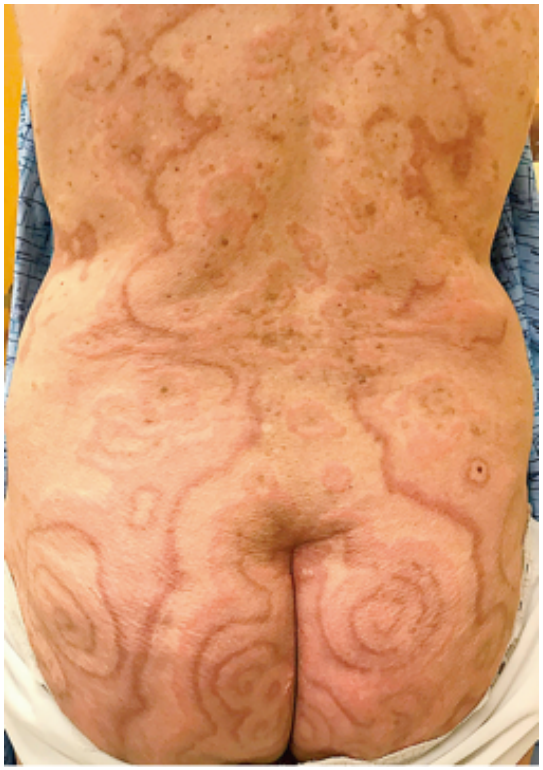
A 73-year-old woman presented to the dermatology clinic with an 11-month history of an evolving pruritic, erythematous rash on her thighs and buttocks. On physical examination she was noted to have polycyclic erythematous plaques. What is the most likely diagnosis?



Dermatomyositis

Subacute lupus erythematosus

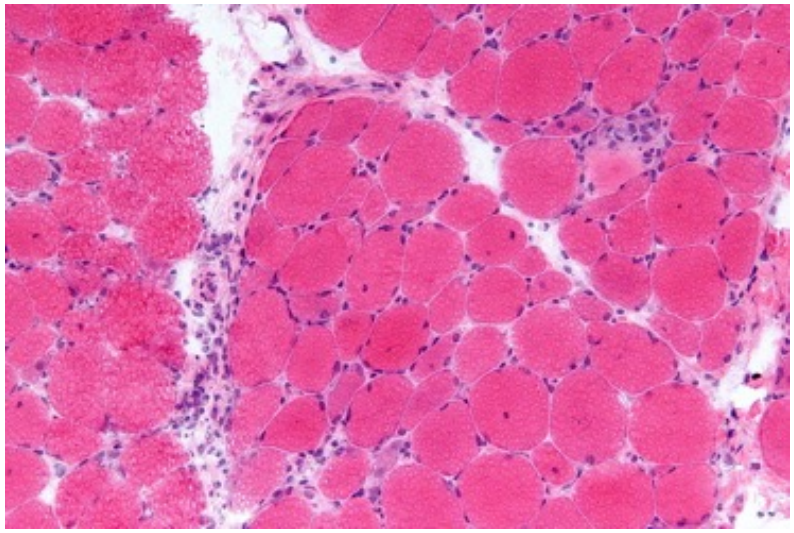
Erythema gyratum repens

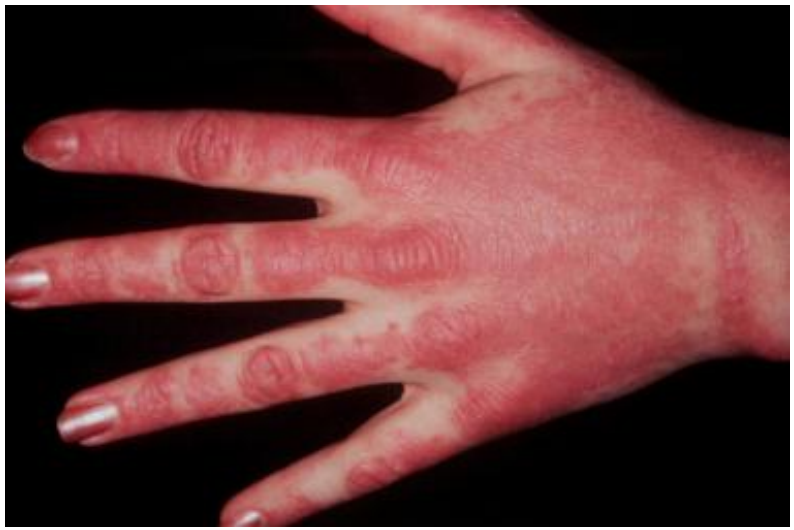
Tinea versicolor

Necrolytic migratory erythema

The patient received a clinical diagnosis of erythema gyratum repens, which is a rare paraneoplastic rash associated with breast, lung, or esophageal cancer. She underwent imaging and colonoscopy before being diagnosed with anal squamous cell carcinoma. The patient was treated with topical glucocorticoids and gabapentin for pruritus. The rash improved after initiation of chemotherapy and radiation.

Die Dermatomyositis (DM, auch Lilakrankheit, Wagner-Unverricht-Syndrom) ist eine idiopathische Myopathie (=Muskelerkrankung) bzw. Myositis (=Muskelentzündung) mit Hautbeteiligung und gehört zu der Gruppe der Kollagenosen. Ist nur die Muskulatur betroffen, so spricht man in der Regel von einer Polymyositis (PM). Aktuelle Studien zur Pathogenese der DM und PM widersprechen sich. Da noch nicht gesichert ist, ob DM und PM die gleiche Pathogenese haben, wird im Folgenden die Dermatomyositis getrennt besprochen und auf die Polymyositis sei nur verwiesen.
Die Erkrankung ist selten und kann in jedem Lebensalter auftreten. Das Häufigkeitsmaximum ist das 50. Lebensjahr, Frauen sind öfter betroffen als Männer (Gynäkotropie 2:1). Bei Kindern liegt das Altersmaximum bei vier bis zwölf Jahren. Bei Haushunden tritt die Dermatomyositis nahezu ausschließlich bei Welpen und Junghunden auf.
Sie wurde von Ernst Leberecht Wagner (1821–1888) 1863 beschrieben und weiter von Heinrich Unverricht untersucht.
Ungefähr 50 % der Dermatomyositiden sind mit Tumoren assoziiert. Besonders hervorzuheben sind dabei Ovarialkarzinome. Es ist deswegen nötig, bei neu aufgetretener Dermatomyositis nach Tumoren zu suchen. Allerdings ist der zeitliche Bezug zum Auftreten der Dermatomyositis zu dem des Tumors extrem variabel – die Haut- und Muskelerkrankung kann dem Tumor sowohl vorausgehen, als auch nachfolgen oder sich zeitgleich manifestieren. In manchen Fällen kann das Wiederauftreten einer Dermatomyositis nach zwischenzeitlicher Heilung von einem Tumor dessen Rezidiv, d. h. Wiederkehr, anzeigen. Die im Rahmen einer Neoplasie auftretende Dermatomyositis ist nach Entfernung der Neoplasie vollständig reversibel.

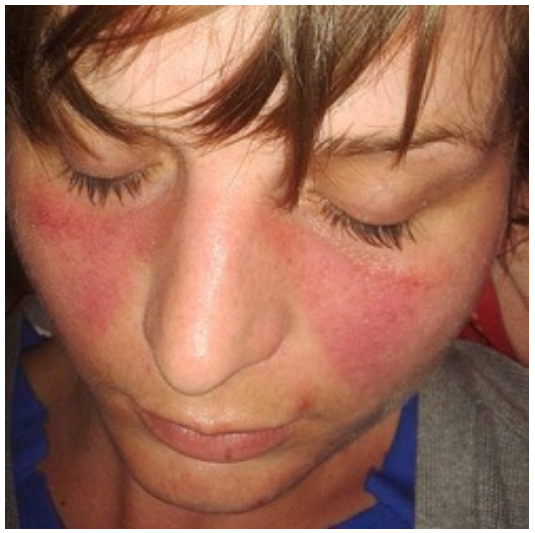


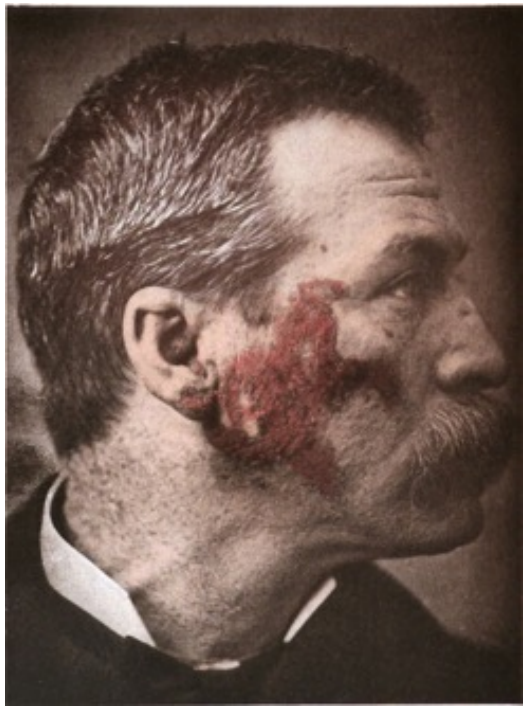


Der Lupus erythematodes (lateinisch lupus, deutsch ‚Wolf', und altgriechisch ἐρυθηματώδης erythēmatṓdēs aus ἐρύθημα erýthēma, deutsch ‚Röte', und Suffix -ώδης -ṓdēs, deutsch ‚ähnlich wie'), auch Schmetterlingsflechte, ist eine seltene Autoimmunerkrankung. Beim Lupus erythematodes ist das körpereigene Immunsystem fehlreguliert: Es richtet sich hierbei gegen gesunde körpereigene Zellen. Dadurch werden Organe und Organsysteme, z. B. die Haut, geschädigt.

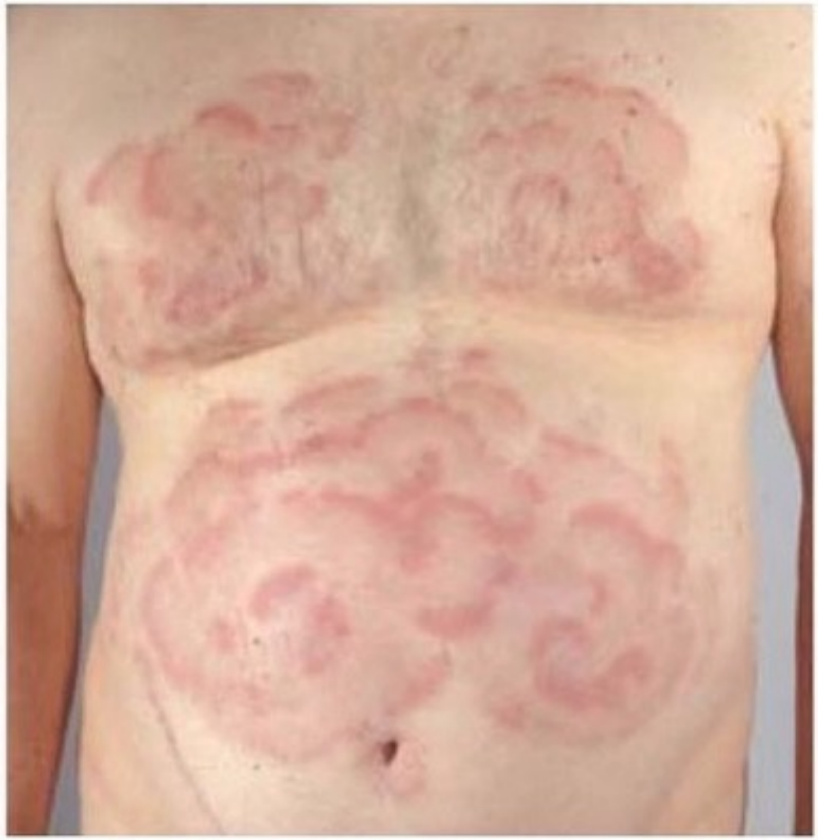
Es gibt unterschiedliche Formen des Lupus erythematodes: Die verschiedenen Formen des kutanen Lupus erythematodes (CLE) befallen üblicherweise nur die Haut. Der systemische Lupus erythematodes (SLE) kann alle Organe befallen. Er gehört zur Gruppe der Kollagenosen. Als Kollagenose gehört der systemische Lupus erythematodes zu den Erkrankungen des rheumatischen Formenkreises. Der neonatale Lupus erythematodes bei Neugeborenen ist eine Folge der mütterlichen Lupus-erythematodes-Erkrankung.

Der Name Lupus wurde von dem lombardischen Chirurgen Roger Frugardi (um 1140–1195) eingeführt, ist aber auch schon im 10. Jahrhundert belegt. Der Begriff Lupus leitet sich vom lateinischen Namen für den Wolf ab. Früher verglich man die Narben, die nach dem Abheilen der Hautschäden verbleiben, mit Narben von Wolfsbissen.

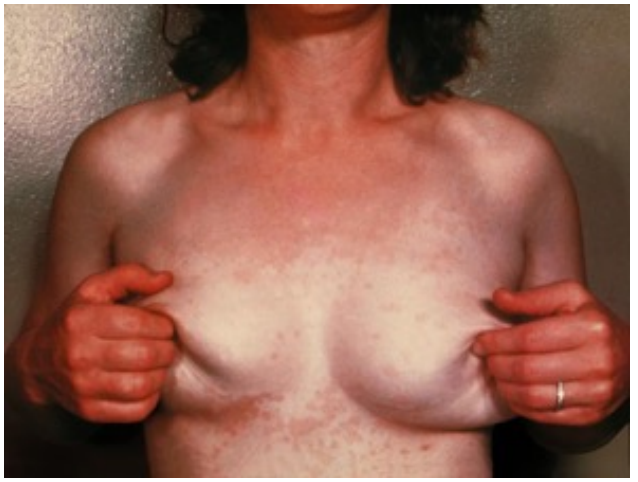


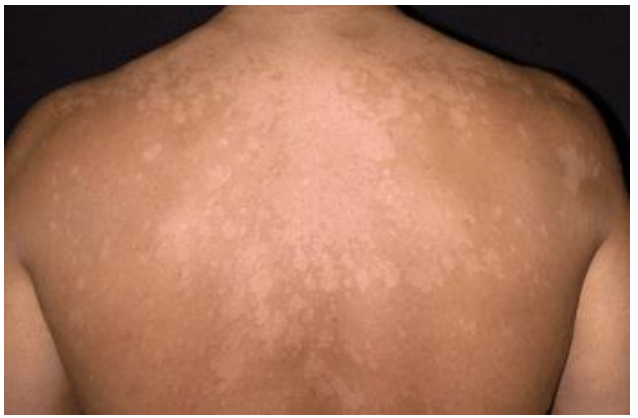


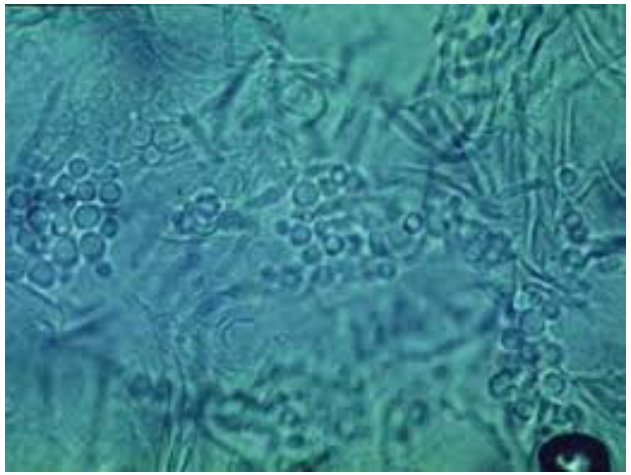
Das Erythema gyratum repens gehört zu den figurierten Erythemen. Es tritt paraneoplastisch auf, vor allem bei Bronchial- und Mammakarzinomen sowie bei malignen Tumoren des weiblichen Genitales, des Ösophagus oder des Magens. Die Hautveränderungen können dem Tumorleiden 4-8 Monate vorausgehen.
Das Eyrthema gyratum repens tritt vor allem bei Erwachsenen zwischen dem 40. und 60. Lebensjahr auf.
Das Erythema gyratum repens präsentiert sich als urtikariell eleviertes, rasch wanderndes (in Stunden), 1-2 cm breites, streifiges Erythem. Die Effloreszenzen sind anulär, girlandenartig oder spiralig ineinander geschwungen und erinnern an Holzmaserungen. Im Randbereich weisen sie eine halskrausenartige Schuppung auf. Das Erythema gyratum repens tritt bevorzugt im Bereich des Körperstamms und an den proximalen Extremitätenabschnitten auf.
Die Ursache für das Erythema gyratum repens ist unklar. Vermutet wird eine immunologische Reaktion auf Antigene wie z.B. Verbindungen, die von Tumoren produziert werden. Die Hautveränderung kann schon mehrere Monate auftreten, bevor andere Symptome einer Tumorerkrankung auffallen. Der Primärtumor ist meist ein Karzinom (Mamma-, Magen-, Lungen-, Prostata-, Ösophagus-, Genitalkarzinome), seltener werden andere Neoplasien wie ein Melanom oder ein Plasmozytom gefunden.



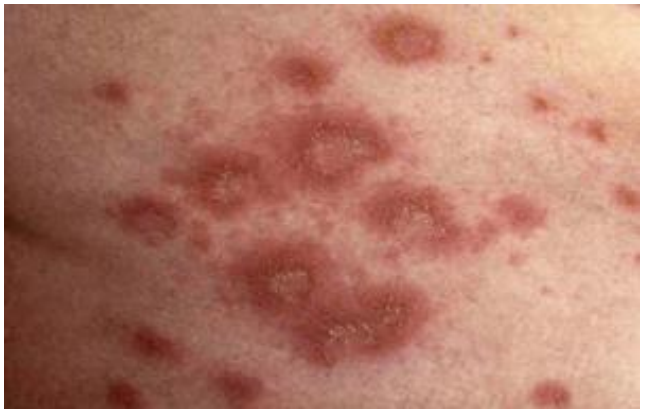
Pityriasis versicolor (Kleienpilzflechte, auch: Kleieflechte) ist eine häufig vorkommende Pilzinfektion der obersten Hautschicht (Epidermis). Der Erreger dieser Hautmykose ist Malassezia furfur (früher u. a.: Pityrosporum orbiculare bzw. Pityrosporum ovale). Der Pilz bleibt als Hefe im einzelligen Stadium, bildet also keinen Fruchtkörper und kein Mycel aus. Es gibt von Land zu Land unterschiedliche Prävalenzen für die versch. Malassezia-Spezies. Die Erkrankung ist harmlos und nicht ansteckend.
Malassezia-Hefen gehören bei annähernd 100 % der Bevölkerung zur normalen Hautflora. Die Gründe, warum sie bei manchen Menschen pathogen (krankhaft) werden, sind nicht ganz geklärt. Es wird jedoch beobachtet, dass die Hautmykose verstärkt in den Sommermonaten und bei Menschen mit Neigung zu starkem Schwitzen auftritt. Auch eine Verbindung mit hoher Schilddrüsenfunktion wird angenommen. Es bildet sich ein Pilzrasen, der zum einen physikalisch Licht blockiert, zum anderen toxisch die Melaninproduktion hemmt. Bei Sonnenkontakt bräunt die befallene Haut weit weniger als die umgebenden Partien, wodurch weiße Flecken (Maculae) entstehen. Diese können linsengroß sein oder sich zu einer landkartenartigen Marmorierung der Haut ausweiten. Die Diagnose wird vom Dermatologen meist als Blickdiagnose gestellt und kann durch das Abkratzen von Hautschuppen und die Begutachtung unter dem Mikroskop bestätigt werden. Die Pilzzellen sind als traubenförmige Kugelhäufchen zu erkennen.



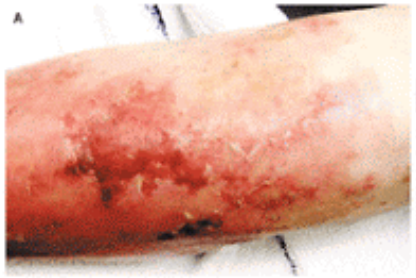


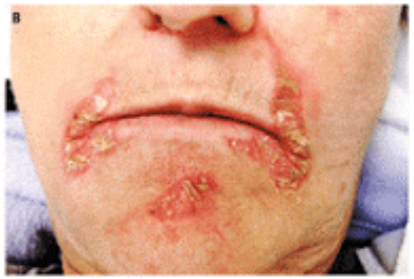


Erythema necrolyticum migrans

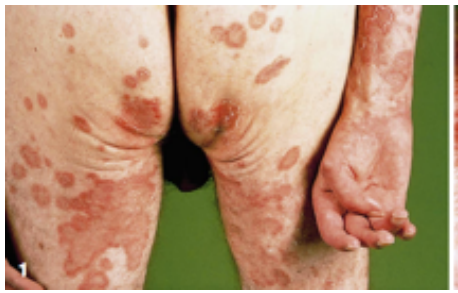


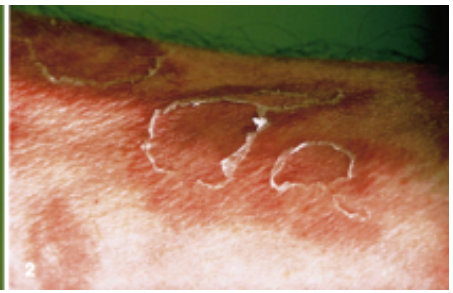
Bei Glukagon-produzierenden Tumoren (Glukagonom) auftretendes paraneoplastisches Syndrom der Haut mit erythematösen bogenförmigen Arealen mit Krustenbildung und langsamer Ausbreitungstendenz. Weitere mögliche Erscheinungen sind Cheilitis, Nageldystrophien, Stomatitis, Diarrhö, Thromboseneigung, Diabetes mellitus, Hyperglukagonämie und B-Symptomatik. Diagnostiziert wird klinisch, laborchemisch und histologisch. Das Glukagonom wird gesucht und saniert. Bizarr geformte zirzinäre Erytheme mit zentrifugaler Ausbreitung und Pustelbildung.
Erythema necroticans migrans; Fünfte obligate kutane Paraneoplasie; Impetigo circinata; Necrolytic migratory erythema; Nekrolytisches migratorisches Erythem; Paraneoplasie fünfte obligate kutane; Staphylodermia superficialis circinata.



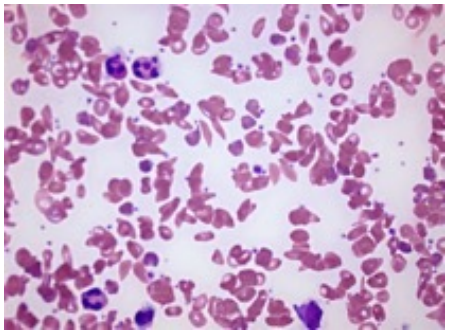


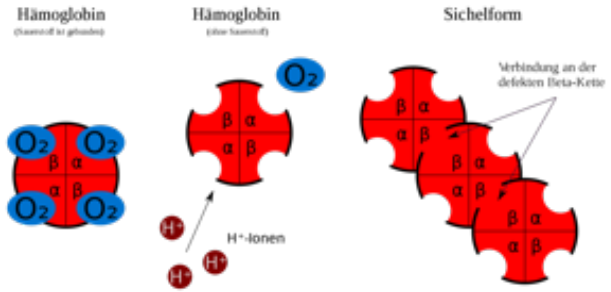
Postuliert wird durch das erhöhte Glucagon eine katabole Stoffwechsellage mit einem Mangel an Zink und verschiedenen Aminosäuren. Für diese These spricht das rasche Ansprechen der Hautverändeurngen auf Aminosäure-Substitutionen. Bemerkenswert ist, dass sich das klinische und histologische Bild nicht von Hautverändeurngen bei Zinkmangelsyndrom oder Biotin-Mangel unterscheidet.

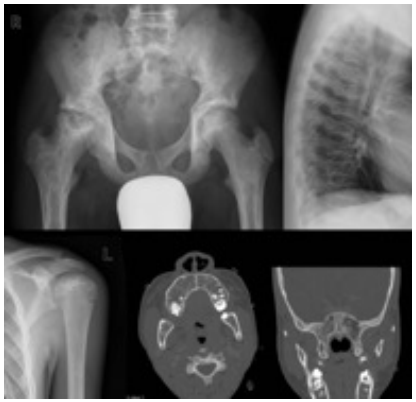




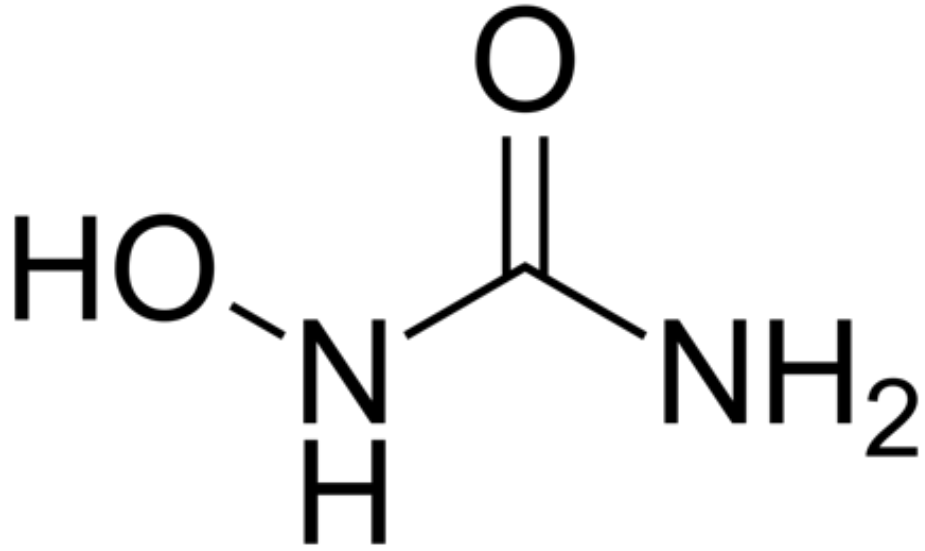
Die Sichelzellkrankheit oder Sichelzellenanämie (medizinisch Drepanozytose), auch Sichelzellanämie ist eine erbliche Erkrankung der roten Blutkörperchen (Erythrozyten). Sie gehört zur Gruppe der Hämoglobinopathien (Störungen des Hämoglobins) und führt zu einer korpuskulärenhämolytischen Anämie. Bei den Betroffenen liegt eine Mutation der β-Kette des Hämoglobins vor. Es können entweder alle β-Ketten betroffen sein (schwere, homozygote Form) oder nur ein Teil (mildere, heterozygote Form). Die Krankheit tritt vor allem bei dunkelhäutigen Personen aus Subsahara-Afrika und deren Nachfahren, aber auch in Teilen des Mittelmeerraums und des Nahen Ostens bis Indien auf und wurde durch Migration global verbreitet. Sie ist nach wie vor in den Entwicklungsländern mit einer hohen Mortalität verbunden. Die Krankheit wurde 1910 von James Herrick und Ernest Lyons bei einem Patienten aus der Karibik beschrieben und die Bezeichnung Sichelzellenanämie wurde zuerst von Vernon Mason 1922 benutzt. Die Betroffenen bilden ein abnormes Hämoglobin (Sichelzell-Hämoglobin, HbS), das bei Sauerstoffmangel zur Bildung von Fibrillen neigt. Dabei verformen sich die roten Blutzellen durch die enthaltenen Fasern zu sichelförmigen Gebilden, verklumpen miteinander und verstopfen kleine Blutgefäße, wodurch eine Entzündungentsteht. Durch die Verklumpung und Gefäßverstopfung kann es bei der homozygoten Form zu anfallsartigen schmerzhaften, z. T. lebensbedrohlichen Durchblutungsstörungen (Sichelzellkrisen) kommen, die unter anderem zu venösen Thrombosen führen können. Aufgrund einer Punktmutation auf Chromosom 11 ist bei der Sichelzellenanämie an der Position sechs der β-Globin-Protein-Untereinheit des Hämoglobins die Aminosäure Glutaminsäure durch Valin ersetzt. Die Bezeichnung dieser Variante in offizieller genetischer Nomenklatur lautet HBB-p.E6V. Die betroffenen Erythrozyten verformen sich bei abnehmendem Sauerstoffpartialdruck sichelförmig, verfangen sich leicht in den Kapillaren und lysieren überdies sehr schnell. Durch die Hämolyse werden Hämoglobin, Arginase und freie Sauerstoffradikale freigesetzt. Freies Hämoglobin bindet Stickstoffmonoxid etwa 1000-mal stärker als intrazelluläres und Arginase verwandelt Stickstoffmonoxid zu Nitrit und Nitrat. Stickstoffmonoxid ist der wichtigste Vasodilatator, und die Konzentrationsabnahme führt zur Gefäßverengung und somit zu Durchblutungsstörungen.

