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**The Success Story of LDL Cholesterol Lowering**  
From Lipids to Inflammation: New Approaches to Reducing Atherosclerotic Risk  
Imaging Atherosclerosis

*Peter Libby, Karin E. Bornfeldt, and Alan R. Tall, Editors*

## The Success Story of LDL Cholesterol Lowering

Terje R. Pedersen

**Abstract:** We can look back at >100 years of cholesterol research that has brought medicine to a stage where people at risk of severe or fatal coronary heart disease have a much better prognosis than before. This progress has not come about without resistance. Perhaps one of the most debated topics in medicine, the cholesterol controversy, could only be brought to rest through the development of new clinical research methods that were capable of taking advantage of the amazing achievements in basic and pharmacological science after the second World War. It was only after understanding the biochemistry and physiology of cholesterol synthesis, transport and clearance from the blood that medicine could take advantage of drugs and diets to reduce the risk of atherosclerotic diseases. This review points to the highlights of the history of low-density lipoprotein-cholesterol lowering, with the discovery of the low-density lipoprotein receptor and its physiology and not only the development of statins as the stellar moments but also the development of clinical trial methodology as an effective tool to provide scientifically convincing evidence. (*Circ Res.* 2016;118:721-731. DOI: 10.1161/CIRCRESAHA.115.306297.)

**Key Words:** atherosclerosis ■ cholesterol, LDL ■ coronary artery disease ■ primary prevention  
■ secondary prevention

During the past 3 decades, we have witnessed an impressive development in the battle against atherosclerotic diseases with the use of new medications that seem to retard or even halt the progression of the atherosclerotic process with a resulting improvement in health and longevity for millions

of individuals. This remarkable progress in medicine did not happen without controversies. The question of whether reduction of cholesterol levels in the blood would be helpful for people in general and for patients, in particular, remained one of the most controversial questions during much of the 20th

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From the Oslo University Hospital, Ullevål, Center For Preventive Medicine and University of Oslo, Institute for Clinical Medicine, Oslo, Norway.

Correspondence to Terje R. Pedersen, MD, PhD, Oslo University Hospital, Ullevål, Bldg 19, Kirkeveien 166, NO-0450 Oslo, Norway. E-mail t.r.pedersen@medisin.uio.no

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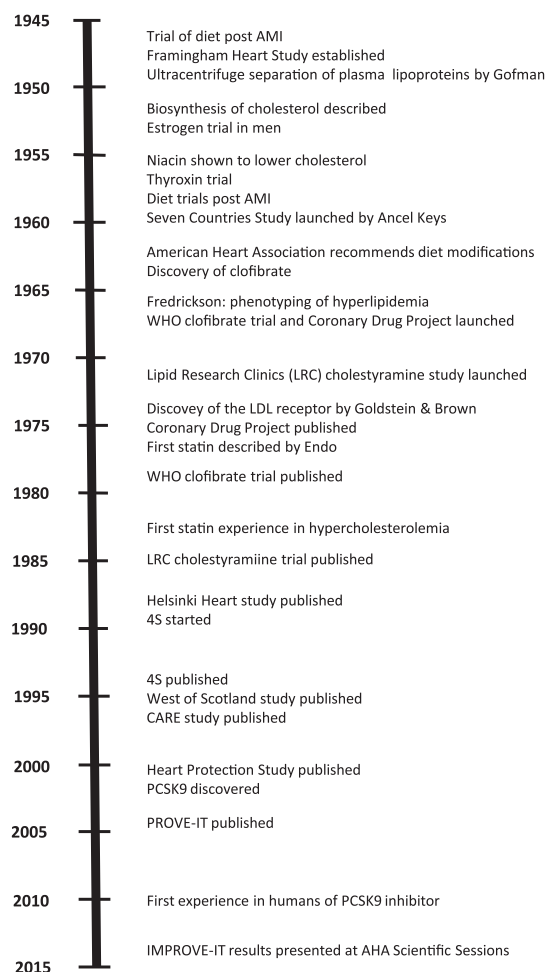
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**Nonstandard Abbreviations and Acronyms**

<b>4S</b>	Scandinavian Simvastatin Survival Study
<b>CDP</b>	Coronary Drug Project
<b>CHD</b>	coronary heart disease
<b>HMG-CoA</b>	$\beta$ -hydroxy- $\beta$ -methyl glutaryl-CoA
<b>LDL</b>	low-density lipoprotein

century. Looking back in the history of cholesterol research and development of medical sciences, many remarkable incidents, debates, failures, and successes deserve further interest.

