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Do Cholesterol Drugs Do Any Good?

Research suggests that, except among high-risk heart patients, the benefits of statins such as Lipitor are overstated

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By John Carey for *BusinessWeek*

Martin Winn's cholesterol level was inching up. Cycling up hills, he felt chest pain that might have been angina. So he and his doctor decided he should be on a cholesterol-lowering medication called a statin. He was in good company. Such drugs are the best-selling medicines in history, used by more than 13 million Americans and an additional 12 million patients around the world, producing $27.8 billion in sales in 2006. Half of that went to Pfizer (PFE) for its leading statin, Lipitor. Statins certainly performed as they should for Winn, dropping his cholesterol level by 20%. "I assumed I'd get a longer life," says the retired machinist in Vancouver, B.C., now 71. But here the story takes a twist. Winn's doctor, James M. Wright, is no ordinary family physician. A professor at the University of British Columbia, he is also director of the government-funded Therapeutics Initiative, whose purpose is to pore over the data on particular drugs and figure out how well they work. Just as Winn started on his treatment, Wright's team was analyzing evidence from years of trials with statins and not liking what it found.

Yes, Wright saw, the drugs can be life-saving in patients who already have suffered heart attacks, somewhat reducing the chances of a recurrence that could lead to an early death. But Wright had a surprise when he looked at the data for the majority of patients, like Winn, who don't have heart disease. He found no benefit in people over the age of 65, no matter how much their cholesterol declines, and no benefit in women of any age. He did see a small reduction in the number of heart attacks for middle-aged men taking statins in clinical trials. But even for these men, there was no overall reduction in total deaths or illnesses requiring hospitalization—despite big reductions in "bad" cholesterol. "Most people are taking something with no chance of benefit and a risk of harm," says Wright. Based on the evidence, and the fact that Winn didn't actually have angina, Wright changed his mind about treating him with statins—and Winn, too, was persuaded. "Because there's no apparent benefit," he says, "I don't take them anymore."

Wait a minute. Americans are bombarded with the message from doctors, companies, and the media that high levels of bad cholesterol are the ticket to an early grave and must be brought down. Statins, the message continues, are the most potent weapons in that struggle. The drugs are thought to be so essential that, according to the official government guidelines from the National Cholesterol Education Program (NCEP), 40 million Americans should be taking them. Some researchers have even suggested—half-jokingly—that the medications should be put in the water supply, like fluoride for teeth. Statins are sold by Merck (MRK) (Mevacor and Zocor), AstraZeneca (AZN) (Crestor), and Bristol-Myers Squibb (BMY) (Pravachol) in addition to Pfizer. And it's almost impossible to avoid reminders from the industry that the drugs are vital. A current TV and newspaper campaign by Pfizer, for instance, stars artificial heart inventor and Lipitor user Dr. Robert Jarvik. The printed ad proclaims that "Lipitor reduces the risk of heart attack by 36%…in patients with multiple risk factors for heart disease."

So how can anyone question the benefits of such a drug?

For one thing, many researchers harbor doubts about the need to drive down cholesterol levels in the first place. Those doubts were strengthened on Jan. 14, when Merck and Schering-Plough (SGP) revealed results of a trial in which one popular cholesterol-lowering drug, a statin, was fortified by another, Zetia, which operates by a different mechanism. The combination did succeed in forcing down patients' cholesterol further than with just the statin alone. But even with two years of treatment, the further reductions brought no health benefit.

Doing the Math

The second crucial point is hiding in plain sight in Pfizer's own Lipitor newspaper ad. The dramatic 36% figure has an asterisk. Read the smaller type. It says: "That means in a large clinical study, 3% of patients taking a sugar pill or placebo had a heart attack compared to 2% of patients taking Lipitor."

Now do some simple math. The numbers in that sentence mean that for every 100 people in the trial, which lasted 3 1/3 years, three people on placebos and two people on Lipitor had heart attacks. The difference credited to the drug? One fewer heart attack per 100 people. So to spare one person a heart attack, 100 people had to take Lipitor for more than three years. The other 99 got no measurable benefit. Or to put it in terms of a little-known but useful statistic, the number needed to treat (or NNT) for one person to benefit is 100.