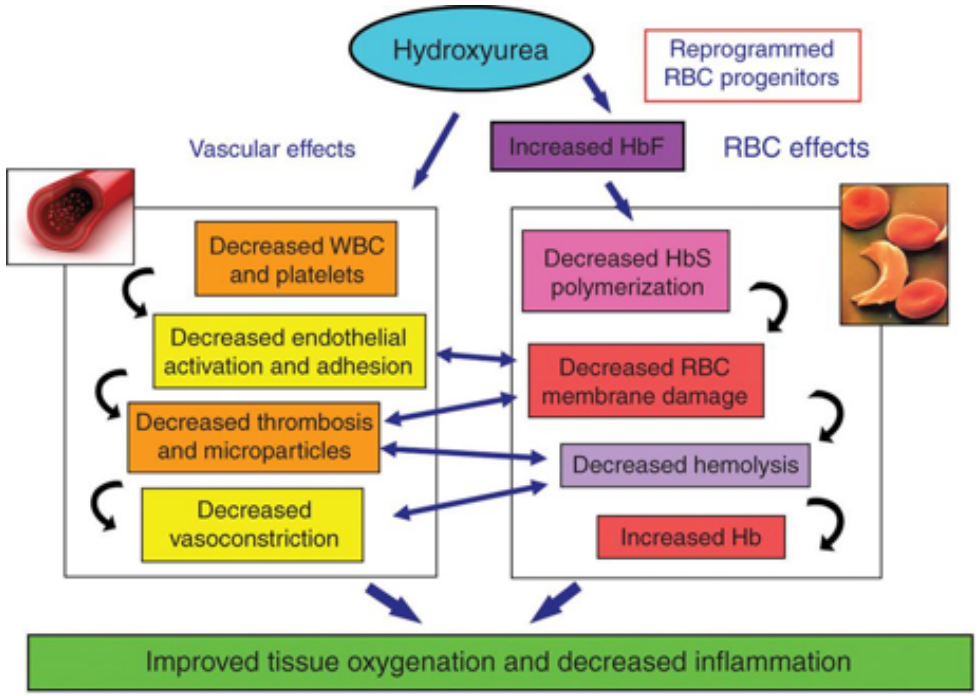


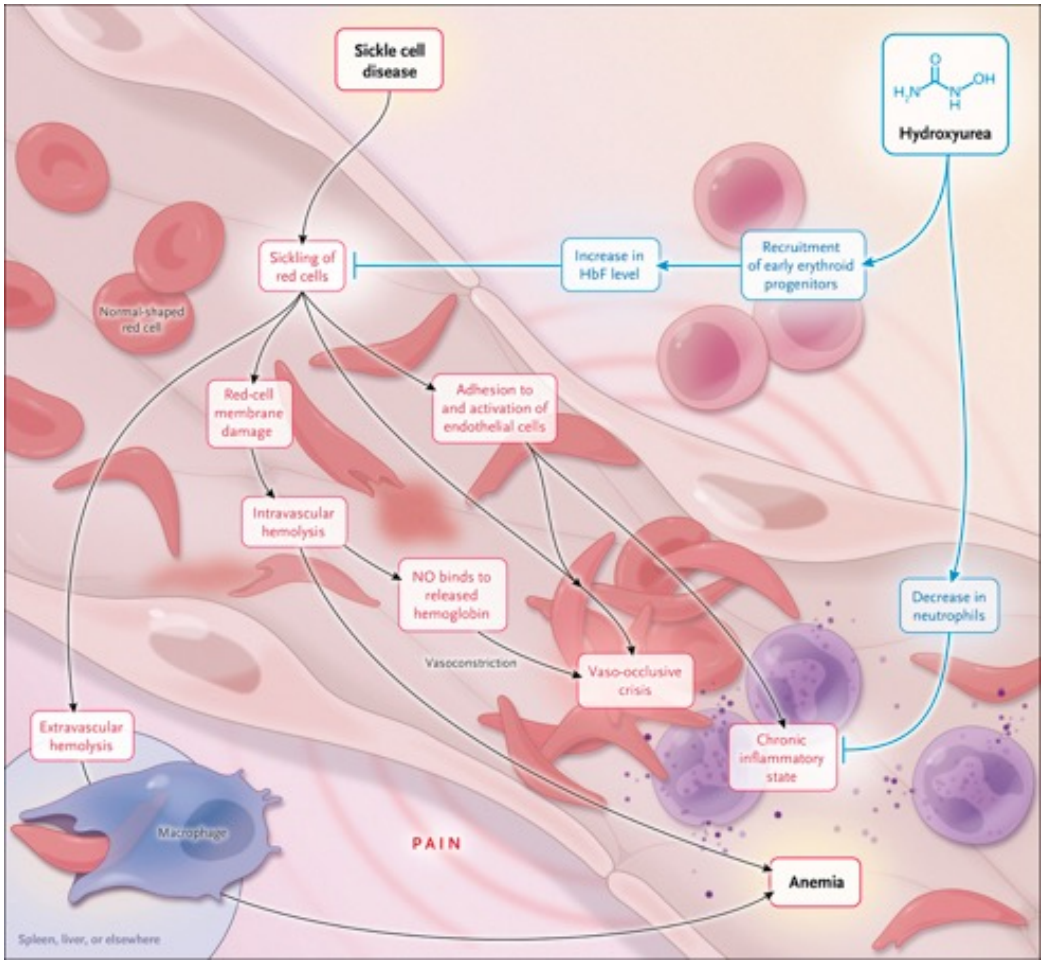




Hydroxycarbamid (INN),
auch Hydroxyharnstoff oder Hydroxyurea, ist
ein Zytostatikum, das zur Behandlung insbesondere
von malignen Bluterkrankungen
(Leukämien, Myeloproliferative Neoplasien) eingesetzt
wird. Es ist auch für die Behandlung
der Sichelzellanämie zugelassen. Im Rahmen von
experimentellen Studien wurde es für die antiretrovirale
Behandlung bei HIV-Infektion getestet. Die Wirkung der
Substanz beruht auf der Hemmung des
Enzyms Ribonukleotidreduktase, welche die Ribose zur
Desoxyribose reduziert. Diese verläuft über einen
radikalischen Mechanismus, der die Bildung eines
Tyrosinradikals im aktiven Zentrum des Enzyms
erfordert. Das stabile Tyrosinradikal entsteht durch ein
nahegelegenes Eisenzentrum, welches aus zwei
Fe3+ besteht. Hydroxyharnstoff komplexiert das Eisen
und bewirkt die Reduktion des Eisens zum Fe2+,
wodurch die DNA-Synthesekapazität der jeweiligen
Zelle deutlich eingeschränkt wird. Durch die
europäische Arzneimittelbehörde EMA wurde die
Substanz auch zur Behandlung der Sichelzellanämie
zugelassen. Hydroxycarbamid erhöht die fetale
Hämoglobin-Synthese (Hb F) im Blut. Ein prozentual
erhöhter Anteil von Hb F im Blut wirkt protektiv
gegenüber der Polymerisation von Sichelzellen. In
mehreren klinischen Studien konnte die Wirksamkeit im
Rahmen vaso-okklusiver Krisen gezeigt werden.







Modification of the Pathophysiology of Sickle Cell Disease by Hydroxyurea.
All the manifestations of sickle cell disease depend, directly or indirectly, on sickling, which in turn is produced, as red cells deliver oxygen to tissues, by the polymerization of deoxyhemoglobin S. Sickled red cells may become stuck in capillaries and, by jamming small vessels, may cause vaso-occlusion and consequent pain crises. Sickled red cells may undergo lysis within the bloodstream (intravascular hemolysis), whereby hemoglobin released in the plasma will bind nitric oxide (NO), resulting in vasoconstriction that will further favor vaso-occlusion. Sickled red cells will also be phagocytosed by macrophages (extravascular hemolysis); together with intravascular hemolysis, this causes anemia, often severe. Sickled red cells will also adhere to the endothelium, causing a chronic inflammatory state that is associated with neutrophil leukocytosis. The main action of hydroxyurea is to cause an increase in the intracellular concentration of fetal hemoglobin (HbF), which interferes with the deoxyhemoglobin S polymer formation, reducing the rate of sickling. Through this mechanism, hydroxyurea affects the very source of all the pathologic features of sickle cell disease. In addition, hydroxyurea lowers the neutrophil count, thus reducing the chronic inflammatory state.

Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa

Hydroxyurea is an effective treatment for sickle cell anemia, but few studies have been conducted in sub-Saharan Africa, where the burden is greatest. Coexisting conditions such as malnutrition and malaria may affect the feasibility, safety, and benefits of hydroxyurea in low-resource settings. We enrolled children 1 to 10 years of age with sickle cell anemia in four sub-Saharan countries. Children received hydroxyurea at a dose of 15 to 20 mg per kilogram of body weight per day for 6 months, followed by dose escalation. The end points assessed feasibility (enrollment, retention, and adherence), safety (dose levels, toxic effects, and malaria), and benefits (laboratory variables, sickle cell–related events, transfusions, and survival).
Retention of Participants in the Trial. The shaded area represents the 95% confidence interval for death or withdrawal from the trial. The inset shows the same data on an enlarged y axis.

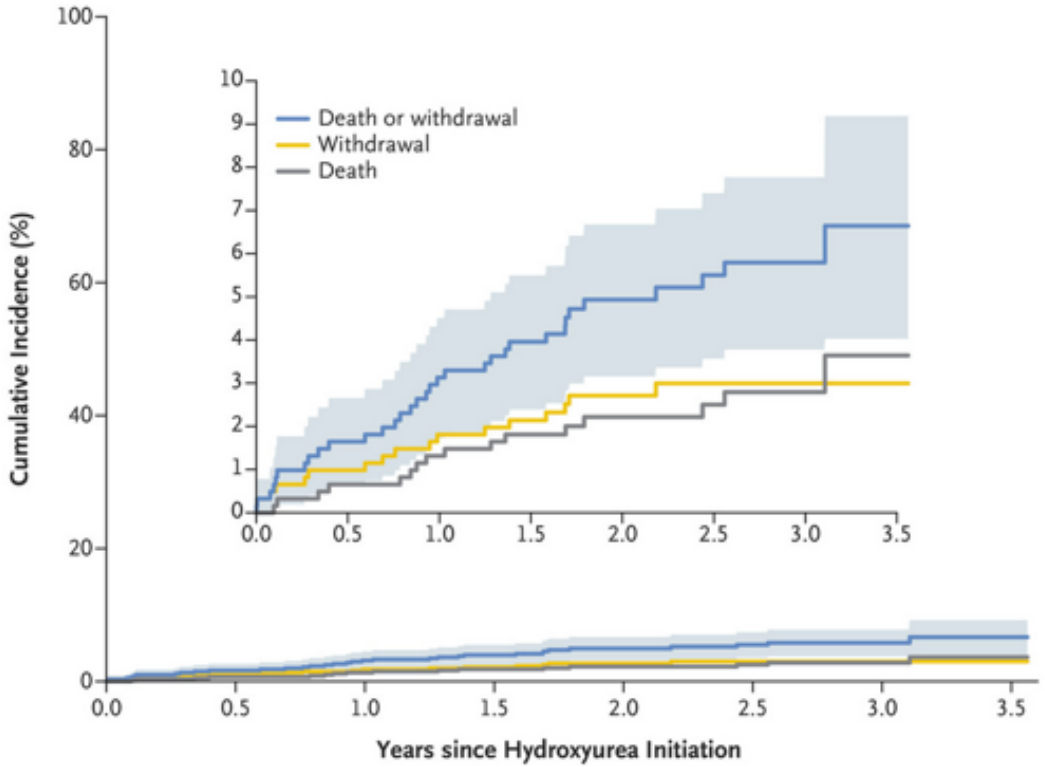


Table 1. Laboratory and Clinical Adverse Events.*

Event	Screening Phase			Treatment Phase			Incidence Rate Ratio (95% CI)
	No. of Events	No. of Participants	Rate	No. of Events	No. of Participants	Rate	
			no. of events per 100 patient-yr			*no. of events per 100 patient-yr*	
Dose-limiting toxic effect	23	20	20.7	302	159	20.6	1.00 (0.62–1.61)
Anemia	8	8	7.2	86	61	5.9	0.82 (0.40–1.71)
Reticulocytopenia	3	3	2.7	72	61	4.9	1.82 (0.58–5.68)
Neutropenia	1	1	0.9	48	40	3.3	3.59 (0.50–25.71)
Thrombocytopenia	11	11	9.9	96	61	6.5	0.66 (0.34–1.25)
Clinical adverse event	342	234	308.4	2507	527	170.7	0.54 (0.48–0.62)
Grade 2	293	212	264.2	2354	513	160.2	0.60 (0.52–0.68)
Grade 3	48	43	43.3	150	112	10.2	0.24 (0.17–0.33)
Grade 4	1	1	0.9	3	3	0.2	0.23 (0.02–2.18)
Serious adverse event	12	12	10.8	65	58	4.4	0.47 (0.25–0.90)
Grade 3	8	8	7.2	24	23	1.6	0.23 (0.10–0.51)
Grade 4	0	0	0.0	25	21	1.7	NA
Grade 5 (death)	4	4	3.6	16	16	1.1	0.30 (0.10–0.88)
Clinical sickle cell–related event	127	107	114.5	779	359	53.0	0.47 (0.38–0.57)
Vaso-occlusive pain or dactylitis	109	92	98.3	655	323	44.6	0.45 (0.37–0.56)
Acute chest syndrome or pneumonia	10	10	9.0	73	56	5.0	0.55 (0.28–1.05)
Acute splenic sequestration	2	2	1.8	16	12	1.1	0.60 (0.13–2.75)
Stroke	2	2	1.8	11	10	0.7	0.42 (0.10–1.67)
Other sickle cell–related event	3	3	2.7	15	13	1.0	0.38 (0.11–1.34)
Any event of grade ≥3	26	23	23.4	104	85	7.1	0.30 (0.19–0.48)
Additional clinical events							
Malaria	52	50	46.9	336	200	22.9	0.49 (0.37–0.66)
Nonmalaria infection	158	138	142.5	1322	429	90.0	0.62 (0.53–0.72)
Any infection of grade ≥3	32	31	28.9	118	96	8.0	0.28 (0.19–0.42)
Septicemia	16	15	14.4	37	34	2.5	0.18 (0.09–0.32)
Transfusion	48	43	43.3	209	149	14.2	0.33 (0.23–0.47)

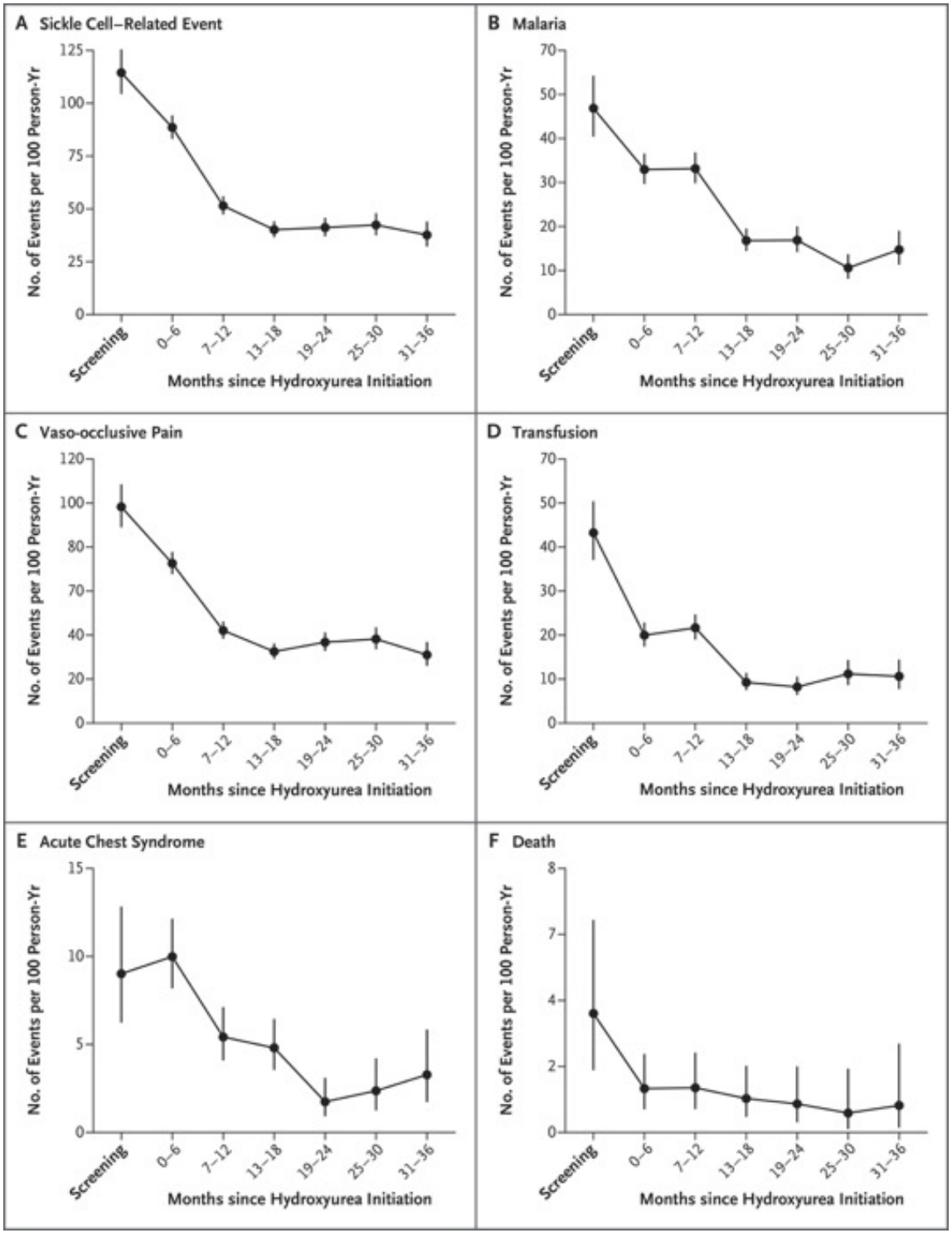
* The screening phase included 111 patient-years, and the treatment phase 1469 patient-years. The confidence intervals were not adjusted for multiple comparisons. NA denotes not applicable.

Table 2. Laboratory Effects of Hydroxyurea Treatment during the Trial.*

Variable	Month 0	Month 3	Month 6	Month 12	Month 24	Month 36	Change from Months 0 to 12 (95% CI)†
Hemoglobin (g/dl)	7.3±1.1	8.0±1.2	8.1±1.3	8.3±1.4	8.3±1.3	8.3±1.3	1.0 (0.8 to 1.0)
Mean corpuscular volume (fl)	77±9	84±10	85±10	89±12	91±13	91±13	13 (12 to 13)
Fetal hemoglobin (%)‡	10.9±6.8	17.3±8.2	19.3±8.7	23.4±9.1	23.4±9.6	21.2±8.8	12.5 (11.8 to 13.1)
White cells per mm^3	16,500±8000	12,700±5300	12,500±5000	10,100±4200	9400±3700	9400±3400	−6300 (−6900 to −5600)
Absolute neutrophil count per mm^3	6800±3000	5200±2700	5300±2700	4200±2200	4100±2100	4300±2300	−2500 (−2700 to −2200)
Platelets per mm^3	411,000±171,000	372,000±173,000	381,000±174,000	343,000±174,000	353,000±166,000	365,000±193,000	−67,000 (−82,000 to −52,000)
Absolute reticulocyte count per mm^3	344,000±147,000	233,000±104,000	220,000±85,000	187,000±77,000	180,000±77,000	176,000±65,000	−157,000 (−169,000 to −145,000)
Alanine aminotransferase (U/liter)	24±33	24±34	23±14	23±15	25±28	21±11	−1 (−4 to 2)
Creatinine (mg/dl)	0.41±0.15	0.40±0.13	0.43±0.20	0.42±0.16	0.43±0.14	0.44±0.14	0.02 (0.00 to 0.03)

* Plus–minus values are means ±SD. Time points refer to the duration since treatment initiation (month 0).
† The 95% confidence interval is for the difference between month 0 and month 12. Confidence intervals were not adjusted for multiple comparisons.
‡ The fetal hemoglobin level was calculated as follows: fetal hemoglobin÷(fetal hemoglobin+sickle hemoglobin).

During hydroxyurea treatment, the white-cell count, absolute neutrophil count, and absolute reticulocyte count significantly decreased, reflecting the intended mild bone marrow suppression, and these effects were sustained over time. The overall rate of sickle cell–related events was significantly reduced (114.5 vs. 53.0 events per 100 patient-years; incidence rate ratio, 0.47; 95% CI, 0.38 to 0.57), and the rates of vaso-occlusive pain and the acute chest syndrome were both reduced. The rates of infection also declined, including rates of nonmalaria infection (142.5 vs. 90.0 events per 100 patient-years; incidence rate ratio, 0.62; 95% CI, 0.53 to 0.72) and severe infection of grade 3 or higher (28.9 vs. 8.0 events per 100 patient-years; incidence rate ratio, 0.28; 95% CI, 0.19 to 0.42). Analyses of additional key clinical events revealed significant reductions during hydroxyurea treatment in the rate of malaria infections (46.9 vs. 22.9 events per 100 patient-years; incidence rate ratio, 0.49; 95% CI, 0.37 to 0.66), blood transfusion (43.3 vs. 14.2 events per 100 patient-years; incidence rate ratio, 0.33; 95% CI, 0.23 to 0.47), and death (3.6 vs. 1.1 events per 100 patient-years.

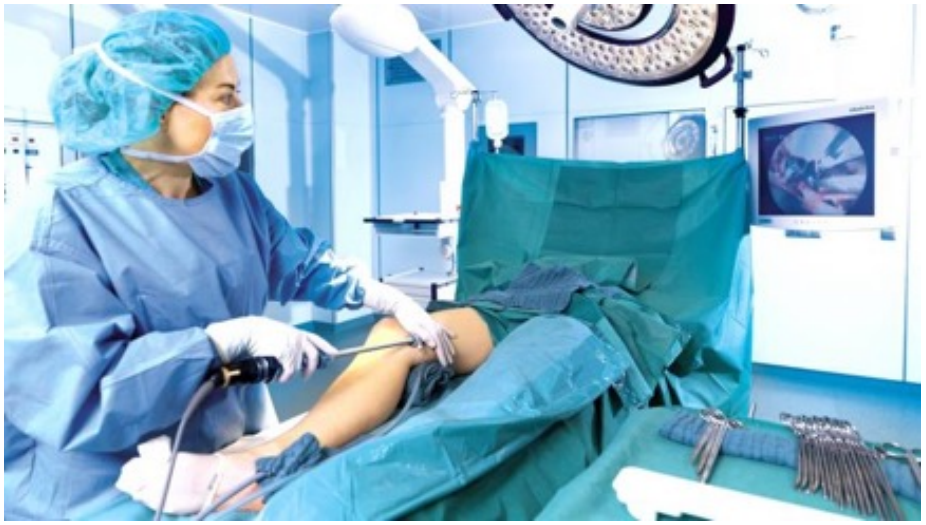


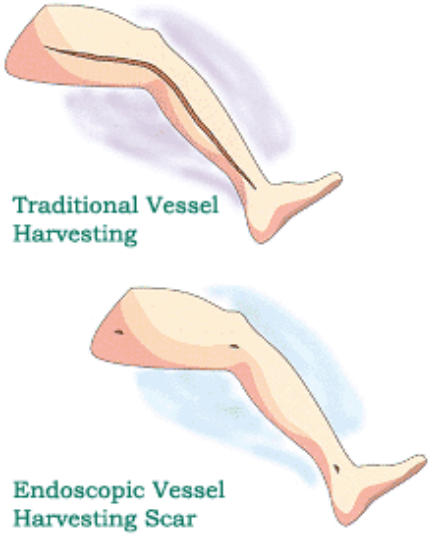
Adverse Events before and during Hydroxyurea Treatment. Error bars indicate 68% confidence intervals, which correspond to approximately 1 standard error.

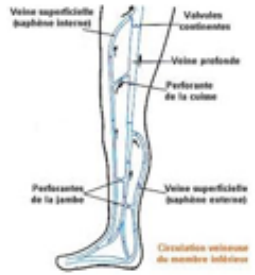
In this trial involving children with sickle cell anemia living in sub-Saharan Africa, we found that hydroxyurea treatment was feasible, reasonably safe, and had both laboratory and clinical benefits. Specifically, as compared with pretreatment rates, the rates of clinical events, including vaso-occlusive pain, infection, malaria, transfusion, and death, declined after 1 year of hydroxyurea treatment.

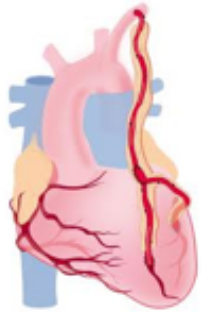
In conclusion, our results show that daily hydroxyurea treatment was feasible and safe for children with sickle cell anemia in sub-Saharan Africa. Moreover, hydroxyurea treatment reduced the rates of painful events, infection, malaria, transfusion, and death. Despite the recognition that 50 to 90% of affected children in Africa die before the age of 5 years, sickle cell anemia remains a neglected disease for which safe and effective treatment options are needed.

The choice of the graft conduit for coronary artery bypass grafting (CABG) has significant implications both in the short- and long-term. The patency of a coronary conduit is closely associated with an uneventful postoperative course, better long-term patient survival and superior freedom from re-intervention. The internal mammary artery is regarded as the primary conduit for CABG patients, given its association with long-term patency and survival. However, long saphenous vein (LSV) continues to be utilized universally as patients presenting for CABG often have multiple coronary territories requiring revascularization. Traditionally, the LSV has been harvested by creating incisions from the ankle up to the groin termed open vein harvesting (OVH).
These concerns regarding wound morbidity and patient satisfaction led to the emergence of endoscopic vein harvesting (EVH). Published experience comparing OVH with EVH suggests decreased wound related complications, improved patient satisfaction, shorter hospital stay, and reduced postoperative pain at the harvest site following EVH. Despite these reported advantages concerns regarding risk of injury at the time of harvest with its potential detrimental effect on vein graft patency and clinical outcomes have prevented universal adoption of EVH.









Randomized Trial of Endoscopic or Open Vein-Graft Harvesting for Coronary-Artery Bypass

The saphenous-vein graft is the most common conduit for coronary-artery bypass grafting (CABG). The influence of the vein-graft harvesting technique on long-term clinical outcomes has not been well characterized. We randomly assigned patients undergoing CABG at 16 Veterans Affairs cardiac surgery centers to either open or endoscopic vein-graft harvesting. The primary outcome was a composite of major adverse cardiac events, including death from any cause, nonfatal myocardial infarction, and repeat revascularization. Leg-wound complications were also evaluated.

