anything like that on them. They just have some little typewritten thing and that's that. So, there is a tendency to lose track of that when you throw it together in a single pill. So, I just didn't want any of us to have the wrong idea about expectations here about what the patient is actually going to see.

DR. BORER: Two issues relevant to that. As a point of information, is it possible to mandate that typed labels in a pharmacy must contain certain information about a certain product?

DR. TEMPLE: Well, we think so. But whether the established mechanism for insisting is available here is not clear. There's something called a med guide that we can require when certain serious hazards would occur if the patient didn't understand certain things. Given the uncertainty about whether discontinuing is critical or not, it would be hard to make the case that you need a med guide.

On the other hand, it's clear that you want patients to understand that they are, in fact, on aspirin and be able to tell their doctor. And companies can agree to have a package insert that is part of their labeling, whether it's a med guide or not.

The next question is how you can provide any assurance that patients will get it. Under the med guide

rule, pharmacists are required to hand it out. Now, what that means if they don't is not completely clear, but they are required legally to attach the med guide which is a patient package insert.

My own view is that if you really care the best way to assure it is to make it part of the distributed package. That doesn't mean a pharmacist couldn't pour it out and put it into another bottle, but they wouldn't have any reason to. So, you create unit-of-use packaging which is how drugs are distributed in most of the world, just not here.

DR. FIEDOREK: We certainly would agree to abide by that and try to work to get appropriate labeling for the combination tablet.

DR. BORER: Another issue here. No single mechanism, except maybe unit-of-use packaging, is going to overcome the possibility totally that somebody is not going to know what he's taking. People have a lot of ways to not know what they're doing.

But another safeguard perhaps could be in the trade name. In this case, it's fortunate that most people understand what the word aspirin means. I suppose, although I have no idea how you make up trademarks, a name that emphasized the component that's of some concern might be helpful in identifying it for patients. So, it's just

something to consider. I don't know if you've thought about your trade name yet.

Are there any other comments? We've raised this as an important issue about recognition. Any other comments, Tom?

DR. PICKERING: Just one naive question. Isn't it likely that when the pharmacist prints out the patient's label with the instructions, they'll paste it right over your very nice label saying aspirin three times?

DR. BORER: If it's unit-of-use packaging then the directions presumably are on the --

DR. TEMPLE: The patient insert can be attached as a pull-out. It depends on how big it is, but it can be attached in a way that it's relatively large print and relatively easy to see.

DR. BELDER: I would also like to mention that this package will actually contain a blister pack and every time the patient punches through a tablet, it will say pravastatin or aspirin. So, even then as you punch through the tablets, as you get the blister pack in your hands, both components are indicated.

DR. TEMPLE: And you see the same thing for the fixed combination in a single tablet?

DR. BELDER: As I said, we haven't developed the packaging yet. We can discuss that, of course.

DR. TEMPLE: But I think that's what people are concerned about.

DR. BELDER: We'll be more than willing to work with the agency to develop clear identification.

DR. TEMPLE: Can I ask the committee one question, Jeffrey? Part of the argument here is that we think it won't be any worse than it is already because aspirin is ubiquitous. The second part is that, yes, probably some people won't realize they're on aspirin, but given the state of what people's views are, that's probably not that bad. We don't even know that's bad for you.

DR. LORELL: I'll take objection to that.

DR. TEMPLE: Well, I'm not endorsing it. I'm just saying I thought that was part of the argument and that they would do their best to make sure people understand it, but that it wouldn't be an unmitigated disaster if somebody slipped through. That's part of the argument I hear. I just want to know what people thought of it. So, I guess I'm about to hear.

DR. LORELL: Yes. Let me respond to that. I think that there is no disagreement with anyone in this room in the cardio-renal field of the extraordinary importance of the use of aspirin and statin lipid-lowering agents for secondary prevention. None of us has to be convinced of that.

I think the data that were presented as supplements clearly raise the issue that there is still a lot of controversy, disagreement about the risk of continued antiplatelet agent use, whether it is aspirin or a newer agent, in the context of minor surgery, major surgery, and biopsies. So, the answers to that are not yet known.

There clearly can be risk in an individual patient of having very adverse outcomes, and I think for many patients the risk of even an increase in -- or any transfusion requirement might be looked at as a major adverse event.

I think one of the things that I'd like to hear your comments on is the safety data that was presented in detail and alluded to here in the earlier presentation this winter that comes from the Pravachol secondary prevention trials. One of the dilemmas there that I'm wrestling with, regarding the use of aspirin, was that aspirin was individually manipulated by the physicians. It was not part of trial design as being a mandated Pravachol alone, Pravachol plus aspirin, or aspirin alone.

So, I think a concern that might be discussed by the committee is that we really don't have data, either retrospectively or prospectively, about the sort of forced co-use of both drugs without individual manipulation. So,

I think although we're all encouraged by the data that at least for vascular operations, continuation of aspirin in the net may be beneficial. There are many other kinds of procedures where that risk-benefit is very unclear.

DR. FIEDOREK: Yes. In the trials you're referring to, the pravastatin trials, the aspirin use may have been done by the patients themselves.

I'd like to ask if Dr. Dacey would care to comment on this from the point of view of cardiovascular surgery, and we can then get to some of the other aspects.

DR. DACEY: Sure. At least in the cardiovascular field, specifically coronary bypass, we found in northern New England -- we talk about continuing aspirin was beneficial with about a 27 percent reduction in operative mortality just being on aspirin as opposed to patients that had the aspirin stopped and had no increase in transfusion, no increase in chest tube drainage, no increase in re-exploration. Indeed, over time, as the slide alluded to, the incidence of re-exploration has continued to go down despite increased aspirin use.

It's not a finding unique to us. The Society of Thoracic Surgeons keeps a database. When they looked at this last in over 78,000 patients, they also found about a 30 percent risk reduction for mortality in patients that take aspirin.

We looked at our own data in northern New England over the last -- I believe it's 5 years, over 13,350 patients or so. Again, about a 28 percent risk reduction in mortality in patients who are on aspirin prior to surgery. Again, we've noted no harmful effects to this.

I know the company is not touting aspirin is a good thing, but certainly in our literature, preoperative aspirin definitely decreases mortality with no discernible adverse effect that we can surmise. So, indeed, we actually encourage our patients, if they're not taking aspirin, to take it right up to and through surgery.

DR. FIEDOREK: Dr. Avorn, would you care to make any comments on this?

DR. AVORN: I think the most relevant piece of this is not whether it is necessarily for nonvascular surgery a good thing or a bad thing to continue aspirin because, as was mentioned, the data simply don't exist, but rather whether the co-packaging or combination of these two products together, as proposed, would increase, decrease, or leave unchanged the likelihood of inadvertent misadventures.

One of the compelling pieces for me is that right now we're dealing with a situation where patients often don't know what they're taking, as the Cook paper demonstrated. Physicians often don't know what the patient

is taking. If it's a surgeon who gets a med list and aspirin is not on it, they may not know what the patient is taking.

So, without taking a stand on whether aspirin should always or never or sometimes be continued through an operation, I think the point here is that this packaging will make it more likely that the doctors involved in the patient's care will be able to make a proactive decision on their own part, whatever their own lights tell them they ought to be doing, and it's giving them more information and that's probably the key distinction.

DR. FIEDOREK: Dr. Chaitman, would you care to comment at all?

DR. NISSEN: Rather than having --

DR. BORER: Just a second, Steve. We have several people. Why don't you finish your response and then we have Mike and Steve and Beverly.

DR. FIEDOREK: I was just wondering, Dr. Chaitman, if you had any answers. No, okay.

DR. BORER: Mike.

DR. ARTMAN: My point was raised already.

DR. BORER: Okay. Steve.

DR. NISSEN: I wanted to explore this a little bit further with you. Dr. Dacey, your data is not prospective, randomized data. Is that correct? It's

observational?

DR. DACEY: That's correct. Both in New England and STS, it was all observational.

DR. NISSEN: So, how do we know that the patients in whom aspirin was continued weren't different from the patients in whom aspirin was stopped?

DR. DACEY: The one paper that we looked at in detail looking at perioperative characteristics, there's no significant difference between those two patients. So, again, there's always a chance of bias, but as far as we can tell as confounding, we didn't find any confounding.

DR. NISSEN: Wouldn't you think that a surgeon that thought a patient that was at particularly high risk for bleeding might stop aspirin and a patient that was at particularly low risk for bleeding might continue it? Obviously, observational data like that has some significant limitations.

I guess I wanted to follow on with that. Would you have different recommendations if a patient were going for, let's say, reoperation?

DR. DACEY: No.

DR. NISSEN: Would you be more likely to stop aspirin in patients undergoing reoperation?

DR. DACEY: Absolutely not. The only possible scenario I could think of would be a Jehovah's Witness, and

then I think you're still dealing with a mortality tradeoff versus bleeding. But reops, anybody else, we always keep it going.

DR. NISSEN: The other issue was I heard said several times that there was no prospective randomized data, and I guess, as I read through the manuscripts -- and I also did my own literature search -- there is some. The VA cooperative study was prospective and randomized. I think it's important at least we put the issue on the table.

As I read the study, in that study, in patients who were randomized to aspirin, there was a 6.6 percent risk of having to go for reoperation, and those that were not aspirin had a 1.7 percent risk of reoperation. So, the risk ratio was about 4 to 1 for having to go back to the operating room and have their chest reopened if they were on aspirin. Now, that's prospective randomized data.

I think it's important that we not trivialize the issues involved here. If you look at the manuscript -- and I'd like to just call your attention to page 237 of the handout -- the differences were highly significant, p values of .0001 for red blood cell transfusions, for platelet transfusions, cryoprecipitate administration, fresh frozen plasma, but not necessarily for whole blood. So, something like cryoprecipitate obviously means that

when you see significant increases in the use of cryoprecipitate, you're talking about a pretty important clinical effect.

