The NEW ENGLAND JOURNAL of MEDICINE

Perspective

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# Naked

Atul Gawande, M.D., M.P.H.

There is an exquisite and fascinating scene in *Kandahar*, a movie set in Afghanistan under the Taliban regime, in which a male physician is asked to examine a female patient. They are separated by an opaque screen. Behind it, the woman is covered from head to toe by her burka. The two do not talk directly to each other. The patient's young son serves as the go-between. She has a stomachache, he says.

"Does she throw up her food?" the doctor asks.

"Do you throw up your food?" the boy asks.

"No," the woman says, perfectly audibly, but the doctor waits as if he has not heard.

"No," the boy tells him.

For the exam, the doctor has cut a two-inch circle in the screen. "Tell her to come closer," he says. The boy does. She brings her mouth to the opening, and through it he looks inside. "Have her bring her eye to the hole," he says. And so the exam goes. Such, apparently, can be the demands of decency.

When I started my surgical practice two years ago, I was not at all clear about what my own etiquette of examination should be. Expectations are murky; we have no clear standards in the United States; and the topic can be fraught with hazards. Physical examination is deeply intimate, and the way a doctor deals with the naked body — particularly when the doctor is male and the patient female — inevitably raises questions of propriety and trust.

No one anywhere seems to have discovered the ideal approach. A surgical colleague who practices in Iraq told me about the customs of physical examination there. He said he feels no hesitation about examining female patients completely when necessary, but because a doctor and a patient of opposite sex cannot be alone together without eyebrows being raised, a family member will always accompany them for the exam. Women do not remove their clothes or change into a gown for the exam, and only a small portion of the body is uncovered at any one time. A nurse, he said, is rarely asked to chaperone: if the doctor is female, it is not necessary, and if male, the family is there to ensure that nothing unseemly occurs.

In Caracas, according to a Venezuelan doctor I met, female patients virtually always have a chaperone for a breast or pelvic exam, whether the physician is male or female. "That way there

are no mixed messages," the doctor said. The chaperone, however, must be a medical professional. So the family is sent out of the examination room, and a nurse brought in. If a chaperone is unavailable or has refused to participate, the exam is not done.

A Ukrainian internist told me that she has not heard of doctors in Kiev using a chaperone. If a family member is present, he or she will be asked to leave. Both patient and doctor wear their uniforms — the patient a white examining gown, the doctor a white coat. Last names are always used. There is no effort at informality to muddy the occasion. This practice, she believes, is enough to solidify trust and preclude misinterpretation of the conduct of care.

A doctor, it appears, has a range of options.

In 2003, I set up my clinic hours, and soon people arrived to see me. I was, I realized, for the first time genuinely alone with patients. No attending physician in the room or getting ready to come in; no bustle of emergency room personnel on the other side of a curtain. Just a patient and me. We'd sit down. We'd talk. I'd ask about whatever had occasioned the visit, about past medical problems, medications, the family and social history. Then the time would come to have a look.

There were, I will admit, some awkward moments. I had an instinctive aversion to examination gowns. At our clinic they are made of either thin, ill-fitting cloth or thin, ill-fitting paper. They seem designed to leave patients exposed and cold. I decided to examine my patients while they were in their street clothes. If a patient with gallstones wore a shirt she could untuck for the abdominal exam, this worked fine. But then I'd encounter a patient in stockings and a dress, and the next thing I knew, I had her dress bunched up around her head, her tights around her knees,

and both of us wondering what the hell was going on. An exam for a breast lump one could manage, in theory: the woman could unhook her brassiere and lift or unbutton her shirt. But in practice, it just seemed weird. Even checking pulses could be a problem. Pant legs could not be pushed up high enough. Try pulling them down over shoes, however, and . . . forget it. I finally began to have patients change into the damn gowns. (I haven't, however, asked men to do so nearly as often as women.)

As for having a chaperone present with female patients, I hadn't settled on a firm policy. I found that I always asked a medical assistant to come in for pelvic exams and generally didn't for breast exams. I was completely inconsistent about rectal exams.

I surveyed my colleagues about what they do and received a variety of answers. Many said they bring in a chaperone for all pelvic and rectal exams — "anything below the waist" — but only rarely for breast exams. Others have a chaperone for breast and pelvic exams but not for rectal exams. Some did not have a chaperone at all. Indeed, an obstetrician–gynecologist estimated that about half the male physicians in his department do not routinely use a chaperone. He himself detests the word "chaperone" because it implies that mistrust is warranted, but he offers to bring in an "assistant" for pelvic and breast exams. Few of his patients, however, find the presence of the assistant necessary after the first exam, he said. If the patient prefers to have her sister, boyfriend, or mother stay for the exam, he does not object — but he is under no illusion that a family chaperone offers protection against an accusation of misconduct. Instead, he relies on his reading of a patient to determine whether bringing in a nurse–witness would be wise.

One of our residents, who was trained partly in London, said he found the selectivity here strange. "In Britain, I would never examine a woman's abdomen without a nurse present. But in the emergency room here, when I asked to have a nurse come in when I needed to do a rectal exam or check groin nodes on a woman, they thought I was crazy. 'Just go in there and do it!' they said." In England, he said, "if you need to do a breast or rectal exam or even check femoral pulses, especially on a young woman, you would be either foolish or stupid to do it without a chaperone. It doesn't take much — just one patient complaining, 'I came in with a foot pain and the doctor started diving around my groin,' and you could be suspend-

ed for a sexual-harassment investigation."

Britain's standards are stringent: the General Medical Council, the Royal College of Physicians, and the Royal College of Obstetricians and Gynaecologists specify that a chaperone must be offered to all patients who undergo an "intimate exam" (i.e., involving the breasts, genitalia, or rectum), irrespective of the sex of the patient or of the doctor.[1,2] A chaperone must be present when a male physician performs an intimate exam of a female patient. The chaperone should be a female member of the medical team, and her name should be recorded in the notes. If the patient refuses a chaperone and the examination is not urgent, it should be deferred until it can be performed by a female physician.

In the United States, we have no such guidelines. As a result, our patients have little idea of what to expect from us. To be sure, some minimal standards have been established. The Federation of State Medical Boards has spelled out that touching a patient's breasts or genitals for a purpose other than medical care is a disciplinable offense. So are oral contact with a patient, encouraging a patient to masturbate in one's presence, and providing services in exchange for sexual favors. Sexual impropriety — which involves no touching but is no less proscribed — includes asking a patient for a date, criticizing a patient's sexual orientation, making sexual comments about the patient's body or clothing, and initiating discussion of one's own sexual experiences or fantasies.[3] I can't say anyone taught me these boundaries in medical school, but I would like to think that no one needed to.

The difficulty for those of us who do not behave badly is that medical exams remain inherently ambiguous. Any patient can be led to wonder: Did the doctor really need to touch me there? Even when doctors simply inquire about patients' sexual history, can anyone be certain of the intent? The fact that all medical professionals have blushed or found their thoughts straying during a patient visit reveals the potential for impropriety in any encounter.

The tone of an office visit can turn on a single word, a joke, a comment about a tattoo in an unexpected place. One surgeon told me of a young patient who expressed concern about a lump in her "boob." But when he used the same word in response, she became extremely uncomfortable and later made a complaint. Another woman I know left her gynecologist after he made an offhand, probably inadvertent, but admiring comment about her tan lines during a pelvic exam.

The examination itself — the how and where of the touching — is, of course, the most potentially dicey territory. If a patient even begins to doubt the propriety of what a doctor is doing, something is not right. So what then should our customs be?

There are many reasons to consider setting tighter, more uniform professional standards. One is to protect patients from harm. About 4 percent of the disciplinary orders that state medical boards issue against physicians are for sex-related offenses. One of every 200 physicians is disciplined for sexual misconduct with patients sometime during his or her career.[4] Some of these cases involve such outrageous acts as having intercourse with patients during pelvic exams. The vast majority of cases involved male physicians and female patients, and virtually all occurred without a chaperone present.[5] About one third of cases studied in one state involved actual sexual intercourse with patients; two thirds involved sexual impropriety or inappropriate touching short of sexual contact. Another goal might be to reduce false accusations arising from misinterpretation.

Nonetheless, eliminating misconduct and accusations would be the wrong aim to guide medical care. The trouble is not that such acts are rare (though the statistics suggest they are), nor that total prevention — zero tolerance — is impossible. It is that, at some point, the measures required to achieve total prevention will approach the Talibanesque and harm care of patients.

Embracing more explicit standards for medical encounters, however, might actually improve relationships with patients — and that does stand as a worthy goal. The new informality of medicine — with white coats disappearing, and patient and doctor sometimes on a first-name basis — has blurred boundaries that once guided us. If physicians are unsure about what is appropriate behavior for themselves, is it any surprise that patients are, too? Or that misinterpretation can occur? We have jettisoned our old customs but have not bothered to replace them.

My father, a urologist, has thought carefully about how to avert such uncertainties. From the start, he felt the fragility of his standing as an outsider, an Indian immigrant practicing in a rural Ohio town. In the absence of guidelines to reassure patients

that what he does as a urologist is routine, he has made painstaking efforts to avoid question.

The process begins before the exam. He always arrives in a tie and white coat. He is courtly. Although he often knows patients socially and doesn't hesitate to speak with them about personal matters (the subjects can range from impotence to sexual affairs), he keeps his language strictly medical. If a female patient must put on a gown, he steps out while she undresses. He makes a point of explaining what he is going to do during the examination and why. If the patient lies down and needs further unzipping or unbuttoning, he is careful not to help. He wears gloves even for abdominal examinations. If the patient is female or under 18 years of age, then he brings in a nurse as a chaperone, whether the exam is "intimate" or not.

His approach has succeeded. I grew up knowing many of his patients, and they trust him completely. I find, however, that some of his practices do not seem quite right for me. My patients are as likely to have problems above the waist as below, and having a chaperone present for a routine abdominal exam or a check of groin pulses feels to me absurd. I don't don gloves for nongenital exams. Nonetheless, I have tried to emulate the spirit of my father's visits — the decorum in language and attire, the respect for modesty, the precision of examination. As I think further about his example, it has also led me to make some changes: I now uniformly use an assistant not just for pelvic exams but also for rectal exams of female patients and as patients desire, for breast exams as well. For the comfort and reassurance of patients, these seem to be reasonable customs, even expectations, for more of us to accept.

A professor once told my medical school class that patients can tell when you've seen a thousand naked patients and when you haven't. I now know that's true. But I have also come to recognize that no patient has seen a thousand doctors. They therefore have little idea, coming to a doctor's office, of what is "normal" and what is not. This we can change.

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**1.** Intimate examinations. London: General Medical Council Standards Committee, December 2001.
**2.** Gynaecological examinations: guidelines for specialist practice. London: Royal College of Obstetricians and Gynaecologists, July 2002.
**3.** Ad Hoc Committee on Physician Impairment. Report on sexual boundary issues. Dallas: Federation of State Medical Boards of the United States, April 1996.
**4.** Dehlendorf CE, Wolfe SM. Physicians disciplined for sex-related offenses. JAMA 1998; 279:1883-8.
**5.** Enbom JA, Thomas CD. Evaluation of sexual misconduct complaints: the Oregon Board of Medical Examiners, 1991 to 1995. Am J Obstet Gynecol 1997;176:1340-8.

# Medical Marijuana and the Supreme Court

Susan Okie, M.D.

Angel McClary Raich, a California woman at the center of the recent Supreme Court case on medical marijuana, hasn't changed her treatment regimen since the Court ruled in June that patients who take the drug in states where its medicinal use is legal are not shielded from federal prosecution. A thin woman with long, dark hair and an intense gaze, Raich takes marijuana, or cannabis as she prefers to call it, about every two waking hours — by smoking it, by inhaling it as a vapor, by eating it in foods, or by applying it topically as a balm. She says that it relieves her chronic pain and boosts her appetite, preventing her from becoming emaciated because of a mysterious wasting syndrome. Raich and her doctor maintain that without access to the eight or nine pounds of privately grown cannabis that she consumes each year, she would die.

Although Raich has embraced a public role advocating the medicinal use of marijuana, she says that her health suffered during the hectic days following the announcement of the Court's decision, when a whirlwind schedule of press conferences and congressional meetings in Washington prevented her from medicating herself with cannabis as regularly as she needed to. "My body was shutting down on me," she said in an interview from her Oakland home last month. "I'm scared of my health failing. I'm scared of the federal government coming in and doing more harm. [Recently,] the city of Oakland warned there were going to be some raids" on marijuana dispensaries. "We're all just waiting. Sitting on the frontline is extremely stressful."

In the Supreme Court case

*Gonzales* v. *Raich*, the justices ruled 6 to 3 that the federal government has the power to arrest and prosecute patients and their suppliers even if the marijuana use is permitted under state law, because of its authority under the federal Controlled Substances Act to regulate interstate commerce in illegal drugs. In practical terms, it is not yet clear what effect the Court's decision will have on patients. An estimated 115,000 people have obtained recommendations for marijuana from doctors in the 10 states that have legalized the cultivation, possession, and use of marijuana for medicinal purposes. Besides California, those states are Alaska, Colorado, Hawaii, Maine, Montana, Nevada, Oregon, Vermont, and Washington. (Three weeks after the decision was announced, Rhode Island's legislature passed a similar law and soon afterward overrode a veto by the state's governor.)

**Vaporizer System for the Administration of Marijuana.**

The cannabis is placed in the chamber and heated to a temperature below that required for combustion. The balloon fills with vapor that contains the active ingredients without the tar or particulates thought to be responsible for most of the drug's adverse effects on the respiratory tract. The patient inhales the vapor from the balloon.

Photo courtesy of Storz and Bickel.

Immediately after the news of the high court's ruling, attorneys general in the states that have approved the use of medical marijuana emphasized that the practice remained legal under their state laws, and a telephone survey of a random national sample of registered voters, commissioned by the Washington-based Marijuana Policy Project, indicated that 68 percent of respondents opposed federal prosecution of patients who use marijuana for medical reasons. Nationally, most marijuana arrests are made by state and local law-enforcement agencies, with federal arrests accounting for only about 1 percent of cases. However, soon after the decision was announced, federal agents raided 3 of San Francisco's more than 40 medical marijuana dispensaries. Nineteen people were charged with running an international drug ring; they allegedly were using the dispensaries as a front for trafficking in marijuana and in the illegal amphetamine "ecstasy."

In California, the raids were widely viewed as a signal that federal drug-enforcement agents intended to crack down on abuse of the state's medical marijuana program. California has an estimated 100,000 medical marijuana users. Its 1996 law grants doctors much greater latitude in recommending the drug than do similar laws in other states, and the U.S. District Court for the Northern District of California ruled in 2000 that doctors who prescribe marijuana are protected from federal prosecution under the First Amendment, provided that they do not help their patients obtain the drug. In San Francisco, some journalists or investigators who posed as patients have reported that they had little difficulty obtaining a recommendation for medical marijuana, which allows the holder to purchase the drug from a dispensary. "We're empathetic to the sick," the Drug Enforcement Administration's Javier Pena told reporters after the raids, "but we can't disregard the federal law."[1]

Even before the Supreme Court decision, many Californians had been calling for stricter state regulation of medical marijuana. Some cities have banned marijuana dispensaries, and many counties and cities — including San Francisco — have imposed moratoriums on the opening of new ones. Some local jurisdictions register and issue identification cards to patients who use marijuana for medical reasons, and state officials have been working on a voluntary statewide registration program. However, the officials recently put the program on hold, citing concern that the issuance of identification cards to patients might put state health officials at risk of prosecution for aiding a federal crime and that federal drug-enforcement agents might seek state records in order to identify medical marijuana users. Registration of patients and the issuance of identification cards by the state are required in seven other states that have legalized the medical use of marijuana; patients can show the card as a defense against arrest by local or state police for possession of the drug. Maine and Washington do not issue identification cards to patients.

Conditions for which marijuana is commonly recommended include nausea caused by cancer

chemotherapy; anorexia or wasting due to cancer, AIDS, or other diseases; chronic pain; spasticity caused by multiple sclerosis or other neurologic disorders; and glaucoma. Frank Lucido, a Berkeley family practitioner who is Raich's doctor, said that so far, the Court ruling appears to have had little effect on his patients who use medical marijuana. About 30 percent of Lucido's practice consists of evaluating patients who want a recommendation for the drug. He said in an interview that he will not issue such a recommendation unless a patient has a primary care physician and has a condition serious enough to require follow-up at least annually. About 80 percent of his patients who use medical cannabis have chronic pain; a smaller number take the drug for muscle spasms, mood disorders, migraine, AIDS, or cancer. "My patients probably average in their 30s," Lucido said. "I have had probably five patients who are under 18. These are people with serious illnesses, where parents were very clear that this would be a good medication for them."

Peter A. Rasmussen, an oncologist in Salem, Oregon, said he discusses the option of trying marijuana with about 1 in 10 patients in his practice. "It's not my first choice for any symptom," he said in an interview. "I only talk about it with people if my first-line treatment doesn't work." Rasmussen said marijuana has helped stimulate appetite or reduce nausea in a number of his patients with cancer, but others have been distressed by its psychological effects. Some express interest in trying marijuana but have difficulty getting the drug. "Most of my patients who use it, I think, just buy the drug illegally," he said. "But a lot of my patients, they're older, they don't know any kids, they don't hang out on the street. They just don't know how to get it."

Clinical research on marijuana has been hampered by the fact that the plant, which contains dozens of active substances, is an illegal drug classified as having no legitimate medical use. Researchers wishing to do clinical studies must first get government permission and obtain a supply of the drug from the National Institute on Drug Abuse. In a report published in 1999, an expert committee of the Institute of Medicine expressed concern about the adverse health effects of smoking marijuana, particularly on the respiratory tract. The report called for expanded research on marijuana's active components, known as cannabinoids, including studies to explore the chemicals' potential therapeutic effects and to develop safe, reliable, rapid-onset delivery systems. It also recommended short-term clinical trials of marijuana "in patients with conditions for which there is reasonable expectation of efficacy."[2]

There has been some progress toward those goals. The Center for Medicinal Cannabis Research (CMCR), a three-year research initiative established in 1999 by the California state legislature, has funded several placebo-controlled clinical trials of smoked marijuana to treat neuropathic pain, pain from other causes, and spasticity in multiple sclerosis, and the results are likely to be available soon. The National Institute on Drug Abuse provided both the active marijuana and the "placebo," a smokable version of the drug from which dronabinol ($\Delta^9$-tetrahydrocannabinol, or THC) and certain other active constituents had been removed. "It's like decaf coffee or nicotine-free cigarettes, and it tastes the same [as marijuana]," said Igor Grant, a professor of psychiatry at the University of California, San Diego, and director of the CMCR. He said additional studies of the whole plant, as well as its individual components, are still needed. "It's still the case that we don't know which components of botanical marijuana have beneficial effects, if any," he said.

In an open-label trial, oncologist Donald I. Abrams of the University of California, San Francisco, found evidence of marijuana's effectiveness in the treatment of neuropathic pain among HIV-infected patients and has just finished a placebo-controlled trial that he intends to publish soon. Abrams has also shown that cannabinoids that are smoked or taken orally do not adversely affect drug treatment of HIV,[3] and he is completing a study that compares blood levels of cannabinoids among volunteers who inhaled vaporized marijuana with similar levels among volunteers who smoked the drug. Vaporizers heat the drug to a temperature below that required for combustion, producing vapor that contains the active ingredients without the tar or particulates thought to be responsible for most of the drug's adverse effects on the respiratory tract.

Meanwhile, a new marijuana-derived drug is on the Canadian market and may soon be considered for approval by the Food and Drug Administration. Sativex, a liquid cannabis extract that is sprayed under the tongue, was approved in Canada in June for the treatment of neuropathic pain in multiple sclerosis. Its principal active ingredients are dronabi-

nol and cannabidiol, which are believed to be the primary active components of marijuana. The drug's manufacturer, GW Pharmaceuticals of Britain, is also testing it for cancer pain, rheumatoid arthritis, postoperative pain, and other indications. Marinol, a synthetic version of dronabinol supplied in capsules, is approved in the United States for chemotherapy-associated nausea and for anorexia and wasting among patients with AIDS.

On the day the Supreme Court ruling was announced, John Walters, President George W. Bush's "drug czar," issued a statement declaring, "Today's decision marks the end of medical marijuana as a political issue. . . . We have a responsibility as a civilized society to ensure that the medicine Americans receive from their doctors is effective, safe, and free from the pro-drug politics that are being promoted in America under the guise of medicine." Nine days later, the House of Representatives, for the third year in a row, defeated a measure that would have prevented the Justice Department from spending money to prosecute medical marijuana cases under federal law.

Nevertheless, marijuana advocates insist that the long-running battle between federal and state governments over the medicinal use of marijuana is far from over. Activists next plan to focus on getting more states to pass laws legalizing medical marijuana, according to Steve Fox, former director of government relations for the Marijuana Policy Project.

It is surprising that the Supreme Court decision does not necessarily spell the end even of Angel Raich's legal case. Raich and another California patient, Diane Monson, who initially sued to prevent the Justice Department from prosecuting them or their suppliers, won a favorable ruling in 2003 from California's Court of Appeals for the Ninth Circuit. The Supreme Court's reversal now sends their case back to that court. Raich said that she, Monson, and their attorneys will ask the appeals court judges to consider other legal arguments, such as whether prosecuting patients who use marijuana to relieve pain violates their right to due process of law. "Previous decisions have established that there is a fundamental right to preserve one's life and avoid needless pain and suffering," explained Boston University's Randy Barnett, a constitutional lawyer who argued the women's case before the Supreme Court. "Federal restriction on accessibility to medical cannabis is an infringement" on that right, he said.

Raich vowed to continue her personal battle. "I'm stubborn as heck, so I don't plan to give it up that easily. I plan to fight until I can't fight anymore," she said.

Dr. Okie is a contributing editor of the *Journal*.

**An interview with Dr. Donald Abrams can be heard at www.nejm.org.**

**1.** Finz S. 19 Named in medicinal pot indictment. San Francisco Chronicle. June 24, 2005:B4.

**2.** Joy JE, Watson SJ, Benson JA, eds. Marijuana and medicine: assessing the science base. Washington, D.C.: National Academy Press, 1999.

**3.** Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Ann Intern Med 2003;139:258-66.

# THIS WEEK *in the* JOURNAL

ORIGINAL ARTICLE

## Comparison of Sirolimus-Eluting and Paclitaxel-Eluting Stents

Sirolimus-eluting stents and paclitaxel-eluting stents both reduce the risk of restenosis after percutaneous coronary intervention as compared with bare-metal stents. In a randomized trial, the two types of drug-eluting stents were compared in patients undergoing revascularization. The sirolimus-eluting stents were associated with fewer major adverse cardiac events at nine months, primarily as a result of reductions in the rates of clinical and angiographic restenosis.

SEE P. 653; EDITORIAL, P. 724; CME, P. 747

ORIGINAL ARTICLE

## Paclitaxel-Eluting Stents Compared with Sirolimus-Eluting Stents in Diabetic Patients

Drug-eluting coronary-artery stents are more effective than bare-metal stents in reducing the frequency of coronary restenosis in patients with diabetes. In a randomized, controlled trial in patients with diabetes, the sirolimus-eluting stent was associated with a smaller extent of late luminal loss than was the paclitaxel-eluting stent, suggesting that the risk of restenosis was also reduced.

SEE P. 663; EDITORIAL, P. 724

SPECIAL ARTICLE

## Sex and Racial Differences in the Management of Acute Myocardial Infarction, 1994–2002

This study compared treatments and outcomes after myocardial infarction according to sex and race from 1994 through 2002. As compared with white men, black men and both white and black women had lower rates of reperfusion therapy and coronary angiography, and black women had higher mortality. Sex and racial differences did not change substantially between 1994 and 2002.

SEE P. 671; EDITORIAL, P. 727

SPECIAL ARTICLE

## Racial Trends in the Use of Major Procedures among the Elderly

More than a decade ago, it was established that there were significant differences in the rates of major surgical procedures between blacks and whites. These investigators examined nine surgical procedures and found that the racial differences noted in 1992 persisted in 2001.

SEE P. 683; EDITORIAL, P. 727

SPECIAL ARTICLE

## Trends in the Quality of Care and Racial Disparities in Medicare Managed Care

In this study examining trends from 1997 to 2003 for white patients and black patients enrolled in Medicare managed care, performance on all nine quality measures improved for both blacks and whites, and racial disparities narrowed for seven of the nine measures. These findings suggest that efforts to improve care for all patients result in reductions in racial disparities.

SEE P. 692; EDITORIAL, P. 727

MEDICAL PROGRESS

## Soft-Tissue Sarcomas in Adults

Soft-tissue sarcomas have traditionally been managed by wide excisional surgery and radiotherapy, with chemotherapy reserved for advanced disease. However, advances in multidisciplinary care have improved the evaluation and treatment of patients with this uncommon tumor. Limb-conserving surgery, superior radiotherapy delivery, and novel adjuvant agents for specific tumors are now available. This article reviews the current understanding and treatment of soft-tissue sarcoma, with an emphasis on recent advances.

SEE P. 701; CME, P. 745

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## A Man with Prolonged Fever and Weight Loss

A 40-year-old man was admitted to the hospital because of fever and weight loss of two months' duration. He had been well until an episode of gastroenteritis, after which daily fever, anorexia, and weight loss developed. A laparoscopic appendectomy was performed, but symptoms persisted. Repeated imaging showed occlusion of the portal vein.

SEE P. 713; CME, P. 746

The NEW ENGLAND JOURNAL of MEDICINE

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# Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization

Stephan Windecker, M.D., Andrea Remondino, M.D., Franz R. Eberli, M.D., Peter Jüni, M.D., Lorenz Räber, M.D., Peter Wenaweser, M.D., Mario Togni, M.D., Michael Billinger, M.D., David Tüller, M.D., Christian Seiler, M.D., Marco Roffi, M.D., Roberto Corti, M.D., Gabor Sütsch, M.D., Willibald Maier, M.D., Thomas Lüscher, M.D., Otto M. Hess, M.D., Matthias Egger, M.D., and Bernhard Meier, M.D.*

## ABSTRACT

### BACKGROUND

Sirolimus-eluting stents and paclitaxel-eluting stents, as compared with bare-metal stents, reduce the risk of restenosis. It is unclear whether there are differences in safety and efficacy between the two types of drug-eluting stents.

### METHODS

We conducted a randomized, controlled, single-blind trial comparing sirolimus-eluting stents with paclitaxel-eluting stents in 1012 patients undergoing percutaneous coronary intervention. The primary end point was a composite of major adverse cardiac events (death from cardiac causes, myocardial infarction, and ischemia-driven revascularization of the target lesion) by nine months. Follow-up angiography was completed in 540 of 1012 patients (53.4 percent).

### RESULTS

The two groups had similar baseline clinical and angiographic characteristics. The rate of major adverse cardiac events at nine months was 6.2 percent in the sirolimus-stent group and 10.8 percent in the paclitaxel-stent group (hazard ratio, 0.56; 95 percent confidence interval, 0.36 to 0.86; P=0.009). The difference was driven by a lower rate of target-lesion revascularization in the sirolimus-stent group than in the paclitaxel-stent group (4.8 percent vs. 8.3 percent; hazard ratio, 0.56; 95 percent confidence interval, 0.34 to 0.93; P=0.03). Rates of death from cardiac causes were 0.6 percent in the sirolimus-stent group and 1.6 percent in the paclitaxel-stent group (P=0.15); the rates of myocardial infarction were 2.8 percent and 3.5 percent, respectively (P=0.49); and the rates of angiographic restenosis were 6.6 percent and 11.7 percent, respectively (P=0.02).

### CONCLUSIONS

As compared with paclitaxel-eluting stents, the use of sirolimus-eluting stents results in fewer major adverse cardiac events, primarily by decreasing the rates of clinical and angiographic restenosis.

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*A list of persons who contributed to the study is provided in the Appendix.

N Engl J Med 2005;353:653-62.

THE USE OF DRUG-ELUTING STENTS that deliver site-specific, controlled release of therapeutic agents[1-10] has significantly reduced the problem of restenosis inherent to bare-metal stents.[11-16] As compared with a bare-metal stent, a polymer-encapsulated stent releasing sirolimus reduced the rate of angiographic and clinical restenosis in several randomized trials.[1,2,5,7,9] Similarly, a polymer-based, paclitaxel-eluting stent consistently reduced the rate of restenosis and the need for repeated revascularization procedures, as compared with a bare-metal stent.[3,4,10] A recent meta-analysis of trials of drug-eluting stents confirmed that sirolimus-eluting stents and paclitaxel-eluting stents reduced the rate of restenosis.[17] The rates of death and myocardial infarction were similar to those with bare-metal stents, attesting to the safety of these devices.

Although the therapeutic benefit of sirolimus stents and paclitaxel stents over bare-metal stents is well established, there may be differences between the two devices.[18] We therefore conducted a randomized, controlled, partially blinded trial comparing the safety and efficacy of the sirolimus and paclitaxel stents in patients undergoing percutaneous coronary intervention.

## METHODS

### STUDY POPULATION

Patients with either stable angina or an acute coronary syndrome were eligible to participate if they had at least one lesion with stenosis of at least 50 percent in a vessel with a reference diameter between 2.25 and 4.00 mm that was suitable for stent implantation. The time from the onset of symptoms to treatment was less than 24 hours in patients classified as having a myocardial infarction characterized by ST-segment elevation. There were no limitations on the number of lesions or vessels or on the length of the lesions. Exclusion criteria were allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, sirolimus, or paclitaxel; participation in another coronary-device study; and terminal illness.

The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at the University Hospital Bern and the University Hospital Zurich, both in Switzerland. All patients provided written informed consent. There was no industry involvement in the design, conduct, financial support, or analysis of the study.

### RANDOMIZATION, STENT IMPLANTATION, AND ADJUNCT DRUG THERAPY

Randomization was performed after the diagnostic angiography and before percutaneous coronary intervention. Sealed, opaque, sequentially numbered allocation envelopes were used. The allocation schedule was based on computer-generated random numbers, stratified according to trial center and blocked, with block sizes of 6 and 10 varying randomly. Patients were assigned on a 1:1 basis to treatment with a polymer-based, sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson) or a polymer-based, slow-release, paclitaxel-eluting stent (Taxus, Boston Scientific). Sirolimus-eluting stents were available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 33 mm. Paclitaxel-eluting stents were available in diameters of 2.25 to 3.50 mm and in lengths of 8 to 32 mm.

Percutaneous coronary intervention was performed according to standard techniques. No mixture of drug-eluting stents was permitted except in the case of an inability to insert the assigned study stent, when crossover to another stent was allowed.

Before or at the time of the procedure, patients received at least 100 mg of aspirin, a 300-mg loading dose of clopidogrel, and unfractionated heparin (70 to 100 U per kilogram of body weight). Glycoprotein IIb/IIIa antagonists were used at the operator's discretion. A 12-lead electrocardiogram was obtained after the procedure and before discharge. Levels of creatine kinase, its MB isoenzyme, and troponin I were assessed 8 to 16 hours and again 18 to 24 hours after the procedure. At the time of discharge, all patients were receiving 100 mg of aspirin once daily for an indefinite period, as well as 75 mg of clopidogrel daily for 12 months.

### STUDY END POINTS AND DEFINITIONS

Adverse events were assessed in the hospital and at one, six, and nine months. An independent clinical-events committee whose members were unaware of the patients' treatment assignments adjudicated all clinical end points. An independent data and safety monitoring board reviewed the data periodically to identify safety issues, but there were no formal stopping rules. All patients were asked to return for an angiographic follow-up study at eight months.

The prespecified primary end point was a composite of major adverse cardiac events (death from cardiac causes, myocardial infarction, and ischemia-driven revascularization of the target lesion) by nine months. Secondary end points included ischemia-driven revascularization of the target lesion, target-vessel revascularization, and target-vessel failure (defined as a composite of death from cardiac causes, myocardial infarction, and ischemia-driven target-vessel revascularization).

The diagnosis of myocardial infarction was based on the presence of new Q waves in at least two contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of myocardial infarction was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin I.

Target-lesion revascularization was defined as revascularization for a stenosis within the stent or within the 5-mm borders adjacent to the stent. Revascularization of the target lesion and vessel was considered to be driven by ischemia if the stenosis of any target lesion or vessel was at least 50 percent of the diameter of the vessel on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms or if the stenosis was at least 70 percent of the diameter of the vessel even in the absence of ischemic signs or symptoms. We specified post hoc an alternative definition of the primary end point: a composite of death from cardiac causes, myocardial infarction, and clinically driven revascularization of the target lesion with stenoses of at least 50 percent in the presence of ischemic signs or symptoms; revascularization events were disregarded if ischemic signs or symptoms were absent.

The principal secondary end point of the angiographic substudy was late luminal loss within the stent as well as within the 5-mm margins proximal and distal to the stent ("in segment"). Other angiographic end points were late luminal loss within the stent ("in stent"), in-stent and in-segment stenosis, and in-stent and in-segment binary restenosis (described below).

Successful stenting was defined as a final stenosis of less than 50 percent of the vessel diameter after implantation of the study stent, and treatment success was defined as a final stenosis of less than 50 percent of the vessel diameter with the use of any percutaneous intervention. Stent thrombosis was diagnosed as an acute coronary syndrome with angiographic documentation of either occlusion of the target lesion or thrombus within the previously stented segment.

### QUANTITATIVE CORONARY ANGIOGRAPHY

Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and were assessed at the angiographic core laboratory of the University Hospital Bern. Angiogram readers were unaware of the type of stent implanted. The projection that best showed the stenosis was used for all analyses. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, nontapered tip of the catheter was used for calibration. Digital angiograms were analyzed with the use of an automated edge-detection system (CAAS II, Pie Medical Imaging). The intraobserver and interobserver reliabilities of the quantitative measurements have been reported previously.[19]

Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, the extent of stenosis (defined as the diameter of the reference vessel minus the minimal luminal diameter, divided by the reference diameter and multiplied by 100), and late luminal loss (the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up). Binary restenosis was defined as stenosis of at least 50 percent of the minimal luminal diameter in the target lesion at angiographic follow-up. All angiographic measurements of the target lesion were obtained in the stented area and within the margins 5 mm proximal and distal to each stent edge.

### STATISTICAL ANALYSIS

On the basis of results from RAVEL (the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions)[1] and the TAXUS II trial,[4] we assumed an incidence of major adverse cardiac events of 6 percent in the sirolimus-stent group and of 12 percent in the paclitaxel-stent group. Enrollment of 1010 patients would provide the study with a statistical power of 90 percent to detect this difference with a two-sided significance level of 0.05. All enrolled patients were included in the analysis of primary

**Table 1. Baseline Clinical Characteristics.***

| Characteristic | Sirolimus Stent (503 Patients) | Paclitaxel Stent (509 Patients) |
|---|---|---|
| Age — yr | 62±11 | 62±12 |
| Male sex — no. (%) | 382 (75.9) | 399 (78.4) |
| Diabetes mellitus — no. (%) | 108 (21.5) | 93 (18.3) |
| Hypertension — no. (%) | 302 (60.0) | 317 (62.3) |
| Hyperlipidemia — no. (%) | 305 (60.6) | 290 (57.0) |
| Current smoking — no. (%) | 184 (36.6) | 181 (35.6) |
| Previous myocardial infarction — no. (%) | 145 (28.8) | 151 (29.7) |
| Stable angina pectoris — no. (%) | 246 (48.9) | 246 (48.3) |
| Acute coronary syndromes — no. (%) | 257 (51.1) | 263 (51.7) |
| Unstable angina — no. (%) | 28 (5.6) | 30 (5.9) |
| Non–ST-segment elevation MI — no. (%) | 112 (22.3) | 123 (24.2) |
| ST-segment elevation MI — no. (%) | 117 (23.3) | 110 (21.6) |
| Time from onset of symptoms of MI to percutaneous coronary intervention — no. (%)† | | |
| <24 hr | 192 (38.2) | 180 (35.4) |
| 24–72 hr | 29 (5.8) | 39 (7.7) |
| >72 hr | 8 (1.6) | 14 (2.8) |
| Glycoprotein IIb/IIIa antagonists — no. (%) | 171 (34.0) | 147 (28.9) |
| Distal-embolization–protection devices — no. (%) | 33 (6.6) | 31 (6.1) |
| Multivessel disease — no. (%) | 300 (59.6) | 301 (59.1) |
| Left ventricular ejection fraction | 0.57±0.12 | 0.57±0.12 |

* Plus–minus values are means ±SD. There were no significant differences between groups. MI denotes myocardial infarction.
† Percentages refer to all patients and not only to patients with myocardial infarction.

and secondary clinical outcomes according to the intention-to-treat principle. We used a Cox proportional-hazards model to compare clinical outcomes between the groups. We assessed the assumptions of the Cox model statistically on the basis of Schoenfeld residuals and graphically using log-log plots and found them to be approximately satisfied for all variables. We prespecified stratified analyses of the primary outcome at nine months according to the presence or absence of two characteristics: diabetes and an acute coronary syndrome.

Analyses of outcomes of the angiographic substudy were not based on the intention-to-treat principle but were restricted to patients who returned for follow-up angiography. A patient could have had more than one lesion in which a stent was implanted. Therefore, in the analysis of the quantitative angiographic data, we used maximum-likelihood logistic and linear-regression models based on robust standard errors that allowed the correlation of multiple lesions within a patient to compare the characteristics of lesions between groups at baseline and follow-up.

Trial data were held by the trial-coordination center at the University Hospital Bern. Analyses were performed with the use of Stata software by an analyst who was unaware of the type of stent implanted. No adjustments were made for multiple comparisons in secondary analyses. All P values are two-sided. As principal investigator, Dr. Windecker had full access to the data and vouches for the data and the analysis.

## RESULTS

Between April 2003 and May 2004, 1012 patients (1401 lesions) were enrolled; 503 patients (693 lesions) were randomly assigned to receive a sirolimus-eluting stent, and 509 patients (708 lesions) to receive a paclitaxel-eluting stent. A total of 98.4 percent of lesions were located in a native coronary artery. The groups had similar baseline clinical and angiographic characteristics (Tables 1 and 2). Procedural characteristics, including the number of lesions per patient, the number of stents per lesion, the length and diameter of the stents, and the rate of direct stenting, were also similar in the two groups (Table 2). The rates of stenting success and treatment success were similar for the two types of stents.

### CLINICAL OUTCOME

Major adverse cardiac events during follow-up are listed in Table 3. At one month, there was no trend favoring either group for any of the clinical end points.

The primary end point (death from cardiac causes, myocardial infarction, or ischemia-driven target-lesion revascularization at nine months) occurred in 6.2 percent of patients receiving sirolimus stents and 10.8 percent of patients receiving paclitaxel stents (hazard ratio, 0.56; 95 percent confidence interval, 0.36 to 0.86; P=0.009) (Fig. 1 and Table 3). This difference was driven by a 44 percent reduction in the relative risk of target-lesion revascularization in favor of the sirolimus stent (4.8 percent vs. 8.3 percent; hazard ratio, 0.56; 95 percent confidence interval, 0.34 to 0.93; P=0.03). Analysis of the alternative definition of the primary end point,

**Table 2. Baseline Characteristics of Lesions and Procedural Results.***

| Characteristic | Sirolimus Stent (693 Lesions) | Paclitaxel Stent (708 Lesions) |
|---|---|---|
| Target-lesion coronary artery — no. (%) | | |
| Left main | 13 (1.9) | 10 (1.4) |
| Left anterior descending | 326 (47.0) | 325 (45.9) |
| Left circumflex | 135 (19.5) | 133 (18.8) |
| Right | 208 (30.0) | 228 (32.2) |
| Bypass graft | 11 (1.6) | 12 (1.7) |
| ACC–AHA lesion class — no. (%) | | |
| A | 131 (18.9) | 153 (21.6) |
| B1 | 300 (43.3) | 307 (43.4) |
| B2 | 173 (25.0) | 155 (21.9) |
| C | 89 (12.8) | 93 (13.1) |
| Approximate duration of total occlusion — no. (%) | | |
| <3 mo | 129 (18.6) | 108 (15.3) |
| ≥3 mo | 8 (1.2) | 17 (2.4) |
| Thrombus present — no. (%) | 163 (23.5) | 155 (21.9) |
| Bifurcated lesion — no. (%)† | 61 (8.8) | 56 (7.9) |
| Ostial lesion — no. (%) | 48 (6.9) | 58 (8.2) |
| Calcification — no. (%) | | |
| None or mild | 439 (63.3) | 480 (67.8) |
| Moderate | 232 (33.5) | 200 (28.2) |
| Severe | 22 (3.2) | 28 (4.0) |
| Before procedure | | |
| Lesion length — mm | 11.8±6.8 | 12.4±7.2 |
| Diameter of reference vessel — mm | 2.82±0.40 | 2.82±0.43 |
| Minimal luminal diameter — mm | 0.52±0.45 | 0.53±0.43 |
| Stenosis — % of luminal diameter | 81.7±15.1 | 81.5±14.5 |
| During procedure | | |
| No. of lesions treated per patient | 1.4±0.6 | 1.4±0.6 |
| No. of stents per lesion‡ | 1.1±0.4 | 1.2±0.5 |
| Maximal stent diameter — mm | 2.9±0.4 | 2.9±0.5 |
| Length of stent per lesion — mm | 18.7±10.3 | 19.0±10.7 |
| Maximal pressure — atm§ | 14.4±3.2 | 14.1±2.9 |
| Direct stenting — no. (%) | 222 (32.0) | 235 (33.2) |
| Successful implantation — no. (%) | 686 (99.0) | 698 (98.6) |
| Treatment success — no. (%) | 689 (99.4) | 701 (99.0) |
| Intraprocedural complications — no. (%) | 14 (2.0) | 14 (2.0) |
| Immediately after procedure | | |
| Final minimal luminal diameter — mm | | |
| In stent | 2.65±0.37 | 2.68±0.39 |
| In segment | 2.56±0.41 | 2.60±0.44 |
| Final stenosis — % of luminal diameter | | |
| In stent | 7.2±4.7 | 6.8±5.5 |
| In segment | 8.8±7.2 | 8.4±6.6 |
| Acute gain — mm | | |
| In stent | 2.13±0.52 | 2.15±0.51 |
| In segment | 2.08±0.53 | 2.08±0.56 |

* Plus–minus values are means ±SD. ACC denotes American College of Cardiology, and AHA American Heart Association.
† Bifurcated lesions required double wiring.
‡ P=0.09 for the comparison between groups.
§ P=0.04 for the comparison between groups.

**Table 3. Clinical Events during Follow-up.**

| Event | Sirolimus Stent (503 Patients) | Paclitaxel Stent (509 Patients) | Hazard Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| **Events at 1 mo** | | | | |
| Death | 0 | 4 (0.8) | 0.11 (0.01–2.08) | 0.12 |
| Death from cardiac causes | 0 | 4 (0.8) | 0.11 (0.01–2.08) | 0.12 |
| Myocardial infarction | 12 (2.4) | 13 (2.6) | 0.93 (0.43–2.04) | 0.86 |
| Q-wave | 6 (1.2) | 4 (0.8) | 1.52 (0.43–5.37) | 0.52 |
| Non–Q-wave | 6 (1.2) | 9 (1.8) | 0.67 (0.24–1.89) | 0.45 |
| Target-lesion revascularization | 11 (2.2) | 10 (2.0) | 1.11 (0.47–2.62) | 0.81 |
| Percutaneous | 11 (2.2) | 9 (1.8) | 1.23 (0.51–2.98) | 0.64 |
| Surgical | 0 | 2 (0.4) | 0.20 (0.01–4.21) | 0.50 |
| Target-vessel revascularization | 12 (2.4) | 10 (2.0) | 1.22 (0.53–2.81) | 0.65 |
| Percutaneous | 12 (2.4) | 9 (1.8) | 1.35 (0.57–3.20) | 0.50 |
| Surgical | 0 | 2 (0.4) | 0.20 (0.01–4.21) | 0.50 |
| Stent thrombosis | 9 (1.8) | 7 (1.4) | 1.30 (0.48–3.49) | 0.60 |
| Major adverse cardiac events | 15 (3.0) | 19 (3.7) | 0.80 (0.41–1.57) | 0.51 |
| Target-vessel failure | 15 (3.0) | 19 (3.7) | 0.80 (0.41–1.57) | 0.51 |
| **Events at 9 mo** | | | | |
| Death | 5 (1.0) | 11 (2.2) | 0.45 (0.16–1.31) | 0.14 |
| Death from cardiac causes | 3 (0.6) | 8 (1.6) | 0.38 (0.10–1.42) | 0.15 |
| Myocardial infarction | 14 (2.8) | 18 (3.5) | 0.78 (0.39–1.57) | 0.49 |
| Q-wave | 6 (1.2) | 5 (1.0) | 1.21 (0.37–4.00) | 0.75 |
| Non–Q-wave | 8 (1.6) | 13 (2.6) | 0.62 (0.26–1.50) | 0.28 |
| Target-lesion revascularization | 24 (4.8) | 42 (8.3) | 0.56 (0.34–0.93) | 0.03 |
| Percutaneous | 22 (4.4) | 36 (7.1) | 0.61 (0.36–1.03) | 0.06 |
| Surgical | 3 (0.6) | 9 (1.8) | 0.33 (0.10–1.22) | 0.10 |
| Target-vessel revascularization | 30 (6.0) | 47 (9.2) | 0.63 (0.40–1.00) | 0.05 |
| Percutaneous | 28 (5.6) | 41 (8.1) | 0.68 (0.42–1.10) | 0.11 |
| Surgical | 3 (0.6) | 9 (1.8) | 0.33 (0.10–1.22) | 0.10 |
| Stent thrombosis | 10 (2.0) | 8 (1.6) | 1.26 (0.50–3.20) | 0.62 |
| Primary end point† | 31 (6.2) | 55 (10.8) | 0.56 (0.36–0.86) | 0.009 |
| Alternatively defined primary end point‡ | 29 (5.8) | 49 (9.6) | 0.59 (0.37–0.93) | 0.02 |
| Target-vessel failure | 35 (7.0) | 59 (11.6) | 0.58 (0.38–0.89) | 0.01 |

* Hazard ratios and P values are from the Cox proportional-hazards model. CI denotes confidence interval.
† The prespecified primary end point was a composite of major adverse cardiac events (death from cardiac causes, myocardial infarction, and ischemia-driven target-lesion revascularization).
‡ The alternative primary end point, defined post hoc, was a composite of death from cardiac causes, myocardial infarction, and clinically driven target-lesion revascularization.

which included clinically driven rather than ischemia-driven revascularization of the target lesion, yielded similar results (5.8 percent in the sirolimus-stent group, as compared with 9.6 percent in the paclitaxel-stent group; hazard ratio, 0.59; 95 percent confidence interval, 0.37 to 0.93; P=0.02).

In a stratified analysis of the primary end point, the difference between sirolimus and paclitaxel stents was more pronounced among the 201 patients with diabetes (hazard ratio, 0.31; 95 percent confidence interval, 0.12 to 0.78) than among the 811 patients without diabetes (hazard ratio, 0.66; 95 percent confidence interval, 0.40 to 1.09), but confidence intervals were wide, and the result of

a test of interaction was not significant (P for interaction=0.13). Conversely, the difference between the sirolimus and paclitaxel stents appeared less pronounced among the 520 patients presenting with an acute coronary syndrome (hazard ratio, 0.84; 95 percent confidence interval, 0.46 to 1.51) than among the 492 patients presenting without an acute coronary syndrome (hazard ratio, 0.34; 95 percent confidence interval, 0.17 to 0.68). Here, the test of interaction reached borderline significance (P=0.05).

The rates of death and myocardial infarction were low and the estimates of hazard ratios imprecise (Table 3). The cumulative frequency of stent thrombosis was 2.0 percent with the sirolimus stent and 1.6 percent with the paclitaxel stent (hazard ratio, 1.26; 95 percent confidence interval, 0.50 to 3.20; P=0.62), and the rates of acute, subacute, and late stent thrombosis were similar in the two groups. The rates of antithrombotic treatment were similar in the two groups during the nine months of the study.