Characteristic	Open Harvesting (N=574)	Endoscopic Harvesting (N=576)	All Patients (N=1150)
Age — yr†	66.6±7.1	66.2±6.7	66.4±6.9
Male sex — no./total no. (%)	571/574 (99.5)	572/575 (99.5)	1143/1149 (99.5)
Smoking status — no. (%)			
Lifelong nonsmoker	123 (21.4)	137 (23.8)	260 (22.6)
Current smoker	151 (26.3)	164 (28.5)	315 (27.4)
Former smoker	296 (51.6)	274 (47.6)	570 (49.6)
Missing data	4 (0.7)	1 (0.2)	5 (0.4)
Race or ethnic group — no. (%)‡			
White, not of Hispanic origin	484 (84.3)	490 (85.1)	974 (84.7)
Missing data	0	1 (0.2)	1 (0.1)
Body-mass index§	30.6±5.2	30.3±5.2	30.4±5.2
Diabetes — no. (%)			
No history of diabetes	277 (48.3)	295 (51.2)	572 (49.7)
Insulin-dependent diabetes	137 (23.9)	125 (21.7)	262 (22.8)
Non–insulin-dependent diabetes	160 (27.9)	155 (26.9)	315 (27.4)
Missing data	0	1 (0.2)	1 (0.1)
Hypertension — no./total no. (%)	515/574 (89.7)	521/575 (90.6)	1036/1149 (90.2)
Hyperlipidemia — no./total no. (%)	502/574 (87.5)	491/575 (85.4)	993/1149 (86.4)
Peripheral vascular disease — no./total no. (%)	80/574 (13.9)	80/575 (13.9)	160/1149 (13.9)
Previous stroke — no./total no. (%)	48/574 (8.4)	48/575 (8.3)	96/1149 (8.4)
Previous myocardial infarction — no./total no. (%)	207/573 (36.1)	219/575 (38.1)	426/1148 (37.1)
Previous PCI — no./total no. (%)	158/574 (27.5)	160/575 (27.8)	318/1149 (27.7)
NYHA functional class — no. (%)¶			
No heart failure	285 (49.7)	284 (49.3)	569 (49.5)
Class I	68 (11.8)	60 (10.4)	128 (11.1)
Class II	151 (26.3)	167 (29.0)	318 (27.7)

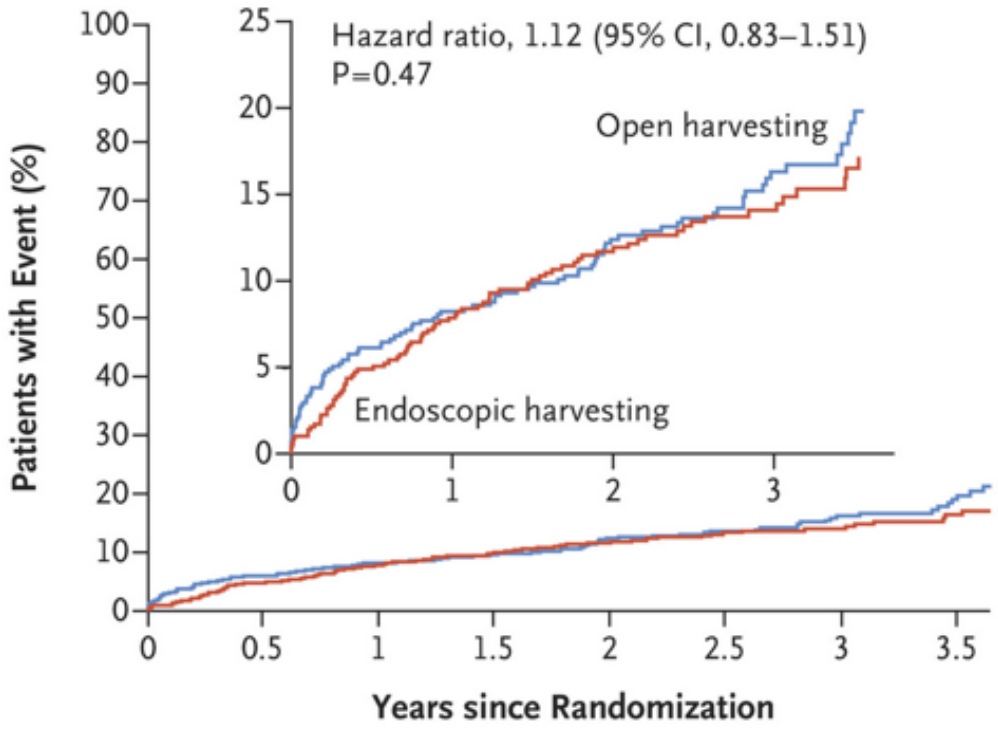
Characteristic	Open Harvesting (N=574)	Endoscopic Harvesting (N=576)	All Patients (N=1150)	P Value
No. of days from randomization to surgery	0.1±2.4	0.0±0.0	0.1±1.7	0.06
Status of index CABG procedure — no. (%)				0.56
Elective	423 (73.7)	415 (72.0)	838 (72.9)	
Urgent	151 (26.3)	160 (27.8)	311 (27.0)	
Missing data	0	1 (0.2)	1 (0.1)	
Combined CABG plus mitral-valve repair — no. (%)	1 (0.2)	2 (0.3)	3 (0.3)	>0.99
Coronary artery disease territories — no. (%)				0.11
Single-vessel disease	12 (2.1)	4 (0.7)	16 (1.4)	
Double-vessel disease	119 (20.7)	129 (22.4)	248 (21.6)	
Triple-vessel disease	443 (77.2)	442 (76.7)	885 (77.0)	
Missing data	0	1 (0.2)	1 (0.1)	
Left main coronary artery disease — no./total no. (%)†	168/572 (29.4)	187/575 (32.5)	355/1147 (31.0)	0.25
SYNTAX score — no. (%)‡				0.83
<22	166 (28.9)	164 (28.5)	330 (28.7)	
22–32	218 (38.0)	228 (39.6)	446 (38.8)	
>32	188 (32.8)	181 (31.4)	369 (32.1)	
Missing data	2 (0.3)	3 (0.5)	5 (0.4)	
Ejection fraction — %§	54.4±9.3	53.7±10.4	54.0±9.9	0.59
No. of grafts per patient¶	3.1±0.8	3.2±0.8	3.1±0.8	0.63
Bilateral internal thoracic artery grafts used — no./total no. (%)	55/571 (9.6)	63/574 (11.0)	118/1145 (10.3)	0.45
Radial artery graft used — no./total no. (%)	6/571 (1.1)	7/574 (1.2)	13/1145 (1.1)	0.79
Off-pump procedure performed — no. (%)	5 (0.9)	1 (0.2)	6 (0.5)	0.12
STS predicted risk of death — %‖	0.97±0.87	0.92±0.85	0.94±0.86	0.73
VASQIP predicted risk of death — %**	0.98±0.88	1.01±1.00	0.99±0.95	0.82
Vein harvesting time — min††	61.4±28.7	57.5±24.4	59.4±26.7	0.01
Cross-clamp time — min‡‡	75.5±31.7	76.6±29.8	76.1±30.7	0.39
Cardiopulmonary bypass time — min§§	107.9±36.4	108.8±35.2	108.4±35.8	0.65
Endoscopic harvesting device type — no. (%)				
Maquet Vasoview	—	548 (95.1)	—	—
Terumo Virtuosaph	—	24 (4.2)	—	—
Missing data	—	4 (0.7)	—	—
Endoscopic harvesting conversion to open harvesting — no. (%)	—	32 (5.6)	—	—
Reason for conversion				
Bleeding	—	6 (18.8)	—	—
Unacceptable duration of endoscopic procedure	—	3 (9.4)	—	—
Insufficient amount of usable vein from endoscopic procedure	—	7 (21.9)	—	—
Harvester unable to locate vein	—	5 (15.6)	—	—
Other	—	11 (34.4)	—	—
Need for procedure to harvest additional conduit after successful endoscopic harvesting — no. (%)	—	4 (0.7)	—	—

Leg-wound infections occurred in 18 patients (3.1%) in the open-harvest group and in 8 patients (1.4%) in the endoscopic-harvest group (absolute difference, 1.7 percentage points; relative risk, 2.26; 95% CI, 0.99 to 5.15). Incisional leg pain had little or no effect on functioning at 6 weeks after surgery in 62.2% of the patients in the open-harvest group, as compared with 79.1% of those in the endoscopic-harvest group (relative risk, 0.79; 95% CI, 0.73 to 0.85). Antibiotics were administered at follow-up to 14.4% of the patients in the open-harvest group and in 4.6% of the patients in the endoscopic-harvest group (relative risk, 3.15; 95% CI, 2.06 to 4.82).

Table 3. Major Adverse Cardiac Events during Active Follow-up.

Event	Open Harvesting (N=574)	Endoscopic Harvesting (N=576)	Hazard Ratio (95% CI)
	number of patients (percent)		
Primary outcome: death from any cause, nonfatal myocardial infarction, or repeat revascularization	89 (15.5)	80 (13.9)	1.12 (0.83–1.51)*
Death from any cause	46 (8.0)	37 (6.4)	1.25 (0.81–1.92)
Myocardial infarction	34 (5.9)	27 (4.7)	1.27 (0.77–2.11)
Repeat revascularization	35 (6.1)	31 (5.4)	1.14 (0.70–1.85)

* P=0.47 in the unadjusted Cox proportional-hazards model for the primary composite outcome.

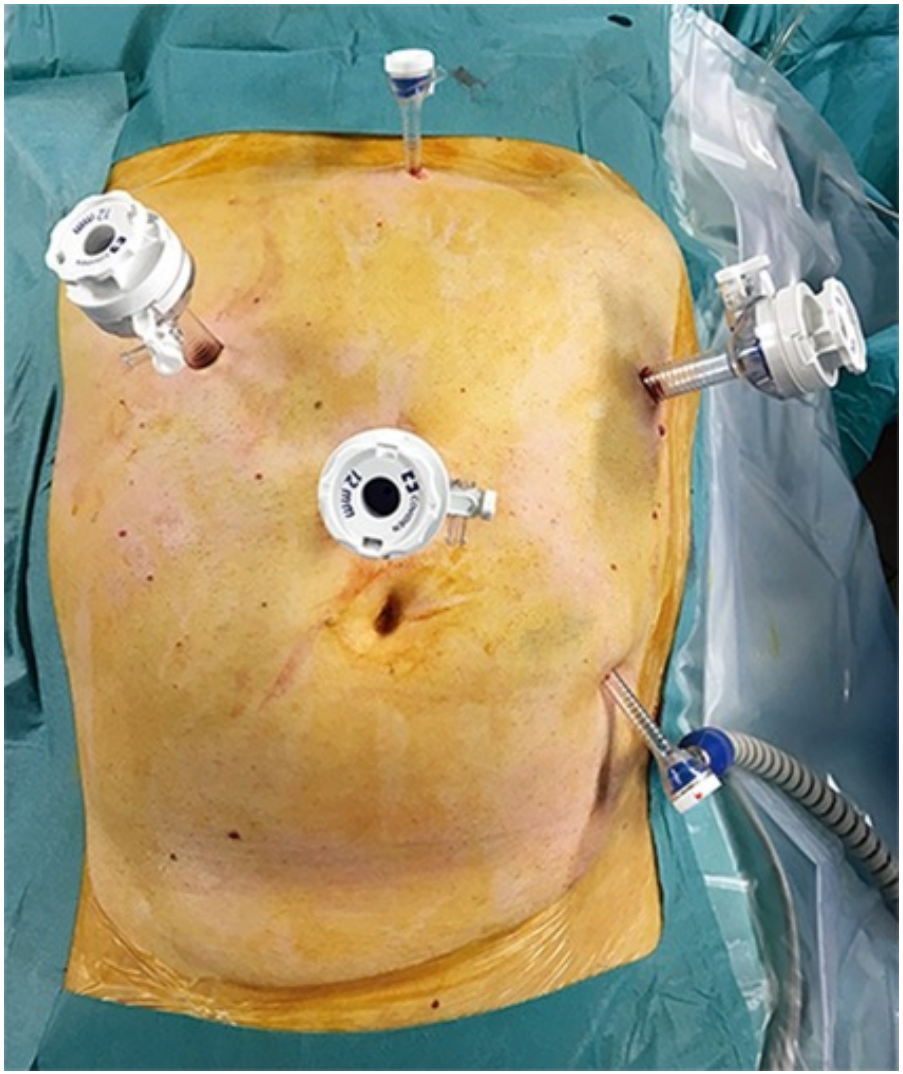


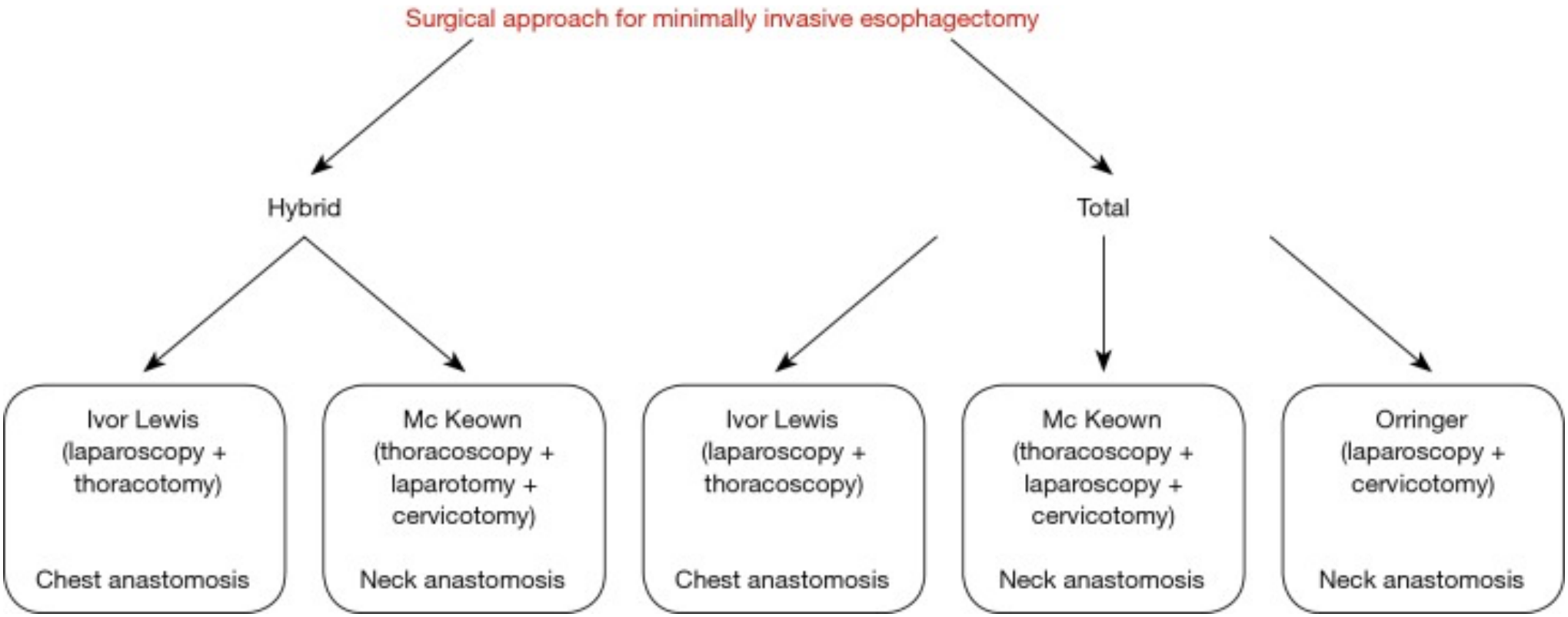
In this trial, in which vein-graft harvesting for CABG was performed by operators with documented experience, we did not find any significant difference between open and endoscopic vein-graft harvesting in the rate of major adverse cardiac events over a median follow-up of 2.78 years. We found a trend toward lower rates of major adverse cardiac events in association with the endoscopic technique when recurrent events were compared between the two treatment groups, although longer-term follow-up will be necessary to determine whether this finding is persistent. Endoscopic harvesting resulted in better harvest-site healing than did the open approach, a finding consistent with previous observations.

In conclusion, our trial did not show a significant difference between endoscopic and open vein-graft harvesting in the rate of major adverse cardiac events among patients undergoing CABG surgery during a follow-up period with a median duration of 2.78 years. The rate of wound complications was lower in the endoscopic-harvest group than in the open-harvest group. Further studies are needed to establish standards for harvester expertise to ensure the safety of patients and effectiveness of the procedure.

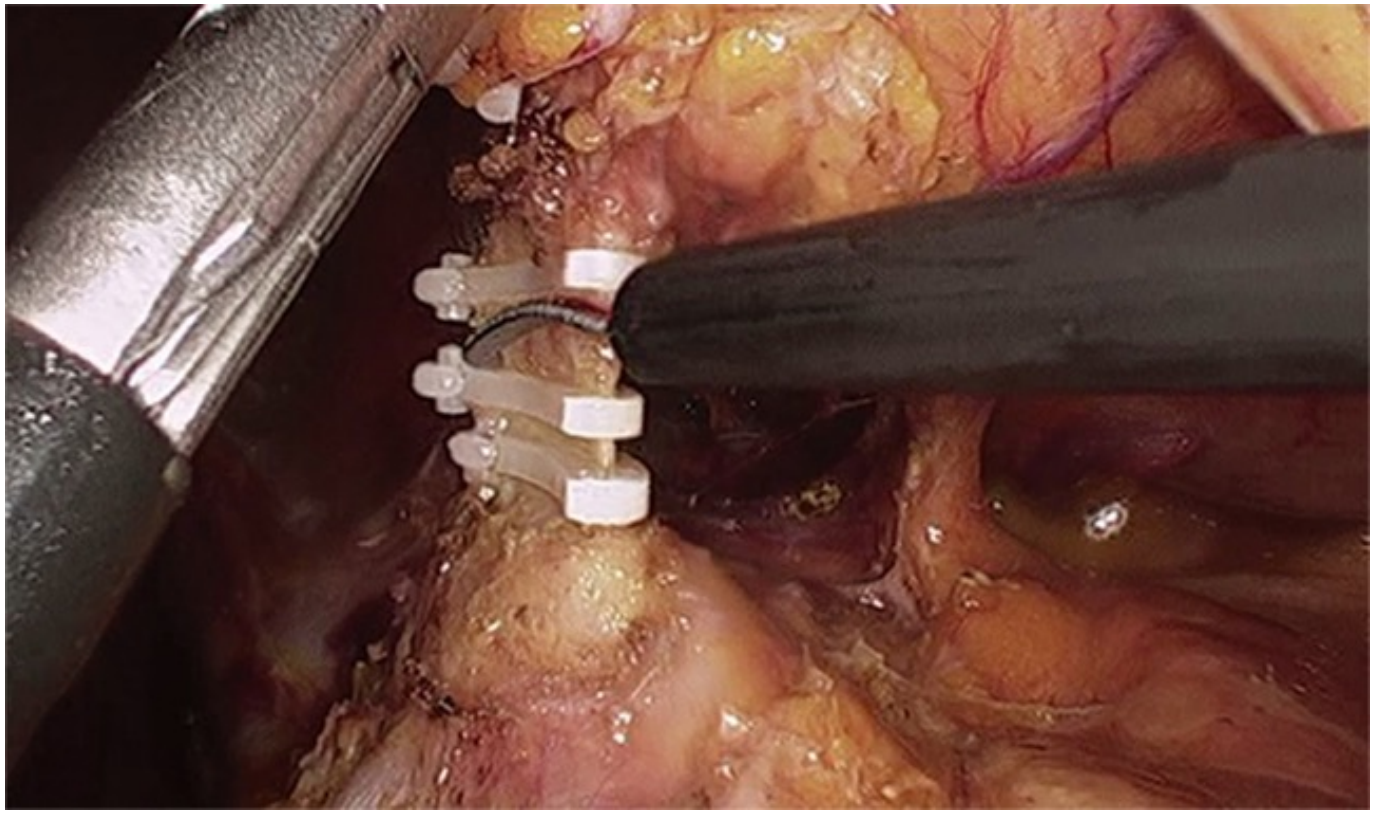
Hybrid and total minimally invasive esophagectomy: how I do it

Esophagectomy is a major surgical procedure associated with a significant risk of morbidity and mortality. Minimally invasive esophagectomy is becoming the preferred approach because of the potential to limit surgical trauma, reduce respiratory complications, and promote earlier functional recovery. Various hybrid and total minimally invasive surgical techniques have been introduced in clinical practice over the past 20 years, and minimally invasive esophagectomy has been shown equivalent to open surgery concerning the short-term outcomes. Implementation of a minimally invasive esophagectomy program is technically demanding and requires a significant learning curve and the infrastructure of a dedicated multidisciplinary center where optimal staging, individualized therapy, and perioperative care can be provided to the patient. Both hybrid and total minimally invasive techniques of esophagectomy have proven safe and effective in expert centers. The choice of the surgical approach should be driven by preoperative staging, tumor site and histology, comorbidity, patient's anatomy and physiological status, and surgeon's experience.

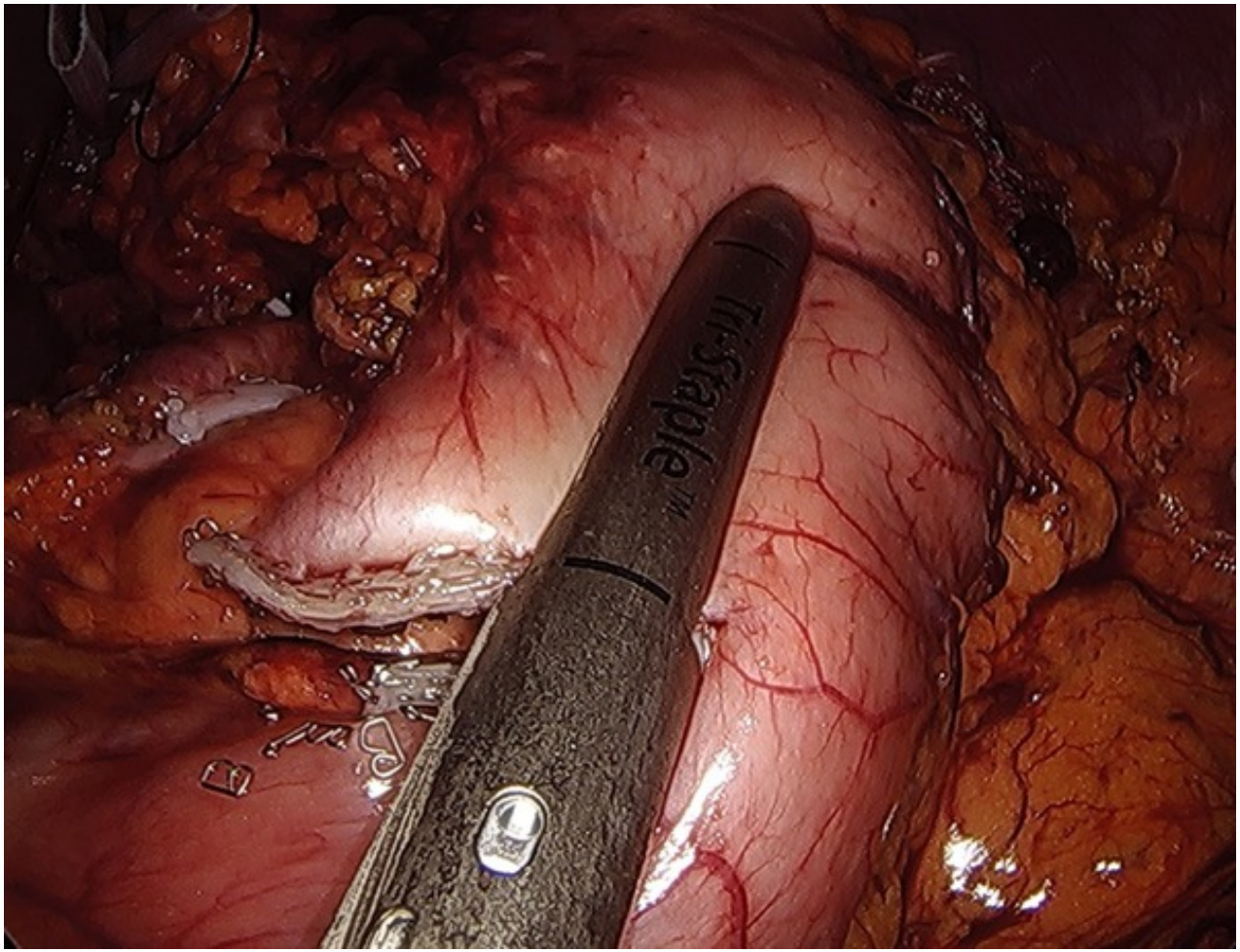




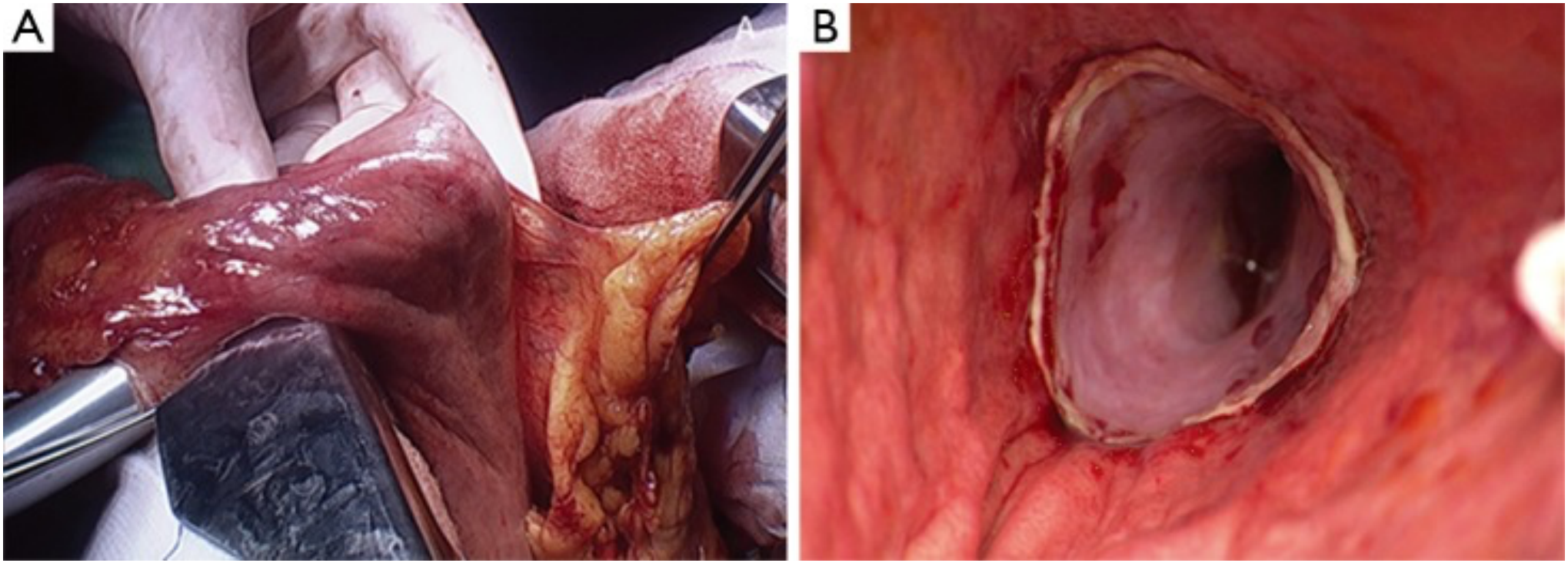
Preoperative staging and tumor characteristics influence the choice of the surgical strategy, i.e., a 2-stage or a 3-stage procedure. In some circumstances, starting with laparoscopy or thoracoscopy may be useful to provide the ultimate staging. Initial laparoscopic approach for gastric conduit preparation, as part of a hybrid or total minimally invasive Ivor Lewis operation, is feasible in the majority of patients with esophageal adenocarcinoma.



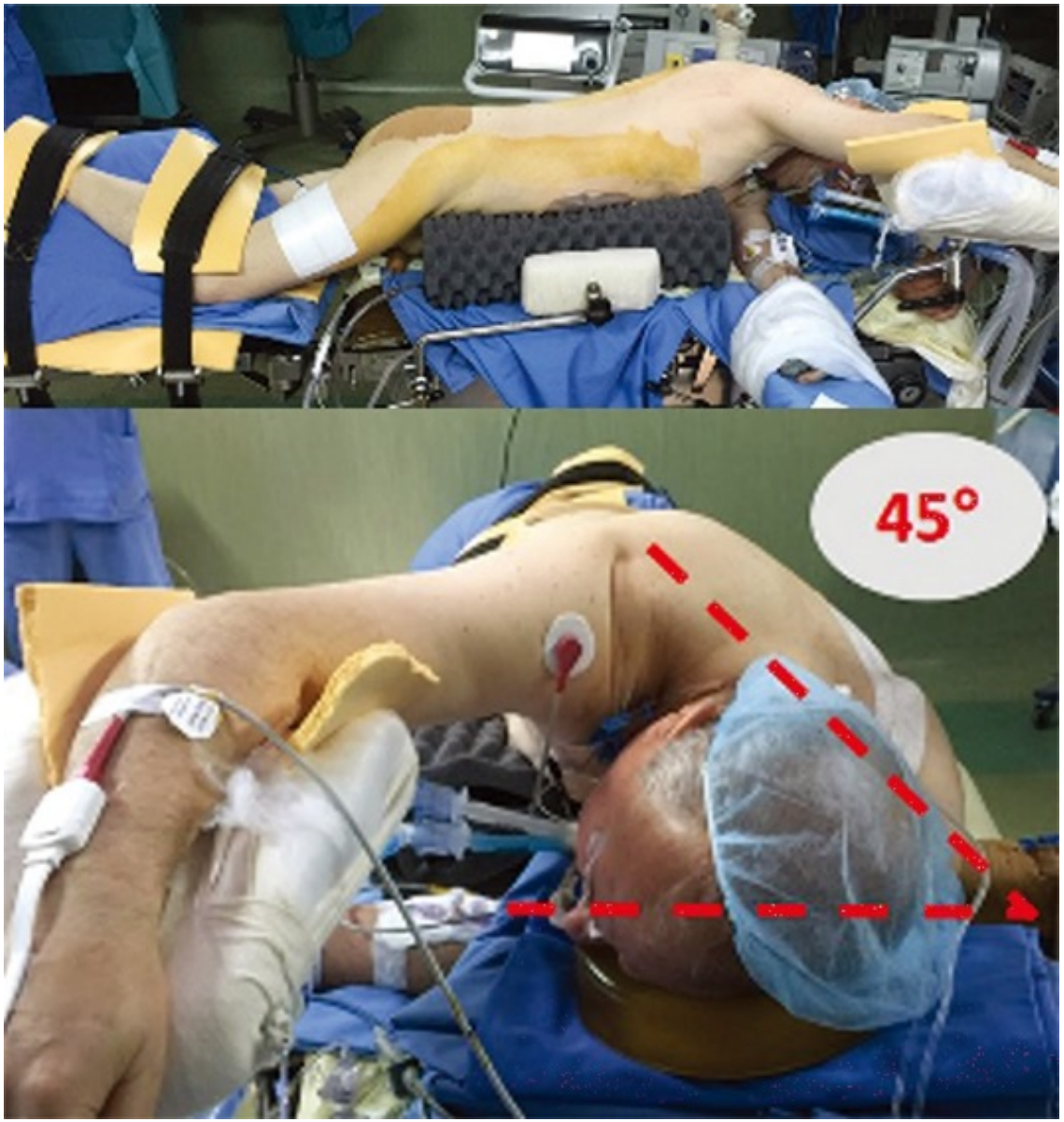
Laparoscopic division of the left gastric artery between Hemolock clips.



