LDL is not changing at all. So, I agree with you that percent of patients with their LDL below is a more exact number than the mean.

DR. LORELL: Just to make a real brief comment, I think it's a really important issue because we're not being asked to approve here an escalating set of packaged products, and I think it's also very important because it's not the sponsor's job to defend or discuss other companies' products, but this is not a unique drug. There are other choices available that, in the current United States managed care environment, allow you to get to goal often with one prescription and documenting it with a single blood test. So, I think it's really important, if we can, to know the data from the LIPID experience.

DR. BORER: Blase, and then Ray.

DR. CARABELLO: Now that the issue of compliance in pill-taking is on the table, it would seem to me that this opens a Pandora's box. We're being asked to consider the co-packaging and co-production of two different pharmacologic agents that are focused on the same goal. As you point out, many of our patients should be on an ACE inhibitor, a beta-blocker, a statin, and an aspirin, and does that mean that we should co-package and co-produce three or four different agents in the same pill?

DR. BORER: If you want to answer, just make it

with a yes or no. If you don't, it's okay, but the question remains.

Ray?

DR. LIPICKY: There are a couple of things, I guess, to talk about, and one of them might be a whole day. But you're not being asked to approve a drug that would be a product, a fixed-dose combination that would be used instead of the individual ingredients. The labeling would say, if you are on these doses of pravastatin or on these doses of aspirin, take me because I am convenient. That's what you're being asked to approve.

The questions that you will be addressing will ask you, do you think this will lead to bad practice? But you are not being asked to approve, put people on this combination product first.

There's a long line of fixed-dose combination products that are anti-hypertensive, ACE inhibitors and diuretics and so on and so forth. Years ago those products were labeled with black boxes that said, do not use me first. Titrate with individual components. Eventually that got to a place where that sort of got modified and changed, and there is a fixed-dose combination antihypertensive product that is in fact for initial therapy. That is, it says, use me instead of an ACE inhibitor or instead of a hydrochlorothiazide product, and

it is a fixed-dose combination. Very special reasoning that got it there.

That's not what this is. This isn't use me first. This is use me if these doses are what your patient is getting because it's easier. That's the first thing to point out.

The second thing, I guess, which might be a day-long discussion, is I think it is inappropriate to think about guidelines, and it is inappropriate to think about percent of patients who would fall below something. Guidelines are okay for guidelines, but we, last time this committee met, looked at an antihypertensive drug where all patients were below guidelines for what blood pressure should be, but in fact, although all patients were there, there was a difference in blood pressure control below the guidelines, and that could have been the real clinical benefit.

So, a number is sort of inappropriate to look at, I think, and when we look at antihypertensive drugs, every single sponsor puts in data that say what fraction of patients are controlled, namely 140 over 90. And I have never looked at those numbers. I have advised all our reviewers to never look at those numbers because if it was 141 over 89, it would be a different fraction. If it was 142 over 92, it would be a different fraction. It's a

totally arbitrary mind set.

If you in fact even thought that, people would start on the combination product first, and there were doctors looking after patients, there isn't any reason they couldn't add another dose of pravastatin, add more aspirin, add more diet because doctors have to look after patients. Right?

But you will be asked, would the existence of this thing in your judgment alter practice, and you'll be able to make a judgment. But I don't think you need to look at this as the initial therapy of people until doctors know what the response is.

DR. LORELL: Well, Ray, I think your comments are well taken, but in the spirit of this group having to ask the question, will it alter practice, I think it would be helpful as a component in our decision making to know the proportion of people who were or were not below 100.

I also think that although in an ideal world components are, indeed, titrated and used separately, the presentation that we just heard emphasized the clinical care component of initiating these agents at the time an acute life-threatening event occurs. In fact, in real world practice and in my practice as an interventional cardiologist, it is extraordinarily common for the dose of both aspirin and a statin that is started to be the one

that is continued for a very, very long time. So, in terms of helping in our clinical decision making, I think these data would really be helpful.

DR. BORER: Let's go to Bob and then Tom and Steve, and then we'll stop because we have another speaker.

DR. TEMPLE: To some extent, the questions raised go to the entire existence of pravastatin. I am absolutely positive you'll find more people reach goal on a different drug. But the expectation is that people will actually measure the effect and see if they consider it adequate, and they might perhaps be influenced by the fact that this drug has much more outcome data than any other drug.

So, it strikes me there's some tension between meeting the guideline with a drug that's never been studied for outcome, or hardly, and instead trying first to get to guideline with one that has a lot of outcome data, and obviously doctors have to figure out what they want to do in that case.

But putting this in a combination with aspirin really doesn't change anything much. 40 milligrams used to be the top dose of this drug. Well, so be it. That didn't get everybody to goal, I'm sure, and then they'd have to decide whether to switch to something else or use it off-label at a higher dose or any of those things, and they

would still have to do all this. As Ray said, you have to decide whether the existence of this will keep people from doing what's right, but our assumption is that you're supposed to check the cholesterol levels even when you use a combination, just as you would when you're using it alone.

As Ray said, it is important to us to know whether you think this will alter practice in a bad way, but some of the questions raised really go to the whole question of the drug itself.

DR. BORER: Tom?

DR. FLEMING: Ray, you've said it's not really integral for us to know what fraction of people, if they take the 40 milligram dose, will achieve targeted levels, will achieve a goal, and I understand what you're saying. You're saying the way you're going to label this would be, if in fact in your judgment a 40 milligram dose is what you should be taking of pravastatin and aspirin, then this is the pill for you.

And yet the way that I understand this has been presented to us as the motivation, as one of the critical motivations for doing this, is it's going to enhance accuracy and adherence. Adherence to what? Well, I assume adherence to an intervention that will allow you to achieve what the targeted goal is. If in fact the 40 milligram

dose does that in the vast majority of people then I am persuaded that this will enhance accuracy and adherence. But if in fact a substantial fraction won't achieve targeted goal, then why is it I should still think that this strategy is going to provide enhanced accuracy and adherence?

DR. TEMPLE: I think that's the question I was addressing. If you think that this drug doesn't get enough people to goal at 40 milligrams -- maybe now at 80 milligrams it does -- I guess you're proposing to advocate that it be removed in favor of putting everybody on atorvastatin, even though there's no outcome data. What's the implication of your --

DR. FLEMING: No.

DR. TEMPLE: You're absolutely right. It won't get everybody to goal. That's true. So, are we in a position or are you taking a position that you want only the drug that gets the most people to goal?

DR. FLEMING: I'm saying when one thinks about what one is achieving here which, if I understand, is accuracy and adherence enhancement, it seems to me, to have a sense of what the level of that up side is, I have to have a sense of whether or not this packaged product is largely going to achieve the intended outcome. If in fact it's largely going to achieve the intended outcome, then I

am persuaded that it's plausible to assume I'm going to get enhanced accuracy and adherence. If, on the other hand, it isn't then I'm thinking this is not necessarily going to have an up side.

DR. TEMPLE: But it can't be better than pravastatin alone at getting you to goal. How could it? It's going to have exactly the same effect on lipids as the drug does.

DR. FLEMING: My question is what happens. If you take the 40 milligram dose with aspirin, in what fraction of people do you achieve goal, or at least a level that care giver and patient would be satisfied, and if they're not, what would they typically do? And I want to have a sense of whether or not there is a large fraction of people that would be satisfied with this combination. If so, then it's plausible.

DR. TEMPLE: You're really asking -- and as Ray said, we are interested in this. If you think this would distort behavior because of the enormous convenience of this, then we would be interested in that concern.

DR. BORER: And we're going to get to that in questions, and the company has already told us they don't have the data we want, so we're going to have to go with what we've got.

DR. BELDER: We have one number: 75 percent

for CARE. For LIPID, we're trying to get that number to you in due course.

DR. THOMPSON: I'd like to submit that we're talking about the wrong goal. The goal is to prevent coronary recurrent events and not necessarily a lipid goal. That's the data I think we've been presented to some extent. The issue is not whether pravastatin is an effective drug. The issue is whether the combination of them is better at reaching the true goal, rather than some guideline goal.

DR. BORER: Steve?

DR. NISSEN: Let me see if I can help make both Ray and Bob a little more comfortable. In a perfect world everybody gets titrated. You know what the goal is and everything is easy and your patient comes in, you check their lipids. If they're not there, you do some intervention and so on. But we know there's abundant data that the first dose that patients are started on is often the dose that they stay on.

What we're trying to get a feeling for is the concern that if a product is available and offers a lot of convenience, is widely marketed and available, that there's a certain inertia that's created. It's already a lot of inertia about up-titration and getting people to goal. We know from Tom Pearson's work that most people don't get to

goal, unfortunately. What you have to do is, if you get them on this combination product and they're not at goal, you've got to stop that. You've got to start another statin, co-administer aspirin with it, get another set of lipid values.

I'm worried that, on balance, that the societal result, the public policy result will be that fewer patients will get where we want them to be than we get now. That wouldn't be a good decision if that were the case.

Now, I had one other question that I want to raise, and I think to me it's actually not trivial. The major side effect of both statins and aspirin is GI intolerance. A certain number of patients -- I think, Paul, you do this for a living. He can tell you that people come in, particularly with initiation of therapy. If patients are on the combination and they get GI intolerance, then they stop both agents. It gives me a little bit of worry here that patients may stop aspirin because they have GI side effects and continue their statin, or vice versa. But when you put things together, you may lose both components if a patient has a gastrointestinal side effect. It just makes me slightly nervous, and I wonder if anybody else is nervous about that as well.

DR. THOMPSON: You know, I do do this for a

living and I'm impressed that we're making it tougher than it needs to be. We're not going to change slovenly medical practice one way or the other. There is this incredible failure to move. I agree with you. I don't think we're necessarily going to make it worse, nor do I think we're going to make it better with an agent such as this. But are we not making it tougher than it necessarily needs to be?

We have an approved drug that may not be the most powerful statin around, but does lower lipid levels, and people use it and there's evidence to support its use. We have another agent that all of us would agree with. Aspirin is effective in secondary prevention. Even though the meta-analysis we were shown raises some questions, none of us on the basis of that meta-analysis would stop giving aspirin after our angioplasties or anything else. So, that's making it more complex.

All we're saying is that there are a lot of people -- and I've left three charts undictated yesterday to get my plane, so I do this every day with a lot of patients. I can tell you that just yesterday somebody said, you're going to give me something else? I'm already taking seven drugs. There is a small group -- not a big group -- that this affects how they think about themselves and their medications, and combining two proven, effective

drugs into one may not be a blockbuster seller or whatever, but it's not probably going to be more dangerous, et cetera.

Now, what about the GI bleeding and stuff like that? Even though I'm the one who's kind of picked on the general practice doctrine and said that doctors who do research do better -- I believe they do. But we have to give some credit to these folks out there to notice that if there is a GI intolerance that they're going to stop the combination and put them on the pravastatin alone. I think we also forget that you can add additional doses of another agent if you wanted to. I mean, you could do other things to potentially get these patients to goal.

DR. BORER: We're going to have just one more comment from Ray, and then I want to ask Dr. Pedersen to present his data because they really do get to the heart of the issue, no pun intended, that Beverly has raised several times here.

DR. LIPICKY: Well, you'll come back to this, I'm sure, but the difference, at least from my perspective, from what you're seeing here is that -- I ought to start from some place different.

Coming back to the antihypertensive model, ACE inhibitors and diuretics are approved drugs, and they are taken together, and it's reasonable to do so. My point of

view: before one would advocate that one should take both by producing a fixed-dose combination, you ought to have the data you need that says that both are contributing to the good of the product -- and in fact that is a regulation that says that both ingredients have to be working in the product you're approving -- and that you ought to know something about the dose of each that you need to give when they are combined, because it might be different than when they are single.

We have accomplished that with antihypertensives, and we've accomplished that with, say, diuretics and triamptyrine, the potassium-retaining thing. Essentially we knew that both ingredients contributed to the product, and we knew roughly what dose you would need to use of each in combination.

