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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

82nd MEETING

Friday, October 24, 1997

9:05 a.m.

National Institutes of Health
Clinical Center-Building 10
Jack Masur Auditorium
9000 Rockville Pike

Bethesda, Maryland

                          PARTICIPANTS

Milton Packer, M.D., Chairperson
Joan C. Standaert, Executive Secretary

MEMBERS

          Robert Califf, M.D.
          Thomas Graboys, M.D., (Consumer Representative)
          John DiMarco, M.D.
          Marvin Konstam, M.D.
          JoAnn Lindenfeld, M.D.
          Lemuel Moye, M.D., Ph.D.
          Ileana Pina, M.D.
          Dan Roden, M.D.C.M.
          Udho Thadani, M.D., FRCP

TEMPORARY VOTING MEMBER

          Ralph D'Agostino, M.D., Ph.D. (Chair, OTC
          Committee)

FDA

          Robert R. Fenichel, M.D., Ph.D.
          Raymond Lipicky, M.D.
          Robert Temple, M.D.

C O N T E N T S

Open Public Hearing

**NDA 20-839: CLOPIDOGREL (PLAVIX)
SANOFI PHARMACEUTICALS, INC.**

**TO BE INDICATED FOR THE PRESENTATION OF VASCULAR
ISCHEMIC EVENTS IN PATIENTS WITH A HISTORY OF
SYMPTOMATIC ATHEROSCLEROSIS**

Sponsor's Presentation

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

2   **Introductory Remarks**

3   DR. PACKER: This is the second day of the 82nd

4   meeting of the Cardiovascular and Renal Drugs Advisory

5   Committee. We will have Joan read the conflict of interest

6   and administrative issues for this morning's meeting. Joan?

7   MS. STANDAERT: Thank you. The following

8   announcement addresses the issue of conflict of interest

9   with regard to this meeting, and is made part of the record

10   to preclude even the appearance of such at this meeting.

11   Based on the submitted agenda and information

12   provided by the participants, the Agency has determined that

13   all reported interests in firms regulated by the Center for

14   Drug Evaluation and Review present no potential for a

15   conflict of interest at this meeting, with the following

16   exceptions. In accordance with 18 USC, full waivers have

17   been granted to Drs. Milton Packer, Dan Roden, Lemuel Moye

18   and Ralph D'Agostino. A copy of these waiver statements may

19   be obtained from the Agency's Freedom of Information Office,

20   Room 12A-30 of the Parklawn Building.

21   We would like to also like to disclose for the

22   record that Dr. Robert Califf and his employer, the Duke

23   University Medical Center, have interests which do not

24   constitute a financial interest within the meaning of 18

1   USC, but which could create the appearance of a conflict.

2   The Agency has determined, not withstanding these

3   involvements, that the interest of the government by Dr.

4   Califf's participation outweighs that the integrity of the

5   Agency's programs and operations may be questioned.

6   Therefore, Dr. Califf may participate in today's discussion

7   of Plavix.

8   There has been a waiver granted for Dr. Cindy

9   Grines but since she will be absent from this meeting, that

10 is not relevant.

11   In the event that the discussions involve any

12 other products or firms not already on the agenda for which

13 an FDA participant has a financial interest, the

14 participants are aware of the need to exclude themselves

15 from such involvement and their exclusion will be noted for

16 the record.

17   With respect to all other participants, we ask in

18 the interest of fairness that they address any current or

19 previous financial involvement with any firm whose products

20 they may wish to comment upon.

21   That concludes the waiver for October 24th.

22   DR. PACKER: As far as our conventional agenda, we

23 now reserve time for public comment, and I understand there

24 is public comment at this particular point in time.

1   **Open Public Hearing**

2   MS. TRUJILLO: Hi. I am Rochelle Trujillo. I am

3 the communications director for the National Stroke

4 Association. Stroke has a devastating impact on

5 individuals, their families and our nation. Despite

6 important advances in stroke prevention and treatment, it

7 continues to be one of our nation's greatest healthcare

8 problems. In our country, stroke is the third leading cause

9 of death. Stroke is the number one cause of adult

10 disability. Stroke touches the lives of four out of every

11 five American families. Stroke strikes someone every

12 minute. Stroke costs more than $30 billion annually. Four

13 million stroke survivors are living in the United States

14 with varying effects from stroke.

15   Additionally, after a 35-year decline, the stroke

16 mortality rate appears to be increasing. Lower death rates

17 for heart disease and cancer continue to decline. Adults

18 over age 50 is the fastest growing segment of our population

19 and, as a result, the trend of escalating stroke deaths is

20 not expected to retreat any time soon unless newer therapies

21 are made available to doctors and patients.

22   The mission of the National Stroke Association is

23 to reduce the incidence and impact of stroke in our nation.

24 While the National Stroke Association is encouraged by

 1 recent advances in the acute treatment of stroke, the best

 2 treatment is still a stroke that doesn't occur. The need

 3 for prevention is even more urgent for those Americans who

 4 are at higher risk because they have already suffered a

 5 stroke or experienced stroke symptoms. Fully one-third of

 6 these patients will experience a recurrent stroke within

 7 five years after the original event.

 8   Antiplatelet and anticoagulant therapy, combined

 9 with other medical and life style modifications can

10 significantly reduce the odds of a second stroke. These

11 high risk patients have an urgent need for availability of

12 safer, more effective antiplatelet agents. Being prescribed

13 a drug which can lower the risk of recurrent stroke with

14 side effects could mean the difference between life and

15 death for many of America's four million stroke survivors.

16   A newly approved antiplatelet agent that reduces

17 the chance of a second stroke could also have a significant

18 impact on the $30 billion invoice that stroke issues our

19 national healthcare system annually. For every stroke that

20 is averted, an average of $15,000 for the first 90 days

21 alone could be saved.

22   More importantly, preventing a stroke also means

23 preventing the devastation and destruction that accompany

24 it. Patients and their doctors need new approaches to

 1 stroke prevention.

 2   On behalf of the National Stroke Association, we

 3 urge your full consideration and look forward to your

 4 carefully evaluated recommendation. Thank you.

 5   DR. PACKER: Is there any other public comment?

 6 If not, we will proceed with the main topic for today's

 7 meeting, which is the evaluation of clopidogrel, and Dr.

 8 Clay will begin the presentation by the sponsor.

 9   **NDA 20-839, Plavix (clopidogrel)**

10   **Sanofi Pharmaceuticals, Inc.**

11   **Introduction**

12   (Slide)

13   DR. CLAY: Dr. Packer, Dr. Lipicky and Dr. Temple,

14 members of the Advisory Committee and guests, I am George

15 Clay, Vice President of Regulatory Affairs at Sanofi

16 Pharmaceuticals, and we are here today to discuss

17 clopidogrel with you.

18   Clopidogrel is an antiplatelet drug that has been

19 jointly developed by Sanofi and the Bristol-Myers Squibb

20 Company for the prevention of vascular ischemic events,

21 myocardial infarction, stroke and vascular death in patients

22 with a history of symptomatic atherosclerotic disease.

23   Our presentation today has been structured to

24 address what FDA and we agreed were the pivotal issues.

1   While we will not dwell on such issues as clinical

2   pharmacology or detailed discussion of safety parameters, we

3   will be happy to answer more detailed questions that may

4   arise in a question and answer fashion.

5   (Slide)

6   The first presentation this morning will be an

7   overview of the CAPRIE study. That is the large, single

8   pivotal safety efficacy study that comprises the majority of

9   the clinical data contained in our NDA. This will be

10 presented by Dr. Donald Easton, who is Chairman of Neurology

11 at Brown University and a member of the CAPRIE steering

12 committee.

13   Statistical interpretation of selected topics

14 relating to CAPRIE will be presented by Dr. Lloyd Fisher.

15 Dr. Fisher is Professor and Associate Chair at the

16 Department of Biostatistics at the University of Washington,

17 and is a consultant to Sanofi on several issues of interest

18 in this NDA.

19   The clinical interpretations of our results will

20 be presented by Dr. Alison Pilgrim, who is Vice President of

21 Cardiovascular Clinical Research for Sanofi Research.

22   (Slide)

23   Consultants seated in the audience who are

24 available to us to answer questions are Dr. Michael Gent,

1 who is the principal investigator and chairman of the CAPRIE

2 steering committee. Dr. Grossman is from the University of

3 California, and is a consultant to us in cardiology.

4   (Slide)

5   Dr. Harker was a member of the CAPRIE steering

6 committee and was involved in the issue of safety

7 evaluation. Dr. Virmani is an expert in cardiovascular

8 pathology, and her research interests include factors that

9 affect the structure of plaque.

10   Our presentation this morning has been designed to

11 address several key points, as was previously mentioned.

12 These points will be covered by all three speakers, and we

13 ask your consideration in allowing us to make the complete

14 presentation on these issues this morning before we answer

15 questions. Thank you.

16   DR. PACKER: As Dr. Easton is coming to the

17 microphone, let me just comment to the Committee that the

18 presentations of Drs. Fisher and Pilgrim are primarily

19 focused on the issue of heterogeneity. So, I would ask the

20 Committee to hold questions about heterogeneity until those

21 presentations are made, but I think that any other issues

22 related to the CAPRIE trial can be asked prior to their

23 presentations. So, let me again say that questions about

24 heterogeneity should be held so that there is an orderly

1 progress of the discussion for this morning's meeting. Dr.

2 Easton?

Overview of CAPRIE

4   DR. EASTON: Thank you, Mr. Chairman. Good

5 morning.

6   (Slide)

7   My responsibility for the next few minutes is to

8 give you an overview of the CAPRIE trial. I will begin with

9 a few comments about atherosclerosis and atherothrombosis.

10   (Slide)

11   We know that atherosclerosis is the major

12 pathological process underlying stroke and myocardial

13 infarction. We know that it is usually a generalized

14 process, affecting more than one vascular bed. There is a

15 high annual incidence of stroke and myocardia infarction in

16 Western countries.

17   Platelets play a pivotal role in acute thrombotic

18 events and, therefore, antiplatelet agents are the primary

19 treatment for preventing these events. So I would like to

20 spend a few minutes on what we know about antiplatelet

21 agents in general.

22   (Slide)

23   The antiplatelet trialists' collaboration

24 conducted an overview analysis of antiplatelet agents across

1 a spectrum of atherosclerotic diseases. They published the

2 results of this meta-analysis in 1994, but it included all

3 of the published and unpublished unconfounded, randomized

4 trials through March of 1990. These trials were identified

5 not only from the medical literature but from trial

6 registries and inquiry of individual investigators and

7 pharmaceutical manufacturers.

8   So they ended up with more than 73,000 patients

9 and 142 randomized trials. They had very clear definitions

10 of endpoints in this overview analysis, and well-defined

11 statistical methodology.

