadir of limb volume is attained, the patient can be transitioned to self-care. A cohort study in which patient condition was assessed before and after the implementation of a program involving comprehensive lymphatic therapy showed lower edema volume, enhanced lymphatic function, fewer symptoms, improved function and quality of life, and a lower incidence of cellulitis after implementation of the program than at baseline before treatment was initiated. A meta-analysis of seven RCTs showed no significant reduction in arm edema with manual lymphatic drainage as compared with standard treatment, but many of these trials were small and had other methodologic limitations.

Conclusions and Recommendations

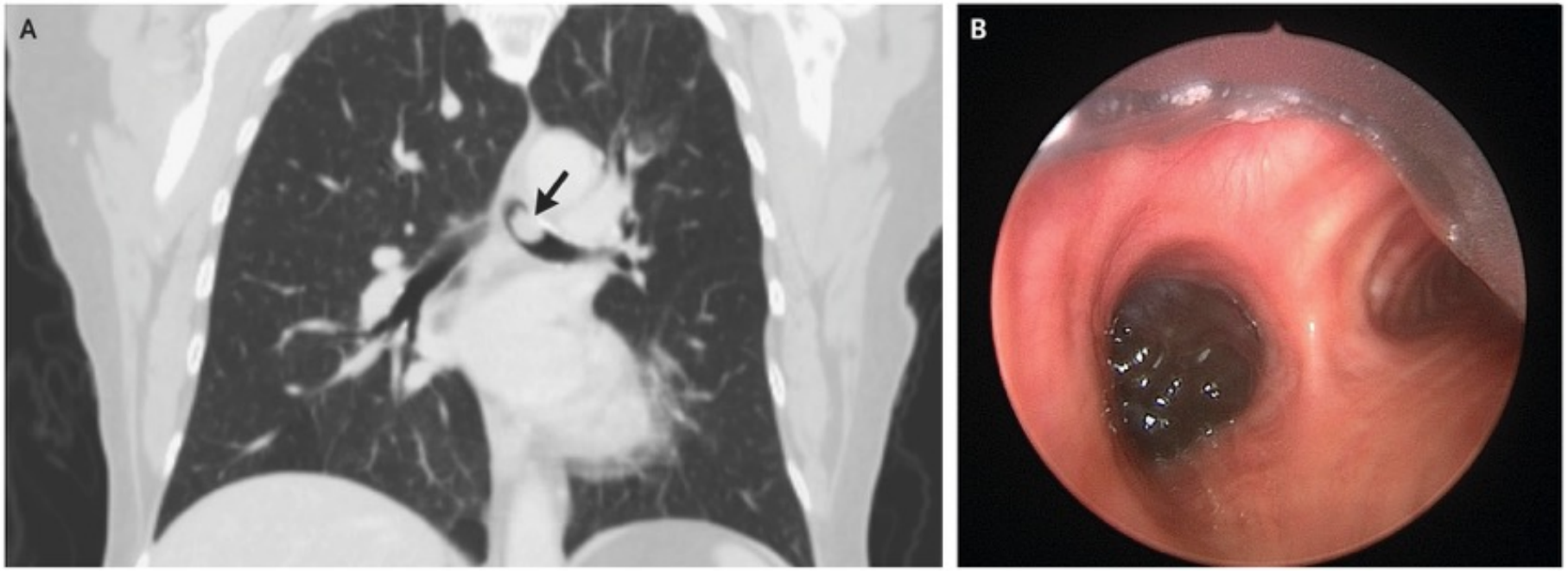
The patient described in the vignette is at increased risk for the development of lymphedema owing to her elevated BMI and her history of axillary lymph-node dissection, nodal metastasis, and radiotherapy. I would recommend a surveillance program that includes quarterly assessment of bioimpedance during this first year after treatment, which is when the majority of cases appear. There should also be prompt use of compression garments and, as necessary, use of decongestive physiotherapy for symptoms or for worrisome changes in bioimpedance. The patient should be encouraged to attain and maintain an ideal body weight through diet and regular exercise. The uncertain merits of conventional risk-reduction behaviors, including the use of a prophylactic compression sleeve, should be explained to the patient so that she can make informed, personalized decisions as to whether she should incorporate these strategies into her plans for aftercare.



Das Lipödem (von altgriech. „Fettschwellung“, aus λίπος lípos „Fett“ und οἴδημα, oídēma, „Schwellung“; in der Umgangssprache fälschlich auch als „Reithosenfettsucht“, „Reiterhosensyndrom“ oder „Säulenbein“ bezeichnet) ist eine voranschreitende Erkrankung. Sie ist gekennzeichnet durch die atypische, symmetrische Häufung von Fettgewebe seitlich an den Hüften und Oberschenkeln und kann aus der Lipohypertrophie hervorgehen[1]. Weiterhin können die Oberarme und im späteren Verlauf auch die Unterschenkel, Unterarme und der Nacken betroffen sein.

Das Lipödem tritt fast ausschließlich bei Frauen auf, nach der Pubertät, nach einer Schwangerschaft oder im Klimakterium. Hormonelle Veränderungen und Gewichtszunahme werden als Ursachen vermutet, ebenso eine genetische Prädisposition.

Das Lipödem ist nicht die Folge von Übergewicht. Es ist im Bereich seitlich an den Hüften und Oberschenkeln angesiedelt, wo eine Gewichtsreduktion generell wenig erfolgversprechend ist.



A 70-year-old woman was referred to the pulmonary clinic with a 2-month history of progressive shortness of breath that had been unresponsive to bronchodilators. Three years before presentation, a melanoma had been excised from her left shoulder. The results of lymph-node dissection at that time were negative for metastases. Physical examination was notable for an inspiratory and expiratory wheeze in the left lung. Computed tomography of the chest showed a polypoid lesion that obstructed the left main-stem bronchus (Panel A, arrow). Rigid bronchoscopy revealed a mobile, pigmented mass arising from the bronchus (Panel B and video). The mass was débrided with an electrocautery snare and argon plasma coagulation. Pathological examination of the mass confirmed a diagnosis of metastatic melanoma, with *BRAF* mutation. The patient's wheezing and shortness of breath completely resolved after the tumor was excised. Treatment of the melanoma with trametinib and dabrafenib was initiated.

Case Studies in Social Medicine — Attending to Structural Forces in Clinical Practice

Many clinicians and trainees see the social world as a messy, impenetrable black box: they may acknowledge its influence on their patients' health, but they lack the understanding and tools for incorporating it usefully into their diagnostic reasoning and therapeutic interventions. But the social sciences of health and medicine provide such tools — theories and methods for understanding social processes and intervening to effect change. Leading organizations in medical education have recommended providing additional training in social medicine, which deploys these approaches to improve health. In this issue, the *Journal* launches Case Studies in Social Medicine, a series of Perspective articles, to highlight the importance of social concepts and social context in clinical medicine. The series will use discussions of real clinical cases to translate these tools into terms that can readily be used in medical education, clinical practice, and health system planning. In their first year in medical school, all students learn to take a social history. As they transform their eyes, ears, and hands into sensors for detecting hidden causes of disease, they also learn to ask probing questions to illuminate patients' social contexts. What pathogenic exposures might a patient face en route to immigrate to the United States from Guatemala, in being subjected to police violence and arrest in a heavily patrolled nonwhite neighborhood, in working in pesticide-laden fields, or as a result of exclusion from health care coverage? Answers to such questions can dramatically change a diagnostic picture or therapeutic plan. Yet by the clinical years of medical school, students learn that the social history is often collapsed into a record of three biobehavioral exposures — to alcohol, tobacco, and illicit drugs. Much of what they read in clinical journals appears to corroborate the assumption that in clinical medicine, the biologic and behavioral world of a patient's body is more important than the social world outside it.

The great promise of precision medicine — that health care will be improved by greater investment in genomic and proteomic knowledge mediated through computational biology — overlooks both the limited contribution that genomics has thus far made to the understanding and treatment of human disease and the uneven uptake of even existing (and relatively inexpensive) diagnostic and therapeutic interventions, let alone the $10,000 blood tests that precision medicine has produced to date. If medicine is to reduce rather than augment health disparities, we will need solutions to both the social and the biologic bases of health and disease.

The goal of Case Studies in Social Medicine is to reunite these two intellectual traditions: the case study as a mode of teaching elements of diagnosis, therapeutics, and prognosis and the exploration of and response to the social forces affecting people's health. The clinical scenarios that will be presented hinge on social forces as much as on natural progression of diseases or twists of therapeutic decision making, demonstrating the inseparability of these forces from the logic of clinical medicine.

Social structures, important forces in determining health, are integral to the problems clinicians face every day. We are convinced that it is time to develop approaches to addressing those forces, allowing clinicians to participate in building more effective health systems and a healthier society.

Medicalization and Demedicalization — A Gravely Disabled Homeless Man with Psychiatric Illness

A 55-year-old man, Mr. N. presented to the UCLA emergency department (ED) reporting auditory hallucinations and thoughts of suicide. This was his sixth visit to the UCLA ED over a period of a few months; each visit was precipitated by his losing his medication and experiencing worsening psychotic symptoms and suicidal thoughts. During all but one of these visits, the examining physicians concluded that Mr. N. did not meet the criteria for psychiatric inpatient care. A typical note read, "He is only in the ER for food and shelter. …He has been homeless for many years. Given that he came to the ER to seek shelter, he has proven himself capable of making plans." Mr. N., first diagnosed with schizophrenia about 30 years earlier, had had numerous hospitalizations. In keeping with trends in the United States toward shorter and less frequent inpatient psychiatric admissions, Mr. N.'s rate of hospitalization had diminished over recent years. The resident who evaluated him this time doubted that he would benefit from hospitalization. She explained to her attending physician that Mr. N. consistently stopped taking prescribed antipsychotics after discharge. She questioned the value of investing resources in an admission, since he would probably be back on the street in a few days, neither taking his medications nor following up on clinic referrals. Suggesting that Mr. N. was more interested in escaping the streets than in psychiatric treatment, and feeling pressure to allocate beds to patients she saw as having more acute medical needs, the resident concluded, "We should give him 10 mg of Zyprexa [olanzapine] now, and he should be more coherent in a few hours so we can let him leave.

This time, however, the attending argued that Mr. N.'s homelessness was as much a symptom of his psychosis as his hallucinations were and that the only way to genuinely treat his complex disease — a disease expressed in both the social register (homelessness, social isolation) and the psychiatric one (auditory hallucinations, suicidal ideation) — was to hospitalize him. At least temporarily, such care could address both social and psychiatric issues, whereas prescribing olanzapine and sending Mr. N. back to the streets was not therapeutic. So the resident placed him on a 72-hour hold for grave disability and ordered that he be admitted.

Social Analysis Concept: Medicalization and Demedicalization

Mr. N.'s case hinges on physicians' interpretations of whether his problems and their possible solutions are or are not medical in nature and therefore whether they are within the scope of practice of medical institutions. This tension can be understood using the paired concepts of medicalization and demedicalization, which social scientists outlined in the 1960s and 1970s.

Demedicalization

Demedicalization is the transformation of problems formerly understood to be medical in nature into problems understood to be nonmedical. Like its opposite, medicalization, demedicalization occurs at multiple levels, ranging from the conceptualization of etiology to the understanding of whether interventions for problems are appropriately medical or nonmedical. From the mid-1960s onward, fiscal crises, federal government policies, and ideological beliefs about community care propelled states to abandon state hospital care. Largely in response to these changes, psychiatrists came to view patients' social ills as outside their purview. Mr. N.'s life over the past 30 years illustrates the receding domain of psychiatric responsibility. Yet demedicalization of the social ravages of psychiatric disease — which enabled physicians to narrow the disease aspects for which they claimed responsibility — deserves equal blame for Mr. N.'s decline.

Clinical Implications

Medicalization was conceived as a critique of medical power's overreach into everyday life. The concepts of medicalization and demedicalization can be useful in questioning our understanding of and care for diseases that blur arbitrary boundaries between the social and the medical. Social scientists generally consider demedicalization of a set of behaviors to be an advance and attribute the original medicalization to cultural ignorance. But demedicalization is not always liberatory and can result in reduced options for people whose suffering from illness is augmented in the process.

Case Follow-up

Mr. N. never returned to the ED and is unlikely to do so for many years: in March, he was arrested and charged with a felony and now resides in Twin Towers Jail in Los Angeles, awaiting trial and with no hope of raising $100,000 for bail.

A 68-Year-Old Woman with Back Pain and a Remote History of Breast Cancer

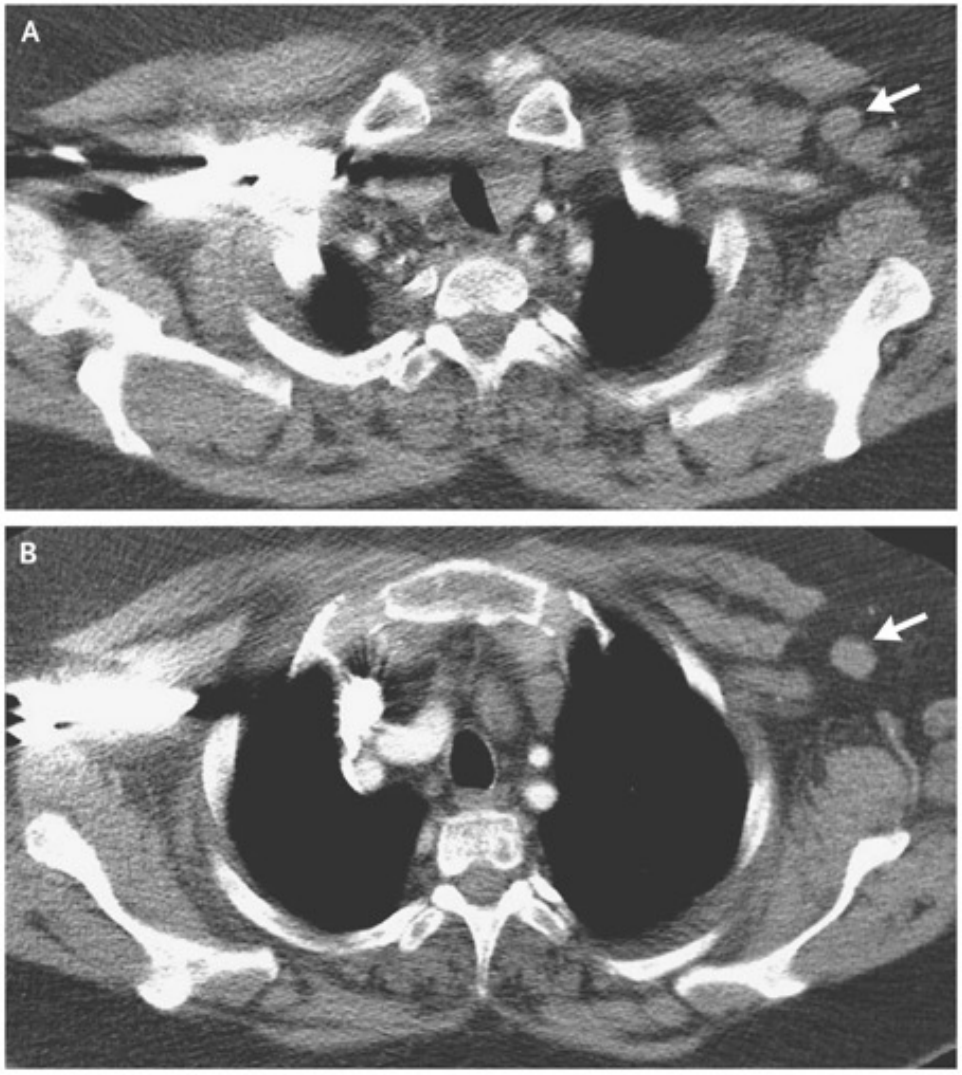
A 68-year-old woman with a history of bilateral breast cancer was evaluated at the oncology clinic of this hospital for back and pelvic pain.

Twenty-five years before the current evaluation, the patient was noted to have a small lump in her left breast during a routine gynecologic examination. A mammogram showed no abnormality. A biopsy of the breast mass was performed, and examination of the biopsy specimen revealed evidence of invasive carcinoma that was estrogen receptor (ER)–positive and progesterone receptor (PR)–positive. Partial mastectomy of the left breast and dissection of axillary lymph nodes were performed, and examination of the specimens revealed the presence of two separate and distinct primary tumors. Histopathological analysis revealed ER-positive invasive ductal carcinoma (first primary tumor, 3 cm in diameter) and invasive lobular carcinoma (second primary tumor, 3 cm in diameter). Of the 10 dissected axillary lymph nodes, 2 were positive for carcinoma. A bone scan and chest radiograph did not show evidence of metastatic disease, and blood electrolyte levels and results of liver- and renal-function tests were normal. The patient participated in a clinical trial, in which she was randomly assigned to receive initial treatment with four cycles of cyclophosphamide, doxorubicin, methotrexate, and fluorouracil followed by radiation therapy of the breast. In accordance with the clinical trial protocol, she did not receive tamoxifen but was monitored regularly with active surveillance.

Twelve years after the initial diagnosis (13 years before the current evaluation), routine surveillance mammography revealed a cluster of calcifications in the right breast. An excisional biopsy was performed, and examination of the biopsy specimen revealed evidence of ductal carcinoma in situ and lobular neoplasia, with positive margins. Genetic testing for a *BRCA* mutation was negative. The patient underwent partial mastectomy of the right breast followed by adjuvant radiation therapy, with a plan to complete 5 years of adjuvant anastrozole therapy.

