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Clinical Article
The Heart Protection Study Findings

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On November 11, 2001 in the ballroom at the Anaheim Convention Center where the American Heart Association was holding its 2001 Scientific Sessions, Professor Rory Collins, head of the Oxford University's Clinical Trial Service Unit, presented the initial findings from the Heart Protection Study (HPS). The audience waited with tense anticipation: would the results of this study, the latest and by far the largest in a series of statin intervention trials confirm previous benefits, would it provide new insights, or raise new questions? The answer was a resounding "yes" to all three questions. In addition the study included an antioxidant therapy arm, and previous clinical trials of antioxidant therapy almost without exception have shown no benefit for cardiovascular disease. Although the results are not yet published and therefore have not been subject to peer review, and many details were not presented, experts who have heard or seen the main results believe that they are extremely important. For this reason the presentation of the HPS initial findings are reviewed here, "hot off the press"!

Background: what is currently known about the benefits of statin therapy

To best appreciate the importance of the HPS results it will be useful to summarize what we know as well as what we do not know about statin therapy. The results of antioxidant treatment in the HPS indicated, once again, that there was no benefit for vascular disease, and will therefore not be a focus of this discussion.

A. Primary Outcome Data

The primary outcome results of a clinical trial are always the most robust, because the study in question will have been designed and powered specifically to test an hypothesis regarding the effect of the intervention on this outcome.

1. The 4S, LIPID and CARE trials used simvastatin (20-40mg) and pravastatin (40 mg) to demonstrate that both hypercholesterolemic (4S, LIPID) as well as normocholesterolemic (CARE) individuals ? mainly men - with coronary heart disease (CHD), had a significant reduction in coronary events (all) or deaths (4S) compared to placebo, in the order of 25-35%.

2. The WOSCOPS and AFCAPS trials utilizing pravastatin (40mg) and lovastatin (20-40mg) respectively, demonstrated that men without CHD but with significant hypercholesterolemia (WOSCOPS), and men and women without CHD but with above

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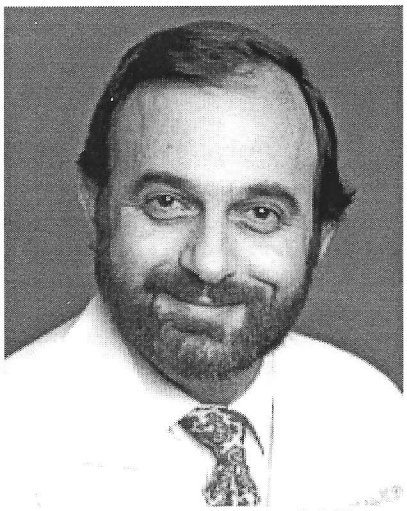
average LDL-C and below average HDL-C (AFCAPS) also had ~25% reduction in the rates of initial cardiovascular events.

B. Secondary Analyses

Secondary analyses of the data are always less reliable than the primary outcomes listed above, because they represent results from studies not specifically designed nor powered to adequately test the hypotheses underlying those analyses.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1. Diabetic subjects with CHD benefit at least equally to non-diabetic individuals. (4S, CARE)

2. Cerebrovascular event rates were reduced ? particularly in those with existing CHD (4S, CARE)

3. Women and older subjects (>60 years of age) benefit equally to the rest of the population (4S, CARE)

4. Healthy subjects with low HDL-C levels benefit more than those with normal values (AFCAPS).

5. Considerable debate has centered around the results of a secondary analysis from CARE which showed that CHD patients with baseline LDL-C in the lowest third of the population (<125mg/dl) do not benefit from pravastatin treatment. Although the data is weak, this has led some to suggest that there is little benefit to be gained from statin treatment below an LDL-C of 125 mg/dl.

Important Unknown Issues

We still do not know the relative impact that the baseline- and post-treatment-LDL-C values, or the percent and absolute reduction of LDL-C levels by statin treatment have on cardiovascular disease event rates. Perhaps the most pressing question for patients with CHD is whether statin treatment should be initiated in all patients with CHD whose LDL-C is less than the NCEP goal of <100 mg/dl, or even <130 mg/dl where it is not considered essential by the latest guidelines, and whether such therapy should be increased in subjects who have reached the LDL-C goal of <100 mg/dl ("how low to go?"). Among subjects without evidence of cardiovascular disease, practitioners are anxious to know whether diabetic and other high-risk patients with 2 or more risk factors should be subject to the same intervention points and targets as those with CHD. Do women and those over the age of 70 years without disease merit the same treatment as younger men?