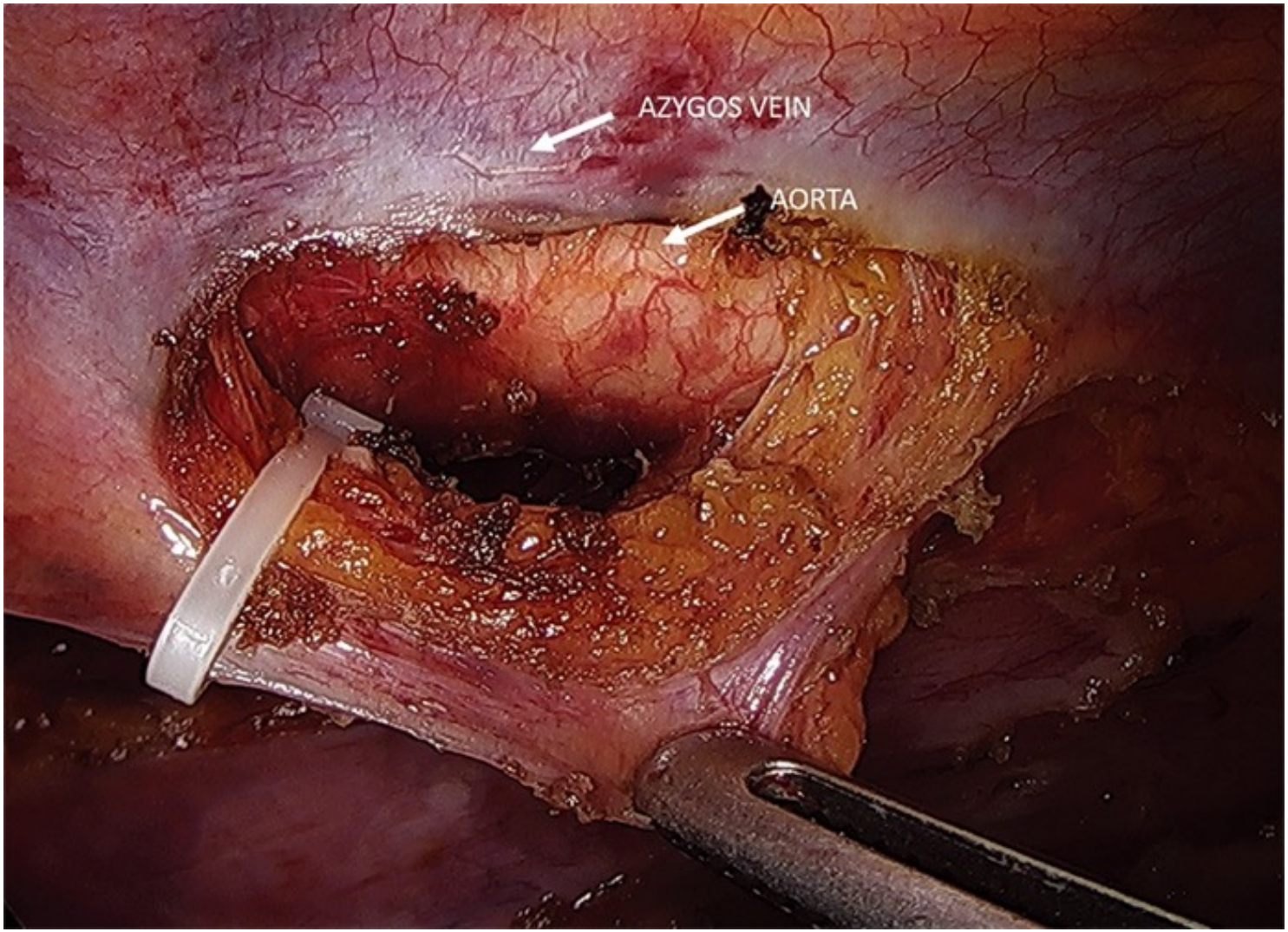
Laparoscopic gastric tubulisation.



Trans-thoracic esophago-gastric anastomosis. (A) Circular stapler introduced into the gastric tube through a gastrotomy at the apex of the lesser curve; (B) the anastomosis as viewed through the gastrotomy site.



Semi-prone patient positioning with a typical 45˚ angle.



The thoracic duct is secured with Hemolock clip at the level of the diaphragm.

Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer

Postoperative complications, especially pulmonary complications, affect more than half the patients who undergo open esophagectomy for esophageal cancer. Whether hybrid minimally invasive esophagectomy results in lower morbidity than open esophagectomy is unclear. We performed a multicenter, open-label, randomized, controlled trial involving patients 18 to 75 years of age with resectable cancer of the middle or lower third of the esophagus. Patients were randomly assigned to undergo transthoracic open esophagectomy (open procedure) or hybrid minimally invasive esophagectomy (hybrid procedure). Surgical quality assurance was implemented by the credentialing of surgeons, standardization of technique, and monitoring of performance. Hybrid surgery comprised a two-field abdominal–thoracic operation (also called an Ivor–Lewis procedure) with laparoscopic gastric mobilization and open right thoracotomy. The primary end point was intraoperative or postoperative complication of grade II or higher according to the Clavien–Dindo classification (indicating major complication leading to intervention) within 30 days. Analyses were done according to the intention-to-treat principle.

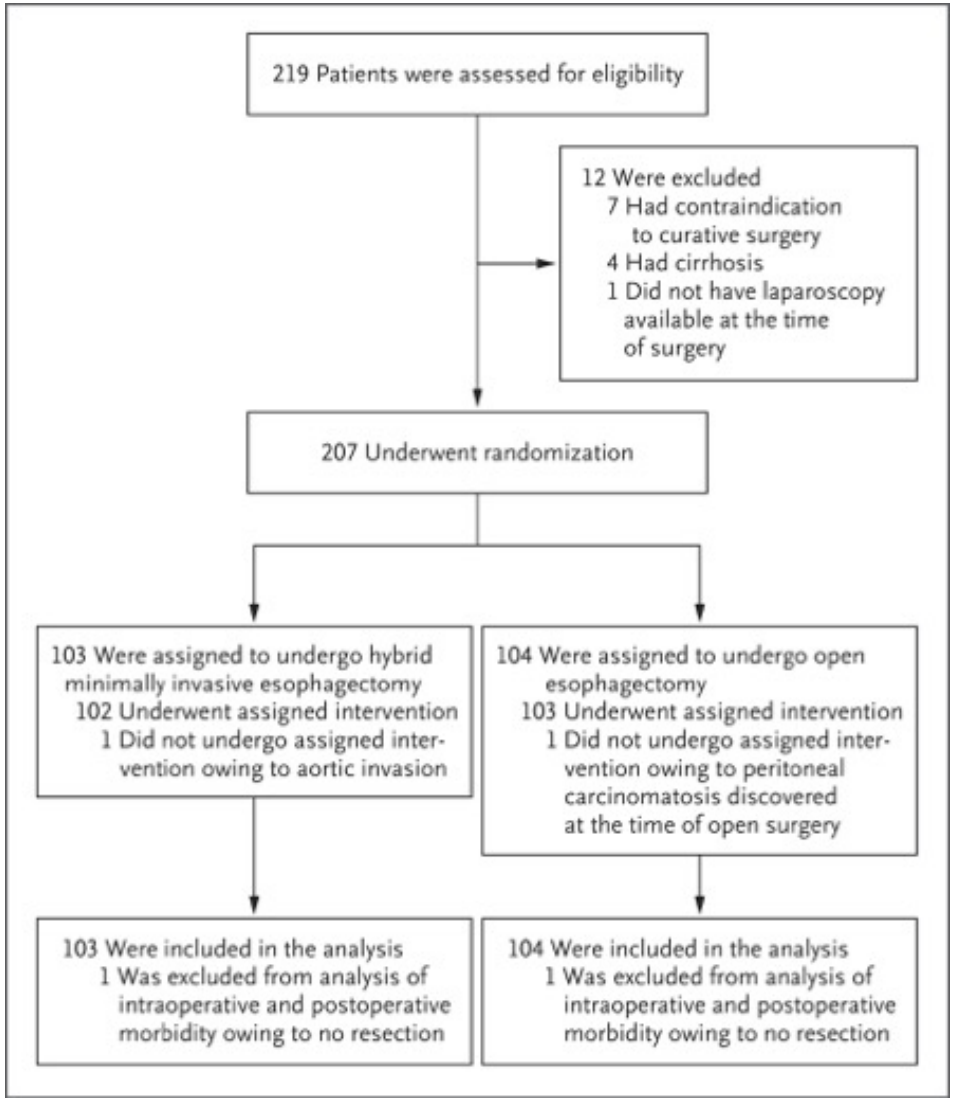


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Total Trial Population (N=207)	Hybrid Minimally Invasive Esophagectomy (N=103)	Open Esophagectomy (N=104)
Age — yr			
Median	61	59	62
Range	23–78	23–75	41–78
Sex — no. (%)			
Male	175 (85)	88 (85)	87 (84)
Female	32 (15)	15 (15)	17 (16)
Body-mass index†			
Median	25	26	25
Range	16–37	16–37	18–35
ASA risk score — no. (%)‡			
1	59 (29)	25 (24)	34 (33)
2	119 (57)	61 (59)	58 (56)
3	29 (14)	17 (17)	12 (12)
WHO performance-status score — no. (%)§			
0	120 (58)	67 (65)	53 (51)
1	79 (38)	31 (30)	48 (46)
2	8 (4)	5 (5)	3 (3)
Clinical tumor classification — no./total no. (%)¶			
cT1	37/198 (19)	18/98 (18)	19/100 (19)
cT2	63/198 (32)	30/98 (31)	33/100 (33)
cT3	98/198 (49)	50/98 (51)	48/100 (48)
Clinical node classification — no./total no. (%)¶			
cN0	89/199 (45)	41/98 (42)	48/101 (48)
cN1	102/199 (51)	53/98 (54)	49/101 (49)
cN2	8/199 (4)	4/98 (4)	4/101 (4)
Tumor histologic findings — no. (%)			
Squamous-cell carcinoma	84 (41)	46 (45)	38 (37)
Adenocarcinoma	123 (59)	57 (55)	66 (63)
Location of tumor in esophagus — no. (%)			
Upper third	1 (<1)	0	1 (1)
Middle third	63 (30)	32 (31)	31 (30)
Lower third	143 (69)	71 (69)	72 (69)
Neoadjuvant therapy — no. (%)			
Chemotherapy	86 (42)	41 (40)	45 (43)
Chemoradiotherapy	66 (32)	36 (35)	30 (29)
None	55 (27)	26 (25)	29 (28)

* There were no significant between-group differences at baseline. 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.
‡ The ASA scoring system is used to assess the physical status of patients before surgery; scores range from 1 to 5, with higher numbers indicating a lower likelihood of survival.
§ World Health Organization (WHO) performance-status scores are assessed on a 5-point scale, with higher numbers indicating greater disability. A score of 0 indicates asymptomatic status, a score of 1 symptomatic but ambulatory and capable of carrying out light work, and a score of 2 symptomatic and in bed less than 50% of the day.
¶ The clinical tumor–node–metastasis (cTNM) classification we used was a combination of the ctTNM classification for carcinoma of the thoracic esophagus (based on Wurtz et al.[37] as modified by Bosset et al.[38]) and of the usTNM classification for carcinoma of the esophagus (based on Tio et al.[39]). The combination of the two, taking into account the most advanced stage, was used in the trial.

The percentage of patients receiving neoadjuvant therapy was similarly high in the two groups (75% in the hybrid-procedure group and 72% in the open-procedure group). A total of 3 patients (3%) who had been assigned to the hybrid-procedure group underwent intraoperative conversion to the open procedure: 1 underwent laparotomy without resection because of advanced disease, 1 underwent intraoperative conversion to the open procedure because of subcutaneous emphysema, and 1 underwent intraoperative conversion to the open procedure, as decided by the surgeon on the basis of intraoperative physiological stress of the patient. According to the intention-to-treat principle, these patients were included in the hybrid-procedure group.

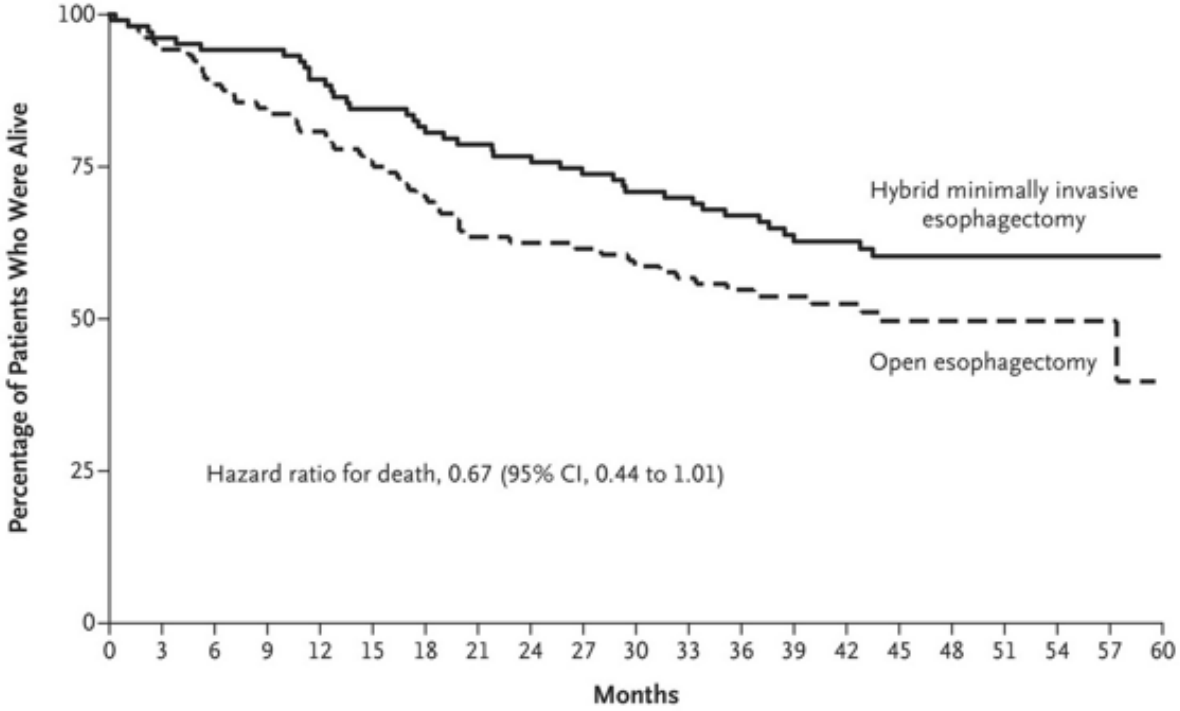
After adjustment for age, sex, American Society of Anesthesiologists risk score, neoadjuvant therapy use, tumor location, histologic subtype, resection-margin status, pathological tumor and node stages, and trial center, we found that minimally invasive surgery was associated with a 77% lower risk of major intraoperative and postoperative complications within 30 days than open surgery (adjusted odds ratio, 0.23; 95% CI, 0.12 to 0.44; P<0.001). Secondary end-point analysis showed no differences between the groups in postoperative mortality at 30 days, intraoperative and postoperative overall morbidity (major and minor) at 30 days, and surgical or medical morbidity. However, hybrid minimally invasive surgery was associated with a lower incidence of major pulmonary complications within 30 days than open surgery (18% vs. 30%). Moreover, the risk of major pulmonary complications within 30 days was 50% lower in the hybrid-procedure group than in the open-procedure group (odds ratio, 0.50; 95% CI, 0.26 to 0.96). Other end points, including operative time and the median length of hospital stay, were similar in the two groups.

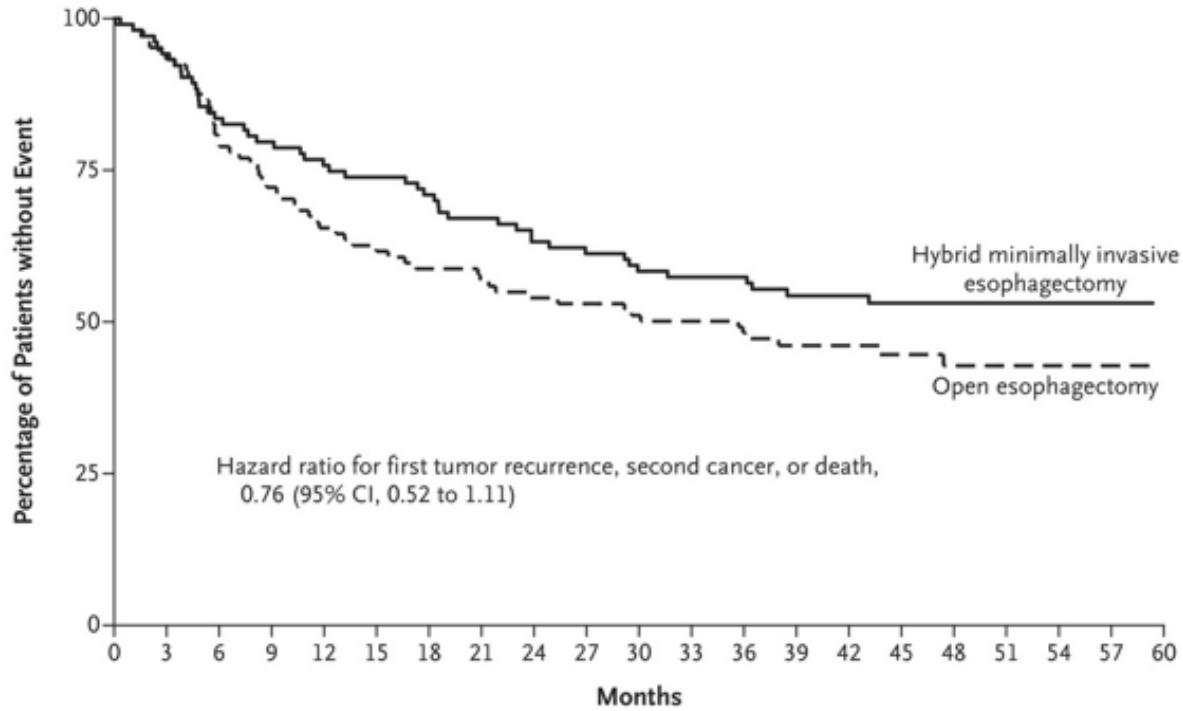
Table 2. Primary and Secondary End Points (Intention-to-Treat Population).*

End Points	Total Trial Population (N = 207)	Hybrid Minimally Invasive Esophagectomy (N = 103)	Open Esophagectomy (N = 104)
Primary end point			
Major complication at 30 days — no. (%)	104 (50)	37 (36)	67 (64)
Secondary end points			
Postoperative death — no. (%)			
At 30 days	3 (1)	1 (1)	2 (2)
At 90 days	10 (5)	4 (4)	6 (6)
Major pulmonary complication at 30 days — no./total no. (%)†	49/205 (24)	18/102 (18)	31/103 (30)
Other end points			
Intraoperative complication — no./total no. (%)†	21/205 (10)	10/102 (10)	11/103 (11)
Total operative time — min			
Median	327	327	330
Range	65–583	103–582	65–583
Abdominal operative time — min			
Median	120	127	110
Range	51–350	60–280	51–350
Length of hospital stay — days			
Median	14	14	14
Range	3–218	7–95	3–218
Surgical complication — no./total no. (%)†	72/205 (35)	32/102 (31)	40/103 (39)
Anastomotic leak	18/205 (9)	11/102 (11)	7/103 (7)
Gastric necrosis	5/205 (2)	2/102 (2)	3/103 (3)
Chylothorax	12/205 (6)	5/102 (5)	7/103 (7)
Delayed gastric emptying	12/205 (6)	3/102 (3)	9/103 (9)
Medical complication — no./total no. (%)†	110/205 (54)	50/102 (49)	60/103 (58)
Respiratory failure‡	21/205 (10)	11/102 (11)	10/103 (10)
ARDS‡	15/205 (7)	8/102 (8)	7/103 (7)
Cardiac arrhythmia	26/205 (13)	12/102 (12)	14/103 (14)
Deep-vein thrombosis	3/205 (1)	2/102 (2)	1/103 (1)
Pulmonary embolus	2/205 (1)	1/102 (1)	1/103 (1)
Infectious complication — no./total no. (%)†	53/205 (26)	24/102 (24)	29/103 (28)

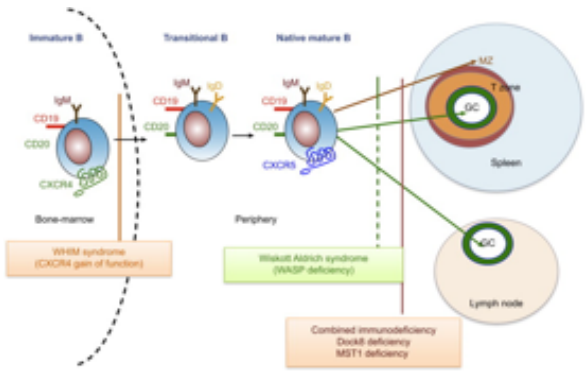
* Data on the total operative time were missing for one patient in the hybrid-procedure group, and data on the duration of abdominal operation and length of hospital stay were missing for one patient in the open-procedure group.
† Data on intraoperative and postoperative complications were not recorded for the two patients (one in each group) who did not undergo resection.
‡ Major bronchial sputum, pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS) were included in the classification of major pulmonary complication. Details are provided in Table S1 in the Supplementary Appendix.

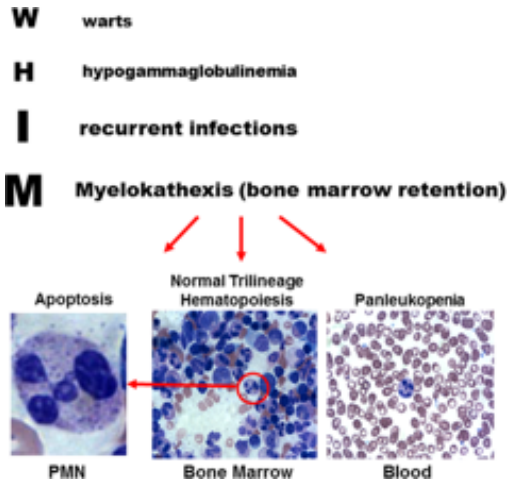
In this multicenter, randomized, controlled trial, we found that hybrid minimally invasive esophagectomy was associated with a 77% lower risk of major intraoperative and postoperative complications than open esophagectomy. Furthermore, minimally invasive surgery was associated with a 50% lower risk of major pulmonary complications than open surgery. Overall survival and disease-free survival were at least as good with minimally invasive surgery as with the open procedure. In parallel to previous findings regarding colorectal resection and gastrectomy, we found that a minimally invasive approach to the abdominal phase of an Ivor–Lewis two-field abdominal–thoracic esophagectomy was associated with substantially lower major morbidity, specifically pulmonary morbidity. In conclusion, this multicenter, randomized, controlled trial showed that hybrid minimally invasive esophagectomy resulted in a lower incidence of major complications (specifically, pulmonary complications) during or after esophagectomy for cancer than did open surgery. The hybrid procedure also resulted in overall survival and disease-free survival that were similar to those observed with open esophagectomy.

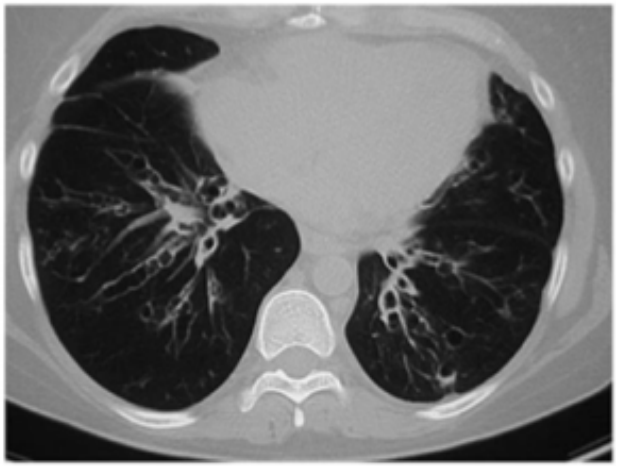




Das WHIM-Syndrom (kurz für Warzen-Hypogammaglobulinämie-Immundefizienz-Myelokathexis-Syndrom) ist eine vererbbare, seltene Immunschwächekrankheit. Charakteristisch für das WHIM-Syndrom ist eine Immunschwäche, die sich in wiederkehrenden bakteriellen und viralen Infektionen äußert. Davon sind insbesondere die Atemwege mit Nasennebenhöhlenentzündungen, Mandelentzündungen und Lungenentzündungen betroffen. Die Patienten sind anfällig für Infektionen mit humanen Papillomaviren, die sich in zahlreichen Warzen, insbesondere im Hand- und Fußbereich, äußern. WHIM-Syndrom-Patienten haben darüber hinaus ein erhöhtes Risiko, an viral-bedingten Krebsarten, wie beispielsweise demCervixkarzinom, zu erkranken. Im Blutserum der Patienten können erniedrigte IgG-Konzentrationen gemessen werden (Hypogammaglobulinämie). Histologisch erscheint das Knochenmark der WHIM-Patienten voller T-Vorläuferzellen. Dem gegenüber kann eine Neutropenie beobachtet werden, die auf eine gestörte Auswanderung und somit Zurückhaltung neutrophiler Granulozyten aus dem Knochenmark zurückgeführt werden kann (Myelokathexis). Das WHIM-Syndrom ist eine autosomal-dominant vererbte Krankheit. Als häufigste Ursache, die bei 92 % der betroffenen Patienten gefunden wurde, werden Mutationen eines Gens auf dem Genlocus 2q21, das den Chemokinrezeptor CXCR4 codiert, angesehen. Diese Mutationen im intrazellulären Teil des membranständigen Rezeptors für das Zytokin CXCL12 (SDF-1) führen zu einem verkürzten Rezeptorprotein, dem die Fähigkeit der Internalisierung nach Aktivierung fehlt. Somit sind Mechanismen der negativen Selbstregulation unterbrochen und der Rezeptor kann dauerstimuliert werden.

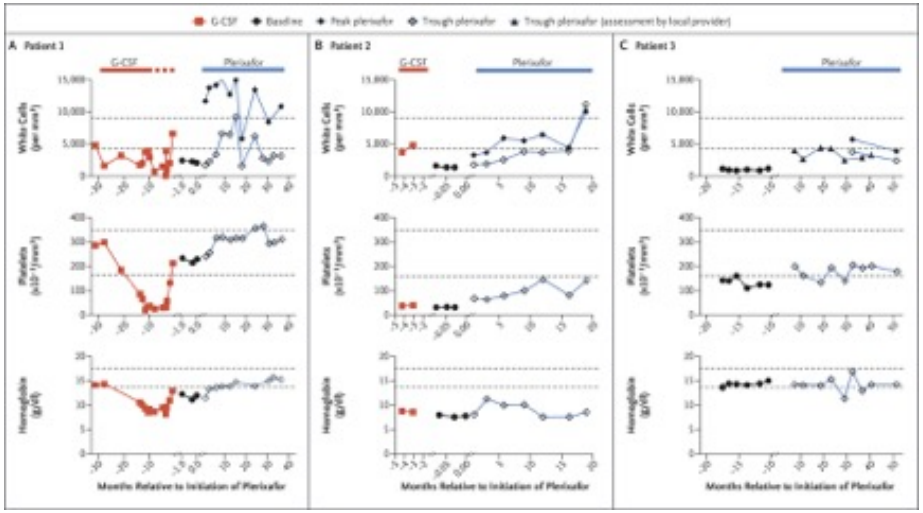




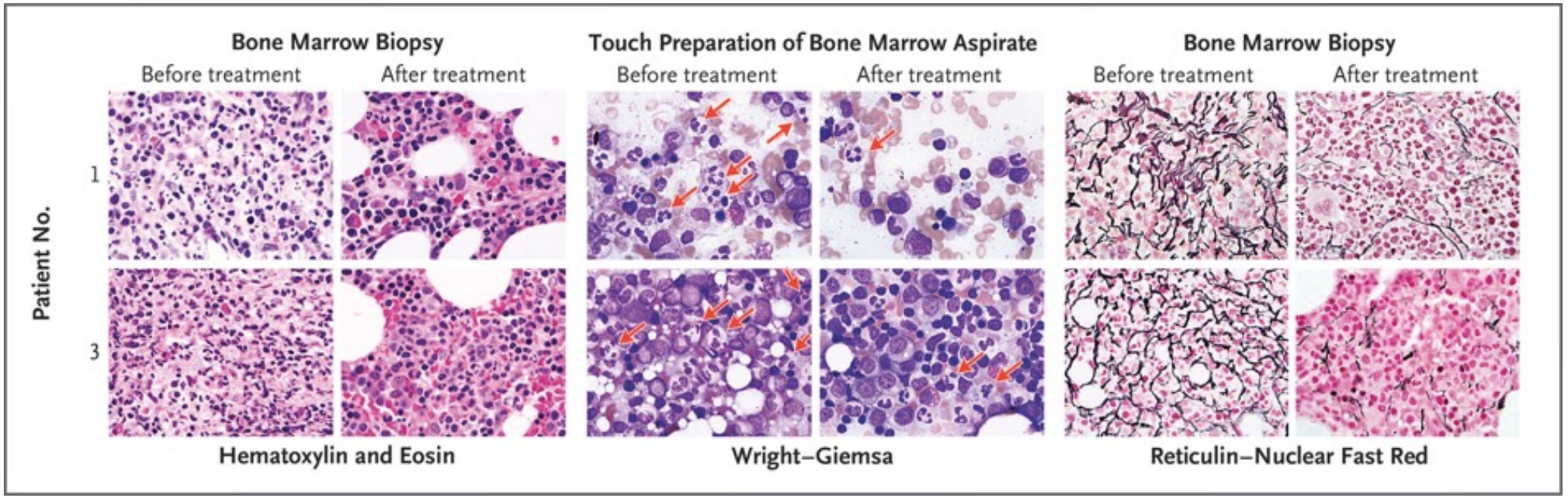


Plerixafor for the Treatment of WHIM Syndrome

WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis), a primary immunodeficiency disorder involving panleukopenia, is caused by autosomal dominant gain-of-function mutations in CXC chemokine receptor 4 (CXCR4). Myelokathexis is neutropenia caused by neutrophil retention in bone marrow. Patients with WHIM syndrome are often treated with granulocyte colony-stimulating factor (G-CSF), which can increase neutrophil counts but does not affect cytopenias other than neutropenia. In this investigator-initiated, open-label study, three severely affected patients with WHIM syndrome who could not receive G-CSF were treated with low-dose plerixafor, a CXCR4 antagonist, for 19 to 52 months. Myelofibrosis, panleukopenia, anemia, and thrombocytopenia were ameliorated, the wart burden and frequency of infection declined, human papillomavirus–associated oropharyngeal squamous-cell carcinoma stabilized, and quality of life improved markedly. Adverse events were mainly infections attributable to the underlying immunodeficiency. One patient died from complications of elective reconstructive surgery.

