EDITORIALS

Primary Prevention of Coronary Artery Disease

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The development and progression of atherosclerosis is an intricate inflammatory process dependent on intimal entry of low-density lipoprotein (LDL) cholesterol. Although myriad genetic and environmental factors modulate this process, the centrality of LDL cholesterol to the physiology of plaque genesis, progression, and instability leads to the notion that reducing serum LDL cholesterol might be an effective way to mitigate or even prevent the disease.

A number of clinical trials have unequivocally demonstrated the clinical utility of lowering LDL cholesterol levels. The three major cholesterol-lowering trials carried out in people without a history of coronary events (primary prevention trials) include the West of Scotland Coronary Prevention Study (WOSCOPS),[1] the Air Force/Texas Coronary Atherosclerosis Prevention Study,[2] and the Anglo-Scandinavian Cardiac Outcomes Trial — Lipid Lowering Arm.[3] Of these trials, WOSCOPS entered people with the highest levels of LDL cholesterol. A total of 6595 men, aged 45 to 64 years, without a prior myocardial infarction, who had a mean plasma LDL cholesterol level of 192 mg per deciliter (5.0 mmol per liter), were randomly assigned to receive 40 mg of pravastatin daily or placebo. Pravastatin lowered serum LDL cholesterol by 26% as compared with no lowering with placebo. After an average follow-up of 4.9 years, there was a statistically significant difference in the rate of the primary end point, nonfatal myocardial infarction or death from coronary heart disease, between the pravastatin group and the placebo group (5.5% vs. 7.9%, $P<0.001$).

In this issue of the *Journal*, Ford and colleagues[4] present the results of a 10-year follow-up of WOSCOPS that included more than 90% of the original trial survivors. The authors found that over the post-trial follow-up period, when treatment was under the control of the patient and his physician, there was a statistically significant reduction in death from coronary heart disease or nonfatal myocardial infarction, from 10.3% in the group originally assigned to placebo to 8.6% in the group originally assigned to pravastatin. Rates of death from cardiovascular causes and mortality from any cause were not significantly lower in the patients assigned to pravastatin during post-trial follow-up; however, significant reductions were maintained for the entire study interval (including both the trial and the post-trial periods). There was no excess of cancer deaths associated with pravastatin.

There are some weaknesses in the study. Perhaps most important, there was a statistically significant (though small) difference between the original pravastatin and placebo groups in the percentage of patients taking statins during follow-up. Patients did not receive specific advice with regard to statin therapy after the trial but were treated at the discretion of their own physicians. This shortcoming does not detract from the important message of this study, which is that the beneficial effect of statin therapy is durable over the long term.

There should no longer be any doubt that the reduction of LDL cholesterol levels has a role in the prevention and treatment of coronary heart disease. The central remaining question is what is the greatest therapeutic benefit that can be gained, particularly for primary prevention of the emergence of clinical coronary disease? This question has two parts: How early should treatment be started? And how low should the target LDL cholesterol level be set?

The data from Ford and colleagues provide

some tantalizing insights into the first question. The fact that the group originally assigned to pravastatin had better outcomes, even after years of similar statin treatment of the placebo group during the post-trial period, suggests the importance of duration of therapy in determining outcome. Earlier initiation of therapy appears to have durably mitigated the atherosclerotic process.

Recently published data from Cohen and colleagues[5] provide strong support for the notion that earlier treatment, even among asymptomatic individuals, may reduce the incidence of clinical coronary heart disease. These investigators examined the effect of two nonsense mutations of the gene coding for the serine protease PCSK9, the resulting inactivation of which lowers the level of LDL cholesterol. One of these mutations was found in 2.6% of blacks in the Atherosclerosis Risk in Communities Study[6,7] and was associated with a 28% reduction in serum LDL cholesterol. The other was found in 3.2% of white subjects and was associated with a 15% reduction in serum LDL cholesterol. In the black subjects, there was an 88% reduction in the 15-year coronary event rate, and in the white subjects, a 50% decrease. The decrease in coronary events is far greater than would be expected (on the basis of data from clinical trials) from the moderate reductions in cholesterol that resulted from mutation of the gene. The data from Cohen and colleagues underscore the possibility that very large reductions in coronary heart disease event rates might be achieved, even with modest LDL cholesterol reductions, if brought about early enough in life.

