titrated to goal if these agents weren't available in a fixed-dose combination.

DR. TEMPLE: Now, how is that different from starting on 40, which is what the recommended starting dose is, and having stopped that and go buy the 80 milligrams or take two of them or something? You think this makes it materially worse because stopping the aspirin and going to the drug store and getting a few aspirin is really hard.

DR. NISSEN: Yes, I do.

DR. BORER: And I would agree with that, and I'd even amplify on it but I don't think I have to.

Tom?

DR. FLEMING: I'd like to probe on this a bit more as well, maybe somewhat along the lines of what Bob was just asking.

Quite frankly, I'm inclined to vote yes in question 9 unless there is a substantial reason given in question 8 to there being a concern with this packaging, and in the context of question 7, the way I've been thinking about this is what's this all about. Why are we considering this packaging?

It needs to be at least reasonably well motivated that there will be an enhanced likelihood of achieving the most favorable benefit-to-risk profile that these agents are capable of providing should you have a

more optimal level of adherence. There needs to be a perception or a reality, better than that, that we have effective agents here that are being underused and as a result, globally we're not achieving the level of clinical benefit that they could potentially provide. If that's not true, we're done.

Now, if in fact that's true, and presumably that would be argued to be true in the sense that when you have a packaged delivery, you're going to make it more convenient and you're going to have a higher level of consistency and accuracy in the delivery of these doses to a larger fraction of the population than currently is getting access to this. That's the pro argument and we've heard that from the sponsor.

The con argument that we're hearing that also seems to be relevant is there's a "yes but." There are circumstances in which this packaged delivery can be nonoptimal, examples being there are certain types of patients that shouldn't be getting antiplatelet therapy and it may be, in fact, not recognized as readily when they are taking a single tablet, or maybe they're getting a nonoptimal antiplatelet agent. Or it may be that we're not achieving an adequate level of targeted goal of lipid reduction and it may become less likely that we would have an altered dose or altered selection if people are choosing

this. I see all of those as relevant concerns, but it is true, somewhat, that when you label things, or at least when you make it as clear as you can that this intervention, this particular package combination isn't necessarily the right choice for all people, that some of these concerns can be offset by intelligent use of this.

So, what I'm left with in the end is the subjective weighing out of what are the benefits that we're going to get when we're using it correctly and it's going to give an enhanced, widespread use of agents that have potential of delivering benefit but they're being underutilized against these instances that we've given where there are concerns. The fact that there are concerns doesn't mean that the benefit-to-risk, so to speak, is negative.

What I'd like to get a sense of from the committee is, is there really an unmet need that's sufficiently substantial such that if this is more convenient, we really will achieve a higher level of adherence and thereby a better benefit-to-risk in the broadest population, but that there are these concerns and in fact they're real but they won't counterbalance the benefit, or are these concerns so real that they will give us no net gain? That's the answer I'd like to hear.

DR. BORER: Tom, let me begin responding to you

by pointing out something. You said get these agents to people. I don't believe we're talking about improving compliance with two agents. I think we're talking about compliance with one agent. The frequency of prescription of statins I don't think is going to be altered one bit by making this combination available. The associated use of aspirin may well be increased. I mean, it may or it may not be. I don't know, but it might be. I don't think the use of statins is going to be altered at all. So, it may be that we might alter the use of aspirin by providing the combination.

I think, though -- and I'd like to hear from everybody else to respond to Tom as well -- that the sense of the people who have spoken, about this among the voting members of the committee, is that perfect is the enemy of good, and we don't know what perfect is, and being on some statin, if you have any of the conditions for which the drug is indicated, is better than being on no statin. We're not going to alter the statin part of this equation here.

What we are going to do, however, we believe, by limiting the dose range of the combination, is making it very likely that people will use this dose even if, left unfettered, their judgment would cause them to use different doses for targets that they may wish to achieve

based on clinical guidelines or whatever else. And it's not that they couldn't make the change, but that it becomes so inconvenient and costly to make the change that they're unlikely to do it and that the patients may not benefit from that.

