FOOD AND DRUG ADMINISTRATION

NINETY-FIFTH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

8:30 a.m.

Friday, January 18, 2002

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue, N.W.
Washington, D.C.

ATTENDEES

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C O N T E N T S

NDA 21-387, Pravastatin/Aspirin
Bristol-Myers Squibb, Co-package,
for Long-term Management to Reduce the Risk of Death,
Nonfatal Myocardial Infarction,
Myocardial Revascularization Procedures,
and Ischemic Stroke in Patients with
Clinically Evident Coronary Heart Disease

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P R O C E E D I N G S

(8:30 a.m.)

DR. BORER: Good morning. We'll begin now the second day of the 95th meeting of the Cardiovascular and Renal Drugs Advisory Committee.

This morning we'll be considering NDA 21-387 for the combination of pravastatin and aspirin. Before we begin, Jaime Henriquez will present the conflict of interest statement.

MR. HENRIQUEZ: Conflict of interest statement. The following announcement addresses the issue of conflict of interest with regards to this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all the financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), a full waiver has been granted to Dr. Alan Hirsch for unrelated speaking for the sponsor. He received between $5,000 and $10,000 a year.

A copy of the waiver statement may be obtained

by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Terje Pedersen would like to disclose that he has lectured for and received speaking fees from Bristol-Myers Squibb.

Dr. Paul Thompson would like to disclose that one of his daughters, age 27, owns 200 shares of stock in Bristol-Myers Squibb. He co-manages the account with her. In addition, he has received grant research support from Bristol-Myers Squibb.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they wish to comment upon.

DR. BORER: Okay. There's no comment about that. We'll move on to the sponsor's presentation.

As I said, there's an application for approval of the combination of pravastatin and aspirin to be co-packaged, first in the same package, then in the same pill, for long-term management to reduce the risk of death, nonfatal myocardial infarction, myocardial revascularization procedures, and ischemic stroke in patients with clinically evident coronary heart disease.

The sponsor's presentation will be introduced by Dr. Fiedorek.

DR. FIEDOREK: Good morning, ladies and gentlemen, committee members, FDA, and everyone else who is here today in Silver Spring. My name is Fred Fiedorek, actually pronounced like the hat "fedora," with an EK instead of an A, and it's my pleasure to be here to talk to you about pravastatin/aspirin as an important product for secondary prevention of cardiovascular disease.

I should add that during my formative years I was also trained at Washington University in St. Louis and the University of North Carolina as an endocrinologist, and so doing research and treating patients primarily with type 2 diabetes makes me aware of the need for secondary prevention in diabetics and other patients with similar problems.

On behalf of my colleagues and our consultant panels here today, I am going to discuss and review with

you an overview of what's going to be presented regarding data, meta-analysis on these data, and the public health and medical need for pravastatin/aspirin. I think we will show you today that there's a strong rationale, based on the best available evidence, to support such a combination product.

However, before I begin, I do want to spend a little bit of time on the scope of this problem in the United States. As you can see in this slide, which documents the top five causes for death in the United States for both men and women, cardiovascular disease and cancer certainly dominate. We're not going to be talking about accidents and why men seem to suffer from accidents and not women. We're focusing on the leading cause, cardiovascular disease for both and strikingly for women, and it's this condition that we're talking about in terms of offering pravastatin/aspirin as a preventative product for secondary prevention to prevent these deaths.

There has been progress in this area, and it's been well documented over the last two decades. The green line here shows a reduction in the age-adjusted mortality rate that really occurs for a variety of reasons, including improvements in acute coronary care, better diet and exercise recommendations, better medicines, and all of this has led to this reduction in age-related mortality.

However, you can see from the blue bars that the overall number of deaths for the whole population, admittedly a population that's increasing in size, has remained constant. So, if you really put these two together and sort of think implicitly about something that's not on this figure, you'll realize that as more and more patients survive acute events, have established clinically evident coronary artery disease, there is a need to prevent them from having recurrent events. In fact, in patients such as myocardial infarction patients, approximately 80 or 90 percent of those patients are the ones that ultimately die from a subsequent cardiovascular event.

So, to move on to the rationale of why we think pravastatin/aspirin will be quite useful in this area of secondary prevention, it's mainly three key points or features that we think will address both the clinical and the public health needs for secondary cardiac prevention.

The main features really in the first set of bullets refer to adherence and accuracy in dosing. Clearly pravastatin and aspirin are two of the core elements in the guidelines for preventing cardiovascular disease in the U.S. population, and this has been repeatedly encouraged over the last several years.

In addition, the availability now of a

combination product, which is a prescription product, will allow for both patients and health care providers the assurance that they're getting correct doses for this secondary prevention problem as well as the correct product. In part of the talk you'll be hearing later, it's actually quite striking that aspirin is recommended for these patients but many times, given the availability of aspirin and OTC substitutes for aspirin, such as Tylenol, many patients actually end up on the incorrect product, not appropriate for secondary prevention in this cardiovascular disease state.

Finally, using primarily sort of a common sense argument, the availability of having one combination product with two core parts of the guidelines to prevent cardiovascular disease, pravastatin and aspirin, does offer a common sense way of reducing pill burden for patients and hopefully enhancing the convenience. Admittedly, when we all were in medical school, those of us who were physicians, this sort of idea runs counter to traditional teaching, where the importance of titrating and dosing individual components separately was emphasized. However, just recently I think it's been recognized that these sort of patients with diabetes, hypertension, cardiovascular disease, all require increasing medicines to manage their problems, and so this should be one way of helping.

Now, if we actually look at the labels for these two products, starting with aspirin approved by this committee in these many different indications over the years, aspirin is indicated for a set of both cardiovascular and cerebrovascular prevention indications in patients with clinically evident coronary heart disease. You'll see that this includes evident heart disease, including myocardial infarction, unstable angina, stable angina, and even patients who've undergone revascularization procedures.

For the prevention of cardiovascular disease, those three or four bullet points at the beginning refer to how aspirin can help in prevention. The fourth one is a much more sort of acute preventative that's been recognized as very important for aspirin.

And the final bullet point refers to how aspirin is very critical in preventing cerebrovascular disease.

If we move on to pravastatin, very similarly pravastatin also possesses an array of indications as secondary prevention for cardiovascular disease. It's indicated to reduce the risk of a variety of subsequent events in patients who have clinically evident coronary heart disease.

So, if we consider what overlap exists for

these two labels -- and we offer you sort of for our combined pravastatin/aspirin product an inner section label, if you will, of both pravastatin and aspirin in a combination tablet -- we're looking to see and provide evidence to support how this co-tablet could be used in the long-term management to reduce the risk of the following cardiovascular events in patients with clinically evident coronary heart disease. These events are death, nonfatal myocardial infarction, revascularization procedures, and ischemic stroke.

I'll add that these four events, in the large pravastatin database that we'll be discussing today, represent both the primary and secondary endpoints that were actually a priori specified for these trials when they were conducted. They're part of the prespecified endpoints, and they're also the subject of the analysis of the data and the meta-analysis of all these studies that we will present today.

Moving on to the population that we want to discuss, again, I've described the indications for secondary cardiovascular disease prevention. And what population in the United States does this entail?

You'll see that the potentially eligible population is approximately 12.4 million subjects, and given the indications described previously for aspirin and

pravastatin, it overlaps to a very large degree. Even if you consider possible contraindications for both aspirin and pravastatin due to the well recognized problems of GI bleeding or aspirin sensitivity for aspirin, and other contraindications for pravastatin, we're still left with a population of approximately 10.4 million patients.

So, when these two therapies are combined, what do we need in terms of the properties for a combination product, either recommended properties or required properties for a combination product?

This list is what we will discuss today, and we will cover how obviously, as is well known to everybody here, aspirin and pravastatin have different mechanisms of action, one through platelet aggregation and platelet effects, and one through lipid lowering and vessel wall effects.

We will also demonstrate data on PK, pharmacokinetics, and pharmacodynamics for these two products when administered concurrently.

We will also review, in the large pravastatin database of approximately 14,000 patients, how the safety and tolerability of these agents do not magnify any of the effects of the agents when given alone.

We will discuss in the recommended combination doses for this product how these are appropriate doses for

pravastatin, given the clinical endpoint data that will be presented, as well as the appropriate doses for aspirin, given its cardiovascular and cerebrovascular prevention indications.

A large part of our presentation today will deal with efficacy, and really there are three core components of this which I'll get to later, but clearly we need to show for a combination product how pravastatin and aspirin contribute ideally in an additive fashion to efficacy, and you'll see this in the data we'll describe today.

Finally, from the point of view of preventing a leading cause of mortality in the United States for both men and women, we think this product addresses an important medical need, public health need, that is also impactful for our discussion.

Helping today in this presentation are our five-member consultant panel. The first two members, Dr. Donald Berry and Dr. Thomas Pearson, will be speakers along with me this morning. Dr. Berry is a biostatistician from the M.D. Anderson Cancer Center and he will be presenting data on the meta-analysis of our large pravastatin database. Dr. Pearson, a preventive cardiologist from the University of Rochester School of Medicine, will follow Dr. Berry and discuss the medical need, both clinical need and

public health need, for this combination product.

Also here with us to answer any questions, should they arise, are Dr. Charles Hennekens from the University of Miami School of Medicine. Dr. Hennekens is founding collaborator of the Antithrombotic Trialists Collaboration and will certainly be well-placed to answer any questions on aspirin.

Additionally here are Dr. Andrew Tonkin and Dr. Frank Sacks. Dr. Tonkin and Sacks respectively were our principal investigators for the large LIPID and CARE pravastatin trials conducted over the last 10 years or so, and they will be able to take any questions specific to these trials or about medical practice for cardiovascular prevention in general.

The agenda this morning essentially mirrors the sort of recommended properties I described for a combination product. My colleague, Dr. Rene Belder, will lead off and talk about the first five bullet points. Dr. Belder has been at Bristol-Myers Squibb for 14 years, and has actually been, over the last several years, the main clinical coordinator for all of the pravastatin clinical trials. He's the glue, if you will, of the pravastatin programs.

When Rene is finished with these five topics, he will then hand over to Dr. Berry, again our

biostatistician consultant, who will deal with the efficacy from the meta-analysis of all these pravastatin trials and the database that it represents, and then also discuss how the efficacy, as evidenced in these trials, particularly ones that last five years or more, really provide evidence of consistent and durable benefit for both pravastatin and aspirin when administered concurrently.

Finally, Dr. Berry will turn over to Dr. Thomas Pearson from the University of Rochester School of Medicine. He will discuss medical need, both in terms of the clinical need and public health need.

Our presentation is meant to last about an hour, assuming no interruptions. If there are interruptions -- you need to interrupt -- we'll certainly be glad to take any questions, and if you do let us go through, you can note that on the bottom of the slide in the lower right-hand corner are numbers and letters that can help you call us back up to, as needed, to answer any specific questions.

With this overview, I now want to turn over to Dr. Belder.

DR. BELDER: Good morning, ladies and gentlemen. It's a pleasure to be here today to share with you some of the results of the clinical development program with pravastatin that spans well over 15 years.

As Dr. Fiedorek already mentioned, I will address these five points with you, the mechanism of action of the components, the possibility of a pharmacokinetic interaction between pravastatin/aspirin, the safety and the tolerability of the combination, the doses that we plan to make available in this combination product, as well as the efficacy based on individual trials.

Starting with the easiest part, every one of you is aware, of course, that pravastatin and aspirin reduce cardiovascular events by different mechanisms of action. Aspirin is, of course, an inhibitor of platelet aggregation. Pravastatin reduces cholesterol levels. One would therefore expect that the benefits that these compounds have on clinical events would be independent from each other.

