Lower LDL Associated with Decreases in Cardiovascular Events Regardless of CRP Level

Heart Protection Study Collaborative Group. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20536 patients in the Heart Protection Study. Lancet 2011;377:469–76.

Study Overview

Objective. To determine whether prevention of cardiovascular events from statin therapy depends on baseline level of C-reactive protein (CRP).

Design. Post-hoc analysis of the Heart Protection Study (HPS), a randomized, double-blind, placebo-controlled trial that enrolled subjects from 1994 to 1997 and followed them for a mean of 5 years. After establishing compliance with a 4-week placebo run-in period followed by a 4- to 6-week simvastatin run-in, researchers randomized subjects to receive either placebo or simvastatin 40 mg. Initial results, published in 2002, found substantial reductions in cardiovascular events in the simvastatin-treated group compared with placebo [1]. This post-hoc analysis examined the effects of simvastatin on cardiovascular outcomes according to baseline CRP level (categorized into 6 strata ranging from < 1.25 mg/L to > 8 mg/L). LDL cholesterol level at baseline and during the last year of follow-up were available for all subjects who completed the trial; CRP levels were available for 18,445 subjects at baseline but only for 2727 subjects in the last year of follow-up.

Setting and participants. 20,469 participants from 69 hospitals in the United Kingdom who were 40 to 80 years old at enrollment with a prior diagnosis of coronary disease, peripheral vascular disease, cerebrovascular disease, carotid artery disease, or diabetes or who were men over age 65 years who were receiving medication treatment for hypertension. Exclusions were for a pre-existing indication for treatment of high cholesterol, chronic liver disease, abnormal liver function tests, chronic kidney disease, inflammatory muscle disease or abnormal creatine kinase levels, concurrent treatment with cyclosporine, fibrates, or high-dose niacin, women of child-bearing age, severe heart failure, conditions that limit compliance such as psychiatric or cognitive disorders, or other life-threatening illnesses [1].

Main outcome measures. Composite of major cardiovascular events, including fatal or nonfatal myocardial infarction, stroke, or a revascularization procedure.

Main results. Each CRP strata had approximately 3000 subjects. Subjects with higher baseline CRP were more likely to be women, have peripheral vascular disease, be on a diuretic, smoke, have low HDL, or have a high BMI, LDL, or triglyceride level. While CRP and LDL were associated, the association was weak ($r = 0.08$). Among the 2727 patients who had both LDL and CRP measured at both baseline and in the last year of follow-up, assignment to the simvastatin arm was associated with a 25% mean reduction in LDL from baseline to follow-up and a 27% mean reduction in CRP ($P < 0.001$ for both). The overall reduction in incidence of first major cardiovascular event after randomization was 24% for the simvastatin group (95% confidence interval [CI], 19%–28%). The reduction in events in the simvastatin group was similar in each of the baseline CRP strata, with no significant trend across the strata. This held for subjects in the lowest CRP strata (< 1.25 mg/L) with a 29% risk reduction (99% CI, 12%–43%; $P < 0.001$). Simvastatin significantly reduced incidence of each of the individual outcome measures as well, including major coronary events, stroke, and first revascularization, and no significant

trend was evident across CRP levels for any of these outcomes. A marginally significant trend in nonvascular mortality was evident across CRP levels, with a greater reduction in groups with higher CRP (marginal significance was attenuated when analyses were corrected for multiple comparisons). To further explore whether simvastatin was more effective in preventing cardiovascular events in some groups, the subjects were stratified into 4 groups based on baseline CRP and LDL levels (below median baseline levels of either, both, or neither CRP and LDL). There was no difference in the reduction in cardiovascular events among any of these groups. Those subjects in the low LDL and CRP group had a 27% reduction in events compared with a 23% reduction for those in the high LDL and CRP group (both $P < 0.001$).

Conclusion. Simvastatin reduced cardiovascular events proportionally at all baseline CRP levels.

Commentary

Clear evidence has emerged that higher levels of CRP are associated with risk for cardiovascular disease, ischemic stroke, and mortality [2]. This association has led to debates about whether CRP should be used in routine clinical practice to determine which patients might benefit from aggressive primary prevention strategies, including use of statin medications. CRP is associated with many other known risk factors for cardiovascular disease, including smoking, diabetes, physical inactivity, and high triglycerides, BMI, or blood pressure [2]. Further, recent evidence has emerged that calls into question a commonly held perception that CRP may be causally associated with cardiovascular disease [3]. However, some studies have found that CRP levels provide added value beyond traditional risk factors to help predict which individuals are at risk for cardiovascular events [4] and who might have lower cardiovascular risk after statin treatment [5]. Among 5742 subjects from the AFCAPS/TexCAPS randomized controlled trial, which compared lovastatin versus placebo for the primary prevention of cardiovascular disease among subjects with average LDL and low HDL cholesterol, subjects in the lovastatin group who had both low LDL and low CRP at baseline had no reduction in cardiovascular events compared with placebo [5], but all other groups (including patients with above average CRP and below average LDL) had a significant reduction in cardiovascular events.

