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Cardiovascular Disease and Lipoproteins: Available Evidence and Remaining Questions. Reactor Panel and Open Forum

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This paper summarizes the responses of panelists and audience to the issues surrounding cardiovascular disease and lipoproteins presented in the previous five papers by Rader, Castelli, Brown, Stein, and Shepherd. Panelists were Virgil Brown, Mark Hlatky, and William Castelli. Sanford Schwartz moderated this session.

Moderator: We will start this session by asking the panelists to share their reactions, thoughts, and comments in the field of cardiovascular disease and lipoproteins.

Mark Hlatky: My research is in the area of outcomes research and I found this presentation very interesting. Different types of evidence were presented, including epidemiological evidence and evidence from laboratory studies and clinical trials. Outcomes research focuses on the bottom line, that is, clinical benefit for the patient. So my tendency is to focus on studies that provide a bottom line answer. Many studies have been conducted in this field with laboratory components, but the key is that we are now seeing very large definitive studies with endpoints measuring clinical benefit meaningful to patients. With the right sort of outcome data, a consensus is now emerging, and people will start changing practices. From an economic point of view, the most compelling evidence comes from large, empirical studies measuring outcomes and economic impact. Economic modeling is also useful but should be kept to a minimum since real data will increase credibility and is the most convincing.

Evan Stein: Jim [Shepherd] presented some interesting hypotheses. The benefit of lipid-lowering therapy was shown to be irrespective of absolute lowering of low density lipoprotein (LDL) cholesterol. Hence, if noncompliers are excluded, any individual taking the drug should have equal benefit. It would be interesting to examine those results divided by quintiles, quartiles, or tertiles. Benefit was also shown to be irrespective of the mechanism involved to lower LDL cholesterol. With respect to the issue on how far can we reduce LDL cholesterol: Is more better? A few trials, such as the Heart Protection Study (HBS2) currently being done in Oxford and the LIPID trial [1], were designed to provide some answers. In a study involving patients with familial hypercholesterolemia [2] (2% of the US population), LDL cholesterol was lowered from about 300 to 200 mg/dL, which was the upper cholesterol level in the West of Scotland Coronary Prevention Study Group (WOSCOPS) [3]. Those patients benefited from this treatment in terms of angiographic reversal. I think benefit is relative for each patient. Even though cholesterol level might remain elevated for some treated individuals, they still benefit from lipid-lowering therapy.

Bill Castelli: In the WOSCOPS study, LDL cholesterol was reduced to 145 mg/dL on average, and about 40% of patients had it reduced to 130 mg/dL. What would happen if the analysis was performed differently, investigating the LDL level at which there was a change in event rate?

Jim Shepherd: The same result was obtained whether we examined absolute or relative reduction. If LDL cholesterol level was lowered by 20 mg/dL, which was the first quintile of reduction, event reduction was minimal. If it was lowered by 35 mg/dL, the highest event reductions were obtained. These reductions were not greater as LDL cholesterol was lowered further in absolute terms.

Moderator: It might be interesting to see if this is also the case in primary prevention versus secondary prevention. In the course of doing economic analysis for the Scandinavian Simvastatin Survival

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Study Group (4S) [4], we observed that if individuals with low LDL cholesterol levels had their levels lowered further, they had fewer cardiovascular events. We may have the opportunity to get some insight into this issue with multiple trials and multiple therapies by performing the same type of analyses as Jim [Shepherd] did for the WOSCOPS study.

Jim Shepherd: This is an important issue because, for ethical reasons, only individuals with LDL cholesterol levels between 170 and 230 mg/dL were enrolled in our trial, limiting the extent of our findings. We need to investigate whether the same kind of benefit can be obtained across a broad spectrum of LDL cholesterol levels by conducting a completely different trial or roll together other trials such as the LIPID [1], CARE [5], and WOSCOPS studies.

Bill Castelli: In a trial where LDL cholesterol levels were not lowered to the goal of therapy for most individuals, one can wonder what would have happened with a more aggressive treatment. Evan [Stein], you mentioned that high density lipoprotein (HDL) cholesterol level was stable during treatment, but LDL cholesterol was lowered and the LDL/HDL ratio was modified. I believe this ratio is the best predictor of what happened in all those studies.

Evan Stein: The most effective way to lower the LDL/HDL ratio is to lower LDL cholesterol level. As Jim [Shepherd] mentioned, it is difficult to alter one type of lipoprotein without altering the others, because they are not discrete parameters; if LDL receptors are increased, other elements are also altered. In the Post-CABG study [6], in the Lifestyle Heart Study [7], and in the STARS diet study [8], HDL cholesterol was essentially the same, whereas LDL cholesterol was lowered and the ratio modified.