With respect to the pharmacokinetic interaction, we did a single dose, three-way crossover study in 30 healthy volunteers. I'll go over this slide with you so that you'll understand the data on this slide.

The left-hand panel on this slide indicates concentrations with respect to the Cmax. The right-hand panel of this slide indicates the AUC, area under the curve.

In the left two bars in each panel, you see the pravastatin concentrations. In the right two bars in each

panel, you see the salicylate concentrations.

Every time you see a green bar, that means the pravastatin and aspirin were dosed at the same time. When you see a blue bar, only pravastatin was dosed. When you see an orange bar, only aspirin was dosed.

Important for the interpretation of the results for this study are the confidence intervals indicated here, here, here and here, and these are the relative concentrations. The confidence intervals indicate that the concentrations were all well within the limits set by regulatory guidelines to declare bioequivalence. So, the conclusion is that there's no pharmacokinetic interaction between pravastatin and aspirin.

With respect to the possibility of a pharmacodynamic interaction between the two products, we had some discussions with the agency before we submitted the NDA. In light of the absence of a pharmacokinetic interaction and in the light of the fact that the ultimate endpoint that we are after is clinical event reduction, we agreed that doing a pharmacodynamic interaction study would not contribute valuable information. However, we are able to show you the effect of pravastatin in the presence or absence of aspirin with respect to the effects on several lipid fractions.

You see the results from the CARE study in this

slide. The green bar again means that pravastatin and aspirin were dosed. The blue bar indicates that only pravastatin was dosed. You see here the lipid-lowering efficacy with respect to total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol. And it's clear from this slide that aspirin does not influence the cholesterol-lowering efficacy of pravastatin. So, with respect to pharmacodynamic interaction, there is no pharmacodynamic interaction between pravastatin and aspirin with respect to the cholesterol-lowering efficacy of pravastatin.

Before I discuss with you the safety findings from the analysis that we did, I would like to briefly introduce to you the clinical program that we did with pravastatin.

The pravastatin atherosclerosis intervention program consisted of seven placebo-controlled trials, all randomized, 40 milligrams of pravastatin versus placebo. Highlighted here on this slide it shows you the three trials that contributed most of the data in this program. Highlighted are the two secondary prevention trials that are the topic of discussion for today. Those were the long-term intervention with pravastatin in ischemic disease study, the LIPID study, involving 9,000 subjects, the CARE study involving 4,200 subjects.

Also part of this program was the primary prevention study, the West of Scotland study, and again is not a topic of discussion for today.

Also part of this program were four regression of atherosclerosis trials. These trials had as the primary endpoint the evaluation of pravastatin with respect to the progression of atherosclerosis in coronary and carotid arteries. The three trials that are highlighted were in a secondary prevention population. These patients had all evidence of coronary artery disease. The trial that is not highlighted, the KAPS study, was a trial in patients who did not have evidence of carotid or coronary disease and was therefore a primary prevention trial. So, only these studies are being discussed today.

To put these trials in perspective and the contribution that they made to the database that we have, we developed this schematic. You can see here that the LIPID and the CARE study contributed 96 percent of the total patient-years of follow-up in these trials, and that the regression trials contributed about 4 percent of the total exposure. In total, it's a very impressive 74,000 patient-years of exposure, so it provides a very robust database to perform analysis on.

I should also emphasize here that the LIPID and the CARE study were designed as clinical event studies, and

therefore complete follow-up of all subjects was attempted. And indeed, in the LIPID and CARE, there was near complete follow-up. Only one subject in the LIPID trial and one subject in the CARE trial escaped the investigators, so the final status of only two subjects was not known at the end of the studies.

This database of 74,000 patient-years of exposure forms the basis of the safety conclusions with respect to the pravastatin/aspirin combination that you see here on this slide. In the interest of time, I do not show you the data that led us to these conclusions, but you can see here the conclusions that we have with respect to some of the events that may be of interest for either a statin or for aspirin.

With respect to CK abnormalities, note that we did not have any case of rhabdomyolysis in any of the trials with pravastatin. So, we have looked at CK abnormalities, liver function test abnormalities, gastrointestinal bleeds, or hemorrhagic stroke. There was no signal with respect to the combination of pravastatin and aspirin, relative to pravastatin by itself or aspirin by itself, that there was an increased incidence of any of these events in the combination group. So, that leads us to the conclusion that the combination of pravastatin and aspirin is safe.

Since this large database was all based on a 40 milligram dose of pravastatin, it's appropriate to consider only a 40 milligram dose in this combination product. 40 milligrams is the approved starting dose for pravastatin. All prevention studies used the same pravastatin dose, 40 milligrams. This dose was extremely well tolerated and very safe and in the trials there was no down titration necessary for safety reasons. In addition, in a population like the elderly, there is no need for a lower dose of pravastatin.

In essence, pravastatin is only indicated at a lower dose in patients requiring complex management, such as patients with renal or hepatic impairment, of patients who have undergone a cardiac transplant who are on cyclosporine. We think that this combination product would not be a good idea to be used in these complex management situations.

With respect to aspirin, the label with respect to the efficacy of aspirin is clear. It advises that aspirin is effective anywhere between 75 and 325 milligrams once daily, and that therapy should be continued indefinitely.

The doses that we have chosen for this combination product are 81 and 325 milligrams. 81 milligrams was chosen because this is the most widely used

dose for secondary prevention in the United States. The 325 milligram dose was chosen because this is the upper end of the approved dose range.

The key question for today may very well be whether or not we have data that show that pravastatin and aspirin is more effective than each of its components. This question can be broken down in two components. The first part is, is pravastatin/aspirin more effective than aspirin by itself? The other part is whether or not pravastatin and aspirin is more effective than pravastatin by itself.

For both of these questions we have evidence from the two largest placebo-controlled randomized trials, CARE and LIPID. I will address the first question on the basis of the LIPID and the CARE study. Dr. Berry will address the second part of the question, also on the basis of the LIPID and the CARE study, but also on the basis of the meta-analysis. In addition, Dr. Berry will address my part of the question also on the basis of the meta-analysis. So, in short, I will present to you the investigation of efficacy of pravastatin in aspirin users based on the data of the randomized controlled clinical trials, CARE and LIPID.

So, how did we define aspirin users in these trials? Aspirin users were defined as those subjects who

were using aspirin at baseline. Aspirin was proactively collected as a concomitant medication in these trials, so we know whether or not the patient was taking aspirin at baseline. However, we did not rigorously collect the dose level that they were using.

We do know that adherence to the pravastatin regimen was very good. 97 percent of the patients who were using aspirin at baseline were still using aspirin at the end of the studies.

The endpoints that we evaluated for this investigation are, of course, the primary endpoints for the individual trials. For LIPID it was coronary mortality. For CARE it was coronary mortality or nonfatal MI.

In addition, we considered several other endpoints for this analysis. These endpoints are based on the overlap of the pravastatin and aspirin labels, and there are two endpoints that are relatively narrowly defined, fatal and nonfatal MI, and ischemic stroke, and a more broadly defined endpoint of coronary mortality, nonfatal MI, revascularization procedures, or ischemic stroke. Each of these endpoints were prospectively defined as endpoints in all of the trials that we included in the analyses.

Starting with the results of the LIPID study, this is a brief overview. The LIPID trial was a trial in

9,000 subjects who qualified on the basis of either myocardial infarction or unstable angina. The mean follow-up was 6.1 years. As said before, the primary endpoint was coronary mortality, and the patients were randomized to 40 milligrams of pravastatin or placebo. 83 percent of the patients were using aspirin.

These are the results for all subjects for the primary endpoint of coronary death. You can see here that pravastatin reduced coronary mortality by 24 percent, which was highly statistically significant, with a p value of .001.

We now investigate the effect of pravastatin on top of aspirin, so we're effectively investigating the combination of pravastatin plus aspirin, versus aspirin by itself. Here again, for the primary endpoint, coronary mortality, we see a 28 percent risk reduction, which was highly statistically significant.

For the other endpoints that we evaluated for this analysis, fatal or nonfatal MI, ischemic stroke, and the composite endpoint, again very similar risk reductions, all of which were statistically significant.

Of note, I would like to point out that despite aspirin use, almost 30 percent of these patients in the placebo group, despite aspirin use, still had an event, and adding pravastatin to the aspirin regimen cut that risk by

one-quarter.

Now going over to the CARE trial, the CARE trial was a trial in 4,200 post-MI subjects. Mean follow-up was 5 years. Patients all had normal cholesterol levels in order to qualify for this trial, and the primary endpoint was nonfatal MI or coronary mortality. Patients were again randomized to placebo or 40 milligrams of pravastatin. 84 percent of the patients were also taking aspirin.

Again, we start with the primary endpoint in all subjects. We see here that for the primary endpoint, nonfatal MI or coronary heart disease death, a 24 percent risk reduction, highly statistically significant.

Now let's investigate the combination of pravastatin plus aspirin versus aspirin by itself. Again, here for the primary endpoint of the CARE study, a 28 percent risk reduction that was highly statistically significant. The other endpoints considered for this analysis, you can see that for these three endpoints there were similar risk reductions that were statistically significant for two out of the three endpoints considered.

The conclusion from these analyses is that the combination of pravastatin and aspirin is significantly more effective than aspirin alone, as evidenced by the randomized comparisons from secondary prevention trials,

LIPID and CARE.

The second part of the question, as I already indicated, is whether or not pravastatin plus aspirin is more effective than pravastatin alone. Ideally one would like to have a database where aspirin therapy was randomized. However, the aspirin trials were conducted before the statins were used, so we couldn't look at these databases. A placebo-controlled trial with aspirin is not feasible because of ethical reasons. However, the pravastatin database, with about 94,000 patient-years of follow-up, provided the robust database to explore this question. Hence, I would like to hand over now to Dr. Berry, who has explored this question, to answer this part of the question.

DR. BORER: Blase?

DR. CARABELLO: You indicated that aspirin was safe. But we're talking now about buffered not enteric-coated aspirin. Is that correct?

DR. BELDER: That's correct.

DR. CARABELLO: And I'm not certain of that. I'd like to see the specific data that compares buffered aspirin with enteric-coated aspirin in terms of safety. So, I hope those data will be forthcoming.

DR. BELDER: Charlie, do you have any comments on that?

DR. HENNEKENS: Well, we didn't specifically study Bufferin against enteric-coated aspirin, but in the Physicians Health Study of 22,071 men, who were randomized to 325 milligrams of Bufferin or placebo on alternate days, after 5 years of treatment and follow-up, the rates of GI upset were virtually identical in the aspirin and placebo groups, a small excess of the Bufferin over the placebo. The rates of GI bleeding were only slightly higher in the 325 every other day versus the placebo, and finally there was only one fatal GI hemorrhage and that was in the placebo group.

Now, I think that while the formulation is important, I think the data suggests that it's the dose of aspirin that's more important with regard to the side effects. The UK trial of TIA, which randomized patients to placebo, 300 milligrams or 1,200 milligrams of aspirin, found that the rate of GI side effects in the placebo group was 24 percent. It was 29 percent in the 300 milligram a day dose and 39 percent in the 1,200 milligram a day dose.

With regard to GI hemorrhages, the rate was 1.6 percent in the placebo group, 2.6 percent in the low dose aspirin group, 300 a day, and 4.9 percent in the 1,200 milligram a day.

So, it's clear that the higher dose is significantly greater than placebo and significantly

greater than the lower dose. So, I think that the doses that are prescribed here in this combination are well within the range where the rate of the side effects are quite low, and I think it's the dose that's more important than the formulation.

