DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM

ADVISORY COMMITTEE

ISSUE: SAFETY AND EFFICACY OF AGGRENOX

(DIPYRIDAMOLE/ASPIRIN CAPSULE (NDA 20-884)

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at

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C O N T E N T S

P R O C E E D I N G S

Call to Order, Introductions

DR. GILMAN: Good morning and welcome. I would like to go around the table and have people introduce themselves. I will start at the left here.

DR. VAN BELLE: Gerald Van Belle, University of Washington, Seattle.

DR. GROTTA: James Grotta, University of Texas Health Center, Houston.

DR. KONSTAM: Marvin Konstam, New England Medical Center, Boston.

DR. LACEY: I am Ella Lacey, Emerita Faculty, Southern Illinois University, Carbondale, Illinois. Consumer Rep.

DR. PENN: I am Richard Penn, Professor of Neurosurgery, Rush University in Chicago.

DR. DRACHMAN: David Drachman, UMASS Memorial Health Care.

DR. CALIFF: Bob Califf, Duke University.

DR. ROBIE-SUH: Kathy Robie-Suh, Division of Gastrointestinal and Coagulation Products, FDA.

DR. TALARICO: Lilia Talarico, Division of Gastrointestinal and Coagulation Products, FDA.

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products, FDA.

DR. GILMAN: Thank you all. Before we get started, let me just lay out a few ground rules. At meetings like this, often two people will want to speak simultaneously. To avoid that, I ask that members of the committee at the table will raise your hand in some way to signal that you would like to speak.

For both the sponsor and the agency, I can assure you from previous experience on this committee that we have read the material thoroughly. We are familiar with it. We have a number of questions and we would like to have our questions addressed.

So when you are speaking, if we ask you a question, and we will--we will interrupt from time to time--please answer our question at that time. Don't say you will get to it in a minute because sometimes those issues disappear and they we are left in our deliberation period not knowing the answer to the question. So please allow us to interrupt and please answer the question as directly as you possibly can.

We have a conflict of interest statement by Sandra Titus, our Executive Secretary.

Conflict of Interest Statement

DR. TITUS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even

the appearance of a conflict at this meeting.

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

In accordance with 18 USC Section 208(b)(3), waivers have been granted to Drs. Richard Penn, Sid Gilman, Claudia Kawas and Marvin Konstam. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

We would also like to disclose that Dr. James Grotta was a local PI on a study of Syntex's Ticlid, a competing product to Aggrenox. Further, we would like to disclose that Dr. Robert Califf is the Director of the Duke Clinical Research Institute at the Duke University Medical Center. The Duke CRI is the coordinating center for numerous clinical trials and it has received funding from various pharmaceutical companies for a study of products unrelated to the product at issue or to the competing product.

Although these interests do not constitute a

financial interest in the particular matter within the meaning of 18 USC, Section 208, they could create the appearance of the conflict. The agency has determined, not withstanding these involvements, that the interests of the government in Dr. Califf's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

Therefore, Dr. Califf may participate fully in the committee's deliberations concerning Aggrenox. In the event the discussions involve any other product or firm not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. GILMAN: Thank you.

We will move right along to Dr. Katz' overview.

Introduction of Issues

DR. KATZ: Thanks. Actually, the agenda is somewhat misleading. I am not going to give an overview. I really just asked for a couple of minutes to welcome folks back. In the Division of Neuropharmacological Drug

Products, we have always considered this committee to be our committee, sort of an extension of the Division. But technically I have been told that is not correct.

From time to time an issue will come before another division, other than ours, that needs to be brought before this committee. That is the case this morning. The NDA for Aggrenox, as Dr. Gilman pointed out, is the Gastrointestinal and Coagulation Drug Products Division. But, because the issues are neurological, it is appropriate to bring it to this committee.

Having said that it is not "our" committee, I still think of it as our committee. So I asked Dr. Talarico, as the Director of the division, if I could just give a welcome. I am pleased to do that.

Dr. Talarico's division and staff have actually reviewed the data and they will be presenting the FDA's view of the results of the trial. Dr. Feeney and I from the Neuropharm Division have consulted with that division and we are available to comment further if needed.

So I really just want to welcome you back, those of you who are coming back. There have been many changes since our last meeting which, as Dr. Gilman reminds me, is quite a while ago.

We have a number of new members. And we have a number of members who are returning. I want to welcome the

new members, Dr. Grotta and Dr. Roy Penix, who, unfortunately, was ill and can't be here. And Dr. Lacey. Welcome. I hope that your serve on the committee is interesting and stimulating. I expect it will be.

Dr. Mike Brooke, Dr. Gerald Van Belle and Dr. Richard Penn are returning to this committee after a numbers of years off and are the inspirations we need to perform three or four more years of thankless, underpaid, government service. So we want to thank them in advance.

There is one other major change in the committee that many of you have probably noticed and that is this is the first meeting of the PCNS Advisory Committee, in over twenty years, in which Dr. Paul Leber is not at the table. As most of you know, Dr. Leber retired a couple of months ago, and this committee, and well as many of you know full well his extraordinary contribution.

Those of us in the division were fortunate to be able to experience his influence on a daily basis, some of us for many, many years. I know that the committee will miss him and we at the division, of course, miss him very much. I guess he is not here in the audience.

But, in any event, I just wanted to welcome you all back, those of you who have been on the committee. And I hope that the discussion is interesting. I expect it will be.

I will go back to Dr. Gilman. Thank you.

DR. GILMAN: Thank you. We have been joined by Dr. Claudia Kawas who is from Johns Hopkins University.

Boehringer is now going to begin with Dr. Manfred Haehl, Senior Vice President, Medical and Drug Regulatory Affairs.

Presentations by Boehringer Ingelheim Pharmaceuticals, Inc.

Introduction

DR. HAEHL: Dr. Gilman, Dr. Talarico, Dr. Titus, members of the committee, good morning and thank you very much for giving us the opportunity to present to you this morning.

[Slide.]

My name is Manfred Haehl. I am the Senior Vice President for Medical and Drug Regulatory Affairs, Boehringer Ingelheim Pharmaceuticals.

[Slide.]

Boehringer Ingelheim seeks approval for Aggrenox and its extended-release formulation product of dipyridamole and aspirin which reduces the combined risk of death and non-fatal stroke in patients who have had transient ischemia of the brain or completed ischemic stroke.

Before we begin the detailed presentation of the data in support of this NDA, let me please read you the rationale for the development of Aggrenox and its potential

for the presentation of stroke.

Ischemic stroke is a serious and devastating event in the larger group of ischemic vascular conditions. Its incidence remains high at about 700,000 per year in this country in spite of risk management and pharmacologic approaches. Therefore, the impact, not only on the patients but also their families and society, is enormous.

There is substantial prior information on the use of anti-platelet agents both alone and in combination. Safety and efficacy of those agents have been established in ischemic diseases in general and in the secondary prevention of stoke particularly.

Aspirin is the most widely studied anti-platelet agent in the prevention of stroke. The most recent FDA rulemaking for the professional labeling was published at the end of last year.

[Slide.]

The indication in this final rule is as follows: to reduce the combined risk of death and non-fatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin-platelet emboli. The dose in this rule is 50 to 325 mg/day. It is important to note that this indication was granted on the basis of a relative risk reduction for the combined endpoint of stroke, TIA and death in the range of 13 to 18 percent.

The trial of aspirin alone in patients with prior TIA or occlusive stroke showed individually and in metaanalyses clear benefits on stroke. However, the results on death were less conclusive. The trials of dipyridamole alone were both fewer and underpowered and basic research suggested that the combination of aspirin and dipyridamole would yield greater benefits than either agent alone.

For these reasons, Boehringer Ingelheim sponsored two large-scale trials. First, the European Stroke Prevention Study No. 1 or, in short, ESPS-1, which has been a combination of aspirin together with immediate-release dipyridamole in one arm against placebo in the second arm. And the second study was the European Stroke Prevention Study 2, or ESPS-2 which was based, in part, on the results of ESPS-1.

ESPS-2 used a two-times-two factorial design of dipyridamole extended-release and aspirin. The combination dose and formulation were chosen to yield maximal and sustained inhibition of platelets together with minimal side effects, less frequent dosing, fewer pills, to enhance long-term compliance.

[Slide.]

You will note that the pivotal trial, ESPS-2, has contributed about 33 percent of the data to the world literature on aspirin and stroke, 3,400 to 5,050 and has

more than doubled the world literature on dipyridamole in stroke.

[Slide.]

ESPS-1 studied the efficacy of the combination of immediate-release dipyridamole plus aspirin as compared to placebo in the prevention of secondary stroke. This study confirms the highly significant benefit of the combination. However, due to its design, it was not able to evaluate the contribution of dipyridamole or aspirin for the observed effects.

[Slide.]

A pivotal study for Aggrenox is ESPS-2. It was designed and it was powered to establish the efficacy of the Aggrenox combination product and of its components, and especially it studied the Aggrenox formulation which is under review today.

[Slide.]

The Aggrenox formulation was designed to combine doses of two active anti-platelet agents with distinctly different modes of action.

[Slide.]

The product is formulated as a hard gelatin capsule containing an immediate-release 25-mg tablet of aspirin surrounded by approximately 700 extended-release granules. These granules amount to 200 mg of dipyridamole

and have different coating to insure sustained release of dipyridamole over the entire dosing interval.

The Aggrenox formulation was desired to enhance compliance over immediate-release dipyridamole formulations which require TID or QID dosing. The 20 mg of aspirin was chosen to insure maximal cyclooxygenase inhibition in the platelet--you know that this is a hit-and-run phenomenon for the lifetime of the platelet--and, on the other hand, to minimize the potential for aspirin-related adverse events.

The scientific hypothesis was that the two distinctly different mechanisms within a rational formulation with no power for kinetic interaction between the two components would actually translate into important benefits in the clinic, benefits which are additive and superior to the monotherapies.

ESPS-2, in pivotal trial, did test for this hypothesis in a double-blind, randomized, four-armed parallel design in over 600 patients with preceding TIA or completed ischemic stroke.

The patients were recruited in 59 centers from 13 countries all over Europe.

[Slide.]

The study demonstrates the highly significant superiority of Aggrenox both over aspirin and dipyridamole in stroke prevention. We will demonstrate to you that this

superiority can be achieved without additional safety risk.

While the outcomes for the prevention of stroke are of powerful significance, the rate for deaths in the study was too low to establish a significantly signature reduction. Nevertheless, the trends, both for Aggrenox and for aspirin, were positive. They were comparable to each other and, even more important, and notably, they were consistent with prior experience and the recently published FDA-approved labeling for aspirin.

[Slide.]

Finally, all significant results in ESPS-2 are robust and reproducible independent and regardless of the statistical methods applied. The powerful superiority results from ESPS for stroke prevention and with the consistent trend for combined death and stroke, we would like the committee to consider that the indication for Aggrenox should be harmonized with the approved indication for aspirin.

[Slide.]

In addition, we would like to ask you to consider how the label for Aggrenox can reflect the robust superiority of Aggrenox for the endpoint of stroke.

Finally, we will show you that ESPS-2 meets the FDA requirements for a single trial to support the approvability of a product as shown on this slide.

[Slide.]

In addition, we will show that Aggrenox complies with the FDA guidance on combination products in which the sponsor must provide evidence of the contribution of each of the components.

[Slide.]

Before I now hand over to the next speaker, I would like to take a moment to mention the academic experts which are in attendance with us today. They are Dr. Donald Easton, Professor and Chairman of Neurology, Brown University, Rhode Island Hospital; Dr. David Sherman, Professor and Chief of Neurology, The University of Texas Health Science Center; Dr. Charles Hennekens, Visiting Professor at Miami and Oxford, U.K.

[Slide.]

Dr. John Pathy, Director and Emeritus Professor, Health Care Research Unit, University of Wales. Dr. Pathy also was the Chairman of the Independent Morbidity and Mortality Assessment Group of ESPS-2.