12   I would say parenthetically that we are going to

13 look in a moment at the results of the meta-analysis, but it

14 is interesting to note that the primary results did not

15 change much from when the analysis was done in 1988 with

16 about 33,000 patients. So, the odds reductions that were

17 looked at have held up over time.

18   (Slide)

19   Here you see the groups of trials: patients with

20 prior myocardial infarction, patients with acute myocardial

21 infarction, prior stroke patients and then an aggregate of

22 "other" high risk patients. The primary outcome that has

23 been looked at in all of these is MI, stroke and vascular

24 death.

1   You see here the cumulative event rates in the

2   control groups. Here are the cumulative event rates in the

3   antiplatelet-treated patients. Overall, there is this

4   reduction from 14.7% down to 11.4% for all these patients in

5   all of these trials.

6   There is good consistency in odds reductions

7   across these various types of patients, as you can see on

8   the right. The sort of bottom line number, in a sense, is

9   this overall 27% reduction in the odds of stroke, MI and

10   vascular death in all of these trials for patients treated

11   with all kinds of antiplatelet agents.

12   (Slide)

13   If you restrict yourself to looking at the trials

14   involving aspirin compared directly to placebo, then there

15   was an overall odds reduction for this same outcome cluster

16   of 25%. The antiplatelet trialists also looked at

17   ticlopidine versus placebo and estimated the odds reduction

18   in those same events to be 33%. This is germane to issues

19   about clopidogrel, as you will see in a moment.

20   In the three trials comparing ticlopidine to

21   aspirin directly, there was a 10% reduction in the odds

22   favoring ticlopidine over aspirin.

23   (Slide)

24   Clopidogrel is a thienopyridine related to

1 ticlopidine. They have a common mode of action in blocking

2 the platelet ADP receptor and, therefore, the ADP pathway to

3 platelet aggregation. This is, of course, different from

4 the cyclooxygenase pathway that aspirin blocks with a

5 possible diesterase pathway that dipyridamole blocks.

6   The dose to be used of clopidogrel was that which

7 was equipotent to the approved dose of ticlopidine, which is

8 100 mg/day, based on platelet aggregation studies and a

9 bleeding time. With this equipotent dose, it was

10 anticipated that we might see an overall odds reduction for

11 the major outcomes somewhere in the neighborhood of what was

12 seen with ticlopidine, namely, 10% over the active agent.

13   (Slide)

14   So CAPRIE was designed to be the pivotal trial

15 demonstrating the efficacy of clopidogrel, clopidogrel

16 versus aspirin in patients at risk of ischemic strokes.

17   (Slide)

18   The rationale for CAPRIE was that patients with a

19 wide spectrum of atherosclerotic disease are at risk of all

20 major atherothrombotic events. The atherothrombotic process

21 is similar regardless of the clinical manifestations of the

22 underlying atherosclerosis and, therefore, clopidogrel would

23 be expected to benefit the entire spectrum of

24 atherosclerotic patients.

1   So, what we are seeing here is that we believe

2   that whether a patient comes into the trial because of a

3   myocardial infarction, because of a stroke, because of

4   severe peripheral arterial disease, the events leading to

5   myocardial infarction should be similar in all of those

6   patients.

7   Similarly, we believe that the pathophysiology and

8   stroke that occurs should be similar in these various groups

9   of patients.

10   (Slide)

11   So, CAPRIE was designed to compare the efficacy

12   and safety of clopidogrel to the active control aspirin. It

13   was a blinded, randomized in 2 parallel groups study;

14   clopidogrel 75 mg/day was compared to aspirin 325 mg/day,

15   and this was a multicenter, multinational trial.

16   The treatment time was approximately a year to 3

17   years of treatment. The mean treatment time was 1.9 years.

18   In the end, there were 19,185 patients enrolled and followed

19   up regardless of discontinuation of study drug. It is thee

20   19,185 patients that were analyzed in the intent-to-treat

21   primary analysis.

22   (Slide)

23   The patients that came in to CAPRIE were from 3

24   different groups: ischemic stroke patients, myocardial

1   infarction patients and peripheral arterial disease

2   patients. These were severe peripheral arterial disease

3   patients with current intermittent claudication or previous

4   claudication with an arterial intervention.

5   Patients with prior atherothrombotic events or

6   atherosclerotic disease in more than one vascular bed were

7   not excluded. In fact, we tried to minimize exclusions of

8   all types. One group of patients that was excluded were

9   those with known intolerance to aspirin. These three groups

10   were chosen just to ensure a spectrum of atherosclerosis in

11   patients that should be at high risk for these outcomes that

12   we are speaking of, myocardial infarction and stroke.

13   (Slide)

14   The outcome events that were looked at in CAPRIE

15   were these: Non-fatal events were MI, stroke, intracranial

16   hemorrhage and leg amputation. On the fatal side, again

17   myocardial infarction, stroke and hemorrhage, and then

18   obvious non-vascular causes of death, such as cancer,

19   trauma, encephalitis and so forth. Any patient that didn't

20   fit into one of these categories of fatality was considered

21   "other vascular." So if there was any doubt about whether

22   it was vascular or non-vascular it was included in this

23   category.

24   Because the term vascular death is used sometimes

1 and other vascular death at other times, I would just like

2 to point out that if you add up the patients with fatal MIs,

3 fatal strokes and other vascular, they constitute the

4 overall group that we call vascular death. Other vascular

5 death, I would just say parenthetically, is congestive heart

6 failure, ruptured aortic aneurism, pulmonary embolus and so

7 forth.

8   (Slide)

9   By protocol, the primary analysis in CAPRIE was

10 this outcome cluster: first ischemic stroke, MI or vascular

11 death. Then there were these other four secondary clusters.

12 The first one is the primary cluster with amputation added,

13 and then vascular death. In this grouping any stroke also

14 then included hemorrhagic stroke, MI and death from any

15 cause. Of course, it is only the primary analysis for which

16 this trial was powered.

17   (Slide)

18   In looking at the 19,000 patients that were

19 randomized in CAPRIE, you can see there was good balance

20 between the 2 treatment groups, and there was also good

21 balance across the qualifying conditions, with a little over

22 6300 patients to the 3 groups.

23   (Slide)

24   In terms of patient accountability, the number of

1   patients that never received study drug was low and equal in

2   the 2 groups. The number of patients lost to follow-up was

3   low and equal in the 2 groups. The number of patients that

4   discontinued study drug for reasons other than outcome event

5   are shown here, and they were equal in the 2 groups and

6   comparable to what we see in other comparable trials, 23.5%

7   and 24.1% of the patients. In terms of the number of

8   patients taking more than 80% of their study drug, that

9   number was high and also comparable in the 2 groups.

10   (Slide)

11   This is the Kaplan-Meier plot of the primary

12 analysis result. What you see is the cumulative event rate

13 for stroke, myocardial infarction and vascular death in the

14 aspirin-treated group. You see below it the cumulative

15 event rate for the clopidogrel-treated patients. The curves

16 separate early, continue to separate and overall there was a

17 risk reduction of 8.7% in this primary outcome cluster

18 favoring clopidogrel in these patients. You can see the p

19 value here and you can see the absolute event rates down

20 here, 5.83% for the aspirin-treated patients per year and

21 5.33% in the clopidogrel patients per year.

22   The comparable analysis for patients on treatment

23 yielded a risk reduction of 9.4%. If you convert this

24 number to an odds ratio rather than a relative risk

1   reduction, the 8.7% becomes 9.4%, which is the number that

2   the antiplatelet trialists have used just for a reference

3   point.

4   (Slide)

5   These are just the absolute numbers of the primary

6   outcomes. You see that there were 1020 stroke, MIs or

7   vascular deaths in the aspirin-treated patients, reduced to

8   939 on clopidogrel. Then here is the reduction in ischemic

9   stroke, 461 to 438. The reduction in myocardial infarction

10 is substantially more, from 333 to 275 first events; and

11 then no difference in the other vascular category between

12 the 2 groups. So the action is in the stroke and myocardial

13 infarction reductions.

14   (Slide)

15   One of the prespecified analyses that was designed

16 to just explore consistency of treatment effect was this one

17 by geographic region. You can see that the groups were

18 divided up into patients from Europe or Australasia and

19 patients from North America. Here is the number of events

20 on aspirin and on clopidogrel. You see relatively

21 comparable reductions across these two groups.

22   (Slide)

23   Another prespecified analysis to explore

24 consistency was this one, the primary outcome by qualifying

1 condition. Here, again, you see qualifying conditions are

2 ischemic stroke, MI, peripheral arterial disease, and here

3 are the relative risk reductions, 7.3% favoring clopidogrel,

4 4% favoring aspirin, 23.7% favoring peripheral arterial

5 disease, with the confidence intervals here.

6   This apparent heterogeneity was unexpected and,

7 consequently, will be addressed in some detail in the

8 subsequent presentations.

9   (Slide)

10   This is designed simply to show that here are the

11 point estimates on an odds ratio depiction of these same

12 groups of patients by qualifying conditions. So, here is

13 the reduction of 8.7%, minus 4% and so on. You can see that

14 the confidence intervals around all of these point estimates

15 include the confidence interval for the primary analysis for

16 which the trial was powered.

17   (Slide)

18   I won't labor the secondary analyses, other than

19 to point out that the results of these analyses were quite

20 consistent with the primary analysis.

21   (Slide)

22   With respect to the adverse events, you can see

23 that we have concentrated here on those adverse events that

24 were significantly different between the 2 treatment groups,

1 any rash and then gastrointestinal difficulties that we will

2 look at. You can see down here the 2 bleeding issues of

3 most importance, gastrointestinal bleeding and intracranial

4 bleeding, and then we wanted to concentration on neutropenia

5 and thrombocytopenia because of what we know about the

6 sister, thienopyridine, ticlopidine.

7   So what we saw here was an increase of 1.4% in

8 skin rashes in those patients treated with clopidogrel over

9 the number for those treated with aspirin. Similarly with

10 the diarrhea, you can see an increase of 1.1% more adverse

11 diarrheas than in the aspirin-treated patients.

12   On the other hand, the gastrointestinal side

13 effects go in the other direction, with an increase in the

14 patients treated with aspirin. In GI ulcers you see the

15 increase in aspirin. These asterisks here are all

16 indicating that these are statistically significant

17 differences in the 2 directions. You see that the GI

18 hemorrhage rate is higher on aspirin than it is on GI

19 bleeding. Although there is a trend for intracranial

20 hemorrhage being a touch higher on aspirin, those are

21 comparable numbers.

22   It is worth noting that in terms of the GI

23 difficulties, including the hemorrhages, aspirin-intolerant

24 patients were excluded from this trial at the outset. It is

1 also interesting to note that in terms of the GI bleeding

2 there is about a 30% reduction in hospitalizations for GI

3 bleeding in the clopidogrel-treated patients.

4   The neutropenia and thrombocytopenia is low in

5 both groups, in spite of the fact that a very intensive

6 effort was made to look for neutropenia and

7 thrombocytopenia, again because of what we knew about

8 ticlopidine. The neutropenia patients will be discussed in

9 more detail at your request subsequently by Dr. Beaumont.

