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Stents to Prevent Stroke

These devices can spring into shape automatically to open arteries blocked with plaque

Stephen P. Lownie and David M. Pelz

As we age, the major arteries of our bodies frequently become thickened with plaque, a fatty material with an oatmeal-like consistency that builds up along the inner lining of blood vessels. The reason plaque forms isn't entirely known, but it seems to be related to high levels of cholesterol inducing an inflammatory response, which can also attract and trap more cellular debris over time. The condition is called *atherosclerosis*, a combination of the Greek words for paste and hardness. As a plaque becomes more advanced, one of two problems can occur. The first and most common is narrowing of the inside of the artery, known as *stenosis*. When severe, blood supply to a body area such as the heart or leg is in jeopardy. The second problem occurs if the plaque ruptures. This event can cause outright blockage of the artery, cutting off blood flow entirely, or give rise to an *embolus*, a piece of debris released from the diseased artery wall. An embolus reduces blood supply once it travels downstream and abruptly blocks smaller arteries there.

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When an artery to heart or leg muscle becomes stenosed, symptoms develop as the muscle works too hard for its limited blood supply. People who have narrowing of these arteries and exert themselves can experience pain in the chest or leg. On the other hand, when an artery supplying the brain becomes stenosed, stroke can occur. But a stroke isn't brought on by thinking too hard. It often comes on like a lightning bolt, and the sudden onset suggests an embolus.

Stroke is the third leading cause of death and disability in the United States and the developed world. The sudden lack of blood flow to the brain causes rapid loss of function, leading to symptoms such as partial paralysis or blindness, or the inability to speak. About one-fifth of strokes are caused by narrowing of the large blood vessels supplying the brain—the carotid arteries—in the neck. American neurologist C. Miller Fisher discovered this cause in the 1950s, at a time when most medical knowledge came from autopsies. Out of sensitivity toward the appearance of the corpse, autopsies on stroke victims almost never involved cutting into the neck. Fisher considered this fact and reasoned that the carotid arteries might provide missing clues. He examined them more closely than anyone had done before, and found evidence of stenosis in a number of cases. Within a few years of Fisher's discovery, surgeons in England and the United States invented operations to restore blood flow through narrowed carotid arteries, called *carotid endarterectomy*. Nowadays the most popular procedure is performed as if removing a banana through a slit in its peel: The plaque is scooped out, usually in one piece, and the opening in the artery is sewn back together *(see Figure 2)*.

When such surgery was first introduced, it was thought that opening up a completely blocked artery in the neck might reverse the effects of a major stroke. This hope proved to be in vain, because the surgery was performed after the stroke damage had already been inflicted. It was soon realized that surgery is best performed after the danger signs—the warning or mini-strokes—had occurred but before a major stroke happened.

Causes of Stroke

Medical researchers sometimes debate whether a stroke has been caused by the plaque creating so much stenosis that it cuts off blood supply, or by an embolus breaking off from the plaque and passing downstream. It may be impossible to tell for certain. In some instances the stenosis caused the stroke. But this scenario is not the norm, because even when a carotid artery becomes totally blocked, a stroke doesn't necessarily occur. Extra blood gets to the brain from other, collateral sources, such as the carotid artery on the other side of the neck. If these collateral sources are sufficient, even a 100 percent carotid blockage can occur with little or no loss of brain blood flow. It is ironic that once a stenosis has progressed to 100 percent occlusion, the risk of future stroke from that artery actually goes down, because the chance of an embolus traveling downstream is reduced.

The collateral blood supply to the brain has been a topic of interest to scientists for almost 500 years. The most important pathway for collateral flow was named the Circle of Willis, in honor of the British physician Thomas Willis (1621–1675) who was one of the first to recognize it in the mid-1600s. The circle itself is centrally located at the base of the brain, but numerous vessels feed into it.

