UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MEETING

MONDAY, DECEMBER 8, 2003

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The Advisory Committee met at 8:30 a.m. in the Ballroom of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Jeffrey Borer, Chairman, presiding.

PRESENT:
JEFFREY S. BORER, M.D., Chairman
PAUL W. ARMSTRONG, M.D., Member
BLASE A. CARABELLO, M.D., Member
SUSANNA L. CUNNINGHAM, Ph.D., Consumer Representative
THOMAS FLEMING, Ph.D., Consultant (Voting)
WILLIAM R. HIATT, M.D., Member
ALAN T. HIRSCH, M.D., Member
JOSEPH KNAPKA, Ph.D, Patient Representative
BEVERLY H. LORELL, M.D., Member
JOHN NEYLAN, M.D., Acting Industry Representative
(Non-voting)
STEVEN E. NISSEN, M.D., F.A.C.C., Member
THOMAS PICKERING,, M.D., Member
EDWARD PRITCHETT, M.D., Consultant (Voting)
RONALD PORTMAN, M.D., Member
ALASTAIR WOOD, M.D., Consultant (Voting)

SPONSOR REPRESENTATIVES:

COLIN BAIGENT, M.D.
JOHN A. COLWELL, M.D., Ph.D.
C. NOEL BAIREY MERZ, M.D.
J. MICHAEL GAZIANO, M.D.
LOREN LAINE, M.D.
THOMAS W. MEADE, D.M., F.R.S.
THOMAS A. PEARSON, M.D., M.P.H., Ph.D.
ERICA PEITLER, Rph
RANDALL STAFFORD, M.D., Ph.D.
GIANNI TOGNONI, M.D.
ERIC J. TOPOL, M.D.

FDA REPRESENTATIVES:

MICHELLE M. JACKSON, Ph.D.
CHENXIONG (CHARLES) LE, Ph.D.
CURTIS ROSEBRAUGH, M.D., M.P.H.
ROBERT TEMPLE, M.D.
DOUGLAS THROCKMORTON, M.D.

AGENDA ITEM PAGE

1 P-R-O-C-E-E-D-I-N-G-S

8:31 a.m.

DR. BORER: We'll begin the Cardiovascular Renal Drugs Advisory Committee meeting. Why don't we introduce the committee members and the FDA Representatives, going around the table. John, we'll start at your end.

DR. NEYLAN: Yes, I'm John Neylan, I am the Acting Industry Representative to the Committee.

DR. CARABELLO: I'm Blase Carabello, a cardiologist from Houston.

DR. KNAPKA: I'm Joe Knapka. I'm a Patient Representative on the Committee.

DR. NISSEN: I'm Steve Nissen, I'm a cardiologist at the Cleveland Clinic.

DR. LORELL: Beverly Lorell, I'm a cardiologist, Harvard Medical School.

DR. PICKERING: Tom Pickering. Hypertension expert at Columbia Presbyterian in New York.

DR. HIRSCH: I'm Alan Hirsch, a Cardiologist and Vascular Medicine Specialist at the University of Minnesota in Minneapolis.

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

DR. BORER: Jeff Borer, Cardiologist at Cornell in New York City.

MS. SPELL-LESANE: Dornette Spell-LeSane, Executive Secretary for the Committee.

DR. CUNNINGHAM: Susanna Cunningham, University of Washington, Consumer Representative.

DR. ARMSTRONG: Paul Armstrong, cardiologist, University of Alberta.

DR. PORTMAN: Ron Portman, pediatric nephrologist, University of Texas in Houston.

DR. PRITCHETT: Ed Pritchett, Cardiology and Clinical Pharmacology at Duke University Medical Center in North Carolina.

DR. WOOD: I'm Alastair Wood, Clinical Pharmacology from Vanderbilt.

DR. HIATT: Bill Hiatt, vascular medicine, University of Colorado.

DR. ROSEBRAUGH: Curt Rosebraugh, Deputy Director, Division of Over-the-Counter Drug Products.

DR. THROCKMORTON: Doug Throckmorton. I'm

the Division Director in the Division of Cardiorenal Drug Products.

DR. BORER: Okay, thank you very much. We'll begin with the Conflict of Interest Statement. Dornette Spell-LeSane, the Executive Secretary will read this.

MS. SPELL-LESANE: The following announcement addresses conflict of interest issues with respect to this meeting and is made a part of the record, to preclude even the appearance of impropriety at this meeting.

The topics to be discussed today, will not focus on any particular product or company, but rather may affect aspirin manufacturers.

The Conflict of Interest Statutes prohibit special government employees from participating in matters that could affect their own or their employer's financial interest.

All participants have been screened for interest in the products and companies that could be affected by today's discussion.

In accordance with 18 United States Code

Section 208(b)(3), the Food and Drug Administration has granted waivers to the following individuals because it has determined that the need for their services outweighs the potential for a conflict of interest.

Thomas Fleming, Jeffery Borer, Edward Pritchett. A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. John Neylan is participating as a non-voting Industry Representative, acting on behalf of regulated industry.

Dr. Neylan is employed by Wyeth Research. In the event the discussions involve products or firms not on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we

ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. BORER: We have some introductory comments and welcome from the FDA Representatives. Doug.

DR. THROCKMORTON: Thanks, Jeff. My comments will be quite brief. I'd just like to take this opportunity to thank the members of the Advisory Committee and the other participants in this meeting today, for coming together to discuss this highly important, highly relevant public health issue. I'm looking forward to a vigorous debate and I much appreciate everyone's participation. Thank you.

DR. BORER: Okay. As it says on the agenda, the committee will assess whether aspirin should be recommended for primary prevention of myocardial infarction in some defined population.

Professional labeling for aspirin currently recommends it's use for prevention of a second myocardial infarction. We'll begin the

sponsor's presentation with Representatives from Bayer. Dr. Peitler.

MS. PEITLER: Mr. Chairman, members of the Advisory Committee, Drs. Rosebraugh, Throckmorton and Ganley, FDA Staff, good morning.

It is an honor to be here today to participate in this public health dialogue. My name is Erica Peitler and I am a Senior Vice President with Bayer Consumer Care, and acting Head of R&D.

Today, it is clear that we have consensus. Aspirin prevents MI. What we are here to consider is how to further expand the professional label for aspirin to include additional individuals.

Those at moderate to high risk for whom the benefits clearly outweigh the risk. Today, in spite of its widely-recognized benefits, aspirin, which costs only pennies per day, still remains underutilized.

There is a significant gap between the aspirin prevention recommendations of major scientific organizations and what happens in actual clinical practice.

Guidelines from the American Diabetes Association, and more recently from the American Heart Association and the United States Preventive Services Task Force, encourage the use of aspirin in moderate risk individuals.

These evidence-based guidelines represent the state of the science within the medical community. But they are not enough to effect the changes required.

Only with FDA approval of an expanded indication to prevent first heart attacks, can there be significant impact. Expanded professional labeling will, first, provide direction and increased clarity for health professionals in determining appropriate individuals for aspirin use.

Second, it will further increase patient awareness and education about cardiovascular risk and it will encourage them to discuss risk management strategies with their physician. In short, expanding the professional labeling for aspirin will help close the gap between the current medical evidence for aspirin and its optimal use.

Over the past two decades, our collective efforts have led to a number of important FDA approvals for the cardioprotective use of aspirin.

Including the prevention of a second heart attack in the 1980s and the prevention of death during an acute MI in the 1990s. And now we come together again.

This time to consider further expansion of aspirin use to prevent a first heart attack. At the center of this discussion, is the issue that we have a gap between the clinical evidence and the current labeling for aspirin.

Current guidelines suggest that patients with a ten year risk of coronary heart disease of at least ten percent, should be on an aspirin regimen, whether or not they have had a previous MI.

This recognizes that an event may be more likely to happen in someone with elevated risk factors than in someone who has already had a heart attack.

Yet, current professional labeling defines eligible candidates for aspirin therapy solely on the presence or absence of a previous event. A

redefinition of patient selection criteria within the aspirin labeling is clearly needed.

To facilitate this change, we have filed a citizen's petition requesting that professional labeling be based on global rather than event-based risk.

In 1989, the Cardio Renal Advisory Committee voted six to two in favor of expanding the professional label to include first MI.

Since that time, three additional trials have been published. The patient database has doubled, from 27,000 to 55,000. The data that will be discussed today, from the five large studies, demonstrate a statistically significant reduction in non-fatal first MI.

Viewed in the context of the totality of the evidence, these five studies advance our understanding of the appropriate patient population who can benefit from an aspirin regimen.

The evidence is in, with respect to moderate and high risk patients; it is now time to take action. To help frame the discussion and

dialogue, Bayer has taken the lead in assembling a group of Researchers and Clinicians.

With us today are the principle investigators from all five studies. We encourage you to take advantage of their expertise in having them further design, in having them further discuss the design features and the findings of their trials.

We also have the guideline authors from the AHA, the ADA, and the USPSTF. We have leading Cardiologists also with us, providing practice perspective. We have experts in GI safety and hemorrhagic stroke, as well as experts who can comment on epidemiology, labeling and utilization.

First this morning, Dr. Thomas Pearson, from the University of Rochester, will discuss the benefits of aspirin to a wider group of eligible patients.

Next, Dr. Colin Baigent, who leads the Antithrombotic Trialists' Collaboration, will comment on the totality of the evidence in both the primary and the secondary databases.

Dr. Noel Bairey Merz, of Cedars-Sinai

Medical Center, will provide insight on what the labeling recommendations should be with respect to women.

Dr. Randall Stafford of Stanford University, will comment on the dramatic underutilization of aspirin in preventing cardiovascular events.

And then Dr. Eric Topol, of the Cleveland Clinic Foundation, will provide a clinical perspective on the proposed labeling change. Bayer is proud to have taken the lead today in building support for this public health partnership.

To more clearly determine appropriate candidates for aspirin therapy. We welcome today's dialogue and we share your sense of urgency about the role of aspirin in addressing this critical public health need. Thank you. Dr. Pearson.

DR. BORER: Does anyone have any overall questions for Dr. Peitler? I have just one, if I might. You made the point that FDA approval would have an impact on patient recognition of the potential role of aspirin. How would that happen?

MS. PEITLER: How would, how would the impact happen? Two things, two very important impacts. One is with the label approval, physicians in clinical practice would have specific clarity and assistance in helping to define and select appropriate patients.

Right now they don't have that specificity. Only an event determines whether aspirin is used or not. So the primary prevention labeling that we're requesting, which is risk-based, will help them decide which patients are at risk and who is appropriate for aspirin use. Second, the educational efforts that will then be rolled out through physicians, ultimately to patients, will raise awareness around risk factors, and engage the physician and the consumer and patients in appropriate dialogue around risk management strategies.

DR. BORER: If professional society guidelines suggest use of aspirin beyond the current label, how will this change cause that second effect. How will the labeling change cause that second effect.

That is that doctors will talk to patients about this, whereas before they wouldn't?

MS. PEITLER: Guidelines are one part of what we think is a collective and collaborative effort. To achieve a public health actionable outcome, it requires not only the guidelines from the leading scientific organizations, it requires FDA labeling.

It requires physician engagement, it requires patient education, to bring those forces together so that behaviors could be changed and appropriate dialogue can take place.

DR. BORER: Any other, yes.

DR. PRITCHETT: I think I heard you say that in 1989, the Committee considered this. And, in fact, I was on the Committee in `89, and I sort of remember this, and that they voted six to two in favor of additional labeling, which never happened, is that correct?

MS. PEITLER: That's correct.

DR. PRITCHETT: Can you or someone explain to us what happened? I remembered the vote as being

five-four, but I'll take your word on it as being six-two.

What, what happened that it never happened?

MS. PEITLER: I think, the short answer, the six to two vote, at the time, the physician's health study and the British doctors trial, were the only two trials that were there.

And I believe that there was some discussion over the divergence of those findings. Today, we bring to the table now three additional published trials, the database which was 27,000 strong at that point, has now advanced to over 55,000.

DR. BORER: Okay.

MS. PEITLER: Thanks.

DR. PEARSON: Dr. Borer, Committee Members, Colleagues, it's my really distinct pleasure to have the opportunity to bring to you what we believe is a strong rationale for the expanded professional, professional labeling of aspirin to include moderate risk patients.

I'm Tom Pearson. I'm a Cardiovascular

Epidemiologist. I run a preventive cardiology clinic at the University of Rochester Medical Center, and it's my opportunity to really describe our thinking on this matter in terms of supporting this labeling.

So we propose to adopt risk labeling for aspirin patient selection, and to include patients with ten year risk of coronary heart disease that exceeds ten percent, where we believe benefits outweigh the risks.

I'd like to outline the rationale that we'd like to bring to you today, and certainly the salient points that I want to make this morning.

First of all, coronary heart disease continues to be a major public health problem. Second is that many patients are at sufficient risk of coronary heart disease to warrant aspirin treatment.

Third is that global coronary heart disease risk and it's an appropriate way to determine the type and intensity of these interventions.

Professional labeling can define moderate and high risk populations where we believe the benefits outweigh the risks. And finally, and a point

that will be made by Dr. Stafford in his studies, is that there is substantial underutilization of aspirin in high and moderate risk patients currently.

I think we all know that for the last, almost the last century, that coronary heart disease has been our leading cause of death. What, perhaps, we aren't quite as aware of is that the Epidemiology of this disease is changing.

Despite previous market reductions in the mortality, I think there is very good evidence to suggest that our incidence is no longer falling.

It's the incidence of coronary heart disease, since about 1990 in this country, as evidenced by community studies in Worcester, Massachusetts and Olmstead County, Minnesota has been flat.

In other words, no further reduction in incidence. With continued fall in case fatality rate, this leads to a rising prevalence of coronary heart disease. And as these patients are of increasing number in our communities, this carries huge implications to direct and indirect costs for our

communities.

Finally, and as you all know in this committee, is that the first presentation of coronary heart disease is often times the last or often times a disabling one. Twenty percent of coronary heart disease initial cases present as sudden death.

And I think you're also aware that your hospitals are full of congestive heart failure patients, which is one of the few, if only, diseases whose incidence prevalence morbidity and mortality have increased every year for the last 25 years.

These are some data from Olmstead County, Minnesota in this paper by Veronique Roger, looking at incidence, not mortality, but incidence of coronary heart disease over the late 1970s through the mid 1990s.

But I think what you can appreciate, that certainly since 1990, you're very hard pressed to suggest any further decline in incidence in men. And, in fact, over this period of time, there's a 35 percent increase in incident coronary heart disease in women.

This is not a disease that is going away. It may be becoming less fatal, but it is certainly not becoming less common. And for the American College of Cardiology, I participated in a working group looking at the implications of the aging of the U.S. population, as well as some of these mortality trends.

Currently, with 12 and a half million Americans carrying the diagnosis of heart disease, that represents 12 percent of men above the age of 45.

And eight percent of women above the age of 45, hearing this diagnosis. We project, as you go through the first half of the 21st century, for a doubling of the prevalence.

Such that the prevalence of coronary disease in the United States will have more people, will number more people than a number of the countries of the world at that period in time.

And this is really a failure of the primary prevention of heart disease. Of turning off the pipeline in the first place and to reduce the number of people in our population with this disabling

and costly disease.

The rationale for primary prevention also includes the fact that we know that heart disease is largely preventable. And it's preventable through relatively simple and inexpensive options, including lifestyle modification.

But I would include aspirin as one of these simple and inexpensive options. The use of safe and effective preventive interventions, will have a significant public health impact.

Anything we can do to turn off that pipeline of cases of coronary disease, I believe to be very worthwhile. Aspirin, we believe, is the most cost-effective pharmacologic option in coronary disease prevention and intervention for, literally, pennies a day.

And finally, we believe that patients at moderate to high risk, can be identified using clinical judgement and risk assessment tools to assist our health care providers in identifying those patients at the right, with the right risk benefit ratio for intervention.

Well, there's been several groups who have recommended guidelines for risk assessment. And the American Heart Association and the United States Preventive Services Task Force, have identified, have adopted guidelines which have encouraged risk assessment and, in those individuals at moderate to high risk intervention with aspirin.

The American Heart Association has recommend adults above the age of 40 should have an absolute coronary risk calculated. And in these individuals with moderate to high risk, there are guidelines for management based on that risk.

You see serum lipids are now, according to the National Cholesterol Education Program Adult Treatment Panel III guidelines are now risk-based. And also with the U.S. Preventive Services Task Force, and with the American Heart Association guidelines for aspirin are also based on these risk calculations.

Now global risk assessment, I believe, can be done easily in the health care provider's office. We believe it should be done at least every five years, or more often if more than two risk factors are

present.

This uses the Framingham Risk Calculation, using age, sex, smoking status, systolic blood pressure, serum cholesterol and HDL cholesterol, to calculate a ten year risk of coronary heart disease, death or myocardial infarction.

I might point out that this is, diabetes is not in this equation, of course, because it is now considered a CHD equivalent, with all of those patients being at high risk.

The risk calculators are available in a variety of forms. They're on the Cholesterol Education Programs's web site, the American Heart Association's web site.

You can beam this on to your Palm Pilot. You can use scoring sheets or a variety of color-coded tables. At the University of Rochester, we have a little color-coded booklet.

Obviously easy to carry around in your coat pocket, and then literally, it takes about 11 seconds to identify, in a color-coded way, an individual to be at low, moderate or high risk.

This is not a difficult or time-consuming enterprise. We do believe it is a valuable enterprise, however, illustrated in this patient's, this next patient's scenario.

Now let's take a patient, and if you were in an internal medicine practice, would certainly not be a rare occurrence.

A middle-aged male who smokes, has moderate levels of systolic blood pressure, moderate elevations of systolic blood pressure and total cholesterol. Perhaps a little lower HDL than we would like.

Nothing extraordinarily extreme in any of those. But if, in fact, you put all of these factors together, you come up with a ten year risk of coronary heart disease of 30 percent.

A risk similar to those of our myocardial infarction survivors. So you can identify, either by clinical judgement or with these risk assessment tools, individuals at moderate to high risk, who have not yet had a coronary event.

Well, this then allows us the

opportunities, as health care providers, to tailor individual treatment decisions based on this.

Both whether to treat and how intensively to treat. Rather than treating no one, or treating everyone to the fullest extent, we are able to stratify the intensity of therapy with the gradations of risk.

And by doing so, we will choose cost-effective therapies. My patients also like to participate in their care. And they like these little tables. They like to understand what their risk is and they like to participate in the selection of risk interventions.

And I think this motivates them to comply with non-pharmacologic and pharmacologic therapies. So I think this is also beneficial as a patient education tool.

We're talking about aspirin today. We're talking about a simple intervention. And we're going to show you a lot of data today, about what is the evidence for aspirin in the prevention of myocardial infarction.

Obviously, the place to start is with the secondary prevention data. Data that we all, including the American Heart Association's Secondary Prevention Guidelines, have agreed is a very important intervention in the prevention of heart disease.

So when you have a large database supporting the safety and efficacy of aspirin in secondary prevention, 150,000 patients from, literally, scores of studies.

And Dr. Colin Baigent today will briefly review some of those data for you. So the American Heart Association and the American College of Cardiology have used these data to recommend aspirin in the patients with established cardiovascular disease.

So one of the things we want to do is ask the question, can we take those data and move them down into other relatively high risk patients. Moderate and high risk patients who have not yet had that cardiac event.

Now obviously the Food and Drug Administration currently approves aspirin to reduce

the risk of MI in patients with a variety of vascular presentations, MI, stroke, angina, revascularizations.

And all these patients have risk above 20 percent. Finally, the American Diabetes Association has also recognized the benefits of aspirin, way back in 1997, when they recommended the use of aspirin for the primary prevention of heart disease in a very high risk group of patients, that is diabetics. Now what we'd like to do is also then, move into the primary prevention issue.

The extrapolation of all we know from second in prevention, down into the moderate risk and high risk primary prevention patients.

And we feel we have a robust and clinically informative database with five trials involving 55,000 subjects. These are well-designed studies with high compliance and follow-up rates.

We think it is a great strength, it comes from a diverse patient population. There are a range of global risks with four studies being in the low risk category and one in the moderate risk group.

And they come from a geographically

diverse group, literally, from all over the world. The number of doses, formulations and primary endpoints have been used.

And we feel, therefore, we have a rich evidence base for our recommendations. Let's talk a little bit about the individual studies that we have to look at.

There are five studies which provide clinically meaningful data on this issue of primary prevention and its safety and efficacy of the use of aspirin in primary prevention. It should be pointed out that at least two of these studies did not reach their predetermined endpoints, because they were stopped by their Data Safety and Monitoring Boards prematurely because of evidence for aspirin effectiveness.

This is the Physician's Health Study in the Primary Prevention Project. So I think it's very important to know that at least within their own studies, at least two, I felt that the data were already significant enough for the benefit of aspirin that they could not continue the trials.

The findings are also consistent with four of the other five studies and all five of these studies have been used in the meta-analysis that Dr. Baigent will be showing you, to more precisely estimate the risk and benefit of aspirin in primary prevention.

The findings, in terms of relative risk reduction of 25 percent are very consistent with those from the secondary prevention trials. Again, a database including 150,000 patients.

And, the American Heart Association, the U.S. Preventive Services Task Force, have used these data to encourage use in moderate risk patients of aspirin.

I chaired the writing group for the American Heart Association. We reviewed the data then. I've had an opportunity to review the data since then, and I am even more convinced now than when I chaired that writing group, that this is the right thing to do.

Let's provide then a little overview of the rationale for this strategy of extending these

benefits into the moderate risk group.

And this is from the U.S. Preventative Services Task Force, which estimates the benefits and harm of aspirin for five years, treating 1,000 patients at various levels of baseline risk for coronary heart disease.

These are a bit modified from the, the Youth Preventative Services Task Force, in that we're using ten year risk here, rather than five year risk in the paper.

So you have two percent, six percent or ten percent, ten year risk. What you have is given a relative risk reduction across all of those risks, it looks like it's pretty stable.

You have increasing numbers of coronary disease events avoided with increasing baseline risk. What doesn't change over those groups, are the number of hemorrhagic strokes and the major gastrointestinal bleeding events, which appear to be stable across these risk strata.

Obviously, the strategy then and we would suggest ten percent and higher, both moderate and high

risk primary prevention patients.

To provide aspirin for those individuals, in which we have a clear benefit, a clear excess of coronary heart disease events avoided, compared to this low baseline risk of GI hemorrhage and hemorrhagic stroke.

And we have experts on all of these areas, basically to comment on issues of both the risks and the benefits. I believe we can classify patients into three buckets.

Three groups of patients, which is what the risk calculator does. I think we tend to overestimate how precise these calculations are. What we're really doing is a risk stratification procedure.

Individuals into the low risk, moderate risk or high risk groups. And I believe these can be identified inexpensively and rapidly in the typical care provider's office.

Now the benefits of intervention, therefore, accrue to those with greatest underlying risk. If there is a stable, 25 percent relative risk reduction, across the risk groups, therefore the

higher the risk you have, going from moderate to high risk, the larger the number of patients who will have MIs prevented per thousand patients treated for ten years.

That's the vertical axis here. Now it turns out, I think, that we have some empirical evidence to support this notion. And these are the secondary prevention trials. Again, 150,000 patients up here, in which, in these high risk patients we know that we prevent a large number of MIs per thousand patients treated per ten years.

We also have the five primary prevention trials. Four in the low risk group, and one in the moderate risk group, which I think support this notion, is that the higher the risk, the higher the numbers of myocardial infarctions potentially prevented.

And these are the data plotted, according to their CHD risk, of the placebo group, and the numbers of MI actually treated, actually prevented per thousand patients treated per ten years.

Now, we also have, and one of the

complexities of this area, is this low underlying risk of hemorrhagic stroke and GI hemorrhage. Here estimated, according to the U.S. Preventative Services Task Force, and agreed by the Antiplatelet Trialists Group, of a four-to-12 range of adverse events, this threshold.

And so clearly what we want to do, and since this is constant, across the risk strata, what we want to do is identify those individuals who are at benefit, rather than at risk, for aspirin.

So basically, what we end up with then is here, with the data shown, superimposed, of the selection of high risk, greater than 20 percent, in primary prevention.

And there are a large number of these patients, obviously, in our practices, who have not yet had an infarction, or moderate risk, greater than ten percent, in which you have obviously a clear benefit, above the line, of the number of MIs prevented compared to their underlying risk of hemorrhagic stroke and GI hemorrhage.

And this is really the rationale for the

recommendations that we're making. And we believe that you can extrapolate this to a broader population. There is a statistically significant benefit to preventing MIs in trials conducted both in primary and secondary prevention.

Even at the low risk, I might say, those four, those four studies, and in the low risk groups in which we're, in fact, not recommending because of the risk benefit ratio.

However, there is homogeneity of the relative risk reductions for coronary heart disease, as Dr. Baigent will show you, across the high and low risk population supporting the usefulness of aspirin therapy, across this continuum.

That in fact there is continued 25 percent risk reduction at all levels of risk. The benefit to risk ratio would be enhanced, therefore, by limiting the use of aspirin to those at least at moderate risk, ten percent or higher, including the high risk individuals in primary prevention.

And also to exclude those patients that we know may have a diathesis for bleeding. So in

conclusion, I think we'd like to make several points very strongly.

One, is that there are robust findings supporting the utility of aspirin for preventing MI across the continuum, 150,000 patients in secondary prevention, 55,000 in primary prevention.

We can prevent this disease with aspirin taken on a regular basis. There is a favorable benefit to risk relationship at moderate risk and higher patients.

Approximately six to 20 MIs can be prevented. And these are MIs which lead to disability and possibly sudden death. And these six to 20 can be prevented for every two to four GI bleeds and zero to two hemorrhagic strokes caused.

A positive risk to benefit relationship. And we believe, that as you get into those higher risk patients, those greater than 20 percent, multiple risk factor patients that we see in our practice, the risk benefit ratio will be even greater.

We believe that there is a major public health benefit to be had here. And we could expect

with the proposed label change, that we'll have increased numbers of patients having their risk assessed.

This continues to be an important opportunity that I think we often times miss in our primary care practices. Second, we'd like to reduce the underutilization of treatment.

In both primary and secondary, these treatment gaps continue. And Dr. Stafford is going to review these data with you.

And then finally, really, and in the end, our goal is to reduce long-term mortality, morbidity and costs from this most common disease, coronary heart disease. Thank you very much.

DR. BORER: Thank you very much, Dr. Pearson. Are there any specific issues? Steve.

DR. NISSEN: Tom, I wonder if you could put up your slide Number 30.

DR. PEARSON: Can we do it? Yes.

DR. NISSEN: Yeah. So, you know, usually, when we're asked to deliberate about, you know, a topic such as this, we want to look at the population

that's going to be treated, and look at the risk benefits in that population.

And, you know, I wonder about your, if you would comment on this. One of the problems that I have here, is in that moderate risk category of ten to 20 percent, we have a single study.

And so, what you're really asking us to do, then, is to extrapolate from studies outside of the range of patients and whom we're really being asked to provide a label, and say, well based upon what happens at risk below and what happens at risk above, that we can then interpret what to do in that group that's in between.

Now really, arguably, there are really two trials. You know, BDT and TPT. Although, BDT doesn't quite make the ten percent risk. One of them looks pretty good, the other one looks pretty bad.

So how do we make this case, when we don't have trials in the range that we're really being asked to label.

DR. PEARSON: I have several responses to that. Number one, is that Dr. Baigent is going to

show you individual study data as well as net analysis data of all of these five studies which basically show that even in this lower risk, there is an efficacy argument in support of aspirin therapy.

So, in all of these five studies, our contention is that we do, on an individual study basis, for two or more trials, have in fact efficacy shown for single.

They may not be in this group, but I don't think, our position here is that these are arbitrary cut points in terms of risk. What we have is a gradation of risk, and we're extrapolating the high risk individuals and the data we have, and the moderate risk into this other's, where the risk benefit ratio is positive.

Secondly is, is that what Dr. Baigent is going to show you, is in fact within all of these five studies including, and Dr. Meade is with us here, and the principle investigators for all of these studies, I might point out, are here today and provide a wonderful opportunity for us to discuss these data.

In addition to this one, I think, quite

convincing, the TPT study, Dr. Meade is with us here from London. And, but in all of these patients there were moderate risk patients within the entire study set.

And these have been taken out in a net analysis and analyzed separately, as virtually a second piece of evidence within this group. And I'd like to not steal Dr. Baigent's thunder, but I think you'll be quite pleased to see that there is also very good evidence within the aggregated data from all five of these studies, that moderate risk patients do in fact benefit.

So, I think there are a considerable number of, there are positive studies in primary prevention. There's one positive study in the moderate risk individuals. And there's positive evidence in the moderate risk patients within the five studies.

DR. BORER: Tom Fleming, you wanted to make a comment about this?

DR. FLEMING: I think Steve's question was right on target. It was exactly my first question as

well. And maybe just to add briefly, at least if we took literally your figure here, then essentially the essence that you would conclude is that where these five studies were performed, there isn't excess benefit relative to risk. In fact, three of them over a region where there would be expected by your own figure to be greater risk than benefit. Are we misinterpreting your figure?

DR. PEARSON: In these two studies, there would be greater risk than benefit. In these three studies there would be "

DR. FLEMING: PHS, HOT and PPP, according to your "

DR. PEARSON: Right, right.

DR. FLEMING: " x-axis?

DR. PEARSON: Right. But this is, again, this is the number of MIs prevented per thousand patients treated. All five of these studies, in fact, show a benefit. The question is do they exceed a threshold of risk benefit?

And three of the five studies do. And again, as the risk of these individuals increase, the

risk benefit ratio becomes increasingly small. Risk benefit ratio.

DR. FLEMING: But in essence, for the area that you're targeting here, which is the moderate risk, you're essentially needing to do an extrapolation with a key study, from the key study data.

DR. PEARSON: By individual study alone, but by looking at individual patients, I don't want to steal Dr. Baigent's thunder "

DR. FLEMING: Okay, all right.

DR. PEARSON: " because he has those data to show you and I think they're quite convincing.

DR. BORER: Okay, we had a number of other questions. I think, Bill Hiatt, you had one initially, and then we'll go to Tom and then Paul and Beverly.

DR. HIATT: My question is, is that we're trying to go from event-driven to global risk-driven assessment. Do you think that the event-driven populations are fundamentally the same as the patients that have this risk continuum?

I know, and so my question is, why is the label being probed just for prevention of first MI, whereas for secondary prevention it prevents MI and death?

DR. PEARSON: I think this is often times a natural history question. Dr. Baigent is going to address this issue looking at, comparing and contrasting the primary and secondary prevention studies for a number of end points, including death and stroke.

And you see a little bit different issues there. My own opinion on this is, of course, is we've converted coronary disease from a fatal disease to a chronic disease. Our case fatality rates for MI, although there is still a very high sudden death occurrence, the case fatality rates have continued to fall.

And therefore, in our powered trials is very much easier to get to an endpoint of reduction and non-fatal MI with relatively fewer of those actually becoming fatal.

So, but there are meta-analyses, again,

bringing all of these data into, into play, in looking at those issues. But I think it's actually kind of a power natural history issue.

You're talking about individuals relatively earlier in the course of what is a disastrous natural history.

DR. HIATT: And qualitatively, you think that they actually look the same?

DR. PEARSON: Yes, and as you know, you've got patients with peripheral arterial disease who haven't had a myocardial infarction, you know what their risk is. It's horrendous.

DR. HIATT: But I also know aspirin doesn't work for those patients. Aspirin has not been approved or labeled or been shown to be effective for those patients.

And, that's a testable hypothesis. So, when you look at global risk as a way to make treatment decisions, that's still a testable hypothesis. And there is a primary prevention study going on in the UK right now, where ABI is being used as a risk stratification, much like Framingham risk is

being done.

And that's a placebo-controlled trial to see if aspirin is effective in those moderate risk patients. So, I think in terms of the Framingham risk, can you tell us about any prospective trials based on that assessment that actually demonstrate aspirin benefit?

DR. PEARSON: Dr. Baigent is going to show you meta-analysis stratified by risk. I guess it doesn't really use the Framingham score, but rather more empiric data from that.

But he will show you the group kind of data of less than one, one to two, and greater than two percent per year risk, and show the relative risk reductions the same across those strata and increasing numbers then of potentially prevented MIs across them.

So the last thing is, the reason you think the label is different now, which is just to prevent non-fatal events, because you've hypothesized the disease has changed. That the mortality has gone down so much, that our goal now is to prevent non-fatal events, not MI, stroke and vascular death which is the

common endpoint for all the other trials that are published.

DR. PEARSON: I believe we will prevent sudden deaths, coronary heart disease deaths in doing so. But I also believe that our primary goal should be to prevent this disease in the first place, given the disability and cost implications of even a non-fatal MI.

DR. BORER: Before we go on to Tom, did Doug or Bob Temple, did you have a clarification to make there?

DR. TEMPLE: I just wanted to add to the peripheral artery disease discussion, because it's of some interest. There's an invitation, not unreasonable in some sense, to extrapolate from data in a variety of populations.

And yet it's unbelievably striking that in the peripheral artery population, who, after all, have coronary heart disease and strokes sort of like everybody else, aspirin in the, in the aspirin trial submitted analysis shows absolutely nothing in about 2,000 patients.

And in trials of ticlopidine, oh, no, clopidogrel, it's very striking that all the benefit of clopidogrel is in the peripheral artery. All the advantage over aspirin is in the peripheral arterial group.

So, it just makes you wonder whether everybody is really as much the same as you'd at first think. And added to that, is that in the Physician's Health Study, which sort of drives a lot of the MI data here, strokes went the wrong way.

Which is really hard, not just hemorrhagic strokes, but what appeared to be, thrombotic strokes went the wrong way.

It just makes you wonder whether people are as much part of a continuum as they appear to be, even though it seems completely logical to say that they would be. I mean, I'd expect it too.

But the data doesn't always come out quite that way.

DR. BORER: Tom?

DR. PICKERING: I have a more general question. The focus of the presentation and also of

the risk equations that we're being encouraged to use, although I suspect very few physicians are actually using them, are heavily focused on coronary heart disease and myocardial infarction.

But if you're a patient or a physician you don't know if the event that that patient is going to have is from coronary heart disease or a stroke.

So, should we not be using risk equations that tell you the overall risk of cardiovascular events as opposed to specifically focusing on MIs.

I mean, I know that the, for instance, blood pressure is more important a predictor of stroke, but again, you don't know, which event you're trying to prevent.

DR. PEARSON: My view of the use of these risk assessment tools is really a group designation. The identification of groups of patients at various risk.

I think the reading of this into a precise estimate of an individual chance of having any specific event, is probably beyond the use of these tools.

What we're really just stratifying a population by three groups to really allow a stratification of the use and intensity of therapies.

So, getting down to some of these other risks of subsets of disease, of other vascular systems of disease, I think should also in general work.

But I think a much more broad look at the way a practicing physician, on Monday morning, when he sees a patient and puts people into a low, moderate or high risk group in very broad a sense.

So that over his entire, his or her entire practice, they would have a better stratification of intensity of therapy by intensity of risk.

DR. BORER: Paul.

DR. ARMSTRONG: Dr. Pearson, you've been thinking about this for a long time and perhaps you have the best overview of any of us.

So, I'm going to ask you a couple of questions that I'm going to return to in relationship to some of the experts that we'll hear from later.

And it relates to the risk of the therapy, not the risk of the disease. What do we know about

the patients who experience intracranial hemorrhage, GI bleeding? And what do we know, if anything, about transfusion requirement?

For example, are these small body weight, elderly ladies over the age of 80? When do they get these side effects in relationship to the exposure over the ten year period that you've elaborated in relationship to the risk of the disease?

And what can we or should we learn about balancing those risks against the benefit that you've elegantly presented?

DR. PEARSON: Would it be an opportunity to call some of our guest Consultants at this time? Is that "

DR. ARMSTRONG: Up to the Chairman. We can defer those questions, if that's your pleasure. I just thought that you would have the best overview of anybody relative to all of these studies.

And it's a composite question related to the risk of the therapy. So, that's up to the Chairman.

DR. PEARSON: It's an important issue and

we're ready and delighted to address that, because I agree with you. It's very important and makes this whole area a little bit more complicated than just all benefit, doesn't it?

DR. BORER: Yeah, perhaps we can wait until your planned presentation of the risk issues, and then we can come back to the composite question.

DR. PEARSON: Let me just, let me just make one overview comment. And that is, is that most of these GI hemorrhages are equated to those requiring transfusion.

So the ones we're talking about, in terms of a definition, is not perhaps a quiet positive stool, but rather a clinical event of meaning.

At the same time, we had a very lively discussion within our group of would you rather have a myocardial infarction or a GI bleed. Your gastric mucosa will heal.

You will have a transfusion requirement. But if you've had a myocardial infarction, as you know, you've lost part of your myocardium permanently and many of those individuals will not heal.

They'll have congestive heart failure and a variety of other sequelae. And that, that risk benefit for that more common adverse affect of GI hemorrhage, should be considered.

Hemorrhagic stroke is another issue. That's obviously a serious catastrophic event. Those are very uncommon. We would want to minimize them by individuals who have a bleeding diathesis and who, for some reason, would believe that they would have an adverse reaction to aspirin.

And we believe that people with a bleeding diathesis, or perhaps a previous history of hemorrhagic stroke, obviously should be excluded from aspirin therapy.

DR. BORER: Beverly.

DR. LORELL: I wonder if we could return to your Slide Number 20, that showed the patient profile. To me, one of the provocative things about the arguments today is not only the difficult dilemma of balancing risk benefit for those patients who sit right on the edge of low and moderate.

But you've alluded to the issue that

current labeling, which is event-based, may also be driving failure to use aspirin in moderate-high and high risk individuals.

To give us a little better handle on that, with such a patient as you've described here, which is bread and butter general medicine and cardiology.

Can you give us any kind of estimate as to what percent of patients like this, may be using aspirin in the United States today and what percent are not?

DR. PEARSON: Yes, Dr. Randy Stafford is going to comment on that specific issue for us later. Let me just talk about the relative number of individuals in the low-moderate risk group.

And that, to some extent, differs by where you are. If you take an NHANES kind of data set, that looks like about 40 percent of individuals are at moderate or high risk pre-MI.

This is not a CHD group. About 40 percent of Americans are at moderate or high risk, adult Americans. If you look at an Internist's Clinic, and we did a survey of 3,200 medical records in 16 primary

care clinics in New York.

It's about one-quarter low risk, one-half non-coronary high risk, and about 25 percent of a typical Internist's practice deals with coronary disease.

So, these are certainly not a minor issue for anyone's cardiovascular practice. Now Dr. Stafford has, and that's his major area of research is looking at the use of these preventive therapies.

And, if I could, I'd like to defer to his presentation.

DR. BORER: Alastair Wood and then Alan Hirsch.

DR. WOOD: I think you've addressed some of the stuff, what I was going to ask. But it does seem to me there's some risk in just adding up different adverse events and without giving them any differential value.

And, you know, without engaging in the vigorous discussion you described that your group had, it does seem to me that preventing an MI has some, has a different value, whether it's better or worse than a

GI hemorrhage.

Do you want to comment on how one could get at that in terms of setting the ten percent level? Because the ten percent level comes essentially from adding up, without any qualitative input, the two different major adverse events.

DR. PEARSON: Right. The ten percent risk level is, according to the Framingham risk, and there have been a variety of Framingham equations, as you know. But the one used by the National Cholesterol Education Adult Treatment Panel III guideline is MI and CHD diff.

So those would be both risks of top end cardiovascular coronary manifestations. This is not angina, this is not positive electrocardiogram or whatever. This is CHD diff and MI.

I agree with you in the sense that we have taken these with virtually no value judgement other than the fact that the GI hemorrhage is usually a serious one requiring hospitalization and transfusion.

And, of course, hemorrhagic stroke is something we'd all like to prevent, particularly with

hypertension control. So, these have been without value, I believe, as you, I think, are eluding to, is that this is conservative.

And, in fact, the U.S. Preventive Services Task Force used a six percent and higher threshold for the use of aspirin.

In our deliberations in the American Heart Association Working Group, we chose a more conservative ten percent, but I would acknowledge this issue of this definition of moderate risk and that at least one professional body has selected, I think, even a less conservative definition of moderate risk.

DR. BORER: Alan.

DR. HIRSCH: Tom, thanks very much. Can we also go back to Slide 20? Or, yes, Slide, excuse me, Slide 30, I believe. Which was a plot of relative risk and adverse event rates.

Like Paul, like the rest of the group, we're trying here today to look at the balance of risk and benefit. And one thing I've struggled with, going through the briefing document is that when we have our enthusiasm to prevent events we tend to look at

relative risk deduction or number of MIs prevented as a laudable goal.

We look at GI bleeds and strokes. We look at annualized event rate. Not relative risk increase, sort of the same figure, or number of events caused.

And I want to again circle back to the same discussion. It seems as though we're asking physicians to do a global risk assessment, looking only again at the sort of risk of the benefit and not calculating it as the risk of the adverse event.

On these plots, is this truly a horizontal line and a stable adverse event rate, or is it a little more honest to plot the accruing risk, in association with the accruing benefit.

And do we truly know that that accruing risk is equal across these categories. There's really two lines that intersect in some different point.

DR. PEARSON: Right. Dr. Hirsch brings up several interesting issues. And let me see if I can tick them off in order. First of all is that Dr. Baigent is going to show you the relative risks, excess relative risks of hemorrhagic stroke and GI

hemorrhage.