Design of the Heart Protection Study

The HPS was a large, randomized placebo-controlled trial of the effects of 6 years of statin and antioxidant therapy in a wide range of subjects at high risk of coronary disease death. A total of 20,536 men and women aged 40-80 years and with LDL-C levels >135 mg/dl were recruited provided that in the opinion of their physicians, they did not have a clear indication (nor contraindication) **for treatment with statins and/or antioxidants.** They were required also to have evidence of cardiovascular disease, namely either CHD, cerebrovascular disease (CVD) or peripheral vascular disease, or be at increased risk because of diabetes (~6000, two thirds of whom did not have CHD) or treated hypertension. The subjects who had cardiovascular disease tended to be elderly, female and to have low LDL-C levels ? the sort of individuals in whom there is more uncertainty about the benefits of statin

treatment. Subjects were randomized into one of 4 groups in a 2 X 2 factorial design to assess the effects of 40mg simvastatin and an antioxidant cocktail (600mg vitamin E, 250mg vitamin C and 20mg beta carotene) versus placebo.

Findings of the Heart Protection Study

A. Antioxidant therapy

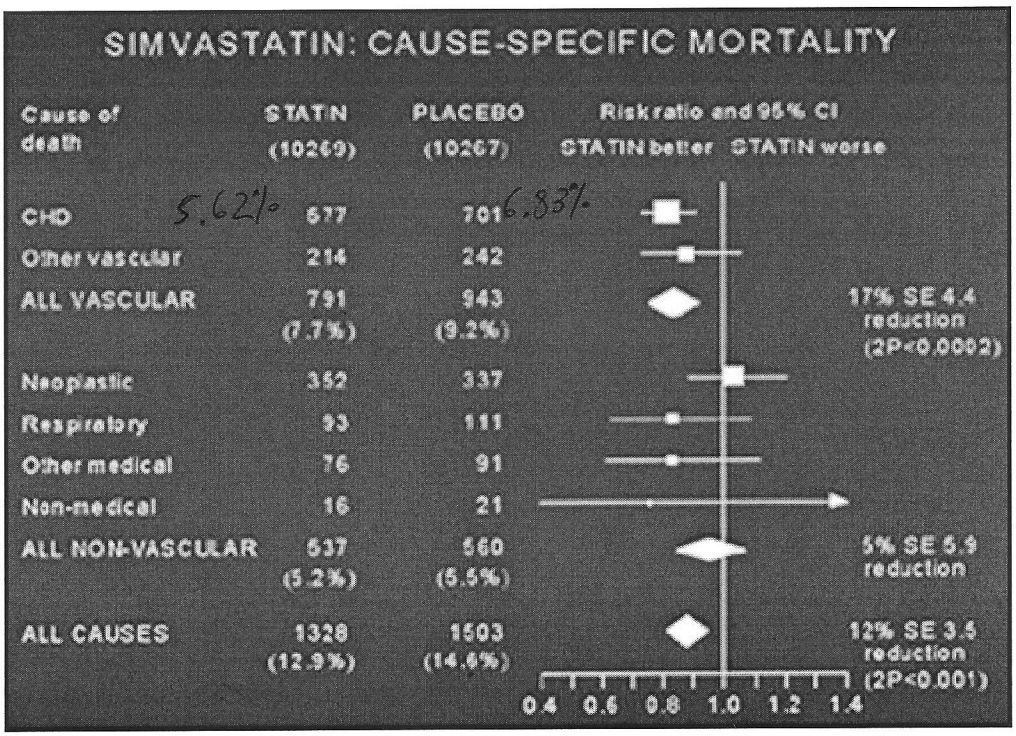
As already mentioned there was no evidence that antioxidant treatment affected either vascular or non-vascular events or mortality beneficially or adversely. Thus while it seemed that antioxidant therapy was without hazard, it had no significant effect in preventing morbidity or mortality in this population.