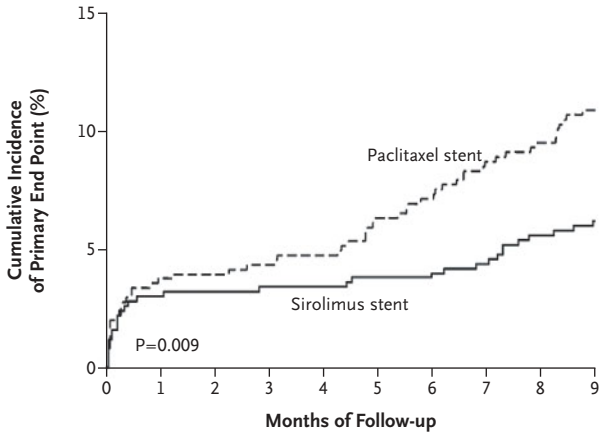


**Figure 1. Kaplan–Meier Cumulative-Event Curves for the Primary End Point of Death from Cardiac Causes, Myocardial Infarction, or Ischemia-Driven Revascularization of the Target Lesion.**

### ANGIOGRAPHIC RESULTS

Angiographic measurements of lesions before and after stent implantation were similar in the sirolimus-stent and paclitaxel-stent groups (Table 2). Angiographic follow-up at eight months was completed in 540 of 1012 patients (53.4 percent), who had 723 of the 1401 lesions (51.6 percent) (Table 4). A total of 267 patients in the sirolimus-stent group (53.1 percent) and 273 patients in the paclitaxel-stent group (53.6 percent) underwent follow-up angiography (P=0.86).

Patients undergoing angiographic follow-up were younger (P<0.001), less likely to have diabetes (P=0.04) or hypertension (P=0.04), and more likely to be male (P=0.004) and to have chest pain (P=0.01) than those who did not return for angiographic follow-up. Among patients undergoing angiographic follow-up, most baseline clinical characteristics and the frequency of chest pain were similar in the two groups, but hypertension was significantly more frequent in the paclitaxel-stent group (P=0.02).

The mean (±SD) in-segment late luminal loss, the prespecified end point of the angiographic substudy, was 0.19±0.45 mm in the sirolimus-stent group and 0.32±0.55 mm in the paclitaxel-stent group (P=0.001). The rate of in-segment binary restenosis was 6.6 percent in the sirolimus-stent group and 11.7 percent in the paclitaxel-stent group (P=0.02). The cumulative frequencies of in-segment stenosis before and after the procedure and at follow-up angiography in the two groups are shown in Figure 2.

## DISCUSSION

In this randomized, controlled, single-blind trial, the use of sirolimus-eluting stents was associated with a 44 percent decrease in the risk of major adverse cardiac events at nine months, as compared with the use of paclitaxel-eluting stents. The therapeutic benefit of the sirolimus stent was primarily driven by a 44 percent reduction in the need for repeated revascularization of the treated lesion.

The rates of clinical and angiographic restenosis were low for both drug-eluting stents, substantiating the results of previous studies.[1-5,7,9,10] A previous small, randomized trial involving 202 patients found a trend toward a higher rate of major adverse cardiac events at six months with the sirolimus stent than with the paclitaxel stent (6 percent vs. 4 percent; relative risk, 1.5; 95 percent confidence interval, 0.44 to 5.16).[20] Notwithstanding this finding, sirolimus stents have consistently been shown to reduce the extent of late luminal loss, a measure of neointimal hyperplasia, more effectively than paclitaxel stents[1-5,7,9,10,18] — a finding corroborated in the present trial.

**Table 4. Angiographic Results of Follow-up.***

| Variable | Sirolimus Stent (348 Lesions) | Paclitaxel Stent (375 Lesions) | Difference (95% CI) | P Value |
|---|---|---|---|---|
| Diameter of reference vessel (mm) | 2.79±0.43 | 2.80±0.45 | –0.01 (–0.08 to 0.06) | 0.74 |
| Minimal luminal diameter (mm) | | | | |
| Proximal margin | 2.64±0.54 | 2.65±0.65 | –0.01 (–0.11 to 0.09) | 0.84 |
| In stent | 2.53±0.50 | 2.44±0.66 | 0.08 (–0.01 to 0.17) | 0.07 |
| Distal margin | 2.49±0.45 | 2.49±0.49 | 0.00 (–0.07 to 0.08) | 0.96 |
| In segment | 2.37±0.57 | 2.28±0.73 | 0.09 (–0.01 to 0.20) | 0.07 |
| Stenosis (% of luminal diameter) | | | | |
| Proximal margin | 11.0±12.2 | 12.7±15.5 | –1.7 (–3.9 to 0.5) | 0.13 |
| In stent | 10.3±12.9 | 14.0±18.9 | –3.4 (–6.3 to –1.3) | 0.003 |
| Distal margin | 9.1±9.2 | 9.2±8.08 | –0.1 (–1.4 to 1.2) | 0.91 |
| In segment | 14.9±16.5 | 19.4±21.7 | –4.5 (–7.5 to –1.6) | 0.003 |
| Late luminal loss (mm) | | | | |
| Proximal margin | 0.12±0.32 | 0.16±0.39 | –0.05 (–0.10 to 0.01) | 0.11 |
| In stent | 0.12±0.36 | 0.25±0.49 | –0.13 (–0.19 to –0.06) | <0.001 |
| Distal margin | 0.07±0.20 | 0.08±0.22 | –0.01 (–0.04 to 0.02) | 0.42 |
| In segment | 0.19±0.45 | 0.32±0.55 | –0.13 (–0.21 to –0.05) | 0.001 |
| Late-loss index | | | | |
| In stent | 0.06±0.18 | 0.13±0.28 | –0.07 (–0.11 to –0.03) | <0.001 |
| In segment | 0.10±0.23 | 0.17±0.32 | –0.07 (–0.12 to –0.03) | 0.001 |
| Binary restenosis (%) | | | | |
| Proximal margin | 3.2 | 4.8 | –1.6 (–4.8 to 1.2) | 0.29 |
| In stent | 3.2 | 7.5 | –4.3 (–7.5 to –1.1) | 0.01 |
| Distal margin | 1.1 | 1.1 | 0.0 (–1.4 to 1.6) | 0.92 |
| In segment | 6.6 | 11.7 | –5.1 (–9.3 to –1.0) | 0.02 |

* Plus–minus values are means ±SD. Late luminal loss was defined as the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up. Binary restenosis was defined as stenosis of at least 50 percent of the minimal luminal diameter in the target lesion at angiographic follow-up. Late-loss index was determined by dividing late luminal loss by acute gain. CI denotes confidence interval.

In our analysis, the rates of restenosis and late luminal loss in the sirolimus-stent group were similar to those in the SIRIUS (Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary-Artery Lesions) trial, the largest previous randomized trial of the sirolimus stent.[2] In contrast, the rates of restenosis and late luminal loss in the paclitaxel-stent group were higher than those observed in the TAXUS IV trial, the largest previous randomized trial of the paclitaxel stent.[10] The reasons for this difference are unclear but may be related to the inclusion in the current trial of patients with more complex conditions and lesions than in the SIRIUS or TAXUS IV trial. The therapeutic benefit of sirolimus stents appears to be particularly apparent in such patients and lesions, perhaps owing to the increased risk of restenosis. Data from the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results–Drug-Eluting Stents for In-Stent Restenosis) trial[18] involving patients with in-stent restenosis, a subgroup of patients at high risk for restenosis, also indicated that the sirolimus stent was more effective than the paclitaxel stent in suppressing neointimal hyperplasia and reducing the need for repeated revascularization. Patients with diabetes represent another subgroup at increased risk for restenosis, even after the implantation of drug-eluting stents. A pre-

specified, stratified analysis in the present trial indicated that differences in favor of the sirolimus stent were more pronounced in patients with diabetes than in those without diabetes.

The rates of death and myocardial infarction were low in both stent groups. The cumulative incidence of stent thrombosis was similar in the two groups, and there was no significant difference in the rates of antithrombotic treatment. Although the overall rate of stent thrombosis was higher than in previous studies of drug-eluting stents, the rate is in keeping with our own experience of 1.6 percent among 6058 patients treated with bare-metal stents.[21] The higher incidence of stent thrombosis in this trial may have been related to the inclusion of patients with more complex conditions and lesions and a higher prevalence of acute coronary syndromes than in most previous studies.

Routine angiographic follow-up is known to increase the rate of target-lesion revascularization, and the incomplete angiographic follow-up in the present trial may have resulted in an overestimation of differences owing to attrition bias.[22] We consider this possibility unlikely, since the difference in major adverse cardiac events in favor of the sirolimus stent over the paclitaxel stent was already apparent at six months, before the scheduled angiographic follow-up (hazard ratio for major adverse cardiac events at six months, 0.56; 95 percent confidence interval, 0.32 to 0.96; P=0.04). In addition, the difference at nine months was significant with the use of an alternative definition of the primary end point, which disregarded target-lesion revascularizations that were driven exclusively by findings on routine angiography.

In conclusion, as compared with polymer-based, paclitaxel-eluting stents, sirolimus-eluting stents resulted in fewer major adverse cardiac events at nine months, primarily by decreasing the rates of clinical and angiographic restenosis.

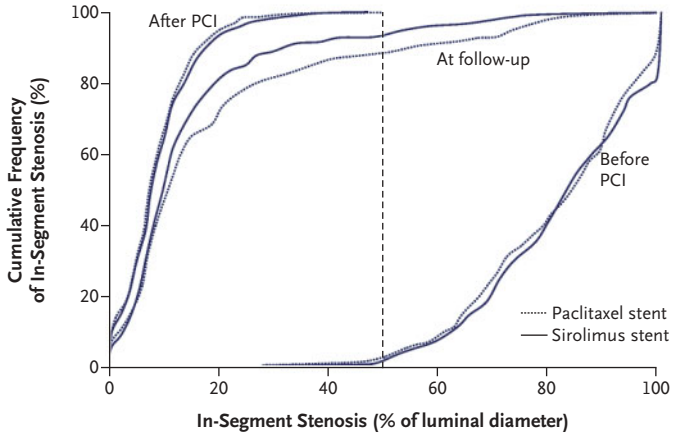


**Figure 2. Cumulative Frequency of In-Segment Stenosis.**

The extent of stenosis was defined as the diameter of the reference vessel minus the minimal luminal diameter, divided by the reference diameter and multiplied by 100. There was no significant difference in measurements before and immediately after the procedure between the two groups. At follow-up angiography, the cumulative distribution curve of in-segment stenosis was shifted to the right for the paclitaxel-stent group as compared with the sirolimus-stent group, indicating that in-segment stenosis was more effectively reduced with the sirolimus stent. PCI denotes percutaneous coronary intervention.

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## APPENDIX

The following persons contributed to the study: **Author Contributions:** *conception and design* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, B. Meier; *analysis and interpretation of data* — S. Windecker, P. Jüni, M. Egger, B. Meier; *drafting of the manuscript* — S. Windecker, P. Jüni, A. Remondino, B. Meier; *critical revision of the manuscript for important intellectual content* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, L. Räber, P. Wenaweser, M. Togni, M. Billinger, D. Tüller, C. Seiler, M. Roffi, R. Corti, G. Sütsch, W. Maier, T. Lüscher, O.M. Hess, M. Egger, B. Meier; *final approval of the manuscript* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, L. Räber, P. Wenaweser, M. Togni, M. Billinger, D. Tüller, C. Seiler, M. Roffi, R. Corti, G. Sütsch, W. Maier, T. Lüscher, O.M. Hess, M. Egger, B. Meier; *statistical expertise* — S. Windecker, P. Jüni, M. Egger; *obtaining of public funding* — S. Windecker, F.R. Eberli, T. Lüscher, O.M. Hess, B. Meier; *administrative, technical, or logistic support* — S. Windecker, P. Jüni, M. Egger, T. Lüscher, O.M. Hess, B. Meier; *acquisition of data* — S. Windecker, A. Remondino, F.R. Eberli, P. Jüni, L. Räber, P. Wenaweser, M. Togni, M. Billinger, D. Tüller, C. Seiler, M. Roffi, R. Corti, G. Sütsch, W. Maier, T. Lüscher, O.M. Hess, B. Meier; **Data and Safety Monitoring Board:** M. Bertrand (Lille University Heart Institute, Lille, France), P. Urban (La Tour Hospital, Geneva); **Event-Adjudication Committee:** A. Garachemani (Sonnenhof Hospital, Bern, Switzerland) and N. Schwick and A. Wahl (University Hospital Bern, Bern, Switzerland).

## REFERENCES


1. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346:1773-80.
2. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349: 1315-23.
3. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003; 107:38-42.
4. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108: 788-94.
5. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093-9.
6. Park S-J, Shim WH, Ho DS, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. N Engl J Med 2003;348: 1537-45.
7. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004; 43:1110-5.
8. Gershlick A, De Scheerder I, Chevalier B, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. Circulation 2004; 109:487-93.
9. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA 2004;292: 2727-34.
10. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.
11. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316: 701-6.
12. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable–stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-95.
13. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496-501.
14. Kimura T, Yokoi H, Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996;334:561-6.
15. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents: a hierarchical Bayesian meta-analysis. Ann Intern Med 2003;138:777-86.
16. Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. JAMA 2000;284: 1828-36.
17. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364: 583-91.
18. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165-71.
19. Togni M, Windecker S, Wenaweser P, et al. Deleterious effect of coronary brachytherapy on vasomotor response to exercise. Circulation 2004;110:135-40.
20. Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXI trial. J Am Coll Cardiol 2005;45:308-11.
21. Wenaweser P, Rey C, Eberli FR, et al. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. Eur Heart J 2005; 26:1180-7.
22. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 2001;323: 42-6.




### CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.

ORIGINAL ARTICLE

# Paclitaxel-Eluting or Sirolimus-Eluting Stents to Prevent Restenosis in Diabetic Patients

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## ABSTRACT

### BACKGROUND

Drug-eluting stents are highly effective in reducing the rate of in-stent restenosis. It is not known whether there are differences in the effectiveness of currently approved drug-eluting stents in the high-risk subgroup of patients with diabetes mellitus.

### METHODS

We enrolled 250 patients with diabetes and coronary artery disease: 125 were randomly assigned to receive paclitaxel-eluting stents, and 125 to receive sirolimus-eluting stents. The primary end point was in-segment late luminal loss. Secondary end points were angiographic restenosis (defined as in-segment stenosis of at least 50 percent at follow-up angiography) and the need for revascularization of the target lesion during a nine-month follow-up period. The study was designed to show noninferiority of the paclitaxel stent as compared with the sirolimus stent, defined as a difference in the extent of in-segment late luminal loss of no more than 0.16 mm.

### RESULTS

The extent of in-segment late luminal loss was 0.24 mm (95 percent confidence interval, 0.09 to 0.39) greater in the paclitaxel-stent group than in the sirolimus-stent group (P=0.002). In-segment restenosis was identified on follow-up angiography in 16.5 percent of the patients in the paclitaxel-stent group and 6.9 percent of the patients in the sirolimus-stent group (P=0.03). Target-lesion revascularization was performed in 12.0 percent of the patients in the paclitaxel-stent group and 6.4 percent of the patients in the sirolimus-stent group (P=0.13).

### CONCLUSIONS

In patients with diabetes mellitus and coronary artery disease, use of the sirolimus-eluting stent is associated with a decrease in the extent of late luminal loss, as compared with use of the paclitaxel-eluting stent, suggesting a reduced risk of restenosis.

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*The Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents (ISAR-DIABETES) study investigators are listed in the Appendix.

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Coronary artery disease is a major cause of complications and death among patients with diabetes mellitus.[1] In particular, patients with diabetes are prone to a diffuse and rapidly progressive form of atherosclerosis, which increases their likelihood of requiring revascularization.[2-4] Percutaneous coronary intervention and aortocoronary bypass surgery are recommended revascularization strategies for such patients. However, because of the increased risk of restenosis after percutaneous coronary interventions in these patients,[5-7] aortocoronary bypass surgery has been considered to be the preferred revascularization strategy for many.[8,9]

Drug-eluting stents markedly reduce the incidence of restenosis as compared with bare-metal stents, both in patients without diabetes and in those with diabetes.[10-17] However, no data are available on the relative efficacy of particular drug-eluting stents in patients with diabetes. This issue has important implications for the selection of the most effective therapy in this high-risk group of patients. We therefore designed a prospective, randomized trial to compare paclitaxel- and sirolimus-eluting stents in patients with diabetes and coronary artery disease.

## METHODS

### PATIENTS

Enrollment of participants began on June 11, 2003, and was completed on March 15, 2004. Two German centers participated in the trial: Deutsches Herzzentrum and First Medizinische Klinik rechts der Isar, both in Munich. Patients were considered eligible if they had diabetes mellitus, presented with angina pectoris or had a positive stress test or met both criteria, and had clinically significant angiographic stenosis in a native coronary vessel. Exclusion criteria included acute ST-segment–elevation myocardial infarction; a target lesion in the left main trunk; in-stent restenosis; any contraindication to the use of aspirin, heparin, or clopidogrel; and lack of consent to participate in the study. The study protocol was approved by the institutional ethics committees at both participating centers. All patients gave written informed consent.

### RANDOMIZATION, INTERVENTIONS, AND ADJUNCT DRUG THERAPY

All patients received a loading dose of 600 mg of clopidogrel at least two hours before undergoing coronary angiography.[18,19] After the guide wire had crossed the lesion, patients were randomly assigned to receive a paclitaxel-eluting stent (Taxus, Boston Scientific) or a sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson) with the use of sealed envelopes containing a computer-generated randomization sequence. The same randomly assigned stent had to be implanted in all lesions in patients who required stenting in multiple lesions; the use of more than one stent per lesion was also allowed.

Periprocedural antithrombotic therapy consisted of intravenously administered aspirin and heparin; abciximab (ReoPro, Lilly) was given only to patients with acute coronary syndromes. After the intervention, the protocol mandated the use of antiplatelet therapy consisting of 100 mg of aspirin twice a day indefinitely as well as 75 mg of clopidogrel twice a day until discharge, followed by a dose of 75 mg a day for at least six months.

### FOLLOW-UP PROTOCOL

After undergoing stenting, all patients remained in the hospital for at least 48 hours. Electrocardiography was performed and blood was collected for the measurement of creatine kinase and its MB isoenzyme before stenting, every 8 hours for the first 24 hours after the procedure, and daily thereafter during hospitalization. A telephone interview was conducted after 30 days to assess each patient's clinical status. All patients were asked to return for coronary angiography between six and eight months after the procedure, or earlier if anginal symptoms occurred. Telephone interviews were repeated nine months after the intervention. Relevant data were collected and entered into a computerized database by specialized personnel at the clinical data-management center. All data were verified with the use of hospital records or the records of family physicians, and all adverse clinical events were adjudicated by an events committee whose members were unaware of patients' treatment assignments.

### QUANTITATIVE CORONARY ANGIOGRAPHY

Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (Deutsches Herzzentrum) with an automated edge-detection system (CMS version 5.1.4.1, Medis Medical Imaging Systems) by experienced personnel unaware of the type of stent implanted. The complexity of the lesions was defined according to the modified grading system of the Ameri-

can College of Cardiology–American Heart Association.[20] The morphologic appearance of in-stent restenosis at follow-up angiography was classified according to the system proposed by Mehran et al.[21] All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin. The same single, worst-view projection was used at all times. The contrast-filled nontapered catheter tip was used for calibration. The reference diameter was determined by interpolation.

The variables that were measured included the reference diameter of the vessel, the minimal diameter of the lumen, the extent of stenosis (the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100), late luminal loss (the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up), and net luminal gain (the difference between the minimal luminal diameter at follow-up and the minimal luminal diameter before the procedure). Quantitative analysis was used to evaluate the stented area ("in stent") and the area that included the stented segment as well as the 5-mm margins proximal and distal to the stent ("in segment").

### STUDY END POINTS, DEFINITIONS, AND DESIGN

The primary end point of the study was in-segment late luminal loss on follow-up angiography. Secondary end points were angiographic restenosis (defined as in-segment stenosis of at least 50 percent on follow-up angiography) and the need for revascularization of the target lesion owing to narrowing of the lumen in the presence of symptoms or objective signs of ischemia during the nine-month follow-up interval.

The diagnosis of diabetes mellitus was considered confirmed in all patients receiving active treatment with an oral hypoglycemic agent or insulin; for patients with a diagnosis of diabetes who were receiving dietary therapy alone, enrollment in the trial required the documentation of an abnormal blood glucose level after an overnight fast or an abnormal glucose-tolerance test.[22] The diagnosis of myocardial infarction during follow-up required the presence of new Q waves on the electrocardiogram or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of the normal range in at least two blood samples (some patients met both criteria).[23]

### STATISTICAL ANALYSIS

The objective of the study was to assess whether the outcome of treatment with the paclitaxel-eluting stent was not inferior to the outcome of treatment with the sirolimus-eluting stent. Calculation of the sample size was based on a margin of noninferiority for in-segment late luminal loss of 0.16 mm. This value is equal to 35 percent of an assumed mean (±SD) late luminal loss of 0.46±0.45 mm in diabetic patients after the implantation of a sirolimus stent, as found in an analysis of a series of diabetic patients treated with sirolimus stents at participating centers in the 10 months that preceded the initiation of the study.

Using a one-sided $\alpha$ level of 0.05, we estimated that 99 patients per group were needed to demonstrate noninferiority of the paclitaxel stent with a statistical power of 80 percent. Expecting that up to 20 percent of the patients would not return for follow-up coronary angiography, we included 250 patients in the study. Sample size was calculated with the use of nQuery Advisor (version 4.0, Statistical Solutions) according to the method of O'Brien and Muller.[24]

Analyses related to angiographic measures were conducted according to the number of patients available for each analyses. All other analyses were conducted according to the intention-to-treat principle. For patients with multilesion interventions, only the data pertaining to the first treated lesion were included in the analysis. The noninferiority hypothesis was assessed statistically with EquivTest (Statistical Solutions) according to the method of Chow and Liu.[25] The differences between the groups were assessed with a two-sided chi-square test or Fisher's exact test for categorical data and Student's t-test for continuous data. The relative risk and its 95 percent confidence interval were computed for outcome measures. The differences in quantitative angiographic results at follow-up between the two study groups were also assessed after adjustment for baseline characteristics by means of multiple linear regression analysis (continuous dependent variables) or multiple logistic-regression analysis (dichotomous dependent variables). All P values were two-sided, and a P val-

ue of less than 0.05 was considered to indicate statistical significance.

## RESULTS

A total of 250 patients were enrolled in the study and randomly assigned to receive either a paclitaxel stent or a sirolimus stent. Table 1 shows the baseline demographic, clinical, and angiographic characteristics of the study population. The procedural characteristics are shown in Table 2. Implantation of the randomly assigned stent was successful in all patients. In 12.0 percent of patients, more than one lesion was treated. There was only one case of early stent thrombosis: in one patient in the paclitaxel-stent group, the stent became occluded five hours after the index procedure.

**Table 1. Baseline Characteristics of the Patients and the Lesions.***

| Characteristic | Paclitaxel-Stent Group (N=125) | Sirolimus-Stent Group (N=125) |
|---|---|---|
| Age — yr | 68.3±9.6 | 67.7±10.2 |
| Female sex — no. (%) | 36 (28.8) | 32 (25.6) |
| Treatment of diabetes — no. (%) | | |
| Dietary therapy alone | 24 (19.2) | 24 (19.2) |
| Oral hypoglycemic agents | 65 (52.0) | 55 (44.0) |
| Insulin | 36 (28.8) | 46 (36.8) |
| Glycosylated hemoglobin — % | 7.4±1.6 | 7.3±1.1 |
| Current smoker — no. (%) | 16 (12.8) | 16 (12.8) |
| Arterial hypertension — no. (%) | 82 (65.6) | 70 (56.0) |
| Hypercholesterolemia — no. (%) | 78 (62.4) | 73 (58.4) |
| Unstable angina — no. (%) | 43 (34.4) | 56 (44.8) |
| Prior myocardial infarction — no. (%) | 49 (39.2) | 39 (31.2) |
| Prior aortocoronary bypass surgery — no. (%) | 13 (10.4) | 16 (12.8) |
| Left ventricular ejection fraction — % | 51.7±13.6 | 50.3±12.7 |
| Target vessel — no. (%) | | |
| Left anterior descending coronary artery | 64 (51.2) | 58 (46.4) |
| Left circumflex coronary artery | 36 (28.8) | 43 (34.4) |
| Right coronary artery | 25 (20.0) | 24 (19.2) |
| Complex (type B2 or C) lesions — no. (%) | 92 (73.6) | 102 (81.6) |
| Vessel size — mm | 2.75±0.56 | 2.70±0.50 |
| Lesion length — mm | 12.4±7.7 | 13.8±7.6 |
| Minimal luminal diameter before procedure — mm | 1.12±0.40 | 1.03±0.37† |
| Stenosis before procedure — % of luminal diameter | 59.4±11.9 | 61.1±13.1 |

* Plus–minus values are means ±SD.
† P=0.09 for the comparison with the paclitaxel-stent group.

### ANGIOGRAPHIC RESULTS

Follow-up angiography was performed in 103 patients (82.4 percent) in the paclitaxel-stent group and 102 patients (81.6 percent) in the sirolimus-stent group. Patients who did not undergo follow-up angiography did not differ significantly from those who did with respect to the baseline characteristics shown in Table 1. Five of the 22 patients who did not undergo follow-up angiography in the paclitaxel-stent group died during the nine-month follow-up period, as did 4 of the 23 such patients in the sirolimus-stent group. No other adverse events were observed among these patients, and none required rehospitalization during follow-up.

The median duration of angiographic follow-up was 196 days (10th and 90th percentiles, 92 and 236) in the paclitaxel-stent group and 196 days (10th and 90th percentiles, 91 and 238) in the sirolimus-stent group (P=0.94). Table 3 shows the results of the quantitative analysis of follow-up angiograms. The mean difference in in-segment late luminal loss between the paclitaxel-stent group and the sirolimus-stent group was 0.24 mm (95 percent confidence interval, 0.09 to 0.39), a result failing to show the noninferiority of the paclitaxel stent and instead demonstrating the statistical superiority of the sirolimus stent (P=0.002) (Fig. 1). This difference remained significant after adjustment for the baseline characteristics of the patients (P=0.001) (Table 3). Figure 2 shows the cumulative rates of in-segment stenosis at follow-up angiography.

Among patients who were receiving insulin, in-segment late luminal loss averaged 0.72±0.66 mm in the paclitaxel-stent group and 0.41±0.42 mm in the sirolimus-stent group (P=0.02). Among patients who were not receiving insulin, in-segment late luminal loss averaged 0.65±0.60 mm in the paclitaxel-stent group and 0.44±0.46 mm in the sirolimus-stent group (P=0.03).

In-segment restenosis was found on follow-up angiography in 17 of 103 patients in the paclitaxel-stent group, as compared with 7 of 102 patients in the sirolimus-stent group (16.5 percent vs. 6.9 percent; relative risk, 2.40; 95 percent confidence interval, 1.04 to 5.55; P=0.03). With respect to the pattern of restenosis on follow-up angiography, all seven of the patients in the sirolimus-stent group

presented with pattern I. In the paclitaxel-stent group, 13 patients presented with pattern I, 1 patient with pattern II, 1 patient with pattern III, and 2 patients with pattern IV.

### CLINICAL OUTCOMES

All patients completed the nine-month follow-up. Six patients (4.8 percent) in the paclitaxel-stent group and four patients (3.2 percent) in the sirolimus-stent group died during this period (P=0.52). Myocardial infarction occurred in three patients (2.4 percent) in the paclitaxel-stent group and five patients (4.0 percent) in the sirolimus-stent group (P=0.72). Target-lesion revascularization was performed in 15 patients in the paclitaxel-stent group, as compared with 8 patients in the sirolimus-stent group (12.0 percent vs. 6.4 percent; relative risk, 1.89; 95 percent confidence interval, 0.82 to 4.27; P=0.13). Among the patients who underwent target-lesion revascularization, the mean extent of in-segment stenosis at follow-up angiography was 65.0±17.0 percent.

## DISCUSSION

In this randomized trial, we compared the efficacy of the sirolimus-eluting stent and the paclitaxel-eluting stent in the prevention of restenosis in patients with diabetes mellitus and coronary artery disease. The paclitaxel stent was associated with a higher rate of in-segment late luminal loss as well as an increased risk of angiographic restenosis. Our study was not sufficiently powered to assess the incidence of clinical restenosis, and we found no significant differences in the rates of clinical end points between the two groups. Nonetheless, our results imply that the sirolimus stent may be preferable to the paclitaxel stent in patients with diabetes who require coronary revascularization.

We chose late luminal loss at follow-up angiography as the primary end point of our trial because it reflects the degree of neointimal proliferation,[26] which is the chief cause of restenosis after stent implantation.[27] Late loss is the most sensitive measure of the antiproliferative effectiveness of drug-eluting stents,[28,29] although in-stent late loss may be a more reliable predictor of restenosis than in-segment late loss.[29] In a recent trial, a 70 percent reduction in the rate of in-segment late luminal loss with the sirolimus-eluting stent was associated with a 75 percent reduction in the rate of target-lesion revascularization as compared with the rates with the control bare-metal stent.[12] However, it should be stressed that late luminal loss constitutes only a surrogate for clinical end points. The limitations of surrogate end points have been well described.[30,31] Our results should be interpreted in this context.

Our calculation of sample size was based on a margin of noninferiority of 0.16 mm for in-segment late luminal loss. This value was selected after an analysis of a series of diabetic patients treated with sirolimus stents at our own institutions. It is also a reasonable margin of difference on the basis of findings in other studies. In the SIRIUS trial, an absolute reduction of 0.57 mm in in-segment late luminal loss was achieved with the use of the sirolimus-eluting stent as compared with the bare-metal stent.[12] Our margin of difference of 0.16 mm represents the preservation of 72 percent of the effect demonstrated by the sirolimus-

**Table 2. Procedural Characteristics.***

| Characteristic | Paclitaxel-Stent Group (N=125) | Sirolimus-Stent Group (N=125) |
|---|---|---|
| Maximal balloon pressure — atm | 14.3±2.6 | 13.7±2.6† |
| Ratio of balloon to vessel | 1.15±0.10 | 1.15±0.10 |
| Length of stented segment — mm | 22.1±9.3 | 23.8±10.2 |
| No. of stents | 1.13±0.36 | 1.15±0.38 |
| >1 Stent implanted — no. (%) | 15 (12.0) | 18 (14.4) |
| Minimal luminal diameter after procedure — mm | | |
| In segment | 2.65±0.52 | 2.59±0.45 |
| In stent | 2.67±0.52 | 2.62±0.46 |
| Proximal margin | 2.70±0.54 | 2.64±0.48 |
| Distal margin | 2.66±0.51 | 2.60±0.46 |
| Stenosis after procedure — % of luminal diameter‡ | | |
| In segment | 9.2±7.2 | 7.9±6.3 |
| In stent | 8.4±7.7 | 7.0±6.4 |
| Proximal margin | 7.5±7.2 | 6.4±6.2 |
| Distal margin | 8.9±7.0 | 7.8±6.5 |
| Abciximab therapy — no. (%) | 24 (19.2) | 25 (20.0) |

* Plus–minus values are means ±SD.
† P=0.08 for the comparison with the paclitaxel-stent group.
‡ The extent of stenosis was defined as the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100.

**Table 3. Results of Quantitative Angiographic Analysis at Follow-up.***

| Characteristic | Paclitaxel-Stent Group (N=103) | Sirolimus-Stent Group (N=102) | P Value | Adjusted P Value† |
|---|---|---|---|---|
| Late luminal loss — mm | | | | |
| In segment | 0.67±0.62 | 0.43±0.45 | 0.002 | 0.001 |
| In stent | 0.46±0.64 | 0.19±0.44 | <0.001 | <0.001 |
| Proximal margin | 0.26±0.70 | 0.06±0.57 | 0.03 | |
| Distal margin | 0.49±0.58 | 0.28±0.46 | 0.006 | |
| Net luminal gain — mm | | | | |
| In segment | 0.90±0.75 | 1.12±0.64 | 0.03 | 0.003 |
| In stent | 1.12±0.77 | 1.38±0.66 | 0.01 | <0.001 |
| Proximal margin | 1.32±0.78 | 1.50±0.74 | 0.08 | |
| Distal margin | 1.09±0.69 | 1.27±0.61 | 0.05 | |
| Minimal luminal diameter — mm | | | | |
| In segment | 2.03±0.78 | 2.15±0.59 | 0.23 | 0.11 |
| In stent | 2.25±0.80 | 2.41±0.62 | 0.12 | 0.05 |
| Proximal margin | 2.43±0.84 | 2.53±0.71 | 0.46 | |
| Distal margin | 2.21±0.75 | 2.29±0.60 | 0.43 | |
| Stenosis — % of luminal diameter‡ | | | | |
| In segment | 31.73±20.87 | 25.74±15.61 | 0.02 | 0.02 |
| In stent | 24.22±21.53 | 16.59±17.22 | 0.006 | 0.004 |
| Proximal margin | 17.18±23.45 | 12.63±19.61 | 0.13 | |
| Distal margin | 25.09±20.09 | 20.74±14.84 | 0.08 | |
| Angiographic restenosis — no. (%)§ | | | | |
| In segment | 17 (16.5) | 7 (6.9) | 0.03 | 0.02 |
| In stent | 14 (13.6) | 5 (4.9) | 0.03 | 0.02 |
| Proximal margin | 1 (1.0) | 1 (1.0) | 1.0 | |
| Distal margin | 2 (1.9) | 1 (1.0) | 0.99 | |

* Plus–minus values are means ±SD. Late luminal loss was defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up. Net luminal gain was defined as the difference between the minimal luminal diameter at follow-up and the minimal luminal diameter before the procedure.
† P values were obtained after adjustment for the baseline characteristics shown in Table 1.
‡ The extent of stenosis was defined as the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100.
§ If angiographic restenosis was detected concomitantly in the in-stent area and any of the margins, it was counted only as restenosis in the in-stent area.

eluting stent in that trial. A new treatment is considered noninferior to a standard treatment when it retains 50 to 80 percent of the superiority that the standard treatment has shown over placebo.[32]

Another issue that requires comment is our observation that the extent of in-segment late luminal loss exceeded the extent of in-stent late luminal loss. This finding differs from the results of most other stenting trials, although a similar result was reported among patients receiving a sirolimus stent in the SIRIUS trial.[12,16] The phenomenon of greater in-segment late loss may be a consequence of two factors. First, after the procedure, the in-stent minimal luminal diameter (2.65 mm) was nearly identical to the in-segment minimal luminal diameter (2.62 mm) — a result that is somewhat unexpected, especially in diabetic patients with diffuse coronary disease. Second, patients with diabetes have a

distinctive, swiftly progressive form of atherosclerosis, which increases the reactivity of the vascular wall to the injury produced by the procedure at the stent margins as well as the rate of natural progression of disease outside the stent, an effect presumably mitigated within the stent by the antiproliferative properties of sirolimus and paclitaxel.

The incidence ratio of target-lesion revascularization to angiographic restenosis in our study was 78.6 percent. In previous randomized trials comparing drug-eluting stents with bare-metal stents, this ratio ranged from 38 and 46 percent[12,13] to 85 percent[33] among patients assigned to receive the drug-eluting stent. It is difficult to be certain of the reason for the higher ratio in our study than in several previous trials. The rate of late loss in our trial was also higher than that in other, similar trials, possibly because we limited our study population to patients with diabetes. The higher rate may reflect not only an increased incidence but also increased severity of angiographically evident restenosis, increasing the likelihood of the need for reintervention. In addition, diabetes mellitus is often perceived as a disease that attenuates anginal symptoms even in the presence of clinically significant coronary artery stenosis. This perception may have induced the clinicians to overestimate symptoms and lower their threshold for reintervention in some patients with angiographically evident restenosis in the present trial.

Although the exact mechanism underlying our findings remains unclear, pharmacologic differences between the two drugs, differences in the dose response of patients with diabetes, or differences in the properties of the two drug-delivery stents (such as release kinetics and polymeric coating) may account for the results. A study of another high-risk subgroup of patients (those with in-stent restenosis) also found sirolimus stents to reduce the risk of target-vessel revascularization more effectively than did paclitaxel stents.[34] These findings, however, cannot be extrapolated to a patient population with a more favorable risk profile. This issue has recently been investigated in other trials, and preliminary results have been presented.[35]

In conclusion, we did not establish the noninferiority of paclitaxel-eluting stents to sirolimus-eluting stents in patients with diabetes and coronary artery disease. Instead, we found that the use of the sirolimus-eluting stent in this setting was associated with a decrease in the extent of late luminal loss, suggesting a reduced risk of restenosis.

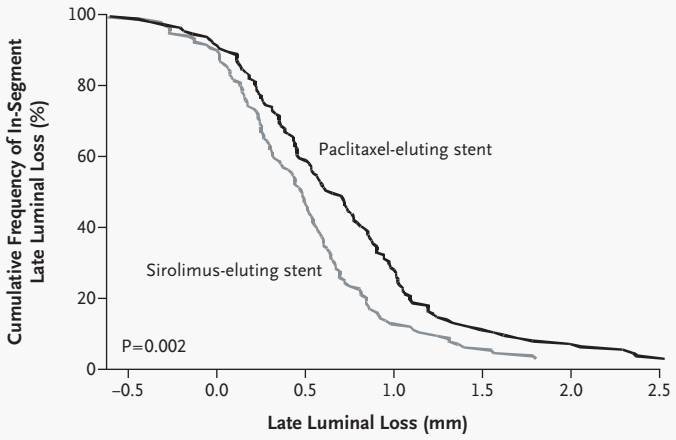


**Figure 1. Cumulative Rates of In-Segment Late Luminal Loss at Follow-up Angiography.**

Late luminal loss was defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up.

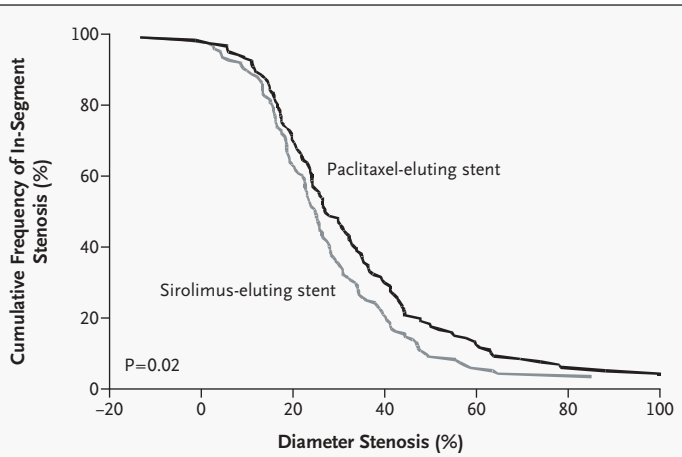


**Figure 2. Cumulative Rates of In-Segment Stenosis at Follow-up Angiography.**

The extent of stenosis was defined as the difference between the reference diameter and the minimal luminal diameter, divided by the reference diameter and multiplied by 100.

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## APPENDIX

The following centers and investigators participated in the ISAR-DIABETES Study: **Steering Committee:** A. Schömig (chair), A. Kastrati (principal investigator); **Event-Adjudication Committee:** J. Dirschinger, H. Schühlen, J. Pache; **Data-Coordinating Center:** J. Mehilli, H. Bollwein, C. Markwardt; **Angiographic Core Laboratory:** A. Dibra, S. Piniek, S. Meier; **Clinical Follow-up Center:** H. Holle, K. Hösl, F. Rodrigues, C. Peterler; **Participating Centers and Investigators:** *Deutsches Herzzentrum, Munich* — J. Pache, C. Schmitt, N. von Beckerath, R. Wessely; *Klinikum rechts der Isar, Munich* — J. Dirschinger, H. Schühlen, M. Seyfarth, M. Karch.

## REFERENCES


**1.** Grundy SM, D'Agostino RB Sr, Mosca L, et al. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood Institute workshop. Circulation 2001;104:491-6.

**2.** Goraya TY, Leibson CL, Palumbo PJ, et al. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. J Am Coll Cardiol 2002;40:946-53.

**3.** Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part II. Circulation 2003; 108:1655-61.

**4.** Hurst RT, Lee RW. Increased incidence of coronary atherosclerosis in type 2 diabetes mellitus: mechanisms and management. Ann Intern Med 2003;139:824-34.

**5.** Carrozza JP Jr, Kuntz RE, Fishman RF, Baim DS. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. Ann Intern Med 1993;118:344-9.

**6.** Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol 1998;32:584-9.

**7.** Elezi S, Kastrati A, Pache J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998;32:1866-73.

**8.** Kuntz RE. Importance of considering atherosclerosis progression when choosing a coronary revascularization strategy: the diabetes-percutaneous transluminal coronary angioplasty dilemma. Circulation 1999;99: 847-51.

**9.** Frye RL, Brooks MM, Nesto RW. Gap between clinical trials and clinical practice: lessons from the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 2003;107:1837-9.

**10.** Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents. Circulation 2003;107:2274-9, 2383-9.

**11.** Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346:1773-80.

**12.** Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349: 1315-23.

**13.** Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221-31.

**14.** Mak KH, Faxon DP. Clinical studies on coronary revascularization in patients with type 2 diabetes. Eur Heart J 2003;24:1087-103.

**15.** Leon MB, Bakhai A. Drug-eluting stents and glycoprotein IIb/IIIa inhibitors: combination therapy for the future. Am Heart J 2003;146:Suppl 4:S13-S17.

**16.** Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 2004;109:2273-8.

**17.** Hermiller JB, Raizner A, Cannon L, et al. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. J Am Coll Cardiol 2005;45:1172-9.

**18.** Kastrati A, Mehilli J, Schühlen H, et al. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. N Engl J Med 2004;350:232-8.

**19.** Mehilli J, Kastrati A, Schühlen H, et al. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. Circulation 2004;110:3627-35.

**20.** Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. Circulation 1990;82:1193-202.

**21.** Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872-8.

**22.** Diabetes mellitus. WHO Tech Rep Ser 1985;727:1-104.

**23.** The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet 1998; 352:87-92.

**24.** O'Brien RG, Muller KE. Unified power analysis for *t*-tests through multivariate hypotheses. In: Edwards LK, ed. Applied analysis of variance in behavioral science. New York: Marcel Dekker, 1993:297-344.

**25.** Chow S-C, Liu J-P. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker, 1992.

**26.** Popma JJ, Leon MB, Moses JW, et al. Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. Circulation 2004;110:3773-80.

**27.** Bauters C, Isner JM. The biology of restenosis. Prog Cardiovasc Dis 1997;40:107-16.

**28.** Regar E, Serruys PW, Bode C, et al. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106:1949-56.

**29.** Mauri L, Orav EJ, O'Malley AJ, et al. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. Circulation 2005;111:321-7.

**30.** Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605-13.

**31.** Psaty BM, Weiss NS, Furberg CD, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999;282:786-90.

**32.** D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues — the encounters of academic consultants in statistics. Stat Med 2003;22:169-86.

**33.** Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788-94.

**34.** Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165-71.

**35.** REALITY at last? REALITY, ISAR-DIABETES, and SIRTAX trials give Cypher an edge, but debate clouds comparisons. The heart.org. (Accessed July 26, 2005, at http://theheart.org/viewArticle.do?primaryKey=397957& from=/searchLayout.do.)

SPECIAL ARTICLE

# Sex and Racial Differences in the Management of Acute Myocardial Infarction, 1994 through 2002

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## ABSTRACT

### BACKGROUND

Although increased attention has been paid to sex and racial differences in the management of myocardial infarction, it is unknown whether these differences have narrowed over time.

### METHODS

With the use of data from the National Registry of Myocardial Infarction, we examined sex and racial differences in the treatment of patients who were deemed to be "ideal candidates" for particular treatments and in deaths among 598,911 patients hospitalized with myocardial infarction between 1994 and 2002.

### RESULTS

In the unadjusted analysis, sex and racial differences were observed for rates of reperfusion therapy (for white men, white women, black men, and black women: 86.5, 83.3, 80.4, and 77.8 percent, respectively; P<0.001), use of aspirin (84.4, 78.7, 83.7, and 78.4 percent, respectively; P<0.001), use of beta-blockers (66.6, 62.9, 67.8, and 64.5 percent; P<0.001), and coronary angiography (69.1, 55.9, 64.0, and 55.0 percent; P<0.001). After multivariable adjustment, racial and sex differences persisted for rates of reperfusion therapy (risk ratio for white women, black men, and black women: 0.97, 0.91, and 0.89, respectively, as compared with white men) and coronary angiography (relative risk, 0.91, 0.82, and 0.76) but were attenuated for the use of aspirin (risk ratio, 0.97, 0.98, and 0.94) and beta-blockers (risk ratio, 0.98, 1.00, and 0.96); all risks were unchanged over time. Adjusted in-hospital mortality was similar among white women (risk ratio, 1.05; 95 percent confidence interval, 1.03 to 1.07) and black men (risk ratio, 0.95; 95 percent confidence interval, 0.89 to 1.00), as compared with white men, but was higher among black women (risk ratio, 1.11; 95 percent confidence interval, 1.06 to 1.16) and was unchanged over time.

### CONCLUSIONS

Rates of reperfusion therapy, coronary angiography, and in-hospital death after myocardial infarction, but not the use of aspirin and beta-blockers, vary according to race and sex, with no evidence that the differences have narrowed in recent years.

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In recent years, attention has been focused on variations in the treatment of coronary heart disease that are related to the sex and race of the patient. Landmark studies in the late 1980s and early 1990s reported differences in treatment according to sex and race.[1-4] In the past decade, other investigations have described a generally consistent pattern of less intensive treatment of acute myocardial infarction in women, as compared with men,[5-11] and in blacks, as compared with whites,[8,9,12-17] across a variety of settings. Efforts to remedy racial and sex differences in health care use have received prominent attention, including a recent Institute of Medicine report[18] and the Public Health Service's Healthy People 2010 initiative.[19]

Although sex and racial differences in the treatment of coronary heart disease have been documented for more than a decade, little is known about whether these differences have persisted in more recent years. We assessed temporal trends in sex and racial differences in the use of guideline-based management for patients hospitalized with acute myocardial infarction.

## METHODS

### PATIENTS

Since July 1, 1990, hospitals participating in the National Registry of Myocardial Infarction (NRMI) have enrolled consecutive patients with myocardial infarction, as previously described.[20] Because NRMI-1 (July 1990 through May 1994) collected little information on patients' characteristics, we restricted our analysis to the 1,724,984 patients from 1917 hospitals who were enrolled in NRMI-2 (June 1994 through March 1998), NRMI-3 (April 1998 through June 2000), and NRMI-4 (July 2000 through May 2002). We excluded 12,132 patients with erroneous discharge dates and 381,018 patients who were transferred from another acute care hospital because their early treatments were not documented. We also excluded 131,474 patients who survived less than 24 hours because of insufficient time to begin treatments; 40,881 patients of unknown age, sex, race, or survival status; 60,689 patients whose race was not recorded as white or black; and 55,316 patients with missing data for model covariables. We restricted our analysis to 658 hospitals (out of 1917 hospitals) participating in NRMI for the full study period, resulting in a final sample of 598,911 patients. NRMI data collection has previously been validated by comparison with the Cooperative Cardiovascular Project.[21] This protocol was deemed exempt from review by the institutional review board at Emory University.

### TREATMENT OF MYOCARDIAL INFARCTION

Patients were evaluated for the use of treatments recommended by the American College of Cardiology–American Heart Association (ACC–AHA) guidelines for the treatment of myocardial infarction since 1990.[22-24] These included acute reperfusion therapy for patients with ST-segment elevation within 24 hours of admission, the administration of aspirin and beta-blockers within 24 hours of admission, and coronary angiography during hospitalization. As secondary treatment end points, we examined the frequency of coronary-artery bypass graft (CABG) surgery and percutaneous transluminal coronary angioplasty (PTCA) (except for primary PTCA, which was included in our definition of reperfusion therapy) during hospitalization.