It is now 170 years since Vogel demonstrated that cholesterol was present in arterial plaques, but the modern story of cholesterol as a contributor to the formation of arteriosclerosis started in 1913 with the publication of the finding of Antischkow in St. Petersburg that feeding of rabbits with cholesterol caused atherosclerosis.<sup>1,2</sup> This discovery was soon afterward confirmed by C.H. Bailey in San Francisco,<sup>3</sup> and the same year that Anitschkow published his experiments with rabbits; Bacmeister and Henes,<sup>4</sup> using new methods of analysis, demonstrated that elevated blood levels of cholesterol were associated with certain diseases, such as atherosclerosis, diabetes mellitus, and chronic kidney disease. According to the pathologist William Dock, there was general acceptance in the medical field in the beginning of the 1920s that lipid-rich intimal lesions that caused arterial obstruction were because of infiltration of plasma lipids and could be caused by hyperlipidemia because of diet.<sup>5</sup> But soon the pathologists came in doubt about this theory as they were unable to reproduce Anitschkows findings in rats and dogs, the most commonly used animals in medical research. Leary<sup>6</sup> summarized the skepticism in a review in *JAMA* in 1935 that pathologists in general did not think that the rabbit was a suitable animal for atherosclerosis research, that the early results were explained by the use of perverted diets, and that the lesions in rabbits did not correspond to the lesions of human atherosclerosis. Leary<sup>6</sup> thought that atherosclerosis was a metabolic disease, but mistakenly also thought that high blood cholesterol levels was the result of overdosing of cholesterol in the diet, reflecting the general belief that the human body was unable to synthesize cholesterol. The issue grew to one of the major controversies in modern medical history, and it was not until after World War II that new interest in the cholesterol and diet/fat hypothesis rose among clinicians (Figure). During the 1940s Konrad Bloch and Feodor Lynen revealed the mechanism of synthesis and regulation of cholesterol and fatty acid in the body (for which they received the Nobel Prize). William Dock wrote an editorial in *JAMA* in 1946 where he concluded that “The familial incidence of coronary disease, undoubtedly related in part to inherited peculiarities of cholesterol metabolism, to dietary habits or to tendency to hypertension...”<sup>7</sup> Still, the question of atherosclerosis developing from dietary habits remained highly controversial. One reason for this was that a large proportion of individuals developing atherosclerotic disease had blood cholesterol levels in the normal range. Second, a majority of subjects that in experiments were given diets with added cholesterol had no or only modest increase in their blood cholesterol levels.



**Figure. Important milestones in the post World War II history of cholesterol research.** 4S indicates Scandinavian Simvastatin Survival Study; AHA, American Heart Association; AMI, acute myocardial infarction; CARE, The Cholesterol and Recurrent Events Trial; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL, low-density lipoprotein; LRC, lipid research clinics; PCSK9, proprotein convertase subtilisin/kexin type 9; and PROVE IT, The Pravastatin or Atorvastatin Evaluation and Infection Therapy.

## Diet Trials

The first clinical trial with diet was performed by Morrison who from 1946 alternately allocated 100 consecutive patients with recent acute myocardial infarction to a low fat, low cholesterol diet, or the usual American diet with normal intake of cholesterol and fat and followed up them for 3 years.<sup>8</sup> Of the 50 patients allocated to low fat to low cholesterol diet, 7 died, whereas of the 50 allocated to normal diet, 15 died. In this pre-randomized controlled trial era, this finding was highly publicized and inspired many clinicians in the Western World to introduce similar programs. A dozen controlled clinical trials of dietary interventions after myocardial infarction were published in the subsequent 15 years, most of them including <300 subjects, and the number of events was too small to show statistically significant benefit of the cholesterol-lowering diets. One of largest was a randomized controlled trial by Leren,<sup>9</sup> who included 412 men 1 to 2 years after a first myocardial infarction. After the first 5 years of follow-up, the group who received

advice of a diet low in animal fats and rich in vegetable oil had a mean serum cholesterol level that was 29% reduced when compared with the group allocated to the usual diet. There was a statistically significant lower incidence of major coronary heart disease (CHD) relapses in the diet group, but mortality was not significantly reduced. After a further 5 to 6 years of follow-up, significantly lower myocardial infarction mortality was demonstrated in the diet group but neither the total mortality nor the total number of fatal myocardial infarction and sudden death were significantly reduced.<sup>10</sup> A Finnish study was performed in 2 mental hospitals that alternately were allocated to a cholesterol-lowering diet or normal diet.<sup>11</sup> In this study, a reduced mortality from CHD was observed while the hospitals were using a cholesterol-lowering diet, but all-cause mortality was not significantly affected. After the series of dietary trials with either disappointing or only borderline convincing results, a review report in the *New England Journal of Medicine* in 1977 brought fuel to the fire with the title Diet-Heart: End of an Era by Mann.<sup>12</sup> In this report, the author ridiculed that attempts to reduce the risk of CHD through a cholesterol-lowering diet were futile and contended that such diet might even increase the risk of cancer. This allegation was based on meta-analysis of 5 dietary trials (among them Leren's) where results from 1 trial indicated a slightly higher incidence in the diet groups although not statistically significantly so.<sup>13</sup> According to Leren,<sup>9</sup> his letter of response to the Editor was 1 of only 7 to be published in the *New England Journal of Medicine*, but the journal allegedly received >1500 responses.

### Early Drug Trials

Since it was an acknowledged fact that CHD was much less prevalent in women than in men, trials of estrogen administration to men at high risk of CHD were initiated already in the early 1950s.<sup>14–16</sup> Two of the trials were small and showed no clinical benefit from the reduced serum cholesterol levels obtained. The largest trial included 275 men with previous myocardial infarction randomly allocated to either placebo or mixed conjugated equine estrogens. Five-year follow-up of patients revealed reduced mortality from all causes in the estrogen group, but increased early mortality in the subgroup starting on a high dose. Another hormone, dextrothyroxine, was tested in a small trial with 38 men with previous myocardial infarction and was found to have a moderate cholesterol-lowering effect.<sup>17</sup> Results from these trials in the early stages of modern drug development were not convincing to the medical community. In the field of preventive cardiology, it was only after the drug clofibrate became available that clinical trial methodology made a substantial step forward.<sup>18</sup> In the United States, a large clinical trial was established through a grant from the National Institute of Health in the United States in 1965 and the first patient entered the trial in 1966.<sup>19</sup> The Coronary Drug Project (CDP) was a nationwide collaborative clinical trial in men with previous myocardial infarction and was set up to evaluate the preventive effect of not only clofibrate but also other drugs that were in the focus for potential effects on prognosis. For the first time in cardiology, a proper sample size calculation was performed with the estimate of a 5-year mortality rate in the placebo group of 30%, all-cause