So, regardless of what decision we make -- and I think the arguments are understood about whether or not this product represents an increased risk or not. There are reasons why people on this committee have been concerned about this, and they relate to some of the data that's available out there.

DR. DACEY: I guess my only rebuttal is sort of in the current era, we just looked at other, again, observational data. And I admit that we looked at over 10,000 patients and have a 2.6 bleeding percent for patients who were not on aspirin, 2.7 percent for patients who were on aspirin, and no statistical difference. At least in the current era, it doesn't seem to be a problem.

DR. BORER: Blase and then Beverly.

DR. CARABELLO: I think it's fair to point out, though, that that VA study is an old study. Surgery has changed. At least the field of surgery that I'm interested in, which is valve surgery, has changed so dramatically since those data were reported, that it's likely that other fields of surgery have also changed.

DR. BORER: Beverly.

DR. LORELL: I think one way that might be

helpful of thinking about this as a safety issue is there really are at least a couple of components here. One is the ambiguity and uncertainty about the risk of inadvertent, which is a little different from what you're talking about, continuation of aspirin for surgery, biopsies, major invasive procedures. Perhaps your comments I think are very important for how we practice but may not be quite to point for this issue because I think in the current era, most cardiologists, cardiac surgeons, vascular surgeons actually make quite a deliberate, focused decision about inclusion or exclusion of aspirin or other platelet agents. So, I think the broader issue for a combination drug that's not intended for use short term but for a very long term is the much broader issue of risk of inadvertent use of aspirin, perhaps for nonvascular procedures.

I think the second safety issue that is still not really fully addressed is the issue -- it's been postulated that there would be less confusion in a prescription drug as to whether aspirin was present or not compared to current over-the-counter use of aspirin for secondary prevention.

But I'm concerned that we really don't have data to support that one way or another. One could make the argument that in a 70-year-old woman who's showing up for a colonoscopy or a major breast biopsy, that she might

report that she's taking an anticholesterol drug. She might not even know the name of that drug or bring the drug with her to the doctor. It's a common scenario.

So, I think the second, very separate safety issue is the issue of whether there is a safety problem regarding ambiguity of combining a very potent antiplatelet agent in a pill with something else. I guess it would have been nice or might be nice to actually have some data to address that. We have only hypothesis right now.

DR. BORER: One of the issues that you may want to talk about, if you have some specific information to bring to bear -- and I think you hit upon this in some of your discussions thus far -- is what is the likelihood of this happening, given that multiple layers of communication that you're suggesting will be brought to bear here, in comparison with the likelihood that somebody who might well benefit from the combination therapy will not be getting one component if the convenience of a combination product isn't made available. You did discuss this to some extent in your first presentation several months ago.

And I think to put this in context -- just as Beverly says, it's a very important issue. I don't have a sense of the magnitude of the likelihood that with the prescribing doctor knowing what he or she gave and the patient having been told and the package saying something

-- with all those levels, I don't know what the magnitude is of the likelihood that somebody will slip sure although, sure enough, somebody will and probably several.

There is, as against that, the benefit to that patient for having been taking the combination therapy that maybe wouldn't have been taken, which we also can't determine the magnitude of. And I'd like to hear a little bit of discussion about that. Perhaps, Charlie, you may want to comment on that.

DR. FIEDOREK: Dr. Topol or Dr. Hennekens, does anybody care to comment?

DR. HENNEKENS: I think, Jeff, as you're pointing out, the overriding benefit of improving compliance overall has to be put in context with the concerns about safety. But I do think, going back to Bev's comments about titration, that in fact the ability to have a low-dose aspirin new data from the CURE study helps in that regard with respect to enhancing safety. And I'd like to just review that, if I could get the slides just to point out.

As you know -- and I think Dr. Lorell mentioned, of course, the acceptance of aspirin in antiplatelet therapy. One important point from the recent meta-analysis from the antiplatelet group -- and as you know, this is a very large collation of data, over 212,000

patients in 287 trials.

What you can see in these data, of course, the first thing of note is that the lower-dose aspirin in all of these trials actually fared somewhat better. This is not a direct comparison, but the dose of one or two baby aspirin, less than 160, had the highest evidence of reduction of vascular death, MI, or stroke, as compared to the dose of greater than that level.

But importantly, as I mentioned, the next slide shows recent data that's been available from this trial. The first point, of course, is that this is not a randomized dose of aspirin, but it's the best we have today as of July 2002. It's a large population of 12,500 patients. Of course, in this particular study, it was at the physician's discretion as to what dose of aspirin to use. So, that's important. While not randomized, there were no differences in the three different arms here with respect to the patient characteristics, demographics, or risk.

But as you can see, the efficacy of either 80 or 160 milligrams -- this was an international trial. There are some doses outside the U.S. of 100 milligrams, for example, or 150. The efficacy was at least as good at the low dose.

And then most importantly, again to address the

concern regarding bleeding -- and this goes back to Steve Nissen's point on the VA trial and Blase Carabello's -- that that study at the VA was a very high dose of aspirin. Now, as it turns out, the dose of aspirin of 325, greater than 200, is associated with the highest risk of life-threatening and major bleeding. And as one goes down to a dose of 81 milligrams, the bleeding risk is considerably reduced. So, you can see for life-threatening bleeding, it's half as much as the 325 milligram dose or in that dose group and also for major bleeding. This would be associated with biopsies or any other procedures that Dr. Lorell is concerned about. The bleeding is considerably less.

So, while the questions have been focusing on the bleeding risk, my concern of course is enhancing compliance. As you know, in the Heart Protection study just published, only 68 percent of patients who were on statins or study drug were taking aspirin. So, the compliance still today remains low. All the recent studies suggest 70 percent for statins of the 100 percent who should use them and at best 85 to 90 percent of aspirin use in, again, 100 percent of patients who should be in that group. So, the idea of improving compliance and particularly stressing low-dose aspirin, which I think all the data suggests converges on a lower risk of bleeding, is

particularly attractive.

And I think this is one thing that the dose, although many have been put into the idea of six different doses of 20, 40, 80 of pravastatin and 81 and 325 of aspirin, but actually most attractive is the 40 milligram pravastatin anchor which has been tested in all the trials and 81 milligrams of aspirin which shows to be the best efficacy and safety tradeoff. So, it seems there's a lot of data to support that as a very viable and helpful combination not only to improve compliance, but to markedly be associated with improved safety.

DR. BORER: Yes. I think you've hit the data that would cover the specific issue I wanted to raise and that is the benefit to the individual patient. Someone who slips through the safety net may be at risk of excessive bleeding if a procedure occurs, but up until that point, that patient presumably has benefitted from the combination. And it's that benefit-risk relation which may be worth our considering as well.

Also, I want to share with everyone an experience that I had recently that changed a little bit the way I think about this. I have a patient, a very prominent movie actor, whose name you would know, who is on a statin to lower his very high cholesterol and I wrote a prescription for that. I also prescribed aspirin, 81

milligrams a day. When I last saw him, we went through, as we always do, his medications, and he had bought an over-the-counter product. I don't write a prescription for aspirin. The way he described it was different from my understanding of the way an 81 milligram tablet looks. So, I asked him to go back home and call up with the dose.

Well, he was taking 325 milligrams of aspirin a day, not what I had told him to take, not what I suggested. Had I written a prescription, I'm reasonably confident that he would have been taking the combination that I wanted him to take.

That's an anecdote, but I think we do have to consider the possibility, as you've mentioned in several other contexts today, that with aspirin being available in many forms, many doses over the counter, even if we tell people what it is we want them to take to co-administer with the prescribed statin, they may not do that. So, that makes the decision-making tree just a little bit more complicated I think.

Tom.

DR. FLEMING: Jeff, I'm glad you're bringing these issues up because I wanted to revisit them as well today. What we're balancing, as I understand, is what I think we referred to a lot on January 18th as accuracy and adherence, and you've really alluded to the fact that it's

not just adherence. There is, in fact, a potential for accuracy against these safety risks that we've been spending a lot of time talking about for inappropriate use in given settings.

So, I wanted to revisit what you've already largely touched on and that is what is our best sense in the intended target population here in secondary prevention that statins and aspirin would be used. I'm hearing 70 percent statins, 85 percent aspirin.

My understanding -- correct me if I'm wrong -- is that a combination might enhance adherence to both people that would be using aspirin but wouldn't have been using statins now would adhere to statins; people that would be using statins but not aspirin now would be adhering to aspirin. Is that the logic here behind this argument?

In particular, if we're trying to enhance the aspirin use such that in settings in which it should be used, as Eric Topol is arguing, we're going to achieve an added benefit there and one has to look at whether that benefit exceeds the hypothetical or real risk when it's being used inappropriately -- and I'm trying to get a better sense of how much benefit there really is. If in fact we would enhance proper aspirin use, that's a real plus. But are these 15 percent who aren't using aspirin

within the 30 percent who aren't using statins? Hence, you're not going to increase aspirin use at all. What do we know about who these people are and the relationship between the group not using aspirin and the group not using statins?

DR. BORER: Do you want to try that?

DR. FIEDOREK: I think we'll call on Dr. Hennekens to answer that.

DR. HENNEKENS: The utilization patterns in secondary prevention range for aspirin from a high of about 77 percent, but these are in the registry data from academic centers that are participating in randomized trials, to perhaps 51 percent in general population surveys. That's the range of aspirin utilization in secondary prevention today.

Secondly, with regard to the patients achieving their -- on statin therapy, I think Tom Pearson has published some data that suggests that it maybe as low as 37 percent. So, if you did nothing more than to increase the utilization of aspirin and statins in the population that's already receiving aspirin, with whatever benefits and risks are attendant there, you'd avoid over 10,000 premature deaths in the United States each year. Now, that has to be weighed against the hazards, but the benefits I think are large.

