CHD of moderate versus more aggressive lowering of LDL-C. Large-scale end point studies investigating this issue are currently underway and will provide answers over the next few years. There are, however, several completed studies reporting the effects of moderate versus aggressive LDL-C lowering on the progression of arterial disease as assessed by angiography or ultrasound.

One such study was the Postcoronary Artery Bypass Graft Trial (10), which followed 1,351 patients who had undergone bypass surgery 1 to 11 years previously. Participants had at least one patent vein graft as seen on angiography. The lipid-lowering treatment was lovastatin supplemented, if necessary, with cholestyramine to generate two groups. In one group the mean LDL-C was 93 to 97 mg/dl, while in the other group the LDL-C was 132 to 136 mg/dl. Angiography was repeated an average of 4.3 years after commencing the therapy. The mean percentage of grafts with progression of atherosclerosis was 27% for patients whose LDL-C level was lowered with aggressive treatment compared with 39% for those who received moderate treatment; this difference was significant (p < 0.001). Furthermore, the rate of revascularization over four years was significantly lower in the group whose LDL-C level was lowered aggressively than in the group receiving moderate treatment.

Another study investigating this issue was the Atorvastatin Simvastatin Atherosclerosis Progression (ASAP) study (11). Conducted in 325 patients with familial hypercholesterolemia, the study was designed to compare the effects of moderate versus aggressive lowering of LDL-C in a population with very high baseline levels of LDL-C. Participants were randomized to receive daily doses of atorvastatin 80 mg or simvastatin 40 mg. The primary end point was the change in carotid intima media thickness (IMT) as determined by quantitative B-mode ultrasound. The LDL-C level in the atorvastatin group was reduced 50.5% from a baseline of 310 mg/dl to an on-trial level of 150 mg/dl, whereas in the simvastatin group the LDL-C was reduced 41.2% from a baseline of 322 mg/dl to an on-trial level of 186 mg/dl. The high density lipoprotein cholesterol was increased by about 13% in each group. Overall, IMT decreased by a mean of 0.031 mm in the aggressively treated group but increased 0.036 mm in the group in which the LDL-C lowering was more moderate. This difference was statistically significant. Regression of carotid IMT was seen in 106 of the 160 subjects in the aggressively treated group and in 65 of the 165 patients on moderate therapy. The change in IMT correlated significantly with the percent of LDL-C reduction.

Despite the impressive reduction in LDL-C concentration in the aggressively treated group in the ASAP study, the on-trial concentration of LDL-C was still well above the target level recommended in the NCEP-ATP-III guidelines. The obvious question arises: Would regression have been even greater had the LDL-C been reduced to ≤100 mg/dl? And if it would, how can such levels of LDL-C be achieved in patients with familial hypercholesterolemia, many of whom have baseline LDL-C levels >300 mg/dl? As indicated in a study in this issue of the Journal (12), one possible approach is to supplement drug therapy with LDL-apheresis.

The study reported by Matsuzaki et al. (12) utilized a combination of drugs and LDL-apheresis to lower the level of LDL-C in patients with familial hypercholesterolemia. This study included 19 patients, all of whom had manifest CHD. All were receiving treatment with a statin (either simvastatin 10 mg per day or pravastatin 20 mg per day) at the time of commencing the study. In an attempt to achieve much lower levels of LDL-C, all patients were recommended to receive LDL-apheresis in addition to the drug therapy. This option was taken up by 12 of the subjects,
with 11 of the 12 completing the study. The remaining seven subjects who declined LDL-apheresis continued to take their lipid-lowering medication and were followed as a control group.

The LDL-apheresis was performed using an automated system in which plasma was passed through two columns containing dextran sulfate covalently bound to cellulose beads. The procedure was conducted biweekly in an outpatient clinic, with an amount of plasma >1.5 times the plasma volume being treated at each session. This procedure resulted in a reduction of the plasma total cholesterol to <100 mg/dl immediately after the LDL-apheresis.

The group receiving medication alone had an LDL-C level that did not change over the year of follow-up (174 mg/dl at the beginning and 181 mg/dl at one year), while the group receiving LDL-apheresis in addition to the drug therapy had a substantial further reduction in concentration of LDL-C. Because the rebound after LDL-apheresis was not linear, the LDL-C concentration in the apheresis group was expressed as a time-averaged value. According to this method of expression, the concentration of LDL-C was reduced by LDL-apheresis from a baseline level of 213 mg/dl to a treatment level of 140 mg/dl.

Coronary angiography was performed at baseline and again one year later to determine the minimum lumen diameter (MLD). Intravascular ultrasound of coronary arteries was also conducted at baseline and after one year to determine the plaque area, the lumen area and the vessel area. The MLD was significantly increased in the LDL-apheresis group but was unchanged in the medication-only group. The plaque area was significantly decreased in the LDL-apheresis group but significantly increased in the group receiving medication alone. Lumen areas and vessel areas did not change significantly during the year of study in either group. The combined use of angiography to assess lumen diameter and intravascular ultrasound to define changes in the plaque is a strength of the study by Matsuzaki et al. (12).

The study provides information of interest and potential importance, although the conclusions are limited by deficiencies in the experimental design. For example, the sample size was small and the subjects were not randomly allocated to the two groups. Nor were the two groups matched in terms of severity of coronary artery disease or plasma lipid levels, although the fact that the LDL-apheresis group had higher LDL-C levels and displayed more severe coronary atherosclerosis at baseline would have masked rather than exaggerated the possible effects of the treatment. Despite the problems with experimental design, the Matsuzaki et al. (12) study does provide evidence of a benefit of LDL-apheresis in patients with familial hypercholesterolemia.

The superiority of LDL-apheresis plus medication over medication alone adds to a growing body of evidence that the benefits of lowering the level of LDL-C are related to the magnitude of the reduction. To this extent, the results of the Matsuzaki et al. (12) study support the conclusion drawn from the ASAP study (11), which used two regimens of drug therapy to compare the effects of aggressive versus moderate LDL-C lowering in hypercholesterolemic patients.

The investigation by Matsuzaki et al. (12) is not the first to suggest cardioprotective effects of LDL-apheresis. Mabuchi et al. (13) reported a six-year nonrandomized study of 130 patients with familial hypercholesterolemia in whom 87 received cholesterol-lowering drugs alone, while 43 received drug therapy plus LDL-apheresis. Greater reductions in LDL-C and lower on-trial LDL-C levels in the apheresis group were associated with a 72% reduction in the coronary event rate (defined as a composite of nonfatal myocardial infarction, revascularization and CHD death). Other reports have suggested benefits of LDL-apheresis (14,15), although these studies were not designed to compare the apheresis with other modes of therapy.

If confirmed, the study reported by Matsuzaki et al. (12) supports a role for LDL-apheresis in patients with familial hypercholesterolemia in whom levels of LDL-C remain above target values despite aggressive lipid-lowering medication. However, the possible advantages of LDL-apheresis have to be weighed against the intrusive nature and the cost of the procedure. It will also need to be demonstrated that the benefits of LDL-apheresis are substantial when used in the setting of a much more aggressive drug regimen than the relatively low doses of statin drugs used in the study reported by Matsuzaki et al. (12). Whether LDL-apheresis will have an additional effect when combined with the highest doses of the newer superstatins remains to be determined. Such a study will need to be conducted before drawing conclusions about the role of LDL-apheresis as therapy to lower the concentration of LDL-C in patients with familial hypercholesterolemia.

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