Then it was sort of reasonable to advocate that this fixed-dose combination should be used, and it explicitly said whether you should titrate with individual components first, and if you turned out to be on the particular dose that was available, to then allow that to be used as a convenience. You know, there's a difference between doctors can use something together and saying they should use something together, and that's a subtle difference.

Now I've lost my train of thought.

DR. BORER: You'll find it again. It's okay. Let's go on to Dr. Pedersen, please, and thank you very much, Dr. Pearson. After Dr. Pedersen, any questions anybody has for him, we'll break for lunch, because the FDA has to eat, I'm told again, and then we'll come back and finish up.

DR. PEDERSEN: Thank you very much. I was invited mainly to present my view on whether a fixed dose of 40 milligrams of pravastatin would be appropriate in the majority of the target population, and the invitation came from the FDA. I have the feeling that this question has already been debated into exhaustion, but to justify the airline ticket, I will still give my presentation. It will be short.

As you know, there have been, until two months ago, five large scale, long-term clinical trials with statins in patients at high risk of CHD. I will not talk about the heart protection study because it hasn't been presented in writing yet and it's not important for this presentation either.

These five clinical trials included patients with a variety of LDL baseline levels. The 4S with simvastatin included the relatively high cholesterol level population. The two trials that are combined for the meta-analysis of this meeting, LIPID and CARE, ranged between

100 milligrams per deciliter in LIPID, approximately, and up to about 200 approximately.

The majority of patients were around 150, and for the total meta-analysis, the mean LDL cholesterol level was 148, with a standard deviation of 26. So, the mean plus two standard deviations would be exactly 200. Therefore, for the meta-analysis of the pravastatin trials in this context, extremely few patients have been studied with an LDL cholesterol level above 200 milligrams per deciliter.

Now, from a lot of epidemiological studies, it is known that about one-fourth to one-fifth of patients with acute coronary syndromes or acute MI coming into the coronary care unit have some inherited disorder of hyperlipidemia. The majority have familial combined hyperlipidemia, at least 20-25 percent, and they usually have LDL cholesterol levels about 200 milligrams per deciliter. The rest are made up by familial hypercholesterolemia and other disorders. So, approximately 20 to 25 percent, maybe a smaller proportion in the United States than in Europe, have very high levels of LDL cholesterol levels, which have not been studied with pravastatin.

Now, there is from the epidemiological data good evidence to suggest that the lower the cholesterol,

the lower the risk of having a heart attack. However, there is very little data from randomized trials to support the concept of a target level. Neither the European target of 3 millimolar per liter or the U.S. target of 100 milligrams per deciliter of LDL has very good support from randomized data. As you may know, at present there are five large-scale, randomized clinical trials addressing this question, randomizing a total of 40,000 patients. But the results of these trials will not be clear until 2004, 2005.

There is, as I said, a lot of epidemiological evidence, and one European study suggests that once you get below 75 milligrams per deciliter of LDL cholesterol, other risk factors lose their importance. Whether you are a smoker, have hypertension, diabetes, once you get below 75, the risk is so low that you can ignore it.

The studies done with other lipid-lowering drugs like simvastatin in 4S indicated that in the internal analyses, the lower the simvastatin group got in the percent reduction of LDL cholesterol, the lower was the risk. The tertile in the simvastatin group who, after one year achieved an LDL cholesterol lowering of between 44 and 70 percent, had a lower incidence of coronary artery disease in the next 4 years than the two other tertiles. So, in 4S there was a linear relationship between the level

reached after 1 year and the risk; the lower you could get, the better. But this is observational data.

In the two trials with pravastatin that have done similar analysis, the CARE study and the West of Scotland study, this finding was not confirmed. On the contrary, in the CARE study, there didn't seem to be much difference of risk reduction whether you had reached a level of 120 or 80 milligrams per deciliter in the pravastatin group compared to those who remained high. A similar finding was done in the West of Scotland trial, where it seemed like about a 12 to 24 percent reduction in LDL cholesterol was enough to achieve the same risk reduction as those who had greater reduction in cholesterol.

So, in an editorial where all these three papers were presented two or three years ago, Scott Grundy suggested that we now have three different models for whether there is a threshold or a target level or not. The evidence from 4S indicating a linear model, the evidence from the pravastatin trial indicating a threshold at approximately 130 milligrams per deciliter of LDL cholesterol, whereas all the epidemiological evidence seemed to indicate an exponential relationship between LDL cholesterol level and risk.

However, the meta-analysis performed with all

types of lipid-lowering trials, including the statin trials, would indicate that there is an almost linear relationship between the percentage reduction in LDL cholesterol and the benefit achieved from the side of the patients.

I'm not going to talk about baseline levels, but the clinical practice to date is that patients with familial hypercholesterolemia and familial combined hyperlipidemia are actually rarely treated with less potent statins. They are usually treated with a high dose of highly potent statins or a combination of drugs. Therefore, for about one-fourth of the target population who are discharged from a coronary care unit with acute coronary syndrome, this type of drug would probably not be considered by physicians, or if they are considering this drug, the patients might not be given what is today regarded as the optimal treatment.

However, we will not know until three years from now whether the concept of a target level is correct or not. And until that, I will not press my point very hard about this.

But my final summary is that there is not very good clinical trial evidence on the use of pravastatin 40 milligrams and its efficacy in about one-quarter of the patients with coronary care unit disease.

DR. BORER: Thank you very much, Dr. Pedersen.

Are there any questions from members of the committee for Dr. Pedersen?

I have just one question that really is sort of not totally relevant here. If one were to measure the cholesterol at the time that statins commonly are begun now in the coronary care unit, if one were to do that, and recognizing that at least in acute myocardial infarction, there's an important change in cholesterol when measured immediately after the event, to what extent, if you can actually provide an estimate, would the estimate be incorrect that you were using as your baseline in cholesterol?

DR. PEDERSEN: I believe that most coronary care units today do measure cholesterol on admission into the coronary care unit. And that measurement would be fairly accurate as to what the usual level of that patient is. It is only after about 24 hours that cholesterol levels tend to drop, and they can drop quite considerably by more than 1.5 millimolar per liter over the next few days, and then gradually get back to the baseline level again after about 6 weeks. But if you measure within 24 hours of onset of symptoms, you get a fairly accurate estimate of what the actual level used to be.

DR. BORER: Steve?

DR. NISSEN: Professor Pedersen, difficult question for you, but it relates to your own practice. Is there a level of LDL cholesterol above which you would not use pravastatin personally?

DR. PEDERSEN: Well, first of all, I rarely use pravastatin at all because my experience is mainly with simvastatin. But if a patient has FH or familial combined hyperlipidemia, which means LDL cholesterol levels around 250, I start with a high dose of simvastatin or atorvastatin, usually at least 40 milligrams. And if it's very high, I start right away with 80 milligrams because the probability to get cholesterol levels down to target level, if you think that's important, is very small with prava 40.

DR. BORER: If there are no more questions for Dr. Pedersen, what we'll do now is break for -- dare I say it -- lunch, early. Let's be back here at 12:30 to begin again.

(Whereupon, at 11:32 a.m., the committee was recessed, to reconvene at 12:30 p.m., this same day.)

AFTERNOON SESSION

(12:37 p.m.)

DR. BORER: We'll reconvene. We have a little bit more discussion and some data to be presented prior to going to the formal questions that we've been given, but I think the discussion won't take us very long and then we can move on to the questions. It is to be hoped that nobody will have to leave early before we get through.

There are two issues. First, the sponsor has data in response to Beverly and Tom's question, and maybe you want to present that briefly, if you would, about the percentage of patients who achieved 100 milligrams percent of LDL cholesterol in the two trials.

DR. TONKIN: Essentially as you heard this morning, in CARE it was 75 percent of people who achieved an LDL cholesterol of less than 100. I should say that the exclusion criteria for CARE were an LDL above 175 milligrams per deciliter, and that's important.

In LIPID, a total of 53 percent of those on pravastatin achieved an LDL of less than 100, and the question was also asked about the LDL of 110, and that was 68 percent. The exclusion criteria for LIPID were a total cholesterol above 271 milligrams per deciliter.

The other comment that I'd make is that these are intention-to-treat analyses, so this does not -- for

example, this 53 percent -- account for the 19 percent of patients who were assigned pravastatin who dropped out from that treatment limb.

If I could show a little bit more data dissecting the material around LIPID a little bit further. There was a lot of discussion about what was the value or the validity, if you like, and how should we look at LDL as against the other part of the argument of whom should be treated. And this is an analysis in LIPID, and I would stress that I do believe that primarily trials examine intervention and not the mechanisms by which they treat.

With that caveat, this is analysis of the lipid parameters, on-study lipid levels, 12 months after recruitment to the study, and looking at the proportion of treatment effect which is explained by those on-study lipid levels at 12 months with respect to coronary events from 12 months over the next 5 years to the end of the study. Because this is a nonrandomized comparison, we adjust for baseline risk factors in all the models.

The proportion of treatment effect, and here's the 95 percent confidence intervals, is the proportionate reduction in the treatment arm effect when one factors in not only the other baseline risk factors, but the particular lipid parameters.

The point I want to particularly make -- a few

points, one of which is that the proportion of treatment effect explained by LDL, although it's 38 percent, has very wide confidence intervals. It might even account for the fact that none of the benefit of pravastatin was related to the LDL lowering.

Also, though, the importance of HDL and other parameters that might be there, and I guess to me the most outstanding example of the fact that it is not just LDL lowering that's important is VAhit, which shows a benefit with gemfibrozil in secondary prevention when there is no effect on LDL. So, I think that what this says to me is that we really have to say that there is a lot of uncertainty about what might be the extent to which LDL lowering is important.

What is fascinating to me is the fact that the guidelines are based on this very endpoint data, data from 4S, data from West of Scotland, and these are the hard clinical endpoint data in LIPID, reduction in deaths, reduction myocardial infarction, stroke, need for revascularization. No evidence of any heterogeneity in treatment effect in any prespecified subgroup, and extraordinarily safe. No cases of rhabdomyolysis, et cetera.

DR. BORER: Steve?

DR. NISSEN: I take it from your comments then

you don't agree with the guidelines.

DR. TONKIN: No, I think that guidelines are guidelines. I myself am involved in generating and chaired our own working group in developing the LIPID guidelines in Australia, but they are guidelines. I think what we also say in the guidelines is that these actually define what might be reasonable practice. They are not prescriptive.

But I really do believe that there is much more data about hard clinical endpoints, much, much more data about safety, and the two aspects of the lipid-lowering guideline, if you like, in terms of secondary prevention, should treatment be started, an extraordinary wealth of data in terms of what should the goal be.

I think we need to await the trials that have been discussed. We know, for example, there is an effect on inflammatory markers. We haven't discussed that at all. In CARE the benefits were restricted to those people who had high levels of CRP, serum amyloid A protein, et cetera. I think that we've got to be very careful in not going beyond the endpoint data in saying that this is the mechanism by which the treatment is working.

DR. BORER: Thank you very much.

There's one additional safety issue that we didn't touch on this morning. In the sponsor's book, it was suggested that combined treatment could be given at any

time of day, and for safety with aspirin, it was necessary to take the aspirin with water. I'm not a gastroenterologist, but common clinical practice, at least where I come from, is to suggest that aspirin be taken with food. Until very recently, the labeling for pravastatin was that it should be given at night because of the somewhat greater efficacy at that time. So, there's some question about giving the combined product any time of day, or giving the two components at night, or at any other time.

Beverly, you had pinpointed this issue, and Beverly actually got a copy of the new proposed label to look through, and perhaps you want to say something about this.

DR. LORELL: Perhaps we could just hear a brief clarification from the sponsor. It's my understanding -- and correct me if I'm wrong on this -- that in the LIPID trial Pravachol was given at nighttime. The current brand-new labeling for Pravachol in the instructions to the patient comments now that it can be administered as a single dose any time of day with or without food. However, in the paragraph describing the pharmacokinetics and metabolism, there is a discussion that says explicitly, "The efficacy of pravastatin administered once in the evening, although not statistically significant, was

marginally more effective than that after a morning dose." It appears that information was acted on in the design of the trial.