Compare that with, say, today's standard antibiotic therapy to eradicate ulcer-causing H. pylori stomach bacteria. The NNT is 1.1. Give the drugs to 11 people, and 10 will be cured.

A low NNT is the sort of effective response many patients expect from the drugs they take. When Wright and others explain to patients without prior heart disease that only 1 in 100 is likely to benefit from taking statins for years, most are astonished.

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Many, like Winn, choose to opt out.
Plus, there are reasons to believe the overall benefit for many patients is even less than what the NNT score of 100 suggests. That NNT was determined in an industry-sponsored trial using carefully selected patients with multiple risk factors, which include high blood pressure or smoking. In contrast, the only large clinical trial funded by the government, rather than companies, found no statistically significant benefit at all. And because clinical trials themselves suffer from potential biases, results claiming small benefits are always uncertain, says Dr. Nortin M. Hadler, professor of medicine at the University of North Carolina at Chapel Hill and a longtime drug industry critic. "Anything over an NNT of 50 is worse than a lottery ticket; there may be no winners," he argues. Several recent scientific papers peg the NNT for statins at 250 and up for lower-risk patients, even if they take it for five years or more. "What if you put 250 people in a room and told them they would each pay $1,000 a year for a drug they would have to take every day, that many would get diarrhea and muscle pain, and that 249 would have no benefit? And that they could do just as well by exercising? How many would take that?" asks drug industry critic Dr. Jerome R. Hoffman, professor of clinical medicine at the University of California at Los Angeles.

Drug companies and other statin proponents readily concede that the number needed to treat is high. "As you calculated, the NNT does come out to about 100 for this study," said Pfizer representatives in a written response to questions. But statin promoters have several counterarguments. First, they insist that a high NNT doesn't always mean a drug shouldn't be widely used. After all, if millions of people are taking statins, even the small benefit represented by an NNT over 100 would mean thousands of heart attacks are prevented.

That's a legitimate point, and it raises a tough question about health policy. How much should we spend on preventative steps, such as the use of statins or screening for prostate cancer, that end up benefiting only a small percentage of people? "It's all about whether we think the population is what matters, in which case we should all be on statins, or the individual, in which case we should not be," says Dr. Peter Trewby, consultant physician at Darlington Memorial Hospital in Britain. "What is of great value to the population can be of little benefit to the individual." Think about buying a raffle ticket for a community charity. It's for a good cause, but you are unlikely to win the prize.

Statin proponents also argue that when NNTs are calculated after the drugs have been taken for just three or five years, they're misleadingly high. Pfizer says that even though only one heart attack was prevented per 100 people in its trial, "it may be a possibility that several or even all [100] benefit" by reducing their risk of a future heart attack. And the benefit grows when the drugs are taken for more years, backers believe. "It does not make sense to take a statin for five years," says Dr. Scott M. Grundy, chair of the NCEP committee that called for more aggressive statin treatment and director of the Center for Human Nutrition at the University of Texas Southwestern Medical Center at Dallas. "When you take a cholesterol-lowering drug, it is a huge commitment," he says. "You take it for life." Grundy figures the chances of having a heart attack over the course of a lifetime are about 30% to 50% (higher for men than women). Statins, he argues, reduce that risk by about 30%. As a result, taking the drugs for 30 years or more would bring 9 to 15 fewer heart attacks for every 100 people. So only 7 to 11 people would have to take the drugs for life for one to benefit.

Critics reply that this rosier picture requires several leaps of faith. A 30% reduction in heart attacks "is the best-case scenario and not found in many of the studies," says Wright. What's more, statins have been in use now for 20 years, and there's little evidence yet that the NNT decreases the longer people take the drug. Most important, the statin trials of people without existing heart disease showed no reduction in deaths or serious health events, despite the small drop in heart attacks. "We should tell patients that the reduced cardiovascular risk will be replaced by other serious illnesses," says Dr. John Abramson, clinical instructor at Harvard Medical School and author of Overdosed America.