DR. BELDER: In the trials that we did obviously we don't know which formulation of aspirin that patients were using. Just aspirin as a concomitant medication was collected, so it could have been any formulation that's on the market.

DR. LORELL: Thank you for a very clear presentation.

You presented very clear data from the LIPID and CARE trials regarding efficacy on endpoints. However, since those trials were done, there are now guidelines from the ACC and American Heart Association that are followed across the country, that for secondary prevention, each of us should be trying to lower LDL cholesterol to a value of less than 100. It would be very nice to see today what the probability is of achieving that explicit goal, with the use of Pravachol 40 milligrams in your data sets. I didn't see that data clearly in either your presentation or the next one, so perhaps that can be brought back to the meeting a little later.

DR. BORER: Steve and then Susanna.

DR. NISSEN: I recognize that you don't have specific information about aspirin dosages in the trials. Do we have a range? For example, were any of the people receiving, say, 650 milligrams of aspirin? Do we have any information at all about the dose of aspirin that was used in those trials? And I'm specifically interested in whether there are significant numbers of patients who had substantially higher doses of aspirin.

DR. BELDER: We don't have information about that.

DR. CUNNINGHAM: I was noticing also that these studies are predominantly male, somewhere in the range of 85 percent, 84, something like that. Do you have any data on what happens with women?

DR. BELDER: Yes, we do have a subgroup analysis in women. These are the numbers of patients in the various groups, male and female. As you can see, the split is indeed what you indicated.

Here you see the results for the expanded endpoint. Here are men, pravastatin plus aspirin versus aspirin by itself. These are the comparisons that we have so far discussed. Dr. Berry will obviously discuss the comparisons that you see here indicated in blue, which are the observational comparisons.

The point here is that for both men and women

there were significant reductions.

DR. BORER: Bob?

DR. TEMPLE: Maybe I should save this for the discussion, but I think one of the presumptions of this whole thing is that aspirin is approved for these uses at doses anywhere between 80 and 325. I don't think we're primarily asking whether aspirin is effective or safe at those doses. I mean, obviously there's some GI bleeding, et cetera. The question here relates to putting them together in what is essentially a fixed combination. So, some of those things I'm not sure need to be revisited.

The other thought was, if some people took more than 325 milligrams of aspirin and you still saw an added effect of the pravastatin, that wouldn't undermine the observation, the point they're trying to make, which is that when you add to an effective dose of aspirin or even maybe super-effective dose of aspirin you get a further effect.

DR. BORER: Can I ask you how many people in your data set were over 65 and how many were over 75? Just a number. I don't need a slide.

DR. BELDER: I'll show you the slide because I don't know it by heart. Above 65 you see the numbers here.

DR. BORER: And above 75?

DR. BELDER: I don't know. I believe none.

DR. BORER: None?

DR. BELDER: None.

DR. BORER: And we have a statement here that says there is no need for lower doses in the elderly. How many additional drugs were these patients over 65 and the 0 over 75 taking? How many other drugs were they taking?

DR. BELDER: I don't know it by heart.

DR. BORER: Well, I think we ought to know. And what were those drugs? Do we know that? What pathway of metabolism did those drugs use? Which ones interfered with the CYP 450 system?

DR. FIEDOREK: Well, Rene, you might comment about the PROSPER study, which we don't have finished.

DR. BELDER: We have currently in a study ongoing -- actually a study we'll have last patient visits in April. In 5,800 patients, on the age --

DR. BORER: But you have data now?

DR. BELDER: Let me answer one of the questions that you raised, is the CYP 3A4 interaction. Pravastatin is not metabolized by CYP 3A4, and therefore there's no potential for interactions with inhibitors of 3A4. pravastatin, with respect to drug-drug interaction pravastatin is extremely clean. In that sense our current label has a statement about the use of pravastatin in the elderly, indicating that pravastatin is safe in the elderly

population.

DR. BORER: Okay. So, the statement here is that we have sufficient data so that we know there will be no drug-drug interaction, not only to alter the pravastatin level, but to alter the level of other drugs that could be concomitantly taken in the elderly. We know that.

DR. BELDER: And that was part of the original application with pravastatin, to make sure that pravastatin would not alter drugs like digoxin, warfarin.

DR. BORER: Right. And therefore, there's no need to be able to titrate the dose of pravastatin in these people.

DR. BELDER: In elderly, no.

DR. BORER: Is that a statement that the FDA is in concordance with, can I ask?

DR. LIPICKY: I do not know. I cannot answer that.

DR. BORER: Anybody here from metabolic and endocrine?

DR. KREISBERG: It's my understanding that as the drug is approved for utilization, there is no specific statement that titration is unnecessary.

DR. BORER: Unnecessary.

DR. KREISBERG: That it is unnecessary. I believe that the data that has been presented is impressive

data that deals with a fixed dose, but it does not address the issue that was raised by my colleague down the table here about how this fits in with the NCEP adult treatment 3 guidelines, and whether it avoids or perpetuates the idea that the goals proposed by them are unnecessary.

DR. BORER: Yes. The efficacy issue is a very important one. I'm concerned with the relation of safety and efficacy here. Bob maybe can --

DR. TEMPLE: Well, I don't think anybody could say there's never a reason to use a different dose. I doubt the company would say that, and they've asked for and gotten approval of an 80 milligram dose, so obviously there are other doses that are useful.

Fixed combinations of this kind may very well say -- that all depends on what you all think -- that the fixed combination is appropriate only for people who need those relevant doses.

Now, one of the concerns that I guess you'll hear Ray talk about is that we don't want to have the convenience of the formulation constrain people unduly. So, as you see, there are two doses of aspirin because we don't want the existence of the combination -- and we talked to the company about this -- to mean everybody has to get 80 or everybody has to get 325, when both doses are currently recommended in labeling for aspirin.

And that's a fair question to ask about the prava dose. If the enormous majority of people need 40 then you might think that's reasonable. If that really keeps you from meeting some appropriate guideline because you can't go high enough, then you might consider that desirable, or you might handle that by saying the whole idea's a bad idea, or by putting something in labeling that says something. Those are all perfectly good things to think about.

But one of the principles that we've enunciated is that you shouldn't force people to use the wrong dose by having a combination. And for any hypertensive combinations, for example, we try to assure that there are dosage forms that have appropriate levels of each of the components. Not everyone necessarily, but a pretty good range.

DR. BORER: Alan?

DR. HIRSCH: Let me follow u, Bob, on your ideas a little bit. I'm going to ignore achieving guideline goals that I'm sure we'll get to later, but I just want to take a moment and stay on the safety issues. I think when we package things together, we're assuming obviously the patient should take them in that combination.

So far I think we were presented in slide B-4 with the pharmacokinetic crossover study, which looks very

clean. But let me just tease this a little bit further for fun and interest.

We see no change in Cmax or area under the curve for these doses in the small study. The question, I guess, is, do we have any evidence in any way that prava affects aspirin's effect on platelets? In other words, I might hypothesize doing an aggregation study, and again demonstrating either with blood from the patient or in vitro that there is no effect on the platelet wall. Any thoughts? Platelet activation.

DR. BELDER: Well, that's a hypothetical possibility, and we think that is very unlikely. In addition, in the analysis that we did, we see a treatment effect of aspirin. Dr. Berry will, of course, go into further detail on that. That is very similar to the treatment effect of what one would have expected. So, in that respect we don't think that there is any diminished effect of aspirin.

With respect to the possibility of a potentiated effect of aspirin, we are fairly encouraged by the safety signals that we see. Perhaps we can show the slide with the hemorrhagic strokes. This is the fatal and nonfatal ischemic and hemorrhagic strokes. I haven't put them on a slide to put them in perspective with respect to how many hemorrhagic strokes we saw and how many ischemic

strokes we saw. But clearly in this part of the panel, there's no evidence that the combination would lead to an increased bleeding. We have a similar picture for gastrointestinal bleeds.

You may think the fatal events look differently, but -- I think we have the next slide, fatal events. This is for fatal ischemic and hemorrhagic strokes, and again, you don't see any evidence of a signal here.

DR. HIRSCH: No, I agree. I've never seen, in the data sets you've given, that evidence of clinical signal, but I was looking for mechanistic interactions.

Let me take that another way as well, in vitro. We're obviously implying with this that 40 milligrams is the dose that should be used, but patients obviously don't comply with our recommendations. Sometimes they take too little, sometimes they take too much.

So, in these pharmacokinetic studies, again, do we have a dose response? If patients did take 80, or if we administered greater amounts of pravastatin, can we achieve an interaction with differing doses? In other words, how far have you tested the interaction between the two in a dose-response manner?

DR. BELDER: From a pharmacokinetic perspective?

DR. HIRSCH: Kinetic, and then --

DR. BELDER: We did it with a single dose. At the point that we did the study, 40 milligrams was the highest approved dose. We have not done a pharmacokinetic interaction study with the 80 milligram dose. However, based on the pharmacokinetic profile of pravastatin and aspirin -- they're both very short-lived -- one would not expect that at the 80 milligram dose the results would be different.

DR. BORER: One final question before you move on. This is really for Dr. Fiedorek, I guess. What data set were you referring to when you said that patients commonly take Tylenol rather than aspirin with a statin?

DR. FIEDOREK: Yes, I was actually foreshadowing to the fourth talk. Dr. Pearson will talk about that data. It's not in any data in the pravastatin data set. It's a publication on consumer use. Dr. Pearson can answer.

DR. BORER: Are we going to see numbers about that?

DR. FIEDOREK: Actually I'll refer to Dr. Hennekens, who actually did the study, even though Dr. Pearson is going to talk about it. I'll let Dr. Hennekens answer.

DR. HENNEKENS: Working with Nancy Cook at the

Brigham and Women's Hospital, we had the opportunity to review a large national sample of people who had been prescribed aspirin for secondary prevention. In that data set that Dr. Pearson will speak about in detail later, fully 15 percent of people who were told that they should be taking aspirin by their health care provider were mis-medicated. They were mis-medicated either with acetaminophen or with nonsteroidal anti-inflammatory drugs. The other point in that survey is only 51 percent of the people who really should have been taking aspirin were taking it. So, there was both under-utilization of aspirin and mis-medication with aspirin in the very population for which this indication is being sought.

DR. BORER: Charlie, do you know how many of these people had statins prescribed concomitantly?

DR. HENNEKENS: No, but I can tell you -- I don't want to be stealing Dr. Pearson's thunder here. I think a major point is in recent databases suggesting maybe that 77 percent of people are really taking aspirin in secondary prevention who should be getting it, and only 37 percent are getting statins. So, if a combination product did nothing more than achieve that 77 percent of people who were on aspirin who needed the statin were also on the statin, narrowing that treatment gap from 37 percent to 77 percent, that translates to probably over 5,000 premature

deaths prevented each year in the United States alone.

DR. BORER: Okay. Why don't we move along to Dr. Berry.

DR. BERRY: Thank you. Good morning, ladies and gentlemen. I'm a statistician and I work with cancer. I'm especially interested in and passionate about breast cancer, but I work on other diseases as well.

I'm interested in Bayesian statistics. The Bayesian approach is particularly appropriate for synthesis of information in the sense Bayesian analysis is meta-analysis. However, I will be presenting standard frequentist multivariate analyses and expanding the assumptions, dropping assumptions, expanding the model to consider Bayesian analyses as well.

Dr. Belder has addressed the question of pravastatin on top of aspirin, a randomized comparison. I'll address that comparison in the context of all five secondary prevention studies, and I'll also address the issue of aspirin use among those assigned to pravastatin, and finally I'll address the question of the persistence of the effect over time.