With this issue of giving both drugs at the same time, although some patients do take their aspirin at night, I think that in general practice in the United States, it is the practice to take aspirin in the morning, not on an empty stomach at nighttime, and usually to take it with food. I guess as the chair brought up, it would be helpful to have some discussion in using a fixed combination about both the issue of time of day and what it should be taken with.

DR. BORER: Does the sponsor have a brief response to that, or any other committee members after that?

DR. BELDER: Yes. The efficacy of pravastatin, when given at night or in the morning, there was a difference of about 2 percent in LDL-C lowering, and our reason to broaden the label to dosing any time of day was based on that very marginal difference, and the fact that perhaps some patients like taking their medications in the morning instead of at night.

When the statins were first developed, there was the at least theoretical thought that since cholesterol synthesis primarily happens during the night that you would

expect a greater benefit, a greater efficacy when you would dose it at night, and that's basically how most of the trials were done. But if you then look back at the data that was actually generated, there was no evidence that there was a difference if you took it either twice a day, at night, or in the morning. The confidence intervals of the point estimates were all overlapping, and that's why we asked the FDA to change our label and we were granted to do so.

DR. BORER: Are there any other questions about this or any other issues before we go on to the formal?

DR. LORELL: [Question off microphone.]

DR. BORER: Well, the issue of the aspirin you mean? It becomes moot if you can actually take pravastatin any time of day with food. Then we can tell people to take aspirin however we want them to take it.

Alan, you'll be happy to see that you'll be opining again. The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of a fixed-dose combination product consisting of pravastatin and aspirin for use in patients who are prescribed these two products as individual entities. It's common knowledge that FDA will accept applications for fixed-dose combination products when two or more approved drugs are commonly prescribed together for convenience and perhaps for better

compliance.

In discussion of such products, we've said that availability of such convenience formulations should not alter health care providers' prescribing practices, that is, by not providing a full range of useful doses. Generally that means that a full range of dosing strengths of each individual entity should be available for the combination product, thereby providing convenience but not influencing selection of doses or dosing regimens of individual entities. And we've heard some discussion specifically about that point, and we will again in responding to the questions.

Further, the division has asserted that it should be well established that both entities should be taken concomitantly, since the existence of a fixed-dose combination product implies that they should be taken together, not just that they can be taken together. Generally speaking, the division has required for fixed-dose combination antihypertensive products that the effects of the combination, A plus B, must be greater than the effects of either one alone, A or B. Moreover, the effects of several doses of A in combination with several doses of B must be evaluated, often in a factorial trial, so that some description of the use of A plus B can be compared with either A or B alone.

The sponsor has chosen a single dose of pravastatin, 40 milligrams, and two doses of buffered aspirin, 81 and 325 milligrams, to combine. Thus, there will be two formulations of the fixed-dose combination marketed, 40 milligrams of pravastatin with 81 milligrams of buffered aspirin, and 40 milligrams of pravastatin with 325 milligrams of buffered aspirin. Although initial marketing will be accomplished by co-packaging, formulations of fixed-dose combinations have been prepared and are awaiting completion of stability studies. The fixed-dose combinations will be marketed as soon as data are available. Although the application is for a co-packaged product, the advisory committee is asked to consider the issue the same as that of marketing a fixed-dose combination product.

Pravastatin is approved for use in: A, primary prevention in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary – I guess in the presence or absence of coronary heart disease and other risk factors; B, for secondary prevention of cardiovascular events, total mortality and stroke; and C, for the treatment of hyperlipidemia.

Aspirin is for use in the following patient populations. Secondary prevention of death and stroke in

patients who have had transient ischemic attacks or stroke, all CNS indications related to thrombotic events. B, secondary prevention in patients who have survived a myocardial infarction, and C, patients who are suspected of having an acute infarction, patients with unstable angina, and patients who are having revascularization procedures, coronary or carotid, who have underlying occlusive vascular disease. Aspirin is given for life, according to the dosing and administration section, for patients who have had unstable angina or PTCA.

Given that preamble, can we define a patient population for whom pravastatin plus buffered aspirin would be indicated, and if yes, we need to define the population or populations. Second, are there populations where there might be net harm from giving both pravastatin and buffered aspirin together, and can we define some of those populations.

The committee reviewer is Alan Hirsch. Alan, why don't you go ahead and we'll see if everybody buys into your answers.

DR. HIRSCH: The reason Minnesotans like to opine is because we have lots o' pines in our state.

(Laughter.)

DR. HIRSCH: So, to start this off, it's easy to define the population. I think the sponsor has helped

us with that. This combination would be used in those individuals with established coronary heart disease, and though not explicitly stated, I think there is an assumption that it is also patients with established heart disease with an elevated cholesterol level.

DR. BORER: Okay. Is everybody reasonably in agreement with this? I think that's pretty much agreed upon.

And 1.2, are there patients where there might be net harm from giving the two?

DR. HIRSCH: The contraindications are, I think, in this case the same as the individual contraindications. There's no additive contraindication. So, no specific population beyond the individual.

DR. BORER: Susanna?

DR. CUNNINGHAM: I have a question. What I'm wondering, and I don't know that we have an answer to this, but I'm wondering if there is actually a combined preparation, that people will actually know that they're on aspirin. And therefore, if they were to have surgery or some other event where someone might say, are you taking aspirin, I'd like you not to take any, or the surgeon might request that, will people know? Because I think patients don't always understand what medications they're on, and so it's kind of a puzzle.

DR. BORER: So, that might be a population for whom at least transiently there would be net harm.

Steve?

DR. NISSEN: Actually, Susanna, it's a very perceptive comment. You know, it's been our practice to withhold aspirin for a period of days prior to cardiac surgery because there's very good prospective data to suggest that if you're on aspirin, your chances of having a major or even catastrophic intraoperative bleed are increased. That is a down side of the fixed combination, that both the physician and the patient -- it may tend to obscure a little bit what the components are. It's one of the reasons why in practice I tend to avoid fixed combinations because you may lose track of the individual components that you're giving.

Is it a huge issue? No, but it could be a problem and it could be even a lethal problem under the wrong circumstances.

DR. CARABELLO: Well, in that same vein, or artery, what we don't know is then what would be the down-side risk of discontinuing the statin agent, let's say three or four days ahead of time of surgery, considering its endothelial effects and other effects. I'm making this up, but it's possible that there would be risk involved.

DR. HIRSCH: This sounds like a labeling

question, but so we can go one step further, I want to make sure everyone heard me. The sponsor's proposed population was long-term management to reduce the risk of cardiovascular events in patients with clinically evident coronary heart disease. I added the phrase, with elevated cholesterol levels.

Based on the discussion, I thought someone was going to stop me and say, moderately elevated cholesterol levels. Does anybody want to add a population based on that?

DR. LORELL: Dr. Hirsch, I would welcome thoughts of others on the committee on that issue. I think the other issue on which I would welcome some comments from Ray is, he made a very, I think, clear statement that he would view appropriate use of this medication in line with the FDA's opinions that fixed combinations are usually used after safe and efficacious titration of the individual components.

Since this affects so many patients in the United States, is this an indication issue or a labeling issue that clinically evident coronary heart disease following successful titration and safety in the use of Pravachol and aspirin?

DR. BORER: This is not an indication issue really. The fact is that this is a convenience

preparation. There's nothing, as Bob said earlier, that would prevent you from giving an extra dose or changing the statin, adding a statin, doing something else, if you thought that your cholesterol goal wasn't being hit. So, I don't think it's an indication issue.

It might be, however, a concern in terms of altering usual practice, and that's something we're going to have to consider. Does the presence of the fixed dose combination make it less likely that doctors will do the titration? That's something that we're going to have to think about and give an opinion about.

Yes, Alan?

DR. HIRSCH: I'm going to try to take your point, Bev, which you've come at fervently, and take it one step further. We're asked as a committee to define the population and the approvability based on a really very elegant, well-done series of meta-analysis we'll get to in a minute, but in the absence of a prospective trial. So, another way of ignoring guidelines is to say, if we decide later that we have safety and efficacy data that should be applied to the population studied. In other words, the sponsor said there's 12.4 million Americans at risk and 10 million who might not have contraindications. The question is, is that the population that this is going to be used for, or really is it the set examined in CARE and LIPID?

We'll come back to that later.

DR. LIPICKY: Just for the sake of the record, what you were asking about usually goes into the dosing and administration part of a label. So, it is always included, but it is in a different part.

DR. BORER: Yes, Bob?

DR. TEMPLE: I think the assumption on these convenience preparations, where you're hoping to get the effect of each drug in an appropriate population, is that the indications for pravastatin are unaltered. You do have to say something about using the two drugs together, for example, titrate separately or things like that. But the pravastatin-receiving population here should be the same people who get pravastatin any other time, one would think, except that in addition they need aspirin. Or someone thinks they need aspirin.

DR. BORER: Mike.

DR. ARTMAN: Along those lines, Bob, though, pravastatin is indicated and approved for primary prevention. I think there's controversy about the use of aspirin in primary prevention. So, I wonder about that population. And are we going to extend the use of aspirin in primary prevention?

DR. TEMPLE: No, we're not, until aspirin gets that claim.

DR. BORER: The fact is that people can choose to take the two sets of indications and find out where they intersect and give the drug that way. I think that's fine. I don't think that's our big issue.

Do we believe that the data support the concept that you could define such a population? And even though a randomized, controlled, prospective trial hasn't been performed, I think what we're hearing here is yes, you could define such a population. We might argue a little bit about what the edges are, but you could define such a population.

I'd like to focus just a little bit more about populations for whom there might be net harm. We've heard a couple, and I want to ask the opinion of the committee about another, and then Dr. Kreisberg will have another opinion.

That is, in the elderly on polypharmacy. I would suggest that we don't really have a lot of data about that population, and it's a relatively high-risk population, so I can't say that there's net harm in the whole population or subset of the population for whom aspirin and/or pravastatin might be indicated among people who are over age 75, if we accept that as elderly, or whatever we accept as elderly now. But I think that it's something that we ought to talk about a little bit, again,

in part because the average number of drugs that people at that age receive is at least five prescription drugs. I'm a little concerned about that, and I think we don't have enough data to be able to say.

Dr. Kreisberg?

DR. KREISBERG: Well, I'm not sure that this is directly relevant to what you've just discussed, but it seems to me that there's a lot of uncertainty vis-a-vis the NSAIDs and the cox-2 inhibitors that will also play into this, although that's not part of the issue that needs to be considered.

I'd like to amplify on Steve's comment about patients undergoing coronary artery bypass. That's actually a small subset of patients who are having procedures. There are dental procedures and there are minor dermatologic procedures and there are colonoscopies and a variety of other things that occur in these patients that will require a specific set of instructions or understanding about the inflexibility of being on this particular preparation when it comes time to temporarily discontinue a component of the pill.

DR. BORER: Ray?

DR. LIPICKY: Well, Jeff, your concern seems to me to be part and parcel of the individual entities. That's true whether it's a combined product or not. So,

I'm not sure that it's a specific concern for thinking about a fixed-dose combination.

DR. BORER: Yes, that's true. I don't think that the concern is specifically because of the fact that the drugs are combined, but if given in a combined product, we do have to be concerned, where we might not be so concerned if we could just give one or the other, which we can because this is a convenience product.

DR. LORELL: Question. I guess I'd like to hear your comments a little bit further. I hadn't thought about this point until it was brought up today about the notion of withdrawal of drug, but I think one of the points that your comment made me think about is that in the older patient there are many instances for procedures, when integrated over time, over six months or a year, where aspirin may be stopped for a period of anywhere from three days for the dentist, or for two weeks or more for a major operation.

It's an interesting comment, given the meta-analyses that we showed today, and were shown, which indicated a very persuasive effect of Pravachol in isolation without aspirin, that there is a protective effect there in those meta-analyses, although the effect of both is clearly greater.