Bill Castelli: We know from the work of Connors that HDL cholesterol increases in individuals consuming cholesterol. This explains why levels in America are much higher than in central China. When cholesterol level is lowered, HDL cholesterol also goes down. However, LDL changes at a rate four to five times greater than HDL, so when you lower LDL with diet, you do lower HDL. Still, the ratio does improve.

If we make an analogy with pneumonia and say that a treatment is available to cure this disease in 30–40% of cases, we would not consider it a good therapy. Why do we not obtain better results with lipid-lowering therapies. Probably other particles are involved that we have not yet taken into consideration.

Evan Stein: To treat pneumonia, the responsible organism is first isolated and identified; otherwise a broad-spectrum antibiotic must be used. Before antibiotics were available, it was difficult to save any individual affected with pneumonia; and if, at that time, a treatment had been available to reduce the death rate by a third, it would have been considered a good start. Today, some individuals still die of pneumonia because of unidentified or resistant micro-organisms. But there are a variety of antibiotics now available to treat identified organisms. For coronary artery disease (CAD), we have identified at least one agent involved, that is, LDL cholesterol. For lipid-lowering therapy, there is a need to conduct additional trials to investigate the role of other factors.

Jim Shepherd: I would like to expand on the issue of the dose used in our study. The WOSCOPS trial was not aiming for a target lipid reduction, so our study does not tell us what would have happened if we had prescribed 20 mg or 80 mg of pravastatin rather than a fixed dose of 40 mg. However, response to the treatment in our study can be considered in two ways. Either individuals with the best response to pravastatin were subjects in whom its ancillary action on other issues such as endothelial function and platelet adhesion was more important; or, the drug was more effectively switching on the LDL receptors of these individuals. In the second case, if an individual received half of the treatment dose with the same reduction in cholesterol, or in particle distribution, he would achieve the same benefit in terms of event reduction since changes in the lipoprotein profile would produce changes in event rates. Beyond measuring LDL cholesterol, we need to measure changes in triglyceride-rich particles. Investigating the ultimate target(s) of this drug, which goes beyond LDL cholesterol, is a crucial issue for understanding drug dosage.

Virgil Brown: Jim [Shepherd], what about quintile values? How many events occurred in the treated group versus the placebo group in each quintile, and how close was that to statistical significance?

Jim Shepherd: The total number of events was about 180 divided into quintiles. Half of those events occurred in the first quintile; only a few in the other quintiles.

Virgil Brown: So, with a very small number of events in those quintiles, results were more hypothesis generating than providing answers.

Jim Shepherd: Absolutely. We need to conduct a clinical trial to investigate the effect of drug dosages on event reduction rates. For example, two subgroups could be defined: one group would receive 10 mg of a lipid-lowering drug and the other group would receive 80 mg of the same drug.

Virgil Brown: There is a definite need for dose-ranging studies where one could examine whether the hypothetical parameters identified in the WOSCOPS study and other parameters can be linked with the drug. WOSCOPS is an interesting study that can help us focus on new questions pertaining to those other 70% of events observed as occurring in the treated group.

Concerning the time factor, the first 6 months were not considered in WOSCOPS. Did you perform an analysis of the number of events that occurred during the second half of the study, when most of the benefit of the treatment could be observed? Also, was there any confounding by the fact that subjects in the first 6 months already had some effective treatment?

Jim Shepherd: We excluded people in the first 6 months because we did not have information on their lipid levels. Obviously, as the study went on, the patients aged and the number of events per treated patient increased. However, we did not evaluate just the second half of the study in terms of event reduction. That is something we could do.

Mark Hlatky: It would be interesting to hear more about potential mechanisms and drug dosages. In the old days, a number of interventions were available but they were not very effective in terms of clinical benefit. Powerful drugs are now available which appear effective in reducing clinical events. Can we generalize from a couple of studies conducted with a specific drug and particular doses to all other statins? What about drugs with different mechanisms?

Jim Shepherd: Statins are certainly different from each other in their pharmacology, in their tissue distribution, and presumably in their local effects. Whether those differences translate to clinical variations is unclear. A few trials should be performed for each drug before we can answer that.

Moderator: There are a series of questions we should address. What is the mechanism of action of lipid-lowering drugs? To what extent is more better? What are the changes in cost effectiveness of the intervention as cholesterol is increasingly lowered.

Dan [Rader]: With respect to the mechanisms involved, there is no clinical evidence that statins in general have a direct effect on the vessel wall. Jim (Shepherd) presented a post-hoc analysis suggesting that possibility, but obviously other interpretations can be made. Is it biologically plausible, how can one prove it, and is it important? Statins do have effects on cells in culture in vitro. But concentrations needed are very high; can concentrations achieved in vivo come close enough to those in vitro to relate at least part of the benefit to LDL reduction?