The collateral blood from the Circle of Willis also comes into play during

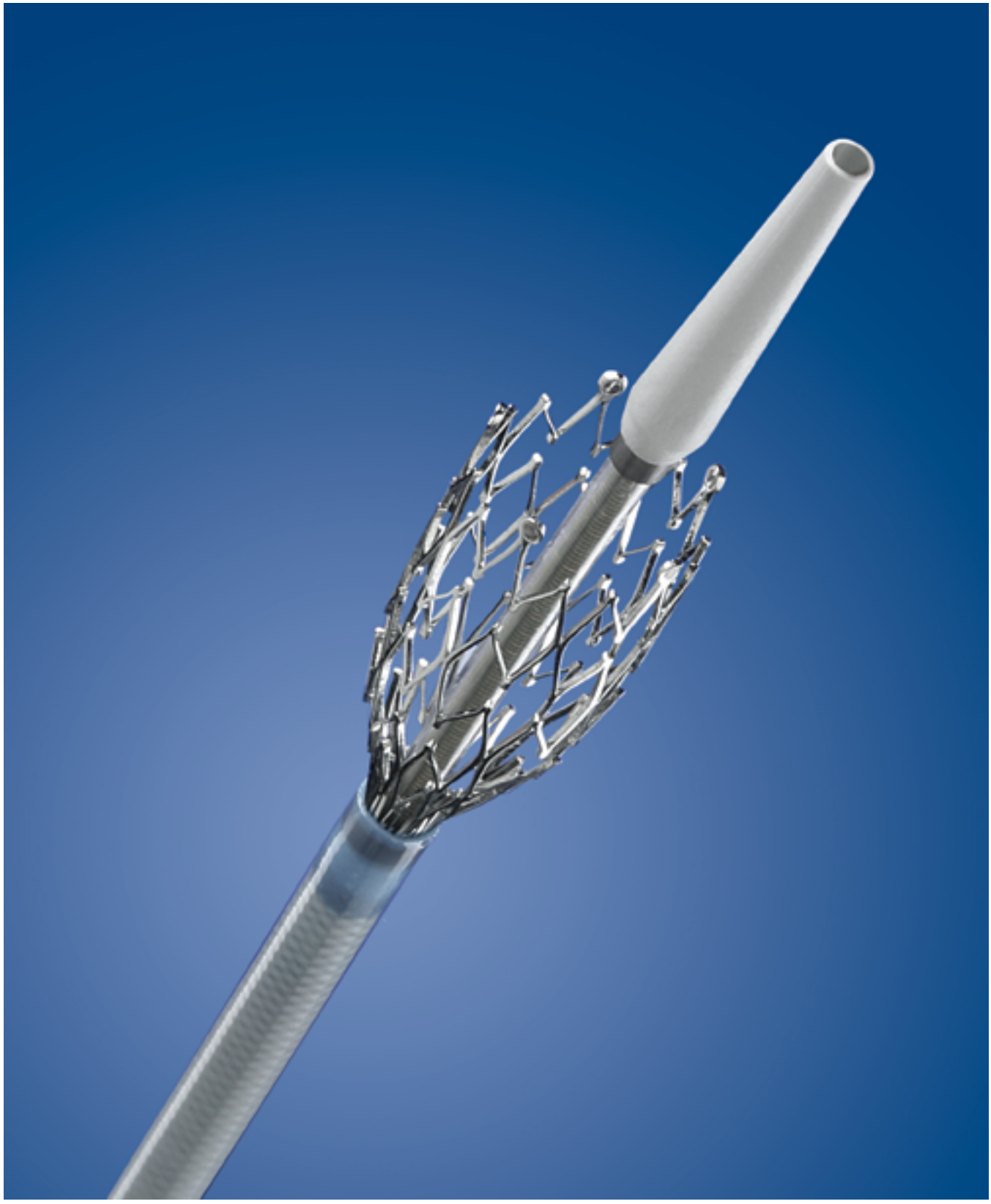

Figure 1. Stents are tubular wire mesh structures sometimes used to hold arteries open. Self-expanding versions of stents were originally designed for use after a balloon had first opened a blockage in the artery. These stents are first compressed into a catheter that can be fed through an artery to a site that is blocked with plaque. The stent in this image is shown partially released from the catheter, and demonstrates that the devices naturally spring back to their original form as they are unsheathed. Stents were developed initially for use in peripheral arteries, such as in the leg, or to hold open the clogged outlets of organs such as the bladder or liver, but studies have demonstrated that they are also useful in managing blockages in major arteries, such as the carotids in the neck, to prevent strokes. Self-expanding stents are less invasive than other interventions and have been shown to expand to their full diameter over time—as long as plaques have not become hardened with calcium. (Photograph courtesy of Covidien.)

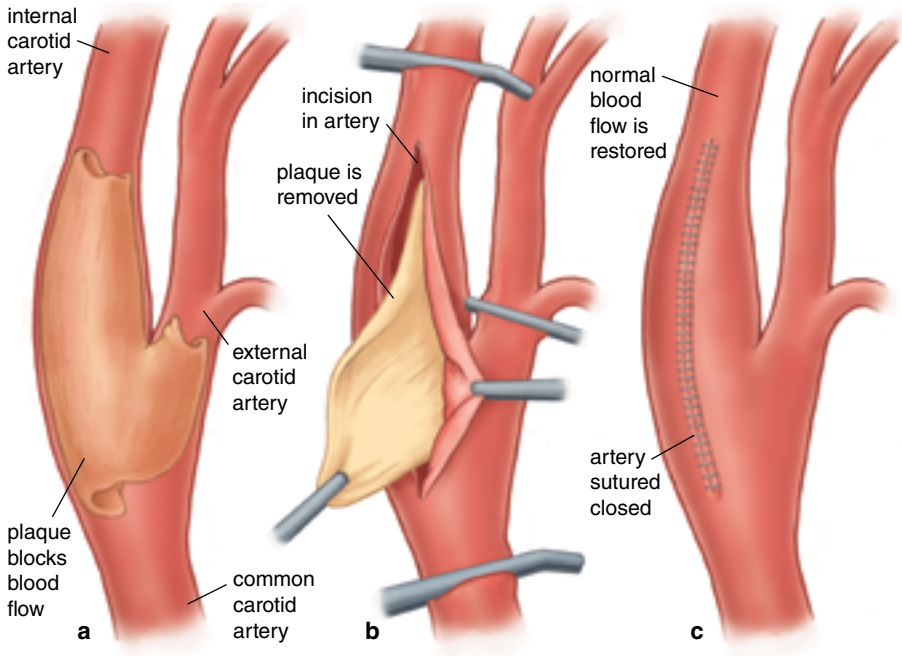

Figure 2. A blocked carotid artery can be cleared with a surgical procedure called endarterectomy, which in essence is like removing a banana through a slit in its peel. The artery is first exposed *(left)* and opened *(middle)* once clamps have temporarily cut off blood flow. The plaque blocking the artery is then cleaned out, usually in one piece, from the inside of the blood vessel. Once the artery has been sutured closed *(right)*, normal blood flow is restored.

carotid surgery. To remove the plaque, the artery must be clamped off for a period of time. Thirty minutes isn't unusual; even up to an hour may be required to perform a clean removal of the plaque. Yet the procedure does not have to be done quickly, because in most instances the Circle of Willis provides sufficient collateral blood flow to prevent a stroke during the operation.