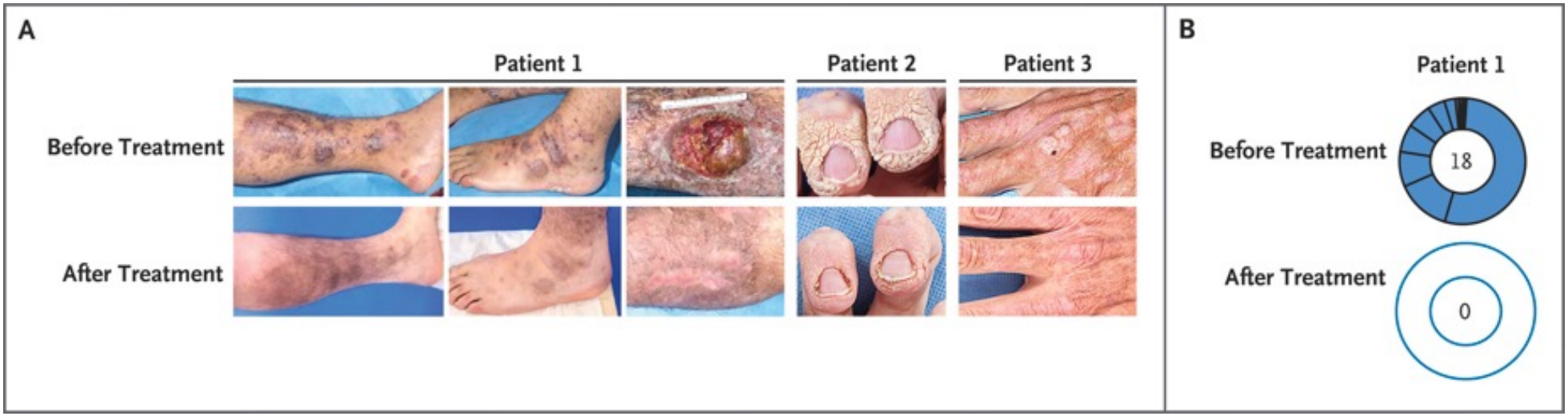


The periods of treatment with granulocyte colony-stimulating factor (G-CSF) and plerixafor are demarcated by the red and blue bars at the top of each corresponding column of graphs. The dotted portion of the red line for Patient 1 denotes the time when high-dose G-CSF treatment (300 µg subcutaneously every day) was interrupted owing to severe thrombocytopenia and the drug was given at a reduced dose (150 µg subcutaneously every other day) only during episodes of cellulitis. Horizontal dashed black lines in each graph designate the upper and lower limits of the normal range for each variable, as determined by the National Institutes of Health (NIH) Clinical Center Clinical Hematology Laboratory. Baseline values were assessed when neither drug was being taken (solid circles). All values for Patients 1 and 2 at baseline and during plerixafor treatment were determined at the NIH. Peak refers to values obtained approximately 3 hours after plerixafor administration, the time of the peak white-cell count, as defined previously. Trough refers to values obtained approximately 12 hours after a dose of plerixafor was administered. Most white-cell values for Patient 3 were determined at trough by the local provider in Germany owing to travel limitations; exceptions are designated by the peak and trough symbols in the figure key, and these values were determined at the NIH.



Amelioration of Myelokathexis and Myelofibrosis during Long-Term, Low-Dose Plerixafor Treatment.

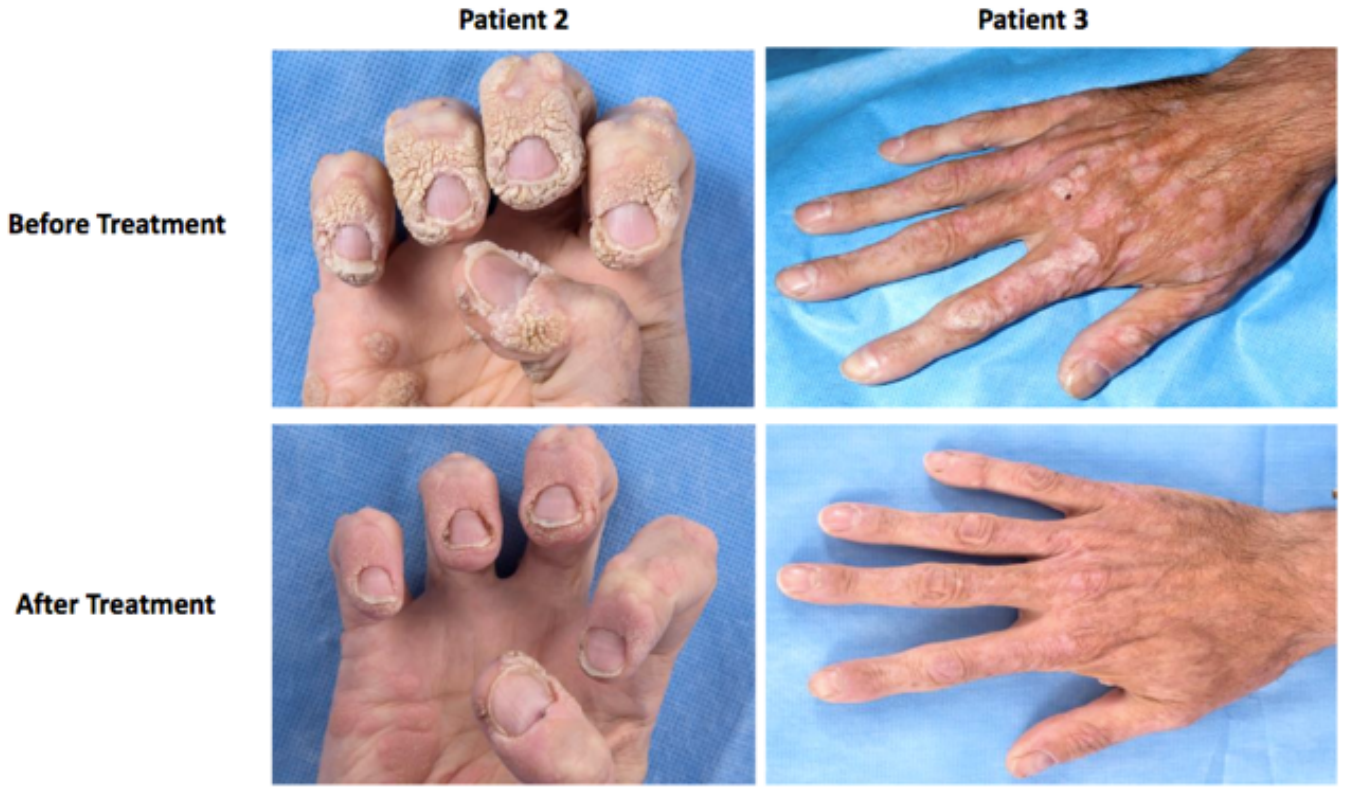
Core bone marrow–biopsy samples were obtained from Patients 1 and 3 approximately 3 days before starting plerixafor (before treatment) and 24 and 52 months after starting plerixafor (after treatment) for Patients 1 and 3, respectively. Pretreatment hematoxylin and eosin–stained biopsy samples from both patients show markedly hypercellular marrow with granulocytic hyperplasia, right-shifted myelopoiesis, an elevated myeloid-to-erythroid ratio of approximately 5:1, and abundant neutrophils consistent with myelokathexis. This pattern was found in approximately 90% of the pretreatment marrow but in only 40 to 50% of the post-treatment marrow. The post-treatment images depict areas of normocellular marrow with normal myelopoiesis and a normal myeloid-to-erythroid ratio of 2:1. The pretreatment touch preparations of bone marrow aspirate (Wright–Giemsa stain) show frequent atypical neutrophils with pyknotic nuclear segments connected by thin, wispy strands of chromatin that are characteristic of myelokathexis (red arrows). These neutrophils can still be seen in the post-treatment samples but are less frequent. Both patients had severe myelofibrosis as defined by pretreatment dense reticulin staining of bone marrow; myelofibrosis was ameliorated after plerixafor treatment. All images are at 1000× magnification.



Amelioration of Skin Pathologic Conditions during Long-Term, Low-Dose Plerixafor Treatment.

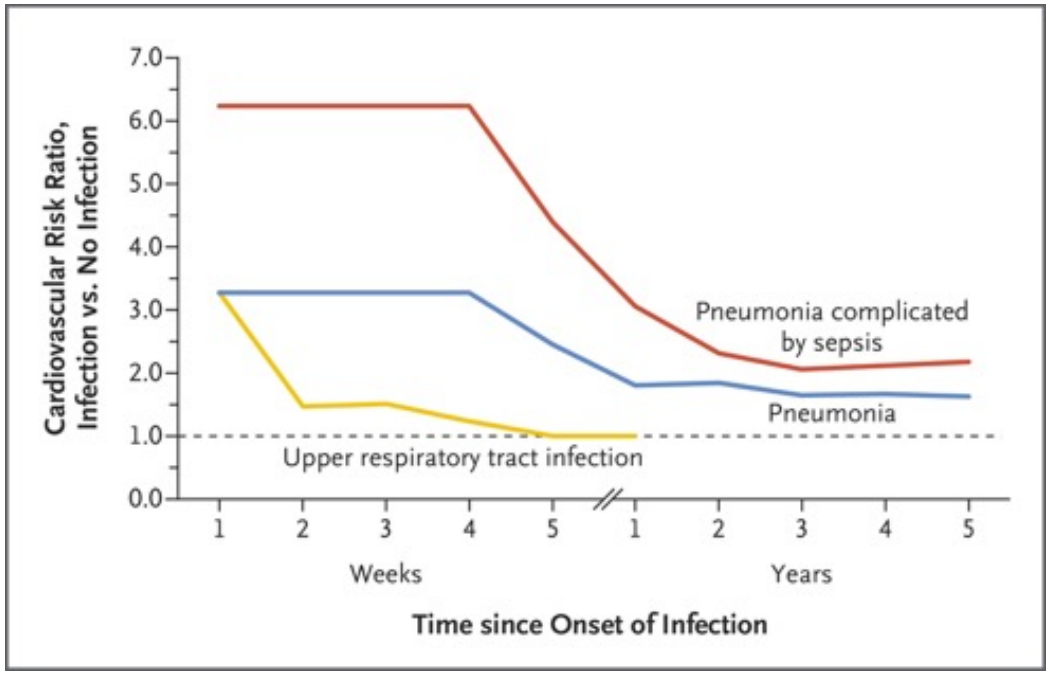
Panel A shows the left medial lower leg, left foot, and right medial lower leg of Patient 1 both before starting plerixafor and after 36, 36, and 28 months of plerixafor therapy for the left, middle, and right post-treatment images, respectively. The fingers of Patient 2 are shown before plerixafor was started and after 9 months of treatment, and the hand of Patient 3 is shown before plerixafor was started and after 32 months of treatment. Patient 1 had chronic eczematoid dermatitis associated with recurrent cellulitis for 6 years. The left and middle post-treatment images of this patient show resolution of inflammation, with residual areas of hyperpigmentation probably representing uncleared hemosiderin; recurrent cellulitis ceased. The right pretreatment image of this patient shows a chronic inflammatory mass centered at a site of recurrent cellulitis and saphenous-vein insufficiency that was removed surgically 6 months after plerixafor was started. The surgical wound (16 × 10 × 2 cm) healed completely (right post-treatment image). Patients 2 and 3 had a reduced cutaneous wart burden after plerixafor therapy. Both patients also received topical imiquimod, and Patient 2 received human papillomavirus (HPV) vaccination during treatment. Panel B shows clearance of 17 HPVs and *Trichodysplasia spinulosa* polyomavirus in Patient 1 after 18 months of plerixafor therapy. The relative abundance of each of the viruses detected is conveyed by the arc length on the donut plot. The number in the center is the number of different HPV types plus polyomavirus species detected.

We describe the CXCR4 antagonist plerixafor as a mechanism-based therapy for three patients with WHIM syndrome who could not receive G-CSF. There was a reduction in the frequency of infection in all three patients; resolution of chronic, progressive, multifocal eczematoid and follicular lesions in Patient 1, associated with clearance of TSPyV and 17 HPV types; a reduction in the wart burden in Patients 2 and 3; and a partial response of head and neck squamous-cell carcinoma in Patient 2. All three patients reported improved quality of life. Further controlled assessment of the safety and efficacy of plerixafor in patients with WHIM syndrome is a challenge because the disease is extremely rare. Nevertheless, our phase 3 trial of G-CSF versus plerixafor in WHIM syndrome is designed to permit this assessment.

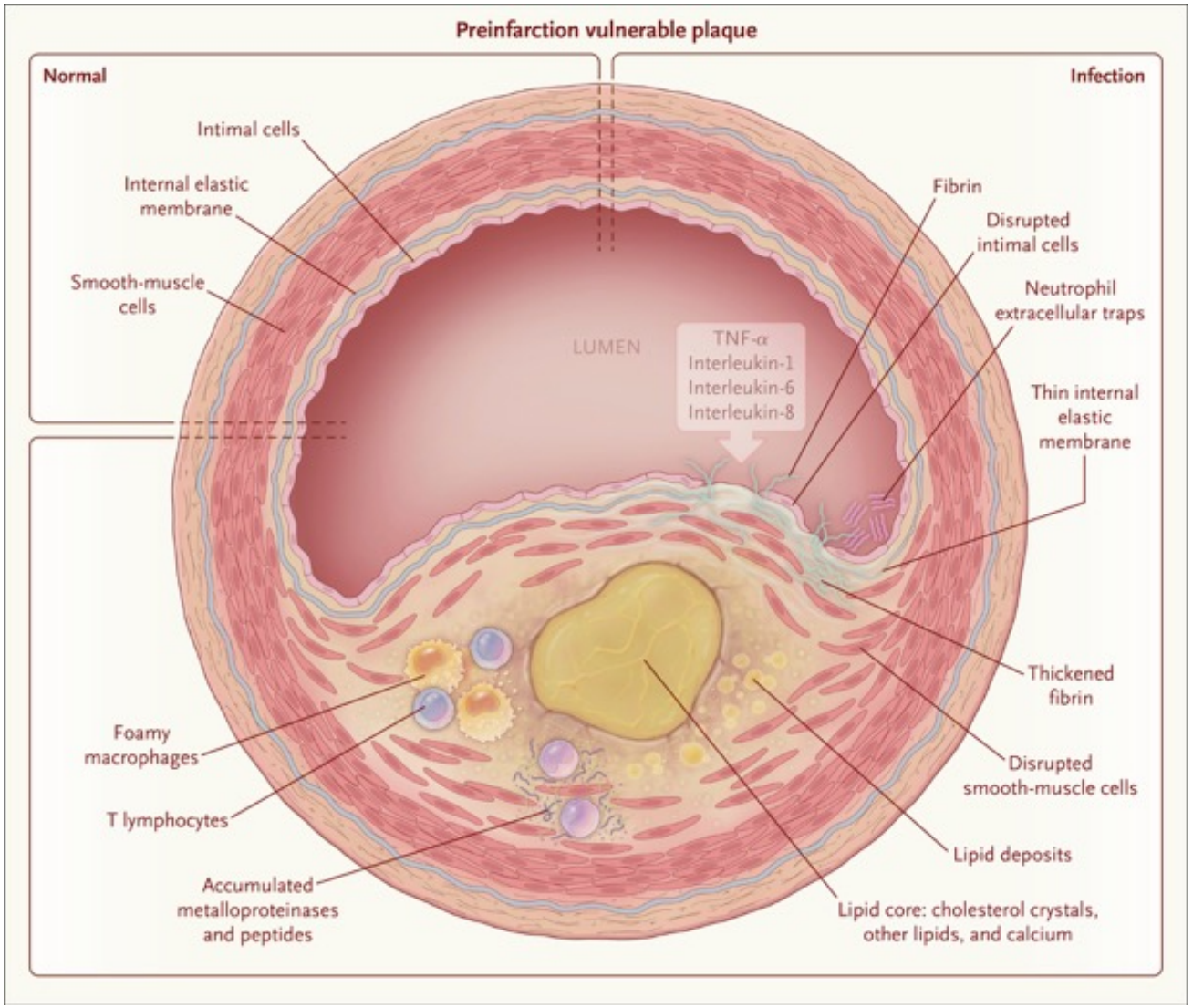


Acute Infection and Myocardial Infarction

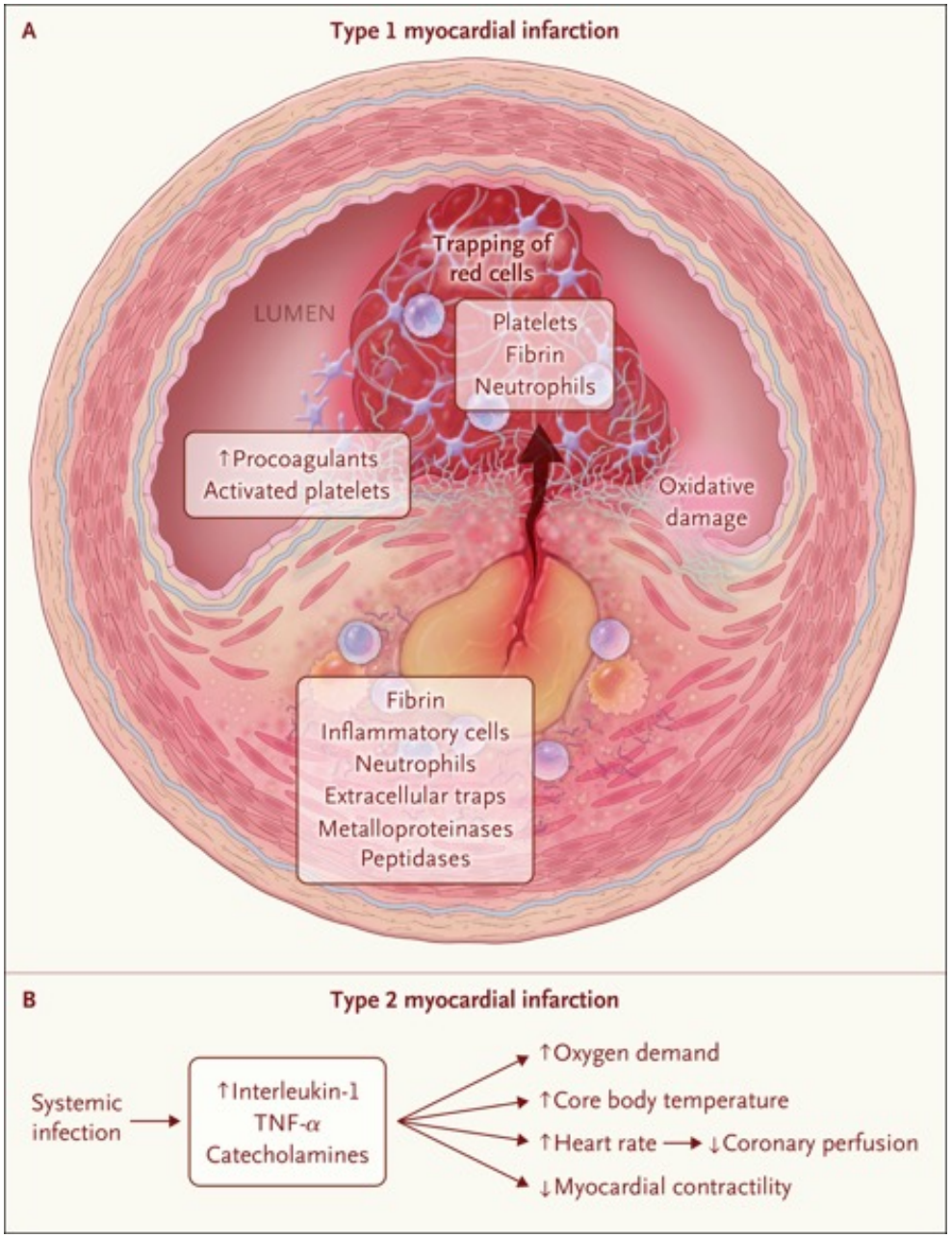
Until the early 20th century, the human life expectancy was less than 50 years, and infections were often fatal. Only in the past century have humans, on average, lived long enough for cardiovascular disease to develop regularly and have antimicrobial therapies made survival from infection the norm. Furthermore, sophisticated techniques for assessing myocardial damage have evolved during the past 50 years. It is therefore not surprising that an association between acute infections and myocardial infarction has been appreciated only in the past few decades. We will review the evidence that acute bacterial and viral infections are associated with an increased risk of myocardial infarction in the short, intermediate, and long term, and we will then discuss mechanisms that might explain this association.



Temporal Pattern of Cardiovascular Risk after the Onset of Acute Infection. The risk of a cardiovascular event is several times higher after the onset of respiratory infection than in the absence of infection. The risk of a cardiovascular event is proportional to the severity of the infection. The risk returns to baseline over a period of weeks after an upper respiratory tract infection. However, the time required for the risk to return to baseline is prolonged after a severe infection, such as pneumonia.

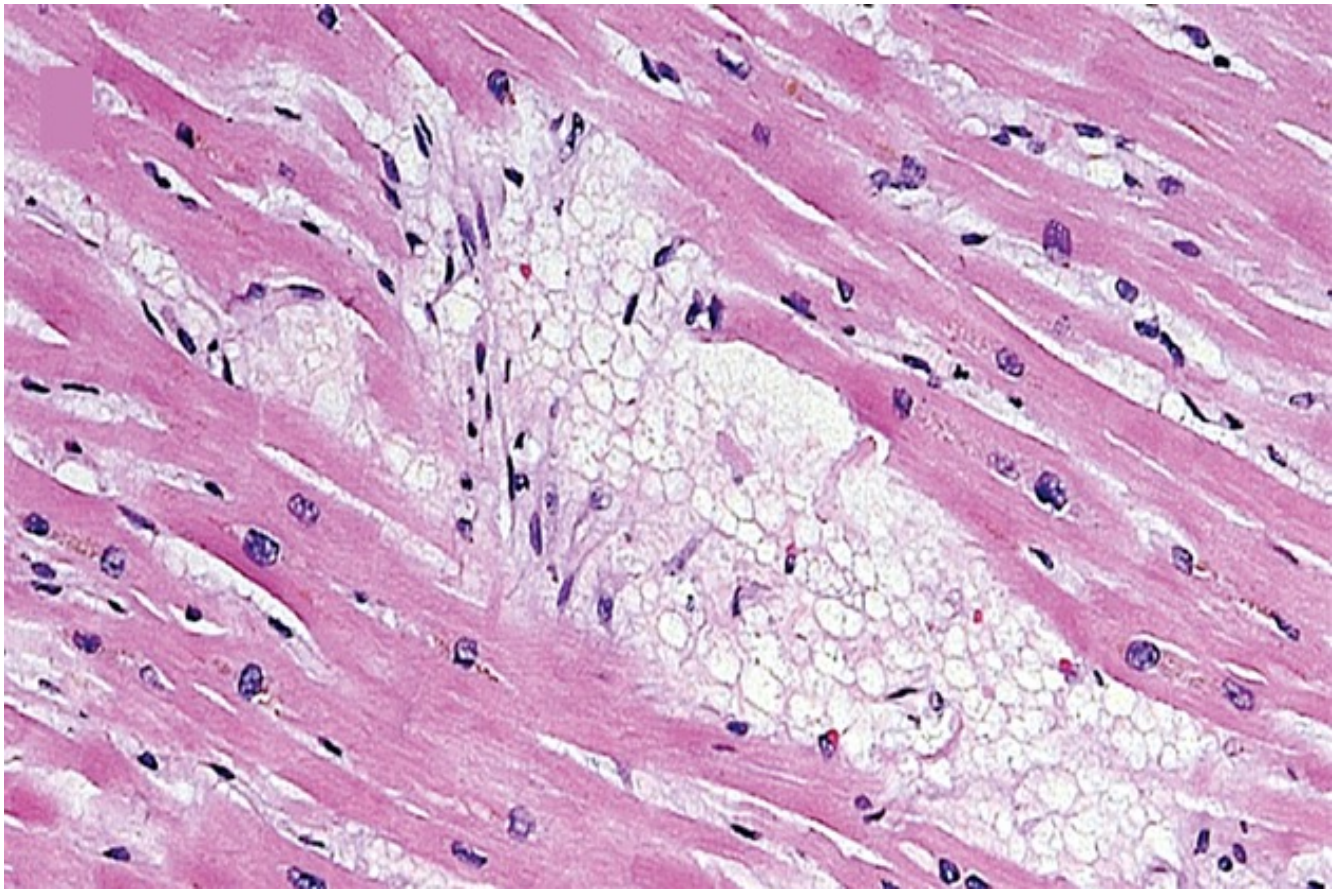


Features Present at the Time of Cardiac Involvement in Acute Infection. Shown is a vulnerable plaque (thin-cap fibroatheroma) during early infection before the development of myocardial infarction. Lipids have already accumulated in the wall of the coronary artery, with thinning of the internal elastic membrane, disruption of intimal and smooth-muscle cells, and fibrin deposition. Also present are foamy macrophages, T lymphocytes, metalloproteinases, peptidases, and neutrophil extracellular traps. In the lumen are inflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukins 1, 6, and 8, that result from sepsis elsewhere in the body.



Mechanisms of Cardiac Involvement in Acute Infection.

Panel A shows rupture of an atheromatous plaque, the mechanism of type 1 myocardial infarction. As a result of the inflammation that develops with infection, the thin-cap atheroma ruptures, releasing inflammatory cells and fibrin into the lumen. In the presence of circulating procoagulants and activated platelets, this release causes immediate accumulation of platelets, fibrin, and neutrophils and trapping of red cells, all of which cause acute obstruction of the coronary arteries. Panel B shows the process of demand ischemia, the mechanism of type 2 myocardial infarction. Acute infection causes the release of interleukin-1, TNF-α, and catecholamines, which increase the core body temperature, oxygen demand, and heart rate. Coronary perfusion declines because of decreased filling time. Cytokines also act to suppress cardiac output. These factors, taken together, cause a mismatch of oxygen needs and oxygen supply, resulting in demand ischemia.



Features Present after Cardiac Involvement in Acute Infection. Shown is an example of direct myocardial involvement in pneumococcal pneumonia. In the heart of a patient who was treated with antibiotic agents but still died from pneumococcal pneumonia, there are disrupted myocytes and there is a relative absence of neutrophil infiltration. In addition, in experimentally induced infection and without treatment, microcolonies of *Streptococcus pneumoniae* were present.