Now, Beverly and Steve and the others here, maybe you may want to add to that.

DR. NISSEN: Well, I think you said it very well. Tom, let me see if I can help you with this.

There are two sides to this equation. Will the combination improve safety or make safety more of a concern? We're talking about weighing, pluses and minuses. I think for that one it's pretty clear to me that the likelihood that people will get aspirin inappropriately and therefore raise a safety problem goes up not down. I think the likelihood that a primary prevention patient who shouldn't get aspirin will and the chances that a patient will get aspirin when having a surgical procedure that shouldn't will are both worse with the combination. So, on the safety side, it's not a plus.

What about efficacy? Efficacy would mean that more patients that ought to have co-administered aspirin would and that more patients would be more likely to get to those lipid targets that we've spent the last 7 or 10 years trying to get people to follow. And I have concerns that

the net balance on the efficacy side will be worse. Yes, a few more patients may get aspirin, but the burden of then having to go through this process of stopping a combination product, switching to a different statin, and co-administering aspirin will be enough of an impediment in primary care and in other settings that fewer patients will actually get to the goals that we want, and so therefore, this combination will have an adverse effect on overall efficacy.

So, I think for me it loses on the safety side and it loses on the efficacy side.

DR. THOMPSON: Jeff, I'm a non-voting member, but can I comment?

DR. BORER: Yes, sure, Paul.

DR. THOMPSON: Because I'd like to make two comments.

First of all, I always tell people that there are two devils in this world. There's the devil you know and there's the devil you can speculate about. When we look at the devil we know and we look at slide D-13, we see that among those patients -- now, this is 1999 data -- with known cardiovascular disease, only 51 percent reported that they were taking aspirin or an equivalent. So, that's a large gap. And we also know that 15 percent of those who said they were taking aspirin were taking something else.

They were taking a non-aspirin compound. So, I think we're actually speculating a fair amount about things that are possible, devils that we're actually imagining, as opposed to facing devils that we can see and have data in.

Now, a couple other small comments. We're talking a lot about the safety of withdrawing a statin, for example. I do that in my lipid clinic all the time because people always doubt whether the statin is responsible for their effect. So, I stop it to show them that indeed the statin was effective.

We're also talking about the negative stuff of aspirin in primary preventions. Well, it's news to me. It's one of the few things I do for myself. I think most cardiologists do take aspirin for primary prevention. So, perhaps there's some data that wasn't presented that I didn't know.

Then finally, what I always do and I tell my children to do when I have to make a decision is I make up a list of pros and cons, and I'm glad to share that with you, if you'd like. But I've listened to the cons during the day that aspirin might be taken by those who are at risk to bleed, and there are all those sorts of risks. But when you take and you make up your benefit-risk thing, even with the fact that convenience for a patient is a benefit -- I thought this was actually a slam dunk when I read this

stuff at home before coming here. I had no idea.

But when you look at the pros and the cons, I find it hard to worry so much about these devils unknown as opposed to the devils we actually see in the data and the efficacy of the combination shown from the meta-analysis, which we all agreed that we liked.

I'll go through my pros and cons, but I don't want to take more time. I'm a nonvoting member, but I've listed to everything such as that you lack flexibility. But that lack of flexibility with a 40 milligram dose may get doctors start with 40 milligrams as opposed to 20 milligrams. So, for most of the things we've talked about as a negative, there's also the potential benefit.

No data on aspirin effect when given together, but actually we do have some data. It looks like it decreases the event rates. And this was the stuff on platelets. In other words, people were talking about the fact that there was no effect on the platelet effect. Well, there's no in vitro studies, but there are in vivo studies showing that that combination looked better. Now, if you give me a choice between some Bademan's platelet chamber versus some human being, I'm going to take the human being studies.