So, I really hadn't thought about this until

today, but it raises the issue over a long period of time, the indication of long-term management, that there may be quite a substantive amount of time in some patients' existence where they would lose the protection even of Pravachol in isolation, in addition to aspirin. So, I think it's an interesting point to think on.

DR. BORER: Okay, let's go on to the second question. There are no data from any trial prospectively designed to test the hypothesis that pravastatin at any dose, plus buffered aspirin at any dose produced a better clinical outcome measured by any clinical endpoint than either pravastatin or buffered aspirin alone. Therefore, is that sufficient reason to cease consideration of approval of the fixed-dose combination product? In other words, is it necessary to have the results of specifically designed controlled clinical trials to consider approval of this fixed-dose combination product? If not, what might be sufficient. Alan?

DR. HIRSCH: I think this is an easy question. We wouldn't have a whole day of discussion if we didn't believe that we could look at the database that exists and consider it, but obviously it's preferred to have a prospective trial.

DR. BORER: Tom, do you have any thoughts about this particularly?

DR. FLEMING: I'm a little uncertain about the lead-in paragraph.

DR. HIRSCH: Where is he taking us in this question? Is there something we're missing?

(Laughter.)

DR. FLEMING: It's my sense that, of course, we'd all love to have had a two-by-two factorial design. It's clear, though, how things evolved in time. We had comparative trials of aspirin against nothing, and then with that being accepted, when pravastatin came along, we had comparative trials of pravastatin, yes versus no, allowing for what was in this case the majority of patients being on aspirin. So, those don't provide for us a randomized comparative assessment of one critical issue, which is, what does aspirin add to pravastatin.

But I would say they do provide us a randomized comparison of what does pravastatin add when you have a population of people who would be on aspirin. So, I would think at least one of the dimensions, we do have randomized trials.

DR. LIPICKY: That's correct. When I transmitted these questions by e-mail to get published, I chose the wrong file. And what you just said was part of the edit that I missed.

DR. BORER: Before we get to you, Steve,

though, why don't we deal with the sense of the question, though. We don't have a randomized, prospectively designed trial to test the effect of aspirin added to pravastatin. Is that a show-stopper, or can we deal with this?

DR. FLEMING: I don't believe it's a show-stopper. Certainly we strongly urge randomized trials to give us far more interpretable data and a much greater sense of confidence in the results, but there certainly are settings where adequate evidence can be provided in the absence of randomized trials.

DR. BORER: Steve?

DR. NISSEN: I think as usual, Tom, you offer lots of wisdom there. I would suggest, however, that there are some issues, and that is that if we aren't going to have randomized data, prospective data, the data should be very solid, well documented, and fairly compelling.

And there's something we didn't talk about very much today that does bother me. We really haven't the faintest idea what dose of aspirin was used, even what the range of doses were. We only know what the aspirin administration was at one time point, which is the time that it was assessed at the beginning of the trial. We don't know if people dropped in and dropped out of aspirin use during the course of the trial.

So, I think the data is actually weakened

substantially from the level of evidence that I would like to see by the fact that we -- I mean, if they had annual assessment of concomitant medicines and could tell us at each year of the trial who was on and who was not on aspirin -- I didn't see any of that data today.

DR. BELDER: We have the data.

DR. NISSEN: Well, you didn't provide it us.

DR. BELDER: You didn't ask for it. I did say that 97 percent of the patients who were taking aspirin at baseline were still taking aspirin at the end of the trial. I said a couple of times that the patients who were not taking aspirin, there was significant drop-in rate. If you want to see the data, we can show you the slides.

DR. NISSEN: There was or was not a drop-in rate?

DR. BELDER: There was a drop-in rate. We can show you the data.

DR. NISSEN: I don't know whether we can do this now or not, Jeff, but to me, if there is a lot of drop-in and drop-out, it's a significant confounding variable. I don't know, Tom, if you could help me with that, but does it confound the data?

DR. FLEMING: It's certainly relevant when I think in terms of what we didn't get by not having a randomized trial. Two of the features are that, on the one

hand, we don't have the assurance that those on intervention, in this case aspirin and those not aspirin, are comparable in ways other than they're receiving aspirin.

The other feature is one you're getting at, Steve, and that is we would ideally like to have had a better managed adherence to the interventions. My own sense about that, though, is if we're relying on these 14,000 patients from LIPID and CARE to not only address the question they're obviously designed to address, which is what does pravastatin do, and in most cases in addition to aspirin, but we're also going to use it to try to learn what does aspirin do in addition to pravastatin -- my own sense is if we had actually designed that as a factorial design, we probably would have had more adherence to the distinction between being on aspirin versus not being on aspirin.

In this setting if there is -- we're hearing that in fact those on aspirin, to a great extent, did continue to adhere. We're hearing it was 97 percent. We're hearing, though, that the aspirin patients did have cross-ins. Wouldn't that dilute the effect that we would be looking for? As a result, if you ended up seeing an effect of those on aspirin and pravastatin versus those on pravastatin alone at baseline, wouldn't the sense be that

this is then good evidence that there is an effect? It would have been even larger had there been better adherence to non-aspirin?

DR. BERRY: Mr. Chairman, may I address that?

DR. BORER: No, not at this moment, please. I'm sorry, it's my fault. I should have pointed out that once we begin the questions, this is a committee discussion. If we need more information, we'll ask for it.

Dr. Pedersen, you wanted to make a comment here?

DR. PEDERSEN: Well, under these circumstances it may not be appropriate that I comment, but I was just thinking that it would be really too much demand a large-scale randomized clinical trial with a combination, considering the cost and the resources required to do such a trial.

However, since the main argument for bringing this combined treatment to the market is that it will increase the compliance with treatment and also the proportion of the population to be treated, one would think that a trial to prove that might be appropriate. And a trial of compliance wouldn't need more than maybe 100-200 patients, looking at proportion of patients reaching certain LDL targets, proportion of patients actually taking aspirin. You could randomize to the combined treatment or

to the usual care, and that would be a simple and inexpensive trial.

DR. BORER: Alan, and then Bob.

DR. HIRSCH: I just want to reemphasize a point for the completeness of the discussion, I think, that Tom made, and in a sense defend my colleague to my left, which is, we looked very carefully at the data for treatment, and I must say I also was not quite aware, other than hearing the 97 percent number, that I knew the aspirin compliance rates.

The question we're asked is, in the absence of a prospectively designed trial, can we consider approval of a combination product with these kind of data. I think that we are going to be, especially if we vote yes, increasingly faced with questions. There are these two anti-ischemic or anti-atherosclerotic interventions. Can they be combined? That's where we started today. Increasingly, there will not be prospective randomized trials. So, this question will, I think, arise again.

So, I think the sense of the committee, despite an elegant presentation and a wonderful data set, is that when there's two treatments in a trial that are going to be expected to be combined, I think this committee probably would like to see compliance rates clearly prospectively collected and presented, so we can have a higher level of

confidence.

DR. BORER: I think Bob has a comment about this, but I do want to make the point that nothing in any law or regulation says that you need to have randomized, prospectively designed, placebo-controlled or any other controlled trials. It just says you have to have adequate evidence, and I think that what Tom is suggesting.

And what I think I'm hearing from around the table is that this issue is not a show-stopper. You could use this kind of evidence, but the confidence that we have in the precision of the conclusions that we draw or the accuracy of the conclusions we draw is less than what we might have or would like to have, certainly with prospectively designed trials.

Bob?

DR. TEMPLE: We actually, in most cases where it was considered an issue, have asked for randomized trials showing the contribution of each. But sometimes, for example, you already know that one of the components doesn't contribute. So, for Sinemet, you don't really need to show that carbidopa doesn't have an effect in Parkinson's disease. It's not intended to. So, all you have to do is do the two components, showing that one adds.

So, one of the questions here is, where are we? Are we at the level of, well, we know that, as the

question is asked, because it's obvious, because they've done these meta-analyses that strongly support the argument, or do you actually need a trial? Of course, the difficulty here is nobody is going to do that trial. You're not going to leave aspirin out.

I want to make a couple of observations. One, to the extent you think compliance is a problem, as Tom said, that weakens the association. If you still find the association, that's not an argument against it, although we may need to inquire just who was counted as being on aspirin. Does that mean aspirin once, aspirin ever, aspirin all the time? I can't tell the answer.

DR. HIRSCH: But Bob, the noncompliance issue works against efficacy but also impedes the safety analysis.

DR. TEMPLE: Well, again, it's not that you might not want to worry about it, but all the advice people give everybody in the world is, if you need these two drugs, take them. So, why do you have a new safety question about low-dose aspirin? It's the same aspirin that 90 percent of the population is supposed to take. So, I'm not sure why that's a new question.

I just want to make an observation and see what you think about it. It's sort of a problem. It's the difference between doing something under the FDA rules and

doing something just because you're a knowledgeable expert. The whole world tells everybody, take aspirin, take a lipid-lowering drug, take ramipril if you need it, get your blood sugar controlled. And they just do that and they give advice and everybody follows it because it seems sensible.

When someone comes to us asking to put those into a fixed combination, we say, well. And I think that's appropriate because marketing something for a particular reason does mean that you have a particular reason for using those drugs together, and we've always taken that position.

I do just want to point out that that raises a problem when it becomes impossible to demonstrate the effect in a formal randomized trial. I don't think you'll find anybody who will do a trial leaving aspirin out of an appropriate population. I don't believe I'd allow myself to be randomized, and I usually take that to mean that most people wouldn't like that trial.

So, the question is what we do in a situation like that. Does that mean you just can't do it? Which is not an impossible conclusion. Or do you find other data that you do your best to probe?

DR. LIPICKY: You've said that you can do it, and so it's time to go to question 4.

DR. BORER: Right, but it's question 3 we're on. Thank you.

DR. FLEMING: Just briefly, though, before we go on. In 2.2 I'd just like to briefly add. Whereas in 2.1 as we've said, it isn't a show-stopper, I would like to reinforce what Steve was saying, in a sense as an answer to 2.2, if not, what might be sufficient? In my own sense, what might be sufficient, of course, is something that would be somewhat setting-specific, but if one has randomized trials for certain elements, and one has for other elements randomized trials in sufficiently closely related settings, and if one has observational studies and properly conducted meta-analyses where, by properly conducted, I mean using a choice of studies and a choice of endpoints that all of us would accept are an appropriate representation of relevant data, and if those analyses provide very strong evidence of benefit, and if in addition to that, one has very strong biological evidence based on complementary mechanisms of action, that's an illustration of some of the types of information that could be persuasive in the absence of formal randomized trials for all of the elements.

DR. BORER: Okay. Now we'll go on to 3.0. One could argue that for the patient population you've defined since the purported mechanisms of action for the

demonstrated clinical benefit of each agent are very different, something to do with lipids for pravastatin, maybe even something more than that, and something to do with platelets for aspirin, and maybe something more than that, showing that there were no important pharmacokinetic or pharmacodynamic interactions using surrogates would be an adequate basis for approval of the fixed-dose combination product.

Do you agree with this, and if so, are there -- well, first let's see. Do you agree with this, Alan?

DR. HIRSCH: I found the question again to be intriguing because I think we were told at the beginning that we should be thinking about fixed combinations in the context not just of the lack of interaction but also in the context of finding some evidence that there's beneficial clinical synergy or benefit in compliance.

DR. BORER: No.

DR. LIPICKY: No.

DR. TEMPLE: Synergy is too much to expect. It's rarely encountered. You just want to know that the two drugs do something that neither drug does alone.

DR. LIPICKY: This was written in the sense that you know aspirin works and you know pravastatin works, that you have the trials that demonstrate that. If you know those two things, which is the basis for people

prescribing them both, would you be satisfied for purposes of a fixed-dose combination, with something less than bodies? Namely, there's no pharmacokinetic interaction, and the platelet effects of aspirin aren't blocked, and the lipid-lowering effects of pravastatin aren't blocked. This is a hierarchical question, to try and find out what's enough.