In the Antiplatelet Trialists Collaboration, as Eric pointed out, two to three years of aspirin therapy were associated with 31 percent reductions in MI, 25 percent reductions in stroke, 15 percent reductions in vascular deaths, and less than 1 percent are serious bleeds. Indeed, that included patients who went on to have surgery and either did or did not stop their aspirin.

So, I agree with Jerry Avorn that when one considers that minority of patients who are going to undergo surgery and may be inadvertently using aspirin when you wished they weren't, that has to be viewed in light of whether having this drug in the hands of a physician as a prescription product would make it better, worse, or the same than right now, when in our data so many people who are told by their doctor to take aspirin are actually on other agents and they don't know that some of the things that they're taking contain products that range from a low of 81 milligrams up to maybe 650 milligrams.

As Eric pointed out, while the benefits of aspirin are similar across a wide range of doses, the risks are related to the dose, and there are people who are not only taking enough of it but people who are taking too much of it. I think to put this in the real of the health care provider would, on balance, be a net benefit.

But I don't mean to sweep under the rug the

concern about those surgical patients. I think that's a real concern, but I think as Dr. Fleming pointed out, that has to be viewed in light of the overall picture of how much benefit there would be to getting better utilization of these lifesaving drugs.

DR. FLEMING: Charlie, I'd like to just follow up on this. Maybe two questions.

The first is the figures you've just given of the prevalence of use of aspirin seem lower than what we had heard a few minutes ago. If I understood, you were saying it's in the 51 to 77 percent range?

DR. HENNEKENS: What I'm saying is that if you look the surveys of registries of patients who were being considered for randomized trials, not necessarily of antiplatelet therapy, just randomized trials in academic centers, you might see numbers as high as 77 percent in that subset of the general population. But in our survey that was done in the general population of secondary prevention patients, 51 percent of them had been told to be on aspirin.

DR. TOPOL: The numbers that I mentioned were best case scenarios, the 75 percent statins and up to 90 percent use of aspirin. Those are the highest that have been published to date in recent studies.

DR. FLEMING: What I actually want are real

world scenarios. So, let me come back to this because others may have insight on this.

I would think a really critical point would be among statin users what fraction are using aspirin. It's entirely possible that we would only have 70 percent of people using aspirin but the nonusers tend to be the non-statin users as well. So, are the statin users also achieving only 50 percent or 75 percent? If the statin users have 95 percent aspirin adherence, then if I understand the logic here, then there wouldn't be so much of an up side. Do you have specific data on the relationship of where these nonusers of aspirin fall relative to users and nonusers of statins?

DR. HENNEKENS: Well, in secondary prevention in my view, the nonusers of statins are much greater than the nonusers of aspirin to begin with. So, it can't be that 95 percent of the users of aspirin are taking statins. It's just not possible.

DR. FLEMING: But what is still possible is amongst the smaller group that you're saying are using statins, a substantial fraction, a high fraction of them may be on aspirin, and the non-aspirin users are falling into this large non-statin-using group. So, we still don't know from anything that's been said whether or not that's not true. If my concern were true, then the logic that,

when you put the two together, you're going to enhance adherence to aspirin doesn't seem to be as compelling to me.

DR. HENNEKENS: What we do know from the randomized trials of pravastatin are that on balance 80 percent of the patients who were randomized to a statin were on aspirin, but again, these are academic medical centers that are enrolling patients in randomized trials where the utilization pattern is higher. That, as Eric pointed out, may also be a best case scenario as well, that of the people on statins, 80 percent of them are on aspirin.

DR. FIEDOREK: Dr. Avorn, do you have a comment to add?

DR. AVORN: Yes. In the materials that were in the appendix to the briefing book, we were able to get some data which are, unfortunately, not yet published -- but we're in the process -- that were drawn from a set of questionnaires sent out to about 26,000 people as they enrolled in various insurance programs that asked them what medications are you on both over the counter and prescription. I think the data that point to the question that you're asking is on the top of page 3. When we crossed aspirin use with statin use -- this is the percent of people who were not taking aspirin among statin users --

46 percent of men and 61 percent of women who were on statins were not on aspirin. Granted, they may have had a reason not to be on aspirin, but those are awfully big proportions, and we can assume that a huge number of those were secondary prevention patients.

There's other data presented there about people who have a history of MI, diabetics, and so forth. But the sense that we get from those data is that people who are on statins are not, by self-report, taking aspirin, and probably if there is a bias, given that it is an observational study, if anything, the bias would be in the direction of these being the boy scouts and girl scouts because they sent in the questionnaire, they were responsive, they filled in all the blanks, and they were the ones who said that they were not taking aspirin in these proportions.

So, I think the data need to be drawn from recent data, and this is about 2000 and 2001 and was mentioned by Dr. Topol and Dr. Hennekens from typical settings. One of the problems in the literature is that those of us who live in university settings do studies of university patients, but most people in the country are not university patients.

I guess the last thing I wanted to mention was in response to Bev's concern, which I share, about

inadvertent use around operations. I think what we need to think about is really the incremental risk versus the incremental benefit of the combination because the concerns that Bev raised were really about the prophylactic use of aspirin, period. That somebody may not tell their colonoscopist that they are taking baby aspirin or some other version because in my experience as a primary care doc, patients don't tell you about their over-the-counter drugs. So, the issues you raised really are worries about the use of prophylactic aspirin, period, because patients go off and do things and don't tell doctors.

I think the question to really focus on is will the incremental risk -- that is, how much more of that will go on -- be worse or better than the current situation, and as was mentioned by the chair, how will that relate to the incremental benefit of will more people be getting this product and will that benefit offset the incremental risk.

DR. FLEMING: So, if I could just close this follow-up discussion of this then. If I'm following the logic here, what we're saying is with this combination, if someone would have been inclined to be using aspirin, then the combination might provide a greater level of adherence to the statin, and if somebody would have been inclined to have been using the statin, if we take at face value what you said, only half of them would be using aspirin, then in

this cohort of people that would be inclined to use statins, we have in half of these people an enhanced likelihood that they would be achieving a strikingly improved adherence to aspirin. And that benefit would have to be viewed in the context of the alleged potential risks associated with inadvertent continued use of that aspirin in those patients in the setting of surgery. Is that a fair summary?

DR. BORER: Exactly. Before we go on to Susanna, with regard to Dr. Avorn's last statement, while I think it's very important for us to think in public health terms how many people are going to be benefitted versus how many people are going to be put at risk, again I think we have to focus on the individual patient too and the individual patient who's on what we may accept as appropriate prophylactic therapy for coronary events is benefiting. At some point there is a risk if an operation occurs and the patient doesn't tell anybody about the drug, or the doctor doesn't know about the drug, there's a risk. But that risk has to be weighed against the benefit in that individual, not just the benefit for society at large, and I think that's an important thing for us to consider.

Susanna and then Tom.

DR. CUNNINGHAM: Yes, I have two points.

One is I'm ongoingly concerned about the lack

of randomized controlled data here because that's just a real problem. We don't really know what we're talking about for sure.

The second thing. We've been talking about people not taking aspirin. I'm wondering about the problem of people on the other side who are prescribed this medication who have seen the package, it floated by, and long since they're not looking at, and now they may make a decision to take aspirin on top of it. How big is that problem going to be? Because people are not going to necessarily remember, even though the packaging is stellar, that it's in there. And then they're going to be trying to be good and take it. You know, it's a pretty common product out there.

DR. BELDER: I would like to comment on that because we believe that these situations are currently already ongoing. The patients may take Goody powder for their headache, but they take Nuprin for their backache, and they will take a variety of products for various reasons, some of which will contain aspirin, and they may not know that it's aspirin because in some of these products, the aspirin is indicated as acetyl salicylic acid, and the patient will not know that it is actually aspirin.

I think as Dr. Topol already indicated, the

prescription use of a low dose of aspirin will probably diminish the likelihood that patients are taking multiple products at the same time because now there's only 81 milligrams of aspirin for their heart instead of currently a lot of 325 in addition to 650 milligrams of aspirin for the headache and perhaps some other use of aspirin for backache. So, we believe that there should not be an additional risk by providing this prescription product.

Yet, we do agree and, as we have indicated before, we are committed to make sure that patients will realize that it is aspirin that they're taking by developing packaging, patient information leaflets, and again working with the agency, once we have the fixed combination tablet, the clear indications will continue.

DR. CUNNINGHAM: But there's not much likelihood that we're going to change their using headache and backache powders I wouldn't expect.

DR. BELDER: Correct.

DR. BORER: Tom.

DR. PICKERING: I wanted to address this issue of the number of patients who should be taking aspirin and statins together but who aren't. There seems there are two issues here. One, as we've heard, the physicians are not prescribing either of these drugs enough, and the other is the adherence or compliance which is sort of a related but

separate issue.

I haven't heard anything to convince me that having the physician being able to write one prescription as opposed to writing two prescriptions or writing a prescription for the statin and then saying take aspirin is actually going to make the physician more likely to do this.

DR. BORER: Do we have any survey or other information relevant to this issue? Is it likely that doctors will begin -- there's no way to answer the question I suppose -- prescribing a combination product, if it becomes available, rather than doing whatever they're doing now?

DR. TEMPLE: Someone will certainly tell them to.

DR. BELDER: There is one way to find out I guess. Obviously, we're going to investigate what happens should this product indeed be approved. We hope that it will stimulate more physicians to do the right thing.

DR. BORER: It seems to me that we have no idea whether doctors will prescribe more, but again, there is a difference, I think, in the compliance part of the equation that you mentioned, Tom, if doctors prescribe both rather than prescribing one on a piece of paper and telling the patient about what to take without writing it on the piece

of paper for the second component. Doctors who would give both are going to be sure that the patient is getting both, which is perhaps a different situation than we have now.