It is now generally accepted that the majority of carotid strokes are caused by embolus arising from plaque, rather than stenosis. This view was first supported by the surgical observation of "ulcers" or craters within the plaque, by surgeons Albert Hall and Wesley Moore of the University of California at San Francisco in the early 1960s. Ulcers contain loose debris that can spill out and embolize. More recently, medical scientists in the 1970s and 1980s—notably neurologist Henry Barnett at the University Hospital in London, Canada—recognized and proved that aspirin prevents strokes. This finding also supported the embolus side of the debate because blood thinners such as aspirin prevent emboli but do not have any effect on stenosis.

Yet surgery to correct the stenosis by removing the plaque is remarkably effective at preventing stroke. By the 1990s scientific studies on both sides of the Atlantic had proven that surgery dramatically reduced the chance of a major stroke, compared to aspirin therapy alone. The success with surgery can probably be attributed to the removal of the source of further embolus. The correction of the stenosis may be only an added benefit.

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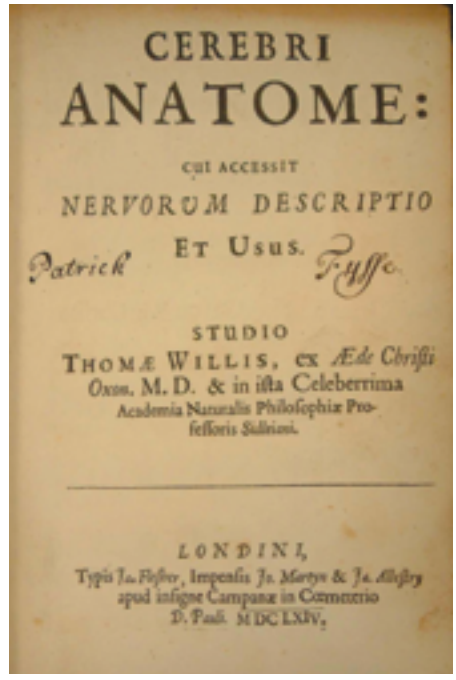
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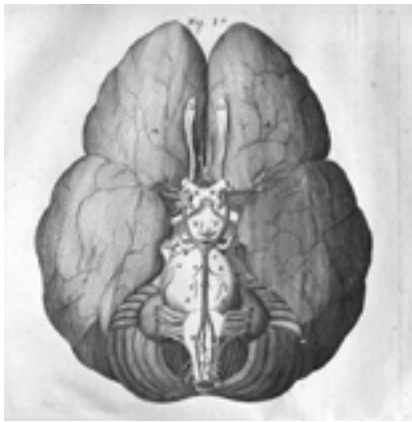


Figure 3. Thomas Willis *(above left)* was a British physician in the mid-1600s. In his book *Cerebri Anatome (above right)*, Willis included an illustration (engraved by Christopher Wren) of the blood vessels at the base of the brain *(left)*. Willis was one of the first to recognize a ring of vessels that is now called the Circle of Willis in his honor. This ring constitutes a collateral blood supply to the brain, providing redundancy should any one vessel fail. The Circle of Willis explains why even a full occlusion in one carotid artery may not result in a stroke, because blood still gets to the brain from other sources. (Top right image courtesy of the Monro Collection, Special Collections, University of Otago.)

Ballooning Options

Meanwhile, new technologies to combat atherosclerotic plaque were already coming onto the scene. Beginning in the United States in the 1960s and later in Europe, American physicians Charles Dotter and Melvin Judkins, and German cardiologist Andreas Gruentzig, pioneered the

use of balloons rather than scalpels to open blocked arteries of the leg and heart. The procedure, called *balloon angioplasty*, uses a catheter to deliver a tiny balloon to a stenosed area, which, when inflated, pushes the plaque aside and dilates the vessel. Although exciting, these approaches didn't catch on in stroke prevention for another 10 to 20 years. Surgeons who operated on the carotid artery and regularly saw the oatmeal-like debris in the ulcers were reluctant to try it. They were concerned that balloons might dislodge plaque debris and lead to embolus.

Gradually things changed, partly due to the success achieved when open surgery was too risky and balloons were the only option. What was also found was that the plaques are often quite rubbery. Even after inflating a balloon with up to six atmospheres of pressure, the plaque would often simply return to its original narrowed shape. Also, x rays of some plaques showed a lot of calcium buildup. To get a calcified plaque to open it might be necessary to crack it apart with repeated high-pressure inflations of the balloon. That procedure might be acceptable in a leg artery, but it's a bit concerning with an artery going to the brain. What if the cracking dislodged an embolus?