B. Statin therapy

At the end of the first year of treatment the average LDL-C was reduced 55 mg/dl in the simvastatin group. By the end of the second through six years the average LDL-C reduction had fallen to ~40 mg/dl. This reduced efficacy over time was shown to result from non-compliance in about one-sixth of the 10,269 participants allocated to 40 mg simvastatin therapy. In addition, one sixth of the placebo group started to use a non-study statin. Combining these "positive" and "negative" non-compliance rates means that about a third of the study population were non-compliant with the assigned study treatment. The investigators reasoned that the full effect of 40 mg of simvastatin on LDL-C lowering would be expected to be closer to 60 mg/dl if 100% compliance of simvastatin treatment was achieved, combined with zero use of statins in the placebo group. They also extrapolated from these estimates that the benefits of simvastatin treatment compared to no treatment would be increased by about one third if full compliance were attained. Given the well-known non-compliance of tablet takers this extrapolation may only have theoretical importance.

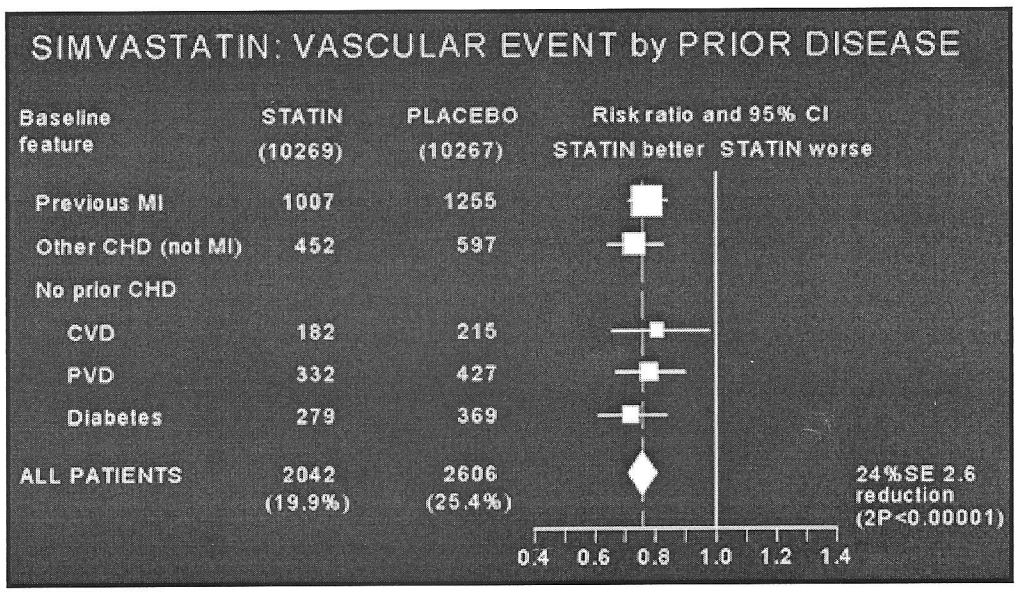
1. Effects on Mortality:

Overall 14.6% of the placebo-treated population died during the 6 years follow-up period, and most (9.2%) were cardiovascular deaths. As seen in Fig 1, there was a highly significant, 12% reduction in total mortality associated with simvastatin treatment that largely reflected a substantial 17% reduction in cardiovascular mortality, more than two thirds of which were CHD deaths. This is similar to the results in LIPID, but less than the benefit in the hypercholesterolemic subjects of 4S. Full compliance to 40mg simvastatin daily might be expected to yield a one third higher reduction in vascular activity overall, that is ~25%, compared to untreated individuals. If an extra 10 million people with high risk for cardiovascular disease were to be treated with simvastatin 40 mg, these results extrapolate to the prevention of 50,000 deaths per year.