Ladies and gentlemen, unfortunately, I have to tell you that Dr. Diener from the University of Essen, who was one of the principle investigators of ESPS-2, wanted to attend but could not come because his mother had to undergo acute surgery.

[Slide.]

Following this introduction, four additional speakers will now present to you. Dr. Greg Albers of Stanford will present an overview of the current management of recurrent stroke and where Aggrenox will fit. He will be followed by Dr. Thomas Muller from Oldenburg, Germany, who will review the pharmacological and the pharmacokinetic rationale for the formulation of Aggrenox. The clinical efficacy and the clinical safety will be presented by Drs. Street and Rakowski from Boehringer Ingelheim Pharmaceuticals. I will follow with concluding remarks.

Ladies and gentlemen, I would like to conclude my introduction with my sincere appreciation to the committee for their consideration and for their advice.

Finally, I would like to introduce Dr. Greg Albers, Director of the Stanford Stroke Center, who was the lead author of the recently published American College of Chest Physicians Sixth Consensus Conference on Antithrombotic Agents in the Management of Stroke.

Dr. Albers will review the current treatment of stroke and place in perspective where Aggrenox might fit in the treatment armamentarium.

Thank you for your attention.

DR. GILMAN: Dr. Haehl, please don't leave the podium just yet. We have been joined by Drs. Houn and Temple. Could you introduce yourselves.

DR. HOUN: Florence Houn, Office of Drug Evaluation III. Thank you.

DR. TEMPLE: I am Bob Temple. I am Associate Director for Medical Policy. Thank you.

DR. GILMAN: Dr. Haehl, you mentioned a number of issues that I think, perhaps, we should ask you about at this point unless you prefer to defer to some of your colleagues. Question 1 concerns one of your slides where you described Aggrenox's proposed indication is to reduce the combined risk of death and non-fatal stroke in patients who have had transient ischemia of the brain or completed ischemic stroke.

The original protocol, as I understand the situation, specified two endpoints. One is stroke. The second is all-cause death. Then, later, a third endpoint was added, apparently, which would be the composite endpoint stroke and/or death.

What you have shown is that there is an effect upon stroke that seems beneficial to your ingredient components. But I don't believe that you have shown that, in fact, it is effective for the combined problem of stroke and/or death.

Could you address that question? It had a couple of parts. One is is this a reasonable request or reasonable indication in light of the findings, first. And, second,

can you explain the change in the endpoints?

DR. HAEHL: Dr. Gilman, you find me in a conflict now. The conflict is should I obey to your suggestion to immediately answer or should I tell you that we have prepared a presentation which will address that.

I will try to answer briefly and attend to it and then more extensively later. Yes, the primary endpoints of the study ESPS-2 were conducted in stroke endpoints and mortality. This was a European study. When we decided, because of the very, very significant and beneficial outcome of the study, that we would not want to hesitate to also propose this formulation for registration in the U.S., we had a pre-NDA meeting with the FDA.

In the flavor of also looking at the effects of aspirin where ESPS-2 has shown a major contribution of the data available for aspirin, it was agreed to also look at the endpoint combined stroke and death. Dr. Street will address this in detail.

DR. GILMAN: Is it your view that the results of this trial, ESPS-2, in fact, did show that this medication is effective in patients for the combined risk of death and non-fatal stroke?

DR. HAEHL: Our assessment is that the results obtained for ESPS-2 for this combined endpoint are absolutely consistent to prior experience which was in the

aspirin label. Therefore, we consider that as a confirmation of the database.

DR. GILMAN: Questions from the rest of the committee?

DR. DRACHMAN: I have one question. Would you say something about the most frequent cause of death, meaning those with stroke, and the relation of aspirin to heart disease, the dosage levels?

DR. HAEHL: Could you repeat precisely for me your question. Are you talking about the results of ESPS-2 and--

DR. DRACHMAN: That, or more generally, the reason for death in most people with stroke--in other words, if this formulation was designed to prevent death, then one needs to think of why those with stroke die and, given that, how this medication would relate to those known causes of death.

DR. HAEHL: I would like--Dr. Street, could you show your slide on the mortality outcome in ESPS-2?

[Slide.]

DR. HAEHL: I am showing you a slide which will come up in the later presentation and maybe will somewhat disrupt the presentation and take it out of context.

DR. GILMAN: Please answer the question, if you can, even briefly now. You can get back to it later.

DR. STREET: I believe I am not prepared with the

slide here. We have only the total mortality slide. We examined that. My presentation, that would be figure No. 24 of my slides. The primary factorial analysis is where the supportive pairwise comparisons start at 26. First maybe we should start with the slide to get a picture of the overall mortality.

[Slide.]

Here we see that there are very few little differences between the curves. This is the aspirin curve on top in yellow. The green is Aggrenox. By the end of the two years, the planned endpoint of the study, most of the curves have converged. Placebo in blue is slightly less. These amount to very few patients' deaths saved per thousand treated.

I could look those up if you wish, but approximately 10 on aspirin--13 on aspirin, 10 on Aggrenox--but very moderate-sized reductions.

DR. DRACHMAN: The question was what did they die of? What are the diagnoses leading to death? What did they die of?

DR. HAEHL: Since this is a clinical question, may I ask Dr. Hennekens to give us his perspective on that, if you permit.

DR. HENNEKENS: First, by way of background, I chaired an aspirin strategy group that petitioned the FDA

for indications for aspirin in this situation. The same issue came up with the aspirin data which related to the fact that the trials are designed to test a particular outcome and all-cause mortality is certainly not an outcome for which trials of the usual size will have adequate power, let alone cause specific mortality.

So, I think that with that as the caveat, there was no significant reduction from aspirin alone on death, but the combined endpoint of stroke plus death in patients with TIA and stroke did show a significant result, and the labeling indication was granted. So, I think that is background.

Now, with regard to the causes of death, there is a variety of causes of death that basically are a major contributor here is death from stroke, and it shows the expected reduction, however, the numbers are just insufficient on which to make a firm judgment for death alone, let alone cause specific mortality, and I think that is an important methodologic point that has to be given, yet the data are consistent with reductions in stroke deaths.

DR. GILMAN: Dr. Temple had a question.

DR. TEMPLE: Actually, I have a comment.

In devising endpoints for these intervention trials, historically, people have tried to identify cause-specific mortality, that is, the person died of a heart

attack, the person died of sudden death, the person died of a stroke, and it is treacherous business, so the advice we often give--not always accepted I should tell you--is that you should look at total mortality, and not worry too much about your ability to separate the causes of death, because it is very difficult, it is after the fact, and you often can't do it.

So, it is not uncommon in a lot of the trials we give advice about for the endpoint to be total mortality plus the event of interest, such as stroke. You know, one can even make a case for throwing MIs into that endpoint, too, because the populations get all of these things.

Overviews of aspirin data, for example, have consistently shown that people with stroke get heart attacks and stroke and die of what appear to be heart attack, stroke, and things like that, and people with heart attacks get stroke and die of heart attack, stroke, and all those things.

So, the causes of death in these atherosclerotic populations are pretty similar across the board, but the main thing I want to say is our experience has told us it is not easy to figure out the cause of death after the fact. It is very difficult. So, often total mortality is the endpoint chosen or the component chosen.

DR. GILMAN: Since we are talking about this, that

is a point, how, in fact, did the sponsor determine the cause of death. Sometimes these would happen at home, sometimes in hospital, yet, you had regular follow-up visits, how was it ascertained what the cause of death might have been in this trial.

Dr. Haehl.

DR. HAEHL: We had a morbidity and mortality assessment committee, and Professor Pathy was the chairman of this committee, and I would invite Professor Pathy to comment how the cause of death was assessed.

DR. PATHY: Thank you, Chairman.

Firstly, of course, the trialist reported back on the cause of death as he saw it, but the MMAG had to make certain clear-cut definitions to ensure consistency of reporting. Thus, anyone having an endpoint stroke is very likely to have other events, such as pneumonia, particularly aspiration pneumonia, equally somebody having a myocardial infarction is likely to have congestive heart failure.

Therefore, we made a very clear-cut decision that a patient having a stroke, an endpoint stroke and dying within 30 days of that stroke would be classified, the death would be classified as stroke, though the trialist may have written down chest infection, but we would still label it as death from stroke if it occurred within 30 days.

Similarly, if a patient died within 30 days of a

myocardial infarction, despite the fact that the trialist might label it as congestive heart failure, we would label the cause of death as a myocardial infarction.

So, we had to have long-term consistency in the trial a certain specific criteria, diagnostic criteria.

DR. GILMAN: Thank you. That does help.

Dr. Katz, did you want to comment?

DR. KATZ: I just was going to, before this last comment, reiterate that the comment that Dr. Temple gave, which is that it is true that it is difficult to ascribe any sort of a cause to mortality, and it is also true for stroke, because that is going to be an issue about stroke-related death, and it is very difficult, and the comment we just heard suggested that there were some criteria, where there were some prospective criteria, I guess there were, about what was a stroke-related death, that is arbitrary, as well, and doesn't necessarily mean that the deaths were actually related to stroke.

I think again, as Dr. Temple pointed out, I don't know how important this question is really in the overall schema. I mean we are looking over a mortality which is probably a reasonable way to look at deaths.

DR. GILMAN: Dr. Haehl, you commented when you were discussing the use of DP and aspirin in combination that you view these as mutually beneficial approaches drugs,

but you haven't commented on the rationale for the dose.

Why did you choose 25 milligrams of aspirin, 200 of DP? Did you do dose finding studies?

DR. HAEHL: I explained that from the development point of view, we chose the 25 mg b.i.d. because we expected that, first of all, 50 mg daily would completely suffice to knock out cyclooxygenase in the platelet, and that is an effect which will last for the whole lifetime of the platelets or nine days roughly, and this is an important contribute to platelet aggregation.

Secondly, we were convinced that 25 mg b.i.d. are an effective dose of aspirin, however, would minimize the risk for the aspirin-induced adverse events, and again I would like to ask Dr. Hennekens to comment and share with us his experience and his interpretation of the dose response of aspirin as to safety.

DR. HENNEKENS: In the antiplatelet trialist collaboration, we found that the benefits of aspirin were present across a wide range of doses, from about 30 to 50 mg up to really several grams a day, but the most striking finding was the difference in the side effect profile.

In addition, working with Paul Ridker, we did plated aggregability and bleeding times for a dose of 50 mg a day for the Women's Health Study of aspirin in 40,000 women funded by the NIH, which is giving 50 mg of aspirin a

day and placebo, and found that we got complete inhibition of platelet-dependent cyclooxygenase for the life of the platelet.

These data in our small pilot are consistent with the prior seminal work of Garrett Fitzgerald of Carlo Patrono and Babette Wecksler confirming that this dose will give inhibition to platelets, and also from the antiplatelet trialist data at minimal side effects, so it is an optimal dose with regard to inhibiting platelet aggregation and minimizing side effects from aspirin.

DR. GILMAN: Thank you. And dipyridamole, how did you choose the dose of dipyridamole?

DR. HAEHL: Dipyridamole, we choose with respect to its ability to inhibit adenosine uptake, and again here the rationale, where Dr. Muller will refer to and show you also slides to that, was that we wanted to obtain an 80 percent inhibition of adenosine uptake because we believed that 80 percent is a relevant inhibition which will translate into clinically important inhibition of platelet aggregation. Just to tell you that we have determined IC50 values for this mechanism, and we translated that into concentrations which we would need in plasma.

DR. GILMAN: So you did no dose finding studies then.

DR. HAEHL: For outcome studies of this type, we

did not feel the possibility to do Phase II-A type dose finding studies.

DR. GILMAN: Dr. Califf.

DR. CALIFF: I guess we are covering a lot of background things, so I will just keep going here for a little bit.

There were two questions I had that are less-- well, that I would regard as background that I would like to hear a little discussion on.

One is the use of placebo. How is the use of placebo justified in light of all the other data about the efficacy of aspirin for patients with vascular disease?