10   (Slide)

11   So in terms of what we know about safety, we have

12 15,000 patient-years of experience on clopidogrel. There is

13 good overall tolerability for the drug. There is a low

14 discontinuation rate due to adverse events, and it was

15 similar to that for aspirin. There was a low incidence of

16 rash or diarrhea. You saw those numbers. There was no

17 excess of thrombocytopenia or neutropenia in the two groups.

18 You will hear more about that. There was significantly less

19 GI bleeding and better overall GI tolerability for

20 clopidogrel than for aspirin.

21   (Slide)

22   The key points that I would make would be that

23 this was a large, well-conducted study, we say modestly.

24 Clopidogrel was compared with an effective active control,

1 namely aspirin. Clopidogrel was more effective than aspirin

2 in the predefined primary analysis, and clopidogrel has a

3 safety profile at least as good as aspirin.

4   Thank you very much.

5   DR. PACKER: I would like to pause at this point

6 in time, and have Dr. Easton remain at the podium, and open

7 the discussion of CAPRIE to the entire Committee. Again, in

8 order to try and establish some orderly discussion of

9 issues, I would still ask the Committee to leave the issue

10 of heterogeneity as well as the issue of a comparison to a

11 putative placebo to a little bit later on in today's

12 presentation because we will be getting additional relevant

13 presentations on these issues. But we can discuss any other

14 issues which are of relevance to the trial at this

15 particular point in time.

16   Let me ask Dan Roden, who is the primary medical

17 reviewer for the Committee, to begin the discussion. Dan?

18   DR. RODEN: I promised I wasn't going to say very

19 much because I don't really want to hear my own voice, and I

20 want to hear the discussion of the heterogeneity issue

21 because I think the two issues that Milton has told us we

22 are not allowed to discuss are the ones that are key to the

23 decision we are going to make.

24   Just let me ask though about the issue of sudden

1 death.   Is this the right time for that?   There is an excess

2 of sudden death in the clopidogrel-treated patients and I

3 would just like some comment from that end.

4   DR. EASTON: Whatever is your preference. Dr.

5 Pilgrim is prepared to speak to that issue in whatever

6 detail you would like. So, you may either have it now or

7 wait until she has made her presentation, whichever you

8 prefer.

9   DR. PACKER: I think we need to have some

10 discussion on the specific issues related to the general

11 topic of endpoints because the issues of endpoints cover a

12 number of varied aspects of that. So, this would be a good

13 time to do that. So, if the sponsor has data on the issue

14 of sudden deaths, this would be a good time to present that

15 data.

16   DR. PILGRIM: I am Alison Pilgrim, Vice President

17 of Cardiovascular Clinical Research at Sanofi.

18   We have looked at the events reported in the

19 CAPRIE trial in considerable amount of detail.

20   (Slide)

21   I think the best way to address this question is

22 to show the individual endpoints that were reported during

23 the trial, and breaks them down across the three qualifying

24 condition subgroups.

1   Deaths in the CAPRIE trial were classified into

2   five different categories, and that was the only

3   classification that was required under the protocol. They

4   were grouped as fatal myocardial infarction, fatal ischemic

5   stroke, death from hemorrhage, death from clear non-vascular

6   causes, and there has to be a substantiated cause of death

7   and then, finally, other vascular death. This last category

8   was really a category by exclusion. It was deaths that

9   failed to meet the first four categories.

10   Overall, in the primary endpoint cluster there

11 were 226 other vascular deaths on clopidogrel and 226 on

12 aspirin. However, they were not distributed absolutely

13 evenly between clopidogrel and aspirin in each individual

14 subgroup. We saw similar numbers in the stroke subgroup, an

15 excess on clopidogrel in the myocardial infarction subgroup,

16 and an excess on aspirin, a similar size excess, in the

17 peripheral arterial disease group.

18   Having seen some variation between the subgroups

19 which, with the small number of events we observed, could

20 very well have been a chance random variation, we did,

21 however, ask our central validation committee, who had

22 validated on a blinded basis all the primary outcome events

23 in the CAPRIE trial, to go back and have another look at the

24 other vascular deaths.

1   (Slide)

2   The way that these were classified relates more to

3   the circumstances of death than to specific diagnosis. It

4   was based on information that was originally provided by the

5   investigator to the validation committee and at that point

6   we were merely seeking to make the distinction between fatal

7   MI, fatal stroke, hemorrhage, non-vascular and other

8   vascular.

9   The validation committee went back and used this

10   information to put the other vascular deaths into the

11   categories shown on the left. Many of the sudden deaths

12   that were reported in this further subclassification were

13   not witnessed. They simply indicated that the patient

14   seemed well and was usually found dead the following

15   morning. As you can see, there is a slight excess of

16   witnessed deaths, but it is only 4 events more in the

17   clopidogrel group than in the aspirin group, and also a

18   slight excess in the unwitnessed group. But most of these

19   patients did not have autopsies performed. So, we don't

20   know what the actual mechanism of death was. It could be a

21   massive MI; it could be a stroke. There could be many

22   causes of that sudden death.

23   DR. PACKER: Dr. Pilgrim, I am sorry, I think this

24   slide refers to deaths which were part of the primary

1 endpoint definition --

2   DR. PILGRIM: Yes, it does.

3   DR. PACKER: Do you have a categorization of all

4 deaths in the trial?

5   DR. PILGRIM: Of? Sorry?

6   DR. PACKER: All deaths?

7   DR. PILGRIM: All deaths?

8   DR. PACKER: Yes. These are --

9   DR. PILGRIM: These are the people that were

10 included in the primary cluster.

11   DR. PACKER: Right, this is only deaths that

12 represent the first event.

13   DR. PILGRIM: Yes.

14   DR. PACKER: But these are not all deaths that

15 occurred in the trial.

16   DR. PILGRIM: No.

17   (Slide)

18   We only have a more detailed slide that breaks

19 this down by qualifying condition, as well as giving the

20 totals at the end. The findings are not very different from

21 the first events. Again, there is a slight excess on

22 clopidogrel for both witnessed and unwitnessed sudden deaths

23 but the numbers change very little.

24   It is difficult to read from here, but we have 45

1 witnessed sudden deaths on clopidogrel compared to 40 on

2 aspirin, and 67 versus 62 for unwitnessed sudden deaths. So

3 the difference between the 2 treatment groups is very small.

4   DR. PACKER: Dan, I think the issue that you were

5 asking about was the MI subgroup, the difference between 22

6 and 10 and 24 and 9.

7   DR. RODEN: Yes. The other question I have is

8 what the definition of death was due to myocardial

9 infarction because this is the other vascular deaths. Was

10 there a protocol specified death due to myocardial

11 infarction? Were there criteria set out to define those

12 deaths, or was that just an investigator judgment?

13   DR. PILGRIM: No. We had very specific criteria

14 that had to be met by any myocardial infarction in the

15 study, and we have those on a slide.

16   (Slide)

17   Basically, the event had to have at least two of

18 characteristic chest pain, enzyme elevation, clear-cut new

19 ECG changes. Then to be categorized as a fatal myocardial

20 infarction, death had to occur within 28 days of the acute

21 MI, in the absence of other causes or explanations for

22 death.

23   DR. RODEN: So, in your subgroup you had 26

24 patients with ischemic chest pain who died. Those were not

1 sudden deaths but you didn't document myocardial infarction?

2   DR. PILGRIM: If we could go back to the previous

3 slide?

4   (Slide)

5   DR. RODEN: It says ischemic chest pain. That is

6 not a myocardial infarction and not a sudden death?

7   DR. PILGRIM: Well, it didn't meet the validation

8 criteria for myocardial infarction but the patient was

9 reported to have ischemic chest pain prior to death.

10   DR. DIMARCO: So go back to the next slide that

11 you showed.

12   (Slide)

13   I guess this is not a question of philosophy --

14 well, maybe it is. Death is death I suppose, but that

15 second bullet category, I would maintain, is more likely to

16 be arrhythmic than anything else, death 28 days after

17 myocardial infarction without other causes. Is there any

18 way to break that out, that particular bullet?

19   DR. PILGRIM: No, the central validation didn't

20 break that category down.

21   DR. DIMARCO: Well, it is probably a small point.

22   DR. CALIFF: I have two questions about endpoints,

23 I have a million other questions but just on the endpoints.

24 The first would be just a good description of the process of

 1   the endpoint determination. You say it was blinded. Was

 2   that always the case? How were disagreements handled? I am

 3   particularly interested, which is really the second

 4   question, in events that were classified non-vascular death,

 5   and I would be interested in the rest of the Committee's

 6   opinion. An endpoint was chosen of vascular death, which

 7   bothers me because patients don't generally care how they

 8   die if they are dead and they are randomized to one

 9   treatment or the other. It looks like if non-vascular death

10   is included the results are not -- if you believe in 0.05,

11   you might not get exactly the same result in the trial. So

12   one is the process of validation and the second is what

13   these non-vascular deaths were, if they can be broken out

14   further.

15   DR. PILGRIM: Dr. Easton was deputy chairman of

16   the validation committee so I think it is best if he

17   addresses how events were actually validated.

18   DR. EASTON: When forms came in to the data center

19   in Hamilton for any outcome event, fatal or otherwise they

20   were then expunged of all identifying data that would

21   suggest who the patient was. Of course, the entire trial

22   was blind all the way to the very end. Then they were sent

23   out to two reviewers. If it was a stroke event they were

24   sent out to a neurologist. If it was a myocardial

1 infarction event according to the investigator, it was sent

2 out to two cardiologists. If the reviewers, the two

3 reviewers agreed with each other and with the investigator,

4 that was the end of it. If the two reviewers agreed with

5 each other but didn't agree with the investigator, then the

6 central office went back to the investigator to request

7 additional information and clarification, and sometimes the

8 investigator would agree that a mistake had been made and

9 they just mis-checked it, or whatever.

10   But to get at what might be your main question, if

11 it came to an issue that the two adjudicators centrally and

12 the investigator disagreed, that case came to the committee,

13 the whole committee, was reviewed and then the final

14 judgment was made by the central validation committee.

15   As it turns out, at the end of the trial we know

16 that the result is identical whether we look at the

17 adjudicated events or whether we just take the raw

18 investigator events. I don't know if I have answered your

19 question.

20   DR. CALIFF: Yes.

21   DR. EASTON: But we did simply categorize the

22 patients into one of those death categories, and we did not,

23 for example, try to identify in the other vascular deaths

24 precisely what kind of a vascular death it was. In other

 1 words, we didn't have specific criteria to identify sudden

 2 death. If the investigator said it was a sudden death and

 3 the adjudicators agreed that it was another vascular death,

 4 then that closed the category.