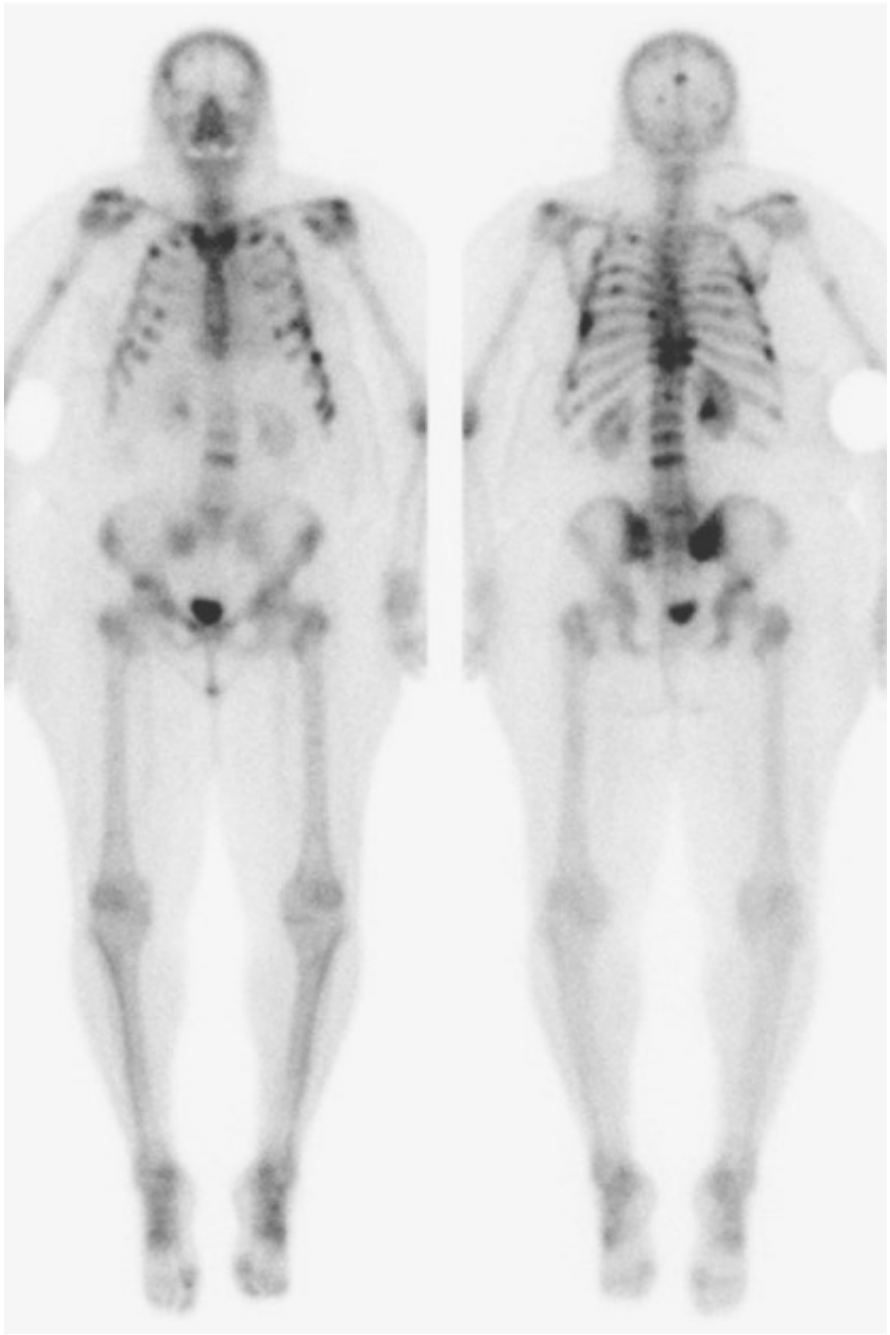
Four years later (9 years before this evaluation), the patient had exertional dyspnea for 3 weeks. A ventilation–perfusion scan showed that there was a high probability of pulmonary embolism, and a d-dimer test was positive; the patient received a diagnosis of pulmonary embolism.

Eight months before the current evaluation, pleuritic chest pain and axillary pain developed, and recurrent pulmonary embolism was again suspected. Repeat mammography and breast ultrasonography were performed and revealed an enlarged left axillary lymph node (13 mm by 11 mm) that corresponded to one of the nodes seen on chest CT.



CT Scan of the Chest. Eight months before the current evaluation, a CT scan of the chest was obtained after the intravenous administration of contrast material. Axial images show enlargement of a left axillary lymph node (Panel A, arrow) and of a left subpectoral lymph node (Panel B, arrow). These findings arouse concern about metastatic disease.

Repeat mammography and breast ultrasonography were performed and revealed an enlarged left axillary lymph node (13 mm by 11 mm) that corresponded to one of the nodes seen on chest CT. Given the depth of the lymph node, biopsy with ultrasonographic guidance was considered to be too technically difficult to perform, particularly since the patient was receiving warfarin therapy and had an increased risk of bleeding. After the patient's surgical oncologist was consulted, a plan for short-term surveillance with imaging studies was implemented.



Whole-Body Bone Scan. A whole-body technetium-99m–methylene diphosphonate bone scan, obtained in anterior and posterior views, shows multiple sites of increased uptake in the calvarium, thoracolumbar vertebral bodies, bilateral ribs, right scapula, right humeral diaphysis, and pelvis. These findings are consistent with osseous metastases.
A focal hypodensity (12 mm in diameter) was present in the left lobe of the liver but could not be further characterized. A follow-up whole-body bone scan with technetium revealed multiple sites of increased uptake throughout the axial and appendicular skeleton.

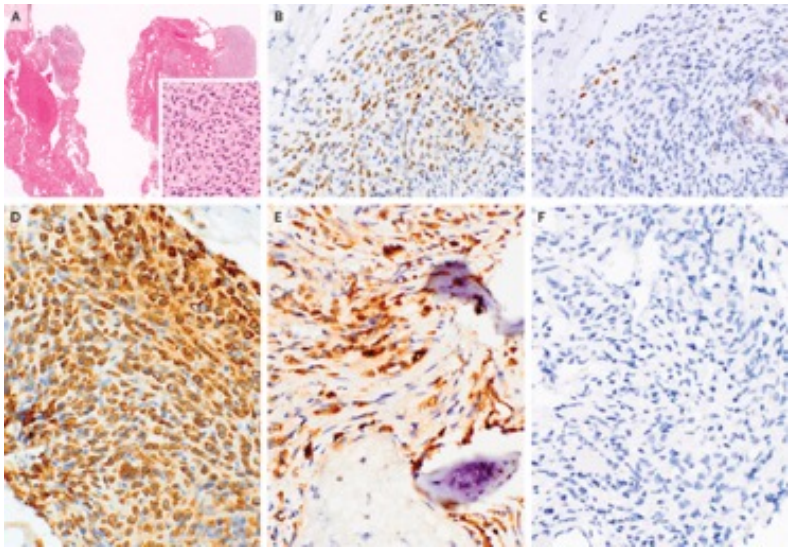
In addition, we would now test the tumor tissue for the presence of human epidermal growth factor receptor 2 (HER2), because the test result would guide the decision regarding whether to administer anti-HER2–directed therapy, such as trastuzumab. We would administer chemotherapy before radiation therapy, rather than radiation therapy before chemotherapy, since the approach of chemotherapy before radiation is associated with a lower incidence of distant metastasis. Finally, we would recommend adjuvant endocrine therapy, such as an aromatase inhibitor, for at least 5 years to lower the risk of disease recurrence.

Biopsy of the sacrum was performed, and examination of the biopsy specimen revealed medium-sized dyshesive tumor cells in a single-cell pattern. On immunohistochemical staining, the tumor cells showed expression of cytokeratin, mammaglobin, and ER and PR proteins and did not show expression of E-cadherin or overexpression of HER2 protein. These findings support the diagnosis of metastatic breast carcinoma of the lobular type.[14] Although the risk of recurrence in women with breast cancer is correlated with clinicopathological features such as tumor size and lymph-node status, the risk of late recurrence (after 5 years) is especially associated with hormone receptor–positive breast cancer.

Table 1. Laboratory Data.

Variable	Reference Range, Adults*	This Hospital, on Evaluation at Oncology Clinic
Hemoglobin (g/dl)	12.0–16.0	9.9
Hematocrit (%)	36.0–46.0	30.3
White-cell count (per mm^3)	4500–11,000	5030
Differential count (%)		
Polymorphonuclear cells	40–70	58.8
Lymphocytes	22–44	30.8
Monocytes	4–11	5.9
Eosinophils	0–8	3.2
Basophils	0–3	1.1
Platelet count (per mm^3)	150,000–400,000	167
International normalized ratio	0.9–1.1	2.4

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

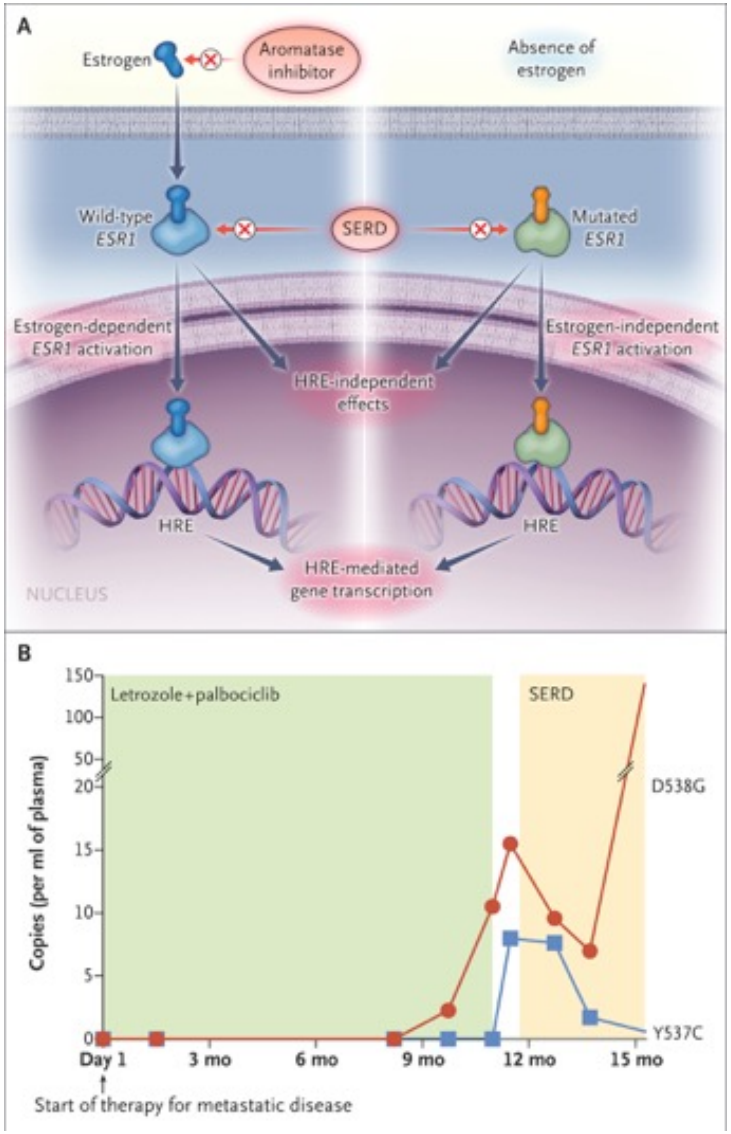


Biopsy Specimen of the Sacrum. Hematoxylin and eosin staining of the sacral mass shows evidence of metastasis of lobular carcinoma infiltrating the bone (Panel A); the inset shows metastatic tumor at higher magnification. Immunohistochemical stains are positive for estrogen receptor protein (Panel B), progesterone receptor protein (Panel C), cytokeratin (Panel D), and mammaglobin (Panel E) and negative for E-cadherin (Panel F).

Several clinical trials show prolonged progression-free survival with the addition of a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, or abemaciclib) to endocrine therapy in patients with ER-positive metastatic breast cancer. On the basis of these findings, therapy with palbociclib and letrozole was started in this patient. Palbociclib was discontinued after a month because of clinically significant side effects, including nausea and dry heaves; letrozole was continued. The patient's disease status was monitored closely, and a year later, restaging scans unfortunately showed evidence of disease progression with new sites of bone metastasis. Letrozole was discontinued, and we reviewed second-line therapeutic strategies, including fulvestrant and exemestane plus everolimus.

Pathological Discussion

A "liquid biopsy" was performed to obtain a specimen containing circulating tumor DNA (ctDNA) for genotyping analysis. Analysis of a blood specimen containing ctDNA was performed with a commercially available, Clinical Laboratory Improvement Amendments–certified, next-generation sequencing–based assay that can detect mutations in 70 genes. Two mutations in the estrogen receptor 1 gene (*ESR1*), encoding ER alpha protein, were detected: *ESR1* ENST00000440973 c.1610A→G, ENSP00000405330 p.Y537C (Y537C) and *ESR1* ENST00000440973 c.1613A→G, p.ENSP00000405330 p.D538G (D538G), in trans. These findings suggest potential resistance to aromatase inhibitors. I suspect that treatment with letrozole resulted in the emergence of *ESR1* mutations as a mechanism of acquired resistance.



A shows the effect of an aromatase inhibitor and a selective estrogen-receptor degrader (SERD) in wild-type and mutated *ESR1*. Mutated *ESR1* leads to activation of the estrogen receptor (ESR1) even in the absence of estrogen. Panel B shows the effect of letrozole plus palbociclib (with palbociclib discontinued after 1 month of treatment) and a SERD in this patient, who had two *ESR1* mutations (D538G and Y537C).

Given the patient's interest in trials of genotype-directed targeted therapy, she was enrolled in a clinical trial evaluating a new SERD (ClinicalTrials.gov number, NCT01823835). Initially, she did well, with evidence of disease control noted on restaging scans. However, a few months later, restaging scans showed evidence of disease progression with new liver metastasis. A liver biopsy was performed (according to an institutional review board–approved protocol) to evaluate for potentially actionable mutations and to gain an understanding of therapeutic resistance.

Mutational analysis of the breast cancer metastasis to the liver was performed on formalin-fixed, paraffin-embedded tissue with the SNaPshot next-generation sequencing assay, a clinical DNA-based assay that detects single-nucleotide variants and insertions and deletions in 91 genes. A pathogenic frameshift variant in the *CDH1* gene, encoding cadherin 1, was detected (*CDH1* ENST00000261769.5 c.1947dupT, ENSP00000261769.4 p.Ile650TyrfsTer13), a finding that supports the diagnosis of lobular carcinoma. Two additional variants of unknown clinical significance were identified: an in-frame deletion in the *PIK3CA* gene, encoding phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA* ENST00000263967.3 c.328_330delGAA, ENSP00000263967.3 p.Glu110del), and a splice-site variant in the *AURKA* gene, encoding aurora kinase A (*AURKA* ENST00000395909.4 c.566+1G→A). Finally, manual review of codons 537 and 538 in the *ESR1* gene revealed wild-type sequences.

Capecitabine therapy was started in this patient. She was recently seen in the medical oncology clinic and was doing well. We are actively monitoring her disease status closely, using standard imaging tests and circulating biomarkers, while also monitoring the latest research developments in precision oncology.

Final Diagnosis

Hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer of the lobular type, with *ESR1* mutations.

Capecitabin ist eine Vorstufe (Prodrug) von 5-Fluoruracil und wird im Tumor in die aktive Substanz umgewandelt. Die Substanz ist oral wirksam und wird zur Therapie von metastasiertem Dickdarmkrebs, metastasiertem oder lokal fortgeschrittenem Mammakarzinom und zur palliativen Therapie des Magenkarzinoms eingesetzt.

Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial

Preterm delivery during pregnancy (<37 weeks' gestation) is a leading cause of perinatal mortality and morbidity. Treating bacterial vaginosis during pregnancy can reduce poor outcomes, such as preterm birth. We aimed to investigate whether treatment of bacterial vaginosis decreases late miscarriages or spontaneous very preterm birth. PREMEVA was a double-blind randomised controlled trial done in 40 French centres. Women aged 18 years or older with bacterial vaginosis and low-risk pregnancy were eligible for inclusion and were randomly assigned (2:1) to three parallel groups: single-course or triple-course 300 mg clindamycin twice-daily for 4 days, or placebo. Women with high-risk pregnancy outcomes were eligible for inclusion in a high-risk subtrial and were randomly assigned (1:1) to either single-course or triple-course clindamycin. The primary outcome was a composite of late miscarriage (16–21 weeks) or spontaneous very preterm birth (22–32 weeks), which we assessed in all patients with delivery data (modified intention to treat).

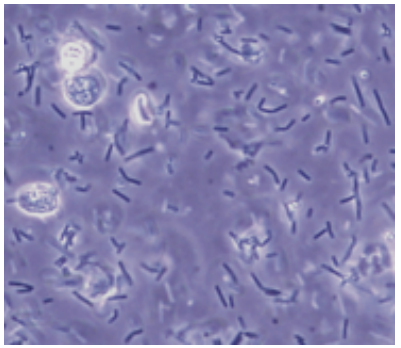
Bacterial vaginosis is an excessive growth of certain vaginal bacteria leading to a major imbalance of the vaginal microbiota, characterised by a decreased abundance of *Lactobacillus* species and an increased abundance of anaerobes and genital mycoplasmas. Bacterial vaginosis can be diagnosed either clinically, with the Amsel criteria (ie, presence of clue cells, a vaginal pH greater than 4·5, profuse white discharge, and a fishy odor.

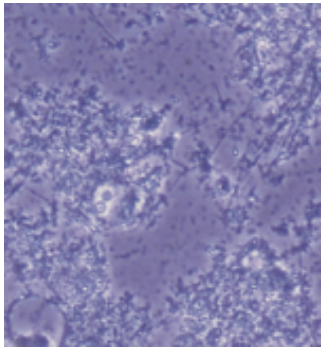
		One course (n=943)	Three courses (n=968)	Total (n=1911)	
Mean gestational age at randomisation, weeks		12·3 (2·2)	12·4 (2·1)	12·3 (2·2)	12·4 (2·1)
Mean maternal age, years		27·9 (5·4)	28·0 (5·4)	28·0 (5·4)	27·7 (5·5)
Educational level					
	Primary school	85 (9·0%)	82 (8·5%)	167 (8·7%)	90 (9·4%)
	High school or technical school	399 (42·3%)	459 (47·4%)	858 (44·9%)	418 (43·6%)
	Higher education	458 (48·6%)	425 (43·9%)	883 (46·2%)	446 (46·6%)
Nulliparous		471 (49·9%)	498 (51·4%)	969 (50·7%)	521 (54·3%)
Smoking at the beginning of pregnancy		323 (34·2%)	346 (35·7%)	669 (35·0%)	287 (30·0%)
History of miscarriage <16 weeks		207 (22·0%)	195 (20·1%)	402 (21·0%)	174 (18·2%)

Der Nugent Score

Die vaginale Mikrobiota der gesunden Frau unterliegt ethnischen, genetischen und äußeren Einfüssen. Laktobazillen dominieren dabei meist in einem balancierten Ökosystem. Bei BV/Dysbiose erstarken *L. iners* und zahlreiche BV-assoziierte Bakterien, meist mit *G. vaginalis*, und bilden ab einer kritischen Mindestmenge und Zusammensetzung polymikrobielle Bioflme. BV disponiert zu aszendierenden Infektionen und Akquisition von STIs sowie zu Spätaborten, Frühgeburten und puerperalen Infektionen. Zur Therapie kommen Clindamycin vaginal, Metronidazol oral oder vaginal oder Dequaliniumchlorid vaginal infrage. Zur Reduk-tion von Frühgeburten eignet sich oral Clindamycin im 1. Trimenon. Oral oder vaginal verabreichte Laktobazillen sind geeignet, die Heilungsergebnisse von Dysbiosen und der BV nach leitliniengerechter Therapie zu verbessern. Das Nativpräparat bleibt die klinisch bedeutsamste diagnostische Maßnahme zur Unterscheidung von normal und abnormal. Unter dem Einfuss von Östrogenen proliferiert das Vaginalepithel und speichert Glykogen. Progesteron fördert die Zytolyse. So wird Glykogen für Laktobazillen frei und von ihnen zu Glukose und Maltose gespalten. Dabei entsteht Laktat und schaft den physiologischen pH-Wert von 3,8–4,4.