Secondly, in the population data at least that I saw, there is really a very homogeneous cultural ethnic background of the population, and would you propose that extend the findings to all races and ethnic backgrounds based on these data?

DR. HAEHL: The ESPS-2 was a study which was performed all over Europe, and coming from Europe, I would consider that Europe is a relatively large pool, genetic pool, and it covered all ethnic groups of Europe.

However, clearly, we don't have information on ethnic groups, especially specific to America or the United States, so we certainly do not have included African-Americans in this study.

From the preclinical data, from pharmacokinetic data which we have, and from based on the pharmacologic mechanisms, we do not believe--and I underline we do not believe--that there is an important difference in the clinic between ethnic groups, but specifically for those in America, we have not investigated that.

Again, I would like to ask one of our clinician advisers, Dr. Albers maybe, whether he could comment on his interpretation of differences both in the treatment of stroke and also in the ethnic differences and the effects of Aggrenox between the two continents.

DR. ALBERS: I don't think we have data from any of the antiplatelet stroke prevention trials to suggest that there is a different response between different ethnic populations. One of the issues with ethnic compilations that some of them have more risk factors, and we have evidence from the ESPS-2 trial that patients with risk factors, particularly hypertension, diabetes, did appear to respond in a similar manner. I think that is as close as we are going to be able to come to extrapolating and saying that we don't have anything specific that would indicate that different populations would be expected to respond differently, although, as mentioned, there is no specific data in African-Americans.

DR. HAEHL: I didn't answer your first question as

to placebo, the use of placebo. May I have a slide.

[Slide.]

I think we have to separate between our today's point of view and the point of view when the study was initiated. That holds true for the inclusion of placebo. It also holds true for several other aspects of the methodology of clinical trials.

The placebo was included because of, at that time, conflicting results from previous stroke trials. The placebo comparison was perceived to be necessary to assess the potential benefits of low-dose aspirin at that time, and at the beginning of the trial, all 60 independent ethical review committees agreed that the use of placebo was appropriate, as did the Central Ethics Review Committee, and as did, of course, all the participating investigators.

It is clearly an issue from today's point of view and especially with the results of ESPS-2 in hands, we would never suggest to do again a placebo-controlled trial, but that is the development of knowledge and experience.

DR. GILMAN: Thank you.

Dr. Katz.

DR. KATZ: A couple of questions. About the statement that there were no evidence that there were racial differences in response, has that been actually investigated, or has that question really not just been

examined adequately?

DR. ALBERS: It is extremely difficult to examine because of the sample sizes needed to show a benefit of an antiplatelet agent for stroke prevention. You generally need studies of several thousand patients in the trial minimum to show a benefit.

So, conceiving of doing a trial where you are going to have that appropriate power in individual racial groups, that hasn't been done, although currently there is an ongoing study that is looking just at African-Americans with two different antiplatelet agents.

But the point that I was making is within the limitations of the study, which clearly are underpowered limitations, no obvious differences have been noted in terms of one racial group responding differently to an antiplatelet agent than another.

DR. KATZ: Let me just ask you, I don't know those data, the representation, the degree of representation, let's say, of African-American patients is presumably quite small. I mean it is one thing to say within the limits of the data there is no obvious difference, but if the data are so limited, it's hard to say anything about it presumably, so I mean are they that limited?

DR. ALBERS: In most of the stroke prevention trials, specifically African-Americans have been very

limited. I think that was one of the rationale for the NIH to fund a specific trial looking just at African-Americans.

DR. KATZ: What about in-vitro work and the effect on cyclooxygenase activity or whatever else you look at with these agents, using platelets from African-Americans, has that been looked at?

DR. ALBERS: I don't have any data on that. I don't know if any of the other experts know of any specific studies that have looked at that issue.

DR. HAEHL: We have information that pharmacokinetically, it behaves--dipyridamole behaves in the same way in whites and in African-Americans.

DR. KATZ: Kinetically, but not necessarily mechanistically?

DR. HAEHL: I am not aware that we have investigated platelets of different ethnic origin.

DR. KATZ: I just had another question earlier about the dose response.

DR. HAEHL: To the question under discussion, Dr. Gilman, Dr. Hennekens would want to comment.

DR. GILMAN: Yes, please.

DR. HENNEKENS: I wanted to emphasize Dr. Albers' important point. It is true that there is a difference in the rates of these diseases that are occurring by ethnic group, but the question is do we have a priori any reason to

suspect that there is a difference in the relationship of the agent to the disease, not the disease incidence itself.

My own view of this is I feel that a study that includes 5 percent or even 10 percent of African-Americans is potentially more damaging than one that excludes them completely. If you want to get the answer, you must have a sufficient number of people to answer that question definitively, and the inclusion of 5 percent or 10 percent is not going to answer that question.

I think it may be politically correct, but I think it is scientifically incorrect. I think the way to do the study is the way the NIH is doing it in that population to get a reliable answer to that question.

DR. KATZ: I don't disagree. I am just trying to make, to sort of bring out the point that there really is not very much known about the effects in that population, and if the intention is to rely on one trial done not in this country, these are issues that I think are worth thinking about.

The question I had also, if I could, about dose response in aspirin and the choice of the dose, are there any trials that look directly, compare directly within one trial, various doses of aspirin, and has a dose response been shown in those?

Just the other half of that question is what about

the side effect. You say there is a dose response with side effect, but what does that look like? I mean where does that start, where does the dose of aspirin start to be a problem?

DR. ALBERS: In terms of the efficacy comparison, there are three trials that have given head-to-head comparisons of aspirin dose. There was a Dutch TIA trial, which was a large study, looking at a 30-mg dose versus about a 300-mg dose, showing no difference.

There was a trial in the UK that looked at about a 300 mg dose versus a dose close to 1,000 mg, so medium versus high dose, and showed no difference in efficacy, and then I will show you some data in a few minutes about a more recent study that looked at carotid endarterectomy patients and compared low doses to high doses, and actually showed benefit of low doses over high doses.

Do you want to comment further about the side effect profile?

DR. HAEHL: Dr. Albers, I would just put up a slide in support of your--so that is the summary on a slide for the different doses in terms of efficacy for doses from 100 mg up to 900 mg.

DR. HENNEKENS: With regard to the side effects issue, in the UK TIA trial, approximately 800 patients were randomized to placebo to 300 mg a day or 1,200 mg a day.

With regard to GI side effects, the rates were 24 percent in the placebo group, 29 percent in the low-dose aspirin group of 300 a day, and 39 percent in the 1,000 mg a day.

Now, if one looks at those differences, they are statistically significantly different, not just between the high dose and placebo, but between the high dose and low dose, and the low dose was closer to the placebo in frequency than it is to the high dose.

With regard to GI bleeding, it was 1.6 percent in placebo, 2.6 percent in the low dose, and 4.9 percent in the high dose. Furthermore, in the antiplatelet trial--those are direct comparisons--the indirect comparisons in the antiplatelet trial as collaborations show that the lower doses were associated with even fewer side effects, and also that 30 to 50 mg is enough to maximally inhibit platelet-dependent cyclooxygenase for the life of the platelet.

So, I think there are compelling reasons for this dose with regard to efficacy and with regard to safety, as well.

DR. GILMAN: Dr. Drachman and then Dr. Penn.

DR. DRACHMAN: I am a little puzzled. If 50 mg totally suppresses cyclooxygenase, what is the basis of more bleeding with larger doses? What are the other effects of aspirin on bleeding tendency?

DR. HENNEKENS: There is evidence there are direct

toxic effects of the aspirin, for example, in the stomach, and that is also related to the dose, so that we have--

DR. DRACHMAN: On bleeding effects.

DR. HENNEKENS: Yes, on bleeding, yes.

DR. GILMAN: Do you want to address that question? Go ahead, Bob.

DR. TEMPLE: If you do endoscopy studies with NSAIDs and aspirin, you find local punctate ulcerations and things like that, so they have direct effects in addition to the effect on bleeding. I doubt 300 mg once a day has a major effect of that kind, but at 1,200 or so, you definitely can get that.

DR. GILMAN: Let's stay on this issue. Dr. Califf.

DR. CALIFF: I am buying the argument related to platelet function and cyclooxygenase, but I mean there are major questions about how aspirin works in the first place now with the evidence of the role of inflammation, and I don't know if we have similar kind of data about inflammation, so I am very skeptical of relying on some sort of biological measurement to tell us what the right dose of aspirin is in the first place.

DR. GILMAN: Another issue. Dr. Penn.

DR. PENN: Yes, I just want to make sure that I understand the data on myocardial infarction and aspirin

dose. Is there a relationship between aspirin dose and myocardial infarction and death or is it just a trend as is indicated here?

DR. HAEHL: In ESPS-2, we have no significant result for the reduction of myocardial infarction, and we believe that that is also what you would not expect in a population with prior stroke or TIA. That would not be the population where you would investigate the efficacy in preventing myocardial infarction.

DR. PENN: My question is, is there going to be a different dose of aspirin recommended for myocardial infarction than the dose that we are now suggesting that you give for stroke.

DR. HAEHL: On behalf of Aggrenox, I can only suggest the dose of 50 mg for stroke prevention. I have to forward the question as to the most adequate dose for the prevention of myocardial infarction to the clinical experts.

DR. HENNEKENS: Just as Dr. Albers participated with the American College of Chest Physicians, I, with Phal Fuster and Mark Cyken, wrote the AHA guidelines for aspirin and the citizens' petitions to the FDA.

Our view of the totality of evidence indicates that a dose of 50 mg a day is sufficient, and in the absence of any acute symptoms, whether or not you survived a prior heart attack, a prior occlusive stroke, a prior TIA, have

chronic stable or unstable angina, a bypass or an angioplasty, that 50 mg of aspirin a day will suffice to maximally inhibit platelets, give the clinically beneficial effect, and minimize the side effects.

The place where the issue is different is if you are having an acute occlusive event, then, Fitzgerald has shown in healthy volunteers, as well as those with unstable angina, that while this dose is sufficient to get that effect, it takes about two days to occur from the time you start the first dose.

Therefore, you need a dose of at least 162.5, as was used in IC, 325 in GC, so for acute occlusive events, a dose of aspirin of about 325 in a regular aspirin is optimal to get a rapid clinical antithrombotic effect, whereas, for the prevention of occlusive events, the 50 mg dose, possibly with an enteric coat, might minimize the side effects even further.

So, for the vast majority of people who are treated with aspirin for the long term, 50 mg enteric is sufficient. When you are having an occlusive event, regardless of the vascular bed, I think a 325 dose of regular aspirin is imperative, and if the patient can't swallow it, to at least dissolve it under the tongue.

DR. GILMAN: Dr. Konstam.

DR. KONSTAM: Dr. Hennekens, I am getting more

confused, because I follow what you are saying, but I am having trouble following how much of it is on the basis of physiologic information and how much of it is on the basis of clinical data.

So, if I am not mistaken, the doses of aspirin approved are down to 75 mg a day. Is that not right?

DR. TEMPLE: They vary by indication. I mean in the monograph, we are very empirical. If 300 is what has been studied, that is sort of what the claim gets even though everybody believes, just the way Charley does, that 75 is probably enough.

Now, Rob just suggested, well, maybe you shouldn't believe that and you should stick with empiricism.

DR. KONSTAM: I just want to know what the data are. Can you just stick to the clinical trial data supporting the 50 mg dose?

DR. HENNEKENS: Well, the data that have been studied go as low as 30 mg on clinical endpoints and show clinical benefits, and I think that--you know, I take your point. When we were designing the Women's Health Study and had it funded by NHLBI, Dr. Lenfant created another expert advisory committee that had us kick out the 325 every other day dose, because as Dr. Temple said, that was the dose we had shown in the Physician Study to be beneficial on acute MI. We wanted to make sure to have that dose and frequency

studied, and the expert committee was so convinced both on clinical data and on some of the biochemical correlates that they asked us to kick out the 325 every other day.