mortality being the primary end point. The size of each treatment group was calculated to give a 95% power to detect a 25% relative risk reduction in comparison with placebo. The placebo group was 2.5 times larger than any of the treatment groups to minimize the variance of observed differences in mortality rates. Also, to allow for a 5-year 30% dropout rate, the total sample size was calculated to be 8379 patients with 2793 in the placebo group and 1117 in each of the 5 drug groups. Apart from clofibrate, these were mixed conjugated estrogen at 2 dosage levels, 2.5 and 5.0 mg/day, dextrothyroxine and nicotinic acid. The first patient entered the study in March 1966 and enrolment at 53 clinical centers was complete in October 1969. In May 1970, an excess number of nonfatal myocardial infarction and other thromboembolic events was detected in the group receiving estrogen 5 mg daily.<sup>20</sup> It was therefore decided to discontinue this regimen when average follow-up was 18 months. At the same time, a subgroup of patients in the dextrothyroxine-treated patients, those with frequent ventricular ectopic beats, experienced higher sudden death rate than the placebo subgroup, and the regimen was also discontinued in this subgroup. After an average of 36-month follow-up, a decision was made to discontinue treatment in the entire group receiving dextrothyroxine because of a significantly higher mortality rate than the placebo group.<sup>21</sup> Finally, in February 1973, after an average follow-up of 56 months, it was decided to discontinue medication in the estrogen 2.5-mg group also because of a trend toward a higher mortality than the placebo group.<sup>22</sup> In 1974, the remains of the CDP were concluded, and when reported in January 1975, it was clear that neither clofibrate nor niacin had any significant effect on the primary end point all-cause mortality.<sup>23</sup> Clofibrate produced an average reduction in total cholesterol of 6.5% from baseline and a 22.3% reduction in triglyceride, whereas niacin treatment resulted in a 9.9% decrease in cholesterol and 26.1% decrease in triglyceride. The niacin group experienced a nominally significant 26% relative risk reduction in nonfatal myocardial infarction.

Shortly before the CDP was recruiting its patients, 2 other trials with clofibrate were initiated in the United Kingdom. The Newcastle trial included 497 patients with various forms of ischemic heart disease that were randomized to placebo or clofibrate and followed up ≤5 years.<sup>24</sup> The other trial conducted in Scotland randomized 717 patients with ischemic heart disease (myocardial infarction, angina, or both) to placebo or clofibrate treatment for 6 years.<sup>25</sup> The results of both trials were published in the same issue of the *British Medical Journal* in 1971. The authors were puzzled by an apparent differential effect among patients with myocardial infarction and those with angina pectoris. In the Newcastle trial, there was a statistically significant reduction in mortality in the clofibrate group when compared with the placebo group, but this was not evident in the Scottish trial.<sup>26</sup> However, in both trials, there was benefit of clofibrate when examining the subgroups of patients with angina and excluding patients with myocardial infarction only. In retrospect, it is clear that the trials were statistically underpowered to allow for such overinterpretation of the details. In the final report of the CDP, the findings of the Scottish trials were reviewed.<sup>23</sup> When combining the result of

the 2 UK trials with exclusion of women, patients receiving anticoagulants and patients without myocardial infarction at entry there were similar rates of death and nonfatal myocardial infarction in the placebo and clofibrate groups. The results of the 2 trials were dismissed by the CDP authors as results that simply were not confirmed by the CDP.

### The World Health Organization Clofibrate/Cholesterol Trial

The lead investigator of the Scottish trial, Oliver<sup>27</sup> realized that a larger trial would be necessary to provide convincing evidence for the beneficial effects of clofibrate in primary prevention, and in 1965, he organized a large clinical trial: the World Health Organization clofibrate trial. The results of this trial should turn out to have profound importance for the cholesterol controversy in the ensuing decades. Participants were healthy men, 30 to 59 years of age recruited in Edinburgh, Budapest, and Prague on the basis of serum total cholesterol levels. After screening 30 000 volunteers, the primary study group were  $\approx 10\,000$  individuals with cholesterol levels in the upper third of the distribution who were randomly selected for treatment with either clofibrate or placebo (similar capsules as clofibrate, but containing olive oil). A further 5000 men from the lower third of the cholesterol distribution were selected to act as a reference group. Clofibrate produced a mean reduction in total cholesterol of 9%. The study was closed down between the summer of 1975 and 1976, and published in the *British Medical Journal* in 1978.<sup>28</sup> The incidence of ischemic heart disease was reduced by 20% in the clofibrate group when compared with the high cholesterol placebo group which was statistically significant, but this effect was confined to nonfatal myocardial infarction. There was no effect of treatment on fatal myocardial infarctions. Furthermore, there was a statistically significant increase in all-cause mortality in the clofibrate group, mostly because of neoplasms and other non-vascular causes. The experience with the WHO clofibrate trial converted Professor Oliver<sup>29–32</sup> into the leading skeptic toward cholesterol lowering as reflected by numerous editorials and letters to editors in leading medical journals.