And so, by, again, our desire is to really give the Advisory Committee a full look at the data, but keep in mind, those relative risks are based on a low absolute risk rate. Okay?

So one per thousand, I believe, is the figure that Dr. Baigent's going to give you. And so the relative risk above that is a, you know, it's like a one to 1.6 increase in, say, GI hemorrhage.

And he's going to show you that for both primary and secondary prevention. If you've had an MI, you can still get a GI hemorrhage on aspirin, obviously. So he's going to show you that. And it does, in fact, I think, support this idea that this risk is stable across the way.

So in looking at this, and this is one of the reasons I'm pleased that these have stimulated a discussion and hopefully a conceptualization.

I would say the accruing risk is here. So it's this. So if you got out your ruler and, again, and this is the scale, this is four to 12 is what U.S. Preventive Services Task Force, the range of adverse

events.

Again, not weighted by severity. We take that, but I think in a conservative sense. And so as you go above that, and this is why, again, we're into the moderate risk, is that this is the accrued benefit.

And that's why we've shown it this way. And obviously what we'd like to do is have a positive benefit to risk ratio.

DR. BORER: John and then Steve.

DR. NEYLAN: Actually, I'd like to revisit your first question, Jeff, to the previous speaker. And could you put up Slide 21.

And that is, Dr. Pearson, as an author of clinical practice guidelines and as one who incorporates this kind of global risk assessment into day-to-day practice, can you speak about the practical implications of what the difference would be in terms of having this kind of labeling as opposed to where we are today without that labeling?

DR. PEARSON: Thank you. I think it's very important for us all to be speaking the same language

and all to be on the same page.

And I think currently this was an issue that we actually addressed when the U.S. Preventive Services Task Force came out while the American Heart Association guidelines were still being written.

And we felt that it was very important to look at these data and to have all of our recommendations on the same page. And our writing group basically agreed that there did appear to be a positive benefit to risk ratio, using the same risk cut points as we recommended as those of the National Cholesterol Education Program guidelines.

Again, a broader use of this risk stratification paradigm. And so I think it's very important that as our patients look at the labeling as our quality assurance agency's look at labeling using these four quality assurance measures, that we're all on the same page. The regulatory agencies, the professional societies and the scientific bodies are really all saying the same thing, based on the same evidence.

And our feeling is that the evidence in

this instance, supports the use of aspirin in primary prevention in these individuals.

I think it is important.

DR. BORER: Steve.

DR. NISSEN: I wonder if we could see your Slide 25, and I had a couple of questions. Could you give me a relatively precise definition of what is meant in this slide by major gastrointestinal bleeding events? So, a definition.

DR. PEARSON: I believe the, and certainly Dr. Baigent is going to show you very similar data from their meta-analysis, is a GI hemorrhage requiring transfusion.

DR. NISSEN: Okay, I would like to see, before the day is out, more complete data, including those patients who are hospitalized for gastrointestinal hemorrhage, but maybe never get a transfusion.

So, in other words, there's obviously a health care cost around being admitted for a GI hemorrhage. And that is not just patients who bleed to the point of requiring a transfusion, that's

everybody who has to go into the hospital for a gastrointestinal hemorrhage.

And so, I know you may not be the proper person, but I want to drill down a little bit further towards understanding the spectrum of adverse events that we're having to weigh here.

Including hospitalizations for a GI hemorrhage, even if they don't involve requiring a transfusion.

DR. PEARSON: Yes, thank you, Dr. Nissen, and I think we have the opportunity here, if I could defer this to the question and answer period.

We have Dr. Pignone from one of the leaders of the U.S. Preventive Services Task Force Writing Group, who can address this issue. And the Antiplatelet Trialists Group also looked at this issue in terms of adverse events so defined.

So, I believe we have the actual primary collectors of those data with us, and including the principle investigators. And I think this is an important issue.

Again, our feeling in terms of the

magnitude of risk, the absolute magnitude of the risk, it's about one-tenth or so of that of the MI risk, in terms of serious medical reactions.

DR. BORER: All right, we'll probably have, we will have the opportunity to revisit this question after the data presented. And that may be more efficient. Susanna and then Dr. Knapka.

DR. CUNNINGHAM: Tom, is it true that if you have on GI event you don't have any increased risk for another, so you go back to zero, if they've had a GI bleed?

DR. PEARSON: There are some risk groups that, and several of them are treatable, like with H.pylori, in which I guess theoretically you would have a risk for, but those are usually at the time of a, one of these issues also treated for it.

We have three gastrointestinal consultants with us for the question and answer period in terms of the risk for recurrent GI bleed.

I think the other issue is if you had a GI hemorrhage, that may be a contraindication to further aspirin use. Unless there's some extraordinary, I

think the other point is if there's an extraordinary benefit to be accrued to aspirin, there are also ways to minimize that GI hemorrhage recurrence through a variety of therapies that you could use to reduce the risk of ulcers.

But we have our GI consultants for that if we could, they could address that. If we could mark that as a question that we should come back to.

DR. BORER: Dr. Knapka, and then Bill Hiatt, again.

DR. KNAPKA: Just one quick question. We talk about risks, and I realize that these heart episodes are caused both genetic and environmental.

Now, is anybody, or are there any genetic markers that can really identify the people that are real high risk for these events?

Or are they looking for genetic markers and are there any?

DR. PEARSON: We should possibly defer that question to our colleagues from Cleveland Clinic, who have been in the media about this recently.

They are, and perhaps the person sitting

next to you, as well. But the, there is obviously an avid search for genetic markers. And there clearly are some families, and we see them in the clinic, where everybody's had an early coronary death.

And these are obviously where the use of that is. I am a public health person, and I've been very struck with, such as the Nurses Study, that if you exercise, you don't smoke, you eat a good diet, you perhaps have moderate alcohol consumption and you have a normal body weight, that you have one-seventh of the risk of all those women that don't do that.

And so I think the evidence still is that our coronary epidemic in this country is not because we've had an in-migration of a lot of high risk families, but because our behaviors certainly aren't what they should be.

DR. HIATT: I'm still bothered by the concept that patients that have had events, are exactly the same as patients who haven't had events, but are high risk.

So that just a few days ago, there's a publication in Diabetes Care about a secondary

analysis from the Primary Prevention Project, where they look at people with diabetes separately from the rest of the population.

And if you look at all the diabetes guidelines there's no coronary equivalent and they should all be on risk reduction therapies including aspirin.

But this subgroup analysis, which is just another post hoc thing, demonstrates absolutely no benefit of aspirin in those patients with diabetes.

And that bothered me. I mean I'm just, I'm just not convinced that you can identify these high risk groups that haven't had events, and think that they're going to respond exactly the same way as people who had events. And this is another example from just recent evidence, that that's not true. Can you help me with that?

DR. PEARSON: Yes, well, what I'd like to is maybe defer that, as well, to our group of experts. We have Dr. Colwell, who is representing the American Diabetes Association, and also has another larger study in diabetics from earlier, the 1980s, in fact,

which influenced the American Diabetes recommendations for the use of aspirin in primary prevention.

And he can share with you, in fact, that strikingly positive study in individuals treated with 650 milligrams of aspirin versus placebo.

And so we would like to delve into the diabetic issue, it's an important issue. We also have the principle investigator for the Primary Prevention Project with us today.

And I think it would be most appropriate for him to comment on the, on the sub-analysis of that population, if we could.

DR. BORER: Tom.

DR. PICKERING: The patient that you showed with the 30 percent risk, had a systolic pressure of 148. So, by most definitions, he had uncontrolled hypertension, and I'm sure we're going to talk about this later, but whether or not these people should be included or excluded.

Can you say how many of the people in the moderate risk group you think are there because of some degree of hypertension?

DR. PEARSON: Hypertension, of course, in this country, as you have contributed to the literature, obviously is a very prevalent condition and therefore is a major determinant about getting into that moderate risk group.

In fact, it would be one of the ways to get into that group along with cigarette smoking, which is independent of your lipids and was one of the reasons why we recommended everyone above the age of 40.

Not just someone with hyperlipidemia, but everyone above the age of 40 should have an absolute risk score for primary prevention.

Let me also say that we have Professor Zanchetti with us from the HOT Trial. A trial that I'm sure you're familiar with, which of course, included aspirin in a largely hypertensive group in terms of the primary prevention opportunities there.

And I think this is relevant to that group. Clearly, that patient in my clinic, we have a lot of work to do. The point of that slide, however, and it's not just aspirin, it's many things.

But clearly the point of that slide, though, was that individuals with several modestly elevated risk factors, clearly, positively elevated, but modestly so, in fact contributes greatly to their overall risk for a cardiac event.

DR. BORER: Okay, thank you very much, Dr. Pearson, that was a wonderful overview and perhaps we can go on to Dr. Baigent.

As we get prepared to do that, I would observe that the questions that are being asked around the table are crucial questions. Very important, and they'll need to be answered before we can respond to the FDA's questions.

But, these aren't the kinds of questions we usually can ask and expect answers to, particularly with regard to safety, when we review NDAs on drugs.

Because the exposure isn't in large, well-controlled clinical trials. It isn't anything near what we're seeing here. So we have an extraordinary and relatively unique opportunity here and I think we'll hear more about it right now.

DR. BAIGENT: Dr. Borer, Committee Members,

ladies and gentlemen, what I'd like to do today is to describe to you the work that's been conducted by the Antithrombotic Trialists' Collaboration, which has ultimately, I think, led to some insights on which types of patients might benefit from aspirin.

So I'm going to start off by describing to you the Antithrombotic Trialists Collaboration, which incidentally used to be called the Antiplatelet Trialists Collaboration, and I'm going to describe what we see in high risk patients and then explain to you why we then moved on to look at moderate risk patients.

In doing that, I'll be describing the balance of the benefits and the risks. And already we've had discussion about this very point. It's absolutely crucial to our deliberations that we understand that balance.

Now first of all, I need to tell you about how the Antithrombotic Trialists' Collaboration started. Right back in the mid `80s, we had a few studies of aspirin and other antiplatelet agents, and those studies were, on their own, too small to tell us

about the detail of who to treat with aspirin.

And so the whole thrust of the Antithrombotic Trialists Collaboration, or the ATT for short, has been to try to put together all the randomized evidence in ways that are reliable. By going to the individual investigators. By getting their protocols, by getting their collaboration. By having individual patient data provided in a standard format, using uniform definitions.

By doing all that, we were able to put together a unique database that's uniquely able to answer particular questions about who to treat.

As Clinicians and as health professionals we really want to know who to treat. We can get information about the general impact of a drug, but we need to know who to treat.

So right back in the mid `80s, we defined outcomes that we would give most emphasis to. And the main outcome that we, right back in the early days, defined was this one, serious vascular event.

Which is a combined outcome of non-fatal MI, non-fatal stroke or vascular death. We did not

include silent MI, nor have we ever since. So right at the very beginning we decided to stick to clinical outcomes that would be, thought to be clinically relevant.

We're also able to look, once we have large amounts of data, remember we're talking about, in the high risk studies, about 17,000 vascular events.

That means a hell of a lot of days in which we were able to explore events in particular. So we were able to look at myocardial infarction in particular. Stroke, in particular.

And subdivide stroke subtypes. So the large amount of data enables us to look in detail at the effects of aspirin on particular outcomes. We're able to look at mortality and we're able to look at major extracranial bleeding.

Right back in the beginning we defined major extracranial bleeding as bleeding due to hemorrhage. Over the years we have stuck to that definition. And so we're talking about a clinically significant adverse event.

So we're going to look at two sources of evidence today. The first of these is the evidence in high risk patients, by which we mean people with a definite history of occlusive arterial disease.

I'm going to describe the results in general terms, because we're mainly wanting to focus on moderate risk patients in this deliberation. Overall, in the most recent cycle of our analyses, remember we've done this over a number of years.

The first publication was in 1988. Subsequently in 1994, and most recently in 2002. And as Dr. Pearson has pointed out, there are about 135,000 patients in over 100 trials.

So, really large numbers of trials were able to contribute to this analysis. Overall, we saw one course of reduction in serious vascular events in a wide range of high risk patients.

Those benefits clearly outweighed the risks. And I think most clinicians now accept, that for a wide range of high risk patients, people with previous events, their benefit to risk ratio is very, very clear.

We're also able to demonstrate that if you are at high risk, it doesn't matter how you got to be high risk. So, in particular, if you're at high risk for some reason, it doesn't it matter if you're a woman. You're at high risk.

And we were able to show, among those 17,000 vascular events, by looking in great detail at individual patient data, we were able to show that the benefits were similar irrespective of age.

Irrespective of whether you're a man or a woman. Irrespective of blood pressure, at least within the range studied. And irrespective of the presence of diabetes.

So that database is really important when you start to think about the implications of lower level, moderate risk patients.

Most recently, when we published this paper, we pointed out that actually many patients, who haven't yet had an event, have already been studied within this high risk group.

We're talking about people with chronic stable angina. We're talking about people with

intermittent claudication. These people are at high risk, and we already routinely treat them with aspirin as is appropriate.

But we also realized, there are many patients, many people out in the community, who, for various reasons, have an agglomeration of risk factors that also puts them at increased risk of vascular events.

We'd like to be able to prevent that. We can't get at that information by looking at the high risk studies, but we what we can do is look at the so-called primary prevention trials.

Many of which have actually targeted people at increased risk of a vascular event. So, again, I would emphasize we set out to do this a priori. We wanted, as a collaboration, among the five principle investigators already here today to answer questions, we pre-specified our outcomes. We put together a protocol. We met several times.

We most recently met in October. And what I'm showing you today is the results on behalf of that collaboration, based on individual patient data.

We are preparing a manuscript at the moment, but I'm going to show you the results as they currently are. Let's start with thinking about what the results tell us from high risk patients.

This is a summary of the absolute benefits of aspirin or antiplatelet therapy. About two-thirds of the trials were aspirin trials in the high risk group.

And what you see here, and you have these in front of you, so you're able to look at the detail. I realize you may not be able to read the numbers, but they're in your pack.

You see along here the absolute benefits per thousand patients treated with aspirin. And the yellow bar is the aspirin bar and the control bar is in red.

So over about 27 months, in a prior MI patient, patient with a previous MI, you get about 36 events avoided per thousand patients treated. And you get similar size benefits. The difference between the yellow and the red bar is similar in size in people with cerebrovascular disease. And also in a range of

other conditions.

So what I want to emphasize from this slide, is that if you annualize this, then roughly speaking, you're talking about a benefit in vascular events of between ten and 20 events avoided per year.

And that is something that we need to bear in mind when thinking about the calculus in people at somewhat lower risk. Now I mentioned that we were able to demonstrate that if you are at high risk, then it doesn't matter how you got to be high risk.

Your particular demographic features don't appear to influence the benefit of aspirin. And here we see that for the split between men and women. In fact, women were at higher risk in this group here and we see that they have as much benefit as men do.

So it's a really important point that we need to keep coming back to throughout the day, I believe, that if you are at moderate or high risk, then it doesn't matter how you got to be that way.

After all, women do have platelets and we'd expect benefit in women in they are at high risk. Similarly in elderly people, the benefits seem to be

as large as they are. In younger people, similar relationship for diastolic blood pressure.

Of course, people who are really hypertensive never get into these trials, at least not until they've had their blood pressure controlled.

But certainly within the range studied, we see similar benefits. And similarly for diabetes, if you are at high risk, it doesn't matter whether you are diabetic or not, you still benefit from antiplatelet therapy.

So these are really important points because they tell us that we can define the group of high risk patients a clear benefit from aspirin.

What about the negative side, and it's quite proper that we do consider the negative side. Actually, that is one of the key questions for this committee.

Well, in the meta-analysis that we did in high risk patients, we showed that there was a 1.6-fold increase in the risk of serious extracranial bleeding.

And that absolute excess risk translates

to about one per thousand per year. It's very similar actually to what you see in the observational studies. About one per thousand per year is a good benchmark to have in mind. IF you compare that to the benefit of ten to 20 vascular events prevented per thousand per year, you can see that the benefit to risk ratio is actually extremely clear and favorable, and that is why it's appropriate to use aspirin so widely in people at high risk of vascular disease.

Now once we'd completed the most recent exercise, we felt that we'd actually not addressed a very important question. We showed, we thought, that for certain types of patients who already have clinical symptoms such as angina or intermittent claudication, that they would benefit from antiplatelet therapy.

But we felt that we should be trying to identify people who are at similar absolute risk, but who have not yet had an event and don't have any clinical symptoms.

After all, why would you not want to prevent an event in that type of person. It's

obvious, from a public health standpoint, that you'd want to do that.

So, as I said, we brought together the principal investigators of those studies, the primary prevention studies, and these are the details of those studies that you're, no doubt, familiar with. You have all the details in your pack.

But just to remind you, The British Doctor Study and the Physician's Health Study, in the early days, looked at a relatively healthy group of patients, and more recently we've had studies, these three studies, the Thrombosis Prevention Trial, the HOT Study and the Primary Prevention Project, have all set out to identify people who have risk factors.

And therefore, they are specifically trying to do what we're all trying to do, identify people who might benefit from aspirin.

So, they generally studied a middle-aged group. They included some women and very few patients had a history of vascular disease. It's simply not the case that the results are driven by people who had vascular disease, who got included in these studies.

Most of the impact is in people who did not have recorded vascular disease at baseline. And we do have some people with diabetes.

We had individual patient data from all the investigators, and they spent a good amount of effort, actually working with us to make sure that data were absolutely straight.

So we've been liaising with them over the last couple of years to get the data straight. Extensive checking and validation of the data has gone on. And this is the knock out point.

Around one-fifth of these individuals were actually at moderate risk of a vascular event, a CHD event, rather. And that means that we have certainly got substantial amount of information that we're able to bring to bear on this problem.

We did not include silent MIs, I specifically mentioned earlier. But in doing this exercise, we also wanted to make a direct comparison, within the same project, of the effects of aspirin among post MI patients and post TIA patients.

So when I come on to my slides showing you

the actual results, you will see secondary prevention as the second section of the figures. And that relates to the affects of aspirin in post MI and post TIA patients, just by way of comparison, so that you can see how the data shape up.

Now you may want to refer to your notes here, because the figures are quite tiny on the screen. Even standing here, I have difficulty seeing them.

This is the result on vascular events for the Primary Prevention Trials. In each of the five trials, what we have is an aspirin column here, a no aspirin column here. You're looking at events per patient-years, a follow-up and that enables you to look at an annualized event rate.

You can see that actually what's most striking is the similarity of these results. Overall, we get a 15 percent reduction. About four standard deviation, so statistically pretty clear.

And if you do a test for heterogeneity the similarity of results, it's clear that these results are completely compatible with each other.

So we're seeing something really striking. That there is similarity among these trials, they've looked at primary prevention patients.

But we want to go further than this. The whole point of this exercise is that if we have a large amount of data on vascular events with a similar comparison, aspirin versus control, we should be able to look at specific types of events.

We should be able to look at cardiac events, we should be able to look at strokes. And bring the data to bear on trying to understand why we see this result. Which, after all, is slightly less than the 25 percent reduction that we see in second prevention.

DR. HIATT: Sorry, what vascular events are you showing us here? MI, stroke and vascular death.

DR. BAIGENT: Exactly the same definition that we've used all along. Serious vascular events, non-fatal MI, non-fatal stroke or vascular death.

DR. HIATT: So those p-values, just aren't consistent with what's been published.

DR. BAIGENT: I'm sorry? This is the

Primary Prevention Trial. These data have not been published before.

DR. HIATT: The MI, stroke and vascular death.

DR. BAIGENT: That's correct.

DR. HIATT: Hmm.

DR. BAIGENT: This is serious vascular events, non-fatal MI, non-fatal stroke or vascular death in prime prevention, 15 percent reduction. In secondary prevention, the high risk studies that I showed earlier, we see about a 25 percent reduction.

DR. HIATT: But you're saying that four out of those five trials were statistically significant across that competent endpoint.

DR. BAIGENT: I'm saying for each of these studies, what you see is a square, which is the point estimates, and the confidence interval. And 99 percent confidence interval is the line.

DR. HIATT: Well, the British Doctors was clearly negative. But the other four studies were negative on their primary endpoints. But you're making the composite endpoint and telling us, even

though those composite intervals cross one, in all but the U.S. Physicians, that they are statistically significant.

DR. BAIGENT: I think what's important to recognize is that when, first of all these are 99 percent confidence intervals. So they, you would, if you had something that was completely clear of the line of no effect, then it would be significant at the one percent level.

As is appropriate, when you're looking at lots of analyses, you want to have a one percent alpha error rate, so that you can avoid concluding, inappropriately, the particular sub-root findings.

So that's why we've traditionally used a 99 percent confidence interval. So you can't say anything about whether these are significant at the five percent level, from this particular figure.

But what I think you can say and it's really important to look at the overall picture, is that you can see consistency of findings here.

There is no significant heterogeneity among these risk reductions. You see a very clear

effect overall. And this is telling us something about aspirin working in people who are within the prime prevention population.

Now we move on to looking at the overall data subdivided by their predicted risk of coronary heart disease. So, just to take you through this figure, you're looking at the Primary Prevention Trials here, and we're look at affects on coronary heart disease events.

Remember, we're now subdividing the data because we understand that there is an affect on vascular events. We now want to look at specifically whether that affect is driven by coronary affects of by affects on stroke or both.

So now we're looking at coronary heart disease events. And what we've done, we've developed a model, prognostic model within the database, to look at patients who are at low risk, that is less than one percent per annum which I think there's a fairly strong conviction should not be treated.

The moderate risk patients that we're aiming to focus on and a small number of patients who

actually were at high risk of a coronary heart disease event, this is the classification that's been used by the American Heart Association.

We wanted to be consistent with that to enable this committee to try to make a judgement based on similar data. Now we're looking at the second prevention trials, the post-TIA patients and the post-MI patients.

And you can see here, if you look at your figures within the pack, the absolute risks of an event are much higher. This is seven and a half percent per annum in the post-MI trials.

Remember, these are quite old now, so these rates would be lower now. And in the post-TIA patients, it's somewhat lower, about three percent per annum.

But if you look in these risk groups, then the risk in the placebo group of the high risk group is 2.4 percent. So that's clearly high risk. Moderate risk group, 1.3 percent, clearly a moderate risk. And low risk, only a half of a percent per annum.

So we successfully divided up the population into three different groups. And what's striking then, is when you look at this, it's absolutely straight, bang down the line, for all the risk groups we are getting a reduction in CHD events of a round about a quarter.

And that's very, very striking. And it's even more striking when you look at non-fatal MI. If we divide up the data and look at non-fatal MI, then what about that.

It's absolutely extraordinary. I think it is a very, very interesting figure. We see a one-quarter reduction in non-fatal MI, right across the different levels of risk.

And in the secondary prevention trials also. So this is telling us something very important about the affects of aspirin, I believe, among a wide range of different risk groups.

In stroke, things are a little bit different. In the secondary prevention context, we know, from previous analysis published in 2002, that roughly speaking, stroke is reduced by around about a

sixth, around a quarter rather.

And in the context of primary prevention, we don't seem to have a significant effect on stroke. Is that because we have an increased risk of hemorrhagic stroke? The answer to that is no.

By the way, I should say that there was an error in your handout. So, if you try to look at the stroke result, I don't think you have the right figure. You need to go back, and we can put the slide up if there's any questions about that one.

If we look at stroke, then, it's clear that there's no significant effect because of hemorrhagic stroke. And as we expect, there's about a third increase in the risk of hemorrhagic stroke, an one-third proportional increase in the risk of hemorrhagic stroke.

But the absolute excess risk of hemorrhagic stroke, which is what matters in public health terms, is tiny. We're talking about 61 events here versus 49, it's less than .1 percent per annum.

So it's really a very small risk. It's not irrelevant, but in terms of weighing public health

benefit, it is relatively less important.

If we look at vascular death, then similarly we say although we, in the high risk studies saw around about a one-sixth reduction in vascular death, there's no significant fate vascular death within the primary prevention studies.

Now, importantly, you also have to look at the risk of major extracranial bleeds. Again, defined in precisely the same way as we've defined it overall, transfusion-related bleeding.

You see around about a two-thirds increase. Obviously we're just looking at the aspirin studies here, we don't get very many bleeds.

We need to look at the high risk database overall to get a two-thirds increase in the risk of bleeding. Which is exactly similar to what we see in primary prevention.

So there's no concern that the proportional increase in the risk of bleeding might be different in primary prevention.

How does this all weigh up? Well, what we see here is particular outcomes. Non-fatal MI,

stroke, vascular death and major bleeds.

In primary prevention, what is similar to secondary prevention is that we get a one-third reduction in non-fatal MI. And we get a two-thirds proportional increase in major bleeding, which translates to about one per thousand excess per year.

What's different is that we don't seem to have any significant effect. We can't really say for certain what the effects are, but it doesn't seem to be significant for stroke or vascular death.

Which is in contra-distinction to what we see in secondary prevention. Of course, it may well be that this is a quirk of the data, since we don't have that many events. But at the moment, there's no clear evidence of any benefit or harm on stroke or vascular death.

We now need to do some calculus to work out which types of patients who are at moderate risk, who, after all, we've demonstrated have clear benefit on non-fatal MI, which types of patients should be treated.

Well this figure shows you the risk

groups. This is the coronary heart disease event rates. These should be percentage events up here.

You have one per thousand benefit here in low risk patients, so probably no clear argument for those patients being treated, since there's a one per thousand excess risk of major bleeding which balances that.

On moderate risk, however, we have three per thousand events prevented per year. And set against that one per thousand, you see there's a three-to-one ratio, which is quite clear.

If we also accept the major extracranial bleeding is perhaps of less importance in avoiding a non-fatal MI, then we can see that by setting three to one, we're actually being conservative, because we're weighing a major extracranial bleed as being similar to a non-fatal MI.

So this is actually a conservative estimate of the type of benefit you might see. And then in high risk patients, six per thousand benefit is really very clear.

So, I think this is probably the most

important slide of all, the weighing of benefits and risk for high and low risk patients.

For high risk patients, that is either greater than 20 percent or people who've already had an event, then we're talking about avoiding 25 to 50 vascular events per thousand patients treated.

And also an additional effect on the ischemic stroke if patients have already had an event, but not if they haven't. And against that, we said over five years you will see one extra hemorrhagic stroke and five bleeds.

So this is clear. On the negative side, this is clearly outweighed by the benefits. In moderate risk, we see that we're preventing around about 14 coronary heart disease events, most of which are non-fatal MIs.

And against that, this is over five years. Against that we're weighing one hemorrhagic stroke and five major bleeds. And again, I reiterate what I say about being conservative by treating them as similar events.

We actually need to be conservative in

making public health policy. And by doing it this way, we are doing that.

However, in low risk patients, it's quite clear that we should not be treating widely with aspirin, because the benefits are similar to the risks.

So to conclude, in the high risk patients, the benefits do clearly outweigh the risks. And I think most people are using aspirin widely in high risk patients.

In moderate risk, I believe that the Antithrombotic Trialists Collaboration analyses have helped us to see that there is a definite group of moderate risk patients that can be identified, not in a substantial group of patients in primary prevention, who could benefit from aspirin.

And that would be of substantial public health benefit. In low risk, however, we are not arguing that aspirin should be widely used, in fact we're arguing the opposite.

The balance is too fine and we would be potentially causing harm in this population. So, I'm

going to close my talk there, thank you very much.

And pass over to Dr. Merz, from Cedars-Sinai Medical Center to talk about the issue in women.

DR. BORER: Doctor Baigent, I think we'll have several questions for you before the next speaker. And I'd like to begin with sort of, with an overarching question, and I'd be very interested in Tom's comment as well, when you're finished.

We have here studies, controlled clinical trials, involving thousands and thousands and thousands of patients. And that's very useful for us because we have a point estimate of risk for the entire group that's been treated that's a lot stronger than we usually see when we consider benefit to risk issues.

But this very large population was very important to have, because the rate of primary events, the outcome events is low. You know, populations with a two percent per year risk. A one percent per year risk or less than that.

And therefore, to obtain a large number of events, we need to study a large number of people.

And one of the issues that everyone is grappling with, and I think it's implicit in the comments that Bob Temple made and the question that Bill raised about strokes and peripheral arterial disease, respectively, is that there, if you look at the individual trials, there is a variability in outcomes, in effect on outcomes in secondary analyses.

And presumably we gain greater clarity by pooling these data and doing meta-analyses, particularly when you use uniform criteria as you did, in the post hoc analysis.

So, I'd like a comment on the, from the point of view of a statistician, epidemiologist, etcetera, on the weight we should give in judging the variation we see among the individual trials for these relatively uncommon events that go one way or the other with treatment on secondary analysis versus the weight we should give to the pooled data.

I know that statisticians often argue about this, and I'd like to hear your opinion. That's one question, and while you're considering that, I have a second question that I'd like you to follow up

on, follow up with.

Silent myocardial infarction was excluded as an endpoint here. And I can understand why that might have been. Some estimates suggest that as many as half the infarcs that occurred are silent.

If that's true, I think it's implausible to suggest aspirin would do anything bad to those people, but, although I can't say that rigorously, but if you assumed that aspirin had no effect, most conservative estimate, had no effect on those silent MIs and we had missed half the events, what impact would that have on the conclusions that you would draw about the benefits of aspirin for prevention of myocardial infarction.

So, two questions. Once you begin, then I'd like to hear what Tom has to say.

DR. BAIGENT: Okay, to deal with the issue about heterogeneity, that once these meta-analyses, I mean one would expect to see variability in the size of an affect on the treatment, on a particular outcome.

What is important to recognize is there

will always be heterogeneity. It's whether that heterogeneity is striking in ways that help you understand the data that is really what we need to tease out.

So, if a set of trials are too small, when taken individually, to look at a particular outcome, then by putting them all together in a meta-analysis, one actually can pick out a true effect.

We have done that many times within the Antithrombotic Trials Collaboration. But we've also, specifically, always looked to see whether there is important heterogeneity that we can detect within that group of trials. And whether that leads us towards an important clinical message is something that we try to explore.

So I think we expect to see variation. Whether it's striking enough to warrant further attention is something that it behooves us to look at.

Your question about silent MI, it may well be the case that there are many silent MIs going on and their clinical relevance may well be worth debating.

But the fact is, that none of these trials, certainly none of the high risk trials, and only a few of the primary prevention trials, set out to record silent MI.

And they were only able to do so by taking ECGs at regular intervals. We cannot ascertain the date of the silent MI. Furthermore, many patients who have a silent MI, subsequently go on to have a clinical event.

And it's clinical events that we want to weigh as being important outcomes that affect patients. So I think that, actually, although there are things going on within our patients, that we can't record, we are getting into the nitty gritty, by looking at clinical outcomes.

And I don't think that in any way is detrimental to our analysis that we don't have information on silent MI available.

DR. BORER: Tom, do you have some comments about this, then we'll go on to Doug and Bob and Steve.

DR. FLEMING: Well, let me just make a few,

brief, initial comments about your question, Jeff, and assume that a lot more detailed response will come during the day.

I think it's important when you have designed, large key studies, as these five studies have been designed. I think it's important to learn the very most you can from them and certainly analyzing them individually and looking carefully at what their primary intended outcomes were, is one critical feature of how we should be focusing in our interpretation.

Certainly, though, those studies may be under-power to address some very specific additional issues and meta-analyses can be extremely important in expanding our understanding.

Realizing, however, that you may be pooling different sources of information that are somewhat different. But, my own sense is, it is important to look at both the individual studies and what they were intending to address, and then also to look at meta-analyses.

One of the specific features that has been

brought out, is these individual studies were all focusing in a primary sense on primary endpoints that had cardiovascular mortality as either the sole aspect of them or a major driving aspect.

And when you start looking at meta-analyses and then start looking at subcomponents, it's very important to realize you may have more statistical power but you also may be led down certain pathways to look at secondary measures.

One of the key issues here is if we're looking at non-fatal MIs, how important were non-fatal MIs in the overall view and the design of trials, in the context of the totality of the endpoints.

We have non-fatal MIs. We have non-fatal strokes. We have fatal events. I might have classified those in exactly that order in terms of their clinical relevance.

And so, as I look at these individual trials and the meta-analyses, one of the things that is important to my way of thinking is the meta-analysis has somewhat shifted the focus on what it was that these individual trials were intending to get at.

Let me just bring up one more feature. The silent MIs. And that's not a trivial issue, because one gets a very different picture in some analyses, in particular the one that the FDA has had a chance to go through in some depth. The HOT Trial, where you actually have an excess of events that are silent MIs, in the aspirin category, those may in fact be somewhat less clinically compelling than non-fatal MIs.

But non-fatal MIs, if you're only affecting non-fatal MIs, and not affecting fatal MIs or stroke or overall death, shouldn't that too, also be given somewhat less emphasis.

So it's a continuum here. And I think we'll discuss these issues in greater depth as the day goes on.

DR. BORER: Thank you. We'll go Doug, to Bob, to Steve, to Tom.

DR. THROCKMORTON: Thanks. I just had a little, a housekeeping issue. I wanted to ask you a little bit about the data presentation that you just made.

Do the analyses that you've shown us differ from the analyses you reported in the 2002 article? Do these come from that same analysis, or are these an extension of that?

DR. BAIGENT: The data we reported in 2002, did not look at time-to-event analyses. The data I've shown you today are limited for the post-TIA and post-MI trials, to trials of aspirin versus control, and they do have information on time-to-event.

So, they are from the same data search, but they, the results are likely to differ in only a few percentage points, because of that different method of answers.

DR. THROCKMORTON: Right, no, I was just curious. Were these submitted as a part of the package to the FDA? I don't remember if they were?

DR. BAIGENT: I'm sorry, I didn't hear that?

DR. THROCKMORTON: Were they submitted to the Agency. I don't remember seeing these particular analyses before. Do you know if they've been submitted to us?

DR. BAIGENT: What I provided from the Antithrombotic Trialists Collaboration for that package was a summary of the general findings. I obviously, in order to make it more informative for this committee, I'm showing you a little more detail now, so that you can flesh out that.

DR. THROCKMORTON: Right, sure. Okay, thanks. I just didn't want to think I'd missed something. Thank you. I have one other small thing. If you go to Slide 55, I'm sure it's just something I don't understand.

What are the two bars? What is the yellow and the red bar? Events preserved, what does that mean?

DR. BAIGENT: The left-hand axis shows you the percentage number of people who had a coronary heart disease event. And so what one sees is the yellow bar is aspirin therapy and the red bar is control therapy.

And that means that there's a difference of point one percent between aspirin, the proportion of CHD events. And so events prevented is actually a

slightly misleading way of presenting it.

DR. THROCKMORTON: Okay, thanks, I was a little confused. Thank you. Bob.

DR. TEMPLE: There's information, at least in some settings, post-procedurally, anyway, that very small MIs that no one could detect, but that are detectable only by troponin excess, may have some implications for outcome and mortality in particular.

So, my assumption is that if you had good data on silent MIs, which you don't, you might well have used it. I understand how difficult it is if you don't have the data.

And it's particularly difficult if you're doing an analysis looking at events over time. But you were content in earlier analyses with analyses that weren't over time, but that were just total.

So, at least where the data were available, you actually could do that, I assume. And it seems not easy to argue that losing some myocardial tissue, but not having pain, isn't an event that matters. You'd think it would, usually.

But I guess the data aren't available for

anybody, but the HOT Study.

DR. BAIGENT: We didn't seek information on silent MI from those studies that recorded it, because we felt a great strength around ours was that we had pre-specified, many years ago, when I was at medical school, asserted that we would only look at these types of events.

And I think that's been a great strength of the ATT over the years, that we've stuck to a consistent measure. And have brought all available studies together so that the public health community can see results in one chunk.

DR. TEMPLE: Did I understand that Slide 50 that was handed out, was just wrong and that you showed the correct slide?

DR. BAIGENT: Yeah, I'm sorry, that was a slip.

DR. TEMPLE: It seems to show a stroke affect, but there isn't. Do you have a slide for just thrombotic stroke?

DR. BAIGENT: We do have a slide.

DR. TEMPLE: This was total, and you showed

hemorrhagic.

DR. BAIGENT: I believe it may be, I don't have my crib sheet here, but there is a back-up slide available to us on ischemic stroke. But I can tell you what it shows.

It shows no affect. Obviously, if you have no affect on any stroke, which is most of the strokes, and the ischemic stroke is most of those.

And you have a tiny, actually an excess risk of hemorrhagic stroke. And it implies that there cannot be any affect on ischemic stroke. Now the reason for that, we are exploring in more detail, as best we can, from the available data.

But at this point, it doesn't seem to be any obvious reason. For example, if you subdivide people by their baseline characteristics, you might want to try and identify people who are more likely to have a reduction in ischemic stroke.

We've not been able to find any such evidence that there is a particular group who do avoid ischemic stroke within that group. But I have to say, of course, that we have a limited number of strokes

within the primary prevention database and so we're probably torturing the data more than we should in looking at that kind of level of detail.

DR. TEMPLE: One of the questions that will face the committee later, is the question, how much comfort should you take from the previous data in the sicker people, in the secondary prevention population.

And that's intended to be a question for discussion, but it does seem on its face that the failure to find what everybody knows is true and ask them if you've had stroke, in the primary prevention group, must shake one a little. So I just wondered what you would say about that.

DR. BAIGENT: I think it's an interesting finding. But we need to remember that we've got clear evidence on non-fatal MI, and that's a substantial protective effect.

We've got neutral results on stroke. There's no evidence that we're causing ischemic stroke. There's evidence that we might be causing a few, a very small number of hemorrhagic strokes.

And there's evidence that we might be

causing some extracranial bleeds, which is obviously important to weigh. There's no evidence at this stage that we're preventing much death, although we would expect that to be an effect of aspirin, even in primary prevention. It may be we just don't have enough numbers.

One technical issue I think is worth considering, when we think about effects on death, and that is that many of the patients who had non-fatal events, non-fatal MI in particular, subsequently went on to die.

And so when we consider death on its own, we may well have the phenomenon whereby patients who have a non-fatal event then start active treatment.

And so the failure to find an effect on mortality, may in part be related to that technical issue. And so I think that what we're seeing is clear effects on MI. No concern that we might causing an excess risk of stroke or vascular death, and clear effects on bleeding.

And what we need to do is focus on those two things, where we have a clear signal and try to

weigh those in ways that are sensible.

DR. TEMPLE: And so just, my last question. That's how we should take, I take it, the effect on vascular events slide, Number 47. Obviously the beneficial effects are driven mostly by effects on MI?

DR. BAIGENT: Yeah.

DR. TEMPLE: And you're saying well, the other events, mortality, don't take that benefit away, even if they don't add much to it.

So is that how one should look at Slide 47?

DR. BAIGENT: Have you got 47 there? Oh, no, you need to go to another presentation. Yeah, we're saying that most of this is driven by effects on coronary heart disease, that's important to understand we get that from this meta-analysis.

We can decided, from this meta-analysis, that this is a clear signal, that it's really important to emphasize that this comes from dominantly non-fatal MI.

DR. TEMPLE: You could add, I guess, I'll add it for you, that four out of the five studies, by

that measure anyway, whatever one thinks of that measure, achieve nominal significance, you know whatever their other "

DR. BAIGENT: That is certainly a true statement. But, I would argue that "

DR. TEMPLE: It wasn't the primary, I know, I know.

DR. BAIGENT: Yeah, you know what my arguments are. I think that we're throwing out information if we just adhere to that kind of approach to interpreting data.

DR. BORER: Steve and then Tom Pickering, Blase, and Tom Fleming.

DR. NISSEN: From a regulatory policy point of view, one of the questions that we face here is when do you use a meta-analysis in deciding about regulatory policy.

And so I want to test a question on you. And the question is shouldn't we restrict such use to situations where there's not a testable hypothesis that can be answered with an appropriately designed prospective clinical trial.

And so the question I would ask is, is the question of whether there is a benefit over risk in the group with the ten to 20 percent risk? Is that a testable hypotheses? I mean could you design a trial?

I'm going to do some power calculations later myself, because I'm going to use your data and I'm going to go back and actually ask that question.

And so if it's a testable hypothesis, then I would ask you, why not test the hypothesis?

DR. BAIGENT: Well, I think there are trials going on at the moment that have identified this as being an important question and they were mentioned, I think, by Dr. Pearson earlier, that there is a trial--no, one of the speakers over there, mentioned that there was a trial in peripheral vascular disease going on Scotland. There's a trial in the elderly that's proposed, that will be looking at precisely that group.

You could think of other groups that would be interesting to have information. But I think that the principle that you might be able to ask physicians, identify particular patients within your

practice who you consider to be at moderate risk, and that you feel might be able to benefit from aspirin, is a good one. And supported by the data.

DR. NISSEN: Sure, but it relates to whether that's something that might appear in a guideline written by an organization or something that would reach the level of evidence that a regulatory agency would want to provide a label for.

And I'm asking the question. I mean, most of the time what we're faced with here at this committee is, there's a hypothesis, the hypothesis is tested.

We have that data. We look at it, and we analyze it and we decide whether it meets the level of evidence required or not. And you know, you would agree here, that there is no trial that's tested the hypothesis that's being asked here.

Which is whether or not a group of people selected, for having a ten to 20 percent risk, have a benefit over the risk.

DR. BAIGENT: I think the objective of the trials that have been published most recently, the HOT

Study, the Primary Prevention Projects and the Thrombosis Prevention Trial, was actually to identify such a group.