So, we are study 50 mg versus placebo in 40,000 women in prevention. But the totality of evidence on this question includes not just basic research and clinical studies, but there are clinical trial suggesting that the lower doses will give net clinical benefits, as well.

The question in my mind, frankly, as a scientist, is whether higher doses, which might also potentially have antiatherogenic effects while having more side effects that we know might have greater benefits. That has never been tested in direct head-to-head comparison.

DR. KONSTAM: Just to follow up, I mean I think these points are all very well taken, we don't know what the ideal dose is. There is a lot of reason to believe that lower doses may be beneficial, and you have made those points eloquently.

I guess this question arose--and I think it is important--is that what are we going to be recommending for the atherosclerotic population, and here, we are going to wind up focusing on patients with past TIAs and strokes, but there are broad questions here.

So, the question is what is the recommendation for aspirin going to be in that, and that is going to wind up

being on the basis of clinical trial data.

DR. HENNEKENS: Well, the FDA--and I agree with their recommendations--have recommended 50 to 325 based on the range of low doses that have shown clinical benefits in trials, and I agree with that.

What I am saying further is that especially when you are looking at a combined preparation with another mechanism of action, you want to minimize the side effects from this one component.

So, I think that from a purely scientific basis--and I wasn't asked about this until a week ago--but if I had been, I would have suggested 50 mg of aspirin as the component in Aggrenox. I think it is the wisest scientifically with regard to maximizing benefits and minimizing side effects, and that is all I can say about it.

DR. GILMAN: To go back to a comment that Dr. Haehl made, in fact, this would be the very population that you would be concerned about myocardial infarction, and these are people who have had stroke or TIA, and they are at risk for myocardial infarction.

DR. HENNEKENS: Yes, I think that is an excellent point, and these are people that this dose of aspirin should from the totality of evidence, not from ESPS-2, but from the totality of evidence from the antiplatelets trial is give benefits without side effects.

Furthermore, as has been asked by the other panelists, if this patient then, nonetheless, despite being on this prophylactic dose to prevent stroke and death, does exhibit symptoms of MI, that person should have a 325 mg of aspirin within 24 hours of onset of those symptoms.

DR. GILMAN: Well, that still raises the question about the wisdom of 50 mg of aspirin in people who are at risk for myocardial infarction.

DR. HENNEKENS: Well, perhaps I am not understanding the controversy here, because for the long term prophylaxis, you want to get the benefits with minimal side effects, and frankly, although we test at 325 every other day, 325 now, in 1999, is a dose that will show a benefit, but will also have a side effect profile that is higher than the 50 mg.

So, to keep this person for long-term prophylaxis, both prevented with regard to occlusive complications with minimal side effects, I think the 50 mg dose is optimal. If that person, despite this prevention, does develop acute symptoms, then, a high dose then would be necessary to get the maximal protection over that acute event, but for the chronic prophylaxis, it is the low dose that gives the benefits with minimal side effects in my view.

DR. GILMAN: Thank you.

Yes, Dr. Lacey.

DR. LACEY: I have a question which is on something that was presented a little bit earlier. On addressing the issue of the percentage of African-Americans in a study, the statement was made that 5 to 10 percent inclusion would be more damaging than exclusion, I would like to ask if that is without regard to the size of the study or did you mean related to this intended population of 7,000.

DR. HENNEKENS: I will give you an example. In the 1980s, the FDA prescription-labeled aspirin for the treatment of TIAs in men, but not in women, and it was based on a totality of evidence that was driven by a Canadian study that had a number of women that, in my view, was inadequate to answer the question in women, let alone answer the question whether women were significantly different from men.

So, from 1980 to 1998, we said TIAs could be treated with aspirin in men, but not women. Then, when a sufficient totality of evidence emerged from numerous trials that studied women, it was clear that the benefit in women was exactly the same as the benefit in men.

So, what I am saying generically is that I would favor a study in African-Americans that can answer the question definitively in African-Americans, and if I wanted to test whether African-Americans were different from non-

African-Americans, I would power my sample size overall to answer the overall question, and I would want 50 percent of that population to be African-American compared with the comparison group to get the most powerful test.

When you have small numbers, I think there is so much variability in the numbers of endpoints and in the data that you might not get the right answer, and I am concerned that a lot of treatment decisions are being made based on the inclusion of 5, 10, 15 percent of a population in an overall study that simply can't with assurance answer that question. It is a methodologic concern.

DR. LACEY: But I am still not clear. Are you saying that regardless of the study, 5 to 10 percent would always be unmeaningful and significant?

DR. HENNEKENS: No. What I am saying is that if a study is powered to get an overall result, and with 10 percent of that total sample can be shown to give not just a significant result in that subset, but a significantly different result if one exists between that subset and the rest of the population, then, I am satisfied.

In my experience, that hardly ever occurs by the inclusion of 10 percent of anything in a study the way they are designed.

DR. LACEY: But conceivably if the study were large enough, 5 to 10 percent--

DR. HENNEKENS: If it were, but if I really wanted to answer the question about whether African-Americans were different from non-, I would do a 50-50 split.

DR. GILMAN: Dr. Califf.

DR. CALIFF: I don't want to belabor this now, but I think it will be important to come back to this issue later because for those designing studies that will come before panels in the future, this is a very important question, and I share Dr. Hennekens' frustration with the way things have been done in the past, but I am not sure of what the guidance ought to be. I think it will be worth discussing later.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Well, I don't really want to beat this to death, but--but most of my patients with strokes and TIAs are hypertensive diabetics who have had one MI. What are we to do? And, furthermore, we learned, right or wrong, that the most common cause of death with stroke is MI.

Would you recommend that my patient with an MI, with an old MI and with a new TIA or stroke be put on this drug and aspirin, or what do we do?

DR. HAEHL: If you allow, Dr. Easton would like to answer that question.

DR. EASTON: Well, I am here today on behalf of stroke prevention. I was here for ticlopidine, I was here

for clopidogrel, I am here for this.

I think Dr. Drachman's question is germane and let me give you the numbers since we don't seem to have it on a slide, just so we know what it was in ESPS-2.

It turns out that there were 757 deaths, and of those, 176 were due to stroke. The next largest group was 143 due to infection, and we heard what the issues might be around that, how many of those were actually stroke.

The next largest group is sudden death, and there were 69 myocardial infarctions as compared to the 176 strokes.

DR. KONSTAM: Sudden death?

DR. EASTON: I am sorry, sudden death was 107.

DR. KONSTAM: 107 sudden deaths and 69 MIs.

DR. EASTON: That is correct. And then we have heard previously about how likely they are to reflect what actually happened to the patient, as I think Dr. Katz pointed out.

Those are the large ones, and then there are a smattering of other issues in the tables here, if you would like me to leave it with you just to look at in this trial.

DR. GILMAN: Thank you.

Dr. Haehl, thank you for your forbearance. You have answered a number of questions that were pressing us.

So, shall we move on to Dr. Albers?

DR. HAEHL: Yes. Thank you very much.

Clinical Overview

DR. ALBERS: Good morning.

[Slide.]

Stroke occurs when there is an abrupt disruption of the blood flow to the brain that is severe enough to cause brain injury that will give lasting neurologic deficits.

Most strokes are due to blood vessel occlusions, but about 15 percent are due to ruptures of blood vessels, and this can either be within the parenchyma of the brain or in the subarachnoid space surrounding the brain. We are going to ignore those and focus on the 85 percent of strokes are ischemic or due to blood occlusions.

These occlusions typically occur because of atherosclerosis involving either the cervical or the intracranial vessels, and atherosclerosis can cause embolic or thrombotic occlusion of the vessels because of aggregates of platelets, fibrin, and debris from these atherosclerotic plaques.

[Slide.]

Here is the diagram that shows the most common causes of ischemic stroke. About 15 percent of ischemic strokes are due to emboli from the heart. Cardiac emboli that typically occur because of atrial fibrillation, heart

valve disease, or myocardial infarction can lead to clots that break loose and travel to the brain, but most strokes, as mentioned, are due to atherosclerosis either of the aorta, the cervical vessels, or the large or small intracranial vessels.

This atherosclerosis can cause flow-limiting reductions, but more commonly it causes artery to artery emboli from the atherosclerotic plaques.

[Slide.]

A TIA has a very similar pathology to a stroke. With a TIA there is a transient occlusion of an intracranial artery that is severe enough to cause focal neurologic symptoms, but these symptoms resolve rapidly because of fragmentation and dissolution of microemboli or thrombi.

TIAs typically last about 10 to 20 minutes. It is very unusual for a TIA to last longer than an hour.

[Slide.]

Stroke, as you know, is a very devastating disease. It is the leading cause of long-term disability worldwide, and it is the third leading cause of death in the United States. If you look on neurology wards, more than half of the beds are filled with stroke patients.

[Slide.]

Stroke is increasing in incidence. The current estimates from the American Heart Association are that there

are about 730,000 strokes occurring in the United States each year, but most patients from stroke, as we have already mentioned, don't die.

Only about 150,000 of those patients die, which leaves a large number of patients living with neurologic deficits due to stroke, and the current estimates are that there are 4 million Americans living with stroke-related disabilities, and since the population is rapidly aging, the prediction is the incidence of stroke is going to go up considerably in the next couple of decades.

[Slide.]

The economic burden of stroke is also very frightening. Current estimates are that the total cost of stroke in the United States is over $40 billion each year, and this breaks down to a per-event cost of about $60,000 per stroke. This can be divided into the direct costs, which involved the care and treatment of the patient, and that is about $40,000 a case, as well as the indirect costs including lost productivity of about $20,000 per stroke. So, it is a phenomenally expensive disease.

[Slide.]

As we have been talking about, the major threat to the stroke patient, particularly in the short term, over the first few years, is not having a myocardial infarction or a vascular death. The major threat, by far and away, is that

they are going to have a recurrent stroke.

Some studies have shown that recurrent strokes are 10 times more likely than a myocardial infarction during the first few years after having a stroke. Later on, they often die of a myocardial infarction or another vascular death, but the key early problem that a stroke patient faces is that they are going to have another stroke and be living with disability from two strokes.

Fortunately, there has been a lot of progress in stroke prevention for patients who have had a recent stroke or TIA. Over the last decade, we have had a lot of progress specifically, carotid endarterectomy has shown to be highly beneficial for patients who have a stenosis of greater than 70 percent which has caused a stroke or a TIA, and recent data suggest that even patients in the 50 to 70 percent stenosis range can benefit if they are properly selected for surgery.

Also, patients with cardioemboli as the source of their stroke, such as atrial fibrillation, can have dramatic reductions in stroke risk with oral anticoagulation therapy, but unfortunately, these two categories, high-grade carotid stenosis and cardiac emboli, only account for a minority of strokes. Most strokes are due to atherosclerosis that is not appropriate for endarterectomy, and for these patients, antiplatelet agents are the treatment of choice, so we are

going to focus on those.

[Slide.]

We now have four different antiplatelet agents that have been shown to be effective for preventing stroke in patients who have a TIA or an ischemic stroke. These include aspirin, ticlopidine, clopidogrel, and dipyridamole particularly when it is combined with aspirin.

[Slide.]

Now, I want to look at a little bit of the data regarding the efficacy of antiplatelet agents for preventing the combined outcome of stroke, MI, and vascular death in patients of different types. This data comes from the Antiplatelet Trialists Collaboration last published in 1994.

What this group did was they looked at a large number of studies, over 140 studies, that took patients with a wide variety of different vascular diseases - myocardial infarction, stroke, peripheral arterial disease. They combined these mixed vascular disease populations together and looked at the efficacy of all antiplatelet agents compared with placebo for preventing this combined vascular outcome.

What they reported was an odds reduction of a 27 percent, which translates to a relative risk reduction of 22 percent for preventing all these events in a mixed population with a mixed population of antiplatelet agents.

Now, what we are interested in are the stroke and TIA patients, and among these studies there were 18 studies that specifically looked at patients with stroke or TIA, and if you look at all antiplatelet agents in these patients, the benefit appears to be a little bit less, specifically, a 22 percent odds reduction or a 17 percent relative risk reduction.