### Further Clinical Trials

As the WHO clofibrate trial was ongoing, several new clinical trials were initiated, using various cholesterol-reducing methods. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was initiated in 1973 after an initiative of a task force on arteriosclerosis recommended to the US National Heart and Lung Institute to develop a program to assess the impact of cholesterol lowering on CHD.<sup>33</sup> It was decided to use cholestyramine resin, developed in the 1950s and 1960s,<sup>34</sup> as this seemed to be the most effective drug available for the reduction of low-density lipoprotein (LDL)-cholesterol in plasma.<sup>35</sup> The trial was performed at 12 lipid research clinics in the United States over a 10-year period and randomized 3806 middle-aged men with primary hypercholesterolemia to receive  $\leq 24$  g/d (6 packets divided into 2–4 equal doses) of cholestyramine or placebo.<sup>36</sup> At baseline, after a cholesterol-lowering dietary period, the mean LDL-cholesterol level was 205 mg/dL. When compared with

the placebo group, the cholestyramine group reduced mean LDL-cholesterol level by 39.4 mg/dL (21%) after 1 year, but over course of the entire study, LDL-cholesterol levels were only 11% lower. The incidence of CHD was 19% lower in the cholestyramine group than in the placebo group. This difference was barely statistically significant with Z score of 1.92, which gave a  $P < 0.05$ . The number of CHD deaths was 30 in the cholestyramine group when compared with 38 in the placebo group. All-cause mortality was reduced by only 7% in the cholestyramine group. Oliver<sup>30</sup> was not impressed by these results and pointed to the fact that in the statistical analysis a 1-sided test of significance had been used; a more appropriate 2-sided test would not be significant at the 0.05 level.

A more courageous approach to the problem was taken by the surgeon Buchwald,<sup>37</sup> who already in 1963 started to perform partial ileal bypass in patients with severe hypercholesterolemia. In the first patient series, 57 severely hypercholesterolemic individuals (total cholesterol  $363.3 \pm 136.8$  mg/dL) underwent surgery to reduce the effective absorbing length of the small bowel with one third. This resulted in a mean reduction in total cholesterol of 34%. Encouraged by the initial results, a randomized multiclinic trial of partial ileal bypass surgery was initiated in 1975, and data were published in 1990.<sup>38</sup> Ileal bypass surgery was performed in 421 patients, whereas 417 patients served as control in a randomized design. After 5-year follow-up, the surgery group had a 37.7% lower mean LDL-cholesterol level than the control group. The results were nonsignificant ( $P = 0.164$ ) after 10-year follow-up, 21.7% risk reduction in the primary end point all-cause mortality. When overall mortality was combined with confirmed myocardial infarction, the difference was 141 end points in the control group against 97 in the surgery group ( $P > 0.001$ ). These results were published at a time when statins became available and the method was never widely adopted.

### Other Fibrates

In the 1970s, Park Davis Research Laboratories had started a search for lipid-lowering compounds and came across gemfibrozil, which was selected for further development.<sup>39</sup> Gemfibrozil seemed to be more potent than clofibrate in reducing triglycerides in laboratory animals, and trials on humans were initiated. The first large clinical trial was the Helsinki Heart study that comprised 4081 asymptomatic men aged 40 to 55 years with non-high-density lipoprotein-cholesterol levels  $> 200$  mg/dL.<sup>40</sup> In this randomized double-blind placebo-controlled trial using 1200-mg gemfibrozil, daily LDL-cholesterol levels were reduced on average 10% and high-density lipoprotein-cholesterol levels were increased 14% whereas triglyceride levels were reduced by 43%. During the 5-year follow-up period, the overall reduction in cardiac end points was 34% ( $P < 0.05$ ), but the death rate was similar in the 2 groups. Significantly more patients in the gemfibrozil group experienced moderate to severe upper gastrointestinal problems. A later analysis suggested that the changes in both high-density lipoprotein-cholesterol and LDL-cholesterol were associated with the reduction in CHD events.<sup>41</sup> This study was later followed by the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention



Trial (VA-HIT) using the same dose of gemfibrozil in men <74 years of age with a history of CHD.<sup>42</sup> The changes in lipid and lipoprotein levels were more modest than in the Helsinki Heart study. Still, after a median follow-up of 5.1 years of the 2531 men, those randomized to gemfibrozil had a 22% significantly reduced rate of nonfatal myocardial infarction or coronary death when compared with the placebo group ( $P=0.006$ ).

### The Cholesterol Controversy Hardens

In the United States, a consensus conference by the National Heart, Lung, and Blood Institute in 1984 concluded that the evidence supporting a causal relationship between blood cholesterol and coronary heart was established beyond any reasonable doubt.<sup>43</sup> Several recommendations on the change of diet and use of drugs were made. The majority of clinicians in general and cardiologists, in particular, were still unconvinced on the use of drugs to reduce cholesterol, even in patients with CHD. Daniel Steinberg, one of leading lipidologists of the NHBLI consensus conference, reminded cardiologists about the importance of cholesterol in an editorial in *Circulation* in 1989 called The cholesterol controversy is over, why did it take so long?<sup>44</sup> Instead, the controversy hardened. Following the Helsinki Heart study, a kind of meta-analysis of selected clinical trials and surveys with cholesterol lowering as a theme was published in the *British Medical Journal* indicating that cholesterol lowering increased the risk of cancer, death by accidents, depression, and suicide.<sup>45</sup> This report was widely publicized in lay media. A long-term follow-up of 1222 male business executives with cardiovascular disease risk factors that had either participated in a control group or a multifactorial intervention group showed a significantly increased risk of death in the intervention group.<sup>46</sup> The results were commented by Oliver<sup>47</sup> in an editorial in the *BMJ* who warned that multiple interventions in middle aged men may do more harm than good.