These prior studies led to the important JUPITER study, which was a randomized, placebo-controlled trial of rosuvasatin therapy among 17,802 apparently healthy subjects with low LDL (< 130 mg/dL) and high CRP (≥ 2.0 mg/L) and triglycerides < 500 mg/dL [6]. The rosuvastatin-treated group had a 44% lower rate of a first major CVD event (hazard ratio, 0.56; 95% CI, 0.46–0.69; $P < 0.001$) or a rate of 0.77 per 100 person-years of follow-up in the rosuvastatin group versus 1.36 for the placebo group. Each of the individual components of the composite end point also was significantly lower in the rosuvastatin group. The trial led researchers and clinicians to conclude that CRP can help predict which patients will benefit from statins, and that patients with traditionally low levels of LDL cholesterol were among those who stood to benefit. The American College of Cardiology and American Heart Association recently released a guideline [7] stating that it is "reasonable" based on strong but imperfect evidence (Class IIa recommendation, B evidence) to use CRP to help guide decision making about statin use among "men 50 years of age or older or women 60 years of age or older with low-density lipoprotein cholesterol less than 130 mg/dL" who are not on lipid-lowering, hormone replacement, or immunosuppressant therapy and without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins, a recommendation taken directly from JUPITER. They issued a Class IIb recommendation (B evidence) that use of CRP "may be considered" to evaluate cardiovascular risk in asymptomatic, intermediate-risk men ≤ 50 years and women ≤ 60 years. However, the ultimate meaning of the JUPITER trial remains undetermined. JUPITER did not include subjects with low LDL cholesterol and low CRP. Could it be that CRP should not be the determinant of statin treatment but rather that we should simply be more aggressive about lowering LDL levels in patients previously considered to be at low risk for cardiovascular events?

This study by the HPS Collaborative Group echoes the concern about over-interpretation of the JUPITER trial (and the preceding AFCAPS/TexCAPS trial). In the HPS, which included over 20,000 individuals, subjects benefited from statin therapy regardless of baseline CRP level. Even subjects with the lowest CRP level had a benefit from statin therapy, as did subjects with low LDL cholesterol and low CRP. The HPS was large enough to ensure large sample sizes in each of the CRP strata, with about 3000 subjects in each, and events were common due to the higher-risk nature of subjects in this study compared with JUPITER and AFCAPS/TexCAPS. When stratified by both LDL and CRP, the low LDL and low CRP group had nearly 4000 subjects, more than double the subjects in this group in the AFCAPS/TexCAPS study. More than 15% of these low LDL/low CRP subjects in HPS had cardiovascular events. Perhaps the AFCAPS/TexCAPS study was similarly underpowered and had too few cardiovascular events to find a difference in this low LDL, low CRP group.

The primary limitation of this study is the use of a post-hoc analysis design, which can lead to biases in the interpretation of results. However, the CRP-related analysis of the AFCAPS/TexCAPS study was similarly post-hoc so the results

are comparable in that regard. The study sample in HPS was high risk, compared with the average-risk groups in both the AFCAPS/TexCAPS and JUPITER trials. Based on current guidelines, most of the subjects in the HPS would qualify for statin treatment based on their prior history alone.

This HPS study provides an important contribution to the debate about the role of CRP in clinical practice. The findings are consistent with prior data suggesting that most of the reduction in cardiovascular events from statins can be attributed to the achieved LDL level [8] and that nearly 90% of achieved reductions in CRP levels from statins can also be attributed to LDL changes [9]. However, other studies, including JUPITER, have found that subjects who achieve a lower CRP level on statin treatment have lower cardiovascular event rates than those with higher achieved CRP levels, regardless of achieved LDL level [10,11]. Yet these studies are observational and do not prove causation between lower achieved CRP and fewer cardiovascular events.

Overall, studies have now repeatedly shown the benefits of statins in many risk groups. Heretofore, we have operated under the impression that statins likely have no role in low- or average-risk patients who have no clear risk factors for cardiovascular disease, including having low CRP levels. This situation calls out for a large-scale trial, with appropriate power, using statins for primary prevention in subjects who by all accounts are low- to average-risk. Only with the results of such a trial can we determine once and for all the role of CRP in clinical practice and in whom statins should be used for primary prevention of cardiovascular events.

Applications for Clinical Practice

Statin treatment appears to be equally beneficial in preventing cardiovascular events in high-risk individuals, regardless of baseline CRP levels. Further studies should evaluate the impact of statin treatment among low-to-average–risk individuals, with low CRP, to establish a clear understanding of how many individuals might benefit from statin therapy and how to use CRP in routine clinical practice. Until such a study is available, it seems reasonable to use CRP in a targeted way to determine whether individuals at average risk for cardiovascular events may benefit from a statin.

—Review by Jason P. Block, MD, MPH

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