Dr Maciejko: The Heart Protection Study (HPS) data indicate that in both the placebo and treatment arms, the incidence of coronary heart disease (CHD) events increased with time. Although the treatment group experienced a lesser increase, Dr Robertson points out that the incidence never actually reached a plateau or waned. Dr Robertson, what do you believe to be the significance behind this finding?

Dr Robertson: Obviously, cumulative incidence can never truly plateau, as some events will always occur, but the rate of decline appeared constant over time for treatment versus placebo. This study did not appear to indicate an accumulating benefit, suggesting a steeper event rate reduction for the first year or 2, then a lesser event rate reduction as the disease process stabilized.

Dr Maciejko: Another possible explanation for the incidence of coronary events not reaching a plateau in the lipid-lowering arm of the HPS is the likelihood that the majority of the participants designated as being free of clinically evident CHD at baseline had asymptomatic, undiagnosed coronary atherosclerosis. The lipid-lowering treatment in this study actually reduced the rate of coronary events, which would be defined here as progression of coronary atherosclerosis to coronary artery disease. If this is the case, in order to observe either a plateau or a decrease of coronary events in a treated group compared with a control group, a study population free of coronary atherosclerosis at baseline is necessary. With a cohort completely free of coronary atherosclerosis, those receiving lipid reduction would develop coronary atherosclerosis at a reduced rate compared with the control group. Fewer participants in the treated group would have the potential to develop a coronary event compared to the control group. This would translate to a plateau in the coronary event curve in the treated group relative to the control group.

The recent data from The Cleveland Clinic would lead one to believe that many of the participants of the HPS designated as being free of coronary artery disease actually had coronary atherosclerosis. Of approximately 260 heart transplant recipients, virtually all of the donor hearts had coronary atherosclerosis, which was determined by intravascular ultrasound performed following coronary angiography about 30 days after transplantation. Even the hearts from donors ages 13 to 19 were affected, with approximately 20% showing
evidence of coronary atherosclerosis. Virtually all hearts from donors older than 40 years of age showed coronary atherosclerosis.

The data from this study suggest that CHD prevention studies may need to be looked at differently, not as primary prevention. What these studies have actually observed is that cholesterol reduction prevents atherosclerosis from becoming coronary artery disease.

**Dr Robertson:** With acute coronary syndromes in stable patients, the greatest benefit is most likely during the first 6 or 12 months, and treating for the next 10 years offers relatively less benefit on a per-year basis. I would have expected to see the placebo patients catching up in some way, but perhaps the cost of delay simply cannot be overcome, which the 4S [Scandinavian Simvastatin Survival Study] investigators suggested. In the other end-of-study follow-up analysis of 4S, patients who had been assigned to intervention and stayed on intervention had an advantage that could never be approached by the patients who had been assigned to placebo, then had the opportunity to begin treatment at the end of the study. The advantage just kept widening. Even though the placebo patients eventually had the opportunity to start therapy, they never had the chance to catch up. That again brings up the issues of how early and how aggressive therapy should be to achieve the greatest benefit for the most patients.

**The Value of Testing for Low-Density Lipoprotein Particle Size**

**Dr Blumenthal:** Although it was criticized for methodology flaws, the Campos study yields some very fascinating findings. Essentially, the study suggests that relative risk for coronary heart disease was 4 times higher in patients with large LDL-C [low-density lipoprotein cholesterol] particle size than in those with small LDL-C particles. From a clinical perspective, if you are treating patients with similar triglyceride levels, would you then go on to evaluate those patients to assess LDL-C particle size?

**Dr Robertson:** The study suggests to me that particle size, as a single factor, is quite useful in screening an otherwise unselected group of patients. For any given group of 100 people, the 40 with the smallest, densest LDL-C particles most likely have a family history of diabetes, hypertension, smoking, and central obesity—all risk factors for developing CHD. These people can be identified as at-risk based solely on presence of small, dense LDL-C particles. However, if the patient is already known to be at high risk, what added benefit is derived from characterizing the particle size?

My concern about doing advanced lipoprotein testing and telling the patients they have to get their particle size above a certain threshold for their risk to be resolved or improved is that I do not know if that is, in fact, true. Secondly, the patient's genetically determined apo B [apolipoprotein B] level may make maintaining a large, fluffy population of LDL-C particles simply impossible. And, I do not know if these individuals are still at high risk for coronary disease simply because they are not maintaining large LDL-C particle size.