### Statins

During the 1950s, the pathway of cholesterol synthesis had been fully revealed, and the rate-limiting step had been shown to be the transformation of  $\beta$ -hydroxy- $\beta$ -methyl glutaryl-CoA (HMG-CoA) to mevalonate.<sup>48</sup> The rate-limiting enzyme HMG-CoA reductase caught the interest of the Japanese biochemist Endo<sup>49</sup> who hypothesized that certain fungi suppressed HMG-CoA reductase, possibly as a defense mechanism against other microbes. At the Fermentation Research Laboratories of Sankyo in Tokyo, he searched for a suitable fungus among 6000 fermentation broths during 2 years. Together with Masao Kuroda, he finally detected that the fungus *Pythium ultimum* produced citrinin that turned out to inhibit HMG-CoA reductase and was a relatively strong inhibitor of cholesterol synthesis in rats.<sup>50,51</sup> The major inhibiting compound was the component ML-236B later known as mevastatin. ML-236B was also discovered in cultures from *Penicillium brevicompactum* by Brown et al<sup>52</sup> and was named compactin for a while. After further search Endo<sup>53</sup> detected that a strain of *Penicillium citrinum* also produced ML-236B. In 1978, it was shown that ML-236B lowered cholesterol in patients with familial hypercholesterolemia.<sup>54</sup> In 1976, a

confidential collaboration between Sankyo and Merck Sharp & Dohme was initiated after Merck learned about ML-236B.<sup>49</sup> Merck started a search for fungi that could produce similar cholesterol-lowering compounds. In 1978, Endo<sup>55</sup> left Sankyo and started to work at Tokyo Noko University. He continued his search for compounds to lower cholesterol, and in a broth of *Monascus ruber*, he isolated monacolin K that was slightly more effective in inhibiting HMG-CoA reductase than ML-236B and was filed for patent in February 1979. In the meantime, Merck had detected that an extract of a soil fungus, *Aspergillus terreus* strongly inhibited HMG-CoA reductase and were able to isolate the inhibitor called mevinolin that they filed for patent in June 1979.<sup>56</sup> It was soon discovered that monacolin K and mevinolin was the same molecule. Sankyo obtained the patent from Endo<sup>49</sup> but did not commercialize the drug, whereas Merck was granted patent rights in the United States and several other countries that gave priority to time of invention rather than to time of application. In 1980, Merck began clinical studies of mevinolin, whereas Sankyo stopped their clinical program on mevastatin because they discovered serious side effects in dogs (possibly intestinal tumors). When Merck learned about this they also halted the clinical development program on mevinolin. Clinicians at lipid clinics were, however, eager to get mevinolin for compassionate use for patients with severe hypercholesterolemia and obtained this from 1982.<sup>57</sup> Mevinolin turned out to be effective with few adverse effects, and in 1983, formal clinical trials were started again. Because of the patent conflict with Sankyo who maintained the patent for mevinolin in 30 countries, Merck developed synvinolin, later to become simvastatin and mevinolin changed name to lovastatin. Both drugs were approved by Food and Drug Administration and came on the market in 1987, simvastatin was first marketed in Sweden.

Preceding the early developments of statins, Brown and Goldstein<sup>58,59</sup> detected the LDL receptor and the strong connection between HMG-CoA reductase activity and the functioning of the receptor, a discovery that won them the Nobel Prize in 1985. It was soon thereafter shown that the HMG-CoA reductase inhibition increased messenger RNA for LDL receptors in the liver and increase the density of LDL receptors on the surface of liver cells.<sup>60,61</sup>

### Statins and the Muscle Problem

When mevinolin was tested in lipid clinics, it was primarily given to patients who were not adequately controlled by other lipid-lowering drugs. These were mostly niacin, cholestyramine, and fibrates, and in the beginning of the 1980s, the most popular was gemfibrozil. At that point of time, relatively little was known about the catabolism and interaction of various drugs used in medicine. The first cases of rhabdomyolysis were reported in heart-transplant recipients treated with cyclosporine in addition to several other drugs; in many cases, gemfibrozil, who were given lovastatin.<sup>62,63</sup> When Merck summarized the experience in 2000 lovastatin-treated patients, the risk of myopathy with concomitant cyclosporine treatment was  $\approx 30\%$ , and with gemfibrozil, it was  $\approx 5\%$ .<sup>64</sup> Lovastatin was later tested at 4 different dose regimens in a placebo-controlled clinical trial with >8200 patients where only 5

patients of the 6600 allocated to lovastatin developed muscle symptoms with CK elevations >10 times the upper limit of normal.<sup>65</sup> Muscle symptoms with any elevation of CK above the upper limit of normal were not significantly different from the placebo group. At this time, however, clinicians had been sensitized on the potential muscle problem with statins and routinely warned patients participating in trials or receiving statins for hypercholesterolemia about muscle pain.