- grau-weißer Fluor,
- fischiger Geruch,
- pH > 4,5 (besonders wenn 10%ige Kalilauge zugeführt wird) und
- mindestens 20 % „Schlüsselzellen“ (Abb. 2





Score	Laktobazillen (grampos. Stäbe)	Gramneg. Stäbchen (Gardenella, Prevotella etc.)
0	> 30 / Feld : 4 x	0
1	5–30 : 3 x	< 1 / Feld : 1 x
2	1–5 : 2 x	1–5 : 2 x
3	1 : 1 x	5–30 : 3 x
4	0	>30 : 4 x

Pregnancy primary and secondary outcomes in the modified intention-to-treat population

Primary outcome						
Late miscarriage or spontaneous very preterm delivery 16–32 weeks (plus 6 days) *		8 (0·8%)	14 (1·5%)	22 (1·2%)	10 (1·0%)	1·10 (0·53–2·32); p=0·82
Secondary outcomes						
Hospitalisation for threatened preterm delivery		71 (7·4%)	93 (9·7%)	164 (8·6%)	80 (8·4%)	1·03 (0·77–1·38); p=0·83
Hospitalisation for premature rupture of membranes ≥24 h		25 (2·7%)	28 (2·9%)	53 (2·8%)	30 (3·1%)	0·88 (0·55–1·44); p=0·29
Mean number of days of hospitalisation for premature PROM or PROM		3·6 (3·6)	4·2 (4·5)	3·9 (4·1)	5·6 (12·7)	NA; p=0·17
Prenatal signs of chorioamnionitis †		14 (1·5%)	10 (1·0%)	24 (1·3%)	8 (0·8%)	1·51 (0·65–3·67); p=0·31
Abruptio placentae		5 (0·5%)	8 (0·8%)	13 (0·7%)	11 (1·2%)	0·59 (0·25–1·42); p=0·20
Premature rupture of the membranes		147 (15·6%)	128 (13·3%)	275 (14·4%)	141 (14·7%)	0·98 (0·78–1·22); p=0·82
	<37 weeks	21 (2·3%)	21 (2·2%)	42 (2·2%)	18 (1·9%)	1·18 (0·65–2·13); p=0·57
	≥37 weeks	126 (13·4%)	107 (11·1%)	233 (12·2%)	123 (12·9%)	0·94 (0·74–1·20); p=0·63
Preterm delivery 22–36 weeks (plus 6 days)		62 (6·6%)	66 (6·9%)	128 (6·7%)	56 (5·9%)	1·15 (0·85–1·56); p=0·37
	Spontaneous	43 (4·6%)	48 (5·0%)	91 (4·8%)	39 (4·1%)	1·17 (0·81–1·69); p=0·40
	Induced	19 (2·0%)	18 (1·9%)	37 (1·9%)	17 (1·8%)	1·09 (0·62–1·93); p=0·76
Hyperthermia during labour (≥38°C)		22 (2·3%)	37 (3·8%)	59 (3·1%)	31 (3·2%)	0·95 (0·61–1·48); p=0·83
Maternal postpartum fever (≥38°C)		26 (2·8%)	31 (3·2%)	57 (3·0%)	24 (2·5%)	1·20 (0·74–1·94); p=0·46
Abscess of abdominal wall or episiotomy (post-partum)		3 (0·3%)	4 (0·4%)	7 (0·4%)	3 (0·3%)	1·17 (0·30–4·52); p>0·99

Fetal and neonatal secondary outcomes according to maternal treatment assignment (≥22 weeks)

		Clindamycin			Placebo (n=955)	Relative risk (95% CI); p value
		One course (n=945)	Three courses (n=953)	Total (n=1898)		
Fetal death ≥22 weeks		4 (0·4%)	5 (0·5%)	9 (0·5%)	6 (0·6%)	0·75 (0·27–2·11); p=0·59
Admission to neonatal intensive care unit		71 (7·5%)	70 (7·3%)	141 (7·4%)	59 (6·3%)	1·20 (0·89–1·60); p=0·23
Neonatal pulmonary disease						
	Need for ventilation (≥24 h)	15 (1·6%)	16 (1·7%)	31 (1·6%)	20 (2·1%)	0·78 (0·43–1·42); p=0·38
	Mean duration of ventilation, days	10·7 (17·0)	13·0 (21·6)	11·9 (19·2)	5·2 (9·8)	NA; p=0·10
	Oxygen therapy ≥36 weeks	1 (0·1%)	4 (0·4%)	5 (0·3%)	4 (0·4%)	0·60 (0·14–2·64); p=0·48
Neonatal sepsis *		21 (2·2%)	27 (2·8%)	48 (2·5%)	31 (3·3%)	0·77 (0·49–1·22); p=0·27
	Suspected	19 (2·0%)	23 (2·4%)	42 (2·2%)	27 (2·9%)	0·78 (0·46–1·31); p=0·31
	Proved	2 (0·2%)	4 (0·4%)	6 (0·3%)	4 (0·4%)	0·75 (0·19–3·18); p=0·74
Severe lesions on transfontanellar ultrasonography		5 (0·5%)	1 (0·1%)	6 (0·3%)	0	NA; p=0·19
Neonatal death ≥22 weeks		2 (0·2%)	1 (0·1%)	3 (0·2%)	2 (0·2%)	0·75 (0·10–6·44); p>0·99
	Early (0–6 days)	2/2 (100%)	0	2/3 (67%)	1/2 (50%)	..
	Late (7–28 days)	0	1/1 (100%)	1/3 (33%)	0	..
	>28 days, before discharge	0	0	0	1/2 (50%)	..

Interpretation

Systematic screening and subsequent treatment for bacterial vaginosis in women with low-risk pregnancies shows no evidence of risk reduction of late miscarriage or spontaneous very preterm birth. Use of antibiotics to prevent preterm delivery in this patient population should be reconsidered.

Evidence before this study

When we planned our study in 2005, the meta-analysis of Leitich and colleagues (2003) had shown a strong association between bacterial vaginosis and preterm birth before 37 weeks (odds ratio 2·19, 95% CI 1·54–3·12). The same year, Ugwumadu and colleagues published the results of a large randomised controlled trial, in which participants received either clindamycin 300 mg or placebo orally, twice-daily for 5 days. The authors showed a significant reduction in miscarriages or spontaneous preterm birth in the clindamycin group. These results were taken into account in a 2005 Cochrane meta-analysis, which showed the need to focus on early detection and treatment of bacterial vaginosis in large trials. We searched PubMed using the terms “bacterial vaginosis” and “preterm birth”, for articles published before 2006. While enrolment in this study was ongoing, two meta-analyses reported conflicting results for use of clindamycin in this patient population. Lamont and colleagues showed a significantly reduced risk of preterm birth before 37 weeks and late miscarriage when clindamycin was given before 22 weeks' gestation to women with bacterial vaginosis; Brocklehurst and colleagues showed no difference for any preterm birth.

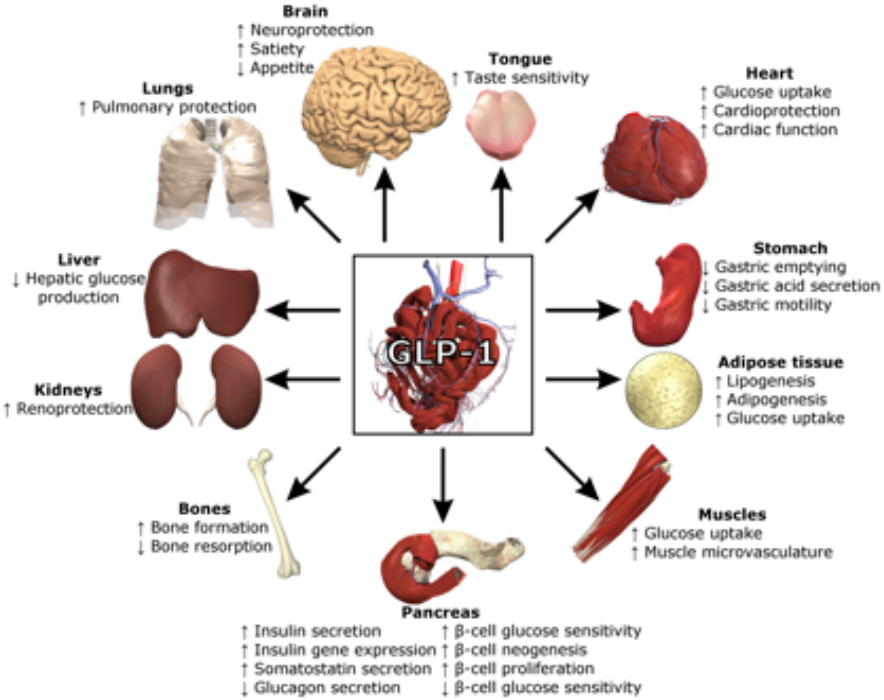
Added value of this study

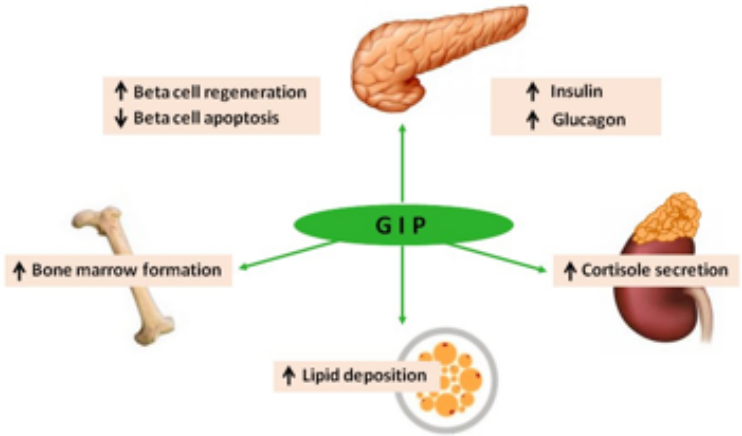
To our knowledge, PREMEVA is the only large trial in this field. We screened 84 530 pregnant women before 14 weeks' gestation and randomly allocated 2869 women with bacterial vaginosis to receive clindamycin or placebo. This strategy also does not reduce late miscarriage or preterm birth before 33 weeks or 37 weeks.

Implications of all the available evidence

Future guidelines should take these results into account. The findings from PREMEVA provide support for the national recommendations that asymptomatic women without a history of previous early delivery should not be screened or treated for bacterial vaginosis.

Das Protein Glucagon-like Peptid 1, kurz GLP-1, ist ein Peptidhormon, das im Darm (L-Zellen von Ileum und Kolon) produziert wird und eine wichtige Rolle bei der Steuerung des Glukosestoffwechselsspielt. GLP-1 gehört zu den Inkretinen.
Glucagon-like Peptid 1 ist ein Polypeptid, dessen Aminosäuresequenz durch das Proglucagon-Gen determiniert ist. Die biologisch aktiven Formen sind GLP-1-(7-37) and GLP-1-(7-36)NH2.
GLP-1 wird von den neuroendokrinen L-Zellen des Darms synthetisiert und während der Nahrungsaufnahme in den Blutkreislauf freigesetzt. Dort hat es nur eine sehr kurze Halbwertzeit: Es wird innerhalb weniger Minuten von der Dipeptidylpeptidase 4 (DPP 4) abgebaut.
Glucagon-like Peptid 1 (GLP-1) hat unter anderem folgende Wirkungen:
Stimulation der Insulinsynthese in der Bauchspeicheldrüse
Senkung des Glucagonspiegels
Verzögerung der Magenentleerung
Hemmung des Hunger- und Durstgefühls
Das Glukoseabhängige insulinotrope Peptid (GIP), früher mit dem gleichen Akronym als Gastroinhibitorisches Peptid oder Gastrointestinales inhibitorisches Peptid bezeichnet, besteht aus 42 Aminosäuren und ist ein in den K-Zellen des Zwölffingerdarms(Duodenum) gebildetes Peptidhormon. Heute ist als Hauptwirkung eine Stimulation der Insulinausschüttung in den B-Zellen der Bauchspeicheldrüse (Pankreas) nach Nahrungsaufnahme nachgewiesen.

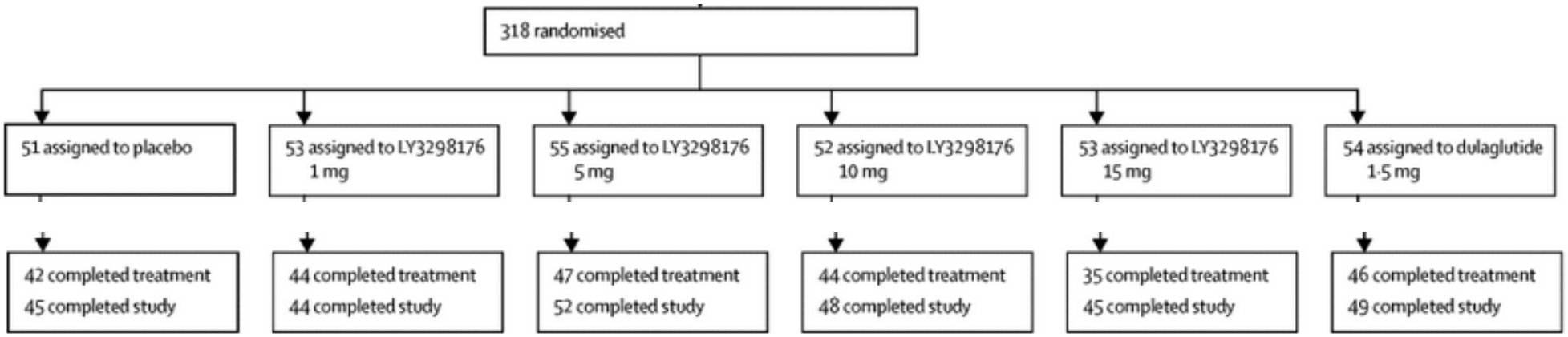


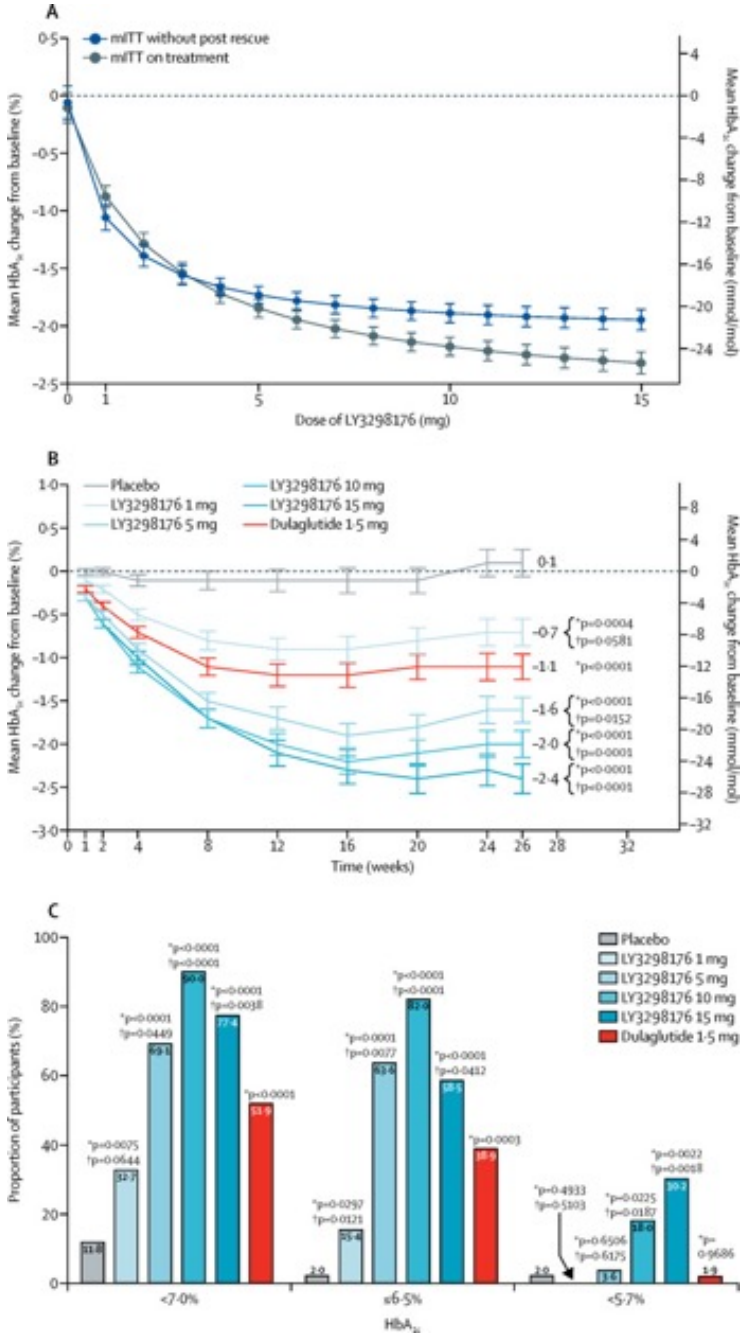


LY3298176, a novel dual GIP and GLP-1 receptor agonist

LY3298176 is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for the treatment of type 2 diabetes. We aimed to examine the efficacy and safety of co-stimulation of the GLP-1 and GIP receptors with LY3298176 compared with placebo or selective stimulation of GLP-1 receptors with dulaglutide in patients with poorly controlled type 2 diabetes.

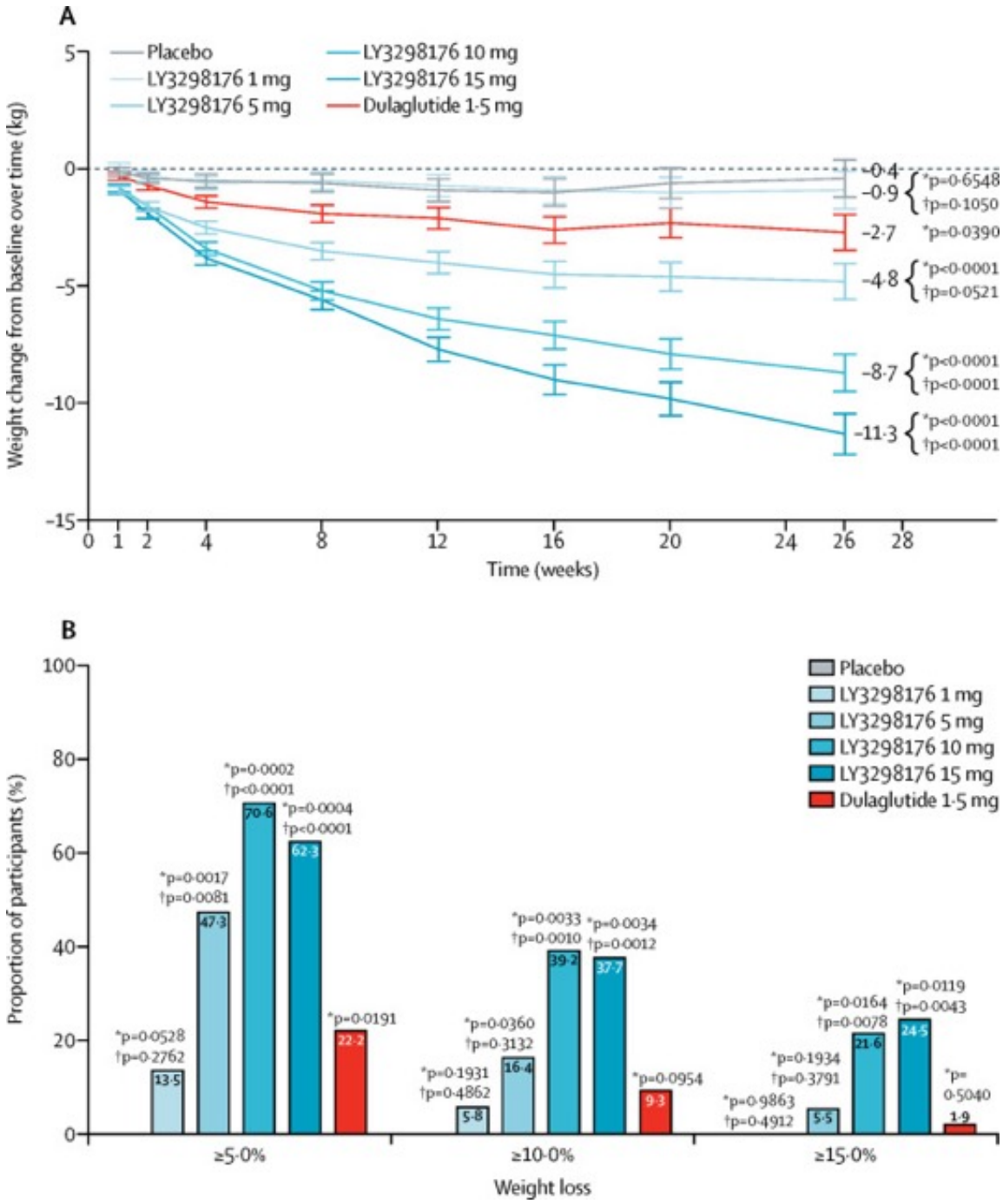
Patients with type 2 diabetes were randomly assigned to receive either once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1·5 mg), or placebo for 26 weeks. Assignment was stratified by baseline glycated haemoglobin A_{1c} (HbA_{1c}), metformin use, and body-mass index (BMI). Eligible participants (aged 18–75) had type 2 diabetes for at least 6 months (HbA_{1c} 7·0–10·5%, inclusive), that was inadequately controlled with diet and exercise alone or with stable metformin therapy, and a BMI of 23–50 kg/m^2. The primary efficacy outcome was change in HbA_{1c} from baseline to 26 weeks. Secondary endpoints, measured in the mITT on treatment dataset, were change in HbA_{1c} from baseline to 12 weeks; bodyweight, fasting plasma glucose, waist circumference, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and proportion of patients reaching the HbA_{1c} target (≤6·5% and <7·0%) from baseline to weeks 12 and 26; and proportion of patients with at least 5% and 10% bodyweight loss from baseline to 26 weeks.