Vaccination

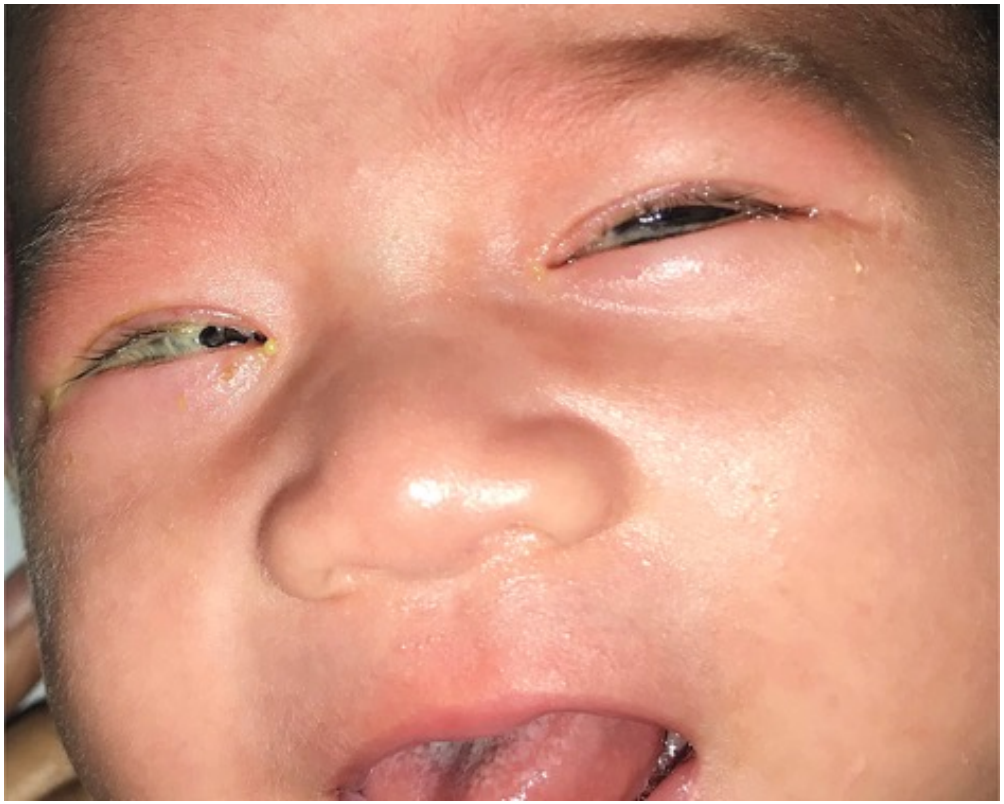
A meta-analysis of five randomized trials showed a 36% lower risk of a composite of cardiovascular events among adults who had received influenza vaccine than among those who had not. The benefit was even greater when the analysis was limited to persons with known coronary artery disease. In contrast, there are limited data from randomized trials regarding the effect of pneumococcal vaccination on cardiovascular risk. A meta-analysis of eight observational studies, all of which were published after 2000, showed a 17% lower risk of myocardial infarction among patients 65 years of age or older who had received pneumococcal polysaccharide vaccine than among those who had not.[40] The lack of a more prominent effect may reflect the decline in the prevalence of pneumococcal pneumonia in recent decades.

Summary

Practitioners may be able to influence the risk of postinfection myocardial infarction if they remain mindful of the increased risk of myocardial infarction during and after acute infections and if they do not dismiss elevated troponin levels as "troponin leak." Among patients with acute infection who have clinical indications for statins and aspirin, these medications should be continued (if the patient is already receiving them) or may be initiated if no contraindications are present.

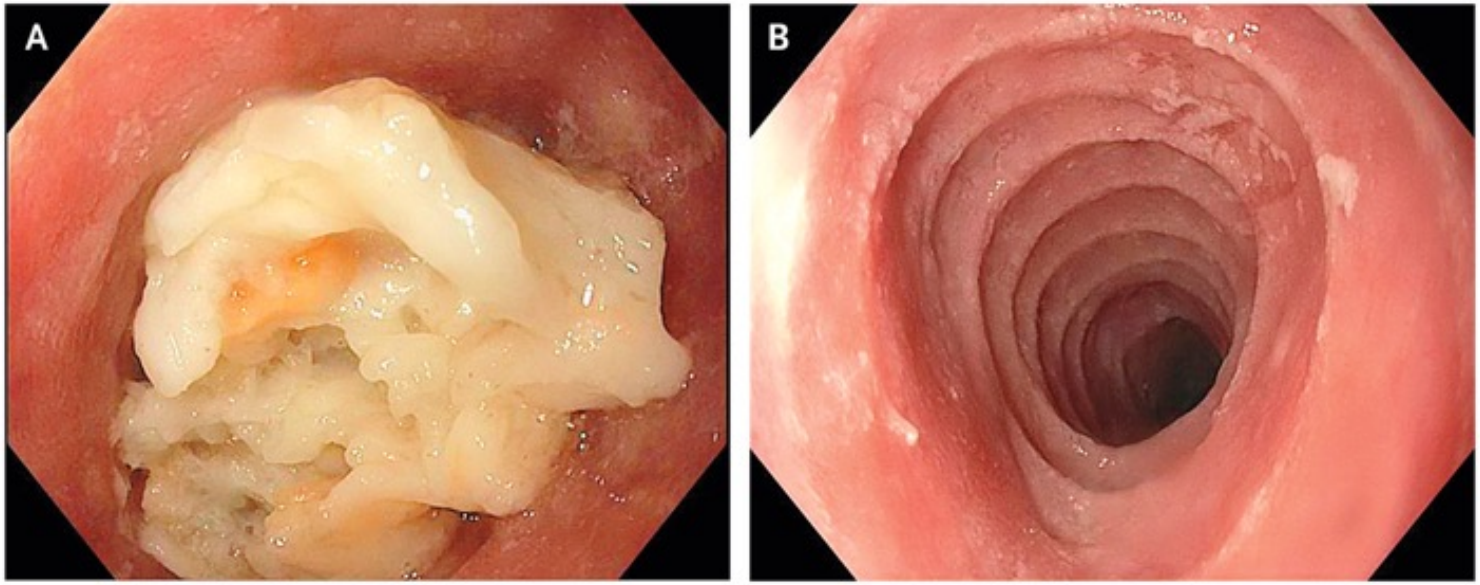
Finally, because the risk of other cardiovascular events — such as heart failure, arrhythmias, and strokes — also increases after acute infection, the mechanisms that account for these associations need to be characterized. This is especially important in the case of heart failure, because after pneumonia the risk of worsening heart failure is even higher than the risk of myocardial infarction. An integrated understanding of the interplay between acute infections and the cardiovascular system should facilitate efforts to reduce the risk of myocardial infarction and other cardiovascular events after acute infections.

Ophthalmia Neonatorum



A 2-week-old baby girl with a 3-day history of purulent discharge from both eyes was brought by her parents to the ophthalmology clinic. The baby had been born at full term by means of spontaneous vaginal delivery. She had not received ocular prophylaxis after delivery, and the mother had not undergone prenatal testing for chlamydia or gonorrhea infection. An eye-discharge sample obtained from the baby and an endocervical swab obtained from the mother tested positive for *Chlamydia trachomatis* DNA and negative for *Neisseria gonorrhoeae* DNA by polymerase chain reaction. Perinatal transmission of *C. trachomatis* or *N. gonorrhoeae* can result in neonatal conjunctivitis, known as ophthalmia neonatorum. The ongoing incidence of ophthalmia neonatorum caused by *C. trachomatis* or *N. gonorrhoeae* can be addressed by routine maternal prenatal screening for and treatment of sexually transmitted infections and by postpartum neonatal ocular prophylaxis against *N. gonorrhoeae*. In addition to treatment of the baby, which included a 2-week course of oral erythromycin, a single dose of oral azithromycin was given to each parent. The baby's symptoms resolved within 5 days after the initiation of treatment, and she remained healthy at follow-up 2 weeks later.

“Trachealization” of the Esophagus



A 32-year-old man presented to the emergency department with difficulty swallowing oral secretions and the feeling that food was stuck in his throat after he ate a pizza roll. The patient reported that similar episodes had occurred previously, but in each instance the feeling resolved spontaneously, and he did not seek medical care. At the time of presentation, the patient was drooling. Upper endoscopy revealed impacted food material (Panel A) and prominent mucosal rings extending 20 cm from the incisors to the level of the gastroesophageal junction, with two discrete areas of narrowing and associated linear furrows (Panel B). Biopsy specimens were obtained, and esophagitis was observed, with more than 40 eosinophils per high-power field. An endoscopic finding of fixed esophageal rings, or “trachealization,” is suggestive of eosinophilic esophagitis, although a definitive diagnosis is made on the basis of clinical presentation, histologic findings, and the exclusion of other causes of esophageal eosinophilia, such as proton-pump inhibitor–responsive esophageal eosinophilia. The patient was treated with an 8-week course of omeprazole, but there was no symptom resolution or histologic improvement on repeat endoscopic biopsies, which confirmed the diagnosis of eosinophilic esophagitis. He was started on an 8-week course of both swallowed fluticasone and a six-food elimination diet (elimination of the six most commonly identified types of allergenic food — wheat, milk, soy, nuts, eggs, and seafood). No additional endoscopies were performed after completion of treatment with fluticasone and the elimination diet. At a 1-year follow-up visit, the patient reported no further symptoms of food impaction.

Das United States Army Special Forces Command (Airborne) (USASFC; deutsch Luftlande-Sondereinsatzkommando des Heeres der Vereinigten Staaten; kurz Special Forces oder USSF) ist die dienstälteste Spezialeinheit der US Army. Ihre etwa 10.000 Soldaten werden aufgrund ihres grünen Baretts auch Green Berets genannt. Es handelt sich dabei ausschließlich um Kampftruppen, die für ihre Aufträge von anderen Einheiten des United States Army Special Operations Command (USASOC) „Sondereinsatzkräfte des Heeres der Vereinigten Staaten“ unterstützt werden. Bis zum 27. November 1990 hieß die Einheit United States Army 1st Special Operations Command. In der Diktion der US-Streitkräfte steht der Begriff Special Forces traditionell ausschließlich für das USASFC (Green Berets). Die anderen Sondereinsatzkräfte des Heeres, zum Beispiel das 75th Ranger Regiment oder das 160th SOAR, sowie die Spezialeinheiten der anderen Teilstreitkräfte werden unter dem Begriff Special Operations Forces subsumiert. Seit ihrer Aufstellung waren die Special Forces an allen militärischen Konflikten und Kriegen der Vereinigten Staaten mit Ausnahme des Einsatzes in Mogadischu 1993[A 1] beteiligt und leisteten weltweit in über 70 Nationen Militärberatung, infrastrukturelle und humanitäre Hilfe.

A 34-Year-Old Veteran with Multiple Somatic Symptoms

A 34-year-old man was evaluated at this hospital because of headaches, cognitive changes, mood symptoms, flashbacks, chest pain, arm tingling, and gastrointestinal symptoms. The patient had served as a special operations combat medic in the U.S. Army Rangers for 8 years. He was wounded several times.

He served in Operation Iraqi Freedom, completing three tours of duty. The patient had had multiple traumatic injuries and experiences during training and deployment. Nine years before the current evaluation, during a parachute-jump training, he had a syncopal episode. Afterward, he could recall only that he had awoken on the ground while a colleague was packing his parachute. He had 3 weeks of headaches, stiffness of the cervical and thoracic spine, and difficulty sleeping. Eight years before the current evaluation, the patient was hit by an explosive blast wave. Afterward, he reported "cloudy" mentation. While he served as the company medic, he was a first responder in two cases in which a soldier had committed suicide. Three years later, during his third deployment, the patient was involved in a motor vehicle accident as a helmeted back-seat passenger. The armored fighting vehicle rolled approximately 9 m into a canal, and the patient was pinned under several men. He had blunt trauma to the head and reportedly lost consciousness for 20 minutes; he had a concussion and traumatic injuries of the head and face, including a hard-palate fracture. He subsequently had headaches and difficulty eating and breathing because of lip and nose swelling.

After the patient's third deployment ended, his wife noticed that he placed kitchen items in the wrong location, became lost while grocery shopping, and was unable to recall the birth of his first daughter. The patient expressed difficulty adjusting to a postdeployment routine, which included child care. He mentioned that he missed his level of entrusted responsibility in the Army Rangers platoon. He reported having "deep, lingering pain at deaths of friends and exposures to children in dire circumstances" and "thinking philosophically about death" but did not report suicidal or homicidal ideation.

Between 3 and 5 years before the current evaluation, while the patient was still in the military, he sought medical and psychiatric care on three occasions. During the first evaluation, duloxetine was prescribed, but it resulted in a rash and peeling of the skin. Three years before the current evaluation, he received inpatient treatment at a military hospital, which included psychotherapy sessions and muscle relaxation and breathing exercises. Two years before the current evaluation, various medications — including sumatriptan, ibuprofen, prednisone, topiramate, and amitriptyline — were tried, with varying degrees of success.

Table 1. Laboratory Data.*

Variable	Reference Range, Other Hospital	13 Mo before Current Evaluation, Other Hospital	1 Mo before Current Evaluation, Other Hospital
Hemoglobin (g/dl)	13.7–17.5	16.7	16.6
Hematocrit (%)	40.1–51.0	49.3	48.7
White-cell count (per mm^3)	4060–9400	7200	10,500
Platelet count (per mm^3)	124,000–335,000	307,000	338,000
Sodium (mmol/liter)	135–145	138	138
Potassium (mmol/liter)	3.5–5.0	4.5	3.9
Chloride (mmol/liter)	100–110	103	102
Carbon dioxide (mmol/liter)	20–30	26	26
Urea nitrogen (mg/dl)	7–25	12	11
Creatinine (mg/dl)	0.5–1.5	1.1	0.9
Glucose (mg/dl)	65–100	97	91
Aspartate aminotransferase (U/liter)	5–34	27	17
Alanine aminotransferase (U/liter)	7–52	62	21
Alkaline phosphatase (U/liter)	40–150	57	58
Thyrotropin (μIU/ml)	0.35–5.00	1.84	0.91
Cholesterol (mg/dl)			
Total	<199	236	
High-density lipoprotein	>40	36	
Low-density lipoprotein	0–129	123	
Triglycerides (mg/dl)	<149	386	
25-Hydroxyvitamin D (ng/ml)	20–50	24.3	
Cortisol, morning (μg/dl)	6–28	6.9	
Calcium (mg/dl)	8.5–10.5		10.4
Total protein (g/dl)	6.0–8.5		8.0
Albumin (g/dl)	3.5–5.0		4.9
γ-Glutamyltransferase (U/liter)	10–65		24
Total bilirubin (mg/dl)	0.2–1.2		1.2
Lipase (IU/liter)	8–70		27
Glycated hemoglobin (%)	4.0–5.7		5.4

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

Twenty-two months before the current evaluation, the patient was honorably discharged from the military, and he moved to New England. Thirteen months before the current evaluation, his condition was assessed by a social worker, psychologist, physical therapist, and neurologist at another hospital. He reported being “constantly on guard” and “easily startled,” as well as having anhedonia, detachment, difficulty concentrating, anorexia, and fatigue. He reported using sarcasm, defensiveness, and intellectualization as coping mechanisms. A review of systems was notable for a reduced ability to move the head and neck to the left and “clicking” with motion of the neck, both of which diminished modestly with physical therapy. Laboratory test results are shown.

A 34-Year-Old Veteran with Multiple Somatic Symptoms

Five months before the current evaluation, the patient reported having flashbacks (*Wiedererleben* oder *Nachhallerinnerung*) with associated emesis. The next month, he reported that his previous concussion was "acting up." He described having a "hazy" feeling, verbal stuttering, and severe headaches, which he rated at 10 on a scale of 0 to 10 (with 10 indicating the most severe pain). The headaches lasted for days and were associated with sonophobia and photophobia; he used ice and ibuprofen for relief. He also began to have panic attacks in association with recall of memories. He described having a "rush of visions" of traumatic memories from childhood and the military and being "not able to turn them off"; lorazepam was prescribed. Recurrent pain and tingling of the left anterior chest and left anterior arm developed in association with these memories and later occurred independently of the memories. The patient treated himself for these symptoms with fans, cold baths, and benzodiazepines.

The patient's father had depression, and his mother, father, and paternal uncle each had a history of alcohol and drug use disorders. The patient had been raised by his grandparents. A sister had died in her 20s from bone cancer. The patient lived with his wife and two healthy young children. He had not worked outside the home since his honorable discharge from the military, instead performing child care duties while his wife worked. He had completed 3 years of college; he had thought about additional schooling but felt discouraged because of forgetfulness. The patient had used chewing tobacco in the past but had not used any in 2 years. He consumed up to four caffeinated drinks daily and had only three or four alcoholic drinks monthly, which was a reduction from his past alcohol consumption. He smoked marijuana daily but used no illicit drugs. Medications included nortriptyline, omeprazole, pantoprazole, sucralfate, ondansetron, and as needed, simethicone.

On examination, the temperature was 37.1° C, the heart rate 94 beats per minute, the blood pressure 109/74 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The weight was 86 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 26.4. The patient was well groomed, alert, cooperative, oriented, and lucid, with coherent speech. He was described as fidgeting, anxious, and irritable. The remainder of the cardiovascular, pulmonary, abdominal, and musculoskeletal examination was normal. A urine toxicology screen was positive for cannabinoids and negative for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and phencyclidine. A diagnosis was made.

Neurologic Diseases

Cerebral aneurysm, vascular dissection, hemorrhage, ischemia, infections (meningitis and encephalitis), and pseudotumor cerebri can all cause headaches, mood symptoms, and cognitive changes. Tumors of the central nervous system (CNS) can cause these symptoms along with emesis and weight loss. Severe headaches or headaches in combination with certain "red flags," such as focal neurologic signs or systemic illness, may indicate the presence of one of these serious underlying causes. Although imaging studies of the head would be obtained in this case to rule out a clinically significant abnormality of the brain or CNS, the chronic nature of this patient's symptoms and the absence of other relevant findings most likely rule out a catastrophic neurologic diagnosis.

Gastrointestinal Diseases

Inflammatory bowel disease could explain the presence of gastrointestinal symptoms. However, although the onset of this disease can occur at any age, it typically occurs before 30 years of age, and the disease is usually associated with blood in the stool and not with vomiting or constipation, which were described by this patient.

Endocrine Diseases

Hyperthyroidism could explain this patient's mood symptoms, anxiety, insomnia, diarrhea, and weight loss. However, he had a normal thyrotropin level, a finding that rules out this diagnosis.

Toxic Exposures

Veterans who served in Operation Iraqi Freedom have a number of potential toxic exposures, including depleted uranium, lead, sand and dust particles, burn pits, oil-well fires, and agents of chemical warfare. However, these exposures are known to result in rashes, widespread pain, respiratory problems, or persistent fatigue, in addition to headaches and cognitive changes. The patient's symptoms and the timeline of illness are inconsistent with these exposures.

Mood and Anxiety Disorders

Bipolar disorder, major depressive disorder, and persistent depressive disorder could each explain the presence of mood changes and insomnia. A family history of depression and ongoing anxiety increase the likelihood of a mood disorder.

Traumatic Brain Injury

Traumatic brain injury (TBI) has developed in 19% of veterans who served in Operation Iraqi Freedom or Operation Enduring Freedom and is the signature wound of these wars. Cognitive consequences of TBI (known as neurocognitive disorder due to TBI) include decreased attention, executive function, learning, memory, language, and social cognition.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is present in 13 to 17% of veterans who served in Operation Iraqi Freedom or Operation Enduring Freedom. PTSD occurs after exposure to a traumatic event and is characterized by re-experiencing of the event (often with physiologic reactions to trauma cues), avoidance of trauma-related thoughts and external reminders, negative alterations in cognition or mood, and hyperarousal.[4] PTSD could explain this patient's mood symptoms, insomnia, flashbacks, hypervigilance, startle, and panic attacks (with associated chest pain and tingling). Furthermore, veterans with PTSD are 4 times as likely to have chronic headaches and 3.5 times as likely to have irritable bowel syndrome as veterans without PTSD.[8,9] A diagnosis of PTSD is the most parsimonious explanation of this patient's panic attacks (a physiologic reaction to trauma cues), rather than an independent panic disorder.

A patient must meet eight DSM-5 criteria for the diagnosis of PTSD to be established. The first criterion is direct exposure or indirect exposure (e.g., involving a family member) to a traumatic event. In patients with PTSD, the constellation of symptoms must lead to functional impairment or distress. In addition, to establish the diagnosis of PTSD, substance use and other medical conditions must be ruled out.

Table 2. Diagnostic Criteria for Post-Traumatic Stress Disorder.*

Criterion	Description	Characteristics of This Patient
Trigger	Patient has had direct or indirect exposure to a traumatic event, e.g., death of another person or threatened death, serious injury, or sexual violence.	He was a combat medic who, in the course of work, was exposed to major trauma and responded to suicides.
Symptoms that begin after trauma		
Intrusion	Patient has ≥1 of the following: involuntary recurrent memories, flashbacks, nightmares, or physical or emotional reactions to traumatic reminders.	He had intrusive thoughts and flashbacks, including scenes of death, and nightmares.
Avoidance of stimuli associated with the traumatic event	Patient has ≥1 of the following: avoids trauma-related thoughts and feelings or avoids cues and reminders.	He was guarded about previous experiences and avoided crowds and driving.
Negative alterations in cognition and mood	Patient has ≥2 of the following: amnesia in response to trauma, self-blame for trauma, inflexible negative beliefs, anhedonia, isolation, or difficulty expressing positive emotions.	He had thoughts of death and dying, self-blame for deaths of military friends, persistent negative emotional state, anhedonia, and detachment and isolation from his family.
Marked alterations in arousal and reactivity	Patient has ≥2 of the following: hypervigilance, startle behavior, aggressive or self-destructive behavior, difficulty concentrating, or sleep impairment.	He had irritability, hypervigilance, enhanced startle response, difficulty concentrating, and sleep disturbances.
Duration of symptoms	Patient has symptoms for >1 mo.	He had symptoms for 8 yr before the current evaluation.
Effect of symptoms	Patient has functional impairment or distress.	He had difficulty connecting with family, communicating, and performing tasks such as shopping and cooking.
Exclusions	Other underlying medical conditions and substance use have been ruled out.	His use of alcohol and marijuana was probably not a major contributing factor, and no other primary medical cause was identified.

* Criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[4]

Discussion of Management

Dr. Mireya F. Nadal-Vicens: Management of PTSD starts with a combination of psychotherapy and treatment with a selective serotonin-reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor. In addition, mirtazapine, prazosin, tricyclic antidepressants, or phenelzine may be administered. At this patient's initial evaluation, mirtazapine therapy was started, given its soporific and appetite-stimulating effects, but treatment was complicated by the development of a facial rash. Escitalopram therapy was started and was associated with no allergic reactions or unacceptable side effects.

A key component of the patient's treatment was completion of 12 weekly 90-minute sessions of prolonged exposure therapy, which is an evidence-based, trauma-focused method of psychotherapy whose effectiveness is based on mechanisms of habituation and learning. During prolonged exposure, patients are required to confront traumatic memories through repeated imaginal exposures and to decrease avoidance by engaging in feared activities in a hierarchical manner (in vivo exposures). In addition to receiving these interventions, patients who undergo prolonged exposure therapy receive extensive psychoeducation regarding the nature of the effects of trauma and the mechanisms through which prolonged exposure exerts positive effects. Patients are given realistic expectations regarding the degree of difficulty of the treatment.

Unfortunately, PTSD is highly prevalent among U.S. veterans. One study showed that among nearly 4.5 million patients who were treated at Veterans Affairs primary care clinics in 2010 to 2011, approximately 9% had a diagnosis of PTSD, more than 25% had depression, 8% had a substance use disorder, and 5% had anxiety. However, among veterans who had returned from service in Iraq, the rate of PTSD was 16% — nearly twice the rate among all veterans.

This patient had somatic symptoms, which are very common manifestations of PTSD. Back pain is nearly twice as common among patients with positive PTSD screens as among those with negative PTSD screens (occurring in 40% vs. 22%), and so is joint pain (50% vs. 26%). Headaches are 3 times as common (32% vs. 10%). Gastrointestinal symptoms such as stomachache, nausea, and constipation are also common among patients with PTSD.

In response to these statistics, the Veterans Health Administration enacted a collaborative care model in which behavior health specialists were located in the same place as primary care practitioners and were immediately available for visits. The model was designed to improve the identification and treatment of veterans who have PTSD, as well as those who have depression, anxiety, and substance use disorders. Thereafter, mental health care was provided to nearly 6% of patients who were treated at Veterans Affairs primary care clinics, and the results of such treatment suggest decreased substance use, increased adherence to antidepressant regimens, enhanced patient engagement, and reduced stigma against accessing mental health services.

What is Vaping?

Vaping is the act of inhaling and exhaling the aerosol, often referred to as vapor, which is produced by an e-cigarette or similar device. The term is used because e-cigarettes do not produce tobacco smoke, but rather an aerosol, often mistaken for water vapor, that actually consists of fine particles. Many of these particles contain varying amounts of toxic chemicals, which have been linked to cancer, as well as respiratory and heart disease.

Vaping has grown in popularity with the rise of e-cigarettes, which were introduced to the mass market in the U.S. in 2007. Vaping devices include not just e-cigarettes, but also vape pens and advanced personal vaporizers (also known as ‘MODS’). E-cigarettes, which resemble smoked cigarettes, and vape pens, which resemble large fountain pens, are typically simpler in design and less expensive than devices that have been customized by the user.

Generally a vaping device consists of a mouthpiece, a battery, a cartridge for containing the e-liquid or e-juice, and a heating component for the device that is powered by a battery. When the device is used, the battery heats up the heating component, which turns the contents of the e-liquid into an aerosol that is inhaled into the lungs and then exhaled.

Adolescent „Vaping“ and Nicotine Use in 2017–2018 — U.S. National Estimates

A rapid increase in the prevalence of vaping among adolescents has aroused public health concern. Adolescents who “vape” use a device such as an electronic cigarette to inhale a heated aerosol, which typically contains nicotine. In 2017, vaping was the most common use of any tobacco-like product among adolescents. This is a rapid rise from a near-zero prevalence of vaping in 2011. We assessed whether the prevalence of nicotine vaping increased among adolescents from 2017 to 2018.

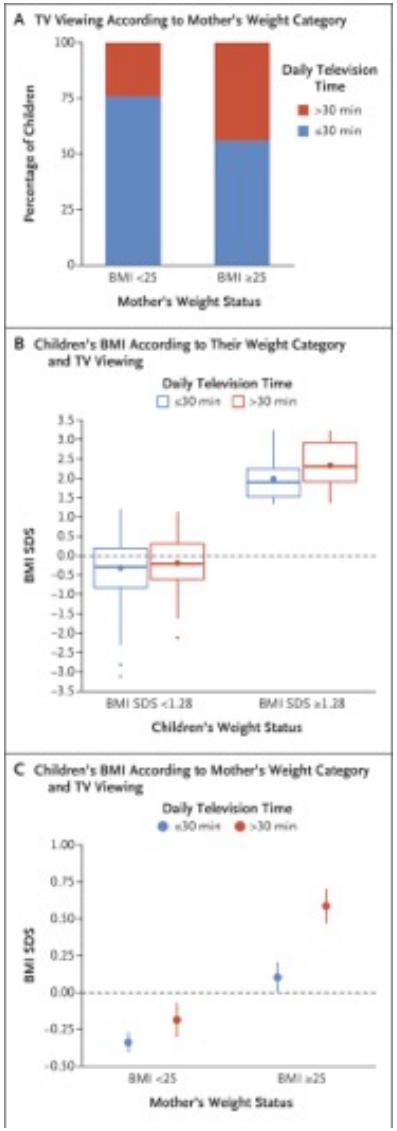
Data for our study came from Monitoring the Future, which annually surveys nationally representative, independent samples of students in the 12th, 10th, and 8th grades. Analyses were based on a total of 13,850 respondents. A randomly selected half of the 12th-grade respondents in this study answered a group of questions on vaping as well as on six common forms of tobacco use, which allowed for the assessment of overall nicotine use with any nicotine product.

Substance and School Grade	Prevalence in 2017 (95% CI)	Prevalence in 2018 (95% CI)	Change from 2017 to 2018 (95% CI)
	percent		*percentage points*
Vaped nicotine			
12th grade	11.0 (9.2–13.0)	20.9 (17.7–24.6)	10.0 (6.5–13.4)
10th grade	8.2 (6.6–10.2)	16.1 (14.0–18.6)	7.9 (5.6–10.2)
8th grade	3.5 (2.9–4.2)	6.1 (5.1–7.4)	2.6 (1.4–3.8)
Vaped flavoring			
12th grade	9.7 (8.4–11.0)	13.5 (11.8–15.4)	3.8 (1.8–5.9)
10th grade	9.2 (7.7–10.8)	13.1 (11.5–15.0)	3.9 (1.8–6.1)
8th grade	5.3 (4.5–6.3)	8.1 (6.8–9.6)	2.8 (1.2–4.3)
Vaped nicotine or flavoring†			
12th grade	15.2 (13.3–17.4)	25.0 (21.6–28.7)	9.8 (6.1–13.4)
10th grade	12.0 (10.2–14.1)	20.3 (17.9–22.9)	8.3 (5.6–11.0)
8th grade	6.3 (5.4–7.3)	9.7 (8.2–11.4)	3.4 (1.7–5.1)

Persistence of Obesity from Early Childhood Onward

Geserick et al. (Oct. 4 issue) report tracking body-mass index (BMI) in individual children over time. However, they did not use longitudinal analytic strategies. Although Figures 1 and 2 (available with the full text of their article at NEJM.org) suggest longitudinal modeling of the data, these data should in fact be presented in bar charts. Moreover, 28% of the data points that met the criteria for inclusion were excluded (multiple visits in a given age group). Longitudinal analyses that include all available data would be more efficient and compelling.

Even though we do not have continuously tracked data throughout childhood for all the children studied, the sample sizes for each year-of-age group (e.g., >3000 for 2-year-old children, which was the smallest sample size) are high as compared with other studies that span more than 13 years of observation and are sufficient to detect even small effects (phi=0.1, power=90%, number required >1051) when tracking obesity from childhood to adolescence. Further, the congruency of the data reassured us that there is a high likelihood of persistence if obesity sets in during early childhood.