The possibilities. Pravastatin was randomized with placebo in all the trials we'll be talking about. Aspirin use and non-use was also measured, and so we have four categories. The combination. We'll be comparing the

combination with placebo, the randomized comparison that Dr. Belder talked about. We'll also be comparing the combination with pravastatin alone, the observational comparison.

Placebo seems left out of this, and indeed, in most of the comparisons we'll be talking about the combination on top of a single agent, but at least once in the presentation I'll compare back to placebo. It's an important benchmark.

The question is, is the combination more effective than pravastatin alone. We have LIPID and CARE. The event rates in LIPID and CARE suggest that indeed that's the case, and you see that here. Both of these are observational comparisons. This is with respect to the primary endpoints in LIPID, which was coronary death, and in CARE, coronary death or nonfatal MI. The rates here are greater, but the effect of aspirin, the reduction among those using aspirin is about 35 percent in both of these studies.

Now, you're worried, of course, that the patients who took aspirin had different characteristics from those who didn't take aspirin. Perhaps they had better prognoses, perhaps they had worse prognoses. An approach to take into account the possibility that aspirin use was differentially applied in these studies, that

patients took aspirin for a reason associated with the extent of their disease is to adjust for the various covariates, the patient characteristics.

You see here we adjust in the multivariate models for age, gender, previous MI, smoking, baseline lipids, baseline blood pressure. So, every analysis that I do and every comparison that I do will be taking these into consideration.

There are other variables that might affect aspirin use. For example, you'll notice if you have looked at the submission that among patients taking aspirin as opposed to not, those taking aspirin had a slightly higher incidence of revascularization procedures. So, that suggests that we take into account other things that might be used in assigning aspirin. Revascularization, diabetes, obesity, these variables we had in the two principal studies, in LIPID and CARE. We did not have them in the other three, the smallest studies. We've done separate analyses addressing specifically these, and also the use of ACE inhibitors, and I can tell you about that if you're interested.

The bottom line is that qualitatively there's no difference in the conclusion within LIPID and CARE considering these variables in addition to these as opposed to just these. So, we can talk about that if you'd like,

but the rest of my presentation this morning will be focusing on those.

Now, no multivariate analysis can turn an observational comparison into a randomized comparison. However, if we look at subsets and we see the same thing from one subset to the next, which is in fact what we do see and you saw an example of that with the breakdown by gender, then that gives more confidence that in fact the result is real.

These are the five studies. Dr. Belder has talked about LIPID and CARE. LIPID and CARE consist of approximately 90 percent of the population and you see that here, 13,000 or so from the 14,500, the total being 14,600. The percent of aspirin use varied, approximately 83-84 percent, as Dr. Belder indicated, in LIPID and CARE, but somewhat less in the other studies varying down to 43 percent in PLAC II. Overall, about 80 percent of the patients were taking aspirin at baseline.

Now, in two of the models that I'll be talking about, we worry about the possibility that the trials are heterogeneous, that there are different characteristics of these trials somehow, even if we adjust for the covariates, that there is an additional trial effect that could affect the conclusions. So, we're going to allow for the possibility of heterogeneity.

However, the trials, the five trials, had lots of commonalities, and these are listed here: similar entry criteria, similar types of patients, of course a randomization of pravastatin versus placebo, long-term follow up, endpoints. We'll consider particular endpoints or others that you may be interested in and we can show you. These endpoints were all measured in the trials, the covariates recorded. The data analysis for each of these trials was conducted independently of the sponsor, separate from the sponsor. However, the sponsor has combined the data into a single data set with all of the variables in question to facilitate the meta-analysis.

These are the endpoints we're considering, three: fatal and nonfatal MI, ischemic stroke, and then a composite including these, but also including any coronary death and the vascularization procedures.

The first model that I want to talk about is the standard one, the one that is familiar to most of you, I suspect. It is a multivariate Cox proportional hazards model, which will include all of the covariates that I talked about before. The patients are combined across the trials. We're considering the single data set, but we also consider trial as an effect, so trial is one of the covariates that we are adjusting for in the model.

This is for fatal or nonfatal MI. This, the

yellow comparison is the one that Dr. Belder talked about. It is the randomized comparison of pravastatin on top of aspirin. So, this is restricted to the patients taking aspirin. What is the benefit of adding prava? And you see that it is a 31 percent for fatal or nonfatal MIs, a 31 percent reduction.

This is the observational comparison. Among those patients who were randomized to pravastatin, 80 percent of them were taking aspirin. The benefit of aspirin amongst these patients was about 26 percent. This is the value 1. The fact that the confidence interval does not include 1 means that it is statistically significant in this multivariate analysis.

The next endpoint is ischemic stroke. The confidence intervals are wider because there are fewer events in ischemic stroke. Again, this is prava on top of aspirin, a 29 percent reduction. This is aspirin on top of prava, a 31 percent reduction. And again, statistically significant.

The composite endpoint, of course more events, smaller confidence intervals, the reduction due to pravastatin on top of aspirin, 24 percent; 13 percent aspirin on top of pravastatin. And again, statistically significant.

Now one of the questions of interest to the FDA

is, is this one study? Is it two studies? And to address that, we've broken out into LIPID and CARE separately. So, the analyses that you've seen on the previous slide, I'll repeat on the next two slides. This is the randomization. See, all yellow? This is the randomization comparison, the benefit of pravastatin on top of aspirin for LIPID and CARE, LIPID and CARE, LIPID and CARE for the three endpoints that we're talking about. This is the number 1, so statistical significance if it overlaps the number 1 for these studies separately.

So, for example, you see in LIPID about a 24 percent reduction in the composite events for pravastatin on top of aspirin, about a 24 percent reduction, the same for pravastatin. This is pravastatin on top of aspirin in CARE and in LIPID.

The observational comparisons in blue, and the composite endpoint of 14 percent reduction of aspirin on top of pravastatin in LIPID, a 22 percent reduction for aspirin on top of pravastatin in CARE. And again, both statistically significant.

This is the second model I want to consider and it is an extension in the following way. It's a Bayesian hierarchical model. It allows for the possibility of heterogeneity in the studies, in the various trials. It treats really two experimental units. This is a

hierarchical model. There are two levels of experimental unit. One is patient within trial, but trial itself is an experimental unit. There is more information in a trial with larger sample size, but the trial is counted as much as any other trial of the same size.

Now I want to show you the comparisons here. This is the cumulative proportion of events -- this is for fatal or nonfatal MI -- out to 5 years for the randomized comparison of the combination versus aspirin alone. So, this is prava adding to those patients taking aspirin. This is the 31 percent reduction out here at year 5. It's easiest to see the 31 percent reduction in event rates, as well as in hazard.

The other randomized comparison is for prava for non-aspirin users, prava versus placebo. And here the reduction -- actually we haven't shown you that -- is about 20 percent.

Any comparison of a dotted line with a solid line is an observational comparison because it compares aspirin versus not. I said I'd mention placebo. The effect of aspirin alone is a reduction here of this extent. The effect of prava alone is a reduction of this extent. If you add those two together, you get something, I don't know, about down here. What we're looking at in the combination is something that is at least additive.

This is for ischemic stroke. Again the randomized comparison of pravastatin on top of aspirin, and this was I think a 29 percent reduction. This is the randomized comparison for the non-aspirin users, and the benefit here, I think it was like a 29 percent reduction in risk for patients in comparison of aspirin alone versus those who were taking pravastatin plus aspirin.

And the composite endpoints, I think similar. This was like a 24 percent reduction, and this is like the 14 percent reduction that we saw a couple of slides ago.

So, the same thing is happening in model 2 as model 1. The analyses that we did in model 2, allowing for this study heterogeneity, reinforced the comparisons in model 1. So, the combination provides an benefit for all three endpoints, the benefits ranging from 24 percent to 34 percent comparing the combination to aspirin, and 13 percent to 31 percent comparing the combination to pravastatin. The benefit was similar in models 1 and 2. And this benefit was consistent within the studies, LIPID and CARE, considered individually.

Now, a possibility that you might worry about -- we're doing proportional hazards. And so these are cumulative proportion of events for model 2, very similar for model 1, and you see that these lines don't cross. Roughly speaking the hazards are the derivatives of the

slopes of these lines. These are the hazards by year for the first year, the second year, up to the fifth year. And you see that these things are proportional for each of the treatment groups. That is one of the assumptions of model 2 as well as model 1. You see a drop in hazard. In the first year, all these have a higher hazard. Presumably the mixture of patients is heterogeneous and the patients are at high risk, at least some of the patients are at high risk, in the first year. And they recur. When we go to the second year, the hazard is calculated by redefining the denominator so that we're looking only at at-risk patients. The hazards drop and presumably start to increase with the force of mortality. People are getting older.

And so we introduce model 2. And one of the concerns that you might have is, well maybe one of these agents, say aspirin, works early on and then doesn't work anymore. And pravastatin works late on and doesn't work early on. So, maybe you can take aspirin first, and then after a few years convert to pravastatin. And so far, we've not worried about that possibility. I want to worry about that possibility. We want to extend model 2, all of the multivariate modeling aspects of model 2, to allow for the hazard ratios within treatment to vary over time.

This is the cumulative proportion of events from model 3. These are estimates. I can tell you what

the probabilities are for comparing these curves at any of these time points if you are interested.

These are the hazards. The hazards, now you see there's a great deal more noise because we are modeling these things individually. We're modeling the hazard in year 1, separate from year 2, separate from year 3. So, there's a good deal more variability and crossing here of some of the hazard functions. For example, it happens in year 3 that the hazard for aspirin alone is actually slightly greater than placebo alone. You expect that sort of thing because there's a good deal of noise here.

There are several amazing things about this picture. One is that the combination is better in each one of these years. The combination is better than any one of the other treatment groups in every year. These are like five separate studies. The events in this group in the first year are distinct from the second year or distinct from the third year, etc. So, we sort of start over again. And when we start over again in the second year, again the combination wins.

Now, I can quantify that for you if you like, I can tell you what the probability is that in this particular year the hazard is better for the combination than, let's say, for aspirin alone. But the important thing to me is that the hazard is better for the

combination group in each one of these years. It shows the persistence of the effect.

Another interesting thing about this picture is it shows what doesn't happen. I mean, one of the things that you see in the first year is that the combination lowers the hazard. What does it do? Does it extend the period of time before the event occurs? So, does it push it into the future a year or two? If that were the case then you would expect this bump coming later. That doesn't happen here.

So, the conclusion of the hazard analysis over time, the benefit of the combination over aspirin was present in each year of the 5-year duration of the trials and the same is true for the combination over pravastatin. The benefits estimated for model 1, the confidence intervals in particular, were confirmed by the more general models and fewer assumptions. When we dropped the assumption of proportional hazards, for example, we observed the same thing.

So, we've observed benefits in the meta-analysis. We've observed the same benefits within the studies considered separately. We allowed for heterogeneity in a number of ways, but in fact these studies are quite homogeneous with respect not only to the baseline characteristics but also the results.

And so now I'd like to turn the podium over to Dr. Tom Pearson who will discuss medical need.

DR. BORER: Are there any questions for Dr. Berry? Ray.

DR. LIPICKY: I guess I missed it when I first looked at the thing, but you actually think the analyses suggest that there's a super-additive effect or a synergistic effect between prava and aspirin and that you could --

DR. BERRY: Dr. Lipicky, between you and me, the answer is yes. I think there is a super-additivity.

DR. BORER: I'd like to extend the question I asked earlier. You had 1,600 people who were over age 65. 3 percent of your total population had liver enzymes that were at least three times the upper limit of normal or CK at least four times greater than the pretherapy level. How many in the above age 65 group had these abnormalities? Do you have that breakdown?