To exclude racial or sex variations in treatment that may reflect differences in the proportion of patients for whom treatment is considered appropriate, we identified subgroups of patients who were ideally suited for each management strategy — in other words, patients with the strongest indications for treatment (ACC–AHA class I) and without major contraindications, according to guidelines published in 1990,[22] 1996,[23] and 1999.[24] When variations were present in the three sets of guidelines, the 1996 guidelines were followed, since they are similar to the 1999 guidelines and were published closest to the beginning of our observation period.

To avoid bias in regard to the availability of services, rates of coronary angiography were calculated among patients admitted to facilities with full capability of performing invasive cardiovascular procedures. Rates of use of CABG and PTCA were calculated among patients admitted to these facilities who were "ideal candidates" for coronary angiography and who underwent angiography. Because information was lacking on angiographic findings, we were not able to define further patient eligibility for revascularization. The only contraindication to the use of aspirin in the initial management of myocardial infarction is true allergy to salicylates, which is uncommon and was not recorded in NRMI. Therefore, no ideal-candidate subgroup was created for aspirin.

### IN-HOSPITAL MORTALITY

We examined trends in hospital mortality according to sex and race. This analysis was restricted to patients who were not transferred to another acute care hospital, since the survival status of transferred patients in the second hospital was unknown.

### STATISTICAL ANALYSIS

We categorized patients into four groups according to race and sex: white men, white women, black men, and black women. Sex and racial differences in demographic and clinical factors and in the characteristics of hospitals were assessed over the full study period and stratified according to year of treatment (with a year defined as the period from June through May). We calculated crude rates of treatment and in-hospital mortality for the selected subgroups of ideal-candidate patients in the four groups.

We used logistic-regression models to derive the likelihood of treatment and death for the four groups.[25] We tested whether differences in the use of treatments according to sex and race changed over time by including a three-way interaction term reflecting the sex and race of patients and the year. Three consecutive models were constructed for each end point. Model 1 included sex, race, year, and all two-way and three-way interaction terms among sex, race, and year; model 2 expanded the data in model 1 to include other demographic and clinical factors; and model 3 expanded the data in model 2 to include characteristics of the hospitals. To assess whether the clustering of patients within hospitals affected our results, analyses were repeated with the use of generalized-estimating-equation models. The results were similar and are not reported. All analyses were performed using SAS software (version 8.2).

## RESULTS

### CHARACTERISTICS OF PATIENTS AND HOSPITALS

The mean age of patients did not change substantially over time, but the prevalence of most coronary risk factors increased in all subgroups (Table 1), whereas there was a decline in the proportion of patients with ST-segment elevation or Q waves on initial electrocardiography. The four subgroups showed similar time trends in most factors, as shown by the nonsignificant interaction among sex, race, and year. In all years combined, there were substantial differences in many factors according to sex and race. For example, women in both racial groups were older than men, whereas blacks in both sex groups were younger than whites. As compared with white men, fewer female and black patients had ST-segment elevation or Q waves on initial electrocardiography, but women and blacks had more risk factors, a higher Killip class, and a longer delay to reach the hospital. As compared with whites, black patients tended to be hospitalized more often in facilities that were used for teaching, were affiliated with medical schools, were located in urban areas, and had equipment for performing cardiovascular procedures.

### IDEAL CANDIDATES FOR TREATMENTS AND PROCEDURES

The proportion of patients qualifying as ideal candidates for reperfusion and the administration of beta-blockers was 50 percent or less and declined over time in all groups. At each time point, women and blacks were less likely than white men to be ideal candidates (Fig. 1). Approximately 10 percent of patients were classified as ideal candidates for coronary angiography. This percentage was similar in all sex and racial groups and fairly constant over time.

### TREATMENTS AND PROCEDURES AMONG IDEAL CANDIDATES

In the unadjusted analysis, treatment rates differed according to sex and race, with rates highest in white men and lowest in black women (Table 2). Differences were larger for rates of reperfusion therapy and coronary angiography, particularly for black women, but smaller for the use of aspirin and beta-blockers. The use of aspirin and beta-blockers increased over time, whereas rates of reperfusion therapy remained stable and those of coronary angiography decreased slightly, with similar time trends in the four demographic groups. As a result, there was no significant variation over time in treatment differences according to sex or race.

Results that were adjusted for the characteristics of patients and hospitals were similar (Table 3). Because models 2 and 3 provided almost identical results, only the results of model 3 (adjusted for both patient and hospital characteristics) are presented. The interaction among the factors of sex, race, and year, as well as all other pairwise interactions, were not significant, indicating that racial and

**Table 1. Demographic and Clinical Characteristics of Hospitalized Patients According to Sex, Race, and Study Year.***

| Characteristic | White Men | | | | | White Women | | | | | Black Men | | | | | Black Women | | | | | P Value‡ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years† | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years† | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years† | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years† | |
| **Patients** | | | | | | | | | | | | | | | | | | | | | |
| Mean age (yr) | 65.1 | 65.9 | 66.9 | 67.4 | 66.4 | 72.9 | 73.4 | 74.4 | 75.0 | 74.0 | 60.5 | 60.8 | 61.4 | 62.0 | 61.3 | 66.6 | 66.8 | 67.6 | 67.9 | 67.3 | 0.96 |
| Primary medical insurance (%) | | | | | | | | | | | | | | | | | | | | | 0.46 |
| Age <65 yr and commercial insurer or PPO | 24.2 | 21.7 | 21.8 | 21.0 | 22.1 | 10.9 | 9.8 | 9.7 | 9.5 | 9.9 | 21.0 | 18.1 | 19.2 | 18.2 | 19.0 | 13.1 | 10.6 | 10.5 | 11.0 | 11.2 | |
| Age <65 and HMO | 6.8 | 8.7 | 9.6 | 8.9 | 8.6 | 3.2 | 4.1 | 4.5 | 4.2 | 4.0 | 8.6 | 10.9 | 12.4 | 11.6 | 11.0 | 6.6 | 6.8 | 8.2 | 7.9 | 7.5 | |
| Age <65 yr and Medicaid | 1.5 | 1.4 | 1.3 | 1.4 | 1.4 | 2.0 | 1.8 | 1.7 | 1.7 | 1.8 | 4.7 | 4.3 | 4.3 | 5.0 | 4.6 | 7.1 | 6.9 | 6.4 | 5.9 | 6.5 | |
| Age <65 yr and other type of insurance | 10.8 | 9.5 | 7.0 | 6.7 | 8.4 | 5.5 | 4.8 | 3.4 | 3.1 | 4.1 | 17.7 | 17.8 | 14.1 | 13.1 | 15.5 | 10.1 | 10.7 | 8.3 | 7.0 | 8.8 | |
| Medicare, age ≥65 yr | 56.7 | 58.7 | 60.3 | 62.0 | 59.6 | 78.5 | 79.4 | 80.6 | 81.5 | 80.1 | 48.1 | 48.9 | 50.1 | 52.1 | 49.9 | 63.0 | 65.0 | 66.5 | 68.2 | 66.0 | |
| Medical history (%) | | | | | | | | | | | | | | | | | | | | | |
| Myocardial infarction | 27.5 | 27.9 | 27.5 | 27.6 | 27.6 | 23.6 | 23.9 | 23.7 | 24.0 | 23.8 | 24.9 | 26.5 | 24.9 | 26.1 | 25.6 | 25.2 | 25.6 | 23.0 | 24.1 | 24.3 | 0.04 |
| Angina | 18.5 | 17.7 | 14.0 | 12.5 | 15.5 | 19.9 | 18.8 | 14.1 | 12.4 | 15.9 | 14.2 | 13.9 | 11.5 | 9.2 | 12.0 | 16.8 | 16.6 | 12.0 | 9.5 | 13.2 | 0.25 |
| Heart failure | 10.9 | 12.1 | 14.2 | 15.8 | 13.4 | 19.2 | 20.2 | 23.3 | 24.7 | 22.1 | 12.5 | 15.1 | 18.1 | 18.7 | 16.4 | 21.4 | 23.0 | 24.8 | 27.4 | 24.5 | 0.64 |
| PTCA | 8.9 | 10.3 | 12.3 | 14.5 | 11.6 | 5.6 | 6.9 | 8.3 | 9.6 | 7.8 | 6.6 | 8.0 | 10.1 | 11.9 | 9.5 | 6.0 | 6.6 | 7.7 | 10.1 | 7.8 | 0.54 |
| CABG | 14.6 | 15.8 | 17.5 | 18.8 | 16.8 | 8.2 | 9.5 | 10.2 | 10.9 | 9.8 | 6.6 | 7.7 | 9.1 | 10.2 | 8.5 | 5.8 | 6.4 | 7.3 | 8.4 | 7.2 | 0.63 |
| Stroke | 7.1 | 8.0 | 9.3 | 9.2 | 8.5 | 9.8 | 10.6 | 12.6 | 12.4 | 11.5 | 9.5 | 10.2 | 12.5 | 12.3 | 11.3 | 12.2 | 14.1 | 15.4 | 14.8 | 14.3 | 0.17 |
| Diabetes | 22.3 | 23.8 | 26.4 | 28.0 | 25.3 | 29.8 | 30.2 | 32.0 | 32.2 | 31.2 | 31.2 | 31.0 | 34.6 | 34.4 | 33.0 | 45.8 | 47.1 | 45.4 | 47.5 | 46.5 | 0.36 |
| Hypertension | 44.6 | 47.6 | 51.3 | 55.3 | 49.9 | 56.5 | 59.8 | 63.5 | 66.8 | 62.1 | 62.9 | 65.9 | 68.1 | 70.8 | 67.3 | 74.3 | 77.0 | 78.5 | 81.5 | 78.3 | 0.61 |
| Current smoking | 30.4 | 29.3 | 27.3 | 27.1 | 28.4 | 20.1 | 19.5 | 18.0 | 17.6 | 18.7 | 39.5 | 38.6 | 36.2 | 36.2 | 37.5 | 22.5 | 22.9 | 21.9 | 22.0 | 22.3 | 0.04 |
| Hypercholesterolemia | 25.8 | 29.3 | 32.6 | 36.4 | 31.3 | 24.1 | 27.0 | 28.1 | 30.7 | 27.7 | 18.7 | 22.7 | 23.4 | 27.4 | 23.3 | 20.4 | 22.7 | 23.7 | 27.2 | 23.9 | 0.32 |
| Time from onset of symptoms to arrival at hospital | | | | | | | | | | | | | | | | | | | | | |
| Mean (hr) | 5.3 | 5.2 | 5.2 | 5.1 | 5.2 | 6.3 | 5.9 | 5.9 | 5.6 | 5.9 | 6.2 | 5.7 | 5.9 | 5.2 | 5.8 | 6.5 | 6.6 | 6.6 | 5.9 | 6.4 | 0.03 |
| Not available (%) | 21.8 | 25.0 | 32.1 | 38.1 | 29.6 | 28.7 | 32.6 | 40.7 | 47.4 | 38.2 | 26.9 | 31.9 | 39.3 | 46.0 | 36.8 | 33.7 | 39.3 | 46.4 | 52.7 | 44.3 | 0.26 |
| Chest pain on presentation (%) | 76.5 | 73.7 | 68.3 | 66.2 | 70.9 | 67.0 | 64.0 | 56.5 | 53.8 | 59.7 | 71.8 | 69.7 | 65.0 | 62.8 | 66.9 | 64.4 | 61.6 | 55.2 | 54.5 | 58.2 | 0.30 |
| Changes in first electrocardiogram (%) | | | | | | | | | | | | | | | | | | | | | |
| ST-segment elevation | 44.8 | 40.7 | 33.6 | 28.3 | 36.4 | 40.2 | 35.6 | 27.6 | 22.5 | 30.7 | 41.0 | 38.4 | 30.5 | 25.1 | 33.1 | 33.6 | 31.1 | 23.7 | 19.2 | 25.9 | 0.17 |
| ST-segment depression | 28.3 | 29.4 | 28.4 | 27.3 | 28.3 | 28.3 | 29.1 | 27.6 | 25.8 | 27.6 | 24.6 | 25.5 | 23.3 | 21.8 | 23.7 | 23.6 | 24.7 | 23.1 | 20.8 | 22.9 | 0.34 |
| Q wave | 12.0 | 10.2 | 8.7 | 7.8 | 9.6 | 10.8 | 9.0 | 7.0 | 6.5 | 8.1 | 9.7 | 9.1 | 7.3 | 6.4 | 8.0 | 7.9 | 7.9 | 5.4 | 5.6 | 6.5 | 0.32 |
| Left bundle-branch block | 5.3 | 5.6 | 5.4 | 3.6 | 5.0 | 7.5 | 7.9 | 7.6 | 4.8 | 6.9 | 3.5 | 4.4 | 3.9 | 3.0 | 3.7 | 6.2 | 6.0 | 5.6 | 3.4 | 5.1 | 0.03 |
| Killip class (%) | | | | | | | | | | | | | | | | | | | | | 0.72 |
| 1 (No heart failure) | 78.9 | 78.6 | 78.1 | 78.1 | 78.4 | 67.9 | 68.3 | 68.0 | 68.6 | 68.2 | 75.9 | 76.2 | 74.2 | 75.2 | 75.3 | 67.1 | 66.5 | 68.1 | 67.6 | 67.4 | |
| 2 (Heart failure) | 14.2 | 14.4 | 14.7 | 15.0 | 14.6 | 20.9 | 20.8 | 21.0 | 21.3 | 21.0 | 16.0 | 15.7 | 17.3 | 17.1 | 16.6 | 20.2 | 20.8 | 19.4 | 20.8 | 20.3 | |
| 3 (Pulmonary edema) | 6.1 | 6.3 | 6.4 | 6.1 | 6.2 | 10.2 | 10.0 | 10.2 | 9.3 | 9.9 | 7.7 | 7.3 | 7.8 | 7.2 | 7.5 | 12.0 | 11.9 | 11.8 | 10.9 | 11.6 | |
| 4 (Cardiogenic shock) | 0.8 | 0.7 | 0.8 | 0.8 | 0.8 | 1.0 | 0.9 | 0.7 | 0.8 | 0.8 | 0.5 | 0.7 | 0.7 | 0.6 | 0.6 | 0.7 | 0.9 | 0.7 | 0.7 | 0.8 | |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean systolic blood pressure (mm Hg) | 144.9 | 145.1 | 144.3 | 143.7 | 144.5 | 145.5 | 146.3 | 145.6 | 145.1 | 145.6 | 149.9 | 148.4 | 147.7 | 147.6 | 148.3 | 150.5 | 150.9 | 151.1 | 151.2 | 151.0 | 0.008 |
| Mean pulse (beats/min) | 84.2 | 84.9 | 86.1 | 86.4 | 85.5 | 89.0 | 89.8 | 91.0 | 91.4 | 90.4 | 86.4 | 87.0 | 88.9 | 88.8 | 87.9 | 90.0 | 91.5 | 92.1 | 92.2 | 91.6 | 0.16 |
| Creatine kinase or creatine kinase MB ≥2 times normal (%) | 85.6 | 86.0 | 80.3 | 76.2 | 81.9 | 82.1 | 82.3 | 74.3 | 69.2 | 76.5 | 85.6 | 85.4 | 79.5 | 76.5 | 81.4 | 82.7 | 82.7 | 75.0 | 70.4 | 76.9 | 0.96 |
| Ejection fraction (%) | | | | | | | | | | | | | | | | | | | | | 0.32 |
| ≥0.40 | 42.1 | 45.4 | 47.3 | 52.2 | 46.9 | 38.5 | 42.9 | 45.6 | 50.4 | 44.8 | 42.0 | 43.6 | 46.4 | 49.7 | 45.8 | 41.7 | 42.5 | 46.9 | 50.3 | 46.0 | |
| <0.40 | 15.3 | 17.5 | 19.4 | 22.4 | 18.8 | 14.7 | 16.8 | 18.4 | 21.6 | 18.2 | 17.4 | 19.9 | 23.9 | 26.4 | 22.3 | 16.1 | 19.0 | 20.0 | 23.9 | 20.2 | |
| Not assessed | 42.6 | 37.2 | 33.3 | 25.4 | 34.3 | 46.8 | 40.3 | 36.0 | 28.0 | 37.0 | 40.6 | 36.5 | 29.8 | 23.8 | 31.9 | 42.2 | 38.5 | 33.0 | 25.8 | 33.8 | |
| **Hospitals** | | | | | | | | | | | | | | | | | | | | | |
| Staffed beds >200 (%) | 72.9 | 72.7 | 73.1 | 73.7 | 73.1 | 71.7 | 72.4 | 71.8 | 72.3 | 72.1 | 84.4 | 85.2 | 86.5 | 86.6 | 85.8 | 85.6 | 85.4 | 86.9 | 86.8 | 86.3 | 0.47 |
| Medical-school affiliation (%) | 42.5 | 43.3 | 45.3 | 44.6 | 44.0 | 42.4 | 43.6 | 44.7 | 43.6 | 43.7 | 55.8 | 56.6 | 58.2 | 58.6 | 57.4 | 58.2 | 59.3 | 59.9 | 60.4 | 59.6 | 0.95 |
| Teaching facility (%) | 8.5 | 9.7 | 8.4 | 8.7 | 8.8 | 7.7 | 9.2 | 8.1 | 8.6 | 8.4 | 18.0 | 20.5 | 17.5 | 18.7 | 18.6 | 19.1 | 22.6 | 18.8 | 18.6 | 19.7 | 0.01 |
| Urban location (%) | 83.0 | 82.6 | 83.7 | 84.4 | 83.5 | 81.9 | 81.8 | 82.5 | 83.3 | 82.4 | 88.5 | 88.4 | 89.8 | 91.1 | 89.6 | 90.2 | 88.5 | 89.8 | 91.0 | 89.9 | 0.08 |
| Facilities for cardiovascular procedures (%) | | | | | | | | | | | | | | | | | | | | | 0.31 |
| None | 17.1 | 15.7 | 13.8 | 11.7 | 14.5 | 19.0 | 17.1 | 15.5 | 13.8 | 16.1 | 9.8 | 7.9 | 8.7 | 7.9 | 8.5 | 8.8 | 7.1 | 7.9 | 7.4 | 7.7 | |
| Coronary catheterization only | 27.3 | 27.3 | 24.2 | 20.1 | 24.6 | 29.0 | 28.8 | 26.4 | 23.0 | 26.5 | 25.9 | 25.8 | 23.7 | 19.4 | 23.4 | 25.9 | 25.9 | 24.7 | 20.6 | 24.0 | |
| PTCA, no open heart surgery | 7.1 | 6.3 | 5.9 | 7.3 | 6.6 | 7.3 | 6.4 | 6.1 | 7.5 | 6.8 | 8.7 | 6.9 | 6.2 | 9.7 | 7.9 | 8.4 | 6.9 | 7.3 | 10.5 | 8.4 | |
| PTCA and open heart surgery | 48.5 | 50.7 | 56.1 | 60.8 | 54.3 | 44.7 | 47.7 | 52.0 | 55.6 | 50.5 | 55.5 | 59.4 | 61.4 | 63.0 | 60.2 | 57.0 | 60.0 | 60.1 | 61.4 | 59.9 | |
| Quartile of myocardial-infarction volume (%)§ | | | | | | | | | | | | | | | | | | | | | 0.15 |
| ≤79 | 5.5 | 4.8 | 4.0 | 3.4 | 4.4 | 6.0 | 4.9 | 4.5 | 3.9 | 4.7 | 3.0 | 3.0 | 2.8 | 2.4 | 2.8 | 3.5 | 2.8 | 3.6 | 2.5 | 3.1 | |
| 80–135 | 14.3 | 13.5 | 12.2 | 11.9 | 12.9 | 14.7 | 14.1 | 13.3 | 13.4 | 13.8 | 14.8 | 13.9 | 13.3 | 11.5 | 13.2 | 14.8 | 12.7 | 13.4 | 12.1 | 13.1 | |
| 136–228 | 26.6 | 25.1 | 24.8 | 24.4 | 25.2 | 28.1 | 26.3 | 25.6 | 26.0 | 26.4 | 32.1 | 29.4 | 29.6 | 28.9 | 29.9 | 30.3 | 31.4 | 31.7 | 30.8 | 31.1 | |
| ≥229 | 53.6 | 56.6 | 58.9 | 60.2 | 57.5 | 51.2 | 54.7 | 56.5 | 56.8 | 55.1 | 50.1 | 53.7 | 54.2 | 57.2 | 54.1 | 51.5 | 53.1 | 51.3 | 54.6 | 52.7 | |
| Hospital ownership (%) | | | | | | | | | | | | | | | | | | | | | 0.77 |
| Public | 12.6 | 12.9 | 11.6 | 11.0 | 12.0 | 12.3 | 12.4 | 11.3 | 10.6 | 11.6 | 16.4 | 19.1 | 18.6 | 15.9 | 17.5 | 16.6 | 20.3 | 17.2 | 16.8 | 17.7 | |
| Private, not-for-profit | 82.5 | 81.9 | 82.7 | 83.5 | 82.7 | 83.3 | 83.0 | 83.6 | 84.5 | 83.6 | 79.7 | 75.2 | 76.7 | 79.8 | 77.9 | 79.3 | 75.3 | 78.3 | 79.6 | 78.2 | |
| Private, for-profit | 4.8 | 5.2 | 5.7 | 5.5 | 5.3 | 4.4 | 4.6 | 5.1 | 4.9 | 4.8 | 3.9 | 5.7 | 4.6 | 4.3 | 4.6 | 4.1 | 4.4 | 4.6 | 3.6 | 4.2 | |

* The study period was June to May, so there is overlap in years. HMO denotes health maintenance organization, PPO preferred provider organization, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass grafting. Because of rounding, not all percentages total 100.

† P<0.01 for the comparison of white men with white women, black men, and black women for all years combined, except for P values for creatinine kinase levels, which were two or more times the normal level among black men (P=0.33).

‡ P values indicate whether there is a significant difference in the trend over time for factors among the four subgroups defined by sex and race.

§ Volume denotes the number of patients admitted with myocardial infarction per year.

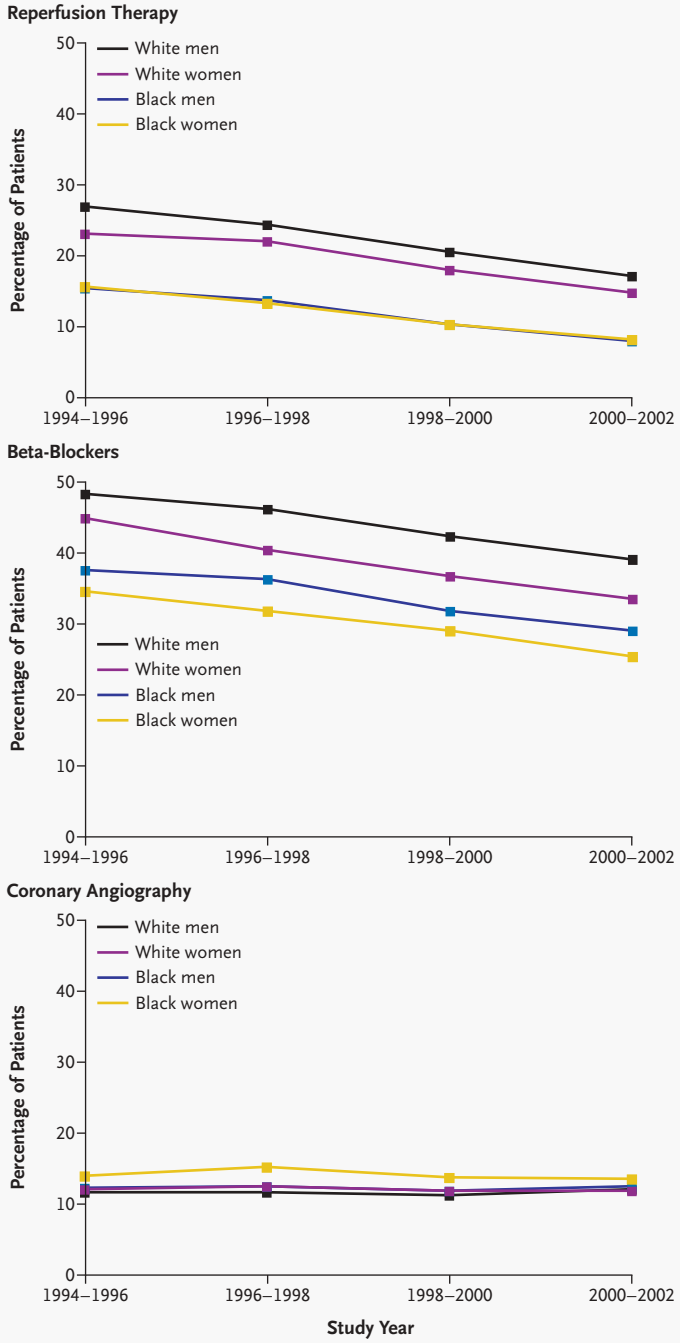


**Figure 1. Proportions of Patients Considered Ideally Suited for Treatments and Procedures after Acute Myocardial Infarction, According to Sex and Race by Study Year.**

A year was defined in this study as the period from June through May.

sex differences in treatment did not change over time. In absolute terms, black women remained the group with the lowest rate of use of interventions. As compared with white men, the adjusted risk ratio for the use of reperfusion therapy in all years combined was 0.97 for white women, 0.91 for black men, and 0.89 for black women ($P<0.001$ for all comparisons). For coronary angiography, corresponding estimates were 0.91, 0.82, and 0.76 ($P<0.001$ for all comparisons). Adjusted differences for the use of aspirin and beta-blockers were small. For the use of aspirin, the risk ratio during the entire period was 0.97 for white women, 0.98 for black men, and 0.94 for black women, as compared with white men ($P<0.001$ for all comparisons). For the use of beta-blockers, corresponding figures were 0.98 ($P<0.001$), 1.00 ($P=0.55$), and 0.96 ($P<0.001$). Preferences of patients with respect to reperfusion therapy were recorded starting in 1998. These data show few refusals for reperfusion therapy (less than 0.5 percent) in each sex-and-race subgroup.

Analysis of secondary treatment end points indicated lower rates of use of CABG as compared with white men, with an adjusted risk ratio of treatment for white women, black men, and black women of 0.73, 0.74, and 0.63, respectively ($P<0.001$ for all comparisons). Adjusted differences in rates of PTCA according to sex and race were small, except for black women (risk ratio, 0.89; 95 percent confidence interval, 0.83 to 0.95); white women had slightly higher rates of PTCA than did white men (risk ratio, 1.06; 95 percent confidence interval, 1.04 to 1.08). Data on the use of stents were available starting in 1998. There was a steady increase in stent use over time, from 73.1 percent in 1998 to 87.3 percent in 2000 through 2002. Similar proportions of patients undergoing PTCA received stents regardless of sex or race, with similar time trends. Racial and sex differences in the use of CABG and PTCA did not change over the study period.

### MORTALITY

Overall, 21.7 percent of patients were transferred to other hospitals and excluded from assessment of in-hospital mortality. The proportion of patients who were transferred varied among groups according to race and sex: 23.2 percent for white men, 18.0 percent for white women, 18.3 percent for

**Table 2. Unadjusted Rates of Treatments, Procedures, and Outcomes among Hospitalized Patients, According to Sex, Race, and Study Year.***

| Characteristic | White Men | | | | | White Women | | | | | Black Men | | | | | Black Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years |
| | *percent* | | | | | | | | | | | | | | | | | | | |
| Primary treatment end points | | | | | | | | | | | | | | | | | | | | |
| Reperfusion therapy in first 24 hr for ideal candidates† | 87.4 | 87.4 | 84.1 | 86.8 | 86.5 | 84.9 | 83.8 | 81.6 | 82.6 | 83.3 | 80.4 | 80.8 | 79.8 | 80.7 | 80.4 | 79.6 | 78.4 | 74.5 | 78.8 | 77.8 |
| Aspirin in first 24 hr, all patients | 80.7 | 85.4 | 86.8 | 84.2 | 84.4 | 73.5 | 80.1 | 81.3 | 78.8 | 78.7 | 79.5 | 84.1 | 85.1 | 84.5 | 83.7 | 72.2 | 79.8 | 80.4 | 79.3 | 78.4 |
| Beta-blockers in first 24 hr for ideal candidates‡ | 54.7 | 63.2 | 69.3 | 79.7 | 66.6 | 49.7 | 59.7 | 65.6 | 76.0 | 62.9 | 57.1 | 62.9 | 71.2 | 80.0 | 67.8 | 49.8 | 60.7 | 69.1 | 75.6 | 64.5 |
| Coronary angiography for ideal candidates§ | 72.3 | 72.3 | 67.0 | 65.4 | 69.1 | 58.0 | 59.7 | 54.5 | 52.7 | 55.9 | 68.5 | 65.6 | 62.0 | 61.1 | 64.0 | 59.5 | 56.4 | 54.8 | 51.1 | 55.0 |
| Secondary treatment end points | | | | | | | | | | | | | | | | | | | | |
| CABG (excluding immediate CABG) for catheterized patients¶ | 25.5 | 26.6 | 26.4 | 28.1 | 26.7 | 22.4 | 22.3 | 23.1 | 23.3 | 22.8 | 19.5 | 21.6 | 20.5 | 22.7 | 21.1 | 15.9 | 18.2 | 23.7 | 20.4 | 19.8 |
| PTCA (excluding primary procedure) for catheterized patients¶ | 44.5 | 45.0 | 48.2 | 46.7 | 46.1 | 43.6 | 45.1 | 46.6 | 44.5 | 45.0 | 39.6 | 44.7 | 48.5 | 43.0 | 44.0 | 39.8 | 33.4 | 37.8 | 41.5 | 38.1 |
| In-hospital mortality for all patients | 8.8 | 8.5 | 9.1 | 8.8 | 8.8 | 13.7 | 12.3 | 12.2 | 11.4 | 12.3 | 6.8 | 6.8 | 7.5 | 7.8 | 7.3 | 10.5 | 10.5 | 11.3 | 10.5 | 10.7 |

* The study period was June to May, so there is overlap in years. CABG denotes coronary-artery bypass grafting and PTCA percutaneous transluminal coronary angioplasty.

† Patients were considered ideal candidates for reperfusion therapy if they were less than 75 years of age, had ST-segment elevation on the first echocardiogram, presented within 12 hours after the onset of symptoms, did not have documented contraindications to fibrinolytic therapy (i.e., active internal bleeding or known bleeding diathesis; a history of stroke, recent surgery, or trauma; intracranial neoplasm; severe uncontrolled hypertension; or other documented contraindication), and did not decline to receive treatment.

‡ Patients were considered ideal candidates for beta-blocker therapy if they had a pulse of at least 60 beats per minute; did not have evidence of heart failure, shock, or hypotension (i.e., systolic blood pressure <100 mm Hg); and presented within 12 hours after the onset of symptoms.

§ Patients were considered ideal candidates for coronary angiography if they were admitted to hospitals fully able to perform invasive procedures and if they had had any of the following conditions: hypotension requiring intervention, recurrent angina, ischemia or infarction, cardiogenic shock, and hemodynamic instability.

¶ Patients were considered ideal candidates for coronary angiography and had undergone the procedure.

black men, and 14.4 percent for black women (P<0.001). Among patients who remained in the same hospital, overall unadjusted mortality was 10.2 percent, ranging from 7.3 percent among black men to 12.3 percent among white women (Table 2). After adjustment for differences in age and other characteristics of patients and hospitals, the death rate in hospitals was similar among black men (risk ratio as compared with white men, 0.95; 95 percent confidence interval, 0.89 to 1.00) and white women (risk ratio, 1.05; 95 percent confidence interval, 1.03 to 1.07), but higher among black women (risk ratio, 1.11; 95 percent confidence interval, 1.06 to 1.16). Racial and sex differences did not change over time.

## DISCUSSION

There were notable differences and similarities in the treatment and outcome of myocardial infarction according to race and sex from 1994 through 2002. As compared with white men, fewer black men and black women received reperfusion therapy and coronary angiography, whereas black women had the highest adjusted mortality rate among all sex and racial groups. In contrast, differences in treatment and mortality between white women and white men were generally small, as were differences between any of the four racial and sex groups in the use of aspirin and beta-blockers. Racial and sex differences were essentially unchanged between 1994 and 2002.

Management differences were greater when patients were compared according to race within each sex (black men vs. white men and black women vs. white women) than when they were compared according to sex within each race (black men vs. black women or white men vs. white women), suggesting that disparities according to race may be more important than disparities according to sex. Black women had the highest risk of not receiving reperfusion therapy and coronary angiography. Several previous studies also documented less aggressive management of coronary disease in both women[5-11] and blacks.[8,9,12,14,15] The few studies that examined subgroups classified according to both sex and race also found the lowest rates among black women.[13,26,27]

Treatment differences according to sex and race persisted without much variation between 1994 and 2002. Although several studies investigated time trends in management of acute myocardial infarc-

**Table 3. Unadjusted and Adjusted Risk Ratios for Treatments, Procedures, and Outcomes among Hospitalized Patients Classified According to Sex, Race, and Study Year.***

| Characteristic | White Women | | | | | Black Men | | | | | P Value† | Black Women | | | | | P Value‡ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years§ | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years§ | | 1994–1996 | 1996–1998 | 1998–2000 | 2000–2002 | All Years§ | |
| | *risk ratio* | | | | | | | | | | | | | | | | |
| **Primary treatment end points** | | | | | | | | | | | | | | | | | |
| Reperfusion therapy in first 24 hr for ideal candidates | | | | | | | | | | | | | | | | | |
| Unadjusted | 0.97 | 0.96 | 0.97 | 0.95 | 0.96 | 0.92 | 0.92 | 0.95 | 0.93 | 0.93 | 0.34 | 0.91 | 0.90 | 0.89 | 0.91 | 0.90 | 0.68 |
| Adjusted¶ | 0.98 | 0.97 | 0.98 | 0.95 | 0.97 | 0.90 | 0.91 | 0.94 | 0.90 | 0.91 | 0.26 | 0.91 | 0.90 | 0.87 | 0.89 | 0.89 | 0.67 |
| Aspirin in first 24 hr for all patients | | | | | | | | | | | | | | | | | |
| Unadjusted | 0.91 | 0.94 | 0.94 | 0.94 | 0.93 | 0.98 | 0.98 | 0.99 | 1.00 | 0.99 | 0.30 | 0.90 | 0.93 | 0.93 | 0.94 | 0.93 | 0.56 |
| Adjusted¶ | 0.96 | 0.97 | 0.97 | 0.97 | 0.97 | 0.97 | 0.97 | 0.98 | 1.00 | 0.98 | 0.55 | 0.90 | 0.94 | 0.93 | 0.96 | 0.94 | 0.38 |
| Beta-blockers in first 24 hr for ideal candidates | | | | | | | | | | | | | | | | | |
| Unadjusted | 0.91 | 0.94 | 0.95 | 0.95 | 0.94 | 1.04 | 0.99 | 1.03 | 1.00 | 1.02 | 0.80 | 0.91 | 0.96 | 1.00 | 0.95 | 0.97 | 0.78 |
| Adjusted¶ | 0.96 | 0.98 | 0.98 | 0.98 | 0.98 | 1.00 | 0.96 | 1.00 | 1.00 | 1.00 | 0.38 | 0.88 | 0.95 | 0.98 | 0.96 | 0.96 | 0.75 |
| Coronary angiography for ideal candidates | | | | | | | | | | | | | | | | | |
| Unadjusted | 0.80 | 0.83 | 0.81 | 0.81 | 0.81 | 0.95 | 0.91 | 0.92 | 0.93 | 0.93 | 0.07 | 0.82 | 0.78 | 0.82 | 0.78 | 0.80 | 0.62 |
| Adjusted‖ | 0.91 | 0.93 | 0.93 | 0.89 | 0.91 | 0.82 | 0.78 | 0.84 | 0.86 | 0.82 | 0.055 | 0.82 | 0.73 | 0.77 | 0.77 | 0.76 | 0.25 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Secondary management end points** | | | | | | | | | | | | | | | | | | |
| CABG (excluding immediate CABG) among catheterized patients | | | | | | | | | | | | | | | | | | |
| Unadjusted | 0.88 | 0.84 | 0.88 | 0.83 | 0.85 | 0.76 | 0.81 | 0.78 | 0.81 | 0.79 | 0.62 | 0.68 | 0.90 | 0.73 | 0.74 | 0.89 | 0.42 | |
| Adjusted‖ | 0.76 | 0.71 | 0.77 | 0.71 | 0.73 | 0.69 | 0.78 | 0.73 | 0.77 | 0.74 | 0.50 | 0.57 | 0.78 | 0.63 | 0.63 | 0.88 | 0.41 | |
| PTCA (excluding primary procedure) among catheterized patients | | | | | | | | | | | | | | | | | | |
| Unadjusted | 0.98 | 1.00 | 0.97 | 0.95 | 0.98 | 0.89 | 0.99 | 1.01 | 0.92 | 0.95 | 0.89 | 0.74 | 0.78 | 0.89 | 0.83 | 0.08 | 0.52 | |
| Adjusted‖ | 1.06 | 1.10 | 1.04 | 1.04 | 1.06 | 0.92 | 0.99 | 1.02 | 0.92 | 0.97 | 0.98 | 0.79 | 0.81 | 0.94 | 0.89 | 0.049 | 0.48 | |
| **In-hospital mortality for all patients** | | | | | | | | | | | | | | | | | | |
| Unadjusted | 1.52 | 1.42 | 1.33 | 1.29 | 1.38 | 0.77 | 0.81 | 0.82 | 0.88 | 0.82 | 1.19 | 1.23 | 1.24 | 1.19 | 1.21 | 0.80 | 0.72 | |
| Adjusted¶ | 1.10 | 1.10 | 1.01 | 0.99 | 1.05 | 0.92 | 0.94 | 0.92 | 0.99 | 0.95 | 1.03 | 1.11 | 1.14 | 1.11 | 1.11 | 0.73 | 0.31 | |

* Patients were considered ideal candidates for reperfusion if they were less than 75 years of age, had ST-segment elevation on the first echocardiogram, presented within 12 hours after the onset of symptoms, did not have documented contraindications to fibrinolytic therapy (i.e., active internal bleeding or known bleeding diathesis; history of stroke, recent surgery, or trauma; intracranial neoplasm; severe uncontrolled hypertension; or other documented contraindication), and did not decline to receive treatment. The study period was June to May, so there is overlap in years. CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

† P values are for the interaction between sex and race.

‡ This P value indicates whether there is a significant difference in the trend over time for treatments or procedures among the four subgroups defined by race and sex.

§ P<0.01 for the comparison of white men with white women, black men, and black women, for all years combined, except for beta-blockers in black men (unadjusted P=0.05; adjusted P=0.55), PTCA in black men (unadjusted P=0.09; adjusted P=0.26), PTCA in white women (unadjusted P=0.02), and mortality in black men (adjusted P=0.06).

¶ Risk ratios were adjusted for age, insurance status, medical history (a history of myocardial infarction, angina, heart failure, stroke, diabetes, hypertension, or hypercholesterolemia; current smoking status; and previous CABG or PTCA), severity characteristics on admission (Killip class, systolic blood pressure, pulse, chest pain, left bundle-branch block, creatine kinase levels, location of anterior or septal infarct, and left ventricular ejection fraction [classified as <40 percent, ≥40 percent, or missing]), time from the onset of symptoms to hospital arrival (<3 hours, 3 to 6 hours, >6 to 12 hours, >12 hours, or not available), and hospital characteristics (number of beds; medical-school affiliation or teaching status; urban location; availability of invasive procedures, including catheterization, CABG, and PTCA; annual quartiles for the volume of myocardial infarction, and hospital ownership [including public, private not-for-profit, and private for-profit]).

‖ Risk ratios were adjusted for the same factors as those listed above, except that availability of invasive procedures was not included among hospital characteristics, since only patients admitted to hospitals fully able to perform invasive procedures were examined for the use of cardiovascular procedures.

tion,[28-30] none examined such trends with respect to patients' sex or race. Studies of patients who were referred for cardiovascular evaluation[31,32] found little difference in management according to sex, with little variation over time. One study that was based on administrative Medicare databases found smaller differences between blacks and whites in the use of coronary angiography and revascularization procedures in 1997 than in 1986.[33] Since results were adjusted only for sex and age, variations over time may reflect variations in the characteristics of patients or in their diagnoses, rather than in patterns of use in health care.

Despite considerable debate, reasons for these differences are largely unknown. Potential explanations are sex and racial differences in eligibility for treatment, clinical contraindications, and confounding by other clinical factors.[34] We mostly excluded these possibilities by focusing on ideal candidates and by adjusting for characteristics of patients and hospitals, although some misclassification is possible. It seems unlikely that misclassification affected our conclusions, because such errors should not have occurred differentially according to sex, race, or study year.

The preferences of patients regarding therapy may play some role in the treatment differences that were observed. Data on patients' preferences in NRMI were limited to reperfusion therapy in the latest years; therefore, we could not account for the preferences of patients in our analysis. However, available data indicated very low rates of refusal (less than 0.5 percent) in all sex and racial subgroups. Incomplete information regarding the time of the onset of symptoms could also contribute to differences in reperfusion therapy. These data were more often missing for white women, black men, and black women than they were for white men. To minimize potential bias, only patients with complete information regarding this factor were considered ideal candidates for reperfusion.

Probably, persistent differences in treatments and procedures according to sex and race reflect some unmeasured characteristic of patients or a health care factor that has not changed over time. There may be differences according to sex and race in the early presentation of myocardial infarction that lead to a delayed diagnosis in black women, white women, and black men. This may affect early treatment in these groups, particularly the use of reperfusion. Similarly, unmeasured health care factors may lead to inequalities in the delivery of care among demographic groups. A recent study found that black patients tend to be treated by primary care physicians with lower qualifications and to have less access to subspecialist care, diagnostic imaging, and nonemergency hospital admissions.[35] Although these results cannot be extrapolated to acute inpatient care, provider-level differences according to race may exist during an admission for myocardial infarction — for example, the likelihood or timing of referral to a specialist. Hospital-specific effects may also account for a large portion of racial and ethnic disparities in the time to reperfusion therapy,[36] suggesting important unmeasured hospital-level factors — perhaps poorer-quality centers treating a disproportionate number of minority-group patients. This, however, is not consistent with our observation of larger treatment disparities, in comparison with white men, for black women than for black men, two groups who presumably have similar rates of use of hospitals that serve members of racial minorities.

The lack of narrowing in some differences in treatment according to sex and race in recent years is a cause for concern. Differences in treatment paralleled to some extent differences in mortality in our study, since black women were also the group with the highest adjusted in-hospital mortality rate. A full understanding of the reasons underlying such differences requires further study.

Although clinical guidelines for the treatment of acute myocardial infarction changed somewhat during the study period, that change should not affect our results, since we focused on patients who, at each time point, were ideal candidates for each intervention and since the definition was the same for each sex and racial subgroup. We lacked information on whether a history of asthma, chronic obstructive pulmonary disease, dementia, or conduction disorders may have limited the use of beta-blockers or whether a history of hypersensitivity to salicylates or active ulcer disease may have discouraged the use of aspirin. There is no reason to expect that these contraindications differed according to sex or race over time. We also lacked data on socioeconomic factors, such as education and employment status, and were unable to separate the role of sex or race from these factors. Information regarding the time of the onset of symptoms was not available for all patients. The quantity of these missing data increased over time in all sex and racial sub-

groups with similar trends, making it unlikely that missing values introduced bias. Finally, we did not have access to angiographic data, so we cannot exclude the possibility that observed differences in rates of revascularization after coronary angiography reflected overuse of procedures in white men, rather than underuse in other groups of patients. For this reason, rates of revascularization procedures were considered secondary end points.

Differences in some treatments and procedures, particularly reperfusion therapy and coronary angiography, according to sex and race persist after myocardial infarction, with no substantial changes from 1994 to 2002. Black women, the group with the lowest rate of use of interventions, have higher mortality rates than do other groups. Although the reasons for these differences are unknown, their persistence emphasizes the need for a continued search for explanations so that inequities in clinical care may be eliminated.

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## REFERENCES


1. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. N Engl J Med 1991;325:221-5.
2. Steingart RM, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease. N Engl J Med 1991;325:226-30.
3. Wenneker MB, Epstein AM. Racial inequalities in the use of procedures for patients with ischemic heart disease in Massachusetts. JAMA 1989;261:253-7.
4. Whittle J, Conigliaro J, Good CB, Lofgren RP. Racial differences in the use of invasive cardiovascular procedures in the Department of Veterans Affairs medical system. N Engl J Med 1993;329:621-7.
5. Yarzebski J, Col N, Pagley P, Savageau J, Gore J, Goldberg R. Gender differences and factors associated with the receipt of thrombolytic therapy in patients with acute myocardial infarction: a community-wide perspective. Am Heart J 1996;131:43-50.
6. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). Am J Cardiol 1996;78:9-14.
7. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of acute myocardial infarction and 30-day mortality among women and men. N Engl J Med 2000;343:8-15.
8. Weitzman S, Cooper L, Chambless L, et al. Gender, racial, and geographic differences in the performance of cardiac diagnostic and therapeutic procedures for hospitalized acute myocardial infarction in four states. Am J Cardiol 1997;79:722-6.
9. Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: the TIMI III registry. JAMA 1996;275:1104-12.
10. Kostis JB, Wilson AC, O'Dowd K, et al. Sex differences in the management and long-term outcome of acute myocardial infarction. Circulation 1994;90:1715-30.
11. McLaughlin TJ, Soumerai SB, Willison DJ, et al. Adherence to national guidelines for drug treatment of suspected acute myocardial infarction: evidence for undertreatment in women and the elderly. Arch Intern Med 1996;156:799-805. [Erratum, Arch Intern Med 1996;156:1920.]
12. Canto JG, Allison JJ, Kiefe CI, et al. Relation of race and sex to the use of reperfusion therapy in Medicare beneficiaries with acute myocardial infarction. N Engl J Med 2000;342:1094-100.
13. Schulman KA, Berlin JA, Harless W, et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. N Engl J Med 1999;340:618-26. [Erratum, N Engl J Med 1999;340:1130.]
14. Chen J, Rathore SS, Radford MJ, Wang Y, Krumholz HM. Racial differences in the use of cardiac catheterization after acute myocardial infarction. N Engl J Med 2001;344:1443-9.
15. Epstein AM, Weissman JS, Schneider EC, Gatsonis C, Leape LL, Piana RN. Race and gender disparities in rates of cardiac revascularization: do they reflect appropriate use of procedures or problems in quality of care? Med Care 2003;41:1240-55.
16. Peterson ED, Wright SM, Daley J, Thibault GE. Racial variation in cardiac procedure use and survival following acute myocardial infarction in the Department of Veterans Affairs. JAMA 1994;271:1175-80.
17. Hannan EL, van Ryn M, Burke J, et al. Access to coronary artery bypass surgery by race/ethnicity and gender among patients who are appropriate for surgery. Med Care 1999;37:68-77.
18. Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, D.C.: National Academy Press, 2003.
19. Department of Health and Human Services. Healthy People 2010: understanding and improving health. 2nd ed. Washington, D.C.: Government Printing Office, 2000.
20. Rogers WJ, Bowlby LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993): observations from the National Registry of Myocardial Infarction. Circulation 1994;90:2103-14.
21. Every NR, Frederick PD, Robinson M, Sugarman J, Bowlby L, Barron HV. A comparison of the National Registry of Myocardial Infarction 2 with the Cooperative Cardiovascular Project. J Am Coll Cardiol 1999;33:1886-94.
22. Gunnar RM, Passamani ER, Bourdillon PD, et al. Guidelines for the early management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee to Develop Guidelines for the Early Management of Patients with Acute Myocardial Infarction). J Am Coll Cardiol 1990;16:249-92.
23. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1996;94:2341-50.
24. Ryan TJ, Antman EM. 1999 Update: ACC/AHA guidelines for management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890-911.
25. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.
26. Arnold AL, Milner KA, Vaccarino V. Sex and race differences in electrocardiogram use (the National Hospital Ambulatory Medical Care Survey). Am J Cardiol 2001;88:1037-40.