Beverly.

DR. FIEDOREK: Can I call on Dr. Pearson? He'd like to make a comment about that.

DR. PEARSON: We'd like to show a slide that was, I think, presented in the initial presentation of these data. I think the questions here are very important.

I think you could argue that the noncompliance and the stoppage of essential therapies is a much bigger issue than many of these side effects we've been talking about in terms of the potential of lives lost. In that context, it's interesting there's a minimal amount of data on the effect of combination therapies on compliance. It's really quite an interesting deficit, I think, in our knowledge.

There are three diseases here, two of which are getting close, diabetes and hypertension. The other is HIV which, of course, nowadays is the penultimate in combination therapies. I think you can see from these four studies that there was an improvement in compliance and consumption. Certainly in our writings of how to boost compliance with preventive cardiologic therapies, the number of different preparations and the number of

individual pills that a patient is requiring to take is a major determinant of noncompliance. I think the clinical epidemiology of noncompliance has shown that. These suggest from a more randomized trial kind of period that you can do something about it, and that is reduce the number of pills by putting combination pills together. The data are slim. I think this is what we have.

DR. LORELL: Well, I think we've moved really into sort of a little different arena, talking about issues of compliance. I think it's interesting that if one steps back and looks at this, as Susanna pointed out, we don't have data regarding prospective effects on efficacy of major endpoints regarding co-packaging versus individual manipulation and prescription of aspirin and a statin-lowering agent. We can speculate but we don't have prospective data regarding safety from either bleeding side effects or much more rare statin side effects of individual prescribing or explicit prescribing and manipulation of the two agents separately versus in combination. So, we're now on an argument that is somewhat compelling that as for individual patients and for a broader public health issue, that we would enhance compliance with the use of two agents that clearly reduced cardiovascular risk.

But I think if the issue of compliance is on the table, whether we're talking about broad populations or

the individual patient like your patient that you brought up, we have to bring to the table that there are several components of patients complying with what a physician prescribes.

One of them is the benefit that's been mentioned of potentially having fewer drugs to take and less pills piled up on the counter. And that's very compelling.

But the other issue that all of us around the table face with individual patients and compliance is in fact an economic one, that if a patient is given a prescription for something that is costly, that prescription may not even be filled or may be filled once and not renewed. So, I think that it had not been my intention to bring this up, but I think if we're arguing that a strong rationale is compliance and enhancing that piece of nonusers to be users, I think one concern is the risk, a real risk, that a patient might not fill or use a prescription drug compared to the ability to utilize two drugs separately, one of which costs pennies.

DR. FIEDOREK: I'd like to address that. We didn't bring that up as well, and we understand the issue of medical economics is very real. Since we've been asked, I would like to mention that we intend to offer the pravastatin-aspirin combination. The aspirin component

will be offered at no additional cost to pravastatin as it currently is available. So, that's one of the things that I know would be a concern and that's our intention.

DR. NISSEN: Well, I had a debate with myself about 3:00 a.m. last night about whether I was going to bring this up or not, but since the cat is out of the bag, I think it's time to talk about it. Let me see if I can articulate a question. Again, I recognize this is not a regulatory issue.

Let me also compliment the sponsor on doing a nice job of resubmitting this and answering many of our questions from the first time around. I think the availability of multiple doses and so on is a very useful thing.

But as I understand the situation, pravastatin, which has been a very effectively used agent for quite a number of years now, is due to go off patent within the next several years. When that happens, typically a drug falls in price by about 80 percent.

I would personally think it's important to provide the medical community with some reassurance here, and the reassurance would be that if patients in the next, say, two years are switched from brand Pravachol to brand combination and then subsequently the drug becomes genericly available, then the pharmacist will be precluded

from substituting generic pravastatin. It's essentially an evergreening of the patent on the drug.

Since we are talking about compliance and Bev raised the issue, if the combination product is, say, four or five times more expensive than the generic pravastatin plus generic aspirin, won't compliance potentially go way down? Patients are really worried about the cost of medications.

I know, Bob and Doug, that this is not a regulatory and approval issue, but I guess I feel in the interest of public discourse on this topic -- and we represent the public interest not just advising a regulatory agency -- I need some reassurance here that what we're doing is not to dramatically increase health care costs by approving a combination product.

DR. FIEDOREK: Dr. Belder.

DR. BELDER: I can give an answer to that. The approval of this product would perhaps lead to some additional exclusivity that entirely falls within the current patent life of pravastatin, and generic companies would be able to come up with a combination product as well after the patent life of pravastatin is over.

DR. NISSEN: That's very reassuring. Thank you. I'm glad I asked. I wasn't going to ask, but I'm glad I did ask.

DR. TEMPLE: I was just going to express some slight discomfort because the setting could be considered somewhat coercive as to the response. After all, they're seeking approval and we really don't get to regulate that. You did point out it could affect compliance which is a sort of wedge, if you like, but I just want to express some nervousness about this direction.

DR. NISSEN: Yes. And knowing that nervousness, I literally had a little debate in the middle of the night about whether it was even appropriate to bring it up.

The major case for this is compliance. And since this is a factor in compliance, I felt it was a nice time to maybe get those issues out on the table.

DR. TEMPLE: It is true, though, whatever exclusivity becomes associated with this product -- and I would not be prepared to say what it would be because I don't know -- it ends after an absolute maximum of three years, barring some patent thing that I don't understand. And then other people could make the same combination.

DR. NISSEN: So, in fact, my fear here has been -- you reassured me that fears of a large increase in the overall cost of these agents is unlikely to occur as a consequence of any approval of this combination.

DR. TEMPLE: Or perhaps not for too long.

DR. NISSEN: Yes, I understand, but I want to make sure that that's on the table.

DR. BORER: In the interest of Steve's sleep tonight and Bob's, I want to reassure the sponsor that nobody is trying to coerce anybody into anything.

I'd like to ask a slightly different question. You dealt with this, as I recall, in January, but I just want to hear it restated. I think that at that time Dr. Belder presented data about the timing of administration of pravastatin during the day since, for a long time, the short-acting statins had been recommended for administration in the evening, and I believe you showed data that it really didn't make much difference. But it may make a difference in terms of safety when the aspirin is taken. One would not want to take it on an empty stomach at night. So, can you tell us what you're going to be recommending about the timing of administration of the combination product?

DR. BELDER: The recommendation with respect to the timing of the combination product will be identical to that currently existing for aspirin. I'm afraid that I do not know that by heart.

DR. BORER: That's fine. That's good enough.

Are there any other questions?

DR. CUNNINGHAM: I have a question. I would

like the sponsor to review for me -- you probably did this in January; I don't recollect -- what the data for women is on secondary prevention using aspirin. A lot of the data that you include is for men, so I'd like for you to remind me what all we have for women.

DR. BELDER: In the pravastatin trials?

DR. CUNNINGHAM: No. Aspirin.

DR. BELDER: Aspirin trials.

DR. CUNNINGHAM: I'm just interested in the randomized, controlled trial data.

DR. HENNEKENS: In the randomized trials of secondary prevention, a significant proportion were women and the FDA has prescription-labeled aspirin for the secondary prevention of MI, stroke, and vascular death in women as well as men.

DR. TEMPLE: Correcting a longstanding error.

DR. HENNEKENS: Well, that's an excellent point. In 1980, there was approval of aspirin for the treatment of TIAs in men but not in women based largely on a Canadian study that was woefully underpowered to address the issue in women, but after the two cycles of the Antiplatelet Trialists Collaborations increasing the sample size of women, it showed benefits that were quite similar to those in men. So, the indications in secondary prevention for men and women are identical.

DR. BORER: Any other issues that we need to raise?

(No response.)

DR. BORER: If not, is that the conclusion of your formal presentation?

DR. FIEDOREK: That's it. That's the conclusion, yes.

DR. BORER: Then let's go on. It says that there's a break at 3 o'clock, and remembering what happened the last time when I tried not to have a break, I think we will. It's now 2:52. At 3:02 -- no. Let's make it 3:07 we'll be back here.

(Recess.)

DR. BORER: We'll structure our final discussion around the questions.

Oh, sorry. I can't forget this one. Are there any comments from the public about the topic under discussion? There were no requests for presentation, but I'm asking now if there are any impromptu requests.

(No response.)

DR. BORER: If not, we'll move on to the committee discussion, and we'll use the questions as the format. We'll have Beverly, as the committee reviewer, go through them. I'll read the preamble here.

The Cardio-Renal Advisory Committee is asked to

reconsider the co-packaged product of pravastatin and aspirin, based on the additional materials and references provided by the sponsor.

This product was previously presented to the advisory committee on January 18. At that meeting, there was general agreement that a population could be defined for which the co-packaged would be indicated. There was also general agreement that the sponsor's meta-analysis of the five lipid-lowering studies in a secondary prevention population -- and they're listed -- demonstrated that both pravastatin and aspirin individually contributed to the beneficial cardiovascular outcomes seen in the separate trials. The advisory committee also endorsed the choice of the two doses of aspirin.

The advisory committee, however, felt that the risk-benefit ratio of marketing the co-packaged product was adverse based on the following considerations:

First, the potential for excessive bleeding should the product be discontinued prior to a surgical procedure.

Second, the potential for inappropriate discontinuation of the pravastatin should the patient need to temporarily discontinue aspirin.

Third, the use of the single fixed dose of the 40 milligram pravastatin dose, where a higher or lower dose

of pravastatin would be more appropriate for the individual.

And fourth, the potential for use of this co-packaged product in an inappropriate population such as for primary prevention of cardiovascular events.

Not all members of the advisory committee applied equivalent weight to each of the above concerns.