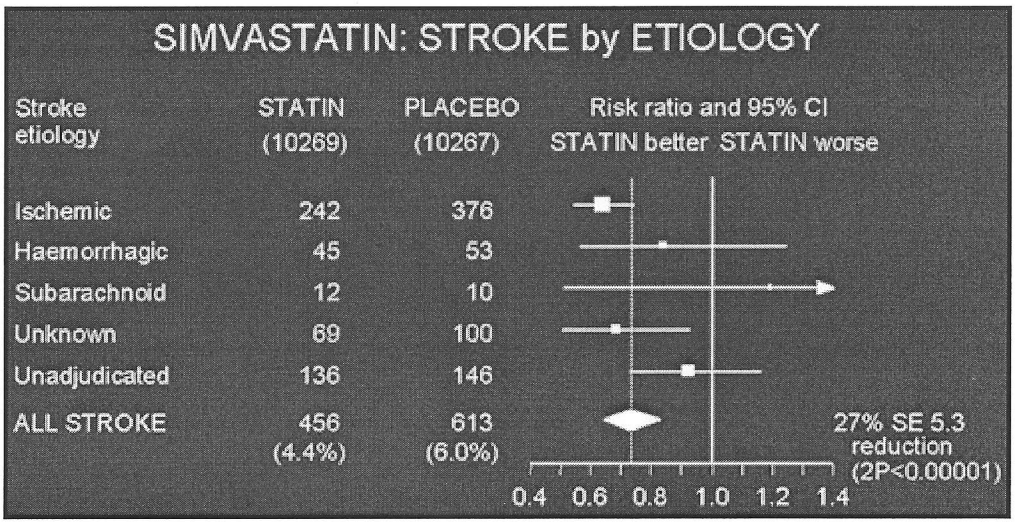
2. Effects on Cardiovascular Events in Subjects with Prior Cardiovascular Disease

By study end, 25.4% of the placebo group had experienced a cardiovascular event. Simvastatin treatment was associated with ~25% reduction in CHD events in subjects with prior myocardial infarction as well as those with other prior CHD manifestations such as coronary revascularizations (Fig 2). This is very similar to the effect of pravastatin in the CARE study. Although the baseline LDL-C concentration was approximately the same in these two trials (~130-136 mg/dl), the cohort with CHD in the HPS apparently contained more women and elderly subjects and had a lower baseline LDL-C than did the entire study population (unfortunately these details were not presented). Thus the results appear to extend beyond what was found in the CARE trial.



The data in Fig 3 reveal for the first time in a clear and unequivocal manner that

statin treatment prevents stroke. Simvastatin treatment reduced the occurrence of stroke by about 25% from the 4.4% total stroke incidence in the placebo group. The lower frequency of stroke was due entirely to a reduced incidence of ischemic stroke. There was also no significant effect on hemorrhagic stroke, a result dispelling fears that lowering cholesterol might increase the incidence of this finding.