**27.** Giles WH, Anda RF, Casper ML, Escobedo LG, Taylor HA. Race and sex differences in rates of invasive cardiac procedures in US hospitals: data from the National Hospital Discharge Survey. Arch Intern Med 1995;155:318-24.
**28.** Rogers WJ, Canto JC, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the U.S. from 1990 through 1999. J Am Coll Cardiol 2000;36:2056-63.
**29.** Heidenreich PA, McClellan M. Trends in the treatment and outcomes for acute myocardial infarction: 1975-1995. Am J Med 2001;110:165-74.
**30.** Spencer F, Scleparis G, Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Decade-long trends (1986 to 1997) in the medical treatment of patients with acute myocardial infarction: a community-wide perspective. Am Heart J 2001;142:594-603.
**31.** Miller TD, Rogers VL, Hodge DO, Hopfenspirger MR, Bailey KR, Gibbons RJ. Gender differences and temporal trends in clinical characteristics, stress test results and use of invasive procedures in patients undergoing evaluation for coronary artery disease. J Am Coll Cardiol 2001;38:690-7.
**32.** Roeters van Lennep JE, Zwinderman AH, Roeters van Lennep HWO, et al. Gender differences in diagnosis and treatment of coronary artery disease from 1981 to 1997: no evidence for the Yentl syndrome. Eur Heart J 2000;21:911-8.
**33.** Escarce JJ, McGuire TG. Changes in racial differences in use of medical procedures and diagnostic tests among elderly persons: 1986-1997. Am J Public Health 2004;94:1795-9.
**34.** Rathore SS, Krumholz HM. Differences, disparities, and biases: clarifying racial variations in health care use. Ann Intern Med 2004;141:635-8.
**35.** Bach PB, Pham HH, Schrag D, Tate RC, Hargraves JL. Primary care physicians who treat blacks and whites. N Engl J Med 2004;351:575-84.
**36.** Bradley EH, Herrin J, Wang Y, et al. Racial and ethnic differences in time to acute reperfusion therapy for patients hospitalized with myocardial infarction. JAMA 2004;292:1563-72.

SPECIAL ARTICLE

# Racial Trends in the Use of Major Procedures among the Elderly

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## ABSTRACT

### BACKGROUND

Differences in the use of major procedures according to patients' race are well known. Whether national and local initiatives to reduce these differences have been successful is unknown.

### METHODS

We examined data for men and women enrolled in Medicare from 1992 through 2001 on annual age-standardized rates of receipt of nine surgical procedures previously shown to have disparities in the rates at which they were performed in black patients and in white patients. We also examined data according to hospital-referral region for three of the nine procedures: coronary-artery bypass grafting (CABG), carotid endarterectomy, and total hip replacement.

### RESULTS

Nationally, in 1992, the rates of receipt for all the procedures examined were higher among white patients than among black patients. The difference between the rates among whites and blacks increased significantly between 1992 and 2001 for five of the nine procedures, remained unchanged for three procedures, and narrowed significantly for one procedure. We examined rates of CABG, carotid endarterectomy, and total hip replacement in 158 hospital-referral regions (79 hospital-referral regions for black men and white men and 79 for black women and white women) with an adequate number of persons for each procedure. We found that in the early 1990s, whites had higher rates for these procedures than blacks in every hospital-referral region. By 2001, the difference between whites and blacks (both men and women) in the rates of these procedures narrowed significantly in 22 hospital-referral regions, widened significantly in 42, and were not significantly changed in the remaining hospital-referral regions. At the end of the study period, we found no hospital-referral region in which the difference in rates between whites and blacks was eliminated for men or women with regard to any of these three procedures.

### CONCLUSIONS

For the decade of the 1990s, we found no evidence, either nationally or locally, that efforts to eliminate racial disparities in the use of high-cost surgical procedures were successful.

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Black Americans have a much lower life expectancy and worse health outcomes than white Americans. Large differences in health outcomes between races have raised obvious questions about differences in health care that might contribute to these patterns. Numerous studies have documented racial disparities in the use of major, high-cost surgical procedures that are not explained by differences in patients' clinical characteristics.[1,2] The racial differences in the use of surgical procedures occur for a broad range of clinical indications and are largely independent of the level of physician discretion involved in a procedure.[3] Although overuse of these procedures in white patients may explain some of the disparity, studies suggest that black patients undergo fewer clinically important, evidence-based procedures than white patients.[4-7]

Studies showing racial disparities in care have received wide attention in the media since the early 1990s, prompting the federal government to develop several initiatives to address this problem. In 1993, the National Institutes of Health started requiring that minority patients be adequately represented in clinical studies, and funds were allocated specifically to improve the health of members of minority groups. In 1996, the Department of Health and Human Services renewed its efforts within the Office of Minority Health to eliminate racial and ethnic disparities in health care with added funding and new initiatives to collaborate with local agencies to improve care for members of minority groups who have diabetes or cardiovascular disease.[8] At least 34 states have established offices of minority health, whose purpose, at least in part, is to reduce disparities in care.[9] Recently, the Institute of Medicine called for the health care system to take on the challenge of eliminating racial disparities.[10]

Despite clinical evidence collected over many years showing important racial disparities and high-profile initiatives to reduce them,[8] we do not know whether the inequities between blacks and whites in the rates of procedures have begun to narrow, and we are not aware of any prior studies that focused on changes in the use of procedures since 1997.[11] In this study, we examined how racial differences in the receipt of nine major surgical procedures among Medicare beneficiaries have changed over the past decade. Analysis of trends in the use of these procedures over time provides evidence of whether initiatives to reduce disparities have begun to work. Given substantial regional variation in the patterns of disparities,[12] we also studied local regions, where initiatives might be most effective, in order to detect whether in those regions racial disparities might have been reduced or increased.

## METHODS

### PATIENTS AND PROCEDURES

We used all data for Medicare beneficiaries enrolled in fee-for-service programs from 1992 through 2001 to calculate the rates of performance of nine procedures. We chose these particular procedures because they are common, relatively expensive, and associated with significant rates of disease and death and because previous studies have found racial differences in their rates of use.[1,3,12-14] The rates of the procedures we evaluated (categorized according to the coding of the *International Classification of Diseases, Ninth Revision* [ICD-9]) were the following: abdominal aortic aneurysm repair (ICD-9 codes 38.44 and 39.25 restricted to the diagnoses of 441.3 to 441.9); back surgery (03.0x, 03.1x, 03.2x, 03.32, 03.39, 03.4, 03.5x, 03.6, 03.93, 03.94, 03.96, 80.5 to 80.59, and 81.0 to 81.09); coronary-artery bypass grafting (CABG) (36.10 to 36.19); percutaneous transluminal coronary angioplasty (36.01, 36.02, and 36.05); cardiac valve replacement (35.20 to 35.24); carotid endarterectomy (38.12); total hip replacement (81.51, 81.59 excluding diagnosis of 820 to 821.39, and 996.0 to 996.99); total knee replacement (81.41 and 81.54); and appendectomy (diagnosis-related groups 164 to 167).

We used the denominator file of all Medicare beneficiaries to identify resident persons 65 years of age or older who were enrolled in Medicare between 1992 and the end of 2001. Any person who was not listed in the denominator file as being enrolled on June 30 of a given year (either because of enrollment in a health maintenance organization or enrollment late in the year) was excluded from the numerator (number of procedures) and denominator (total number of persons eligible for the procedure) for that year. We focused our analysis on comparisons between black persons enrolled and nonblack persons enrolled. However, as others have done,[15] we refer to the nonblack population as white, even though approximately 5.5 percent of such subjects in 2001 were members of other races or ethnic groups.

### VARIABLES

Race (black or white) according to data collected for Medicare enrollment, age (in categories of 65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years, and 85 to 99 years), sex, and ZIP Code were determined with the use of the denominator files. ZIP Code was linked with data from the 2000 Census to obtain the median income of people living within a ZIP Code. The outcome was whether a person enrolled in Medicare had a procedure or did not have the procedure. The primary outcome, the difference between whites and blacks (or the white-minus-black gap) according to sex, was the difference in the age-adjusted rate of the procedure between whites and blacks enrolled in a given year.

We defined health care markets as hospital service areas and further aggregated these areas into 306 hospital-referral regions, as previously described for the Dartmouth Atlas of Health Care project.[16] Hospital service areas are defined on the basis of patterns of travel to receive hospital care among those enrolled in Medicare, and hospital-referral regions are defined on the basis of travel for tertiary care among those enrolled in Medicare. We restricted regional analyses to hospital-referral regions in which the expected number of procedures among both black patients and white patients was at least 25.[12]

### ANALYSIS

We examined the Medicare enrollee census for each year from 1992 through 2001 and calculated the annual age-adjusted rates for each procedure according to race and sex separately. Rates were calculated by dividing the number of procedures (numerator) by the total number of patients eligible for the procedure (denominator) within each category (age, race, and sex) aggregated nationally. We used indirect standardization to create national age-adjusted rates for each group according to race and sex for each year.[17]

Our primary aim was to determine whether the gaps in rates between blacks and whites increased or decreased over time for each procedure. We built linear regression models for men and women separately in which we used age-adjusted differences between whites and blacks in the rates of procedures as the outcome and year (the continuous variable) as the main predictor. We also plotted the rates over time for three procedures (CABG, total hip replacement, and carotid endarterectomy) to understand better the evolution of patterns of care. We chose these three procedures because they are common and represent both cardiovascular and orthopedic conditions.

We also sought to determine whether there were changes in the gaps between whites and blacks in the rates of procedures over time within local regions. We limited the analyses to CABG, total hip replacement, and carotid endarterectomy in hospital-referral regions in which the expected number was at least 25 procedures for each group according to race and sex. We began by pooling data from 1992 through 1994 to achieve an adequate sample size

**Table 1. Characteristics of the Study Population of Fee-for-Service Patients Enrolled in Medicare, According to Year.***

| Characteristic | 1992 (N=29,247,133) | 1995 (N=29,248,026) | 1998 (N=27,041,785) | 2001 (N=27,656,346) |
|---|---|---|---|---|
| | | *percent* | | |
| Age | | | | |
| 65–69 yr | 30 | 29 | 27 | 27 |
| 70–79 yr | 46 | 46 | 47 | 46 |
| ≥80 yr | 24 | 25 | 26 | 28 |
| Female sex | 60 | 60 | 60 | 60 |
| Black race | 7 | 7 | 7 | 7 |
| Region | | | | |
| West | 26 | 25 | 25 | 26 |
| Midwest | 23 | 24 | 25 | 24 |
| South | 26 | 26 | 27 | 28 |
| Northeast | 25 | 25 | 23 | 23 |

* Percentages may not total 100 because of rounding.

and adequate stability of the rates of procedures for each group within each hospital-referral region. The rates of procedures among blacks and whites were then indirectly standardized according to age, and these standardized rates were compared with the use of a log transformation and the usual formula for the standard error.[18] We report both the number of hospital-referral regions in which the procedure rate among whites exceeded that among blacks and the number of hospital-referral regions for which the difference in rate is significant at the level of $P<0.05$.

Other outcomes included whether the difference in the rate of procedures between whites and blacks changed over time in each hospital-referral region. We performed a linear regression analysis for each hospital-referral region with the yearly difference between whites and blacks in the standardized rates of procedures as the dependent variable and the year (from 1992 to 2001) as the independent predictor. We report the number of hospital-referral regions in which the gaps between whites and blacks in the use of a procedure widened over time and the number in which the gaps narrowed over time as well as the number in which these changes were statistically significant at the level of $P<0.05$.

Finally, we pooled data from the last three years of the study (1999 through 2001) to determine the number of hospital-referral regions in which the gaps still favor white patients and in how many regions these gaps remain statistically significant. To illustrate the changes in rates over time (on the basis of the data for 1992 through 1994 and those for 1999 through 2001) and for comparisons between white patients and black patients, we plotted the rates for 1992 through 1994 against those for 1999 through 2001 for each hospital-referral region and race according to sex and procedure.

**Table 2. Rates and Changes in Rates of Procedures among Men and Women Enrolled in Medicare, 1992 and 2001.***

| Procedure | 1992 | | | 2001 | | | Change in Gap per Year† |
|---|---|---|---|---|---|---|---|
| | Whites | Blacks | Difference | Whites | Blacks | Difference | |
| **Men** | | | | | | | |
| Repair of abdominal aortic aneurysm | 2.10 | 0.57 | 1.53 | 1.59 | 0.51 | 1.08 | –0.45‡ |
| Angioplasty | 21.34 | 11.86 | 9.48 | 28.19 | 19.67 | 8.52 | –0.96 |
| Back surgery | 3.05 | 1.59 | 1.46 | 4.70 | 2.51 | 2.19 | 0.73 |
| CABG | 9.01 | 2.72 | 6.29 | 9.80 | 4.11 | 5.69 | –0.60 |
| Carotid endarterectomy | 3.13 | 0.82 | 2.31 | 4.42 | 1.44 | 2.98 | 0.67 |
| Total hip replacement | 1.96 | 0.86 | 1.10 | 2.60 | 1.08 | 1.52 | 0.42‡ |
| Knee replacement | 3.47 | 1.19 | 2.28 | 5.05 | 1.85 | 3.20 | 0.92‡ |
| Valve replacement | 1.43 | 0.48 | 0.95 | 1.91 | 0.73 | 1.18 | 0.23‡ |
| Appendectomy | 0.46 | 0.32 | 0.14 | 0.55 | 0.31 | 0.24 | 0.10‡ |
| **Women** | | | | | | | |
| Repair of abdominal aortic aneurysm | 0.39 | 0.23 | 0.16 | 0.37 | 0.25 | 0.12 | –0.04 |
| Angioplasty | 11.68 | 10.07 | 1.61 | 16.83 | 17.35 | –0.52 | –2.13‡ |
| Back surgery | 2.62 | 1.48 | 1.14 | 4.33 | 2.37 | 1.96 | 0.82‡ |
| CABG | 3.14 | 1.80 | 1.34 | 3.70 | 2.82 | 0.88 | –0.46 |
| Carotid endarterectomy | 1.59 | 0.64 | 0.95 | 2.42 | 1.15 | 1.27 | 0.32 |
| Total hip replacement | 2.36 | 1.24 | 1.12 | 3.33 | 1.86 | 1.47 | 0.35‡ |
| Total knee replacement | 4.32 | 3.47 | 0.85 | 6.61 | 5.10 | 1.51 | 0.66‡ |
| Valve replacement | 0.89 | 0.39 | 0.50 | 1.17 | 0.64 | 0.53 | 0.03‡ |

* CABG denotes coronary-artery bypass grafting.
† The gap was calculated as the procedure rate among whites minus that among blacks; a minus sign signifies a narrowing of the difference between whites and blacks in the rates of a procedure.
‡ P for trend <0.05 in the multivariable linear regression models.

## RESULTS

There were approximately 29 million enrollees in our denominator files for each year from 1992 through 2001. During the 1990s, the percentage of those enrolled in Medicare in the oldest age groups (80 to 99 years of age) rose from 24 to 28 percent, whereas the percentage in the youngest age group declined (Table 1). The percentages of enrollees who were female or white remained relatively constant.

### NATIONAL RATES OF PROCEDURES

National rates of the use of the procedures among Medicare enrollees increased during the study period from 1992 through 2001 for eight of the nine procedures studied (i.e., all except repair of an abdominal aortic aneurysm), and the increases were generally present for each group according to sex and race (Table 2). Among men, the rates for all nine procedures were higher among whites than among blacks in 1992. The difference in rates between whites and blacks (the rate for whites minus the rate for blacks) widened significantly for five procedures, narrowed significantly for one procedure, and did not change significantly for three procedures (Table 2). For example, the gap in the rate of repair of an abdominal aortic aneurysm narrowed significantly (gap among men, 1.53 procedures per 1000 enrollees vs. 1.08 procedures in 1992 vs. 2001; change, −0.45 procedure per 1000 enrollees; P=0.03). The findings among women were similar.

When we examined the rates for CABG, total hip replacement, and carotid endarterectomy in greater detail (Fig. 1), we found that the patterns of use over time varied according to procedure. There were steady increases in the rates of total hip replacement among white women, white men, and black women, but those among black men remained relatively stable (Fig. 1A). In contrast, there was a sharp rise in rates of carotid endarterectomy from 1993 through 1995 for all groups, although the increase was much more pronounced among whites than among blacks (Fig. 1B). These changes followed the publication of the results of two clinical trials that expanded the indications for carotid endarterectomy.[19,20] The rates for CABG remained relatively stable from 1992 through 2001, with small increases early in this period for all groups and small decreases late in the period (Fig. 1C).

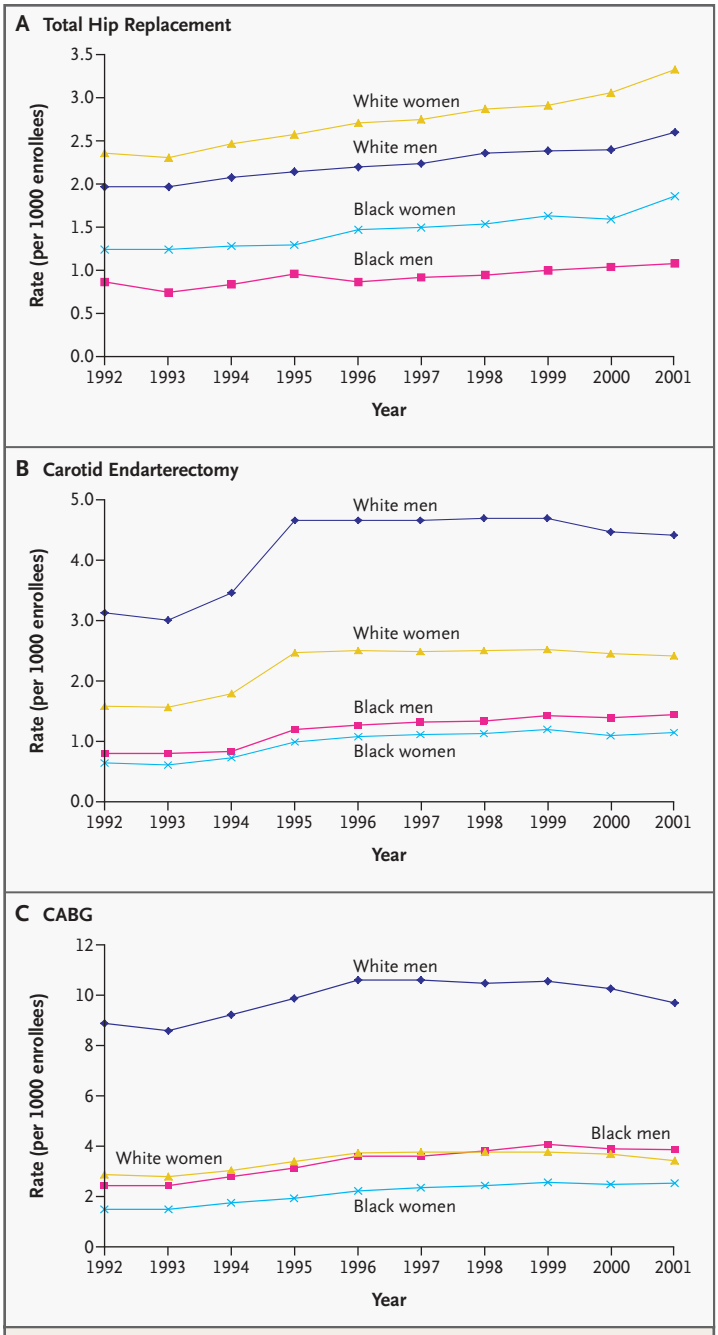



**Figure 1. Age-Adjusted National Rates of Total Hip Replacement (Panel A), Carotid Endarterectomy (Panel B), and Coronary-Artery Bypass Grafting (CABG) (Panel C) per 1000 Persons Enrolled in Medicare, 1992 through 2001.**

### PROCEDURES WITHIN HOSPITAL-REFERRAL REGIONS

When we examined hospital-referral regions that had an adequate number of persons for the analysis of the frequency of CABG, total hip replacement, and carotid endarterectomy, we noted several findings (Table 3). First, whites underwent a greater number of these three procedures than blacks in every hospital-referral region from 1992 through 1994. For example, among men, in all 20 hospital-referral regions that had an adequate sample size, whites had more total hip replacements than blacks, although the racial difference was statistically significant in only 17 of these hospital-referral regions (Table 3). Next, we found that during the study period, the gap between whites and blacks for total hip replacement widened in 17 of these 20 hospital-referral regions (in 5, the changes were statistically significant) and narrowed in 3 (none were statistically significant) (Table 3). The majority of the hospital-referral regions also showed a widening gap between whites and blacks for carotid endarterectomy, although for CABG, a majority of the hospital-referral regions showed a narrowing of the gap. Finally, from 1999 through 2001, more of each of the three procedures were performed among white men than among black men in every hospital-referral region, and most of the differences in the rates of use were statistically significant. In our analyses of hospital-referral regions according to procedures performed among black women and white women, the trends in racial differences in rates of use of these procedures were qualitatively similar.

We also examined the stability of the rates at the start of the study (between 1992 and 1994) and at the end of the study (between 1999 and 2001). Hospital-referral regions that had high rates of procedures among white patients also had relatively high rates among black patients (Spearman correlations ranging from 0.20 to 0.60 according to sex and procedure in the early period, and from 0.50 to 0.86 in the later period). Similarly, the rates at the start of the study period closely predicted the rates at the end of the study period (Fig. 2); this was true among both whites and blacks. Whereas the rates of the use of the procedures were higher among whites than among blacks in each hospital-referral region, blacks in a few regions had higher rates than did whites in other regions, a phenomenon that was true for both periods examined (Fig. 2). The variation in the rates of procedures among hospital-referral regions was also substantial for each race.

**Table 3. Increase, Decrease, or Elimination of Racial Difference in the Largest Hospital-Referral Regions.***

| Procedure | Gap between Whites and Blacks in HRRs† | | | |
|---|---|---|---|---|
| | Gap >0, 1992–1994 | Gap Widened | Gap Narrowed | Gap >0, 1999–2001 |
| | *no. of HRRs (no. with significant result)‡* | | | |
| Men | | | | |
| Total hip replacement (20 HRRs) | 20 (17) | 17 (5) | 3 (0) | 20 (18) |
| Carotid endarterectomy (19 HRRs) | 19 (19) | 15 (8) | 4 (0) | 19 (19) |
| CABG (40 HRRs) | 40 (40) | 17 (8) | 23 (7) | 40 (40) |
| Women | | | | |
| Total hip replacement (20 HRRs) | 20 (18) | 17 (13) | 3 (1) | 20 (19) |
| Carotid endarterectomy (19 HRRs) | 19 (19) | 14 (6) | 5 (2) | 19 (19) |
| CABG (40 HRRs) | 40 (39) | 9 (2) | 31 (12) | 40 (39) |

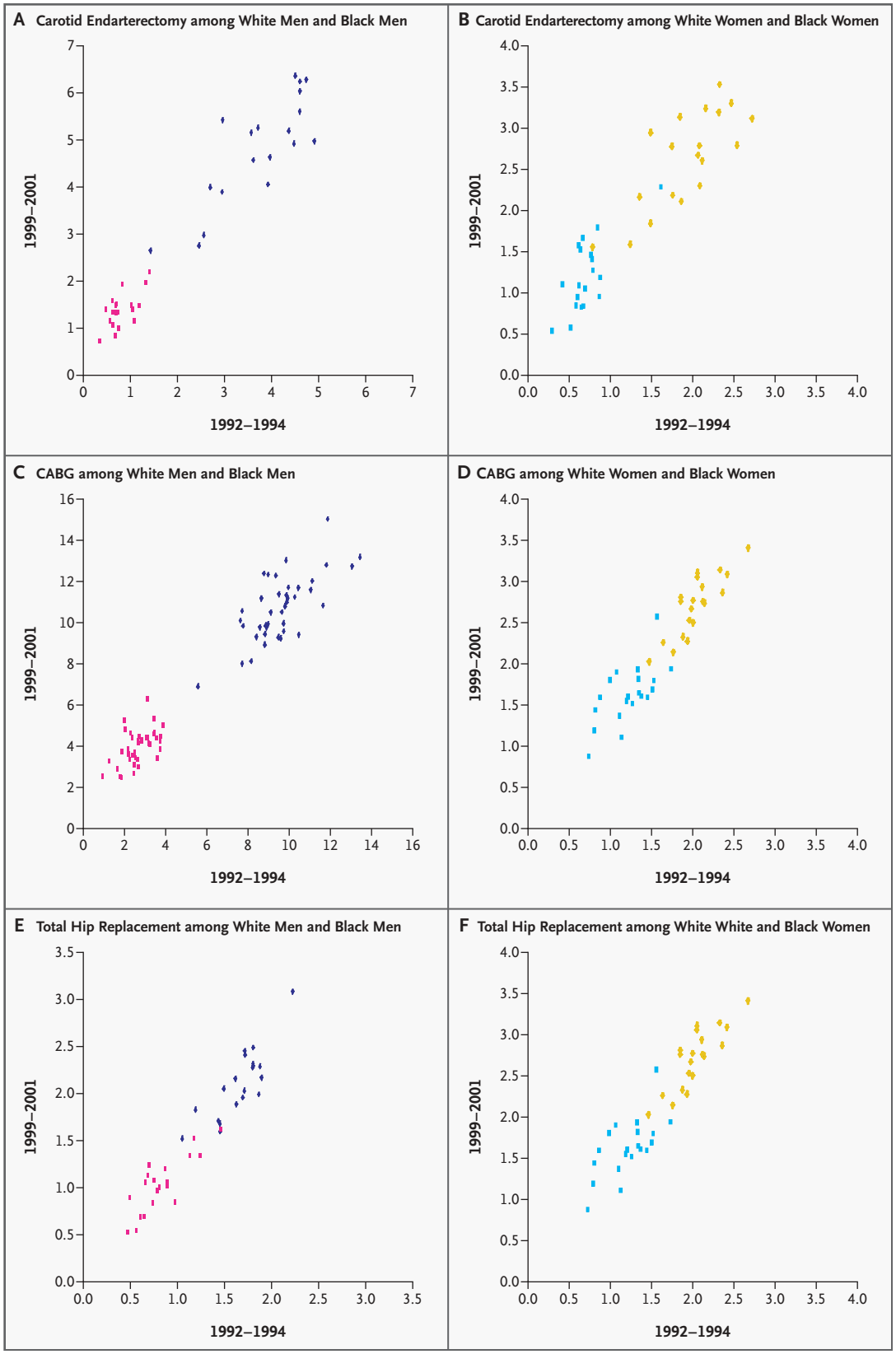
* HRRs denotes hospital-referral regions, and CABG coronary-artery bypass grafting.
† The gap was calculated as the procedure rate among whites minus that among blacks.
‡ P<0.05 was considered to indicate a statistically significant result.

## DISCUSSION

We examined trends in the rates of use of nine major procedures among black persons and white persons enrolled in Medicare between 1992 and 2001 and found that racial differences in these rates did not narrow meaningfully during this decade. The

**Figure 2 (facing page). Comparisons of the Rates of Three Major Surgical Procedures Performed in Two Periods (1992 through 1994 and 1999 through 2001) among Black Men and White Men and among Black Women and White Women per 1000 Persons Enrolled in Medicare.**

Panel A shows the rates in selected hospital-referral regions of carotid endarterectomy among black men (red squares) and white men (dark blue diamonds), and Panel B shows the rates of this procedure among black women (blue squares) and white women (yellow diamonds). Panel C shows the rates in selected hospital-referral regions of CABG among black men and white men, and Panel D shows the rates of this procedure among black women and white women. Panel E shows the rates in selected hospital-referral regions of total hip replacement surgery among black men and white men, and Panel F shows the rates for this procedure among black women and white women.



rates of the procedures performed were greater among whites than among blacks for every procedure examined. Racial differences in these rates widened for five procedures, narrowed for one, and remained statistically unchanged for three. We found no local regions in which racial differences in care were eliminated altogether by 2001.

More than 600 studies have documented racial and ethnic differences in health care dating back at least to the 1980s.[1] These studies suggested that racial and ethnic differences reflect, in part, underuse by black patients, who fail to receive these procedures when their use is clinically appropriate. In response to this evidence, numerous national and local initiatives have been developed to reduce racial differences in health care. Our findings show that, despite these efforts, differences between white Medicare enrollees and black Medicare enrollees in the rates of major procedures did not change meaningfully in the 1990s. Moreover, we did not find a single hospital-referral region (in the 158 sex-specific and procedure-specific analyses performed) in which the difference in rates (the white-minus-black gap) of the use of CABG, total hip replacement, or carotid endarterectomy was eliminated.

Previous studies[5,13,21-25] have suggested that racial gaps in the use of the procedures we evaluated are unlikely to represent only differences in disease incidence or in patients' preferences. Numerous studies have shown that differences in rates of cardiovascular procedures represent a mix of overuse among whites and underuse among blacks.[5,13,21-23] Likewise, racial differences in rates of total knee replacement and total hip replacement are unlikely to be due to differences in disease incidence, given that the incidence of osteoarthritis among blacks is similar to if not greater than that among whites.[24,25]

Appendectomy is traditionally considered a procedure that involves little physician discretion, although two prior studies have found results consistent with ours.[3,26] Whether the incidence of appendicitis differs between whites and blacks is unknown. Blacks are more likely than whites to have a ruptured appendix at the time of appendectomy,[27] indicating either delayed presentation or a greater reluctance among surgeons to perform the procedure. Whites are more likely than blacks to have false negative appendectomies,[28] indicating either differences in clinical presentation or a lower threshold to perform surgery. The combination of these findings suggests that there are likely clinically important racial differences in the care of patients with appendicitis.

Although procedure rates among blacks increased for all procedures in the 1990s, this increase did not reduce the racial gaps, because rates among white patients increased even faster than those among black patients for all procedures except repair of an abdominal aortic aneurysm. For example, the rates of carotid endarterectomy substantially increased in 1995, soon after the publication of major trials showing benefits of this procedure in patients with carotid-artery stenosis.[19,20] However, most of this increase in rates of carotid endarterectomy occurred among the white population, perhaps because white patients were more aggressive in seeking surgical remedies after the data were released or, alternatively, because the doctors who cared for white patients were early adopters of a more aggressive surgical approach. Surgical repair of an abdominal aortic aneurysm was the one procedure in which the gap between whites and blacks for the use of a procedure decreased. The narrowing of this gap occurred in the late 1990s and was associated with the disproportionate receipt among whites of procedures involving new endovascular techniques instead of the traditional surgery for repair of an abdominal aortic aneurysm.[29]

Our study has important limitations. First, we could not differentiate between overuse among white patients, underuse among black patients, or some combination of the two. We can only show that whites and blacks continue to receive very different care. Further, it is possible that the clinical indications or patients' preferences for the procedures examined have changed in ways that explain the persistence of gaps between their use in white patients and black patients. However, there are no data on how clinical indications or patients' preferences have changed over time. Finally, because we could examine individually only those hospital-referral regions with an adequate number of persons that would allow for statistically precise estimates of rates of procedures, changes in gaps in their use between blacks and whites in other regions are possible.

In conclusion, we studied racial differences in the receipt of nine major surgical procedures among persons enrolled in Medicare and found that there have been no meaningful, consistent reductions in the gaps in care between black enrollees and white enrollees. Although substantial local and national

attention has been paid to the issue of racial disparities, we found no evidence that the disparities in the rates of use of the procedures examined have been reduced. Numerous other studies have shown that the gaps in care represent, in part, both underuse among black persons and overuse among white persons. New efforts toward a better understanding of and closing of these gaps in care between black persons and white persons are needed.

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## REFERENCES


1. Kressin NR, Petersen LA. Racial differences in the use of invasive cardiovascular procedures: review of the literature and prescription for future research. Ann Intern Med 2001;135:352-66.
2. Escarce JJ, Epstein KR, Colby DC, Schwartz JS. Racial differences in the elderly's use of medical procedures and diagnostic tests. Am J Public Health 1993;83:948-54.
3. Mort EA, Weissman JS, Epstein AM. Physician discretion and racial variation in the use of surgical procedures. Arch Intern Med 1994;154:761-7.
4. Canto JG, Allison JJ, Kiefe CI, et al. Relation of race and sex to the use of reperfusion therapy in Medicare beneficiaries with acute myocardial infarction. N Engl J Med 2000; 342:1094-100.
5. Schneider EC, Leape LL, Weissman JS, Piana RN, Gatsonis C, Epstein AM. Racial differences in cardiac revascularization rates: does "overuse" explain higher rates among white patients? Ann Intern Med 2001;135:328-37.
6. Epstein AM, Ayanian JZ, Keogh JH, et al. Racial disparities in access to renal transplantation — clinically appropriate or due to underuse or overuse? N Engl J Med 2000; 343:1537-44.
7. Epstein AM, Ayanian JZ. Racial disparities in medical care. N Engl J Med 2001;344: 1471-3.
8. Department of Health and Human Services. The initiative to eliminate racial disparities. (Accessed July 21, 2005, at http://raceandhealth.hhs.gov.)
9. Trivedi AN, Gibbs B, Nsiah-Jefferson L, Ayanian JZ, Prothrow-Stith D. Creating a state minority health policy report card. Health Aff (Millwood) 2005;24(2):388-96.
10. Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, D.C.: National Academy Press, 2003.
11. Escarce JJ, McGuire TG. Changes in racial differences in use of medical procedures and diagnostic tests among elderly persons: 1986-1997. Am J Public Health 2004;94: 1795-9.
12. Skinner J, Weinstein JN, Sporer SM, Wennberg JE. Racial, ethnic, and geographic disparities in rates of knee arthroplasty among Medicare patients. N Engl J Med 2003;349:1350-9.
13. Epstein AM, Weissman JS, Schneider EC, Gatsonis C, Leape LL, Piana RN. Race and gender disparities in rates of cardiac revascularization: do they reflect appropriate use of procedures or problems in quality of care? Med Care 2003;41:1240-55.
14. Mahomed NN, Barrett JA, Katz JN, et al. Rates and outcomes of primary and revision total hip replacement in the United States Medicare population. J Bone Joint Surg Am 2003;85:27-32.
15. Baicker K, Chandra A, Skinner JS, Wennberg JE. Who you are and where you live: how race and geography affect the treatment of Medicare beneficiaries. Health Aff 2004;Web Exclusive. (Accessed July 21, 2005, at http://www.healthaffairs.org.)
16. The Dartmouth atlas of health care. Chicago: American Hospital Publishing, 1996.
17. The Dartmouth atlas of health care, 1998. Chicago: American Hospital Publishing, 1998.
18. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987. (IARC scientific publications no. 82.)
19. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325: 445-53.
20. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-43.
21. Hannan EL, van Ryn M, Burke J, et al. Access to coronary artery bypass surgery by race/ethnicity and gender among patients who are appropriate for surgery. Med Care 1999;37:68-77.
22. Peterson ED, Shaw LK, DeLong ER, Pryor DB, Califf RM, Mark DB. Racial variation in the use of coronary-revascularization procedures: are the differences real? Do they matter? N Engl J Med 1997;336:480-6.
23. Laouri M, Kravitz RL, French WJ, et al. Underuse of coronary revascularization procedures: application of a clinical method. J Am Coll Cardiol 1997;29:891-7.
24. Tepper S, Hochberg MC. Factors associated with hip osteoarthritis: data from the First National Health and Nutrition Examination Survey (NHANES-I). Am J Epidemiol 1993;137:1081-8.
25. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the First National Health and Nutrition Examination Survey (HANES I): evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988; 128:179-89.
26. Gittelsohn AM, Halpern J, Sanchez RL. Income, race, and surgery in Maryland. Am J Public Health 1991;81:1435-41.
27. Braveman P, Schaaf VM, Egerter S, Bennett T, Schecter W. Insurance-related differences in the risk of ruptured appendix. N Engl J Med 1994;331:444-9.
28. Flum DR, Koepsell T. The clinical and economic correlates of misdiagnosed appendicitis: nationwide analysis. Arch Surg 2002;137:799-804.
29. Anderson PL, Arons RR, Moskowitz AJ, et al. A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. J Vasc Surg 2004;39:10-9.

SPECIAL ARTICLE

# Trends in the Quality of Care and Racial Disparities in Medicare Managed Care

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## ABSTRACT

### BACKGROUND

Since 1997, all managed-care plans administered by Medicare have reported on quality-of-care measures from the Health Plan Employer Data and Information Set (HEDIS). Studies of early data found that blacks received care that was of lower quality than that received by whites. In this study, we assessed changes over time in the overall quality of care and in the magnitude of racial disparities in nine measures of clinical performance.

### METHODS

In order to compare the quality of care for elderly white and black beneficiaries enrolled in Medicare managed-care plans who were eligible for at least one of nine HEDIS measures, we analyzed 1.8 million individual-level observations from 183 health plans from 1997 to 2003. For each measure, we assessed whether the magnitude of the racial disparity had changed over time with the use of multivariable models that adjusted for the age, sex, health plan, Medicaid eligibility, and socioeconomic position of beneficiaries on the basis of their area of residence.

### RESULTS

During the seven-year study period, clinical performance improved on all measures for both white enrollees and black enrollees ($P<0.001$). The gap between white beneficiaries and black beneficiaries narrowed for seven HEDIS measures ($P<0.01$). However, racial disparities did not decrease for glucose control among patients with diabetes (increasing from 4 percent to 7 percent, $P<0.001$) or for cholesterol control among patients with cardiovascular disorders (increasing from 14 percent to 17 percent; change not significant, $P=0.72$).

### CONCLUSIONS

The measured quality of care for elderly Medicare beneficiaries in managed-care plans improved substantially from 1997 to 2003. Racial disparities declined for most, but not all, HEDIS measures we studied. Future research should examine factors that contributed to the narrowing of racial disparities on some measures and focus on interventions to eliminate persistent disparities in the quality of care.


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Despite decades of impressive scientific and clinical innovations, substantial deficiencies persist in the quality of health care in the United States,[1-3] and troubling disparities exist in the quality of care for racial and ethnic minorities.[4-8] Efforts to improve the quality of health care and attempts to reduce disparities in treatment may be connected, because variations in appropriate care that are not caused by clinical factors or by the informed preferences of patients are, by definition, indicators of suboptimal care.[9]

Recently, signs of an improved quality of care have been evident both within and outside managed-care settings.[10-12] These improvements may be related to efforts to measure and report clinical performance. However, little is known about whether general improvements in the quality of care are also accompanied by reductions in racial and ethnic disparities. Quality-improvement efforts may reduce such disparities, but they also may have no effect or even increase disparities.

A recent study of patients with end-stage renal disease suggested that broadly targeted interventions to improve the quality of care were associated with reduced racial disparities in hemodialysis dosing.[13] However, an analysis of the administration of influenza vaccine to Medicare beneficiaries showed that higher rates of vaccination in managed-care plans, as compared with the rates in fee-for-service plans, were not associated with reduced disparities on the basis of race.[7]

Within the Medicare program, managed-care plans provide an opportune setting to examine the relation between improvements in the quality of health care and changes in racial disparities. Health plans are particularly well positioned to improve care, because they finance and monitor the provision of health services to enrollees.[12,14] Since 1997, all health plans participating in Medicare have been required to submit publicly reported performance measures from the Health Plan Employer Data and Information Set (HEDIS) developed by the National Committee for Quality Assurance (NCQA). In previous studies of HEDIS measures, black enrollees were less likely to receive beta-blockers after myocardial infarction, eye examinations after receiving a diagnosis of diabetes, follow-up care after hospitalization for mental illness, and influenza vaccinations.[6,8]

In this study, we report on trends in the quality of care provided to enrollees in Medicare managed-care plans from 1997 to 2003 and assess whether racial disparities in quality changed during this period. Evaluation of HEDIS performance trends by race can provide important information about whether broad improvements are associated with narrowed or widened racial disparities in the quality of medical care.[15]

## METHODS

### STUDY POPULATION

We obtained HEDIS data for Medicare managed-care plans from the Centers for Medicare and Medicaid Services (CMS) covering seven reporting years (1998 to 2004) with information regarding clinical care that was delivered from 1997 to 2003. These data contained 2,691,482 observations for enrollees who were eligible for at least one of the nine HEDIS indicators described in Table 1. Each observation included the patient's health identification code and health plan, as well as variables indicating eligibility for and adherence to each HEDIS measure.

NCQA developed detailed specifications for measures that define criteria for inclusion in the sample and the method for the calculation of adherence to each HEDIS quality indicator. To ensure that health plans prepared data in accordance with NCQA specifications and that the data would be valid for use in health plan comparisons, the CMS conducted two audits of HEDIS reporting by Medicare managed-care plans during 1998. The audits included a review of data systems, interviews with health plan personnel, and a centralized review of medical records. In the initial phase of these audits, 90.3 to 96.6 percent of health plans that reported data were fully compliant with the technical specifications of the three HEDIS measures of effectiveness of care. After completion of the audit, all plan-reported rates were within 1 percentage point of audit-derived rates.[16]

Using the health identification code, we matched each enrollee with HEDIS data on at least one measure with the file of Medicare enrollees for the corresponding year to obtain demographic information on the race, age, sex, and ZIP Code of residence of beneficiaries and to ascertain whether they also had Medicaid coverage. We achieved a match rate of 96 percent, or 2,573,166 observations. We excluded 229,938 observations for enrollees who were under the age of 65 years, 201,323 observations for enrollees who were of a race or ethnic background other than black or white, and 44,150 observations

**Table 1. Description of HEDIS Measures of Quality of Care.***

| Measure | Description | Years |
|---|---|---|
| Breast-cancer screening | | |
| Mammogram | Mammography within the past two years for women 65–69 yr | 1997–2003 |
| Diabetes care | | |
| Eye examination | Retinal examination by an eye care professional within the past year | 1999–2003 |
| Testing of glycosylated hemoglobin level | Testing of glycosylated hemoglobin within past year | 1999–2003 |
| Control of glycosylated hemoglobin level | Levels of glycosylated hemoglobin below 9.5% | 1999–2002† |
| Testing of LDL cholesterol level | Testing for LDL cholesterol within past year | 1999–2003 |
| Control of LDL cholesterol level | Level of LDL cholesterol below 130 mg/dl | 1999–2003 |
| Cardiovascular care | | |
| Beta-blocker use | Receipt of a prescription for a beta-blocker within seven days after discharge from hospital for treatment of acute myocardial infarction | 1997–2002† |
| Testing of LDL cholesterol level | Testing of LDL cholesterol after discharge from hospital for treatment of acute myocardial infarction, coronary-artery bypass graft, or percutaneous transluminal coronary angioplasty | 1998–2003 |
| Control of LDL cholesterol level | Level of LDL below 130 mg/dl after discharge from hospital for treatment of acute myocardial infarction, coronary-artery bypass graft, or percutaneous transluminal coronary angioplasty | 1999–2002†‡ |

* LDL denotes low-density lipoprotein.
† Data for 2003 were excluded because NCQA changed its specifications for measurement, which prevented a comparison with rates in previous years. For the measure of glycosylated hemoglobin levels, the adherence threshold was lowered to less than 9.0 percent in 2003. For the beta-blocker measure, the exclusion criteria of congestive heart failure, left ventricular dysfunction, and diabetes were removed and chronic obstructive pulmonary disease was added for the denominator population. For the measure of LDL cholesterol after myocardial infarction or a coronary procedure, the adherence threshold was lowered to a level of less than 100 mg per deciliter.
‡ Data from 1998 were excluded for the initial year, since health plans reported incomplete data. Information for this measure was not publicly reported by NCQA for this year.

for enrollees who died during the year of measurement (with some overlap of enrollees in these three exclusion categories). This process yielded a total study sample of 2,122,809 observations, of which 9.2 percent were for black enrollees. To reduce the likelihood that trends in performance and disparities might be a result of the entrance and exit of health plans from Medicare, our primary analysis excluded 319,358 observations from health plans with less than five years of continuous participation in Medicare managed care. (In a secondary analysis, we did not exclude health plans with less than five years of participation and instead included observations for eligible patients from all health plans that participated in Medicare managed care for at least one year during the study period. Results were similar and are not shown.)

The primary study sample included 1,803,451 observations (9.4 percent for black enrollees) from 183 health plans for the nine HEDIS indicators. The sample size of observations over the entire study period ranged from 79,133 for the beta-blocker measure to 1,035,946 for the breast-cancer-screening measure.

### STUDY VARIABLES

Our dependent variables were the receipt of each HEDIS indicator (Table 1) by eligible enrollees. Our chief independent variable was black or white race, and these designations are highly accurate in Medicare enrollment data.[17] Covariates included age, sex, enrollment in Medicaid, the percentage of persons 65 years of age or older within the enrollee's ZIP Code with an income of less than the federal poverty level, the percentage of persons 65 years of age or older in the enrollee's ZIP Code who had attended college, and urban residence. Data on poverty, educational level, and urban residence within a particular ZIP Code were obtained from the 2000 U.S. Census.

### STATISTICAL ANALYSIS

We assessed demographic and socioeconomic characteristics of the population that was eligible for each HEDIS measure. For white enrollees and black enrollees in each year, we calculated the performance for each HEDIS measure as the percentage of eligible enrollees who were reported to have achieved the performance measure.

**Table 2. Demographic Characteristics of the Study Population as Measured by HEDIS, by Year.***

| Measure (Initial Year–Final Year) | Whites | | Blacks | |
|---|---|---|---|---|
| | Initial Year | Final Year | Initial Year | Final Year |
| | *no. of patients* | | | |
| **Breast-cancer screening (1997–2003)** | | | | |
| Sample size | 92,894 | 148,577 | 6,775 | 11,494 |
| Mean age — yr | 67 | 67† | 67 | 67† |
| Medicaid recipient — % | 2 | 4† | 9 | 10† |
| Below poverty level — % | 8 | 8† | 16 | 14† |
| Some college or above — % | 39 | 36† | 29 | 30† |
| Urban residence — % | 91 | 84† | 97 | 97† |
| **Diabetes care (1999–2003)** | | | | |
| Sample size | 77,154 | 61,998 | 12,663 | 8,647 |
| Mean age — yr | 69 | 70† | 69 | 69† |
| Female sex — % | 48 | 48 | 59 | 59 |
| Medicaid recipient — % | 4 | 6† | 12 | 13 |
| Below poverty level — % | 8 | 8† | 16 | 14† |
| Some college or above — % | 36 | 36† | 28 | 30† |
| Urban residence — % | 87 | 87† | 95 | 97† |
| **Beta-blocker prescribed after myocardial infarction (1997–2003)** | | | | |
| Sample size | 8,864 | 8,686 | 510 | 686 |
| Mean age — yr | 74 | 75† | 73 | 74† |
| Female sex — % | 42 | 45† | 51 | 50 |
| Medicaid recipient — % | 3 | 5† | 12 | 15 |
| Below poverty level — % | 8 | 8† | 17 | 17† |
| Some college or above — % | 36 | 34† | 27 | 26† |
| Urban residence — % | 89 | 88† | 98 | 97† |
| **Cholesterol management after myocardial infarction or coronary procedure (1999–2002)** | | | | |
| Sample size | 18,326 | 20,029 | 1,048 | 1,414 |
| Mean age — yr | 70 | 70† | 70 | 70† |
| Female sex — % | 34 | 34 | 49 | 50 |
| Medicaid recipient — % | 3 | 5† | 13 | 16† |
| Below poverty level — % | 8 | 8† | 16 | 16† |
| Some college or above — % | 36 | 35† | 27 | 27† |
| Urban residence — % | 88 | 87† | 97 | 97† |

* Classification regarding patients' socioeconomic level, educational attainment, and residence in an urban area was performed on the basis of ZIP-Code data from the 2000 U.S. Census.
† The number is significantly different from that in the initial year ($P<0.05$).

