Use of Statins and Aspirin to Reduce Risks of Cardiovascular Disease

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In numerous randomized trials, some of cholesterol lowering with statins (1) and others with aspirin (2), each agent alone reduces risks of subsequent occlusive cardiovascular disease (CVD) events. In patients with prior myocardial infarction (MI), treatment with statins reduces the risk of coronary events by about a third as well as stroke and total mortality by about a fourth (1). In primary prevention, treatment with statins results in an approximate one-third reduction in initial coronary events. Treatment with aspirin in patients with prior CVD results in reductions of about a third for subsequent nonfatal MI, a fourth for nonfatal stroke, and a sixth for vascular death (2). In primary prevention, treatment with aspirin results in about a one-third reduction in first MI (3). This commentary provides a theoretical basis to explain why it is plausible to expect additive benefits of statins and aspirin to reduce risks of cardiovascular diseases.

For virtually all cases of occlusive CVD, the underlying cause is atherosclerosis whereas the proximate cause is thrombosis. The statins have pleiotropic effects, but their main property in long-term therapy is to cause marked reductions in total cholesterol and, in particular, low-density lipoprotein (LDL) cholesterol, thus retarding atherosclerosis, the underlying cause (4). Aspirin, in contrast, reduces platelet aggregation thus inhibiting thrombosis, the proximate cause of virtually all cases of occlusive vascular disease (5). Statins and aspirin have different biological mechanisms of action that suggests that their beneficial effects on CVD are, at least, additive. In addition, recent findings suggest that anti-inflammatory effects may contribute to the benefits of both the statins and aspirin on the risk of CVD. First, C-reactive protein (CRP), a marker of inflammation, has been demonstrated to predict future risks of CVD. Second, the benefits of both the statins and aspirin on the risk of CVD appear to be modified by underlying inflammation. Third, there is evidence that both these agents reduce CRP levels. All these research considerations are likely to have future clinical relevance.

The evidence for the anti-inflammatory effects of the statins on risk of coronary disease includes analyses of baseline bloods in the Cholesterol and Recurrent Events (CARE) trial (6). In this trial, patients with a prior history of MI who had a total cholesterol of less than 240 mg/dL and LDL cholesterol levels between 115 and 175 mg/dL, were randomized to either 40 mg pravastatin or placebo. In a nested case-control study (7), patients who subsequently developed a recurrent nonfatal MI or fatal coronary event, had significantly higher baseline levels of CRP and serum amyloid A, another marker for inflammation, than did age- and sex-matched controls (P = 0.05). Individuals in the highest quintile of CRP had a significant 77% increase in risk, and those in the highest quintile of serum amyloid A, a significant 74% increase in risk, as compared to those in their respective lowest quintiles. Further, the benefits of pravastatin on the risk of MI were modified by underlying inflammation. The proportion of recurrent coronary events prevented by pravastatin was 54% in patients with evidence of inflammation, as compared to 25% among patients without evidence of inflammation, even though baseline levels of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were similar in those with and without evidence of inflammation.

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In subsequent analyses of the CARE data (8), CRP levels tended to decrease over the 5-year follow-up period among patients assigned to pravastatin but to increase among patients assigned to placebo. Thus, although there were no differences in mean CRP levels at baseline, the mean CRP level was 37.8% lower at 5 years of follow-up in those allocated to pravastatin as compared to those on placebo. These effects persisted in analyses stratified by age, body mass index, smoking status, blood pressure, and baseline lipid levels. While most patients were receiving concurrent aspirin at entry, randomization, as expected, yielded nearly identical distributions of aspirin use in the statin and placebo groups.

In an analysis of CRP in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), stratification of patients by CRP and lipid levels, suggested that statin therapy may be effective in the primary prevention of coronary events in patients with elevated CRP levels but without hyperlipidemia (9). Finally, in the most recently reported Pravastatin Inflammation/CRP Evaluation (PRINCE trial) the effects of pravastatin on high-sensitivity CRP levels were evaluated among patients with elevated LDL cholesterol levels and no apparent coronary disease to assess changes in CRP levels independent of changes in lipid levels (10). Pravastatin reduced CRP by 16.9% ($P < 0.001$) at 24 weeks, reflecting a decrease of 0.02 mg/dL in the pravastatin group as compared to no change in the placebo group. These changes were largely independent of pravastatin-induced changes in LDL cholesterol. A similar reduction in CRP levels was also observed in a secondary prevention cohort treated with open-label pravastatin.

With respect to aspirin and CRP, the available epidemiologic data derive mainly from observational data within two primary prevention trials of aspirin and cardiovascular disease—the Physicians' Health Study (11) and the Womens' Health Study (12)—as well as a small, randomized, crossover trial of aspirin in patients with chronic stable angina (13). All these trials of aspirin preceeded the development of statins so there was no concurrent use.