 5   DR. CALIFF: That sounds like a great process and

 6 you should be commended on really doing it the way you did

 7 it. I was more interested though in the non-vascular deaths

 8 which seemed to be a little bit maldistributed against

 9 clopidogrel. Are those broken down? I mean, you know, auto

10 accidents?

11   DR. EASTON: Yes. Yes, they are. I don't know if

12 we can produce a slide of that for you but, for example, I

13 think even on some of the things we would call obvious we

14 often struggled with a patient with terminal cancer who then

15 has a stroke, and we argued about whether this is

16 prothrombotic state due to the cancer. The issue is that,

17 first of all, we tried to always go with the judgment of the

18 investigator when that was possible but even with an

19 automobile accident there would be times when the patient

20 clutched his chest and slumped over the steering wheel and

21 drove off the road, and there would be times when it was a

22 single care accident and they were drinking. So, again, a

23 judgment would be made. But if it required a judgment, then

24 the patient was put in the other vascular death category.

 1 You had to be really able to say with confidence that this

 2 was a non-vascular death. Otherwise, it went into the other

 3 vascular death category.

 4   DR. CALIFF: This just a point for the Committee,

 5 and this is always confusing but this is the reason why I

 6 always favor total death instead of vascular death in how it

 7 should be considered because there is an excess of 21 in the

 8 non-vascular death category. I don't know what that means.

 9   DR. PACKER: Let's discuss it because it is an

10 important issue not only for this trial for trials in

11 general. Let me ask a question on that because I think this

12 is on the minds of the entire Committee.

13   Just suppose a patient was hospitalized for sepsis

14 and died of a pulmonary embolism. How is that death

15 categorized?

16   DR. EASTON: That would be a septic death. I say

17 this now. As you can imagine, there was great discussion

18 that took place on a case like this. In general, my

19 response to that would be an attempt was made to determine

20 what the illness was without which the patient would not

21 have died. So, in your case I think it would have been

22 sepsis.

23   DR. PACKER: And if a patient was hospitalized for

24 bypass surgery and developed pneumonia?

1   DR. EASTON: Developed pneumonia after the

2 surgery?

3   DR. PACKER: Sure.

4   DR. EASTON: Any death that was linked to surgery

5 for a vascular cause was called a vascular death. In this

6 case other vascular because it is not MI or stroke.

7   DR. RODEN: And how about a patient who is at home

8 three weeks following a myocardial infarction and is found

9 dead the next morning?

10   DR. EASTON: That patient would have been called a

11 myocardial infarction death if it occurred within 28 days

12 and he didn't have a gunshot wound or something.

13   DR. RODEN: I guess this goes back to what Rob

14 said, and having gone through this exercise a number of

15 times, I think in the end there is something perverted about

16 voting about the cause of death. People die for some

17 reason; we just don't know what it is but I would have

18 certainly called that a sudden death, not a myocardial

19 infarction death.

20   DR. PACKER: Rob, you congratulated the sponsors

21 on doing it the way they did. But I am curious, what did

22 they achieve by doing it the way they did?

23   DR. CALIFF: Well, I congratulated then on the

24 process of having blinded reviewers. Actually, I think one

1 of the most important things, to me, which we may get to

2 later is understanding the certain cases, the uncertain

3 cases, and validating that the result was the same by the

4 investigator call and a blinded adjudication. I did not

5 congratulate them on the choice to not have all-cause

6 mortality as a component of the primary endpoint. I think

7 that is a terrible idea, to have only vascular death, for

8 the reason that we just discussed. You never really know

9 and you end up voting. You know, if somebody runs off the

10 road and into a stop sign, was it a sudden death? You have

11 been over these a hundred times. Unfortunately, in this

12 particular trial it looks like if you look at all-cause

13 mortality the results are basically the same, if you are

14 really hung up on p values of 0.05. I am not sure from what

15 I have read but you might have that data. It may be

16 slightly over 0.05.

17   So, there are two different things. The process I

18 think is really worthwhile because we have seen a number of

19 trials where the results looked different by the

20 investigator and a blinded reviewer, and I think that is

21 important to know. When they look the same, that really

22 adds, from my perspective, credibility to the way the trial

23 was done and I think that is a big plus for this trial.

24   DR. PACKER: John, you mentioned, which has now

 1   emerged many times, does it really matter to the patient how

 2   they die. A dead patient is a dead patient.

 3   DR. DIMARCO: Yes, I agree completely with Rob.

 4   Total mortality is the thing that is the most meaningful

 5   here. But I also agree that looking at the mechanisms of

 6   death can pick out outliers. There we had 121 versus 114

 7   neoplasms. If you had seen 191 neoplasms versus 100 that

 8   would give you some further ideas if there was a change in

 9   total mortality. So, I agree that classifying the deaths is

10   useful. It just makes a problem when it is used as your

11   primary endpoint, and total mortality should probably be the

12   primary endpoint.

13   DR. PACKER: Are you saying that sponsors or

14   investigators should classify death or subclassify death not

15   as an establishment of efficacy as an endpoint, but as an

16   insight into what mechanisms might be operative if one had

17   an effect on all-cause mortality?

18   DR. DIMARCO: Yes, because I think there is just

19   so much more uncertainty in the classification that I,

20   frankly, can't decide a lot of times what it is and when you

21   are voting, you know, and you get a 4-3 vote, which is not

22   uncommon on these committees, you just have a lot more

23   uncertainty with mechanisms, particularly when you have 20

24   different mechanisms. So, it is not always clear and total

1   mortality is a thing you are pretty sure of.

2   DR. TEMPLE: One of the things about

3   classification is that they are not necessarily mechanistic.

4   My assumption is that most people who die of an MI, or at

5   least a large fraction of them, have arrhythmic deaths. So,

6   the distinction between two isn't particularly mechanistic.

7   The division by particular cause of death is

8   almost always a big problem. A lot of trials have

9   distinguished vascular deaths from others. That is still a

10 problem too. It is worth remembering, and I am sure Dr.

11 Gent will remember this, that when we looked at ticlopidine

12 the survival advantage -- I may have this slightly wrong --

13 in one of the studies was driven almost entirely by non-

14 vascular deaths. I remember Dick Kronmal arguing, hey, that

15 was our endpoint; we have to go with it. But the Committee

16 was nervous because it was sort of improbable.

17   So, you can pay in a variety of ways. I mean, it

18 would be sort of implausible that an antiplatelet drug would

19 beat another drug by decrease in cancer death. That would

20 be a novel hypothesis. In that case, use of all-cause

21 events would raise some eyebrows, for what it is worth.

22   DR. PACKER: I think it gets a little confusing

23 also because I think in the document when investigators were

24 asked to categorize death as an adverse reaction, sudden

1 death was put into the category of non-vascular death but it

2 was out into the category of death in body as a whole which

3 is a true statement, of course --

4   (Laughter)

5   -- but not particularly useful. Marv?

6   DR. KONSTAM: Yes, I just have two comments. My

7 main comment is going to be really supportive of what others

8 have said. I do want to say that I am looking forward to a

9 statistical discussion of the validity of the results, and

10 we have had a lot of discussion on the panel about the

11 importance of examining the prestated primary endpoint in

12 terms of first assessing is it a positive or negative trial.

13 I don't think any of my colleagues on the Committee are

14 going to digress from that statistical point. I just wanted

15 to say that.

16   Having said that, I really do want to confirm and

17 support really what the other panelists have said, that in

18 conducting trials and designing primary endpoints I

19 personally would urge sticking to all-cause mortality and

20 looking for causes of death, as Milton suggests, as some

21 kind of indicator, hypothesis generator about what is going

22 on.

23   I will just point out as a point of evidence that

24 experiments have been done where adjudicated causes of death

1 have been performed and then sent blindedly to other pseudo-

2 endpoint committees and the results have come out very

3 discrepant. So, I think this is evidence for what the other

4 panelists are saying, urging that primary endpoints really

5 include all-cause mortality.

6   DR. DIMARCO: Can I ask one more question about

7 the deaths? Do we have any idea how many of these occurred

8 in hospital or out of hospital?

9   DR. EASTON: The all-deaths?

10   DR. DIMARCO: All deaths.

11   DR. EASTON: Can anyone answer that question? In-

12 hospital mortality? We can certainly seek that out for you

13 to see if we can answer it.

14   DR. DIMARCO: You know, one of the things is

15 getting information back. The committee may be great and

16 the committee may have no biases, but the information you

17 get from the field is often very poor. Obviously, in the

18 hospital is sometimes better than outside the hospital but

19 it really gets to be a real problem.

20   DR. MOYE: I wonder if I could just change the

21 direction of the conversation for a moment.

22   DR. PACKER: Entirely for purposes of organized

23 flow, I would like this to focus on the endpoint issue, if

24 we could.

1   DR. MOYE: Yes, but it is another issue involved

2   in the endpoints. I wonder if I could hear some comment

3   from the investigators about their expectation of efficacy.

4   Sizing these large trials is a very delicate business, and

5   from what I gathered in the protocol the trial was sized

6   originally at 15,000 patients, and the expectation was that

7   they would be able to demonstrate an efficacy of about 12%.

8   Now, I understand the sample size has been increased to just

9   over 19,000. But I didn't see any change in the expectation

10   of efficacy. So my belief is that the investigators were

11   looking for a 12% efficacy, and there being any efficacy

12   less than 12% would not fall in the critical region and,

13   essentially, was a finding not worth noting. Yet, at the

14   end of the trial we have an efficacy of 8.7%. Now, that

15   happens to be statistically significant because you don't

16   have 15,000 patients; you have over 19,000 patients. But

17   still the efficacy, seems to me, to be a third less than

18   what the investigators had initially stated was the basis on

19   which they sized the trial and, in fact, would have been a

20   finding that would have been non-significant in the original

21   design. So, should we be impressed with 8.7% efficacy if

22   that is a third less than what the investigators themselves

23   said was the efficacy worth detecting?

24   DR. EASTON: Well, I have a couple of responses to

1   that. It would go like this, first of all, as I mentioned,

2   I think there is the 8.7% relative risk reduction. I

3   mentioned that if you convert that to an odds ratio

4   reduction it becomes 9.4% and that is very consistent with

5   what was seen with ticlopidine across all the trials with

6   ticlopidine. So, the expectation would be that we would see

7   that number.

8   Now, if you also recognize that we used the

9   ischemic stroke, MI or death, whereas the antiplatelet

10 trialists used all stroke, including hemorrhagic stroke,

11 when we add in the hemorrhages to ours, that raises the 9.4

12 to 10.2. So, I think that the comparability of what we saw

13 to what has been seen previously with the sister drug was

14 nearly identical.

15   I think the issue with the patient number was that

16 we were recruiting at 138% of what we expected to recruit

17 and it was clear that we had the 15,000 patients in, in 2

18 years and 3 months when we really expected to get them in

19 for 3 years. That resulted in a lot of patient-years at

20 risk that needed to be adjusted for.