Their event rates were somewhat lower than they had hoped for, but that was the objective of those trials. And we can find a group, within those trials, you know, a randomized comparison within those trials, where those patients were studied.

So I think, you know, we already have randomized data within, looking at that very question.

DR. NISSEN: I guess the other question I wanted to ask is with the Thrombosis Prevention Trial, there are two p-values provided. One for coronary death and fatal and non-fatal MI. And that p is equal to 04.

And then there's a p of equal to 07 when you include silent MI. And I'd like to know which of those analyses was the primary pre-specified analysis of interest here? What did they pre-specify in the trial?

DR. BAIGENT: Well, we have Dr. Meade present in the audience, but I think I know what he

will answer, so I can tell you the answer is that they did not plan to look at silent MI as their primary outcome. So it was specifically aimed, maybe Dr. Meade would want to come to the microphone and just affirm that that was the case. But it was not planned to look at silent MI.

PROFESSOR MEADE: Yes, I'm Professor Meade. It was not pre-specified. It was analysis that was actually carried out by your statistician, and which I actually think was inappropriate.

DR. NISSEN: Well, if it wasn't pre-specified, why would anybody have gotten all those EKGs and looked at it? I mean obviously somebody was interested enough in it to get a bunch of electrocardiograms.

PROFESSOR MEADE: We were carrying out serial ECGs throughout the follow-up of our trial participants, and it seemed to me an obvious question that people would ask about silent MIs.

The result we got was no effect at all. To me it doesn't actually follow, although we know about the significance of silent MIs that aspirin are

necessarily going to influence silent MI.

But in any case, it was simply provided because people we discussed it with said, well, it would be interesting to show that.

It's not pre-specified. It was an analysis carried out by the FDA Statistician and which I take rather serious exception.

DR. BORER: Tom Pickering.

DR. PICKERING: I have a question about the blood pressure. In Slide 41, in the high risk patients, you said the benefit was the same whether or not the diastolic pressure was above or below 90.

Nowadays, as you know, we tend to focus on systolic pressure, in fact, some hypertension experts have said we don't even need to measure diastolic pressure.

So, can you tell us about systolic pressure, and also, you also said that if patients were really hypertensive, they didn't get into these studies.

So what sort of range of blood pressures are you talking about in this analysis?

DR. BAIGENT: Well, this particular analysis was done for the 1994 cycle analyses. In that stage we didn't analyze systolic blood pressure, although we could have done.

I haven't repeated these analyses specifically for this committee for looking at systolic blood pressure. I can't give you an answer to your question. However, we have looked in the primary prevention trials at whether systolic blood pressure is associated, no, raised systolic blood pressure is associated with any attenuation of benefit.

And we did not find that. We found similar benefits irrespective of blood pressure. That's to say within a particular risk level, the influence of blood pressure was not to attenuate benefit.

In terms of, so that answers, I hope answers your question about the effects of aspirin at different levels of blood pressure.

In terms of range of blood pressures that would typically be included in trials, you're as

familiar as anyone with the types of patients who are excluded from aspirin or antiplatelet trials.

Generally speaking, people specify an upper limit. For example, 180 systolic, 200 systolic. It varies between trials. But generally speaking, we see an average of something like 140 over 80 in most trials.

And you might see systolic blood pressures going up to, you know, 160, 170, but not much higher than that. That's the range of values seen.

DR. BORER: Blase.

DR. CARABELLO: Out of these trials, the British Doctors Trial is the odd person out. And today it might be easier to blow it off because we have five trials and it's only one of those five.

But 14 years ago it was one of the two trials available. And at that time the committee still voted in favor of broader labeling.

I realize that a number of the physicians involved stopped taking their aspirin, and that might be one excuse. But as I read through that trial, I just found it hard to understand why it failed to come

up with a difference.

And I was wondering if you or its PI could address that trial specifically, as it is the outlier here.

DR. BAIGENT: Okay, well I'm flattered that you say that I'm PI. I'm representing the British Doctors Study. Actually, I wasn't born when that was started.

(Laughter.)

DR. BAIGENT: Sir Richard Doll still comes into work every day and he has the office next to me. And still works longer hours than I do, so he is the principal investigator.

And I think what he would say is that there was an issue with compliance in the British Doctors Study. We really can't explain why this result is out of line with the others.

It may be to do with doctors starting treatment, you know how they are always the first to act on guidelines that have not yet been written.

And certainly I think that there was this phenomenon in the UK whereby some of the doctors

accepted the evidence at an early stage.

We have actually gone to quite a lot of trouble to get the data from individual records out of the basement where they're still kept in Oxford.

And we, actually quite a lot of work went into trying to put the data together so that they could be analyzed as part of this work.

So I think if there was anything particularly striking, we would probably have discovered it during the course of doing that work. But nothing that we've analyzed has given us any clue at to why that study is a bit out of line.

DR. BORER: Tom Fleming.

DR. FLEMING: I have a couple of quick issues and then maybe one or two more detailed issues. Just very quickly, could you remind us the year in which you said you pre-specified your analysis plan for the analysis of these five primary prevention trials.

DR. BAIGENT: We did that and we met in 2000, I believe, January, 2000, February, 2000. But actually we've been, I mean that's really a bit

misleading. Because I've been working on this for the last decade.

And after the high risk paper in 1994, we felt that we should be looking again at the high risk trials in a new cycle of analyses, and that was what we published in 2002.

But we also felt that in the 2002 paper, we should separate out the primary prevention trials. So, in some ways, we have been planning for some years, before that, to look at the primary prevention trials separately, knowing that particular new studies had been planned and were ongoing.

DR. FLEMING: And certainly we know from a scientific perspective, if we're looking at evidence to be interpreted as confirmatory, as opposed to exploratory, we like to have pre-specified hypotheses.

Usually we think of that pre-specification meaning before the data are unblinded, how we struggle when we're doing meta-analyses of studies that have been essentially completed.

The meta-analysis is pre-specified, but the data are out there, and so it's not rocket science

to get a sense of what kinds of hypotheses are likely to be supported or not supported.

The second issue is as you did these analyses, some of these patients that came from these five primary prevention trials were in fact post-MI or secondary, in particular, PHS, that's true.

Did you exclude all of those patients when you did these meta-analyses?

DR. BAIGENT: We didn't exclude them. We had information about those patients or those individuals who had inadvertently been entered into the trials.

And what we have done is we've analyzed the data among those patients who had a history of vascular disease and among those patients who didn't have a history of vascular disease.

And we've been able to show, and I can make the data available to the committee. We've been able to show that the results were entirely similar in both groups.

And, moreover, the results are not explained by an effect only in those patients who had

a history of vascular disease.

I note that Dr. Gaziano has come up to the microphone. I believe he probably wants to make a comment about the types of patients who were included in the U.S. Physicians Study. So, Mike, you might want to say a few things.

DR. GAZIANO: Yes, I represent the Physicians Health Study. I'm Mike Gaziano, the current PI of the study. And I take issue with the notion that there was a substantial number of individuals with prior MI in the Physicians Health Study.

It was a very low risk group of individuals. After very careful review of all records for any reported MI during the study, we've located one individual who's had a confirmed MI prior to the start of the study.

And there were no other clinical evidence of prior MI. In the study, in general, it was a very low risk group of people. We had about 15 percent of the overall anticipated mortality for an age-matched male group.

So it's a very low risk group. There were about 333 individuals with angina at baseline. But, in general, it was a very low risk primary prevention group.

DR. FLEMING: I'm not talking about the totality of the study distribution. I'm talking about whether there were a fraction of these patients in this study that, in fact, are in, what we would call secondary prevention categories for which we've already had approvals.

You're saying there are almost none, you're saying?

DR. GAZIANO: Almost none. Almost none. There were 333 who had pre-specified angina out of 22,000, and one MI. So it's a primary prevention trial, largely.

In those 333, there were 28 MIs.

DR. FLEMING: Could I have you go to Slide 50, actually I'm going to want to quickly scan through 50, 51, and 52. While you're going to that, one of the struggles here, and we alluded to this earlier on, is that we've got five studies in primary prevention

and those primary prevention studies, as Dr. Pearson's slide previously showed, are heavily weighted toward what we would call low risk patients for whom we're not specifically advocating aspirin use.

I think you've indicated that as you've divided these patients up into low risk, moderate risk and high risk, in terms of person and years of follow up, I think only one-eighth of this population falls into the moderate risk group, and only three percent into the high risk group.

So certainly any conclusions particularly we would make about high risk, are extraordinarily fragile. And what we see about intermediate or moderate risk is, again, based on only one-eighth of these five.

But what's interesting is that at least for me, one of the issues that is very important here is that, in looking at a composite endpoint, not all components of the composite are of equal clinical relevance.

We've got, in your composite here, we're focusing on non-fatal MI. We're focusing on stroke

and we're focusing on fatal events. And these data point out that when you do subdivide and take your seven-eighths of the population that you consider at less than one percent, and then your one-eighth of the population at one to two percent, which is your target group.

If we looked at the aggregate, one disconcerting element here is that we're not seeing even a positive trend for fatal MIs, for stroke and for overall cardiovascular death.

When you've done your meta-analysis here and you look at stroke, it looks even less favorable in your moderate group than in the low group. If we go to the next slide.

When you look at hemorrhagic stroke, it looks less favorable as well. Next slide. When you look at vascular death, it looks less favorable as well.

So, when we look at this entire data set, including the primaries, you see something very inconsistent with secondary. You don't see trends for beneficial effects on these very important elements.

And now when you subdivide it into primary, into low risk against moderate, on these critical features, moderate looks even worse. Am I misinterpreting or is that, in fact, a fair interpretation?

DR. BAIGENT: Well, I would interpret it a bit differently. If we could go back to the first one on stroke. If I'm understanding you correctly, you're concerned that the moderate risk patients are having a less favorable effect than the low risk patients, is that correct?

DR. FLEMING: What's your interpretation of it?

DR. BAIGENT: Well, I would say that this is likely to be the result of having subdivided the data in many ways. I mean we are looking at several hundred analyses here. We have to, I think, be careful about making errors by going into the data in too much detail.

I mean maybe one sign of that is that actually, although these moderate patients appear to be a little adverse, when you go to the higher risk

patients they appear to be going back the other way.

Surely this is more likely to be due to random error, that we need to be careful that we don't make mistakes by looking at that kind of level of detail of the data.

DR. FLEMING: When we were talking to Dr. Pearson, we were, some of us were concerned that we're being asked here today to look at whether or not there is an adequately favorable benefit to risk profile in moderate risk patients, that an approval should be provided, this should be added the indication.

And we were concerned that the preponderance of evidence in these five studies comes from what you might call low risk. And we were told, well, wait for your presentation because you're going to pull out those moderate risks, and you're going to be able to show us the insights from that moderate risk.

So, I'm left on the one hand with my understanding that we are to look at these data in the moderate risk category and put some credibility as we make our assessment as to whether the label should be

extended to this cohort.

And yet, when the results look more, look less favorable here, now you're telling me something that I understand. Which is gee don't overinterpret subgroups because this is going to be particularly unreliable, especially when it's such a small subgroup.

I understand that. But then I'm left with the thought that what little evidence is here, doesn't look good, how am I supposed to interpret this evidence then in some way as being the basis for an extension of the label?

DR. BAIGENT: Well, I believe I have shown you the moderate risk group in the context of the other risk groups. And that was my aim all along to, and the aim of the ATT, has been to try and present all of the available evidence to pick out the moderate risk group as being indicative of a general pattern.

Can we go back one or two slides, I think -- this one here. I never argued that this particular result should receive emphasis.

This particular one here, which happens to

be three standard deviations in favor, a non-fatal MI. I didn't pick that out. But what I pointed out and I think is really important for this committee to understand, is that the results on non-fatal MI are similar across a wide range of risk levels.

And that is one piece of evidence we need to weigh. And then we need to think, well, what does that imply for the benefit to risk ratio?

We obviously need to consider stroke and vascular death as part of that overall evidence. But I would argue for looking at all the risk levels and trying to reach a synthesis of the data by looking at all the different risk levels and picking out how the benefit to risk ratio is favorable within particular risk groups.

And we're arguing that you should be conservative and say moderate risk seems to be about three to one. That seems to be a good level to pick.

If you go lower than that, then you may be causing significant harm.

DR. FLEMING: So essentially in Slides 50, 51 and 52, where these patterns look unfavorable, your

overall sense is we should proceed with caution here because this subgroup is a fairly limited fraction of the total of this meta-analysis. Did I interpret you correctly?

DR. BAIGENT: I think they should be treated with caution, yes, because they are relatively small numbers of events.

DR. BORER: Paul.

DR. ARMSTRONG: Dr. Baigent, I've got two questions. Almost half of the population that you've presented were male doctors. And arguably, some would say that doctors are smarter than patients and some would say not.

(Laughter.)

DR. ARMSTRONG: And some would say that the applicability of treatments in doctors to the general population that we're considering is perhaps questionable.

And it leads to my second question. But the issue is surveillance as it relates to side effects, which I'm still trying to get a handle on, and the extent to which compliance and recognition of

side effects, such as mylina or other things that might lead to more catastrophic events, might have been more sensitively surveyed by the receiver of the medicine.

So I'd like you to comment on that, and I'd like you to comment on the rigor with which surveillance, as it relates to these uncommon but important issues that we're grappling with, were actually detected or looked for in the broad cross-section of studies and patients which we're reviewing. So, if you could deal with that question first and then I have a second one.

DR. BAIGENT: Okay. We specifically asked people to give us information on serious bleeding, by which we meant typically transfusion.

There may occasionally be bleeds that don't need a transfusion that are serious, that are not cerebral, but we asked for serious bleeding and generally we got transfusion-related bleeding.

So that was the same for the U.S. Physicians and the British Doctors Study. We went to some length actually to ensure that numbers were

transfusion-related.

So the absolute risks I've shown you are based on that specific outcome. And I don't believe surveillance would have accounted for much variation in the way in which people interpreted that.

DR. ARMSTRONG: And there was no heterogeneity across the doctor, non-doctor studies as it relates to the side effects? Because I couldn't get at that from your presentation.

DR. BAIGENT: Well, we could put up the slide on major bleeding. Actually, no, we don't have the individual studies available to look at.

But my recollection is, and I can get the data for you after the break, if you would permit that, is that there wasn't any heterogeneity between the studies.

DR. ARMSTRONG: My second question, in your 2002 BMJ work, you talk about the risk being similar across a wide category of patients, at least as it relates to extracranial bleeding.

And I'm still, and you mentioned in your presentation that you do have now time-to-event data.

And so what I'm trying to get at is time-to-event as it relates to intercranial hemorrhage and GI bleeding, and bleeding requiring transfusion and the extent to which we can learn something from that relative to, for example, small, elderly females of low body weight for whom bleeding is of concern in relationship to other studies, as you well know.

So, do we have that information, sir?

DR. BAIGENT: We certainly have the information available that would enable us to do those analyses. We haven't done them as yet. But we've looked at the variation in the relative risk of hemorrhagic stroke and of extracranial bleeding according to baseline features, and we did not find any statistical heterogeneity among the different subgroups. So however, whatever type of person you are, the relative risk increase of each of those types of outcomes doesn't appear to be predicted by your particular baseline features.

However, the absolute risk of those events is modified by that, and that is something that we could look at. I should say that we have looked at

time-to-event analyses of those adverse events and we find that they accrue uniformly over time.

So it's not as if we get a massive hit in the first year after starting treatment. They accrue over time.

DR. ARMSTRONG: That's helpful, thank you.

DR. BORER: Bob Temple.

DR. TEMPLE: I just wanted say, mention a couple of historical things. The idea that something like 500 of the patients in the Physicians Health Study had a prior MI was based on an onsite review by someone who is now dead, and who, therefore, cannot defend it anymore, but I can tell you she was a very careful reviewer. So, I can't say too much more about it than that. But that's what she thought when she did an on-site inspection of the records.

I guess I want to make the second observation that having one study go the wrong way is not unprecedented in the aspirin world. The largest secondary prevention study, AMIS, had mortality going adversely and didn't have a favorable effect overall.

So it's not so odd that that could happen,

the rest of the studies looked much better. And I just want to say something about meta-analysis, really following up what Steve was saying.

As a general rule, I can't, I don't know enough to say that there's no exception. We have thought there ought to be some studies, how many to be debated, that actually show the effect of interest on their own.

And as Tom was saying before, that doesn't mean you can't learn a great deal from subsets and all kinds of other things that meta-analyses are done for.

But it would be unusual, I can't say never, to reach a conclusion based entirely on the meta-analysis of studies. Now, I don't, that's partly a reading of the law and it's partly nervousness about how meta-analyses come to be.

You usually know the results before you do them. It's worth noting, for example, that in secondary prevention there is no specific mortality claim in the current aspirin labeling. There is a claim for the sum of MI and mortality, because that endpoint is solid in many individual studies. But

although the overall analysis clearly shows, I mean the meta-analyses clearly show a mortality effect, that is not in the label.

And the reason for that is the one I just gave you. No individual trials managed to show that. So you could describe that as an excess of caution or a lot of things, but there is some nervousness about not being able to see it in individual trials.

One last bit. The reason, when we saw only two studies, the British Doctors and the Physicians Health Study, we were not overimpressed was that, remember, the Physicians Health Study failed on its primary endpoint, because there weren't enough deaths.

We were too healthy. That's because we're too smart. I believe the first explanation is the best. I'm still in that study. When you actually, when you go to find an alternative endpoint, a good question is should you pick the one that knocks your eyes out, or should you have a broader endpoint which is stroke, hemorrhagic and non-hemorrhagic, death and MI.

Well, when you do that, you just saw the number, you get a .01. That doesn't necessarily overcome the British Doctor Study. That's not so powerful that it looks persuasive.

And I think that's why we were a little skeptical back then. Of course now there are three more studies and that's a lot more information.

DR. BORER: Before we go on to Bill, Tom, you wanted to comment on that?

DR. FLEMING: Just among the things that Bob Temple was just saying. Just to add a little bit to one point. You were talking about the Physicians Health Study and you were, I think what you had said was the mortality endpoint, the doctors are too healthy, there weren't enough deaths and so it wasn't positive because of that.

You're mic is not on.

DR. TEMPLE: Some of us think there were enough deaths.

DR. FLEMING: Well, I guess what I want to lead to is "

DR. TEMPLE: I'm just kidding. It was good

to have a healthy population.

DR. FLEMING: There's a difference between a non-significant result that's really trending and suggesting benefit, but you're underpowered, versus a study that's suggesting no difference.

And there were equal numbers of deaths in that study. So it is in fact true that that study needed to have more deaths to be able to be adequately powered to show differences it was targeted to be able to show.

On the other hand, it did show that in the substantial number of deaths that were there, they were balanced. And so that's, you know, it's important to say that a study that doesn't achieve statistical significance isn't the same as another one.

There is still information in there.

DR. PEARSON: I was wondering if I would invite Professor Meade to the microphone at this juncture. Because our point is, we have one moderate risk study which in fact, using predetermined endpoints, does show a significant effect.

And if we could perhaps have him give a couple of comments relative to Dr. Temple's point.

DR. BORER: We will want to hear that. Is that not part of any of your presentation later? No?

DR. PEARSON: No.

DR. BORER: Okay, let's hold off for one second and hear the other two questions which may relate to that same issue, and then we'll have Dr. Meade speak. Bill.

DR. HIATT: Just back to slide 47. I just want to understand your data analysis. Because when I look back at the trials themselves, on the composite endpoint, MI, stroke, vascular death, Physicians Health Study was positive.

HOT was positive if you exclude silent MIs. Looking at the Primary Prevention Project, Table 2 of the efficacy results, in the article itself, with the composite cardiovascular death, non-fatal infarction, non-fatal stroke, it's a non-significant with the confidence intervals up to 1.04. Your results show something different than that, which is why I asked the question when you presented it. I'm

sorry I had to interrupt. And so that was confusing.

If you look at the TPT Study on Page 237 of that article, it says aspirin without warfarin reduced all ischemic heart disease. So that's fatal, non-fatal MI, excluding stroke, by 23 percent, but it's minus 42.

So that also crossed the one. So according to the actual primary articles, those two composite endpoints were statistically negative, but you're presenting them as positive. I didn't understand that.

DR. BORER: Before you answer the question, can I, you're referring back to the original article that presented the data on this trial.

If I'm not mistaken, in the ATT you pulled out segments of each of these trials, did you not? To look at the moderate risk patients, or do I misunderstand that?

DR. BAIGENT: This particular figure is showing all the available data. And I can't comment on individual numbers. I can certainly explore what you're saying, in more detail.

In the break, I can look at the numbers and try and explain why they differ. All I can say is that the principle investigators of these, of all the studies confirmed the data that we had presented were correct.

So, there maybe minor differences in definition that have accounted for those differences. We asked for particular outcomes to be provided and analyzed them de novo using our own definitions.

And that may account for some differences. But I would, I will look and see during the break.

DR. HIATT: Well, it might in fact, because the Primary Prevention Project was very close on that composite endpoint and the risk reduction was very close to what you present.

So maybe your analysis explains that. But it was just in contradistinction to the actual articles and FDA's statistical analysis were different from what you're presenting. And that's why I was just asking that question.

DR. BAIGENT: Naturally there will be, there will be minor differences. There shouldn't be

major differences.

DR. HIATT: A related question is in the 2002 publication of the Antithrombotic Trialists Collaboration. The result of peripheral arterial disease is a 22 percent or 23 percent odds reduction. But that's when you include all the other antiplatelet drugs in addition to aspirin.

So, ticlopidine, dipryridamole, clopidogrel. If you continue to call off just the aspirin effect in those patients in your publication is that any different than it was in the earlier publication which was not significant?

DR. BAIGENT: The argument that we put in the 2002 publication was the same essentially as we argued all along. But what we're seeing is an antiplatelet effect of aspirin.

If we analyze all the, if we set out to analyze all the antiplatelet drugs together, get an estimate of the facts and then we examine in a separate analysis whether there was any evidence that aspirin working differently to other, had different effects to the other antiplatelet agents that are

available.

We concluded from that analysis that the evidence among about two-thirds of the trial was using aspirin were similar to the other trials.

So that's been the basis for arguing that aspirin is an example of an antiplatelet effect. It's the most widely used example, it would be expected to produce results that are largely similar to the overall findings of the 2002 results.

DR. HIATT: So it wasn't driven by the same data from the CAPRI where clopidogrel was clearly superior to aspirin in that population? And ticlopidine had similar kinds of differences, but when they compare it with aspirin.

DR. BAIGENT: Yeah, the clopidogrel turned out to be very slightly more effective than aspirin in the range of patients they studied in CAPRI. It formed part of the evidence for the comparison of a different antiplatelet agent with aspirin.

But it was not, there was no evidence from the trials comparing an antiplatelet agent versus control. The effects varied according to the

antiplatelet agent.

So overall, we had some limited evidence that could prove it might be more effective in particular types of patients. But generally speaking, the effect of antiplatelet drugs appeared similar across the board.

DR. BORER: Alastair.

DR. WOOD: Yeah, could you put up Slide 30, again. It seems to me that what the committee is struggling with is the lack of data in the pale yellow section.

And I guess what I expected and from the trailer for your talk was that you were going to fill that in by taking the data from all of the studies and give us some data on that.

Can you sort of verbally do that now and give us a sense of what that data would look like in the absence of a slide? And before you get to that, I guess the second thing it seems to me is you've all locked yourself into this ten percent as the cut point.

And at the same time you're offering all

of the variables as a continuum. And which seems to me a mistake in some ways. But to go back to my point, I was expecting to see you fill this in.

DR. BAIGENT: If I could go back to the, if we bear that in mind, the light yellow section, the middle section is the second line on each of my figures.

So, if we go back to Slide 50, say, could you do that for me? Maybe one before that. Consistently throughout the talk, what I've been trying to do is show you, this is the section on the left-hand side, the low risk group.

This is the moderate risk group and this is the high risk group. As Dr. Pearson said, I was going to describe what happens in this group, but in fact what I've aimed to do through the talk is actually describe a continuum.

I tried to get the overall picture which is of consistency in non-fatal M, and then to argue that this has implications for considering this moderate risk group, and indeed for the high risk group, where some people would say that, you know, the

issue is less, less contentious.

But for the moderate risk group, this is the relevant line. And I have a hope being able to show that the effects are similar throughout the board including this middle section for non-fatal MI.

It's not appropriate, in my view, to take this group here in isolation and start chopping it up. I think, I hope Dr. Fleming would agree that that would be inappropriate. We'd be looking in far too much detail at a relatively small number of events, when treated in isolation.

That actually would be over-analyzing a group of patients from within the overall context of the study.

DR. FLEMING: Indeed, I do share your caution when you point that when we take a meta-analysis and then we look at one-eighth of it, which is the moderate group, the middle group as you're pointing out, that we'd hoped to have filled in, and then the high risk which is three percent, you've got to be extremely cautious.

The issue, though, is this, to come back

to Alastair's point, my understanding too was we were going to be led down a path that was going to show us how we could use these data which were predominantly in a low risk group, to try to have insight about risk benefit in this moderate risk group.

So the tension here is I share your concern about viewing this with great caution, but these are the data that we have to use, most importantly, to draw our conclusions.

And when you go beyond 49 and you look at Slide 50, if we could just, one more time, look at Slide 50, one of the issues here that is of concern to some of us, is that there seems to be an inconsistency between what we see in secondary prevention, which is, yes, you have a reduction in non-fatal MIs, but you correspondingly have a reduction in fatal MIs, in stroke, and in overall vascular death.

And that's not showing up in the meta-analysis of these five studies in primary prevention. So I was hoping to be led down a path here at least, granted, I have to view this with caution, that might suggest a continuum here.

And there isn't. It gets actually worse when you look at your moderate group on these measures that aren't showing benefit in the overall primary prevention meta-analysis.

Now I subdivide into the 13 percent that are the moderate target group, and I see even more concern. Granted, viewed with caution, that on this slide and the next two slides, the key most important endpoints seemingly are even more problematic.

DR. BORER: Steve, let's hold your issue until after a break, which I haven't called yet. But if we don't do it soon, we won't have one. Let's take a ten-minute break, we'll reconvene at 11:15 and we'll begin with Steve's question.

(Whereupon, the foregoing matter went off the record at 11:06 a.m., and went back on the record at 11:20 a.m.)

DR. BORER: So, if we can assemble, I will begin with Steve Nissen's question.

DR. NISSEN: We need a responder at the microphone, though.

DR. BORER: I think he's coming. Why don't

you ask the question. A response will appear from somewhere.

DR. NISSEN: Okay. Well, I want to see Slide 50 again. This is a follow on to Tom Fleming's earlier question, which is what appears to be, I'll use the word signal, although it's obviously kind of a weak way to do it, that there is excessive stroke risk in that one to two percent category. And this is to some extent a rhetorical question, but there is a formal test for heterogeneity here.

And I know you did that for all of these, and I'd like you to maybe make sure everybody here understands what the results of that heterogeneity test is for this particular analysis.

In other words, is this, is there heterogeneity here or is there not?

DR. BAIGENT: Yes, there is. We tested between this result here and this result here. So the second prevention trial is a 90 percent reduction and the primary prevention trial is a five percent increase, non-significant increase.

If you test for heterogeneity between

these two, that is to say is there any evidence that these differ. And you do get a p-value of .01. So it's clear evidence heterogeneity "

DR. NISSEN: So clearly it is heterogeneity. I wanted to make sure everybody saw that, Tom.

DR. FLEMING: And it's even worse because that strength of evidence for heterogeneity is just looking at the five percent against the 19 percent.

And within the five percent, we see additional evidence that is, in fact, inconsistent with a linearity here. What you've got is the critical group of interest to us here is a subgroup within the group of five percent that looks even worse than the five percent.

DR. BAIGENT: I do think we need to, we must not lose sight of the fact, though, that we are arguing that we can prevent non-fatal MI. And that is worthwhile. We are also arguing that we have no clear evidence that we're causing ischemic stroke, and that is something that we'd like to have, but we don't have. So I do think there's been a little bit too

much emphasis on this particular result and the result on vascular death.

Whereas we have something which is extremely striking in non-fatal MI, and we must not forget that.

DR. NISSEN: I have to follow up just a second on that and say you're getting pretty close there on that one to two percent category.

It's not quite significant, but it is really pretty close, isn't it?

DR. BAIGENT: Yeah, but we've looked at several hundred analyses. I mean, you know, you expect to see a little bit of garbage when you do that.

I mean if you torture the data enough, it will eventually confess. And, you know, I think we do need to bear in mind, I mean, you know, I think pretty much everyone agrees that there have been a lot of analyses here and, sure, we're going to see some apparently striking findings if we over analyze it.

DR. BORER: As a follow on to that, your Slide 55 where you look at CHD events, this presumably

includes MI death and, non-fatal MI, non-fatal stroke and death.

And you've come up with a three, a benefit of three patients per thousand per year reduction. Is that correct for all events?

DR. BAIGENT: That is correct, yes. We did that because coronary heart disease event rates stratification is used by all the guidelines's bodies. So we wanted to make it easy for these data to be compared with other guidelines.

DR. BORER: Yeah, my only point was that this presumably is an integrator of all the good and bad things that happen.

DR. BAIGENT: This combines non-fatal MI and coronary heart disease death. It has a clear effect on non-fatal MI, there's no clear effect on coronary heart disease death.

Many patients who had a non-fatal MI go on to have a coronary heart disease death. So we're looking at the time to first of those events.

DR. BORER: I'm sorry, then I misunderstood. This is non-fatal MI and death.

DR. BAIGENT: Or coronary death, yes.

DR. BORER: Or coronary death, but does not include strokes.

DR. BAIGENT: No, it doesn't.

DR. BORER: Okay. Why don't we go on to the next, oh, I'm sorry, Bob.

DR. TEMPLE: Slide 47 shows study-by-study results for the combined endpoint of vascular events. Is there a similar table for just, a study-by-study now, not be risk, for the coronary events?

DR. BAIGENT: Yes, there is. If we, I mean I haven't got it available for you in this presentation, but I can tell you that it shows a similar pattern, a very similar pattern in fact.

As you'd expect because you're not getting much effects on stroke, you're not getting much effects on death, you're getting an effect on coronary heart disease.

And that's consistent throughout the study. So you see a similar sort of pattern with not much effect in British Doctors, and a clearer effect in the other studies.

And that reduction is around about a quarter.

DR. TEMPLE: Okay, and the other studies all achieve nominal significance, do they?

DR. BAIGENT: I couldn't tell you offhand. But they are very consistent and there's no heterogeneity among them, yeah.

DR. TEMPLE: Okay, I mean, that is the endpoint we're talking about here, so.

DR. BAIGENT: Coronary heart disease events is the one that we "

DR. TEMPLE: Yeah, I don't feel embarrasses about asking. I mean, wouldn't, I guess I'm puzzled. Why wouldn't you show the results of each individual study for the endpoint that we're talking about, that we're hoping to get approval for?

DR. BAIGENT: Well, I said right at the start that we, right from the very beginning, had looked at vascular events as our primary outcome, as our main focus, right back to the early days when we started the ATT, APT.

And so I felt it was most appropriate, the

least misleading, to show right up front what we saw in vascular events. We then planned to go into more detail with the data.

Obviously, in 15 minutes I can only show you a fraction of the several hundred or so analyses we've done. But I felt that by going straight to the issue, which is stratification by risk, we would actually, probably see more interesting information.

DR. TEMPLE: It's probably my hangup on individual studies, but, okay.

DR. BORER: On Page 35 of our background document, although p-values aren't in there, the absolute numbers are for all the trials for non-fatal MI are shown.

DR. BAIGENT: It should be pointed out that that is not the analyses you've seen today. This is a meta-analysis conducted by the Antithrombotic Trialists' Collaboration, I'm showing you.

You get very similar results when you look at the published data which is what previous authors have done. You know, qualitatively get similar results.

We've been able to look in a bit more detail because we have the individual data.

DR. BORER: I'm sorry, Tom, Tom Pickering.

DR. PICKERING: Yeah, could you show us the data on the overall vascular events divided into the three risk groups? I don't think we've seen that.

DR. BAIGENT: I think we have it as a backup slide. Can you access that? I mean, again, it's very similar to what you see on coronary heart disease events.

And won't add very much more to understanding because there's a neutral effect on strokes and a neutral effect on vascular deaths.

So, you see the same patterns, really. That's coronary heart disease events by risk. What we see is, so what we're looking for is vascular events in the same mode, okay.

Keep going, keep going, I think it might be the next one. No, not that one, not that one, not that one, keep going. Oh, I don't have it here.

It's very similar pattern to the coronary heart disease events, essentially similar. And, you

know, I don't think there's anything more to say, really.

There is no qualitative difference between what we see for vascular events and coronary events. We just see a slightly smaller signal for vascular events, because we're mixing together something on which we have no effect and something on which we have a clear effect.

That's all that happens. It's not as if we're trying to hide anything. There's just a smaller effect, that's all.

DR. THROCKMORTON: The FDA analyses are in the statistical review, I think on Page 13.

DR. BAIGENT: I'm sorry, I didn't catch that? Was a point being made?

DR. TEMPLE: No, it's just those numbers are going to differ because they include silent MIs, where we knew them. So, I'm just explaining why it would look different.

DR. PEARSON: Mr. Chairman, just a point of clarification, should we go ahead with our core presentation, or would you like to have the individual

addressings of specific questions.

DR. BORER: Why don't we try and complete the core presentation now, if we can before lunch, and then we'll, during the question and answer period we can have the individual PIs respond to specific issues that have come up.

DR. PEARSON: Excellent, thank you.

DR. MERZ: Hi, let me introduce myself. I'm Dr. Noel Berry Merz. I am a Clinical Cardiologist on faculty at Cedars-Sinai Medical Center.

I'm also a Scientific Investigative Cardiologist and Chair of the NHLBI-sponsored WISE Study, which is the Women's Ischemia Syndrome Evaluation Study, a prospective multi-center study of over 1,000 women.

I'm trying to understand better the different manifestations, if they are in women. So, with that expertise, I'll go ahead. One of my sort of introductory comments would be that this very good debate this morning basically is asking a basic question at a lot of different levels about lumping and splitting. And you're being asked to consider

lumping for what is perceived as an important public health policy issue.

I'm going to talk to you about some of the hazards of splitting, specifically with the regard to how we have not adequately served women with their leading health care threat.

And also, why we really need to focus on aggregates because it's such an important public health problem.

Since 1984, more women than men have died annually of heart disease.

You can see from this figure where men are shown in the black bars and women in the gray hatched bars, that from an absolute number, women now comprise 52 percent annually of all heart disease deaths.

This is of course related to the aging of America, our obesity epidemic, our rising rates of diabetes as well as renewed interest in smoking. But this will worsen as this bolus in the python of baby boomers goes through.

And we've estimated in terms of man/women power, cardiovascular specialists, as well as hospital

beds, we don't have enough to take care of this public health crisis that really has already started.

What do we know about the current status of primary prevention in women? Women are more likely now to die of sudden death prior to hospital arrival. These are new CDC statistics out analyzing data from 1999.

This is really for the first time. Men have always taken the prize for out-of-hospital sudden cardiac death, until this recent analyses.

Women historically, and this data goes back to the 1970s, have always taken the lion's share of cardiovascular health care costs. Now, because we are the dominant majority, but historically because we're so much more expensive to take care of when we do get a cardiovascular disease.

Fifty percent of women, from a primary care standpoint, greater than 55 years old, do have a high risk cholesterol level.

And within this age group as well, one-third of 55 years olds have a global CHD risk score that's greater than six percent. And this is why the

American Heart Association and the American Preventive Services Task Force made these recommendations.

And they made them for men and women, they did not split. Women see primary care physicians more often than men for both routine and symptom related care. They're also actually quite a bit more compliant with preventive health care recommendations.

We now have something as simple as a screening annual mammography rates compliance up to 70 percent, where men are not as good with their prostates.

Women can also show that they're more compliant with more complex recommendations. For example, women are more compliant with these complex nutritional guidelines, which was really leading the charge for the cholesterol falls that we've seen, from a dietary standpoint, in the last decades.

Yet, women are less likely to receive appropriate care that is preventive, including aspirin, when indicated. And we have national survey data that when a women is at equal high risk, compared to a man, she is less likely to be given many

different types of appropriate care, including aspirin.

Well, what are some of the issues to consider when we evaluate the data. Dr. Colin Baigent, showed us gender specific data.

Issues to consider when evaluating the data. Throughout a lot of investigation women have received what I call special population treatment, where women are considered a minority subgroup, and yet, we are the majority. We are the majority of the general population at 51 percent.

And we are now the strong majority at 52 percent of all cardiovascular disease. And upwards of 60 percent of our health care expenditure in terms of cardiovascular disease.

We also have had the pedestal treatment, where risk avoidance in women is factored relatively higher, shifting the perceived risk benefit ratio, such that effective treatments are less utilized.

And we can't tell you why physicians are not telling women to take their aspirin as much as men, but this would certainly be a concern.

Yet, when we examine the data, as we just did, there were no significant differences in either magnitude of risk or benefit between women and men in either the primary or secondary prevention aspirin trials, and indeed leading our authoritative bodies not to stratify by gender.

There's also no biological basis for a gender difference in aspirin benefit or risk. And again, it does not make sense that there should be.

So, in conclusion, the aging of America necessitates a focus on the majority, which is now women, and this will only become stronger. It is not just politically correct, and as my daughters say, with a smile on their face, girls rule.

And in a lot of ways we need to be very careful about how we lump and split now. Because our CCUs are going to be increasingly filled with women. And if we don't know what to do with them, we are not going to serve ourselves as well as them.

Risk stratification does exist. Women are amenable to preventive practices and yet therapies are underutilized.

There are similar favorable risk benefit ratios for women and men, for aspirin as primary prevention. We have the opportunity today to close what we consider is a very big evidenced-based practice gap, as well as to rectify special population and pedestal treatments, where the largest group afflicted by heart disease, which is women. I will close with that.

DR. BORER: Thank you very much, Dr. Merz. I think we'll hold any questions, because there will be some specifically about the data on which the similar, the conclusion of similar favorable risk benefit ratios is based.

But we'll hold that until the question and answer period later, only because we do have a published time of 1:00 at which we need to have public comments.

So why don't we move on to the next formal presentation and we'll hold the questions until later.

DR. MERZ: Which is Dr. Randall Stafford.

DR. STAFFORD: Dr. Borer, and other members of the Advisory Committee. My name is Dr. Randall

Stafford. I serve as Director of the Program on Prevention Outcomes and Practices within the Stanford University Prevention Research Center.

I practice in the Stanford Preventive Cardiology Clinic as well. My presentation focuses on enhancing appropriate aspirin utilization with CHD risk-based therapy.

In brief, my presentation will address the following areas. Our study to examine national patterns of aspirin use, suggests a role for evidence-based labeling as a strategy for improving what is currently sub-optimal aspirin use.

What is the rationale for this study? The concept of global risk implies that a continuum of risk exists that can be used to tailor the intensity of clinical management.

More effective care results when patients at higher risk are treated more aggressively across multiple risk-reduction strategies. As you know, aspirin's role in secondary prevention for high risk patients is well-established.

Substantial benefits also exist for

moderate risk patients, without known CVD events. There is a need to solidify physician recognition of risk stratification as a key tool in disease management.

Despite substantial efforts to develop the evidence concerning appropriate aspirin use, little is actually known about current physician aspirin utilization practices. Particularly for this moderate risk group.

This project's specific aims include first to evaluate 1992 through 2001, aspirin use in, by cardiovascular disease risk status.

We focus in particular on moderate risk patients. Second, to identify patient and physician characteristics associated with aspirin use.

Data sources for this study include the federally conducted National Care Surveys. These surveys are conducted in the settings of private physician offices, for NAMCS and hospital outpatient departments for the NHAMC study.

Patient visits are the unit of analysis. Annual samples of between 45 and 50,000 visits are

available from these two surveys together. Visit specific information is included about patient demographics and diagnoses, physician activities and new or continuing medications.

While these surveys have been validated against other national data sources, there are inherent difficulties in assessing the use of over-the-counter medications.

Including uncertain reporting of aspirin use. Given the data elements that were available in these surveys, we define cardiovascular risk categories as follows.

High risk was defined as patients with existing coronary heart disease or other clinical forms of atherosclerosis. Moderate risk patients were defined as those with diabetes who had no coronary heart disease, or patients with two or more coronary heart disease risk factors among younger patients, and among older patients, one or more risk factors.

The remaining patients are low risk. Regarding the likelihood of aspirin use, by cardiovascular risk category, several conclusions can

be drawn from the observed data on national practices.

There is dramatically lower than expected reported use of aspirin, both in high risk groups as well as moderate risk patients. For high risk patients, aspirin use was reported in only 25 percent of these patients.

For patients with diabetes and no CHD, six percent. For other patients in a moderate category on the basis of other risk factors, only seven percent were reported to be using aspirin.

We can see also that for low risk patients, less than one percent were reported to be using aspirin. We also see here, that over this ten year period there's been relatively modest increase in the use of aspirin.

We also examined aspirin use among patients taking statins. Use of these lipid-lowering drugs by these patients, indicates that they are not only at elevated risk, but that they are already receiving pharmacotherapy to modify their risk.

We see here that aspirin use in those patients with known CVD is around 30 percent. In

those patients at moderate risk, here including those patients with diabetes, aspirin use was reported in only 16 percent in the most recent data. Although, you can see that there has been some increase over time.