Additive Effect of Endogenous and Acquired Risk Factors for Obesity in Early Childhood. Panel A shows the daily television viewing time of children according to maternal body-mass index (BMI, the weight in kilograms divided by the square of the height in meters; BMI ≥25 indicates overweight). Children of mothers with a BMI of 25 or higher watched more television than children of mothers with a BMI of less than 25 ($P<0.001$). Panel B shows children's BMI standard deviation score (SDS; BMI ≥1.28 SDS indicates overweight) according to television viewing time.

These observations of clustering and tracking of risk factors for childhood obesity suggest that it is reasonable to initiate preventive action in at-risk preschool children, particularly in those with upward deviation of BMI centiles.

Question of the Week

In addition to aspirin and a statin, which one of the following medications is most appropriate for a patient with known coronary artery disease who has stable exertional angina?

- Metoprolol
- Lisinopril
- Isosorbide dinitrate
- Candesartan
- Diltiazem

Your answer is correct.

Metoprolol
Lisinopril
Isosorbide dinitrate
Candesartan
Diltiazem

Key Learning Point

View Case Presentation ›

In addition to aspirin and a statin, the type of medication routinely recommended for a patient with symptomatic coronary artery disease is a beta-blocker.

Detailed Feedback

A beta-blocker is first-line therapy for patients with symptomatic coronary artery disease, especially those with concomitant hypertension. Beta-blockers decrease myocardial oxygen demand by decreasing blood pressure, heart rate, and myocardial contractility.

Long-acting nitrates (such as isosorbide dinitrate and isosorbide mononitrate) and calcium-channel blockers (such as diltiazem) can be added if the beta-blocker does not sufficiently control the angina.

Angiotensin-converting–enzyme inhibitors (such as lisinopril) and angiotensin-receptor blockers (such as candesartan) are useful adjunctive therapies in patients with coronary disease who have hypertension or left ventricular dysfunction, but they are not anti-anginal agents. Whether they reduce the incidence of myocardial infarction independent of their blood-pressure–lowering effects is controversial.

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined. We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with type 2 diabetes.

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10142	17160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

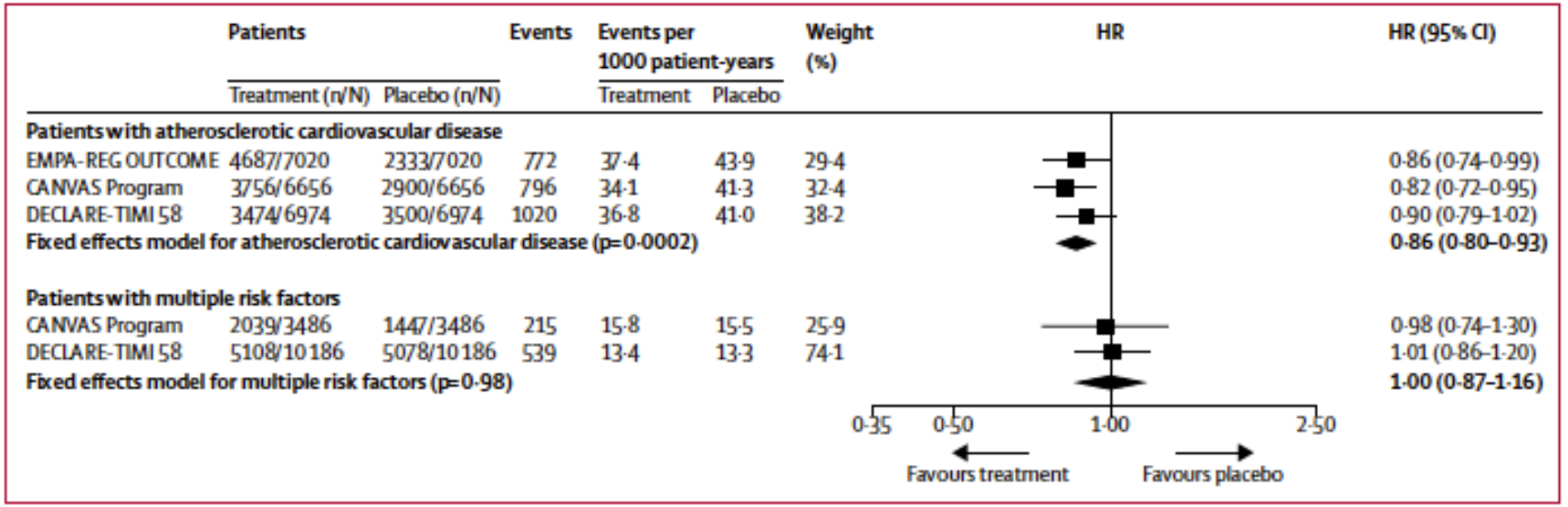
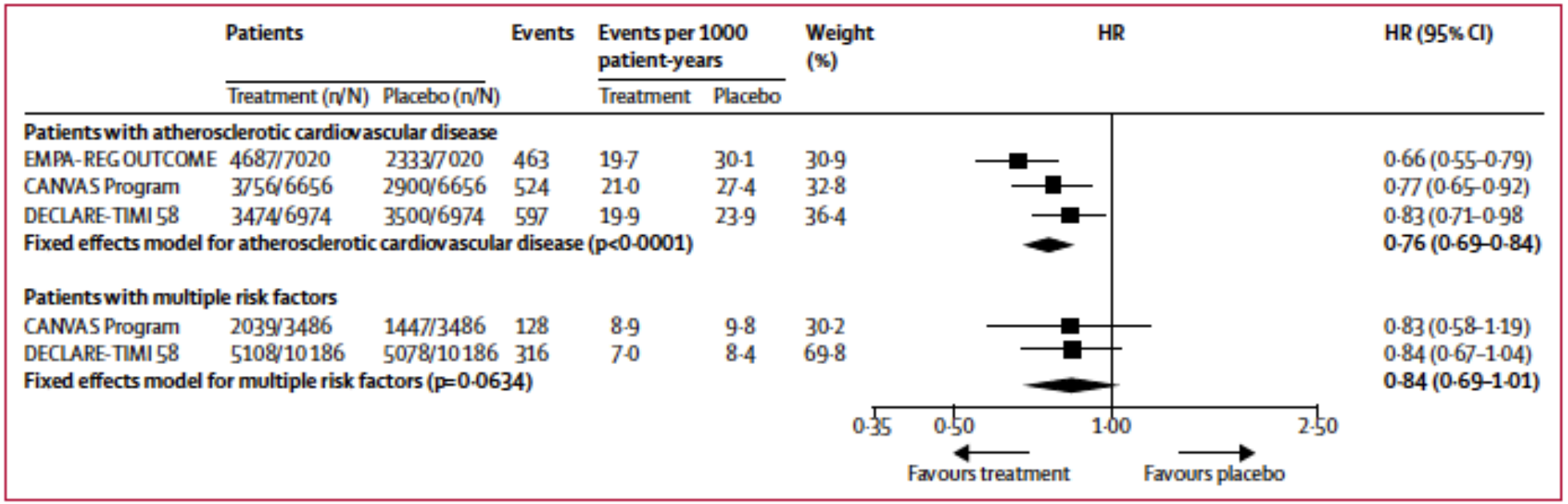


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**



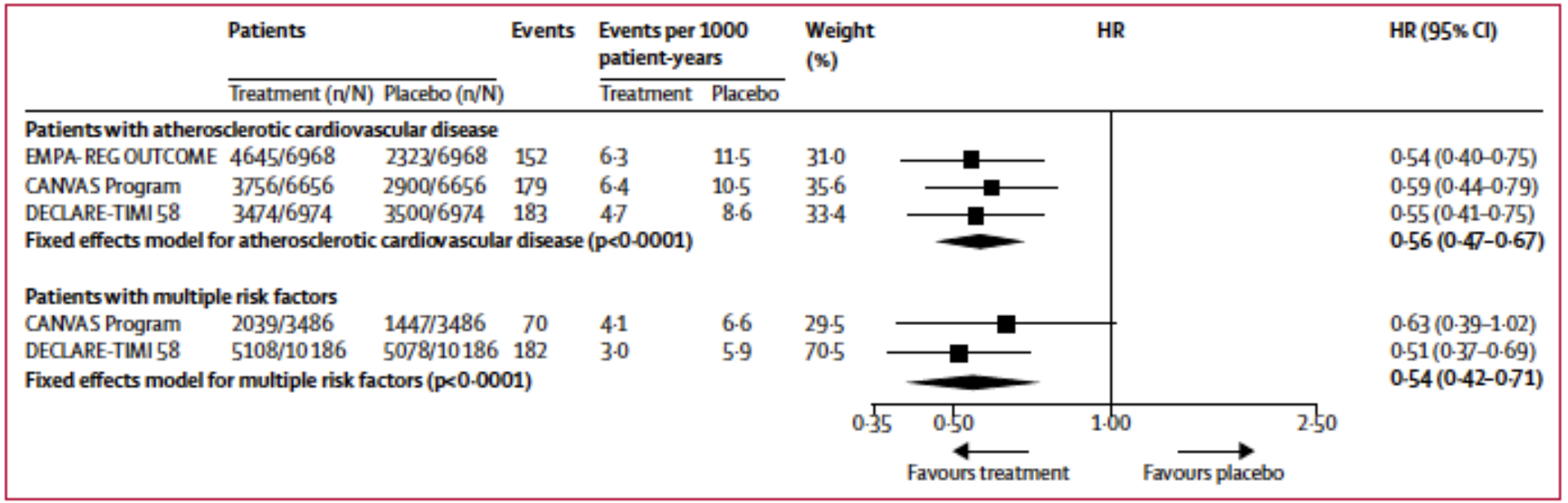


Figure 4: **Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease**

A glance at solely a fraction of the sponsors

Daiichi Sankyo, Eisai, Eli Lilly, and Janssen, grants, personal fees, and other from Merck, and personal fees from Aegerion, Allergan, Angelmed, Boehringer Ingelheim, Boston Clinical Research Institute, Icon Clinical, Lexicon, St Jude Medical, and Xoma outside of the submitted work. IR reports personal fees from AstraZeneca and Bristol-Myers Squibb during the conduct of the study. IR also reports personal fees from Boehringer Ingelheim, Concenter BioPharma—Silkim Ltd, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk Inc, Orgenesis, Pfizer, Sanofi, SmartZyme Innovation Ltd, Panaxia, FuturRx Ltd, Insuline Medical, Medial EarlySign Ltd, CameraEyes, Exscopia, Dermal Biomics Inc, Johnson & Johnson, Novartis Pharma AG, Teva, Glucome Ltd, and DarioHealth outside of the submitted work. MPB reports grants from Amgen, AstraZeneca, Merck, and Pfizer, and personal fees from Aralez, Amgen, AstraZeneca, Bayer, Janssen, Pfizer, and Sanofi during the conduct of the study. OM reports grants and personal fees from AstraZeneca and Bristol-Myers Squibb during the conduct of the study. OM also reports grants and personal fees from NovoNordisk and personal fees from Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Jansen, and Novartis outside of the submitted work. ETK reports personal fees from AstraZeneca, Ono Pharmaceutical, Daiichi Sankyo, Bristol-Myers Squibb, and Tanabe-Mitsubishi Pharma outside the submitted work. AC reports personal fees from Novo Nordisk, Eli Lilly, Sanofi, Boehringer Ingelheim, Merck Sharp & Dohme, and Glucome, and grants and Development LLC, Sanofi US, Merck Sharp and Dohme, Eli Lilly, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai Inc, Esperion, Metavant, and Pfizer outside of the submitted work. JPW reports personal fees and other from Brigham and Women's Hospital during the conduct of the study JPW also reports grants, personal fees, and consultancy fees paid to his institution from AstraZeneca, Novo Nordisk, and Takeda, personal fees and consultancy fees paid to his institution from Boehringer Ingelheim, Lilly, Janssen, Napp, Mundipharma, and Sanofi, and consultancy fees paid to his institution from Wilmington Healthcare outside of the submitted work. MSS reports grants and personal fees from Amgen, AstraZeneca, Intarcia, Janssen Research and Development, The Medicines Company, Medimmune, Merck, and Novartis, grants from Daiichi-Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Takeda, Abbott Laboratories, Bayer, Critical Diagnostics, Genzyme, Gilead, and Roche Diagnostics, and personal fees from Bristol-Myers Squibb, CVS Caremark, Dyrnamix, Esperion, Alnylam, Ionis, and MyoKardia outside of the submitted work. KI and ELG report grants to their institution from Abbott Laboratories, Amgen, AstraZeneca, Bayer, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, Gilead, GlaxoSmithKline, Intarcia, Janssen Research Development, the Medicines Company, MedImmune, Merck, Novartis, Pfizer, Poxel, Roche Diagnostics, and Takeda outside of the submitted work.

Acknowledgments

Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma

There are few effective treatment options for patients with recurrent or metastatic head-and-neck squamous cell carcinoma. Pembrolizumab (PD-1) showed antitumour activity and manageable toxicity in early-phase trials. We aimed to compare the efficacy and safety of pembrolizumab versus standard-of-care therapy for the treatment of head-and-neck squamous cell carcinoma.

Methods

We did a randomised, open-label, phase 3 study at 97 medical centres in 20 countries. Patients with head-and-neck squamous cell carcinoma that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or progressed within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease, were randomly assigned (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive pembrolizumab 200 mg every 3 weeks intravenously or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab (anti EGFR) intravenously (standard-of-care group). The primary endpoint was overall survival in the intention-to-treat population. Safety was analysed in the as-treated population.

Median overall survival in the intention-to-treat population was 8·4 months (95% CI 6·4–9·4) with pembrolizumab and 6·9 months (5·9–8·0) with standard of care (hazard ratio 0·80, 0·65–0·98; nominal p=0·0161). The most common treatment-related adverse event was hypothyroidism with pembrolizumab (in 33 [13%] patients) and fatigue with standard of care (in 43 [18%]). Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events.

Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial

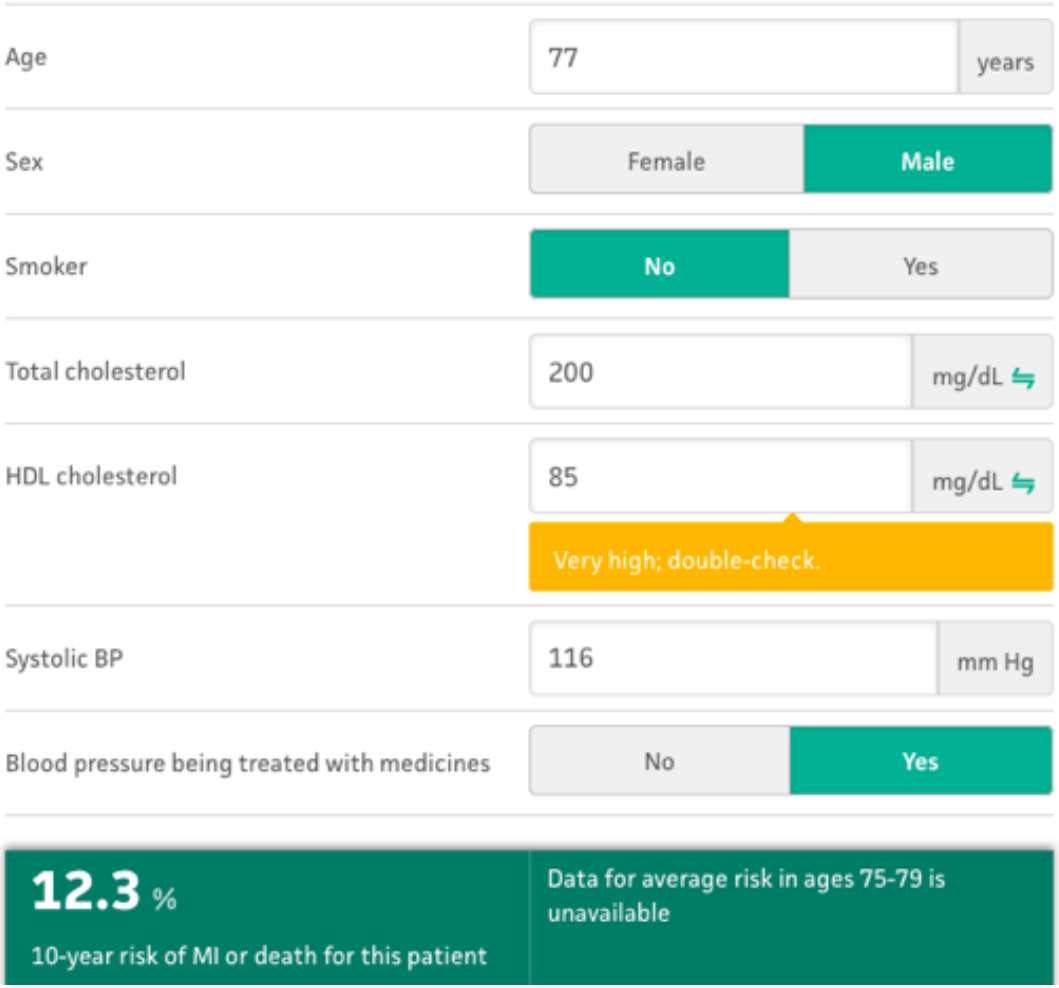
Primary prevention of cardiovascular disease often fails because of poor adherence among practitioners and individuals to prevention guidelines. We aimed to investigate whether ultrasound-based pictorial information about subclinical carotid atherosclerosis, targeting both primary care physicians and individuals, improves prevention.

Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) is a pragmatic, open-label, randomised controlled trial that was integrated within the Västerbotten Intervention Programme, an ongoing population-based cardiovascular disease prevention programme in northern Sweden. Individuals aged 40, 50, or 60 years with one or more conventional risk factors were eligible to participate. Participants underwent clinical examination, blood sampling, and ultrasound assessment of carotid intima media wall thickness and plaque formation. Participants were randomly assigned 1:1 with a computer-generated randomisation list to an intervention group (pictorial representation of carotid ultrasound plus a nurse phone call to confirm understanding) or a control group (not informed). The primary outcomes, Framingham risk score (FRS) and European systematic coronary risk evaluation (SCORE), were assessed after 1 year.

3532 individuals were enrolled between April 29, 2013, and June 7, 2016, of which 1783 were randomly assigned to the control group and 1749 were assigned to the intervention group. 3175 participants completed the 1-year follow-up. At the 1-year follow-up, FRS and SCORE differed significantly between groups (FRS 1·07 [95% CI 0·11 to 2·03, p=0·0017] and SCORE 0·16 [0·02 to 0·30, p=0·0010]). FRS decreased from baseline to the 1-year follow-up in the intervention group and increased in the control group.

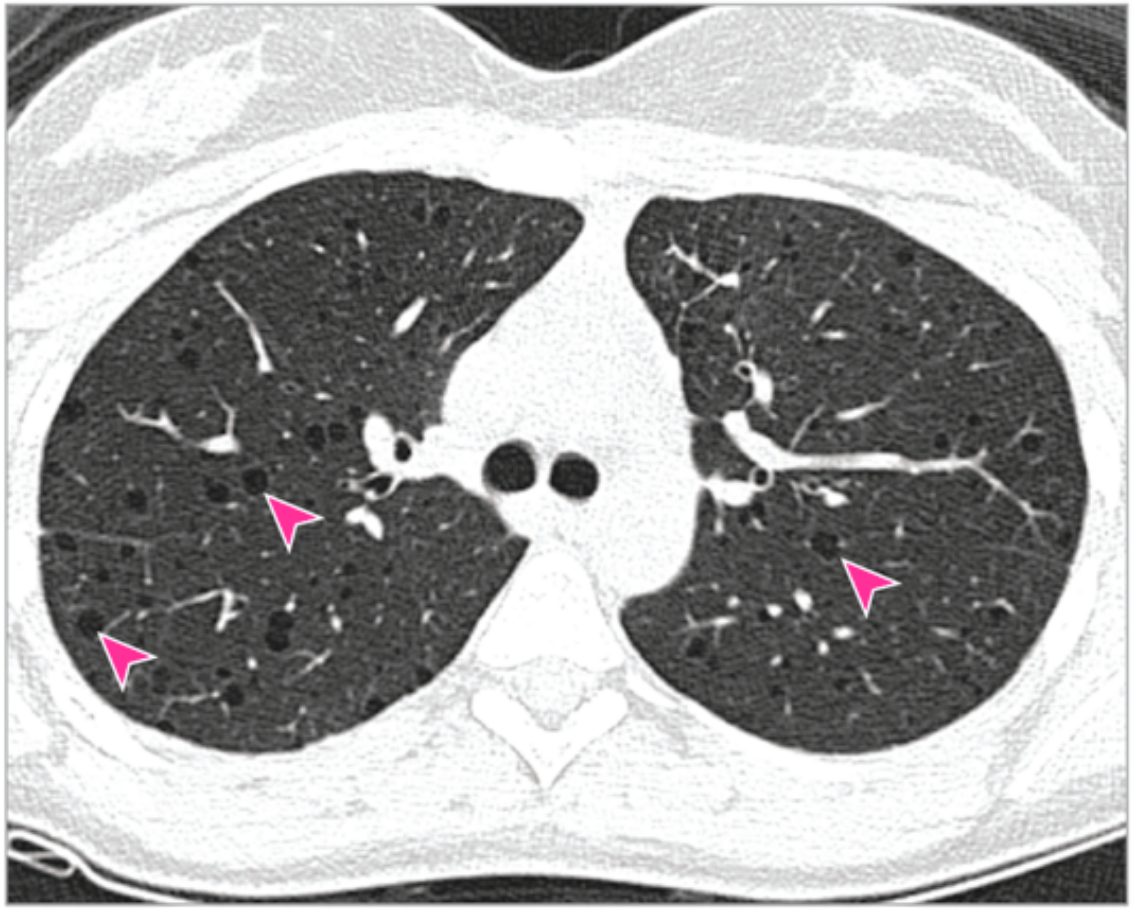
Framingham Risk Score for FCL

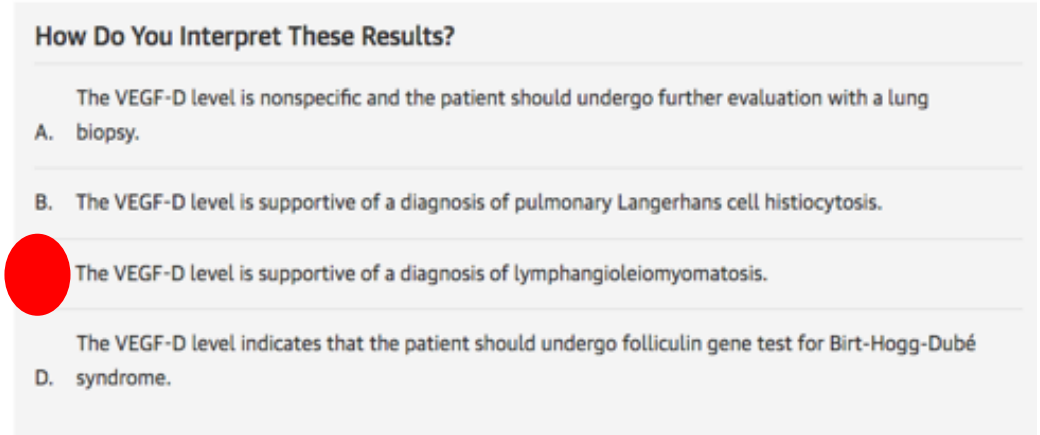
Der Framingham Risk Score (FRS) berücksichtigt das Alter, Geschlecht, Gesamt-Cholesterol, HDL-Cholesterol, Blutdruck und das Rauchen und errechnet das 10-Jahres-Risiko für einen Myokardinfarkt. Der Modifizierte Framingham Risk Score schließt zusätzlich noch eine Diabetes-Erkrankung ein.
Von einem hohen Risiko muss ab einem FRS von über 20%, von einem niedrigen bei einem Wert unter 10% ausgegangen werden.



Case

A 28-year-old nonsmoking woman was referred to the pulmonary clinic for further evaluation of shortness of breath with exertion. She had slowly progressing dyspnea over the past year and general fatigue. She did not report a history of xerostomia, keratoconjunctivitis sicca, pleural effusions, pneumothoraces, seizure, cognitive impairment, recurrent sinopulmonary infections, or previous autoimmune disease diagnosis and had no relevant family history of lung disease. Her physical examination findings were unremarkable and there was no evidence of cutaneous lesions. A high-resolution computed tomographic (CT) scan of her chest revealed diffuse thin-walled pulmonary cysts without nodules, parenchymal changes, or lymphadenopathy (Figure). Imaging of her abdomen did not show kidney lesions or abdominal masses. The patient's serum vascular endothelial growth factor D (VEGF-D) level was elevated at 1300 pg/mL (reference range, <600 pg/mL).





Pulmonary cysts are characteristic of different diseases that include, but are not limited to, Langerhans cell histiocytosis, lymphangioleiomyomatosis (LAM), and Birt-Hogg-Dubé syndrome. Pulmonary Langerhans cell histiocytosis is a rare lung disease characterized by accumulation of Langerhans cells in small airways and is usually seen in young adult smokers. High-resolution CT images commonly demonstrate nodules and upper and middle lobe cysts that may progress to a thick, irregular-walled, bizarre-shaped appearance. Birt-Hogg-Dubé is an autosomal dominant syndrome characterized by multiple irregular lung cysts commonly found in the peripheral lung zones at the lung bases and along the mediastinum, and it is associated with cutaneous fibrofolliculomas, spontaneous pneumothorax, and kidney cancer. LAM is a rare disease that predominantly affects women of childbearing age, with a prevalence of approximately 3 to 8 cases per million women. LAM may occur sporadically or in association with tuberous sclerosis complex. A diagnosis of LAM can be confidently made with characteristic high-resolution CT image findings of diffuse thin-walled pulmonary cysts surrounded by normal lung parenchyma and 1 of the following: renal angiomyolipomas, chylous effusions, lymphangioleiomyomas, or a diagnosis of tuberous sclerosis complex. In the absence of these other findings, a lung biopsy may be required to differentiate the symptoms from other cystic lung diseases. More recently, serum VEGF-D testing has emerged as a noninvasive means of confirming the diagnosis in a subset of patients with cystic lung disease in whom the level is documented to be elevated.

The New York Times

Top Sloan Kettering Cancer Doctor Resigns After Failing to Disclose Industry Ties

Dr. José Baselga stepped down as the chief medical officer of Memorial Sloan Kettering Cancer Center.
Thos Robinson/Pershing Square Sohn Cancer Research Alliance, via Getty Images

Dr. Baselga, a prominent figure in the world of cancer research, omitted his financial ties to companies like the Swiss drugmaker Roche and several small biotech start-ups in prestigious medical publications like The New England Journal of Medicine and The Lancet. He also failed to disclose any company affiliations in articles he published in the journal Cancer Discovery, for which he serves as one of two editors in chief.

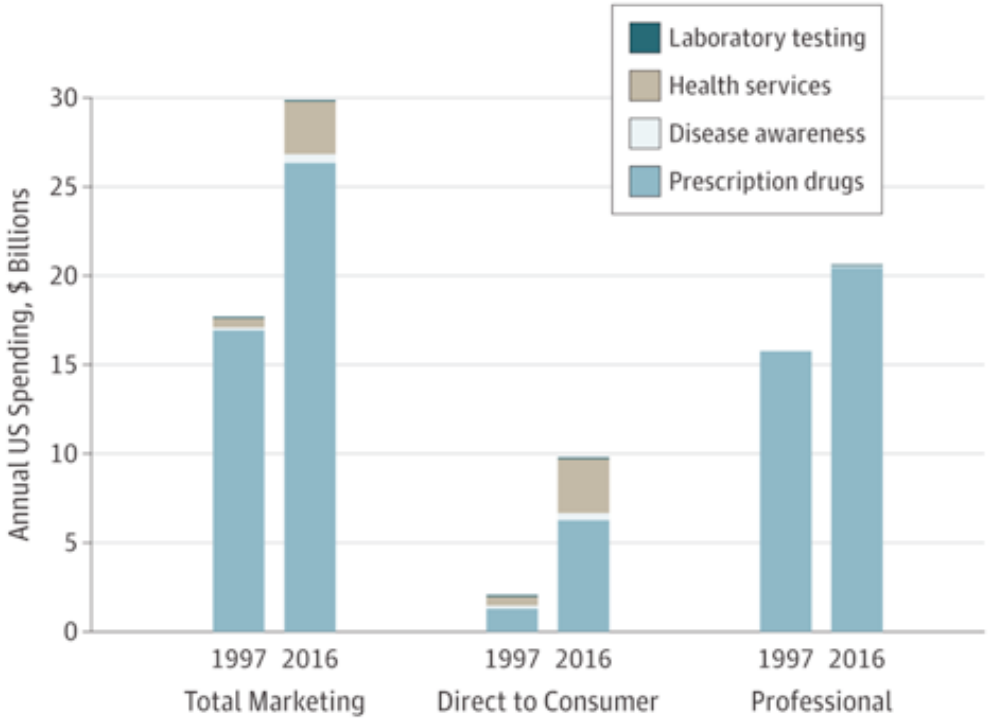
José Baselga (born 3 July 1959) is a Spanish medical oncologist and researcher focused on the development of novel molecular targeted agents, with a special emphasis in breast cancer. Baselga served as Physician-in-Chief at the Memorial Sloan Kettering Cancer Center until his resignation in September 2018 after it was reported that he had failed to disclose millions of dollars in financial ties with pharmaceutical companies in his research. On January 7, 2019, AstraZeneca announced that they had hired him as head of research and development in oncology.