So, I've listened to the two sides of it, but I'm surprised a little bit.

DR. BORER: Tom, did you have some comments here?

DR. FLEMING: Jeff and Steve, I wanted to just follow up for clarification on your insights.

I understand, Jeff, from what you're saying is that you see the most substantive impact of this would be potentially increased adherence to the aspirin, that the lipid-lowering intervention will essentially, in terms of its overall coverage, largely stay the same.

DR. BORER: Yes. Anything else would have to be a result of marketing, and I don't think we can make any guess about the impact of marketing, how it's going to be done, or whatever. But logically there should be no impact on the use of the statin. It really should be only on the impact of the use of the aspirin.

DR. FLEMING: So, if I go with that, Steve, what I heard was a concern in terms of the safety side in particular being that if there isn't an as flexible an adjustment of the regimen for a lipid-lowering agent, that could have adverse effects on efficacy and safety.

DR. NISSEN: No, I'm sorry. The safety issue related to the aspirin. I'm very comfortable with the safety of pravastatin and, frankly, the other statins as well.

DR. FLEMING: All right. So, basically it

would be a concern about potential loss of efficacy on the lipid-lowering side, the statin side. When we see data, as we were just referred to, D-13, and we see estimates of about 50 percent underuse of aspirin, even though I appreciate that there are settings you've described where aspirin use could be inappropriate and hence larger use could lead to then some instances of adverse effects, if it truly is 50 percent, isn't the up side for increased adherence to aspirin far greater than the down side?

DR. BORER: I don't know. I really don't know. First of all, we have no idea what the impact on aspirin use would be. We heard that in Sweden there wasn't much impact, not that those are primary data, and yes, this is a convenience product.

DR. FLEMING: I am persuaded by what was said earlier and that is if you make this available and it's not in fact used, then that's a marketing issue. That's not an issue as to whether this had the potential of providing benefit. In fact, there's no harm, in a sense, done if you make this available and no one uses it. We just didn't provide any benefit.

My concern is if we make this available and it is used, is this in fact going to achieve more net benefit than harm, and the benefit would allegedly be, if I focus on the way you think this is going to go, Jeff, it has the

potential at least of substantially increasing adherence to aspirin which, if we believe the efficacy data, has the potential of providing meaningful benefit on major events. But then there is the offsetting aspect that in some of these cases, there may be some safety concerns, and in the lipid-lowering case, there may be lack of as effective adjustments that could provide some offsetting.

So, is that the benefit-to-risk that we would have to say when we --

DR. BORER: As far as I'm concerned, you've pretty much noted the elements, and I would go one step further. I'd be a lot happier, because I think the problem would be obviated, if the sponsor provided pravastatin at several doses with aspirin attached to it so that I could give the dose that I want to give.

DR. NISSEN: We don't know what percent of that 50 percent not on aspirin also require co-administration of statins. You understand that that data is not statin data. That's aspirin data. So, there's an unknown here, and that is how many of those people would be even eligible for a combination product, and we have not been provided with any information about that.

DR. FLEMING: A very important point. Is there anybody that has that data? If this 50 percent doesn't apply to our population and we need to know what percent of

the people on statins are not using aspirin, which is very relevant.

DR. ARTMAN: Just go back to D-10, the sponsor showed us data from 167,000 patients who had had an MI at discharge, and 77 percent of them were receiving aspirin and only 37 percent were receiving statins. So, I don't see this as an underutilization of aspirin. I see it as an underutilization of statins. And I think the sponsor is probably not going to go out promoting aspirin. They're going to go out promoting pravastatin.

DR. BORER: Which they could do anyway.

DR. ARTMAN: Which they could do anyway.

You know, this was prefaced to us with this treatment gap and it's a public health issue, and it's not because the drugs aren't available. These drugs are available. It's educating the physicians and, these days, educating the consumers directly. So I think, Tom, this maybe is more reflective of the proper patient base.