DR. HIRSCH: Well, so I'll answer that, and I was ambivalent. I was probably trying to dodge an answer.

DR. FLEMING: Before you do, could I just also ask just to make sure that I'm understanding this, Ray? My understanding of this question says, suppose you have done properly controlled trials that establish each of the individual components is effective individually.

DR. LIPICKY: No. It is in the sense that Bob is saying now.

DR. TEMPLE: Let him finish. He's going to get to where you want him to.

DR. FLEMING: And if in fact you have properly controlled studies that show each of these components is effective individually, and if you then have data on PK and PD that indicates there's no interaction, are those sources of information alone adequate without knowing anything about combination efficacy?

DR. LIPICKY: That's correct. Without ever

doing the meta-analysis.

DR. TEMPLE: Together with the fact that they work in a completely different way, which you might choose to believe means that their independent effects will be manifested, even without measuring that. That's the question.

DR. HIRSCH: I'm going to keep the discussion going by simply charging in and saying I waffle. It might be under certain circumstances.

DR. LIPICKY: Under this circumstance.

DR. HIRSCH: This very circumstance?

DR. LIPICKY: Yes.

DR. HIRSCH: I would not be personally prone yet.

DR. BORER: That means no.

DR. HIRSCH: It's a no.

DR. BORER: We'll go around and get some comments about this because this is an important point.

And I'll tell you that I certainly wouldn't agree with this either, that this alone would be adequate because there are several other issues that we're going to get into, specifically one that was highlighted in your preamble about affecting practice patterns that would be necessary to make some judgment about in order to determine whether the specific combination on the table was

approvable. There may be other issues as well, but the point is, I wouldn't agree with this.

Steve, you want to make a comment?

DR. NISSEN: Yes. I would emphatically think it's not adequate, and I'm going to give you an example, although it's a controversial one. There's some data out there that suggests that aspirin works, that ACE inhibitors work, and there's also some data that suggests that when you give ACE inhibitors with aspirin, it reduces the effectiveness of the ACE inhibitor.

Now, I think that's controversial, but there certainly are plenty of examples out there where two drugs that independently are active, that when combined, if studied carefully enough, would show less combined effect than the individual components. So, I would feel very strongly that we should not set the standard so low.

DR. BORER: But this question specifically states there are no important pharmacokinetic or pharmacodynamic interactions.

DR. NISSEN: Yes, but it doesn't have to be pharmacokinetic or pharmacodynamic. It can be biological. That somehow or other, that biologically, when you combine two drugs, it does something you didn't anticipate to the biological system that makes one or another of the components work less well, and it has nothing to do with PK

or PD.

DR. HIRSCH: It could be biobehavioral. It could be, again, how the patient actually then, therefore, is taking the two tablets and how they're given or withdrawn in real life.

DR. THOMPSON: Anything is possible, but we don't have any evidence to suggest that, and do we put any credence into the fact that this is a common, widespread clinical combination, that every one of us as clinicians would do? How does that figure into this?

DR. BORER: Just one second, Paul. I think that the issue here is first a generic one, and second, applying it to this particular concern. I think what we're hearing from Steve and from Alan and from me so far is that no, for perhaps different reasons, just knowing that there are no pharmacokinetic and no pharmacodynamic interactions of the two entities isn't sufficient by itself as a basis for approval. It might be, but it isn't sufficient.

DR. TEMPLE: Can we just tease two parts of that? You're going to come back to the question of whether the fact that they're in a fixed combination screws up your ability to use them properly. Perfectly good question. I think this was intended to ask, do we know that these drugs, used properly, will have an additive effect because they work differently and because they're well studied

alone.

And I've heard several different answers. Your particular answer was, well, I might believe they would work, but I'm very worried about whether I'm going to change people's behavior. Perfectly good question. See, you could have a well-designed factorial study and still worry about that.

So, they're really a separate question. One is, do I know that the two will work. A second very interesting question is, will people use these properly if they're available in a fixed dose? But I think that's a separate question.

DR. BORER: Beverly?

DR. LORELL: Well, I think that in adhering to the strict wording of this question, and in responding to Ray's comments, I think we were provided with very clear data regarding the peak levels of the two drugs when given at the same time, and the area under the curve. I don't think we were quite provided with one of the things that Ray mentioned that I would like to have seen, and that was that giving the two drugs at the same time does not modify standard indices of aspirin's effects on platelet activation and aggregation. It may not, and my best guess, if I had to make a guess -- does it? The answer is probably no. But we weren't shown that data.

In argument that it should be shown, there are studies, not with this combination but with other agents that have been in the literature recently, suggesting that the timing of when one gives common other used drugs, in addition to aspirin, can profoundly modify the pharmacokinetic activity of aspirin on the platelet.

So, this is not a minor point if in the trials Pravachol was given in the evening, and in large amount of patient practice, they can't tell us how and what time aspirin was given, but it is widespread practice for aspirin to be given about 12 hours apart in the morning.

So, I would like to have seen pharmacokinetic data demonstrating very clearly that when you give both together you're obligated, you're getting them there at the same time, that you don't alter the pharmacokinetic activity on the platelet.

DR. BORER: What if you had had those data? What if you had, by whatever standard you wanted to set, adequate pharmacokinetic and pharmacodynamic data indicating no interaction? Would that alone be sufficient?

DR. LORELL: I think this question is asking something different. It's saying, are there sufficient data to support the presence or lack --

DR. BORER: No. That's 3.1. 3.1 is, do you agree with this, which is the statement that the surrogate

pharmacodynamic data and pharmacodynamic data, if you had them, would be adequate. Then we go to this product.

So, would you agree with the idea that you could approve a combination of two different drugs, drugs that presumably act differently, if you know that there are no pharmacodynamic and pharmacokinetic interactions. Then we get to the issue of whether that applies to this drug. Would you accept?

DR. LORELL: It would have helped me to say there are both sufficient data to support the lack of a significant interaction, as well as it would have helped me think about answering number two.

DR. LIPICKY: But the question that was answered was I don't care if they had it, that wouldn't be enough. So, it's a matter of would that be enough if they had whatever it was you wanted. Then you deal with do they have this and do they have this.

DR. LORELL: I would say it's a component of additional data I would like to have.

DR. LIPICKY: No. Enough, enough.

DR. LORELL: It wouldn't have been enough in isolation.

DR. LIPICKY: That's the question.

DR. HIRSCH: Let's take each part of the question in turn and come around.

DR. BORER: Okay. What Beverly has just said is that these data alone would not have been enough.

Susanna?

DR. CUNNINGHAM: I'm just curious. I believe that this says a lipid effect and the platelet effect, but I believe, but I don't know for sure -- and somebody else can give me more information -- that both drugs also have an anti-inflammatory effect. And what do we know about their interaction in terms of enhancing each other's action as in anti-inflammatory drugs?

DR. BORER: My guess is we know very little. But again, I think just in terms of getting through this thing efficiently, let's say we knew all that stuff. Would knowing that there were no important pharmacokinetic interactions and no pharmacodynamic interactions in two molecules that act differently be enough to allow approval of putting them together in a fixed-dose combination to be given to people? Several people have said, no, that's not enough.

Then we go on to are there sufficient data here. If it wouldn't be enough, you don't have to go on to ask if we had sufficient data here.

DR. CUNNINGHAM: I don't know if I know enough to answer that.

DR. BORER: Okay.

How about the others at the table who haven't commented yet? Mike?

DR. ARTMAN: I think I agree with the sort of sense of unease that I've heard so far, and I would say no.

DR. BORER: Blase?

DR. CARABELLO: Yes, I also would say no.

DR. BORER: Tom?

DR. FLEMING: I say no, but I would like to be real precise about what I'm saying no to.

My interpretation of this question, right or wrong, is if we know we have two agents and individually we know that those two agents are effective, and in addition to that now we're adding that we know that they have purported different mechanisms of action and we have done PK and PD studies to show no interaction, is that information in its own right adequate to approve a fixed-dose combination?

By the way, I would say all of those pieces are very important to ultimately having what's adequate, but those pieces themselves aren't sufficient in my view. There is additional insight I would like to have directly clinically about what the combination does as the additional piece to add on to those important elements to come up with what is sufficient. Hence, with that interpretation of the question, my answer is no.

DR. BORER: Paul?

DR. THOMPSON: Yes. I would say that there's sufficient data to answer 3.1.1, that there's a lack of significant pharmacokinetic interaction, and I would suggest that --

DR. BORER: But we're not at 3.1.1. We're at 3.1. Do we agree --

DR. THOMPSON: No, I don't agree with that.

DR. BORER: Okay. Then we don't have to go to 3.1.1 because if you don't agree those data would be enough, then we don't have to determine whether they have those data or not yet.

Dr. Kreisberg?

DR. KREISBERG: My answer is no.

DR. BORER: No, okay. So, I think it's unanimous. Everybody said no.

Now, Ray, do you want a response to the subsidiary questions?

DR. LIPICKY: No.

DR. FLEMING: Could I have a clarification of that?

DR. BORER: Yes.

DR. FLEMING: At least in my own answer, I said those conditions aren't sufficient, but they are certainly relevant to ultimately what I want to consider as what may

be sufficient.

DR. BORER: So, you may get back to 3.1.1.

DR. FLEMING: Eventually we're going to have to answer 3.1.1 and 3.1.2. At least I want to answer 3.1.1 and 3.1.2.

DR. LIPICKY: Well, we don't want your answer, Tom.

(Laughter.)

DR. BORER: And as advisors we can only give the advice we're asked for.

DR. TEMPLE: Jeffrey, it is important and it's important to other potential convenience preparations because there's always going to be a rationale like this. You know, one lowers lipids, one lowers this, one lowers that. And so, figuring out how far you think we should go with that information alone is of considerable interest to us. But I'm sure, as Tom was about to say before he was interrupted, you can keep those things in mind even while you consider the adequacy of the other data. I'm sure everybody will.

DR. LIPICKY: And there isn't any question about the importance of all that stuff. I'd just like to get to question 5.

DR. BORER: That's good. Well, we're at question 4 right now actually.

The sponsor has provided three different meta-analyses, data from five placebo-controlled trials, the total number of randomized patients being 14,617, that address whether or not administration of pravastatin plus buffered aspirin has a greater effect than either buffered aspirin or pravastatin alone. Some of the selected trials required that patients have greater than normal levels of serum cholesterol; others did not.

4.1. Do these 14,617 randomized patients represent a reasonable approximation of the patients for whom this combination product would be indicated?

Alan?

DR. HIRSCH: Yes, but I was again very bothered by the relative lack of women and minorities, and when we talk about generalization to the American population, we've got to do better. But knowing that the general database we always look at is not much better than this, I'll say yes.

DR. BORER: What about the fact that there were upper limits on cholesterol levels?

DR. HIRSCH: My understanding of the word "reasonable" is not all-inclusive, broadly representative, but let's hear everybody else's opinions.

DR. BORER: Steve?

DR. NISSEN: It weakens it a little bit, not a huge amount. You'd like to have all comers, but these

trials, at the time they were designed, were designed around, some of them, fairly narrow ranges. We heard from Dr. Pedersen that a quarter of the patients that come in with myocardial infarction have LDLs of over 200, and those people would have been excluded from at least some of these trials.

So, I think when you pull all these patients together in a meta-analysis and you've restricted the lipid range for some of those components, it's a source of uncertainty. I don't think it's a huge source of uncertainty, but there is some uncertainty related to that.

DR. BORER: But the sense is that this is not a show-stopper either I take it. Does anybody disagree with that or have any other opinion about this?

(No response.)

DR. BORER: Let's go on to 4.2 then.

From the results of the meta-analyses, do you conclude that the data show that pravastatin plus buffered aspirin has a greater effect than either buffered aspirin or pravastatin alone? And there are two subheads to that, and I'll read them first because I think the answer is all-inclusive here.