We analyzed the independent impact of a range of factors on aspirin use. We found that aspirin use increased from moderate and high risk patients. It also increased with increasing patient age. Independent of all the other factors, aspirin use was less likely in women.

It was more likely in those patients with either private or public health insurance, and it was more likely in those patients who were visiting cardiologists as opposed to primary care physicians.

These patterns suggested that while overall aspirin use is sub-optimal, patterns for some sub-populations are even less optimal. As you've seen, aspirin is dramatically underused in the prevention of CHD in appropriate patients.

There's minimal inappropriate use in low risk patients and the extent of underutilization has

improved only modestly over the past decade, in spite of accumulating evidence of benefit.

Greater aspirin use was independently associated with higher CVD risk, advanced age, male gender, health insurance coverage and cardiologist care.

Our study has limitations that are part and parcel of examining OTC drug use. There is possible under-reporting of aspirin use because of the over-the-counter status of this drug.

While the magnitude of under-reporting is unknown, it is telling that a physician would neglect reporting such an important therapy were it truly being used.

Even with this limitation, these are likely the best data we have available to assess aspirin use. They indicate that aspirin is under-used, particularly in moderate risk patients.

Well, what causes sub-optimal aspirin use. Possible contributors include lack of knowledge about existing evidence, lack of incentives and/or accountability for evidence-based practice.

It's true that both patients and physicians may unduly focus on acute issues. And the process of balancing costs, risks and benefits, may not always be straightforward.

Finally, aspirin is not labeled for primary prevention, despite available evidence of its benefits. How can we improve appropriate aspirin utilization?

Well, clearly only part of this puzzle, unambiguous labeling supporting the appropriate use of aspirin, will give both patients and physicians an unequivocal message regarding aspirin's role.

As you are considering today, it is vital to expand labeling to include moderate risk patients. Other strategies may include physician and patient education and engagement, including better incentives for attaining recommended practices.

We also may need to think about supplementing current mechanisms by which prevention services are delivered. For example, employing Nurse Case Managers to manage chronic issues and improve patient adherence.

With these and other strategies, I have no doubt that aspirin can come closer to fulfilling its promise as an effective an inexpensive therapy, capable of drastically reducing cardiovascular disease risk.

It's my pleasure to introduce Dr. Eric Topol of the Cleveland Clinic Foundation.

DR. TOPOL: Thanks very much, Randall. It's been difficult to sit through the morning, having much to say, but of course I'm trying to come to a point where we try to process a lot of this information.

I'm only going to make just a few remarks, but first to point out that we're all students of aspirin and antiplatelet therapy over, really, a couple of decades.

And I think the most important signal that we've seen, and of course a lot of that was the classic article that has been commented on of the Oxford Group in 2002 BMJ, is that the most important effect of aspirin, throughout all of its applications has been in the reduction of non-fatal MI.

And that is greatly overriding that of stroke or a vascular death. Which of that tripartite endpoint has been the one that the Oxford Group introduced many years ago.

So it's no surprise to me, to see that in the population under discussion today, and it's been a great discussion, very intellectually charged.

I knew it would be good, but it's even exceeded the dissection that I had anticipated. That non-fatal MI, is the signal that we're looking for. This is a much lower risk population.

So with that background, let me just try to sum up a few key points. The first is that we have a body of data that you've seen, with five trials.

It was the decision to present all the trials, although, for this particular extended label, it could have just been the thrombosis prevention trial.

And in retrospect, it might just be that trial. Because that is the one that directly addresses this moderate risk group. And the greater than one percent risk per year, ten percent risk per

decade. So, in effect, if you just like to drill down on that trial, that will answer a lot of the comments that have been made throughout the course of the morning.

Particularly Tom Fleming's and Steve Nissen's and others. But in the totality, we have over 55,000 patients from five trials. And these five trials have been published in the, I think the most respected peer review journals.

And they include the New England Journal of Medicine, Lancet and British Medical Journal. Why they have not been reviewed by this supreme court, if you will, they certainly have undergone a strict peer review.

And no trial, and I've watched many clinical trials in the cardiovascular medicine space and medicine throughout the last couple of decades has been pristine, without any warts or glitches. I think you all would acknowledge that.

They are diverse populations, which is a great thing. It's a major strength of these trials, rather than a detractor as has been pointed out or at

least suggested.

Now the most important point about these trials, which is the most salient aspect of the thrombosis prevention trial, which you'll hear separately from Professor Meade again, later today, is that this unequivocal, 30 percent reduction in non-fatal MI. Now this is so important because, as you've seen, this is the same proportionate reduction as is seen with secondary prevention, post-MI.

So this 30 percent reduction is important and it's a log order greater than the risk of a serious cataclysmic side effect that is of hemorrhagic stroke.

And the issue about the silent MI is somewhat disturbing to me. And that's because these trials did not use silent MI in their endpoint, their primary endpoint. And from the very outset, as Colin reviewed this morning, that has never been part of the endpoint, outcome data of these trials.

And we only have some data for two of the trials, and that data, of course, is compromised because of the lack of time to event and the lack of

ability to define a silent infarction.

These are all clinically manifested non-fatal MIs, 30 percent reduction, and that's just right concordant with the overall effect of antiplatelet therapy and aspirin in particular.

And I also want to emphasize, I hope this is something we all have learned over the years about interpretation of clinic trials. That this subgroup issue is counterproductive and certainly can be quite misleading. And Noel emphasized that earlier with respect to the women, that applies to many other subgroups as well.

Now these data have been raked over considerably. They are five groups of individual societies or groups, clinical trial groups that have gone over the same data that you're going over, perhaps processed a little bit more up-to-date, a little more recent, but nonetheless, essentially the same data.

The American Heart Association, the American College of Cardiology, the American Diabetes Association, the U.S. Preventive Services Task Force

and the Antithrombotic Trialists' Collaboration. And each of these groups have made specific recommendations regarding the use of primary prevention, suppression of infarcs with aspirin.

Now in the real world, interestingly, the medical community, and to a large extent the lay community, already accept primary prevention of aspirin.

So, although, not sanctioned by the regulatory authority here in the United States, the medical, and to a large proportion the lay public accept aspirin as a prevention tool.

Americans are, of course, empowered now and they have accepted this. So many are taking aspirin, more than 20 million Americans are taking aspirin on a daily basis to suppress events. And this, a large proportion of those are primary prevention by individuals.

But there is an inconsistent message. Because if you turn to any of the lay media, such as magazines like Good Housekeeping, the Reader"s Digest, the Consumer Reports on Health, Prevention Magazine,

Ladies" Home Journal, you will see recommendations from physician advisors about taking aspirin.

Yet, this is all off label. This is all not sanctioned by the regulatory oversight. And so it's, of course, an inconsistent message which we'd like to get concordant, get on cue, get to be homologous.

That all of the responsible parties believe in the same thing. If that's possible. Now acute MI is something that we need to prevent much better, because recently, much work has gone in in clinical trials and little progress has been made.

So, here it is towards the end of `03, and as we look into the future, we know that platelet-thrombus is the proximate cause. So there is an obvious connection with the action of aspirin.

There has been no significant reduction in mortality in many recent trials, randomized clinical trials. And, in fact, over the last ten years, there was no incremental reduction of mortality through any new therapeutic intervention.

Once CMI has been initiated, bad outcomes

are frequent and that's best exemplified by the recent VALIANT Trial which follow post-MI heart failure with a very high rate of death, quite alarming, over its extended follow up.

And then finally, as I think you would agree, the only meaningful way to deal with MI in the future, and much more effectively, is to prevent these events.

So which of the recommendations should we accept, assuming we're accepting one of them. That, of course, is not entirely clear from the discussion this morning, but at least we can consider three different strata or levels.

The U.S. Preventive Services Task Force, as you recall, recommended the threshold of .6 percent per year or six percent over a ten year period.

That was the most aggressive recommendation, that is published in the Annals of Internal Medicine in `02. Then there was the AHA and ACC recommendations, which, as Tom Pearson summarized, were less aggressive. That was a one percent per year.

And you've seen from Colin's review of the individualized data, and I would also add to the point, that having individualized data in this meta-analysis gives us a lot more to work with.

I think it makes the meta-analysis another credible tool to support the Thrombosis Prevention Trial, the primary body of data for this discussion.

But what you'll see is with this one percent threshold or ten percent over ten year anticipated event rate, there will be a 35 percent reduction of non-fatal MI.

That's three per thousand events reduced per year, with the average individual living a 20 year or longer life span. So this is a very large proportion of events over the course of that individual's lifetime.

And then two percent per year, which is perhaps the least aggressive, but certainly a supported threshold. This is not the one that is really been under discussion, but it would be the most conservative threshold. But it would yield an even higher proportionate reduction, as you noted in that

analysis of non-fatal MI, is a 43 percent reduction.

That's six per thousand events per year accruing over many years as an individual's life goes on. Now, in addition to the benefit, which I would say in this population is solely related to the non-fatal MI protection, suppression of those events. The risks are that of bleeding, particularly the one that we are most concerned about, in terms of frequency, is that of GI bleeding.

Now it's important to recognize that since there is this relationship of a tradeoff, that the overriding myocardial infarcs are titrated in part by the incidents of GI bleeding. And these are GI bleeds that lead to hospitalization with or without transfusion.

But the point is that a GI bleed, and Alastair would have made this point earlier, is not necessarily as bad an outcome as an MI, even if they are equivalent, and they're not.

In fact, in this moderate or intermediate primary prevention risk group, there is a great excess of reduction of the events of MI, as compared to any

type of GI bleeding.

The second point has to do with the lower doses of aspirin, and having been now in two recent trials, been shown to reduce the rate of bleeding as compared to 325. And I also would mention that the British Doctors Trial, used 500 milligrams.

That's an outlier and that also may have interfered with some of the efficacy in that trial. But nonetheless, the bleeding clearly does appear to have a relationship in the BRAVO and CURE Trials that were recently published back-to-back as far as the aspirin dose data output.

And that the preservation of aspirin does appear efficacy at doses as low as 75 to 81 milligrams. So to summarize, the most important direction in the future of medicine is primary prevention, without any question.

And this, of course, is really pushing the envelope and raising the bar in some respects. Because we're now, by definition, dealing with low event rate populations.

And there's only so long these clinical

trials can go on in our lifetime. And as you can recognize, two of these trials of the five were stopped prematurely by their data and safety monitoring board and the steering committee because it had exceeded the expectations of their primary endpoint, or of a cardinal endpoint.

Secondly, that the ongoing large trials, such as CHARISMA, which several of you are involved in the CHARISMA trial, that's already accepted that aspirin is the backbone strategy for primary prevention.

In one arm of the CHARISM trial of over 15,000 patients is aspirin, and that's now being compared to aspirin plus a second antiplatelet, in this case clopidogrel. So we already have gone past aspirin. At least many of use, as Clinical Investigators in this field, thinking that this is a sure foundation strategy.

And so soon, if this is not recognized as a foundation strategy we'll have a runaway train, if you will, with respect to the new comparators.

And then finally, aspirin, I do believe,

is a cornerstone of prevention of myocardial infarction. And that shouldn't be considered as secondary prevention, but also fully incorporated in our primary prevention strategies. Thank you for your attention.

DR. BORER: Okay, thank you very much, Dr. Topol. And also Dr. Stafford. There will be some questions about some aspects of these presentations. I think Dr. Stafford responded directly to Alan Hirsch's question earlier.

But it's noon and at 1:00 we have published the fact that we'll be having public comment. So, we're going to break now for lunch. We'll come back at 1:00, and after the public comments are concluded, we'll continue questions and hear from the PIs.

(Whereupon, the foregoing matter went off the record at 11:59 a.m., and went back on the record at 12:59 p.m.)

AFTERNOON SESSION

(12:59 p.m.)

CHAIRMAN BORER: We'll begin the afternoon portion of the meeting now. The meeting will be open for public hearing, for public statements. Several people have indicated their desire to make a statement for which three to five minutes per statement is available.

I'm going to read to you a guidance here regarding the public statements.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any

company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first of the speakers is Nathaniel G. Clark, National Vice President, Clinical Affairs and Community Programs of the American Diabetes Association.

Dr. Clark.

** DR. CLARK: Thank you very much for allowing me to speak on this important issue.

I just want to tell a bit about what my title means. Being the National Vice President for Clinical Affairs for the American Diabetes Association

means that it is my responsibility to oversee our development and promotion of our clinical practice guidelines, one of which deals with the use of aspirin.

There are two comments I want to make briefly before beginning the remarks that I planned to make prior to the meeting beginning. The first is to urge the committee very carefully to consider the position of patients with diabetes who are in this very odd position, given the discussion this morning, of being at moderate or most would say high risk for the development of cardiovascular disease and yet have not had a documented event, and therefore, for those with diabetes, primary prevention, in fact, is secondary prevention.

And on behalf of the 18 million Americans with diabetes, what you will think about and decide today will have a great deal of importance in terms of their future health.

The second comment I wanted to make has to do with a question that came at the beginning in terms of what is the actual effect of what the FDA says on

this topic if many of the professional bodies have already issued guidelines, and this is a case where I'd urge you to consider that there are two issues.

One is what did the FDA say, and the second is what did the FDA not say. If you had not recently reviewed the very same evidence that various bodies had looked at to make their guidelines, then the guideline issuing body, such as the American Diabetes Association, could say, "Well, I know there isn't actually an FDA indication for the use of aspirin as primary prevention, but we believe based on the evidence that this is reasonable."

If you today decide to not grant primary prevention as an indication, that will be a significant detriment as we move forward, and I believe it will significantly contribute to the lack of compliance which already has been documented as poor to this guideline.

In terms of my previous remarks that I planned to make, I want to first say that the American Diabetes Association enthusiastically supports the proposed change, both as we believe it will benefit

patients with diabetes, but also because if the FDA speaks, I believe this will help in regard to compliance to the guideline we have issued.

Second, that diabetes is a major risk factor for cardiovascular disease is well known to all of you and has been brought out. When NCEP ATP III defined diabetes as a coronary risk equivalent, thereby saying that those with diabetes based on that fact alone had a risk of cardiovascular disease of 20 percent or greater, this was tremendously important in regard to the need for patients with diabetes to understand the benefits of aspirin.

Cardiovascular disease is a major complication and the major complication for those with diabetes. We now talk about the treatment of diabetes to prevent cardiovascular disease as having many components. Currently the buzz word is to talk about the ABCs, A standing for A1C, a measure of blood sugar control; B being blood pressure; and C being cholesterol.

But equally important would be aspirin and smoking reduction.

Our current recommendation and guideline in regard to aspirin for those with diabetes is that all adults should be on aspirin essentially. We specifically state that those over the age of 40, regardless of any past cardiovascular history should receive an aspirin, and those younger than 40, those still adults, should be considered for aspirin if they have an additional cardiovascular risk factor in addition to their diabetes, and these are enumerated as a family history of cardiovascular disease, a history of dislipidemia, hypertension, microalbuminuria, or smoking.

So, in summary, I would urge you most strongly to consider the evidence that's been presented and to grant the proposal as stated and to enlarge the indication for aspirin to include primary prevention for cardiovascular disease.

Thank you very much.

CHAIRMAN BORER: Thank you, Dr. Clark.

The next statement is from Dr. Charles Curry of the Association of Black Cardiologists.

** DR. CURRY: Thank you very much.

Today I serve as a consultant for Bayer, and at this time, I represent the Association of Black Cardiologists.

I sit on the National Heart Attack Alert Program Committee for the National Medical Association, and on that committee we see all of the data that represents the millions of Americans who die of coronary artery disease annually, and one cannot help but be extremely concerned and hopeful, particularly when we've heard today that the mortality rate does not appear to be going down, as one would expect, with all of the great interventions that we have.

The African American community is a high risk community. As you all know, 50 percent of African Americans age 50 will have hypertension. Hypercholesterolemia is a major problem; cigarette smoking; all of the risk factors that we hear so much about and I truly believe in are in abundance in the African American population.

We also know that nine of ten patients with MI, with acute coronary syndrome will have at

least one major risk factor. So it seems reasonable that somewhere in the spectrum of coronary artery disease and sudden death and myocardial infarction and angina there must be a pool of people who simply have a lot of risk factors and they're waiting to develop an acute coronary syndrome.

And it seems to me that this committee today has an opportunity to approve a form of primary prevention that has been used in millions of people, and it's clearly not malignant.

I know how much the FDA likes studies. I heard Dr. Temple say once he liked to see two studies better than .05 P values, but we have studies, and I don't think that we're likely to get any additional major studies because I don't believe you'll find a control group in the United States.

So I think we would like to endorse the recommendations of the American Heart Association and hope that you can find enough evidence to convince you to help further reduce the incidence of coronary artery disease in the American population.

Thank you.

CHAIRMAN BORER: Thank you very much, Dr. Curry.

The next speaker is Dr. W. Fred Miser of Ohio State University.

** DR. MISER: Dr. Borer, members of the Advisory Committee and FDA staff, good afternoon. It's an honor to be here today, even if it's just after lunch, to urge you to approve aspirin therapy as primary prevention of myocardial infarction.

My name is Dr. Fred Miser. I'm a Board certified family physician, a Diplomat and Fellow of the American Academy of Family Practice, and an associate professor of family medicine at the Ohio State University College of Medicine and Public Health.

I was invited here today by the Bayer Corporation, who assisted in my travel and lodging here because of an editorial that I wrote last year for the American Family Physician. This peer reviewed journal, published by the American Academy of Family Physicians, is distributed to over 192,000 physicians and health care providers.

In its editorial entitled "An Aspirin a Day Keeps the MI Away for Some," I reviewed the latest recommendations by the third U.S. Preventative Services Task Force which found good evidence that the potential benefit of daily aspirin therapy in persons of moderate to high risk for a cardiovascular event outweigh the potential harm.

I then went on to review other studies including the ATT and summarized by acknowledging that aspirin is not a panacea, and as with all therapies, we as physicians are obligated to spend time with our patients discussing the advantages and disadvantages of this treatment and assist them in making wise decisions.

As you know, the 90,135 family physicians here in the United States provide the vast majority of primary care. Our focus is on the care of the whole person. Not only do we provide for acute care needs and managed chronic disease. We also provide advice in promoting health and hopefully attempt to prevent disease.

In terms of coronary heart disease, which

despite modern medical technology continues to be the most common cause of death and disability in the U.S., our goal is to keep our patients away from you, the cardiologist, nothing personal, by attempting to modify these known cardiac risk factors to prevent their first MI.

On a daily basis we care for our individuals, just like the one described earlier today by Dr. Pearson. We encourage our patients to stop smoking, to get off the sofa and get some moderate exercise, and to eat wisely. We also make therapeutic decisions about controlling their blood pressure and their lipids.

The decision to treat these conditions with medicines comes as we assess their overall risk with the potential benefit of the therapy. As physicians, we can easily identify those for whom the MI clock is ticking, which leads me to aspirin therapy.

As with all therapies, we understand that aspirin has its benefits and its risks, and as with all therapies, we are obligated to use aspirin wisely.

Daily we use clinical guidelines and decision rules to guide our therapy for a myriad of conditions.

Likewise, we are capable of deciding who is at moderate and high risk for coronary artery disease using the coronary risk assessment tools, whether it be in paper format or on our PDAs or on the Internet.

Our patients, likewise, are smart and often use these tools on their own. Using this tool allows us to sift through the 30 to 40 patients that we see daily to stratify and identify those at cardiac risk and to tailor our treatment based on that risk, which brings me finally to the labeling issue for aspirin as primary prevention.

As you know, there's a dramatic lag between when research shows a benefit and when that science is actually put into practice. Many of our patients who would benefit from aspirin therapy are not on aspirin, and many are taking aspirin inappropriately who may not benefit.

This change in labeling, I believe, would dramatically raise the awareness of appropriate use of

aspirin both for the physician and the patient. As noted by the patient education handout developed by the American Academy of Family Physicians called "Coronary Heart Disease, Reducing your Risk" one of the recommendations is ask your doctor about taking a low dose of aspirin each day. Aspirin helps prevent coronary heart disease, but taking it also has some risks.

This open dialogue between a physician and patient is crucial. This alliance, combined with the wise use of clinical judgment, can identify those who will benefit from aspirin as primary prevention or preventing those who are not at risk for harm.

I am convinced as a family physician that this change in labeling is crucial, and I urge you to approve this change, and, yes, I do take my daily baby aspirin.

Thank you.

CHAIRMAN BORER: Thank you, Dr. Miser.

The next speaker is Eric Topol of the Cleveland Clinic, who has spoken with us a little earlier.

** DR. TOPOL: Thanks very much, Dr. Borer.

I want to first acknowledge that I have worked as a consultant to both Bayer and to McNeil and my time is reimbursed. I also at this juncture am speaking not only in behalf of McNeil's view, but also of mine as to build on some comments earlier regarding selection of patients, that is, the clinical criteria apart from such things as a Framingham score, and also the improved risk-benefit ratio in recent times.

So first I just want to talk about the charisma trial very briefly. This is a large-scale trial that has been conducted. The enrollment phase has been complete. It's one of the most rapid enrollment trials that has ever been performed. Nine hundred hospitals across six continents in 32 countries, and it is comparing aspirin plus placebo as compared to aspirin plus clopidogrel.

Now, instead of using any kind of Framingham risk score or other risk scores, we actually use a combination of major and minor criteria, and so in going along with the American Diabetes Association recommendations, diabetes as a

major criteria; also an abnormal ankle-brachial index, asymptomatic carotid stenosis, or abnormal carotid plaque by ultrasound. Those are major. One of those plus two minor or two major would constitute sufficient enrollment criteria.

And the minor criteria include systolic blood pressure abnormality, hypercholesterolemia, smoking, current smoking, and age by gender.

So these criteria, that is, three minor or combinations of major and minor, were the enrolling population. What I wanted to tell you is that we had a chance to look at this population now which just completed its enrollment in November, just a few weeks ago, and there were over 15,600 patients enrolled. Of these patients, the population, 21 percent constituted a primary prevention cohort never having had any type of vascular event.

And the main event rate for the trial is death of any cause, MI or stroke, and interestingly, despite the use of evidence based medicines that included statins in 67 percent, ACE inhibitors or angiotensin receptor blockers in 67 percent, and beta

blockers in 48 percent, we still see a very high event rate.

So the point is that even in 2003 with all of the other evidence based medicines, things that might go into the "polypill" some day, which include low dose aspirin, we see a very high event rate.

Now, the other thing I wanted to just build on was a comment I made earlier regarding tradeoff, and I want to just review the two studies that have shown what I believe are the best evidence we have today: that aspirin at lower doses within the 75 to 325 range is associated with even less bleeding hazard.

And what you can see, these are data from the BRAVO trial, which was another large trial over 9,000 patients conducted worldwide in which we were looking at an oral 2B3 inhibitor, lotrafiban plus aspirin, versus aspirin and placebo. These are the aspirin only patients, and it was at the discretion of the treating physician investigator to use a lower dose or the dose that was over the 162 threshold, which was largely 300 or 325.

And it turned out by multivariate analysis, by propensity analysis there was no difference between these patients with respect to the aspirin compartment, and what you can see is that there was a significant gradient of bleeding: serious bleeding requiring a hospitalization; transfusion; and any bleeding, favoring the lowest dose aspirin.

In addition, the CURE trial the week after we published BRAVO in Circulation, the CURE trial investigators published their experience with aspirin, and what you can see, again, is a very important relationship between aspirin dose and bleeding.

But also I call your attention to the relationship to the major events of death, MI, stroke, because at the low dose of less than 100 milligrams, again, the patient is not being demographically different at all at the lowest dose. This is obviously not a randomized trial, but it's the best data that we have today. It's in a cumulative 20,000 patients.

You can see the event rates were not compromised, but on the other hand, major bleeding was

substantially less at the lowest dose of aspirin.

And as you can see, in summary, the actual data for the dose of aspirin and major bleeding, you see the gradient goes up very sharply from 1.9 to 3.7 for aspirin alone, and then the combination also follows that same trend.

So just to summarize the important points is that apart from using risk scores, very straightforward, simple, clinical criteria can distinguished patients at increased risk and also to emphasize it, the current use of evidence based medicine does not appear to preempt or reduce that risk to any significant degree. That is, it's very easy still today to find a population of primary prevention with high hazard.

And secondly, that the efficacy of aspirin does appear to be well preserved at doses less than 162 and even doses of 75 or 81 milligrams, and that bleeding complications, particularly gastrointestinal bleeding, serious bleeding, is markedly reduced associated with this less dose of aspirin.

Thank you.

CHAIRMAN BORER: Thank you, Eric.

The next speaker is Suzanne Hughes of the Preventive Cardiovascular Nurses Association.

DR. HIATT: Is it possible to comment on these or not?

CHAIRMAN BORER: I'm sorry?

DR. HIATT: Is it possible to ask questions or do you want to wait until the end?

CHAIRMAN BORER: Why don't we wait until the statements are made and then we can raise the questions generically?

** MS. HUGHES: Good afternoon. I'm Suzanne Hughes, and I'm a registered nurse at Akron General Medical Center in Akron, Ohio, and today I represent the Board of Directors of the Preventive Cardiovascular Nurses Association.

Our group does not have a financial relationship with Bayer, and the expenses related to my attendance here today are the responsibility of the Preventive Cardiovascular Nurses group.

We are pleased to have the opportunity to address this committee on the use of aspirin for

primary prevention of acute myocardial infarction. Heart disease and stroke affect over 61 million Americans and cost more than $350 billion annually. In order to change the tide of this epidemic, we must develop and implement safe, efficacious, and cost effective primary interventions.

Our organization's mission is to improve the health of all Americans through the reduction of cardiovascular disease risk factors. We achieve our mission through professional and public education, dissemination of national guidelines, and public awareness campaigns.

We fully support the American Hearth Association's 2002 guidelines for primary prevention of cardiovascular disease and stroke 2002 update. A key feature of this guideline is the identification of persons who are at substantial risk for a primary cardiovascular event in the next ten years. This is defined as a risk of greater than or equal to ten percent based on age, gender and various coronary risk factors. The recommendations for this group include the use of low dose aspirin.

Eidelman and colleagues recently published a meta analysis of five large, randomized trials of aspirin in the primary prevention of cardiovascular disease. Fifty-five thousand five hundred and eighty men and women were included in this analysis. Aspirin users were found to have a 32 percent reduction in nonfatal myocardial infarction. Their recommendations are similar to those of the American Heart Association.

In summary, we support the use of low dose aspirin in the primary prevention for persons at moderate to high risk of acute MI. This is, of course, with full recognition that there are persons in this risk group in whom aspirin even at low dose could be associated with gastrointestinal bleeding or even hemorrhagic stroke.

We feel that the net benefit in the group described above has been clearly demonstrated. The challenge that we face as health care professionals is the dissemination of this information to the public and to our colleagues in a way that they fully understand both the risks and the benefits of this

therapy.

We are prepared to be an active partner in educating nurses and other health care providers about the measurement of global risk and the potential benefit of aspirin in moderate to high risk persons.

In addition, we will seek ways to educate the public about aspirin and to encourage those at risk to seek the advice of their health care provider regarding aspirin use.

Thank you.

CHAIRMAN BORER: Thank you, Ms. Hughes.

Our next speaker is Dr. Michael Pignone from the University of North Carolina at Chapel Hill, Division of General Internal Medicine.

** DR. PIGNONE: Thank you, Dr. Borer.

I'm Mike Pignone from the University of North Carolina. I'm a general internist and clinical epidemiologist, and I was the lead author on the evidence report for the U.S. Preventative Services Task Force, which you've seen some of the results today, and was posted in Annals of Internal Medicine.

I just wanted to reinforce really three

points from the Preventive Services Task Force Process. Number one, they considered three main questions: is there benefit in the prevention of cardiovascular or CHD events with aspirin? Are there known harms associated with aspirin? And, third, what's the benefit-to-harm ratio?

As part of that process, they considered the same evidence as being considered here today. The Preventative Services Task Force felt strongly that there was good evidence supporting the benefits of aspirin in reducing nonfatal myocardial infarction. They also agreed with the results presented earlier today, suggesting that there were known harms, including a relative risk of approximately 1.6 for GI bleeding and approximately 1.3 for hemorrhagic strokes, leading to in excess of one per 1,000 per year for GI bleeding and one per 1,000 over five years for hemorrhagic strokes.

I believe that really all of the evidence you heard today has been consistent with those findings and consistent with good scientific and epidemiologic principles. The difficult issue is to

consider where the benefit-to-harm ratio should be drawn for a recommendation of aspirin to the general public, particularly in adults who might be at increased risk of cardiovascular disease.

The U.S. Preventive Services Task Force did not want to define a strict criteria below or above which people would receive aspirin. Instead they recommended that at high risk people be counseled that aspirin is potentially beneficial. At very low risk, they should be counseled that aspirin probably is not beneficial and that there is an area in between for which shared decision making would be appropriate.

For that reason, the risk threshold use for the discussion of the benefits and harms of aspirin is slightly lower, 0.6 percent over ten years, than that considered by the American Heart Association. This should in no way be interpreted as being differential interpretation of the data or different findings, but rather answering slightly different questions that are actually quite compatible with one another.

So I hope that additional information is

helpful to the deliberation of the FDA committee. The Preventive Services Task Force for those of you who are not aware is an independent, government sponsored body, sponsored under HHS and the Agency for Health Care Research and Quality that has been tasked with evaluating preventive care for a variety of different preventive services, including aspirin as well as several screening tests, and is made up of mostly physicians, nurses, and other public health experts who consider preventive care strategies.

Thank you.

CHAIRMAN BORER: Thank you, Dr. Pignone.

The next speaker is Dr. Noel Bairey Merz who we heard from a little while ago.

** DR. MERZ: I'm here now representing the American College of Cardiology and do need to declare a conflict that Bayer assisted with my travel to this meeting.

I am pleased to speak on behalf of the American College of Cardiology. I am a Fellow in the ACC and have served as the past chair of its Prevention of Cardiovascular Disease Committee.

I also serve as a member of the board of trustees. I am the current American College of Cardiology representative to the National Cholesterol Education Program, chaired the 33rd Bethesda Conference entitled "Preventive Cardiology: How Can We Do Better?" and was a participant author in the 27th Bethesda conference matching the intensity of risk factor management to the level of risk.

I was a recent reviewer on the soon to be published American Heart Association primary prevention of coronary heart disease in women guidelines and participated as the ACC representative in the 1997 aspirin for primary prevention hearings.

The American College of Cardiology appreciates the opportunity to offer its comments regarding this Food and Drug Administration's consideration for the labeling of low dose aspirin, 81 to 325 milligrams daily, for the primary prevention of a first myocardial infarction in moderate risk subjects. The ACC is a 25,000 member, nonprofit, professional medical society and teaching institution whose mission is to foster optimal cardiovascular care

and disease prevention through professional education, promotion of research, leadership in the development of standards and guidelines, and formulation of health care policy.

The ACC represents more than 90 percent of the cardiologists practicing in the United States. Our interest and concern about the FDA's labeling of low dose aspirin grows out of our primary responsibility as cardiovascular specialists to insure the patients have the best care available to them, care that is safe, effective, appropriate and comprehensive, and our testimony today is with that responsibility clearly in mind. We are advocates of good drug therapy because we know that when appropriately utilized they can substantially improve patient outcomes.

Within that framework, we testify here regarding support for the labeling of low dose aspirin for the prevention of first myocardial infarction in these moderate risk subjects. We in the cardiovascular community work each day to close the gap between evidence based guidelines for CHD

prevention and the hard realities of practice. Today we have the opportunity to help close that gap.

We believe that the FDA's current approach to regulating over-the-counter drug products works to insure that such products are safe, effective, and offer safeguards to insure that consumers receive care that is appropriate and comprehensive. We agree that it's appropriate for the FDA to examine its overall philosophy and approach to regulating these drug products in the light of continuous changing health care environment and including the growing self-care movement.

Furthermore, we find that the FDA's current approach insures that consumers have easy access to certain drugs that can be used safely for conditions that consumers can self-treat without the help of a health care practitioner and that this is the correct approach to regulating drug products that are over the counter.

The American College of Cardiology joins other authoritative organizations, such as the American Heart Association and the U.S. Preventive

Services Task Force, in supporting the labeling of low dose aspirin for the prevention of first myocardial infarction in moderate risk subjects. The following reasons outline the rationale for this support.

Number one, coronary heart disease is the leading cause of death and disability in this country. Rates of coronary heart disease are rising again in this country due to aging, the obesity epidemic, and a resurgence of cigarette smoking. Strategies to reduce CHD must be taken undertaken urgently to counteract this growing epidemic.

Number two, aspirin is effective in reducing first myocardial infarction in subjects at an appropriate level of risk. Eight randomized controlled trials demonstrate absolute benefits that outweigh risks for subject at high, as well as moderate and low global risk of coronary heart disease.

Number three, current authoritative organizations, including the American Heart Association, the American Diabetes Association, and the U.S. Preventive Services Task Force, using expert

consensus, evidence based review, currently recommend low dose aspirin for both the high, above 20 percent, ten-year risk, as well as the moderately low, six to 20 percent ten-year CHD risk subjects.

Number four, current use of low dose aspirin in appropriate risk subjects is poor with national surveys indicating less than 50 percent of the eligible high risk subjects using low dose aspirin. Aspirin use is even lower in the moderate-low risk subjects, as low as under eight to ten percent.

Number five, health care professional and consumer global CHD risk assessment is available in print media and internet formulations. Women over 60 and men over 50 years of age with at least one risk factor often typically fit within this moderate risk level and should be considered for low dose aspirin therapy.

Six, and finally, alignment of aspirin labeling with current scientific knowledge and evidence based clinical practice guidelines would strengthen both physician and consumer knowledge in

the appropriate use of aspirin. Significant public health benefit in terms of reductions in coronary heart disease, as well as coronary heart disease related health care costs could be expected.

We look forward at the American College of Cardiology to working further with the FDA as it continues to review its labeling of aspirin, and I'm happy to take any questions when appropriate, Chairman.

CHAIRMAN BORER: Thank you very much, Dr. Merz.

We have a final scheduled speaker, Dr. Udho Thadani, who is a professor of medicine at the University of Oklahoma.

** DR. THADANI: Mr. Chairman, ladies and gentlemen, you heard from other speakers today's conflict of interest. I am on the Speakers Bureau for several companies. I've acted as advisor to several companies, including Bayer in the past. I've been on the FDA committee 1995 and '99, and special government agent.

But today I'm not a hired gun from any of

the companies. I paid my own way to be here.

I think you have already heard a very positive note from a lot of speakers, and I really come here to say what my view is and what my patients ask me. There is no doubt this data on aspirin was presented in 1997 to the committee on secondary prevention, and there was no doubt that the drug was definitely effective when it was approved.

Here we're talking about primary prevention, and the data from the five studies, what you're seeing, shows that it does reduce the clinical infarcts, but not the silent infarct at this point, one, and the patient might pay a little bit higher price that he might get a stroke or may go to hospital with a GI bleed.

And if I ask my patient, give them option of taking aspirin when he doesn"t for primary prevention, and if I tell him, "Look. You may not get a heart attack and go to hospital, but you might get a heart attack on your electrocardiogram which you may not know," and we know a lot of diabetic patients have no symptoms or they get short of breath and they don't

go to hospital, and you do an ECG and they've got a QA infarction.

And then I tell him, "Look. You know, there's a chance that you get a stroke," and the answer usually is, "Forget about the infarct. I do not want to get a stroke," because stroke is devastating. Patients are incapacitated, and a lot of patients with a big hemorrhagic stroke would rather die than get an infarct.

So I think you have to keep that in perspective, although the data here has shown there's 30 percent reduction in clinical infarcts, but when you look at the silent infarct, the data is not so overwhelming, and yet when you look at the stroke, that's going in the wrong direction.

So I think the committee has to put a balance before they certainly recommend on the basis of these trials, and then we have heard that subgroup analysis, stroke is going in the wrong direction, that we should ignore it as all garbage, and Dr. Eric Topol, who is a very important committee cardiologist has said that perhaps infarction is worse than

bleeding. I'm not sure that one could accept that because if you have a GI bleed and get a transfusion, there are risks involved with that.

So I think one has to be balanced. Obviously the benefit is greater.

Then if infarctions are so important, why they do not transmit into saving lives? We have heard and we have read the literature that slight bump in troponin translates into saving lives, and yet despite a reduction in infarcts of 30 percent, there is no improvement in survival, and you might have a negative impact on stroke.

So I think there are different issues. I'm a fellow of the Canadian Cardiovascular Society as well as American Heart Association, ACC. I'm sure I"ll be kicked out. So these are my views.

(Laughter.)

DR. THADANI: Have nothing, nothing to do with the society views, but I think if I look at it, clearly I think one has to be very careful because the guidelines are written by very prominent, important people. I have done research in ischemic heart

disease for 34 years, and if the guidelines are not driven by the solid evidence of data, then it's expert opinion.

So I think committee members here have to make a judgment which is driven by the data and not by suggestions by different people.

Thank you for your time.

CHAIRMAN BORER: Thank you very much, Udho.

That concludes the list of speakers who have applied to make comments. Is there anyone else who has a comment to make, a member of the public?

(No response.)

CHAIRMAN BORER: If not, we'll move ahead. Dr. Pearson, you indicated that the PIs of the five relevant trials are here. We don't need a presentation of the data, although it would have been interesting to hear that in the primary presentation, but I'm sure we'll talk a little bit more about it after the FDA presentation.

But there were specific issues that came up, and I think we would benefit from hearing a

response to those issues from the PIs of their specific studies.

** DR. PEARSON: Thank you, Mr. Chairman.

And I just wanted just to put this into the context again about what the issues are and where our principal investigators will be commenting on specific questions.

Our feeling is that we have proof of efficacy in the high risk individuals. We have proof of efficacy from a moderate risk trial, the TPT trial that you're going to hear from in a moment from Dr. Meade. We have evidence of efficacy from those individuals in the low risk studies which, in fact, are at moderate risk, and in fact, we have efficacy from several of the low risk studies.

So the issue is not efficacy. The issue is risk-benefit, with this underlying risk of hemorrhagic stroke and GI hemorrhage, and obviously it's arbitrary where you cut the line. The American Heart Association writing group cut it at ten percent, the U.S. Preventive Services at six percent.

So what we want to do is now frame this

discussion and solidify these issues of efficacy, and I'd like to invite Professor Tom Meade to talk about the TPT trial at the microphone in terms of some of the issues related to this being a moderate risk trial with predetermined endpoints.

Dr. Meade.

DR. MEADE: Thank you very much.

I am, as you've heard, Tom Meade. I'm emeritus professor of epidemiology now in London University. I was the principal investigator of the Medical Research Council, the British Medical Research Council's thrombosis prevention trial at the time that I was Director of the council's epidemiology and medical care unit. And thank you very much for allowing me to say a few words about the trial which I will outline very briefly because of the time question, but in view of the importance that I think is being attached to it I obviously need to say a few words.

As you know, this was a trial carried out in moderate risk patients, and the events that would be prevented, as you've seen on this slide which was

just up, are approximately equal to those in secondary prevention, although none of the people in our trial had previously had an event.

It was carried out in general practice, and it had a 50 percent take-up of those who are eligible to take part, which is a very high proportion for a trial making the demands on the participants that this did.

Ninety-five percent of the or 98 percent of the population in the U.K. are registered, and we conducted this trial in 108 practices throughout the whole of the United Kingdom. So it is a very representative result in the U.K., and as you know, we use 70 milligrams of aspirin a day.

Now, I will briefly show the main results in a moment, but I believe that saying a word or two about this trial does fulfill what I understand to be one of the FDA's requirements for at least one trial in the relevant category that meets the criteria and satisfies the endpoints.

But I think I should say a little first about some of the concerns about the trial which are

in the documentation that you've had, and I hope that this will help to allow the committee to view our results without misapprehensions about some of the points that have been made.

There is a statement that neither the protocol nor the data were available. I wasn't actually asked for either of those, and the data, of course, have now gone to Colin Baigent at CTSU, and I think that that is actually an overriding way of looking at the question that we're talking about.

The protocol and the paper both say that we would look at fatal and nonfatal MI, and we do that on the same footing as all events, in other words, the combination of the two, and there's a very good reason for that which was that there was already evidence from the 1994 ATT paper and now from the 2002 that the effects on fatal events are considerably less than nonfatal.

So it would seem inappropriate for us to look at the results for all coronary events without looking at those two contributory subgroups.

So the trial, in fact, did have a primary

endpoint of myocardial infarction which answers, I think, your question in 2.1.3 of the questions that you've sent us.

Now, silent MI was not mentioned in the protocol, and it was not included in our results, our main results, which was made quite clear in the paper. So I think that the .07 significance value which is being mentioned in the FDA's questions is actually inappropriate.

We looked at the data on silent MIs because we had got serially ECGs throughout the seven-year follow-up, and it was pretty clear that I think if we hadn't shown those data somebody would have asked us to do so.

And if I may say in a friendly but firm context of a scientific discussion with people who I can hope are called colleagues, we did, in fact, put in the results about silent MI really almost as a footnote about the main coronary heart disease results, and given the emphasis that there has been from members of the questioning group about pre-specification, I could have dealt with that, but in

the absence of the protocol, you weren't able to see what we said, and so I really don't think it was correct for the .07 result to have been shown, and I hope you'll disregard it.

