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says Ioannidis. "Someone who is independent should do this."

But GSK doesn't think that crunching studies together is in itself the best way to find side-effects. "We don't think meta-analysis is the best way to address this," says GSK spokeswoman Alice Hunt. Clinical trials, she argues, are the only way to achieve a definitive answer. GSK is in the middle of a clinical trial of more than 4,000 patients that is aimed specifically at assessing the cardiovascular effects of Avandia (compared with more than 10,000 patients in Nissen's number crunch). *The Lancet* editorial also recommends waiting for these results — although the news of the new findings has reportedly led to volunteers dropping out of the trial.

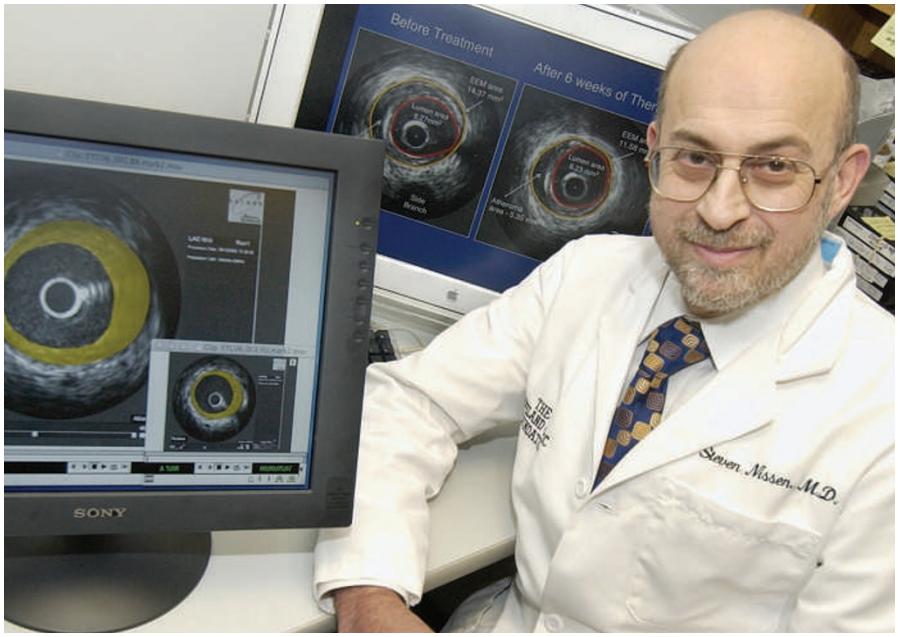
Preliminary results of the trial, scheduled to finish in 2008, have been shared with the FDA, says Hunt. "They could potentially be released, but that's not being looked at, at the moment," she adds.

The FDA will not as yet comment on the ongoing trial, to "preserve the study integrity", but it does have additional data on the drug. Without seeing the results for themselves, some doctors find it hard to know how to judge FDA assurances that the additional data it has do not point to a significant risk of heart attack. "They are unpublished, uncited data that are not available to the public. I've heard the same story before: 'We know there are weapons of mass destruction in Iraq. We can't tell you how we know, but we know'," says Nissen.

For some, even a preliminary analysis is reason enough to avoid the drug, if only because there is an alternative medication — pioglitazone, marketed under the name Actos in the United States — that has not yet been associated with cardiovascular risks. Nissen's analysis was enough to convince Harlan Krumholz, a cardiologist at Yale University: "When you're talking about safety and you're talking about a drug for which there are alternatives, you have to ask yourself, who has the burden of proof here?"

Although Avandia's fate remains unclear, Nissen's study has served to raise the profile of meta-analyses. Roger Chou, a clinician at the Oregon Evidence-based Practice Center in Portland notes that at the moment, independent analyses such as this are done on an ad-hoc basis. "Right now, it's really just when somebody's interested in it, or when there's something that's making people concerned," he says. But there is a growing interest in independent groups monitoring drug safety in this way — and, importantly, signs of increased funding from organizations such as the US Agency for Healthcare Research and Quality to support meta-analyses. ■

Heidi Ledford



A. SANCETTA/AP

Man on a mission

It isn't every clinical scientist who in the space of a month sends a major drug company's stock plummeting, is invited to testify at Congress and is crowned one of the world's 100 most influential people by *Time* magazine. But then, they aren't Steven Nissen, the cardiologist who last week fingered the diabetes drug Avandia as carrying a possible risk of heart attacks (see opposite).

"He will persevere for what he believes is right."

This is not the first or most famous case for Nissen, 58, who is based at the Cleveland Clinic in Ohio. In 2001, while serving on a committee of external advisers to the US Food and Drug Administration (FDA), he raised concerns about the safety of a painkiller called Vioxx. Before then, he had made his name pioneering an ultrasound technique that allowed doctors to see fatty plaques of atherosclerosis (see *Nature Med.* 11, 700; 2005).

Since Vioxx, Nissen says that he has become more concerned about the scientific rigour of drug regulation, prompting him to dig into clinical-trial data that suggest hidden drug risks. "I don't go looking for these things, but they sure seem to find me," he says. Between running trials for several drug companies, he has flagged cardiovascular risks in drugs for everything from attention deficit hyperactivity disorder to heart failure itself, often costing companies millions in the process.

His fans praise him for refusing to pull his punches. "He will persevere for what he believes is right, regardless of the toes on which he may tread," says Peter Libby, chief of cardiology at Brigham and Women's Hospital in Boston, Massachusetts, who has worked with Nissen for twelve years.

But his methods have earned him enemies, too, many of whom contend that he is more interested in felling the next Goliath than in seeking scientific truth. "The caped crusader Nissen is at it again," groused a critic on the *Wall Street Journal's* health blog on 21 May. Bob Temple, director of medical policy at the FDA's drug review centre, has also taken a shot at Nissen. Temple told *RPM Report* that he was "sort of stunned" by Nissen's suggestions to Congress that senior FDA officials had overruled their underlings' safety concerns. "I can tell you, he didn't see that," Temple said.

Nissen certainly isn't always right. Speaking to journalists last October, he put Pfizer's cholesterol drug torcetrapib, for which he was overseeing a clinical trial, at the top of a list of hot stories that reporters should watch in 2007. Weeks later, Pfizer pulled the plug on the drug when it was found to raise death rates in late-stage trials (see *Nature* 444, 794–795; 2006).

"After the torcetrapib business, I thought I would lay low for a while," Nissen said last week. "Then I stumble across this [Avandia] problem and here we are again." ■

Meredith Wadman