21   In addition, we were looking blinded at the

22 overall event rate, both groups together, and could see that

23 it was running lower than that which was predicted. So, the

24 adjustment upward was based on the fact that the trial was

1 outperforming itself and the patients were healthier than we

2 had anticipated they would be at the beginning.

3   So, my sense of it is that no modification in the

4 expectation took place. I happen to think we were unlucky

5 at the end of the trial in seeing 8.7 instead of 10.7, but

6 that is a guess.

7   DR. FISHER: May I make a comment?

8   DR. EASTON: Sure.

9   DR. FISHER: I have a little trouble understanding

10 your comment, Lem, for the following reason: As we all

11 know, approximately half the time the observed rate will be

12 less than the true rate and about the other half will be

13 greater. When a trial is powered, part of the point of the

14 power is so that the times you get these lower estimates, if

15 you want 90% power, is to get out there. So there is

16 nothing surprising about this. Indeed, if you look at the

17 confidence intervals there certainly is no proof whatsoever

18 the true rate is not greater or less than the observed

19 estimated, but I have never heard of something like that

20 actually said -- well, do you still believe your trial

21 because you came out a little bit less. There are

22 substantive arguments I think and issues we have to address

23 but, to me, this isn't one of them.

24   DR. MOYE: Well, it just seems that the

1 investigators do have the authority at the beginning of the

2 trial to state their expectation of the benefit they would

3 like to see from the intervention, and the expectation here

4 was that they would see 12% reduction.

5   DR. FISHER: I thought their expectation was that

6 the true rate was 12% and that they would see variability

7 about that, which both of us could compute based on the

8 number of events.

9   DR. MOYE: Well, there was certainly variability

10 about the event rates, but about the benefit that was seen,

11 which is essentially the boundary for the critical region,

12 there really isn't much variability about that. Right? I

13 mean, the variability has to do with the actual test

14 statistic. What the investigators had to say was that they

15 were looking for 12% reduction.

16   DR. FISHER: Well, if that is what they actually

17 did, and I know Dr. Gent is smarter than this, but if they

18 thought the true rate was 12% and they were absolutely

19 determined to observe it they were in a tough position

20 because with any sample size, as I mentioned, half the time

21 you are going to observe less. I am not clear what critical

22 region you are talking about. Apparently it is not the

23 critical region for the test statistic it is, rather, some

24 clinical benefit below which they wanted to observe things.

1 I don't know if that was specified. I can't recall reading

2 that in the protocol.

3   DR. PACKER: Udho, is the issue on endpoints?

4   DR. THADANI: Yes.

5   DR. PACKER: Okay.

6   DR. THADANI: I think it would be nice to look at

7 the data with the total deaths included in the primary

8 endpoint. The question I will ask is about another primary

9 endpoint, myocardial infarction. In their criteria they are

10 using enzymes or Q-wave. There are a lot of missing data

11 points. Patients were not seen at each visit if they

12 dropped out, for whatever reason. The question comes up how

13 many could have been missed who had infarction and were not

14 in the data base. I realize this was in both groups. So, I

15 think the missing data points, how many patients were not

16 followed after they dropped out, and how that could have

17 influenced it, I need some reassurance on that. At least

18 that the ECG were reviewed or the patients were never seen

19 at the last entry point, and I think that will have

20 important implications in many trials, including this one.

21   DR. EASTON: Right. Well, every patient in this

22 trial was followed, whether they were on or off therapy, to

23 all of the scheduled visits. The issue of how many visits

24 were missed is an issue that we have specifically been asked

1 to addressed, and it is going to be addressed shortly.

2   DR. PACKER: Can we hold on that issue for a

3 moment because it is not an issue directed to what we really

4 want to focus on now, which is the endpoint issue. So, with

5 your indulgence, hold your response on that just for a few

6 minutes because I really want to keep the Committee focused

7 on what the issues are in an orderly fashion.

8   Udho, aside from the endpoint?

9   DR. THADANI: Yes, I think the other thing is if a

10 patient had chest pains three days before the visit, and you

11 happened to see him and he said, oh, I had half an hour

12 pain. The question always comes up in this so-called

13 endpoint, but in my judgment, you know, it is difficult to

14 know if the patient had an infarct or not because you are

15 using the criteria of enzyme plus duration of pain. So, is

16 there any data on how much that happened? I presume you

17 kept diaries on duration of pain. It would be nice to know

18 how many patients could have been missed who had complained

19 of prolonged pain and the enzymes are missing, or something.

20 This is in addition to those patients who actually came to a

21 visit. It is not that there are missing data points but

22 they could have come for a visit and had some episode but do

23 not meet the criteria.

24   DR. EASTON: I will see if we can give you an

1 absolute number on that but there is no question about it.

2 A patient could have come in, talked about chest pain two

3 weeks ago, had no enzymes, no cardiographic change and,

4 therefore, a suspect MI but that couldn't be documented.

5   Similarly with the stroke patients, they may have

6 come in and told you about an episode of left-sided

7 weakness. They tell you it all went away in 24 hours and

8 you don't really know whether it did or didn't when you are

9 seeing them a month later. So, it is possible that they

10 actually had a mild stroke rather than a TIA.

11   To answer your question about whether we have

12 absolute numbers on those kind of events, I would think the

13 answer is no, but it is low. Can someone help me with that?

14 We do not have that. But as you point out, they should have

15 been equal in the two groups.

16   DR. THADANI: We don't know that. I am presuming

17 that the number might be the same. The problem with

18 endpoints, you know, death is one thing; stroke is another.

19 I think that becomes very relevant when you are combining

20 the endpoint results, at least for myself.

21   DR. D'AGOSTINO: I would just make a comment about

22 the overall deaths. I think overall deaths is very

23 important obviously. It is a different endpoint and it is a

24 different study. So, when we look at the primary analysis

1 and we look at the p values and so forth, I don't think we

2 can then say let's replace the primary analysis with overall

3 deaths. I think it is very important for us to say how the

4 overall deaths fit into the full picture. I think it is

5 very important to understand that.

6   The thing that I was caught in reading the

7 material was that when there was a discussion about the

8 death and there was a lack of clarity, it was always put

9 into the vascular deaths, and you have said that again. I

10 guess I would just like a sense of how often that happened

11 because, again, being involved in some of these endpoint

12 committees and what-have-you, oftentimes people just sort of

13 shrug their shoulders and go along with it; other times they

14 are really hard-nosed, and I would just like to get a sense

15 when it was not clear what the deaths were how many times

16 the vascular was, in fact, used.

17   DR. EASTON: I think I can only give you a sense

18 at this moment. I can certainly tell you that the agreement

19 rate between the investigators and the reviewers was

20 extremely high over this issue of whether it was a vascular

21 death or non-vascular death. In fact, when there was an

22 identified disagreement, often when you went back it was

23 that someone had misinterpreted the criteria and it was

24 resolved by discussion.

1   I am trying to get a handle on giving you an

2   honest answer on the question of how often did you struggle

3   over whether the automobile death was due to a stroke or due

4   to --

5   DR. D'AGOSTINO: Well, the point is that there is

6   a difference of 21 deaths in the 2 groups. It could have

7   been a difference of 55 and so forth, and these p values

8   would jump all over the place depending on that. So I think

9   we really do need some comfort in how rigorous that endpoint

10 was. I think it is very important to get a handle on the

11 sense of it, and I think you are giving us an answer.

12   DR. CALIFF: Ralph, actually this is a question

13 for you based on what you said, because I don't pretend to

14 know the answer and I hope that in the process of going

15 through this trial we will learn something that can be

16 applied in the future. But you said we shouldn't try to

17 replace the primary endpoint just because we think, as a

18 panel, we know one that is better. Obviously it was

19 specified. But if you have a case where the primary

20 endpoint is vascular death and it is statistically

21 significant, and then you look at all-cause mortality as

22 part of the endpoint and it is not, what would you conclude?

23 Would you conclude that the treatment reduces vascular death

24 but not your total risk of being dead?

1   DR. D'AGOSTINO: That is one possible explanation.

2 Another possible explanation is that the sample size isn't

3 big enough to have the impact of the cardiovascular death

4 show itself in the total mortality. By looking at vascular

5 versus non-vascular and putting the two together you

6 introduce another source of variation and you just may not

7 have a big enough study to swing the vascular deaths showing

8 themselves through the total mortality.

9   DR. CALIFF: I guess later we will get

10 specifically to what you concluded about this.

11   DR. PACKER: Well, Rob, this is an important

12 issue. Although we will have an opportunity to answer

13 specific questions posed to the Committee by the Agency, the

14 issue that we are talking about now is an issue that is very

15 relevant to CAPRIE but also very relevant to all trials that

16 are being conducted now, and in the future, in

17 cardiovascular disease that have cause-specific events.

18 When I say cause-specific events I don't mean composites; I

19 mean that the events which are included in the primary

20 endpoint are events which are of a specific cause as opposed

21 to taking all-comers. Rob and Marv and John and many others

22 on the Committee, and I think I heard no member of the

23 Committee that actually advocated using cause-specific

24 classifications. I think every member of the Committee said

 1 that they preferred a less categorized approach to the

 2 finding of the primary endpoint.

 3   So, for example, a less categorized approach in

 4 CAPRIE would be all deaths plus all MI and all strokes.

 5 That would be a less categorized approach that would include

 6 all deaths so that one would avoid partially the potential

 7 bias that is inherent in the classification process, and if

 8 not bias, then arbitrariness at least.

 9   So, my question to the Committee that I would like

10 some comment on because it has very important implications

11 for trial design is that you are telling sponsors now, and

12 there are lots of sponsors in the audience, that you would

13 like to see primary endpoints which are more general and,

14 therefore, less potentially biased, but you have one here

15 that is very cause-specific but it was their primary

16 endpoint. We already know that we need to be careful about

17 substituting our primary endpoint for their primary

18 endpoint. So my question is if we tell the sponsor, please,

19 go out and take a more general approach to the

20 classification of primary endpoints, and they say, sorry, we

21 are not going to do it; we are going to specify our endpoint

22 and we will make it as cause-specific as we want because if

23 we win on it, we have won. Then how does our opinion

24 matter? How does the message of what is desirable about a

1 general endpoint get transmitted to the community so that

2 the kind of endpoints that are developed are more in keeping

3 with the minimization of bias? Rob?

4   DR. CALIFF: Based on the discussion, it would be

5 interesting for the investigators to say why those cause-

6 specific events. The intent of the trial was to tell a

7 doctor what to advise the next patient. I would have

8 thought the patient would want to know what is my risk of

9 being dead, not what is my risk of dying of some particular

10 cause. So, I am interested in what the investigators think.

11 But, you know, I would think the answer to your question is

12 that we will deliberate, I guess, on how we interpret this

13 particular result and that will send a message to people, at

14 least about this particular Committee. It may not be true

15 of all committees in the future, and we have limited terms.