To determine adjusted rate differences between white enrollees and black enrollees, we fitted separate linear models predicting receipt of each HEDIS measure to each year's data. To assess trends, we fitted models to combined data from the first and last usable year for each measure. We assessed the overall trend in the quality of care by testing the significance of the year effect in the model without a race-by-year interaction. To assess changes in racial disparity on the risk-difference scale, we tested the significance of a race-by-year interaction term.

In order to determine the adjusted effect of variables regarding demographic characteristics, health plan, and socioeconomic factors on racial dispari-

ties in the quality of care, we fitted three versions of each of these linear regression models. Adjusted rates and differences then corresponded to those predicted at the mean values of the adjuster variables. The first model adjusted for age and sex. The second model added to the first model variables for rural residence and health plan (defined as a Medicare managed-care contract). Because each contract is typically limited to a specific state (except for a few health plans that serve contiguous areas in adjacent states) and the addition of variables by state did not significantly alter regression results after controlling for health plan, we did not include further geographic controls. The third model added to the second model variables for Medicaid eligibility and ZIP-Code-level variables for income and education. All analyses were performed using SAS statistical software (version 9.1) and are reported with two-tailed P values. Our study protocol was approved by the Human Studies Committee of Harvard Medical School and the CMS Privacy Board.

## RESULTS

The demographic and socioeconomic characteristics of the enrollees who were eligible for each of the four categories of HEDIS measures during the initial and final years of measurement are shown in Table 2. As compared with the proportion of white enrollees, a higher proportion of black enrollees was female, eligible for Medicaid, and living in urban areas that had higher rates of poverty and lower rates of educational attainment. Black enrollees made up a higher proportion of the sample for diabetes-related measures — a finding that probably reflects the higher prevalence of this disease among blacks. The demographic characteristics of white enrollees and black enrollees were very stable during the seven-year study period, except for an increase in the percentage of Medicaid recipients and a decrease in the percentage of white women in urban areas who were eligible for the breast-cancer-screening measure.

The quality of care improved during the study period on all measures for both blacks and whites (P<0.001 for all time trends) (Table 3). For black enrollees, the absolute improvement ranged from 6 percent (for the completion of mammography) to 43 percent (for a level of low-density lipoprotein [LDL] cholesterol <130 mg per deciliter for patients with diabetes). For white enrollees, the absolute improvement ranged from 3 percent (for comple-

**Table 3. Adherence to HEDIS Measures by Race and Year.***

| Measure (Initial Year–Final Year) | Initial Rates | | | Final Rates | | | Change in Disparity |
|---|---|---|---|---|---|---|---|
| | White | Black | Disparity | White | Black | Disparity | |
| | *percent* | | | | | | |
| Breast-cancer screening | | | | | | | |
| Mammogram (1997–2003) | 74 | 69 | 5 | 77 | 75 | 2 | –3† |
| Diabetes care | | | | | | | |
| Eye examination (1999–2003) | 64 | 55 | 9 | 72 | 70 | 2 | –7‡ |
| Testing of glycosylated hemoglobin level (1999–2003) | 75 | 71 | 4 | 90 | 88 | 2 | –2‡ |
| Control of glycosylated hemoglobin level (1999–2002) | 71 | 67 | 4 | 82 | 75 | 7 | +3‡ |
| Testing of LDL cholesterol level (1999-2003) | 70 | 61 | 9 | 94 | 92 | 2 | –7‡ |
| Control of LDL cholesterol level (1999–2003) | 36 | 23 | 13 | 73 | 66 | 7 | –6‡ |
| Cardiovascular care | | | | | | | |
| Beta-blocker prescribed (1997–2002) | 76 | 64 | 12 | 94 | 93 | 1 | –11‡ |
| Testing of LDL cholesterol level (1998–2003) | 58 | 40 | 18 | 84 | 75 | 9 | –9‡ |
| Control of LDL cholesterol level (1999–2002) | 47 | 33 | 14 | 68 | 51 | 17 | +3 |

* LDL denotes low-density lipoprotein.
† P=0.002.
‡ P<0.001.

tion of mammography) to 37 percent (for LDL cholesterol <130 mg per deciliter for enrollees with diabetes).

The disparity between blacks and whites narrowed significantly for seven of the nine measures in the study (P<0.01). However, for control of levels of glycosylated hemoglobin, the disparity between blacks and whites increased from 4 percent to 7 percent (P<0.001). For the measure of the percentage of enrollees who achieved an LDL cholesterol level of less than 130 mg per deciliter after a myocardial infarction or a coronary procedure, racial disparities were statistically unchanged (P=0.72).

Table 4 summarizes the results of the multivariable models. Adjustment of the HEDIS performance rates for age and sex (model 1) had little effect on estimated disparities. Additional adjustment for the enrollee's health plan and rural residence (model 2) reduced the disparities between blacks and whites in the initial and final year for six of the nine HEDIS measures and rendered the race-by-year interaction for control of glycosylated hemoglobin levels no longer statistically significant. Additional adjustment for the socioeconomic indicators of Medicaid coverage and residence in high-poverty and low-education areas (model 3) further reduced the magnitude of disparities between blacks and whites in both the initial and the final year. In all models, however, the decrease between the initial and the final year in the magnitude of disparities remained statistically significant for seven of the nine HEDIS measures we studied (P<0.01 for all race-by-year interaction terms).

Figure 1 illustrates two patterns of time trends in the quality of care for blacks and whites who were enrolled in Medicare managed care. For the testing of LDL cholesterol among enrollees with diabetes (Fig. 1A), improvements for white enrollees and

**Table 4. Racial Differences in HEDIS Performance Adjusted for Demographic, Socioeconomic, and Health-Plan Effects.***

| Measure | Racial Disparity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Model 1 | | | Model 2 | | | Model 3 | | |
| | Initial Year | Final Year | Change in Disparity | Initial Year | Final Year | Change in Disparity | Initial Year | Final Year | Change in Disparity |
| | *percent* | | | | | | | | |
| Breast-cancer screening | | | | | | | | | |
| Mammogram† | 5.5 | 1.5 | −4.0‡ | 2.8 | −0.7 | −3.5‡ | −0.2 | −2.6 | −2.4‡ |
| Diabetes care | | | | | | | | | |
| Eye examination | 9.0 | 2.2 | −6.8‡ | 1.8 | −0.3 | −2.1‡ | 4.7 | −1.4 | −6.1‡ |
| Testing of glycosylated hemoglobin level | 4.8 | 2.2 | −2.6‡ | 3.7 | 1.3 | −2.4‡ | 2.2 | 0.8 | −1.4‡ |
| Control of glycosylated hemoglobin level | 3.6 | 6.5 | 2.9‡ | 4.7 | 5.2 | 0.5 | 3.8 | 4.3 | 0.5 |
| Testing of LDL cholesterol level | 8.8 | 2.7 | −6.1‡ | 9.0 | 2.4 | −6.6‡ | 7.0 | 1.8 | −5.2‡ |
| Control of LDL cholesterol level | 12.3 | 6.6 | −5.7‡ | 8.4 | 7.3 | −1.1‡ | 7.2 | 6.6 | −0.6‡ |
| Recent myocardial infarction | | | | | | | | | |
| Beta-blocker prescribed | 11.8 | 0.4 | −11.4‡ | 5.0 | −0.4 | −5.4‡ | 4.1 | −1.6 | −5.7‡ |
| Recent myocardial infarction or coronary procedure | | | | | | | | | |
| Testing of LDL cholesterol level | 17.9 | 9.2 | −8.7‡ | 12.7 | 7.2 | −5.5‡ | 11.3 | 6.0 | −5.3‡ |
| Control of LDL cholesterol level | 13.2 | 16.3 | 3.1 | 10.6 | 12.2 | 1.6 | 7.3 | 8.8 | 1.5 |

* Racial difference is defined as the rate for white patients minus the rate for black patients. Model 1 is adjusted for age and sex; model 2 is adjusted for all characteristics in model 1, plus the type of health plan and residence in a rural area; model 3 is adjusted for all characteristics in model 2, plus the level of income and education and eligibility for Medicaid. LDL denotes low-density lipoprotein.

† Models predicting receipt of mammography did not include terms regarding age and sex, since the eligible population was restricted to women between 65 and 69 years of age.

‡ P<0.01 for race-by-year interaction term in models predicting adherence to HEDIS measures.

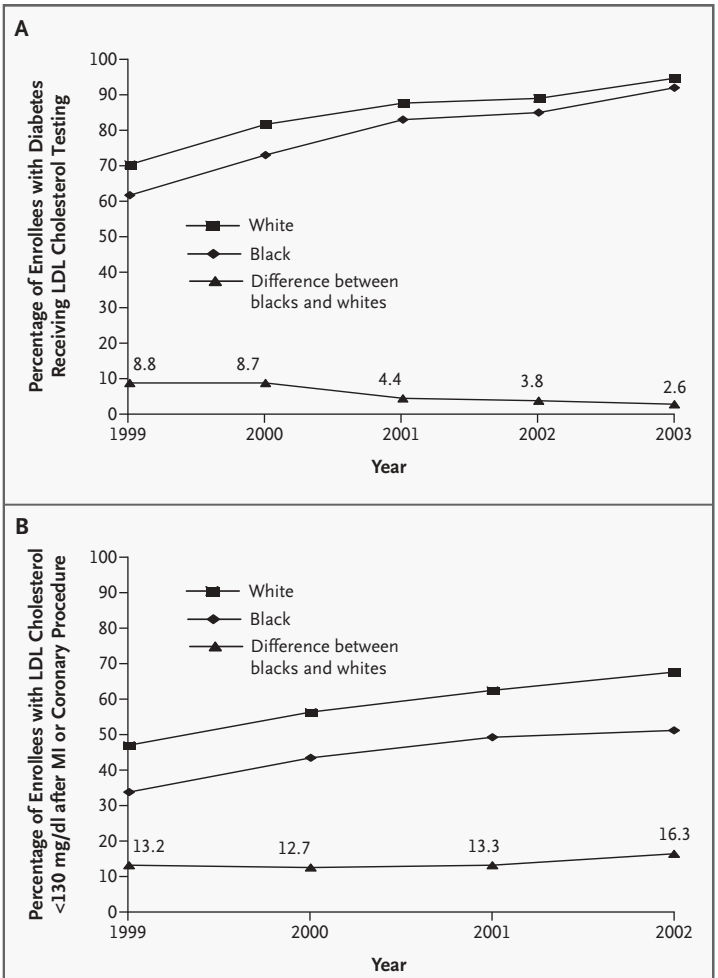


**Figure 1. Trends in Receipt of Two HEDIS Measures for Enrollees in Medicare Managed-Care Plans, by Race.**

Panel A shows large overall improvements in the quality of care by year and a significant narrowing of the disparity between blacks and whites in testing for levels of low-density lipoprotein (LDL) cholesterol among patients with diabetes (P<0.001). Panel B also shows large overall improvements in the quality of care by year but no narrowing of the disparity between races in the control of LDL cholesterol below a level of 130 mg per deciliter after myocardial infarction (MI) or a coronary revascularization procedure (P=0.72).

black enrollees were accompanied by a reduction in the racial disparity between these two groups from 1999 to 2003. In contrast, for the control in levels of LDL cholesterol below 130 mg per deciliter after a myocardial infarction or a coronary procedure (Fig. 1B), clinical performance improved substantially for both white enrollees and black enrollees but with no reduction in the disparity between blacks and whites from 1999 to 2002.

## DISCUSSION

In this time-trend analysis of nine clinical performance measures for enrollees in Medicare managed-care plans from 1997 to 2003, quality of care improved on all nine measures and was accompanied by a significant reduction in the disparities between blacks and whites on seven of the measures. Both trends were substantial and were not explained by changes in the sociodemographic characteristics of enrollees or in the health plans that participated in the Medicare managed-care program during the study years. In contrast, racial disparities did not decrease over time for two HEDIS measures assessing clinical outcomes for diabetes and heart disease.

An adjustment for rural residence and health plan narrowed the observed magnitude of racial disparities for most HEDIS measures — a finding suggesting that part of the racial disparity was related to the disproportionate enrollment of black beneficiaries in health plans or in regions with lower performance on these measures. Even the adjusted models, however, showed decreased racial disparities over time.

In spite of observed improvements, performance as measured by HEDIS indicators approached or exceeded 90 percent on only three measures (testing of glycosylated hemoglobin and LDL cholesterol for patients with diabetes and the frequency of prescribing beta-blockers for patients with cardiovascular disorders). On the other six measures, performance was less than 82 percent for both white enrollees and black enrollees. For these important clinical services, gaps between actual and optimal care remained substantial.[2]

Although racial disparities decreased to 2 percent or less for five of the six process measures, disparities remained at 7 percent or greater for the three measures assessing clinical outcomes (control of LDL cholesterol for enrollees with either diabetes or heart disease and control of glycosylated hemoglobin) in the most recent study years. Although we controlled for socioeconomic variables, the financial burden of the use of lipid-lowering and glucose-lowering medications may have contributed to the greater disparity we observed on these outcome measures, which often require sustained therapy in addition to intermittent testing.[18,19]

Our findings are consistent with the proposition that improvements in the quality of care are as-

sociated with reductions in racial disparities.[9] By increasing the consistency of the delivery of care, interventions such as the use of reminder systems, disease management programs, and feedback to health care providers may decrease variation on the basis of nonclinical factors such as race.[20-24] A greater awareness among beneficiaries or their health care providers about appropriate services for breast-cancer screening, diabetes control, and cardiovascular care could also explain our results.

We believe that the observed declines in racial disparities were unlikely to have resulted from specific health plan programs tailored to improve care for black enrollees. The representatives of nearly half of the health plans who responded to a recent survey did not collect data regarding race and ethnic background of enrollees.[25] In addition, efforts by health plans to develop programs to eliminate disparities in the quality of care on the basis of racial and ethnic factors are relatively recent.[26] Since late 2003, the CMS has provided data regarding enrollees' race and ethnic background to participating health plans and has required that they conduct at least one project to reduce disparities.[27] However, the reduction in disparities we observed largely preceded these efforts.

The strengths of this study were the inclusion of a large, nationally representative sample of enrollees and the use of quality measures that have been audited and publicly reported by health plans for several years. Since all health plans participating in Medicare were required to report data regarding the quality of care, we avoided the selection bias associated with voluntary reporting programs.[28] We were able to adjust for health plan effects and several measures of socioeconomic position that may have confounded or mediated the relationship between race and the quality of care. By limiting our primary analysis to plans with five or more consecutive years of participation in Medicare, we addressed the possibility that changes in the quality of care or reductions in disparities might be an artifact of health plans' selectively entering or exiting the Medicare program.

Our study had several limitations. It was not designed to address the factors that may have caused the observed results or to determine whether similar trends would have been observed for aspects of the quality of care beyond those assessed by the public reporting of HEDIS measures. Furthermore, patients in Medicare fee-for-service and non-Medicare settings were not included in the HEDIS data set. Previous studies have shown similar racial disparities in fee-for-service and managed-care settings,[7,29] but whether our finding of decreasing racial disparities over time extends beyond Medicare managed care remains an open question.

Because enrollment data for Medicare did not reliably identify enrollees who were Hispanic, Asian, or Native American during our study years,[17] we chose not to analyze trends among these ethnic and racial groups. Such studies are clearly needed. The data also lacked detailed clinical information to provide risk-adjusted outcome measures. Although unmeasured clinical factors might partially explain cross-sectional differences in outcome measures by race, such factors would be less likely to explain changes in racial disparities over time.

Several studies have suggested that racial differences in the quality and outcomes of care may be related to differences in the site of care between white and minority patients.[30,31] Although we were able to analyze the contribution of health plans to racial variation in the quality of care, the current HEDIS reporting protocol does not collect information on providers and practices within plans. In addition, the attitudes of patients about health in general or about their ability to modify their diet or physical activity[32,33] may contribute to racial disparities in clinical outcomes, but these variables were not available in our analysis.

Our findings have two important policy implications. For policymakers, health plan leaders, purchasers, and providers who are concerned with improving the quality of care and with reducing disparities, appropriate data are essential to gauge progress on each of these objectives. Measures of quality should be stratified by race, ethnic background, and socioeconomic position — an approach that is now rarely possible with publicly reported data on the quality of care.[9,34,35] Second, although racial disparities decreased on some measures of quality, interventions that are focused on black enrollees or their health care providers may still be necessary to eliminate the disparities that remain.

In summary, improvements in the quality of care among enrollees in Medicare managed-care plans since 1997 have been accompanied by reduced racial disparities in most, but not all, measures of clinical performance we studied. Effective collaborative efforts by policymakers, health-plan administrators,

clinicians, and patients may be needed to eliminate these disparities entirely.

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## REFERENCES

1. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, D.C.: National Academy Press, 2001.
2. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348:2635-45.
3. Jencks SF, Cuerdon T, Burwen DR, et al. Quality of care delivered to Medicare beneficiaries: a profile at state and national levels. JAMA 2000;284:1670-6.
4. Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, D.C.: National Academy Press, 2003.
5. Ayanian JZ, Weissman JS, Chasan-Taber S, Epstein AM. Quality of care by race and gender for congestive heart failure and pneumonia. Med Care 1999;37:1260-9.
6. Schneider EC, Zaslavsky AM, Epstein AM. Racial disparities in the quality of care for enrollees in Medicare managed care. JAMA 2002;287:1288-94.
7. Schneider EC, Cleary PD, Zaslavsky AM, Epstein AM. Racial disparity in influenza vaccination: does managed care narrow the gap between African Americans and whites? JAMA 2001;286:1455-60.
8. Virnig BA, Lurie N, Huang Z, Musgrave D, McBean AM, Dowd B. Racial variation in quality of care among Medicare + Choice enrollees. Health Aff (Millwood) 2002;21(6):224-30.
9. Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. JAMA 2000;283:2579-84.
10. Jencks SF, Huff ED, Cuerdon T. Change in the quality of care delivered to Medicare beneficiaries, 1998-1999 to 2000-2001. JAMA 2003;289:305-12. [Erratum, JAMA 2003;289:2649.]
11. Lied TR, Sheingold S. HEDIS performance trends in Medicare managed care. Health Care Financ Rev 2001;23:149-60.
12. Jha AK, Perlin JB, Kizer KW, Dudley RA. Effect of the transformation of the Veterans Affairs health care system on the quality of care. N Engl J Med 2003;348:2218-27.
13. Sehgal AR. Impact of quality improvement efforts on race and sex disparities in hemodialysis. JAMA 2003;289:996-1000.
14. Baker LC, Hopkins D, Dixon R, Rideout J, Geppert J. Do health plans influence quality of care? Int J Qual Health Care 2004;16:19-30.
15. Zaslavsky AM, Ayanian JZ. Integrating research on racial and ethnic disparities in health care over place and time. Med Care 2005;43:303-7.
16. Health Care Financing Administration. Medicare HEDIS3.0/1998 data audit report. (Accessed July 22, 2005, at http://permanent.access.gpo.gov/websites/www.hcfa.gov/quality/3i2.htm.)
17. Arday SL, Arday DR, Monroe S, Zhang J. HCFA's racial and ethnic data: current accuracy and recent improvements. Health Care Financ Rev 2000;21:107-16.
18. Federman AD, Adams AS, Ross-Degnan D, Soumerai SB, Ayanian JZ. Supplemental insurance and use of effective cardiovascular drugs among elderly Medicare beneficiaries with coronary heart disease. JAMA 2001;286:1732-9.
19. Persell SD, Maviglia SM, Bates DW, Ayanian JZ. Ambulatory hypercholesterolemia management in patients with atherosclerosis: gender and race differences in processes and outcomes. J Gen Intern Med 2005;20:123-30.
20. Kiefe CI, Allison JJ, Williams OD, Person SD, Weaver MT, Weissman NW. Improving quality improvement using achievable benchmarks for physician feedback: a randomized controlled trial. JAMA 2001;285:2871-9.
21. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998;280:1311-6.
22. Grimshaw J, McAuley LM, Bero LA, et al. Systematic reviews of the effectiveness of quality improvement strategies and programmes. Qual Saf Health Care 2003;12:298-303.
23. Weingarten SR, Henning JM, Badamgarav E, et al. Interventions used in disease management programmes for patients with chronic illness — which ones work? Meta-analysis of published reports. BMJ 2002;325:925-33.
24. Weiner M, Callahan CM, Tierney WM, et al. Using information technology to improve the health care of older adults. Ann Intern Med 2003;139:430-6.
25. America's Health Insurance Plans and The Robert Wood Johnson Foundation. Collection of racial and ethnic data by health plans to address disparities: final summary report. (Accessed July 22, 2005, at http://www.rwjf.org/files/research/080504AHIPFinalSummary.pdf.)
26. Hassett P. Taking on racial and ethnic disparities in health care: the experience at Aetna. Health Aff (Millwood) 2005;24(2):417-20.
27. Medicare, Medicaid, and SCHIP Benefits Improvement and Protection Act of 2000, § 1852.
28. McCormick D, Himmelstein DU, Woolhandler S, Wolfe SM, Bor DH. Relationship between low quality-of-care scores and HMOs' subsequent public disclosure of quality-of-care scores. JAMA 2002;288:1484-90.
29. DeLaet DE, Shea S, Carrasquillo O. Receipt of preventive services among privately insured minorities in managed care versus fee-for-service insurance plans. J Gen Intern Med 2002;17:451-7.
30. Bach PB, Pham HH, Schrag D, Tate RC, Hargraves JL. Primary care physicians who treat blacks and whites. N Engl J Med 2004;351:575-84.
31. Bradley EH, Herrin J, Wang Y, et al. Racial and ethnic differences in time to acute reperfusion therapy for patients hospitalized with myocardial infarction. JAMA 2004;292:1563-72.
32. Ayanian JZ, Landrum MB, McNeil BJ. Use of cholesterol-lowering therapy by elderly adults after myocardial infarction. Arch Intern Med 2002;162:1013-9.
33. Persell SD, Keating NL, Landrum MB, et al. Relationship of diabetes-specific knowledge to self-management activities, ambulatory preventive care, and metabolic outcomes. Prev Med 2004;39:746-52.
34. Ver Ploeg M, Perrin E, eds. Eliminating health disparities: measurement and data needs. Washington, D.C.: National Academies Press, 2004.
35. Zaslavsky AM, Hochheimer JN, Schneider EC, et al. Impact of sociodemographic case mix on the HEDIS measures of health plan quality. Med Care 2000;38:981-92.

REVIEW ARTICLE

MEDICAL PROGRESS

# Soft-Tissue Sarcomas in Adults

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SOFT-TISSUE SARCOMAS ARE UNCOMMON TUMORS THAT HAVE TRADITIONALLY been managed by wide excisional surgery and radiotherapy; the use of chemotherapy has been reserved for advanced disease. Advances in multidisciplinary care have improved the evaluation and care of patients with this disease. Limb-conserving surgical paradigms, superior radiotherapy delivery, and novel adjuvant agents for specific tumors are now available. This overview is intended as a review of current understanding and treatment of soft-tissue sarcoma, with an emphasis on recent advances.

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Although soft-tissue sarcomas can arise anywhere in the body (Table 1), the majority occur in the limb or limb girdle or within the abdomen (retroperitoneal or visceral and intraperitoneal). Benign soft-tissue tumors, especially lipomas, are 100 times as common. Soft tissue in this context is defined as nonepithelial extraskeletal tissue, including muscle, fat, and fibrous supporting structures, arising mainly from embryonic mesoderm, with some neuroectodermal contribution.

Accurate pretreatment evaluation is critical for treating soft-tissue sarcomas. Surgery for localized disease is often curative, alone or in combination with radiotherapy and chemotherapy in selected patients. Function-preserving limb conservation is the goal of treatment for soft-tissue sarcomas of the limbs. Intraabdominal tumors pose treatment challenges because of the proximity of adjacent vital organs. Half of patients with soft-tissue sarcomas will die from this disease, a statistic that has changed little in recent decades.[1]

Soft-tissue sarcomas are best treated in multidisciplinary centers that specialize in treating this disease,[2-6] have experience with functional limb preservation, and have low rates of local recurrence and good rates of overall survival.[3] The management of this tumor at other types of centers may lead to inappropriate tests,[2] positive margins after surgical resection, and a reduced likelihood of radiotherapy.[6] Patients with soft-tissue sarcomas are reportedly willing to travel greater distances in order to receive care in a specialty center.[4] Specialists who preserve the function of a given site can work cooperatively with oncologists to enhance the likelihood of a good outcome.

## DEMOGRAPHIC AND ETIOLOGIC CHARACTERISTICS

Soft-tissue sarcomas account for only about 1 percent of all cancers.[7] Approximately 8700 new cases of soft-tissue sarcoma are diagnosed each year in the United States[7] and about 1500 in the United Kingdom. The relative frequency and response of each subtype vary according to age. For example, soft-tissue sarcomas in children, particularly rhabdomyosarcomas, more often respond to chemotherapy than do those in adults.[8] The overall incidence of soft-tissue sarcoma has been increasing,[9] perhaps as a result of the increase in Kaposi's sarcoma, which is often associated with the acquired immunodeficiency syndrome (AIDS),[9,10] as well as improved recognition and diagnosis.

Most soft-tissue sarcomas are sporadic; few have an identifiable cause. There is an association between certain viral infections (notably Epstein–Barr virus in those with AIDS) and leiomyosarcoma.[11] Sarcoma may develop 3 to 15 years after therapeutic ir-

**Table 1. Distribution of Soft-Tissue Sarcoma.***

| Site | Incidence |
|---|---|
| | % |
| Lower limb and girdle | 40 |
| Upper limb and girdle | 20 |
| Retroperitoneal and intraperitoneal sites† | 20 |
| Trunk | 10 |
| Head and neck | 10 |

* Percentages are approximate.
† These sites include gastrointestinal stromal tumors.

radiation for lymphoma, cervical cancer, testicular tumor, or breast cancer. However, the benefits of radiotherapy in such circumstances outweigh the minimally increased[12] risk of sarcoma. Chronic lymphedema-associated angiosarcoma (Stewart–Treves syndrome) usually occurs as a rare complication of treatment for breast cancer. Some genetic disorders are associated with soft-tissue sarcomas. For example, neurofibromatosis type 1 carries a 10 percent lifetime risk of malignant tumors of the peripheral-nerve sheath. Children with hereditary retinoblastoma (owing to a germ-line mutation in the *RB1* tumor-suppressor gene) face an exceptionally high risk of osteosarcoma and soft-tissue sarcoma, which is further increased by the receipt of radiotherapy.[13] Sarcoma has also been reported in patients with the Li–Fraumeni syndrome, which is caused by a germ-line mutation in the *p53* tumor-suppressor gene.[14]

## CLINICAL FEATURES, ROLE OF IMAGING, AND DIAGNOSIS

The clinical symptoms accompanying the diagnosis of soft-tissue sarcoma are nonspecific. The most common finding at presentation is a painless, gradually enlarging mass. The size of the tumor at diagnosis varies according to the site; tumors of the distal limbs and head or neck are usually smaller because they are likely to be noticed earlier, whereas tumors of the thigh and retroperitoneum may become huge before they are detected. Soft-tissue sarcomas expand in a spherical fashion but infiltrate the tumor pseudocapsule and, occasionally, adjacent structures. Accordingly, patients with these tumors may present with site-dependent symptoms of increased pressure, such as paresthesia, distal edema, or bladder symptoms.

The growth rate of soft-tissue sarcomas varies with the aggressiveness of the tumor. Low-grade tumors may evolve over a long period and may be mistaken for benign tumors, especially lipomas. Such a mistake may delay referral to a specialist center.[15] Indeed, the identification of soft-tissue sarcoma relies on clinical examination, imaging, and histologic analysis. Examination and imaging can be used to define the tumor's relationship to surrounding structures.

Plain radiographs may be used to rule out bone neoplasms and detect calcifications characteristic of soft-tissue osteosarcoma or synovial sarcoma. A chest radiograph is essential, though preoperative computed tomography (CT) of the thorax is preferable for detecting metastases. CT and magnetic resonance imaging (MRI) are used to image the primary tumor; neither offers an overall advantage.[16] CT is usually performed to identify intraabdominal tumors, such as liposarcoma, the most common retroperitoneal tumor. The multiplanar images and better anatomical definition possible with the use of MRI are its key advantages; this approach is preferred for the diagnosis of soft-tissue sarcoma of the limbs. Advances in these two approaches now permit faster acquisition of images and better spatial resolution.[17] Dynamic gadolinium-enhanced MRI can be used to identify early enhancement of viable tumor tissue as compared with surrounding reactive tissues. Additional imaging approaches offer future promise. A recent meta-analysis of the results of positron-emission tomography (PET) with fludeoxyglucose F 18 concluded that routine use is currently unjustified.[18] Combining functional information obtained from PET with anatomical detail from CT[19] or MRI[20] may increase the usefulness of these techniques. Magnetic resonance spectroscopy may be useful in some circumstances, such as when one is assessing a patient's response to chemotherapy when resection has not been performed.[21]

With few exceptions, histologic examination of a tumor specimen is required before treatment is initiated. Percutaneous core needle biopsy is safe and effective[22,23] and can be performed with the use of local anesthesia on an outpatient basis for palpable tumors of the arms and legs. The biopsy site should be chosen so that it will lie within the area of a possible subsequent en bloc resection of the tumor. The subtype and grade of the tumor can be determined in 80 percent of core needle biopsies,[22,23] and pathologists experienced in examining soft-tis-

sue sarcomas have a diagnostic accuracy of 95 to 99 percent. So-called small round-cell tumors (embryonal rhabdomyosarcoma, Ewing's sarcomas, and lymphoma) can be identified by needle biopsies, permitting nonsurgical induction therapy (Fig. 1). Currently, incisional biopsy is less common than needle biopsy at many centers. In the hands of a nonexpert, incisional biopsies have a higher rate of complications than core needle biopsies[2] and thus should be performed only in exceptional circumstances, ideally by the surgeon planning the definitive resection. Cytologic analysis of fine-needle aspirates alone can be used to diagnose recurrent tumor[24] or nodal metastases. Regardless of how biopsy material is obtained, the specimen is best evaluated by a pathologist specializing in soft-tissue diseases.[2,25]

If imaging suggests that a retroperitoneal tumor is most likely a resectable soft-tissue sarcoma (Fig. 2), biopsy should not be performed, given the potential for transperitoneal spread and track implantation.[26] Exceptions include suspected lymphoma or germ-cell tumors, which usually appear as paracaval or paraaortic masses on CT, and masses tentatively identified as sarcomas for which preoperative chemotherapy or radiotherapy is contemplated. A biopsy should be considered if a gastrointestinal stromal tumor is suspected on radiologic grounds,[27] if metastatic disease is suspected, or if the tumor is unresectable.

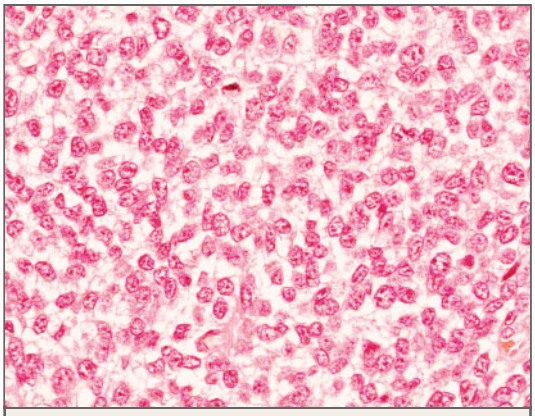


**Figure 1. Photomicrograph of Ewing's Sarcoma, a Type of Small Round-Cell Tumor (Hematoxylin and Eosin).**
Small round-cell tumors can be diagnosed with the use of core needle biopsy, making possible the initiation of appropriate therapy.

## PATHOLOGICAL FEATURES

The World Health Organization[28] has defined approximately 50 tumor subtypes relevant to soft-tissue sarcomas; these are named largely according to the tissue they most closely resemble. A three-step grading system devised by the French Federation of Cancer Centers Sarcoma Group[29] is widely used and takes into account the degree of differentiation, the mitotic count, and the extent of necrosis. Four-step grading systems are also in use.[30] It is difficult to grade tumors previously treated with radiotherapy or chemotherapy and recurrent tumors.

Determining the stage of a tumor allows physicians to estimate the prognosis. The staging system devised by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) (Fig. 3)[30] combines the most important determinants of survival in localized soft-tissue sarcomas of the limbs: the grade, depth, and size of the tumor. Large series confirm that grade and size are of similar prognostic importance.[31,32] Five-year survival rates for stages I, II, III, and IV are approximately 90, 70, 50, and 10 to 20 percent, respectively, and are further modified by the type and site of the tumor and other factors.[33] Prognostic algorithms derived from large databases can be used to provide longer-term survival estimates.[34]

The use of conventional staging systems for retroperitoneal tumors is less accurate prognostically, but a method based on grade, the completeness of resection, and the presence or absence of metastases can be used to identify groups with different outcomes.[5] Other risk factors are relevant to certain tumors; for example, tumor size and mitotic count are used to assess risk in cases of localized gastrointestinal stromal tumors.[35]

The classification and characterization of soft-tissue sarcomas have evolved as the information supplied by histologic analysis has been supplemented with that provided by immunohistochemical analysis and with an improved understanding of the underlying genetic changes. Identification techniques are increasingly applicable to formalin-fixed, paraffin-embedded material. Genetic aberrations have been described in many soft-tissue tumors and help identify tumors that were previously difficult to classify, especially pleomorphic soft-tissue sarcomas.[36] Aberrations can be hereditary or acquired.[14,37-39] Consistent, specific translocations resulting in new fusion genes characterize some sarcomas (Table 2). Genetic information can facilitate the diagnosis (especially in the case of small

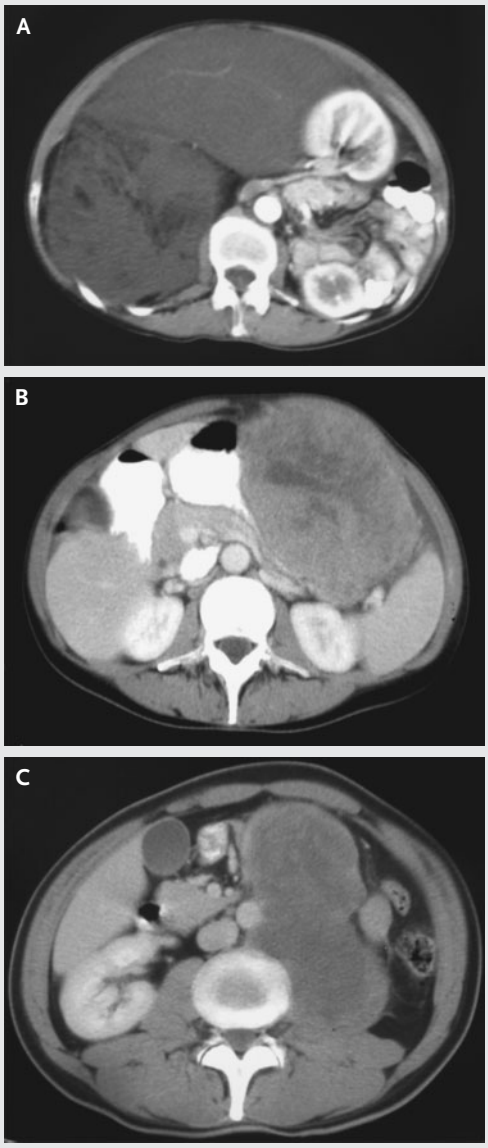



**Figure 2. CT Scans of Large Retroperitoneal Masses Suggestive of Soft-Tissue Sarcoma.**

Panel A shows a liposarcoma with characteristic features. The tumor has caused the right kidney to rotate and overlie the left kidney. Panel B shows a huge mass of borderline resectability. Percutaneous core needle biopsy confirmed the diagnosis of gastrointestinal stromal tumor, and imatinib therapy was initiated. Panel C shows an unresectable mass in psoas muscle; the aorta is displaced. Core needle biopsy revealed a malignant germ-cell tumor treatable with chemotherapy. Levels of tumor markers were elevated, and ultrasonography showed that the left testis was abnormal.

round-cell tumors), confirm relationships between morphologic subtypes, and predict the behavior of specific sarcomas beyond that provided by the general features of grade, size, and depth.[40] One emerging application is mutational analysis of gastrointestinal stromal tumors, in which mutations in the *KIT* gene appear to have a major effect on treatment response and survival.[41] Emerging gene-array and proteomic techniques are being applied to identify potential treatment targets, which may help to individualize therapy.[42,43]

## TREATMENT

Surgery — supplemented when necessary by adjuvant radiotherapy — is often curative for localized soft-tissue sarcomas. As already discussed, treatment is best planned in a multidisciplinary setting, which facilitates consideration of the need for preoperative induction treatment, discussion of reconstructive strategies, and planning for rehabilitation. This assessment should include histologic review by an expert on soft-tissue sarcoma to verify or alter the classification or grade of the tumor[25]; a change in the grade or class may necessitate a change in the treatment plan.

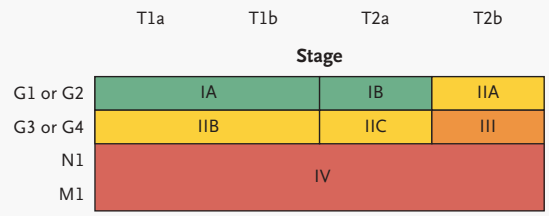
Although local treatment of primary soft-tissue sarcoma of the limbs influences the likelihood of local recurrence, limb salvage, and functional outcome, the metastatic potential is mainly determined by the grade and size of the primary tumor. There is little evidence that local recurrence increases the likelihood of metastatic spread, although debate on this point continues.[32,44] Except for rhabdomyosarcomas and Ewing's sarcomas, the use of adjuvant chemotherapy generally does little to influence the natural history of the disease.

### SURGERY

Surgical resection involving wide margins, with or without radiotherapy, offers the best chance of cure in the absence of metastatic disease. The operation should be planned by an experienced surgical team after careful study of the scans. Because soft-tissue sarcoma can occur at any site, every operation will be different, though common surgical oncologic principles prevail.

Because soft-tissue sarcomas expand spherically and along tissue planes, their centrifugal growth creates a false capsule, or pseudocapsule, of com-

| Grade and TNM | Description |
|---|---|
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Undifferentiated |
| T1 | Tumor ≤5 cm in largest dimension |
| T1a | Superficial to deep fascia |
| T1b | Deep to deep fascia (includes retroperitoneal, intrathoracic, and most head and neck tumors) |
| T2 | Tumor >5 cm in largest dimension |
| T2a | Superficial to deep fascia |
| T2b | Deep to deep fascia (includes retroperitoneal, intrathoracic, and most head and neck tumors) |
| N1 | Regional nodal metastasis |
| M1 | Distant metastasis |




| 5-Yr Survival | |
|---|---|
| Stage | % |
| I | 86 |
| II | 72 |
| III | 52 |
| IV | 10–20 |

**Figure 3. Descriptions of Stages, Grades, and the Tumor–Node–Metastasis (TNM) System of the American Joint Committee on Cancer for Soft-Tissue Sarcoma and the International Union against Cancer.**
Data have been modified from Greene et al.[30]

pressed surrounding tissue. Malignant cells penetrate this pseudocapsule.[45] Simple removal of visible tumor in this plane leaves microscopic disease in situ, and 90 percent of tumors recur unless there is further treatment. Over 30 percent will recur even after further excision of the tumor bed,[46] and the subsequent use of radiotherapy does not compensate for the presence of unplanned positive histologic margins.[47] (In contrast, leaving a carefully considered positive margin adjacent to a critical structure to facilitate limb preservation results in rates of local recurrence of only approximately 4 percent when planned irradiation is carried out.[46]) Thus, the goal of surgery is to resect the tumor with wide (2 to 3 cm) margins when possible, removing at least one uninvolved tissue plane circumferentially.

Approximately one third of patients with a low- or intermediate-grade tumor and wide resection margins will not require further treatment (including radiotherapy). It is rarely necessary to reconstruct major vessels or to resect major nerves unless they are encased by tumor. However, resection of some major nerves generally results in surprisingly little disability; therefore, resection should be considered if amputation is the alternative.[48] If it is safe from an oncologic perspective, preserving one innervated muscle in any compartment results in better function than a more radical approach.[49] Although tumors are usually smaller in the distal limbs than in the proximal limbs, it is more difficult to preserve function in the distal limbs, especially the forearms and hands. Preoperative induction treatment may reduce the size of tumors of distal limbs and facilitate better functional results.

Amputation is ultimately required in 5 to 10 percent of patients with sarcoma of the limbs, usually after previous limb-salvage operations.[50] In such cases, major amputations (forequarter, hindquarter, or through-hip amputation) are often necessary, because recurrences are generally proximal. Such procedures are tolerated remarkably well and provide excellent local control.[51]

The skin is rarely involved in soft-tissue sarcoma and can usually be preserved. Skin and soft-tissue reconstruction is required in 10 to 20 percent of patients and can reduce complications or avert amputation, especially in the case of recurrences in previously irradiated locations. Transposed myocutaneous or fasciocutaneous flaps are commonly used, but it is sometimes necessary to transfer free tissue. In selected cases, early involvement of surgeons with expertise in reconstructive surgery optimizes functional and cosmetic results[52] while preserving reconstruction options. Site- and organ-specific lesions are often managed with the help

**Table 2. Chromosomal Translocations in Soft-Tissue Sarcomas.***

| Type of Tumor | Translocation | Genes Involved |
|---|---|---|
| Synovial sarcoma | t(X;18)(p11.2;q11.2) | *SSX1* or *SSX2*, *SYT* |
| Myxoid or round-cell liposarcoma | t(12;16)(q13;p11) | *CHOP*, *TLS* |
| | t(12;22)(q13;q11-q12) | *CHOP*, *EWS* |
| Ewing's sarcoma or peripheral primitive neuroectodermal tumor | t(11:22)(q24;q12) | *FLI1*, *EWS* |
| | t(21:22)(q22;q12) | *ERG*, *EWS* |
| | t(7;22)(p22;q12) | *ETV1*, *EWS* |
| | t(2;22)(q33;q12) | *FEV*, *EWS* |
| | t(17;22)(q12;q12) | *E1AF*, *EWS* |
| Desmoplastic small round-cell tumor | t(11;22)(p13;q12) | *WT1*, *EWS* |
| Alveolar rhabdomyosarcoma | t(2:13)(q35;q14) | *PAX3*, *FKHR* |
| | t(1;13)(p36;q14) | *PAX7*, *FKHR* |
| Extraskeletal myxoid chondrosarcoma | t(9;22)(q21-31;q12.2) | *CHN*, *EWS* |
| | t(9;17)(q22:q11) | *CHN*, *RBP56* |
| Clear-cell sarcoma | t(12;22)(q13;q12) | *ATF1*, *EWS* |
| Alveolar soft-part sarcoma | t(X;17)(p11;q25) | *TFE3*, *ASPL* |
| Dermatofibrosarcoma or giant-cell fibroblastoma | t(17;22)(q22;q13) | *COL1A1*, *PDGFB1* |
| Infantile fibrosarcoma | t(12;15)(p13;q25) | *ETV6*, *NTRK3* |
| Low-grade fibromyxoid sarcoma | t(7;16)(q34;p11) | *FUS*, *BBF2H7* |

* The translocations should be read, for example, as follows: t(X;18)(p11.2;q11.2) is a translocation between chromosomes X and 18 involving the short arm at region 11.2 and the long arm at region 11.2.

of other specialists, including head-and-neck surgeons, gynecologists, and urologists.

Surgery is the mainstay of treatment for soft-tissue sarcomas of the retroperitoneum (15 percent of soft-tissue sarcomas). En bloc resection of adjacent viscera is frequently required, but complete tumor resection (with negative histologic margins) is difficult, owing to the proximity of vital structures.[53] Retroperitoneal sarcoma remains an insidious disease, with a generally inexorable course. Most of these tumors will recur, eventually causing death, underscoring the need for better control.[54-56]

## RADIOTHERAPY

The cytotoxic effects[57] and therapeutic role[58] of radiotherapy in treating soft-tissue sarcomas are well described. Radiotherapy should be considered for high-grade tumors of the limbs (unless margins are very wide) and for intermediate-grade tumors of the limbs with close or positive histologic margins.[44] Radiotherapy has little role in primary low-grade soft-tissue sarcoma, although it should be considered for a recurrence.

Radiotherapy is delivered as either external-beam therapy or brachytherapy. The latter involves the insertion of radioactive "seeds" or wires (usually iridium-192) into surgically placed catheters traversing the tumor bed. Brachytherapy has theoretical advantages postoperatively, given the hypoxic nature of the wound and the radiobiologic characteristics of the inverse-square law (local doses are high, but the dose decreases proportionally with increasing distance from the tumor). These advantages are even more important in patients who have already undergone external-beam radiotherapy.[59] No randomized clinical trial has compared these types of delivery. Not all sites are suitable for brachytherapy, and many units prefer to perform external-beam therapy with its use of standardized fields. Occasionally, both methods are combined — for example, when a large external-beam field is used with a brachytherapy boost to a specific area.