The sponsor amended their application by a response addressing aspects of these concerns, including the following: a proposal to include in the pravastatin-aspirin co-packaged product two new doses of pravastatin, that is, 20 and 80 milligrams, in addition to the originally proposed 40 milligram dose, to be co-packaged with 81 and 325 milligram doses of aspirin; and submission of numerous publications.

So, we are asked to respond to two questions. First, to what extent has the sponsor's submission addressed your concerns regarding the following. And, Beverly, why don't you go through them one at a time and we'll see if we have any comment.

Just before I do, Doug, which, if any, of these do you need formal votes on?

DR. THROCKMORTON: Certainly the second question.

DR. BORER: Okay. Beverly.

DR. LORELL: Do you wish me to go through each of these?

DR. BORER: One at a time so that we can get other comment if there is any.

DR. LORELL: The first question is to what extent has the sponsor's submission addressed concern regarding the potential for excessive bleeding should the pravastatin-aspirin not be discontinued prior to surgery?

My comment is based on the assumption that we're discussing a single pill or capsule and not a co-packaging of two distinct, different tablets. To my mind, this concern has not yet been adequately addressed. I think one could speculate in either direction regarding issues of patient and provider recognition of the use of aspirin and the separate issue regarding the magnitude of risk if aspirin is inadvertently continued. In total, I don't feel that this concern has been adequately addressed for inclusion of a potent antiplatelet agent in the same pill with a drug that acts very differently.

DR. BORER: Can I ask is it possible, if the committee recommended such a thing and you agreed, for the dispensers of this medication to be mandated to provide with each box, each package, however it's distributed, in large, bold type an insert or a piece of paper that says, if you're going to have an operation, you must talk with

your doctor about stopping this drug at the appropriate time? That kind of warning. I'm thinking about the mandate that was approved with cilostazol, for example, where it was absolutely necessary that something go in that warned people about heart failure issues.

DR. THROCKMORTON: Well, certainly the PPIs, the patient education materials, answer questions like that aimed to sort of address issues that are identified as concerns for a patient to understand.

I think probably less than the format necessarily, for today the most useful thing would be to have committee members identify those aspects of education that you see as most critical and then exactly how those things might be addressed. Again, Bob had pointed out some things might be best addressed with unit-of-use packaging. Other things might be addressed in patient education or something like that. That would be something we'd work with the sponsor on, but to hear the concerns I think is going to be the most relevant thing for sure.

DR. TEMPLE: Jeffrey, the direct answer is we can require material accompanying the dosage form. That's not that common but we can.

DR. BORER: Number one, would the inclusion of such material, appropriately designed with appropriately big letters, help alleviate some of your concerns? And if

it would, can you begin to list the specific kinds of issues you'd like to see in such a patient education material piece?

DR. LORELL: I think that's a tough question. There's no question that a very vivid and clear labeling with the word "aspirin" in several places, as well as a patient alert, as described would be helpful.

I think I am still concerned for two reasons. One is that in my experience as a clinician for many years, with chronic use of combination agents, regardless of what they are, there is confusion on the part of patients as to what they are taking. So, I am not confident that even the most vivid packaging, such as the potential example that we were shown today, would mitigate against this.

I think the second concern is --

DR. TEMPLE: Bev, can I just ask something?

DR. LORELL: Yes.

DR. TEMPLE: If there were unit-of-use packaging, this would come with each new refill.

DR. LORELL: Well, I think the second issue is that in some context in pharmacies, unit-of-use vivid packaging is actually repackaged, as we've heard earlier, into labeled bottles.

DR. BORER: Not unit-of-use, no. It's when it's not unit-of-use that it's repackaged in general, I

think.

DR. LORELL: I'm sorry. I'm talking more about one way of potentially managing this would be to have it in very distinctive kind of packaging with sort of blister units so that the packaging itself contained vivid reminders. But even that I think is a bit of a concern because of the potential that the drug could be repackaged in a standard bottle with labeling in small letters. So, it would help, but it wouldn't completely erase my concern.

DR. BORER: Can we just clarify that for everybody? Because I think this is a key point in terms of assuaging some concerns about safety. If unit-of-use packaging is mandated and agreed upon by the sponsor, that would make it very difficult, nigh impossible for a pharmacist to repackage it. Am I incorrect about that?

DR. TEMPLE: I don't think we totally know, or at least I don't totally know. I have heard that sometimes, for example, if there's an odd number of pills, not what's in the unit of use, that they will sometimes put it into their own plain bottle. I can't swear to you that that never happens. No, a blister pack would be more difficult. I can't imagine anybody doing that. But they didn't describe a blister pack for the single pill. Is that what you said?

DR. BELDER: We haven't developed the packaging

for the single pill. The current co-packaged product is a blister pack, and every time a patient punches out a tablet, they will see aspirin or pravastatin.

DR. TEMPLE: That would be a relatively unusual packaging for just plain, old, single pills, not that it couldn't be done. And that would make it more difficult. It also makes it bulky.

DR. BORER: But I thought that what you had said was that you would work with the agency to deal with this, if that's what was mandated.

DR. BELDER: Absolutely.

DR. LORELL: Jeff, I think the second issue -- and I want to try to be articulate about this. I think that issue number 1 is, would very clear packaging that was quite vivid help? Yes, it would.

The second issue, though, is that we're not talking about short-term, 2-week or 30-day use of a drug. We're talking about this drug being used for months to years. This is a setting where a patient may well be dealing with several different physicians, be dealing with a colonoscopist, a surgeon, someone doing a biopsy, other than the primary prescribing physician or cardiologist to whom the patient is going to be reporting what drug they are taking. I am concerned that even with the most very meticulous and careful packaging that in long-term patient

reporting of what drug they're taking, that there is potential for confusion or mistake that they are taking an antiplatelet agent. So, that's the second level of my concern.

DR. BORER: JoAnn.

DR. LINDENFELD: Well, I share Bev's concerns somewhat, but I think this problem might be helped if the labeling said to notify your physician if surgery is planned. I think there's a jump from the patient knowing they're on aspirin to being worried about surgery. But at least for myself, I find patients pick up those kind of signals quite clearly and often will tell me that if surgery were planned rather than, wait a minute, I'm on aspirin. So, that would be one labeling thing I might think would be very clear to the patients that would help somewhat with this concern.

DR. BORER: Are there other issues of that level of concern that ought to be flagged that way? I mean, I could conceive of a warning like the one you just stated being printed right on the outside of a box if unit dosing is used. What other issues, if any, do you think need to rise to that level of patient education?

DR. LINDENFELD: I think that's the major one. The major one we've discussed is bleeding. So, that would be the major one.

DR. BORER: Beverly are there any other specific issues besides the "talk to your doctor if you're going to have an operation"?

DR. LORELL: Well, I think we haven't talked too much about this today. I guess there's the formal potential for confusion of a patient who thinks they're taking prescription fancy aspirin and not recognizing or forgetting that they're taking a statin regarding the concerns that we all instruct our patients very explicitly about warnings to report with use of statins. So, one might consider -- I certainly haven't fully thought this out -- but whether such unusual packaging might also include a very clear warning, alert your physician if you have myalgias, you know, the similar warnings that we talk about with statins to a patient.

DR. BORER: Steve.

DR. NISSEN: I wanted to bring this up earlier, but low-dose aspirin is associated with some increase in gastrointestinal bleeding and so on, and I think it would be nice to put in there that you should inform your physician if you have abdominal pain, black, tarry stools, that sort of thing because some of these patients will, in fact, have that complication and you want to make sure that it's brought to somebody's attention.

DR. TEMPLE: As part of the patient

information.

DR. NISSEN: Yes, I think so.

DR. TEMPLE: Yes. That would be consistent with the eventual aspirin labeling. It doesn't really have that yet, but it will.

DR. NISSEN: I think it's the right thing to do because if people don't know about that, they may not bring it to their physician's attention. All the studies I'm aware of do show that that's a well-defined, not an enormous risk and usually not life-threatening, but it can be.

DR. BORER: Are there any other major concerns that have to be flagged in patient education materials, forgetting about the specific format for the moment, but by some appropriate format should be flagged at a very high level so they're not likely to be missed? We've hit three.

(No response.)

DR. BORER: Okay. Then let's go on to 1.2.

DR. LORELL: The second question is the concern regarding the potential for inappropriate discontinuation of pravastatin during times when aspirin is temporarily discontinued.

To my mind, this is much less of an issue. I think there's very little information in the literature regarding risk, if any, of temporary discontinuation of a

statin. We actually didn't discuss it during the discussion, but there is a paper that appeared in Circulation that was part of our data to review that raised the question as to whether temporary discontinuation of a statin conferred an increased cardiovascular risk in a population of patients with unstable syndromes. That paper I would view as being a very provocative and a very important hypothesis to be tested, but I don't think it's to point in this discussion about co-packaging.

DR. BORER: Also, the concern is raised in the context of purposeful temporary discontinuation, which might be less likely to happen if somebody was having crescendo angina when his or her doctor told them to stop the drug. Okay, so that's less of a concern.

Does anyone else have any other comments about that particular concern or are we all satisfied that that's a lesser issue? Tom.

DR. FLEMING: Is it fair to say that there's a key distinction between question 1 and 2? Question 1 relates to an important safety concern that can arise with inappropriate continuation of aspirin, whereas question 2 relates to -- is it correct to interpret this as a potential loss of more full efficacy if there is inappropriate temporary discontinuation of the statin?

DR. LORELL: I interpreted it slightly

differently. Really the question as to whether statins are providing a very important short-term, stabilizing factor on unstable plaque as opposed to issues of lowering measured lipids. So, this is a concern that I think many have as to whether or not there is both short-term risk of stopping a statin for a period of several days in patients who are undergoing vascular surgery or other high-risk surgery.

The converse of that, not relevant today, is whether there's short-term benefit of aggressively starting a statin very early in a high-risk population.