Lifestyle Changes

In its written response, Pfizer did not challenge this key assertion: that the drugs do not reduce deaths or serious illness in those without heart disease. Instead, the company repeated that statins reduce the "risk of death from coronary events" and added that Wright's analysis was not published in a peer-reviewed scientific journal.

If we knew for sure that a medicine was completely safe and inexpensive, then its widespread use would be a no-brainer, even with a high NNT of 100. But an estimated 10% to 15% of statin users suffer side effects, including muscle pain, cognitive impairments, and sexual dysfunction. And the widespread use of statins comes at the cost of billions of dollars a year, not just for the drugs but also for doctors' visits, cholesterol screening, and other tests. Since health-care dollars are finite, "resources are not going to interventions that might be of benefit," says Dr. Beatrice A. Golomb, associate professor of medicine at the University of California at San Diego School of Medicine.

What would work better? Perhaps urging people to switch to a Mediterranean diet or simply to eat more fish. In several studies, both lifestyle changes brought greater declines in heart attacks than statins, though the trials were too small to be completely persuasive. Being physically fit is also important. "The things that really work are lifestyle, exercise, diet, and weight reduction," says UCLA's Hoffman. "They still have a big NNT, but the cost is much less than drugs and they have benefits for quality of life."

Difficult risk-benefit questions surround most drugs, not just statins. One dirty little secret of modern medicine is that many drugs work only in a minority of people. "There's a tendency to assume drugs work really well, but people would be surprised by the actual magnitude of the benefits," says Dr. Steven Woloshin, associate professor of medicine at Dartmouth Medical School.

A good example: Beta-blockers are seen as essential in treating congestive heart failure. Yet studies show that an average of 24 people must take the drugs for seven months to prevent one hospitalization from heart failure (thus, an NNT of 24). And 40 people

must take it to prevent one death (NNT of 40). "Even for medications we consider effective, we see NNTs in the 20s or higher," says Dr. Henry C. Barry, associate professor of family medicine at Michigan State University College of Human Medicine.

For many other drugs, the NNTs are large. Take Avandia, GlaxoSmithKline's (GSK) drug for preventing the deadly progression of diabetes. The blockbuster, with $2.6 billion in U.S. sales in 2006, made headlines in 2007 when an analysis of clinical trial data showed it increased the risk of heart attacks. The largely untold story: There's little evidence the drug actually helps patients. Yes, Avandia is very good at lowering blood sugar, just as statins lower cholesterol levels. But that doesn't translate into preventing the dire consequences of diabetes, including heart disease, strokes, and kidney failure. Clinical trials "failed to find a significant reduction in cardiovascular events even with excellent glucose control," wrote Dr. Clifford J. Rosen, chair of the Food & Drug Administration committee that evaluated Avandia, in a recent commentary in The New England Journal of Medicine. "Avandia is almost the poster child for everything wrong with our system," says UCLA's Hoffman. "Its NNT is close to infinite."

Regarding Avandia, Dr. Murray Stewart, Glaxo's vice-president for clinical development, says that the evidence of its benefits against heart disease and other major complications of diabetes "is still inconclusive." But the drug has other benefits, he argues, such as delaying the need to take insulin.

When other medications widely believed to be effective were put to the test of a clinical trial, they flunked. Hormone replacement therapy didn't protect against heart disease. Anti-psychotic drugs were actually less effective than a placebo in reducing aggression in patients with intellectual disability.

The truth about drugs' effectiveness wouldn't be as worrisome if consumers and doctors had an accurate picture of the state of knowledge and could make rational decisions about treatments. Studies by Darlington Hospital's Trewby, UBC's Wright, and others, however, show that patients expect far more than what the drugs actually deliver.