16   DR. KONSTAM: To me, the issue is a statistical

17 question and then clinically relevant questions. I think

18 that in trying to interpret the statistical validity and

19 strength of the primary observation, my own feeling is we

20 are going to wind up having to stick to the predefined

21 primary endpoint. Then in terms of clinical interpretation

22 and deciding what this really means, we will have to move to

23 really scrutinizing what we believe are clinically relevant

24 endpoints.

 1   But I just want to point out one thing that ought

 2   not to be lost sight of in addressing Rob's question about

 3   what you do when the vascular deaths drift to the other

 4   direction and you go to all deaths. I just want to point

 5   out that deaths of any variety are not really driving this

 6   primary endpoint. I just don't want to lose sight of that

 7   point. The vascular death story is not driving the primary

 8   endpoint. If you shift gears to all-cause mortality, it

 9   shifts a little bit but not by much. So, I think this is an

10   extremely important discussion statistically and then

11   clinically conceptually, but I don't want to lose sight of

12   the fact that the fatality thing is not really driving the

13   primary endpoint in the aspirin-clopidogrel comparison.

14   DR. PACKER: Marv, that may be true and, by the

15   way, I do think that the concept of taking sort of a duality

16   of prospective approaches is useful, but death is always the

17   worst outcome. It is always includable in any definition --

18   DR. KONSTAM: It is the most important one.

19   DR. PACKER: And the most important one. So,

20   although a sponsor may produce a result which is totally

21   neutral on mortality and, therefore, all of the action is in

22   the non-fatal events, mortality is so important that if it

23   were totally neutral and became even more neutral if you

24   included all deaths, the effect on non-fatal endpoints may

1 be of minimal clinical relevance.

2   DR. KONSTAM: Yes, i agree with that completely.

3 You may wind up concluding that you have a positive trial of

4 no clinical importance. No, I fully agree with that. Just

5 to focus on the issue of what happens here when we move --

6 and I agree with completely with everything everybody said -

7 - moving from vascular deaths to all-cause mortality which I

8 would have preferred to be included in the primary endpoint.

9 I just don't want to lose sight of the fact that when we

10 come back to the primary endpoint, yes, it does move from a

11 p of 0.04 to 0.06 or something, but it doesn't move much.

12   DR. LIPICKY: Before you send the total message, I

13 am a little bit worried from the vantage point that I could

14 conceive of totally wiping out all cardiovascular problems

15 in people, but I know they would all die, and total

16 mortality would be the same in both groups depending on the

17 time course of the trial.

18   DR. PACKER: Only a hundred years later.

19   DR. LIPICKY: Well, okay, maybe. Depending on the

20 time course of the trial. Things other than the thing that

21 may be affected by the therapy are noise in the background.

22 Don't misunderstand, I understand total mortality; I am more

23 comfortable with that but we are sort of making it sound

24 like it is the only thing one should do. I would like a

1 little longer discussion and more careful thought and not

2 have it come out as a transient to another deliberation.

3   DR. PACKER: Ray, let me clarify what I think the

4 Committee is saying, but let's make sure that, in fact, the

5 Committee is saying this. What we are not saying is that we

6 want every trial to be a survival trial for all-cause

7 mortality. We are not saying that. We are saying that

8 composite endpoints are perfectly rational approaches to

9 deciding whether there has been a drug effect. What we are

10 saying is that how one chooses the component of the

11 composite, one needs to be careful.

12   DR. FISHER: Could we put up a slide on all the

13 deaths in the trial, just to put it in perspective?

14   DR. PACKER: Lloyd, hold on; we are having a more

15 general discussion now as opposed to the specific discussion

16 on CAPRIE, just for one moment.

17   What we are saying is that when one chooses the

18 components, the more one selects cause-specific components

19 the more concern one raises about the generalizability and

20 clinical relevance of the result. Is that a fair statement?

21 Does the Committee feel comfortable with that statement?

22 Udho?

23   DR. THADANI: Obviously, mortality is a very

24 relevant issue because it is in the primary endpoint, but

1 take patients with some neurological other causes of death,

2 even with neoplasia, one doesn't know if the neoplasm was

3 terminally responsible or if those patients could have died

4 of other vascular reasons -- you know, aortic aneurism

5 rupture. So, the important issue, unless you do autopsies

6 on everybody, is that one is never going to be sure

7 absolutely, although one might guess. So, unless you

8 mandate that every patient who dies in a trial will have, as

9 far as possible, autopsy, it becomes an issue again of

10 concern. So we are still guessing to some extent.

11   If you are going to make a composite endpoint, as

12 Milton said, I would like to see total mortality. I realize

13 it may make the trial more difficult and sample size might

14 go up. But at least it gives one confidence that you are

15 benefiting some and not harming some, whatever it is.

16   DR. FENICHEL: I think there is obviously a sort

17 of tension here between the discomfort with having the trial

18 of a cardiovascular product made foggy by the noise that is

19 unavoidable in traumatic deaths, and suicides and what-not.

20 On the other hand, one is uncomfortable with watching people

21 make judgments.

22   It seems to me that there are at least two ways to

23 deal with that. I don't mean to tell the Committee what

24 might be an appropriate decision on this matter, but it

1 seems to me, of the two ways, the sponsor has chosen the

2 better one. Certainly, we have seen trials where the causes

3 of death that are known, or the events that are known are

4 analyzed, strokes, say; let's say ruptured aneurisms, other

5 various specific vascular things, and then residual. The

6 question is do you include the residual or do you exclude

7 the residual.

8   Here, that is not what they have done. What was

9 set out in this protocol is things which could possibly be

10 vascular are included in vascular deaths, and the judgments

11 are of a different kind because they are not picking up

12 things and, well, maybe you didn't get all of those. They

13 are excluding things which one would perhaps always agree

14 were noise. So, there is a little difference of nuance

15 here.

16   DR. PACKER: Bob, there may or may not be. I will

17 give you an example. This is a trial in which a patient who

18 had a non-fatal intracranial hemorrhage, which I think all

19 of us would agree is a vascular problem, was not included in

20 the primary endpoint because they said it was not going to

21 be included in the primary endpoint, and it causes a general

22 problem. If a sponsor knows the pharmacological action of a

23 drug, both in terms of its efficacy and its safety, one

24 could define a primary endpoint so selectively that the

1 actions on efficacy would be easily identified and refined

2 and any adverse effect that would fall even in the same

3 system would, therefore, be excluded because the protocol

4 said so a priori.

5   DR. FENICHEL: Right. That is certainly true but

6 that is a slightly different point. I was just talking

7 about deaths.

8   DR. CALIFF: Actually, there is an issue here on

9 how you do interpret the small differences in deaths. But I

10 think we would all be more comfortable, since we give drugs

11 to effect total health and not some component of health,

12 people are concerned with how they are doing altogether. So

13 if you did have all-cause mortality and it was a significant

14 result, that would be the best you could do.

15   DR. FENICHEL: Oh, absolutely.

16   DR. CALIFF: You are saying if you are doing a

17 mechanistic trial where you want to understand mechanism,

18 looking at excluding the noise and the potential for noise

19 is good, in this case the investigators and sponsors took a

20 very conservative and laudable approach by putting

21 everything in vascular death unless they could specifically

22 target it, and I would agree with that.

23   DR. DIMARCO: The only thing is that when you do

24 that, you know, you have 28 deaths and we are attributing

1 that to drug and the 11 or 17 deaths excess we are saying is

2 chance. Somehow that strikes me. I think my feeling would

3 be that if you are going to include mortality in an endpoint

4 in a trial where there is a lot of mortality, you should

5 probably take all-cause, and you open yourself up to bias.

6 There are a lot of conditions where you don't expect a lot

7 of mortality and your endpoint is not going to be a fatal

8 endpoint and then you have to look at it, but it shouldn't

9 be a part of the primary endpoint. But if mortality is in

10 your endpoint I think you would probably want all-cause

11 mortality.

12   DR. TEMPLE: This isn't the first time this issue

13 has been discussed, obviously. There are a couple of

14 components of cause-specific mortality that need to be

15 addressed. One is the possibility that the assignment is

16 biased, and there is certainly a living, breathing example

17 of that. The mechanisms used here probably protected

18 against that, and that is highly relevant.

19   There is also some distinction between cause-

20 specific at the level of MI, sudden death etc., and all

21 vascular versus other. The former is almost certainly bogus

22 because most of the distinctions aren't meaningful. If you

23 die of an arrhythmia after an MI, why is that different from

24 dying from an arrhythmia without an MI? Well, it is

 1 different but it doesn't seem very meaningful. But the

 2 distinction between vascular and other is certainly present

 3 in an awful lot of trials. I guess I would say maybe there

 4 should be a workshop on that and important discussions, but

 5 that is a major issue.

 6   We always advise people in a trial where you don't

 7 expect too many other kinds of deaths to use all because it

 8 is easier and raises fewer questions of the kind that have

 9 come up today. But there is a lot of water under the bridge

10 and a lot of large trials that have used all vascular. I

11 guess one should consider the largeness of the problem.

12   The other point I guess I would make goes to what

13 Udho was saying. There are always events that you may not

14 detect in these things, that were below the limit of

15 detection. In general that is probably not a problem unless

16 there is a biased ascertainment or conclusion. If you set

17 an enzyme level for what is an MI, then you miss MI's that

18 don't reach that enzyme level. That is true but it may not

19 matter.

20   DR. PACKER: But, Bob, I do think this probably

21 does deserve a workshop because there are a lot of layers

22 and complexities to this issue and I think all of us who

23 would admit to having spent their time classifying events,

24 and most of us would like to probably forget that

1   experience, have questioned at the end of hours and hours of

2   spending time whether the process was worthwhile because

3   there is so much of that process which is arbitrary.

4   DR. TEMPLE: In trials like this where most of the

5   deaths were vascular you do have the luxury of using an all-

6   cause mortality endpoint. If you had a different

7   population, one that was susceptible to a lot of oncologic

8   deaths and things like that, you may make it impossible to

9   do a trial realistically by insisting on all-cause

10 mortality.

11   DR. CALIFF: Yes, but those are exceptions in this

12 forum.

13   DR. TEMPLE: In people with cardiovascular risk

14 factors you don't have to do that.

15   DR. LIPICKY: I suppose since that choice is

16 always there irrespective of what arbitrary decision one

17 uses to make what the primary endpoint, both analyses should

18 be done. As is usually the case, if there is discrepancy

19 between those two analyses then you wonder what is going on.

20 It is not clear to me that one has to make the decision and

21 say that one must always do something, all that one has to

22 do is say you have to look at both components.

23   In the case in point, when you do that it doesn't

24 really change the inference. So, although this is a general

1 problem, maybe we could go on.

2   DR. FISHER: I would just like to throw up one

3 slide because I think the Committee has been laboring under

4 a slight misconception, and the misconception I think arose

5 because if somebody had a primary event of MI and then died

6 three months later, they were not counted as a death.