Radiotherapy alone is considered when surgery is inappropriate or declined by the patient; it achieves rates of local control of 30 to 60 percent.[60] More commonly, operative treatment is coupled with adjuvant radiotherapy on the basis of evidence demonstrating similar survival rates after limb-conserving surgery with radiotherapy and after amputation.[44,61] Optimal timing remains unclear. A lower total dose of radiotherapy (50 Gy) is required when it is delivered preoperatively. Postoperatively, a total of 60 to 66 Gy is usually delivered to maximize killing of hypoxic tumor cells. One trial of external-beam therapy in patients with soft-tissue sarcoma of the limbs demonstrated similar effectiveness whether therapy was administered preoperatively or postoperatively. Functional outcome in the group treated preoperatively was slightly better but was associated with a doubling in the incidence of wound-healing problems.[62] Counterintuitively, delaying postoperative radiotherapy does not significantly worsen the rate of late control of local disease.[63]

Because patients with retroperitoneal soft-tissue sarcoma generally die from a local recurrence, improved local control could have a great effect. Postoperative radiotherapy presents particular challenges at this site; large areas generally require irradiation, and the occurrence of side effects in many organs limits the doses. The preoperative[64] or intraoperative[54,56] use of radiotherapy theoretically overcomes these problems, but improvements have been minimal in practice. Enhanced targeting and delivery of radiotherapy with the use of intensity-

modulated techniques represent a potential advance.[64]

### CHEMOTHERAPY

Whereas the goal of surgery and radiotherapy is local control of the tumor, the aim of chemotherapy is systemic control, which may be therapeutic, adjuvant, or palliative. Although some subtypes of soft-tissue sarcoma are sensitive to chemotherapeutic agents, the outcome of therapeutic chemotherapy is unsatisfactory overall, and the use of adjuvant chemotherapy is controversial. A meta-analysis of adjuvant chemotherapy did not demonstrate an overall survival advantage, although progression-free survival improved.[65] One small study of adjuvant chemotherapy reported a small survival benefit (but an identical rate of metastases) in selected patients with high-grade soft-tissue sarcoma of the limbs treated with an intensive regimen.[66]

Small round-cell tumors are treated initially with combination chemotherapy. This approach has dramatically improved overall survival among patients with Ewing's sarcoma, from under 10 percent before the introduction of systemic treatment to greater than 60 percent. The use of local therapy remains important. Radiotherapy alone is inferior to surgery for local control in patients with Ewing's sarcoma. Improved survival is associated with increased rates of surgical intervention.[67] Cyclophosphamide and ifosfamide, vincristine, doxorubicin, dactinomycin, and etoposide have all been used to treat these tumors.[68] Prognosis is predicated on the size, site, and stage of the tumor, and the histologic response to induction chemotherapy is the most important prognostic factor on multivariate analysis — histologic examination of tumors resected after induction therapy showed that necrosis of greater than 90 percent of the tumor confers a significantly better outcome than lesser degrees of necrosis, irrespective of tumor size.[69] Patients with Ewing's sarcoma may benefit from intensive regimens that include ifosfamide. High-dose chemotherapy with salvage of autologous peripheral-blood progenitor cells may be useful and is being compared prospectively with maintenance therapy in a multicenter study in Europe and North America (intensive induction therapy with vincristine, ifosfamide, doxorubicin, and etoposide is followed by high-dose melphalan with busulfan).[70]

The use of traditional generic approaches to chemotherapy belies the heterogeneity of soft-tissue sarcomas. Chemosensitivity varies according to the tumor subtype, and the likelihood of a response and survival is further influenced by the tumor grade, the patient's age, performance status, and the timing of metastatic disease.[71] Leiomyosarcoma, for example, responds variably to conventional chemotherapy, depending on the site and grade of the tumor. Uterine leiomyosarcoma is particularly aggressive, but it may respond to high-dose gemcitabine with docetaxel.[72] Facial and scalp angiosarcoma may respond to paclitaxel,[73] and taxanes may have broader utility against angiosarcomas at other sites. A pegylated liposomal formulation of doxorubicin (with reduced toxicity)[74] has also been reported to be active against angiosarcomas.[75]

Chemotherapy is palliative for most patients with unresectable or metastatic disease. Ifosfamide and doxorubicin are routinely used in this setting; doxorubicin as a single agent is considered the drug of choice. Recent studies have reevaluated ifosfamide dosing,[76] and high-dose ifosfamide with doxorubicin is commonly used for younger patients with aggressive tumors; response rates of approximately 50 to 60 percent have been reported.[77] It remains unclear whether this approach improves survival, which is on the order of 12 months in this situation.[71]

Trabectidin (Yondelis, PharmaMar), a natural product from the marine tunicate *Ecteinascidia turbinata* that selectively inhibits DNA transcription,[78] is a new agent that has shown some activity in advanced disease refractory to conventional cytotoxic drugs. It appears to induce a low rate of objective remission (4 percent) but a high rate of disease stabilization (a 24 percent rate of progression-free survival at six months), though it is moderately toxic.[79]

### TARGETED MOLECULAR THERAPY

Encouraging progress is occurring with the use of therapies directed against specific molecular targets associated with soft-tissue sarcoma. Gastrointestinal stromal tumor, the best-known example, is largely driven by activating mutations in the proto-oncogene *KIT*, a receptor tyrosine kinase, as reported by Hirota et al. in 1998.[80] Immunohistochemical detection of the resultant protein, KIT, is a reliable means of identifying this tumor.[81] The protein tyrosine kinase inhibitor imatinib is the treatment of choice for advanced inoperable or metastatic gastrointestinal stromal tumor, and its role in the preoperative and adjuvant setting is under evaluation. Trials have defined side-effect profiles,[82] response rates (more than 60 percent),[83] and dose–response

**Table 3. Effect of *KIT* Mutations on the Response to Imatinib in Patients with Gastrointestinal Stromal Tumors.***

| Exon | Site | Incidence | Response |
|---|---|---|---|
| | | *percent* | |
| 11 | Juxtamembrane domain | 67 | 85 |
| 9 | External domain | 17 | 45 |
| 13 | *TK1* | 2 | ? |
| 17 | *TK2* | 2 | ? |
| None | —† | 13 | 10 |

* Data are from Heinrich et al.[41] More than 90 percent of patients with gastrointestinal stromal tumors have activating *KIT* or *PDGFRA* mutations.
† Some tumors may have mutant *PDGFRA*.

relationships. One trial comparing daily doses of 400 mg and 800 mg suggests that the higher dose improves progression-free survival and that patients whose disease progresses during treatment with the lower dose may have a response to the higher dose.[84]

The specific molecular alteration in gastrointestinal stromal tumors is a critical determinant of response. Mutations in exon 11 of *c-KIT* (coding for the intracellular juxtamembrane domain) account for nearly 70 percent of cases and are associated with a rate of response to imatinib of 85 percent (Table 3). However, imatinib is less effective in tumors without *KIT* mutations or other mutations.[41] Activating mutations in the platelet-derived growth factor receptor $\alpha$ (*PDGFRA*) gene may also drive gastrointestinal stromal tumors.[85] Since PDGFRA is also an imatinib substrate, some tumors without *KIT* mutations respond to imatinib, owing to the inhibition of PDGFRA. However, unlike *KIT* mutations, most *PDGFRA*-activating mutations occur in the kinase domain, and such mutations are unresponsive to imatinib.[41]

Other subtypes of soft-tissue sarcoma with specific molecular targets have been identified. Dermatofibrosarcoma protuberans and the related giant-cell fibrosarcoma are driven by a translocation causing fusion of the collagen I type 1$\alpha$ (*COL1A1*) and platelet-derived growth factor $\beta$ (*PDGFB*) genes (Table 2). The resultant fusion protein is processed to functional PDGFB.[86] Since imatinib inhibits the receptor of PDGFB, it can be effective in the treatment of dermatofibrosarcoma protuberans[87]; this agent might be useful for patients with locally recurrent inoperable disease or metastatic spread. Synovial sarcoma is associated with a translocation resulting in fusion of the synovial sarcoma genes *SYT* and *SSX1* or *SSX2*,[40] with the fusion protein capable of acting as a transcriptional regulator. Synovial sarcomas may express epidermal growth factor receptors,[88,89] and the epidermal growth factor receptor inhibitor gefitinib is currently being evaluated in a phase 2 trial of patients with synovial sarcoma conducted by the European Organization for Research and Treatment of Cancer (EORTC).

Angiogenesis is a potential therapeutic target. Soft-tissue sarcomas express vascular endothelial growth factor.[90] The efficacy of a vascular endothelial growth factor–neutralizing antibody (bevacizumab) in other tumors[91,92] raises the possibility that the angiogenic process could also be inhibited in sarcomas. One current National Cancer Institute trial (03-C-0110) is evaluating bevacizumab in patients with Kaposi's sarcoma, and the EORTC is setting up clinical studies of inhibitors of vascular endothelial growth factor receptor tyrosine kinase in other sarcomas.

## FOLLOW-UP

Post-treatment surveillance (by means of clinical examination and chest radiography or CT) is recommended to detect treatable recurrence and metastasis.[93] Recurrence rates of 5 to 10 percent might be expected after optimal treatment of soft-tissue sarcomas of the limbs. The utility of CT and MRI for detecting subclinical local recurrence has not been established, but these approaches may be more useful for detecting deep lesions. Since two thirds of recurrences occur within two years,[33] follow-up should be most intense during this period.

Planned post-treatment surveillance enables rapid enlistment of palliative options in patients with incurable disease. However, there is little evidence that early detection of recurrence has a major influence on survival. For every patient whose life is saved by amputation, pulmonary metastasectomy, or aggressive chemotherapy, many others undergo ultimately futile therapies with little benefit — patients need appropriate information from their clinicians in order to choose the best treatment options. Issues related to the quality of life deserve careful consideration.[94]

## OPTIONS FOR ADVANCED DISEASE

All three major approaches to treatment — systemic chemotherapy, radiotherapy, and surgery — may prove useful in patients with advanced disease, de-

pending on the circumstances. Systemic chemotherapy has a palliative role, as was discussed earlier. Radiotherapy may provide substantial control of symptoms, particularly for patients with inoperable localized symptomatic disease.

Surgery with a goal of limb salvage is useful for locally recurrent disease. Reconstruction is more frequently needed in this setting. Amputation should be considered in patients with advanced disease, if severe pain, fungation, or bleeding is present. Nodal metastasis occurs in only 1 to 5 percent of patients with soft-tissue sarcoma, most frequently in those with epithelioid sarcoma or rhabdomyosarcoma.[95] Nodal involvement is classified as stage IV disease, equivalent to distant metastatic disease, although the prognosis for patients with the former is perhaps slightly better.[96] Therapeutic nodal dissection provides adequate local control in most patients. Pulmonary metastasectomy may benefit certain patients, resulting in medium- to long-term survival for some patients (with few metastases appearing late after primary resection).[97,98]

Isolated limb perfusion is appropriate for some patients with advanced soft-tissue sarcoma of the limbs. Isolated limb perfusion delivers high regional doses of chemotherapeutic agents through an extracorporeal circuit.[99] Melphalan is most commonly used, and the addition of tumor necrosis factor $\alpha$ (licensed in Europe but not in the United States) may further improve results: limb salvage is reported to be possible in 80 percent of selected patients who receive perfusion who would otherwise have required amputation or functionally debilitating treatment.[99] Tumor necrosis factor $\alpha$ targets the tumor neovasculature, causing vasodilatation and increasing vascular permeability (increasing the penetration of melphalan into the tumor), followed by prompt shutdown of measurable metabolic activity in the tumor.[100]

## CONCLUSIONS

Surgery is the mainstay of treatment for soft-tissue sarcomas; radiotherapy is useful in selected cases. Conventional chemotherapy has little effect on the outcome of most tumors, but the availability of novel targeted agents may drastically improve the prognosis of some soft-tissue sarcomas, as has been demonstrated with imatinib in the case of gastrointestinal stromal tumors. Prompt diagnosis and referral are desirable, since the size of the tumor at presentation is a continuous variable for the risk of local recurrence and metastatic disease.

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## REFERENCES

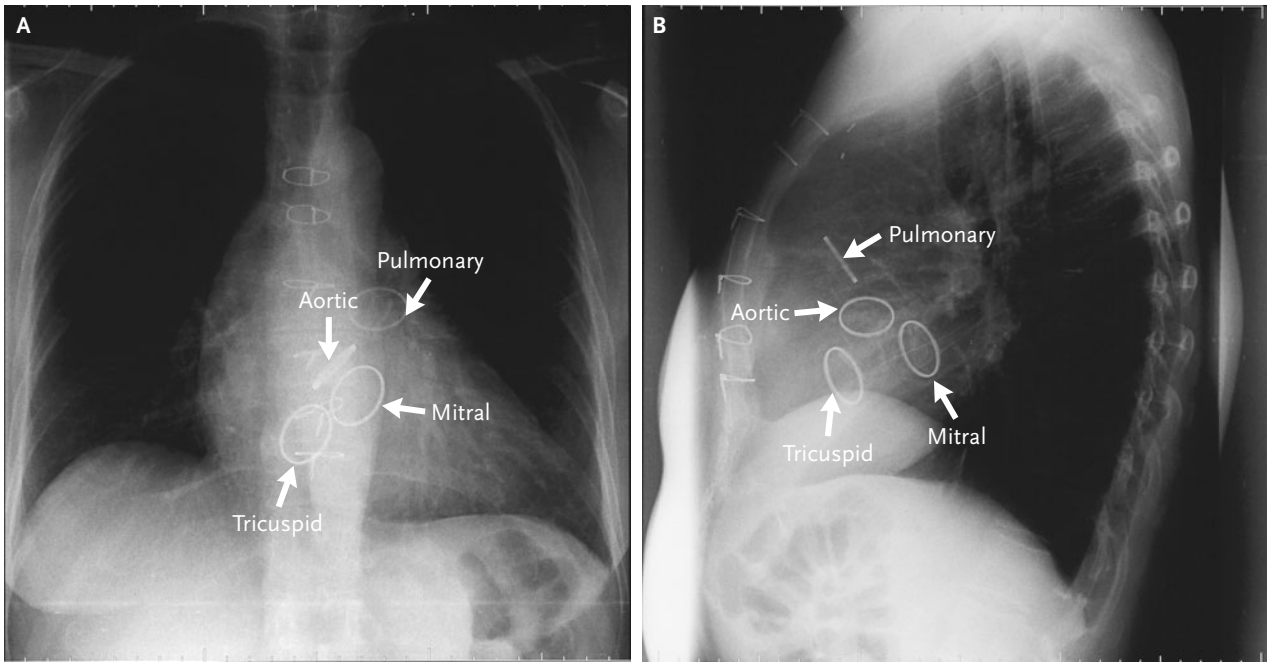
1. Wietz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 2003;21:2719-25.
2. Mankin HJ, Mankin CJ, Simon MA. The hazards of the biopsy, revisited. J Bone Joint Surg Am 1996;78:656-63.
3. Ray-Coquard I, Thiesse P, Ranchère-Vince D, et al. Conformity to clinical practice guidelines, multidisciplinary management and outcomes of treatment for soft tissue sarcomas. Ann Oncol 2004;15:307-15.
4. Rydholm A. Centralization of soft tissue sarcoma: the southern Sweden experience. Acta Orthop Scand Suppl 1997;273:4-8.
5. Van Dalen T, Hennipman A, Van Coevorden F, et al. Evaluation of a clinically applicable post-surgical classification system for primary retroperitoneal soft-tissue sarcoma. Ann Surg Oncol 2004;11:483-90.
6. Clasby R, Tilling K, Smith MA, Fletcher CD. Variable management of soft tissue sarcoma: regional audit with implications for specialist care. Br J Surg 1997;84:1692-6.
7. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004; 54:8-29.
8. Arndt CAS, Crist WM. Common musculoskeletal tumors of childhood and adolescence. N Engl J Med 1999;341:342-52.
9. Zahm SH, Fraumeni JF Jr. The epidemiology of soft tissue sarcoma. Semin Oncol 1997;24:504-14.
10. Levi F, La Vecchia C, Randimbison L, Te VC. Descriptive epidemiology of soft tissue sarcomas in Vaud, Switzerland. Eur J Cancer 1999;35:1711-6.
11. McClain KL, Leach CT, Jenson HB, et al. Association of Epstein–Barr virus with leiomyosarcomas in young people with AIDS. N Engl J Med 1995;332:12-8.
12. Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. Arch Surg 1992;127:1379-85.
13. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma: radiation dose and sarcoma risk. JAMA 1997;278:1262-7.
14. Strong LC, Williams WR, Tainsky MA. The Li-Fraumeni syndrome: from clinical epidemiology to molecular genetics. Am J Epidemiol 1992;135:190-9.
15. Rydholm A. Improving the management of soft tissue sarcoma: diagnosis and treatment should be given in specialist centres. BMJ 1998;317:93-4.
16. Demas BE, Heelan RT, Lane J, Marcove R, Hajdu S, Brennan MF. Soft-tissue sarcomas of the extremities: comparison of MR and CT in determining the extent of disease. AJR Am J Roentgenol 1988;150:615-20.
17. Sanders TG, Parsons TW III. Radiographic imaging of musculoskeletal neoplasia. Cancer Control 2001;8:221-31.
18. Bastiaannet E, Groen H, Jager PL, et al. The value of FDG-PET in the detection, grading and response to therapy of soft tissue and bone sarcomas: a systematic review and meta-analysis. Cancer Treat Rev 2004; 30:83-101.
19. Bar-Shalom R, Yefremov N, Guralnik L, et al. Clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management. J Nucl Med 2003;44:1200-9.
20. Somer EJ, Marsden PK, Benatar NA, Goodey J, O'Doherty MJ, Smith MA. PET-MR image fusion in soft tissue sarcoma: accuracy, reliability and practicality of interactive point-based and automated mutual information techniques. Eur J Nucl Med Mol Imaging 2003;30:54-62.
21. Vaidya SJ, Payne GS, Leach MO, Pinkerton CR. Potential role of magnetic reso-

nance spectroscopy in assessment of tumour response in childhood cancer. Eur J Cancer 2003;39:728-35.
**22.** Hoeber I, Spillane AJ, Fisher C, Thomas JM. Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors. Ann Surg Oncol 2001;8:80-7.
**23.** Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 1997;4:425-31.
**24.** Trovik CS, Bauer HC, Brosjo O, Skoog L, Soderlund V. Fine needle aspiration (FNA) cytology in the diagnosis of recurrent soft tissue sarcoma. Cytopathology 1998;9:320-8.
**25.** Alvegard TA, Berg NO. Histopathology peer review of high-grade soft tissue sarcoma: the Scandinavian Sarcoma Group experience. J Clin Oncol 1989;7:1845-51.
**26.** Clark MA, Thomas JM. Portsite recurrence after laparoscopy for staging of retroperitoneal sarcoma. Surg Laparosc Endosc Percutan Tech 2003;13:290-1.
**27.** Burkill GJC, Badran M, Al-Muderis O, et al. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. Radiology 2003;226:527-32.
**28.** Fletcher CDM, Unni KK, Mertens F, eds. Pathology and genetics of tumours of soft tissue and bone. Vol. 5 of World Health Organization classification of tumours. Lyon, France: IARC Press, 2002.
**29.** Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997;15:350-62.
**30.** Greene FL, Page DL, Fleming ID, et al. eds. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag, 2002.
**31.** Ramanathan RC, A'Hern R, Fisher C, Thomas JM. Modified staging system for extremity soft tissue sarcomas. Ann Surg Oncol 1999;6:57-69.
**32.** Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679-89.
**33.** Stojadinovic A, Leung DH, Allen P, Lewis JJ, Jaques DP, Brennan MF. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. J Clin Oncol 2002;20:4344-52.
**34.** Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20:791-6.
**35.** Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol 2002;33:459-65.
**36.** Segal NH, Pavlidis NA, Antonescu CR, et al. Classification and subtype prediction of adult soft tissue sarcoma by functional genomics. Am J Pathol 2003;163:691-700.
**37.** Stratton MR, Moss S, Warren W, et al. Mutation of the p53 gene in human soft tissue sarcomas: association with abnormalities of the RB1 gene. Oncogene 1990;5:1297-301.
**38.** Kruzelock RP, Hansen MF. Molecular genetics and cytogenetics of sarcomas. Hematol Oncol Clin North Am 1995;9:513-40.
**39.** Karpeh MS, Brennan MF, Cance WG, et al. Altered patterns of retinoblastoma gene product expression in adult soft-tissue sarcomas. Br J Cancer 1995;72:986-91.
**40.** Ladanyi M, Antonescu CR, Leung DH, et al. Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. Cancer Res 2002;62:135-40.
**41.** Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
**42.** Lee YF, John M, Edwards S, et al. Molecular classification of synovial sarcomas, leiomyosarcomas and malignant fibrous histiocytomas by gene expression profiling. Br J Cancer 2003;88:510-5.
**43.** Nielsen TO, West RB, Linn SC, et al. Molecular characterisation of soft tissue tumours: a gene expression study. Lancet 2002;359:1301-7.
**44.** McCarter MD, Jaques DP, Brennan MF. Randomized clinical trials in soft tissue sarcoma. Surg Oncol Clin N Am 2002;11:11-22.
**45.** Bowden L, Booher RJ. The principles and technique of resection of soft parts for sarcoma. Surgery 1958;44:963-76.
**46.** Gerrand CH, Wunder JS, Kandel RA, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br 2001;83:1149-55.
**47.** Schwartz DL, Einck J, Bellon J, Laramore GE. Fast neutron radiotherapy for soft tissue and cartilaginous sarcomas at high risk for local recurrence. Int J Radiat Oncol Biol Phys 2001;50:449-56.
**48.** Bickels J, Wittig JC, Kollender Y, Kellar-Graney KL, Malawer MM, Meller I. Sciatic nerve resection: is that truly an indication for amputation? Clin Orthop 2002;399:201-4.
**49.** Pitcher ME, Thomas JM. Functional compartmental resection for soft tissue sarcomas. Eur J Surg Oncol 1994;20:441-5.
**50.** Clark MA, Thomas JM. Amputation for soft-tissue sarcoma. Lancet Oncol 2003;4:335-42.
**51.** Merimsky O, Kollender Y, Inbar M. Is forequarter amputation justified for palliation of intractable cancer symptoms? Oncology 2001;60:55-9.
**52.** Langstein HN, Robb GL. Reconstructive approaches in soft tissue sarcoma. Semin Surg Oncol 1999;17:52-65.
**53.** Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg 2003;238:358-71.
**54.** Alektiar KM, Hu K, Anderson L, Brennan MF, Harrison LB. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys 2000;47:157-63.
**55.** Rossi CR, Deraco M, De Simone M, et al. Hyperthermic intraperitoneal intraoperative chemotherapy after cytoreductive surgery for the treatment of abdominal sarcomatosis: clinical outcome and prognostic factors in 60 consecutive patients. Cancer 2004;100:1943-50.
**56.** Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas: final results of a prospective, randomized clinical trial. Arch Surg 1993;128:402-10.
**57.** Lichter AS, Lawrence TS. Recent advances in radiation oncology. N Engl J Med 1995;332:371-9.
**58.** Strander H, Turesson I, Cavallin-Stahl E. A systematic overview of radiation therapy effects in soft tissue sarcomas. Acta Oncol 2003;42:516-31.
**59.** Janjan N, Crane C, Delclos M, Ballo M. Brachytherapy for locally recurrent soft-tissue sarcoma. Am J Clin Oncol 2002;25:9-15.
**60.** Tepper JE, Suit HD. Radiation therapy alone for sarcoma of soft tissue. Cancer 1985;56:475-9.
**61.** Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305-15.
**62.** O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002;359:2235-41.
**63.** Ballo MT, Zagars GK, Cormier JN, et al. Interval between surgery and radiotherapy: effect on local control of soft tissue sarcoma. Int J Radiat Oncol Biol Phys 2004;58:1461-7.
**64.** O'Sullivan B, Ward I, Catton C. Recent advances in radiotherapy for soft-tissue sarcoma. Curr Oncol Rep 2003;5:274-81.
**65.** Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997;350:1647-54.
**66.** Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 2001;19:1238-47.
**67.** Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2003;55:168-77.
**68.** Kolb EA, Kushner BH, Gorlick R, et al. Long-term event-free survival after intensive

chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol 2003;21:3423-30.
**69.** Oberlin O, Deley MC, Bui BN, et al. Prognostic factors in localized Ewing's tumours and peripheral neuroectodermal tumours: the third study of the French Society of Paediatric Oncology (EW88 study). Br J Cancer 2001;85:1646-54.
**70.** Strauss SJ, McTiernan A, Driver D, et al. Single center experience of a new intensive induction therapy for Ewing's family of tumors: feasibility, toxicity, and stem cell mobilization properties. J Clin Oncol 2003;21: 2974-81.
**71.** Van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens — a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 1999;17:150-7.
**72.** Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20: 2824-31.
**73.** Fata R, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer 1999;86:2034-7.
**74.** Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2001;37:870-7.
**75.** Eiling S, Lischner S, Busch JO, Rothaupt D, Christophers E, Hauschild A. Complete remission of a radio-resistant cutaneous angiosarcoma of the scalp by systemic treatment with liposomal doxorubicin. Br J Dermatol 2002;147:150-3.
**76.** van Oosterom AT, Mourisden HT, Nielsen OS, et al. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer 2002;38:2397-406.
**77.** Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. Am J Clin Oncol 1998;21:317-21.
**78.** D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. Expert Opin Investig Drugs 2003;12:1843-53.
**79.** Yovine A, Riofrio M, Blay JY, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol 2004;22:890-9.
**80.** Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577-80.
**81.** Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152:1259-69.
**82.** van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 2001;358:1421-3.
**83.** Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-80.
**84.** Verweij J, Casali PG, Zalcberg J, et al. Early efficacy comparison of two doses of imatinib for the treatment of advanced gastrointestinal stromal tumors (GIST): interim results of a randomised phase III trial from the EORTC-STBSG, ISG, and AGITG. Proc Am Soc Clin Oncol 2003;22:814. abstract.
**85.** Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299:708-10.
**86.** Shimizu A, O'Brien KP, Sjoblom T, et al. The dermatofibrosarcoma protuberans-associated collagen type I alpha1/platelet-derived growth factor (PDGF) B-chain fusion gene generates a transforming protein that is processed to functional PDGF-B. Cancer Res 1999;59:3719-23.
**87.** Maki RG, Awan RA, Dixon RH, Jhanwar S, Antonescu CR. Differential sensitivity to imatinib of 2 patients with metastatic sarcoma arising from dermatofibrosarcoma protuberans. Int J Cancer 2002;100:623-6.
**88.** Gusterson B, Cowley G, McIlhinney J, Ozanne B, Fisher C, Reeves B. Evidence for increased epidermal growth factor receptors in human sarcomas. Int J Cancer 1985; 36:689-93.
**89.** Nielsen TO, Hsu FD, O'Connell JX, et al. Tissue microarray validation of epidermal growth factor receptor and SALL2 in synovial sarcoma with comparison to tumors of similar histology. Am J Pathol 2003;163: 1449-56.
**90.** Hayes AJ, Mostyn-Jones A, Koban MU, A'Hern R, Burton P, Thomas JM. Serum vascular endothelial growth factor as a tumour marker in soft tissue sarcoma. Br J Surg 2004;91:242-7.
**91.** Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti–vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003;349:427-34.
**92.** Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
**93.** Whooley BP, Gibbs JF, Mooney MM, McGrath BE, Kraybill WG. Primary extremity sarcoma: what is the appropriate follow-up? Ann Surg Oncol 2000;7:9-14.
**94.** Merimsky O, Kollender Y, Inbar M, Chaitchick S, Meller I. Palliative major amputation and quality of life in cancer patients. Acta Oncol 1997;36:151-7.
**95.** Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults: analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993;217:72-7.
**96.** Behranwala KA, A'Hern R, Omar AM, Thomas JM. Prognosis of lymph node metastasis in soft tissue sarcoma. Ann Surg Oncol 2004;11:714-9.
**97.** Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999; 229:602-12.
**98.** Temple LKF, Brennan MF. The role of pulmonary metastasectomy in soft tissue sarcoma. Semin Thorac Cardiovasc Surg 2002;14:35-44.
**99.** Eggermont AMM, de Wilt JHW, ten Hagen TLM. Current uses of isolated limb perfusion in the clinic and a model system for new strategies. Lancet Oncol 2003;4: 429-37.
**100.** Sijens PE, Eggermont AM, van Dijk PV, Oudkerk M. 31P magnetic resonance spectroscopy as predictor of clinical response in human extremity sarcomas treated by single dose TNF-alpha + melphalan isolated limb perfusion. NMR Biomed 1995;8:215-24.

IMAGES IN CLINICAL MEDICINE

# Four Artificial Heart Valves

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A 67-YEAR-OLD WOMAN REPORTED HAVING PROGRESSIVE SHORTNESS OF breath over several months, three years after undergoing aortic-valve replacement for aortic insufficiency. The patient had migraine headaches for which she had received 2 mg of ergotamine tartrate daily for many years. On physical examination, her blood pressure was 170/95 mm Hg. She had elevated jugular venous pressure, and grade 2/6 systolic and diastolic murmurs were noted along the right sternal border. The results of laboratory analysis for 5-hydroxyindoleacetic acid were normal. Echocardiography showed a normal aortic-valve prosthesis and thickened mitral, pulmonary, and tricuspid valves with severe insufficiency. Cardiac catheterization revealed elevated right atrial pressure and normal coronary arteries. On rethoracotomy, all three native valves were found to be severely thickened and were replaced with St. Jude Medical prostheses. The patient had an uneventful recovery, and her symptoms improved from New York Heart Association class IV to class I. A follow-up radiograph of the chest shows the position of all four prosthetic valves (arrows, Panels A and B). Pathological examination showed changes compatible with the long-term use of ergotamine. A review of the pathological report from her initial aortic-valve surgery three years earlier demonstrated findings consistent with ergotamine toxicity as well. The patient continues to do well at one year and uses paracetamol for management of migraine pain.



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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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# Case 25-2005: A 40-Year-Old Man with Prolonged Fever and Weight Loss

Dennis L. Kasper, M.D., Dushyant Sahani, M.D., and Joseph Misdraji, M.D.

## PRESENTATION OF CASE

A 40-year-old man was admitted to this hospital because of persistent fever, night sweats, anorexia, and weight loss.

The patient had been in excellent health until eight and a half weeks before admission, when fever, chills, severe headache, and diarrhea developed the day after he and his family ate in a fast-food restaurant. Others in the family had similar symptoms. The headaches and diarrhea resolved after five days, but the fever persisted, with nightly temperatures of 38.9°C to 39.4°C associated with drenching night sweats. The fever responded to ibuprofen and did not occur during the day. Anorexia developed, with a weight loss of 6.4 kg, and the patient felt some pressure in the right upper abdominal quadrant. He noted a brownish-orange color to his urine. Evaluation by his primary care physician two and a half weeks after the onset of symptoms (six weeks before admission to this hospital) revealed normal vital signs and normal findings on physical examination; laboratory-test results are shown in Table 1. Computed tomographic (CT) scanning of the abdomen and thorax showed no abnormalities except for patchy, nonspecific heterogeneous attenuation in the liver, which was thought to suggest fatty infiltration.

Two weeks later, four weeks before admission, persistent symptoms prompted referral to a second physician for consultation. The results of the physical examination were again normal. Serum levels of electrolytes, calcium, phosphorus, glucose, urea nitrogen, and creatinine were normal. The results of tests for C-reactive protein, alpha$_1$-antitrypsin, alpha-fetoprotein, ceruloplasmin, and thyrotropin were normal. Assays for the presence of IgG antibodies to Epstein–Barr virus (EBV) latent membrane protein and EBV nuclear antigen were positive; those for IgM anti-EBV antibodies, hepatitis B antigen and antibody, and antimitochondrial antibodies were negative. Antinuclear antibodies were present at a titer of 1:32 in a speckled pattern. Urinalysis was positive for urobilinogen (+) and was otherwise normal. Other results from this second round of laboratory tests are shown in Table 1.

Repeated CT scanning of the abdomen, performed after the administration of intravenous contrast material as well as oral contrast material, showed inflammatory changes around the cecum and possibly the terminal ileum. The liver showed diffuse low attenuation in the center without biliary obstruction or a focal mass. The gallbladder was absent. The spleen, pancreas, adrenal glands, and kidneys were normal. A biopsy

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**Table 1. Hematologic Laboratory Values.**

| Variable | Six Weeks before Admission | Four Weeks before Admission | On Admission to the Other Hospital | On Admission to This Hospital | Second Hospital Day |
|---|---|---|---|---|---|
| White-cell count — per mm³ | | 10,200 | 7,000 | 10,300 | 12,600 |
| Red-cell count — per mm³ | | 4,290,000 | 3,910,000 | 3,870,000 | 3,890,000 |
| Hemoglobin — g/dl | 12.6 | 11.6 | 10.4 | 10.2 | 10 |
| Hematocrit — % | | 35.4 | 31.8 | 30.8 | 31 |
| Mean corpuscular volume — μm³ | | 83 | 81 | 79 | 80 |
| Mean corpuscular hemoglobin — pg/red cell | | 27.0 | 26.6 | 26.3 | 25.8 |
| Mean corpuscular hemoglobin concentration — g/dl | | 32.8 | 32.7 | 33.1 | 32.4 |
| Platelet count — per mm³ | 613,000 | 376,000 | 386,000 | 398,000 | 397,000 |
| Differential count — % | | | | | |
| Neutrophils | | 77 | 70 | 84 | 81 |
| Lymphocytes | | 17 | 24 | 12 | 12 |
| Monocytes | | 6 | 6 | 2 | 5 |
| Eosinophils | | | | 2 | 2 |
| Basophils | | | | 0 | 0 |
| Erythrocyte sedimentation rate — mm/hr | 67 | 115 | 120 | 123 | 124 |
| Prothrombin time — sec | | 13.1 | 13.1 | 13.9 | 14.0 |
| International normalized ratio | | 1.2 | | 1.3 | 1.3 |
| Partial-thromboplastin time — sec | | 31.2 | 27.0 | 29.2 | 29.9 |
| Prothrombin gene mutation G20210A | | | | | Normal |
| Partial-thromboplastin time–lupus anticoagulant screen* | | | | | Negative |
| Antithrombin III (functional) — %† | | | | | 84 |
| Protein C (functional) — %‡ | | | | | 72 |
| Activated protein C resistance§ | | | | | Ratio, 2.5 |
| Protein S (functional) — %¶ | | | | | 100 |

* This test is based on partial-thromboplastin–time screens for the presence of lupus anticoagulants.
† The normal range is 80 to 130 percent.
‡ The normal range is 70 to 140 percent.
§ The normal ratio is greater than 2.0.
¶ The normal range is is 70 to 140 percent.

specimen of bone marrow showed normal hematopoiesis and increased iron storage.

Colonoscopy, esophagogastroduodenoscopy, and endoscopic retrograde cholangiopancreatography performed during the following week showed no abnormalities except for a few erosions in the gastric antrum; the pancreatic ducts and bile ducts had no filling defects. A biopsy specimen from the liver was reported to show a nonspecific increase in inflammatory cells. An upper gastrointestinal series with small-bowel follow-through showed that the terminal ileum was never well distended and had some mucosal irregularity. About six weeks after the onset of his illness, the patient was admitted to another hospital for exploratory laparoscopy. An inflamed retrocecal appendix was removed; there was evidence of periappendiceal and pericolonic inflammation. Pathological examination of the appendix was reported to show inflammation and cancer.

Within 24 hours, the patient reported improvement in his symptoms, and he was discharged to his home. He felt well for about one week; then the fever and night sweats recurred. Repeated CT scanning of the abdomen and pelvis at that time, after the administration of oral and intravenous contrast material, showed no opacification of the main portal and superior mesenteric veins and stranding of

the peripancreatic and periportal fat. The patient was referred to this hospital the next day, and he was admitted.

The patient had undergone laparoscopic cholecystectomy two years earlier. He did not smoke, drink alcohol, or use illicit drugs, and he drank minimal amounts of coffee. He was married, with two children; all three family members were well. He worked as a mechanic but had been unable to work for the past month because of his illness. An uncle and a grandmother had had lung cancer, and the patient's father had died at 64 years of age of lung disease related to asbestosis and emphysema. His mother and three siblings were in good health. He had not traveled outside the United States for 13 years. He had no pets, no exposure to animals, and no known tick bites. The family's drinking water came from a well. He had no nausea or vomiting, diarrhea, hematochezia, hematemesis, muscle weakness, joint problems, or neurologic symptoms. He took no medications.

On examination, the blood pressure was 115/70 mm Hg, the pulse 105 beats per minute, the respiratory rate 18 breaths per minute, the temperature 37.3°C, and the oxygen saturation 100 percent while the patient was breathing room air. He was in no acute distress. The skin was pale, with no rashes, lesions, or jaundice. An examination of the head, eyes, ears, neck, and chest revealed no abnormalities. The heart rate and rhythm were regular, with no murmurs, gallops, or rubs. The abdomen was soft, nontender, and nondistended, with normal bowel sounds. The liver and spleen were not palpable. The extremities appeared normal. Neurologic examination revealed no abnormalities. Specimens of blood were drawn for culture. Laboratory-test results are shown in Table 2.

Magnetic resonance imaging (MRI) of the liver on the day after admission (before and after administration of intravenous gadolinium) showed a nonenhancing thrombus in the main portal vein that extended into both the right and left intrahepatic branches. No mass lesion, focal abnormality, or dilatation of the bile ducts was present in the liver. The hepatic arteries, hepatic veins, and splenic vein were patent.

A diagnostic test result was reported.

## DIFFERENTIAL DIAGNOSIS

*Dr. Dennis L. Kasper:* This patient and his family probably had food-borne infectious diarrhea, and this patient's subsequent problems may well have resulted from complications of this primary infection.

The differential diagnosis of food-borne infections is wide, with possible pathogens ranging from bacterial to viral to protozoan. These causes may be clinically indistinguishable; stool cultures would have been useful and might have been diagnostic earlier in the course of the illness. The persistence of this man's symptoms for weeks, with fever and subsequent complications, limits the scope of the diagnostic possibilities. Overall, this complex clinical course is most consistent with a bacterial cause of diarrhea. Salmonella, campylobacter, and yersinia would be at the top of my list of possible causes.[1] In the United States, salmonella and campylobacter are much more common food-borne pathogens than yersinia.[2]

This case begins to distinguish itself from routine infectious diarrhea in its subsequent course. The weight loss and pressure in the right upper quadrant that the patient had after the diarrheal illness are unusual and suggest other problems that may have been initiated by the original gastrointestinal infection.

### PERSISTENT SYMPTOMS WITH ABNORMAL RESULTS ON LIVER-FUNCTION TESTS

The increased serum level of alanine aminotransferase and a borderline low serum level of albumin, along with the weight loss and pressure in the right upper quadrant, suggest the evolution of a new process involving the liver or perhaps the presence of underlying liver disease that predisposed the patient to more severe infection. The incubation period was too short for hepatitis to have been acquired during the patient's recent contact with apparently contaminated food. The workup for hepatitis B and EBV-related hepatitis was negative. A workup for hepatitis A was not done.

Liver disease due to iron overload or hemochromatosis would predispose a patient to yersiniosis. Yersiniae exploit host iron and use it to enhance their virulence. The detection by CT of nonspecific heterogeneous liver attenuation suggests a diffuse hepatic process. Heterogeneous attenuation, as compared with homogeneous attenuation, is less consistent with infiltrative disease due to iron deposition and more consistent with a vascular process. The patient's serum iron levels and total iron-binding capacity make hemochromatosis an unlikely diagnosis, and no aspect of his history suggests iron overload.

**Table 2. Blood-Chemistry and Immunologic Laboratory Values.***

| Variable | Six Weeks before Admission | Four Weeks before Admission | On Admission to the Other Hospital | On Admission to This Hospital | Second Hospital Day |
|---|---|---|---|---|---|
| Protein (g/dl) | | | 7.3 | 8.5 | 8.1 |
| Albumin | | 3.3 | 3.4 | 3.1 | 2.9 |
| Globulin | | | 3.9 | 5.4 | 5.2 |
| Alanine aminotransferase (U/liter) | 270 | 244 | 352 | 195 | 175 |
| Aspartate aminotransferase (U/liter) | 80 | 113 | 78 | 75 | 63 |
| Alkaline phosphatase (U/liter) | 230 | 610 | 439 | 431 | 468 |
| Lactate dehydrogenase (U/liter) | | 536 | 430 | 133 | |
| Iron ($\mu$g/dl) | | | 19 | 15 | 18 |
| Iron-binding capacity ($\mu$g/dl) | | | 356 | 228 | 217 |
| Ferritin ($\mu$g/liter) | | | 566 | 649 | 618 |
| Vitamin $B_{12}$ (pmol/liter) | | | 741 | | |
| Folate (nmol/liter) | | | 11.9 | | |
| Homocysteine ($\mu$mol/liter) | | | | | 8.1 |
| Anti–smooth-muscle antibodies | | | | | Positive at 1:20 dilution |
| Anti–liver-kidney microsomal antibodies | | | | | <1:40 |

* To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791. The normal range for homocysteine is 0 to 12 $\mu$mol per liter.

### DETERIORATION OF LIVER FUNCTION

Over the next few weeks, the results of tests of liver function became increasingly abnormal. Alkaline phosphatase rose to a very high level, and the level of lactate dehydrogenase was high, with ongoing elevation of hepatocellular enzymes. The erythrocyte sedimentation rate continued to rise, suggesting an ongoing inflammatory process. A process that connects the diarrheal disease to the abnormal results on liver-function tests must be considered. Although pyogenic liver abscesses would have been high on my diagnostic list, repeated CT two weeks after the initial CT did not support this diagnosis. It did show ongoing inflammatory change around the cecum and possibly the terminal ileum, suggesting that the initial infection may not have resolved. The liver continued to show low-level heterogeneous attenuation, with no abscesses or biliary obstruction.

A liver biopsy showed a nonspecific increase in inflammatory cells. Without definitive pathological findings in the liver, vascular disruption causing diffuse heterogeneous liver changes must be strongly considered. The development of liver disease after infectious diarrhea, the subsequent radiologic studies, and the continuing fevers all suggest the portal venous system as a site where infection might arise, where organisms might disseminate from the bowel to the systemic circulation, and where vascular occlusion may develop, possibly as a result of portal-vein thrombosis.

### ILEOCECITIS AND PERIAPPENDICITIS ASSOCIATED WITH FOOD-BORNE PATHOGENS

The upper gastrointestinal series with small-bowel follow-through showed a lack of distention in the terminal ileum, as well as mucosal irregularities. At this point, a possible link between the diarrheal illness and the continuing mucosal irregularities in the small bowel becomes more apparent. Yersinia, salmonella, and campylobacter have been associated with ileocolitis, periappendiceal inflammation, and appendicitis following acute infection.[3-12] Clinically, these gastrointestinal infections may be indistinguishable once appendicitis develops.[5] Of these three organisms, yersinia is most often associated around the world with subsequent inflammation of the appendix, periappendiceal areas of the ileum, or mesenteric lymph nodes.[4,13] In the United States, *Yersinia enterocolitica* has reportedly been found in up to 9 percent of appendixes re-

moved because of symptoms of appendicitis.[4] It is not clear whether *Y. enterocolitica* is the causative agent of appendicitis in these cases. *Y. pseudotuberculosis* is a pathogen that is found primarily in animals and rarely in humans.[8] *Y. enterocolitica* is usually transmitted to humans from domestic and wild animal reservoirs by way of food consumption. Although self-limited enterocolitis is much more commonly caused by *Y. enterocolitica* than by *Y. pseudotuberculosis*, the latter is more often associated with mesenteric lymphadenitis and terminal ileitis.[8]

Salmonella, which can cause pseudoappendicitis or even an illness mimicking inflammatory bowel disease,[10] may have initiated the disease process in this patient. In the United States, several studies indicate that diarrheal disease due to campylobacter is more common than that due to salmonella and shigella combined.[6] *Campylobacter jejuni* is the principal diarrheal pathogen belonging to this genus; it causes tissue injury in the jejunum, ileum, and colon and has also been associated with pseudoappendicitis.[6]

During an exploratory laparotomy, an inflamed retrocecal appendix was removed. Periappendiceal and pericolonic inflammation was reported. The disease process in the ileal and appendiceal areas was probably associated with the original infectious cause of diarrhea. In spite of an initial postoperative improvement, fever and night sweats recurred.

A workup at this hospital included what turned out to be an unremarkable medical history and an essentially normal physical examination. However, MRI of the liver with gadolinium contrast material yielded findings of interest. May we review these studies?

*Dr. Dushyant Sahani:* Contrast-enhanced CT of the abdomen, performed in arterial and portal venous phases of liver enhancement on the day before admission, showed heterogeneous enhancement of the liver parenchyma in the arterial phase (Fig. 1A). However, in the portal venous phase, the liver enhanced homogeneously. An occlusive thrombus was identified in the left main branch of the portal vein and a nonocclusive thrombus in the superior mesenteric vein (Fig. 1B). In addition, there was stranding in the fat, which indicated inflammation in the right lower quadrant, along the medial aspect of the cecum (Fig. 1C). There was no ascites.

One day after admission, a contrast-enhanced MRI of the liver confirmed the finding of a nonenhancing, occlusive thrombus in the portal vein. When this scan was compared with the CT scan, progression of the thrombus in the main portal vein, intrahepatic branches, and the superior mesenteric vein (Fig. 2) was evident.

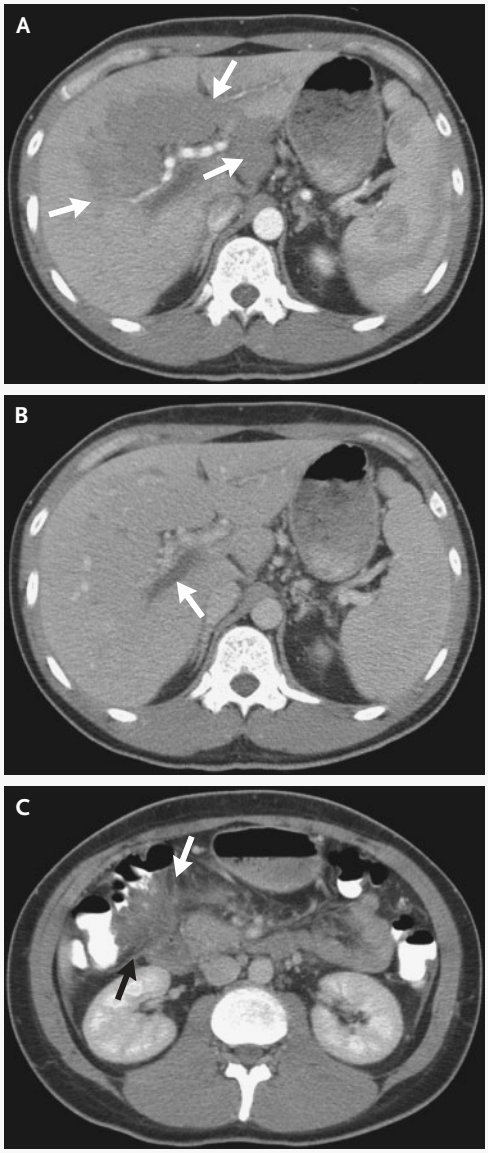


**Figure 1. Contrast-Enhanced CT Images of the Liver Obtained One Day before Admission.**

The arterial-phase image (Panel A) shows heterogeneous enhancement of the liver parenchyma at the level of the porta hepatis (arrows). In the subsequent image from the portal venous phase (Panel B), a filling defect, or thrombus, is evident in the main portal vein and the left branch (arrow). In an image obtained at the level of the right lower quadrant (Panel C), there is stranding in the pericecal fat (arrows), indicating inflammation.

### PYLEPHLEBITIS FOLLOWING APPENDICITIS

*Dr. Kasper:* The imaging tests and the case presentation are consistent with pylephlebitis (septic thrombophlebitis of the portal veins). This condition appears to have developed as a result of the appendicitis and periappendicitis, which were probably due to one of the diarrheal pathogens I have already mentioned. It is less likely, but possible, that these food-borne organisms were responsible for the pylephlebitis. Only rarely do case reports describe pylephlebitis as having been caused by salmonella[14]; yersinia and campylobacter are also unlikely suspects. Appendicitis itself is a well-known cause of pylephlebitis.[15] The venous drainage from the appendiceal area and terminal ileum flows directly into the portal system (Fig. 3). Bacteroides species are components of the normal ileal and cecal flora.[16] In appendicitis, both vascular flow to the appendix and vascular leakage of bacteria are increased. In one series of appendicitis cases in Croatia,[17] portal-vein bacteremia was found in 19 of 50 cases, but patients had systemic bacteremia in only 3 of the cases. Bacteroides and *Escherichia coli* predominated among the isolates.

In a 1995 review of 19 cases of pylephlebitis reported in the literature after 1979,[15] appendicitis was second only to diverticulitis as a predisposing condition for pylephlebitis. The organisms most frequently cultured from the blood were bacteroides (especially *Bacteroides fragilis*) and *E. coli*. Pylephlebitis often leads to inflammation and, not uncommonly, to abscess of the liver.

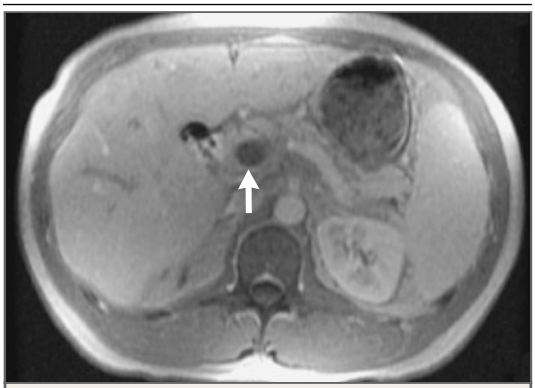

**Figure 2. A Dynamic Contrast-Enhanced MRI Scan of the Liver Obtained on the Second Hospital Day.**
An occlusive thrombus is present in the superior mesenteric vein (arrow).