### Other Statins

Several other companies started developing their own statins when Merck continued developing mevinolin (lovastatin). Sankyo developed pravastatin, a derivative of monakolin later to be licensed by Bristol Meyer Squibb. Because of the patent conflict with lovastatin, Merck developed simvastatin, a semi-synthetic derivative of lovastatin, whereas the next generation of statins, fluvastatin, (appeared 1994), atorvastatin (1997), cerivastatin (1998) rosuvastatin (2003), and pitavastatin (2003) are all synthetic. The different statins vary in their way of metabolism, interaction with other drugs and elimination. There is a general warning to combine any statin with any drug without checking for problematic interactions. Any drug combination that is rising the serum concentration of a statin might induce myopathy. Cerivastatin was withdrawn from the market in 2001 because of high incidence of rhabdomyolysis, in particular, with the combination with gemfibrozil.<sup>66</sup>

### The Statin Trials Era

In 1987, it was becoming known that statins would become available on the market within short. Because of the cholesterol controversy, I urged the director of Merck in Scandinavia, Per Wold Olsen to perform a large clinical trial with all-cause mortality as the primary end point rather than any other type of study.<sup>67</sup> Olsen was able to convince Merck Research Laboratories to perform the trial in the Nordic countries, based on a draft protocol I had hastily put together. After having recruited every university hospital in the Nordic countries Denmark, Finland, Iceland, Norway, and Sweden in addition to several nonteaching clinical centers (94 in total) for the study, the Scandinavian Simvastatin Survival Study (4S) was initiating recruitment of patients in February 1988.

On the basis of a protocol revised by the Steering Committee, the participants were patients with a history of myocardial infarction or angina pectoris with serum total cholesterol level of 5.5 to 8.0 mmol/L (212–309 mg/dL) after a 8-week run-in dietary advice period and 2 weeks on placebo tablets.<sup>68</sup> Randomization of the last of 4444 patients took place in August 1989. Several comparisons of the patient population were made with the myocardial infarction register at Göteborg Post-Myocardial Infarction Clinic in Sweden to estimate the mortality rate in the study population. It was estimated that a total of 440 deaths was needed to have a 97% power to detect a 30% reduction in total mortality at  $\alpha=0.05$ . The double-blind period ended on August 1, 1994. The results were presented at the American Heart Association Scientific Session in Dallas November the same year and published in the *Lancet* 2 days later.<sup>69</sup> There was an immediate relief among the believers of the cholesterol hypothesis, and many thought that the

controversy was solved. But it was not until the second and third statin trials appeared that the use of statins started to take off, because at that point of time, statins were regarded as expensive drugs and reimbursement from third parties were not available everywhere.

The West of Scotland study started randomization in February 1989 to treatment with pravastatin 40 mg daily or placebo in 6595 men, 45 to 64 years of age. The participants were selected after screening >80000 men and those without any history of CHD, but with plasma cholesterol levels at least 6.5 mmol/L (252 mg/dL) were given dietary advice and asked to return on 3 more screening visits. Those who still had LDL-cholesterol levels of 4.0 mmol/L (155 mg/dL) at the fourth visit were included in the study and followed up for  $\leq 6$  years. The mean reduction in LDL-cholesterol was 26% in the pravastatin group. The primary end point was myocardial infarction or death from CHD combined, and this end point was reduced 31% when compared with the placebo group. There was no increase in mortality from noncardiovascular causes, and all-cause mortality was reduced by 22% ( $P=0.051$ ).<sup>70</sup>

One year later in October 1996, the results of The Cholesterol and Recurrent Events Trial (CARE) study appeared.<sup>71</sup> This study comprised 4159 men and women with myocardial infarction between 3 and 20 months before randomization who were aged 21 to 75 years and had plasma total cholesterol levels <240 mg/dL (6.2 mmol/L) and LDL cholesterol levels of 115 to 174 mg/dL (3.0–4.5 mmol/L). This study started in December 1989 and was ended in February 1996 with a median follow-up duration of 5 years. Pravastatin 40 mg daily lowered the mean LDL cholesterol of 139 mg/dL (3.6 mmol/L) by 32%. Pravastatin treatment lowered the incidence of the primary end point, fatal coronary disease or confirmed myocardial infarction by 24% ( $P=0.003$ ).

At this point, cholesterol lowering with statins had been proven beneficial and effective for 2 different drugs, for both men and women over a wide age range, and in primary and secondary prevention, and the knowledge was wide spread among both lay and professionals. Statins were soon to become the most widely prescribed class of drugs in both the United States and Europe. The question quickly arose: at what level of plasma LDL-cholesterol would statins begin to be beneficial? In the 4S, no patients with relatively low levels of LDL-cholesterol had been included, but an analysis of relative risk by quartile of baseline total cholesterol or LDL-cholesterol showed no significant difference in treatment effects.<sup>72</sup> The next question was How low should one go with LDL-cholesterol. All 3 trials published their post hoc analysis in the same issue of *Circulation*.<sup>73–75</sup> The 4S results indicated that the preventive effect was determined by the magnitude of the reduction in LDL-cholesterol with no threshold at which further lowering was not effective. The analysis of the 2 pravastatin trials, on the contrary, indicated that there was a threshold where no additional benefit was achieved. In the West of Scotland study, this threshold was estimated to be 24% reduction in LDL-cholesterol. In the CARE study, the threshold was estimated to be at LDL-cholesterol of  $\approx 125$  mg/dL (3.2 mmol/L). This threshold was not confirmed in a similar analysis of The Long-Term Intervention with Pravastatin

in Ischemic Disease (LIPID) study that included 9014 patients with known CHD and also used pravastatin against placebo.<sup>76,77</sup> The most likely explanation for the failure of the first 2 pravastatin trials to detect this relationship was the lack of statistical power as they both had much fewer end points than 4S and LIPID.