Efficacy outcomes of treatment with LY3298176 at week 26 after once-weekly subcutaneous administration

(A) Bayesian dose response efficacy curve of LY3298176 by dataset. Data are posterior mean, with SD error bars. (B) Mixed model repeated measures analysis of the mITT on treatment dataset. Data are least squares mean, with SE error bars. (C) Last observation carried forward endpoint data of the mITT on treatment dataset. HbA_{1c}=glycated haemoglobin A_{1c}. mITT=modified intention-to-treat. *p values versus placebo. †p values versus dulaglutide 1·5 mg.



Bodyweight outcomes of treatment with LY3298176 at week 26

(A)Mixed-effect model for repeated measures analysis of the mITT on treatment dataset. Data are least squares mean, with SE error bars. (B)Last observation carried forward endpoint data of the mITT on treatment dataset. mITT=modified intention-to-treat. *p values versus placebo. †p values versus dulaglutide 1·5 mg. HbA_{1c}=glycated haemoglobin A_{1c}. (C)Gastrointestinal events (nausea, diarrhoea, and vomiting) and decreased appetite were the most common treatment-emergent adverse events; the incidence of these events was higher for the LY3298176 and dulaglutide groups than for the placebo group. The incidence of nausea, diarrhoea and vomiting were 15·4% for 1 mg LY3298176, 25·5% for 5 mg LY3298176, 39·2% for 10 mg LY3298176, 60·4% for 15 mg LY3298176, 35·2% for dulaglutide, and 5·9% for placebo.

Evidence before this study

We searched PubMed on July 17, 2018, using the terms “liraglutide”, “exenatide”, “lixisenatide”, “dulaglutide”, “albiglutide”, “semaglutide”, “glucagon-like peptide-1 receptor agonist”, and “type 2 diabetes” with no date or study duration restrictions. Non-English references were excluded. The published literature describes glycated haemoglobin A_{1c} (HbA_{1c}) reductions (depending upon baseline HbA_{1c}) of up to 1·5 %, and bodyweight reduction up to 5 kg (on average, large interindividual differences) with the most effective glucagon-like peptide-1 (GLP-1) receptor agonists being liraglutide, dulaglutide, and semaglutide. Four small studies have reported on dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists. A 6-week study with a pegylated dual agonist showed clinically relevant glucose reduction and weight loss with a relatively low incidence of gastrointestinal side-effects. A 12-week study with a dual agonist, and balanced activity at the two receptors, showed similar glycaemic efficacy and modest weight loss compared with liraglutide. In a single ascending dose study and a 14-day multiple ascending dose study, another dual GIP and GLP-1 receptor agonist, RG7697, showed glycaemic improvement and weight loss.

Added value of this study

LY3298176 is a novel dual GIP and GLP-1 receptor agonist balanced towards GIP. In this study, we compared LY3298176 with dulaglutide, a selective GLP-1 receptor agonist, and placebo. We show that simultaneous stimulation of both receptors by LY3298176 caused a statistically significant and clinically meaningful improvement in glucose lowering and bodyweight reduction, compared with selective agonism at the GLP-1 receptor with dulaglutide. Notably, these results are consistent with observations reported in preclinical studies of GIP and GLP-1 costimulation, suggesting its potential for greater metabolic effects versus selective GLP-1 receptor stimulation, especially for weight reduction. To confirm the superior clinical profile of LY3298176, additional clinical studies versus the most potent GLP-1 receptor agonists are warranted. When compared with dulaglutide, LY3298176 had a greater effect on both homeostatic model assessment of pancreatic β-cell function and insulin resistance and caused a greater reduction in glucagon concentration. Although we did not assess the effect of LY3298176 on appetite and food intake, the multifold increase in the reporting of reduced appetite as an adverse event with LY3298176, compared with dulaglutide, suggests that the effect on appetite might contribute to the metabolic effects of LY3298176.

Implications of all the available evidence

Our findings show that treatment with LY3298176, a novel dual GIP and GLP-1 receptor dual agonist, resulted in statistically significant and clinically meaningful control of HbA_{1c} with greater weight loss and an acceptable tolerability profile, as compared with dulaglutide, a GLP-1 receptor agonist. Larger confirmatory studies are needed to assess whether LY3298176 has advantageous therapeutic effects with regard to glycaemic control and bodyweight reduction when compared with the selective GLP-1 receptor agonist class of agents in patients with type 2 diabetes.

Adverse outcomes after arthroscopic partial meniscectomy: a study of 700 000 procedures in the national Hospital Episode Statistics database for England

Arthroscopic partial meniscectomy is one of the most common orthopaedic procedures worldwide. Clinical trial evidence published in the past 6 years, however, has raised questions about the effectiveness of the procedure in some patient groups. In view of concerns about potential overuse, we aimed to establish the true risk of serious complications after arthroscopic partial meniscectomy. We analysed national Hospital Episode Statistics data for all arthroscopic partial meniscectomies done in England between April 1, 1997, and March 31, 2017. Simultaneous or staged (within 6 months) bilateral cases were excluded. We identified complications occurring in the 90 days after the index procedure. The primary outcome was the occurrence of at least one serious complication within 90 days, which was defined as either myocardial infarction, stroke, pulmonary embolism, infection requiring surgery, fasciotomy, neurovascular injury, or death. Logistic regression modelling was used to identify factors associated with complications and, when possible, risk was compared with general population data.

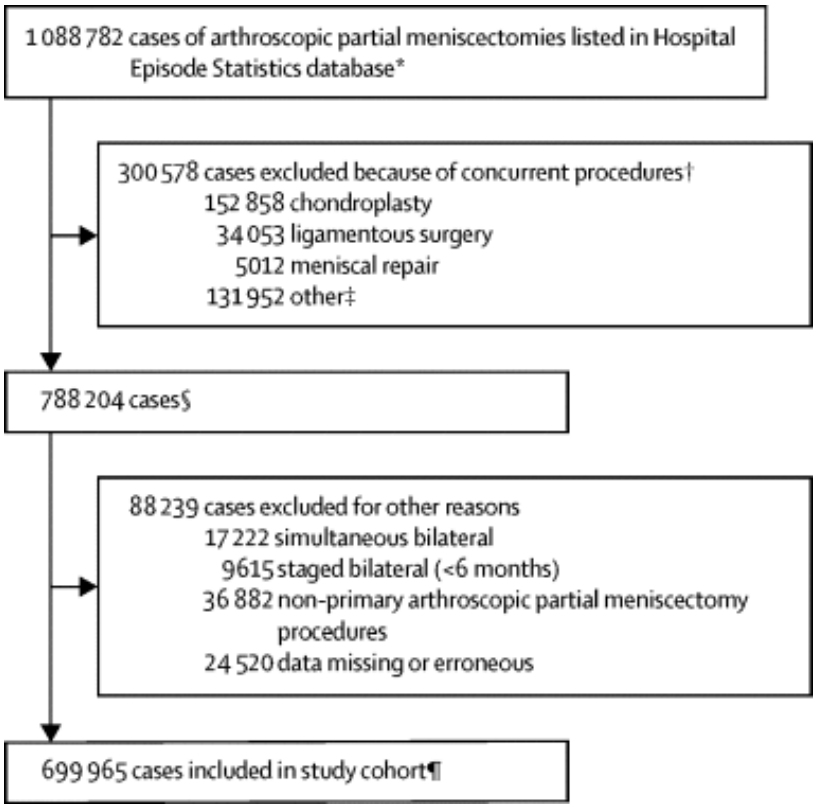


Table 1 Demographics and descriptive statistics

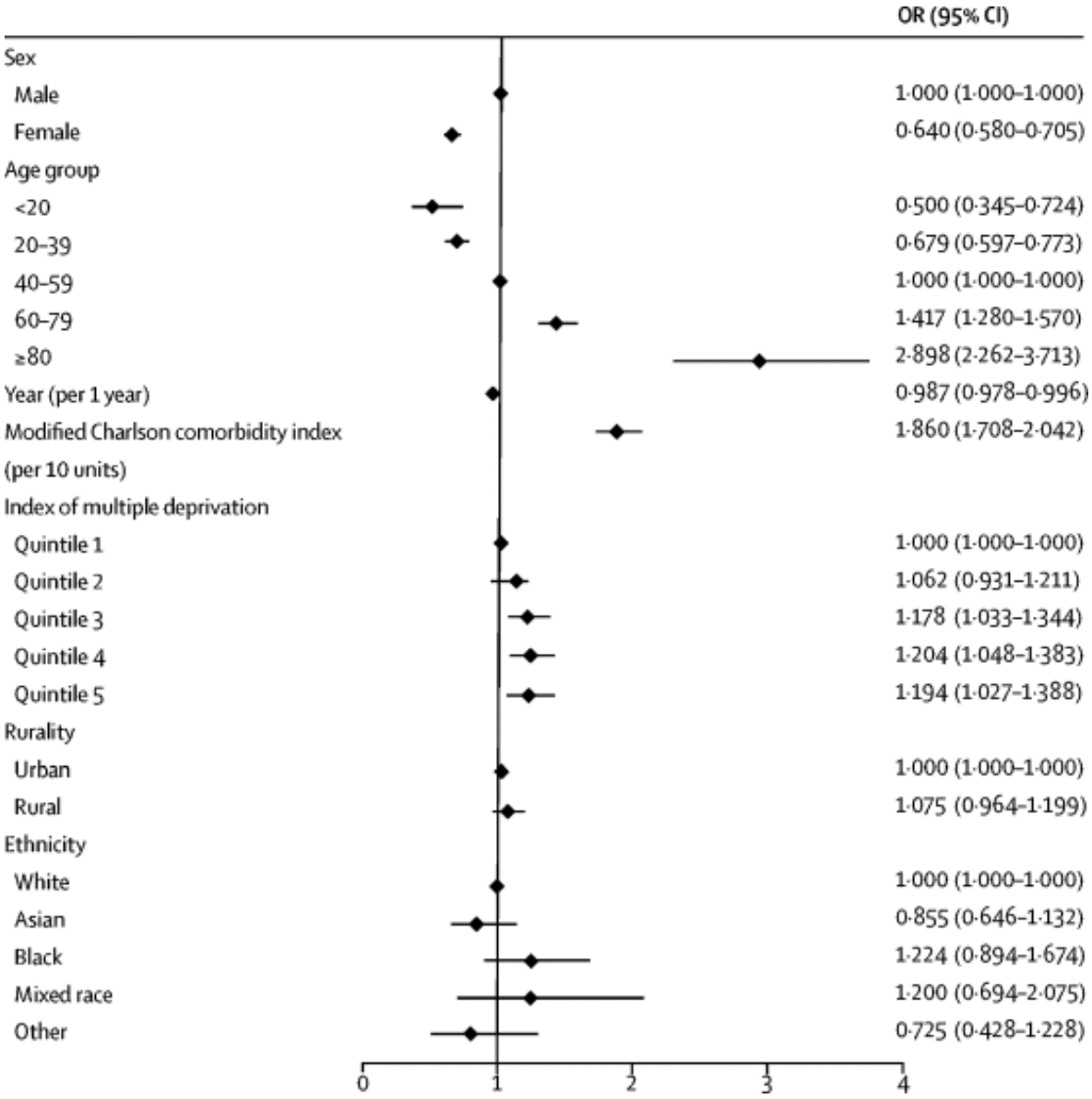
		All procedures	Serious complications*
Overall		699 965 (100%)	2218 (0·32%, 0·30–0·33)
Sex			
	Male	453 726 (64·82%)	1545 (0·34%, 0·32–0·36)
	Female	246 239 (35·18%)	673 (0·27%, 0·25–0·29)
Age group, years			
	<20	21 798 (3·11%)	32 (0·15%, 0·10–0·21)
	20–39	172 636 (24·66%)	356 (0·21%, 0·19–0·23)
	40–59	330 752 (47·25%)	988 (0·30%, 0·28–0·32)
	60–79	167 287 (23·90%)	766 (0·46%, 0·43–0·49)
	≥80	7492 (1·07%)	76 (1·01%, 0·80–1·27)

Data are n (%) or n (%, 95% CI)

Table 2 Complications within 90 days

	n (% [95% CI])
Any reoperation*	4239 (0·606% [0·588–0·624])
Serious complication†	2218 (0·317% [0·304–0·330])
Infection‡	944 (0·135% [0·126–0·144])
Lower-respiratory-tract infection	931 (0·133% [0·125–0·142])
Urinary tract infection	647 (0·092% [0·085–0·100])
Pulmonary embolism	546 (0·078% [0·072–0·085])
Myocardial infarction	279 (0·040% [0·035–0·045])
Mortality	217 (0·031% [0·027–0·035])
Stroke	208 (0·030% [0·026–0·034])
Acute kidney injury	206 (0·029% [0·026–0·034])

N=699 965.



Procedure-level multivariable logistic regression model adjusted for sex, age group, year, modified Charlson comorbidity index, index of multiple deprivation, rurality, and ethnicity. Error bars show 95% CIs. OR=odds ratio.

Table 3 Unadjusted and adjusted odds of serious complications

	Serious complication*		Pulmonary embolism		Myocardial infarction		Stroke	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjuste (95% CI
Sex								
Male	1·00	1·00	1·00	1·00	1·00	1·00	1·00	1·00
Female	0·802 (0·733–0·878)	0·640 (0·580–0·705)	1·311 (1·106–1·555)	1·021 (0·848–1·228)	0·571 (0·433–0·752)	0·406 (0·303–0·543)	1·325 (1·006–1·745)	0·818 (0·611–1
Age group, years								
<20	0·491 (0·345–0·698)	0·500 (0·345–0·724)	..	..	..	..	..	..
20–39	0·690 (0·611–0·779)	0·679 (0·597–0·773)	0·482 (0·369–0·631)	0·481 (0·358–0·646)	0·029 (0·007–0·116)	0·015 (0·002–0·109)	0·133 (0·054–0·329)	0·157 (0·063–(
40–59	1·00	1·00	1·00	1·00	1·00	1·00	1·00	1·00
	1·535	1·417	1·524	1·422	1·933	1·794	3·077	2·425

Procedure-level multivariable logistic regression model adjusted for sex, age group, year, modified Charlson comorbidity index, index of multiple deprivation, rurality, and ethnicity. OR=odds ratio.

*** At least one serious complication within 90 days, defined as either pulmonary embolism, myocardial infarction, stroke, infection requiring surgery, fasciotomy, neurovascular injury, or death.**

† Infection requiring surgery (open or arthroscopic washout).

Table 4 90-day adverse event rates in the general population *vs* a matched sample of the study cohort

		General population risk % (95% CI)	Study cohort risk % (95% CI)	Risk ratio (95% CI)
Mortality[30*]				
	Overall	0·158% (0·157–0·159)	0·031% (0·027–0·035)	0·20 (0·17–0·22)
	<20 years	0·007% (0·007–0·008)	..	..
	20–39 years	0·011% (0·011–0·012)	0·009% (0·005–0·015)	0·81 (0·49–1·32)
	40–59 years	0·043% (0·042–0·044)	0·021% (0·017–0·027)	0·50 (0·40–0·63)
	60–79 years	0·233% (0·230–0·236)	0·061% (0·050–0·074)	0·26 (0·22–0·32)
	≥80 years	2·043% (2·026–2·060)	0·360% (0·238–0·524)	0·18 (0·12–0·26)
Myocardial infarction[31†]				
	Men (<80 years)	0·058% (0·049–0·067)	0·046% (0·040–0·052)	0·79 (0·64–0·97)
	Women (<80 years)	0·028% (0·022–0·035)	0·024% (0·019–0·031)	0·88 (0·63–1·23)

*** Mortality data are Office for National Statistics population-level data for England, 2016, excluding death from cancer.**

† Excludes iatrogenic causes.

Evidence before this study

A meta-analysis of studies of adverse events after knee arthroscopy, published in 2015, included summary estimates of deep vein thrombosis (0·413% [95% CI 0·178–0·960]; five studies of 432 663 patients or procedures), pulmonary embolism (0·145% [0·059–0·354]; six studies of 736 823 patients or procedures), venous thromboembolism—ie, deep vein thrombosis or pulmonary embolism—(0·568% [0·296–1·090]; six studies of 571 793 patients or procedures), infection (0·211% [0·080–0·556]; four studies of 946 230 patients or procedures), and death (0·096% [0·004–2·390; two studies of 106 967 patients or procedures). Heterogeneity (I^2) in all these estimates exceeded 90% and the included studies had several limitations. Studies had inconsistent inclusion criteria, often included patients undergoing complex arthroscopic procedures (such as ligament reconstruction), and had different outcomes, endpoints, and units of analysis (ie, patient or procedure). The completeness of case capture in insurance company databases was also of concern (where applicable). Thus, CIs were wide, the range of complications reported was incomplete, and the generalisability of the findings to patients undergoing the most common procedure, arthroscopic partial meniscectomy, in isolation was unknown. We did an updated search of MEDLINE, Embase, CENTRAL, and CINAHL on Feb 8, 2018, and followed the published search strategy from the previous meta-analysis of harms. We identified four subsequent studies of venous thromboembolism and one study of infection, in which the frequencies of these complications was similar to those in the previous meta-analysis. In a cohort study of 45 943 patients, myocardial infarction occurred in 23 (0·05%) within 30 days of knee arthroscopy. For comparison, in the general population, the previously reported 90-day risk of mortality is 0·158%, of myocardial infarction is 0·058% (in men younger than 80 years; the corresponding frequency in women is 0·028%), of pulmonary embolism is 0·006%, of stroke is 0·034%, and of non-iatrogenic septic arthritis is 0·001%.