### BACTEROIDES AND THROMBOTIC DISEASE

Anaerobic infections are strongly associated with thrombotic diseases. Thrombophlebitis is found in as many as 5 to 12 percent of cases of anaerobic bacteremia.[18] The responsible mechanism is not fully understood, but several factors may contribute. Bacteroides species elaborate enzymes that degrade heparin.[19] Bacteroides can accelerate coagulation in mice, as shown by decreased clotting time; this acceleration is secondary to a cell-wall component.[20] Surface components of bacteroides substantially enhance fibrin clotting, probably in tandem with a capsular component that activates macrophages and initiates the clotting cascade.[21] *B. fragilis* expresses capsular polysaccharides that have structural characteristics that make them fibrinogenic and thus capable of facilitating abscess formation[22,23]; the underlying mechanism is probably quite similar to that which enables the organism to cause thrombophlebitis.[21] The unique immunologic properties found in the capsular zwitterionic polysaccharides of *B. fragilis* promote this procoagulant activity.[23] Although I would usually be inclined to favor a unifying diagnosis, in this case I think the probability of two more common associations — food-borne infection causing appendicitis and *B. fragilis* causing pylephlebitis — is greater. Therefore, I believe that the most definitive diagnostic test in this case was the blood culture, which I suspect grew *B. fragilis* (although it may have grown yersinia, salmonella, or campylobacter).

*Dr. Nancy Lee Harris* (Pathology): Dr. Ivers, you were the infectious-diseases fellow who cared for this patient; can you give us your clinical impressions?

*Dr. Louise Ivers* (Infectious Diseases): We reviewed the patient's radiology images from previous admissions with radiology staff members on the day of admission. On the basis of the finding of portal-vein thrombosis in combination with the history of subacute appendicitis and prolonged fever, our leading differential diagnosis was septic portal-vein thrombosis. Since the patient was clinically stable, we recommended that antibiotics be withheld for the first 24 hours after admission while blood cultures were obtained.

*Dr. Harris:* Would stool cultures have been of any use in determining what caused the patient's original diarrhea?

*Dr. Kasper:* The patient still had signs of active ileocecitis, as seen in the CT scan. I would like to know whether stool cultures were done.

## CLINICAL DIAGNOSIS

Pylephlebitis.

## DR. DENNIS L. KASPER'S DIAGNOSIS

Ileocecitis with appendicitis in association with infection by yersinia, salmonella, or campylobacter, leading to pylephlebitis with *B. fragilis* bacteremia.

## PATHOLOGICAL DISCUSSION

*Dr. Joseph Misdraji:* The specimen obtained during liver biopsy is perhaps most remarkable for the absence of pathological findings in the portal vein, given the imaging studies that showed complete occlusion of this vessel. The portal tracts are edematous and the bile ducts appear reactive and injured. Inflammatory cells are sparse, but a few neutrophils infiltrate the bile duct epithelium (Fig. 4A). Although these changes are not well developed, they raise the possibility of some degree of bile-duct obstruction. In the setting of portal-vein thrombosis, this may be due to a condition known as portal biliopathy, in which extrahepatic biliary obstruction results from an engorgement of collateral veins around the bile duct.[24]

The appendix showed areas of mucosal ulceration (Fig. 4B), associated with hemosiderin deposition, and periappendiceal fat necrosis, indicating an acute and chronic inflammatory process. In the periappendiceal fat, there was a thrombosed vein (Fig. 4C), which is of interest in the context of the patient's portal-vein thrombosis. As Dr. Kasper predicted, a blood culture yielded *B. fragilis*, establishing the diagnosis of pylephlebitis as a result of infection with *B. fragilis.*

Pylephlebitis begins with thrombophlebitis of the small veins draining the infected site, which in this case was the appendix. The involvement, by extension, of larger veins leads to septic thrombophlebitis of the portal vein, and further extension to the large mesenteric veins may result in bowel ischemia — a rare complication that carries a high risk of death. Embolization of an infected thrombus results in liver abscesses.[25] The organisms that are most often cultured from the blood are *E. coli* and *B. fragilis.* Although the role of these organisms in precipitating appendicitis is controversial, their role in abdominal infectious complications of appendicitis has been well established; these two organisms are those most frequently recovered from inflamed, gangrenous appendixes or the peritoneal fluid in cases of appendicitis.[26-33] Clinical trials have shown that the use of antibiotics with activity against *B. fragilis* in the treatment of complicated appendicitis can reduce the rate of postoperative infectious complications.[34,35]

## DISCUSSION OF MANAGEMENT

*Dr. Harris:* Dr. Kasper, could you discuss your recommendations for the management of bacteroides pylephlebitis?

*Dr. Kasper:* In a case such as this one, until culture results are known, metronidazole and a quinolone agent should be administered to treat bacteroides and food-borne infection, respectively. If the blood yielded only a food-borne pathogen, metronidazole would not be needed. Anticoagulant therapy in this clinical setting has not been proved essential but has been associated with improvement in the condition of some patients, with a decrease in septic embolization to the liver from infected portal thrombi and consequent prevention of liver abscesses. Many patients respond to antibiotics alone, whether or not they receive heparin.[15]

*Dr. Harris:* Dr. Ivers, would you tell us how you treated this patient's condition and how he is doing?

*Dr. Ivers:* Anticoagulation with intravenous heparin was begun. When we received the positive results of the blood cultures, we started treatment with cefepime and metronidazole and switched to levofloxacin and metronidazole after the identification of *B. fragilis.* The patient's fever immediately resolved. Subsequent blood cultures were negative. Although the infectious-diseases consultants had requested stool cultures, these were not done. A transthoracic echocardiogram did not suggest the presence of valvular vegetations. Esophagogastroduodenoscopy revealed grade 1 esophageal varices. The heparin was ultimately discontinued and oral warfarin was begun. A workup to evaluate the presence of a hypercoagulable state revealed a mildly elevated titer of anticardiolipin IgM, which was to be followed up after discharge. The patient was discharged to his home. He was well and preferred to follow up with his physician in his home city, who reported that the patient was doing well. The testing for hypercoagulability has not been repeated.

*Dr. Sahani:* Follow-up CT scans performed at another hospital two and a half months after the pa-

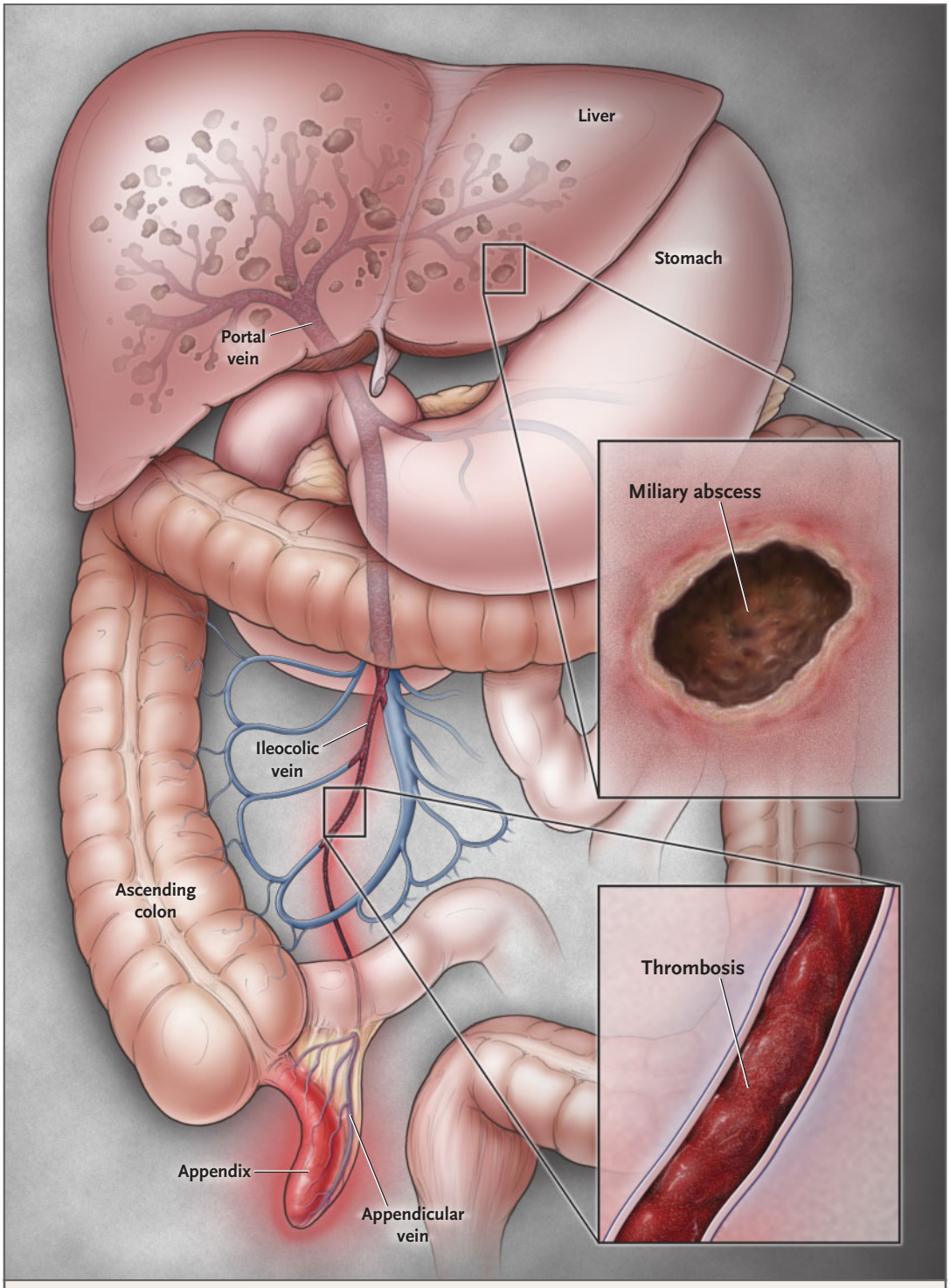


**Figure 3. The Pathogenesis of Pylephlebitis and Liver Abscess after Acute Appendicitis.**

Infection in the appendix can result in bacterial leakage into the portal venous system. Bacteroides species, particularly *B. fragilis,* have unique virulence factors that contribute to thrombosis.

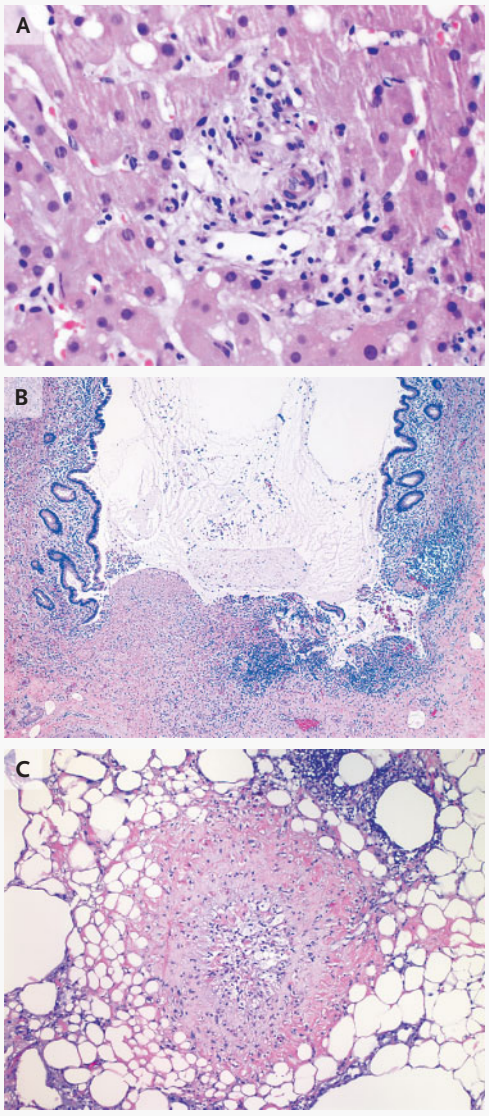


**Figure 4. Biopsy Specimens from the Liver and the Appendix (Hematoxylin and Eosin).**

The specimen from the liver biopsy (Panel A) contains an edematous portal tract. The bile-duct epithelium shows reactive changes with nuclear enlargement, irregular nuclear placement, and cytoplasmic eosinophilia. A very few inflammatory cells are seen infiltrating the duct epithelium. The specimen from the appendix (Panel B) shows patchy mucosal ulceration consistent with appendicitis. A vein in the periappendiceal fat (Panel C) reveals a vein occluded by loose fibrous tissue, indicating an organized thrombus.

tient was discharged showed a persistent portal-vein thrombus, with the development of venous collaterals or cavernous transformation of the portal vein, suggestive of portal hypertension, as well as evidence of chronic liver disease, with enlargement of the caudate lobe (Fig. 5).

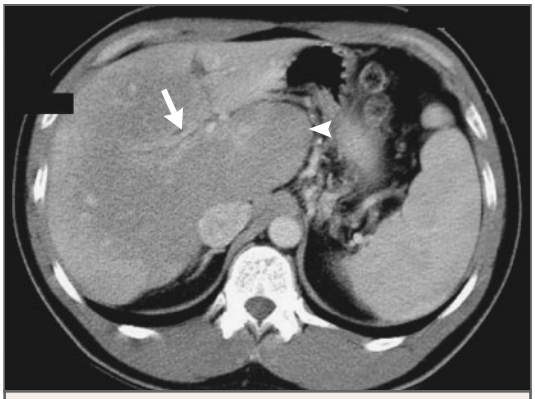

**Figure 5. A Contrast-Enhanced CT Scan Obtained Two and a Half Months after the Patient's Discharge.**

There are signs of chronic portal hypertension, including the development of venous collaterals around the thrombosed portal vein (arrow) and hypertrophy of the caudate lobe of the liver (arrowhead).

*Dr. Kenneth McIntosh* (Pediatrics, Children's Hospital): Had blood cultures been done before the patient's admission to this hospital?

*Dr. Ivers:* No cultures were done before his admission here. It appeared from the record that the primary concern of the physicians caring for him before the laparoscopy was that he had an occult malignant condition — in particular, lymphoma.

*Dr. Nesli Basgoz* (Infectious Diseases): Should people with a thrombotic complication of infection be investigated for a hypercoagulable state? Is there any reason to expect that such patients are uniquely susceptible to thrombotic conditions because of preexisting hypercoagulable states?

*Dr. Kasper:* Not to my knowledge. It is the infection with *B. fragilis* that predisposes the patient to hypercoagulation. I know of no association of the organism with a preexisting hypercoagulable state or the subsequent development of thrombotic disease.

## ANATOMICAL DIAGNOSIS

Portal-vein thrombosis due to *B. fragilis* infection.

Dr. Kasper reports having received consulting fees from Chiron Vaccines and reports holding patents in several areas of group B streptococcal vaccines and in zwitterionic polysaccharides as immunomodulators. Dr. Sahani reports having received grant support from Bracco Diagnostics.

## REFERENCES


1. Butterton JR, Calderwood SB. Acute infectious diarrheal diseases and bacterial food poisoning. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson LJ, eds. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill, 2005: 754-9.
2. Preliminary FoodNet data on the incidence of infection with pathogens transmitted commonly through food — selected sites, United States, 2003. MMWR Morb Mortal Wkly Rep 2004;53:338-43.
3. Arda IS, Ergin F, Varan B, Demirhan B, Aslan H, Ozyaylali I. Acute abdomen caused by *Salmonella typhimurium* infection in children. J Pediatr Surg 2001;36:1849-52.
4. Bennion RS, Thompson JE Jr, Gil J, Schmit PJ. The role of *Yersinia enterocolitica* in appendicitis in the southwestern United States. Am Surg 1991;57:766-8.
5. Blakelock RT, Beasley SW. Infection and the gut. Semin Pediatr Surg 2003;12:265-74.
6. Blaser MJ. Infections due to Campylobacter and related species. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson LJ, eds. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill, 2005:907-9.
7. Chandler ND, Parisi MT. *Yersinia enterocolitica* masquerading as appendicitis. Arch Pediatr Adolesc Med 1994;148:527-8.
8. Dennis DT, Campbell GL. Plague and other Yersinia infections. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson LJ, eds. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill, 2005:921-9.
9. Deutsch A, Wasserman D, Ruchelli E, Johnson J, Broussard DL. An uncommon presentation of Salmonella. Pediatr Emerg Care 1996;12:285-7.
10. Lesser CF, Miller SI. Salmonellosis. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson LJ, eds. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill, 2005:897-902.
11. Naktin J, Beavis KG. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. Clin Lab Med 1999;19:523-36.
12. Puylaert JB, Van der Zant FM, Mutsaers JA. Infectious ileocecitis caused by Yersinia, Campylobacter, and Salmonella: clinical, radiological, and US findings. Eur Radiol 1997; 7:3-9.
13. Dionisio D, Belli A, Dionisio A, et al. Appendicitis: microbial interactions and new pathogens. Recenti Prog Med 1992;83:330-6. (In Italian.)
14. Knobel B, Sommer I, Menashes Z. A rare presentation of systemic salmonellosis. Infection 1985;13:70-2.
15. Plemmons RM, Dooley DP, Longfield RN. Septic thrombophlebitis of the portal vein (pylephlebitis): diagnosis and management in the modern era. Clin Infect Dis 1995; 21:1114-20.
16. Hentges DJ. Anaerobes as normal flora. In: Finegold SM, George WL, eds. Anaerobic infections in humans. San Diego, Calif.: Academic Press, 1989:37-53.
17. Juric I, Primorac D, Zagar Z, et al. Frequency of portal and systemic bacteremia in acute appendicitis. Pediatr Int 2001;43:152-6.
18. Gorbach SL, Bartlett JG. Anaerobic infections. N Engl J Med 1974;290:1289-94.
19. Gesner BM, Jenkin CR. Production of heparinase by Bacteroides. J Bacteriol 1961; 81:595-604.
20. Bjornson HS, Hill EO. Bacteroidaceae in thromboembolic disease: effects of cell wall components on blood coagulation in vivo and in vitro. Infect Immun 1973;8:911-8.
21. Rosenthal GA, Levy G, Rotstein OD. Induction of macrophage procoagulant activity by *Bacteroides fragilis*. Infect Immun 1989; 57:338-43.
22. Tzianabos AO, Onderdonk AB, Rosner B, Cisneros RL, Kasper DL. Structural features of polysaccharides that induce intra-abdominal abscesses. Science 1993;262: 416-9.
23. Choi Y-H, Roehrl MH, Kasper DL, Wang JY. A unique structural pattern shared by T-cell-activating and abscess-regulating zwitterionic polysaccharides. Biochemistry 2002; 41:15144-51.
24. Perego P, Cozzi G, Bertolini A. Portal biliopathy. Surg Endosc 2003;17:351-2.
25. Slovis TL, Haller JO, Cohen HL, Berdon WE, Watts FB Jr. Complicated appendiceal inflammatory disease in children: pylephlebitis and liver abscess. Radiology 1989;171: 823-5.
26. Martirosian G, Bulanda M, Wojcik-Stojek B, et al. Acute appendicitis: the role of enterotoxigenic strains of *Bacteroides fragilis* and *Clostridium difficile*. Med Sci Monit 2001; 7:382-6.
27. Mosdell DM, Morris DM, Fry DE. Peritoneal cultures and antibiotic therapy in pediatric perforated appendicitis. Am J Surg 1994;167:313-6.
28. Rautio M, Saxen H, Siitonen A, Nikku R, Jousimies-Somer H. Bacteriology of histopathologically defined appendicitis in children. Pediatr Infect Dis J 2000;19:1078-83.
29. Heseltine PN, Yellin AE, Appleman MD, et al. Perforated and gangrenous appendicitis: an analysis of antibiotic failures. J Infect Dis 1983;148:322-9.
30. Bennion RS, Baron EJ, Thompson JE Jr, et al. The bacteriology of gangrenous and perforated appendicitis — revisited. Ann Surg 1990;211:165-71.
31. Pieper R, Kager L, Lindberg AA, Nord CE. Acute appendicitis and *Bacteroides fragilis*. Scand J Infect Dis Suppl 1979;19:92-7.
32. Pieper R, Kager L, Weintraub A, Lindberg AA, Nord CE. The role of *Bacteroides fragilis* in the pathogenesis of acute appendicitis. Acta Chir Scand 1982;148:39-44.
33. Elhag KM, Alwan MH, Al-Adnani MS, Sherif RA. *Bacteroides fragilis* is a silent pathogen in acute appendicitis. J Med Microbiol 1986;21:245-9.
34. Wilson SE, Boswick JA Jr, Duma RJ, et al. Cephalosporin therapy in intraabdominal infections: a multicenter randomized, comparative study of cefotetan, moxalactam, and cefoxitin. Am J Surg 1988;155:61-6.
35. Bennion RS, Thompson JE, Baron EJ, Finegold SM. Gangrenous and perforated appendicitis with peritonitis: treatment and bacteriology. Clin Ther 1990;12:Suppl C:31-44.

**CORRECTION**

## Case 25-2005: A 40-Year-Old Man with Prolonged Fever and Weight Loss

Case 25-2005: A 40-Year-Old Man with Prolonged Fever and Weight Loss . On page 714, lines 4 through 6 of the right-hand column should have read, ``Pathological examination of the appendix was reported to show inflammation and no cancer,´´ rather than ``. . . inflammation and cancer,´´ as printed. We regret the error.

N Engl J Med 2005;353:2827-a

EDITORIALS

# Healing Achilles — Sirolimus versus Paclitaxel

David J. Moliterno, M.D.

Since the inception of percutaneous coronary intervention (PCI), restenosis leading to repeated target-lesion revascularization has been the primary weakness of the procedure and has been repeatedly referred to as its Achilles' heel. Placement of a coronary-artery stent has emerged as the technique of choice for PCI, because it provides a substantial reduction in the percentage of patients who need subsequent target-lesion revascularization — from 25 to 35 percent after balloon angioplasty alone to 10 to 15 percent after stenting. Most of the luminal loss after stent placement is clinically evident in the first six to nine months after the placement and is the result of proliferative neointimal tissue growth in response to strut-associated injury and inflammation. Most recently, antiproliferative agents, such as sirolimus (an immunosuppressant) and paclitaxel (an antineoplastic agent), have been coupled with polymers that elute or slowly release these inhibitors from the stent surface. Drug-eluting stents have effectively reduced the need for target-lesion revascularization to an even lower rate (approximately 4 to 6 percent).[1-3] In this issue of the *Journal*, Windecker et al. and Dibra et al., who respectively conducted the SIRTAX (Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization)[4] and ISAR-DIABETES (Intracoronary Stenting and Angiographic Results — Do Diabetic Patients Derive Similar Benefits from Paclitaxel-Eluting and Sirolimus-Eluting Stents)[5] studies, report their findings from randomized, head-to-head comparisons of a sirolimus-eluting stent (Cypher; Cordis, Johnson & Johnson) with a paclitaxel-eluting stent (Taxus, Boston Scientific).

In the trial reported by Windecker et al., with 1012 patients and using a composite primary end point of death from cardiac causes, myocardial infarction, and ischemia-driven target-lesion revascularization at nine months, there were fewer events with sirolimus-eluting stents than with paclitaxel-eluting stents (6.2 percent vs. 10.8 percent), mainly as a result of a lower rate of target-lesion revascularization in the group with sirolimus-eluting stents (4.8 percent vs. 8.3 percent). There also was less in-segment late luminal loss, the prespecified end point of the angiographic substudy, with sirolimus-eluting stents than with paclitaxel-eluting stents (0.19 mm vs. 0.32 mm). During a similar interval, the ISAR-DIABETES investigators enrolled 250 patients with diabetes, a PCI cohort known to be at particularly high risk for restenosis as defined in both angiographic and clinical assessments. The study's primary end point of in-segment late luminal loss was measured by computer-assisted quantitative angiography and revealed that there was less late loss with sirolimus-eluting stents than with paclitaxel-eluting stents (0.43 mm vs. 0.67 mm). The corresponding rates of target-lesion revascularization were 6.4 percent and 12.0 percent (P=0.13). Though not of adequate power to assess specific end points related to ischemia, such as death, myocardial infarction, and stent thrombosis, neither trial observed a difference in these outcomes.

Considering the clinical implications of these trials, we can agree that patients will be unconcerned about a 130-μm increase, on average, in late luminal loss with paclitaxel-eluting stents, as seen in SIRTAX, unless this increase translates into a consistently higher risk of repeated target-lesion revascularization. The extent of late luminal loss with both bare-metal and drug-eluting stents has been correlated with the frequency of repeated revascularization, although as the average for late luminal loss and target-lesion revascularization moves closer to zero with drug-eluting stents, the statistical correlation between the two becomes less straightforward.[6] With this in mind, the higher incidence (by 3.5 percentage points) of target-lesion revascu-

larization among patients with paclitaxel-eluting stents than among those with sirolimus-eluting stents in Windecker and colleagues' study seems to fit, yet it contrasts with the preliminary details from the largest study of sirolimus-eluting stents versus paclitaxel-eluting stents, known as the REALITY (Prospective Randomized Multicenter Head-to-Head Comparison of the Sirolimus-Eluting Stent [Cypher] and the Paclitaxel-Eluting Stent [Taxus]) trial.[7] In REALITY, with 1353 patients and 92 percent angiographic follow-up, greater late loss was observed in the group that had paclitaxel-eluting stents, but this loss was not associated with a higher rate of target-lesion revascularization.

This seeming contradiction between trials may be a consequence of the underlying risk of restenosis and the severity of late luminal loss. Among nearly all patients at low risk for restenosis, who have low-average levels of late loss, the residual coronary artery lumen remains ample. Therefore, subsequent rates of target-lesion revascularization should be low and should not vary much with small differences in late loss. With higher levels of late loss, the picture changes. Indeed, reviewing the five recently reported randomized clinical trials of sirolimus-eluting stents versus paclitaxel-eluting stents that included end points relating to angiographic findings and repeated target-lesion revascularization among 3467 patients[4,5,7-9] (Fig. 1), a pattern can be seen. In the REALITY trial (a mixed-patient cohort, but a cohort that probably had low risk overall), differences in in-lesion late loss did not overtly affect the rate of target-lesion revascularization. In trials of patients at particularly high risk for restenosis, such as ISAR-DESIRE (Intracoronary Stenting and Angiographic Results — Drug-Eluting Stents for In-Stent Restenosis),[8] involving patients being treated for in-stent restenosis, and ISAR-DIABETES, differences in average in-segment late loss appear to be more strongly associated with differences in the rate of target-lesion revascularization. The patient population studied by Windecker et al. probably fell into the mid-range of risk; they showed a less marked but detectable difference in the rate of target-lesion revascularization. So, on the basis of these observations, it is evident that trials comparing sirolimus-eluting stents and paclitaxel-eluting stents need to be large or include a cohort at relatively high risk for restenosis to allow effective evaluation of a significant difference in rates of repeated target-lesion revascularization.

When the data from six randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents that were reported this year[4,5,7-10] are examined together, a higher rate of repeated target-lesion revascularization after placement of paclitaxel-eluting stents is apparent (Table 1). A formal meta-analysis has been performed.[11] A similar trend is suggested by the largest registry of sirolimus-eluting stents versus paclitaxel-eluting stents published so far, the Rotterdam Cardiology Hospital registry,[12] which observed rates of 3.7 percent and 5.4 percent, respectively, of repeated target-lesion revascularization at one year among 1084 patients. According to these reports collectively, if a true difference exists between the currently available sirolimus-eluting stents and paclitaxel-eluting stents, it is more likely than not to favor the sirolimus stent.

What explains the difference between the sirolimus-eluting stents and the paclitaxel-eluting stents as observed in the two current trials?[4,5] There are several possibilities, because every component of

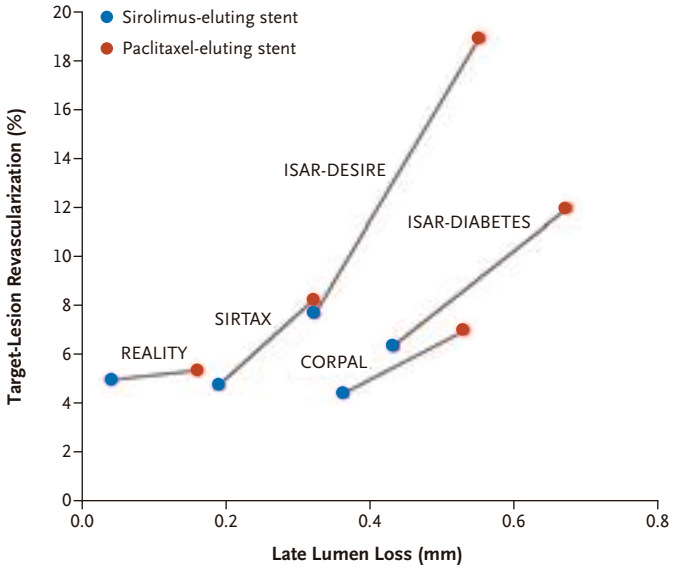


**Figure 1. Angiographic Assessment of Late Lumen Loss and Associated Rates of Repeated Revascularization Procedures, as Reported in Recent Trials.**

ISAR-DESIRE denotes Intracoronary Stenting and Angiographic Results — Drug-Eluting Stents for In-Stent Restenosis, ISAR-DIABETES Intracoronary Stenting and Angiographic Results — Do Diabetic Patients Derive Similar Benefits from Paclitaxel-Eluting and Sirolimus-Eluting Stents, SIRTAX Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization, CORPAL Drug-Eluting Stent for Complex Lesions: Cordoba–Las Palmas Study, and REALITY Prospective Randomized Multicenter Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel-Eluting Stent (Taxus).

**Table 1. Target-Lesion Revascularization.***

| Randomized Trial | Number of Patients in Trial | Target-Lesion Revascularization | | Odds Ratio (95% CI) |
|---|---|---|---|---|
| | | Sirolimus-Eluting Stents (%) | Paclitaxel-Eluting Stents (%) | |
| ISAR-DESIRE | 200 | 8.0 | 19.0 | 0.37 (0.15–0.89) |
| TAXi | 202 | 2.0 | 1.0 | 1.98 (0.18–22.19) |
| ISAR-DIABETES | 250 | 6.4 | 12.0 | 0.50 (0.20–1.23) |
| SIRTAX | 1012 | 4.8 | 8.3 | 0.56 (0.33–0.93) |
| CORPAL† | 652 | 4.2 | 7.1 | 0.57 (0.29–1.13) |
| REALITY† | 1353 | 5.0 | 5.4 | 0.92 (0.57–1.49) |
| Pooled | 3669 | 4.9 | 7.5 | 0.64 (0.48–0.84) |

* CI denotes confidence interval, ISAR-DESIRE Intracoronary Stenting and Angiographic Results — Drug-Eluting Stents for In-Stent Restenosis, TAXi Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology, ISAR-DIABETES Intracoronary Stenting and Angiographic Results — Do Diabetic Patients Derive Similar Benefits from Paclitaxel-Eluting and Sirolimus-Eluting Stents, SIRTAX Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization, CORPAL Drug-Eluting Stent for Complex Lesions: Cordoba–Las Palmas Study, and REALITY Prospective Randomized Multicenter Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel-Eluting Stent (Taxus).
† Data are from a preliminary report.

the two drug-eluting stents — the underlying stent, the drug-delivery polymer, and the antiproliferative agent — is different. Although both stents have a closed-cell design, they differ in cell geometry and strut thickness. In another comparison, whereas both antiproliferative agents are cell-cycle inhibitors, their mechanisms of action as well as the timing of their polymer-based delivery differ substantially.[13] Sirolimus-eluting stents are coated with 140 μg of sirolimus per square centimeter, and it slowly elutes over the course of four to six weeks; paclitaxel-eluting stents are coated with 100 μg of paclitaxel per square centimeter, and it has a bimodal release that is completed in approximately two weeks.

The other possibility is that these two trials, like any study, have limitations that affect the reliability of their findings. For example, the reported difference in late luminal loss is based on incomplete observations: 47 percent of the patients in Windecker and colleagues' study and 18 percent in ISAR-DIABETES did not have angiographic follow-up. In addition, the number of patients studied was moderate, and each trial was limited to two study centers. The end point of ischemia-driven target-lesion revascularization, which affected a difference in the composite end point in the study by Windecker et al., is important but soft, as compared with the end points of death, myocardial infarction, and stent thrombosis.

In summary, terrific strides have been made in the battle against restenosis with the development of drug-eluting stents. The analogy of Achilles and restenosis may be more fitting today than it was when PCI was first developed. Thetis, in an attempt to give her newborn son immortality, grasped his heel and immersed him upside down in the river Styx. Unfortunately, the area under her hand was not exposed to the magical waters, and Achilles was left vulnerable in a small but distinct area. So too, drug-eluting stents have conquered restenosis except in a small percentage of patients. The data overall, from randomized clinical trials and from registries, suggest that the currently available sirolimus-eluting stents provide an angiographic and clinical edge over the currently available paclitaxel-eluting stents. In contrast, the currently available paclitaxel-eluting stent holds an edge on availability, deliverability, and cost. Whereas a large-scale, randomized trial may help settle this score more definitively, the testing of second-generation drug-eluting stent platforms, with various stent struts, polymers, and drugs is already well under way.

Dr. Moliterno reports having received compensation for serving on data-safety monitoring committees for stent manufacturers, including Boston Scientific and Guidant.

From the Gill Heart Institute and Division of Cardiovascular Medicine, University of Kentucky, Lexington.

1. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583-91.
2. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with

the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation 2004;109:1942-7.
3. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315-23.
4. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653-62.
5. Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663-70.
6. Kereiakes DJ, Kuntz RE, Mauri L, Krucoff MW. Surrogates, substudies, and real clinical end points in trials of drug-eluting stents. J Am Coll Cardiol 2005;45:1206-12.
7. Morice M-C, Serruys PW, Colombo A, et al. Eight-month outcome of the REALITY Study: a prospective, randomized, multi-center head-to-head comparison of the sirolimus-eluting stent (Cypher) and the paclitaxel-eluting stent (Taxus). Presented at the 2005 Annual Scientific Session of the American College of Cardiology, Orlando, Fla., March 6–9, 2005. (Accessed July 27, 2005, at http://www.clinicaltrialresults.org/home.htm.)
8. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165-71.
9. de Lezo JS, Medina A, Pan M, et al. Drug-eluting stent for complex lesions: latest angiographic data from the randomized rapamycin versus paclitaxel CORPAL study. J Am Coll Cardiol 2005;45:Suppl A:75A-76A. abstract.
10. Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. J Am Coll Cardiol 2005;45:308-11.
11. Kastrati A, Dibra A, Eberle S, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. JAMA 2005;294:819-25.
12. Ong AT, Serruys PW, Aoki J, et al. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. J Am Coll Cardiol 2005;45:1135-41.
13. Rogers CD. Drug-eluting stents: clinical perspectives on drug and design differences. Rev Cardiovasc Med 2005;6:Suppl 1:S3-S12.


# Health Disparities — Less Talk, More Action

Nicole Lurie, M.D., M.S.P.H.

During the past decade, hundreds of articles have been published documenting the existence of racial and ethnic disparities in health and health care — a data deluge that has led many observers to suggest that it is time to stop documenting disparities and turn our efforts to doing something about them. Three articles in this issue of the *Journal* once again document the existence of disparities — albeit with a slightly different twist — by looking at time trends.[1-3] For most of the areas studied, disparities between white patients and black patients have not substantially improved during the past decade or so. Rather than simply dismissing these findings as more documentation, how might we use them to enhance our knowledge and inform strategies to eliminate disparities?

Jha et al.[1] examined trends in the use of important surgical procedures from 1992 to 2001 and found that the gap between whites and blacks has not narrowed in most regions of the United States. Vaccarino et al.[2] examined trends in the quality of care for myocardial infarction from 1994 to 2002 and report persistent racial differences in the use of reperfusion therapy and coronary angiography and in hospital mortality but no differences in the number of prescriptions given for aspirin and beta-blockers. Such enduring trends suggest that the adage "The system is perfectly designed to get the results that it does" is once again applicable here. As Satcher et al.[4] point out in documenting the lack of substantial improvement in the racial gap in mortality during the past 40 years in the United States, "this complex system is consistently producing a predictable result." Aspects of the system are so ingrained that many physicians remain unaware of these disparities. As recently as last year, only a third of cardiologists who responded to a survey agreed with the statement that "clinically similar patients receive different cardiovascular care based on what their race and ethnic background is."[5] In short, the articles by Jha et al. and Vaccarino et al. strongly suggest that we will not make progress in eliminating disparities simply by tinkering with the system.

On a more encouraging note, Trivedi et al.[3] report on the quality of care for whites and blacks in Medicare managed-care plans from 1997 to 2003 and show that overall clinical performance improved on all measures for both white and black enrollees. In addition, the racial gap actually narrowed for seven of the nine measures that were studied. However, for two of the three outcome measures — control of levels of glycosylated hemoglobin for patients with diabetes and of low-density lipoprotein cholesterol after myocardial infarction — the disparities actually increased slightly. It is likely that some change in systems led to the improvements. Indeed, since 1997, managed-care plans administered by Medicare have been required

to measure and issue public reports on such quality measures. This reporting has been shown to be associated with an improved quality of care. Although the behavior of physicians is notoriously hard to change, ordering a test or writing a prescription is a relatively uncomplicated activity and is amenable to change with appropriate incentives and modifications to systems. The control of levels of glucose and lipids and the performance of a revascularization procedure after myocardial infarction are much more complex challenges, suggesting that we need to approach these persistent racial disparities as multifaceted system issues. The level of complexity suggests that no one party is to blame, even though it has been convenient to blame doctors, patients, or society at large. As we have learned from other areas of quality improvement, it is not that simple.

These three articles tell us about fundamental components of systems that will be critical in the elimination of disparities in care. First, the research could not have been done without data on the race or ethnic background of patients; two of these studies relied on data available to Medicare. Second, measurement and reporting, and their associated quality-improvement activities, have led to improvement in the quality of care overall as well as to the narrowing of racial disparities. However, until very recently, the bulk of the delivery system had no data on race and ethnic background, so it has been virtually impossible to examine, let alone publicly report, data on the quality of care for various racial and ethnic groups. The use of available data and standard quality-improvement methods constitutes a good start, although these approaches alone may not get us where we need to go. Additional work will be required to understand why the process measures have changed even though the outcomes have not. This problem will probably require analysis of the root causes of the persistence of these differences in control — a study that is not easily accomplished with administrative data.

An important article that was published last year may shed additional light on the systems issue. Bach et al.[6] reported that a minority of physicians care for the overwhelming majority of black patients in the United States. Physicians who care for black patients were more likely to report that they had difficulty mustering adequate resources — subspecialty referrals, diagnostic imaging, high-quality ancillary services, or hospital admission — for their patients. The systems analysis will need to examine structural factors in the delivery system and look for modifiable root causes that extend beyond the immediate control of the physician's office or hospital. Systems analysis, as well as systems change, may need to involve the community as well as the delivery system.

There are good reasons to be optimistic about

**Table 1. Members of Groups Working on Racial Disparities in Health Care.***

| National Health Plan Collaborative on Health Disparities | Best Clinical and Administrative Practices Workgroup: Improving Health Care Quality for Racially and Ethnically Diverse Populations |
|---|---|
| Aetna | Molina Healthcare |
| Anthem Blue Cross and Blue Shield | Monroe Plan for Medical Care |
| Cigna HealthCare | Helix Family Choice |
| Harvard Pilgrim | Neighborhood Health Plan of Rhode Island |
| HealthPartners | UPMC Health Plan |
| Highmark Blue Cross and Blue Shield | LA Care Health Plan |
| Kaiser Permanente | Medica |
| Molina Healthcare of California | Network Health |
| United Healthcare | Blue Cross of California |
| WellPoint | Oregon Collaborative (Oregon Office of Medical Assistance, CareOregon, Family Care, and Providence Health Plan) |
| | Healthfirst |
| | SoonerCare |
| Total number of enrollees covered: 76,748,227 | Total number of enrollees covered: 3,154,748 |

* Anthem and WellPoint have merged. UPMC denotes University of Pittsburgh Medical Center.

some aspects of systems change. The leadership of health insurance plans, including the commercial insurers and Medicaid plans listed in Table 1, now understand that in order to make further improvement in the quality of care and respond to a more demographically diverse marketplace, they need to make progress in racial disparities. They have also realized that they cannot make progress without being able to measure and monitor that progress, which means that they need information about the race and ethnic background of enrollees. Working in two collaborative efforts,[7] they have started to obtain and use such data. In the case of Medicaid plans, these data are now available through most state Medicaid agencies. The commercial insurers have either begun to ask enrollees to supply information voluntarily on their race or ethnic background or they have used sophisticated geocoding and surname-analysis techniques to estimate the racial composition of their enrollees. But regardless of the methodology, all participating health plans have begun to move toward systematically examining the quality of care for important subgroups of their enrollees with chronic illnesses. Furthermore, recognizing that measurement alone will be insufficient to produce results, they are designing and testing a variety of interventions to address the disparities they have found. Although it is too soon to know how successful these efforts will be, the plans, which collectively cover 90 million people, are consciously changing their systems.

Insurers and health care providers working together may be able to make substantial progress in health care disparities, but they cannot solve this problem alone. In many areas of the country, employers are joining in the effort. However, more widespread redesign of systems — particularly, outside of the traditional health care system — will be required to address the complex interplay of social determinants of health and health care outcomes, and this change will probably be longer in coming. Meanwhile, those of us working within the health care system need to test and implement effective strategies for the reduction of disparities. We will continue to rely on trend data, such as those reported in this issue, either to document our progress or to point us in additional directions for solutions. Regardless, we cannot give up until the job is done.

From RAND, Arlington, Va.

1. Jha AK, Fisher ES, Li Z, Orav EJ, Epstein AM. Racial trends in the use of major procedures among the elderly. N Engl J Med 2005;353:683-91.
2. Vaccarino V, Rathore SS, Wenger NK, et al. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. N Engl J Med 2005;353:671-82.
3. Trivedi AN, Zaslavsky AM, Schneider EC, Ayanian JZ. Trends in the quality of care and racial disparities in Medicare managed care. N Engl J Med 2005;353:692-700.
4. Satcher D, Fryer GE, McCann J, Troutman A, Woolf SH, Rust G. What if we were equal? A comparison of the black-white mortality gap in 1960 and 2000. Health Aff (Millwood) 2005;24(2):459-64.
5. Lurie N, Fremont A, Jain A, et al. Racial and ethnic disparities in care: the perspectives of cardiologists. Circulation 2005;111:1264-9.
6. Bach PB, Pham HH, Schrag D, Tate RC, Hargraves JL. Primary care physicians who treat blacks and whites. N Engl J Med 2004;351:603-5.
7. Major health plans and organizations join AHRQ to reduce racial and ethnic disparities in health care. Press release of the Agency for Healthcare Research and Quality, Rockville, Md., December 14, 2004. (Accessed July 28, 2005, at http://www.ahrq.gov/news/press/pr2004/dispcolpr.htm.)

CLINICAL IMPLICATIONS OF BASIC RESEARCH

# Nitric Oxide–Eluting Polyurethanes — Vascular Grafts of the Future?

Subodh Verma, M.D., Ph.D., and Philip A. Marsden, M.D.

Aristotle said, "In all things of nature there is something of the marvelous." Nitric oxide is one such marvel. Few could have predicted that one atom of nitrogen and one of oxygen would together be a fundamental regulator of the human body. Among the endogenous defenses against vascular injury, inflammation, thrombosis, and atherosclerosis, nitric oxide assumes the dominant role. Its release from the endothelium counters the activation and adhesion of leukocytes, limits platelet aggregation and thrombus formation, and maintains the vascular smooth muscle in a nonproliferative state, thereby maintaining the integrity of blood vessels and guarding against adverse vascular remodeling. These characteristics suggest that nitric oxide may improve the biologic properties of cardiovascular biomaterials,[1] and a recent report by Jun and colleagues[2] provides support for this hypothesis.

Autologous vessels, such as the internal thoracic artery and saphenous vein, are routinely used in coronary and peripheral arterial bypass surgery. Unfortunately, some patients do not have enough vessels for transplantation or they have preexisting disease in these vessels. Furthermore, the relative paucity of nitric oxide production by saphenous veins as compared with arterial conduits may contribute to early graft failure. Synthetic materials such as polyethylene terephthalate (Dacron) and expanded polytetrafluoroethylene (Teflon) are used for large-diameter (more than 6 mm) vascular substitutes, but these are prone to thrombosis, intimal hyperplasia, and thus, failure in small-diameter applications, especially coronary-artery bypass grafting. Perhaps a graft that releases nitric oxide would address these problems.

Jun et al.[2] incorporated a nitric oxide donor (called diazeniumdiolate) into a polyurethane and then assessed its interactions with platelets, vascular smooth-muscle cells, and endothelial cells — all of which are critical to graft occlusion (Fig. 1). The anionic portions of diazeniumdiolates, which contain the $[N(O)NO]^-$ functional group, spontaneously decompose in solution to release nitric oxide.

The authors found that the mechanical properties of the synthesized polymer were similar to those of commercial polyurethane vascular grafts and that nitric oxide was released in two phases: a rapid burst during the first 48 hours, followed by a slower, sustained release over a two-month period. During both phases, endothelial cells exposed to the nitric oxide–eluting polyurethane films showed enhanced rates of proliferation and increased rates of migration and coverage of the synthetic surface, as compared with cells exposed to control polyurethane films. The development of a nascent endothelial lining within vascular conduits forms a physiologically relevant interface between blood and the vessel wall that is similar to that of native vessels and is considered to be a pivotal event required to protect against early thrombosis and graft occlusion. In addition, vascular smooth-muscle cells showed a reduced rate of proliferation when exposed to nitric oxide–eluting polyurethane films during both phases of the release of nitric oxide, indicating that the use of a nitric oxide–eluting polyethylene graft may limit the formation of occlusive scar tissue and neointimal hyperplasia. Finally, the level of platelet adhesion was significantly lower on nitric oxide–eluting polyurethane films than on control polyurethane films during both phases of nitric oxide release. This finding, too, predicts that the use of nitric oxide–eluting polyurethane grafts will inhibit the formation of occlusive thrombus.

The synthesis of a bioactive, nitric oxide–eluting polyurethane serves as a first step toward the generation of a synthetic, small-diameter vascular graft for use in bypass procedures involving small-caliber arteries. The concept is tantalizing, but several questions remain. Will the in vitro effects of nitric oxide–eluting polyurethane be maintained when the films are formed into cylindrical vascular grafts? And what about the effect of the physical forces of

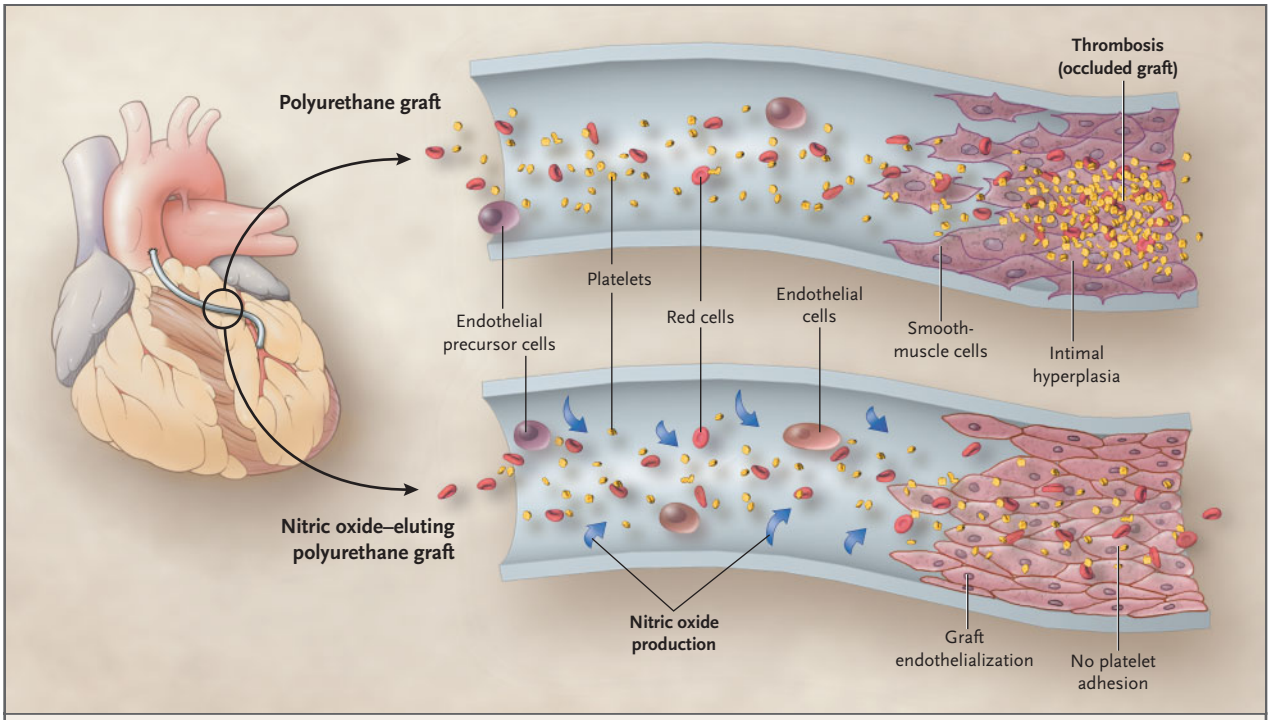


**Figure 1. The Effect of a Nitric Oxide–Eluting Polyurethane Graft.**

The synthesis of a nitric oxide–eluting polyurethane by Jun et al.[2] presents the intriguing possibility of manufacturing a synthetic, small-diameter vascular graft for use in bypass procedures that would avert rapid occlusion and graft failure. Studies suggest that a small-caliber synthetic polyurethane graft without a thrombosis-resistant surface is quickly occluded when used to bypass a coronary vessel. In vitro experiments carried out by Jun et al.[2] suggest that a graft composed of nitric oxide–eluting polyurethane may limit graft occlusion by promoting early endothelialization of the synthetic surface and inhibit the adhesion, aggregation, and activation of platelets.

the circulation, especially shear stress, on the in vivo antithrombotic and antiocclusive properties of the polymer? Similarly, we need to determine the response of bone marrow–derived endothelial progenitor cells to nitric oxide–eluting polyurethane. These stem cells participate extensively in the reendothelialization of damaged vascular surfaces and actively contribute to the processes of neointimal formation, restenosis, and atherogenesis.[3] The sustained release of nitric oxide may favorably influence this cell population, because endothelial nitric oxide synthase is critical for the activity of endothelial progenitor cells.