So, I interpreted this maybe a little differently, Tom, not as whether you were going to impede the long-term kind of benefit that's been observed in clinical outcome trials, but whether there was a special kind of niche safety risk in stopping a statin in unstable patients.

DR. FLEMING: Well, that's the clarification that I was hoping to get. Essentially what you're saying is the issue here is not so simple as if there's inappropriate discontinuation, you are getting a level of nonadherence to an intervention, hence you're getting less than fully optimal efficacy. You're saying there could actually be a safety risk associated with these temporary discontinuations.

DR. LORELL: Yes. That's the issue -- I'm sorry we didn't have a little more discussion about this earlier -- that was raised in the Circulation paper that's gotten a great deal of attention. This was a retrospective analysis not a prospective study.

DR. FLEMING: That's paper number 1, wasn't it?

DR. LORELL: Exactly. But it suggested some very worrisome trends in terms of major adverse coronary outcomes in patients who had discontinuation of statins. So, it's a very different issue I think.

DR. FLEMING: Although unfortunately, as is the case with the aspirin data, this is nonrandomized and it's entirely possible that this is a very biased assessment.

So, just to close my thoughts on this, the way I had been thinking about this issue was that you're presumably intending to get meaningfully enhanced adherence to the statins with the combination. One then has to look at whether that benefit achieved by higher adherence to statins overall exceeds the risks associated with potential discontinuation in some patients.

DR. BORER: We don't actually know the risks. The risks are largely theoretical and were heightened by this article. But I think in all fairness, if they should prove to be important, there is an obvious remedy. Since the patients would be stopping their drug in most cases,

not all, because they had been told to do so, they can be told to take the single component pravastatin by itself in the interim.

DR. LORELL: There's another theoretic risk that I'm sure all have thought about. Let me see if I can articulate this.

In the use of a combination antihypertensive medication or a combination antidiabetic medicine, I think the way most clinicians use those medicines is to start the two not only independently but often at different points in time. In fact, in the use of aspirin and lipid-lowering agents, that is also not an uncommon scenario. Some physicians will start both at the same time, but it is not uncommon and I would argue, in fact, often quite common to start one first and then to secondarily add on the second.

The advantage of that strategy clearly seen in the antihypertension combinations is that one has a track record with a patient regarding both tolerance and knowing that there are not major side effects that would require one or the other drug to be stopped.

I suppose there is a formal possibility with this drug that for secondary prevention, it might be started right off the bat as the first drug being prescribed for the patient, and we could think of some very common scenarios for that. A patient presents with new

onset angina and then is begun on this combination agent as part of other therapies.

So, there is some formal risk -- I don't know what it is -- that when a combination drug is started without first starting the drugs independently and getting a clinical track record, that if there's an adverse event -- let's say the patient develops severe GI indigestion or develops a rash, even non-life-threatening -- that both drugs might be permanently stopped because of reluctance to rechallenge with the individual agents. So, that's an unusual possibility with this drug that I think might not have been seen by the agency in other combination products that are prescription drugs.

DR. BORER: So, we've listed several concerns that might be at least mentioned in packaging at some level so that physicians would be aware of the possibilities and perhaps could take some remedial action.

Let's go on to 1.3.

DR. LORELL: 1.3 asks about the concern about the inappropriate use of a lower or higher dose of pravastatin than is necessary or safe for a given patient.

This is a tough issue and I think it is one that a lot of time was spent on in the winter meeting and none today. It goes to the issue of what is the goal in secondary prevention, how do you use a statin, and do you

aim simply for reduction to a goal measurement of either total cholesterol, LDL, or elevation of HDL. We now have a more recent study presented this fall that actually suggests that use of absolute measurements may be challenged.

So, I think that one of the concerns that was raised by the committee last time is the scenario that if a patient were started on this combination agent -- let's take the scenario that one was using the highest dose of pravastatin and had not yet achieved current guidelines for secondary prevention. Would there be some risk that the convenience factor would mitigate against the hassle factor of getting the patient to transition to a different agent and aspirin use separately?

I think that is some risk. However, I think that's actually probably no more or less a risk than in prescribing of any statin when you don't get to goal and being willing to make a change and convince the patient to change. So, I look at this, yes, it is an issue, but I look at it as a lesser one.

DR. NISSEN: I think the sponsor has been actually as responsive as they could here. One of the objections I had to the first application was it was that one dose. We've really been trying to educate our colleagues to treat to a target with statins. So, I really

didn't like the original application in large part because of that. Now we have the three commonly used doses of pravastatin available and actually we have a total of six combinations.

Now, there still may be patients in whom the LDL is particularly high, in whom the highest dose of pravastatin is not adequate to get to goal, and those people have to be transitioned, hopefully, to something else. But what the sponsor has done is they've been very responsive to those concerns by offering us choices, and I think that's all we can ask of them.

The concern doesn't totally go away here. If you give this combination product to somebody with an LDL of, say, 240, the odds are pretty good you're not going to get to an LDL of 100. But hopefully physicians are savvy enough not to do that.

DR. BORER: Does anybody have any lingering concerns about this issue? Doug.

DR. THROCKMORTON: Jeff, I guess I'd like just a little more conversation around sort of a related issue. I heard two visions of how you would write a description of how to use this drug. One model is the combination antihypertensive model where the notion is usually you push one drug to maximal dose and then you add a second agent, and if that combination is available as a combination,

that's when we recommend you use the combination as a possible convenience.

An alternative model would be to say -- and it might be more appropriate here -- a lot of people are going to come in on one or the other of these therapies at a dose that's not driven by any measure, that is, no change in blood pressure like you would have from hypertension. It may be a change in LDL, but some of the dosing may not be driven by that necessarily. It might be driven more by safety concerns or driven by your following the outcome data. How would you write a label for how you'd choose which of these doses to use?

DR. BORER: Maybe I can take a quick crack at that, and then we can have some other comments.

I don't see this as being a major concern. I think that as Steve just pointed out, there is now the entire range of labeled pravastatin doses, and if you score the tablets, even below the lowest labeled dose is available. For the lipid-lowering drug, which presumably one might choose to titrate to a total cholesterol or LDL goal, and the aspirin usage associated with that is now up to the doctor because all the options are available. So, I don't think that's a problem.

Yes, it's true that 80 milligrams a day of pravastatin may not get every individual to the goal that

his or her physician has set for treatment for hyperlipidemia. Then one would perhaps go off to the use of a different statin and have to use a separate aspirin tablet. But that's what medical practice might demand. That's not an argument against making the convenience product available.

I'm not particularly concerned, although I think Beverly's example is absolutely on target. There might be a rare toxic reaction that couldn't be clearly ascribed to either component. Both components might be stopped and the patient might be denied the benefits that might accrue from one or the other. That's possible. And I'm sure that appropriate wording can be added in the label to suggest that doctors might then want to rechallenge with one or the other. They might do it; they might not. That's true.

But as you say, in the case of other more commonly used combination products that we're more accustomed to hearing about in cardiovascular medicine, specifically antihypertensive drugs, there is a measure. There is a goal. It's blood pressure. For aspirin there is no measure. We're basing the use of aspirin and the dosing of aspirin on well-controlled trials showing a benefit, and we really don't have dose-response data. So, there is no goal. It's merely the fact that we believe

that aspirin is more likely to be beneficial than detrimental for everyone for whom secondary prevention is indicated.

Again, for cholesterol we do have a target, perhaps, that some people might use, and one can titrate the drug as necessary to achieve that target if it's achievable with this product and not alter the aspirin usage.

So, I'm not concerned about the co-administration of the two, starting the two at the same time. I think Beverly's point is very well taken and that information should be given to physicians to encourage them to rechallenge if one of these rare problems occurs, but I don't see it as a show stopper.

Beverly.

DR. LORELL: I think it's an interesting question. I guess I would be interested in knowing what the rest of the panel thinks as to whether or not the optimum use for efficacy, as well as safety, would be to formally treat this drug the way we do antihypertensive combinations and to advise in patient and physician education and marketing that the two should be started separately, and if the desired level of lipid reduction is achieved, then to move to the combination using the precedent from antihypertensives.

DR. TEMPLE: That's not quite the precedent. That's one way, but it also acknowledges that you can titrate, for example, the diuretic by giving combinations with increasing doses of diuretic. So, in this case, you could accomplish the same thing, since there's nothing to measure with the aspirin, by moving up the lipid combinations, and it would more or less be equivalent to what you do with the antihypertensives, mostly because there isn't anything to follow for the aspirin part.

DR. BORER: Paul.

DR. ARMSTRONG: Doug's question raises, in my mind, another issue which we haven't talked about and that is the patient who arrives with an acute coronary syndrome on prior aspirin therapy, which we know is a risk factor for an unfavorable event. In large part, although the data I don't know is all that well known, many of these patients would be on 325 or more of aspirin and not on 81. So, in the event that a patient then arrives on this new combination of 40 and 81, under those circumstances -- and there's a literature, of course, around aspirin resistance -- the issue would be would a physician under those circumstances be wise to prescribe a larger dose of aspirin with the notion that there might be a better balance between efficacy and safety in the context of a presenting acute coronary syndrome. So, that's one situation where I

can conceive that this issue might come to quite a sharp focus.

DR. BORER: Blase.

DR. CARABELLO: Obviously, the combination here is being initiated for secondary prevention. So, it's hard to think of a secondary prevention patient where aspirin wouldn't be indicated. So, that's pretty much part of the deal. I think most of the time you would start at 81 milligrams. You're not really titering to anything. You leave that in place and then titrate the pravastatin portion of the drug, which now the sponsor has given us the ability to do, to the usual targets. Since the indication here is secondary prevention, almost 100 percent of those people need to be on aspirin. Unlike the hypertension situation where you might start with hydrochlorothiazide and then add enalapril and then finally have the combination drug.