The solution to the problem of rubbery plaque came with the development of stents. Broadly, a *stent* refers to any type of scaffolding used in dental, skin or facial surgery. The term evolved to include tubular wire mesh structures that were developed to open up blocked arteries supplying the leg as well as clogged outlets of the bladder and liver. Balloon-expandable stents are mounted on the same balloons used to open up the blockage, and are opened by the balloon itself. Self-expanding stents are designed to open up on their own. These stents are compressed into the catheter before insertion and naturally spring back to their original form as they are unsheathed.

Once stents were used alongside balloons for the carotid artery, results improved dramatically. Stents helped keep the artery open. Over the past 10 years carotid stenting has improved to a level almost as good as established carotid surgery. But balloons are still the most forceful part of the procedure, and as the plaque is pushed apart, fragments can dislodge and pass up to the brain, leading to stroke. Efforts to limit this problem have included the development of tiny umbrella-like sieves, placed downstream before the balloon is inflated. These *embolic protection devices* are designed to trap larger bits of debris while allowing normal blood cells to pass through to the brain.

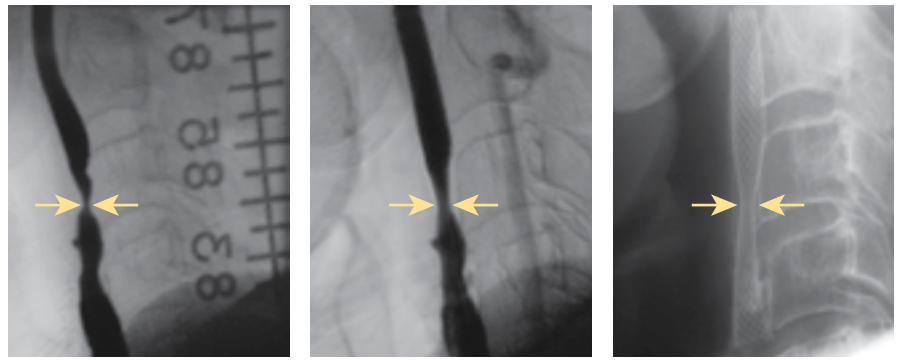


Figure 4. Angiograms (which are taken using an injected dye) of the carotid artery of a 72-year-old man named Joe show that the vessel was significantly narrowed before treatment *(left).* During the procedure to place a stent in the blocked area, the stent expanded partially *(middle).* An x ray following the procedure showed that the stent still maintained a residual hourglass narrowing in its shape, indicating that it had not fully expanded at this point *(right).* (Unless otherwise indicated, images are courtesy of the authors.)

An Expanded View

At the beginning of our own experience with carotid stenting a dozen years ago, we took care of a 72-year-old man named Joe. He had undergone carotid surgery 18 years earlier but his artery had narrowed again and he had experienced a small warning stroke. At the time a radiologist, Suleyman Men from Ankara, Turkey, was visiting our unit. He and his group had made an interesting discovery concerning the use of self-expanding stents for cancer. Tumors such as those in the pancreas can become enlarged and squeeze off the bile duct that drains the liver, causing a backup of bile, liver trouble and jaundice. Men and his colleagues used a balloon to dilate the narrowed bile duct. They then placed a stent to hold the duct open, preventing sludgy bile from clogging up and blocking things again. But after a while the group stopped using balloons altogether. They found that the stent opened up the bile duct because of its own springy outward force. The stents even continued to open for a few days after being deposited, expanding out to at least 85 percent of their maximum diameter. Balloons weren't needed to achieve an acceptable result.

Intrigued by this finding, we wondered whether narrowing of the carotid artery might respond the same way. But cancerous narrowing of the bile duct is decidedly different from the hardening

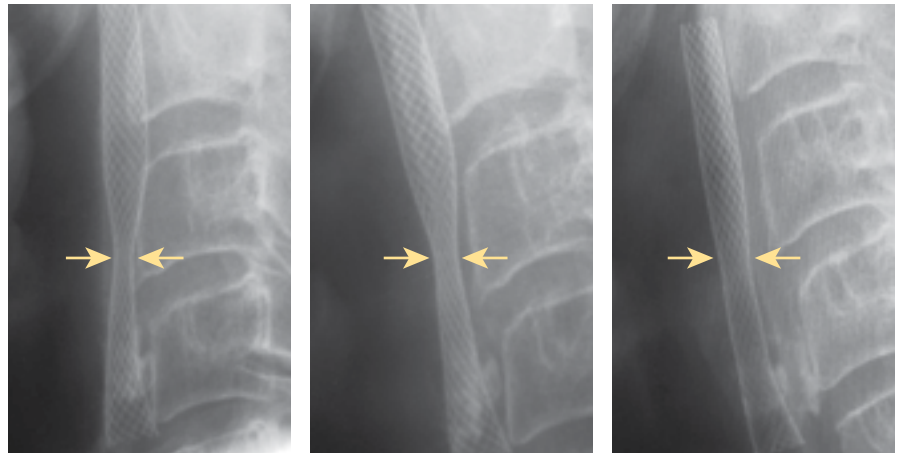


Figure 5. Joe's carotid artery immediately after stent deployment still showed some narrowing *(left).* Two days after the procedure, x rays prove that the stent continued to open under its own natural inclination to return to its original shape *(middle).* After three months, imaging demonstrates the stent sides are virtually parallel and the stent appears widely open *(right).*