Added value of this study

We assessed a wide range of serious complications in a cohort restricted to patients undergoing arthroscopic partial meniscectomy only. To our knowledge, our study is the largest reported single database cohort so far of knee arthroscopy procedures (699 965 cases). Arthroscopic partial meniscectomy was associated with a 0·317% risk of serious complications within 90 days (pulmonary embolism, myocardial infarction, stroke, fasciotomy, neurovascular injury, infection requiring surgery, or death). Increasing age was associated with an increased risk of serious complications, and female patients were at decreased risk of serious complications. Compared with the general population, arthroscopic partial meniscectomy was associated with an increased risk of septic arthritis and pulmonary embolism, and neither risk has improved over time despite modern prophylactic methods. For every 1500 fewer knee arthroscopies done, one pulmonary embolism and two native knee joint infections could be prevented.

Implications of all the available evidence

Overall, our findings suggest that arthroscopic partial meniscectomy is a low-risk procedure, and should continue to be used in carefully selected patients. However, the increased risks of pulmonary embolism and septic arthritis, rare but serious complications, are important to consider because up to 2 million knee arthroscopies are done worldwide each year. Our data will help to inform patient decision making and consent. Continued focus on the development of refined patient selection criteria is justified to avoid exposure to potentially avoidable risks.

Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries

Universal health coverage has been proposed as a strategy to improve health in low-income and middle-income countries (LMICs). However, this is contingent on the provision of good-quality health care. We estimate the excess mortality for conditions targeted in the Sustainable Development Goals (SDG) that are amenable to health care and the portion of this excess mortality due to poor-quality care in 137 LMICs, in which excess mortality refers to deaths that could have been averted in settings with strong health systems. Using data from the 2016 Global Burden of Disease study, we calculated mortality amenable to personal health care for 61 SDG conditions by comparing case fatality between each LMIC with corresponding numbers from 23 high-income reference countries with strong health systems. We used data on health-care utilisation from population surveys to separately estimate the portion of amenable mortality attributable to non-utilisation of health care versus that attributable to receipt of poor-quality care.

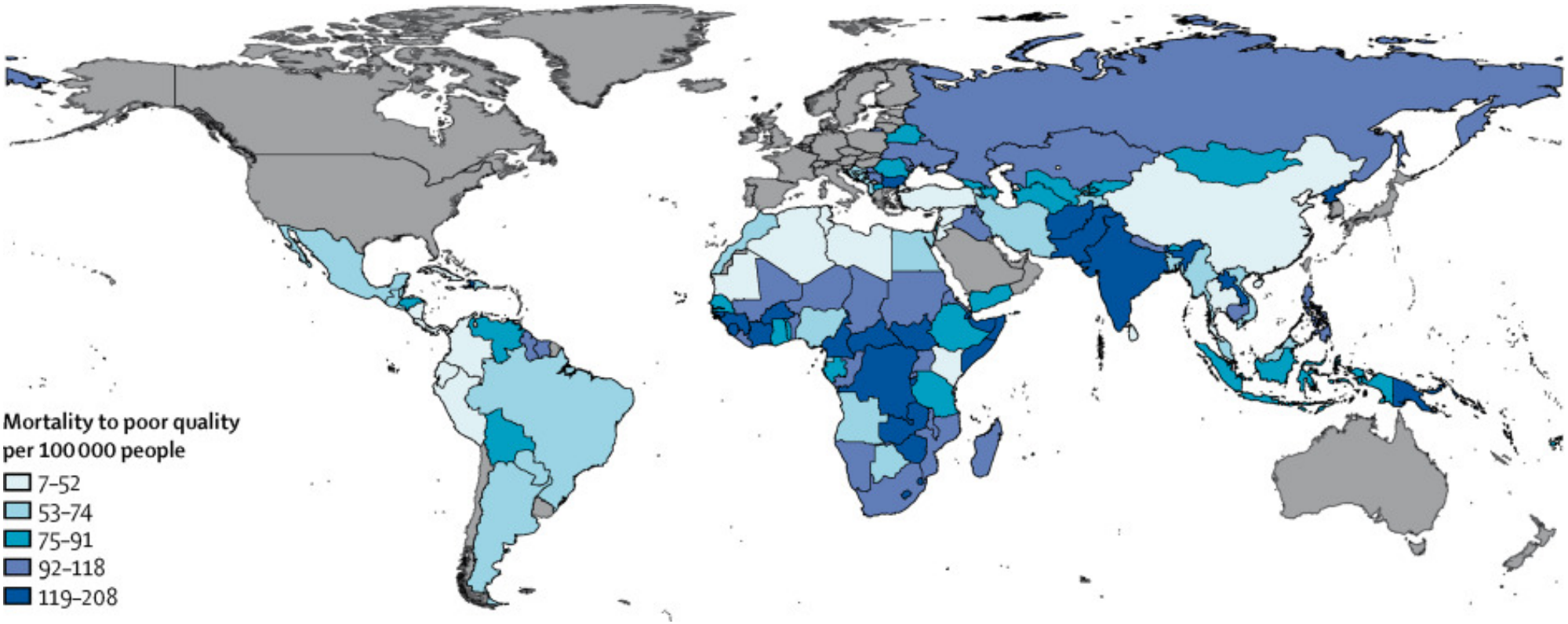
Table 1 Conditions amenable to health care

		Age range
HIV or AIDS		0–74
Tuberculosis		0–74
Vaccine preventable diseases		
	Hepatitis B	0–74
	Meningitis	0–14
	Diphtheria	0–14
	Otitis media	0–74
	Varicella and herpes zoster	0–74
	Whooping cough	0–4
	Meningococcal meningitis	0–14

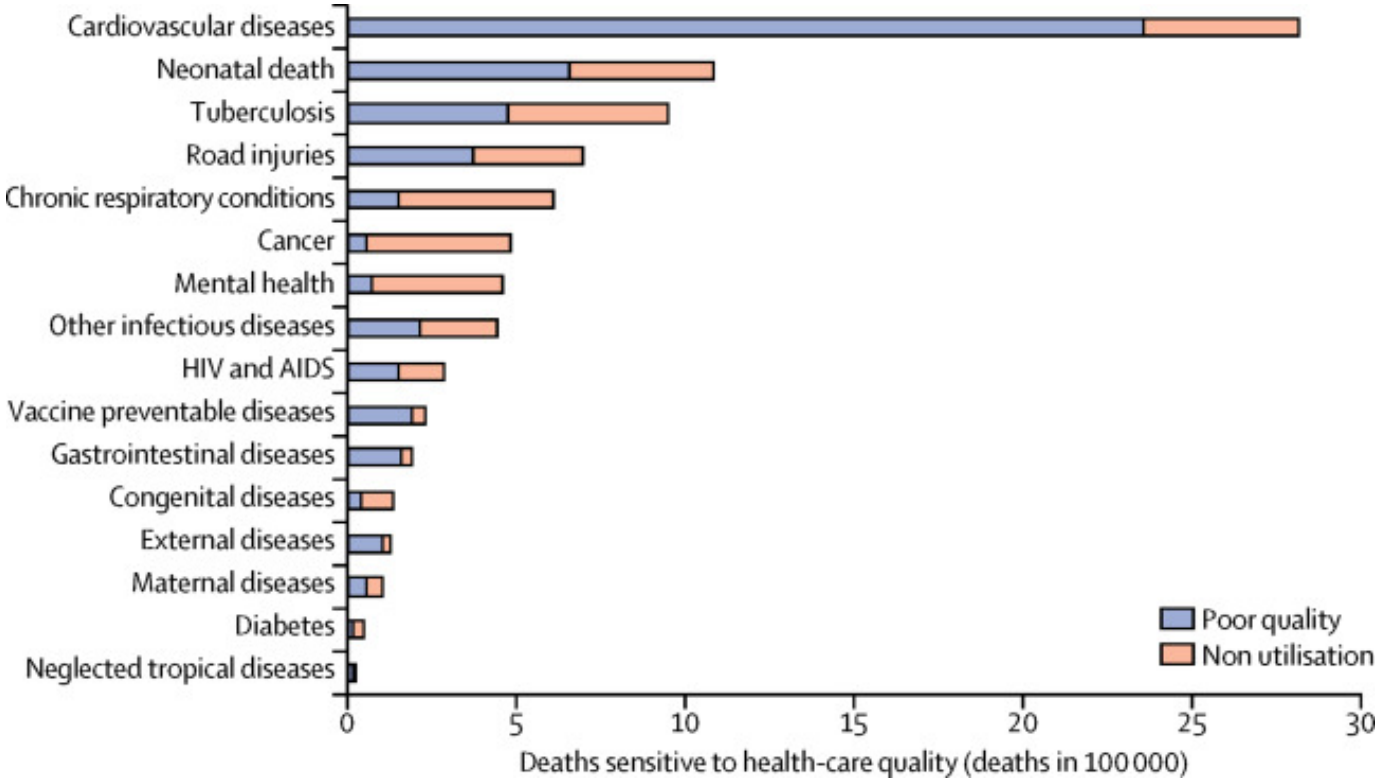
Cardiovascular diseases		
	Rheumatic heart disease	0–44
	Ischaemic heart disease	0–74
	Hypertensive heart disease	0–74
	Ischaemic stroke	0–74
	Intracerebral haemorrhage	0–74
	Congenital heart anomalies	0–14
	Chronic kidney disease due to hypertension	0–49
Gastrointestinal disorders		
	Peptic ulcer disease	0–74
	Appendicitis	0–74
	Inguinal and femoral hernia	0–74
	Gallbladder and biliary diseases	0–74
	Paralytic ileus and intestinal obstruction	0–74
Diabetes		

Of the 19·3 million total deaths in 2016 in LMICs from the 61 specific causes and age groups considered in this study, we estimated that there were 15·6 million avertable deaths in LMICs (95% uncertainty interval [UI] 15·4–15·9 million), including 7·0 million deaths preventable through public health intervention (UI 6·8–7·2 million), and 8·6 million amenable to health care (UI 8·5–8·8 million). The amenable deaths should be viewed as a conservative estimate because some deaths currently counted under preventable could have been averted through primary prevention in the health system. Of the excess deaths amenable to health care, an estimated 3·6 million were due to non-utilisation of health care services (UI 3·5–3·7 million), and 5·0 million were due to poor quality of available care (UI 4·9–5·2 million). 224 million YLL (UI 219–230 million) were due to poor quality of available care.

South Asia had the greatest mortality due to use of poor-quality health care at 1·9 million deaths (39% of global poor-quality service access mortality). Central Europe and Latin America had the highest percentage of amenable mortality due to receipt of poor-quality health services, whereas sub-Saharan Africa had the lowest, where a greater percentage were due to non-utilisation of services.



The figure presents the mortality due to access to poor-quality services and non-utilisation of health services by condition type. Cardiovascular disease deaths made up 33% (2 817 000) of the amenable deaths in the total health system, of which 84% (2 358 000) were caused by use of poor-quality health services. After cardiovascular disease, deaths from neonatal conditions, tuberculosis, and road injuries comprised the most amenable deaths, with a total of 1·5 million deaths due to use of poor-quality services and 1·2 million deaths due to non-utilisation of health services. Only 11% (53 000 of 477 000) of amenable cancer deaths and 15% (69 000 of 455 000) of amenable mental and neurological deaths were due to use of poor-quality health care, reflecting the low utilisation of health services for these conditions



Mortality due to poor quality versus non-utilisation of health care by condition type

Reproduced from Kruk and colleagues,
by permission of Elsevier. External factors deaths are those due to poisonings and adverse medical events. Other infectious diseases deaths are those due to malaria, diarrhoeal diseases, intestinal infections, and upper and lower respiratory infections.

Evidence before this study

Although amenable mortality has been estimated and discussed in high-income countries for several decades, the concept has only recently been extended to low-income countries. We searched PubMed for the terms “amenable mortality” and “quality” for studies published in English from 1990–2018 and reviewed citations in relevant articles. Nolte and McKee have developed the concept of amenable mortality to estimate the number of deaths that could be averted by health care in Organisation for Economic Co-operation and Development countries. In 2016, the Global Burden of Disease (GBD) group extended this concept to low-income and middle-income countries (LMICs) and developed an access and quality index to compare performance. Multicountry studies, such as those by Souza and colleagues and Biccard and colleagues, have shown that in some LMICs mortality is higher for people receiving care in facilities than in high-income countries, even after adjusting for morbidity. Alkire and colleagues found that worldwide 8 million deaths were amenable to health care, resulting in estimated welfare losses of US$6·0 trillion to LMICs in 2015.

Added value of this study

This study reports the number of deaths amenable to health care in LMICs and is the first to estimate the proportion of these deaths due to poor quality of care versus non-utilisation of care. This finding has important policy implications for countries pursuing universal health coverage as increased access to poor quality of care is unlikely to improve health outcomes. Our study found that nearly 8 million people die every year because of a lack of access to high-quality care. We found a higher proportion of amenable deaths are among health system users than non-users in LMICs. Deaths caused by poor-quality health care spanned the conditions included in the Sustainable Development Goals, including cardiovascular diseases, neonatal conditions and road traffic accidents. Although the 2016 GBD study did not report numbers of amenable deaths or partition these deaths into the separate contributions of quality of care and utilisation, it did observe substantial disparities in amenable mortality across regions and related to levels of development.

Implications of all the available evidence

Although our findings cannot be directly compared to the study by Nolte and McKee because the conditions they reported were different in high-income settings, the authors made different adjustments for public health interventions, and the settings of care were much better resourced than in many countries in our study, and they found that mortality in 21% of men and 30% of women under the age of 75 years is amenable to good health care; the corresponding figure from our study is 56% (all amenable deaths/avertable deaths).

The 2016 GBD paper concluded that despite progress since 1990, improved access to care and quality of care received has a large potential for improving outcomes in low-income and middle-income countries, although there is a large and growing heterogeneity of performance across countries. Specifically, although many countries lag behind peers in their income group, some middle-income countries with recent health system reforms appear to be realising outsized health gains. Our estimate that 55% of all avertable mortality for Sustainable Development Goal conditions can be addressed by good health care is somewhat higher than the Nolte and McKee study estimates and suggests that health systems are just as crucial for overall mortality reduction in lower-income countries as they are in high-income countries. Our paper uniquely estimates the portion of amenable mortality due to non-utilisation of available care versus utilisation of poor quality of care. We conclude that access is no longer the only binding constraint for improving survival in LMICs—health system quality must be improved simultaneously. This is particularly trenchant as countries embark on universal health coverage, which has been characterised in terms of improved coverage and reduced financial risk. Our work, in combination with past research, shows that improving health system quality is an immediate priority if countries hope to succeed in reaching the third Sustainable Development Goal.

Implementation research: new imperatives and opportunities in global health

Summary

Implementation research is important in global health because it addresses the challenges of the know–do gap in real-world settings and the practicalities of achieving national and global health goals. Implementation research is an integrated concept that links research and practice to accelerate the development and delivery of public health approaches. Implementation research involves the creation and application of knowledge to improve the implementation of health policies, programmes, and practices. This type of research uses multiple disciplines and methods and emphasises partnerships between community members, implementers, researchers, and policy makers. Implementation research focuses on practical approaches to improve implementation and to enhance equity, efficiency, scale-up, and sustainability, and ultimately to improve people's health. There is growing interest in the principles of implementation research and a range of perspectives on its purposes and appropriate methods. However, limited efforts have been made to systematically document and review learning from the practice of implementation research across different countries and technical areas. Drawing on an expert review process, this Health Policy paper presents purposively selected case studies to illustrate the essential characteristics of implementation research and its application in low-income and middle-income countries. The case studies are organised into four categories related to the purposes of using implementation research, including improving people's health, informing policy design and implementation, strengthening health service delivery, and empowering communities and beneficiaries. Each of the case studies addresses implementation problems, involves partnerships to co-create solutions, uses tacit knowledge and research, and is based on a shared commitment towards improving health outcomes. The case studies reveal the complex adaptive nature of health systems, emphasise the importance of understanding context, and highlight the role of multidisciplinary, rigorous, and adaptive processes that allow for course correction to ensure interventions have an impact. This Health Policy paper is part of a call to action to increase the use of implementation research in global health, build the field of implementation research inclusive of research utilisation efforts, and accelerate efforts to bridge the gap between research, policy, and practice to improve health outcomes.

Key messages

- Implementation research offers a way to understand and address implementation challenges and have a positive effect on people's health by contributing to building stronger and more responsive health systems within the realities of specific contexts.
- Implementation research can lead to positive health outcomes, inform policy design, improve health management and service delivery, and support and empower communities and beneficiaries.
- Implementation research uses multidisciplinary approaches and a range of empirical and systematic methods to document, analyse, and address key health problems and test technical health interventions and contextually tailored innovative strategies within the foundations of local context.
- Implementation research can be used to evaluate the feasibility, adoption, and acceptance of interventions and their coverage (particularly in reaching disadvantaged groups), quality, equity, efficiency, scale, and sustainability.
- Implementation research involves an approach to doing research that fosters ownership, collaboration, and influence; policy makers, implementers, communities, and researchers should work together throughout the research and implementation processes to build trusting partnerships and encourage the coproduction of knowledge.
- Implementation research involves some key trade-offs to consider, including rigour versus usefulness of the research, fidelity versus adaptation of an implementation component, embedded versus externally objective approaches, seeking generalisable knowledge versus context-specific problem solving, and incentives versus disincentives for researchers and implementing agencies.

Conclusion

The case studies show the wide range of implementation research processes in terms of scale, topics, methods, and range of impacts in global health. The effects of implementation research do not always fit neatly into the categories we have used to describe them. The same research can affect health outcomes while also informing policy, improving health management and service delivery, and empowering communities and beneficiaries. Many of the case studies illustrate how implementation research can be used to improve health service delivery within specific contexts and discuss the processes that can inform scale-up and efforts in other settings. Some of the case studies focus on vertical or disease-specific interventions (eg, smallpox, HIV, or onchocerciasis), and other case studies focus on broader health systems strengthening (eg, the national balanced scorecard for basic health services in Afghanistan and district level cases). In the case of disease-specific interventions, implementation focus brings in the need to acknowledge and address the broader health system factors that can either enable or inhibit effective action, and raises other areas for important consideration, such as community ownership and adaptation to community needs.