DR. BERRY: One thing. Not in direct answer to that question, but we have done a separate analysis of the over 65 with respect to what I've shown, if you're interested in seeing that. You don't care about that.

DR. BORER: I'm not because I believe you. And I don't disbelieve anything I've heard. You know, we're talking about a single dose to be mandated as part of a

combination that could conceivably alter practice patterns, and I want to know about the safety of doing that relative to the effectiveness which we're going to hear more about. Bev has already raised that issue.

DR. BELDER: Perhaps I can tell you what currently the pravastatin label states about geriatric use. It says the following. Two secondary prevention trials with pravastatin, CARE and LIPID, included a total of 6,593 subjects treated with pravastatin 40 milligrams for periods ranging up to 6 years. Across these studies, 31 percent of pravastatin subjects were age 65 or older and .8 were age 75 and older. The beneficial effects of pravastatin in elderly subjects in reducing cardiovascular events and in mollifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

DR. BORER: Okay. Do you have the numbers I asked for, or not?

DR. BELDER: So, in the two trials there was – we didn't do an analysis of CK by age, no.

DR. BORER: Okay. Or liver enzymes. No.

DR. BELDER: Well, with respect to liver

enzymes, the current pravastatin label does not require liver enzymes to be measured after initiation of therapy, and that applies to all ages.

DR. TONKIN: Perhaps if I could make some comments about the safety database and also about the issue around age. LIPID contributed 68 percent of the data that you're seeing. In fact, at baseline there were 1,511 patients age 70 or over. They were followed for a mean of 6 years, and then in fact after that, we approached all patients, including those who had been randomized to placebo, to see whether they would be agreeable to go on to open-label pravastatin, specifically to get more data about safety, including the elderly, more data about cost effectiveness. In fact, we have 95 percent of the initial cohort who had survived who hadn't died who agreed to that further follow-up. So, the safety danger in LIPID now goes out to where patients may be 83 or so. We see no signals.

But the important point, I think, is that what we did in LIPID was we said, what is the effect of pravastatin in a dose of 40 milligrams against placebo against the background of usual therapy. So, the individual clinicians had to make the decision about whether or not patients should be on aspirin. The trial didn't mandate it. We left that decision to the clinician. So, undoubtedly, a number of people who would not be

treated with aspirin are not getting into the data set.

With respect to the overall data set with pravastatin, if one includes also the West of Scotland study with LIPID and CARE, there is 112,000 person-years of experience comparing pravastatin, a dose of 40 milligrams, against placebo. In fact, there are many patients who remained on pravastatin as remained on placebo at the end of the study. Extraordinary tolerance. There was not a single case of rhabdomyolysis in that 112,000 patient-years of experience.

If you took those patients who had abnormal liver function tests at baseline, there was no difference between placebo and pravastatin on top of that in terms of deterioration.

So, I think the experience with respect to safety is extraordinary. What really this is about is ensuring the patients would receive the dose that is proven in the studies, that against what would be the position of judgement, if you like, about usage of aspirin.

DR. BORER: Bev, did you have a comment? Or Susanna?

DR. LORELL: I guess one of the comments in the geriatric use paragraph that was read, in the next paragraph there actually is a comment that mean AUCs were slightly higher in elderly subjects.

DR. BELDER: That's correct. There is quite some variability in the AUC levels of pravastatin. However, as Dr. Temple indicated before, we have recently gained approval of pravastatin at 80 milligrams. In addition, we are collecting quite a substantial safety database on pravastatin of 1,260 milligrams, and so far we do not observe any safety signal with pravastatin.

Again, I don't think that the safety of pravastatin in whatever population is an issue. Pravastatin has been proven to be extremely safe in a variety of patient populations.

DR. BORER: Okay. Tom.

DR. FLEMING: Don, I had a couple questions. I appreciate and thank you for the very nice presentation of these three models. Certainly they are very informative.

As you note, the major challenge here is really trying to understand what aspirin adds to pravastatin in the absence of randomized trials. These models make an attempt to make adjustments for the imbalances that may exist between those who elect to use aspirin versus those who don't.

You have adjusted for a number of factors and I think you've really acknowledged this. What concerns most of us about observational data and analyses and models such as this is that they are informative and helpful, but we

worry about whether we're adjusting for differences that are the tip of the iceberg.

You have noted that demographics -- smoking, revascularization procedures -- were important elements to adjust for. I understand you have adjusted for all of those in the model.

Some of the other things that we might think about are, for example, differences in other interventions, baseline treatments. We see, for example, in the FDA briefing document on pages 37 and 38, we see differences in beta blockers that are more frequently being used in those who are choosing to use aspirin and those who are not.

How have you addressed the potential impact of differences in concomitant meds between those electing to use aspirin and those not?

DR. BERRY: We did an analysis within LIPID and CARE separately for ACE inhibitors. I can't remember. Did we also do beta-blockers? Can you bring those slides?

All of these are within model 1, that is, the standard proportional hazards model. Model A is what we talked about. Everything that you've seen is model A. Model B includes these other issues of diabetes, the revascularization procedures, BMI, obesity, stroke, dyspnea, angina. Model C includes the same as model B, but also beta-blockers and ACE inhibitors.

And this is CARE. The variables in CARE are slightly different, as you see here. We didn't have some of the same variables. There are additional variables in LIPID as opposed to CARE. And so I'll show you these things separately. These are separate models and it's awfully busy. Let's see if we can focus on, say, the composite endpoint.

This is the composite endpoint and we are now talking about LIPID. And so in LIPID this is what you saw before. This is somewhat different now because it doesn't include all of the other studies. This is just LIPID separately. There was a 24 percent reduction in pravastatin on top of aspirin and a 14 percent reduction in aspirin on top of pravastatin. That was model A. If we incorporate the second tier of variables, we get something which is comparable. If we go to model C, which also includes the beta-blockers and the ACE inhibitors, we see something that is very similar.

DR. FLEMING: While we're here then, essentially model C is the direct answer to this specific question.

DR. BERRY: Right.

DR. FLEMING: But also let's look at CARE.

DR. BERRY: CARE, in fact, gets even stronger. The conclusion is even stronger.

DR. FLEMING: So, they go in a bit the opposite direction?

DR. BERRY: Right.

DR. FLEMING: With CARE, adjusting for beta-blockers and ACE inhibitors, there seems to be an enhanced effect. With LIPID, there seems to be a somewhat diminished affect.

DR. BERRY: Only slightly diminished. If you go back, you'll see that it's not changed. It is slightly diminished.

DR. FLEMING: 14 to 11 to 12 to 9.

DR. BERRY: Slightly diminished, 35 to 30.

DR. FLEMING: And this is using as covariates beta-blockers and ACE inhibitors as reported at baseline.

DR. BERRY: That is correct.

DR. FLEMING: Second question. If we look at the raw data, the conclusions, Don, that these analyses have presented, not too surprisingly, are fairly consistent with an impression you get when you just look at the raw data. One place that that is presented is in the FDA briefing document on pages 41 to 43 for each of the five major endpoints that were considered. And it's really worth perusing that data for a moment on pages 41 to 43 because it really shows an intriguing pattern.

What it does is it breaks the data out into

groups by pravastatin plus aspirin, pravastatin alone, aspirin alone, and neither, which ideally we would have liked to have had in a true factorial design. Of course, what we know is that this is based on pravastatin to placebo randomization where aspirin use is observational.

As you scan through these three pages and you're looking at each of these endpoints, what you find, which is somewhat similar, Don, to your comment a bit early about there maybe being a positive synergy here, is for each of these five endpoints, you find that when you add aspirin to pravastatin, you get a much more vigorous or substantial improvement and outcome than when you're adding aspirin to control.

In a sense, that's reassuring because the really relevant question here is, what does aspirin add to pravastatin, not what does aspirin add to nothing. And yet, what we're dealing with here, as you've acknowledged, is we're out on the end of a limb here because we're really trying to determine what the effect of aspirin is in nonrandomized data. Where we do have randomized data is looking at the effect of aspirin alone.

So, what concerns me is, when I look at these five endpoints on pages 41 to 43, when I'm making the comparison from aspirin against nothing, I'm seeing essentially no effect on any of these five endpoints. Not

only is it less effect than what aspirin does in the presence of pravastatin, but what aspirin does in the absence of pravastatin in these data is essentially nothing.

What concerns me is that's not consistent with what we've seen from randomized trials looking at aspirin. We do have evidence about what aspirin does in randomized trials, but it's in the absence of pravastatin. So, now that we're in this realm and we're using these data out on the end of this limb to say what aspirin does in the presence of pravastatin, and we look also at what these data are saying about what aspirin does in the absence of pravastatin, and we see an answer that's inconsistent with the randomized trials, how do we reconcile this? In your exploration of these data, can you tell us why aspirin doesn't add anything in the absence of pravastatin?

DR. BERRY: Yes. First of all, the group that you're looking at is the smallest group. It's the set of patients who were not taking -- let me start over again.

DR. FLEMING: It actually is half of the group.

DR. BERRY: Yes, it's half of the group. That's why I'm starting over again.

The effect of aspirin. If you looked at this study and said -- I think we have a slide on this -- let's look at aspirin alone, 80 percent versus 20 percent, what

is the effect of aspirin? The effect of aspirin alone is the mixture of, or the average of the effect of aspirin for those patients who were taking pravastatin plus the effect of aspirin for those patients who were not taking pravastatin.

And so you correctly say that the benefit -- let's think about the composite endpoint where the comparison that you're making is most pronounced, and actually why don't we show that slide, the one where the composite endpoints, model 3. It's one of the late ones, like C-20 or so.

So, this is what Dr. Fleming is talking about. If you compare placebo and aspirin alone, there's very little difference. In fact, I think it was like 3 percent reduction due to aspirin. If you compare, however, the pravastatin, the affect of aspirin here, it's -- I don't know -- 13 percent or so. And so if you ask the question, what is the overall benefit of aspirin in this study, it's about a 10 or 11 percent reduction, 13 percent average with 3 percent, but with the greater weight on the other one. As to why this is not different, I'd give it to small sample size.

Let me say one other thing about that. In terms of the composite endpoint, the composite endpoint includes the revascularization procedures. And we have a

slide, which we can show for the various endpoints, which indicates that in fact aspirin has no benefit on revascularization procedures. In fact, if you took these out, there would be a separation here.

DR. HENNEKENS: Can I make another point, Don?

DR. FLEMING: Oh, Charlie.

DR. HENNEKENS: I just want to make another point on Tom's question because this issue was troubling to me when I first looked at these data as well.

My own looking at it is as follows. If we look at the randomized comparisons in the Physicians Health Study, the time course to benefit, we began to see that over 40 percent benefit within 6 months of taking the aspirin. Then it persisted over the 5 years until the trial was stopped because of the statistical extreme nature of that finding, with more endpoints developing.

I think it's important to point out that in the CARE study, the time of randomization was 10 months after the event and the time to randomization in LIPID was 13 months after the event. So, I think one of the issues to consider is that the major benefits that aspirin conferred may have occurred already before these trials began.

DR. FLEMING: Charlie, are you suggesting then that this might be true here, that after you've been on a certain period of time, continued use of aspirin is not --

DR. HENNEKENS: No, I think that these data -- I think Rene was going to show that these data also show benefits among the aspirin users compared with the non-users. However, the ability to study this, I guess you'd call it, interaction would be best, as you point out, in a randomized, double-blind factorial trial where everyone is assigned to the agents at the same time. And here we have a disconnect because we have, in my view, predominantly anti-atherogenic effects of the statin drug that takes some delay until it occurs, and the predominantly antithrombotic effects of the aspirin, and the time course of that large benefit is within the first several months of starting it, which would be at the time these people were started, I think. It's just a methodologic point I wanted to add to the discussion.