### The-Lower-the-Better Trials

The differing results of the 3 first statin trials gave ammunition to a marketing competition between the pharmaceutical companies producing different statins. Bristol Meyers Squibb funded The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial to demonstrate that the more potent statin atorvastatin was not superior to their less potent pravastatin. Pfizer and Warner Lambert, bringing atorvastatin to the market in 1997, on the contrary, wanted to demonstrate that the highest dose was superior to the lowest dose and that their highest dose was superior to the simvastatin doses used in 4S and supported the Treating to New Targets (TNT) and the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) studies. Merck supported a similar trial comparing simvastatin 20- and 80-mg doses and also a trial comparing an early and high-dose simvastatin strategy with a 4S-like strategy using only 20 mg and starting only after 4 months of acute myocardial infarction. The first of these trials to report results was the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial.<sup>78</sup> This study enrolled 4162 patients with a recent acute coronary syndrome, who were randomized to treatment with pravastatin 40 mg daily or atorvastatin 80 mg daily. Median LDL-cholesterol levels achieved during treatment was 95 mg/dL (2.46 mmol/L) in the pravastatin group and 62 mg/dL (1.60 mmol/L) in the atorvastatin group. Designed to show noninferiority of pravastatin, the result was surprisingly a highly statistically significant superiority of atorvastatin 80 mg with a reduction of the composite primary end point of 16% ( $P=0.005$ ) relative to pravastatin. Shortly thereafter, phase Z of the Aggrastat-to-Zocor Trial (A to Z) trial was published, randomizing 4497 patients with acute coronary syndrome to an early and intensive treatment regimen with simvastatin 40 mg daily for 30 days and thereafter 80 mg daily or placebo for 4 months followed by simvastatin 20 mg daily.<sup>79</sup> After 2 years of follow-up, there was a trend similar to the PROVE IT study that the early and more intense regimen was superior, but this difference did not reach statistical significance. One reason might have been that one third of the participants stopped taking the study medication during the trial.

The TNT study compared atorvastatin 10 mg and 80 mg daily in a double-blind fashion in 10001 patients with previous CHD.<sup>80</sup> The mean LDL-cholesterol levels during the study were 101 mg/dL (2.6 mmol/L) and 77 mg/dL (2.0 mmol/L) in the 10-mg and 80-mg groups, respectively. This difference led to 22% relative reduction in the primary composite end point of CHD ( $P<0.001$ ) over a total follow-up period of 6 years. With exception of more frequent elevation of liver enzymes in the group receiving the 80-mg dose, there were only small differences between the groups in occurrence of

adverse events. The IDEAL study randomized 8888 patients with previous myocardial infarction to open-label prescription of either simvastatin 20 mg daily or atorvastatin 80 mg daily.<sup>81</sup> End points were classified by a committee blinded to treatment. The dose of simvastatin could be increased to 40 mg, and the dose of atorvastatin could be reduced to 40 mg daily. At 1 year, the mean level of LDL cholesterol was 102 mg/dL (2.64 mmol/L) in the simvastatin group and 79.1 mg/dL (2.04 mmol/L) in the atorvastatin group. The primary end point major coronary event (CHD death, nonfatal myocardial infarction, or cardiac arrest with resuscitation) was reduced by 11% ( $P=0.07$ ). The difference in other coronary end points was the same as seen in the TNT study. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) study compared treatment with simvastatin 20 mg and 80 mg in 12064 survivors of myocardial infarction in a double-blind trial.<sup>82</sup> At 2-month follow-up, there was a mean 0.51 mmol/L (19.7 mg/dL) lower LDL-cholesterol level in the 80-mg simvastatin group, but this difference was reduced over the next 5 years to only 0.29 mmol/L (11.2 mg/dL). There was a nominally significant reduction in nonfatal myocardial infarctions, but the primary end point of major vascular events was reduced only 6% in the 80-mg group ( $P=0.10$ ). In this trial, definite myopathy was observed in 54 patients in the 80-mg group and in 2 patients in the 20-mg group. The results of the 5 trials were combined in a meta-analysis that showed a further proportional risk reduction of 15% associated with a mean 0.51 mmol/L (19.7 mg/dL) reduction in LDL-cholesterol ( $P<0.0001$ ) in favor of the high-dose statin.<sup>83</sup>

### Other Statin Trials

As the more versus less statin trials were ongoing, several randomized clinical trials were under way. Of the larger studies with clinical end points were the following: The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) randomized 5608 men and 997 women without previous CHD and with average LDL-cholesterol levels (130–190 mg/dL [3.36–4.91 mmol/L]) to treatment with placebo or lovastatin 20 mg daily.<sup>84</sup> The lovastatin dose was titrated to 40 mg daily if the LDL-cholesterol level was  $>110$  mg/dL (2.84 mmol/L) at 3 months. Major coronary events were reduced by 37% with lovastatin when compared with placebo ( $P<0.001$ ). The LIPID study (see above) was also confirming the results of the first trials. The randomized clinical trials with statins that reported cardiovascular outcome are listed in the Table. More than 190000 subjects have been randomized into these trials. Only in few of them was there little or no effect of therapy. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial (ALLHAT-LLA) failed to show a significant benefit.<sup>92</sup> In this large open-label trial using pravastatin against usual, care there was a substantial dropin and dropout of statin therapy during the trial, causing a difference in LDL-cholesterol between treatment groups that was much less than in other trials. Statins did not seem to have a preventive effect in patients with advanced chronic disease such as patients with diabetes mellitus on renal dialysis or patients with advanced heart failure. The other studies that included patients with diabetes mellitus,