There are some inaccuracies following that in the footnotes to Tables 9 and 10 in your statistical review. We did also, incidentally show the results for fatal and nonfatal strokes combined which arises in your questions and is shown in our trial not to have been done.

In the memorandum, it's stated that aspirin caused more bleeding independent of site and severity, and that also is not correct. For example, hematuria occurred slightly more frequently in those on aspirin than those who are not, although it wasn't a significant or very big difference, and it was only the bleeding events which we call minor events which differed significantly between aspirin and not aspirin.

The differences between the major and the intermediate bleeding results are not significant, although a case of major result of bleeding episodes,

fortunately we had very few events.

And then finally, I think at this stage there is the slightly downbeat comment at the end of one of your documents that gives a quote from our paper. Results give limited, if any, agreement for the general use of aspirin regardless of risk. In other words, in those who are not at increased risk where the benefit and the harm might be more equal.

That sentence doesn't mean obviously that aspirin shouldn't be used in those who are at high risk. It obviously should be.

Now, if I could have Slide 158, please, I have four slides to show quickly. As you know, the trial was a factorial trial involving warfarin as well, and there were four treatment groups, and I only want to say that the letters in the right hand of each line there describe the four groups which I'll show in a moment.

WA refers to those who are on both warfarin and aspirin. W are to those who are on warfarin only, A to those who are on aspirin only, and P to those who were on placebo.

And if I could have the next slide, 159, please, there's a summary of what was our main statistical analysis, which was according to the main effects, and so for aspirin we compared everybody who was on aspirin, WA, and warfarin -- I beg your pardon -- WA and W against A plus P. Whereas for aspirin, it was WA and A against W plus P, having demonstrated that the effect of one agent does not influence the other. In other words, there's no interaction.

The point that was made earlier about the A versus P in the separate group's comparison not being significant, I think, is actually not appropriate. We simply describe that to show that the effect -- I think it's a 23 percent reduction in all events -- was very much the same as what we had when we looked at the main effects, but it's the main effects which are the principal approach to our analysis.

Well, so for the results. First of all, if I could have Slide 172, please. You can see -- I'm sorry -- I hope you can see that down at the bottom there is the effect in the log rank presentation of

aspirin on nonfatal events, significant at the .004 level.

Next above that is the to me unexpected but nevertheless real absence of any effect of aspirin on fatal events, and at the top is the sum of those two which in my view is actually perhaps no longer a very appropriate analysis to do, but nevertheless is significant according to all our criteria and specifications at the .04 level.

I have got results on stroke and major bleeds. We've showed no significant reduction in stroke attributable to aspirin, and there was no significant difference in major bleeds between aspirin and placebo, although the number of events were fortunately very small.

So in conclusion, I think there's no doubt about the value of aspirin in reducing nonfatal myocardial infarction in those who are at moderate risk, according to our trial. It would be nice if it also reduced fatal events, but if it doesn't I don't know the explanation for that, and I think the reduction in nonfatal events is certainly a worthwhile

achievement.

Thank you very much.

CHAIRMAN BORER: Thank you, Dr. Meade.

Let's limit any questions we have to clarifications of what Dr. Meade has said instead of value issue.

Tom?

DR. FLEMING: Well, just on this last issue where you were referring to the fact that there isn't an adverse or a positive effect on fatal events and you showed that second figure there, well, globally if I'm following it in your Lancet publication in 1998, if I count up in your table the listing of all deaths that are cardiovascular deaths, there's a 101 versus 81 excess. So there's a substantial excess of deaths in the aspirin group in cardiovascular deaths.

DR. MEADE: Well, if I could have slide 169, please.

This shows the results in the previous slide, the log rank demonstrations, but in fact, yes, there was in our data a nonsignificant adverse effect

of aspirin on fatal events. That's absolutely true.

DR. FLEMING: There you're only giving the MI, fatal MIs.

DR. MEADE: Yes.

DR. FLEMING: The total, however -- and that's 60 versus 53 -- the total, however, for all fatal cardiovascular events is 101 versus 81.

DR. MEADE: Could you just refer? Which table are you looking at?

DR. FLEMING: I'm looking at page 238 in your Lancet publication. It's Table 3, Table 3, Lancet.

DR. MEADE: Yes, I have that.

DR. FLEMING: 1998, under deaths.

DR. MEADE: Yes.

DR. FLEMING: I'm summing the one, two, three, four columns that relate to various subcategories of cardiovascular death, and when you sum them up, it's 101 against 81.

(Pause in proceedings.)

DR. MEADE: Yes. You've done a calculation which is not actually shown in the paper,

and you've included the noncardiovascular events.

DR. FLEMING: Correct.

DR. MEADE: And some other categories. That's not talking about coronary events specifically, which is what I've been addressing.

DR. FLEMING: It's IHD or stroke, stroke, or other cardiovascular.

DR. MEADE: Yes. Well, I would want to check those figures myself, but I think already answered the question in that you've included several categories there. I've just been talking about the MI question.

DR. FLEMING: That is correct, and that's why I wanted to clarify, because you're only talking MI, but if we look at all cardiovascular deaths, it's 101/81.

DR. MEADE: Well, again, that was not a specified endpoint in our trial, and I think it points up the importance of contributing these data to Colin Baigent's overview.

CHAIRMAN BORER: May I ask for a clarification? As you said, Dr. Meade, we don't have

the protocol, but if I understood correctly the prespecified primary endpoint was combined events.

DR. MEADE: No. We made it clear in the protocol and the paper that we would put all coronary events, fatal events and nonfatal events, on the same footing, and I've explained why that was, because in the secondary prevention --

DR. THROCKMORTON: The endpoints are specified in the first part, the endpoints part of the paper. If you want to read that out loud, it does -- I mean, the paper says the primary endpoint was all IHD deaths defined as the sum of fatal and nonfatal events, i.e., coronary death and fatal and nonfatal MI.

Now, that seems to differ from some of the things you've said.

DR. MEADE: No, but it also goes on to say that fatal and nonfatal events separately were also to be examined.

I think that absolutely rigid adherence to rules like prespecification and definition and so on are a good servant but a bad master, and I have

explained, I think, a very reasonable reason why we separated out fatal and nonfatal, because we had an indication already that the effect of aspirin might be different.

DR. TEMPLE: Were the fatalities just what appeared to be fatal infarctions or all cardiovascular --

DR. MEADE: No, fatal infarctions.

DR. TEMPLE: Okay. So if someone dies suddenly, that doesn't get counted?

DR. MEADE: No, that does get counted because we thought that most sudden deaths were coronary events, and the ones that the adjudicators thought weren't were omitted.

DR. TEMPLE: Okay. So all seven of unobserved deaths were counted.

DR. MEADE: Yeah, yeah, yeah.

DR. TEMPLE: Okay. So that could include some strokes or as long as you don't --

DR. MEADE: But not in the coronary events.

DR. TEMPLE: Well, no, that's what I'm

asking. The primary endpoint included heart attacks, okay? Coronary events that you survived.

DR. MEADE: Yeah.

DR. TEMPLE: And which fatal events?

DR. MEADE: Fatal events that are attributed to coronary disease.

DR. TEMPLE: Well, that turns out to be a huge problem in knowing how to attribute it. I can give you documentation for that, but what did you count?

DR. MEADE: We got all of the information that we could from coroners and hospitals, submitted them to an independent adjudicator, and if he decided they were due to coronary disease, they went in. If he decided on the few cases that they weren't, they didn't.

DR. TEMPLE: Did you do an analysis that included all fatal events or all fatal cardiovascular events plus nonfatal coronary events?

DR. MEADE: No, we didn't.

CHAIRMAN BORER: Okay. Well, we'll get back to this after a bit, but let's go through the

other issues that were raised if we can.

DR. PEARSON: Yes. I'd like to introduce Dr. Michael Gaziano who is the principal investigator for the physicians health study currently and particularly deal with issues of why they stopped this trial early and this issue of the disagreement about the prevalent coronary patients.

Dr. Gaziano.

** DR. GAZIANO: Thank you very much. This has been a very stimulating discussion.

The first point I'd like to make is that the physiology of myocardial infarction and other major important events is the same in physicians as it is in anyone else.

(Laughter.)

DR. GAZIANO: I would like to respectfully disagree with the assertion that there were 500 prerandomized MIs. That can unequivocally not be the case. We had a total of 139 events in one group, 239 in the other group, a total of 378 incident myocardial infarctions. All of the physicians reported these events. They were confirmed at a rate of about 80

percent. None of the physicians on their initial questionnaires either at randomization or at run-in reported a prior myocardial infarction.

I don't know how the number of 500 could have been achieved. We get records only on the reported cases, which would have been some 400-odd reported myocardial infarctions and some 250 reported strokes, of which about 70, 80-plus percent were confirmed.

So I have no idea where that number could have come from, but it absolutely could not have been 500. We have identified one myocardial infarction that was reported after randomization, that the date was confirmed prior to randomization.

The second point is with respect to the endpoints. The information on vascular death does not provide informative results from this study. The data monitoring board voted six to two, with all six members who were present voting for termination and the two absent members voting for continuation based on the 44 percent reduction that we see in the previous slide on myocardial infarction.

The power for fatal events was not what was anticipated in the original trial, and I don't think that this data can be interpreted in this study or in PPP that was also terminated early as indicating proof of a lack of benefit.

Here you see the fatal events in the physicians health study. Total cardiovascular events, 81 versus 83. All the way down at the bottom, total deaths, 217 and 227.

These findings are consistent with an effect of the 44 percent reduction in fatal and nonfatal myocardial infarction translated to a low risk population, which would be quite consistent with the data that we've seen in secondary prevention.

So I don't think that the lack of statistically significant difference on cardiovascular death or total death provides an informative information, and the most informative information that we get here is on myocardial infarction.

The third point is that in my opinion the physicians health study and the other trials must be interpreted not in isolation as if this were a new

drug, but in the context of the wealth of over 300 secondary prevention trials, the basic science data suggesting that there is a consistent effect of each of the individual trials and the pooled analysis.

And the utility of the pooled analysis in my mind is not that it provides new and unique information overall. It's that it provides the best quantitative estimates for the reduction in the risk for myocardial infarction in primary prevention, which is very consistent with the secondary prevention data. The trials like the physicians health study were not well powered for risk. So, therefore, the pooled analyses are also better estimates.

But I also think you take that information that we get from the primary prevention trials with the secondary prevention trials on a risk to come up with the best estimate so that we could come to a conclusion about whether or not there would be a risk versus a benefit and where that break point might be in primary prevention.

I think that these trials individually provide very important information and its pooled

data.

Lastly, were we asked to do a similar trial in an intermediate risk population, the feasibility of that trial logistically and also ethically would be questioned, and we have recommendations from the ACC "- from the AACHA and from the U.S. Preventive Task Force. I think it would be very difficult for us to take a moderate risk population and randomize them not only because there would be a lot of drop-in in that group, but also because I think it would be difficult for us to get it behind, to get backing of our institutional review boards.

In primary prevention, I think that this series of five trials alone and collectively in the pooled analysis represent very good primary prevention data suggesting that the physiology is the same in primary prevention. They provide useful information, but not the totality of information on risk, and it's my opinion that there is a point at which we can find a benefit-to-risk ratio based on the existing primary prevention data, which is very difficult to achieve

and which has been done in five trials and in which we'll get more information in the coming years with a couple of ongoing trials.

Thank you.

CHAIRMAN BORER: Thank you.

Doug?

DR. THROCKMORTON: Yeah. I'll just make a couple of general comments to sort of clear up some of the small things because I think the committee probably has important things to talk about later on here.

First, as regards the individuals that were thought to have had prior MIs, as best as can be made out, again, Dr. Temple pointed out that the reviewer is no longer with us. That was based on the use of PTCA or CABG, the individuals that had been enrolled in the trial. That's not the same thing, I grant you, as knowing that those individuals had had MIs as the basis for either of those interventions, but that accounts for the 40 individuals that Dr. Triantas -- sorry -- 38 of the 40 that Dr. Triantas identified as having had a prior MI. I take the point

that that's not quite the evidence for that that you might like unless there's other data that we don't have access to at this point.

And then the second issue, this issue of the .07 P value. I think this was the TPT comment that was made previously. I'd agree that without access to the primary data, it's hard for us to be precise on that value, and other than saying in general the value was higher than .04, it's probably best to leave it there.

Thanks.

DR. GAZIANO: Well, we collect information on revascularization procedures. We certainly don't consider those myocardial infarctions although they are important events, and there would likely have been a small number of P randomization vascular interventions.

DR. THROCKMORTON: Yeah, I think we're probably asking that a trial of this age to bear up more than maybe we would be able to recover at this point.

DR. GAZIANO: Absolutely. I think our

definition of MI has changed over the years. There are smaller events that we might have called unstable coronary syndromes historically which now with troponin we might call a myocardial infarction. The numbers would have been different, but I don't think the answer would have been any different.

CHAIRMAN BORER: Bob.

DR. TEMPLE: There was a lot of discussion and publication about the new analysis of the physicians health study when it was terminated. There's no question that there was no possibility of reaching the primary endpoint.

The choice of the secondary endpoint, however, as nonfatal MIs is of some interest. I mean, the primary endpoint had failed. So that was out, and then you have some choices as to the secondary endpoint or the new primary endpoint.

It could have been fatal and nonfatal MI, fatal and nonfatal stroke plus other cardiovascular events. It could have been any of those things. We know that if you do the latter and be more inclusive, the P value comes out .01. So it's not a negative

study even in those terms.

But can you say any more about how it happened to be the choice of the one thing that turned out absolutely best instead of something that seems a little more logical?

DR. GAZIANO: It was not as you point out the one thing that turns out to be the best. It was not nonfatal myocardial infarction. It was total myocardial infarction.

DR. TEMPLE: Actually the fatal MIs come out very well.

DR. GAZIANO: The fatal ones do come out very well, ten versus 28, but the endpoint that we showed -- could I have Slide 71? -- the endpoint that we showed, 139 versus 239, is totally myocardial infarction including both fatal and nonfatal myocardial infarction.

DR. TEMPLE: Right, but those come out really great. I mean, those are the best flexible numbers that --

DR. GAZIANO: The choice of that endpoint, the choice of that endpoint, that was a prespecified

secondary endpoint, and it was actually the data monitoring board's emphasis on that particular event.

DR. TEMPLE: Yeah, I know. There was discussion about it though at the time.

DR. GAZIANO: For which the investigators had little control, and then if you look at important vascular events, which was also a prespecified endpoint and an endpoint that Colin Baigent talked much about, this includes not only nonfatal myocardial infarction, but nonfatal stroke where we're anticipating seeing perhaps some benefit as well as some risk. So I think it's a very valuable and important.

Composite risk shows also a clinically relevant 18 percent reduction in risk with a P value of .01.

DR. TEMPLE: Yeah, I don't disagree with that, and the reviewer actually thought that .01 was the right P value for this trial because she thought why wouldn't you count fatal and nonfatal MIs and other cardiovascular fatalities and strokes since we don't know what we're doing here and we're off the

primary effort.

DR. GAZIANO: Now, you mentioned subsequent other analyses that are relevant, and I wish Nancy Cook were here to address those, but if you look at compliance adjustment, obviously the effects get much stronger, although this was an intention to treat analysis and none of those analyses were included, and then if you look at the combination of the first five years plus the seven years of follow-up that obviously it's observational data, you get a statistically significant reduction in cardiovascular mortality as well.

So we get a very consistent story from the physicians health study.

CHAIRMAN BORER: Tom Fleming.

DR. FLEMING: It might be useful though for a little bit of a statistical clarification on this. I thought where you were headed in your questions, Bob, were certainly consistent with my own thought.

It's interesting that the domain that was chosen when the primary endpoint was lurking around at

81 against 83, was the endpoint for which we had the most positive signal, and indeed, yes, the team included the fatal MIs that were in the right direction at ten against 26, but interestingly everything else looked pretty unimpressive if you look at deaths due to sudden death, stroke, or other cardiovascular. They were just as strong in the other direction, the 47 against 30, so that overall mortality showed no difference, and stroke was in the wrong direction.

And if you pool together the endpoint of 307 against 370, the positive is entirely driven by what they chose as the endpoint for positivity. This level of difference wouldn't have justified early termination by a group sequential monitoring procedure, i.e., if you had gone with this endpoint, with a P of .01, .01 is not impressive statistically, an interim monitoring aspect for group sequential.

So you were right, I believe. They went in the only direction they could have that would have given this the evidence needed to say it's conclusive on that specific endpoint.

You talked about 81-86, and you're right. This study in not conclusively ruling out benefit on mortality or on cardiovascular mortality. It's certainly though suggestive of no difference, and it contributes 160 events. You would need fivefold that though basically to rule out a 15 percent reduction, which is close to what you might see in a secondary prevention setting, but, oh, by the way, you do have fivefold that many when you do the meta analysis, and it shows the same thing that the 81 against 83 shows.

DR. GAZIANO: I would say that, again, the choice of myocardial infarction, total myocardial infarction being the dominant particularly in a male population, the dominant cardiovascular event driving this analysis was one that was prespecified, and it was the data monitoring board that felt it was unethical to continue a trial with such a dramatic reduction in one of the important prespecified secondary endpoints when the primary endpoint was not likely to provide meaningful information within the context of the duration of the trial.

But I would argue that the 81 versus 83

should not in any way be interpreted as proof of lack of benefit is very analogous to the early cholesterol reduction trials where we saw clear reduction in CHD risk, and we saw no benefit in total mortality, and there were those that interpreted that as proof of lack of efficacy on total mortality. Therefore, there must be excess vascular risk, and it wasn't until we got large enough trials with big enough agents that proved that those original interpretations were not correct, that the data for the early primary intervention clusteral (phonetic) trials were consistent with the secondary prevention trials and did not disapprove the benefit on total mortality. They were just not designed to show that.

This study was designed --

DR. FLEMING: The monitoring committee did not have access to the totality of what we have access to today in terms of total numbers of cardiovascular events, which is 900. They only had access to 160. Those data certainly do not rule out benefit. They don't conclusively establish no effect. They suggest no difference in this context, and the monitoring

committee made a judgment based on what they had at the time.

We know much more at this point in time, including the fact that we now have 900 events showing the same pattern of no effect which now does have a confidence interval that could rule out about a 15 percent reduction, which is on the range of what you could get in secondary prevention.

So now you do have the kind of evidence that you were saying you didn't have at the time that the monitoring committee had to make this judgment.

DR. GAZIANO: I would just have to disagree that that taken out of context of what we know about the effect of aspirin in secondary prevention, that still these effects are not inconsistent with an overall effect in MI and an overall effect in cardiovascular events.

CHAIRMAN BORER: Dr. Pearson, do we have some additional comments?

DR. PEARSON: In addition, we'd like to move on to another principal investigator, Dr. Dianni Tognoni from Milan, and the PPP trial, again, another

trial that was stopped early. I'd also like him to comment on the subanalysis published recently on the issue of the diabetics.

DR. TOGNONI: Thanks.

As you say, the group I am representing here, the PPP, is the general practice oriented group of the GC group who has been working for trials in myocardial infarction. We applied to the testing of this primary prevention, the same methodology we had applied for.

Myocardial trials, they are very pragmatic trials in a real condition of care. So I think that I would like just to underline some of these points because of the definition of the population and because that is relevant for the reason why we were requesting them to stop.

General practitioners, as you have seen passing in the publication, would ask to include patients who they believed to be at the sufficiently high risk despite the background treatment for background condition for which statins and antihypertensive therapy, to be exposed to aspirin

against no treatment.

The trial was a self-tutorial (phonetic) of whether those general practitioners randomized those patients, and at the occasion of an interim analysis the request was made to the same committee to consider stopping the trial because of what we could call something between ethical or futility reasons.

On one side there was a strong internal consistency of results pointing to positive effects in the primary endpoint, which was associated with increasing external evidence of recommending aspirin for primary prevention. The TPT results were published. There were already some recommendations and guidelines, and the general practitioners were asking whether it was still ethical to go on with a trial if the trial could add any new, important information based on that.

The final decision was to stop the trial before the planned number of events, and as you have seen the results, the collection of all the events which were foreseen in the primary endpoint confirmed the internal consistency of results both for the

combined endpoint and for the separate endpoint of cardiovascular death.

On the other side, there was no evidence posed with the opposite of risk associated with aspirin therapy with respect to the stroke, which was obviously the risk. The HOT results were already published.

Also we had for the stroke in our population difference in favor of aspirin both in overall stroke and hemorrhagic stroke.

Within the population just for information, and I have to confirm what Dr. Meade said before, our database also is perfectly available obviously for whatever inspection that has been done for other occasions for FDA for the trial.

We had made also some evaluation on the attributability of the benefit-to-different risk integrity. We have also prepared risk chart with the database of the study showing that the benefit is there across the different categories and obviously the absolute benefit is better with what could be called here moderate categories.

The second observation for the recent publication in this group of diabetes patients, I think that here as it's said clearly in our paper and in the accompanying editorial, there are general caveats about subgroup analysis.

As you have seen for general presentation, the diabetes patient represents approximately 20 percent, one-fifth of the population. So that's a subpopulation for which there was no preplanned analysis.

The general analysis was suggested first because there was a specific interest of adding something on diabetes because we are working on diabetes and then I think as the editorial points out in our comments, we see that as kind of a research issue in the framework of the formulation of the what is called now the aspirin resistance and whether or not the background diabetes condition could be seen as a situation where to investigate, but our interpretation is in general -- that's the subgroup analysis -- is not against the general classical interpretation of main trial result because that has

been proposed is after the main analysis.

CHAIRMAN BORER: Thank you.

Dr. Pearson, do we have any other comments? Can we focus them specifically on the issues that were raised rather than a summary?

DR. PEARSON: Yes. The issue raised there was this diabetes issue, and I did want to ask Dr. Colwell, if I might, to just comment on another issue relative to diabetics if we could quickly show his one slide.

DR. COLWELL: Well, thank you.

I'm John Colwell. I'm professor of medicine at the Medical University of South Carolina, and I was the lead author on the initial position paper that the ADA put out in 1997 about primary prevention for cardiovascular events in people with diabetes at high risk.

The deliberations at that time were, of course, the recognition which you've heard over and over again today that people with diabetes are at tremendously high risk for cardiovascular events, perhaps two to fivefold above control groups, and that

we needed to look at every possible way to prevent cardiovascular events that we could.

At that time we were impressed by the analysis that Dr. Baigent showed from the antiplatelet trialists and secondary prevention trials where the diabetics seemed to do better with aspirin therapy.

And there was one trial specifically in diabetes. If we could see one slide, it's Slide 262. It may have escaped people's notice. This was the early treatment diabetic retinopathy study. This is a large study done by the ophthalmologists, the National Eye Institute, and of course, they were interested in whether aspirin would prevent progression of retinopathy. So this was the primary reason for an aspirin versus placebo study in this group.

They were also studying various forms of laser therapy and pre-proliferative diabetic retinopathy, but they agreed to monitor cardiovascular events because of the prediction that aspirin might be protective in terms of cardiovascular event in this high risk group as a secondary analysis, of course.

But there were 3,711 patients. About 30

percent of them had Type I diabetes. The rest had Type II. They had pre-proliferative retinopathy. So they're fairly advanced. About half of them had hypertension. A fair number had lipid disturbances, hemoglobin A1Cs, and about half of them were above ten percent, and so forth.

So this was a high risk diabetes group, but only ten percent of them had a previous history of cardiovascular event. So in a sense it's mixed primary and secondary prevention trial in a high risk group.

A large dose of aspirin was used, 650 milligrams a day versus placebo, and the five-year follow-up.

In terms of myocardial infarction, the aspirin group, 9.1 percent had MIs, fatal and nonfatal. In the placebo it was 12.3 percent. Relative risk was .83, and the confidence limits just went past one in this particular study.

We were impressed that this went along with previous studies. There's one other subgroup study, if I could have the next slide, which is in the

primary prevention trial, the U.S. physicians health study. The diabetics in that group are shown in this slide.

There were 533 people with diabetes in that slide, and we know about the design. In terms of myocardial infarction within the people with diabetes, it was four percent on aspirin and ten percent in the placebo group with a relative risk of .39. Obviously this is a very small subgroup study, but it did influence the committee at the time. So this, along with the ETDRS and the meta analysis from the antiplatelet trialists, were really the reasons why the ADA came up with their position statement that high risk diabetics should be put on aspirin therapy.

Thank you.

CHAIRMAN BORER: Steve, clarification question?

DR. NISSEN: Yes, clarification on those last two slides. Could you tell us about the P values and the other events?

I mean, obviously, again we've gotten a very clear focus on myocardial infarction, but we're

trying to make a decision here on the basis of a totality of evidence, and so if you go back one slide, I'd like to know what the P value was for that comparison, and I'd also like to know what happened with the other events like stroke, hemorrhagic stroke, et cetera.

DR. GAZIANO: The P value in that comparison was about .0038, and the other comparisons were not significant, but there was no --

DR. NISSEN: So if you look at the totality of cardiovascular events, including stroke, was it significant or not?

DR. GAZIANO: Not significant.

DR. NISSEN: Okay, and how about the next study? Can we see that?

DR. GAZIANO: That is the study you just heard about.

DR. NISSEN: Yes.

DR. GAZIANO: I don't know what happened to the diabetic subgroup in this particular study. It has not been published, and we didn't analyze that.

DR. NISSEN: Okay. Because I think

obviously when we see numbers like this, we have to understand what the confidence intervals are around those numbers, and I think, you know, I'm concerned that we not look just at one type of event, myocardial infarction. We're really trying to balance here in this committee a balance of risk and benefit for all kinds of events and not just myocardial infarction.

So you know, if you're going to show us this, then show us everything. Don't show us a piece of the data.

CHAIRMAN BORER: Okay. Thank you very much.

Dr. Crawford, Dr. Pearson, are there any other focused comments?

DR. PEARSON: Yes. Professor Zanchetti, also from Milan and principal investigator of the HOT study, has to give a talk tomorrow morning in Rome and had to leave early. He was here earlier. I'd just like to, at his urging, I'd like to just show you two slides.

One, oh, two, and this gets at the question from the panel about this inclusion of or

this discussion of whether or not silent MIs should be considered separately.

And prior to unblinding of results, they had -- their statistical analysis group had made the decision not to include silent MI, and the reason for this was their inability to include this in meta analysis because no other antihypertensive or antiplatelet therapy trials had included silent MI among the endpoint.

Particularly, this point has not been covered by the group yet, and they considered silent MI a soft endpoint because nonfatal MI was defined by the usual two or three criteria, chest pain, elevated enzymes and ECG changes, whereas silent MI was only one, and they considered this a soft endpoint.

Silent MI, again, you heard about the time dependent issue, and of course, they had 14 percent of ECGs could not be obtained.

With that, if I could have slide 101, please, that trial obviously showed then a 15 percent reduction in major cardiovascular event and a 36 percent reduction in all MI. Again, this lack of

certainly no evidence of detriment, but certainly not any cardiovascular mortality findings.

But I did want to point this out, that this is the fourth trial, again, with evidence suggestive of the ability to prevent MI.

I had one other group that I wanted to address relative to questions from the panel, and I'd like to call Dr. Laine to talk really about some of the questions I believe Dr. Cunningham had raised about the issues related to GI toxicity.

DR. LAINE: Very briefly, I promise.

I'm a gastroenterologist from USC. That's known for being cheated by the BCS. In any event --

(Laughter.)

DR. LAINE: And with a clinical research interest in ulcer disease and upper GI bleeding.

And Dr. Nissen asked a question about what were the levels of, quote, hospitalized bleeding, serious bleeding. The data that you were shown was actually the investigators gave their numbers for serious bleeding, such as transfusion requiring, but frankly, it's not clear how many of them were

transfusion, how many events were called serious.

If we look at the literature, one of the best epidemiologic groups is Garcia Rodriguez. They have recently published a meta analysis with the endpoint of hospitalization for upper GI bleeding. They suggest about a twofold increased risk. That's 2.2 relative risk, and they also have about a baseline in the normal population of about .1 percent.

So given those data, the suggestion is about .1, just over .1 percent per year, though admittedly within that analysis there's a range up to as much as a third of a percent in a Denmark study, a large cohort study from Denmark.

If we want to just look at any mention of GI bleeding, maybe the best is to look at a meta analysis in the BMJ by Derry and Loke, and they suggest perhaps as much as, again, a one-third of one percent any GI bleeding increase.

I think it was Dr. Cunningham who asked about the long-term risk and what we do with people who come in with GI bleeding. Based on the latest data from HCUP project of the Agency for Health Care

Research and Quality, it says the mortality for upper GI bleeding due to ulcers has really dropped below five percent now. So that we always read about ten percent in textbooks. It's probably somewhat lower in the United States now.

The other important thing is although I would never trivialize upper GI bleeding -- it's one of my favorite things -- once people get out of the hospital and their ulcers heal, there is no residual damage there. There is no doubt there's marked increased recurrence rate, but the way we handle that is we go at the three pathophysiologic mechanisms, if you will.

One, get rid of H. pylori if present. There is a study, at least one, in the New England Journal that says you can decrease risk by doing that.

Two, avoid NSAIDs, which increase the risk of aspirin bleeding by two to fourfold.

And, three, give potent antiacid treatment with things like proton pump inhibitors, again, at least one study in the New England Journal showing a significant decrease.

So I wouldn't trivialize it. I would just say that we can at least decrease the risk, although not get rid of it.

CHAIRMAN BORER: Thank you very much.

Okay. Paul.

DR. ARMSTRONG: Is this the time to pursue to GI bleeding issue or not with the expert?

CHAIRMAN BORER: Yes, I think this may be our only time. So you go ahead.

DR. ARMSTRONG: In the trials that we're reviewing, there are a variety of exclusion criteria, some of which have been published and some not. I'm trying to understand the patient population that we're asked to make a judgment on relative to the patient population for the proposed label, and I'd appreciate your comments on the homogeneity versus the heterogeneity of the exclusion criteria in the five trials. That's the first question.

The second is we are looking at two other trials that Dr. Topol showed us: one, the CURE trial and the other the BRAVO trial in which the frequency of serious bleeding, most of which was GI

substantially in excess of the bleeding in the prevention trials.

There are exclusion criteria and patient populations described in those studies, but the bleeding rates, for example, in BRAVO are 2.4 to 3.3 percent in a population studied for about a year; 1.9 to 3.7 percent in CURE for a population studied about nine months.

Can you help me understand these issues because I'm struggling, and I really need to understand the issue of the frequency of GI bleeding, cure, for example. You need two units to be declared as a transfusion.

DR. LAINE: I think of it some come -- I think we have to be careful --

DR. ARMSTRONG: Of course.

DR. LAINE: -- of on these studies. The real problem is there are so many other risk factors for GI bleeding just in a background population, H., H. pylori. These patients get a number of other anticoagulants, and I also was struck by the high rates. Without a placebo group it's hard to say.

For instance, the placebo bleeding rate in some of these studies can be over half a percent and, you know, in the .5 to one percent range. So I'll let Dr. Topol talk about those.

DR. TOPOL: No, that's a very important point. Of course, those trials were not primary prevention trials, CURE and BRAVO. Most of that bleeding was up front in the hospitalization and included bypass surgery bleeding, bleeding related to other procedures. So it's a different patient population, but nonetheless, it was the gradient of a bleeding relationship as a function of aspirin dose.

But totally different incidence levels as compared to the patients in the primary prevention trials.

CHAIRMAN BORER: Blase.

DR. CARABELLO: Are we asked to approve all aspirin or enteric coated versus not enteric coated aspirin in terms of our risk-benefit analysis? And what is the difference in risk of enteric versus not enteric coated aspirin?

DR. LAINE: That's actually a fairly easy

one in the sense that virtually all of the studies do suggest that at least in terms of clinically important events like bleeding, that there is no significant difference between low dose plain, buffered, or enteric coated aspirin.

DR. PEARSON: I believe Dr. Meade has also comments from his experience with both warfarin and aspirin study.

DR. MEADE: Professor Meade again.

I just have had a chance now to look at the figures which Dr. Fleming raised just now, which I hadn't had a chance to check over, and I thought it might be helpful just to explain those in a bit more detail.

First of all, there were, as you can see, 13 more deaths from MI in the aspirin than the placebo group, and I've referred to that already, although it's a far from significant excess. So that's part of the reason.

Now, the other point is that Table 3, which is the one you were looking at, is one where it is rather important to look at the separate treatment

effects because the WA group there or at least the aspirin group includes the WA group, and there were certain fatal cerebral hemorrhages in the WA group which were attributable to warfarin.

So to that extent the figure where it says IHD or stroke, first event, should allow for those.

Now, if you want to take those figures to one side, it makes the balance much more even, and the other point is that I don't think the other cardiovascular deaths should really be rolled into this because they were nearly all due to ruptured aortic abdominal aneurism, and you know, I don't think that they're really part of the story that we're trying to unravel.

DR. FLEMING: But those other cardiovascular weren't contributing to this excess of 20. There are actually two fewer other cardiovascular on the aspirin. So if we take out that ten and 12, the 101 against 81 becomes 91 against 69, which is slightly a little worse now.

DR. MEADE: No, I think you should also then take out the seven fatal cerebral hemorrhages

because they were definitely due to warfarin.

DR. FLEMING: Well, but this is a factorial design. So you have the same fraction of people in the aspirin group on warfarin as in the controls. So if it's only happening warfarin when they're on aspirin, then that is, in fact, partly causal to aspirin as well.

Your analysis is very appropriate here. Your analysis in this paper captures the power of a factorial design, and it allows you to understand what the effect is of warfarin and what the effect is of aspirin. So this analysis is very appropriate, and it is already balanced for warfarin use.

DR. MEADE: Yes. As I said, I thought I would just -- since this is a calculation which you've done, which I haven't seen and have only had a chance to think about would comment on, and a lot of it is due to the excess of fatal MI events, which I've already referred to.

Why that happened, I don't know, but it was far from statistically significant, and I think that if one is going to start going into aspects of

this sort, you should really look at the deaths from all causes, and of course, they were very equally balanced.

CHAIRMAN BORER: Okay. Thank you very much, Dr. Meade.

I think we're going to have to move on to the FDA presentation. Dr. Jackson and Dr. Le.

DR. JACKSON: Good afternoon. I'm Michelle Jackson with the FDA's division of over-the-counter drug products and the Center for Drug Evaluation and Research.

I'd like to briefly describe the OTC drug review and provide some background on the regulatory history of aspirin. I'll describe the events leading up to this Advisory Committee meeting to discuss the citizens' petition submitted by Bayer Health Care.

What I'm going to discuss includes, first, an overview of the OTC drug monograph process, which will include a general concept of professional labeling for an OTC drug product; then the regulatory history for aspirin leading up to this Advisory Committee meeting; and I'll also mention some

highlights from the 1989 and 1997 Advisory Committee meetings and also briefly discuss the final rule on the professional labeling of aspirin.

The OTC drug review began in 1972 as a four-phase review of the safety and effectiveness of OTC drugs on the market. This is referred to as the OTC drug monograph process.

The first stage of the review involves the advisory review panels made up of independent experts. The panel then submits a report to the FDA with their recommendations.

In the second stage, FDA publishes the panel's report in the Federal Register as the advanced notice of the proposed rulemaking or the ANPR. A public comment period follows, allowing interested persons to submit comments and additional data.

Based on the panel's recommendations and comments received in response to the panel's recommendations, a third stage of the review is that FDA's proposed rule published in the Federal Register as a tentative final monograph are referred to as the TFM or the proposed rule.

This is then followed by a public comment period.

In the fourth stage of the review, FDA considers additional comments, new information submitted in response to the TFM. The agency then develops a final monograph or a final rule which is the final regulation for that particular drug class.

At this point in time, FDA has developed a final monograph with the professional labeling for aspirin, and so today's discussion will be considering an amendment to the current regulation.

Once the comment period for the particular rulemaking is closed, interested parties may still provide comments and additional data to the OTC drug review through the citizens' petition process. The Code of Federal Regulations, the CFR, in Section 10.30 describes in detail how to submit a citizens' petition. Anyone from the public can submit a petition to the agency. Essentially it's the right of citizens to petition the government.

Through this process someone may request that the agency issue, amend, revoke a regulation or

take or refrain from taking certain actions.

Petitions are placed on public display in the Division of Dockets Management. The agency has received a number of petitions to the internal analgesics monograph requesting cardiovascular indication for aspirin.

During the OTC drug review, labeling of the drug product is included in the review. There are two types of labeling: OTC labeling and professional labeling. The difference between the two is that OTC labeling is provided for consumers, and consumers are able to safely self-medicate themselves with the product.

Professional drug labeling is provided for health care professionals only and is not intended for the general public, and advice from a health care professional is needed for the safe and effective use of the drug product.

By the way of introduction, in the next two slides outline the key chronological events leading up to the issues for this Advisory Committee meeting. The regulatory history of aspirin for

today's discussion will mainly focus on cardiovascular issues. I'll briefly run through the key events and then discuss each event in greater detail.

In July 1972, we had the formation of the advisory panel review to the OTC internal analgesic ingredients. In July 1977, we had the publication of the OTC internal analgesics panel's report and the ANPR. This is then followed by a public comment period.

In November 1988, we had the publication of the TFM, also followed by a public comment period. In May 1989, the agency received a comment from the Sterling Drug Company requesting a claim for aspirin for the prevention of primary heart attack.

In October 1989, the Advisory Committee met to discuss the claim for aspirin for the prevention of primary heart attack.

In October 1992, the Aspirin Foundation submitted a citizens petition requesting an aspirin claims for treating acute MI.

In December 1992, the Aspirin Strategy Group also submitted a citizens petition requesting an

aspirin claim for treating acute MI.

In June 1994, the aspirin strategy group submitted another citizens petition, and this time requesting a claim for aspirin for anyone at risk for MI and stroke.

In June 1996, the agency published an amendment to the TFM to include two citizens petition requests to include an aspirin claim for treating acute MI. In January 1997, the Advisory Committee met to discuss an aspirin study group's petition claim for aspirin for treating acute MI.

In January 1997, the Advisory Committee met to discuss an Aspirin Strategy Group's petition claim for aspirin for anybody at risk for MI and stroke. This then led to the October 1998 final monograph for the professional labeling of aspirin.

Now that I've given you a brief overview of what's to come, we'll move on to some regulatory history beginning with the 1977 recommendations of the advisory review panel for the OTC internal analgesics and antirheumatic drug products.

The Advisory Review Panel is responsible

for the evaluation of the safety and effectiveness of OTC internal analgesic drug products containing aspirin. In the Federal Register of July 8th, 1977, the agency published the panel's recommendation in the ANPR to establish a monograph for OTC internal analgesics, anti-pyretic and anti-rheumatic drug products. In its report, the panel extensively discussed antiplatelet effects of aspirin, increased bleeding time, warnings against use in people with GI or bleeding problems or during pregnancy, and there was also no mention of cardiovascular claims and the panel's report at that time.

After reviewing the comments and new data submitted in response to the ANPR, the agency published a TFM in 1988. This document described the agency's position concerning the condition under which OTC internal analgesic drug products are generally recognized as safe and effective.

Some of the highlights included in the TFM is that the agency propose professional labeling for the use of aspirin for reducing the risk of recurrent TIAs or stroke in men, for reducing the risk of death

and/or nonfatal MI in patients with previous infarction or unstable angina, and for rheumatologic diseases.

In response to the TFM, the agency received the following comments that professional labeling be approved for the use of primary prevention of MI under a doctor's supervision, reduce a dose for TIA and stroke from 1,300 milligrams to 300 milligrams per day; and to also include labeling for both men and women.

On October 5th, 1989, the Advisory Committee met to consider data from the physician health study to support the use of aspirin for primary prevention of MI. Some of the highlights and concerns from the committee was that aspirin had no effect on total cardiovascular mortality, and there was no data on aspirin used routinely in men without risk factors and in women, and the committee was concerned that aspirin would be used in healthy people or inappropriate patient population and would, in addition, be advertised for said use.

On June 13th, 1996, the agency proposed to

amend the TFM to include an indication for the use of aspirin in treating acute MI, an initial dose of 160 milligrams to 162.5 milligrams continue daily for at least 30 days.

This proposal was in response to two citizens' petitions submitted by the Aspen Strategy Group and the Aspirin Foundation of American.

On January 23rd, 1997, the Advisory Committee met to consider another citizens petition's request. The citizens petition requested an amendment to the professional labeling for aspirin and secondary prevention of cardiovascular events in patients undergoing coronary, cerebral, peripheral, arterial revascularization procedures with chronic non-valvular atrial fibrillation, and requiring hemodialysis access with fistula or shunt and with elevated risk due to some form of vascular disease.

At the 1997 Advisory Committee meeting, the committee recommended the use of low dose aspirin in patients with stable angina. The committee recommended the use of low dose aspirin in patients with arterial or vascularization procedures, and the

committee also recommended the professional labeling not indicate use in patients with peripheral vascular disease.

The federal notice of 1998 final rule contained the agency's reasons why the claim for a primary prevention of MI was not included in the final monograph. After reviewing the committee's decision on the physicians health study, FDA concluded that some subjects had prior MI and aspirin is already known to reduce the risk of recurrent MI in such patients.

FDA's evaluation showed that eight percent of the subjects who suffered from nonfatal MI during the study also had evidence of a previous MI, and there was no statistically significant effects of aspirin when fatal and nonfatal MI and strokes were combined.