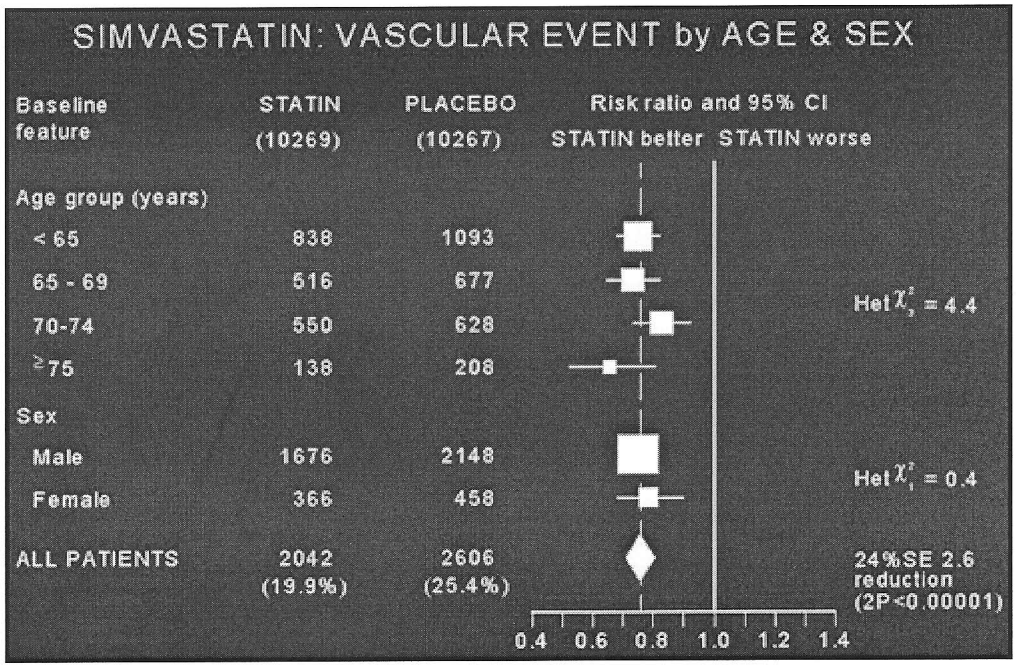


3. Effects on Cardiovascular Events in Subjects without Cardiovascular Disease

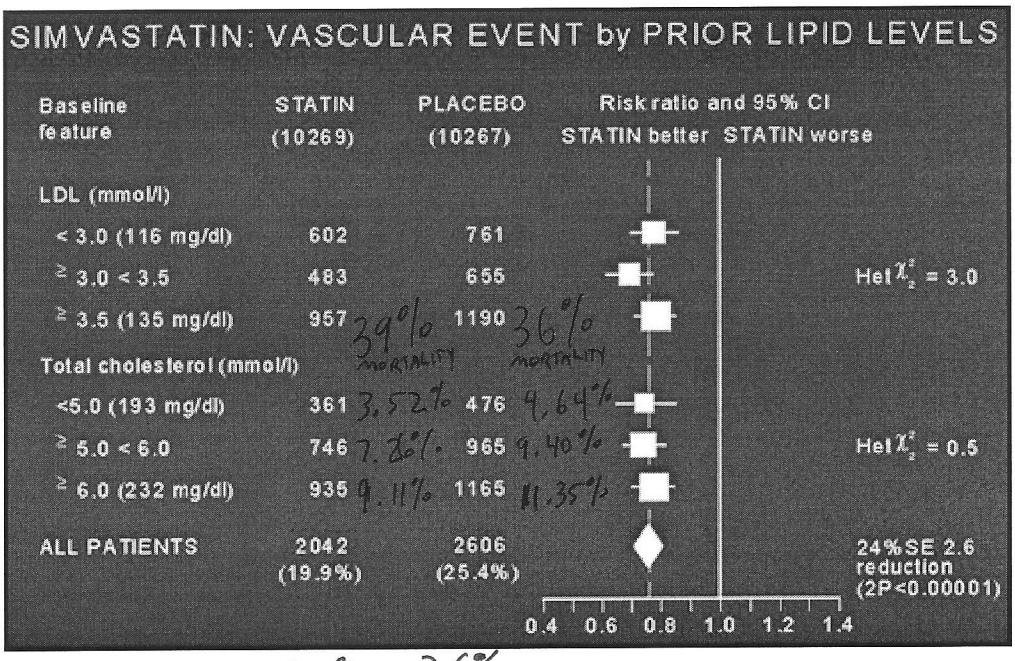
Fig 2 also shows that simvastatin treatment was associated with about a 25% reduction in vascular events in subjects without prior CHD ? such as those who had had a stroke or PVD emphasizing the importance of statin therapy for all forms of atherosclerotic vascular disease. There was also ~25% reduction in vascular events in the 4,000 diabetic subjects (over the age of 40 years) without evident cardiovascular disease. This is by far the largest statin intervention trial for diabetes, and it provides solid evidence for the importance of statin treatment in these patients. Whether benefit accrues from statin treatment in diabetic subjects without vascular disease and with baseline LDL-C levels <130 mg/dl still remains unknown; and further analysis of this group is awaited with interest.

4. Effects of Age, Female Gender and Baseline LDL-C on Cardiovascular Events

There were about 6000 subjects aged 70 years or more, and about 25% of these were older than 75 years. As seen in Fig 4, in both of these age groups simvastatin treatment reduced the rate of vascular events by ~25%, finally demonstrating that maturity of age per se should clearly not be a factor influencing statin treatment decisions. Similarly this is the first study to recruit sufficiently large numbers of women (~5000) to be able to unequivocally demonstrate that even though women have fewer vascular events than men, statin treatment lowers this rate by the same 25% relative risk reduction as seen in men.



The availability for the first time in a clinical trial of a large number of subjects with lower than average LDL-C levels gave the investigators a unique opportunity to evaluate the effects of simvastatin treatment in subjects with baseline LDL-C values at or below NCEP cutpoints for intervention. They chose to examine the effects of simvastatin treatment in groups defined by LDL-C cutpoints of 3.0 and 3.5 mmol/l. This divided the population into 3 approximately equal groups; those with LDL-C <116 mg/dl (mean 105 mg/dl), those between 116-134 mg/dl (mean 124 mg/dl), and those >135 mg/dl (mean 143 mg/dl). Simvastatin lowered LDL-C by 35 mg/dl (mean? is 33%), 37 mg/dl (mean ? is 30%) and 39 mg/dl (mean ? is 27%) respectively in these groups, and as shown in Fig 5, these changes were associated with ~25% reduction of cardiovascular events in each LDL-C subgroup, that is, the same relative benefit was achieved irrespective of baseline LDL-C. This is a striking and somewhat surprising result, but the large numbers of subjects and events in each sub-group make this finding compelling despite it being analyzed post-hoc. Further analysis of the population by NCEP LDL-C cutpoints into groups with LDL-C <100 mg/dl, 100-129 mg/dl and >130 mg/dl yielded essentially the same result, namely that the cardiovascular event rate was reduced ~25% by simvastatin treatment in each subgroup (Fig 6). The implications of these findings is that simvastatin treatment is associated with the same relative reduction in events over a broad range of baseline LDL-C values, and that this extends even to subjects with levels below average.