What is the optimal target for LDL cholesterol? Epidemiologic studies demonstrate a strong, graded association of serum LDL cholesterol and the coronary heart disease event rate without any clear indication of a level below which further lowering of LDL cholesterol fails to further reduce coronary events.[8-11] Consistent with the epidemiologic observations, clinical trials have demonstrated a strong, graded relationship between serum LDL cholesterol and coronary events.[10] However, even though the few major primary prevention trials show a progressive reduction in event rate with decreasing LDL cholesterol, no primary prevention trial provides information about events below an LDL cholesterol level of about 90 mg per deciliter (2.3 mmol per liter), and none of the trials address the issue in adults in their early to middle years.

Interesting data come from studies of hunter-gatherers, Arctic Eskimos, and other civilizations not exposed to the diets and lifestyles of the "modern" industrialized world. In these societies, cholesterol levels remain quite low (with LDL cholesterol in the range of 50 to 70 mg per deciliter [1.3 to 1.8 mmol per liter]),[9] and clinical and postmortem studies show an absence of both the early indications of chronic disease seen in young people in Western societies and the atherosclerosis seen in older people.[12-15] The "Westernization" of such societies results in development of the same diseases that affect our own,[12] a finding that suggests that genetic differences are not the primary reason for the disparity. The lowest-risk segment of the population in the Framingham Heart Study is sometimes cited to support the occasionally offered suggestion that only about half of the risk for coronary events results from known coronary risk factors. This is somewhat akin to comparing cancer rates in heavy smokers with rates in those who smoke less. The "traditional" societies discussed above are far more appropriate comparators. Comparisons with these societies offer the intriguing notion that very large reductions in coronary disease might attend pharmacologic achievement of the LDL cholesterol levels characteristic of those populations.

Is there an LDL cholesterol level below which incident coronary heart disease is essentially eliminated, or does the relationship approach an asymptote at some nonzero risk level? The geometry of the relationship of clinical coronary events and LDL cholesterol, in patients without prior coronary events, has not been studied at LDL cholesterol levels anywhere close to those achievable with modern therapy. If there is a nonzero asymptote, what is it? We can delineate the geometry by performing clinical trials with existing medications. The geometry of the relationship will determine the ultimate impact of lowering LDL cholesterol. One possible result is that sufficient lowering will reduce the incidence of coronary disease to the point that it becomes a relatively uncommon diagnosis.

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Of Attraction and Rejection — Asthma and the Microbial World

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In the first half of the past century, it was thought that asthma was precipitated or prolonged by infection and that infection with several bacteria, including *Streptococcus pneumoniae* and *Haemophilus influenzae,* had a role in asthma.[1] Some investigators had suggested that bacterial allergy or chronic focal infection could be a cause of asthma.[2] More recently, population-based studies relating infections with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* to asthma severity encouraged a resurgent debate, but clinical trials involving various antibiotics failed to demonstrate sustained clinical benefit.[1]

To understand this debate we need to consider asthma and wheeze in children. The greatest incidence of wheeze occurs in children under the age of 4 years.[3] A significant proportion of infants with wheeze outgrow symptoms between 2 and 3 years of age, and this wheezing phenotype has therefore been referred to as "transient wheeze." The remaining children with wheeze have repeated episodes of airway obstruction until school age, in about half the cohort in conjunction with allergen sensitization to food and inhalants.[4] In school-age children, eosinophilic inflammation in the airway is a characteristic feature of asthma, as it is in adults.[5]

Because of the difficulty in performing complex physiological studies in young children, we know very little about the pathogenetic processes occurring in the airways of infants and toddlers with wheeze. Even less is known about the relation between the progression and remission of symptoms and underlying mechanisms. However, some light is shed from studies in which bronchoalveolar lavage was performed in young children with severe wheeze; it is notable that neutrophilic rather than eosinophilic inflammation in the airway has been found at this age.[6] Whether these findings reflect certain phenotypes of severe wheeze that justify invasive bronchoscopy or whether they reflect features of developing asthma is unknown. In adults, neutrophilic inflammation in the airway is seen in the context of asthma exacerbations due to viral infections and in some patients with severe asthma. Since viral infections are the predominant triggers of wheeze in young children, they may induce neutrophilic inflammation in the airway and thereby contribute to the development of asthma in children up to school age.

In this issue of the *Journal,* Bisgaard and colleagues[7] propose an alternative explanation; that is, that bacterial colonization of the airways may induce neutrophilic inflammation in the airways and thereby cause asthma. In their prospective