In the Physicians' Health Study, men without a prior history of MI or stroke were randomized to 325 mg of aspirin or placebo every other day and followed for the development of an initial nonfatal MI, nonfatal stroke, or cardiovascular death. A companion ongoing randomized, double-blind, placebo-controlled trial in women, the Womens' Health Study, is testing 100 mg of aspirin on alternate days in apparently healthy women. In nested case-control studies of baseline bloods from these trials (11,12), CRP levels were higher among cases who subsequently developed MI or stroke than among controls. In the Physicians' Health Study, men in the quartile with the highest CRP values had approximately three times the risk of MI ($P < 0.001$) and two times the risk of ischemic stroke ($P = 0.02$) compared to those in the lowest quartile (11). Further, the use of aspirin was associated with a significant reduction (55.7%) in the risk of a first MI among men in the highest quartile of CRP but with only a small, nonsignificant reduction (13.9%) among those in the lowest quartile. In the Womens' Health Study, there was a 4.4-fold significant increase in the risk of cardiovascular events associated with the highest versus the lowest quartile of CRP values (12).

Aspirin reduced CRP levels in a 6-week small, randomized, placebo-controlled crossover trial in patients with chronic stable angina and demonstrated ischemia (13). Forty patients were randomized to 300 mg of aspirin daily or placebo for 3 weeks followed by assignment to the alternative treatment for an additional 3 weeks. CRP levels were measured at baseline and at the end of each of the 3-week treatment periods. With aspirin treatment, CRP levels were reduced by 29% compared to those assigned to placebo. CRP levels measured at the end of the placebo phase did not differ from the baseline values.

The current evidence suggests that statins and aspirin have at least additive beneficial effects in CVD. This hypothesis could be directly tested in a randomized, double-blind, 2×2 factorial, placebo-controlled trial. Since each of these agents is clearly efficacious, however, it would be neither feasible nor ethical to conduct such a trial. The trials of aspirin were completed in advance of the use of statins, but the statin trials do include large numbers of patients on aspirin. Although these trials are randomized for statins but observational for aspirin, they provide importantly relevant information.

The hypothesis of additive beneficial effects of statins and aspirin on the risk of CVD could be tested by examining cardiovascular outcomes in statin trials in which individuals in the treat and control groups were stratified on the basis of aspirin use at baseline. Using these methods, benefits in individuals on both statins and aspirin could be compared to those assigned to statins alone or aspirin alone. In performing such subgroup analyses, the power of randomization to distribute equally known and unknown prognostic factors is diminished or lost. In addition, self-selected aspirin use has been shown to be associated with CVD risk factors (14) and thus imbalances in risk between those receiving and not receiving concurrent

aspirin therapy in both the statin and placebo groups may be present. If so, then established risk factors for CVD would need to be controlled for in these analyses. Further, drug therapies of proven benefit in reducing risks of cardiovascular diseases such as β-blockers and angiotensin-converting enzyme inhibitors, may well be associated with aspirin use and would need to be carefully controlled in the analyses.

In some of the statin trials, most of the participants were taking aspirin at entry and in others, almost none. For example, in CARE (6) and in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) (15) trials, 83% of individuals were taking aspirin at baseline, whereas in the West of Scotland Coronary Prevention Study (WOSCOPS) (16), only 2.9% of patients were taking aspirin or other antiplatelet agents. It will be important to include in any meta-analysis the few trials, the Scandinavian Simvastatin Survival Study (17) and the AFCAPS/TexCAPS Study (18) in which there was more variation in aspirin use at baseline (37% and 17%, respectively), as well as the other trials with high and low proportions, respectively, of individuals on aspirin therapy at baseline. In older (19) and even very recent (20) meta-analyses of the aspirin trials, the benefits are apparent across a wide range of doses from about 75 mg to several grams daily. Since the adverse effects are clearly related to the dose, most guidelines (21) recommend low doses of aspirin. It is theoretically possible that higher doses would have anti-inflammatory and antiatherogenic effects, but this hypothesis requires testing in randomized trials. In this regard, it would be of great interest to evaluate any effect modification in the statin trials by dose of aspirin.

Interestingly, the recently published guidelines from the National Cholesterol Education Program (NCEP) (22) provide an algorithm derived from the Framingham risk score for establishing the 10-year risk of coronary disease and identifying absolute risks for lipid-lowering therapies in primary prevention. The recommendations are that patients with an absolute 10-year risk of 20% or greater for developing coronary disease are at highest risk and are candidates for drug and dietary therapies. Specifically, primary prevention patients with multiple risk factors may have absolute risks equal to or greater than secondary prevention patients (ie, those who have survived a prior event) without additional risk factors. Further, primary prevention patients with an absolute 10-year risk between 10% and 20% are also candidates for drug and dietary therapy, but in those whose absolute risk is less than 10%, diet therapy alone is recommended. At present, it has been estimated that NCEP guidelines are being achieved by about 37% of primary prevention and 18% of secondary prevention patients (23). These absolute risk categories for lipid-lowering therapies are similar to those recently proposed for the use of aspirin in the primary prevention of MI (24). If these guidelines were implemented, virtually all patients given statins would also be on aspirin. At present, adoption of these guidelines for statins and aspirin would increase the use of both statins and aspirin in primary prevention. This clinical strategy is likely to yield enormous benefits on reducing risks of CVD.

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