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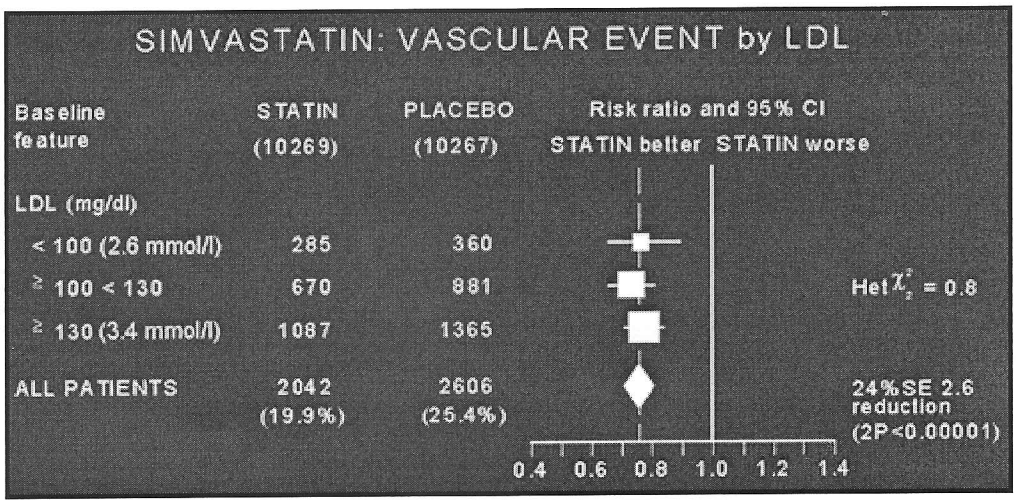
5. Adverse Events

There were very few adverse events. All participants were advised on entry that simvastatin could cause muscle pain and in both the simvastatin and placebo groups about 5% of subjects complained of muscle pain early on. Only 9 out of 10,269 simvastatin-treated subjects (0.09%) and 5 out of the 10,267 placebo-treated subjects (0.05%) were noted to have CPK levels >10X the upper limit of normal, indicating the rarity of statin-induced myositis ? an extremely important finding given the recent scare surrounding the withdrawal of Baycol. There was also a very low incidence of abnormal liver enzymes. Participants were tested four monthly during the first year and six monthly subsequent to that; 77 (0.8%) of the simvastatin-treated subjects and 65 (0.6%) of those in the placebo group had ALT levels >3X the upper limit of normal. These results once again confirm that statin treatment is extremely well tolerated.



Conclusions and Implications

First, the study gave no support to the concept that antioxidant therapy will protect against heart disease. With regard to simvastatin treatment, overall the study showed

that in this high risk population with and without prior vascular disease, 40 mg of daily simvastatin produced a 17% reduction in cardiovascular mortality, and lowered cardiovascular events by ~25% (~35% compared to untreated subjects, and with perfect compliance) irrespective of prior history, age, gender or baseline LDL-C level. This translates into preventing 5 deaths and 70-100 cardiovascular events per 1000 untreated, high risk individuals, a finding that clearly has major public health importance. The demonstration in the HPS that simvastatin reduces cardiovascular disease in a wide range of high risk individuals independent of the baseline LDL-C, brings to mind the use of aspirin to prevent cardiovascular disease. It seems likely that like aspirin, statins will reduce cardiovascular disease in all subjects with increased risk, and from a public health point of view could be recommended to all such individuals irrespective of their baseline LDL-C, particularly since statins have even fewer serious side effects than aspirin. Finally, these findings now logically require us to focus on the need to further our understanding of two critical questions: (1) what constitutes the high-risk patient, and (2) in subjects with normal or mildly elevated LDL-C levels, is more lowering of LDL-C better?

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