DR. FLEMING: Don, while you're speaking, could you put that slide back on again that you just had?

DR. BERRY: Put it on again.

A bottom line that you can read from this is that the only way to get a benefit from aspirin is to take pravastatin with it.

DR. FLEMING: I like your color coding and your interpretation before.

Basically, as I look at this, where at least I feel most comfortable, I have to admit, is where I have

randomized comparative trials.

DR. BERRY: Sure, of course.

DR. FLEMING: And as you note, when we're comparing these solid lines, and in particular the solid orange against the solid green, it's answering an important question and doing so in the context of a randomized trial. What does pravastatin add to aspirin?

The other question that I find very interesting is the dotted purple against the green, which is, what does aspirin add, the dotted purple there, against the green. Which is what does aspirin add to pravastatin?

What's encouraging, as you noted, is that that seems to be greater than what the orange does against the dotted red. If anything there is synergy here. And where my discomforts is I know something about the orange against the dotted red from sources that are much better than this, from randomized trials, and they don't agree with this. So, I'm just left with a sense that when I'm seeing something that I do know about that doesn't agree with this, then where I'm trying to use this, which is the dotted purple against the green, it just makes me a little uneasy.

The good news is, though, that this is underestimating what the effect of aspirin is. So, if I extrapolate that, then one might be willing to say that the

green versus the dotted purple is underestimating, that's one positive way to look at it.

The negative way to look at it is, when I have randomized trials and I have historical evidence or observational evidence and they don't agree, then it makes me more worried about being out on the end of that limb when I'm having to use observational data for the green against the purple.

DR. BELDER: Don, we did a couple of other looks at the data, and perhaps a slide up.

This is all aspirin users and this is what Don already alluded to, that basically the effects on the lines that you see is an average of the aspirin users in pravastatin-treated patients and non. And here you see the effects on the various endpoints of all aspirin users versus non-users, and the treatment effects are actually quite consistent except for the composite endpoint that includes CABG and PTCA. All the other endpoints are very consistent with what you would have expected aspirin to do in this population.

Now, the question may be, well, why doesn't it show up in the previous slide that we had? And one has to realize that we had the non-aspirin users, who were a minority of the population, about 20 percent of the population. In addition, those patients who were not on

aspirin at baseline, many of them started using aspirin as the trials went on. So, particularly in that group we see slowly a treatment effect of aspirin starting to occur. But these data, we believe, present the true effectiveness of aspirin in this population. That's the mix of the pravastatin and placebo users.

DR. FLEMING: Don, I had one more question. I don't know if this is getting at my answer or not. You had given the analyses on three of the major endpoints. The primary endpoint of LIPID was CHD death, and the primary of CARE was CHD death, nonfatal MI. Did you also do your analyses for those endpoints?

DR. BERRY: Yes.

DR. FLEMING: Can you just quickly show us?

DR. BERRY: Can we show those? CHD death, CHD death including nonfatal MI.

DR. BORER: Just a yes or no answer while you're waiting for that. Do you want to put a statement in the label of this combined product that says it shouldn't be used by people who've had a revascularization procedure?

DR. BERRY: No. You're going to answer this, I know, Rene. But I want to distinguish between revascularization procedures at baseline and what we're talking about here. This is an endpoint revascularization procedure. It is not a baseline.

DR. LORELL: A comment on that point. I think that there's even another possibility to interpret that data, if just for a minute we could go back to that slide that broke out bypass surgery and angioplasty. If you're doing an intervention of using aspirin and lipid-lowering therapy that dramatically reduces the risk of acute coronary syndrome, then by definition, in a large or small population, you are going to be doing many fewer interventions for that indication. And you have not shown us that data but I think it would be highly likely that that population of CABG and angioplasty events are enriched by a group for whom the indication was chronic stable angina and it was unenriched by loss of the population of people who had acute coronary syndromes.

In fact, I think -- and maybe Charlie Hennekens can correct me if I'm wrong -- but I don't think there is data that demonstrates that aspirin use alone prevents that piece of the indication for revascularization. In other words, this may be actually a confounding effect on actually changing the kind of pool of people compared to the trial that Dr. Hennekens was discussing.

DR. BELDER: We have thought about this as well, and actually we determined the endpoints that we were looking at before we actually saw the results of the meta-analysis. In retrospect, if we would define the endpoints

again, we probably would take out the revascularization from the endpoint because it is clear that we do not pick up a treatment effect of aspirin. And it's clear that pravastatin has a treatment effect for these events. I think that what you said is a very plausible explanation.

DR. BORER: We have Alan, Bob.

DR. BERRY: Do we have those slides yet for the CHD death?

Okay. So, this is CHD death and nonfatal MI. I guess we don't have it, Tom, combined. Oh, second from the bottom, okay. These are broken out and so if you were to combine these, it would show something similar. If anything, it's a better comparison than including these procedures.

DR. BORER: Bob?

DR. TEMPLE: Well, the only observation I wanted to make is that the effect of aspirin in controlled trials is not perfectly consistent either. What we believe comes mostly from meta-analyses, as everybody probably remembers, the largest secondary prevention trial went the wrong way on survival and was almost dead even on most other things. The results in the Physicians Health Study are completely unmatched by what I consider a fairly similar trial in primary prevention. So, with a small data set, it's not entirely surprising that you might or might

not see something in one of the components.

DR. BORER: Paul?

DR. FLEMING: Before we leave that point, that could be true. One could attribute this to the smallness of the data set. I'm looking at two sources of information. One is this data set here, which is 7,200 people, and then the 20,000 people that were reviewed in the FDA briefing document from the randomized trials.

DR. TEMPLE: Not in the no-aspirin group. I mean, most of the people here got aspirin. So, the comparison with the no-aspirin group is pretty small.

DR. FLEMING: It's 5,800 versus 1,500, right, in this study.

So, I'm saying that is a possible explanation, but across all five endpoints there is, I think, a very discernible difference in terms of lack of effect on any of those five, compared to some of these endpoints that when you look at it in randomized trials, certainly you show considerable effect.

DR. TEMPLE: Looking at the effect of aspirin alone, is what you're noticing.

DR. FLEMING: Correct. Aspirin alone.

DR. BORER: Paul?

DR. THOMPSON: Dr. Berry, could you address the possibility that these studies, done by very knowledgeable,

sophisticated investigators, that the representation or the finding that both the lack of benefit and the super-benefit of aspirin is actually due to the fact that these doctors are making good decisions about who they put people on, and they're deciding not to put either frail or people with GI bleeding or other conditions on aspirin, and that that actually could be a possible explanation for both the high and the low, the over-estimation and the under-estimation?

Really the best utility of these data is to show that something that is a recommended treatment, which is aspirin and a statin, in patients with coronary artery disease doesn't appear to do a whole lot of harm.

DR. BERRY: Can I simply agree?

(Laughter.)

DR. BORER: Yes.

DR. BERRY: I agree. With respect to the frail, we did not have a measurement of frailty per se, but it might be reflected in some of the other covariates that we did measure.

DR. FLEMING: If I could just pursue that, if that's what one were thinking, and if I viewed these four subgroupings as real, then what I would say is the doctor should be saying, if I'm on pravastatin, certainly put me on aspirin. If I'm not on pravastatin, don't put me on aspirin. And yet, in exactly the same proportion of cases

they chose to put you on aspirin, whether or not you're on pravastatin.

DR. BERRY: Of course they didn't know whether --

DR. FLEMING: They didn't know. What was striking to me is in these data, when you've randomized to pravastatin versus control in LIPID and CARE, and it was choice as to whether to use aspirin, the same fraction of people chose to add aspirin whether or not you were on pravastatin or control.

DR. BORER: Perhaps we can move on to the --

DR. TEMPLE: Jeffrey?

DR. BORER: Oh, sorry.

DR. TEMPLE: Just one thing. I thought, Tom, you were making the point you did because it made you wonder about the analysis; that is, the analysis failed to show something we all expect to see.

DR. FLEMING: That's correct.

DR. TEMPLE: The idea that these kind of data can show you, don't use aspirin alone -- maybe everybody was exaggerating.

DR. FLEMING: I will believe the 20,000 people from randomized trials. My whole point is, when I have a randomized trial telling me something about aspirin versus nothing, now I'm using this data set to answer a different

question, what does aspirin add to pravastatin, but it also gives me the same information, imperfect though it may be, about what aspirin adds to nothing, and that information is now inconsistent with my randomized trials about what aspirin does to nothing, it makes me worry about being on the end of a limb when I'm using these data to see what aspirin adds to pravastatin. Not that I have any particular better source of data to use at this point.

DR. TEMPLE: I understand, but the real question is the methodological one. Does this admittedly nonrandomized comparison provide enough assurance so that we really do think that aspirin makes a contribution in the presence of pravastatin. It isn't really to go back and reinspect the advice everybody gives.

DR. FLEMING: Absolutely.

DR. TEMPLE: I'm not referring to what you said.

DR. FLEMING: Absolutely. The comments that I'm making have to do with the reliability of the interpretation of these data in an observational sense, to conclude whether aspirin adds something to pravastatin.

There's a good news and a bad news side to this. Just to summarize, the good news side is, the suggestion is that the effect of adding aspirin is even greater in the presence of pravastatin, and that's the

question I'm really worried about here. The bad news is, where I do have an answer from a randomized trial -- i.e., aspirin versus nothing -- it's not consistent with that answer.

DR. THOMPSON: Dr. Fleming, I'm a little confused about something you said. It seems to me that actually a paucity of people are put on aspirin, if you look at and compare it to the number of people that are in these trials. So, somebody's making a decision. I'm always impressed that people in clinical trials always do better than what we tend to see in practice. I'm moved by the idea that it may be that the doctors that take care of them are doing a better job. So, somebody's making a decision here, and I wonder if that decision isn't what's driving us.

But you said that there was an equal decision to put them on aspirin or not. It doesn't look like it's equal. It looks like it's actually much lower. For example, on the top of page 41. So, I want to just make sure I'm understanding this. It looks like, you know, for example in that last column there are only 1,400 people that were not on pravastatin and not on aspirin compared to almost 6,000 people who were given aspirin when they were on pravastatin.

DR. FLEMING: In these two trials, when you add

them together, you're correct that the largest fraction of people have been provided aspirin. If you break these people into four groups, pravastatin yes-no, aspirin yes-no, and if you believed these data as being true, what you would say is, certainly, use pravastatin. Also use aspirin if you are using pravastatin, but if you're not using pravastatin, don't use aspirin. I'm saying, if the clinicians in fact knew that, then why is it that when pravastatin is used, 80 percent offered aspirin, and when it's not used, still 80 percent offered aspirin?

They're making the right choice in the first case. They're making the wrong choice in the second. However, I want to emphasize what Dr. Temple is saying. I'm not interpreting these data as being the truth. In fact, I believe these data are not reliable in what they're telling us about the effect of aspirin in the absence of pravastatin.

DR. BELDER: Could I make one comment about this because it's only with respect to one particular endpoint, not with respect to the other endpoints. If you look at C-15, please.

The aspirin effect in this endpoint is much more prominent than in the expanded endpoint that includes revascularizations. It's what Dr. Berry indicated earlier, that we do not pick up a treatment effect of aspirin in

revascularizations, and since they are the majority of endpoints that you have in the database, there's a significant dilution.

In addition, I would like to emphasize again that those patients who were not using aspirin at baseline, a significant portion of them started aspirin use as the trials were going on, so we did a very conservative analysis on, if you will, an intention-to-treat basis. So, that, again, would dilute the treatment effect that we would pick up.