DR. FLEMING: I was going to throw something out here because part of where I'm struggling here is I prefer to be looking at quantitative results and we're having to speculate and that's somewhat unavoidable.

We had data presented to us which wasn't certainly as reliable as what we would have had from randomized trials, but it's the best evidence at least that

I have that I can use in a subjective judgment here that says you're going to have on the order of 25 to 33 percent reduction in major events with proper administration of these interventions. If in fact making an intervention that's more convenient does allow for a 25 percent -- and that's a pretty substantial increase -- but a 25 percent increase in adherence from 50 to 75 or whatever, that leads to what one could at least speculate a pretty substantial reduction in the overall rate of occurrence of some of these events.

On the other hand, there are these down sides that occur that relate to safety. It has to be a pretty strong argument I would think, though, that those down sides would be so substantial that they could offset this potential for a very substantial gain by having greater adherence to effective agents.

DR. BORER: To preempt Beverly for just one second here and to try to answer your question, I can't answer the question.

As it was presented, I recognized the same concern that Steve just verbalized, that is, that we were shown the gap for all aspirin users. If you look at the data in the book from LIPID and CARE -- it may not be representative but that's what we've got -- pages 14 and 16 in the briefing book, patients were randomized to

pravastatin or placebo. They may have been on aspirin. 83 percent of the patients in LIPID were on aspirin; 84 percent of the patients in CARE were on aspirin. That's a gap of 16 to 17 percent, not 49 percent.

And I'll tell you my opinion. I can't substantiate it. My opinion. Once somebody is taking a statin drug, their perception of the importance of drug-taking is heightened, and I think it would be more likely rather than less likely that they would take their concomitant aspirin. I don't know if that's true or not, but that's the way I would interpret these data.

DR. FLEMING: Let me reiterate my question then from five minutes ago, which is if it's appropriate to suggest that this 50 percent underuse of aspirin isn't relevant to our context, we need to know, in the context of somebody who would be on lipid-lowering agents, what is our best estimate of that. I understand, from the clinical trials for aspirin, when you have people joining a clinical trial to be randomized to a lipid-lowering agent, 80 percent were using aspirin, but does that represent the real world, which was my question. And then we had reference to data from D-10.

DR. HIRSCH: Tom, you're not going to get an answer to your question. There are various surveys with various aspirin use rates in different populations, and you

can quote figures from 50 to 90 percent. Somewhere between 70 and 80 percent is probably accurate. And you're not going to be able to make your decision based on that. Although you'd like that hard data, sorry, you're not going to get it today.

And I'm going to charge in and make an impassioned plea here. I'm someone, Tom, who also deals with this public health issue of use or not use and filling the gap in underuse of medications. I'm a little surprised at us today. I'm a little surprised that we're going to try to make a decision at this last minute to try to fill this gap with this single product combination because any hope of us changing the outcome of use of aspirin and lipid-lowering agents in America with this decision -- that happens with very long, large-scale NIH, American Heart Association 5- and 10-year, Healthy People 2010 plans. It doesn't happen in a deliberation like this.

I would like to constrain the conversation a little bit and bring it back down to, again like you were saying earlier, is there some evidence of efficacy, what is the safety issue, and do we think physicians can prescribe more or less appropriately, never perfectly.

And with that, Bev, go ahead.

DR. LORELL: Thank you.

I think that in thinking about the data that

we've seen today, we've seen very compelling data from the meta-analysis that the use of Pravachol plus aspirin is efficacious. But I think a very interesting point is that the use of aspirin in the trial data that we have to look at to make our decision was discretionary. It was a high frequency of use that we saw, but it was discretionary and what people were really doing in those trials was taking two separate pills.

