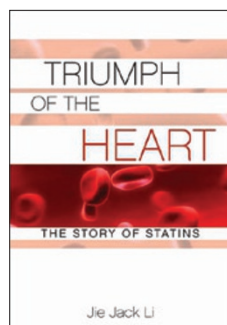


The heart of drug discovery



Triumph of the Heart

Jie Jack Li

Oxford University Press, 2009

224 pp., hardcover, \$29.95

ISBN: 0195323572

Reviewed by Edward A Fisher

Statins are cholesterol-lowering drugs that are the most prescribed class of drugs in the US. *Triumph of the Heart* is a part-science, part-human-interest summary of the development of statins, as well as an appreciation of their incredible financial success. Given the widespread use of statins, the various trade names through the years are familiar to many and include Mevacor, Lescol, Pravacol, Zocor, Crestor, and Lipitor—by far, the most profitable legal drug in history. These drugs collectively represent the most effective agents yet developed to lower low-density lipoprotein (LDL) cholesterol, a major risk factor for coronary artery disease (CAD) and its dreaded consequence, heart attack.

Statins are probably responsible for preventing hundreds of thousands of heart attacks in the US alone. Thus, as Li rightly asserts, the impact of statins on preventive cardiology is undeniable. Yet his title may be a bit overblown, considering Li's admission that statins "reduce the risk of dying from heart disease only 30% or so." In other words, as preventive cardiologists have long known, the majority of people on statins will still have a heart attack. This stark fact blunted the initial hope that CAD would be almost eliminated after the discovery of statins by Akiko Endo and after the brilliant scientific studies of the LDL receptor, including its regulation by statins, conducted by Michael Brown and Joseph Goldstein.

Although we now know that part of the ineffectiveness of statin treatment is due to the relatively low potency of the early drugs, even in the most aggressive, more recent trials there is still an unacceptably high remaining risk in the treated group. As Li points out, this drives both academic and pharmaceutical investigators to discover more of the basic science underlying CAD and identify new targets to halt its progression and even induce regression. Li reviews some of the work on other therapies that have the potential to chip away at the residual risk, particularly those oriented toward the so-called carrier of the 'good' cholesterol, high-density lipoprotein. Although this material will be informative to many readers, especially those not in the field, it is a bit lipid-centric—even to me, a long-term lipid cheerleader!

Reviewed by Edward A. Fisher, Leon H. Charney Professor of Cardiovascular Medicine, Director of the Vascular Biology Research Program and of the Preventive Cardiology Center, New York University School of Medicine, New York, New York, USA.

e-mail: Edward.Fisher@nyumc.org

Li briefly hints at a number of nonlipid factors remaining to be explored in terms of their impact on CAD, including their therapeutic potential. It would have been valuable to have expanded on more of the new directions. For example, it is not until late in the book that he notes that part of the efficacy of statins may include anti-inflammatory effects on the heart attack-causing plaques in the coronary arteries. Inflammation, or, more precisely, the failure to resolve it in plaques, is an active area of research, with myriad discovery programs in the pharmaceutical industry in various stages of translation to clinical use. The emerging and yet-to-be-identified compounds are intended to directly target inflammatory pathways in plaques with a potency greater than that of statins in reducing CAD risk.

Given that Li has been a medicinal chemist in a pharmaceutical company, he is best at describing the structure-function relationships between compounds and their targets and how they can be exploited by stereochemical and chemical modifications. Another strength of the book is the 'fly-on-the-wall' view we get of the often rough-and-tumble road to US Food and Drug Administration (FDA) approval and the subsequent marketing of a drug. The story of the persistence of Bruce Roth and Roger Newton and their close colleagues at Parke-Davis in the discovery and preclinical testing of atorvastatin (Lipitor) is a highlight of the book. Using Lipitor as an example, Li goes into engrossing detail about the gauntlet of daunting steps, each of which must be successful before a drug can go to market—the discovery process, the ability to scale up synthesis in a cost-effective manner, the required results at the preclinical level needed to go forward to clinical testing, and the efficacy and safety trials in humans required to garner FDA approval. In addition to reviewing the objective criteria used to evaluate progress at the various steps of development, Li does an excellent job in describing the more subjective influences by people along the way and even beyond to the marketing phase of the drug—the arguments, lobbying and politicking.

Although the book is short, parts of it do drag. In particular, the detailed descriptions of other drugs made by the statin companies were too long. I realize that Li wanted to give historical and contemporaneous contexts to the development of statins, but I found some of these stretches distracting or boring. Also, some of the language in the sections on compound synthesis sometimes veered toward overly technical descriptions, not optimal for a book intended for a mixed audience, presumably including the lay public. There were some inconsistencies in the evaluation of the financial success of a drug—for example, on one page a billion-dollar-a-year drug is a blockbuster, but on another page, it is a disappointment.

Overall, I found this to be a useful narrative, but did not find it as "fascinating" or "riveting" as the distinguished endorsers on the back cover did. Nor do I think that this is the "first time the fascinating story of statins" is told, as claimed on the fly leaf. In fairness, my limited enthusiasm may be partly related to my general familiarity with much of the material because of my professional work, but the weaknesses described above certainly contributed.

COMPETING FINANCIAL INTERESTS

The author declares competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturemedicine/>.