Context is crucial to the implementation research endeavour, and the case studies make context explicit. Many of the case studies include implementation research processes across different county contexts and programmatic objectives. There are strategic opportunities to learn lessons across diverse contexts. The case study examples of national nutrition systems, iCCM, and strengthening health systems at the district level illustrate a cumulative and growing body of knowledge about developing the health system's organisational capacity across multiple contexts and issues. Implementation research allows the documentation of processes to ensure that the depth and detail of what has been done is made explicit, so that adaptation to other contexts can be considered. Earlier work in this area has emphasised the importance of context and local and ongoing adaption. For example, a systematic review of 150 strategies to strengthen health services in LMICs highlighted much higher implementation outcomes with flexibility and modification through stakeholder feedback, constraints reduction plans, initial and continuous adaptation of the strategy to the local context, broad-based support of stakeholders, and coordination and community organisation.[31]

Implementation research is about how to improve implementation: testing feasibility, adoption, and acceptance of the intervention; addressing quality, equity, efficiency, scale, and sustainability; and ensuring coverage of all people, even those who are marginalised, with the ultimate goal of strengthening health systems to improve health outcomes. These endeavours involve a range of research methods, shaped according to the questions addressed and further iterative processes linking research, reflection, and action. These processes have important roles in helping policy change to be realised, sustained, and to have an effect.

Conclusion continued

The case studies also show how implementation research involves partnerships across the research and implementation cycles with coproduction and concurrent use of knowledge. Dissemination alone is not sufficient to support real change. The core characteristics of implementation research (panel 4) include the nurturing of trusting partnerships to do real-world, real-time research that addresses relevant implementation challenges. The case studies illustrate the importance of context and how health systems operate as complex adaptive systems,[71] constantly changing and shaped by the activities of a diverse set of actors who have different types of incentives to engage or not to engage in implementation research. The case studies illustrate approaches to complex issues in health systems strengthening, and how different stakeholders can learn from their efforts. Local leadership to support ownership, flexibility, and responsiveness of research to the realities and challenges posed by changing, complex, and adaptive health systems is important. Fragility and disaster bring into sharp focus the importance of trusting relationships and approaches that are both embedded and iterative to address the needs and realities of changing contexts.

The implementation research and delivery science statement released at the Cape Town Global Symposium on Health Systems Research is a call to action to the global health community (including academia, implementers, national and global health institutions, and donors) to take up the challenge of strengthening implementation through productive partnerships between policy makers, implementers, and researchers.[7] Advancing implementation research will require overcoming some challenges, including the misalignment of incentives in some academic institutions, which discourages young academics from creating a career in this area and sharing experiences through networks and publications. The growing effort to produce guidelines for publishing implementation research reveals the limitation of current approaches and recognises the importance of reporting studies in sufficient detail to permit replication or adaptation.[64] This highlights the need for further dialogue between journals and authors on how to report the implementation process and learning from implementation research and the broader field of health policy and systems research. Implementation research, as outlined in this Health Policy paper, presents an opportunity to bridge the know–do gap for the ultimate shared health impact that we researchers, policy makers, programme implementers, and communities seek to achieve.

Universal health coverage: breakthrough or great white elephant?

Introduction

"'Doctor come quickly. You have to do something. That old woman is a witch.' Matron was agitated. 'What is it?' I asked as I hurried after her. 'She has tied her granddaughter's antibiotics in a corner of her cloth and is refusing to give them to us. She says they are too expensive.' The young woman, who had been brought in from a remote village we had never visited before, several days after a home delivery, was restless, with high temperatures and getting delirious. Our limited laboratory could not do blood cultures, but the clinical signs were suggestive of septicemia. In our opinion, the only hope for her lay in powerful, but expensive, modern antibiotics. The wizened old lady, her grandmother, sat by her bed stern faced, oblivious to the agitation of the nursing staff. A young woman, a family member, stood by her with a sickly looking child on her back. I spoke to the old lady. 'Mother, those medicines are hope that your grandchild will live. Why have you tied them in the corner of your cloth?' She replied with an impassive face: 'This child will not survive. I have lived long, and I know death when I see it. She has crossed to where we cannot help her. The young ones were foolish and emotional to have spent so much money on this medicine. There are many mouths to feed and little to feed them with. I will return the medicines and collect the money.' I tried to convince her that though very sick, there was a chance her granddaughter could be saved. The antibiotics held some of that chance. Every minute was important. Finally, she gave us back the medicines. More from our importunity than conviction I thought. The girl died that night and we returned the unused medicines to the old lady to get back what money she could. Whenever I reflected on this case, which continued to periodically haunt me, I found myself sympathising with the staff perception of 'unfeeling old witch'. Until I started working in public health in a poor rural district. I wondered again as I sat in forgotten little villages, with little or no basic health service access, low access to education and poor road networks. I observed the scarcity of cash and peoples' vulnerability. Had she really been an 'unfeeling old witch' or a cynical old woman, hardened by a lifetime of grinding rural poverty and marginalisation into a stoic pragmatism when confronted with catastrophic out-of-pocket expenditure? Would the young woman have died if she and her family had been empowered with education and better socioeconomic circumstances? If communities had universal access to adequate quality essential health services?"[1]

A white elephant is a possession which its owner cannot dispose of and whose cost, particularly that of maintenance, is out of proportion to its usefulness.

Will the Sustainable Development Goal 3 sub-goal “Achieve universal health coverage, including financial risk protection, access to quality essential health care services and…safe, effective, quality and affordable essential medicines and vaccines for all” be judged a breakthrough or a great white elephant in implementation, when we look back with the clear eyes of hindsight in 2030? What are the ways in which this agenda might play out in implementation and why might it do so? Drawing on a desk review, this Essay explores dominant ideas, ideology, institutions, and interests in relation to global versus Ghana national health priorities since the WHO constitution came into effect in 1948, to reflect on these questions.

My work experiences over the years in Ghana have convinced me that it is imperative to work towards assuring universal access to the basic socioeconomic and public health conditions that promote health and prevent illness, as well as quality essential clinical health care when needed without catastrophic out-of-pocket payments. Not to effectively pursue this agenda is to leave large numbers of people living under conditions that are a form of structural violence (social injustice).

What are possible implementation trajectories for UHC over the next decade and a half towards 2030? Can we learn anything from an analysis of dominant global-level and national-level ideology, ideas, and interests in health over time, since the WHO constitution came into effect in 1948, about the possibilities for how the current UHC agenda will play out in implementation? To answer these questions, this Essay explores patterns and trends in global health agendas, and in one lower middle-income country, Ghana, over the seven decades since WHO came into being.

Table summarise dominant ideas and underlying ideologies at the global and national level in Ghana over the period of this analysis. Broadly speaking, two main ideological leanings appear to underlie ideas in global health. They can be categorised as the selective, or vertical, and the systems, or horizontal, ideologies. The selective/vertical ideology and related ideas acknowledge that there are multiple issues and, therefore, interventions that need to be implemented to bring about health status and outcome improvements. However, it is not possible within available resources and weak systems to address them all. It is better, as a pragmatic strategy, to focus on selected and justified priorities, and interventions and technologies that can rapidly address them and produce health improvements.

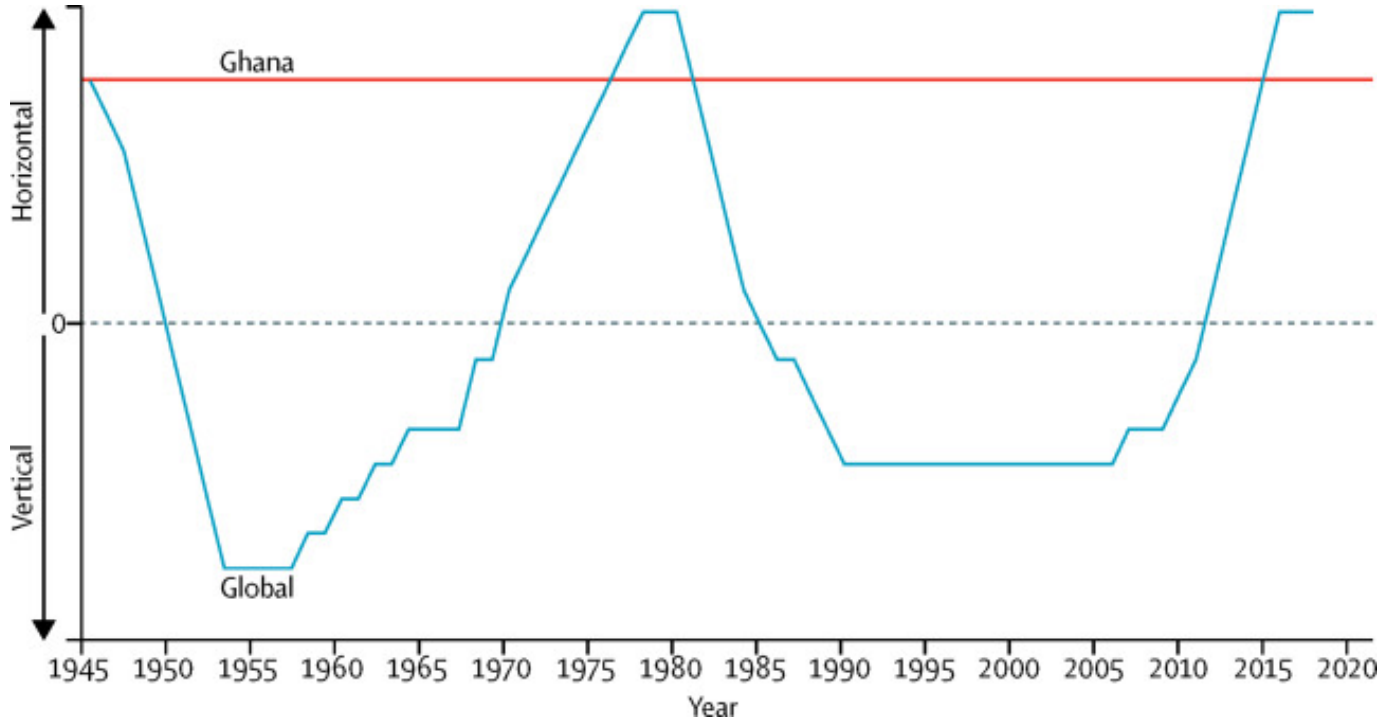
The systems/horizontal ideology emphasises holistic bottom up community engagement approaches, social justice and health as a human right, and strengthening systems as a foundation on which sustainable interventions and health improvements rest.

Table 1 Dominant ideas and underlying ideologies in Ghana and those reflected in global interventions affecting the country, 1945–79

	1945–49	1950–54	1955–59	1960–64	1965–69	1970–74	1975–79
Global							
Dominant ideology	Systems/horizontal	Selective/vertical	Selective/vertical	Selective/vertical	Selective/vertical	Selective/vertical	Systems/horizontal
Dominant ideas	Establishment of global institutions	Communicable disease eradication through mass campaigns	Communicable disease eradication through mass campaigns	Communicable disease eradication through mass campaigns	Communicable disease control	Communicable disease control	Primary health care
Ideas implemented	Establishment of multilateral global health organisations and funds	Mass BCG immunisation starts (1950); global yaws control program starts (1952) me	Malaria eradication programme starts (1955); smallpox eradication programme starts (1958)	Oral polio vaccine licensed (1963)	International Sanitary Regulations renamed International Health Regulations (1951)	Global Expanded Programme on Immunization and global onchocerciasis control programme launched (1974)	First essential medicines list published (1977); Alma Ata International Conference on primary health care (1978)
Global health governance and financing institutions	Multilateral agencies; UNICEF created (1946); UN conference in San Francisco unanimously approves establishment of new autonomous health organisation; WHO constitution comes into effect (1948); World Bank & IMF created at Bretton Woods Conference (1944).	..	..	..	..	..	..
Country level in Ghana							
Dominant ideology	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal
Dominant country ideas	Health System (clinical care and public health development)	Maude Commission report (1952); universal access	Universal access	"The health services in Ghana—a ten-year health programme for Ghana (1961–1970)"; universal access.	"The health services in Ghana—a ten year programme 1961–1970"; universal access.	Konotey-Ahulu committee report on hospital fees [34]	Ghana's 1978 primary health care strategy document
Ideas in implementation	Slow pace of health development by the colonial government, with Christian missions developing mission hospitals and outreach services alongside evangelism	Rapid increase in Human Resources for Health and infrastructure	Rapid increase in Human Resources for Health and infrastructure	Continued increases in Human Resources for Health and infrastructure	Continued increases in Human Resources for Health and infrastructure	Some increases in user fees but still minor	Primary health care; establishment of planning unit in Ministry of Health to lead primary health care development and implementation (1978)
Governance and financing Institutions	British colonial government	British colonial government; independence movement	Multiparty elections; Independence and self-rule on March 6, 1957 (First Republic)	Declaration of one-party socialist state	Military coup in 1966 end First Republic; multiparty elections usher in Second Republic on Oct 1, 1969	Military coup ends Second Republic on Jan 13, 1972	Uprising by junior army officers (June, 1979); military organises multiparty democratic elections; Third Republic commences (September, 1979)

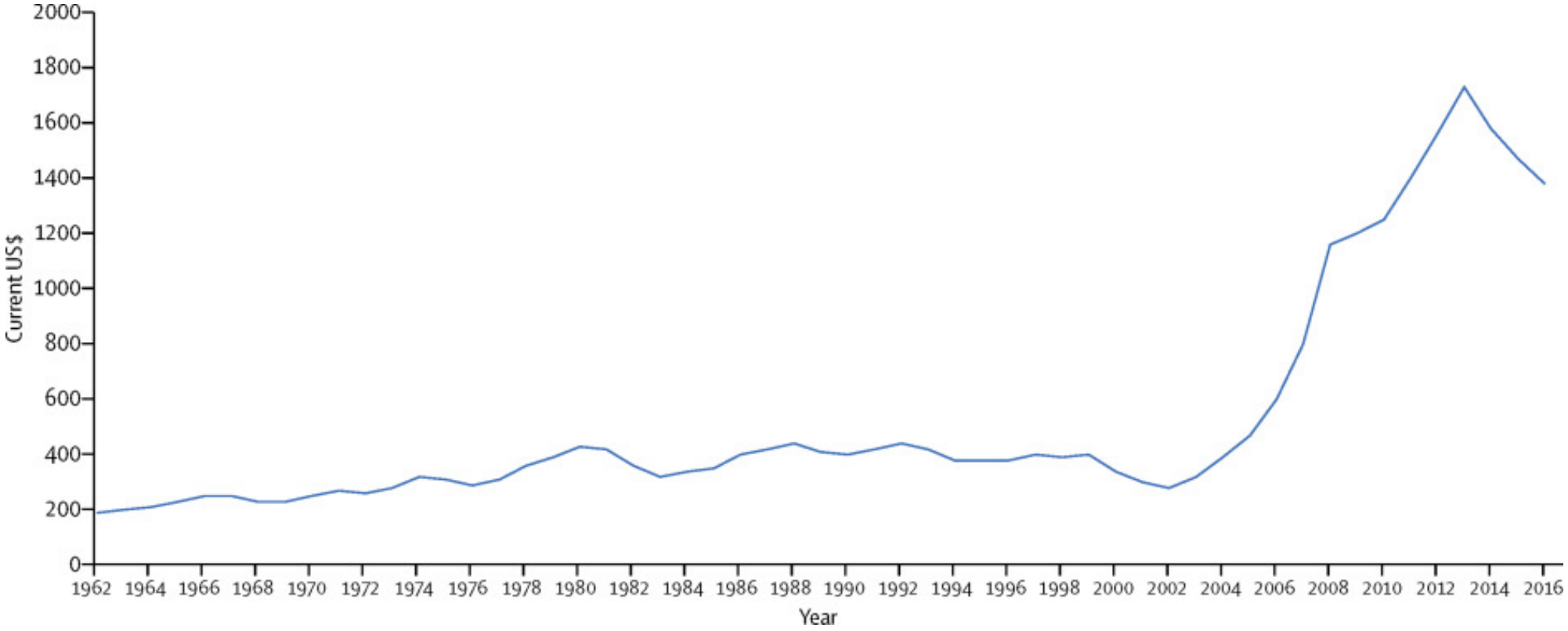
Though ideas related to the comprehensive ideology have never completely gone away, at times they have seemed like a lone voice in the wilderness. Apart from the current SDG period, in which horizontal ideas are once again dominant at global level, they were at their most dominant when the Alma-Ata Declaration of Primary Health Care was made in 1978 and adopted the following year by the WHO member states. At the global level, within a few short years of the Alma-Ata Declaration these ideas had been reframed into the vertical approach of selective primary health care. Despite the pushback by proponents of a more horizontal health systems development approach they never really gained the same dominance until recent times. To borrow the words of Anne Mills: “Gonzalez would no doubt be thoroughly dismayed that that there has been so little progress in 40 years in strengthening health services in low-income counties to maintain the achievements of vertical programs”.

	1980–84	1985–89	1990–94	1995–99	2000–04	2005–09	2010–14	2015–19
Global								
Dominant ideology	Systems/horizontal	Selective/vertical	Selective/vertical	Selective/vertical	Selective/vertical	Selective/vertical	Selective/vertical	Systems/horizontal
Dominant ideas	Selective PHC	Control through global programmes	Control through global programmes	Control through global programmes	Control through global programmes	Control through global programmes	Control through global programmes	UHC; health emergencies and public health (Global Programme of Work 13)
Ideas in implementation	Community health workers; GOBI	Global programme on AIDS commences (1986); polio eradication programme commences (1988)	World Health Assembly adopts resolution to eliminate leprosy (1991)	International commission for certification of Guinea worm eradication established; DOTS for tuberculosis control is launched (1995)	Millennium Development Goals adopted (2000); Commission on Macroeconomics and Health launched (2000)	Millennium Development Goals; World Health Assembly revises and adapts International Health Regulations; Commission on Social Determinants of Health launched (2005)	Millennium Development Goals	SDG adopted (2015); WHO Global Program of Work 13 adopted (2018; UHC, emergencies, public health)
Global health governance and financing institutions	Similar to previous decades (ie, WHO, UNICEF, World Bank, International Monetary Fund, etc)	Similar to previous decades (ie, WHO, UNICEF, World Bank, International Monetary Fund, etc)	Similar to previous decades (ie, WHO, UNICEF, World Bank, International Monetary Fund, etc)	UNAIDS created	Global Fund to fight AIDS, tuberculosis and malaria created (2002); Stop TB Partnership is launched (2000); Global Outbreak Alert and Response network is established (2000); Bill & Melinda Gates Foundation created (2000)	Partnership for Maternal and Child Health launched in 2005	Multilateral (eg, WHO, UNICEF, World Bank, etc) and bilateral institutions of previous decades, with increasing private foundation participation led by the Bill & Melinda Gates Foundation	Multilateral (eg, WHO, UNICEF, World Bank, etc) and bilateral institutions of previous decades, with increasing private foundation participation led by the Bill & Melinda Gates Foundation
Country level in Ghana								
Dominant ideology	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal	Systems/horizontal
Dominant ideas	PHC	PHC	PHC	SWAp with basket funding by several development partners	SWAp with basket funding by several development partners; NHI with ultimate target of universal access (effectively UHC)	Donors in SWAp; move to multidonor budget support at level of Ministry of NHI/UHC	NHI/UHC	NHI/UHC
Ideas in implementation	PHC	PHC	PHC	PHC/SWAp; 5-year POW 1 (1997–2001); integrated, sector-wide, multiyear, Government of Ghana led Program of Work; biannual	PHC/SWAp; 5-year Program of Work 2 (2002–2006); development and introduction of National Health Insurance Scheme	PHC/SWAp; Program of Work 3 (2007–2011); biannual health summits; NHI/UHC	Biannual health summits; PHC/NHI/UHC	Biannual health summits; PHC/NHI/UHC



The is a qualitative visualisation of the information in the table. It makes more visible the fairly steady underlying horizontal focus of dominant national-led ideas versus the fluctuating but largely vertical tendency of dominant global-led ideas.