DR. BORER: Just to save time here, I think we're being perhaps excessively obsessive in tearing these data apart. At the end of the day we're going to have to decide how convincing we are. We have questions that actually cause us to reason through this, and at that point I think we're going to hear a complete analysis. Speculation here is taking a lot of time.

Dr. Kreisberg, you had a comment?

DR. KREISBERG: Well, I was just concerned about the way I heard the conversation going, and maybe Frank Sacks could clarify it. These patients were not treated with aspirin by the investigators. They came to the study, either on aspirin or not on aspirin, and that's the basis of the analysis. Is that not right, Frank? So, it isn't that they get better management from the doctors

who are involved in the study.

DR. THOMPSON: That's not my point. The point is that these are done at institutions that generally have quality of care. They're involved in research. Frequently the patients that are involved in controlled clinical trials appear to do better than those that are not in controlled clinical trials. There are some reasons behind that. One is that they're treated at medical centers that do research. Period.

DR. KREISBERG: I understand that, but most of the patients that are entered in these trials do not come exclusively from academic medical centers, and there are a lot of community participants. It's the academic medical center that serves as a coordinating center.

DR. THOMPSON: I do think we're over-analyzing, but I do think there's a degree of sophistication that goes along with doing controlled clinical trials that benefits patients.

DR. BORER: Alan?

DR. HIRSCH: Well, I don't want to over-analyze how the patients are treated by either academic or primary doctors, but I want to take one of Tom's points just one step further for later discussion. Which is, whenever I see that relative lack of efficacy on the fatal or nonfatal MI endpoint, which would be my signal that I would choose

to look at for the aspirin efficacy, I choose to look at that to make sure that I have some sense that, again, these patients treated by their doctors actually took the drug. I want that signal of efficacy, not again in a small trial to prove that aspirin works -- I can look at the broader database -- but to make sure that in this database that I can then look at the crossover for safety, for a combination package.

So, I again look at page 41 of the FDA briefing booklet at endpoint 2, where I see no signal in the 1,460 non-aspirin treated and 5,833 aspirin-treated patients, no impact on MI rates at all. I say, well, who knows? It's too small a sample size, just the luck of the draw for statistics, the wrong model, or possibly really these are casual patients not really taking their aspirin. Maybe they mistake it for Tylenol. Later when I look over the safety database, I have a little bit of doubt.

I'm expressing this now so that later, when we talk about safety, I can come back to it.

DR. BORER: Dr. Pearson.

DR. PEARSON: Ladies and gentlemen, it's my great pleasure to present the medical need for the pravastatin/aspirin combination.

What I'd like to do is bring the perspective of the preventive cardiologist to this discussion. Certainly

my interest has been in preventive cardiology and the treatment of high-risk patients for about 20 years. I direct a preventive cardiology clinic at the University of Rochester.

I've also been interested in the policy issues related to this and been involved with the development of the basis for the secondary prevention guidelines for the American Heart Association, as well as the first and second iterations of those guidelines. And more recently my research interest has been really in the implementation of these guidelines, as to the extent to which they're getting out to the patients who are eligible for them. So, I'd like to bring the preventive cardiologist's perspective to the medical need for this pravastatin/aspirin combination.

In the first place, to start this discussion, of course, is in the efficacy, and you've just heard these data. It sounds like everyone is a little bit remorseful for not having paid better attention to that multiple regression course in your statistics course, but I think what we've seen here is, I think, very good clinical trial data looking at two individual trials, the LIPID and CARE trials, as well as meta-analyses from three additional angiographic trials with clinical endpoints, that the combination adding pravastatin is more effective than aspirin alone. We just had a very nice discussion of the

observational data, its strengths and weaknesses, as to whether the combination is more effective than pravastatin alone, that is, adding aspirin to the pravastatin, again with single and meta-analyses evidence.

So, I think also it is important, I think, with the second point, to put this into the backdrop of the large clinical trial evidence supporting aspirin use in the secondary prevention of coronary heart disease.

So, the question is, is this a large issue? Dr. Fiedorek presented the initial estimations, and these are the estimations used by the American Heart Association. 12.4 million Americans carry a diagnosis of coronary heart disease. This constitutes, for adults above the age of 45, 12 percent of men and 8 percent of women in the United States. And it's for this reason that many of the public health agencies now are starting to look at these issues of implementation of guidelines as a public health issue, not just a clinical health issue but public health issue.

Even if you were to exclude those individuals who might have contraindications to pravastatin or contraindications to aspirin, usually for GI intolerance, you're still left with about 10 million Americans who would be the eligible population for this combination. The other issue is whether or not this problem is going to be going away, and the answer is no.

This is a small working group that I had the pleasure of participating with for the American College of Cardiology around the end of the millennium, headed by Dr. David Foot, a demographer from the University of Toronto. This basically looks, taking into account the demographics of the United States, the baby boomers, et cetera, at the growth of the prevalence of patients who are going to carry the diagnosis of coronary heart disease. Here we are in 2001 with about 12 million Americans, and over the next 50 years we estimate that this is going to double. About 25 million Americans are going to be carrying this diagnosis. I think this is really the basis for us starting to call this a public health issue as well as a clinical one.

I had, again, the opportunity to head a writing group writing the basis paper for the first secondary prevention guidelines and participated in both iterations since then. I don't remember back in those writings that we ever had much of a question about adding these two issues as important components of those guidelines. First, lipid lowering to achieve an LDL cholesterol of less than 100 milligrams per deciliter, and second, antiplatelet therapy, particularly aspirin, so that these have always been cornerstones of the secondary prevention guidelines as put forth by the American Heart Association and the American College of Cardiology.

What these guidelines do and the wide consensus for their acceptance is for us to look at asking the question, how well are we doing with carrying out these guidelines. And obviously guidelines written, but not implemented, aren't really worth much at all.

I've really had an interest in what we call the treatment gap of the difference between what we recommend and what's actually being done for our patients. And I'd like to make three comments and talk about the relative need of this combination, the three issues.

The first issue I want to talk about is that many patients face a high uphill burden. Obviously, this is and should be a major concern for the medical and nursing communities. This gets at the issue of noncompliance and nonadherence with the recommendations.

Now, let's just consider the typical coronary patient here. And the typical secondary prevention patient might be taking, according to guidelines, a statin, aspirin, an ACE inhibitor and a beta-blocker. If this patient were to have diabetes -- and 25 percent of coronary patients carry the diagnosis of diabetes -- also oral anti-diabetic agents.

Let's consider some of the complications of coronary heart disease: atrial and ventricular arrhythmias, congestive heart failure. A lot of these

patients, 60 percent or so by our calculation, will have hypertension, possibly not totally controlled by this. This is a group where we're going to have a large pill burden. I share with Dr. Borer the concern, particularly in the elderly patient, of drug-drug interactions.

But there's another problem with this, and we all know that one of the risk factors for noncompliance and nonadherence is the number of pills and the complexity of the regimens that patients have to deal with every day. So, this obviously is something that our guidelines are actually asking for, and the question is, what can we do to make this all simple.

The question is, is there any evidence to suggest that putting two agents together in a combination pill helps us with noncompliance and nonadherence? I'd have to say this is a relatively slim data set. Certainly I would like more. The American Heart Association has certainly been very interested in compliance in general. And we were able to find four studies in which combination tablets were compared with dual therapy; that is, individual tablets taken together on compliance.

A study in diabetes showed a 21 percent improvement in tablet consumption over a 6-month period in previously treated patients. There are two hypertensive studies. Obviously, there are some combinations available

for this. One showed a 13 percent improvement in tablet consumption over a 12-month period, and in another kind of measurement setting, another study showed an 11 percent improvement in prescription renewal as a measure of compliance over a 12-month period.

Then finally, and perhaps the most archetypical polypharmacy kind of situation, HIV, there was a 9 percent reduction in missing even a single dose over a 16-week period if it was put together in a combination tablet versus dual therapy. I really think that it's our responsibility, as individuals who want to see our patients do well, to do all we can to improve adherence and compliance.

Let's talk a little bit about another part of the treatment gap, and that is that many patients fail to receive statins or aspirin. There, in fact, turn out to have been quite a large number of studies. We've been involved with a couple of these, but perhaps I'll show you one of the more recent ones, perhaps the largest.

This is from the national registry of myocardial infarction, with 167,000 patients nationwide from 1999 to the year 2000. Again there are many studies looking at this treatment gap. I picked this one because it's the most recent, and it particularly follows the HA medical advisory, which basically suggests that the

initiation of lipid-lowering therapy, particularly statin therapy, in the acute coronary syndrome setting as part of the inpatient discharge regimen, is in fact appropriate. That recommendation predates this study.

Also to point out with this is that this includes coronary patients with no exclusion or contraindications to intolerance of this drug, so that this is in fact the true treatment gap. The treatment gap that is estimated is about 23 percent of patients are going home from their acute coronary syndromes without aspirin, and about two-thirds of them, 63 percent, are going home without a statin. So, the suggestion here then is that this is a large treatment gap, despite our best efforts in implementing our guidelines.

Finally, in addition to this yes-no, are they receiving therapy, there are also additional issues related to how many patients are not optimally medicated. This would include both inadequate and incorrect doses, and just incorrect therapy.

What about statins in this instance? This is a study that I've been involved with, called the lipid treatment assessment program, looking at the use of efficacious statin doses. This was a survey of 4,888 patients from 619 primary care providers around the United States, and of these, 1,460 patients carried the diagnosis

of coronary heart disease.

All patients had to be receiving lipid-lowering therapy to be in this study. This was a study of the clinical epidemiology of lipid management in the United States. And in fact statins were used in 85 percent of the coronary patients.

It turned out that the doses proven to be efficacious in randomized control trials, secondary prevention trials in particular, as we noted in this, were seldom used. The vast majority of patients were not taking doses that the randomized controlled trials demonstrated efficacy in. This in fact was the single largest reason, in my opinion, for these patients not getting to their LDL goal. So, there's another issue in terms of not getting to the LDL goal, and that's the current state of therapy, that many patients are not at LDL goal because they're not even at the doses of therapy for which efficacy has been demonstrated. And this is obviously a big concern.

Well, what about aspirin? Is this any better with aspirin? This is the paper first authored by Nancy Cook for which Dr. Hennekens participated. This was a large consumer survey in which 3,818 patients actually carried the diagnosis of known cardiovascular disease, and only 51 percent of those patients reported taking aspirin or an "equivalent." I think that's worrisome enough, but

of particular concern was of those who thought they were taking aspirin correctly for secondary prevention, actually 15 percent of them were taking a non-aspirin analgesic, especially acetaminophen, which as you know has no secondary preventive benefit. So, we have a concern about not only incorrect doses but incorrect drugs as well in terms of secondary prevention.

So, in summary, the proposal here is that the pravastatin/aspirin combination in coronary heart patients would provide one prescription with two proven therapies, with virtually unexcelled dual efficacy bases. This provides an advantage of making sure that we have proven doses and that we have proven products getting to our patients.

Just several other points in summary. We feel that this will enhance our implementation of the guidelines that we have, unfortunately, pretty good and recurrent evidence to suggest has a treatment gap.

Second, this would provide us the opportunity to assure the appropriate pravastatin dose, at the same time that those exact doses have 112,000 patient-years of observation showing no safety concerns.

Third is that this would provide us with the more appropriate use of aspirin and not provide particularly the elderly patient -- I share your concern,

Dr. Borer, of people who are getting confused about what they should be taking. This would provide them more appropriate use of aspirin at a dose we know has secondary preventive capability.

Then finally, this would provide then enhanced convenience and reassurance for patients and their health care providers in that they are really in fact getting a secondary prevention package.