Still, the publication of this study has prompted me to order more advanced lipoprotein testing; I see LDL-C particle size as an indirect way of estimating particle number, just as the calculated LDL-C is an indirect measure of particle number and true risk. Advanced testing that gives me an estimate of particle number actually helps me know whether I have or have not adequately treated a patient who's calculated LDL-C appears reasonable.

**Dr Blumenthal:** Dr Kwiterovich, in your opinion, can you get the same information by measuring apo B?

**Dr Kwiterovich:** Dr William Connor and associates have studied the Tamar Indians in South America. They consume 85% of their calories as carbohydrates. These people are runners—they are hunters and gatherers—and they have small, dense LDL-C particles. On average, they have HDL-C [high-density lipoprotein cholesterol] levels of 25 mg/dL and triglyceride levels of approximately 120 mg/dL, yet LDL-C levels are generally only 60 mg/dL. Although their LDL-C particles are small and dense, they do not show an increased number of small, dense LDL-C particles.

I agree with Dr Robertson; the important issue is the actual number of small, dense LDL-C particles. The importance of apo B measurement is that it allows an accurate assessment of the number of atherogenic LDL-C particles. Because some evidence has been found that a large number of small, dense LDL-C particles is perhaps more atherogenic than an increased number of larger particles, obtaining a specific measurement of the number of atherogenic LDL-C particles is important. If only the LDL-C measurement is considered, a patient at high risk may be overlooked.
For example, a patient may have an LDL-C level of 120 mg/dL and an apo B of 140 mg/dL, with a lot of atherogenic LDL-C particles.

If more data were available, a more reasonable evidence-based statement could be made as to whether reducing apo B to 70 mg/dL or 80 mg/dL, for example, is appropriate, and if that number should be used as a target for therapy. Unfortunately, those data are not available yet.

**Impact of Combination Therapy on Particle Size and Achieving Therapeutic Goals**

**Dr Kwiterovich:** Zambon's article in Circulation offered a detailed biochemical analysis of the participants in FATS [Familial Atherosclerosis Treatment Study], assessing the combination of colestipol/niacin/lovastatin and cholesterol versus placebo or colestipol alone given to some patients who exhibited high LDL-C levels.1 The investigators evaluated equilibrium density gradient centrifugation and measured hepatic lipase activity. They found that with combination therapy, LDL-C particles became more buoyant, and the hepatic lipase activity decreased to a degree that is highly significant, statistically. In a multiple regression analysis, the strongest predictor of decreased progression of angiographically defined coronary atherosclerosis was the increase in LDL-C buoyancy, and apo B was also a predictor. These findings suggest a constellation of efficacies; combination therapy not only removes LDL-C particles, but also probably decreases overproduction of LDL-C. If LDL-C production is impeded, LDL-C buoyancy will be increased, the number of LDL-C particles will be decreased, and HDL-C levels will be increased, all at the same time.

**Dr Little:** Dr Robertson pointed out that 20% of the patients in the HPS randomized to simvastatin dropped out. Actually, that is very consistent with our observation in treating cardiac patients for secondary prevention; 15% to 20% either cannot tolerate statin therapy or will not take it.

If this kind of dropout rate is seen in the secondary prevention patient population, with patients who should be substantially motivated, the dropout rate for long-term statin therapy must be even higher in the primary prevention population. Does any data support this theory?

**Dr Robertson:** Dropout rates have been quoted as anywhere from 30% to 50% over 1 to 2 years.

**Dr Blumenthal:** Our hope is that with better dissemination of clinical data, patients and providers will be much more apt to maintain therapy and withstand any minor side effects. However, convincing an asymptomatic patient to maintain a cholesterol-lowering therapy is difficult.

**Dr Little:** The message I took away from Dr Robertson's presentation is that although statins are efficacious, they are not the whole answer for treating cholesterol lipid abnormalities. Simple statin regimens bring only half of patients to goal. Combining statins with other modalities can achieve better results than statin monotherapy.

**Dr Robertson:** Relative risk reductions in statin trials rarely exceed 35%. A frequently quoted finding is that a 50% risk reduction was seen for patients with diabetes who participated in the 4S study. What actually occurred was that 50% of the absolute risk was reduced to risk of 25% or less; thus, half of the events that might have occurred actually did occur. Therefore, 25% of the diabetic patients undergoing statin therapy in the 4S study had an event within the 5 years of treatment, despite receiving statins.

Have we addressed the problem of dyslipidemia completely? No. Are we a lot further ahead of where we started? Absolutely. And perhaps we're greedy, but I think that striving for a 50% and greater reduction in event rates is certainly plausible. We will have to be more creative about strategies in order to achieve that goal.

**REFERENCES**