DR. LORELL: I think the issue that was raised in the wintertime about the concern about inappropriate use of the drug with not getting to goal was more the elusive issue, is would there be a very powerful incentive because of the perceived convenience factor by maybe physician and patient, that if you were started on, let's say, the highest dose -- I mean, I think that will happen commonly -- and whatever dose of aspirin you choose, to then not up-

titrate further. So, I think that's the only reason why one could make an argument to start with the individual agent and, if you get to goal, then to move to the combination.

DR. BORER: Steve.

DR. NISSEN: There's at least one other concern about using it as initial therapy, and that is that every drug has a certain number of people who will not tolerate it. Both statins and aspirin actually are both known to produce GI intolerance, and so neither the patient nor the physician will know, when you start a drug at the same time and together in a fixed combination, what the source of that side effect is. In general medical practice, it's always desirable to start agents individually, and then if you find that the right statin dose for this patient is 80 milligrams of pravastatin and then if you want to give them 81 milligrams of aspirin, you then give them the combination for compliance enhancement.

But I don't think you want to mandate it because, in fact, by offering the full dose range, the sponsor has provided us with what I wanted last time around, which is the ability to titrate. We didn't have that before, and we have it now with this new application. I think that enhances the attractiveness of the application significantly.

DR. BORER: Have we given you sufficient guidance with regard to number 1?

Then let's go to the meat of the issue for which we have to vote. Do you recommend the approval of the co-packaged pravastatin-aspirin as therapy for patients for whom both products are indicated? Beverly, why don't we start with you and we'll get a sentence or two from anyone who wants to about why they vote the way they do.

DR. LORELL: Well, I'm going to actually divide that question into two answers. As the question stands there, my answer would be no. I have -- and I've voiced them -- very serious concerns about both long-term patient recognition that they're using aspirin in a combination drug and some of the unanswered speculations and issues about safety. So, as stated, my answer would be no.

As a subquestion, if the common tablet or capsule were packaged somewhat uniquely, to both enhance recognition that aspirin was in the pill and that there were safety issues regarding surgery, as well as recognition of major side effects of statin -- I'm not talking about it being hidden on a small-print package insert that many patients never read -- then my answer for approval would differ and be yes.

DR. BORER: So, would it be reasonable to say that assuming that the outcome of the entire vote was

negative and the FDA went away with that recommendation, that if the sponsor showed you packaging that could answer some of the concerns, that then you would find that acceptable?

DR. LORELL: That's correct.

DR. BORER: Mike.

DR. ARTMAN: Jeff, did we really address 1.4?

DR. BORER: I'm sorry. You know, we did not address 1.4. I'm sorry. We didn't even mention it. My fault.

Do you want to make a comment about that?

DR. ARTMAN: That to me sort of gets at this point number 4 up above that we were concerned about in the January meeting, and I raised the issue at the time about individuals for whom this is going to be prescribed for really primary prevention. I think we need to have a little bit of discussion about that, someone who's going to be given aspirin who simply has elevated cholesterol and who has not had any sort of event. Is that a problem? Are we putting another segment of the population at some risk for the adverse effects of aspirin?

DR. BORER: Is the company planning to remove unmodified pravastatin from the market?

DR. FIEDOREK: No.

DR. BORER: So, anyone who wanted to use

pravastatin for some purpose other than secondary prevention could still do it.

DR. ARTMAN: Sure, I understand that. But I think that again the whole issue is targeting the convenience, et cetera, et cetera. If I'm the only one concerned about that, fine, we'll let that go.

DR. BORER: Does anyone have any comments about that?

DR. TEMPLE: It's only convenient if you were planning to give it off label, which I have absolutely no doubt many people are doing.

DR. BORER: That people will do and perhaps it's the right thing to do.

DR. TEMPLE: It might even be. I'm sure Charlie could give a long lecture on all that.

DR. BORER: But I don't really think that's our concern. That requires an active will by a physician to do something that he or she believes is the right thing to do and for the physician and the patient to accept the potential consequences. That's true with any drug. I don't think there's anything unique about the combination here.

DR. ARMSTRONG: Could I just clarify then, Jeff?

DR. BORER: Yes.

DR. ARMSTRONG: In the event that the indications for statins change and cholesterol becomes an irrelevant target and the sponsor then positions the statin for a different population than is conventional, are we saying that we do not need to be concerned about the linkage to aspirin and that that's not our purview? I just want to understand that.

DR. BORER: I'm not suggesting that the linkage, if the two drugs were prescribed together, might not be a concern in that situation, but rather that if the unmodified drug is available for prescription and if physicians are prescribing drugs for a specific purpose, presumably they must know why they're prescribing the drug and for what. And if they have the capacity to prescribe the unmodified drug, I don't think that the fact that they may inappropriately prescribe a combination precludes the appropriateness of approving the combination. It's just bad medicine.

DR. TEMPLE: What they said is that their labeling will track the current labeling for the single entities. If aspirin changes, their labeling will change. If prava changes, then the combination labeling will change too.

DR. ARMSTRONG: I'm not sure that's wise. That is to say, if we open up the use of statins for all comers,

irrespective of their cholesterol, should aspirin necessarily follow. That's the essence of the question.

DR. TEMPLE: Only if aspirin is indicated in those people, not if it's not. I think Jeff was addressing that. That would represent a decision by the physician to use it in that particular setting, and he should be paying attention to the labeling or deciding to ignore it, whichever he chooses.

DR. LORELL: I think Dr. Artman's comment is very important because to my mind the ante goes up a lot for safety regarding confusion or inappropriate use of aspirin in a primary care population. So, if I'm concerned about that issue in secondary prevention, I'm very concerned about it in a primary care prevention where the potential risk-benefit ratio I think is quite different in a primary population if they're using a statin and forget they're using aspirin. But to my mind, that concern is partially mitigated again by very, very clear and distinctive labeling and warnings.

DR. BORER: Not to disagree with the importance of the concern because it is an important concern, but I don't think it's totally relevant to the approval issue that we're facing here today. To paraphrase some of Dr. Avorn's presentation, how are we going to change the situation that now exists? Aspirin is available over the

counter. If people want to use it for primary prevention because of information they get off the Internet or for any other reason or if doctors want to suggest that it should be used for primary prevention, even though the drug isn't labeled that way, that's going to happen. That isn't the issue I think we're facing. We're facing a different issue.

If two drugs that are appropriate, as we now believe, and labeled for use for a specific indication, are appropriate to be used together and we put them together so that it's easier to take them, is that a reasonable thing to do? The answer that we're going to come to is either yes or no, but I think that's our question, not what if people use it some other way even though the label doesn't say you're supposed to and even though the guidelines for medical practice don't say you're supposed to. I don't think we can deal with that.

DR. ARTMAN: Jeff, the point is you're packaging a drug that's indicated for secondary prevention with a drug that's indicated for either primary or secondary prevention. That's the difference.

DR. BORER: All right. Well, that's reasonable enough. It may be that doctors will choose to prescribe the combination, and maybe they shouldn't be doing that. But that's a matter of physician education I think not of

regulation of drug approval.

DR. ARTMAN: Well, if all this boils down to is physician education, then we really don't need this combination. People know they ought to be giving people aspirin and people know they ought to be using statins.

DR. BORER: No. The issue here is to make the use of drugs that the doctor wants the patient to use and the patient agrees to use more convenient for the patient to use by combining the two pills into one because the pill burden may cause people not to use what seems to be appropriate to use.

Now, the doctor doesn't have to prescribe the combination drug because it's available. The doctor can still say, well, here's your prescription for pravastatin and I want you to go to the drugstore and buy some aspirin. That's still an option. We don't preclude that option by approving the combination. We just make something that's convenient available for people who want to use it. So, I don't think it's quite the same.

Steve.

DR. NISSEN: Michael's concern is not trivial. I'm not saying it's necessarily compelling, but the fact is when you mix together a drug that's designed for primary prevention with a drug that can be used either in primary or secondary, the potential of bleed-over is real. You

know, physicians are creatures of habit. Some physicians -- who knows why -- tend to prescribe one statin versus another statin. Well, now they have two products. They have the pravastatin-aspirin combination; they have pravastatin alone. There may be some tendency, when you have a product of convenience, to use that product in situations where it may not be the right thing to do. I'm not persuaded that that's a huge approvability issue, but there is an issue, and I think that there probably is some risk here that some people will get aspirin that we probably wouldn't want to have get aspirin. When you mix the two together, somebody is going to get it that shouldn't, and maybe it's going to be more people than would get it if you had to separately talk about each of the drugs.

DR. ARTMAN: But your sense is that's not a big issue.

DR. NISSEN: I don't think it's a huge issue, but to say it's no issue I think is wrong.

DR. ARTMAN: Your use of the term bleed-over was intentional?

(Laughter.)

DR. NISSEN: It was not intentional.

DR. CARABELLO: But obviously then that same concern has to be weighed against the number of patients

who should be on the two drugs who wouldn't get the two drugs if you didn't have the convenience of formulating it that way. Goodness knows what that is. Presumably there is a risk in both directions. How you would weigh it, I don't know.

DR. BORER: Mike, have we discussed that 1.4 sufficiently?

If so, let's go on to the vote. Beverly already gave her vote and her reasoning. Mike.

DR. ARTMAN: Beverly voted yes and no. Is that correct?

DR. LORELL: I voted no and yes.

DR. ARTMAN: No and yes, okay.

DR. FLEMING: Just before we go on, Beverly, to clarify, it was yes under what specific packaging restriction?

DR. LORELL: I voted no to the question explicitly, and I voted yes in the context of very distinctive packaging that both clearly alerted the patient that the aspirin was in the pill or the capsule and that secondly had built onto the packaging the warnings that we've discussed. So, to put it another way, I'd be very concerned if this drug ever ended up in a standard CVS or Walgreen's little bottle with the tiny little type label.