The 1965 observation by Gonzalez, that: “Among the many important problems facing the developing nations of the world…is that of the health of their populations…There are two possible approaches to the problem of health in such countries; one is to build up a framework of health services able in due course to cope with the prevalent diseases (horizontal); the other is to attack the principal diseases by mass campaigns” (vertical), could be made in 2018 with only minor variations.



The economy continued to decline and, in the early 1980s, the Government of Ghana entered a classic International Monetary Fund structural adjustment programme. Significant user fees were introduced in the health sector with the aim of recovering at least 15% of operating costs as part of structural adjustment. Health sector resource-mobilisation targets were achieved, but the effects on access, especially for the poorest and most vulnerable, were disastrous.

In Ghana, as in many other low-income and middle-income countries, the global response to the effect of contracting economies on health was a mushrooming of international development assistance, mostly in the form of vertical project support. As a pushback, in the 1990s a sector-wide approach was introduced involving the Government of Ghana and several bilateral donors, such as UK Department for International Development, Danida, and the Royal Netherlands Embassy, as an alternative to the increasingly unmanageable multiplicity of donor-supported vertical programmes. In 1996 Ghana developed Vision 2020, a long term vision for growth and development that included “improve the health status of all Ghanaians” among its objectives with 5-year health sector programmes of work focused on systems building that were part of the sector-wide approach.

Discussion and conclusions

If the patterns of the past are anything to go by, the trajectory of the global UHC agenda cannot be taken for granted at this stage. It could prove a major breakthrough or a great white elephant for low-income and middle-income countries depending on the balance between global-level and country-level leadership, institutions, ideas, interests, and resource priorities. Strong leadership as well as administrative capacity is needed within countries to determine contextually relevant approaches and drive implementation. The global community needs to focus on catalysing and supporting locally driven change through capacity building and empowerment of local actors to lead and drive change. It also needs to resist the temptation to micromanage, lead, and drive national and sub-national level change from the global level using what Olivier de Sardan aptly describes as "'traveling models';…policies and protocols based on 'miracle mechanisms' that have been taken out of their original context but are believed to be intrinsically effective".

Why have agendas for the health sectors of low-income and middle income countries that have an underlying vertical/selective ideology tended to persistently dominate at the global level? Even when a pushback brought comprehensive ideology and ideas into dominance at Alma-Ata, it was eventually reframed in global ideas debate into a vertical/selective approach. Conversely, why at the national level in Ghana has the tendency been towards comprehensive horizontal approaches? Perhaps some of it has to do with incentives, timeframes, and ownership. Financiers of global institutions are an important primary reference group of such institutions. They demand results that can be measurably demonstrated in short-term funding commitments of a few years. Vertical, centrally-controlled, technology-driven programmes, offer the lure of quick visible wins on limited budgets with limited unpredictability. Development of health services and systems, support to bottom-up contextually relevant innovation is a long term effort, and commitment and measurement is often challenging. It requires political and social skills, flexibility, and nimbleness to deal with unpredictability and the vagaries of implementation. Global institutions and their major financiers, in their access to human, financial, and other resources, and the power these confer, are unlike the beneficiaries, institutions, and citizenry of low-income and middle-income countries their decisions and priorities affect.

In 1992, Ghana had moved from military rule to multiparty democratic governance under the Fourth Republic constitution. When one of these two parties won the presidency and the parliamentary majority, despite donor scepticism and in some cases outright opposition, they immediately established policy-making processes and, within 3 years, passed the necessary legislation and commenced implementation of national health insurance. Over time, even the opposing donor community became ardent supporters of the concept of an insurance programme they had initially considered not feasible.

Diclofenac use and cardiovascular risks: series of nationwide cohort studies

ABSTRACT

OBJECTIVE

To examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs, initiation of paracetamol, and no initiation.

DESIGN

Series of 252 nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design).

SETTING

Danish, nationwide, population based health registries (1996-2016).

PARTICIPANTS

Individuals eligible for inclusion were all adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases (that is, with low baseline risk). The study included 1 370 832 diclofenac initiators, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 healthcare seeking paracetamol initiators matched by propensity score, and 1 303 209 healthcare seeking non-initiators also matched by propensity score.

MAIN OUTCOME MEASURES

Cox proportional hazards regression was used to compute the intention to treat hazard ratio (as a measure of the incidence rate ratio) of major adverse cardiovascular events within 30 days of initiation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Diclofenac is the most commonly used non-steroidal anti-inflammatory drug (NSAID) in low, middle, and high income countries

Its cardiovascular risks compared with other traditional NSAIDs have never been examined in a randomised controlled trial, and current concerns about these risks make such a trial unethical to conduct

A series of Danish nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design), included 1 370 832 initiators of diclofenac, 3 878 454 initiators of ibuprofen, 291 490 initiators of naproxen, 764 781 healthcare seeking initiators of paracetamol (matched by propensity score), and 1 303 209 healthcare seeking NSAID non-initiators (matched by propensity score)

WHAT THIS STUDY ADDS

The incidence rate ratio of major adverse cardiovascular events at 30 days among diclofenac initiators increased by 50% versus non-initiators, by 20% versus ibuprofen or paracetamol initiators, and by 30% versus naproxen initiators

The increased risk was observed for atrial fibrillation or flutter, ischaemic stroke, heart failure, myocardial infarction, and cardiac death; both sexes of all ages; and even at low doses of diclofenac.

Risk of upper gastrointestinal bleeding at 30 days with diclofenac was similar to that of naproxen, but considerably higher than for no NSAID initiation, paracetamol, and ibuprofen

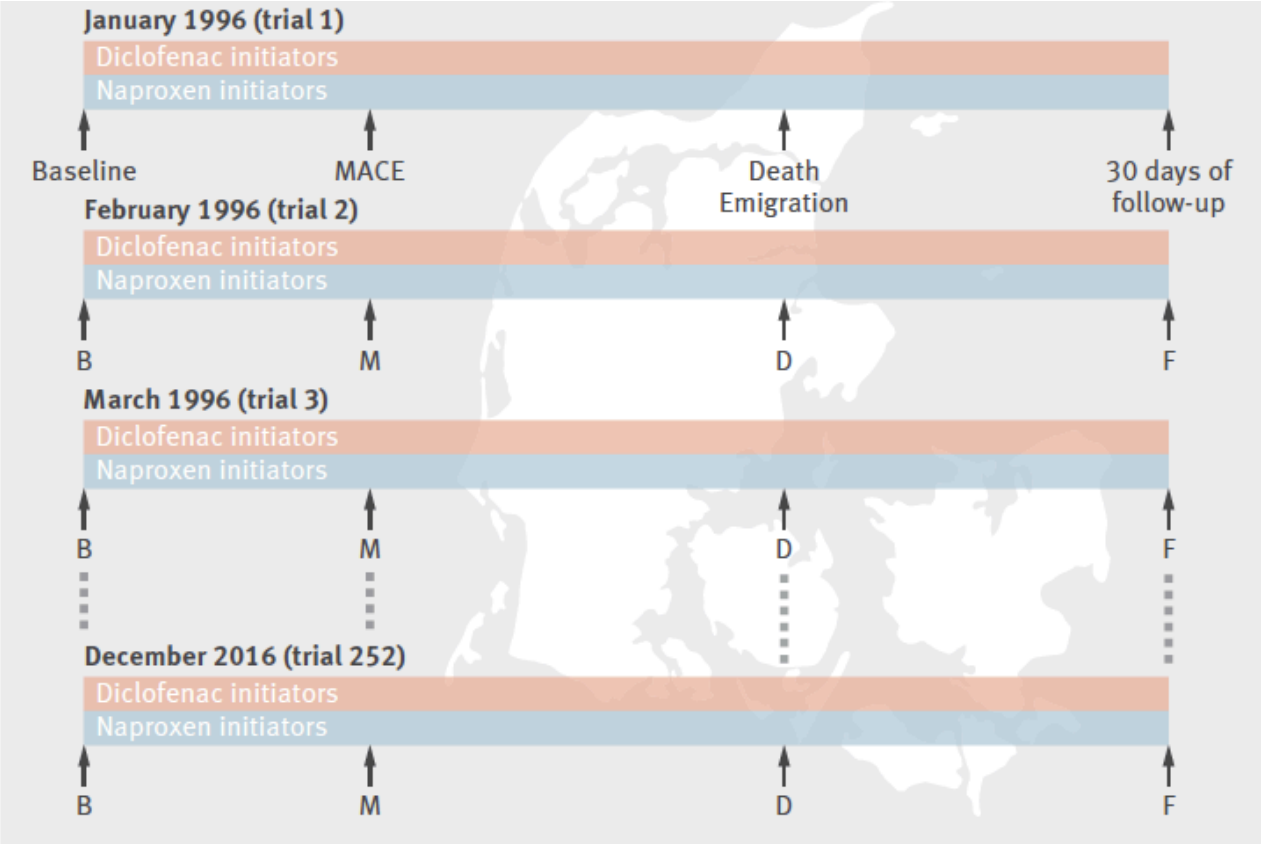
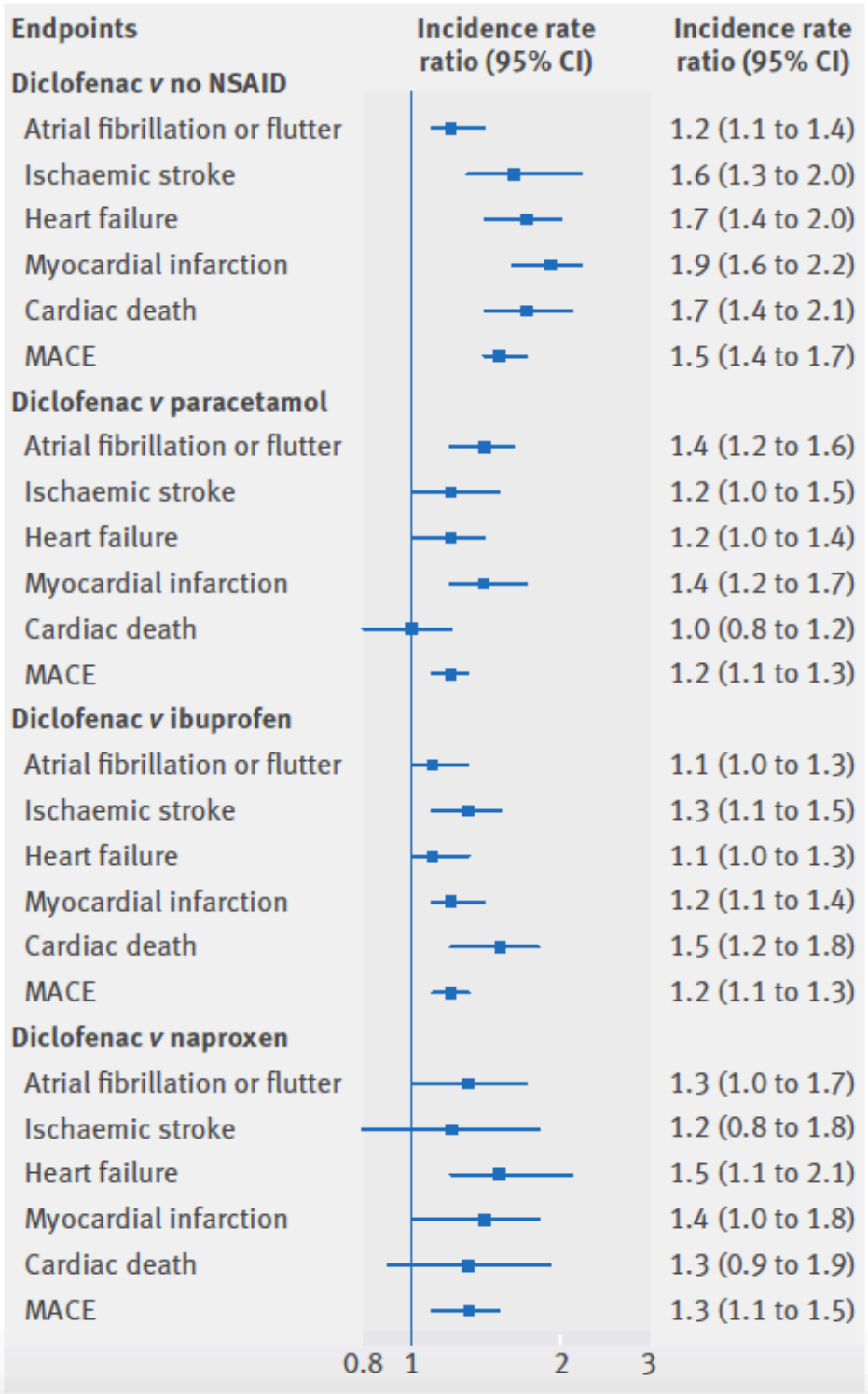


Fig 1 | Emulated trial design, to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs in Denmark. Individual level linkage of nationwide population based registries was used to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a clinical controlled trial. Eligible individuals were aged at least 18 years who had at least one year of prescription history and none of the exclusion criteria. All initiators of diclofenac and naproxen were identified during the month of January 1996. Each person was followed up to a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up. Enrolment was repeated in the months of February and March, and subsequently for every month up to December 2016. The series of 252 emulated trials were then statistically pooled into one model, generating a sample size of 1 370 832 diclofenac initiators and 291 490 naproxen initiators. A similar approach was used to identify ibuprofen initiators (n=3 878 454) and propensity score matched initiators of paracetamol (n=764 781) and NSAID non-initiators (n=1 303 209). B=baseline; MACE=major adverse cardiovascular events; D=death or emigration; F=30 days of follow-up



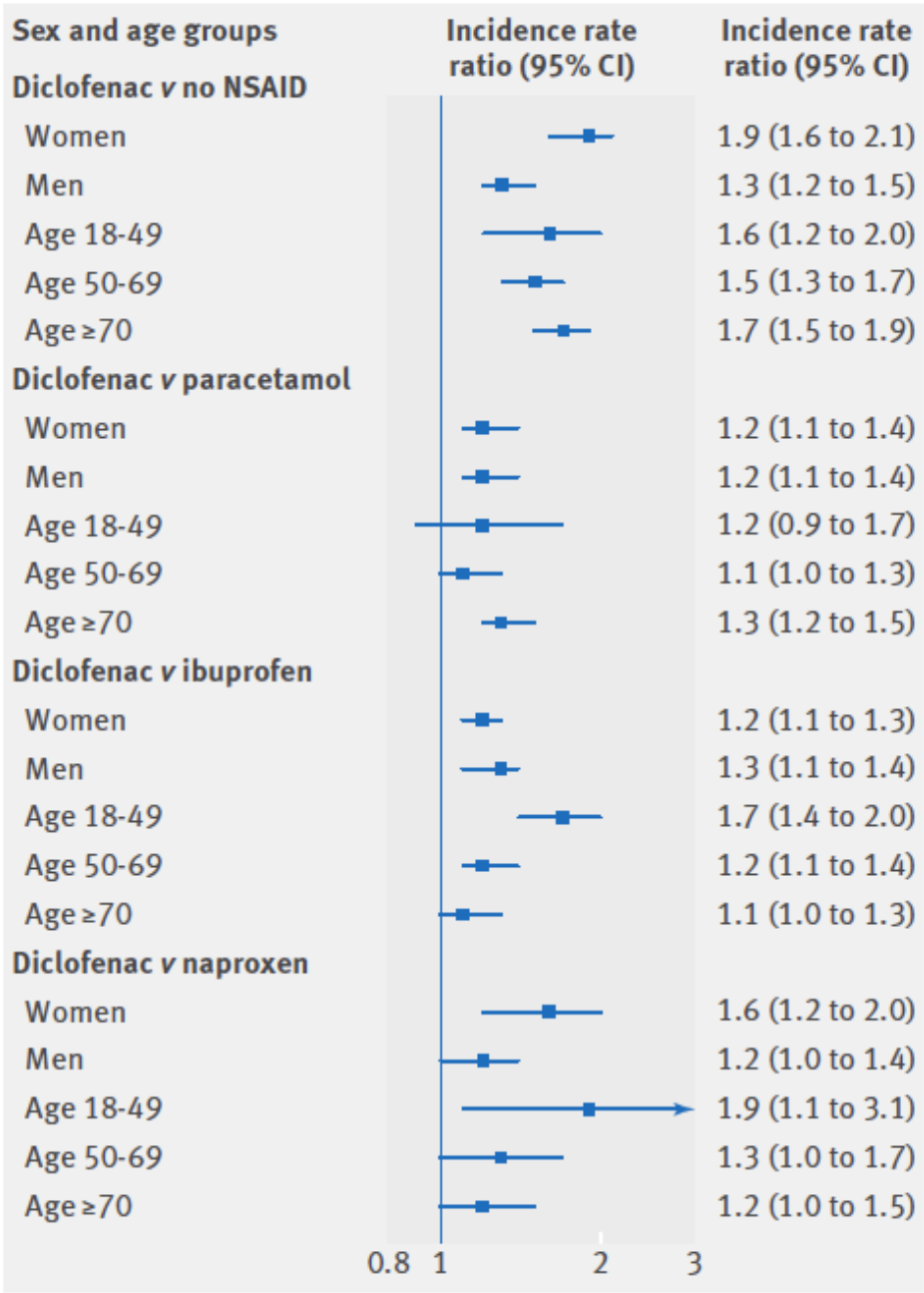


Fig 3 | Risk of major adverse cardiovascular events after diclofenac initiation according to sex and age. NSAID=non-steroidal anti-inflammatory drug