A little more concerning is that when we look at the 10 trials that looked at stroke or TIA patients and evaluated aspirin versus placebo, the relative risk reductions are even more modest, 13 percent relative risk reduction or a 16 percent odds reduction.

DR. GILMAN: What is the confidence interval of the odds reduction, is that 95 percent?

DR. ALBERS: I don't have the confidence intervals on this study. The confidence intervals for this 144 are really quite small. I am going to show you the confidence intervals in just a moment for the specific stroke or TIA trials.

So, one of the questions is why are relative risk reductions lower than odds reductions, and that is because they are calculated differently, and we can talk about that later if there is interest. But you can see that the interpretation of the data can be quite different if you are thinking of a 27 percent reduction versus a 13 percent

reduction.

So, let's look now at the stroke and TIA patients specifically.

[Slide.]

Here are the patients with stroke or TIA who were randomized to an antiplatelet agent versus placebo, and as I reported for aspirin, there was a 13 percent relative risk reduction and for all antiplatelet agents combined there is a 17 percent relative risk reduction.

The reason for the difference is that there are two antiplatelet agents that appeared to be more effective, and that would be ticlopidine and a combination of dipyridamole and aspirin. So, that is why we see the difference between the 13 and the 17. Then, one of the concerns would be the dose which we have been discussing.

DR. GILMAN: That is just the question. So, aspirin, all doses. How about specific doses though?

DR. ALBERS: That is this slide.

[Slide.]

This is a meta-analysis that was performed based on the data from the Antiplatelet Trialist, and here we have the relative risk reductions with the 95 percent confidence intervals, and it is broken into three groups: studies that looked at low doses, less than 100 mg/day; medium dose 300 mg/day, and then the high doses 900 mg or more. These are

the placebo-controlled studies.

Here you can see the point estimates for relative risk: 13, 9, and 14, and now you can see the 95 percent confidence intervals to get a feeling for what kind of differences we have, and then when you combine the all together, you have a 13 percent relative risk, obviously, with narrower confidence intervals.

So, there does not appear from the available data to be a relationship between aspirin dose and benefit for preventing this combined endpoint.

[Slide.]

Now, as I also mentioned earlier, there were three head-to-head comparisons.

DR. GILMAN: What about the 9 percent for 300 mg?

DR. ALBERS: Right. That comes from one study, which was the UK TIA trial, and you can see that this one study in and of itself did not show a statistically significant benefit of 300 versus placebo. That is the only study we have that compares 300 versus placebo.

Then, we have the Dutch TIA trial, a very large study that compared 300 versus 30, a head-to-head comparison there, which showed no difference in the efficacy between 300 and 30, and then there was the study, the UK TIA that compared this 300 to about 1,000 mg of aspirin. Again, there was no difference in the efficacy of the head-to-head

comparison.

[Slide.]

Now, there is one new study that has just come out recently which was a direct comparison of high-dose aspirin versus low dose, and this is in a specific patient population. These are patients who have had a carotid endarterectomy. So, it is looking at preventing stroke, MI, and vascular death over the short term in a patient who has just undergone a carotid endarterectomy. This data have just been presented recently. It is called the ACE trial.

It is a large trial, you can see about 1,500 patients per group, and they were randomized to low-dose aspirin which was either 81 or 325 mg of aspirin, or high dose, and the high dose was either 650 or 1,300 mg of aspirin.

Here you can see the results. At three months, the rate of stroke, MI, or death was 6.2 percent in the low dose and 8.4 percent in the high dose, which was a statistically significant benefit favoring the efficacy of low dose over high dose.

So, the previous low dose/high dose comparisons had shown no difference. In the special circumstance, carotid endarterectomy, short-term follow-up, we see a statistically significant difference favoring the low dose being more effective for preventing these vascular events.

DR. GILMAN: These comments have not dealt with very low dose, such as 50 mg aspirin, though.

DR. ALBERS: The 50 mg, the main effect here against placebo was the SALT trial, which was a 75 mg versus placebo. The main data for the 50 mg against placebo will be the ESPS-2 data, and the relative risk reduction seen with the 50 mg is certainly in the ballpark, if not greater, than the reductions that we are talking about here in the SALT trial, at 75, or these other trials at higher dose.

Then, we had the 30 versus 300 from the Dutch TIA.

DR. GILMAN: Dr. Katz first. Dr. Drachman next.

DR. KATZ: Just a quick question about the Dutch study, the 300 versus the 30. How big a trial was that, and were there numerical differences, you know, sort of a trend in favor of one dose or another?

DR. ALBERS: It was a very large trial, it was over 3,000 patients. Somebody might be able to help me. There was not a trend. It was very comparable. If somebody has the exact numbers?

DR. EASTON: Five percent better in the 30 mg as compared to the--

DR. ALBERS: So, we are hearing 5 percent better in the low dose.

DR. GILMAN: Please use the microphone and repeat what you just said.

DR. EASTON: I will check to confirm this, but with respect to the trend, I believe it was about 5 percent risk reduction favoring the 30 mg dose.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Would you go back one slide. There, is it true that neither of the lower doses quite reached significance, since they overlap zero, is that right or not?

DR. ALBERS: Yes, that is correct. I suspect if you add in the ESPS-2 to this--this was a meta-analysis performed before ESPS-2 was available, and certainly the 50 mg versus placebo had a very statistically significant benefit in ESPS-2, so I would be--I don't know if somebody has done this already, but since it comes very close to meeting statistical significance without ESPS-2, and ESPS-2 being a very large trial, I think it is highly likely that this is now a statistically significant effect if you take all the low dose versus placebo data in stroke or TIA patients.

DR. GILMAN: Dr. Kawas.

DR. KAWAS: I would like some clarification on the next slide actually.

In the low-dose group, can you separate out the two low doses? I mean one of them is not so low, and is that really what is generating the effect of 325?

[Slide.]

DR. ALBERS: There is a number of different analyses that have been done on this, and a study has not been published in full. I understand that for some of the analyses, the 81 looked better, and that other of the analyses, the 325 may have looked a little bit better in terms of trends, but there was not a clear difference, there was not a clear difference saying that one dose was better than the other there.

DR. KAWAS: What was the relative proportion of the two doses in that group that you pooled?

DR. ALBERS: Fifty-fifty.

[Slide.]

So, as already stated, based on the information that we have been discussing in detail, about six months ago the FDA revised the guidelines, and just quoting from the Federal Register, what they now say is that the "positive findings at lower dosages are sufficient reason to lower the dosage of aspirin for subjects with TIA and ischemic stroke."

For ischemic stroke and TIA, 50 to 325 mg aspirin once a day is currently the recommended dose. The drug should be continued indefinitely.

[Slide.]

Other professional groups have also joined this

low dose recommendation. I was part of the American College of Chest Physicians group, and we put out a recommendation that was published essentially simultaneously with the FDA guidelines coming up with the same recommendation, 50 to 325 mg per day for stroke or TIA patients, and the American Heart Association is in the midst of revising their guidelines. The proposed dose that is being finalized right now is the 50 to 325 mg dose, as well.

[Slide.]

Now, there are two other alternative antiplatelet agents that are approved for use in stroke or TIA patients for preventing stroke, and ticlopidine was the first one to be approved, and this drug has some advantages.

It was studied in two large trials. The first was a trial against placebo, looking at patients with completed stroke, ticlopidine versus placebo, a study called CATS. Ticlopidine was found to be statistically significantly more effective than placebo in preventing stroke or stroke and death.

It also was tested against aspirin, and this was the TASS study, another large study comparing patients who had had this time TIA or a recent stroke, ticlopidine versus aspirin, and it was a high dose aspirin that was chosen in the TASS study. Again, ticlopidine was shown to be more effective than aspirin for preventing stroke or stroke and

death.

The disadvantages of ticlopidine are the neutropenia. There is about a 1 percent incidence of neutropenia, which can be very severe, but fortunately, reversible. A little more concerning is the rare side effect which is not always predictable and not always reversible, which is TTP, thrombotic thrombocytopenic purpura, which carries a very high morbidity and mortality.

Because of these hemologic side effects, CBC monitoring is required with this drug, at least six CBCs during the first three months of therapy, and there is also some nuisance side effects that occur at relatively high frequencies, diarrhea and rash. Five to 20 percent of patients will have these type of side effects from ticlopidine.

[Slide.]

Now, there is a related agent which is also approved, clopidogrel, similar to ticlopidine, but it has some substantial advantages in terms of the adverse effect profile. It is much better tolerated than ticlopidine. There has not been a placebo with neutropenia or TTP with this agent, so no hemologic monitoring is required.

The drug has proven efficacy. It was compared in a huge trial against aspirin, the CAPRIE trial, which enrolled patients with stroke, myocardial infarction, or

peripheral arterial disease, and in that combined group of patients, looking at the combined endpoint of stroke, MI, and vascular death, clopidogrel was more effective than aspirin.

Disadvantages of clopidogrel are that it has not yet been tested in a TIA population, so we have no data about clopidogrel in TIA patients, and then although the CAPRIE trial was not powered to look at the individual subgroups, stroke/MI, there were over 6,000 stroke patients and over 6,000 MI patients in the CAPRIE trial, and if you look at those patients as individual subgroups, there was not a statistically significant benefit of clopidogrel over aspirin in those 6,000 patient subgroups.

[Slide.]

Now, this is a slide that needs to be interpreted with great caution. It is a figure that we put together when we made the ACCP guidelines for stroke prevention. What it is an attempt to do is give a general feel for the efficacy data that have emerged from these three alternative antiplatelet agents, ticlopidine, clopidogrel, and dipyridamole-aspirin combination.

It is important to note that there are no head-to-head comparisons. We have no head-to-head comparison of any of these alternative agents one versus the other. We only have comparisons with aspirin. In fact, for each of these

alternative agents, there is one single trial that had TIA and stroke patients and compared the alternative agent head to head with aspirin.

So, for clopidogrel, it is the CAPRIE trial, and here we are looking at just the subgroup of patients who got into CAPRIE because of a stroke. So, that is 6,431 patients. For ticlopidine, there was the TASS trial, and that was 3,000 patients, and then ESPS-2, if we look at the combination versus the aspirin-alone arm, that is about 3,299 patients.

DR. GILMAN: Well, as you say, that really should not be shown here because you have not done head-to-head comparison with these other drugs.

DR. ALBERS: Okay. What this is just an attempt to do is show you what the risk reductions were in these trials.

DR. GILMAN: But they are not comparable.

DR. ALBERS: The trials--and that is a very good point, that is why I said this needs to be interpreted with great caution because these are different trials, they had slightly different inclusion and exclusion criteria. They had different doses of aspirin. They are different studies. So, this is not an attempt at all to say that these are direct comparisons. This is just an attempt to summarize the data for common endpoints that were available from these

trials.

So if you are looking at the endpoint of stroke from these three trials, then, what you can see is that in the stroke subgroup of CAPRIE, there was an 8 percent relative risk reduction over aspirin. Clopidogrel over aspirin was 8 percent.

From the TASS study, ticlopidine over aspirin was 21 percent, the ESPS-2 it was 23 percent.

The numbers for stroke, MI, and vascular death, just to show the results of the trials, are for clopidogrel 7 percent, ticlopidine 9 percent, and then the combination in the 22 percent range.

So, these are the available data, and unfortunately, it is unlikely that we will have head-to-head comparisons between these agents. So, these are the numbers that we have available, but I certainly want to emphasize that these are not--

DR. KONSTAM: What was the dose of aspirin in the CAPRIE trial?

DR. ALBERS: These all have different doses of aspirin. The CAPRIE trial had 325 mg of aspirin.

DR. GILMAN: The question was what was the dose of aspirin in the CAPRIE trial.

DR. ALBERS: CAPRIE. Ticlopidine was high dose aspirin, and then the dipyridamole/aspirin obviously was the

low dose we have been discussing.

DR. KONSTAM: So, in other words, these really are not comparable.