Why the mismatch? Some of the blame goes to the way results are presented. A 36% decline in heart attacks sounds more dramatic and important than an NNT of 100. "It comes as a shock to see the NNT," says Dr. Barnett S. Kramer, director of the office of medical applications of research at the National Institutes of Health. Drug companies take full advantage of this; they advertise the big percentage drops in, say, heart attacks, while obscuring the NNT. But when it comes to side effects, they flip-flop the message, dismissing concerns by saying only 1 in 100 people suffers a side effect, even if that represents a 50% increase. "Many physicians don't know the NNT," says Dr. Darshak Sanghavi, a pediatric cardiologist and assistant professor of pediatrics at the University of Massachusetts Medical School and a fan of using NNTs.
The whole statin story is a classic case of good drugs pushed too far, argues Dr. Howard Brody, professor of family medicine at the University of Texas Medical Branch at Galveston. The drug business is, after all, a business. Companies are supposed to boost sales and returns to shareholders. The problem they face, though, is that many drugs are most effective in relatively small subgroups of sufferers. With statins, these are the patients who already have heart disease. But that's not a blockbuster market. So companies have every incentive to market their drugs as being essential for wider groups of people, for whom the benefits are, by definition, smaller. "What the shrewd marketing people at Pfizer and the other companies did was spin it to make everyone with high cholesterol think they really need to reduce it," says Dr. Bryan A. Liang, director of the Institute of Health Law Studies at the California Western School of Law and co-director of the San Diego Center for Patient Safety. "It was pseudoscience, never telling you the bottom-line truth, [which is] that the drugs don't help unless you have pre-existing cardiovascular disease." The marketing worked, Liang says, "even in the face of studies and people screaming and yelling, myself included, that it is not based on evidence."

Pfizer replies that the industry is "highly regulated" and that every message in ads and marketing "accurately reflects Lipitor's labeling and the data from the clinical trials."

Drugmakers, however, do make sure that the researchers and doctors who extol the benefits of medications are well compensated. "It's almost impossible to find someone who believes strongly in statins who does not get a lot of money from industry," says Dr. Rodney A. Hayward, professor of internal medicine at the University of Michigan Medical School. The NCEP's 2004 guideline update garnered headlines by recommending lower targets for bad cholesterol, which would put more Americans on the drugs. But there was also a heated controversy in the medical community over the fact that 8 of the 9 experts on the panel had financial ties to industry. "The guideline process went awry," says Michigan State's Barry. He and 34 other experts sent a petition of protest to the National Institutes of Health, saying the evidence was weak and the panel members were biased by their ties to companies.

Easy Metrics

The appearance of conflict of interest is "very important to organizations like ours, and we are all taking it seriously," responds NIH official and NCEP coordinator Dr. James I. Cleeman. "But the facts of the science were entirely correct."

Yet Cleeman's confidence is not universally shared. To statin critics, Americans have come to rely too much on easy-to-grasp health markers. People like to have a metric, such as cholesterol levels, that can be monitored and altered. "Once you tell people a number, they will be fixated on the number and try to get it better," says University of Texas' Brody. Moreover, "the American cultural norm is that doing something makes us feel better than just watching and waiting," says Barry. That applies to doctors as well. They are being pushed by the national guidelines, by patients' own requests, and by pay-for- performance rules that reward physicians for checking and reducing cholesterol. "I bought into it," Brody says. Not to do so is almost impossible, he adds. "If a physician suggested not checking a cholesterol level, many patients would stomp out of the office claiming the guy was a quack."

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Yet Brody changed his mind. "I now see it as myth that everyone should have their cholesterol checked," he says. "In hindsight it was obvious. Why didn't I see it before?"

Cholesterol is just one of the risk factors for coronary disease. Dr. Ronald M. Krauss, director of atherosclerosis research at the Oakland Research Institute, explains that higher LDL levels do help set the stage for heart disease by contributing to the build-up of plaque in arteries. But something else has to happen before people get heart disease. "When you look at patients with heart disease, their cholesterol levels are not that [much] higher than those without heart disease," he says. Compare countries, for example. Spaniards have LDL levels similar to Americans', but less than half the rate of heart disease. The Swiss have even higher cholesterol levels, but their rates of heart disease are also lower. Australian aborigines have low cholesterol but high rates of heart disease.

Moreover, says MSU's Barry, cholesterol-lowering medications other than statins "do not prevent heart attacks or strokes." Take Zetia, which blocks absorption of cholesterol from the intestines. Marketed by Merck and Schering-Plough, the drug brought in $1.5 billion in 2006, with sales climbing 25% in the first half of 2007, says IMS Health (RX). The companies combined it with a statin to create a drug called Vytorin, with over $2 billion in sales in 2007.