Jim Shepherd: Improvement in forearm blood-flow or substance penetration into the myocardium is observed when an individual receives a statin. We do not know whether that is an effect of the drug per se, or an effect of lowering cholesterol and altering endothelial function. There may be multiple benefits of statin therapy that go beyond LDL, but no data is available to evaluate effects independent of LDL reduction. Another difficulty lies in extrapolating in vitro observations to clinical practice. So far, differences among statins are unresolved.

Evan Stein: The pleiotropic effects observed on platelets and viscosity certainly may share a pathway with cholesterol reduction in platelet membranes. We know there is a relationship between triglyceride lipoproteins and fibrogenic pathways. We also know that the effect of statin on lipoprotein particles is more important in hypertriglyceridemic patients because more remnants in cholesterol enriched VLDL and small VLDL are removed. With respect to the difference between statins, when cholesterol or lipoproteins in general are lowered, a pleiotropic effect across a wide array of parameters can be observed.

Bill Castelli: To address the question of how soon the effects of a lipid-lowering therapy can be observed in practice, I would like to mention that, in our study [9], after a few months of treatment, some patients had LDL cholesterol levels below 90–100 mg/dL, triglycerides below 90 mg/dL, and they had lost their angina. Improvements in their Doppler flow and other indicators were also observed in a short period of time. Based on previous clinical trial data, we told our patients that years of treatment would be needed to see an improvement in their condition, but that was not true. A

study performed by Lance Gould [10] showed that the positron emission tomography (PET) scan of a patient could be normalized after 3 months of cholesterol-lowering therapy. The therapy was then stopped and the PET scan was abnormal again two months later. In the Andrew's study, a cholesterol-lowering treatment was prescribed for 6 months to 20 patients. Thirteen were cured, two improved, one was stable, and one patient's condition worsened.

Moderator: Virgil [Brown] showed in the CARE study that 2 years of treatment were necessary to see a statistically significant impact of the lipid-lowering treatment on clinical events. In the WOSCOPS study, the curve started separating at 6 months. Obviously, clinical benefits can be observed earlier than statistically significant differences.

Jim Shepherd: I agree with Bill [Castelli]. We conducted a study with 10 patients for whom surgeons could do nothing and who were sent home, essentially to die. Those individuals had a serious problem but did not have a high cholesterol level and nothing else was wrong with them. We gave them a statin and other treatment for several months and we observed all sorts of improvements in their condition. We had to stop the treatment due to funding and the patients died.

Moderator: The session is now open to questions from the public.

Speaker 1: With respect to Jim Shepherd's presentation, I agree with what has been said about subgroup analyses, and I think it is possible that a 25% reduction in LDL might produce a maximum benefit. But we do not know that yet. With respect to the comparison of the Framingham-predicted event rates and the actual pravastatin-treated event rates, I would like to mention that predictions of the Framingham model were pretty good [9]. However, it seems probable that predicted rates matched up with observed rates because it was a clinical trial rather than an observational study.

Jim Shepherd: I presented data with all the possible caveats, but you need to weigh the evidence and decide for yourself. Although our placebo group was not absolutely identical to the Framingham males group, there was a difference between the placebo group and the pravastatin-treated group, independent of how absolute risk was calculated.

Speaker 2: I think that using the simple concept of an event is confusing since all events are not equal. I would be surprised if changes in LDL cholesterol levels had equal effect on the multitude of scored events. The problem is, you would need a huge database that cannot be obtained from a randomized trial to investigate this. I am specifically interested in the distinction between non-Q wave heart attacks and Q wave heart attacks, which I think are two different diseases. I believe that early studies did not consider non-Q wave heart attacks as heart attacks, and I wonder if results would have been different if they had been taken into consideration.

Bill Castelli: They were included as coronary insufficiency, and reported throughout. Heart attacks were part of total CHD, which, in the Framingham study, included angina, coronary insufficiency, myocardial infarction, sudden death from CHD, and nonsudden death. Myocardial infarction did not include non-Q wave heart attacks that were part of the coronary insufficiency syndrome.

Speaker 2: So, definitions and scoring have changed and many more subendocardial infarcts are counted today. In summary, each discrete outcome should be studied rather than generalizing for cardiac events. A huge dataset would then be needed, which means that random control trials will not be sufficient to obtain all the necessary information.

Jim Shepherd: I presented information only on the primary endpoint to keep it simple. An economic analysis of our data including the endpoints you are interested in will be published shortly in the *British Medical Journal.* It will provide far broader insight into benefits of therapy in patients who are making a transition from what we consider to be perfect health to cardiovascular disease.

Mark Hlatky: The use of endpoints with multiple pathophysiologies is an issue, particularly to expand the number of outcomes for smaller studies. We should ensure that those outcomes have a common underlying mechanism. For example, use of coronary revascularization procedure is open to a lot of subjective judgment and should not be used as an endpoint. I think we need to focus on clinical outcomes.