DR. GILMAN: These are not comparable in any way. I am not sure why you are showing these data.

DR. ALBERS: Okay. I am showing the data because these are the three agents that clinicians are faced with in terms of stroke prevention, and a very frequent question that neurologists ask is what were the efficacy of these agents in the trials that they were evaluated. Of course, they have not been evaluated in head-to-head comparisons, so we have no way of comparing the efficacy between these agents. We only have the comparator of aspirin in there different trials with three separate patient populations that were enrolled.

DR. GILMAN: And different doses of aspirin.

DR. ALBERS: And different doses of aspirin if you think that that is an important issue, yes.

DR. GILMAN: Well, that is a question.

DR. CALIFF: You have got me a little revved up here. Just because some neurologists ask stupid questions is not a reason to show the data at a meeting like this, and we will come back to this later.

DR. ALBERS: Whether it is a stupid question or not, I think is another issue. You know, we have choices to

make.

DR. CALIFF: You are saying it is intelligent to do indirect comparisons and put things on a slide that lead people to create images in their mind that are not scientifically comparable.

DR. ALBERS: I think the practical issue is that we have several antiplatelet agents that are available, and from the point of view of the clinician, one needs to try to balance what the perceived efficacy of these agents are, what the perceived side effects are, and what the cost of these agents are.

DR. GILMAN: The clinicians can think for themselves, and by showing these data, it gives the impression of a direct comparison, which is false, it is just not valid.

DR. ALBERS: Okay. We will finish up with the ACCP guidelines.

[Slide.]

The guidelines that were currently agreed upon by the ACCP is that every patient who has had a non-cardioembolic stroke or TIA should be taking an antiplatelet agent daily. It was a very straightforward, high-grade recommendation.

We also felt that aspirin, clopidogrel, ticlopidine, and the combination of aspirin and dipyridamole

had all been shown to be effective for preventing stroke and that they were all acceptable options for initial therapy, and as we have clearly pointed out here, we have no direct comparisons to help determine the absolute efficacy differences.

However, we did have fairly clear safety, we felt, in looking at the ticlopidine side effect profile versus the clopidogrel side effect profile. Even without head-to-head comparison, the incidence of adverse events were so dramatically different between those two agents that we made the recommendation that we would favor clopidogrel over ticlopidine because of that adverse event profile.

Finally, we mentioned--and, again, no specific head-to-head comparison, so nothing that can draw any firm conclusion, but the combination of aspirin and dipyridamole may be more effective than clopidogrel and has a similar favorable adverse event profile.

[Slide.]

So, in summary, you can say that antiplatelet agents are effective in the secondary prevention of nonfatal stroke and death.

The currently approved antiplatelet regimens provide a relatively modest risk reduction.

The hope is that more effective and safer treatments to prevent stroke will be available on the

immediate horizon.

DR. GILMAN: Thank you.

Any other questions for Dr. Albers? Dr. Grotta.

DR. GROTTA: Dr. Albers, you sort of glossed a little bit over the previous dipyridamole data. What about the early dipyridamole trials that were uniformly negative, how would you reconcile the later data with those?

DR. ALBERS: I don't know if we have slides. I am sure this is going to be covered in later presentations, but basically, prior to ESPS-2, when you look at the dipyridamole/aspirin versus aspirin comparison, there were only three trials in cerebrovascular patients, and they all had very wide confidence intervals because of very small samples sizes. When you sum them together, you see a trend in favor of the combination over aspirin, but it is not statistically significant, but the power of those studies to detect a difference is extremely small. I am not sure if somebody has that slide available.

Then, in terms of the combination dipyridamole/aspirin versus placebo, the only large trial, of course, would be the ESPS-1 that has already been shown.

[Slide.]

DR. HAEHL: This slide shows you the patient numbers for the trials which included dipyridamole, to which we referred as being underpowered.

DR. ALBERS: So, you can see that some of these trials were trials on the order of 300 patients.

DR. KONSTAM: What about previous trials of dipyridamole alone, are there such trials?

DR. TEMPLE: Well, there is PARIS. I mean there were studies in the post-infarction setting from a while ago.

[Slide.]

DR. HAEHL: These are the randomized small-scale studies of dipyridamole with or without placebo or aspirin control.

DR. ALBERS: That last slide that had the "omit" written on it really addresses the earlier question. I don't know if we can bring that up.

[Slide.]

It shows the confidence intervals of those trials. Because the numbers were 300 to 400 patients, the confidence intervals are extremely wide. With a 284-patient trial, their chance of showing anything is extremely low. You can see these huge confidence intervals. That is the same with these other.

These are the comparison of dipyridamole and aspirin versus aspirin. These are the previously available data which led to the conclusion before ESPS-2 that there was no clear evidence of a benefit.

You can see if you sum these, you get a small trend in favor of the combination over aspirin, but ESPS-2 overwhelms these because of the large number of patients, and when you have the totality of the evidence, then, you see a statistically significant benefit of the combination of dipyridamole and aspirin compared to aspirin alone.

DR. KONSTAM: Dr. Gilman.

DR. GILMAN: Please follow up, Dr. Konstam.

DR. KONSTAM: You are saying not to look at these, and maybe we shouldn't, but I guess one of the things we are going to have to come back to is that we have a single trial to deal with.

So, I am going to be looking for some evidence elsewhere in the literature or in the data set or somewhere that confirms this. I guess looking at what you just showed in the absence of ESPS-2, it looks like you are right on unity for the comparison. Is that not right?

DR. ALBERS: There is a trend in favor of--

DR. KONSTAM: Do you want to put that up again?

DR. HAEHL: Our interpretation as the company for these trials was that the wide range, which you have seen, actually allows for any conclusion from highly, and therefore, we decided to perform a very large-scale trial.

DR. KONSTAM: I understand that. I will put the question this way. Is there any evidence elsewhere outside

of the ESPS-2 data set that is supportive of the conclusions that you are trying to--

DR. HAEHL: Please put up Slide No. 5. Dr. Hennekens.

DR. HENNEKENS: First, dipyridamole, and then aspirin. On dipyridamole, I think it is very important to understand the totality of evidence in the world literature on dipyridamole alone and dipyridamole plus aspirin had 120 total strokes as the outcome of all the studies in the world put together.

ESPS-2 itself had about I believe 323 strokes in its own entirety, therefore, ESPS-2 swamps the world literature on dipyridamole alone, because it contributes so much information, and I think we have to understand the difference between finding no association and an inability to find an association if one is there because we didn't have enough endpoints. I think that is an important frame of reference for dipyridamole, I think, and for aspirin, I think an important frame of reference is to look at the--

DR. GILMAN: Please continue.

DR. HENNEKENS: We have 3,406. In the eight studies of aspirin in TIA or stroke patients, 3,406 randomized aspirin, 2,584 to placebo, an odds reduction of 18 percent with confidence intervals from 5 to 30.

Now, ESPS-2 on its own has 1,649 randomized to

aspirin and 1,649 to placebo, a 23 percent statistically significant reduction with confidence intervals from 4 to 37.

I believe that the FDA's recommendation to approve aspirin in this indication was based on the totality of evidence that combined the eight other studies with ESPS-2, and this goes back to the dose issue. The dose of ESPS-2 of 50 mg a day is showing a highly significant, very reliable benefit of aspirin.

ESPS-2 is also showing a significant reliable benefit of dipyridamole alone, and therefore, to me at least, what is going on with Aggrenox has to be looked upon in the context of this study showing a clear benefit on stroke of both 50 mg of aspirin and the extended release dipyridamole in this dose.

There are clear and conclusive benefits on stroke for both of these, and they represent--you know, it is not just that it is just one study, it represents such a large contribution to the world literature on the treatment of TIA and stroke patients. So, I think that has to be viewed as beyond the fact that it is just one study.

DR. GILMAN: That is true, however, the benefit is upon stroke, and not stroke and/or all-cause death.

DR. HENNEKENS: Actually, if I remember the data correctly, there is a clear benefit of the combined

preparation on stroke plus death. However, it is not significantly superior to either of the components. However, when looking at stroke, there is a clear and significant benefit of the combination that is not only robust, but it is significantly better than any of its components, and you will save double the number of lives from stroke by treating with the combined preparation, numbers of strokes, not death, but you are quite right, but the study wasn't powered to answer the death question, and in some ways I think it is a catch-22 to ask it to find a benefit on something where it couldn't possibly do so.

DR. GILMAN: But the primary endpoints originally designed were stroke, death, and now later modified to stroke and/or death. That is the point I am making.

DR. HENNEKENS: And I would just like to say on the stroke endpoint, there is not only a significant benefit of aspirin, there is a significant benefit of dipyridamole, and there is a much greater benefit of the combination that is significantly better than either component on the endpoint of stroke.

DR. GILMAN: For stroke.

DR. HENNEKENS: Yes.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: Just a little bit of history. We have major problems with this, as Marv and Rob will know.

We frequently look at combined endpoints, and our inclination is to label a drug that, one, on a combined endpoint with the benefit on the endpoint that was studied in the trial, but it is typical, for example, you don't want to leave deaths out of the combined endpoint, but it is very unusual to have a persuasive effect on death alone.

So, we dance around that. We say the primary endpoint was death plus all stroke, and the study was successful, it reduced that, but you should not there was no significant effect on death alone.

We face this problem with aspirin claim. Most of the individual studies we relied on do not have a significant effect of aspirin on death after MI, in fact, no single study does. If you look at an overview, it sort of does.

But we still use the combined endpoint because, on the whole, that was what was studied, and if you were giving a full explanation, you would say but note there was no significant effect on death alone.

It is just very unclear about what to do. It is sort of a matter of taste, but we face this every time. All of the antiplatelet drugs being studied now are studied on a combined endpoint, and they never show an effect on death alone, but death is always in the endpoint because you can't really leave it out.

So, it is sort of a matter of taste about how you label it. You don't want to mislead anybody into thinking there was an actual effect on death when there wasn't. On the other hand, the combined endpoint may have been the endpoint that was the one of choice, so you feel funny not using it, and there is no perfect answer to this.

DR. GILMAN: Dr. Penn.

DR. PENN: Just from a policy standpoint, can I ask you, are we committed to the aspirin standard where you have added death, as you admit on not compelling data, in our approval here? Do we have to be consistent?

DR. TEMPLE: No. That is sort of why I said it is a matter of taste. I mean probably, in this case, since this is a prescription drug, we can provide a fuller explanation in the Clinical Trial Section if that were the outcome, and say, you know, the main endpoint was a combined endpoint, and the p-values were for that, and on the other hand, almost all the action was on the stroke component. You can give a lot of explanation, so that everybody knows what the truth is.

DR. PENN: But we are going to ask the statisticians if you added some other endpoint other than death--and one can think of lots of other endpoints to put in--the effect was so strong on stroke, that might carry almost any endpoint that was neutral into it.

DR. TEMPLE: Absolutely.

DR. PENN: So, we could talk about dandruff, we could talk about, you know, something else, and that puts us in a difficult situation. I think, knowing from years past, how the panel feels about these issues, we tried to stick to what the data really shows us, and it may be important for the company to tell us how they feel about this particular issue, whether they felt forced into adding death or whether it is something that it would save us a lot of trouble if we just take that indication out.

DR. TEMPLE: Well, we often urge companies to at least include one endpoint that has death in it, and the reason isn't necessarily that you want to show a benefit, it is because when someone dies, I mean, for example, if you had a nice effect on stroke, but death went the wrong way, it would be kind of goofy to say you had done something good.

So, you put deaths in almost to prophylax against their going the wrong way, and yet you may not expect a beneficial effect on death. The action may well all be or primarily be on stroke.

So, no, you are not bound by the way the aspirin thing was written.

DR. GILMAN: Again, I have to point out that one of Dr. Haehl's slides said that this will reduce the

combined risk of death and nonfatal stroke in patients, et cetera.

DR. TEMPLE: That could be true, but irrelevant. You know, you may reach the conclusion that that is not where the action was. That is a possible conclusion to reach.