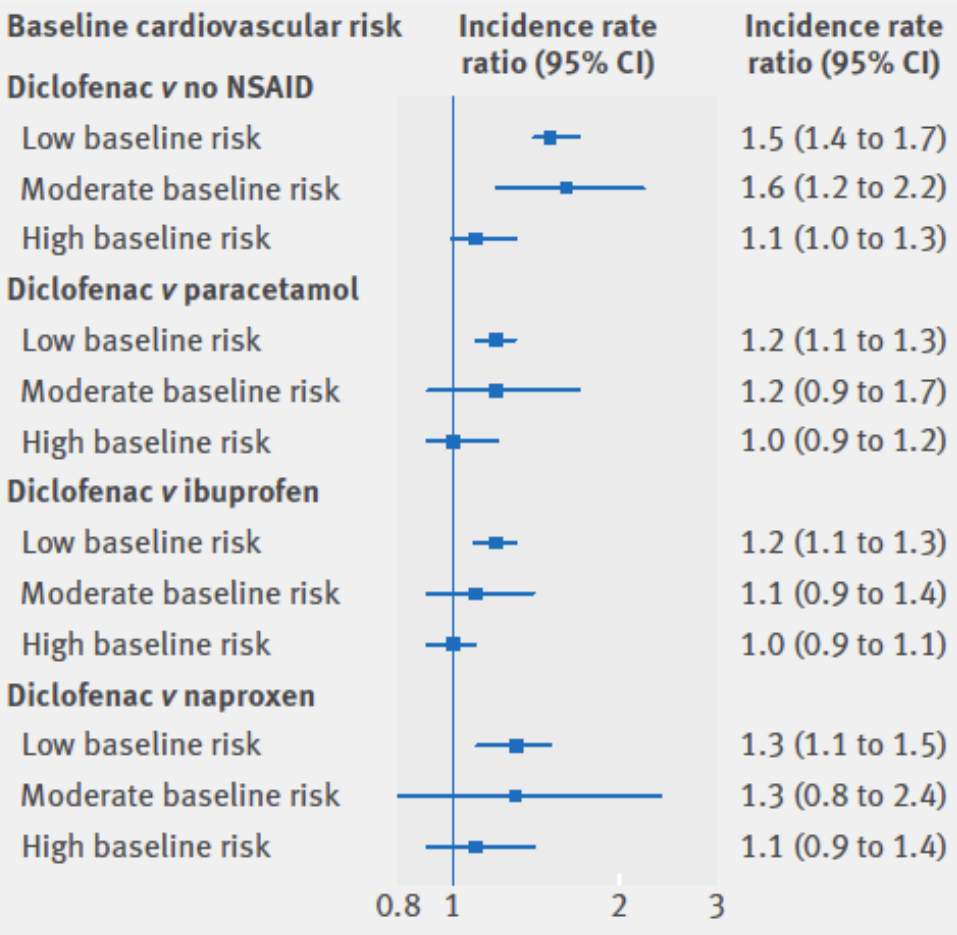


Fig 4 | Risk of major adverse cardiovascular events after diclofenac initiation according to baseline cardiovascular risk. NSAID=non-steroidal anti-inflammatory drug

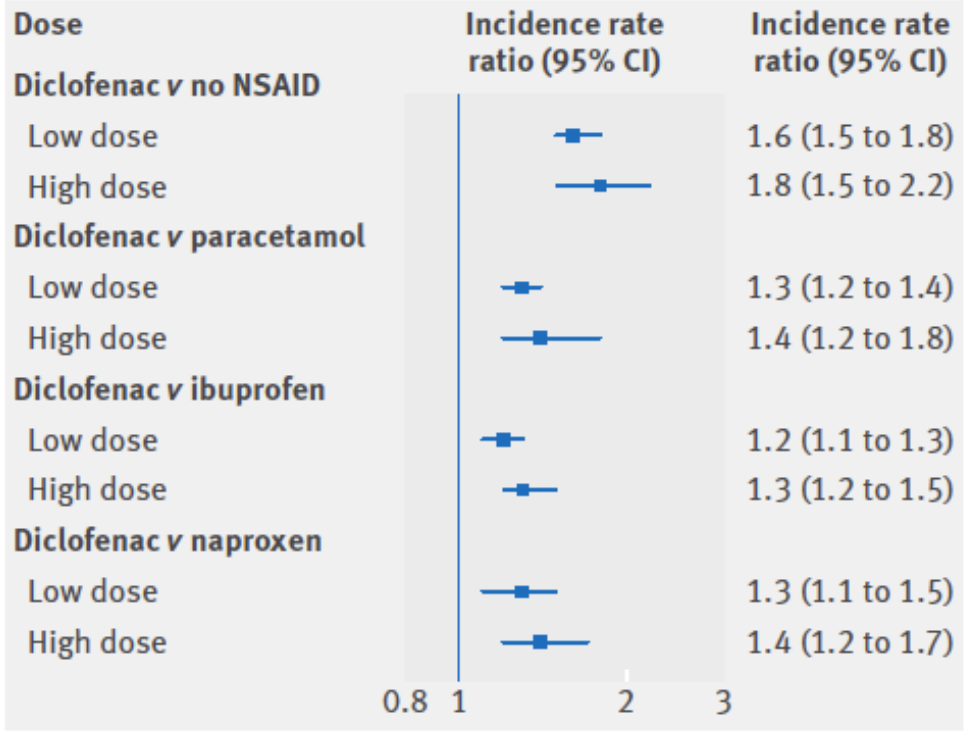


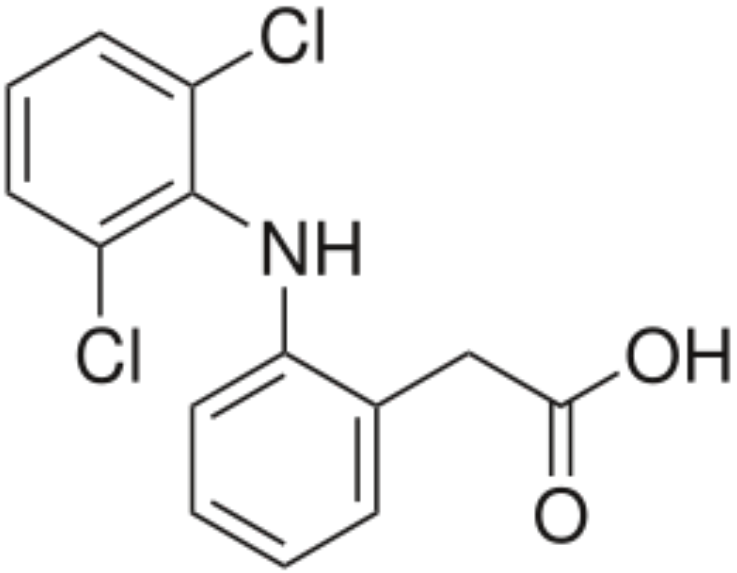
Fig 5 | Risk of major adverse cardiovascular events comparing initiation of low and high dose diclofenac with no NSAID initiation or initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug

Conclusions and implications

Our study provides an overview of the spectrum and magnitude of cardiovascular risks related to initiation of diclofenac. We also showed that diclofenac initiators had an upper gastrointestinal bleeding risk similar to that of naproxen initiators and more than twice the risk of ibuprofen initiators. Treatment of pain and inflammation with NSAIDs may be worthwhile for some patients to improve quality of life despite potential side effects. Considering its cardiovascular and gastrointestinal risks, however, there is little justification to initiate diclofenac treatment before other traditional NSAIDs.

It is time to acknowledge the potential health risk of diclofenac and to reduce its use. Diclofenac should not be available over the counter, and when prescribed, should be accompanied by an appropriate front package warning about its potential risks. Moreover, the choice to use diclofenac as the reference group to provide evidence of safety of selective COX-2 inhibitors represents a potential flaw in safety trials.41-43 Future trials should instead use low dose ibuprofen (≤1200 mg/day) or naproxen (≤500 mg/day) as comparators.4

In conclusion, our data support that initiation of diclofenac poses a cardiovascular health risk, both compared with no use, paracetamol use, and use of other traditional NSAIDs.



Das **Metabolische Äquivalent** (*metabolic equivalent of task*; MET) wird verwendet, um den Energieverbrauch verschiedener Aktivitäten zu vergleichen. Es ist die Beschreibung
des Stoffwechselumsatzs eines Menschen bezogen auf den Ruheumsatz im Verhältnis zu seinem Körpergewicht.
Das metabolische Äqivalent wurde von *Ainsworth* wie folgt definiert: 1 MET entspricht dem Umsatz von 3,5 ml Sauerstoff pro Kilogramm Körpergewicht pro Minute bei Männern, bei Frauen sind es 3,15 ml/kg/min. Eine andere Definition bezeichnet als 1 MET einen Energieverbrauch von 4,2 kJ (1 kcal) je Kilogramm Körpergewicht pro Stunde, beides entspricht in etwa dem Ruheumsatz des Körpers. Moderate körperliche Aktivität hat etwa einen Energieverbrauch von 3 bis 6 METs, intensive Anstrengungen hingegen über 6 METs.
Da der Energieumsatz individuell unterschiedlich ist, eignet sich der Vergleich von Aktivitäten mittels MET nur für den relativen Vergleich des Energieverbrauches einer Person. METs werden als Maß in der Ergometrie genutzt.

Physical activity	MET
Light intensity activities	**< 3**
sleeping	0.9
watching television	1.0
writing, desk work, typing	1.5
walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
walking, 2.5 mph (4 km/h)	2.9
Moderate intensity activities	**3 to 6**
bicycling, stationary, 50 watts, very light effort	3.0
walking 3.0 mph (4.8 km/h)	3.3
calisthenics, home exercise, light or moderate effort, general	3.5
walking 3.4 mph (5.5 km/h)	3.6
bicycling, <10 mph (16 km/h), leisure, to work or for pleasure	4.0
bicycling, stationary, 100 watts, light effort	5.5
sexual activity	5.8[12]
Vigorous intensity activities	**> 6**
jogging, general	7.0
calisthenics (e.g. pushups, situps, pullups, jumping jacks), heavy, vigorous effort	8.0
running jogging, in place	8.0
rope jumping	10.0

The Physical Activity Guidelines for Americans

Importance Approximately 80% of US adults and adolescents are insufficiently active. Physical activity fosters normal growth and development and can make people feel, function, and sleep better and reduce risk of many chronic diseases.

Objective To summarize key guidelines in the *Physical Activity Guidelines for Americans*, 2nd edition (PAG).

Process and Evidence Synthesis The 2018 Physical Activity Guidelines Advisory Committee conducted a systematic review of the science supporting physical activity and health. The committee addressed 38 questions and 104 subquestions and graded the evidence based on consistency and quality of the research. Evidence graded as strong or moderate was the basis of the key guidelines. The Department of Health and Human Services (HHS) based the PAG on the *2018 Physical Activity Guidelines Advisory Committee Scientific Report*.

Recommendations The PAG provides information and guidance on the types and amounts of physical activity to improve a variety of health outcomes for multiple population groups. Preschool-aged children (3 through 5 years) should be physically active throughout the day to enhance growth and development. Children and adolescents aged 6 through 17 years should do 60 minutes or more of moderate-to-vigorous physical activity daily. Adults should do at least 150 minutes to 300 minutes a week of moderate-intensity, or 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. They should also do muscle-strengthening activities on 2 or more days a week. Older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities. Pregnant and postpartum women should do at least 150 minutes of moderate-intensity aerobic activity a week. Adults with chronic conditions or disabilities, who are able, should follow the key guidelines for adults and do both aerobic and muscle-strengthening activities. Recommendations emphasize that moving more and sitting less will benefit nearly everyone. Individuals performing the least physical activity benefit most by even modest increases in moderate-to-vigorous physical activity. Additional benefits occur with more physical activity. Both aerobic and muscle-strengthening physical activity are beneficial.

Conclusions and Relevance The *Physical Activity Guidelines for Americans*, 2nd edition, provides information and guidance on the types and amounts of physical activity that provide substantial health benefits. Health professionals and policy makers should facilitate awareness of the guidelines and promote the health benefits of physical activity and support efforts to implement programs, practices, and policies to facilitate increased physical activity and to improve the health of the US population.

Box 1. New Evidence for Health Benefits of Physical Activity

Improved bone health and weight status for children aged 3 through 5 years

Improved cognitive function for youth aged 6 to 13 years

Reduced risk of cancer at additional sites

Brain health benefits, including improved cognitive function, reduced anxiety and depression risk, and improved sleep and quality of life

Reduced risk of fall-related injuries for older adults

For pregnant women, reduced risk of excessive weight gain, gestational diabetes, and postpartum depression

For people with various chronic medical conditions, reduced risk of all-cause and disease-specific mortality, improved function, and improved quality of life

Adults and Older Adults

- Lower risk of all-cause mortality
- Lower risk of cardiovascular disease mortality
- Lower risk of cardiovascular disease (including heart disease and stroke)
- Lower risk of hypertension
- Lower risk of type 2 diabetes
- Lower risk of adverse blood lipid profile
- Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus,
- Improved cognition
- Reduced risk of dementia (including Alzheimer disease)
- Improved quality of life
- Reduced anxiety
- Reduced risk of depression
- Improved sleep
- Slowed or reduced weight gain
- Weight loss, particularly when combined with reduced calorie intake
- Prevention of weight regain after initial weight loss
- Improved bone health
- Improved physical function
- Lower risk of falls (older adults)

Box 3. Types and Intensity of Physical Activity

Aerobic Activity

An activity in which the body's large muscles move for a sustained amount of time, therefore improving cardiorespiratory fitness. Aerobic activity is also called endurance or cardio activity. Examples include brisk walking, running, or bicycling.

Muscle-Strengthening Activity

An activity that increases skeletal muscle strength, power, endurance, and mass. Examples include weight lifting or resistance training.

Bone-Strengthening Physical Activity

An activity that produces a force on the bones, which promotes bone growth and strength. Examples include jumping rope or running.

Balance Activity

An activity designed to improve individuals' ability to resist forces within or outside of the body that cause falls while a person is stationary or moving. Examples include lunges or walking backward.

Multicomponent Physical Activity

An activity that includes more than 1 type of physical activity, such as aerobic, muscle strengthening, and balance training. Examples include some dancing or sports.

Absolute Intensity

Refers to the rate of work being performed and does not consider the physiologic capacity of the individual. This is often expressed in metabolic equivalent of task (MET) units. Moderate-intensity physical activities such as walking briskly or raking the yard have a MET level of 3 to 5.9 METs.

Box 8. Key Guidelines for Adults With Chronic Health Conditions and Adults With Disabilities

Adults with chronic conditions or disabilities, who are able, should do at least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.

Adults with chronic conditions or disabilities, who are able, should also do muscle-strengthening activities of moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.

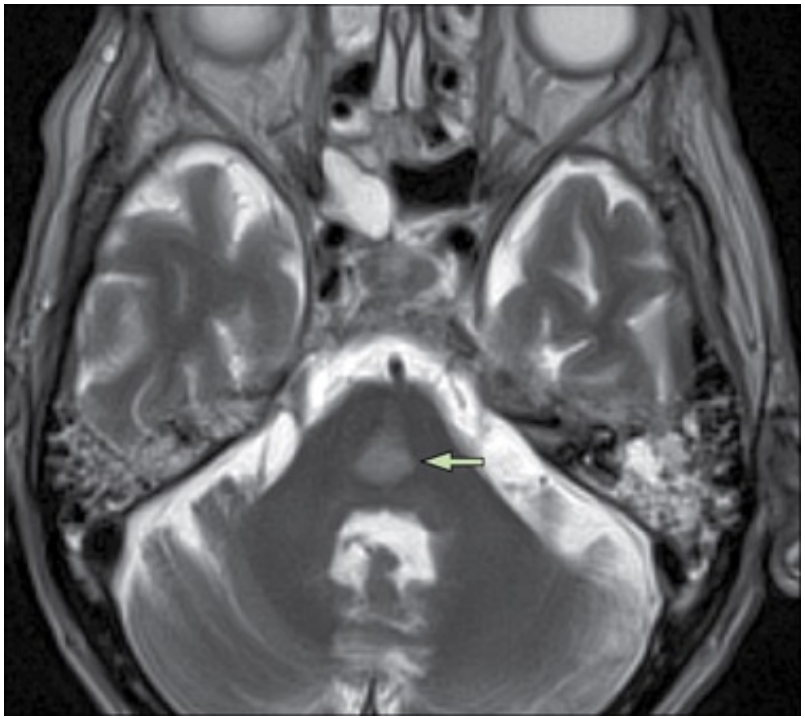
When adults with chronic conditions or disabilities are not able to meet the above key guidelines, they should engage in regular physical activity according to their abilities and should avoid inactivity.

Adults with chronic conditions or symptoms should be under the care of a health care practitioner. People with chronic conditions can consult a health care professional or physical activity specialist about the types and amounts of activity appropriate for their abilities and chronic conditions.

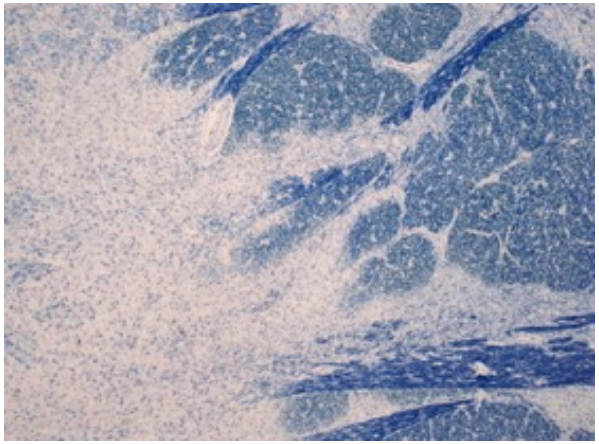
A 62-year-old man with a history of heavy alcohol abuse was admitted to our hospital with chronic diarrhoea, confusion, and weakness in both legs. Initial physical examination showed marked cachexia and decreased strength in both lower limbs. His sensation was intact. Laboratory testing showed several electrolyte abnormalities—presumed to be due to his diarrhoea—including hyponatraemia (130 mmol/L); this was gradually corrected over the course of 4 days, using 0·9% sodium chloride. At the end of this period, the sodium was 140 mmol/L (normal range 135–145 mmol/L). Over the next few days, he continued to be encephalopathic and eventually lost motor function of his arms and legs; his pupils continued to be reactive to light and the function of his extraocular muscles remained intact. An MRI scan of his brain showed restricted diffusion and fluid-attenuated inversion recovery (FLAIR) showed a corresponding abnormality in the central pons that was consistent with a diagnosis of central pontine demyelination. Sadly, the patient died in the intensive care unit after his family decided to pursue palliative care.

An MRI scan of central pontine myelinolysis

T2-weighted fluid-attenuated inversion recovery brain MRI shows a triangular area of increased signal intensity in the pons (green arrow) consistent with central pontine myelinolysis.



Osmotic demyelination syndrome—also known as central pontine myelinolysis or extrapontine myelinolysis—usually occurs after rapid correction of sodium abnormalities, although it might be seen secondary to chronic alcohol use, other severe electrolyte disturbances, and malnutrition. According to one theory, the lack of sufficient energy in malnourished patients leads to suboptimal functioning of the Na+/K+ATPase pump, which subsequently results in imbalances in sodium homoeostasis in the brain. A high degree of clinical suspicion that it is likely to occur in patients with chronic alcohol use and those who are malnourished might help to prevent the development of osmotic demyelination syndrome. Treatment is usually just supportive management. However, there have been some case reports of successful treatment with plasma exchange, methylprednisone, and immunoglobulins. MRI usually confirms the diagnosis, and the FLAIR sequence is used to suppress the effects of cerebrospinal fluid on the image—this is especially helpful in showing subtle changes at the periphery of the cerebral hemispheres and in the periventricular region.



The currently accepted theory states that the brain cells adjust their osmolarities by changing levels of certain osmolytes like inositol, betaine, and glutamine in response to varying serum osmolality. In the context of chronic low plasma sodium (hyponatremia), the brain compensates by decreasing the levels of these osmolytes within the cells, so that they can remain relatively isotonic with their surroundings and not absorb too much fluid. The reverse is true in hypernatremia, in which the cells increase their intracellular osmolytes so as not to lose too much fluid to the extracellular space.
With correction of the hyponatremia with intravenous fluids, the extracellular tonicity increases, followed by an increase in intracellular tonicity. When the correction is too rapid, not enough time is allowed for the brain's cells to adjust to the new tonicity, namely by increasing the intracellular osmoles mentioned earlier. If the serum sodium levels rise too rapidly, the increased extracellular tonicity will continue to drive water out of the brain's cells. This can lead to cellular dysfunction and CPM