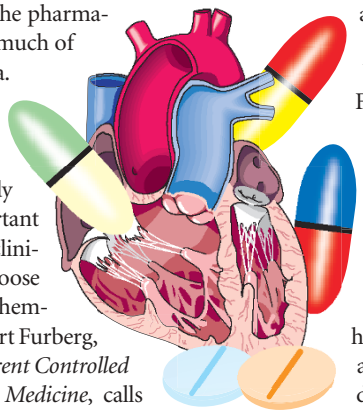
Despite hype, not all statins are the same, experts say

Statins do more than prevent heart attacks—that much is clear. But scientists are just beginning to unravel the drugs' panoply of effects.

In the decade since clinical data confirmed that the drugs could prevent heart attacks in patients with coronary artery disease, they have achieved the status of blockbuster drugs. Now, as a third generation of 'superstatins' come on line, it is increasingly clear that all statins are not the same. They differ in their efficacy and produce a range of effects—both good and bad—beyond cholesterol reduction.

With six different drugs vying for shares of a $20 billion market, the pharmaceutical industry has set much of the statin research agenda. Scientists have been busy comparing the drugs using an array of doses, endpoints and study populations. Still, important questions linger, and clinicians trying to choose between statins find themselves faced with what Curt Furberg, editor of the journal *Current Controlled Trials in Cardiovascular Medicine*, calls the "industry paradox."



"If one member of a class is effective, they say they are all effective," says Furberg, professor of public health sciences at Wake Forest University Baptist Medical Center in North Carolina. "If one member of a class has a bad effect, they will say that they are all different."

Topping the list of ill effects is rhabdomyolysis, a potentially fatal form of muscle toxicity that seems to occur more frequently with the newer, more powerful, drugs. More than 30 fatal cases led Bayer to pull its cerivastatin from the market in 2001, and the US watchdog group Public Citizen wants the Food and Drug Administration to do the same for rosuvastatin. In a searing editorial, *The Lancet* charged AstraZeneca with rushing its rosuvastatin to market without adequate safety or efficacy data (*Lancet* **362**, 1341; 2003). Several insurers refuse to cover the drug, and sales, while robust, have not been as high as predicted.

David Waters of the University of California in San Francisco advocates the aggressive use of statins in high-risk patients, noting that the benefits outweigh the slim possibility of an adverse effect. "Millions of patients have taken statins for longer than a decade now, and the older ones have turned out to be remarkably safe," he says. Still, Waters does not prescribe rosuvastatin.

Statins have also been linked to a range of unexpected health benefits, many of them bolstering the concept of inflammation as a bad player. Scientists are examining the drugs' usefulness in treating multiple sclerosis, some cancers, osteoporosis, Alzheimer disease and memory loss. Meanwhile, a study at the University of California in San Diego is investigating possible links between statins and problems with aggression and memory loss.

Based on statins' ability to lower C-reactive proteins (CRP), Paul Ridker at Brigham and Women's Hospital in Boston is evaluating the role of CRP in heart disease. Statins reduce cardiac mortality in patients regardless of baseline cholesterol levels, suggesting that the drugs' benefit may be due to another mechanism.

"Are we misreading the biology of how these drugs work?" Ridker asks. "If the biology is giving us a signal, let's answer the question."

The JUPITER trial, designed by Ridker and funded by AstraZeneca, will test whether rosuvastatin reduces mortality in healthy patients with normal cholesterol and high CRP levels. It will also supply the safety data many doctors want to see before they consider using the drug.

The demand for superstatins could surge if studies confirm that reducing cholesterol to levels lower than currently recommended can save lives. Three ongoing trials with different doses of the same statin could also help reveal whether the dose—rather than the specific drug—determines how statins work.

A panel of cardiologists, including Ridker and Waters, recently gathered in New Orleans and examined the known differences in the statins. All statins exhibit the same broad pharmacological effects. "Nevertheless, important differences exist," the group wrote in their March report. "For this reason, it is incorrect to view all statins as being interchangeable."

Tinker Ready, Boston

Europe urged to step up applied cardiovascular research

Cardiovascular research in Europe urgently needs funds for continent-wide applied research projects, more than 100 researchers argued at a conference in Brussels in March.

According to John Martin, a researcher at University College London and the European Society of Cardiology's chief liaison to the European Union (EU), the conference's main purpose was to lobby for funds from Europe's Seventh Framework Programme, set to distribute up to €30 billion between 2006 and 2010.

Early ideas for the program have suggested focusing on basic, rather than applied, research, as the former is expected to benefit many diseases. But favoring such 'horizontal' funding over a 'vertical' approach would not sufficiently benefit the fight against cardiovascular disease, Martin said.

Despite declining mortality rates in western and northern countries, cardiovascular disease is Europe's top killer. What's more, said Daiva Rastenyte of Lithuania's Kaunas University, death rates in eastern and central Europe are on the rise.

EU money is needed for large-scale clinical studies not carried out by pharmaceutical companies, said Silvia Priori of the Salvatore Maugeri Foundation. Priori noted that several questions remain over the safety and efficacy of drugs in distinct European populations, women and elderly patients. She also pleaded for surveys of clinical practice across Europe, as notions on optimal therapies vary wildly among countries.

It is not yet clear how the European Commission (EC) plans to respond. Because EU money accounts for just 6% of all European public research funds, the commission's health director, Octavi Quintana Trias, said he would hesitate to divide it into smaller chunks earmarked for many diseases. In principle, he said, the commission tends toward a horizontal approach. But, "we will still need some special attention for diseases that represent a major burden."

The first EC proposal on the Seventh Framework Programme is expected to be published in May.

Peter Vermij, Brussels