Virgil Brown: Given that, it is more impressive when a very consistent change is observed in endpoints that have many other determinants. Changes in cholesterol levels must be very power-

ful to override all of these other variables and give the same response for various endpoints, stroke, for example.

Speaker 3: My primary concern is the clinical significance of these different issues. Could you speak about the significance of some of these other particles you mentioned earlier?

Jim Shepherd: Briefly, some lipoprotein particles in the blood are more atherogenic than others. The intermediate particle between VLDL (which is the source of energy in the circulation in most instances) and LDL (which is the waste product of VLDL metabolism) is very atherogenic, as is the remnant of the VLDL particle. We do have blood samples from patients involved in the WOSCOPS trial and I am planning to measure these different particles to investigate whether these particles are related to event reduction or risk.

Moderator: For the clinician, LDL cholesterol includes most of those particles. In addition, most of the drugs that lower LDL also lower intermediate density and remnant particles. Current guidelines are sufficient since they incorporate these other particles. It would also be very expensive and tedious to perform particle measurements on a regular basis.

Jim Shepherd: If we were to start over again, we might not measure LDL as predictor for risk but we might use a broader measure including LDL, other particles, and VLDL remnants.

Bill Castelli: I think it is important to examine other atherogenic particles, although their measurement is difficult in practice. That is why we also lower triglycerides for coronary patients to reduce all those particles and have a better ratio. To make an analogy with the treatment of hypertension, reduction of blood pressure under 140 and 90 might not be sufficient since, even though the absolute risk is not that high, half of heart attacks and strokes in America occur in individuals with a blood pressure between 120 and 140, and 80 and 90. That is why the Joint National Commission on High Blood Pressure Control (JNC VI) recommendations [11] were set at 130 a few years ago and might be modified shortly. We are taking the same attitude with lipid-lowering therapies to reduce blood lipids to very low levels.

Virgil Brown: I do not have any disagreement with the idea that LDL/HDL ratio is a powerful risk function and is superior to other measurements. However, in the real world, we have not mastered HDL measurement yet. Plasma samples may sit at 98°F from 1 to 72 hours before they get to a laboratory, so I am not sure that measuring remnant fractions is feasible yet.

Speaker 4: I agree with Virgil (Brown) for that reason in particular but also because we incorporate HDL and a lot of other risk factors into our risk assessment model. The ratio is a predictive number, but, clinically, it is more realistic to incorporate HDL as a sole number along with other risk factors, make an overall risk assessment, and base the decision to treat on the overall risk assessment rather than focusing disproportionately on a ratio.

Bill Castelli: The only problem is that if you take multiple risk and get a multiple risk score, you need to define categories to make the decision to treat. Treatments are different whether a patient has hypertension, high blood sugar, or bad lipid profile. For each one of those categories, goals have to be set, therapy initiated, and carried out.

Speaker 5: Evan [Stein], why did you use univariate analysis to perform the LDL cholesterol and triglyceride analysis?

Evan Stein: The researchers of the 4S study performed this analysis. They showed that there was a univariate relationship between triglycerides and LDL and HDL cholesterol levels, but that relationship disappeared when LDL cholesterol was reduced.

Speaker 6: Bill [Castelli], you commented a lot on the HDL/LDL ratio and focused on the Framingham versus WOSCOPS analysis. Following Jim Shepherd's comments on that analysis where they controlled for HDL cholesterol and still observed treatment effects, would you comment on the overlap analysis?

Bill Castelli: The issue is that if an individual's risk is reduced, will he eventually have the same event rate as another individual with the lower number. According to Jim [Shepherd], a treated individual will even have a lower event rate than the untreated one with the low cholesterol level. He might have had beneficial effects on endothelial function and other mechanisms mentioned earlier. It might even be that there was an effect on some of these other parameters that were not considered in the Framingham formula.

Moderator: I think this is an important issue that should be investigated further. If an individual

aged 55 years old with LDL cholesterol of 200 mg/dL receives a treatment to lower this level to 160 mg/dL, his body tolerance might be different than that of a subject with the same age and LDL cholesterol of 160 mg/dL who received no treatment. In fact, the treated person might be at lower risk quantitatively although he appears to be at higher risk. There is a lot to learn from those subgroups.

To close, we have learned a lot since our first hypothesis about the benefits of lipid-lowering therapy for CHD. Many questions have been answered, but many more need response. We have seen that individuals have reached a variety of conclusions after examining data pertaining to lipid-lowering therapy. Importantly, ongoing issues are: (a) the emphasis we put on those conclusions; (b) how we let them affect our clinical judgment and treatments; and (c) whether we are seeing drug class effects, LDL effects, or something else.

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