Using as a standard of two trials at a p less than .05, is the strength of evidence from the meta-analysis as strong as this standard?

Using as a standard of one trial at a p less than .05, is the strength of evidence from the meta-analysis as strong as this standard?

Alan, why don't you go ahead, and if there are some technical issues, we'll ask Tom to comment as well.

DR. HIRSCH: I've learned to give the yes/no first and then to opine. So, I think the answer is clearly no, but let me just say why.

Both in the FDA briefing document, as well as I think what Tom said initially, there are many reasons why meta-analyses cannot hold the weight of a prospective trial in general, and for me, reviewing the application, although I clearly see an efficacy signal for aspirin with pravastatin and not as strong by itself, there's always this weakness in being able to interpret data in a meta-analysis form which I think is also evident in this very robust meta-analysis. So, the answer is no.

DR. BORER: Tom?

DR. FLEMING: Well, this certainly is a difficult issue, difficult question to answer because those of us who believe strongly in the greatly enhanced interpretability of randomized trials struggle mightily when we're faced with a situation such as this. And there is substantial evidence here and there is a strong motivation or rationale for why the more complete access to

fully randomized data would be difficult to achieve, although I'll also argue the fact that it's difficult to achieve something doesn't mean having less than reliable evidence makes it any more reliable.

But I guess my overall sense here, when I look at the data that's been provided, is we look at the progression in clinical practice that led to the nature of the trials that were conducted that provide the evidence that we need to answer this question. So, initially we began with aspirin in placebo-controlled studies and my sense is even though there is some diversity in the level of effect that those trials have established for aspirin, when compared to controls, that when one looks at the aggregate of evidence, I think there is substantial evidence establishing the effect of aspirin in randomized trials when looking at it as aspirin versus control versus nothing.

Aspirin then became quite widely used, and then when pravastatin came and the trials that were being done were assessing the effect of pravastatin, even though in a sense I would have loved to have seen a factorial design conducted at that point, where patients were randomized to aspirin yes-no/pravastatin yes-no, I can understand the rationale by those who were designing the trials to believe that aspirin would be important to provide at least for the

clinical caregiver to choose, whether or not they would use it. As a result, those studies, and most specifically CARE and LIPID, provide I think a very proper and reliable assessment of what pravastatin adds to aspirin, but obviously aren't designed to provide a reliable conclusion about what aspirin does.

We're left, in answering this question, with the need to look at the aggregation of available evidence to answer two questions. What does pravastatin add to aspirin? What does aspirin add to pravastatin? Are they both integral to the combination?

I think doing some kind of meta-analysis formally or informally is a very appropriate way to proceed. Of course, there's always the challenge, as has been clearly and appropriately identified by the FDA review, that when you do a meta-analysis, it's important for us as consumers of that information to be confident that this is a representative summary of relevant information rather than a retrospective choice of those specific studies, subpopulations, and endpoints that might best defend or achieve a conclusion that those that are conducting the analysis would like to achieve.

My sense is that if we're looking at the question that I defined, it is certainly relevant to focus on those studies that the sponsor has put forward, but I'm

open and very interested in comments from my colleagues if they think a different choice would have been more appropriate. I believe the focus on CARE and LIPID is a very logical and appropriate focus here.

I also think with the cross section of endpoints that we've been presented here, which are basically CHD death, fatal/nonfatal MI, ischemic stroke, and the combination that includes revascularization, that that is the array of relevant clinical endpoints as well. So, I'm not particularly troubled by either of those features.

So then I'm, as a result, comfortable in looking at these data particularly in the sense that they were designed. They were designed to address specifically whether pravastatin, in a randomized fashion, adds, and in most cases, adds to aspirin. There are many summaries, but if we look at the model 1 analysis that the sponsor provides, which is the traditional Cox regression analysis, and we see the data on C-11, C-12, and C-13, we see a summary in the yellow bars on those slides as to what the data are showing us about what the effect is of pravastatin when added to aspirin. And we see, I think, consistent evidence of benefit across all of the endpoints.

In particular, when we then divide this in the next slide into LIPID versus CARE to see, whether or not,

in the spirit of are there two studies that are adequate and well-controlled at the .05 level, I see evidence that I view to be adequately convincing. So, when I look at this source of information, I'm persuaded that the standard for strength of evidence has been met for establishing that pravastatin adds to aspirin.

Well, that was the easy part. The tougher part is if we have to rely on this same source of information, is this adequately convincing that aspirin is integral and it adds to pravastatin.

I struggle greatly with this when one looks at the information that's presented here, which are the blue lines -- and in particular, slide C-13 presents for these three primary endpoints, what is the strength of evidence for what aspirin adds to pravastatin, looking separately at LIPID and CARE -- I see evidence, which if I can view this to be reliable -- i.e., if this were from randomized comparisons -- I would view that this strength of evidence is definitely convincing to me that aspirin is, in fact, integral as well to the effect of the combination.

So, that leaves me then with one final dilemma, and that is, these aren't from randomized trials. What is the plausibility that these differences, in fact, could be more due to the systematic differences in patients who chose to use aspirin versus chose not to use aspirin as

opposed to the actual effect of aspirin itself? That's an incredibly difficult question to answer.

I could be readily persuaded that those people who would be put on aspirin wouldn't be randomly done, but I could also be persuaded, although there's really no evidence in the covariates that we have, that those people who were put on aspirin might, in fact, have been more ill.

The other feature here -- and it comes back to something Steve said, but actually it makes me a little more confident in these data -- is we don't have the same level of confidence and adherence to the aspirin versus non-aspirin, and it's the point that was reiterated by Bob Temple. If anything, that would lead me to think that we might be underestimating the effect.

What we have in these analyses is the ability to look not only at what aspirin adds to pravastatin but what aspirin adds to nothing, although it's not as reliable because it's not in a randomized trial. But what's interesting is when you look at what aspirin adds to nothing, you're getting an underestimate of effect. And this was an issue that I was probing at some length earlier, the cup half full/half empty.

It made me, in the cup half empty, a little more skeptical about what we could say about what aspirin adds to pravastatin when we see evidence about what aspirin

adds to nothing as being less than what we would have known from the randomized trials.

But the cup half full says to me, well, but this is consistent with an underestimate of effect that could readily be achieved if those that are being administered aspirin are, in fact, if anything, somewhat more seriously ill or at higher risk, and if those on the control arm had a greater propensity or likelihood of crossing in.

So, when I think about all of those features, it actually leads me to think that the evidence here from this nonrandomized comparison surely is far less reliable than that I would have from a randomized comparison, but the things that I can think of that are the likely systematic biases would tend to make me think that we're getting an underestimate of effect, and the levels of effect that we're seeing, if they were from randomized trials, would meet my sense of standard for strength of evidence.

So, when all is said and done, as rarely as it is for me to be able to say something that isn't randomized probably is adequately convincing when one considers all of this and the fact that you have different mechanisms of action, I think I am persuaded, when I look at all of this information, that yes, each of these components is

contributing.

DR. BORER: Ray, it really isn't necessary, is it, for us to answer precisely 4.2.1 and 4.2.2? I don't think we can provide an equivalence answer. I think either we'll all agree with Tom that the data are adequately compelling to convince us that both components are integral to the combined effect or we're not.

DR. LIPICKY: But Tom gave sort of a binary qualitative answer. I'd like a little bit of a quantitation with respect to the confidence you have in the conclusion you drew.

DR. BORER: Okay.

DR. LIPICKY: And that's what 1.1 and 1.2 are devoted to. It doesn't need much discussion. He just has to say it's sort of one trials, sort of two trials, in between, or it's even better than two trials.

DR. BORER: Okay. Steve?

DR. NISSEN: I wasn't going to take that so much, but I want to remind everybody of something. A few years ago, it was just absolutely clear and obvious from nonrandomized, sort of observational data that estrogen was very good for cardiovascular protection in women. In fact, many women I know in my practice were pressured heavily to take estrogen by their family practice physicians because huge, enormous observational databases showed that women

that got estrogen had a lower incidence of coronary heart disease. And now, as it's tested prospectively, we find out it isn't so.

Now, is it exactly the same situation? Of course, not. But what happened was that women who chose to take estrogens were different from women who didn't. And you raised the question, Tom -- and I agree with you completely -- that people that chose to take aspirin or whose physicians chose to give them aspirin in this trial -- could they have been sufficiently different to account for some of this?

And, Ray, I don't know in any given situation how you ever can correct for that. It's a huge hazard. So, the only question then you have to do is look at it and say how plausible is that possibility. And, boy, we've been wrong. On the estrogen story, we've been as wrong as we could possibly be.

DR. LIPICKY: You can be wrong with a p of .05 in a prospective randomized trial. Okay? So, I just want to get a feeling of how wrong you think you can be. That's all.

DR. BORER: Let me ask Steve then, since he was the last to speak, and therefore it's easiest to keep him going, do you find these data sufficiently compelling so that you can conclude that both components add to the

combined effect of the combination product?

DR. NISSEN: I do, but I'm nervous. And I gave an example of a situation where people who thought they really understood this very, very well turned out to be absolutely dead wrong about another form of therapy.

DR. BORER: So, are you nervous enough to say this is as good as one trial at p less than .05, or are you even more nervous than that? Because nervous I think means you're not willing to say it's as good as two trials at p less than .05.

DR. NISSEN: I'm going to think about that before I answer.

DR. LIPICKY: The point estimate is in the right direction. No question. No one is going to argue about that. The question is do you think that's real, and then how certain are you of that? And are you going to put us in the position of saying, well, you ought to prove things with a single trial of .05?

DR. HIRSCH: Ray, this is about like a single .05 trial, meaning that we have really quite good data with quite good fidelity, with a p value that looks sort of appropriate, but we could be wrong. That's where we are. It's about equivalent to one well-designed trial.

DR. BORER: Blase and then Bob.

DR. CARABELLO: I think the data are

compelling, but I don't think you can compare the apple and orange of randomized trials to a meta-analysis.

But unlike the estrogen situation, all the toothpaste is out of this tube. There is never going to be this trial. There is never going to be a double-blind, randomized, two-pole trial of these two drugs. It's not going to happen. Millions of Americans are already on this combination, and unless and until some data to become available to suggest that maybe they shouldn't to be, to then throw the whole issue back, it just isn't going to happen.

DR. BORER: I'm not sure that that's what we're being asked to do or not to do. I think what we're sort of being asked is should the FDA put its imprimatur behind the combination if we don't have the data that normally -- the evidence of the strength that we normally would require to allow the FDA to come to that conclusion.

DR. LIPICKY: I want to emphasize that Bob said yesterday that a p of .05 single trial was good enough to get approval. So, saying a p of .05 single trial isn't the death, I just want to get a feeling for the strength of evidence. And so far you're telling me, well, I don't know how to tell you what I think. That's what you said so far.

DR. BORER: No, no. Very clearly Alan said, one trial at p less than .05.

Bob?

DR. TEMPLE: Well, you really have to make the same distinction Tom made. On the question of whether prava adds to aspirin, A, you don't need a meta-analysis. Both trials showed it. They showed it for all endpoints. The p values were pretty extreme. And I must say, although we asked it, I find it hard to imagine that anybody doesn't find that part of it convincing. Those trials were mostly done in aspirin users. All the evidence you have on the effect of prava is from trials in which most people got aspirin. So, that doesn't seem hard. It's the other part that seems hard because you're into epidemiology or something.

I just wanted to go back to something Tom said before, which was that he would like to be allowed to think about the fact that the two drugs work in completely different ways and factor that into his thinking, which I'm sure he did. When Ray wanted to pose the one study at .05 versus two, I said, why don't you cross that out? They can't answer that because it is, to a degree, apples and oranges. It seems fairly obvious that one is bringing one's impression about how things work, with all the flaws that that can induce, just as everybody appears to be wrong substantially on what estrogens do. So, that does seem part of it.