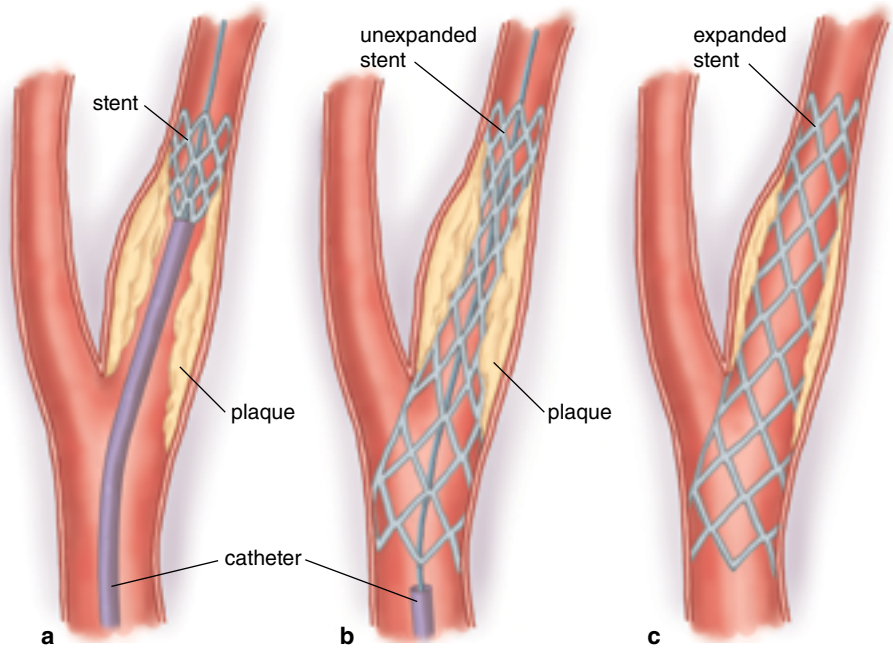


Figure 6. Self-expanding stents provide an alternate treatment for carotid artery blockages in patients who have experienced stroke warning symptoms and for whom surgery might not be the best option. A catheter containing a compressed stent is fed through the artery to the site of the blockage *(a)*. As the catheter is removed and the stent put into place, it initially expands only as far as the boundary created by the blockage *(b)*. However, over time the stent often will fully expand to its uncompressed state, and in the process push aside the plaque in the blockage, restoring normal levels of blood flow *(c)*.

and even calcification seen with atherosclerosis. Could a self-expanding stent alone do the job as effectively as a balloon plus a stent? If so, the procedure would be simplified quite a bit. Simpler could also be safer, although it remains to be proven: Studies have found that emboli during treatment increase in number as more devices are used. Before his treatment, Joe and I discussed this option, agreeing that if the stent wasn't as successful as we would like, he might have to come back for treatment with a balloon at a second session. He understood the rationale and agreed, and his treatment a few days later was uneventful. We were encouraged when the stent expanded partly during the procedure, from a diameter of 0.8 millimeters to 1.2 millimeters *(as shown in Figure 4)*. However there was still a persistent hourglass-type appearance to the stent.

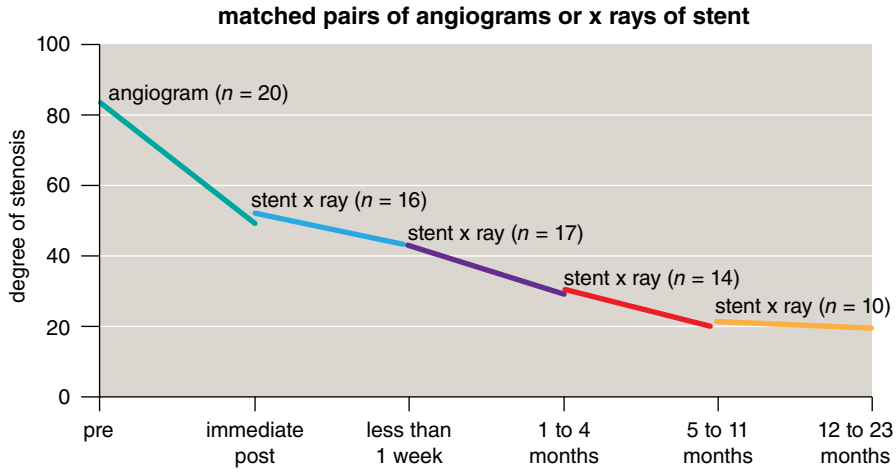


Figure 7. Sequential x ray results in the first 21 patients in which the authors placed self-expanding stents show a progressive reduction in the narrowing (stenosis) of the carotid artery as the stents expand, compared to each patient's radiological results before treatment. About half of the stent expansion occurs immediately, with the rest happening more gradually, for up to 11 months before stabilizing. (Numbers on each colored line segment of the graph indicate the number of patients included in that segment of follow-up radiology.)

We decided to wait and see if the stent might expand further. We kept Joe on some aspirin to prevent any clots from forming along the struts of the stent while it was still a bit compressed. The artery looked narrow but there was excellent blood flow through the stent. We kept monitoring things every few days to see if the stent would expand further under its own *chronic outward force*. Remarkably it opened to 3.5 millimeters after a few days *(see Figure 5)*. By three months it had opened even further, to 4.5 millimeters.