DR. BORER: No trademark names, please.

(Laughter.)

DR. BORER: JoAnn. I'm sorry. Mike.

DR. ARTMAN: I'm not sure that putting these two drugs together will increase the utilization. I think we just don't know. A lot of this is just speculation and conjecture.

I am somewhat reassured by the multiple dosing combinations. I think that is, as Steve mentioned, a big advance.

I'm not quite as concerned as I was before about some of the potential risks. So, on balance, I think I would say yes.

DR. BORER: JoAnn.

DR. LINDENFELD: I would say yes. There are so many things we don't know that have been discussed, but the most common question I get is, can I take fewer pills? Not can I take fewer medications, but can I take fewer pills. So, I think having more people take these two drugs will be beneficial. We don't know how many more that will be, but I think I know that in some patients, who are already getting these two, they will take it more reproducibly if they have a combination available. And none of the safety concerns that we've heard has risen to the surface enough for me to be concerned that there's a safety issue that overcomes that potential benefit.

DR. BORER: Tom.

DR. FLEMING: I vote yes with proper packaging.

Just to quickly summarize and kind of bring in a little bit of the extensive discussion we had back on January 18th as well, I believe we do have a clear indication, secondary prevention with preexisting cardiac conditions, where I think the LIPID and CARE studies do provide considerable evidence of substantial benefit on MI, stroke, and CHD death, 25 to 30 percent with the addition of pravastatin, 15 to 30 percent with the addition of aspirin.

And as best I can understand from now two meetings of discussion, there really does appear to be a substantial medical need as evidenced by substantial fractions of these people who are non-adherent or who are not taking antiplatelet agents, maybe 15 to 50 percent of this targeted population, and lipid-lowering agents, maybe 30 percent.

It's very unclear to what extent this will enhance adherence, but I'm willing to believe that with the magnitude of efficacy that would be achieved, that it's very likely there would be meaningful improvement in adherence. And so, that's the up side.

The down side against that, as we've had a lot of discussions, I think first of all the sponsor's

providing now ability to titrate the statin is an important enhancement to address one of the key issues or concerns in January, and these concerns about excessive bleeding or inappropriate use of aspirin -- it troubles me because of what little we understand about this. It strikes me that it's an issue that is important but one that would be probably intrinsically very difficult to obtain the type of data we really would like to have to understand the magnitude.

But I've been persuaded that with appropriate packaging that clearly would identify the aspirin content and the warnings that Beverly is talking about that the overall evidence at hand then, to my way of thinking, is adequately favorable in benefit to risk to support a vote of approval.

DR. BORER: I vote yes. I think the body of evidence favoring the effectiveness of both components combined is overwhelming even though the studies weren't designed specifically in the way we might have liked them to have been to specifically demonstrate that fact. I think the total body of evidence is overwhelming.

I think that the sponsor is now presenting the product in a way that it is truly a convenience product. That is, it's possible to provide virtually any conceivable combination of doses, the absence of which was my primary

concern in January and, therefore, that the drugs can be used together in whatever way the individual physician and patient believe they should be.

I would share Beverly's concern -- and it's been echoed by others -- about the packaging. I think the caveat to this yes vote is that the sponsor and the FDA come to an agreement about packaging and warnings and labeling and whatever that would deal with the concerns that Beverly listed when she gave them to you, Doug. So, I think that's important.

But there is one other point here, and that is if we do recommend approval to the FDA, this could be seen as precedent-setting in some ways, and I would like to say a word about that.

The fact that we may recommend the approval of this combination product is specific to this combination product by which I mean there are two components all conceivable, currently employed and justifiable combinations of the components are being made available in combination so that the drug doesn't dictate medical practice. I think that's very important.

The fact that we may recommend to you to approve this combination doesn't mean that every time two different components that do two different things but are aimed at the same disease process are put together in the

same pill somehow, that we would necessarily suggest approval of that combination. I think each one has to be reviewed on the basis of its merits and on the basis of the various factors, including the doses involved that we've talked about here. So, I think that should be on the record. The precedent is very limited here.

With that, again my vote is yes.

Paul.

DR. ARMSTRONG: Yes. I'm persuaded by the sponsor's preparation and work that the balance of benefit and risk is supportive of a yes vote. My ancillary comment would be that they have provided information and hypothesis-generating information that such a combination will enhance the way doctors prescribe drugs and the way patients will take drugs. I think they would do a real service to patients and physicians and other sponsors and regulators if they were to test the hypothesis appropriately, starting now. If this is precedent-setting, then why not do the research that's necessary to establish that this idea is verified? You've got a unique opportunity and you would do people a real service to do that.

DR. BORER: My guess is that Charlie already has the protocol written.

Steve.

DR. NISSEN: My original objections in January were most focused on the fact that I was worried that this combination would undermine all the work that many of us have done over the last decade in trying to convince physicians that they should treat to goal for cholesterol. And we have national guidelines and a national cholesterol education program that said treat to goal. What we had in January was one statin dose to choose from, and I was concerned that the convenience of the product would undermine all the efforts that we had made to try to get people to treat to goal. Part of this was exacerbated, if I may speak very candidly, by some of the work that the sponsor has done over the years around the issue of whether it is in fact appropriate to treat to goal. And I just saw that whole issue being revisited.

So, when you reformulated to allow us the ability to give at least three different doses of statin, that went a long way toward reassuring me that this would not undermine current medical practice. And so, that's a big help.

I think you've done a nice job of partially alleviating the safety concerns, but not completely. And I share with Bev some of the concerns about safety. Perhaps there are even some that we didn't talk about, but the notion that some patients are going to get GI intolerance

and they're going to stop this product and they're going to end up stopping both the aspirin and the pravastatin. There are a lot of things to think about here.

On balance, I have been convinced by the presentation today and by the reformulation that more patients will benefit by having this available than will be harmed by it, and I therefore can vote yes.

DR. BORER: Blase.

DR. CARABELLO: I vote yes.

I'm not particularly concerned about the issue of bleeding. I'm sure that aspirin creates some, but I think especially in the modern surgical era, it really doesn't contribute an awful lot to postoperative or intraoperative bleeding.

I think the issue of labeling is an important one, but after the sponsor goes to whatever lengths they go to to label the product, in the end it's up to us to figure out what the patient is taking. Just like Jeff's sophisticated, up-scale patient who was taking the wrong stuff, the only way you would know that is to actually have them drag the pills into your office and see what they are. And I think that's the bottom line. It's the only way to really know what our patients are taking anyway.

I think Paul's comment is very cogent. If we could demonstrate as a medical community that this idea

works, that you can take two agents with entirely different pharmacologic targets that are umbrellaed under the canopy of here's a pill that makes you live longer and that could be extrapolated to other formulations of different drugs, we might be on to something here. It would be nice to see somewhere down the road if in fact this has increased utilization of those types of therapies.

DR. BORER: Susanna.

DR. CUNNINGHAM: Well, I'm just going to be different. I'm going to vote no for the very reason that we don't have any science. It actually says we're hypothesizing this will improve compliance. I hope it does. I think everybody has voted yes. My vote is not going to change anything, but I really am not comfortable with voting for something for which there is no science for the combined. I mean, I know there's all the individual, and I appreciate that and I understand that it may actually have great benefit. But this particular combination has never been studied.

DR. BORER: I think it's been studied. It just hasn't been studied in the format that we might have liked.

Bob.

DR. TEMPLE: It's worth mentioning that the combination policy has never said that there needs to be a demonstration of advantage. Now, I think if you talked

about this more, there would be some desire to have a reason for having a combination because you can immediately think of some potential disadvantages, which certainly have been discussed at great length. So, as a practical matter, maybe you do need to have some sense that it's worth it, but strictly speaking, many combinations couldn't possibly have a medical advantage. They're just the same drug taken in one pill. So, what can they do? And we have never said that they have to. What we have tried to do is make sure that some of the disadvantages are mitigated by having all doses available and perhaps by additional labeling and things like that.

DR. CUNNINGHAM: But aren't those usually just for one thing like hypertension? I mean, here we're treating two different things. Cardiovascular disease, yes, but not just blood pressure and not just cholesterol.

DR. TEMPLE: You're right. Over-the-counter-land drugs for different things are very common, but for prescriptions it's certainly the exception. Almost all of them have been combinations directed at the same thing. So, this has some precedent with respect to that too. You can easily think of a very large number of possible combinations of drugs for treating various people's ills of the elderly.

DR. BORER: I think that Susanna's point is a

very important one, but one might argue that this really isn't different from the combination antihypertensive drug product fundamentally because you're not really treating people for their high blood pressure. You're treating people to reduce strokes, myocardial infarctions, and cardiovascular death, heart failure, and renal disease, five different things here. And this combination is intended to prevent myocardial infarctions, stroke, and cardiovascular death. It's just that in the one case the putative pathophysiology is one set of processes that both drugs seem to hit, and here there are two different processes aimed at the blood vessel in different ways. So, I don't think the differences between the combination products are as great as they might at first seem, but I think the point is still an important one.

DR. TEMPLE: An interesting question could arise. There are other lipid-lowering drugs that don't have as much data on prevention, that have a couple of studies on this and that, or no studies at all. You might see a proposal sometime for a drug that lowers lipids and has aspirin attached to it because aspirin is good for people. That's a different set of considerations. We're actually internally thinking about all this stuff. I ran the numbers. You can think of many thousands of combinations along these general lines.

DR. BORER: Well, that concern is the reason that I said what I did about precedent. You have to see and we then perhaps have to see the data that would support such a combination.

Are there any other comments from the committee?

(No response.)

DR. BORER: If not, I want to congratulate all of you for finishing 45 minutes and 50 seconds early.

(Whereupon, at 4:14 p.m., the committee was recessed, to reconvene at 8:00 a.m., Friday, July 19, 2002.)