DR. GILMAN: That is for this committee then to wrestle with.

Dr. Katz.

DR. KATZ: I was basically just going to say the same thing that Bob just said. The only point I want to make is that as I gather, it is not entirely clear that stroke and death was the primary outcome, so there is even that additional potential problem.

DR. GILMAN: Dr. Califf.

DR. CALIFF: Just to comment that it sounds like we are going to come back to this, but to me it is a bit of a time warp looking at stroke or myocardial infarction as in isolated endpoint. I think it is fraught with so many difficulties that I would never advocate that now in a prospectively designed trial, because these sudden deaths that were mentioned, we have no idea how many of those were sudden deaths due to stroke and how many were sudden deaths due to heart disease.

So, it would be inconceivable to me in a large

trial to design a trial looking at a nonfatal component of a frequently fatal pathophysiologic phenomenon without counting both components in the primary, but we are caught with what was done seven or eight years ago, in a previous time, and it is going to be something we have to come back and wrestle with.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: But, Rob, let's say that is true and therefore you are urging that you use combined endpoints. So, now you do the whole thing, you do the combined endpoint, and the deaths come out neutral. Within the combined endpoint, the combined endpoint wins, let's say, but the deaths come out neutral and all the action seems to be in stroke, so you did the right study, but what do you put on the label?

DR. CALIFF: Well, we got into this because we were doing studies trying to prevent nonfatal MI, and in the end, it actually was a little bit silly to try to prevent nonfatal MI, because people are most worried about the fatal MIs that they may have and we weren't counting those.

When people die, actually, from the statistical point of view, you are left with an odd situation where you are counting people who are dead as not having a endpoint, which is an odd thing.

DR. TEMPLE: That is why you use combined

endpoints.

DR. CALIFF: What is why we used combined endpoints, and I would say that you sort of want to add up to the ultimate, preventing the combined endpoint where most of the effect was on the nonfatal component should just be noted. As you say, most of the effect was on the nonfatal component.

DR. TEMPLE: You have clearly heard other committee members wonder about that policy, and say, well, maybe you should only get the thing that you won on, and I do think it is a matter of taste. There is no single right answer.

DR. CALIFF: This study is raising a number of policy issues, I think.

DR. GILMAN: Dr. Easton wanted to comment?

DR. EASTON: That has resolved.

DR. GILMAN: If there are any presenters for the open hearing, please talk with Sandra Titus.

Do you want to wrap this up? I think we should take a break as soon as we are through with this segment. Dr. Haehl, shall we stop here?

DR. HAEHL: I think the proposal was to have a break and then we will continue with Dr. Muller for the next presentation.

DR. GILMAN: Let's do that. Let's take about a

10-minute break. We will start promptly in 10 minutes.

[Recess.]

DR. GILMAN: We are missing Dr. Califf, but I expect he will be right back.

Please, Dr. Haehl, let's proceed.

DR. HAEHL: Thank you, Mr. Chairman.

I would like now to call Dr. Thomas Muller from Oldenburg, Germany, and he will present the rationale from a pharmacological and from a pharmacokinetic point of view for the formulation of Aggrenox.

Please, Dr. Muller.

Aggrenox Development Rationale

DR. MULLER: Ladies and gentlemen, I want to shortly summarize for you the pharmacologic background for the combination of low-dose aspirin with an extended release preparation of dipyridamole to Aggrenox for the secondary prevention of stroke.

First, I want to demonstrate the superior inhibition of platelet thrombus formation by the combination of aspirin with dipyridamole in a model of plaque vessel wall interaction.

Then, I will shortly address the key mechanism of action of both aspirin and dipyridamole to finally, shortly address pharmacokinetic implications of these very different mechanisms of action.

Before we start, let us turn to the site where all the trouble starts in the patients with TIA and stroke.

[Slide.]

This is a cross-section through a plaque vessel, a very schematic drawing, which demonstrates that the injury of the endothelial cell lining at the interface between the flowing plaque and the vessel wall, that this injury exposes pharmogenic elements of the vessel wall to the flowing plaque. Platelets in the blood adhere to the collagen fibers, they get activated and they start to aggregate. This very local and extremely rapid response to the injury ensures the hemostatic repair. If, however, this process runs out of control, excessive thrombus formation may follow.

[Slide.]

Such a thrombotic occlusion of the blood vessel triggers a cascade of events which finally lead to the complex and diverse clinical manifestations of TIA and stroke.

The clinical evidence just discussed by Dr. Albers for the benefit of antiplatelet agents clearly supports this pathophysiologic concept. Therefore, we have established a model which allows to directly assess the effects of antithrombotic agents on such plaque-vessel wall interaction.

[Slide.]

Human anticoagulated whole blood is allowed to flow over thrombogenic surface and the thrombi attached and adherent to this matrix are measured by quantitative microscopy.

[Slide.]

This is shown in more detail in this slide. The matrix is derived from cultured endothelial cells, and the cell-free matrix is then exposed to the flowing human blood in order to allow for the thrombus formation, and each individual thrombus attached to the matrix is detected by automated fluorescein microscopy.

As you see, most of the platelets and thrombi adherent to this matrix are relatively small, however, there are about 5 percent of these thrombi which are extremely large and which might be biologically, especially important, and it is the unique advantage of this model to allow us to investigate the effects on these very large thrombi.

We have performed a double-blind, randomized, placebo-controlled group comparison with exactly the same medication used in ESPS-2, that is, the combination of low-dose aspirin with extended release preparation of dipyridamole and the individual components.

Each subject was treated with five doses, and the blood was investigated just before the start of treatment

and after the end of the treatment.

[Slide.]

This slide summarizes the results on the mean reduction of the size of all the thrombi detected on the extracellular matrix, and as you see, placebo treatment did not affect the mean size of the thrombi attached to the matrix.

Dipyridamole had an effect. Aspirin showed about a 50 percent reduction, which means that, on average, each thrombus after treatment had only half of the size that it had before the treatment, and it is quite evident that the combination of this low dose of aspirin with extended release dipyridamole clearly shows an additive benefit with regard to the reduction of this mean area of all thrombi.

[Slide.]

I already addressed the issue that there are very large thrombi to be detected on the extracellular matrix in these flow experiments. They represent about 5 percent of all the thrombi and as you see, placebo did not affect at all the proportion of the very large thrombi.

In contrast, the combination of aspirin with dipyridamole was very effect. It reduced the proportion by an absolute number of 4 percent, which means by almost 80 percent, and it is quite evident that concerning the formation of the very large thrombi, the effect of the

dipyridamole and the aspirin treatment is very similar in contrast to the effect on the total number of platelet thrombi.

DR. GILMAN: Dr. Muller, can I ask a question here?

DR. MULLER: Yes.

DR. GILMAN: You are using 400 mg of DP there.

DR. MULLER: Yes.

DR. GILMAN: The formulation is with 200 mg. Can you explain that?

DR. MULLER: I am very sorry. This means per day, so this was administered twice daily, so this refers to the daily dose of dipyridamole. It was exactly the same treatment which has been used in the ESPS-2 study.

DR. DRACHMAN: Would you explain the ordinate? I don't really understand that.

DR. MULLER: Right. The ordinate gives you the absolute reduction in the proportion of very large thrombi. So, the proportion of very large thrombi in the control, in placebo, is normally 5 percent, and the reduction by the treatment was virtually zero.

So, the treatment did not affect the proportion of these very large thrombi, whereas, the combination of aspirin with dipyridamole was very efficient. It reduced the proportion of these very large thrombi by about 4

percent, which means there were only still 1 percent, which represent 20 percent of these large thrombi remaining on the matrix.

DR. GILMAN: This would be a nice model to test various doses, you tried different doses of aspirin or dipyridamole?

DR. MULLER: You are addressing very intriguing point. I have to emphasize these studies were performed in 1988, and at the time, nobody knew about the results of ESPS-2, so when I tried to publish this, everybody was concerned about the positive outcome of dipyridamole in this model, and insofar I refrained from performing more detailed work in this model as I really had problems to get this published.

But now with the data from the ESPS-2, I think it looks very persuasive. That is my problem, I came too late, you are right.

[Slide.]

With this indication of a superior benefit of the combination of aspirin plus dipyridamole, on the mural thrombus formation, I wanted also to now look behind the scene and simply share with you the key biochemical mechanisms, and we already talked in quite some detail about this, so all of you are very much aware that the [exacerbation] of the platelets leads to the generation of

this thromboxane.

Thromboxane is an activator of adjacent platelets, and thereby an almost explosive formation of thromboxane will occur in the close proximity of a growing thrombus. This thromboxane not only activates platelets, it also triggers vasoconstriction.

[Slide.]

Thereby we are very happy that aspirin does a very efficient job with regard to the inhibition of the cyclooxygenase activity, and this has been already addressed in many details, so I need no longer to comment on this.

[Slide.]

But we have to keep in mind that thromboxane is not the only mediator of platelet activation and platelet aggregation. There are quite a number of other ones, and I would like to focus your attention to adenosine diphosphate. This is a molecule which is already stored in the granule of the platelets, and whenever a platelet is activated, it releases ADP from its internal store.

[Slide.]

This is depicted here in this slide, so in the proximity of a growing thrombus, the concentration of ADP, which was released from the granules of the activated platelets, will be converted rapidly to adenosine, and this adenosine is taken up by red blood cells and by platelets.

[Slide.]

Here, dipyridamole comes in. It is a very efficient reversible inhibitor of the adenosine uptake. It has an IC50 of only 0.25 microgram/mL in human plasma, and by inhibiting the elimination of the adenosine in the close proximity of the thrombus, it now can really bind to the platelet and inhibit further platelet activation.

This cycle triggers a very intelligent feedback mechanism, that is, the more platelets are activated, the more ADP will be released and converted to adenosine, and the more adenosine will be accumulating in the presence of dipyridamole to feedback inhibit then further platelet activation and thereby to allow for further growth of the thrombus, and this mechanism only works after some initial thrombus formation, and therefore it nicely explains the preferential inhibition of very large thrombi by dipyridamole.

The implications of the IC50 are that doubling this concentration of 0.25 microgram dipyridamole/mL of plasma, 0.5 microgram/mL, results in an approximately 80 percent inhibition of this mechanism.

[Slide.]

Therefore, it was the target of the development of an extended release preparation of dipyridamole to maintain a plasma level of 0.85 microgram/mL dipyridamole translating

into an 80 percent inhibition of the adenosine uptake over the entire dosing interval, and Dr. Haehl already addressed the convenience of such an extended release preparation which has to be administered only twice daily.

In addition, all the data in the pharmacokinetic demonstrate that there is no interaction, no pharmacokinetic interaction between aspirin and the extended release formulation of dipyridamole in Aggrenox.

[Slide.]

In summary, I would like to emphasize that the suppression of thromboxane by aspirin and the reversible inhibition of the adenosine uptake by dipyridamole, and thus the increase in the local levels of adenosine combines two very independent and efficient mechanisms to express platelet thrombus formation.

The individual doses of the aspirin with its irreversible inactivation of the cyclooxygenase, and the extended release preparation of dipyridamole in order to maintain efficient plasma levels over the entire dosing interval have been selected.

There is no evidence for pharmacokinetic interactions.

[Slide.]

Finally, I have shown that the combination of aspirin with dipyridamole in Aggrenox combines with superior

inhibition of platelet thrombus formation.

With these preclinical results, it is time to turn to the clinical benefits of Aggrenox, and therefore I would like to introduce Dr. James Street, biostatistician, of Boehringer-Ingelheim.

I thank you very much for your attention.

DR. GILMAN: Thank you.

Dr. Grotta, a question?

DR. GROTTA: Yes, two questions. Just coming back to my previous question about the fact that prior to ESPS-1, there were at least two trials that, in aggregate, I thank gave no signal that the combination of aspirin and dipyridamole was superior to placebo or to aspirin alone.

Then, ESPS-1, which I suppose you will show showed some efficacy, and now we have ESPS-2, is there an explanation in your formulation of the drug that might explain this discrepancy and give us greater confidence, to understand this difference over time?