I want to mention one other thing. I somewhat hesitate to do this. There are actually trials in which antiplatelet drugs have been given to people who are on statins, not trials of aspirin, but it's not out of the question we could take a look at trials of clopidogrel and things like that to see whether there was an effect of an antiplatelet drug. It raises some of the same issues as yesterday when you're already on a lipid-lowering drug. We haven't done that. We haven't ask the company to do it, but those data are in the public domain. It might be possible to do that to test the hypothesis.

DR. BORER: I think would think that clopidogrel would be the wrong choice since the drug was approved because of its putative superiority not only to a placebo defined on aspirin, but to aspirin.

DR. TEMPLE: Well, see, that's a good question. It depends on what you think the question is. And I'll tell you what my thought was. We weren't trying to answer the question whether you get precise estimates of what the exact effect of these things are together. It was really a qualitative plus or minus thing, answering the question, if your lipids are under great control, does doing something to your platelets make a difference. So, maybe in that case, another antiplatelet drug, even one that was better than aspirin, might be pertinent.

DR. BORER: I'd like to disagree with that. I think -- and you'll have to correct me if I'm wrong -- that in asking the FDA to approve a combination drug for prevention of events, which is what we're talking about when we add the aspirin on, we'd like to have some sense that there is a quantitative effect, any quantitative effect. And looking at the quantitative effect of a drug that's more potent than aspirin may not tell us that aspirin really adds in an important way to pravastatin in prevention of events. Now, it may add in other ways. It may have platelet active effects, et cetera.

DR. TEMPLE: Jeff, might it not tell you that even if your lipids are just perfect, fixing your platelets makes a difference?

DR. BORER: Yes, it might well.

DR. TEMPLE: In some ways that's the question.

DR. BORER: Well, I'm not sure.

DR. TEMPLE: Not the whole question.

DR. BORER: I'm not sure I'd agree with that.

DR. THOMPSON: Dr. Borer, I'd like to come back to the question --

DR. BORER: Wait, wait. Just a minute, Paul.

I don't want to carry this discussion ad nauseam. The points have been made. I think what we're trying to do here is to determine how compelling we believe

the evidence in favor of an additive effect either way is. And I think we've heard that in general there's evidence, and so far everybody has been willing to accept that there's evidence and both components do add to the effect of the combination of drugs.

The data, as we've heard from Steve and from Alan, aren't as compelling as we usually expect to see, but they're there. That doesn't mean that they're adequate or inadequate, but they're there. And Alan suggested, in terms of the degree to which he's convinced, he's as convinced as he would have been if he had seen one trial at p less than .05.

Let's see if we can sort of narrow the answer to that question, and let's hear from the voting members. Mike?

DR. ARTMAN: What's the question, Jeff?

(Laughter.)

DR. BORER: From the meta-analyses --

DR. ARTMAN: Okay, so you want to answer 4.2.1 and 4.2.2?

DR. BORER: Yes.

DR. ARTMAN: I would agree with what Alan said, that the level of confidence I have in this would be comparable to a single trial at a p less than .05.

DR. BORER: Tom, do you want to finalize your

answer now, or do you want some time to think?

DR. FLEMING: Well, I think I've already said the essence. I'm very comfortable to say that the contribution of pravastatin to the combination has been established by the standards of two studies at the .05 level.

The combination of aspirin is where I struggle greatly. It's extremely rare for me to find nonrandomized data as adequately convincing. The basis that I have judged in this case that it is is essentially built on, A, the fact that I think the evidence is adequately convincing that aspirin, in the absence of pravastatin, is beneficial according to the standards we would usually have for strength of evidence; B, that the biological plausibility that it would maintain that effect in the presence of pravastatin because of different mechanisms of action is relevant; and, C, because the evidence that we do have, flawed as it is because it's not from randomized comparative studies, gives us very favorable point estimates where the best judgment that I can make about where the biases would be, in terms of selection factor as to who got aspirin versus who didn't, and in terms of lack of adherence diluting differences, would if anything dilute the estimates that we came up with, which in fact does appear to be what we're seeing when we look at these data

from the aspirin versus nonaspirin. It's the aggregation of all that that provides me a sense that this is adequate, as incredibly rare as it would be for me to arrive at that conclusion in the absence of randomized comparisons.

And I'm not comfortable, though, stating numerically whether or not this is the same as one or two. It's not nearly as convincing as what you would have if you had had the data from two randomized trials that provided strong evidence of benefit. Nevertheless, it's my sense, for the reasons that I've given, that the aggregation of this evidence is adequately convincing to conclude that both elements contribute to the combination benefit.

DR. BORER: Dr. Kreisberg?

DR. KREISBERG: My answer is yes. I think the preponderance of the data supports the fact that the combination is better than either one alone.

DR. BORER: Are you as convinced as you would be if we had two randomized controlled trials?

DR. KREISBERG: Well, with the proviso to Dr. Nissen about there are things in medicine that make perfect sense but are absolutely wrong, the answer is yes, I'm satisfied with the evidence.

DR. BORER: Beverly?

DR. LORELL: The answer to 4.2 is yes. I thought the data was very compelling that pravastatin plus

buffered aspirin has a greater effect than either buffered aspirin -- either aspirin -- not buffered, but aspirin -- or pravastatin alone.

And for the record, I will say that as a nonstatistician, I cannot feel comfortable answering .1 or .2, but I will say that in this case, there were really two things that I think made this meta-analysis compelling to me as a clinician, not a statistician.

One was that the meta-analysis involved a very large number of patients who were quite well defined.

And the second thing is that I'm always nervous as a nonstatistician when I hear a statistician use a single meta-analysis approach to try and persuade me of something. And I thought it was very valuable in the analysis we heard today that there was an effort to approach this meta-analysis dilemma from three different models.

So, the answer to 4.2 is yes. I can't answer .1 or .2.

DR. BORER: Susanna?

DR. CUNNINGHAM: I would also say that I'm convinced that the pravastatin has a greater effect than aspirin alone, and I also cannot answer the subquestions.

DR. BORER: Yes. I think the question is a little confusing in that it refers in 4.2 to the meta-

analyses. In fact, the meta-analyses really I think properly refer to the pravastatin on top of aspirin rather than the aspirin on top of pravastatin, which I think would be hit in 4.3, but I think the answers have referred to both, if that's okay.

And is it okay if we try not to answer 4.3. I don't think any of us other than Tom can --

DR. LIPICKY: Fine.

DR. FLEMING: Just a simple answer. I find the results from the models as qualitatively consistent.

DR. BORER: Okay.

I think for the record, then, everyone has agreed that there is reasonable evidence that both components contribute to the effect of the combination with varying degrees of enthusiasm, perhaps in general, less than would have been the case had there been two randomized controlled trials to look at, each meeting the p less than .05 standard.

Let's go on to 5.0. Upon what basis was the dose of buffered aspirin chosen for use in the fixed-dose combination product? Do you consider this reasonable? What alternative doses can you recommend? And should one wait prior to approval on settling the question of buffered aspirin dose?

Alan?

DR. HIRSCH: Do you want one or all three?

DR. BORER: Just do all three.

DR. HIRSCH: Well, I think the basis of the choice of antiplatelet dose was retrospectively a combination of the primary aspirin trials, the antiplatelet trialists collaboration, and other meta-analyses and obviously the clinical practice that was both valid in the pravastatin trials.

Do I consider this to be reasonable? Absolutely, acceptable and reasonable.

What alternative doses besides the 81 and 325 would I recommend? I wouldn't. Those would be the appropriate doses certainly in the United States market in any case.

And should one wait prior to approval on settling the question of buffered aspirin dose? I think that in this real world, we have adequate data to be happy with those two choices of doses.

DR. BORER: Is anybody unhappy with that answer? Steve is unhappy.

DR. NISSEN: Well, not completely unhappy, but I must point out that there's an enormous meta-analysis, just published within the last few days, from the Oxford Group that shows that there is a higher risk of the 325 milligram dose and that the dose that seemed to have the

best combination of safety and efficacy was the 81 to 160 milligram dose. So, it's brand new data. It wasn't available to the sponsor when all this was done, and I haven't had a chance to fully analyze that manuscript, but it ought to be at least mentioned.

DR. TEMPLE: That depends a little bit on whether you want to look at a particular dose that was used in a particular setting or, like the collaborations have to do, lump them all together. The current labeling for aspirin says you can do either of those things. Be my guest. And I think that's what we urge: cover the range of doses that are used. There are some things where 150 is the recommended dose.

DR. HIRSCH: Just to come back to the point, our goal was to make sure that were doses available, not to follow another meta-analysis, another guideline. I think the sponsor has done that.

DR. BORER: I think in general then everybody is happy with 5.0. We know how the doses were chosen. We think it's reasonable, no alternatives to recommend, and with the caveat that was just made by Steve and amended by Alan, we don't think it's necessary to beat this one any further.

But 6.0. Upon what basis was the dose of pravastatin chosen for the use in the fixed-dose

combination? Do you consider this reasonable? What alternatives can you recommend, and should one wait prior to approval on settling the question of pravastatin dose?

Keep in mind, in answering this, that putatively this is a convenience product. So, it doesn't mean that everybody has to give this dose.

Alan?

DR. HIRSCH: Yes. I'm collecting my thoughts here.

We spent less time, I thought, than we might have on the discussion of dose, even though we did circulate there. So, this is a question which I would like everyone to weigh in on.

The basis of the choice of dose I presume was a combination of the initial dose-response data the sponsor had, the application of that in the PLAC I, PLAC II, REGRESS, LIPID, and CARE trials.

And do I consider this to be reasonable? Yes, that's reasonable because that's the database we're presented in the meta-analysis.

The hard part is when we get to 6.2 and 6.3 when we're asked what alternatives can you recommend. I suspect there will be some diversity of opinion.

When you lead the question, Jeff, and say it's a convenience dose product, actually there's no need to

recommend alternatives. We're asked for a single dose based on the clinical trials for convenience and we can stop. But I do suspect that the panel members will want to discuss the potential for alternative doses in the prava arm, as well as in the aspirin arm, though many may not want to go there.

I'll charge ahead and go to 6.3. Should one wait prior to approval on settling the question of pravastatin dose? I think not, but I bet you there's diversity of opinion. I could justify that if you'd like.

DR. BORER: I think we've said that the choice of the dose was based on the fact that that was the dose that was used in the prevention trials, and it was reasonable.

There could be alternatives. I don't know if we want to discuss this at this point. There could be, but this is being suggested as a convenience product for people who come to the conclusion that this is the dose that ought to be used.

Yes, Beverly.

DR. LORELL: Had there not been the preamble in the text before that question, I would have answered 6.1 yes. I think there's reasonable logic as to why 40 milligrams were chosen. And for the answer to 6.2, what alternatives would you recommend, I would say none.

But I am concerned that in fact in the text preamble in paragraph 2 that you read was the comment that generally that means that a full range of dosing strengths of each individual entity should be available for the combination product, thereby providing convenience, but not influencing selection of dosing or dosing regimens of individual entities. So, with that preamble to guide us as members of the committee, I would say 6.2 probably does merit some discussion, and the alternative I would recommend would be including consideration of also 80 milligrams with the two options for aspirin. I don't understand the logic for offering a range of aspirin and not offering a range of titration of Pravachol, unless it is the intention to argue that it doesn't matter what your LDL is.

DR. BORER: That issue that you just so beautifully outlined is the sum and substance of question 8.0, and so perhaps, with your permission, we'll wait until 8.0 and discuss that more fully because I think this is really, so to speak, the heart of the matter. Is that okay, Ray?

DR. LIPICKY: Sure.

DR. BORER: 7.0. Assuming that you have concluded something about the strength of evidence that pravastatin and buffered aspirin should be taken together

and that the doses to be available in the fixed-dose combination product are appropriate, what is the strength of evidence that a fixed-dose combination product, taking a single pill, has increased clinical benefit with respect to taking two pills not necessarily together?

To clarify that further, should we require better demonstration of additional benefit provided by convenience, and what kind of demonstration would be better?

Alan, do you want to start out?