In an eagerly awaited trial completed in 2006, the companies compared Zetia plus a statin with a statin alone in patients with genetically high cholesterol. But the drugmakers delayed announcing the results, prompting scientific outrage and the threat of a congressional investigation. The results, finally revealed on Jan. 14, showed the combination of Zetia and a statin reduced LDL levels more than the statin alone. But that didn't bring added benefits. In fact, the patients' arteries thickened more when taking the combination than with the statin alone. Skip Irvine, a spokesman for the joint venture, says the study was small and insists there's a "strong relationship between lowering LDL cholesterol and reducing cardiovascular death."

Irrelevant LDL?

If cholesterol lowering itself isn't a panacea, why is it that statins do work for people with existing heart disease? In his laboratory at the Vascular Medicine unit of Brigham & Women's Hospital in Cambridge, Mass., Dr. James K. Liao began pondering this question more than a decade ago. The answer, he suspected, was that statins have other biological effects.

Since then, Liao and his team have proved this theory. First, a bit of biochemistry. Statin drugs work by bollixing up the production of a substance that gets turned into cholesterol in the liver, thus reducing levels in the blood. But the same substance turns out to be a building block for other key chemicals as well. Think of a toy factory in which the same plastic is fashioned into toy cars, trucks, and trains. Reducing production of the plastic cuts not only the output of toy cars (cholesterol) but also trucks and trains. In the body, these additional products are signaling molecules that tell genes to turn on or off, causing both side effects and benefits.

Liao has charted some of these biochemical pathways. His recent work shows that one of the trucks, as it were—a molecule called Rho-kinase—is key. By reducing the amount of this enzyme, statins dial back damaging inflammation in arteries. When Liao knocks down the level of Rho-kinase in rats, they don't get heart disease. "Cholesterol lowering is not the reason for the benefit of statins," he concludes.

The work also offers a possible explanation of why that benefit is mainly seen in people with existing heart disease and not in those who only have elevated cholesterol. Being relatively healthy, their Rho-kinase levels are normal, so there is little inflammation. But when people smoke or get high blood pressure, their Rho-kinase levels rise. Statins would return those levels closer to normal, counteracting the bad stuff.

Add it all together, and "current evidence supports ignoring LDL cholesterol altogether," says the University of Michigan's Hayward. In a country where cholesterol lowering is usually seen as a matter of life and death, these are fighting words. A prominent heart disease physician and statin booster fumed at a recent meeting that "Hayward should be held accountable in a court of law for doing things to kill people," Hayward recounts. NECP's Cleeman adds that, in his view, the evidence against Hayward is overwhelming.

But while the new analyses may rile those who have built careers around the need to reduce LDL, they also point the way to using statins more effectively. Surprisingly, both sides in the debate agree on the general approach. For anyone worried about heart disease, the first step should always be a better diet and increased physical activity. Do that, and "we would cut the number of people at risk so dramatically" that far fewer drugs would be needed, says Krauss. For those people who still might benefit from treatment, a recent analysis by Hayward shows that statins might better be prescribed based on patients' risk of heart disease, not on their LDL cholesterol levels. The higher the risk, the better the drugs seem to work. "If two patients have the same risk, the evidence says they get the same benefit from statins, whatever their LDL levels," Hayward says.

Ways to fine-tune this approach may be coming soon. The company that first sequenced the human genome, Celera Group (CRA), has found a genetic variation that predicts who benefits from the drugs. Perhaps 60% of the population has it, says Dr. John Sninsky, vice-president of discovery research, and for everyone else, the NNT is sky-high. "It does not relate at all to your cholesterol level," Sninsky adds.

If the drugs were used more rationally, drugmakers would take a hit. But the nation's health and pocketbook might be better off. Could it happen? Will data on NNTs, the weak link to cholesterol, and knowledge of genetic variations change what doctors do and what patients believe? Not until the country changes the incentives in health care, says UCLA's Hoffman. "The way our health-care system runs, it is not based on data, it is based on what makes money."