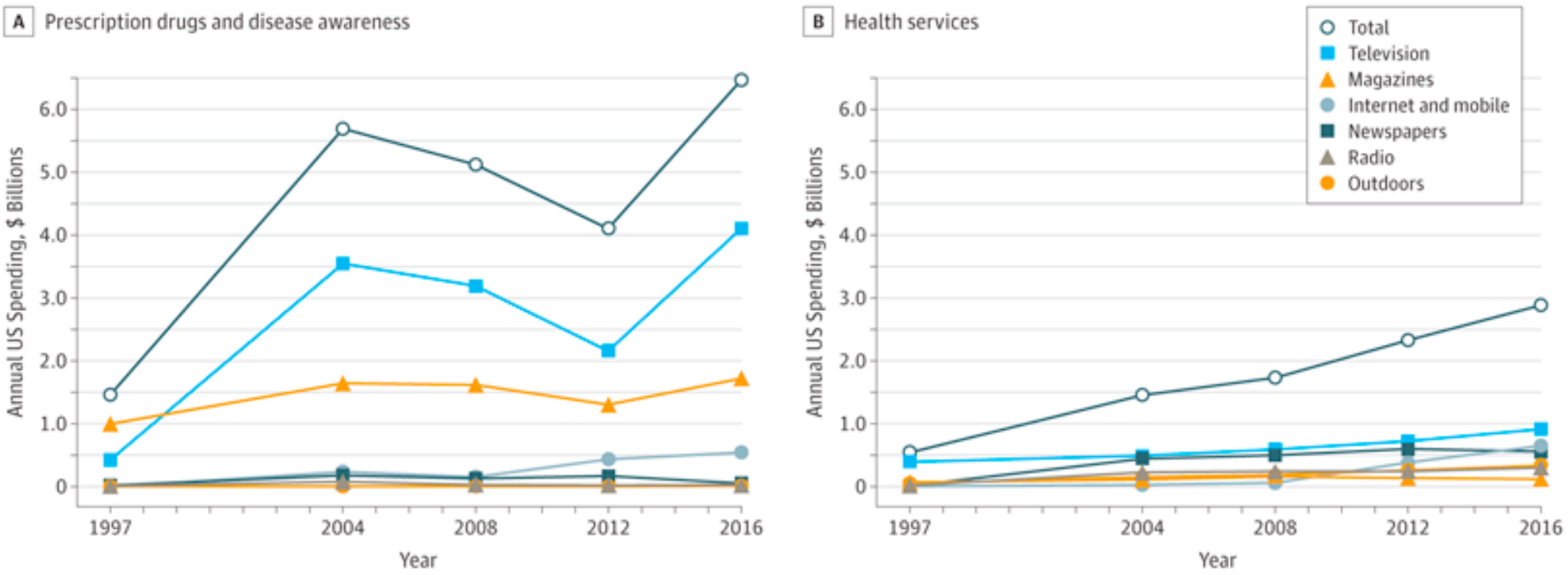
Medical Marketing in the United States, 1997-2016

Importance Manufacturers, companies, and health care professionals and organizations use an array of promotional activities to sell and increase market share of their products and services. These activities seek to shape public and clinician beliefs about laboratory testing, the benefits and harms of prescription drugs, and some disease definitions.

Objective To review the marketing of prescription drugs, disease awareness campaigns, health services, and laboratory tests and the related consequences and regulation in the United States over a 20-year period (1997-2016).

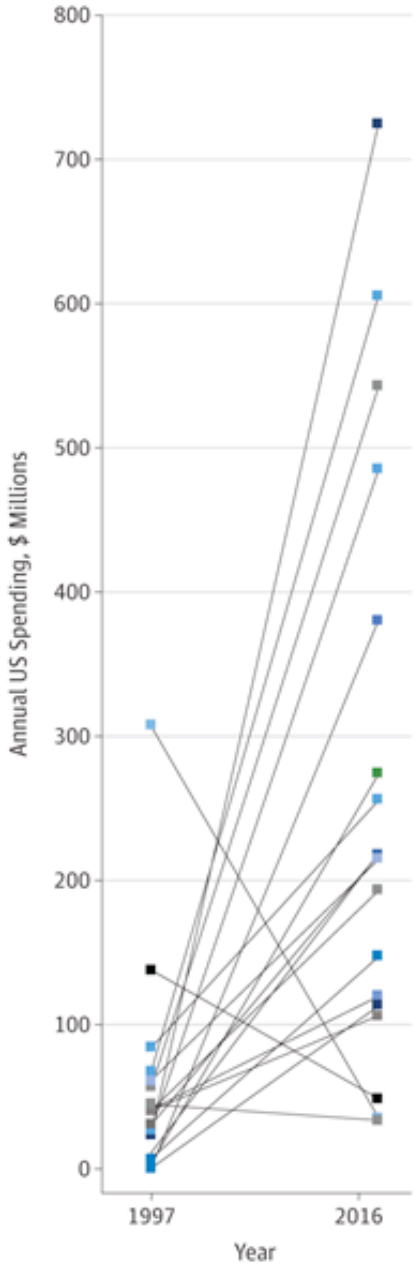
Findings From 1997 through 2016, spending on medical marketing of drugs, disease awareness campaigns, health services, and laboratory testing increased from $17.7 to $29.9 billion. The most rapid increase was in direct-to-consumer (DTC) advertising, which increased from $2.1 billion (11.9%) of total spending in 1997 to $9.6 billion (32.0%) of total spending in 2016. DTC prescription drug advertising increased from $1.3 billion (79 000 ads) to $6 billion (4.6 million ads [including 663 000 TV commercials]), with a shift toward advertising high-cost biologics and cancer immunotherapies. From 1997 through 2016, the number of consumer and professional drug promotional materials that companies submitted for FDA review increased from 34 182 to 97 252, while FDA violation letters for misleading drug marketing decreased from 156 to 11.





Direct-to-Consumer Advertising for Drugs and Health Services

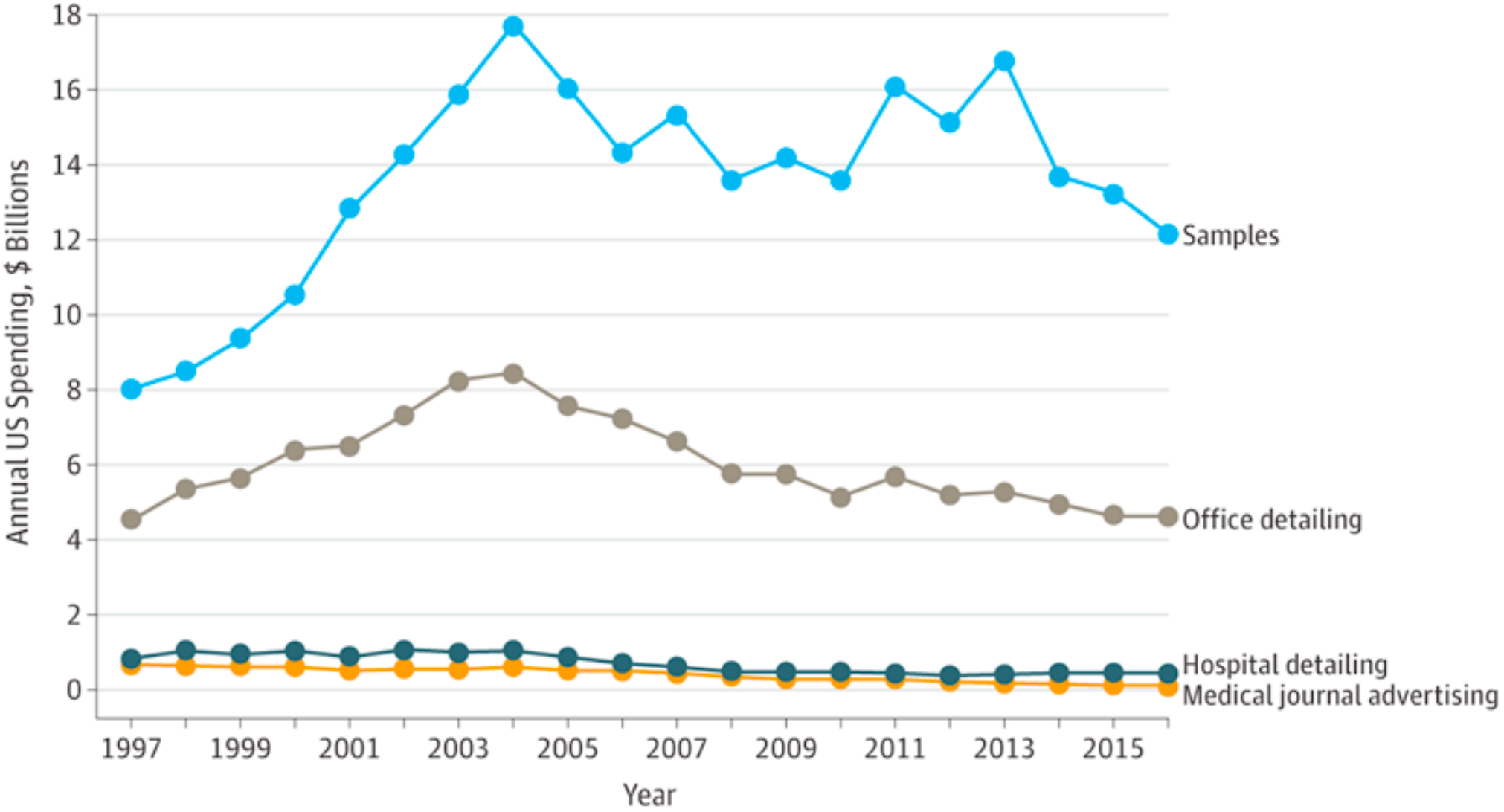
The outdoor category includes billboards and mass transit posters and banners.



Therapeutic Category	US Spending, $ Millions 1997	2016	Top Advertised Drugs 1997	2016
Diabetes/endocrine	23	725	Glucophage, Humalog, Glucotrol XL	Trulicity, Farxiga, Victoza
Dermatology	67	605	Sporanox, Lamisil, Differen	Cosentyx, Humira, Otezla
Pain/central nervous system	56	542	Imitrex	Lyrica, Tecfidera, Botox
Cardiac	0	379	Not applicable	Eliquis, Entresto, Xarelto
Arthritis	27	484	Naprelan, Lodine XL, Relafen	Xeljanz, Humir, Orencia
Cancer	3	274	Novladex, Zofran, Taxol	Opdivo, Keytruda, Ibrance
Respiratory	84	255	Accolate, Serevent, Flovent	Breo, Symbicort, Anoro, Ellipta
Immunology	11	218	Crixivan, Combivir, Norvir	Prevnar, Gardasil, Trumenba
Infection	30	217	Zithromax, Havrix, Denavir	Harvoni, Tamiflu, Neulasta
Gastrointestinal	61	215	Prilosec, Propulsid, Helidac	Humira, Xifaxan, Viberzi
Depression	40	193	Prozac, Serzone, Paxil	Pristiq, Rexulti, Trintellix
Impotence	7	147	Erecaid, Caverject	Viagra, Cialis, Erecaid
Contraception	41	119	Ortho Tri-Cyclen, Depo-Provera, Norplant	Nexplanon, Skyla, Paragard
Ophthalmology	0	113	Not applicable	Restasis, Xiidra, Ciprodex
Menopause	40	106	Prempro, Premarin, Climara	Premarin, Estring, Osphena
Cholesterol	138	48	Pravachol, Zocor	Praluent, Crestor, Repatha
Allergy	307	35	Allegra, Claritin, Zyrtec	EpiPen, Pazeo, Dymista
Osteoporosis	44	33	Fosamax, Miacalcin	Prolia, Forteo, Synvisc

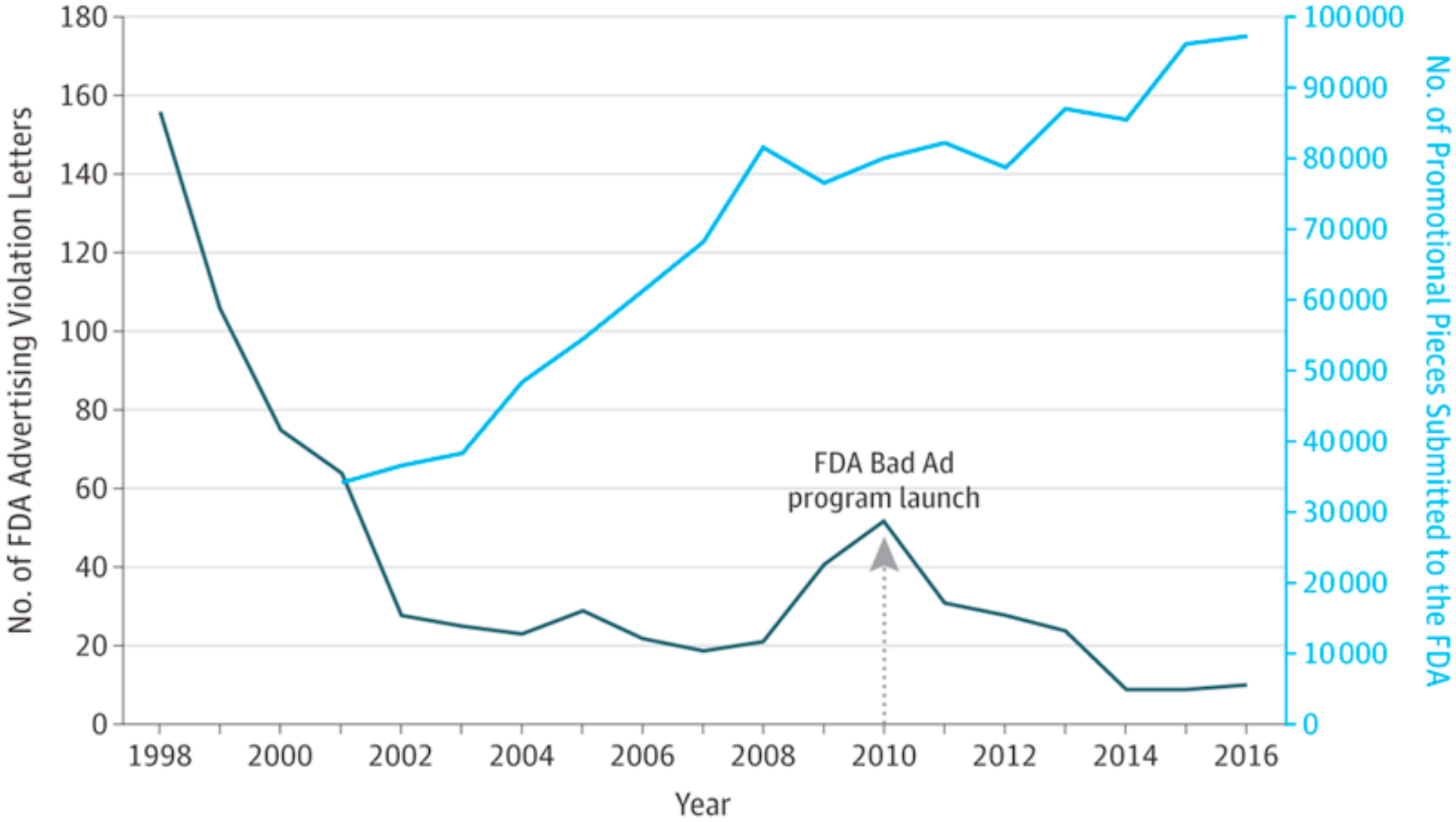
Direct-to-Consumer Drug Advertising by Therapeutic Category

Direct-to-Consumer Drug Advertising by Therapeutic Category



Professional Marketing for Prescription Drugs and Disease

IQVIA provided the yearly data, based on monthly, nationally representative audits of approximately 4000 office physicians in 19 specialties. Sample spending used suggested retail prices except for hospital detailing from 1997 to 2000 (IMS data reported by Kaiser Foundation). Spending for meetings and events was not included (reported to have declined from $2.1 million to $0.8 million between 2001 and 2010;



FDA Prescription Drug Advertising Violation Letters and Promotional Materials Submitted to the FDA

FDA (US Food and Drug Administration). The FDA Bad Ad program teaches prescribers and the public to identify and report misleading promotion.

Disease Awareness Campaigns

Companies often pay physicians to talk or learn about disease diagnosis or treatment. The opioid crisis highlights the potential risks of entangling industry in disease education. Company-sponsored disease awareness fostered an aggressive approach to chronic pain treatment including lower thresholds for opioid use in noncancer pain. In 1996, without supporting evidence, the American Academy of Pain Medicine and the American Pain Society, both substantially funded by opioid manufacturers, issued a consensus statement endorsing opioids for chronic noncancer pain, describing addiction risk as low. The American Pain Society also introduced pain as a fifth vital sign, which was adopted by the Department of Veterans Affairs and endorsed by the JCAHO, encouraging clinicians to screen all patients for pain along with measuring traditional vital signs.108 Between 1996 and 2001, Purdue Pharma (the manufacturer of Oxycontin) paid more than 5000 physicians, pharmacists, and nurses to attend speaker training conferences and sponsored more than 20 000 pain education programs.109 Opioid prescription sales and deaths quadrupled from 2000 to 2015.

Even accredited CME disease education can induce inappropriate diagnosis and treatment. For example, a Medscape-accredited CME program, “Unmasking ADHD in Adults,” funded by Shire (the manufacturer of Adderall), taught primary care physicians that diagnosis can be made in 6 minutes. After questioning, the psychiatrist who created the program reconsidered and repudiated the claim.

Key Points

Question How has the marketing of prescription drugs, disease awareness, health services, and laboratory tests in the United States changed from 1997 through 2016?
Findings From 1997 through 2016, medical marketing expanded substantially, and spending increased from $17.7 to $29.9 billion, with direct-to-consumer advertising for prescription drugs and health services accounting for the most rapid growth, and pharmaceutical marketing to health professionals accounting for most promotional spending.
Meaning There has been marked growth in expenditures on and extent of medical marketing in the United States from 1997 through 2016.

eBox. Strategies to Support Responsible Marketing and Reduce Adverse Consequences

Prescription drugs

Strengthen FDA regulation of promotion

Maintain FDA's jurisdiction over off-label promotion

Prohibit DTC advertising and limit detailing of: highly-addictive drugs, accelerated approvals prior to confirmation of clinical benefit and new drugs during the first few years on the market, institute "black triangle" for new drugs

Require advertising to highlight uncertainties and negative results

Consider banning company sponsored telemedicine visits to prescribe advertised drug

Limit industry influence on prescribing and increase transparency

Establish state'" and institution restrictions or bans on pharmaceutical company detailing visits and gifts to clinicians, and prohibit faculty participation on company speaker bureaus.

Accelerate public reporting of industry payments to physician assistants, nurse practitioners, nurses, pharmacists and patient assistance charities – not mandated to begin until 2022.

Disease awareness campaigns

Clarify regulation of disease awareness campaigns

Coordinate FDA and FTC processes and issue joint guidance for disease awareness campaigns addressing issues such as permissibility of symptom quizzes and scientific standards, fair balance – mention treatment harms, evidence standards for disease prevalence estimates, prominence of company sponsorship.

Reliably tagging awareness websites with "Ad" in search engines.

Establish criteria for trustworthy disease definitions

Adopt National Academy of Medicine and Guidelines International Network[109] principles for trustworthy guidelines in setting quality criteria for new or modified disease definitions by experts without financial conflicts of interest

Health services

Increase awareness of – and surveillance for - "Bad Ads"

Initiate programs such as FDA's Bad Ad initiative for drugs to encourage clinicians and consumers to report misleading health services (or laboratory test) advertisements to FTC and state Attorneys General

Establish proactive review of hospital advertisements by the Joint Commission

Better self-regulation by academic medical centers and hospitals

Encourage "Truth in advertising" pledges by marketing departments and require submission of advertisements (including co-branded ads) to the local IRB or a third-party reviewer for independent assessment prior to dissemination

Laboratory tests

Clarify and enforce regulations about laboratory test approval

Finalize and implement new FDA policy for premarket approval of moderate-to-high risk LDTs to establish reproducibility and predictive value, and monitor for serious adverse events.

Approve individual tests not laboratories (i.e., do not grant "precertification" exemptions after first test approved).

Set and enforce promotional standards`

Issue FDA guidance establishing standards for promotional materials including mention of supporting evidence (e.g. "[Test] approved by FDA based on accuracy – not been shown to improve outcomes"), harms (e.g., false positives or negatives), extent of FDA review, major evidence-based guideline recommendations (e.g. Preventive Services Task Force), and substantiating clinical utility - for tests making health claims.

Enforce regulations forbidding promotional materials for pharmacogenetic tests to claim or imply a clinical benefit unless supported by sufficient evidence noted in the approved label.

Require companies promoting unapproved physician-ordered LDTs to disclose clinician or hospital payments

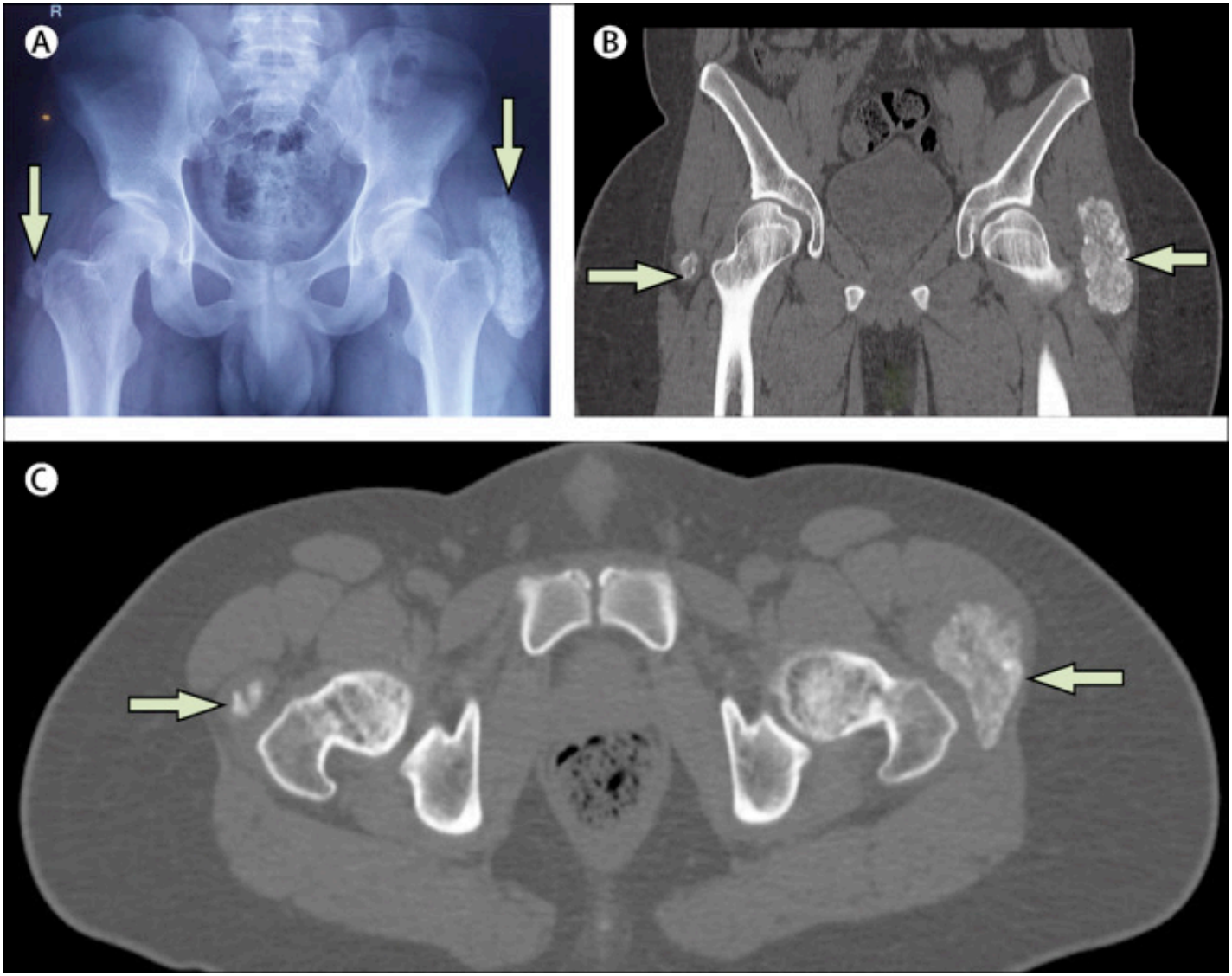
Professional organizations should discourage physicians from being paid to prescribe advertised tests and require physicians identified through companies to disclose to patients how they are being paid

Hyperphosphataemic tumoral calcinosis

An 18-year-old man presented to our department with a 1-year history of pain in the region of his left hip and difficulty in squatting. He reported no history of any local trauma. There was no history suggestive of an autoimmune disorder. Clinical examination found a tender, hard mass in the left greater trochanteric region with painful, restricted rotation and abduction movements of the hip. Both his medical history and family history were unremarkable.

Plain x-ray and CT scans of the pelvis showed bilateral—left greater than the right—and periarticular, lobulated, calcific, soft tissue masses. Serum urea, creatinine, uric acid, total calcium, alkaline phosphate, and parathyroid hormone concentrations were normal. However, serum inorganic phosphorus was elevated at 2·10 mmol/L (normal range 0·81–1·45 mmol/L). The ratio of the renal tubular maximum reabsorption rate of phosphate to corrected glomerular filtration rate was also elevated at 2·16 mmol/L (normal range 1·07–1·89 mmol/L), suggestive of increased renal tubular phosphate reabsorption.
Considering the patient's age, presence of bilateral, and periarticular soft tissue, calcific masses about the hip, hyperphosphataemia with increased tubular phosphate reabsorption, and the absence of indications that the ectopic calcification was secondary to any other causes, the patient was diagnosed with hyperphosphataemic tumoral calcinosis.

The symptomatic, left-sided mass was surgically excised: during the operation it appeared as a cystic mass containing chalky white material. Histological examination showed amorphous and granular calcified material surrounded by histiocytic and giant cell reaction—confirming the diagnosis. Postoperatively, attempts were made to lower the patient's blood phosphate concentration using a combination of a phosphate-restricted diet with less than 800 mg/day tablets of the non-calcium-based phosphate binder, sevelamer hydrochloride—which binds phosphate in the intestine, and oral acetazolamide to induce phosphaturia.



X-ray (A) and CT scans (B and C) of pelvis show bilateral periarticular calcific masses (green arrows) around the hip.

Hyperphosphatemic Familial Tumoral Calcinosis (FGF23, GALNT3, αKlotho)

Familial Tumoral calcinosis (TC) is a rare disorder distinguished by the development of ectopic and vascular calcified masses that occur in settings of hyperphosphatemia (hFTC) and normophosphatemia (nFTC). Serum phosphorus concentrations are relatively tightly controlled by interconnected endocrine activity at the level of the intestine, kidney, and skeleton. Discovering the molecular causes for heritable forms of hFTC has shed new light on the regulation of serum phosphate balance. This review will focus upon the genetic basis and clinical approaches for hFTC, due to genes that are related to the phosphaturic hormone Fibroblast growth factor-23 (FGF23). These include FGF23 itself, an FGF23-glycosylating enzyme (GALNT3), and the FGF23 co-receptor α-Klotho (αKL). Our understanding of the molecular basis of hFTC will, in the short term, aid in understanding normal phosphate balance, and in the future, provide potential insight into the design of novel therapeutic strategies for both rare and common disorders of phosphate metabolism.

GALNT family transfers an N-acetyl galactosamine to the hydroxyl group of a serine or threonine residue in the first step of O-linked oligosaccharide biosynthesis.

Mutations in *FGF23*, GALNT3 and α*KL*

Syndrome	Gene	Mutation	Protein
hFTC	*FGF23*	123c>a	H41Q
hFTC	*FGF23*	160c>a	Q54K
hFTC	*FGF23*	287t>c	M96T
hFTC	*FGF23*	211a>g	S71G
hFTC	*FGF23*	367g>t	G123W
hFTC	*FGF23*	385t>c	S129P
hFTC	*FGF23*	386c>t	S129F
HHS	*GALNT3*	2t>a	M1K
hFTC	*GALNT3*	41–58del	R14fsX21
hFTC	*GALNT3*	484c>t	R162X
hFTC	*GALNT3*	485g>a	R162Q
hFTC	*GALNT3*	516-2a>t	(Splice Site)
hFTC	*GALNT3*	677delC	A226VfsX3
hFTC	*GALNT3*	815c>a	T272K
HHS	*GALNT3*	803_804insC	A268fsX271
HHS	*GALNT3*	839g>a	C280Y
hFTC	*GALNT3*	842a>g	E281G
hFTC	*GALNT3*	966t>a	Y322X
hFTC	*GALNT3*	1076c>a	T359K
hFTC	*GALNT3*	1097t>g	L366R
hFTC	*GALNT3*	1102_1103inst	E375X
hFTC	*GLANT3*	1245t>a	H415Q
hFTC	*GALNT3*	1312c>t	R438C
HHS	*GALNT3*	1313g>a	R438H
hFTC	*GALNT3*	1387a>t	K463X
HHS	*GALNT3*	1392+1g>a	(Splice Site)