We followed Joe's stent over the next four years. It remained widely open and his symptoms did not recur. He remained free of strokes for the rest of his life and ultimately died in his sleep.

Encouraged by this experience, we continued to use a "primary carotid stenting" technique at our institution *(as shown in Figure 6)*. We believed that the intrinsic force of the stent alone would be sufficient to dilate the majority of carotid artery plaques without the use of angioplasty balloons. In each case we performed x rays on the day of treatment, then a day or two later, and then two or three times over the next year. We identified 21 consecutive people between March 2000 and September 2002, all of whom had stroke warning symptoms and severe carotid artery narrowing. Stent deployment was successful in 20; only one individual required a balloon. During treatment the average amount of narrowing was reduced from 83 percent to 49 percent. By a week later this dropped to 43 percent, by four months to 30 percent, and by 11 months to 21 percent on average *(see Figure 7)*. Clearly our belief was justified: The majority of carotid plaques opened up by simply placing a self-expanding stent without a balloon.

The stent expansion was a dual-stage process. The first phase occurred immediately as the stent was deployed in the vessel and accounted for about half of the average overall expansion. The second phase occurred more slowly over subsequent days, weeks and even months. In most placements, the immediate and delayed expansions

were about equal. In a few, there was no immediate response but a marked delayed response.

But in one plaque, in a patient named Emma, there was neither an immediate nor a delayed response; the stent failed to expand at all. This plaque was different from the others in an important way: It was heavily calcified. In Emma's artery, and in some others, the stent remained narrowed in an hourglass shape, in contrast to most stents that opened fully *(see Figure 8)*.

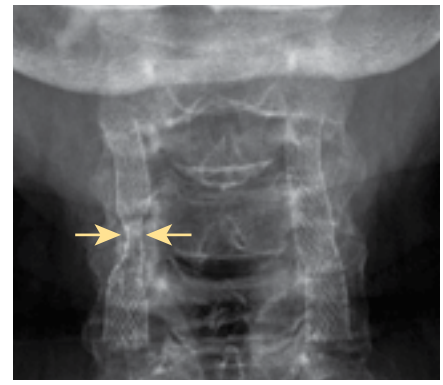
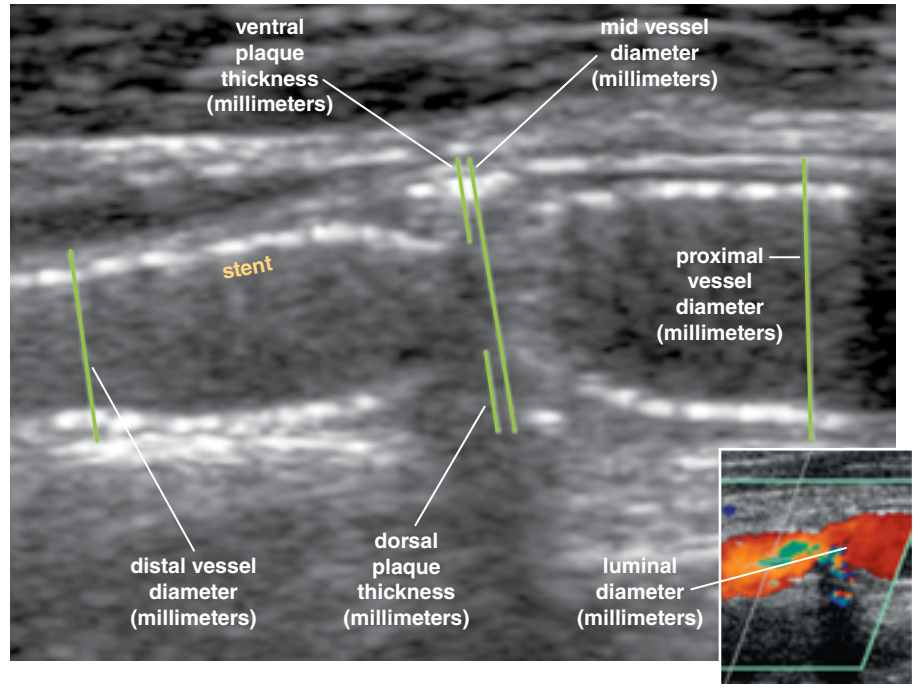


Figure 8. An x ray of a female patient (taken in a frontal view) who had stents placed in both of her carotid arteries shows the influence of plaque composition on the stent's performance. The stent on the right side of the image (in the patient's left artery) was placed first and able to fully open to restore blood flow. The stent on the left side of the image encountered plaque that had been hardened with calcium and was thus unable to fully expand *(arrows)*.

Where the Stents Are

This experience suggested that stents might not be able to dilate heavily calcified plaques. But overall in these first 21 people the x ray results were promising. However, before we could explore the question about calcium any further, another query had to be addressed first. Our colleague Donald Lee wondered whether the x-ray evidence of stent expansion really meant that the internal diameter of the artery was opening up. Or could it be that the struts of the stent were insinuating themselves into the atherosclerotic plaque and not really opening up the inside of the artery at all? The plain x rays could not answer this question, because they only showed the stent struts—not the inner pathway of the artery. Thus it was necessary to turn to ultrasound, a noninvasive imaging technique based on high-frequency sound waves, which can provide information regarding the inside of the vessel in the form of both an image and blood flow velocities through the length of the stent. In the carotid artery, a velocity greater than 250 centimeters per second indicates severe artery narrowing (forcing a moving fluid into a narrower opening causes an increase in speed). In people with diseased carotid arteries, a velocity of 400 centimeters per second or more would be quite common. Therefore we decided to carry out ultrasound tests on our first 21 patients to determine whether the artery was indeed opening up inside *(see Figure 9)*.