7   (Slide)

8   But if you look at the overall total deaths in the

9 CAPRIE study, there are more in the aspirin group than in

10 the clopidogrel group. It is not statistically significant,

11 but the only reason I am putting this up here is it doesn't

12 give one huge cause for concern that there is a tradeoff,

13 that you are preventing vascular events with but the overall

14 net effect might be harmful.

15   So the tenor of some of the things that were said

16 -- I am not arguing with the philosophy and actually I agree

17 with Rob on that, but I would like to point out in this data

18 set that when you look at things overall, all-cause

19 mortality in both groups in the whole study, to the extent

20 that there is an excess, it lies in the aspirin group. Of

21 course, nobody would claim that is a statistically

22 significant difference or that there is a difference in

23 mortality, but it is comforting that it goes in that

24 direction at least.

1   DR. PACKER: Alright, Rob, very brief.

2   DR. CALIFF: I agree with you. I am not concerned

3   about a major tradeoff from an adverse effect. I am really

4   raising the issue because how are we going to interpret this

5   trial with regard to mortality. That is the question I am

6   raising. It is not a big effect to begin with but this is a

7   significant result and, therefore, is part of the composite.

8   If we say there is an effect on death and it is small

9   because the composite is significant, that is one

10   interpretation. Another would be if you put all-cause

11   mortality in the composite is no longer significant and,

12   therefore, we really can't say anything about death. I

13   don't know, I mean, it is confusing to me and I just wanted

14   to have discussion about it. It is not that I am concerned

15   that there is a hazard that would be dangerous to people.

16   DR. PACKER: Let's pause on this and let's go on

17   to the next issue that Udho mentioned, which was the

18   integrity of follow-up issue. Dr. Easton, you were going to

19   respond to the issue of integrity of follow-up?

20   DR. EASTON: No, I mentioned that we actually have

21   a little presentation to make on the issue of integrity of

22   follow-up.

23   DR. PACKER: Can you make that presentation now?

24   **Integrity of Follow-Up**

1   DR. BEAUMONT: My name is Daniel Beaumont. I am

2   Vice President of Cardiovascular Product Management at

3   Sanofi. I will explain how we followed the patients after

4   study drug discontinuation. I have a few slides to walk you

5   through this process.

6   (Slide)

7   The question is could we have missed some events.

8   It is a common concern for all clinical trials because we

9   want to minimize the number of patients lost to follow-up

10   and the number of events we could possibly miss.

11   For the vast majority of CAPRIE patients it was

12   not a concern because they all formal follow-up visits at

13   the study site including the last follow-up visit. However,

14   there was a small group of patients in whom it was more

15   difficult. These patients were those who had discontinued

16   study drug. For some of them, about two-thirds of them, the

17   last follow-up contact was not at the study site, as allowed

18   by protocol, and they could have missed one or more

19   intervening visits and also it was particularly important

20   for those patients who didn't have events counted in the

21   primary analysis.

22   There were an equal number of these patients in

23   both the clopidogrel group and aspirin, overall less than 3%

24   of the total population. But the question was could we have

 1 missed outcome events in these particular patients.

 2   (Slide)

 3   What did we do to minimize any possible loss of

 4 information in these patients? First, each CAPRIE patient

 5 had a defined final follow-up visit date, and investigators

 6 received a list of dates for all of their patients from the

 7 coordinating and method center. For logistical reasons, a

 8 14-day window was allowed around the final follow-up visit

 9 date.

10   Patients who could not have their final follow-up

11 visit date at the study site were followed by a specific

12 procedure in which we requested that contact be made by the

13 investigator or other qualified study personnel by whatever

14 means available. Most contacts were made by telephone, to

15 the patient. Other possible contacts were with the family

16 physician or with the relatives of the patient. In less

17 than 100 remaining patients who could not be located or who

18 refused to respond to our inquiries, we hired an outside

19 agency to help the investigator to complete these contacts.

20   So, we requested information on all of these

21 patients for vital status and non-fatal events. The events

22 we were looking for, as you have seen, are stroke and MI

23 with specific criteria, and these events are catastrophic

24 and probably would have led to hospitalization. It is

1 unlikely that the patient or the physician would have failed

2 to remember them when we contacted them.

3   Of course, any additional events which were

4 detected in that process during the close-out procedures

5 were validated by the central validation committee in

6 exactly the same way as the events detected during the

7 normal course of the study.

8   At the end of this process only 56 patients were

9 truly lost to follow-up, 30 clopidogrel and 26 aspirin.

10 These patients account for only 65 patient-years at risk out

11 of the total of 36,000 in the clopidogrel trial, less than

12 0.2%. So, overall, in CAPRIE in all cases other than these

13 56 the investigator has always indicated on the case report

14 form that he had contacted the patient and that he knew

15 whether or not an outcome had occurred. So, we are

16 confident that with these procedures we have absolutely

17 minimized the possible loss of information on outcome

18 events. Furthermore, the study was blinded throughout the

19 data disclosure and, thus, the manner in which the follow-up

20 visit data was collected was not biased.

21   (Slide)

22   However, the Agency asked us earlier this month if

23 source documents were available to support documentation

24 supplied on the case report form for these particular

1 patients who discontinued drug, and we were asked to verify

2 this in 70 clopidogrel who were selected because they were

3 particularly at risk of missing information. Because these

4 patients had discontinued the drug early their final follow-

5 up visit was not at the study site. They had not reported

6 an outcome event. In addition, they had had no contact for

7 more than one year. So they were particularly at risk of

8 missing information.

9   We also checked and there were 63 such aspirin

10 patients who met the same criteria so, again, the numbers

11 were balanced between the two treatment groups.

12   We gave detailed instructions to the centers to

13 review study documentation in order to confirm how the last

14 contact was made, who was contacted and if there was

15 documentation to the effect that the vital status was

16 checked and non-fatal events were looked for.

17   We have now reviewed all 70 cases in the 52

18 centers involved and the report of the information collected

19 has been provided to the Agency.

20   (Slide)

21   Summarized on this slide is that we have obtained

22 confirmation that there was documentation to support vital

23 status in all 70 patients. As regards non-fatal events,

24 documentation of the lack of an outcome event was complete

1 for 63 patients; 4 patients had uncertain documentation,

2 meaning the investigator could tell us, he knew that the

3 patient had not had a non-fatal event but there was no

4 specific documentation of that. Finally, for 3 patients

5 only the vital status could be determined.

6   The steering committee had prospectively

7 recognized this possibility and determined that it was

8 preferable to include information on vital status only in

9 the primary analysis than to have no information at all.

10   So, finally, 33 of the 63 aspirin patients who met

11 the same criteria were located at the same 52 centers. So

12 we obtained documentation for the 33 patients and the

13 pattern was nearly identical to the 70 clopidogrel patients.

14

15   So, in conclusion, having checked the sample of

16 patients at particularly high risk of missing information,

17 we are further reassured that the close-out procedure was

18 accurately followed by the centers, and that the potential

19 for missing additional outcome events in CAPRIE is very low.

20   DR. PACKER: Can you stand by, please? I just

21 want to clarify for those in the audience what the specific

22 issue is. In most trials for which the primary endpoint is

23 all-cause mortality, it is relatively easy, and is done

24 routinely, to ascertain the vital status of patients at the

1 end of the trial whether or not they had been taking their

2 study medication.

3   In the event that a trial is proposing the use of

4 a composite endpoint, which includes non-fatal events, there

5 has been concern raised by the Agency and by this Committee

6 that there may be incomplete ascertainment of non-fatal

7 events, with are a part of the primary endpoint, in patients

8 who discontinue their study medication because in many

9 trials patients who discontinue their study medication are

10 followed only for vital status and not for the occurrence of

11 non-fatal events which may be of importance, especially if

12 they have events which are part of the primary endpoint.

13   The CAPRIE investigators proactively recognized

14 this issue because in the protocol they prespecify that all

15 patients were to be followed to the planned end of the study

16 whether or not they continued taking their study medication.

17 It was a proactive recognition of the importance of this

18 issue, and the protocol takes pains to say that these

19 patients will be followed in almost exactly the same fashion

20 as if they were taking their study medication.

21   The concern here is not the intent of the CAPRIE

22 investigators which was, in fact, appropriate and honorable,

23 but whether this intent was carried out faithfully. So let

24 me just try and focus on the specific issue. Discussion by

1 the Committee? Udho?

2   DR. THADANI: I think I raised that point about

3 the myocardial infarctions. This is a general comment, and

4 it is absolutely mandatory in trials where soft endpoints or

5 relatively non-hard endpoints are being used like that, that

6 you must follow the patients at the same visits because it

7 is possible, if a patient drops out of the study and you

8 don't see him for six months -- it may be difficult for him

9 to remember if he had a chest pain for 20, 30 minutes. How

10 can one be sure that you didn't miss an infarct because

11 enzymes later on are not going to help, and nobody did them.

12 And the same thing could have happened with TIA. So, I

13 think those are issues one will have to keep in mind, that

14 unless you have visits at regular scheduled visits at the

15 office site, not even a phone contact because I know, I have

16 been in trials and the nurse calls and they talk to a wife

17 or a spouse and they say they are fine, but one doesn't know

18 the true incidence of these relatively hard endpoints but,

19 yet, not so hard as death or infarctions. So, I think there

20 are some concerns. Although the intention is there,

21 patients don't take their medication; they don't come in and

22 we don't try hard enough. So, that is an issue that I think

23 is relevant.

24   DR. TEMPLE: Milton, if I understand these things,

 1   it isn't particularly important whether you miss an endpoint

 2   here. What is important is whether there is bias to miss

 3   it. That is, whether the reason for dropping out has

 4   something to do with whether a person had an endpoint and

 5   whether the losses are what is sometimes called informative.

 6   So, it seems to me, one needs to focus on that. I guess the

 7   question is can one say anything about people who

 8   discontinued early and their prior history is helpful on

 9   that, or is that just not knowable? I mean, if someone was

10   having unstable angina, progressive chest pain and left,

11   that is different from someone who leaves bored and tired

12   and may or may not have had an MI six months later. The

13   latter is really not important. You don't have to capture

14   everything. You just have to have an unbiased capture. The

15   former could matter a lot.

16   DR. PACKER: I think there always is uncertainty

17   about this, Bob. I think that uncertainty is not only

18   heightened by the fact that all of the events which may

19   occur surrounding a patient's discontinuation of study

20   medication may not be known or recorded. But I think there

21   is also the issue that many events are classified as patient

22   refusal to continue, or physician refusal to allow the

23   patient to continue which, in fact, contains in it the

24   potential that the patient is experiencing an event which is

 1 related to the medication they are taking, not recorded but

 2 translated into something which appears to be

 3 administratively more neutral. It is always a concern.

 4   DR. TEMPLE: That is the worry, but what are the

 5 potential remedies? People do drop out of studies. People

 6 refuse to come to clinic. Every trial has that at least to

 7 some degree. You can get their vital status, but what can

 8 one do about the rest of the stuff?