FDA's evaluation of the physician health study show the reduction of the incidence of fatal and nonfatal MI was accompanied by an increase in hemorrhagic stroke, sudden death, and other cardiovascular deaths, and the British doctors trial,

despite its similarities to the physician health study, does not support the use of aspirin to prevent an initial MI. The study revealed no effect on total cardiovascular mortality.

Aspirin as an OTC product is somewhat unique in that the professional labeling information does not appear on the OTC label. The regulation constitutes that labeling be provided to health care professionals by manufacturers. It has a comprehensive prescribing information similar to that found on prescription labels. The professional labeling for the use of aspirin is used for vascular indication and patients that have undergone certain revascularization procedures and rheumatologic diseases.

The professional labeling is similar in structure to the prescription label by providing information on studies supporting efficacy indications, dosage recommendations, and warnings. Listed here are some of the components that go into the professional labeling of aspirin. You have adverse reactions such as hearing loss, dizziness, GI

bleeding and upset stomach; warnings such as de-alcohol and Reye's Syndrome warning, indications such as the vascular and revascularization procedures and arthritis, dosage administration describing the dosage for the indicated use, and dosage describing what actions to be taken, and precautions such as patients with renal failure, patients on strict sodium diets and drug interactions and contraindications that include the allergy and Reye's Syndrome.

This table shows the indication and the recommended daily dose for the use of aspirin in patients who have vascular problems, and listed here are just some of the examples of the vascular indications.

This table shows the indication and the recommended daily dose for aspirin used in patients who have undergone revascularization procedures, and listed here are some of the examples of the procedures.

So in today's meeting, the Division of OTC Drug Products is seeking the committee's perspective and recommendation concerning Bayer Health Care's

request to expand the cardiovascular indications for professional labeling of aspirin for the use of a regime dose of 75 to 325 milligrams for primary prevention of MI in patients at risk for coronary heart disease.

The agency's primary concern is an assessment of the overall data.

Thank you for your attention.

CHAIRMAN BORER: Thank you, Dr. Jackson.

Now we'll have the review by the FDA statistician.

DR. LE: Good afternoon. My name is Charles Le. I'm a statistician at the FDA.

I'm going to talk about the issues with the statistical analysis in this citizens petition. This is the outline of my talk.

First, I will talk about background. Then I will introduce the sponsor's meta analysis peripherally. Next I will talk about the HOT study issues and the pooled analysis issues which are corresponding to the sponsor's meta analysis issues, and then I will talk about the exploratory benefit-to-

risk analysis family summary.

The background. The sponsor requested amendment to the professional labeling for aspirin. The new indication is that low dose aspirin reduces the risk of the first MRI in patients with a coronary heart disease risk of ten percent or greater over ten years or there is a positive benefit risk as assessed by the health care provider.

Five studies were selected to support the petition. Here are the five studies: the BDT, the British Doctors Trial; and the PHS, the U.S. Physicians Health Study; the TPT, the thrombosis prevention trial; the HOT, the hypertension optimal trend study; the PPP, the primary prevention project.

Over the five studies, PHS and HOT are two of the larger ones. Each has approximately 20,000 subjects. Under the other three studies, each has around 5,000 subjects. Combining the five studies, the total number of subjects is more than 55,000.

FDA only has data for HOT. For the other three or four studies, the reviews were based on the published literature.

The agency considered aspirin for this indication before and did not approve it. Dr. Jackson already did a summary listing some of the reasons. At that time, only two studies were available, the BDT and the PHS. The reasons were PHS showed that some patients had a prior MI, and the aspirin is already known to reduce the risk of recurring MI. The PHS did not achieve statistical significance when combined with nonfatal MI and the nonfatal stroke. The BDT, which was very similar to the PHS, was neutral on the effect of -- I'm sorry The BDT was neutral on the effect of aspirin on MI.

So what's new in this petition? Three new studies were included, the TPT, HOT, and PPP. Among the three studies, HOT is the largest one. Under the sponsor's meta analysis of the five studies was submitted to support the petition.

So in the following, I'm going to introduce in the sponsor's meta analysis peripherally, and then I will talk about HOT study issues and come back to the meta analysis issues.

This is the sponsor's meta analysis for a

nonfatal MI. The data from the published literature for HOT under the information for nonfatal MI is not available. So combining the other four studies, the relative risk is .68 and then the 95 percent confidence interval is from -- I'm sorry -- the 95 percent confidence interval is from .59 to .79.

For the composite of MI, stroke, and the cardiovascular death, combining the five studies and the relative risk is .85, and the 95 percent confidence interval is from .79 to .93.

For cardiovascular death, combining five studies the relative risk is .98 and the 95 percent confidence interval is from .85 to 1.12.

Now we talk about HOT study issues. The main issue is the silent MI. In the heart, the primary endpoint was major cardiovascular events. It was the composite of nonfatal and silent MI, nonfatal stroke and cardiovascular death, and the silent MIs were obtained by comparing the ECGs at the baseline with the final visit. The randomization was a one-to-one ratio. Each group had approximately 9,400 subjects.

Here is a silent MI, and the total MI by treatment group. There were 48 percent and 31 percent sudden MIs in aspirin group and placebo group respectively.

These are the efficacy results for the HOT study. If we look at the first column, the difference between the first row and second row is whether we include or exclude sudden MIs. The same thing for the third row and fourth row, and now we have a worst stroke, cardiovascular mortality and total mortality. If we look at the number of P values, this column, only two rows with not enough P values, and that's .05, that's one way to exclude silent MIs.

When we include silent MIs in the lines above, the nominal P values are more than .05. So whether to include or exclude silent MIs is crucial.

The published paper reported that statistical significance was achieved for the composite of nonfatal MI, nonfatal stroke, and the cardiovascular death, and for MI alone and the silent MIs should be included in both efficacy endpoints according to the study protocol. When silent MIs are

included both in the primary endpoint and the MI unknown and not statistically significant.

Now we talk about the meta analysis issues. I called it a pooled analysis. This is the summary for the five studies.

If we look at the patient population for PHS and the BDT, the patient population was apparently healthy male physicians. For TPT, it was mail subjects at high risk of cardiovascular disease, for heart and PPP. The patient population, the patients were at some risk of cardiovascular disease.

The master row is the aspirin dose. It ranges from 75 milligrams per day to 500 milligrams per day, including 325 milligrams every other day. So the patient populations were quite different among five studies, and the aspirin doses varied.

Now if we look at the primary endpoint for each individual study, for PHS and the BDT the primary endpoint was cardiovascular death. For TPT it was fatal and nonfatal ischemic heart disease. For HOT and the PPP, it was the composite of cardiovascular mortality, nonfatal MI, and the nonfatal stroke for

heart. As mentioned before, sudden MIs were included.

Now, the five studies is positive in the sense that the statistical significance is not achieved for the primary endpoint.

Now we look at the MI. MI is one of the secondary endpoints in the five studies. If you look that the five studies individually, all the relative risks are less than one and the PHS has the smallest relative risk at the .58, and the BDT has the largest relative risk at the .96, and if you look at the nominal P values, PHS has a very small nominal P value, less than .0001, and the TPT has a nominal P value at a .04. For the other three studies the nominal values are more than .05.

Now we combine the studies. The first line in yellow is combining the five studies. The relative risk is .77. The nominal P value is less than .0001, and the 95 percent confidence interval is from .69 to .85, and the yellow line in the middle here where you excluded the PHS because PHS has a very small nominal P value; so when you exclude it and combining the other four studies, and then the nominal

P value becomes .011.

And in the last row here, we exclude two studies, PHS and TPT, because the two studies, both have a nominal P value less than .05, and then combining the other three studies, the nominal P value is .096.

There were some issues with the pooled analysis, why and how the five studies were selected. The patient populations were very different and aspirin doses are different.

So what's the evidence for MI? MI is only a second random point in all the five studies, and the silent MI is an issue. If we look at the five studies individually, PHS suggested potential benefit. TPT had a nominal P value at .04. Heart is not clear. BDT and TPT failed to show statistical significance, and then the pooled analysis did not provide any additional information beyond the individual studies.

Finally, we talk about the exploratory rate, benefit-risk analysis. The new indication where you expanded the risk population and the bleeding is one of the known adverse events for aspirin. The

benefit and risk ratios should be considered.

We only have data for HOT. So here is the MI and the major bleeding by treatment group, provided overall for male low and for female low. In each case aspirin has a lower rate for MI and a high rate for bleeding.

So we're trying to quantify the benefit-risk ratios. This method was developed by Andrew Willan and others, published in Controlled Clinical Trials. I listed a reference at the bottom.

That Pt and Ps, the probability of MI free in aspirin and placebo group, respectively, that Qt and Qs is the probability of major bleeding in aspirin and placebo group, respectively. Then a possible measure of benefit-to-risk ratios are -- which is defined as Pt minus Ps over Qt minus QS are defined this way.

Then are measures. How many MIs can be prevented and the cost of one major bleeding by using aspirin, and the confidence interval can be obtained. From the HOT study we got the estimates for all, and the confidence intervals are wide. So they're not

provided here.

For the definition of major bleeding, you can look at the final report for the HOT study. What does this mean?

It means for male and female combined, it is estimated 54 MIs can be prevented and the cost of 100 major bleeds by using aspirin. For male alone, 85 MIs may be prevented at the cost of 100 major bleeds by using aspirin, and for female alone, 14 MIs may be prevented and the cost of 100 major bleeds by using aspirin.

In summary, MI is only a secondary endpoint, and in all of the five studies silent MI is an issue. For primary prevention of MI, PHS suggested the potential benefit. TPT had a nominal P value at the .04. Hot failed to share statistical significance when sudden MIs were included. BDT and the PPP failed to show statistical significance.

The two studies in yellow were considered by the agency before, and there were some issues with the pooled analysis, why and how the five studies were selected, the risk factor of the patient population,

and the aspirin doses, and the pooled analysis does not provide additional information beyond the individual studies.

And finally, the benefit and the risk should be considered.

Thank you.

CHAIRMAN BORER: Thank you very much, Dr. Le.

Yes, Alastair.

DR. WOOD: I have a question. One of the strengths of meta analysis is to take the totality of the data. How do you justify excluding two of the major studies which by my sort of back-of-the-envelope calculation cut by 50 percent the number of patients you had in the study?

DR. LE: The idea is if you've already cut the number of people less than .05, we're trying to get the information from the other three studies, and combining the other studies, the sample size is increased. Hopefully we can get the statistics in significant results to obtain the nominal P values still, .096.

That's the idea, but you've already got that PHS has a very small, nominal P value, and the TPT had a nominal P value at .04.

DR. WOOD: I'm not sure I understood your answer.

DR. TOPOL: Alastair, I think it's an attempt to find a confirmatory meta analysis after you accept the physicians health study. A done deal, and then you see if the rest of it looks like the confirmation.

I think a lot of people --

DR. LE: Right. That's the idea.

DR. FLEMING: I guess I would say in understanding the nature of your question, the estimate is -- the best estimate is the totality of the data. The physicians health study gave a very strong signal. The totality of the data gives a strong signal. It's relevant to get a sense of whether or not there's robustness. If that physicians health study was out, would the remainder of the study still basically themselves be providing a strong signal?

It's in that context, but clearly the best estimate, as I think your intuition is saying is going to be the one based on using all of the data.

CHAIRMAN BORER: Okay. There were -- I'm sorry. Beverly?

DR. LORELL: I think one of the things that I'd like to make a point of in regard to your otherwise excellent analysis is that for the totality of the risk-benefit experience around cardiovascular events, must coronary and MI include subsequent development of heart failure, which confers both morbidity as well as followed out longer than these studies a secondary risk of mortality, as well as stroke?

So I think unfortunately -- and I don't think we can squeeze these trials to get this data -- but it would have been of interest to have actually had some kind of an estimate of prevention of risk of heart failure, morbidity and mortality over both a shorter and a longer range?

So my comment is I think in this risk-benefit equation, this is a component of risk that

we're not able to look at today.

CHAIRMAN BORER: Steve.

DR. NISSEN: Yes. There's sort of an issue on the table that we haven't really talked about, and maybe I can frame it. It is a question really for the FDA and for the OTC group.

And that relates to direct to consumer advertising. I assume that what's really at issue today, which we haven't talked about is what you can do with direct-to-consumer advertising, which I suspect is why this application is here.

And so the question is: if we give this label, are we likely to see direct-to-consumer advertising promoting the use of aspirin in primary prevention, or is that simply not an issue? Is it an issue?

This is professional labeling versus -- I mean I don't understand what the implications of a decision here would be on how this would likely play out.

DR. TEMPLE: Charlie may want to answer more. This was once an issue when there wasn't much

direct to consumer advertising of prescription drugs, but now there's direct to consumer advertising of prescription drugs. There would be direct to consumer promotion of a so-called professional claim in advertising, and I think nothing would stop that any more than direct to consumer advertising of prescription drugs.

So I think the issue here is what's the right statement of what the indications are, which will limit promotion and affect promotion of all kinds to all people, but the DTC thing is really not such a -- I mean, it's not an important question. It will happen, guaranteed.

DR. NISSEN: Well, assuming we give the label it would happen.

DR. TEMPLE: Yeah, yeah. Not unless.

DR. NISSEN: Okay. I just wanted to make sure we understand that, yeah.

DR. TEMPLE: Maybe not unless.

DR. NISSEN: What I'm trying to weigh here as a -- you know, trying to do what I think is in the public interest here and what I'm trying to understand

is what the risks are that people at such low risk that aspirin would increase their risk of harm will get the drug versus more people who would benefit getting the drug, and so this is playing into my thinking here.

DR. TEMPLE: Can I make an observation about that? I mean, to my surprise to some extent almost the entire presentation about this has been who to give the drug to. Usually the first thing you do is you find out whether it works in the population like people who haven't had an MI yet.

And I guess I would urge you to think a lot about that question, and then it's very important who to direct the drug to, and really the presenters have talked a lot about that and who is at great enough risk to do that, and you can advise us on how much emphasis we should put on that, but it's really important to us to know whether you think they've got the data that supports the effectiveness in primary prevention, and I hope you'll concentrate on that and not worry too much about promotion because we'll worry about that.

CHAIRMAN BORER: I promise we'll concentrate on that.

DR. NISSEN: Okay. I just thought that we ought to say something.

DR. TEMPLE: It's not uninteresting. It's very interesting, but where we need help is what to make of the data.

DR. NISSEN: I understand completely, but I just thought it was not being said and it probably ought to be said.

CHAIRMAN BORER: Okay. With that issue having been put on the table, let's move along here. We have some unanswered questions. Bill Hiatt had one, and I think Susanna had one, but what I'm going to propose that we do is to begin discussion of these issues in the context of the FDA's questions. If we require clarification of any points by any of the committee members from the sponsor and its representatives, then we'll do that, but otherwise the sponsor's comments are concluded at this point.

Alastair.

DR. WOOD: I'm sorry. Just before we

leave the sponsor, the presentations were so different. It does seem to me there ought to be a chance from the sponsor to respond to the comments from the FDA.

CHAIRMAN BORER: To which comments?

DR. WOOD: Well, some of the specific comments in the last presentation seem to me to beg for a response, and I think it would be appropriate to hear why they see such a disparity between the two presentations.

CHAIRMAN BORER: Okay. We're not going to do that right now only because I think the discussion will get a little convoluted. The FDA statistical review was available a while ago, and the sponsor gave its views of how the data look. It can respond to the FDA, could have responded to the FDA's statistical review, but I think our discussion will take both of these sets of analyses into consideration, that is, what we've been presented by the sponsor and what we've been presented by the FDA reviewer.

So I think we'll hold off on a specific response right now. As we go along, it may be

necessary to do it.

Okay. Again, if you need clarification from the sponsor about anything, then we can certainly get into that in the context of our consideration.

I'm not going to call for a break right now. If anybody needs to come in and go out, you can certainly do that.

The questions put to the committee are as follows. The Cardiorenal Advisory Committee is asked to give an opinion on the use of aspirin for the primary prevention of myocardial infarction in response to a citizens petition. That petition cites five studies. We've heard a great deal about the five studies. They're summarized on the first page of questions.

The specific characteristics of these studies are presented here on page 4 of the questions, and with these characteristics in mind and with the data that we've heard in mind, are there any other studies that should have been considered?

Is there anyone on the committee who believes that there are studies that should have been

considered that weren't for this purpose?

DR. HIATT: I don't believe so, but I just would point out that there is this subgroup analysis the Primary Prevention Project published in Diabetes Care this month. It maybe has limited value, but it's new.

CHAIRMAN BORER: Okay. Are there any other studies of which anyone is aware that should have been considered in drawing conclusions here?

(No response.)

CHAIRMAN BORER: I will take that as a no.

Number two, in considering how to interpret these trials with respect to primary prevention of MI, whether by formal or informal meta analysis, what is the significance of each of the following?

And I'm going to ask Tom to take the lead in providing a response to these questions and then each of the other committee members can follow up if she or he chooses.

Two, point, one, one, the study protocol is unavailable for BDT, TPT, and PPP. Tom?

DR. FLEMING: Should I group my answers and maybe give a global answer to Question 2 in the efficient use of time here or do you want me to go --

CHAIRMAN BORER: No, you go ahead and group your answers.

DR. FLEMING: Okay.

CHAIRMAN BORER: If you think that's appropriate.

DR. FLEMING: All right. I might try to answer Question 2 by grouping these seven elements into four parts in responding to them in these four part. The first two parts I'll put together. The study protocol was unavailable and the source data are unavailable. What is the significance?

Certainly there is some non-trivial significance. Having been involved in many advisory committees, I've been convinced that what comes forward in a detailed FDA presentation often is substantive additional insight beyond what I might have gotten by reading the published literature presentation of the results.

And an example of this certainly is the

HOT trial is the one that the FDA did give a careful analysis for, and the insights about silent MI that I want to refer back to in subsequent questions as to why I consider it to be of relevance is certainly something that was much clearer when we were seeing the FDA presentation compared to the literature publication of these results.

So I do believe that literature publications are very informative, but from experience, I think there is a substantive added insight that we get when the protocol and source data have been reviewed in depth by the FDA and presented to the advisory committee.

The second and third and fourth components, no study had a primary prevention of MI as the primary endpoint and only one study showed an effect on its prespecified primary endpoint.

My sense about this is these certainly are also relevant facts, as I'll allude to in some subsequent questions. I think the clinical community used considerable judgment in identifying what would be the most appropriate endpoint in each of these five

trials, and those endpoints typically were focusing very much on cardiovascular morality, as well as nonfatal MI and nonfatal stroke, and the fact that none of these were significant, or the way I might put it is the fact that the results on those measures were far less favorable than the result on MI certainly indicates the fact that the more global measures that we were looking at were not nearly as persuasive as the specific subcomponent, which was nonfatal MI.

And this is an issue of considerable significance when we put in the context benefit to risk and the fact that there is increased bleeding and hemorrhagic stroke. So the nature of this significance, I think, will come clear as we also answer subsequent questions.

Part number 215, the studies varied with respect to what MIs were captured, and certainly that is of some significance. In an example of this, the HOT trial did provide us an analysis of the silent MIs as well as other MIs, and that did, in fact, have some relevance or does have some relevance in interpretation.

The final two elements, the dose regimen and biopharmaceutical properties of aspirin varied. The baseline risk factors varied. What is the significance of this?

In fact, I think there's a tradeoff. I think there are some beneficial aspects to this variability. I think it gives us the opportunity to assess at some level how generalizable our results are by looking at the assessments over a range of different regimens and characteristics of participants.

However, this generalizability comes at the risk of greater clarity for any specific setting. So we have less certainty about any specific indication and specific regimen by virtue of the fact that there was this heterogeneity.

I'll stop. Those are the 2.1.

CHAIRMAN BORER: Great. Okay. Does anybody on the committee have any additional comments with regard to 2.1? Remember we will come to these issues again, I think, in Question 6, but specifically I'd like to hear if anyone would like to

comment on 2.13 and 2.1.4. "No study had primary prevention of MI as a primary endpoint, and only one study appears to have shown an effect on its prespecified primary endpoint."

How does that impact on your thinking about the evaluation of what was found? Steve.

DR. NISSEN: Well, like I think Tom, I'm much less comfortable in analyzing data in a clinical trial when the primary endpoint is not met, and I think it should be said that, you know, there are lots of risks of looking at even prespecified subgroups, let along non-prespecified subgroups, but those risks go up, it seems to me, when the primary trial fails to meet its prespecified endpoint.

And so this tends to weaken the overall case, and it's unfortunate that it's true for virtually the entirety of the data, that none of these studies really were a slam dunk for their primary endpoint, and that makes me not want to go into those subgroups with the same level of confidence that I would in a study that actually met its endpoint.

CHAIRMAN BORER: What about the presence

or absence of consistency among the various endpoints, primary or secondary, given the fact that the primary was not met in any of the trials? Does anybody have any thoughts about that, the impact of the consistency or lack of consistency among the various outcome events?

Beverly.

DR. LORELL: Well, I'm not sure if this is precisely what you're getting at, but I did want to comment about the issue of consistency of defining myocardial infarction and to put a little bit of my perspective on the FDA comments here.

I am not troubled by the inclusion or lack thereof of silent MI. It's a whole different issue as to whether or not there was any awkwardness in what was defined in the protocol versus the final assessment, but I'm talking about linking of the clinical totality of our judgment today.

I think it's worth emphasizing that we know a huge amount from many studies and large evidence based trials beyond the studies here about the outcome short and long term of the clinical event

of myocardial infarction.

In contrast, we know remarkably little and the data is conflicting about the long-term clinical outcome of so-called silent infarction and probably could not even reach consensus around this table except in the narrow setting of post PCI experience of how to even define that.

So in responding to query number 2.1.5, I think my own view is I'm not troubled by this issue of silent versus clinical event, and I personally would urge this group to think predominantly about the clinical MI event database.

DR. TEMPLE: I just want to be sure one distinction is made. You may not -- some of the studies don't have any information on silent MIs. So I think you're saying don't discard the studies for that.

What about the studies that do have information about it, but didn't include it? How do you feel about that? I just want to separate those two issues.

DR. LORELL: I think I would say the same

thing, that I think in making a clinically sound decision we have very little data, and it's discrepant about the implications of a silent MI in this kind of prospective primary prevention setting.

DR. TEMPLE: Okay. So you're saying that you think the right endpoint is the clinically manifest MI.

DR. LORELL: In the database that we have today, I do.

DR. TEMPLE: Okay. I'd be interested in being sure how other people feel about that, too.

CHAIRMAN BORER: Paul.

DR. ARMSTRONG: I wanted to respond to 2.1.3, but before doing that, silent MI, of course, expresses itself as sudden death, which is the first manifestation of the disease, and if it uniformly defined as new Q, then it has prognostically meaningful implications that are clear cut.

The complications of myocardial infarction, if they're meaningful, should express themselves in death downstream, and so the consistency issue is potentially troublesome. The point I wanted

to make relative to 2.1.3 was one that I thought Tom would address and I'll ask him directly through you, which is: if you terminate a trial early because of an efficacy endpoint that's not your primary, then there's another layer to this discussion relative to the confidence in the estimate which Steve spoke about, and that, of course, is that you overestimate the extent of the efficacy.

Could you give us some sense based on your experience of the proportion of the estimate of efficacy that's likely overestimated because the trial terminated based on that judgment?

DR. FLEMING: Well, Paul, you're right. If you're monitoring a trial and at an interim analysis you see a result that looks extreme and that triggers a recommendation to terminate, then essentially it's a bit of what you might call a regression in the mean phenomenon.

Essentially your estimate undoubtedly reflects the fact that there's benefit, but probably at a time period where you might be getting a particularly favorable estimate of that benefit. So

you're tending to overestimate the true benefit.

A seat of the pants adjustment is about a ten percent difference. I had mentioned in the PHS trial though that if we're looking -- and I don't think we're going to look at these data purely from the perspective of statistical significance, yes versus no in individual trials, but one has to recognize as well that what you call statistically significant also has to be assessed in a more conservative way, that you need much stronger evidence for you to judge something as statistically significant.

Could I go back though? I thought you raised a really important issue on the silent MIs, and I was wanting to wait until Question 6 to give a basis for why I would view it to be of some relevance, but maybe that's artificially too long.

My own sense is that there's a continuum in the clinical relevance of outcome measures, and I would tend to think most of use would put mortality at the highest, and we may specifically here put cardiovascular mortality there because we're trying to

achieve greater sensitivity by not diluting our mortality on point by those non-cost specific measures.

My sense is we might well put nonfatal strokes then at next in line and that I might be putting nonfatal MIs next in line to that. I would be readily persuaded that silent MIs would then go below the nonfatal MIs in this continuum.

Where I'm struggling is there is a paradox here because when we talk about -- and the sponsor in their documentation says we're trying to deal with morbidity and mortality, and I think if you reduce MIs and even if you're reducing nonfatal MIs, I'm believing we're inclined to think that should translate into some overall mortality trend, and when it doesn't I want to try to probe and find out why.

And in one trial where we're giving evidence, which is the HOT trial, the silent MIs go 75/57 in the wrong direction, and when we look at the PHS trial and we see some positive trends in MI deaths, we're seeing an equal number of excess sudden death and other cardiovascular deaths that are

occurring in the other types.

And so I'm saying: is there a clue here that it may be that silent MIs are, in fact, not as favorably affected, but they too have some effect on subsequent mortality? And so if we're only looking at MIs and nonfatal MIs, and we're getting the impression of benefit, but our mortality data and stroke data say, no, you're not getting benefit, then do the silent MIs help us to address that paradox?

DR. ARMSTRONG: Could I respond to that?

We've heard from some of the PIs that the data is available, but the FDA has not had it, which is a paradox in relationship to discussing this important issue because in that data one would be able to address the robustness and the symmetry with which the silent MI question was, in fact, evaluated, would be, I think, a key issue here.

So I would just make that point in relationship to where we are with this issue.

CHAIRMAN BORER: Yeah, Tom, your response actually got to what I was trying to ask about consistency of the endpoints. The fact that there was

not consistency is a little troubling perhaps.

Tom Pickering.

DR. PICKERING: I just wanted to say I would be somewhat concerned if the way the recommendation went depended on this issue of silent MI since most of the studies didn't evaluate it as far as we know, and in those that did, it was just a single ECG analysis, and I don't know how reliable that is.

CHAIRMAN BORER: Steve.

DR. NISSEN: I wanted to respond to Bob's question about silent MI. I mean, the way I would view this is I would look at the data as it was prespecified, and so in those trials, it's that we're going to include silent MI. Then I would hold them to that, and in trials that said we are not going to include silent MI, I would hold them to that.

You know, I think to me that's the only appropriate standard we can come up with, and I guess my second comment is that we really don't have enough information to know whether silent MI does or does not carry with it the same precise implications as a non-

silent MI, and so in the absence of any data, then you just simply look at what was pre-specified, and you classify them the same.

I don't think we have any basis for making any other judgment, and so let's look at the prespecified endpoints, and it sounds like in HOT clearly they did prespecify that those silent MIs would be included, and I think we should hold them to that.

CHAIRMAN BORER: Bob.

DR. TEMPLE: I have a comment about something else, but I must say given how often an unusual thing occurs in an MI or angina and is confused with esophageal things, it seems odd not to count them just as much, but I'll leave that aside. You know more about that than I do.

I have a question. Even though the endpoints were different in all of the trials, as we saw, most of the trials, but I'll express a reservation about that, do have an endpoint that consists of nonfatal MI and nonfatal stroke and fatal cardiovascular. They all have that, and four of them

were presented as showing at least border line statistical significance.

So I guess my question is maybe that's all just after the fact stuff on my part, but is that somewhat reassuring in that you can find a common, not unreasonable endpoint in all of them, and I just do have to observe that I'm concerned about the thrombosis prevention trial because I don't think we have total cardiovascular mortality data there, and we would surely want to get that, especially if the data become available to us.

But leaving that question aside, if that endpoint were reasonably common to all of the trials, would that help in this discussion, even though it wasn't prospective and even though we're just being wise guys after the fact because it sounds plausible?

Does that help at all?

CHAIRMAN BORER: Alan, do you want to respond to that?

DR. HIRSCH: Well, I have a profound response. Certainly that would help. Let me take the first aspect.

Yes, I think the post hoc recognitional signals for the nonfatal MI is somewhat reassuring. All of us look with our blinders on after the fact, but a secondary endpoint prespecified they had some consistency would be reassuring, I think, to most members of the panel, certainly to me.

CHAIRMAN BORER: Any other responses?

(No response.)

CHAIRMAN BORER: Well, let's move on to number three. Aspirin has a claim for secondary prevention of myocardial infarction. How much, if at all, does this lower the evidentiary burden for primary prevention of myocardial infarction?

Bill, do you want to talk about that?

DR. HIATT: I don't think it changes at all. In fact, the population is so much bigger for primary prevention the burden of evidence should be every bit as strong.

I asked this question early on. It makes intuitive sense that it's a continuum and there are all the same patients, but there may be some qualitative differences from patients who have had an

event, whose plaque has ruptured versus those who have not.

So I was just struggling to look at whether the signals were consistent from those form whom there is approval versus those for whom we're trying to gain approval today, and my questions remain. In women, in people with diabetes, in people with other manifestations of athrothrombosis like peripheral arterial disease, are these populations when they're lumped into the primary prevention cohort really equivalent to just an overall risk score assessment and treatment?

And those questions haven't really been answered.

CHAIRMAN BORER: Yeah. Hold that because we're going to get back to that in Question No. 5, which may be an important issue for us. So we will get back to that.

Does anybody else have any comment on 3.1?

Yes, Alastair.

DR. WOOD: I guess my comment relates to the following. This is not really a primary

prevention in the usual way we think about it. It seems to me that what's being asked for here is moving from an event based prescription strategy to a risk based prescription strategy, which is a little different from just viewing this as primary prevention in itself.

And so it seems to me the real issue we have to debate is whether a risk-based and prescription strategy is appropriate, and if it is appropriate, at what level do you set the risk and for your prescription?

And the problem with setting the risk is that we need to have some value, that we need to have some measure of that risk that takes some value weighted measure of risk, value weighted meaning, you know, that I don't accept an MI the same as a GI bleed, frankly, and equally I don't accept that a GI bleed is the same as a hemorrhagic stroke. I mean, I think I'd value these differently and greater obviously.

And so the primary question is do we move from an event based strategy to a risk based strategy,

and if we do, then at what level do you set the risk?

The whole problem here is and what we're being asked to debate is this finite cut point between ten and 20 percent where the data are all largely below that cut point, but that doesn't bother me so much because if you come in with a lower cut point I might be even more comfortable with that than I would be with a higher end cut point given the data.

And in addition, I'm not sure that the ten percent cut point has much rationale anyway.

CHAIRMAN BORER: Bob.

DR. TEMPLE: Alastair, maybe that's what we should have asked you. We do ask you that in the seventh question, but that question comes only after you are satisfied that the drug works and you haven't had an event yet. Now, maybe that's all stupid of us and the whole question is already answered already because it's really all the same and it doesn't make any difference. That's certainly the presentation we heard, I think.

Don't worry about this particular population. Just try to direct the drug to the right

people in whom the benefits outweigh the risks.

But we really want to know, for reasons Dr. Hiatt suggested, whether these people really do have a benefit of some kind, that is, people who haven't had an identified event yet. Then you can talk about who to direct the drug to.

So we did not ask those questions. We did not ask the question the way Alastair put it. We really want to know whether you think in people who haven't had an identified event yet these drugs prevent events.

And it's not just who to direct it to. That comes only after you answer that first question.

CHAIRMAN BORER: Alan.

DR. WOOD: But that's confusing. I think the albatross in the room, in a sense, was something that Steve mentioned earlier. I think we've all gotten past this idea that it's pure primary prevention or a continuum of risk or secondary prevention.

And I find the word, again, to be distracting here because it really is, going back to

what Bill said, a question of how an OTC medication which will be delivered by the public to itself in a primary prevention motif will be applied in a whole slew of individual, some with diabetes, some with PAD, some with risk factors.

And it is the ability to think we have evidence for primary prevention in those groups consistently that I think confuses this question.

DR. WARD: But there's no suggestion that this would be delivered by patients to themselves without professional intervention.

DR. HIRSCH: Ah, the albatross in the room. I understand that. That is the challenge.

DR. WARD: No, I agree. I don't think we should worry about that at all.

DR. HIRSCH: We need -- look. It may turn out you think this was silly, but the original approval here was for people who had had an event, and it's not completely obvious that those people are just like the other people for reasons Dr. Hiatt has been trying to get everybody to pay attention to. The mortality effect is different. The effect on stroke

is different. Maybe they're not the same and we're not smart enough to figure out why.

In any event what we're really asking is is there evidence for use of the drug in some or all? We'll get to that. That's question seven of the people who have not had an event yet.

Now, I suppose you could tell us that's a stupid question. Of course aspirin works. These people aren't any different from anybody else. If that's what you think, tell us that and we don't have to spend a lot of time worrying about the data because that would not be a data dependent conclusion. So that's all right, too.

But I just want to focus the first six questions are about whether there's evidence that it works in people who haven't had an event yet. Feel free to tell us that's a stupid question, but be specific about it.

CHAIRMAN BORER: Bill and then Paul.

DR. HIATT: Okay. So just to follow up on that, I'll go to 3.2 because it appears to me from the data that if you just focus on nonfatal MI, those

are all prespecified events at some level, and it does appear to be effective.

But I'm not convinced that it doesn't adversely affect mortality or strokes. So if it was really convincing that the effect on those two endpoints was absolutely neutral and all you care about is the bleeding risk and that you're convinced that it doesn't reduce MIs, I'm okay with that.

The question is how far those confidence intervals shift in the adverse direction for the other cardiovascular endpoints that I --

DR. TEMPLE: That's actually why I asked you whether you were impressed by the fact that at least with one exception that I'm not sure of, when you look at fatal and nonfatal MIs and strokes and total cardiovascular mortality, all of them seem to show, except the British doctors study, which doesn't show anything, all of the others seem to show a favorable effect.

Now, one could know, well, they were presented as Ps less than .05. You can debate each one. I guess I offer the proposition that if you

believe there's a persuasive effect on MIs, even though it wasn't the primary endpoint, one might take as reassurance that nothing bad is happening the fact that those things all end up really being driven by the MI. They're not reversed.

That's really what I was asking about, the commonality of that endpoint which I guess I must, you can probably figure out, fine at least somewhat reassuring against what you're worried about maybe, that certain people are disadvantaged badly.

DR. HIATT: So in trying to answer this question on efficacy, not just look at the bleeding risk but look at the stroke risk and the mortality risk, and if those things are convincingly acceptable, then the MI reduction is probably clinically relevant.

CHAIRMAN BORER: Okay. Before we go on to Paul, you wanted to make a clarification, Tom?

PARTICIPANT: No further comment.

CHAIRMAN BORER: Oh, okay. Sorry.

Paul.

DR. ARMSTRONG: The conversation today has been predicated on aspirin's mechanism being clear-

cut, which is an antiplatelet agent. There has been some data from some of these trials suggesting the anti-inflammatory effect is important. It would be helpful in relationship to primary prevention for someone, if there is data, clear data supporting an anti-inflammatory effect that's translated into a vascular benefit to state it, but it hasn't been stated today, and I would just be in terms of extending the indications into an area where there's not much data, it would be helpful to know the answer to that.

CHAIRMAN BORER: That's a very important point, but I think that we have to look first at the data and only after that begin to talk about how it got that way on a pathophysiological basis because I don't think we're going to come to a conclusion about the latter.

DR. CUNNINGHAM: Jeff.

CHAIRMAN BORER: Yes, Susanna.

DR. CUNNINGHAM: This may belong to Question 5, but I'm a little disturbed that we're talking about efficacy for prevention of MI when

there's no data necessarily for efficacy prevention of MI in women. I have yet to see that and the discussion goes on and on, and yet, you know, for 50 percent of the population here, we don't have data that I can tell and only 20 percent of the population that was studied were women. Those were in the last two trials, and there is a published study in sort of a minor journal, a journal of gender specific medicine reporting on the HOT data and saying that there was no benefit for MIs in women, no significant benefit.

So I'm a little concerned that we keep talking about the benefit on MIs when that may not exist in women.

CHAIRMAN BORER: The analyses we were given showed no significant benefit in women, but as I read them, there was at least a nominal reduction in events in women in the analysis that was done. Is that different from the way you viewed it?

DR. CUNNINGHAM: Well, the report that was in this small journal is kind of a minor report, but it says that the reduction in women was .4 MIs per person-years for women, and it was 2.1 per men, and

it was a 19 percent reduction, but it doesn't differentiate in this little report about whether it was all MIs, fatal MIs or exactly what it was. So it's kind of hard to interpret.

I'm just concerned that I haven't yet heard. I heard terminology about women. I heard about women being special population or whatever else. I think in some cases I think they may be second hand rose.

CHAIRMAN BORER: Ron and then Doug.

DR. PORTMAN: Being a pediatrician, prevention is what we're about in large part, and my concern is how long do you treat with aspirin. Forever?

We have a lot of children now that are becoming very high risk. That slide we saw this morning of the 52 year old I could put about 10,000 15 year olds into that same slide with hypercholesterolemia and hypertension and insulin resistance, and so on.

And so do we treat children? And if so, when? At what age? And what marker are we going to

use?

If I treat hypertension, I know what happens to blood pressure. If I treat cholesterol, I know what happens to that. If I use aspirin, I'm looking for the absence of something.

And so I'm waiting for how many years to see that absence. Is there no other marker that we can use for that?

CHAIRMAN BORER: Doug.

DR. THROCKMORTON: Sorry. It was just a comment that Dr. Le had included a subgroup analysis in females from the HOT study on page 15 of his review. I think the sponsor had some materials. I don't remember for sure what those are.

CHAIRMAN BORER: Tom.

DR. FLEMING: Just to respond in general to Question 3.2, it is as we're looking at what influences the evidentiary burden for evidence of primary prevention of MI, as we go from secondary prevention to this primary prevention setting, we're dealing with a situation where the disease rates are lower, and yet where by all indications the safety

risks remain constant, and so to establish favorable benefit to risk, those observations in their own right provide an increased or enhanced burden of establishing efficacy because there has to be an impressive level of efficacy when you're looking at a more rare disease endpoint to offset a constant level of risk.

In that context, when we look at the results or the inconsistency of results on stroke and overall cardiovascular mortality between the secondary and the primary settings, this is very important. In the secondary setting, what we're looking at is about a one third reduction in nonfatal MI and strokes by 20 to 25 percent and cardiovascular mortality by ten to 15 percent. There's a very nice positive reinforcement there.

In this setting, we're looking at suggestions, data that suggest that there isn't a benefit on stroke. In fact, there might be a slightly adverse relative risk, and that overall cardiovascular mortality has a relative risk that's near unit.

And in the meta analysis, it's not that

there's just a trivial amount of information here. We have in nonfatal MIs a thousand events, but in nonfatal strokes, there are 650, and in an overall total cardiovascular mortality, there's 900 events.

These data taken in totality give us confidence intervals that are ruling out the level of benefit that we're seeing in the secondary prevention setting for effects on stroke and overall cardiovascular mortality.

So these observations have a profound effect, I would argue, on what strength of evidence you would need to establish adequate efficacy by just showing what the effects are on primary prevention of MI.

DR. HIATT: Sorry, but just to interpret that comment, so do you believe then that the evidence is very strong that aspirin is neutral on cardiovascular mortality in the primary setting?

DR. FLEMING: We're going to jump ahead, but let me just comment right now. The essence is, in my words, I think these data suggest lack of benefit over the time period that participants were followed

in this study.

And whether we call it compelling is something that could be controversial, but there's sufficient evidence here that we can rule out the level of benefit that at least was seen in the secondary prevention setting.

So it's a considerably strong suggestion for lack of benefit. Now, one of the issues that I struggle with is is it that we followed people an average of five years. What if we follow them an average of seven years or ten years? Might there be some evolving benefit that would occur that we haven't yet weighted to see?

I don't know the answer to that.

DR. HIATT: My question is: have you excluded harm? I think this does do that, right?

Lack of benefit, yes. Have you excluded any adverse effect on CV mortality?

DR. FLEMING: Well, we can certainly exclude just off the top of my head -- and I would have to go back and look at this in a bit more detail -- but you would exclude harm at the level of saying

you're going to double the rate of strokes, and you could actually exclude probably much lesser excesses than that, but you could still have moderate excesses.

And now if there are moderate excesses and there's no positive effect by indication on cardiovascular mortality and you have the bleeding episodes, then what does an effect on nonfatal MI do to offset all of those concerns?

CHAIRMAN BORER: Alastair?

DR. WOOD: Well, while I agree with Tom, I think we have to be careful about carrying that too far. I mean really what you're saying is is prevention of MI an approvable indication, and I think it is. We've approved lots of drugs for indications like prevention for hospitalization for heart failure and in the absence of at that time mortality data, and so on.

So I don't think the absence of positive mortality data and particularly where it's reasonable to say that you were studying a disease an earlier stage in its life cycle should preclude it being approved. We approve drugs every day for non-

mortality driven endpoints.

And then to turn the thing around I'd just echo what Bill I think was saying, that the absence of a mortality signal in the opposite direction certainly provides you with some reassurance that you've not selected some specific indication out here, and that is masking some other encompassed endpoint that would have actually picked up something bad happening.

So I think the question is: is this an approvable indication? My view is it is, the indication of prevention of MI.

And if that's the case, you don't need a mortality endpoint.