Our hypothesis remained valid. The plaques were being forced outward, but gently so, under the natural springiness of the self-expanding stent. But this answer prompted more questions about how the stent interacts with the carotid plaque. Although



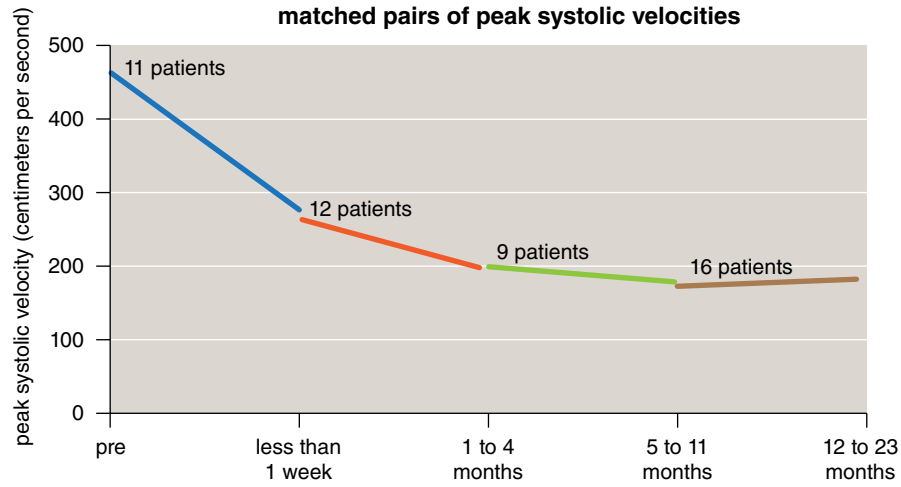


Figure 9. Ultrasound imaging of a stented carotid artery shows the points measured to assess the effect of stents on the carotid artery wall thickness and overall artery diameter *(top)*. The luminal diameter *(inset)* shows the internal size of the artery. Plaque thickness was shown to decrease after stent placement, but overall artery diameter did not change, indicating that the stent had remodeled the plaque but not displaced the normal artery wall. Ultrasound tests on the authors' first 21 patients with self-expanding stents also allowed comparisons of the rate of blood flow within the vessel (peak systolic velocity) before and after stent placement *(bottom)*. Peak systolic velocity above 250 centimeters per second is considered severe. These results showed that the internal diameter of the vessel was indeed being opened by the stent, rather than the stent embedding itself into the plaque.

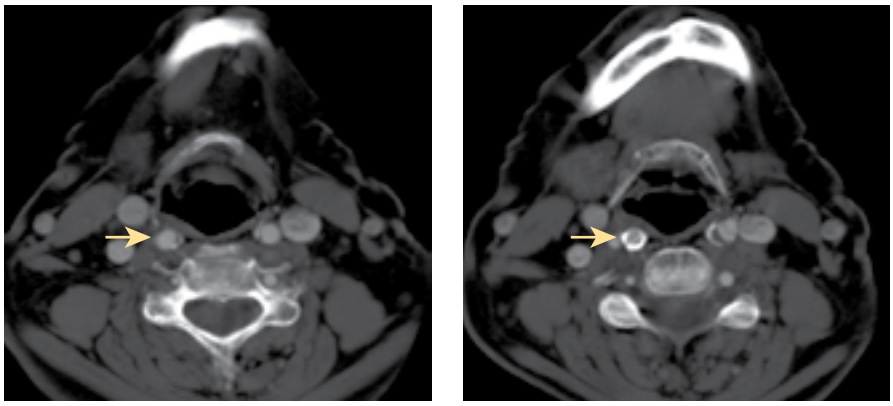


Figure 10. Thinly sliced images from a computed tomography (CT) scan through the carotid arteries are taken at the level of the plaque. On the left image there is no calcium seen in the artery wall *(arrow)*. The right image shows dense white calcium surrounding most of the artery at this level *(arrow)*.

our ultrasound results showed that the artery truly was being opened by the stent rather than it simply embedding itself into the plaque, we still did not know what was happening to the overall size of the carotid artery. Were the stents gradually squeezing or "remodeling" the plaque against the outer arterial wall? Alternatively, was the force of the stent against the plaque also forcing the outer arterial wall outward, leading to a wider overall diameter of the artery? To answer this question we again turned to ultrasound studies. In 30 plaques treated with stents, we performed ultrasound before and after placing stents. We measured the internal diameter of the artery and the thickness of the plaque in front of and behind the stent. The overall artery diameter was also measured *(as shown in Figure 9)*.

As expected, the inside opening increased in size over time due to the self-expanding stent. However, plaque thickness also decreased on both sides of the stent, front and back, so the overall artery diameter did not change. As we had surmised, the stents had remodeled the plaque significantly but had not caused any outward displacement of the normal artery wall.