**Table. Important Randomized Controlled Statin Trials With Clinical End Points**

Year	Trial	References	Patient Category	Statin(s)	n
1994	4S	69	CHD	Simvastatin	4444
1995	WOSCOPS	70	Healthy hypercholesterol.	Pravastatin	6595
1996	CARE	71	CHD	Pravastatin	4159
1997	Post CABG	85	CHD	Lovastatin	1351
1998	AFCAPS/TEXCAPS	84	Healthy	Lovastatin	6605
1998	LIPID	76	CHD	Pravastatin	9014
2000	GISSI Prevenzione	86	CHD	Pravastatin	4271
2001	MIRACL	87	CHD	Atorvastatin	3086
2002	HPS	88	CHD	Simvastatin	20 536
2002	LIPS	89	Post PCI	Fluvastatin	1677
2002	GREACE	90	CHD	Atorvastatin	1600
2002	PROSPER	91	Elderly (70–82 y) high risk	Pravastatin	5804
2002	ALLHAT-LLT	92	Hypertensive high risk	Pravastatin	10 355
2002	ASCOT	93	Hypertensive	Atorvastatin	10 305
2003	ALERT	94	Renal transplant	Fluvastatin	2102
2003	CARDS	95	Diabetes mellitus type 2	Atorvastatin	2838
2004	ALLIANCE	96	CHD	Atorvastatin	2442
2004	PROVE IT	78	CHD	Pravastatin-atorvastatin	4162
2004	A to Z	79	CHD	Simvastatin	4497
2004	TNT	80	CHD	Atorvastatin	10 001
2005	4D	97	Dialysis patients w. diabetes	Atorvastatin	1255
2005	IDEAL	81	CHD	Atorvastatin -simvastatin	8888
2006	MEGA	98	Healthy hypercholesterol.	Pravastatin	8214
2006	SPARCL	99	Stroke	Atorvastatin	4731
2007	CORONA	100	Heart failure	Rosuvastatin	5011
2008	GISSI HF	101	Heart failure	Rosuvastatin	4574
2008	JUPITER	102	Healthy CRP elevation	Rosuvastatin	17 802
2009	AURORA	103	Chronic kidney disease on dialysis	Rosuvastatin	2776
2010	SEARCH	82	CHD	Simvastatin	12 064
2011	SHARP	104	Chronic kidney disease	Simvastatin+ezetimibe	9270
	Total				190 429

A to Z indicates Aggrastat-to-Zocor Trial; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of Lescol in Renal Transplantation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CABG, coronary artery bypass graft; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, The Cholesterol and Recurrent Events Trial; CHD, coronary heart disease; CORONA, The Controlled Rosuvastatin Multinational Trial in Heart Failure; CRP, C-reactive protein; GISSI HF, The Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca; GISSI Prevenzione, The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; GREACE, The Greek Atorvastatin and Coronary Heart-disease Evaluation Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPID, The Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS, The Lescol Intervention Prevention Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study; MIRACL, The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study; PCI, percutaneous coronary intervention; PROSPER, The Prospective Study of Pravastatin in the Elderly at Risk; PROVE IT, The Pravastatin or Atorvastatin Evaluation and Infection Therapy study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SHARP, Study of Heart and Renal Protection; SPARCL, The Stroke Prevention by Aggressive Reduction in Cholesterol Levels study; TNT, Treating to New Targets study; and WOSCOPS, The West of Scotland Coronary Prevention Study.



hypertension, stroke, or healthy people with increase in risk factors such as diabetes mellitus, elevated C-reactive protein or moderate hypercholesterolemia showed a substantial benefit of treatment. The largest of the trials, the Heart Protection Study (HPS) surprised many by showing the same relative risk reduction among patients with low LDL-cholesterol levels as in those with hypercholesterolemia.<sup>88</sup> Several meta-analysis combining results of clinical trials have been published, but the most frequently cited are the analyses performed by the Cholesterol Treatment Trialists' (CTT) Collaboration<sup>83</sup> that includes most of the trials in the Table and a sex comparison in 2015.<sup>105</sup>

### The Present Status and the Future

Today statins are the most widely prescribed class of drugs for chronic use and does not seem to have serious competition from other alternatives. Statins have been successfully implemented in the treatment of children with familial hypercholesterolemia. Recently, ezetimibe was proven to add benefit to statin therapy in patients with recent acute coronary syndrome included in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study.<sup>106</sup> The fibrates have not had much success in trials when added to statin treatment, and niacin has been withdrawn from many markets. However, at present, we are eagerly waiting for the results of ongoing large studies with clinical end points using cholesteryl ester transfer protein inhibitors and inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9). The latter have shown exciting preliminary results in smaller scale trials.<sup>107,108</sup> Because the cost of statin therapy has dropped substantially and because patent rights have been lost, it is still likely that statins will remain the basis for preventive cardiology for a long time.

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