DR. TEMPLE: Jeffrey, we really have never asked people to show that. It doesn't mean we couldn't change our view, so it's worth listening. It's my belief that it would not be easy to do in a controlled trial setting where people tend to be compliant. You'd have to establish so loose a setting that people could just ignore the drugs they're supposed to take. I wouldn't say that's not possible, but there's not a lot of track record on it.

DR. HIRSCH: But you asked the question.

DR. TEMPLE: Yes. I probably tried to cross it out.

(Laughter.)

DR. LIPICKY: Yes. It has to be put in context. The assumption was you were going to come to different conclusions in some of the questions above than

you did and that then you would not be able to assert that you knew that the two ingredients contributed to the effect or that you had more major reservations than you did.

So, the crux of the argument, in part, that was made by the company was that compliance was the benefit here, that this fixed-dose combination -- they didn't think you'd reach the conclusion that they had shown A plus B is better than A or B -- offered compliance advantages. And there was absolutely no data regarding compliance at all for this fixed-dose combination. So, this question was written to find out whether you want data to support your judgments. It probably is out of place now since you answered the questions above in a different fashion.

DR. HIRSCH: I think it's still in place.

DR. TEMPLE: Well, it's still pertinent to the end game where you're going to worry about the fact that they may not know how to stop it properly before surgery, a perfectly legitimate question, and maybe the potential for better compliance --

DR. LIPICKY: Well, okay, fine.

DR. TEMPLE: -- certainly not the documentation of good compliance might be part of what you think in it. But ordinarily in other senses we don't really ask that question.

DR. LIPICKY: But in fact I guess the

presentation disturbed me because what was shown for this general knowledge that combinations are better for compliance was a total of four trials. So, I don't think it is general knowledge or that you can assume that taking one pill instead of two leads to better compliance. And so, it's sort of pertinent to the question of if that were important, what do you think we should have seen.

DR. HIRSCH: Can I rephrase the question a little bit because I think this does merit some discussion based on everything I've heard from the panel? I think the lead-in to this whole discussion was obviously convenience and compliance. So, the question I'd phrase is, when does perceived convenience, really driven I think by patient demands we all hear, actually work for or against a perceived or demonstrated, I should say, health benefit? In other words, does having a convenience product per se, which might potentially improve compliance with one or two drugs, work for or against hitting the endpoint ultimately of a decreased cardiovascular risk?

DR. LIPICKY: I guess the discussion should be would you require seeing data that there is something to that. The question is totally out of context now. So, the subparts are: would compliance data be enough, or would you need to have body counts?

DR. HIRSCH: So, just as my friend Tom

occasionally tells us how we might best think about the statistical considerations, I'd like to just throw some ideas out there for the panel to consider because the sponsor did and I found them intriguing.

There are a lot of hypotheses about why this might be a good thing, and the ones I listed were things like potentially adherence to guidelines because people would actually take their aspirin, for example; perhaps use of the correct dose because it would be formulated correctly; perhaps a decreased pill burden and again a greater daily compliance. There were many others, but I think all of these are basically conjecture at this point. There is not adequate data, having read those primary references as well, to suggest that we achieve that in this particular population with these particular products.

So, with that in mind, when I thought of these questions, I actually did think that we're going to be faced with many potential combinations. From this very data set, we could look at beta-blocker pravastatin in the future. We could look at "prilstatin." This is a large data set. There are many combinations that would be very beneficial.

But before I'm having to face this as a panel member, I actually would like to see some additional data, and I was thinking of a compliance study, Ray, but that may

be unreasonable.

What does everyone else think?

DR. BORER: Are there any other opinions? Dr. Kreisberg?

DR. KREISBERG: Well, there's another element to this and that is cost, which we haven't discussed and maybe we can't discuss. But aspirin is dirt cheap and it's about a penny a day for those people that take it. And we're talking about a combination now, and when you consider that 80 percent of the deaths occur in people over the age of 65 and they have Medicare, the payments that they have to make for these medications become crucially important.

So, one of the questions that I have in my mind is what is the intent of the sponsor with regard to this preparation because if it turns out that a drug like pravastatin will, in the near future, will be a generic and will be allowable with a $10 co-payment through most health plans, but this product is not a generic and it requires a $25 co-payment or a $35 co-payment with the plan, then what is that going to do for the proposed adherence rate that we're contemplating would be of benefit to this type of combination?

DR. TEMPLE: It's not that that's not a perfectly cogent question, but I think we don't consider it

FDA's province to do that.

DR. BORER: Should we require demonstration of additional benefit from a convenience study? I don't know that we need to spend a lot of time on this, but does anybody have any thoughts that they want to share here? Blase?

DR. CARABELLO: I don't think we should because I think that ultimately the sponsor bears that burden. If it turns out that the drug is easier to take and that people like it and use it more, then it will be used. And in fact, if that's not the truth, then the drug will die on the vine and it won't be a consideration.

DR. BORER: We don't have compliance data, and I think speculating about it probably isn't going to be very useful at this point.

But let's get on. The last two questions I think are where the action is.

8.0. How likely is it that the availability of a fixed-dose combination product would encourage inappropriate use of the doses of any of these drugs?

This was the issue that Beverly was getting at earlier and it's what we danced around all day. We heard data from Dr. Pedersen and from the sponsor, and I think this is where we really want to concentrate our discussion.

Alan?

DR. HIRSCH: Do you want us to take these one by one or again the whole packet?

DR. BORER: Take them together.

DR. HIRSCH: Inappropriate use of buffered aspirin for primary prevention. I think the risk is very low.

Inappropriate use of a dose of 40 milligrams of pravastatin. Actually low.

Inappropriate use of a dose of 325 milligrams buffered aspirin. I think equally low.

And the same thing for 8.4.

DR. BORER: I'm sorry. We were given these 8.1 through 8.4. I want to expand a little bit.

DR. HIRSCH: Okay.

DR. BORER: Inappropriate use of a dose of pravastatin. I don't care what the dose is. If only one dose is offered, is it likely that the practice pattern will be that the drug is not used in the way that it otherwise might be used?

DR. HIRSCH: Yes, I think there's a real chance of that.

DR. BORER: Does anybody else want to talk about that? Steve?

DR. NISSEN: Yes. I'm troubled by this, and let me see if I can help.

First of all, I do think that there is a moderate risk of inappropriate use of buffered aspirin, and I think Susanna really was the first to point this up. And I hadn't really thought about it, but the more I've thought about it and heard from other people, I am concerned that people undergoing both minor and major surgical procedures may accidentally -- much more likely accidentally -- be given aspirin as part of a fixed-dose combination.

And what's important for us to understand is that aspirin is not a completely benign drug, that it has very serious consequences in the wrong circumstances. Therefore, when you put it together in a fixed-dose combination, I do think you increase the likelihood that either the patient or the physician will be unaware of the fact that they're taking a potent antiplatelet agent and that someone will forget about that in a circumstance where the patient may be harmed. So, I've got to give that at least some credence.

Similarly, because the dose of 40 milligrams of pravastatin, according to current guidelines -- this speaks to medical practice -- is unlikely to get, in my opinion, the majority of patients to the recommended goals, then I think that encouragement of use of this fixed-dose combination will, in fact, increase the probability that some patients will be undertreated with respect to their

lipids.

So, I would also say -- and we can skip the dose issues -- that both for pravastatin and for aspirin, there is moderate risk here that the agents will be given inappropriately when here in the fixed-dose combination. And the more relevant issue then is how does that risk equate with the benefit that might accrue from this combination, and I will speak to that a little bit later.

DR. BORER: Beverly?

DR. LORELL: I agree with what was just said.

DR. BORER: Mike, go ahead.

DR. ARTMAN: I would just like to get back to the issue of inappropriate use of buffered aspirin for primary prevention, and I raised it earlier and got pooh-poohed a little bit. But I disagree with Alan. I really think that there is that risk, and I think there's a lot of controversy about the use of aspirin for primary prevention. I don't think it's been proven, and I think if this fixed-dose is approved, I can see a big campaign and the detail people talking up this combination for secondary prevention, and oh, by the way, you know pravastatin is approved for primary prevention as well. And I think there's going to be a lot of leak and a lot of bleed over to that, and that concerns me as well as these other issues that Steve and Beverly have raised as well.

DR. BORER: I agree with what everyone has said here, and I would like to add just one additional point. I think that over and above the other aspirin issues that have been raised, aspirin may not be the appropriate drug for every patient who requires a platelet active agent. Clopidogrel is approved for certain, specific situations. Most people who receive an antiplatelet drug like aspirin or clopidogrel require or should receive or do receive lipid-modifying therapy in the form of statins. If a combination product is available that has aspirin attached to it, I'm concerned that in some, admittedly small, segment of the population, the more appropriate drug, which might be clopidogrel, won't be used in favor of the less appropriate drug because of the convenience of giving the aspirin together with the otherwise necessary statin. So, I would just add that to the mix, but other than that, I agree with what's been said here.

Blase?

DR. CARABELLO: Just to reiterate what I said earlier, we have no idea what the sudden withdrawal of the statin agent prior to surgery might do, and so one can easily foresee the cumbersome nature of withdrawing the aspirin part of the product and continuing the statin part of the product by prescribing a single agent. I doubt that anybody would do that. And while I have no knowledge that

the withdrawal of statins might be dangerous, it's open to question. So, that does concern me.

DR. BORER: Just to put this in proper perspective without moving beyond where we are here, right now the sponsor is proposing co-packaging, in which case the issue of stopping aspirin independent of pravastatin wouldn't be a big issue, it wouldn't be a big deal. But you asked us to consider a pill that has both of them in it. You didn't tell us about the form of the pill. Is the aspirin part something that could be broken off? Or are we going beyond, in talking about that, where we should be going?

DR. LIPICKY: I can't answer the question. Clearly aspirin is not going to be in half and prava in the other in your single tablet.

DR. FIEDOREK: Yes. We're still working on the formulation for that, but it will be a combination tablet.

DR. LIPICKY: But you're not going to put aspirin in one half and prava in the other.

DR. FIEDOREK: No.

DR. BORER: No, okay.

So, I think the general sense here is that we have real concern about the range of doses that's available for this product because of the various reasons that have been raised, because of the likelihood that this selection,

this range that's been offered, will potentially adversely affect clinical practice.

DR. LORELL: I think that there was also the separate concern raised about packaging a potent antiplatelet agent with another drug.

DR. TEMPLE: We need to understand this because these are probably the reasons you may give a particular opinion. So, it would be very helpful if we understood those. Let me tell you what I understand.

You haven't addressed the question of whether labeling could overcome this and you might want to think about that.

But one major concern was that having two together really makes it difficult to stop one of them, and you can think of quite bad consequences if people don't realize they're supposed to stop their aspirin prior to surgery and you're not sure that stopping the whole combination is the right thing to do. So, I understand that part. That's pretty clear.

I'm a little foggy on the dose thing, unless you just don't believe people will do it, which might be your explanation. This is going to be labeled as if 40 milligrams is the right dose, you can add them together. So, you must suspect that that will not, in fact, happen.

DR. BORER: Yes.

DR. TEMPLE: I assume that's the reason.

DR. BORER: I think from the discussion that we've had around the table during the day, that would be the presumption.

DR. TEMPLE: Just let me continue. The first one, you might think of ways to label around that, but you'd be suspicious about whether they'd work, I imagine.

This one, is this susceptible to appropriate labeling injunctions, you know, be sure you get the right dose, not everybody needs 40. Or is that just not a possibility?

DR. BORER: We can ask everyone around the table their opinion. My opinion is that the label really won't mitigate that potential problem.

Steve?

DR. NISSEN: Bob, the evidence -- and again, this is an area that I happen to be an expert in -- is that most patients end up on the dose of statin that they're started on, that unfortunately, despite all of our efforts to get people to titrate, they tend not to titrate. So, my concern is that to the extent that this will happen, the inconvenience to the physician and the patient of having to stop the combination, switch to a different statin and then co-administer aspirin will be enough of an impediment that more patients will not be titrated to goal than would be