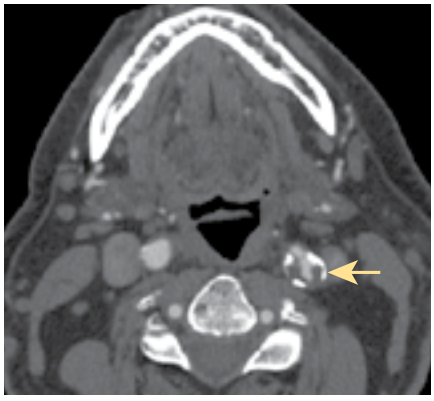


Figure 11. A CT scan slice through carotid artery with plaque shows white flecks of calcium are present *(arrow)* but there are larger, dark areas of "soft" plaque seen adjacent to and beneath the areas of calcium.

Calcium's Impact

We began to wonder how often calcium such as that seen in Emma's plaque might play a role in the stent's ability to expand. Our initial observations were confined to plain x rays taken at the time of treatment. We had no methodological approach to assess plaque calcification. We therefore developed a straightforward classification scheme based on five grades. At the level of the most severe stenosis, we divided the cross-sectional circumference of the artery into four quadrants. Calcium might be observed in none, some or all of these quadrants. We classified a Grade 0 plaque as having no observable calcium. At the opposite extreme, we classified a Grade 4 plaque as having calcium extending continuously through all four quadrants, surrounding the inside wall of the artery like a napkin ring.

In our first 100 cases we found a correlation between the grade of plaque calcium and the ability of the stent to dilate the plaque. Plaques likes Emma's, full of rock-hard calcium, resisted the outward force of the stent.

As imaging technology improved, so did our ability to examine the features of plaque calcium. We turned to thin-slice computed tomography (CT), which provided exquisite detail throughout the length of the plaque on a millimeter-by-millimeter basis *(see Figure 10)*. CT uses x rays but a computer processes them into three-dimensional slices of the body. We classified 75 plaques based on plain x rays and another 102 plaques with CT scanning. We found that if calcium ringed more than 50 percent of the artery, the likelihood of an excellent stent result declined from 75 percent to 38 percent. Calcium did indeed play an important role in stent expansion.

CT scans allowed us to see more details of plaque composition; besides the calcium that appears white, non-calcified plaque shows up as grayish-colored tissue in the scans *(see Figure 11)*. Our previous results had shown that soft plaque could be more easily dilated by a stent's chronic outward force. We incorporated this aspect of the imaging into our plaque classification scheme, based on the presence (Grade A) or absence (Grade B) of soft plaque. We found that in the presence of moderate amounts of soft plaque, the stent showed excellent dilation 63 percent of the time. On the other hand, if soft plaque was absent and calcium ringed at least 50 percent of the artery, only 17 percent had an excellent stent expansion. In hard plaques such as these, balloons might be required, or endarterectomy surgery might be safer than balloons.

Custom Stents

We have learned why stents had varying behavior in different plaques. Calcium is an important determinant, but equally important is the presence of soft plaque. As more becomes known about the properties of carotid plaques, we hope that the results of treatment with a stent in a given individual will be easier to predict. Prior to offering a carotid stent treatment, CT imaging of the plaque is useful. Currently, an individual's age is considered an important factor in whether to recommend surgical plaque removal versus a stent treatment. Stenting is riskier in people over the age of 70. But perhaps as we age, our carotid plaques become more heavily calcified. This situation could increase the risk of stenting, especially if balloons then become necessary, as they are the most dangerous part of the procedure. Is it the individual's age, or the age of their plaque, that is more important? That would be interesting to know.

Finally, for any given carotid plaque, one size of stent may not fit all. The

chronic outward force, responsible for opening up the carotid plaque after a stent has been deployed, is intrinsic to the stent's material and design. A second force associated with self-expanding stents is the *radial resistive force*, which causes a stent to resist compression from the outside environment. Stent designs tend to focus on the radial resistive force rather than on the chronic outward force because engineers design stents to work against compression from the outside environment, such as malignancies in the bile duct. Even when chronic outward force is considered and analyzed in stent design, it tends to be measured after the stent is already 3 millimeters open. Yet most stenosed carotid arteries are narrower than 1.5 millimeters by the time they require treatment. It is tantalizing to think about the design of "plaque-appropriate" stents that could be individually selected based on a plaque's softness and calcification, as well as the remaining diameter of artery through which the stent must safely pass before it is deployed.

Using balloons to make an artery look normal again is probably more important for heart and leg arteries than it is for those going to the brain. Heart and leg muscles are subject to periods of greater physical stress. The brain, with its excellent collateral blood flow, behaves differently. For brain arteries, stents may be all that is necessary to prevent future embolus and stroke. The stent does not have to make the brain artery appear normal again. It simply has to prevent embolic debris from flying up to the brain.

Surgery to remove plaque on the carotid artery remains a very effective strategy to prevent stroke in people who have experienced stroke warning symptoms. But in certain individuals, stents are an effective alternative. We found that through their chronic outward force, stents gently open up most plaques without the added use of balloon inflations. This strategy makes the treatment process simpler and cheaper. We believe it may make it potentially safer as well. Some x-ray features of carotid plaques, including calcium and plaque softness, are highly predictive of the degree to which a stent will open up the artery to near normal again. These features might help guide effective stroke prevention.

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