Then, how stable is this formulation that you are seeing in Aggrenox, was there a change in the formula since it seems to be that that might explain some of these discrepant results? Was the formulation of the drug consistent throughout the trials?

DR. HAEHL: The formulation of Aggrenox was consistent since ESPS-2 when it was first used.

Dr. Sherman wanted to comment on your first question.

DR. SHERMAN: One of the things that I have learned about dipyridamole is that it is a reversible inhibitor of platelets, and the effects on the platelets are dependent on the blood levels, which was something I didn't realize early on.

One could speculate that some of the earlier trials they were using immediately release with the sorts of plasma levels that you saw might have meant that a portion of the time the patients didn't have inhibition of their platelets. It is a potential explanation.

I think maybe a better explanation is just the size of the studies, but from the understanding of the biological mechanism, you could also make that argument, I think.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Would you say a word about the PDE efficacy of dipyridamole?

DR. MULLER: This is an important and interesting issue. I think we all have read in our textbooks of pharmacology that indeed initially it was believed that dipyridamole preferentially inhibits the cyclic AMP dependent phosphodiesterase, however, these observations occur or this inhibition occurs only at plasma levels which

are far above the therapeutic levels.

More recent advances have brought our attention to a different phosphodiesterase, which is the cyclic GMP dependent phosphodiesterase, which is usually busy to degrade cyclic GMP which is generated in the platelet in response to nitric oxide or EDIF, and whenever in the platelet there is an increase in cyclic GMP, dipyridamole does interfere with the degradation of this intraplatelet cyclic GMP, and indeed there is some experimental evidence that this mechanism might also contribute to the antithrombotic activity of dipyridamole, however, to keep the presentation focused, I have concentrated on the adenosine mechanism.

DR. DRACHMAN: This mechanism, I believe is used in another recently accepted drug, namely, sildenafil, better known as Viagra. What is the efficacy of this drug vis-a-vis the erectile dysfunction that is dealt with by sildenafil?

DR. HAEHL: As you know, there are several subtypes of phosphodiesterases, and in addition, we have never investigated that.

DR. GILMAN: Does Dr. Easton want to comment?

DR. EASTON: Just one clarifying comment to Dr. Grotta's question, and that is, if you look at the three previous stroke trials for the endpoint stroke, which is the

focus for the moment, there actually was an odds reduction of 17 percent favoring combination dipyridamole plus aspirin over aspirin alone.

It is clearly just a trend. The confidence intervals do include unity. Now, when you take that and add --and that turns out to be 120 events, and the difficulty now is when you add ESP to that, you have 443 events, and that number moves from 17 to 25, and is statistically significant.

So, the point I would only make is it wasn't negative data. It was lack of data prior to this trial. Similarly, if you do the same numbers for the 14 trials, not just now the three stroke included patients, but all of the patients in combined dipyridamole plus aspirin versus aspirin, again, you see this trend 12 percent reduction in favor of the combination for prevention of the endpoint stroke, and then that number also moves into the highly significant range when you add in the ESPS trial.

So, I think it is fair to say that it was a lack of data with a trend going in the right direction rather than negative data.

DR. GILMAN: Thank you.

Dr. Califf.

DR. CALIFF: I just want to take advantage of this one opportunity to maybe learn a little bit more about

stroke since we are on the mechanisms of action.

You built the whole rationale on antithrombotic effect. I guess it is a three-part question. What do we know about inflammation and risk of stroke? Does dipyridamole add anything to aspirin in terms of antiinflammatory effects, and if so, what?

Thirdly, are you convinced that the only mechanism of action of aspirin is its antithrombotic mechanism in preventing recurrent stroke?

DR. MULLER: We already discussed this issue this morning, that indeed there is current speculation that atherosclerosis may be an inflammatory process. I completely agree on this.

My point was that however the acute reaction to this inflammation that is the rupture of a plaque or any other injury of the vessel wall triggers the instantaneous response of the platelets, and that is where the thromboxane inhibition and where the adenosine uptake inhibition really comes into play.

That, of course, does not rule out any other mechanism, but I think there is a rational basis for that, and as long we don't have any long-term trials which clearly demonstrate a superiority of high doses of aspirin which are antiinflammatory active in the clinical endpoints, I think this remains pure speculation, don't you agree?

DR. CALIFF: Yes, but like most pathophysiology, it is speculation. In the end, we will come back to the clinical data, which I guess we are getting.

DR. HAEHL: I would agree. We made a hypothesis the basis for our formulation, and we tested it in the clinic, and it seems that there is a relation between the hypothesis and the result, but therefore it always is a jump from one side to the other, but it seems to be consistent.

I had the impression that Dr. Hennekens wanted to comment on the aspirin antiinflammatory efficacy.

DR. CALIFF: It would be interesting to know if you have seen the same things that you saw with regard to cardiac events in the stroke events issue.

DR. HENNEKENS: Well, our comparisons about aspirin in the presence of high levels of CRP are sort of post hoc, nonrandomized comparisons. My own view is that I have serious doubts that a dose of 50 to 100 mg of aspirin is having a significant antiinflammatory effect.

I think the alternative hypothesis that at the time of an acute stroke or an acute MI, there is such increased platelet activation that it does go with the data from the antiplatelet trial, that people who were taking aspirin at the time of the event, who were given an acute amount of aspirin, tend to have lowered subsequent clinical outcome, suggesting that there must still be increased

platelet activation and other mechanisms that are occurring around the time of the event that relate to these mechanisms described.

DR. CALIFF: But people with high CRPs also have a high risk of stroke in addition to a high risk of MI.

DR. HENNEKENS: Yes, they do, and we did find that people who were getting either 325 every other day in the physician study or 50 a day in the women's study, that there was some modification of the effect by aspirin, that is, that aspirin seemed to have its greatest benefit in the people with the highest levels, but as I say, they are not randomized comparisons and we need more data on that question.

DR. GILMAN: I would just like to note that Dr. Michael Brooke has joined us. He is from the University of Alberta, flew down this morning. Welcome.

DR. GILMAN: If there are no other questions, let's move on, Dr. Street.

Clinical Trial Efficacy

[Slide.]

DR. STREET: Members of the committee, today, I will present an overview of the design, principal results, and reliability of the Second European Stroke Prevention Study.

This trial was designed to test the safety and

efficacy of the two components of extended release dipyridamole and aspirin, alone and in combination, to prevent stroke and death in patients with prior TIA or ischemic stroke.

There were actually four specific clinical questions to be address by this trial. First, does low-dose aspirin, 50 mg a day, prevent stroke or death, which was not known at the time.

Does extended release dipyridamole prevent stroke or death? That had also not been established.

Are the effects of the two drugs additive when administered in combination?

Finally, is Aggrenox well tolerated?

ESPS-2 provides clear, positive answers to all of these questions. I will address the first three, the efficacy questions, and Dr. Rakowski will follow with a discussion of the tolerability.

[Slide.]

Very briefly, I know you are all familiar with this trial, but just for the record we will briefly summarize.

This was a multicenter, randomized, double-blind, placebo-controlled trial, ranged in a 2 x 2 factorial design of four parallel treatment arms, each containing approximately the same number of patients.

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These patients were recruited from 13 countries, had 59 centers across Europe. The randomization was performed by the European Organization for the Research and Treatment of Cancer, a group which is independent and highly experienced in centralized computer randomization.

This randomization was balanced with respect to four factors: the gender, the age group, type of qualifying event, and the center.

Treatment and follow-up were all to be two years and patients were to be followed for two years regardless of whether they ceased treatment. There were nine visits at one and three months, and then at three-month intervals thereafter.

[Slide.]

This simply summarizes the numbers of patients in the four groups, roughly equal.

[Slide.]

As far as qualifying events which were to be within three months, and most of which occurred--as a matter of fact, the mean time from the qualifying event to randomization was one month. We see perfect balance between the treatment groups, roughly, one-quarter having a TIA, and a little over three-fourths a stroke as their qualifying event.

[Slide.]

The study was to include adult men and women, 58 percent were men, who had had, as I say, an ischemic stroke or TIA within three months. They had to be stabilized from that stroke prior to entry.

Key exclusion criteria were they had had no history of gastric bleeding or other bleeding disturbances, active peptic ulcer, known hypersensitivity to either of the study medications, or any life-threatening conditions.

[Slide.]

Sample size. The protocol-planned sample size was 5,000 patients, 1,250 per treatment arm, the same number as were present in the ESPS-1 design. In addition, this design contemplated one interim analysis in the protocol.

DR. GILMAN: Could I ask about that? Sorry to interrupt you.

DR. STREET: Yes.

DR. GILMAN: I thought you had planned interim analyses yearly.

DR. STREET: No, there were interim safety reports to the ethics committee, but they were not the basis for decisions, nor were they analyzed with p-values or anything like that, so there was only the one that was used as a decision point.

DR. KONSTAM: I am not sure I understand that.

There were interim safety looks you are saying? What were the purpose of these interim looks if you were not looking at the data?

DR. STREET: Can someone actually comment on the nature of the review that was performed for safety?

DR. HAEHL: Dr. Bertrand, would you please comment on the procedures to inform the ethics committee about the conduct of the trial in yearly intervals? For your information, Dr. Bertrand is a co-worker of Boehringer Ingelheim, and he was the responsible monitor for ESPS-2 in Belgium.

DR. BERTRAND-HARDY: Data for the ethics committee, we prepare once a year and the statistician made a review of the main side effects as they were registered in the case report form, mainly headaches, bleeding, gastrointestinal diseases, and so on.

The results were presented to the ethics committee once a year and this committee had to decide whether the study could continue or not on the basis of those data.

DR. KONSTAM: So deaths were reviewed as well, right?

DR. BERTRAND-HARDY: Yes, of course, yes.

DR. KONSTAM: And strokes were not?

DR. BERTRAND-HARDY: And strokes also.

DR. KONSTAM: Were reviewed.

DR. BERTRAND-HARDY: Yes, they were reviewed. But the tables were randomly allocated so as to keep the blindness of the study, so it was not possible to identify the treatment groups.

DR. KONSTAM: But if you had identified a major difference in the endpoint of stroke, let's say, between the two groups at an interim look, might not you have recommended stopping the study?

DR. BERTRAND-HARDY: No, because in the protocol, there would be only one interim analysis, and the rules for treatment cessation, of course, apart from the reason, and for seeing side effects or something which would be very important that the study would be stopped if the statistical significance would reach a value which was lower than p 1 for 1,000. That was the only occasion, and also safety analysis, as far as I know, never the statistician did analyze the efficacy.

DR. GILMAN: But you did compare placebo group, you know which was the placebo, you know which were the--

DR. BERTRAND-HARDY: No.

DR. GILMAN: No, you did not.

DR. BERTRAND-HARDY: Even the statistician did not know that. He knew that there were three groups and named A, B, C, and D, but he could not identify them.

DR. GILMAN: Then, explain how you would determine

safety if you didn't know which was the placebo group.

DR. BERTRAND-HARDY: Just by difference between the groups.

DR. GILMAN: And was there a trigger for stopping the trial?

DR. BERTRAND-HARDY: Yes, well, I mean regarding safety, there was no trigger, just a strong excess of death or something which would not be acceptable, and regarding the efficacy, I told you that was the p-value.

DR. GILMAN: How would you know, what would be your marker for excess, how would you know?

DR. BERTRAND-HARDY: Well, I can't specify exactly, I don't know exactly which was the rules which were applied by the statistician.

DR. GILMAN: Does anybody in the company know what the rules were?

DR. HAEHL: Dr. Pathy, as the Chairman of the Assessment Group, could you comment on that?

DR. PATHY: Chairman, whereas we looked at deaths, we were totally blinded. We didn't know whether the patient was on placebo or active medication. Neither did we know the centers from which the reports were coming. Everything was looked at totally blindly. So, I can't give you an answer to that.

Also, of course, it was the ethical committee that