

Steve Nissen

At ease in the spotlight, cardiologist Steve Nissen has won the trust of many journalists. But his colleagues are still reserving judgment on his celebrated imaging method.

If you work on Wall Street, don't plan on speaking with cardiologist Steve Nissen anytime soon. If you're a journalist, you'd better arrive early to get a good place in line.

On a recent Monday in his office at the Cleveland Clinic, Nissen was being prepped for a television interview. One member of the hospital's communications staff fastened a microphone to Nissen's lapel while a second positioned lights and took his place behind the camera. That day, the embargo was set to lift on a study published in *Circulation* linking the cholesterol drug rosuvastatin (Crestor), the most potent statin on the market, to muscle and kidney damage.

Nissen was not an author on the study, but he spent much of the day commenting on the findings. Thanks to the year-old Cleveland Clinic News Service, journalists can talk to Nissen on speakerphone while staffers tape the interview and transmit the video, edited or uncut, right from the hospital's in-house studio. Nissen even invited *Nature Medicine* to tag along as he examined a patient splayed out on a table for an angiogram.

"I happen to feel very strongly that the public has a right to know more about science, because if the public knows, then people can make informed choices," Nissen says. "So I put some energy into it."

Nissen, who runs the Cleveland Clinic Cardiovascular Coordinating Center, has been forging a visible presence since he moved to Cleveland 13 years ago. Prior to that, he was at the University of Kentucky in Lexington, where he completed his fellowship and later served on the faculty.

Even Nissen's allies readily acknowledge that he loves the limelight. Some critics, while declining to be quoted on the record, take shots at what they call his proclivities for salesmanship and controversy. But all readily acknowledge that he is the primary force behind an imaging technology called intravascular ultrasound (IVUS). The technology allows researchers to see and measure atherosclerosis, the fatty plaque that attaches to the walls of coronary arteries and cannot be detected on an angiogram.

Nissen produced the first images in humans in 1990 and began using IVUS to document the ubiquitous prevalence of coronary artery disease even among teenagers. He then began developing a method to use IVUS in large-scale clinical trials, work he believes could speed the validation of promising new drugs because it requires hundreds of patients over months—rather thousands of patients over years—for a full-scale study.

"Steve saw the importance of studying the pathobiology of atherosclerosis," says Anthony DeMaria, who began mentoring Nissen during his internship at the University of California, Davis.

The approach began to garner big attention when Nissen published two headline-grabbing papers two years ago. In the first, Nissen used IVUS to record a 4% reduction in plaque among 34 heart attack patients given five infusions of Apo-A1 Milano, a variant of the lipoprotein ApoA (*JAMA* **290**, 2292–2300; 2003). The lipoprotein enhanced the ability of HDL, or 'good,' cholesterol to usher fat out of the arteries and into the liver for excretion.

"I actually told my team that I thought the chances of it working was about one in a million—and I really meant it, because it was so radical," he says. The proof-of-concept study raised a host of unanswered questions, but drug giant Pfizer quickly bought Esperion Therapeutics, the tiny company that had produced recombinant Apo-A1 Milano, for \$1.3 billion.

Just 10 days later, at the American Heart Association annual meeting, Nissen presented the so-called reversal trial, a head-to-head comparison

of the statins atorvastatin (Lipitor) and pravastatin (Pravachol) (*JAMA* **291**, 1071–1080; 2004). IVUS images showed that Lipitor had effectively halted the progression of plaque buildup, but coronary disease progressed considerably in those given Pravachol. The study suggested that treatments should aim to lower LDL, or 'bad,' cholesterol levels as much as possible.

"So we showed the benefit of reducing bad cholesterol and raising good cholesterol, and we released both pieces back-to-back," Nissen says. "To have a single laboratory provide you with both pieces of information really put us on the map."

But what's lacking, critics say, is evidence of an air-tight correlation between the IVUS-recorded reductions in plaque, a 'surrogate' outcome, and fewer heart attacks and strokes among patients. "The IVUS exam may not relate to the clinical expression of the disease, and we need more data on that," says DeMaria, who's now at the University of California, San Diego.

Another shortcoming, others say, is that the images' resolution is not sensitive enough to distinguish between fatty and fibrous tissue. Nissen's lab is also one of only a few equipped to interpret the data, making it difficult to get independent confirmation of his findings. "It's like a sole source for a hard scientific point that you need total objectivity for. It makes you nervous," says Larry Rudel, a cholesterol researcher at Wake Forest University who was enlisted to use IVUS on laboratory primates for one of Nissen's studies.

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Already juggling patients, research and teaching, Nissen in March 2006 begins a year's term as president of the American College of Cardiology. "[Nissen] has one of the highest energy levels of any human being on the planet," says his longtime collaborator Peter Libby, chief of cardiovascular medicine at Brigham and Women's Hospital in Boston. "He has a schedule and a workload that would topple many people, yet he's able to thrive."

To elude the many ethical landmines that litter the intersection of science and big business, Nissen says he decided five years ago to stop taking consulting fees. Instead, he directs his clients to donate the fee to charities. "I need a firewall that allows no one to be able to say I have a conflict of interest," he says. "It means giving up a lot of income, but my credibility stems from the belief that when I report something, I don't benefit financially."

Nissen and Eric Topol, the Cleveland Clinic's chief of cardiovascular medicine, found themselves under attack by drug manufacturer Merck four years ago after they raised the first red flag about increased risk of heart attacks among users of the arthritis drugs Vioxx, made by Merck, and Pfizer's Celebrex. "Those companies went after us and it was very uncomfortable," recalls Topol, who later opted out of his consulting deals.

Nissen says he remains on one advisory panel to Merck, but admits some relationships there remain "a little tense." Still, he says, he's sure people understand that his positions are not borne of self-interest. "I'm sure I have enemies because I'm outspoken," he says. "What can I say? But I try to be fair, so be it. I'm willing to take the heat."

Bruce Diamond, Cleveland