I am concerned about the issue that having a single fixed dose carries a risk, as was put well by one of my colleagues, of increasing the likelihood of under-treatment with statins, but I think that my much larger concern that I had not even thought about until I heard the discussions today, is the very real risks of packaging a potent antiplatelet agent with something else. And I would go on record as saying that I have grave concern about packaging aspirin, clopidogrel, or any other antiplatelet agent with anything, whether it be a beta-blocker, an ACE inhibitor, you name it. I use these drugs every day in very high-risk patients. Aspirin is a powerful drug. It carries risks of bleeding. Patients and doctors have to be extremely attentive to its use and the subtle nuances of when to temporarily stop and when to restart it. So, I think my largest concern is I don't think the issue of convenience is outweighed by the very real risk and lack of

data about packaging a potent antiplatelet with something else. To me that's a very major issue.

DR. BORER: Blase, do you have any last comment here?

DR. CARABELLO: No.

DR. BORER: Then let's move on to question 9. We'll go around the table because this is a vote that has to be counted, and we have to have a verbal statement.

Do you recommend approval of a fixed-dose combination product of pravastatin plus buffered aspirin -- I assume the product that we've been given, which is the doses -- yes, right?

DR. LIPICKY: Yes.

DR. TEMPLE: Jeffrey, one thing. We didn't think of this. You ought to address the question of whether it would be different if they made it available with two doses of pravastatin, which they may not want to do, but which is certainly possible.

DR. BORER: Alan, why don't you start?

DR. HIRSCH: Am I'm allowed, Bob, to answer your first question first? I mean your dosing question. Say yes.

DR. LIPICKY: [Inaudible.]

DR. BORER: Why don't we answer this one first? Then we'll go around the room and ask the second one.

DR. TEMPLE: That would be okay. Would your answer be different if they had an 80?

DR. LIPICKY: If you say no, then you can ask what if you had two doses of pravastatin, would that be good?

DR. HIRSCH: I'll need to explain later. I'll say no.

DR. BORER: Let's start with Dr. Kreisberg.

DR. KREISBERG: No.

DR. LORELL: No.

DR. BORER: That was a no from Beverly. Susanna?

DR. CUNNINGHAM: No. I'd really like to have the information that allowed me to vote differently. I would like to know that this was safe and that people wouldn't be put in trouble, and I'd like to know that this actually helped people to take their drugs more. We don't have that information. I'd like to have something that says if it were available as a combined, one, people would take it more often. I don't have that. I hate having to guess, and so I'm going to say no.

DR. BORER: Mike?

DR. ARTMAN: No.

DR. BORER: Tom?

(Pause.)

DR. KREISBERG: Yes or no.

(Laughter.)

DR. FLEMING: Well, there is a third and I'll take that option. I'm to abstain from this. I actually was inclined to vote yes, and I've been persuaded by a lot of comments over the last 20 minutes that this is extremely difficult.

Basically my sense is that if it is, as I would have thought, much more plausible than I'm hearing, that we really would enhance the overall adherence, then I would think that the potential for benefit exceeds the very real and relevant concerns. But what I'm hearing from my clinical colleagues, who have much better insight than I do about the actual real-world reality of this, is it's not very likely we're going to have enhanced adherence, and if that's the case, then I don't believe that it would be a positive step. So, in the absence of being able to make an informed judgment about that, I think I'm going to abstain.

DR. BORER: Blase?

DR. CARABELLO: Yes.

DR. BORER: Steve?

DR. NISSEN: No.

DR. BORER: And I'll vote no. So, we have 7 no, 1 yes, 1 abstain.

Now let's go on to the next issue, which is the

one that Bob just asked, and I'm going to change the question just a little bit. What if we had not two doses but a broader range of pravastatin doses? I don't want to pick the doses, but what if we had a broader range of pravastatin doses available together with aspirin? Would that change the vote?

Alan, why don't you start?

DR. HIRSCH: Yes, and the reason is because pravastatin is safe and effective, aspirin is effective and rather safe. Actually the biobehavioral issues of how patients take drugs and physicians prescribe them are the main ghost in the room. That's what this is all about. For that, I think with a dose range, I would certainly have voted yes.