These I think are the main points that I wanted to cover in talking about the medical need for this combination therapy. Thank you.

DR. BORER: Thank you, Dr. Pearson.

Steve?

DR. NISSEN: Tom, thank you very much. I've long admired your work on the under-treatment of patients with statins, and I want to focus on that a moment.

You've got a lot of data you've looked at on getting patients to goal, and so my first question is a difficult one. What percent of patients in the secondary prevention population would you estimate would get to goal with 40 milligrams of pravastatin?

DR. PEARSON: Let's look at the -- I think the LIPID study would be the best one there. Can we have that slide from the LIPID study?

I might say, Dr. Tonkin, this was almost all

the hospitals in Australia. Is that correct?

I just want to make one point here.

DR. TONKIN: Yes, indeed. In the combined populations of Australia and New Zealand, there were 21 million people, and it was 87 hospitals. So, this wasn't just purely the elite centers.

DR. PEARSON: Can we have that slide? It was about the percent LDL lowering in the LIPID study.

While we're getting there, let me also -- this has to do with the potency of pravastatin 40 and the population distribution of LDLs in coronary patients. Those two things were the two parameters.

I believe, in fact, the LIPID study, despite it's being in Australia, I think has something to tell us in the United States, and that is the average LDL was 146, 142. 40 milligrams of pravastatin, then, provided about a 28 percent LDL lowering, which got the average down to about 103 or so. So, on the average, patients were in fact around the LDL goal.

Now, we all know that there are subsets of patients that don't do so well on the diet, aren't implementing the therapeutic lifestyle change, which should give us another 15 percent reduction in LDL prior to pharmacotherapy. We also know that there are some patients with genetic hyperlipidemias that just need triple drug

therapy in addition to this. So, we all know about this.

But in terms of almost a population-wide intervention as to how many patients are going to be getting to goal, it's my perspective that this is a pretty good look.

DR. TONKIN: It also indicates the dilution because of the drop-ins to those on placebo. There were 23 percent assigned placebo who commenced open-label lipid-lowering therapy and the 19 percent dropouts on pravastatin, which causes the upward drift over the trial.

DR. NISSEN: Would I be correct in interpreting these data to suggest, then, that something less than 50 percent of the patients in the secondary prevention population would get to the recommended guidelines using the 40 milligram pravastatin dose? Would that be correct?

DR. PEARSON: I would suggest that it would be around 50 percent, perhaps a little higher. We're really quite enthusiastic about the ATP-3 guidelines, therapeutic lifestyle changes. We're getting another 15 percent prior to pharmacotherapy. So, if you put all those together, you'll be a little bit more than 50 percent.

DR. NISSEN: There's other published data that would suggest that it perhaps is only as little as 30 percent of patients. Do you think that's possible?

DR. PEARSON: I think that depends on the

population you're starting with, which is the reason why we wanted to look at essentially a community-wide issue here.

DR. NISSEN: An interrelated question, then. So, would you give this combination to a patient with an LDL of, say, 200?

DR. PEARSON: We always look at matching the potency with the intervention. In patients with markedly elevated LDL in my practice I use one of the more potent statins, particularly if the LDL goal is less than 100 or even more. But I would also tell you that we would look at a variety of other issues, including safety and efficacy, the ability to use combination therapies, and a variety of other issues, and we take it really on a case-by-case basis.

DR. NISSEN: Would there be a maximum LDL that you would consider to be inappropriate for the use of this product?

DR. PEARSON: I don't think so.

DR. NISSEN: So, you'd give it to somebody with an LDL of 200 then?

DR. PEARSON: I might, but I'm saying that I think usual practice would be, particularly if we're thinking that we're not going to be using combination therapy, that we'd be looking at probably a more powerful statin in this instance.

DR. NISSEN: If I could just follow up with one more short question, and that is, if you didn't get to goal with this product, if you chose a patient with an LDL of, say, 180, and you gave them this combination and they didn't get to goal, what would you then do?

DR. PEARSON: According to the guidelines, which I think we generally do follow, we would look at a variety of other issues relative to compliance, first of all, if they're complying, and the nonpharmacologic basis of it, but then thereafter the possibility of whether or not a more potent statin would give us as much benefit as perhaps adding another family of lipid-lowering agents to that instance, looking at the HDL and triglyceride and other issues related to that patient. Again, I would do it on an individual basis.

But the answer to your question, would I always change over to a more powerful statin, the answer is definitely no.

DR. SACKS: I'd just like to add a point.

DR. BORER: Wait one moment, please. We have a number of comments and questions from the committee. I'm going to ask the sponsor to just hold off until we hear the entire spectrum of our issues, and then maybe if you want to comment, you can.

Dr. Pedersen was first, and then Bev, Tom,

Blase, and Ray.

DR. PEDERSEN: Tom, do you have any information about the reason why physicians do not prescribe these drugs? Is it actually the number of pills that is the main reason, or are there other reasons?

DR. PEARSON: I wish I could tell you the definitive answer there. It's kind of hard to kind of mind-read why physicians don't meet guidelines. I think certainly with the secondary prevention situation, I would have to say I've been quite optimized about U.S. physicians with increasingly using cholesterol-lowering agents. That 37 percent I think is a composite of a variety of things. But I think there has been some progression of use over time, particularly as efficacy studies come in.

We've looked at a couple of data sets, the American College of Cardiology evaluation of preventive therapeutics, the LTAP study, and our own databases, and there are some others as well. There's a variety of issues. One is a knowledge gap among physicians about whether or not there is efficacy of these drugs.

There continues to be a safety issue, which I think we've shown with the clinical trials. Really we don't exactly understand where that comes from because the safety of these drugs is quite extraordinary.

There is also the gap between the acute care

setting and the picking up of that patient by the primary care provider. This is, I think, a huge abyss in which patients go in possibly, and this is one of the reasons why those guidelines about starting acute therapeutics in people with acute coronary syndromes, cholesterol-lowering therapeutics as part of the in-patient, was so important because then it's part of the coronary care package rather than something you can start 6, 8, 12 months later, which of course we know is not a good idea.

So, I think it's really a variety of issues having patient factors, physician factors, health care system factors. I think it's a worldwide phenomenon. You're seeing some of that from Europe as well. I think it's something we need to continue to look at strategies about how to overcome.

DR. PEDERSEN: The reason I'm asking this question is that I really doubt that there is a host of physicians out in the marketplace waiting desperately for a combination drug. To my knowledge, another pharmaceutical company, Merck, has already brought to the market a combination of simvastatin, which is their statin, with aspirin, tested on a European market in Sweden a couple of years ago. It may be due to lousy marketing, but they experienced a total flop. Swedish physicians didn't want to use this combination, and it was withdrawn again. This

was a test market. I was wondering whether there is a similar experience from the United States, whether you have done some research about combinations of this kind, or whether the company has some experience about it.

DR. FIEDOREK: Well, we're only addressing really the clinical need here. I think we're trying to provide evidence to support the clinical need. If you approve this product, we'll find out.

(Laughter.)

DR. LORELL: Yes, let's return to the clinical need issue. I think you make a very cogent argument for both the need for increased usage of statins in this very high-risk population, as well as issues of the need for enhancing patient compliance once the drug is prescribed. But I'd like to return to the issue of the national guideline goal for this very high-risk population, at a risk for premature death, life-threatening infarction, unstable angina and stroke, for achieving a goal not sort of near 100, but below 100, for LDL-lowering.

I think it's very important for the public record and the public who is listening to understand that this is not sort of a petty adherence to a number, but that the data overwhelmingly supports -- doesn't prove but supports -- the notion that progressive lowering of LDL cholesterol is associated with progressive lowering of risk

for these serious hard endpoints. I would really like to see the data presented by the company from both CARE and the LIPID study as to the percent of patients who achieved an LDL goal less than 100, and the percent who didn't.

The reason I think this is very important is there are definite advantages of combination agents for compliance and ease of use. The flip side of that is that there may be a reluctance and a bit of an impediment to changing therapy when you've got both of them packaged. So, I think we really need to see that data.

DR. SACKS: Just to give you the CARE experience, Bev. The average LDL in CARE on prava 40 was 98, so that would be certainly somewhat more than 50 percent of the patients in the CARE trial achieved goal.

Another interesting aspect of that is, in the CARE trial we excluded over 20 percent of patients because their LDL at baseline was under 115. In most of those patients, the LDL was between 100 and 115. In view of the advisability of getting LDL under 100, I would think in all patients, regardless whether their LDL is 115 or 120 or 150, that would add another pool of another 20 percent of coronary patients that with this dose would get under 100.

DR. LORELL: Frank, I appreciate that comment, but I think what this committee really needs to see are the hard numbers. The percent of people who achieved current

guideline goal and the percent that didn't. And I think we need to see it both for the totality of the experience and broken down for CARE and LIPID because LIPID I think was skewed toward a somewhat higher cholesterol LDL population and CARE was a little bit lower.

DR. PEARSON: Just one comment to put this discussion into perspective, and that is that I think there have been several surveys as to what currently is achieved in terms of coronary patients being at goal in three or four large studies, certainly one of our own. And a number of about 25 percent pops up recurrently. That's basically how we're doing currently in the United States.

Part of the issue here is that part of those individuals aren't at goal, somewhere between one-third and two-thirds of patients, and they aren't being treated with efficacy-proven agents at all or at the levels of those efficacy-proven agents at which efficacy was shown. So, the other issue is we still have quite a large quantitative treatment cap in terms of LDL, and part of that, in fact, I think is approachable with a combination agent with increased convenience of use.

DR. BORER: Tom?

DR. FLEMING: Well, I'm glad I followed Beverly. She got exactly at the issue that I was concerned about. Steve raised this very important point. What is

the amount of impact that we get in LIPID and CARE with the 40 milligram dose reduction, and we saw an average, but an average doesn't tell us specifically how many people in fact aren't going to achieve an acceptable level of reduction.

Exactly as Beverly said was my question. Maybe just to refine it a bit, what I'd like to see is an indication of what percent achieve 100 as a function of what they started at, and what percent achieved at least 110 as a function of what they started at, so that I would get a sense of at least what is the likelihood that if we had a packaged product, people would achieve levels of effect that they would be satisfied with versus needing a change.

Then the second question, for my own statistical sense here, not being a clinician. If in fact you don't achieve 110 or 100, what is the typical approach people would wish to use clinically. Do you switch to a "more potent" statin? Do you increase the dose? What are the consequences, and how would a packaged product impact the flexibility of implementing those alternatives. Two questions.

DR. BORER: Any or all of the above. There are lots of approaches if you don't hit the target. We don't need more information about what -- unless you have the

percentages that were asked for.

DR. BELDER: Yes. For CARE, the percent of patients that were actually reaching goal below 100 was 75 percent. For LIPID, I don't know the number. We will not be able to find out during the lunch break either because we don't have access to the database, but that would be somewhat lower. I think it's bigger than the 50 percent, but it's somewhere between 50 percent and 75 percent.

DR. FLEMING: That seems a little bit surprising in view of the fact that the average was above 100. So, how could you have more well than half achieving below 100?

DR. BELDER: That depends, of course, on how the distribution was of the patients across the cholesterol range, and as Frank already indicated, there's a lot of patients with relatively low cholesterol levels.

DR. FLEMING: Maybe after lunch we can see an exact figure.

DR. BELDER: Well, I'm giving you the exact figure. I can put it on a slide, but it will be the same number: 75 percent for CARE. For LIPID, we don't have the number.

DR. PEARSON: And keep in mind that I believe those average levels were intention-to-treat. Right? So, that would include the noncompliant patients where their