DR. FLEMING: Well, let me clarify what I was saying. I was answering the question specifically do the results on stroke and overall cardiovascular mortality raise the burden absolutely?

Because if, in fact, we say is an effect on MI an adequate efficacy measure upon which an approval could be based, is it possible, of course, but that's not sufficient in answering the question. One has to look at the totality of the efficacy

information. One has to look at the totality of the safety information.

If there weren't evidence here of major bleeds and hemorrhagic stroke, that's going to substantially lower the bar for how much efficacy information or what the level of efficacy benefit we have to see.

Furthermore, if you just told me we saw an effect on MI and that's all you told me, and in fact, when I read the sponsor's document, the suggestion is this is, in fact, evidence of benefit on morbidity and mortality, and you would tend to think it's evidence of benefit on morbidity and mortality, but if I then tell you, "But, oh, by the way, there isn't a mortality benefit," then does that somewhat reduce the overall clinical relevance of an effect on nonfatal MI when there's no overall effect on mortality, particularly in the context where I didn't get it for free. I got it in the context of bleeding and hemorrhagic stroke.

DR. WOOD: Well, not necessarily,. I might make the judgement that preventing me having an

MI was a worthwhile endpoint in itself, provided my risk of mortality wasn't increased, which it is not.

CHAIRMAN BORER: Okay. We'll go on. Steve and Susanna had comments. Can I ask you, Steve, in the context of your comment, can you begin to answer Question No. 4?

DR. NISSEN: Yeah, I was actually going to do that, and, Alastair, I agree with you. Prevention of MI is absolutely an approvable indication, but I would ask you a question, and that is: how often has this committee or any committee granted such an indication when there's not a single trial in which it was the primary prespecified endpoint?

DR. WOOD: Well, carvedilol was approved where the endpoint was not the prespecified endpoint. Isn't that right, Paul? I remember that from my days on the committee.

DR. THROCKMORTON: Yeah, for mortality. The original approval of carvedilol was a mortality endpoint. I think that was not prespecified. Typically in other settings we have sort of said mortality is more or less always primary, but that is

exactly --

DR. WOOD: Right. I remember the discussion then about having spent your P value and so on. There was a non-primary endpoint, which resulted in approval.

DR. NISSEN: But I'm just wanting to point out to you that obviously, while it may be an approvable indication, usually that's supported by testing that question in a prospective way in a clinical trial where that is a prespecified primary endpoint. We aren't given any data here in which that was a primary prespecified endpoint. So we're now being asked to render that opinion based upon analysis of secondary endpoints, not primary endpoints.

CHAIRMAN BORER: How about Question No. 4 here? Do you want to?

DR. NISSEN: You know, it's interesting because I do think there probably is an effect here, but I think it's very difficult to say so from a rigorous statistical vantage point and, again, for the reasons that all of you have said, that, in fact, it was never the primary endpoint for any of these

studies. The messages are kind of mixed.

There's an issue of women versus men. I mean, to me to say that the available data support that, I would sure like to see at least one trial where that was the tested hypothesis of the trial. That to me would be a tremendous boon to making that -- to answering that question.

And you know, I don't know if Tom is going to offer it up, but I mean, I've made some mental calculations over whether that is, in fact, a testable hypothesis, and it is a testable hypothesis in a clinical trial.

CHAIRMAN BORER: Susanna.

DR. CUNNINGHAM: Actually I'm not sure if I had a new comment, but I just want to reiterate the issue that every time someone says preventing MI, that we ought to say preventing MI in men because we don't have that data for women.

CHAIRMAN BORER: Yeah. The data that exists from HOT are on page 15, Table 15 where there's a nominal reduction in events with aspirin, but not anywhere close to a significant change, statistically

significant change.

I'm sorry? Still on four, yeah.

DR. FLEMING: I mean, what I've found very helpful here was to go back to the statisticians, the FDA statistician's review, and thinking through the first three parts of Question 4, the Tables 9, 10, and 11, looking at basically relative risks across all of the studies, and I was answering Question 4 in two subelements, looking at what we know about the effects on nonfatal MI and looking at what we know about the effects on fatal MI, page 13 of 18 and 14 of 18 in the statistical review at the end of our document.

So in Table 10, Table 10 is looking at nonfatal MI. The overall relative risk that the statistical review achieved was 27 percent reduction, somewhat smaller than the estimate of the sponsor, in part, through the inclusion of the silent MIs in the HOT trial.

Certainly the PHS study is a huge, driving power to the strength of statistical evidence, but what this analysis shows is that there still is marginally significant evidence of effects on nonfatal

MI, even eliminating the HOT trial.

But in Table 11, looking at fatal MIs, the relative risk in the totality of the data is .91, and that benefit is entirely due to the PHS trial. If you remove that, the overall relative risk is 1.01. So in the absence of the PHS trial, the overall effect on fatal MI is estimated to be neutral.

Now, that doesn't mean it's appropriate to leave it out. The PHS study is certainly one of the relevant contributors of information, but what's interesting is this positive trend, the positive influence of the PHS study is based on ten versus 26 fatal MIs. That's a reduction of 16, but in that same trial if you're looking at the combination of death due to sudden death, stroke, or other cardiovascular, it's 47/30 in the wrong direction.

So the only study that's contributing to a positive trend on fatal MIs is overall not contributing to any positive net benefit. It's just a cost specific benefit on one type that's offset by another.

So my overall sense here is the answer to

this question is it's certainly appropriate to look at the two components, that there is evidence; there is evidence, I believe, that there is an effect on nonfatal MIs. The strength of that evidence is heavily carried by the PHS trial, but the overall nonfatal MI is very interestingly not affected, and that is what I referred to earlier as part of a paradox that I think is very relevant.

If you just tell me nonfatal MIs are benefitted, that's a different story than if you tell me nonfatal MIs are benefitted, but it's not translating into any kind of mortality benefit.

CHAIRMAN BORER: Okay. Doug, you've asked us how to explain differences in outcome among these studies. Is that a critical question for you to have an answer to?

DR. THROCKMORTON: I think it probably is in sort of a larger context, and maybe in the interest of time and things, I could -- there's another part to some of these questions that I haven't heard a lot of discussion about.

One aspect of several of the questions,

maybe not defined clearly enough, was the thinking that's going behind the answers you'll be asked to give in Question 6 and Question 7. How are you looking at these five trials?

So sort of the first step was just are you going to put them together in some aggregate fashion in a meta-analytic sort of way or is there another way that you're going to think about them in terms of their contribution to efficacy and safety? And just sort of ask everyone to sort of comment on their own thinking.

Can you look at the trials and say, "Nope. They're too heterogeneous. Formal meta analytical approaches don't seem appropriate here, but I've got other ways that with large data sets I feel comfortable understanding their outcomes, and here it is."

Just a little more conversation and I think that would capture what we were at in the question as well.

CHAIRMAN BORER: Okay. I'll start off if you like, and then anybody can jump in.

I would look at the totality of the data, but I'd hope that there was some reasonable consistency at least at the top level among the studies. There is some consistency. There is some consistency. It's not the consistency necessarily that the investigators expected when they began the trials, but there is some consistency.

So I don't feel overwhelmingly concerned about combining them in a meta-analysis. There are some rough edges though. There are some differences. There are some heterogeneity. We're going to be asked about subpopulations where in situations where there wasn't much data to allow us to answer.

But in general, there was some consistency. I am concerned about becoming too detailed in subanalyses. Now, having said that, it appears that each of these studies did subanalyses to come to a positive outcome since the primary analysis wasn't positive in most of the studies.

Nonetheless, there was a consistency in the subanalysis that turned out to be positive. So I don't have an overwhelming problem with combining, and

even in doing a formal meta-analysis the strength of my confidence in the outcome, however, is something that we're going to have to define as we go through these questions.

So I don't have a problem with combining.

DR. THROCKMORTON: Okay. So sorry. Just to press a little more, your consistency you're referring to there is in the results.

CHAIRMAN BORER: In the results, yeah.

DR. THROCKMORTON: And not -- I mean there are sort of two parts to consistency that you might think about for meta-analytic things. You start out saying the trials themselves enrolled populations that were similar enough to be poolable, and then after that you might in some meta-analytic approaches say, "And the results, in fact, give consistent results."

Now, you gave me an answer to that last one. You think that the results at least for some chosen endpoints were consistent enough to be poolable. You're saying then -- I'm inferring the same thing about the trial populations.

CHAIRMAN BORER: Right. You would be inferring correctly. The fact is that these were heterogeneous populations, but in my view the heterogeneity within these populations was not sufficient to negate the capacity to look at them together.

DR. KNAPKA: But what about the difference in dose rate? I mean, I think one of the things I remember in Statistics 101 is that when you're planning your study, that's when you decide what statistics you do, and now they're saying, "Well, we've got some data here. Let's go around and find some statistics and make it look good."

Now, every single -- most of these have different dosages, and that could have some effect. It definitely would; different populations, too.

CHAIRMAN BORER: What do you think about the doses? What conclusions would you draw, if any?

DR. KNAPKA: I don't know, but I think I haven't seen actual statistics, but surely the dose rate was a major difference between these, among them. You know, anything from 75 to 500, and surely that

has to be accounted for in the statistics, does it not?

CHAIRMAN BORER: I would think so, but as I recall the analyses that we were presented, even though there appeared to be a gradient in terms of response depending upon dose, in other words, it looked like maybe there was a dose-response curve and that response was inversely related to dose.

Nonetheless, if you looked at all of the subgroups based on dose, there was a consistency qualitatively in the results. So I mean, it's still a factor, but I'm not as overwhelmingly concerned as I might be, given that consistency.

Steve.

DR. NISSEN: I wanted to directly address Dr. Throckmorton's first part of the question, and that is the populations, and I would point out that if you look at, you k now, Slide 30 from the presentation, the range of risk in the populations varies over a fivefold range from about a two or three percent ten-year risk in HOT to about a 12 percent or so ten-year risk in TPT.

So if you say you want to combine them, well, you're now talking about a sixfold difference across the range of what the actual risk characteristics of the patients were. That suggests that they were pretty heterogeneous.

CHAIRMAN BORER: Just to play the devil's advocate, I would accept that, but I think we have to remember what we're using to define risk. We're using epidemiological data that are inherently somewhat limited, applied to study populations. There's a difference, and, yes, it's fivefold. Is that enough so that you would negate the similarities among these populations?

I would say no, but you could certainly say yes.

DR. NISSEN: Well, no, I'm not talking about estimated risk. I'm talking about actual risk. So --

CHAIRMAN BORER: You mean event number, the incidence of events that we saw?

DR. NISSEN: Yeah, I think. Isn't that right? Isn't there about a fivefold or sixfold

difference in the actual event rates in the patient populations?

I think that's right, and somebody correct me if I'm wrong, but I think we're being asked to put together trials where there is a five X difference in the actual event rates between the least risky trial and the most risky trial, and to me it's not an estimate. That's an actual fact.

CHAIRMAN BORER: Paul.

DR. ARMSTRONG: I think these populations -- I mean, we've heard that the strength of these analyses is the diversity of the population. So if we go back to the question can you group them vis-a-vis meta analysis on a population basis, we have nearly half physicians, and I continue to believe those physicians responded differently as it relates to adherence and complained of side effects.

We don't have many ladies, as my colleague to the right has said. We have a trial of hypertensive patients with concomitant calcium antagonists which have sometimes been reported to exacerbate GI bleeding. So I would think that these

populations are heterogenous.

So that there's a strength in that, and we should explore the diversity, but I'm concerned about grouping them.

DR. THROCKMORTON: Do you have an alternative strategy to a sort of standard grouping thing? We've made it till almost four o'clock without saying "Bayesian." But I mean, is this a time to start thinking of, you know, four out of five sorts of things?

Are there other ways that, Paul, you'd suggest that in the face of, say, we concluded -- say that it was concluded, in fact, that these trials were so heterogeneous that formal pooling strategies weren't appropriate. I'm just saying that. Are there other strategies that the committee might suggest?

DR. ARMSTRONG: I think there are, and that's when I'd go and talk to Dr. Fleming.

DR. HIRSCH: But before we talk to Dr. Fleming, taking the point brought up by Steven again, yes. I mean, one way is to say that we have allowed PHS to sort of drive this as the salient trial that

initiated this discussion, but in that risk continuum, it really is TPT that is germane to the indication we're being asked to look at.

So first I think it's fine to pool and say overall the populations that we're looking at are somewhat similar or diverse, and there's a spectrum. Is the dose ranging acceptable within the range where the clinical effect is known and reasonable?

Is there some signal across all of the trials of nonfatal MIs? Thomas said yes, and then you subdivide out TPT, which is a medium risk population, and you say, "Is it still there?"

And I think we can go around and ask that question, but I think it is.

CHAIRMAN BORER: Tom?

DR. FLEMING: Well, I was commenting earlier that with the heterogeneity that exists between these two trials it's a plus and a minus. The plus is that it does give you an opportunity to generalize or at least have a sense as to whether or not the conclusions or the results generalize to a broader population.

The negative or the minus is that you have much less insight about any specific indication, and my biggest concern here is that you're right, Steve. There is heterogeneity in the baseline rates. I computed them in the control arm, and there's about a fourfold difference from the lowest to the highest.

My biggest concern is the highest, which kind of stands alone, which is TPT, is just barely into the range of what indication that we're being asked to consider.

So there is some heterogeneity here, but a limitation here is that the vast majority of that heterogeneity is covering a region that is low risk, and so we're left with, by the Oxford analysis' own indication, one-eighth of the data in the region that we're being asked to really consider here as moderate risk.

DR. HIATT: Just to clarify heterogeneity, is there any statistical heterogeneity in the results from the FDA analysis? I don't recall hearing that.

DR. FLEMING: I think the answer is no.

DR. THROCKMORTON: Dr. Le could comment.

DR. LE: For all MI, there is a statistical heterogeneity for all MI. For nonfatal MI, there is not.

DR. FLEMING: And certainly one of the areas of heterogeneity is one that Jeff had referred to at the very beginning of the discussion of heterogeneity, which is heterogeneity in the nature of the effect that we're seeing on various endpoints and specifically heterogeneity between how that effect differs from the way the effect was seen in secondary prevention, which is to my view the most important type of heterogeneity. It's an inconsistency in the nature in the nature of intervention effect that we're seeing in the primary prevention setting versus the secondary prevention setting.

And when we do the subgroup analysis, even though we only have 12 percent of the data to do it in the moderate category, we are not reassured. The problems are exacerbated by the fact that where we're seeing lack of benefit, which is on the most important endpoints, I would say, cardiovascular mortality and

stroke, the results tend to be even worse in the moderate risk group compared to the totality of the primary prevention setting.

CHAIRMAN BORER: Go ahead.

DR. HIRSCH: Well, just heterogeneity has benefit if it allows the incremental risk to be linked to sort of an appropriate dose response benefit, and I think what we're not seeing here is heterogeneity helping form us in that direction.

CHAIRMAN BORER: Okay. Let's move on to Question No. 5.

DR. FLEMING: One quick second.

CHAIRMAN BORER: Yes.

DR. FLEMING: Just because Susanna raised an important point and I was waiting to respond until we got to it, which was Question 4.4, which was looking at effect in relevant demographic subgroups. She raised the issue, what about gender, and I would think it's worth at least briefly looking at the FDA medical officer review, page 18, Table D5, where essentially, as you know, we have unfortunately not nearly the evidence we should have in females to be

able to answer the question as to whether the results that we're seeing apply equally to females and to males.

And the largest portion of the data in the females does come from the HOT trial, and so this is an extremely important analysis looking at the relative risk estimate in the females compared to males for the all MI endpoint where there is in this analysis a 20 percent reduction in males and a five percent reduction in females.

I'm going to jump ahead just because you're looking in the right place. On the next page is some information relative to Question 5.1, which is now saying what about safety in subgroups, and the safety evidence in females on fatal bleeds and nonfatal major bleeds is on the bottom of page 19 in Table D8 compared to that in males, and basically from the risk perspective, it looks like there is a substantial risk in both groups.

So the evidence that we have here is suggesting that females endure the same risk that males endure, but are achieving much less benefit. Is

that proven? No, it's not proven, but if the only evidence that we have is suggesting less benefit, it's certainly saying to me we're paying a big price by virtue of the price that many of these studies didn't collect information in females, and we're left with a disturbing position here, which is maybe benefit to risk is the same in females as in males.

The little information that we have at least raises a question as to whether it might be less favorable.

DR. LORELL: Tom, may I ask a question while you are on this point?

Are you helped in any way or not helped in thinking about the analysis you've just done by pulling in the larger experience in the high risk population that was done earlier this morning?

DR. PICKERING: A very good point. To what extent can we be reassured by the high risk? My biggest concern is that the high risk is very inconsistent with the primary prevention data that we have on many key measures, and if in the data that I have I'm seeing a lot of consistencies, then I'm

willing to extrapolate in those settings where I don't have data.

But where I have data, where I have data in the primary prevention setting, there are some very inconsistent results compared to the secondary prevention setting. So that makes me then much less willing to extrapolate in settings where I don't have data in the primary prevention setting using evidence from the secondary prevention setting.

CHAIRMAN BORER: Tom.

DR. PICKERING: On this issue of demographic subgroups, I want to bring up the issue of hypertension again because I think in TPT, it was stated that if the blood pressure was above 145, there was no evidence of benefit, and in one of the subgroup analyses of the HOT trial, the patients who had diastolics between 85 and 90 didn't benefit. It was only the ones who are really very well controlled.

So I think this is a sort of murky issue, and we really don't know what level of blood pressure if we're going to recommend this at all it's safe to recommend aspirin.

CHAIRMAN BORER: Ron.

DR. PORTMAN: We also haven't talked all day about the issue of race, and in the HOT trial, I mean, one of the only significant P values on major cardiovascular events was in the African American, you know, group.

DR. THROCKMORTON: But that's D4 in Dr. Polaya's (phonetic) review also, page 18.

CHAIRMAN BORER: Is that sufficient for us to draw conclusions about the effect of therapy in different racial groups?

DR. PORTMAN: Well, I'm only pointing at the HOT trial. I haven't really seen much analysis if you look at all of the other trials. You know, at least in this booklet there's not much on African Americans there. So I don't think you can.

CHAIRMAN BORER: There won't be either. Most of the trials were done in Europe.

DR. PORTMAN: Right.

CHAIRMAN BORER: Okay. How about H?

DR. ARMSTRONG: Well, exactly. The elderly Oriental or Asian individual who is worried

about ICH, I was looking for stratification of that information according to risk. I see it relative to efficacy, but not safety, and it's critically important, I think.

Where is that data?

CHAIRMAN BORER: So, Paul, could you say what you're worried about there?

DR. THROCKMORTON: Sorry, Paul. Many of us are concerned about the --

DR. ARMSTRONG: Many of us who care for the Asian population where the ICH frequency is much higher and the mode of exit from life more common, there's a special concern in relationship to their management around a host of agents, especially those that reduce the potential for clotting.

So I'm keen to know what the risk of the things we've been talking about is relative to that population.

DR. THROCKMORTON: I confess I was thinking of the international conference on harmonization when you said that instead of intracranial hemorrhage. Thank you. Sorry about

that.

CHAIRMAN BORER: Okay. Let's move on to Question No. 5. What do the available data say about the safety of aspirin in primary prevention? What do you know about?

Well, we've just discussed this to some extent. Risks in demographic subgroups, I think we've discussed that.

Interactions with underlying disease, does anyone have any comment about our knowledge or lack thereof?

DR. WOOD: Well, I think that was the point Tom was making, that there may be an interaction with hypertension. is that right, Tom? I think that was collected from --

CHAIRMAN BORER: Any other important potential diseases that might interact in a way that we want to know about and don't know about?

DR. THROCKMORTON: Yeah, actually that's pretty much a particular thing we were interested in here, and it goes back to previous discussions where we've come before the committee and the committee has

said, "You guys haven't even thought to worry about leading risk perioperatively, for instance."

So if there are drug or disease interactions or other demographic interactions that you believe risk to the level beyond those that were sort of statutorily obligated to be concerned about gender, race, and ethnicity, please, it would be very useful to identify those for us.

Well, I mean, there are 20 million people in this country with chronic kidney disease, a CKD, and they are considered in the highest, you know, cardiovascular risk group, and obviously we're going to have to worry about GFR when we talk about aspirin as to what level we can safely give aspirin, but I think that issue needs to be addressed.

And just since I have the microphone, in concomitant drug issues, I'm concerned, again, as a pediatrician, kind of a naive question, but when we talk about risk and moderate risk, is a patient who is on an antihypertensive and normotensive, on a statin and normocholesterolemic at a moderate risk? Obviously he had it initially, but now he's treated,

and so does he warrant aspirin or not?

CHAIRMAN BORER: Good question.

Blase.

DR. CARABELLO: It's not clear to me whether diabetes is simply off the table by virtue of being high risk to begin with, and do those patients automatically constitute a high risk group that --

CHAIRMAN BORER: Not according to current labeling.

DR. CARABELLO: Well, then I think that's a pretty clear area to think about.

CHAIRMAN BORER: Steve.

DR. NISSEN: Just to be aware of it, there has been some data presented that suggests that giving ibuprofen with aspirin may neutralize its benefit. So there would be some issues there since both agents are available over the counter, and I don't know the extent to which others think that that is convincing or compelling evidence, but I know there is some evidence about mixing and matching over-the-counter analgesics that may take away the benefit of aspirin, and we have to be careful about that.

CHAIRMAN BORER: Yes. Correct me if I'm wrong, Doug, but you know, several issues have been raised: kidney disease, concomitant medications, et cetera, et cetera, about which clearly we don't have sufficient data to make statements. We can only raise concerns.

Unless we think it does, that by itself wouldn't preclude us from determining that in some population that we could define it would be appropriate to use this drug and the labeling could talk about all of the things we don't know if we came to that conclusion; is that correct?

DR. THROCKMORTON: I think in general that is correct. You might say, for reasons that I'm not saying we're in this situation; you might say this demographic is so critical it's going to be entirely used in women and all of the studies have been conducted in men. You know that really has to be addressed before you can think about approving it for this particular indication or something like that.

Short of that, there have been analyses in a lot of these subgroups. We haven't talked about

them today. I don't think the FDA conducted any formal analyses of several of them.

What I'm hearing is concern, interest in information, examination, not that so critical aspect to it. If I'm wrong, it might be worth clarifying, but that is about right.

CHAIRMAN BORER: Okay. We're up to Question No. 6, and for this one, we need specific responses from each committee member. We will start with Tom and go around that way and come back up.

Question No. 6: should professional labeling for aspirin recommend its use for primary prevention of MI? And if so, et cetera, et cetera.

Tom.

DR. FLEMING: Well, in trying to provide some of the logic for the response I'd provide, let me just quickly run through a few issues that we've already discussed in the previous questions that have led up to this.

Starting from the secondary prevention setting, using, for example, the Oxford presentation that we saw today, there is a strong and I would call

consistent signal that's coming across the key traditional measures that we would look at, nonfatal MI reduced by 33 percent, stroke by 20 to 25 percent, cardiovascular mortality by ten to 15 percent. Event mortality in some of the settings is significant, and all of these other measures are significant.

So there is, in fact, a clear message of benefit in the setting of secondary prevention. Not surprisingly to me, in secondary prevention, in secondary prevention, which isn't what we're talking about today, but I'm leading up to where we're going to be, in the five trials on primary prevention it's not surprising to me that these studies had targeted the same global endpoint, two of them essentially focusing on CV mortality and the others basically look at CV mortality and nonfatal MI, nonfatal stroke.

These studies predominantly, certainly those that looked at CV mortality, the BDT and the PHS study, fell well short of showing benefit on that. In fact, suggested lack of benefit on that measure.

The other three that we're looking at, the aggregate all vascular event showed positive trends.

We've talked a lot about the fact that it's important to look at these individual studies being true to how they were designed as we focus on what we can say, but in any clinical setting obviously it is important to learn everything that we can, and so we do appropriately look at some level at aggregate analyses, and the meta analyses in that context do provide us some additional insights, although one has to be extremely careful when the primary endpoints aren't positive and then we can look in some domains and see benefit.

One has to be cautious about the overall interpretation, particularly when those other domains are less clinically compelling than what the primary endpoint was, which is very different from the carvedilol example.

Back on January 7th, at the Cardiorenal Advisory Committee we had a very long discussion about what strength of evidence can we put on secondary measures, and my recollection of that long discussion was, well, if the secondary measure is survival, that is so unique in terms of its overall clinical

relevance that you still pay a price, maybe an order of magnitude greater strength of evidence you would need, but survival is something that can still be persuasive in a secondary endpoint.

My concern is that we're going a bit in the other direction. We're going from an endpoint that certainly had important mortality elements to it, and we're moving away from that to an endpoint that is nonfatal MI.

Well, what do we know? What we know, I believe there is substantial evidence within the context of these five trials to indicate a level of benefit on nonfatal MI, some estimates 32 percent, some estimates 23 percent. By my calculation that translates in the context of these five trials, if you look at these five trials which are predominantly in a lower risk group than what we're asked to focus on as a moderate risk group; by my calculation we get about five events prevented over a five-year period. That's what the meta analysis of these five data would tell us about nonfatal MI.

What about fatal MI? Does nonfatal MI in

some sense correlate or translate into some benefit? Probably at a level that can vary, but we surely hope it does, and I believe part of the overall clinical relevance of a reduction in nonfatal MI is a subtle imputation we make in our mind about what that means about death and fatal MIs.

Well, in these data in the PHS study we have the most encouraging evidence, ten against 26, but for the other five studies, the evidence is there's no reduction in fatal MIs, and as I had mentioned earlier, what's concerning to me is in the one study PHS that did show a fatal MI positive trend where there were 16 less fatal MIs, there are 17 more fatal sudden death strokes or other cardiovascular events.

So even that trial that was sort of the one we hold out shows no net benefit in the evidence in hand in overall fatal cardiovascular events.

Well, globally what about overall cardiovascular death and what about stroke? The evidence that we have in hand is very informative. It may not be conclusive, but it's very informative.

While we have about 1,000 nonfatal MIs in these five trials, we have 650 nonfatal strokes, and we have 1,000 total cardiovascular deaths.

So those latter two measures show relative risk estimates that are just about unity, slightly positive on mortality, somewhat negative on stroke, with however a substantial amount of evidence when you look at the totality of these studies. A lot more than was known to the PHS data monitoring committee at the time that they looked at their data where they only had 160 cardiovascular deaths to look at, we have nearly fivefold that many.

And essentially with this amount of evidence in hand, what we can say is there's fairly substantial evidence that we have (a) lack of benefit on these measures and (b) at a level that's inconsistent with the corresponding level of benefit that we saw on those measures in the secondary prevention setting, and looking in the other setting, we can rule out a 25 to 50 percent harm, but we can't rule out a 20 percent harm. There is, in fact, still some modest harmful effect that these data remain

consistent with on cardiovascular mortality and on overall stroke.

So as I look at all of this and kind of put it together, what do we know? Well, from these five trials that are focusing on an early or low risk primary prevention setting, by my best estimate we're preventing for 1,000 people over five years, we're preventing five nonfatal MIs in this setting.

In turn, it's not translating into any beneficial effect on stroke or any beneficial effect on cardiovascular mortality. That in its own right is of some clinical relevance. Five prevented nonfatal MIs is of some relevance. It is, however, to my way of thinking concerning when there isn't any suggestion that that's translating into any beneficial effect on stroke or on overall mortality.

And there is a price. Hemorrhagic stroke is estimated at one excess event and major bleeds at two to four excess events, and so in the context of this particular set of five trials, I wonder why that is a clear benefit.

Now, the issue is can we extrapolate. Can

we take these data, however, and extrapolate to the setting that we're really asked to focus on, which is moderate risk.

Well, the first issue is the moderate risk group is only 12 and a half percent of the totality of these data. On the one hand, we're asked to use this as a basis of providing extrapolation to the extent that we can argue -- and it has been argued -- that there will be a prevention not only of five events in five years for 1,000 people, but this could be as much as 14.

But this is an extrapolation on a limited amount of data, and this same evidence if we look at stroke and we look at cardiovascular death is suggesting in the moderate group that results are worse than what I was talking about when I said it didn't look like there was harm. Numbers are small, but there's an estimate of a 78 percent increase in hemorrhagic stroke, a 33 percent increase in stroke, and in vascular deaths, whereas it's six percent benefit in the complement, in the low risk group, it's four percent harm in the group that we're targeting.

Now, we're asked, however, look at these data with extreme caution because this is a small subgroup. I acknowledge that, but wait a minute. We have to be consistent. This is the same small subgroup upon which we have to base our extrapolation that this five prevented events if you looked at it in a moderate setting would be 14 prevented events.

And so one of the issues here that I struggle with is do we consider silent MIs. Well, I'm not a surrogate endpoint person. Any of you who have known me on this committee would know that well, and in a certain sense, I would consider silent MIs to be a level of a surrogate less clinically relevant in this continuum.

But when I see nonfatal MI trends that aren't translating into other domains of benefit and then I see the single study that looks at the domain of silent MIs, and it goes 75/57 in the wrong direction, then I begin to wonder whether technically speaking even our measurement of who had an MI or nonfatal MI or not is not capturing the essence of the overall cardiovascular influence that we're having on

these individuals.

And it leaves me in the end with a sense that it just well may be that there's a positive benefit to risk if I can target the right population.

Actually I do think the question today isn't does aspirin work. We know it works, and we certainly know it works in a net benefit to risk positive sense in the secondary prevention setting.

The question is: can we go back now to a primary prevention setting and target a high enough risk group where the effect that we have is going to offset the known and constant negative effects, and what we're left with here is evidence that suggests that the effect that it has is clearly not at all parallel to what the effect is in the secondary prevention setting, in those elements that are most important to the patient.

Oh, I didn't vote.

CHAIRMAN BORER: Right.

(Laughter.)

DR. FLEMING: So my vote is going to be to Question 6, it's going to be no, and I'll have a

comment in 6.2 as to what additional evidence we could get to answer the unknown questions.

CHAIRMAN BORER: Why don't you go ahead and give that answer now?

DR. FLEMING: In 6.2?

CHAIRMAN BORER: Six, point, two.

DR. FLEMING: Well, as I said, my vote of no is not a vote that is based on my conclusion that we've established lack of favorable benefit to risk in this setting. It's rather based on the fact that there is a paucity of data in truth in the setting in which we're really being asked to make a judgment, and what we have to extrapolate is from a primary prevention setting where the overall benefit to risk is five prevented cases for one additional hemorrhagic stroke and two to four additional major bleeds, and that doesn't translate into positivity to me.

And yet my own sense is if we did a trial that would, in fact, truly target these people who were at moderate levels of risk and we, in fact, had sufficient duration of follow-up that we would, in fact, be able to see whether we just didn't look long

enough.

And if we build in an even distribution of males and females so that we can actually understand what's happening in the females, this is, in fact, I think, a doable study, and just very quickly from some crude calculations, if we were doing a study that would have seven years of follow-up -- and I say, in part, seven years of follow-up to give aspirin its best shot, to give it an opportunity to see whether or not these early, nonfatal MIs are going to translate into something that is, in fact, favorable in some of these other domains, such as other cardiovascular or vascular mortality events.

Essentially it"s a study that would require 1,500 events, and so approximately 15,000, and so, in fact, a study that's of the size of what we've heard reported today both in terms of these five and what we've heard from other investigators that under contemplation, and essentially what that would do is it would relieve us from having to do as the Oxford analysis indicated an extrapolation of the data using a fairly small subgroup into being able to actually

have the direct population that we care about and to have them followed for an adequate duration of time; that if there is benefit beyond a nonfatal MI, we'll have greater sensitivity to detect it.

CHAIRMAN BORER: Alan.

DR. HIRSCH: I want to go on record and say we'll never sit to Tom's right again when you call a vote.

It's hard to follow that, Tom.

First, I want to answer backwards. Actually that's very much the study that actually needs to be done. Otherwise I feel like we're dealing a vote in the absence of unambitious data, and this is so important. I believe that one could go that way and perform that ethically.

I expected to come to the room and be overwhelmed by the positivity of the data, by consistency of effects, by subgroups that clarified the relative risk reduction, and that could be applied to this medium risk population for which the application was made, and I'm impressed by the relative paucity of data that actually helps me feel

strong in the vote I'm going to give you in three more sentences.

But I do believe that there is enough signal that is sort of generated iteratively across the studies in the benefit of nonfatal MI. I think we see that. I think we have spoken to it across the panel today.

One word. I actually am troubled by the nonfatal, silent MI Q-wave infarctions. To me that's no surrogate endpoint, and from what I know of cardiology, there should be clinical impact down the road if we followed patients long enough.

I think that's the one trial that was designed correctly and for which we actually gain the greatest amount of information, and I would caution us and those who interpret our panel vote to think clearly about that.

I think there is adequate information to recommend aspirin to prevent nonfatal MI in, I guess, primary prevention, but again, riddled with caution, and maybe if I can jump to 6.1.2 with that caution or 1.1 and 1.2, I can't quite answer the patient

population question, and I'm looking for more discussion because I still don't really know what population achieves that benefit.

So I'm going to dodge that and look for more erudite answers from my counterparts.

The dosing I think was no issue at all really. I think we have from 70 milligrams to 150 to 325, adequate information across the trials to suggest benefit on the nonfatal MI outcome.

So there.

CHAIRMAN BORER: Tom.

DR. PICKERING: I guess if the question was -- the way the question is phrased, primarily prevention of MI, I guess I would say yes, but in this particular population I think the issue is not just the prevention of MI, but we have to look at all vascular events because that also is at high risk for stroke.

And overall I would say the net benefit, not just looking at MI, is so small that I would not support it. I'm still particularly concerned about the patients with uncontrolled hypertension who have

not really been addressed in these studies. I mean what evidence we have is that they don't derive benefit, and whether we like it or not, most of the hypertensives who are in this medium risk group are not adequately controlled.

DR. THROCKMORTON: Sorry, Tom. I don't want to put words into your mouth, but so you're saying that you are unable to define the population that you believe an effect on nonfatal MIs is adequately demonstrated? I'm just trying to understand.

DR. PICKERING: My vote would be no because I don't think, you know, just nonfatal MI is really the right question.

CHAIRMAN BORER: Do you want to talk about the studies that might be done to provide compelling evidence?

DR. PICKERING: Well, I think I would like to see more evidence in patients who have systolic blood pressures that are, say, above 145, which is a large proportion of the hypertensives.

CHAIRMAN BORER: Beverly.

DR. LORELL: I do think the evidence in its totality supports the use of aspirin for primary prevention of nonfatal MI, and that's how I would modify that question. I think Tom has eloquently addressed the fact that the data is ambiguous to neutral on prevention of fatal MI and all cause mortality.

I guess I am more persuaded than I think Tom was. I couldn't quite tell about Alan's thoughts, that there is a continuum at risk. I think that Tom's estimate of benefit is probably and maybe appropriately on the conservative end because the trials we have to look at looked at low risk patients for the large part.

And I guess that was not quite a question that you asked, but I do buy the notion of a continuum of cardiac risk and the ability to get some handle on that with the measures that we talked about this morning.

With regard to a study, I think it would be profoundly difficult in the United States in 2004 to do any study except revisit low risk in those

patients who sit right on the border of low and moderate risk. I think the thing that is driving me in part to make my vote the way it is is my concern that in the United States not only are we not treating these patients on the border of low and moderate, but that we're failing to treat moderate and high risk patients who have not yet had an event.

We have to wait for something that is life threatening to occur to the individual patient before we can treat them.

In terms of defining the population to whom one might target this, I think that here one does have to be conservative and to go back to the characteristics of the patients included in these trials, and including what their exclusionary criteria were for systolic hypertension and for GI bleeding risk.

But I think we do have some data from these low risk population about what levels of patients with hypertension we might want to caution inclusion or not inclusion.

And finally, like Susanna, I am troubled

about the issue of women. I think this becomes a matter of philosophy rather than science. My vote would be to be a lumper rather than a splitter.

My suspicion is that -- and I'm not 100 percent sure about this -- that with further data analysis of the enormous Women's Health Initiative, there may, in fact, come some additional informative data about aspirin/no aspirin with regard to cardiovascular events from that huge database.

But I think that summarizes my answer to that question.

CHAIRMAN BORER: Doug, can I ask for a clarification? Your question specifically says recommend its use for primary prevention of MI. Beverly has modified that to say nonfatal MI. Do you need --

DR. THROCKMORTON: Yeah, I think what Beverly did was modify an answer for both fatal and nonfatal, and that seemed an appropriate modification. If people felt all types of MI, then that's certainly one answer you could give us: a blanket yes.

If you think it's nonfatal, then like

Beverly did, I think that would be useful.

DR. LORELL: Yeah, let me even be clearer. I would say no for all MI because I think the answer Tom eloquently described what we know about fatal MI, and I think we also clearly saw today we don't know enough about silent MI. So I think, you know, I would say no for all MI, but yes for nonfatal MI.

DR. THROCKMORTON: Alan, do you need to clarify your remarks? You were the other person that's voted yes to now.

DR. HIRSCH: If the question were on all MIs or fatal MIs, I would vote no, and it's yes to nonfatal MIs.

CHAIRMAN BORER: Steve.

DR. NISSEN: Well, I'm going to choose not to cherry pick the data for a specific endpoint. You know, for a patient it doesn't matter how you get dead. You're either dead or you're alive, and so I, like Tom, want to look at this as a totality. I don't like the way the question is worded because it really is a question for me of whether this label ought to be extended.

And once you extend it, you've got to take everything that comes with it. It means benefit on MI but maybe some hazard on stroke, and I'm not so sure about total mortality.

So, you know, to me it's really a question of the totality of benefit.

Now, let me just point out something to the rest of the committee. We are being asked to opine on the basis of a group of trials that were largely negative on their primary endpoint. The minute you start to go there, you know, we're in some trouble. I mean, it's a very slippery slope when you try to interpret data from trials where they were negative on their primary endpoints.

So we're going to pick some things out from the trials that look pretty good for a drug, and we're going to choose to emphasize the benefits from those secondary analyses, and that in and of itself is potentially hazardous. The next thing we're going to be asked to do is we're going to be asked to extend that information to the moderate risk group for which the data from those five trials only contains about 12

and a half percent patients in that group.

And so now in addition to taking trials that were largely negative on their primary endpoint, you want us now to take and extrapolate that to a group that they weren't even intended to study, a group with a different risk category, and so that has huge statistical risks associated with it.

And then there's the question of potential for harm. Now, I'm more familiar with the statin world since I tend to operate in that area, and I can tell you we have all been struck by the fact that over the last few years there seem to be a rising number of patients in such trials with stroke as an endpoint compared to MI. The ratio of MI to stroke as patient populations get older, you know, stroke is an increasingly important endpoint and particularly among older patients and among hypertensive patients I worry about hemorrhagic stroke because I know what the consequences of that are, and it is a far worse outcome than a myocardial infarction for most patients. Most MI patients we can get through it. If they have a little heart failure usually it's

treatable. We've got very good drugs now for that, but once you've had a stroke and you can't speak and you can't walk, your life is never the same again.

And I'm not so sure we've excluded the possibility in this population of a moderate harm in that population. So that influences my thinking.

The fourth point is, you know, I've spent a lot of years thinking about silent MI and I went through this gritting of teeth over whether MIs after PCI were important or not, and I looked at the totality of data, and I'm convinced that a myocardial infarction is probably a myocardial infarction.

If you lose myocardium it's not a good thing, and so when a trial prespecifies silent MI, then that's the endpoint I'm going to hold that trial to, and one of the key trials here did, and it certainly did go in the wrong direction.

Finally, does it make sense? Are primary prevention patients different from secondary? Is there a pathophysiological reason why we might expect this to be different?

And the answer is you bet there is, that

once you rupture plaque in the coronary, the underlying pathophysiology of what's happening may well be entirely different from a patient who has never ruptured a plaque in a coronary or in a middle cerebral artery.

And so there is a pathophysiological reason to expect these patients are different.

Number six, could I wrote a label? Do I have enough information here to write a label that would describe how one should use these drugs?

Well, given all of the extrapolation one has to do, I have no idea what to say about women, the elderly, people with concomitant hypertension. How do I write a reasonable or meaningful label for such a use?

And so what I finally come down to is that if in a 55,000 patient meta analysis you can't come to a definitive conclusion, if there is a benefit it's got to be pretty small, and therefore, in order to prove it to my satisfaction, I want a prospective randomized trial because that's the level of evidence that this committee is usually asked to opine about,

and in the absence of data I do not agree with Beverly. I usually do, but I don't here, that I think that when we can't come to a solid conclusion from a 55,000 patient meta analysis, we need a prospective trial, and the NIH or other organizations, as they did in the ALLHAT study involving some 42,000 patients over seven years, we could answer this question. We should answer this question, and if it were a positive study, I would be the first one to line up and give my vote to giving the label.

So I vote no.

CHAIRMAN BORER: Dr. Knapka.

DR. KNAPKA: Okay. I guess I'm in a little strange position here because I am a scientist, a nutritionist, and I'm also a heart patient. I am one who had a silent MI at some point. That's why I don't know when it was.

And I think in those days I know I had hypertension. My father died at age 34 with heart disease. So I was really at high risk, and I think I would have welcomed it if someone would have told me, "Look. If you take aspirin, it will probably really

help you."

So as a scientist I would vote no because I agree that the data is really pretty weak. I think the analysis is bad, although, you know, lumping all of this together I still maintain there's a lot of differences.