DR. KREISBERG: I'll vote no and the reason that I'll vote no is that the only alternate dose is 80 milligrams, at least that's what I'm hearing. And that adds an additional 3 percent LDL cholesterol lowering, and consequently I don't think that's enough of a therapeutic option to make that an attractive one. So, my answer is no.

DR. BORER: Beverly?

DR. LORELL: I would answer no too. I think it still does not address the issue of potential increasing the probability of undertreatment. We were shown no data

addressing that.

And secondly, I still have a major concern about combining, in a fixed-dose combination, with any other drug an antiplatelet agent.

DR. BORER: Susanna?

DR. CUNNINGHAM: No, because it doesn't change the issues I'm concerned with.

DR. BORER: Mike?

DR. ARTMAN: Yes, I would say no as well. I think that again as sort of a clinical pharmacologist, this really goes against one of the principles of rational drug therapy and that is to try and tailor your therapy to each individual patient. And that may change on a month-to-month basis in that given patient.

The other issue is related to the compliance issue. For those who have tried to study compliance in populations who are taking a medication that really doesn't make them feel any different, compliance is a very difficult issue. It's very complicated. And the inference is that just because this patient who is taking four or five drugs now will take three or four drugs instead of four or five will have better adherence to their regimen I think is just a lot of hand-waving. There are absolutely no data to support that, and I think this is the wrong way to go.

DR. BORER: Tom, you already abstained from number one. Do you want to abstain from two?

DR. FLEMING: Yes.

DR. BORER: And Blase, you said yes the first time. So, that's not an issue.

Steve?

DR. NISSEN: No.

DR. BORER: Alan? I'm sorry. Alan already said --

DR. HIRSCH: I did but I could change my mind if you like.

(Laughter.)

DR. BORER: No, no.

I have a very difficult time with this question. I think that it would be reasonable to approve a combination of these two products as a convenience as long as the uncombined drugs remained available and as long as a range of doses and combinations sufficient to suit my purposes as a prescriber were met.

I agree fully with what Bev said. I am concerned about potential problems associated with adding an antiplatelet drug that might not be used appropriately because it's attached to something that the patient may not remember about. But I think I might be able to deal with that or someone might be able to deal with that in certain

situations. And the convenience of having that available might outweigh my concern in some situations. What I was not happy about with the drug that was proposed was that it limited my capacity to manipulate cholesterol the way I might choose to do it.

So, while I still have the safety concerns that have been raised here, and I agree fully with Mike's comment that I don't think the right way to give drugs is in fixed combinations, that you should titrate individually and be able to change doses individually, nonetheless I think the convenience of having the two pills in one would be reasonable and would be sufficient to outweigh my concerns about safety for approvability as long as my capacity to prescribe the doses I want to prescribe wasn't limited. So, I would vote sort of a tepid yes on this last question.

So, I don't think we have to take a big tally on that one. It's not one of the official questions here.

DR. TEMPLE: But you did take a tally, didn't you?

DR. BORER: Well, we have everybody's answer. Do you want me to summarize it for you? We have 3 yeses, 5 noes, and 1 abstain.

DR. TEMPLE: It's late to point out what I'm going to point out, and we obviously should have built it

into the questions. But you may recall that aspirin is available as an over-the-counter drug and whether people take it and under what circumstances they take it and whether their doctor knows they're taking is is not exactly a known quantity at the present time. I don't know if that makes any difference, and we really didn't mention it. But that seems to have something to do with how much anxiety one should have about someone taking aspirin when he shouldn't. I mean, they already are.

DR. BORER: Not to me, for the reasons that Beverly verbalized very well.

I think that we've completed our responses. We'll call the meeting adjourned.

(Whereupon, at 3:05 p.m., the committee was adjourned.)

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