Will nitric oxide–eluting polyurethane grafts offer enduring vascular benefit? Early reendothelialization and inhibition of platelet aggregation should enhance long-term patency by establishing an endothelial environment resembling that of native vessels, but this possibility will require careful study. In humans, the endothelial cells that overlie atherosclerotic plaques in diseased blood vessels do not produce much biologically active endothelial-derived nitric oxide, in part because they express little endothelial nitric oxide synthase.[4] The therapeutic potential of nitric oxide–eluting polyurethane grafts may therefore lie in the hope that they more closely mirror a healthy vascular endothelial phenotype.[5]

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1. Loscalzo J. Nitric oxide insufficiency, platelet activation, and arterial thrombosis. Circ Res 2001;88:756-62.
2. Jun HW, Taite LJ, West JL. Nitric oxide-producing polyurethanes. Biomacromolecules 2005;6:838-44.
3. Sata M, Saiura A, Kunisato A, et al. Hematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis. Nat Med 2002;8:403-9.
4. Wilcox JN, Subramanian RR, Sundell CL, et al. Expression of multiple isoforms of nitric oxide synthase in normal and atherosclerotic vessels. Arterioscler Thromb Vasc Biol 1997;17:2479-88.
5. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation 2003;108:2054-9.

CORRESPONDENCE

# Exhaled Nitric Oxide and Asthma

**TO THE EDITOR:** The landmark study by Smith et al. (May 26 issue)[1] shows that measurement of exhaled nitric oxide ($F_{ENO}$) can reduce the dose of inhaled corticosteroids in patients with asthma without impairing control of asthma and, in particular, exacerbations of asthma. Because of the high variability of $F_{ENO}$ among both healthy persons and patients with asthma, it may make sense to consider a personalized "best" cutoff $F_{ENO}$ level, as seen after the dose-optimization phase or after administration of a dose of oral prednisone. In addition, the relatively high exhalation flow rate used (250 ml per second), as compared with the recommended flow rate of 50 ml per second,[2] may be a factor. The difference in terms of parts per billion between a patient when in stable condition and the same patient in unstable condition will be much smaller, and perhaps less discriminatory, at 250 ml per second than at 50 ml per second.[3] Finally, the numerical trend seen in the reduction of exacerbations suggests that the study was underpowered to assess this outcome.

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1. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352:2163-73.
2. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.
3. Silkoff PE, McClean PA, Slutsky AS, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. Am J Respir Crit Care Med 1997;155:260-7.

**TO THE EDITOR:** Smith et al. compared exhaled nitric oxide with clinical criteria (symptoms, bronchodilator requirements, and pulmonary function) as a guide for adjusting the dose of inhaled corticosteroids in patients with mild-to-moderate asthma. They observed fewer mild exacerbations in the $F_{ENO}$ group than in the control group and similar asthma control with lower doses of inhaled corticosteroids in the $F_{ENO}$ group. For patients with asthma that is not controlled with low-dose inhaled corticosteroids (i.e., 500 μg of beclomethasone or the equivalent), guidelines recommend combining inhaled corticosteroids with long-acting beta$_2$-agonists rather than higher doses of the corticosteroid,[1] since the combination is more effective.[2,3] We believe that had the authors used such a combination for adjustment, they would have obtained different results, given that long-acting beta$_2$-agonists are quite effective in controlling asthma without modifying exhaled nitric oxide.[4]

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THIS WEEK'S LETTERS

1. Global Initiative for Asthma 2002. Update: Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop report 1995. Bethesda, Md.: National Institutes of Health, 2002. (DHHS publication no. (NIH) 02-3659.) (Accessed July 28, 2005, at http://www.ginasthma.org.)
2. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma: Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med 1997;337:1405-11. [Erratum, N Engl J Med 1998;338:139.]
3. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000;320:1368-73.
4. Yates DH, Kharitonov SA, Barnes PJ. Effect of short- and long-acting inhaled beta2-agonists on exhaled nitric oxide in asthmatic patients. Eur Respir J 1997;10:1483-8.

**TO THE EDITOR:** Smith et al. succinctly demonstrate that a management algorithm incorporating the measurement of exhaled nitric oxide enables inhaled corticosteroid doses to be back-titrated without loss of asthma control. The authors' findings also raise the exciting possibility that this easy-to-measure surrogate inflammatory biomarker might guide clinicians in the optimal management of persistent asthma with the use of a low-to-moderate dose of inhaled corticosteroid (step 3 of the national asthma guidelines[1]). Perhaps these symptomatic patients with normal levels of nitric oxide (and probable adequate antiinflammatory therapy) should proceed to a therapeutic trial of a long-acting $beta_2$-agonist.[2] For patients with elevated levels of nitric oxide (suggestive of ongoing inflammation) the inhaled corticosteroid dose could first be increased or a leukotriene-receptor antagonist could be added.

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1. British guideline on the management of asthma. Thorax 2003; 58:Suppl 1:i1-i94.
2. Currie GP, Lee DK, Wilson AM. Effects of dual therapy with corticosteroids plus long acting beta2-agonists in asthma. Respir Med 2005;99:683-94.

**THE AUTHORS REPLY:** Dr. Silkoff raises two important points. First, in any situation where fixed cutoff points are used to determine dose adjustments, outcomes will be significantly influenced by placement of the cutoff points. We acknowledge that this was the case in our study, not only for the $FE_{NO}$ group but also for the control group (in which clinical characteristics were used). The same is probably true of the two earlier "proof of concept" studies.[1,2] Dr. Silkoff advocates the use of "personalized 'best'" $FE_{NO}$ thresholds as the basis for clinical decision making. We agree that a "one size fits all" approach may be rather crude. But it is a first step. Substantial work is required before any alternative can be recommended.

Both Drs. Currie and Lee and Drs. Corbetta and Fabbri highlight the issue of using long-acting $beta_2$-agonists. First, we accept that using these agents in patients who were symptomatic despite their taking 250 μg or more of fluticasone per day would have conformed more closely to international guidelines. Had we taken such an approach, it might indeed have influenced the overall results. However, because of the confounding effect of the use of long-acting $beta_2$-antagonists on the primary end point (exacerbations), we calculated a priori that this approach would have required a tripling of the number of subjects needed for the study. This was beyond our resources. Second, we agree with Drs. Currie and Lee that when $FE_{NO}$ levels are normal, treatment with additional inhaled corticosteroids is unlikely to be beneficial[3]; long-acting $beta_2$-antagonists or leukotriene antagonists are more logical alternatives in such circumstances, and normal $FE_{NO}$ results are therefore informative.

We disagree with Drs. Corbetta and Fabbri's assertion that the overall message of the study is misleading. Our message is quite plain: treatment with inhaled corticosteroids should be tailored for each patient. Nothing less and nothing more. $FE_{NO}$ measurements are a helpful prompt in this regard.

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D. Robin Taylor, M.D.

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1. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. Am J Respir Crit Care Med 1999; 159:1043-51.
2. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360:1715-21.
3. Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med (in press).

**CORRECTION**

## Exhaled Nitric Oxide and Asthma

Exhaled Nitric Oxide and Asthma . In the letter by Smith and Taylor, in the first full paragraph of the right-hand column on page 733, lines 3, 10, and 18 should have read ``long-acting beta-agonists,´´ rather than ``long-acting $beta_2$-agonists´´ and ``long-acting $beta_2$-antagonists,´´ as printed. We regret the error.

# Heart-Rate Profile during Exercise as a Predictor of Sudden Death

**TO THE EDITOR:** The study by Jouven and colleagues (May 12 issue)[1] advances our understanding of the factors involved in the precipitation of sudden death. However, the authors' assertion that exercise-induced changes in heart rate "may have clinical implications in terms of the early identification of high-risk subjects" is untenable given the very low incidence of sudden death in their studied population. Only 1.4 percent of the 5713 healthy middle-aged men died suddenly during the 23-year follow-up. On the basis of the criterion the investigators found most discriminating — subnormal exercise-induced increase in heart rate — 500 men would have to undergo exercise testing in order for 100 men to be classified as belonging to the "high-risk" quintile. During the subsequent 23 years, only 2 of these 100 men would actually die suddenly. Thus, while the risk in this quintile is slightly increased, it is certainly not high, nor is it sufficient to justify stigmatization or the institution of nonvalidated primary prevention.

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1. Jouven X, Empana J-P, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352:1951-8.

**TO THE EDITOR:** The article by Jouven et al. about heart rates during exercise and their relation to sudden death conclusively extends the known risk of poor heart-rate variability in patients with cardiac conditions to middle-aged men without a known history of cardiac disease. In doing so, the authors provide a new target for primary prevention of life-altering cardiac events — one that is thought to be independent from coronary lesions.[1] Just as the patients who have had a myocardial infarction have benefitted from exercise strategies that focus on the autonomic nervous system,[2] so might asymptomatic age-appropriate patients benefit. In fact, exercise has been shown to increase autonomic responses in several asymptomatic groups, including people with diabetes,[3] sedentary postmenopausal women,[4] and healthy young women.[5] Further studies should be undertaken to see whether asymptomatic patients have decreased mortality after engaging in exercise training that targets the autonomic nervous system. In the meantime, physicians should revisit cases in which there were "negative" results on exercise stress tests for signs of poor heart-rate variability. In addition, the "normal" resting heart rate of 75 to 99 beats per minute —which apparently confers an almost fourfold relative risk of sudden death — should be questioned.

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1. Vivekananthan D, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003;42:831-8.
2. La Rovere MT, Bersano C, Gnemmi M, Specchia G, Schwartz PJ. Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. Circulation 2002; 106:945-9.
3. Loimaala A, Huikuri HV, Koobi T, Rinne M, Nenonen A, Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. Diabetes 2003;52:1837-42.
4. Jurca R, Church TS, Morss GM, Jordan AN, Earnest CP. Eight weeks of moderate-intensity exercise training increases heart rate variability in sedentary postmenopausal women. Am Heart J 2004; 147:e21.
5. Goldsmith R, Dardik I, Bloomfield DM, et al. Implementation of a novel cyclic exercise protocol in healthy women. Am J Med Sports 2002;4:135-41, 151.

**THE AUTHORS REPLY:** Dr. Bassan addresses the classic difference between relative and absolute risk. This long-term, prospective study was conducted in a highly selected population of asymptomatic working men; subjects with any cardiac abnormalities at rest or during exercise testing were excluded from the analysis. As is generally the case in studies of risk factors, absolute risk is artificially low. Conversely, populations of patients with cardiac failure or with a history of myocardial infarction have a much higher absolute risk of sudden death (but also numerous confounding factors, including beta-blocker therapy, that challenge the interpretation of the heart-rate profile). Moreover, the strict criteria that were applied for coding sudden death in the current study were responsible for a decrease in sensitivity. Taken together, these points explain why, in the current study, sudden death failed to account for 5 to 10 percent of total mortality, as it is usually reported.[1] Consequently, any attempt to assess the incidence of sudden death

in our study, which was clearly not designed for this purpose, should be regarded with caution.

The assumption made by Dr. Bassan that regular sports activity is a nonvalidated primary-prevention measure is highly debatable. As pointed out in the article, our findings do not address this issue. However, fundamental experimental work by Schwartz et al.[2] and Hull et al.[3] clearly indicates that exercise training is associated with a decrease in sudden death risk, in part through the restoration of autonomic control. In addition, and as stated by Dr. Harnik, the benefit of exercise strategies that target the autonomic nervous system has been observed in high-risk populations. In asymptomatic subjects, regular physical activity has also been associated with an increase in heart-rate variability.[4] Meanwhile, further studies are required to see whether asymptomatic patients show decreased rates of sudden death after exercise training.

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1. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998; 98:2334-51.
2. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death: new insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation 1988;78: 969-79.
3. Hull SS Jr, Vanoli E, Adamson PB, Verrier RL, Foreman RD, Schwartz PJ. Exercise training confers anticipatory protection from sudden death during acute myocardial ischemia. Circulation 1994; 89:548-52.
4. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am J Epidemiol 2003;158:135-43.

## Coronary-Artery Bypass Grafting versus Stent Implantation

**TO THE EDITOR:** The analysis by Hannan and colleagues (May 26 issue)[1] comparing coronary-artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) is seriously flawed. The data were derived retrospectively from two separate New York State registries. The 12 risk factors for increased mortality that made up the propensity model are more common among patients undergoing CABG than among those undergoing PCI. Differences between the two groups in variables such as the incidence of carotid-artery disease (14.0 percent vs. 3.5 percent, respectively) and chronic obstructive pulmonary disease (COPD) (16.4 percent vs. 5.9 percent) have not been previously reported in registries that prospectively assessed risk before revascularization was chosen.[2,3] Among patients in the Bypass Angioplasty Revascularization Investigation registry who underwent CABG or PCI, there was a similar likelihood of peripheral vascular disease (15 percent vs. 14 percent) and COPD (5 percent vs. 4 percent).

The clinical assessment conducted before CABG is more extensive than that before PCI. Ultrasonography and spirometry of the carotid artery are often performed before CABG but not before PCI. Thus, in the study by Hannan et al., risk-ascertainment bias may have caused the substantial differences between the unadjusted and adjusted mortality rates. Furthermore, the public reporting of risk-adjusted, physician-specific mortality rates for CABG and PCI in New York State strongly influences case selection and the reporting of risk factors.[4,5]

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1. Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2005;352:2174-83.
2. Brooks MM, Jones RH, Bach RG, et al. Predictors of mortality and mortality from cardiac causes in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial and registry. Circulation 2000;101:2682-9.
3. Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease: initial results from the era of coronary angioplasty. Circulation 1994;89:2015-25.
4. Narins CR, Dozier AM, Ling FS, Zareba W. The influence of public reporting of outcome data on medical decision making by physicians. Arch Intern Med 2005;165:83-7.
5. Moscucci M, Eagle KA, Share D, et al. Public reporting and case selection for percutaneous coronary interventions: an analysis from two large multicenter percutaneous coronary intervention databases. J Am Coll Cardiol 2005;45:1759-65.

**TO THE EDITOR:** The study by Hannan et al. comparing bypass surgery with percutaneous revascularization provides new insight into the potential efficacy of these two procedures for patients with

multivessel coronary artery disease. In all observational studies, however, a multitude of potential biases can trip up the investigator. In 1991,[1] a colleague and I observed marked differences in behavioral changes in patients who had undergone bypass surgery as compared with those who had undergone angioplasty: whereas 55 percent of patients who underwent bypass surgery quit smoking and had not resumed after one year, only 25 percent of patients who underwent angioplasty did so. Changes in smoking status may reflect multiple behavioral changes by patients that are difficult to quantify and that are more profound after surgery than after angioplasty; such changes may also reflect closer physician follow-up and pharmacologic intervention. All these factors might attenuate risk in the surgical group.

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**TO THE EDITOR:** By searching a public database, www.health.state.ny.us/nysdoh/, for CABG and PCI, we found that the actual number of revascularization procedures performed in New York State from 1996 through 2000 was 75,271 for CABG and 137,798 for PCI. However, the article by Hannan et al. reports the survival for only 37,212 patients who underwent CABG (49 percent of the total) and 22,102 who underwent PCI (16 percent); patients who had prior revascularization, disease of the left main coronary artery, or early acute myocardial infarction were excluded, as were those from out of state.

Although the first three exclusions are appropriate for the comparison of mortality rates associated with these two revascularization procedures, the last seems unwarranted, since data on the deaths of out-of-state patients should be accessible. Regardless, the provision of numbers and clinical characteristics of patients who were excluded would assist the clinician in determining the extent and character of selection bias in this cohort analysis. The absence of this information limits the physician's ability to generalize and apply the study results to choices in coronary revascularization. In addition, the low percentage of cases for both procedures included in the study — particularly for the PCI group — needs to be explained.

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**THE AUTHORS REPLY:** In response to Drs. Flaherty and Davidson: the reason we used a propensity analysis was to adjust for differences in the prevalence of risk factors, which are usually present in observational studies. If there were no differences, there would be no need for propensity analyses. It is not difficult to accept the finding of increased carotid-artery disease in patients who undergo CABG, given the concordant findings of increased rates of stroke, aortoiliac disease, and femoral or popliteal disease, all of which can be easily ascertained by the cardiologist before stenting and are primarily clinical diagnoses. In addition, the easily identified clinical findings of increased age, diabetes, three-vessel coronary disease, and renal failure support the likelihood of more severe carotid-artery disease in the CABG group. We disagree with the contention that public reporting results in the avoidance of PCI in patients at high risk. However, even if this were true, it would seemingly shift the sicker patients to CABG surgery, which undermines Flaherty and Davidson's earlier claim that ascertainment bias is an explanation for differences in risk factors.

Regarding Dr. Crouse's comments: it is possible that differences in the rate of smoking cessation between the CABG and PCI groups could contribute to the superiority of long-term outcomes with CABG. However, if this is the case, we do not regard it as a bias in the study but, rather, as a problem that must be dealt with by improving the outcomes of PCI through closer follow-up.

In response to Drs. Rubin and Mody: there were 137,798 patients who underwent PCI and 75,271 who underwent isolated CABG in New York from 1997 through 2000, the years of the study. After records were combined for patients who had multiple procedures and a relatively small number of patients without valid Social Security numbers were excluded, there were 106,551 patients who underwent PCI and 66,250 who underwent isolated CABG. The relatively low percentage of patients with PCI was a result of the elimination from both procedures of those with single-vessel disease, which resulted in 47,470 patients who underwent PCI and 59,441 who underwent CABG. Another 7255 pa-

tients who did not receive stents were removed from the PCI group, and another 17,279 with stents in the PCI group and 20,747 in the CABG group were removed because of previous revascularizations, left main coronary artery disease, an acute myocardial infarction within 24 hours before the procedure, or all of these. A relatively small number of patients (834 in the PCI group and 1482 in the CABG group) were excluded because they were from outside New York State. We did not have access to the National Death Index because of resource constraints, but earlier studies of ours have demonstrated that the absence of data from this source does not introduce a bias.[1]

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## Circulating Osteoblast-Lineage Cells

**TO THE EDITOR:** The study by Eghbali-Fatourechi et al. (May 12 issue)[1] suggests the presence of circulating osteoblasts that potentially contribute to physiological bone formation. In addition to its association with bone modeling and remodeling, as Canalis discusses in the accompanying editorial,[2] calcification can be observed in blood vessels and heart valves as a common complication of atherosclerosis, diabetes, and end-stage renal disease and is generally considered to be a significant predictor of adverse clinical events. Extraosseous calcification seems to be an active, cell-mediated process within bone-like tissues with marrow, cartilaginous tissue, and osteoblast-like cells.[3] Since naive nonosseous tissues contain no osteoblasts, the origin of ectopic osteoblasts remains unclear. Recent evidence suggests that circulating progenitors contribute to the accumulation of smooth-muscle cells in atherosclerotic lesions.[4,5] It may be plausible that the circulating osteoblast-lineage cells participate in the pathogenesis of ectopic ossification. It is consistent with this notion that extraosseous calcification and osteoporosis tend to occur in the same patients and correlate in severity. Deregulated mobilization, homing, and proliferation of circulating osteoblasts may account for both diseases.[3] Therefore, quantification of circulating osteoblasts in patients with ectopic calcification is worthy of investigation.

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1. Eghbali-Fatourechi GZ, Lamsam J, Fraser D, Nagel D, Riggs BL, Khosla S. Circulating osteoblast-lineage cells in humans. N Engl J Med 2005;352:1959-66.
2. Canalis E. The fate of circulating osteoblasts. N Engl J Med 2005;352:2014-6.
3. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. Arterioscler Thromb Vasc Biol 2004;24:1161-70.
4. Sata M, Saiura A, Kunisato A, et al. Hematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis. Nat Med 2002;8:403-9.
5. Caplice NM, Bunch TJ, Stalboerger PG, et al. Smooth muscle cells in human coronary atherosclerosis can originate from cells administered at marrow transplantation. Proc Natl Acad Sci U S A 2003;100:4754-9.

**THE AUTHORS REPLY:** Circulating mesenchymal cells may indeed participate in ectopic ossification. Mechanisms regulating vascular calcification involve paracrine osteogenic signals (i.e., the bone morphogenetic protein BMP-2 and Wnt proteins)[1]; whether these osteogenic stimuli act primarily on resident stem cells in the vasculature to induce osteogenic differentiation[1] or recruit circulating myofibroblast[2] or osteoblastic progenitors at sites of injury is unknown. These possibilities are not mutually exclusive. For example, since circulating osteoblastic cells are already partially differentiated, they may immediately participate in the response to injury, whether in the vascular tree, fractured bone, or other tissues. By contrast, osteogenic differentiation of resident stem cells at sites of injury may require some time (i.e., weeks); thus, committed osteoprogenitors in the circulation may constitute the early response to injury and then be relieved by progenitors recruited from the local tissues. Accordingly, there is now evidence supporting the

notion that bone marrow harbors subpopulations of tissue-committed cells that participate in the response to injury in a variety of organs[3]; in addition, infused bone marrow stromal cells localize to the fracture callus in mice but largely are replaced by host osteoblastic cells within eight weeks after fracture.[4]

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2. Simper D, Stalboerger PG, Panetta CJ, Wang S, Caplice NM. Smooth muscle progenitor cells in human blood. Circulation 2002; 106:1199-204.
3. Kucia M, Ratajczak J, Ratajczak MZ. Are bone marrow stem cells plastic or heterogenous — that is the question. Exp Hematol 2005; 33:613-23.
4. Devine MJ, Mierisch CM, Jang E, Anderson PC, Balian G. Transplanted bone marrow cells localize to fracture callus in a mouse model. J Orthop Res 2002;20:1232-9.

## Asthma and Invasive Pneumococcal Disease

**TO THE EDITOR:** Talbot et al.[1] (May 19 issue) find that in the absence of coexisting conditions such as diabetes, alcoholism, or infection with HIV, which are known to confer a high risk of invasive pneumococcal disease, the excess presence of invasive pneumococcal disease among persons with asthma is one to three episodes per 10,000 person-years. The presence of coexisting conditions was determined from hospital and pharmacy records for the year before the index date, defined as the date of isolation of *Streptococcus pneumoniae*. However, HIV infection often goes undetected, even in patients receiving medical care,[2] until a known HIV-related illness develops, such as invasive pneumococcal disease.[3] Invasive pneumococcal disease has been estimated to be as much as 100 times more common among persons with HIV infection than in the general population.[4,5] It has been recommended that a diagnosis of invasive pneumococcal disease trigger testing for HIV antibody.[3,5] The restriction of coexisting conditions only to those documented on or before the date of isolation of *S. pneumoniae* may have resulted in substantial underestimation of the incidence of HIV infection. The effect of such an underestimation on the study findings should be considered.

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1. Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med 2005;352:2082-90.
2. Kuo AM, Haukoos JS, Witt MD, Babaie ML, Lewis RJ. Recognition of undiagnosed HIV infection: an evaluation of missed opportunities in a predominately urban minority population. AIDS Patient Care STDS 2005;19:239-46.
3. Garcia-Leoni ME, Moreno S, Rodeno P, Cercenado E, Vicente T, Bouza E. Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. Arch Intern Med 1992;152:1808-12.
4. Redd SC, Rutherford GW III, Sande MA, et al. The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. J Infect Dis 1990;162:1012-7.
5. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000; 132:182-90.

**TO THE EDITOR:** Talbot et al. use a case definition of asthma that relies on medical-record review of the diagnostic codes entered or medication-prescription records, or both. Physical-examination data, pulmonary-function assessment, and laboratory information are not incorporated into the case definition. The decision to use a diagnosis of asthma by a noninvestigator physician as the study case definition may result in the misclassification of study subjects. The authors cite two published reports to support the validity of their choice of case definition.[1,2] However, the current investigation does not, in fact, use the same case definition as was used in those studies. Moreover, the cited investigations studied patients with asthma who were over the age of 65 years, whereas the average age in the current study population is 28 years and persons older than 49 years were excluded. The authors should acknowledge the possibility of mis-

classification of study subjects as a potential limitation of their analysis and cite reports that validate their case definition.

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2. Hartert TV, Speroff T, Togias A, et al. Risk factors for recurrent asthma hospital visits and death among a population of indigent older adults with asthma. Ann Allergy Asthma Immunol 2002;89:467-73.

**THE AUTHORS REPLY:** We appreciate the comments of Dr. Cotton regarding undiagnosed HIV infection as a risk factor for invasive pneumococcal disease. We reexamined the Tennessee Medicaid program (TennCare) records of cases of invasive pneumococcal disease for the years after patients had received a diagnosis of invasive pneumococcal disease for health care visits that recorded a coded HIV diagnosis or a prescription for HIV-specific medications. In 9.8 percent of the patients coded as having invasive pneumococcal disease (34 of 347) and 0.4 percent of the controls without a diagnosis coded as HIV or other risk factors for invasive pneumococcal disease (22 of 5541), patients were later given a diagnosis of HIV infection. Of patients with invasive pneumococcal disease who had asthma, 5.9 percent (3 of 51) were later given a diagnosis of HIV infection, as compared with 10.5 percent of those without asthma (31 of 296). We agree with Dr. Cotton that HIV testing should be strongly considered for persons who present with invasive pneumococcal disease.

Drs. Kuschner and Kuschner appropriately noted the limitations of the use of administrative data and questioned our definition of asthma. A diagnosis of asthma is established on the basis of the patient's history; documentation of reversible airflow obstruction by spirometry, methacholine challenge or another challenge test, or both; and the exclusion of any alternative diagnoses.[1] Previous studies using Medicaid data revealed that diagnostic coding data have an excellent predictive value for asthma diagnosed with the use of these criteria.[2,3] The confirmation of the use of diagnostic codes in a younger cohort (15 to 44 years of age) has also been published.[4]

Those earlier studies also made it possible to assess the validity of our diagnostic algorithm for asthma, which included the use of asthma-specific medications, on the basis of standardized criteria and chart review conducted in an older adult cohort (≥65 years of age) (unpublished data). This was a more sensitive, though less specific, definition in the older group, since it also identified subjects with chronic obstructive pulmonary disease (COPD). These findings provided the rationale for limiting our study to those younger than 50 years of age, among whom COPD is less prevalent.

When we used only diagnostic codes to define asthma, the association between asthma and invasive pneumococcal disease in our cohort remained significant (adjusted odds ratio, 3.1; 95 percent confidence interval, 2.2 to 4.5), as compared with the odds ratio of 2.4 (95 percent confidence interval, 1.9 to 3.1) reported in our article. Our definition of persons with asthma included patients given a medical diagnosis as well as those treated for asthma and probably excluded those with milder disease. Misclassification of asthma due to errors in diagnosis would probably be nondifferential with respect to the incidence of invasive pneumococcal disease and would therefore make an association more difficult to detect.

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2. Hartert TV, Speroff T, Togias A, et al. Risk factors for recurrent asthma hospital visits and death among a population of indigent older adults with asthma. Ann Allergy Asthma Immunol 2002;89:467-73.
3. Hartert TV, Togias A, Mellen BG, Mitchel EF, Snowden MS, Griffin MR. Underutilization of controller and rescue medications among older adults with asthma requiring hospital care. J Am Geriatr Soc 2000;48:651-7.
4. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol 2003;189:1705-12.

# Cerebral Folate Deficiency Syndrome

**TO THE EDITOR:** Ramaekers et al. (May 12 issue)[1] report 28 patients with the cerebral folate deficiency syndrome characterized by decreased levels of 5-methyltetrahydrofolate (5MTHF) in the cerebrospinal fluid caused by autoantibodies' blocking of folate transport into the brain. The patients benefited from folinic acid supplementation.

The clinical features of this syndrome fit with other neurodegenerative disorders. According to previous papers by the authors, the latter disorders can be associated with cerebral folate deficiency as a secondary phenomenon.[2-4] Patients with secondary cerebral folate deficiency (e.g., the Rett syndrome) potentially benefit from folinic acid supplementation.[2-4] The authors do not report the presence or absence of folate-receptor autoantibodies in secondary cerebral folate deficiency. Before claiming that the cerebral folate deficiency syndrome is a separate entity, the investigators should demonstrate that it is a unique, autoantibody-mediated disease, different from secondary cerebral folate deficiency.

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1. Ramaekers VT, Rothenberg SP, Sequeira JM, et al. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. N Engl J Med 2005;352:1985-91.
2. Ramaekers VT, Hansen SI, Holm J, et al. Reduced folate transport to the CNS in female Rett patients. Neurology 2003;61:506-15.
3. Blau N, Bonafe L, Krageloh-Mann I, et al. Cerebrospinal fluid pterins and folates in Aicardi-Goutieres syndrome: a new phenotype. Neurology 2003;61:642-7.
4. Ramaekers VT, Blau N. Cerebral folate deficiency. Dev Med Child Neurol 2004;46:843-51.

**THE AUTHORS REPLY:** Within the group of neuropsychiatric conditions associated with cerebral folate deficiency, infantile-onset cerebral folate deficiency syndrome can be delineated as a separate and recognizable clinical entity, which can begin manifesting itself at the age of four months, when the only identifiable abnormality is a low level of 5MTHF in the cerebrospinal fluid.[1,2] This means that other conditions that involve secondary cerebral folate deficiency must be excluded before a firm diagnosis of infantile cerebral folate deficiency syndrome is established.[2]

The identification of blocking folate-receptor autoantibodies in the serum of most patients with infantile-onset cerebral folate deficiency syndrome merely reflects a specific autoimmune mechanism that explains the blocked folate transfer to the brain. Among the few patients without these folate-receptor autoantibodies, alternative causes may be responsible for the low levels of 5MTHF in cerebrospinal fluid.

Since blocking folate-receptor autoantibodies impair folate transport across the placenta and blood–cerebrospinal fluid barriers,[3] we cannot exclude the possibility that they also play a role in the pathogenesis of secondary cerebral folate deficiency.[4,5]

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2. Ramaekers VT, Blau N. Cerebral folate deficiency. Dev Med Child Neurol 2004;46:843-51.
3. Rothenberg SP, da Costa MP, Sequeira JM, et al. Autoantibodies against folate receptors in women with a pregnancy complicated by a neural-tube defect. N Engl J Med 2004;350:134-42.
4. Ramaekers VT, Hansen SI, Holm J, et al. Reduced folate transport to the CNS in female Rett patients. Neurology 2003;61:506-15.
5. Blau N, Bonafe L, Krageloh-Mann I, et al. Cerebrospinal fluid pterins and folates in Aicardi-Goutieres syndrome: a new phenotype. Neurology 2003;61:642-7.

# Response of a Nonmalignant Pleural Effusion to Bevacizumab

**TO THE EDITOR:** The potential role of vascular endothelial growth factor in malignant as well as nonmalignant pleural effusion[1,2] prompted us to use bevacizumab, a monoclonal antibody against vascular endothelial growth factor, in a 68-year-old man with primary cardiac amyloidosis who had severe dyspnea and underwent repeated thoracenteses for pleural effusions. Cytologic assessments of the

**CORRECTION**

## Cerebral Folate Deficiency Syndrome

Cerebral Folate Deficiency Syndrome . In the letter by Willemsen et al., author Marcel M. Verbeek's name was misspelled.

N Engl J Med 2006;354:215-a

pleural fluid did not detect malignant cells. Primary amyloidosis had been diagnosed by myocardial biopsy four weeks previously, but there were no other manifestations of amyloidosis. At the time of the patient's admission, left ventricular function was moderately reduced (ejection fraction, 40 percent). A radiograph of the chest showed massive pleural effusion in the right hemithorax. The C-reactive protein level was markedly increased (27.2 mg per deciliter), but no inflammatory infiltrate was seen in the radiograph of the lung. Thoracentesis was unsuccessful because of the segmented nature of the effusion. Because of the elevated C-reactive protein level, we began broad-spectrum antibiotic treatment and gave the patient an intravenous diuretic. After five days, the C-reactive protein level was reduced, but the clinical condition, with severe dyspnea, and the chest radiograph remained unchanged. The patient was judged unable to undergo anesthesia for surgical intervention and pleurodesis.

Because the severe dyspnea continued despite intensive conventional treatment for another seven days, we decided to treat the patient with bevacizumab (Avastin, Roche).[3] After obtaining the patient's consent, we administered the dose used for the treatment of colorectal cancer (5 mg per kilogram of body weight given intravenously over a period of 90 minutes).[4] On the first day after the administration of bevacizumab, the patient reported increased urine production and markedly reduced dyspnea. One week after bevacizumab treatment, the chest radiograph showed a dramatic reduction in the pleural effusion. This finding was confirmed in a second radiograph two weeks after the administration of bevacizumab.

To our knowledge, this is the first report of the treatment of a nonmalignant pleural effusion with bevacizumab. Considering the prompt clinical improvement and the reduction in the effusion after administration of the antibody, there is good reason to believe that clinical improvement and diminished effusion were associated with bevacizumab therapy.

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**1.** Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 1983;219:983-5.
**2.** Sack U, Hoffmann M, Zhao XJ, et al. Vascular endothelial growth factor in pleural effusions of different origin. Eur Respir J 2005;25:600-4.
**3.** Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004;3:391-400.
**4.** Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

# BOOK REVIEWS

## FALLING THROUGH THE SAFETY NET: AMERICANS WITHOUT HEALTH INSURANCE

By John Geyman. 222 pp. Monroe, Me., Common Courage Press, 2005. $29.95 (cloth); $18.95 (paper). ISBN 1-56751-255-0 (cloth); 1-56751-254-2 (paper).

## UNINSURED IN AMERICA: LIFE AND DEATH IN THE LAND OF OPPORTUNITY

By Susan Starr Sered and Rushika Fernandopulle. 247 pp. Berkeley, University of California Press, 2005. $24.95. ISBN 0-520-24442-7.

THESE TWO BOOKS DOCUMENT THE CONSEquences of the lack of universal coverage for health care in the United States and then recommend national health insurance. Each book is readable and perceptive and offers fresh information and helpful syntheses of familiar data. Even experts in health policy will find news in these books.

Both books are vague, however, about how to address the fundamental problem of making policy for access to care, which entails mobilizing the political will to achieve substantial reform. The authors of these books, like many before them, imagine (perhaps even hope) that a combination of increasing physical and mental suffering and the rising cost of care will create a crisis. This crisis, they believe, will precipitate a political situation in which thoughtful policy design could overcome the inhibiting effects of ideologies and interest groups.

The authors of each book tell compelling stories of pain and suffering drawn from their interviews with persons who are uninsured. John Geyman includes "more than 30 family stories and patient vignettes"; Susan Starr Sered and Rushika Fernandopulle interviewed "more than 120 uninsured Americans" and "approximately four dozen physicians, medical administrators, and health policy officials." Geyman has read widely about the problems of access to health care and recommendations for solving them in the research literature, the media, and reports commissioned by official bodies and advocacy groups. Starr Sered and Fernandopulle command much of the same information. In addition, they apply the findings of studies of related subjects in the social sciences. Both books argue that a social-insurance entitlement program for health and long-term care is in the best interests of most Americans.

These books contribute to the running debate about health insurance as a method for expanding access to care in America that began in the second decade of the 20th century. Geyman's comprehensive survey and synthesis of an enormous amount of information are marred by a few minor errors (for example, mistitling several people and misstating the governance of a few organizations). He amply documents the negative effects, direct and indirect, on almost everyone in the country of lack of access to care. Geyman criticizes, and occasionally caricatures, interest groups that have opposed proposals for a national program of social insurance or even for near-universal coverage. He is especially offended by the pharmaceutical, insurance, and investor-owned hospital industries.

Starr Sered and Fernandopulle offer an original conceptualization of the poignant stories told to them by uninsured people across the country. They contend that the "current American system in which health care is linked to employment is creating a caste of the chronically ill, infirm, and marginally employed." This caste — a word they chose with care — is experiencing a "death spiral" as a result of which its members are "sucked into a lethal vortex of ill health, medical debt, and marginal employability." Like castes in India, these "millions of Americans" are increasingly set apart from more fortunate Americans by a "physical marker" — for example, "rotten teeth, chronic coughs, bad skin, . . . addiction to pain medication."

Geyman, Starr Sered, and Fernandopulle want to believe that a crisis in the health sector would create incentives for the reform of policy for coverage. The causes of this crisis would be the rising costs of insurance for employers, individuals, and families, in combination with anxiety and untreated illness among increasing numbers of Americans. In the post-crisis politics of health care, masterly public officials, in alliance with leaders of

business and a resurgent labor movement, would overcome resistance to reform, including the inertia that would result from a majority of Americans' believing that they are adequately insured.

Starr Sered and Fernandopulle do not make the observation, however, that none of the 120 uninsured people they interviewed mentioned politics or their elected representatives (and they seem not to have asked about these subjects). None of the persons interviewed, moreover, described a telephone call or a visit to the office of an elected official or mentioned a campaigning politician inquiring about their problems.

In contrast, in my professional work I talk most days with persons who hold leadership positions in state legislatures or have been elected to statewide office. These colleagues, both Democrats and Republicans, have firsthand knowledge of their constituents' problems with access to health care. Moreover, they work hard to ameliorate these problems by making policy and helping individuals receive care. The absence of politics and politicians from Starr Sered and Fernandopulle's account supports my undocumented impression that my colleagues and their constituents are atypical among persons in public office.

But most of my colleagues have been reelected, which suggests practicable next steps in actualizing reform of access to care. The political work of solving the problems of health coverage may have to begin with the organization of individuals, one by one, into coalitions for change in states and communities. Geyman offers examples of such work in several states, but he focuses on results rather than on the hard work of politics (the "slow boring of hard boards," as social scientist Max Weber wrote more than 80 years ago). Elected officials who try to make policy to improve access to care encounter many obstacles, not the least of which are strong opinions that are frequently grounded in ideology about markets and choice and the money and persuasiveness of health-sector interest groups. These officials need all the help they can get from voters, as people with health care needs and as members of organizations that favor policy to expand access to care.

In the absence of a new approach to the politics of access, our pluralistic, expensive, and inequitable methods of paying for health services are likely to survive unchanged during any foreseeable crisis. Patients and families are well acquainted with the suffering described in these books. Communities have the burden of aggregate costs of the schooling, jobs, and productivity lost by people without insurance, as well as the expenses of treating and caring for such people — expenses that are shifted to public and private payers and absorbed by professionals and institutions. There is little reason to believe that patients, families, and communities will not adapt to new crises in the health sector, just as they have adapted in past crises. The most likely alternative to mobilizing sufficient political will to achieve at least near-universal coverage is that, as a society, Americans will learn to tolerate more suffering.

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## ONE NATION, UNINSURED: WHY THE U.S. HAS NO NATIONAL HEALTH INSURANCE

By Jill Quadagno. 274 pp. New York, Oxford University Press, 2005. $28. ISBN 0-19-516039-8.

Over the past century, powerful organizations, industries, and groups have mobilized to oppose the enactment of national health insurance in the United States. Although the players on the opposition team have changed, and their ideologies have shifted, the result has been consistent. Interest groups that have stood to lose with the extension of coverage have ensured that universal coverage would not come to pass. So writes Jill Quadagno in *One Nation, Uninsured*.

Quadagno, a sociologist and an unabashed advocate of universal coverage, is clearly fascinated by this history. She tells it in a readable and engaging fashion. Starting with the failure of the campaign for compulsory health insurance in the Progressive Era and ending with the demise of President Bill Clinton's health plan, the book details the ways in which stakeholders — physicians, the business community, and insurers — have battled to maintain their positions. The victors in the battles have not only won as a result of their sheer financial power; they have also prevailed through coalition building and organizing at the grassroots level.

Much of the material in this book draws on previously published accounts. Some of the most interesting portions come from Quadagno's own ar-

chival searches and her interviews with people who lived the history that she describes. This is a tale that spans nearly a century, and in a short book, some richness is inevitably lost. The material covering the early years tends to be more nuanced than that of more recent events, such as the failure of the Clinton health plan.

One difficulty with the book is that its audience is not clearly defined. On the one hand, Quadagno addresses sophisticated debates in political causality; indeed, in invoking stakeholder politics, one of her objectives is to put forth a kind of "unified field theory" to explain the failure of universal coverage. On the other hand, she takes the time to define rudimentary terms such as "filibustering" and to summarize the very basics of programs such as Temporary Assistance to Needy Families and welfare reform.

For physicians who share Quadagno's taste for universal coverage, this look backward at a series of missed opportunities is rather bleak. This is not a history from which such readers can draw much professional pride. Nor does Quadagno's analysis offer much hope that physicians will be central players in health care reform in the near future, given their current organizational fragmentation. In the final pages of the book, the author looks forward, presenting a brief sketch of how a coalition of diverse groups (including employers, the elderly, organized labor, and the uninsured) might work together to achieve what has repeatedly failed to come to fruition over the past century. Although some readers may consider this an unlikely picture of the near future, Quadagno's sustained focus on interest-group politics seems right on target.

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## CORRECTIONS

Sudden Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both (June 23, 2005; 352:2581-8). On page 2581, lines 9 and 10 in the Results section of the Abstract should have stated that "83 percent of all patients who died suddenly in the first 30 days did so after hospital discharge," rather than "83 percent of all patients who died suddenly did so in the first 30 days after hospital discharge," as printed. We regret the error.

Bites of the Brown Recluse Spider (May 12, 2005;352:2029-30). In the letter by Swanson and Vetter, on page 2029 in the right-hand column, lines 7 through 12 of the second paragraph should have read, "Furthermore, the unverified diagnosis of a spider bite in areas where loxosceles spiders are nonendemic is insufficient proof of the local existence of brown recluse spiders or other allegedly necrosis-inducing spiders . . .," rather than "in areas where loxosceles spiders are endemic," as printed. We regret the error.

Standard and Increased-Dose BEACOPP Chemotherapy Compared with COPP-ABVD for Advanced Hodgkin's Disease (June 12, 2003;348:2386-95). On page 2387, in Table 1, the dose of cyclophosphamide in the regimen of increased-dose BEACOPP should have read 1250 mg per square meter, rather than 1200 mg per square meter, as printed.

## NOTICES

*Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the* Journal*'s Web site (www.nejm.org/meetings). The listings can be viewed in their entirety or searched by location, month, or key word.*

### VA–NATIONAL MEDICAL MUSICAL GROUP

The group is recruiting new members for its symphony orchestra and chorus. The MMG holds concerts around the country and overseas, including annual Flag Day/Independence Day and Veterans' Day concerts. Physicians, dentists, nurses, other healthcare personnel, faculty and students, both VA and non-VA, and their families and friends may apply.

Contact VA–National Medical Musical Group, 1700 17th St., NW, Suite 508, Washington, DC 20009; or call (202) 797-0700; or e-mail vanmmg@hotmail.com; or see http://www.medicalmusical.com.

### LUCILE PACKARD CHILDREN'S HOSPITAL

The following course will be offered: "Palliative and End of Life Care for the Adult and Child" (Kauai, Hawaii, Nov. 7–9). The course is jointly sponsored by Lucile Packard Children's Hospital at Stanford and Stanford University School of Medicine.

Contact Lucile Packard Children's Hospital, CME Programs, 725 Welch Rd., MC 5517, Palo Alto, CA 94304; or call (650) 497-8554; or fax (650) 497-8585; or see http://www.cme.lpch.org.

### RETINAL AND VITREOUS SURGERY

The course will be offered in Prague, Czech Republic, Sept. 3 and 4.

Contact Prof. Ingrid Kreissig, University of Tuebingen, Breuningerbau, 72075 Tuebingen, Germany; or fax (49) 7071-29-5209; or e-mail ingrid.kreissig@augen.ma.uni-heidelberg.de; or see http://kreissig.uni-hd.de/.

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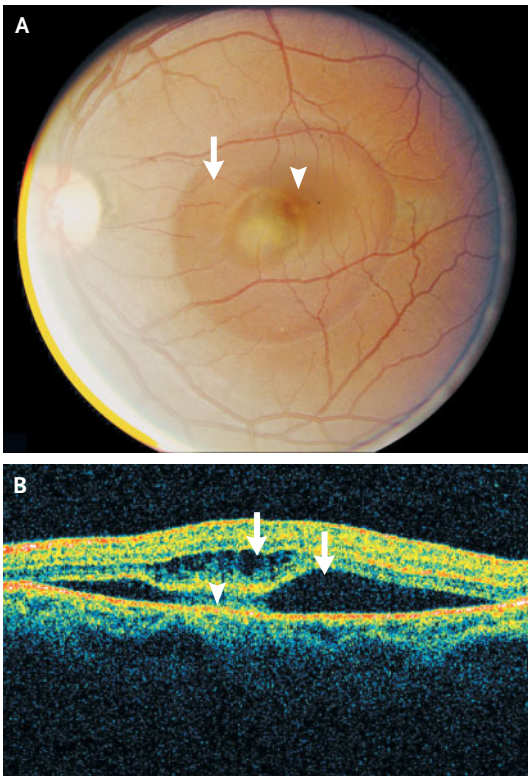
IMAGES IN CLINICAL MEDICINE

# Central Serous Chorioretinopathy in Pregnancy

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A 32-year-old black woman who was seven months pregnant presented with a three-day history of blurring and greenish discoloration of her central vision in the left eye. Visual acuity was 20/70 in the affected eye. After dilation of the pupil, ophthalmoscopic examination revealed a large, serous macular detachment (Panel A, arrow) with central white subretinal exudates (arrowhead). A horizontally oriented optical coherence tomograph of the macula demonstrated both the serous subretinal fluid (Panel B, right-hand arrow) and the area of subretinal exudates (arrowhead). Cystoid changes were also seen within the retina overlying the area of subretinal exudates (Panel B, left-hand arrow). Pregnancy is a well-known risk factor for the development of central serous chorioretinopathy. White subretinal exudates are found in the majority of cases of central serous chorioretinopathy in pregnancy, in contrast to cases not associated with pregnancy. After delivery, the serous macular detachment resolved within 12 weeks, and the patient recovered visual acuity of 20/20.