And as a scientist I'd probably vote no, but as a heart patient and I'm supposed to be representing the patients, I would probably say yes, vote yes with some stipulations.

Number one, only high risk patients should be -- for people at high risk as defined this morning, high risk, and also that there be some follow-up, that people are not just told to take aspirin and never followed. Maybe quarterly they have a blood clot, draw a blood clot in time to try to at least help to prevent some of these others, the bleeding, the stroke, et cetera.

So I think it probably isn't clear. As a scientist, I say no. As a patient, I say yes with these stipulations.

DR. NISSEN: Does he get two votes or one?

DR. THROCKMORTON: Unfortunately we'll ask you to integrate your.

DR. KNAPKA: Give me one half.

DR. THROCKMORTON: I think we really do need to ask for a yes or a no, and your other comments are taken into account. But a yes or a no.

DR. KNAPKA: I would say no.

CHAIRMAN BORER: Blase.

DR. CARABELLO: Well, I certainly agree with Steve that there are plenty of reasons to suppose that primary and secondary prevention could be quite different, and after you've had an MI you begin the cascade of inflammation that leads to yet further disruption of caps and more disease down the road. So I could see why the two things would be different.

My biggest concern and the reason I think I want to vote today yes is I don't believe we can do the trial that Steve thinks we can do. Every guideline organization has come on line is saying that you should give this drug. I have never heard so much public comment in the brief two years I have been on the committee as we had today for incredibly

influential people speaking for the drug's use, and I think in that background it would be very difficult to ever do the trial that we're talking about doing to prove whether or not this stuff works.

I would say yes for nonfatal MIs in men. I don't see any way of labeling it for women where it appears that the risk of hemorrhagic stroke is increased and there's very little evidence of benefit. We just don't have those data.

DR. THROCKMORTON: Sorry. I need to ask you to fill it out. So primary prevention for MI, which was the thing the sponsor was seeking for, which would be total MI, fatal and nonfatal. I need to ask you to comment on that as well.

DR. CARABELLO: I would say yes, but in men.

DR. THROCKMORTON: Yes to fatal and nonfatal MI.

DR. CARABELLO: Yes.

DR. THROCKMORTON: And then populational comment?

DR. CARABELLO: Would be men, and I don't

think you can do the study to hack it out.

CHAIRMAN BORER: John, you cannot vote, but you can comment. So let's hear what you have to say.

DR. NEYLAN: Great. Thanks, Jeff.

It strikes me how voracious we are when it comes to data, and I think about this drug and there's some, I guess, quarter million patients in which it has been studied now low these many decades, and still I have to agree as I sat through this day's session that there is much we still don't know, and so I certainly listened very intently to Tom Fleming's overall exigencies of the status of the statistical knowledge and lack thereof.

That said, I think looking at this new cohort of some 55,000 patients, it strikes me that it would be impossible to see this cohort not included within the professional labeling of this drug within the clinical studies section to speak to the in general trend of direction in which the composite endpoints, at least four of these five studies, have brought us.

There is, I think, good reason why professional societies have taken these data and although they are not ironclad and absolutely foolproof, nor can they ever be, have made the good faith efforts to drive the clinical practice forward with the intent, of course, of reducing cardiovascular morbidity and mortality.

And that's something I think that even as we adhere to the rigors of our science we still have to keep in mind. There is a public health safety issue here. Sure, we can sit back and say the definitive trial has not yet been done and we can say, all right, let's prospectively devise one, but I am in complete agreement with several who have opined so far that actually in today's society and today's world that that is not really a practicality at least for most patients with moderate risk.

While we could design a theoretical trial that would satisfy statistical number and so forth, I don't believe that many IRBs nor many patients would actually agree to that kind of a study.

As we look to where therapies are moving

now, so many of them are now including aspirin as part of the baseline strategy. That train has left the station. So my answer is that although we don't have all the answers, I do believe there is a way to craft a label inclusive of the data coming out of these very important clinical trials that could guide clinicians in the treatment of both fatal and nonfatal myocardial infarction.

CHAIRMAN BORER: Bill.

DR. HIATT: It's my first meeting. Do I have to vote?

(Laughter.)

CHAIRMAN BORER: You've got to vote.

DR. HIATT: As I look at this data coming in, I think Dr. Fleming summarized my impressions before all of the discussion. Although I would differ slightly and think you might have presented the worst case scenario for the limited component of the data, which is the nonfatal events, and it may be preventing five; it may be preventing 14. So I think the point estimate there may be somewhat variable.

I'm convinced it doesn't prevent fatal

events, and I'm uneasy about its effect on safety, and it's not just bleeding, but also strokes.

So my struggle is trying to get what was actually in the label which is defining this intermediate risk group using Framingham to match the data, which I think is fairly consistent in terms of the nonfatal MIs in the population study, which don't exactly match the label that's being proposed; that in these relatively lower risk patients ironically it appears to consistently reduce the risk of nonfatal MI.

And so in that context and in the caveat that it only applies to men that match the inclusion/exclusion criteria that define those trials, can the label actually match the data? If it can't, then I would vote no, and if it can, that it's really clearly disclosed, that there's really very limited value of aspirin in the totality of treating cardiovascular disease prevention limited to a subgroup of people with certain risk characteristics that are defined by a largely male gender, et cetera; that in that context the signal, I think, is robust

enough to support it.

CHAIRMAN BORER: So give us a summary.

DR. THROCKMORTON: So, again, without trying to put words into your mouth, what I'm hearing is that you can -- I'll change it around a little bit -- you can define that a treatment effect exists as regards nonfatal MI. The precise population is sort of another issue, but you believe a population could be defined as relates to the trials that make up this database.

DR. HIATT: Yeah, I think the data support a treatment effect narrowly defined by the population on that one particular endpoint called out in isolation from everything else.

DR. THROCKMORTON: And just to be clear then, so nonfatal MI, you believe that those evidence exist. Fatal MI?

DR. HIATT: No.

DR. THROCKMORTON: Okay. Again, I don't know. I would interpret that as for the question. The question specifically is for all MIs, which is what the sponsor was seeking prevention.

DR. HIATT: Oh, I'd vote no for that.

DR. THROCKMORTON: You would be saying no, but that nonfatal MI was something you thought the data existed for.

DR. HIATT: Correct.

DR. THROCKMORTON: Okay. Thanks.

CHAIRMAN BORER: Alastair.

DR. WOOD: Well, I think it's worth thinking about why we even think about labeling, and you know, as you sit here sometimes it's easy to imagine that this is something that comes down from the mountain on stone tablets. Presumably the purpose of amending a label is to better inform physicians about how to use a drug, and so one question to ask is is there an opportunity here to better inform physicians about how to use aspirin, and I think the answer to that is unequivocally yes.

And I think that obligates us to change the label, therefore, and make changes in a number of directions.

The first one and the place I'm going to start, which is sort of ass-backwards in some ways, is

that it's certainly important to change the label to inform physicians about the kinds of patients you ought not to be treating with aspirin. In other words, given the potential for risk, it's certainly worth informing physicians better as to whom it is improbable that the benefit will exceed the risk, and we can define that however you want, but it's certainly somewhere between five and six percent, I guess, or somewhere around that number.

The second thing is in the same light. I was working here on my Palm Pilot just a minute or two ago just running through the Framingham algorithm that everybody has now, I guess, on their Palm Pilots or whatever. It's worth remembering you get a big hit in risk for having your blood pressure over 140. So you don't necessarily want to put yourself into the high risk group by having your blood pressure over 140 because, like Tom, I'm not persuaded that that's a group I would necessarily want to be treating first.

So I think there's a clear reason to improve the information that's in the current professional labeling for aspirin, and do I believe

that the current data support and indication for a nonfatal MI? Yes, I do actually, and I think there are more patients in these studies than in any study that we've ever seen presented at an advisory committee that I've been on, and these studies also include more women and more of every other group than any study we've ever seen presented.

You know, we can bemoan the fact that there aren't enough women or there are not the same number of women as men, but, God, you know, when we see studies for NDAs that have 2,000 people in them, they don't have this number of women. They don't have this number of people.

And so I think that the data do exist to suggest it should be approved for nonfatal MI, and I also think that I don't agree with the way the question is phrased. Should professional labeling for aspirin recommend its use for primary prevention of MI? Well, there are two ways to approach that. You can tell people what the data as they exist say. That doesn't mean to say you have to recommend it. You can that meta analysis of the 55,000 people or whatever it

is show a benefit in the treatment of nonfatal MI, and I think that's worth informing physicians about.

That's not necessarily the same as a recommendation, and we've done that lots of times before where there are didactic statements made and labels that talk about subgroup analysis that appear to show risk or benefit or whatever that wouldn't stand up to rigorous analysis because they were not primary endpoints.

So I would vote in favor of an approval for a limited indication, and I'd strongly recommend amendment of the label that allows physicians to be informed of the current state of the data.

CHAIRMAN BORER: So that's a yes for nonfatal MI. How about all MI?

DR. WOOD: No.

CHAIRMAN BORER: No for all MI with clear information in the label about what actually is found.

DR. WOOD: And some caution about just using -- that's not been discussed actually in the meeting at all, but these scoring systems all include blood pressure as a heavy weighter for the risk, and

I'm not sure that I necessarily agree that these risks can be uniformly assessed.

CHAIRMAN BORER: Ed?

DR. THROCKMORTON: We'll come back to that. I very much want to hear comments around that. That was part of what we were looking for in the next question.

CHAIRMAN BORER: Ed.

DR. PRITCHETT: Well, this is kind of a remarkable situation for me to be in because I was here at the October 6th, 1989 meeting when we considered this question with far less data available to us, and at that meeting I voted -- I answered this question yes, and today I'm going to answer it no.

And I think before you all run back to Duke and say that Ed has lost his mind, let me try and explain where I'm coming from. One is I think that it's not something that has happened to the data. It's probably something that has happened to me.

One is that I've developed a health skepticism about the sort of exploration of data sets after the primary outcomes fail or even when they're

positive. So I've become much more skeptical of the interpretation of data within clinical trials.

And the other thing is that I've developed almost a reverence for the FDA standard for approval. Frankly, I'm a cardiologist, and I take an aspirin every day, and I have since I was 40 years old. I recommend that my patients do this. I applaud the recommendations of the American Heart Association and the American College and Preventive Health Services Task Force. I support all of them.

I do not think that the evidence presented to us meets the standard that the FDA has required of us in the past or still requires of us. I don't think it's there.

So the answer -- if the question is do I think that aspirin may be valuable in primary prevention of myocardial infarction, I think it is. Do I believe that the regulatory standard has been met? I think it has not, and my vote is no.

DR. WOOD: Ed, can I just challenge you a little bit on that or at least start a conversation?

It seems to me that there is a difference

here between approving a drug for the first time to be used, to be marketed, and one in which we're trying to inform physicians about how they should use the drug, and it disturbs me a lot to hear you say that you would take a drug for an indication, but you wouldn't want to inform other physicians about how appropriate to use that.

So let me niggle you a bit on that.

DR. PRITCHETT: Well, it's just I have no problem with the notion that there are a lot of drugs used; maybe most of the drugs used today are used for what I referred to as off label indications, and in some cases those uses are very well established by many multi-center clinical trials, and in some cases they're established only by hearsay, and that's the way we practice medicine, and I see no conflict there.

I think the question is: are we practicing medicine by, you know, just by what's written in the FDA label? And the answer is, no, we're not.

And so I think if you want someone to say, "This is the way we think we ought to practice

medicine," the Heart Association has done that. The college has done that. The Preventive Health Services Task Force has done that. The FDA standard hasn't been met, and I don't think the FDA standard is different.

If the drug is already on the market and labeled for another indication, we might feel good about it. There are certain even classes of drugs that we feel good about. We feel good about beta blockers. We feel good about statins because those are classes of drugs that have been shown to reduce mortality. So we might smile more kindly or be less concerned about those drugs if they come forward with another indication.

But they're still a standard that has to be met. I don't think it has been met here.

CHAIRMAN BORER: Ron.

DR. PORTMAN: You walk into the doctor's office and after they say, "What brought you here today?" the next question will be, "Now, are you planing on a fatal or a nonfatal MI?"

(Laughter.)

DR. PORTMAN: You know, for those who say, "I'm going to have a nonfatal one," I mean, here's your aspirin. Fine, and for those of you who are going to have a fatal one, well, you don't need an aspirin.

So, I mean, I don't think you can separate it like that. I mean, you either recommend it for the prevention of cardiovascular disease or you don't, and you know, the data that has been presented to me today that I have seen would suggest that there's not enough evidence there to recommend it. I think we really need a study that specifically addresses this question.

And so my vote is no.

CHAIRMAN BORER: Paul.

DR. ARMSTRONG: Not all MIs are the same, Mr. Chairman. I've been caring for them for over 30 years and investigating them, and I don't know what the MIs in this data set consisted of. So I'm troubled by that.

I do know that silent myocardial infarctions are important, and I do know that half of

them are misinterpreted and they're not clinically silent at all. They just don't get to the hospital, and those that survive you learn about later.

I think the definition of MI is changing dramatically, and we are, as you know, working in a consensus group with Europe which will increase the frequency of MI by 30 percent based on new diagnostic criteria, and the MIs that we're looking at, many of which were studied and acquired 15 or 20 years ago were in an environment where prevention and milieu pharmacologically when they occurred was different and, indeed, what we can do now relative to the occurrence of MI is far different than it was then.

I think there is data and gold in these trials that we have not been able to access, and so in relationship to what other information might be germane to the question on the table, I think we've heard from two of the PIs at least that it's there for the FDA to look at, and it might well be revealing on some of these issues, and I would be the first one to want to get down and wrestle with it.

I think Steve Nissan said something that I

believe very strongly, having been in the position of prescribing something that produced a disabling, nonfatal intracranial hemorrhage and stroke, and that is that it's a very devastating, complication of a treatment. It's not valued the same way as a myocardial infarction or a GI bleed, and the transfusions associated with a GI bleed likely have different implications now than they did 20 years ago.

So I have enough doubt and enough uncertainty relative to the likelihood of harm that the small benefit that I think is probably there is not in my view justification to approve this, and if I were, it would certainly be at a dose of 100 milligrams or less.

So I vote no.

CHAIRMAN BORER: Susanna.

DR. CUNNINGHAM: I think the public looks to the FDA for safety as well as efficacy, and I think when the public gets a recommendation from the FDA, they anticipate and they assume that the medication is going to be safe. So if the public knew that the medication that was recommended had a high probability

or some probability, it may not be that high, but some probability of causing them a stroke, which is a devastating event, for some small possibility of maybe preventing an MI, they wouldn't be willing to make that tradeoff.

So I would like to see data that was convincing because I would like there to be a medication that was as useful as aspirin looks to be. I think it's something that the public needs. The public has a hard time with diets and exercise and weight loss, and they would like a medication that worked.

But they wouldn't, I don't think, be willing to take the tradeoff of having a stroke. So I'm unfortunately not convinced by the data. I think that I'd like to be. I'd like there to be more analysis. I hope the Women's Health Initiative has more data. I think women are not served by this data because there's no benefit in the 20 percent of the population who were women. There's no benefit shown.

I'd like there to be benefit for women. So I'd like there to be something there for them. So

my vote has to be no.

The other interesting thing I was thinking about is somewhere it was said, I've heard, there was no such thing as a silent MI just, a caretaker who was unable to hear. So maybe we need to look further at those silent MIs.

DR. THROCKMORTON: Jeff, I'm sorry. We've lost track with the nonfatal and fatal. You said?

DR. CUNNINGHAM: I said I agree with Ron. If the patient walked in the door and I knew what they were --

DR. THROCKMORTON: No, I heard that, and actually that was well put, but we were asking the other members. I guess I'd just invite the last people since Ron said that if their vote was any different for a claim for nonfatal MI.

DR. CUNNINGHAM: I'm going to be no all around until I have better data.

DR. THROCKMORTON: Okay, and Paul and Ed, I guess.

DR. ARMSTRONG: No.

DR. THROCKMORTON: Okay. I just wanted to

make sure that I understand. Thank you.

CHAIRMAN BORER: Okay. I'm in a situation a little bit different from Ed's in that I wasn't here during the 1989 meeting, but I was at the earlier one that wasn't mentioned in any of the reviews when we considered aspirin for secondary prevention after myocardial infarction, which I believe was in 1982, so long ago that everybody has forgotten about it.

DR. NISSEN: I wasn't even born then.

(Laughter.)

CHAIRMAN BORER: Well, I take that under advisement.

Before I give my vote, and I'll go through the reasoning, I want to make a few preliminary statements. First of all, the reason that we have guidelines committees is primarily to obtain a consensus about the best thing to do generally in the absence of dispositive data.

Ultimately a patient comes in to be seen and you have to make a decision: do this, do that. And in the absence of the kinds of data that we'd all like, we make the best decision we can, and in the

current era, guidelines committees are formed to help inform those decisions, and that's fine, and that's good.

Drug approval, however, as Ed said, I think, carries with it the, or always has carried with it and, I think, will continue to carry with it, a sense of adequacy of data to draw a firm conclusion. So I don't think the fact that guidelines committees have come to a conclusion causes the FDA to need to jump on board.

And the fact that a study perhaps cannot be done anymore because of the milieu in which we find ourselves is not an argument. It's not an acceptable argument in favor of granting an approval. We might just say we don't know but, you know, do the best we can with the data we've got.

So I think we have to judge these data as they are, not because of circumscribing situations.

Having said that, I'll go a little bit further. I think nonfatal MI reduction, if that's what has happened here, is a real benefit, and if nothing else happened, everything else was neutral but

nonfatal MI was decreased by treatment, then I would say that's a good thing, and that's an approvable indication.

I think that CVAs are bad things, that strokes are bad things, are very bad things. I think nonfatal strokes are very bad things. Fatal strokes in parallel with what Ron said, if a patient walks into your office dead, I don't think he or she cares how he got there, whether it's a stroke, an MI, or a car accident.

But nonfatal strokes are very bad for all of the reasons that have been said. I don't know what to make of silent MIs, and I don't want to get into a discussion of putative mechanisms because I don't think that we have sufficient data, as I've said so many times about any drug to determine how specific pharmacological effects track with clinical effects. We know they track; we don't know why.

However, I would point out only that the data would be consistent with, not suggestive of, but consistent with some effect of aspirin that reduces the perception of the symptom that's associated with

an MI. You know, aspirin does do that. You know, it's an anti-inflammatory drug that reduces pain.

I'm not suggesting that's what happens here, but you know, we ought to keep it in mind if the silent MI data seem to be discordant, those few data that we have seem to be discordant with the other data.

And I'm very concerned that we don't have sufficient information about women to make a strong statement, although the data we have are at least not inconsistent with there being similar benefit, if there is benefit, in women as in men, but you know, if this drug were to be approved for a new indication, I would certainly make it very clear what we don't know in labeling.

Now, having said all of that, we come down to what the data tell us, and you know, I'm concerned about the fact that the primary endpoints generally weren't met, and I'm concerned about all of these things, but I think that there is a plausible interrelation between the outcome events of greatest interest: cardiovascular death, MI, fatal or

nonfatal, what have you.

So I'm not necessarily a priori opposed to voting for approval of a drug for an indication for use of a drug because it didn't meet the primary endpoint in the various trials. I'm concerned about it, but I'm not a priori against it.

And I look at the numbers that we have here, and I'm going to go through them specifically so I can make a point. The data indicate that for all five trials there was a 27 percent reduction in nonfatal MI. We don't know about silent MI, but the data we have, 27 percent reduction.

For the TPT study, which was the one study perhaps in the population for whom the sponsor would have us aim this drug, the reduction was 32 percent. That's the same.

For all MI, fatal or nonfatal, the entire data set shows a 23 percent reduction in relative risk. The TPT study, 19 percent, I'm going to say that's the same.

For all stroke, the totality of the data shows an increase in all stroke. That's fatal and

nonfatal, a tremendous increase in fatal strokes, but for fatal and nonfatal, five percent. TPT decreased by two percent all stroke. You know, that sounds pretty similar, although it disturbs me that strokes are increased, particularly if they're not fatal.

And then look at all vascular deaths. For the totality of the group, the RR is .98 in favor of aspirin, which is no change at all, but that's where the disturbing point is because TPT increased by 20 percent all vascular death. That would be disturbing to me.

How disturbing? Well, not as disturbing as it might be. The numbers are relatively small, and then we have this confound with the warfarin that, you know, I don't even want to get into that. I don't know how to make any sense of that.

So I'm willing to back off on that concern for the moment. Given all of those numbers that I've given you that seem to be consistent, I would draw from those numbers the conclusion that all MIs are reduced by some proportion. I would say maybe 20 percent, maybe a little bit more, for some population

that's been defined here; that vascular deaths probably aren't changed much for that same population, and that strokes probably aren't changed much. They may increase a little bit, and that's disturbing. That's a real disturbing point.

But when you put it all together as concerned as I am, I would have to say that I think the bulk of the evidence favors benefit over risk for some population. Now, what's the population?

Well, the sponsor would tell us that if we use an algorithm that defines people who have a ten percent, ten-year risk of some CHD event or greater than that, that that's a high risk population, and I'm willing to buy that.

Now, you know, we're going to get into another question here, which is very important, which has to do with how we define that group, whether anybody can use a label indication to define that group, whether anybody will use label indications, but let's say they could.

I would say that that case has been made. So I would vote yes for the question of recommend its

use for primary prevention of MI in a population as I've defined it greater than ten percent ten-year risk, which puts me in the distinct minority because the majority said no.

Now, having said that, Doug, do you want us to move on sine the vote is no? Do you want us to move on?

DR. THROCKMORTON: Let's move on --

DR. CUNNINGHAM: Can I add something?

CHAIRMAN BORER: Yes, sir. Susanna.

DR. CUNNINGHAM: I just want to make one comment that no one else has commented on, and that is that we don't have adequate data for different ethnic groups. Do we have a positive signal for African Americans? But we only have 650 people in that group. We have very few group -- any other data about any other ethnic group.

So I think as the consumer representative, I really want to encourage that we have data for other populations and that we explore further the data in the African American population because if it's a benefit there, that's critically important.

And the elderly, yes.

MS. SPELL-LeSANE: Yes, can Dr. Hirsch and Dr. Fleming vote again for nonfatal MI, please?

DR. THROCKMORTON: Yeah. By my count there were four individuals that voted yes on the question for all MIs: Alan; Dr. Hirsch, you're one; Dr. Lorell, you're one; Dr. Carabello, you're one; and Dr. Borer, you're one.

Several of you voted yes for nonfatal MIs, and I've tried to capture those as well, but just on the strict this was the proposal. I just want to make sure we have the right numbers. Is that a correct understanding of everyone's votes for the question of recommending inclusion of language for fatal and nonfatal, all MIs?

MS. SPELL-LeSANE: Dr. Lorell, you had?

DR. LORELL: I had originally voted no on the totality, but I will change my vote on that to a yes. So yes and yes.

DR. THROCKMORTON: Dr. Carabello?

Okay. Dr. Hirsch?

I'm not putting on anyone else that wants

to change -- clarify their votes should certainly do so as well. I'm just going down the people that I had identified.

DR. HIRSCH: I believe my vote was yes for prevention of nonfatal MI, no for the totality of MI.

DR. THROCKMORTON: Okay. Thank you for clarifying that.

Does anyone else need to clarify their vote? I as well need to make sure that we understand this.

Yours, Dr. Wood was also the same way, no on the total, yes on the nonfatal. Dr. Knapka, I also have you for a no and a yes. Okay.

DR. KNAPKA: Actually overall it's probably no.

DR. THROCKMORTON: You came down on the no at the end of the day.

DR. KNAPKA: But yes if there are stipulations.

DR. THROCKMORTON: Yes.

DR. KNAPKA: The population being well defined and there is some follow-up, and they just

don't say take aspirin and do nothing.

DR. THROCKMORTON: Okay. As I counted then there are three individuals who are saying yes to the proposed labeling. I just want to make sure. Is that everybody's count so that then we can move forward to some more discussion? Because there are at least two other things I really would like to get some input on.

MS. SPELL-LeSANE: I have ten noes and four yeses for the all MIs.

DR. THROCKMORTON: You're going to have to give a list of the names. I have --

MS. SPELL-LeSANE: I have Hirsch, Lorell, Carabello and Borer.

DR. THROCKMORTON: Right, and Dr. Hirsch just clarified that his was a no for all MIs, but was a yes for the nonfatal MIs. So that would reduce that count to three individuals. Okay?

Two things that I wanted to ask, one thing sort of very separately, and we'll come to that at the end, which was to revisit what Dr. Hiatt had raised this morning, the use of our secondary prevention

people differ fundamentally from the primary prevention, but first I want to come back to what Dr. Wood raised and what Dr. Pickering talked about was were an indication to be crafted, how to define risk, how to sort of decide what population would benefit.

Are these instruments that have been proposed by the sponsor -- is that an appropriate way to do that or is it more appropriate, well, along the lines of the Question 7? Are there other tools that may be the more usual way of describing populations that would benefit men, women, that sort of thing, another way to go?

CHAIRMAN BORER: Okay. Bill, why don't you go ahead and then we'll ask for comments if anybody differs with what you say.

DR. HIATT: In contrast to my thinking about the data showing a reduction in nonfatal events, I think the use of a risk stratifying device, whether it's Framingham, whether it's other surrogates of risk, coronary calcium scores, ankle-brachial indices, other risk factors, CRP, for example, these are all testable hypotheses, and I guess for Question No. 7, I

think if the label sticks to the evidence that has actually been studied, that I would have comfort with.

But if it goes to the next level saying you can use this risk score and define the population that really wasn't represented in the trial, I don't think there's any evidence to support that. So I would vote no for using Framingham risk to define the responsive group of people who should take aspirin and haven't had an event.

That is a testable hypothesis. That should be studied.

DR. THROCKMORTON: Are there other ways that you would define -- well, you sort of intimated in your comments on the last question that you'd use I guess I'll call it a more traditional approach of the population studied in the trials. Again, without putting words into your mouth or --

DR. HIATT: If you'd just stick with the data and stick with the efficacy signal in those cohorts and you're careful to define who they are by inclusion and exclusion and demographics, then you're as close to the data as you can get.

But if you use then that to say that in this small minority who were, in fact moderate risk by Framingham, we should apply that to all people in the United States who should take aspirin to prevent a nonfatal event, I don't think that's supported by any of the evidence.

And I do think that there are a number of things, simple things, and I think Al would agree if you did the ankle-brachial index as a way to risk stratify in conjunction with these other risk scores or other kinds of things like that, you could define intermediate populations, and they would be very responsive to a variety of therapies including aspirin or statins or other risk modifying agents.

But that really needs to be prospectively tested.

CHAIRMAN BORER: Let me ask you to answer two additional questions then. So am I understanding that if this drug were to be approved now, and obviously the majority thinks it should not be for this new indication; that if it were to be in the current setting, you would want to see the inclusion

and exclusion criteria for the TPT used as the definition of population since that was the only moderate risk group and showed the biggest --

DR. HIATT: No, I think that that would also be a risk because then you're dropping down to just one trial. So it ought to really reflect the totality of the demographic actually reported, which is mostly the very low risk people.

DR. WOOD: So you'd use just physicians?

(Laughter.)

DR. HIATT: Well, must male physicians. Well, I think that's the bind we're in because I think the evidence looks okay in that cohort. I would not extrapolate.

CHAIRMAN BORER: Okay. Then we won't go on to the next issue, which is can physicians use this, but we'll get to that again and can patients understand it.

Does anyone else have any? Steve.

DR. NISSEN: Yeah. Doug, there's something you've got to be really careful about here. The NCEP guidelines, and I have some knowledge about

how these were framed, the questions that were being addressed were different. We had a class of drugs, statins, which produced pretty uniform benefits, had very, very low risk, I mean, myopathy notwithstanding, and the risks are in the few per million.

And so the question that NCEP was dealing with with the Framingham risk score was cost effectiveness. You know, at what level of risk do you rise to where it's worth spending the amount of money you have to spend on a drug in order to achieve a benefit?

We're asking a different question here. We have a drug which can cause harm and can also do good, and so now we're trying to weigh harm versus benefit, and it's a very different equation. So if you want to take the NCEP Framingham and extrapolate that to a very, very different situation of risk versus benefit where there's harm that could be done, I would have to say that that would be a very dicey proposition to do that because there is a different balance in the potential risks of the drugs involved, between statins and, say, aspirin.

DR. THROCKMORTON: Yeah, you might also argue that those guidelines are actually based on prospectively designed outcome trials that have sort of tested those strategies, if I understand.

DR. NISSEN: Oh, I have already made that argument. That's why I voted no. I mean, I think that if you're going to use some strategy, the strategy ought to have been a tested strategy that there's been some testing of and proof that, in fact, it works.

And we don't know whether a Framingham risk score works as a means to select patients for therapy, which is why I voted no. I don't see how you're going to do this.

DR. THROCKMORTON: Yeah, although probably to be fair, you could have managed -- I mean, the sponsor's argument is that, in fact, a scoring system like this might promote a more appropriate use. That is, a physician that was looking at the data, if you were convinced that, in fact, it was extrapolatable from the identified data and all of those things, you might -- it might be a thing that physicians might

more readily apply and the sort of general practice population might be more likely to have, you know, full use.

I'm not hearing a lot of enthusiasm for that extrapolation, I guess.

DR. NISSEN: I'll shut up in just a minute, but just keep in mind that this is an over-the-counter drug, not one that you have to write a prescription for.

So what's really a question is who's making the decision.

CHAIRMAN BORER: Beverly, then Alastair and then Blase.

DR. LORELL: Yeah, I actually think it is feasible and it's the direction of cardiology in primary care practice today to think about gradations of benefit and risk, and a term was used earlier today, "the intensity of therapy." So I think it would be possible to write a label that were as vague as moderate to high risk and to refer to assorted scoring systems.

I don't think it's in the FDA's business

to put its imprimatur on any single system. To me part of defining the population in which this might be used is defining what we know about safety, and for that being a different issue is we do have safety data, the analysis that Tom did here, in a large number of patients and trials that had exclusion criteria.

So to me a part of writing a label, if one were to do so, would be to look very carefully at this very large database regarding the exclusionary criteria for upper limits of severe, uncontrolled hypertension. These trials did not exclude people with some hypertension, a risk of GI bleeding, et cetera.

So I think there's a very different issue of defining the exclusionary population based on what were used as exclusionary data in these trials versus whom you would include.

And I don't think it is at all out of the question to identify a target population of moderate or moderately high risk.

DR. THROCKMORTON: Sorry. I've got to

press on that. What I heard you say was you should use the exclusion; you should look to the exclusion criteria used in the trials to sort of describe the population that would potentially benefit, but then you turned it around and said, no, I think you should use some sort of scoring or that a scoring system --

DR. LORELL: No. I would use the exclusionary criteria as a way of defining safety boundaries. So you know what happened in terms of adverse events in these trials based on whom was excluded. So among a population who, in other words, did not have exclusionary criteria, you can say something about safety or more specifically what the risks are of hemorrhagic stroke and major bleeding, including GI bleeding.

In terms of the inclusionary criteria, I think it is feasible in 2004 to make a recommendation for use in moderate to high risk patients who have not yet had an event.

DR. THROCKMORTON: Right. So just again to paraphrase, you might say we know a lot about the safety of aspirin in terms of outcomes from a lot of

different places, obviously not just these trials, but you might be able to draw on such a database to inform the kinds of safety in different kinds of populations -- I don't know -- women or people over the page of 75 or whatever.

Help me out now how to move from that to decide who would be receiving the therapy and how to describe that population efficacy-wise.

DR. LORELL: Yeah, I think efficacy-wise you would consider writing recommendation or a labeling trying to get across the notion of balancing potential benefit and risk and targeting from moderate to high risk patients.

And I think primary care physicians, as we heard earlier today in some of the public commentary and cardiologists are becoming increasingly comfortable with doing that in their own practice, and there's several different pathways for doing that.

I think you'd have to have an efficacy statement saying that very clearly the level of confidence of benefit -- there are ways one could word this that are already done in labels -- is much less

certain for women and certain other subgroups.

DR. WOOD: Yeah, I think there's a number of points, Doug. The first is that you can use the scoring system presumably to define futility. It seems to me highly unlikely that you're going to see benefits in a group for whom the risk is less than that of the risk of hemorrhagic stroke and some measure of a GI hemorrhage, and I wouldn't count these, as I said before, equal, but at least, yo know, as you reduce your risk you're certainly not going to get to a point where you could be confident you would exceed in the risk-benefit ratio.

The same question, which I think is what Steve was trying to say as well, does the Framingham algorithm define the group that's going to benefit from aspirin, and I suspect it doesn't although it may be useful to do just what I said a second ago.

And I think we could actually get data particularly from the Oxford group that would help with that. For example, you get a big hit from having a blood pressure greater than 140 on the Framingham data, and yet intuitively one would think that that's

a group that would be at particular risk from hemorrhagic stroke.

Now, that's an answerable question, I guess, from your data, and you could go back and look at that fairly easily.

So I would recommend that that was done, and that we look and see if the group who had a blood pressure greater than 140 or some number were at particular risk for hemorrhagic strokes during aspirin administration.

But that doesn't mean that the scoring system would be valueless because I think it does define groups in whom there's unlikely to be any benefit just because of the sheer futility, and it certainly assists you in defining groups who are at great risk from cardiovascular disease, and physicians tend not to do a very good job of that, I think. They tend to work on specifics. You know, they're treating blood pressure or they're treating cholesterol. They don't sum it all together and put it into a composite score very well, although they could.

DR. THROCKMORTON: So would that be

predictive value or operating characteristics? I mean are those the sorts of words that -- I mean, you define the operating characteristics of this screen whether it's the Framingham study or -- I'll turn my off in a minute and you can have -- I mean, is that sort of what you're saying?

Because I want to hear Dr. Pickering as well. I mean, this is really important because this is a really fairly new thing. Other than NCPT and things like that where they have been prospectively applied to the database, actually taking a population based analysis, you know, set of data like this and saying, "Now I can use a scoring system," is relatively novel and it's really important for us to understand, you know, how you think we should go about doing that.

DR. WOOD: Well, I guess what I'm saying is that the scoring system has potentially two or three benefits. The first benefit is that by looking at the group that's at very low risk and you can probably within a fair degree of certainty say that that group is unlikely to benefit from aspirin, given

the horizontal lines shown on these multiple copies of that slide, that is, they're at constant risk and they're unlikely, therefore, to benefit if the absolute risk is less than the risk of the adverse events.

Does the scoring system define the group that will benefit? I don't think we know that, and all we know is -- and Bill said this earlier -- is the data that were used as the entry criteria for the studies.

That may be okay, but we don't know it with any level of certainty. However, the scoring system by definition is a composite, and we have prima facie reasons, I think, to believe that some of the contributors to that scoring system may actually increase your risk of aspirin rather than decrease it, and I think that's something that needs to be carefully explored before we just blindly go into the scoring system.

CHAIRMAN BORER: We have Blase, Tom, Alan and then I have a comment that I think may end us.

Blase.

DR. CARABELLO: I think it's fine to define or suggest that we use it in moderate or high risk populations, but I wouldn't want to see us go with one scoring system. We all have different ways of risk stratifying.

In the New England Journal article that was included in the packet by Michael Laragh, the 45 year old guy with a densely high positive family history, an LDL of 160, and an HDL of 35, I'd have given him aspirin, and they concluded not to.

So, I mean, I think that I would be very careful about how we define these, or I would leave it broad and not limit it to one system or another.

CHAIRMAN BORER: Tom.

DR. PICKERING: Yeah, we've only been talking about scoring systems for MI, but there have also been algorithms developed for risk of stroke. I haven't seen any that give you overall risk. It would be interesting. There may be some.

But it seems to me there may be patients who on the MI score would be moderate risk and, therefore, according to what we've heard today would

benefit in terms of nonfatal MI, but that patient might also score high on the stroke risk, particularly if their blood pressure is a little high because blood pressure is a more important to stroke than MI.

And in those patients, it may be that aspirin is particularly harmful since we really don't know. So I think, you know, this may depend on which scoring system you happen to prefer for your particular patient.

CHAIRMAN BORER: Alan.

DR. HIRSCH: The fact that we're all having our lights on here pushing six o'clock shows how important this question is to us.

You know, I've been in favor of the use of Framingham risk or as other risk indicators because to me their use is primarily as the sponsor and many of the advocates stated; they're a call to action for complacent physicians to do good things for people at risk.

That said, I wanted to go on record as we're asked to opine that -- I was really troubled by the creative use of the risk or to apply a population

in which it was not pre-hoc defined in any of these trials.

And I just want to echo again there's good reasons to believe that the pathophysiology of effective aspirin would be quite distinct from that from NCP, great reasons to believe it, and these data actually suggest, in fact, that it doesn't work. There was less risk reduction in the population in the medium risk group.

So here's a suggestion. It's a nice hypothesis. You test it in future trials or, you know, there's enough data here in 55,000 individuals probably whom have some blood pressures and some cholesterols. One could actually test this post hoc by an appropriate analysis and come back and inform us in some subsequent publication.

CHAIRMAN BORER: Yes. I will begin with Alan's statement because it was part of my conclusion here.

Let me say at the outset I suggested that there was benefit here and that the benefit outweighed the risk, but I didn't say for whom and I don't know

how to write a label.

I don't think we have the data. I would have to agree with Steve that I don't know who to say should get the drug because I don't know what drove the benefit.

Now, having said that, I think that one rational place to start would be, since the suggestion has been made to use the Framingham score, to go back and apply the Framingham score in the populations that were studied and see what comes out. Maybe it works; maybe it doesn't, but I wouldn't know how to write the label.

And I agree with Blase that I am very worried about a very prescriptive set of criteria in a legal document. I probably wouldn't agree with whatever you wrote, but I don't know what to write, and so even though I voted that there's something here to be approved, I don't know who to approve it for.

So we need more data.

Now, next point because you asked these questions. Let's say we had a scoring system. Let's say it was the Framingham scoring system. Let's say

post hoc you do the analysis and it works beautifully. Can physicians use this?

Well, sort of, maybe. I want to remind you of Dr. Stafford's data. There is a label for aspirin. it says that people who have had an event, people who are at high risk, et cetera, et cetera, that they should get aspirin.

And what we learned was that maybe 20 percent of them do. Maybe 30 percent of them do. So can doctors use it? I mean, people with an event, what could be simpler?

It's a lot simpler than the scoring system, but only 20 to maybe 30 percent of doctors tell patients to use aspirin. So I think it's tough to expect doctors to use a scoring system. That doesn't that, you know, if it works we shouldn't put in the label and prescribe it and whatever.

And can patients understand it? Forget it. I mean it's just not going to happen.

So if the goal of writing guidelines and if the drug were to be approved, one of the benefits that's inferred to occur from having had the drug get

the imprimatur of the FDA for a specific indication is that, you know, a lot more people are going to use it. Well, in absolute terms, a lot more may, but in percentage terms, I think that the response is going to be relatively small at first, and it's going to take a major educational effort for it to be better than that, and I worry a little bit about educational efforts because the principals that they espouse tend to be carved in stone and every patient is an individual, and you have to make individual decisions in the clinical arena.

So having said that, I don't know how to write the label. I think some more work has to be done to determine how to write the label, and once you do, I don't know if it's going to be practical for physicians to apply it or for patients to use it.

I don't see any other lights on. Are there any other comments?

Because if not --

DR. THROCKMORTON: Sorry. One more comment and then I'll let you go, and this comes up just from something that Dr. Hiatt said this morning.

He was expressing concern that looking at the secondary data, you know, there was an obvious continuum as far as secondary prevention down to primary prevention. I was just wondering whether there was some reason to be concerned about that.

And I believe he was expressing some concern about that, and I wondered whether anyone else had any comments about that. Because at least a portion of the argument here has been look at all of the secondary prevention data that is obviously robust and quite impressive, and should we be discounting that in some sense because it's not -- has a different physiology, something like that.

CHAIRMAN BORER: You know, I'll tell you. There may be some pathophysiological differences between the patients who are beneficiaries of aspirin for second prevention and those that we're talking about now. There may well be. I don't doubt that there are.

You know, in general, however, I think that we make a final decision about whether a drug is appropriate for an indication or whether it's not

based on a body count because we don't really know the pathophysiology, I mean, or if we do know it today, we'll know it differently a year from now.

So I would look at the body counts, and to me there is a consistency, albeit there's some noise; there is some consistency across the trials if you go from the high risk to the low risk. So I have a concern, but it doesn't reach the level of concern where I would change my vote that was in the minority.

Steve.

DR. NISSEN: Yeah, I have to try to get the last word in here. You know, the idea that we will go back and now apply some criteria to determine who in that ten to 20 percent group ought to get the drug, I want to point out to everybody that we have very few patients from these five trials in that group, and so now we're going to try to apply a tool to a group of people that perhaps includes maybe 12 percent of that 55,000 patients, and I would guess, just guessing, that it will be very difficult to apply any tool post facto to the data when so little of the data we were presented with actually occurs in the

range that we're most interested in.

And so I'm not very optimistic, Doug, that you're going to be able to go back and figure out some scale to apply here.

CHAIRMAN BORER: Okay, Doug. Any other issues? Have we solved this one for you?

DR. THROCKMORTON: Thanks to everyone very much.

CHAIRMAN BORER: Okay. We'll conclude this session and we'll meet again tomorrow morning.

(Whereupon, at 5:49 p.m., the meeting was adjourned.)