 9   DR. PACKER: I think what one needs to do is try

10 as hard as one can to get all the events and, hopefully, one

11 is at the end talking about a small number and, hopefully,

12 that number will be unbiased. I think the idea here is not

13 to demand perfection but to seek it.

14   DR. CALIFF: Bob, I guess the only thing I would

15 add to what you said is that if you believe in p values of

16 0.05 and you have a robust p value, then the only issue

17 really is bias. But if you are teetering around the point

18 of 0.05 and you think that is the Holy Grail, then loss of

19 ascertainment equally in both groups for endpoints that

20 would have occurred in both groups -- as you know, as you

21 accrue endpoints sort of equally in groups, the p value goes

22 in the wrong direction. So, I think when you have a

23 marginal result, then it becomes a little more important

24 just to make sure that you are not being at all lax about

1 endpoints.

2   DR. TEMPLE: So, what is a reasonable practice?

3 Do you attribute to the missing people the event rate of the

4 whole group to see what difference that might make? Is

5 there any approach that is sensible?

6   DR. CALIFF: I guess my own approach in studies

7 that we look at internally is to do a sensitivity analysis,

8 and first attribute all the missing patients as having had

9 events if they were in the experimental group, and attribute

10 the event rates that were observed, and then assume that the

11 event rates are equal in the two groups, a sort of average.

12 But, see, if you get different answers when you do those

13 three ways --

14   DR. TEMPLE: Of course, you get different answers.

15 How could you not?

16   DR. CALIFF: Not necessarily. If you have a

17 robust p value and you can attribute an event to every

18 missing patient --

19   DR. TEMPLE: Well, it may or may not obliterate

20 the significance but it is certainly going to be different.

21   DR. CALIFF: Then it really doesn't change your

22 interpretation if you believe this 0.05 stuff.

23   DR. GANLEY: I just want to make some comments on

24 what was just stated, and just clarify some things. There

1   is a distinction between the follow-up of patients if you

2   are an early permanent discontinuation. There was the

3   option not to come into the clinic, whereas that option was

4   not available if you were on medication. You had to come in

5   and get medication and the physician or investigator would

6   presumably see you.

7   As far as the comment that the vast majority of

8   the CAPRIE patients came in for a final follow-up visit,

9   that is true because the vast majority were still on

10 therapy. If you look at the last visit for these early

11 permanent discontinuations, I think 3182 were followed up by

12 either a phone call, a letter or something of that sort.

13 Those are not the ones that we had a problem with. It was

14 the ones that were lost to follow-up prior to that because,

15 presumably, the majority of those people were contacted

16 every four months and you could probably get some reasonable

17 history from them. It was a concern with this group of

18 patients that either did not have a follow-up four months

19 prior to that or were lost to follow-up for a long period of

20 time. That number totally 546. The 70 patients were ones

21 that were lost to follow-up for greater than a year.

22   The other issue, which I wasn't going to discuss

23 but which has been brought up, is this issue of loss to

24 follow-up. To me, it is a question of how you define

1 someone who is lost to follow-up. As I showed in the

2 review, every patient was supposed to have a termination end

3 date. They were supposed to be seen within 2 weeks of that.

4 In morbidity and mortality trials we have problems with

5 people who are seen much earlier than that. If you are seen

6 after that date there is no problem because you can

7 generally assess the status. It is that population that is

8 seen before that, and if you look at the numbers it is 944

9 patients who were seen prior to what was specified in the

10 protocol.

11   I agree with you, the protocol was very clear on

12 what was to be done; it is just how it was carried out. Of

13 those 944, 149 didn't even have a year of follow-up. If you

14 look at the review that I gave, there is a sample of the 4

15 people that had the shortest follow-up time, and I think it

16 is fairly clear that in most trials you would not

17 characterize these people as completers, and all of these

18 patients are completers. Patient 3080229 had 301 days of

19 follow-up, who was randomized on December 21, 1994 so

20 technically they should have been seen in December of 1995.

21 Well, this person went on to have a CABAG done in August,

22 was an early permanent discontinuation, and the last follow-

23 up was in October of 1995. So we don't even know the status

24 of that person. That person is considered a completer. In

1 most trials that I have reviewed, the majority of which have

2 been in heart failure, that person would have been lost to

3 follow-up, and we would make them go find out what happened

4 to that patient.

5   There are 944 patients. If you figure out how

6 much time we have lost in follow-up, it comes to around

7 between 13,000 to 14,000 days of follow-up that we have lost

8 in those patients.

9   As far as the 70 patients, they have provided some

10 information on that regarding the follow-up. My sense is

11 that what we are going to find if we look at the document is

12 that we really don't have documentation of specific

13 questions that were asked of a patient or family member when

14 they were contacted. Based on a communication I had with an

15 FDA investigator who went to a site within the past week, I

16 had her looking at some of these for early permanent

17 discontinuation and most of the notes just say the patient

18 is fine. Okay? It doesn't say the patient denies any

19 history of MI or hospitalization. To me, that is analogous

20 to what a first year medical student would put in a note

21 when he goes in and asks a person how they are feeling and

22 they put down that there is no complaint. When a doctor

23 comes in and asks if they had any chest pains in the night,

24 the person gives you this big history of it. So there is a

1 distinction there I think.

2   DR. CALIFF: But before you sit down, if you could

3 maybe help us a little bit. You have raised some issues

4 here. I think we all agree they are not easy issues, and if

5 we were dealing with a result which was striking it probably

6 wouldn't really matter. Is it fair to ask you to provide a

7 little more interpretation on your conclusions? I mean, you

8 have raised some issues --

9   DR. GANLEY: I don't know how to answer them

10 honestly --

11   DR. CALIFF: Okay.

12   DR. GANLEY: -- because I can't say that I have

13 ever experienced -- you know, in most trials that I have

14 reviewed we have generally been able to get almost 100%

15 follow-up and it is very clear that you know the status of a

16 person after their termination or end date. This trial I

17 think is fairly unique and I think the steering committee

18 actually did a very good job. I read through all the

19 minutes of the study. They actually did a very good job of

20 trying to address these issues. I just think that the

21 characterization that there were only 56 lost to follow-up

22 is not by the definition that I, as a reviewer, would

23 normally use.

24   DR. RODEN: Assuming that there is no bias in the

 1 follow-up or in the lack of follow-up, is there a way that

 2 you can correct for that statistically or otherwise, making

 3 some reasonable assumptions and seeing if the trial would

 4 not have worked the same way, Ralph?

 5   DR. D'AGOSTINO: If there is no bias, if it is

 6 randomized lack of follow-up, then what you have you can

 7 analyze and feel comfortable with. The point is if the

 8 noncompliance is tied to a particular treatment, the

 9 reaction to it.

10   DR. RODEN: Does anybody from the Agency have any

11 sense that that is the case?

12   DR. LIPICKY: Can I just say a little bit more

13 than Charlie said, and this is not a settled issue at the

14 moment, but the plan was, as was presented, to look at the

15 group that had been dropped or that had been lost to follow-

16 up for the longest period of time, and to look at the

17 distribution amongst groups, and to look at the way in which

18 the documentation for their status had been determined.

19 That has been submitted and you heard a very brief summary

20 of it. I don't know if, when it is looked at in detail, it

21 will be comforting or not comforting, but at least as looked

22 at on the slide shown, it seemed like that problem would not

23 be likely to have led to bias and that the ascertainments

24 are of a reasonable nature. So, a decision will need to be

 1 made, and it has not been made yet, as to any other people,

 2 any more information that will be needed to be looked at.

 3 That is sort of where it sits. So, at the moment the Agency

 4 has not made a clear decision as to whether this is a big

 5 problem, a little problem or any other kind of a problem.

 6 It has identified that there was one.

 7   DR. RODEN: I will just say that if you want the

 8 best follow-up you should use first year medical students.

 9   DR. PACKER: Dr. Easton, if I could ask, the

10 process that was followed in this trial in terms of follow

11 up was to ask patients in general to come back every four

12 months, and during that period of time to report to the

13 physician anything that had occurred during that four-month

14 period of time. That requires a patient to remember what

15 happened during that four-month period of time. Every time

16 there was a recording of something, in other words, that

17 patient could have had an event but forgot; that patient may

18 have had no events but reported one because they thought

19 they had a heart attack but they didn't have a heart attack.

20 The physician who was the investigator may not have been the

21 patient's physician and, therefore, the patient's physician

22 frequently maybe had a better idea whether there was an MI

23 or stroke than the patient. This is certainly not only the

24 case in the patients who were assessed at the end of the

1 trial who may have not been seen for four months or even a

2 year, but also for any patient who was followed as the

3 protocol said they should be followed, which was every four

4 months.

5   One way of solving that problem would be for a

6 patient or investigator to report an event immediately when

7 it occurs, and not to wait for four-monthly follow-up

8 visits.

9   DR. EASTON: Yes, I think that is a good point.

10 In fact, I suspect that is what actually happened most of

11 the time. Certainly, in our investigator meetings and so

12 forth we direct patients -- I will speak for myself, for

13 example, and my patients, I am telling them all the time

14 what the symptoms are that we are looking for; what the

15 neurologic symptoms are; what the cardiopulmonary symptoms

16 are. If they have any of these symptoms we want to hear

17 about it, and usually do. In fact, we heard about all sorts

18 of things that weren't.

19   But I think what I can't answer for you is the

20 question of was that applied uniformly across the trial and

21 what percentage of patients probably did call when they had

22 numbness on the right side or some chest pain. But,

23 certainly, an effort was made to do exactly that and get

24 those patients in to be seen quickly if they had any

 1 suggestive symptoms of one of the events that we are talking

 2 about.

 3   DR. PACKER: And if that were to occur, was it

 4 reported on the CRF at the time of its occurrence or at the

 5 next scheduled visit?

 6   DR. EASTON: I can't answer that specifically.

 7   DR. PACKER: The protocol implies that that

 8 information was held until the next scheduled visit.

 9   DR. EASTON: Well, if it were an event, of course,

10 an event form would be initiated at that time. If it was

11 determined by the investigator that this was not a TIA, a

12 stroke and so forth, then I believe it did go till the next

13 formal visit and then was recorded on the case report form.

14 I am getting a nodding head to that, so that is correct.

15   DR. PACKER: The only reason for worrying is

16 because, obviously, you are in some cases, and perhaps in

17 many cases, relying on a 4-month memory perspective to

18 collect information, and the only issue in the patients lost

19 to follow-up is that the time period is longer. It could be

20 6 months; it could be 12 months; it could be 18 months. The

21 only observation I think that Dr. Ganley has made is that in

22 the patients that were lost to follow-up more than 6 months

23 there were 179 assigned to aspirin and 205 assigned to

24 clopidogrel, and although that 30 patient difference might

 1 not be very impressive, in a trial in which the treatment

 2 difference is small it raises questions as to whether there

 3 has been complete ascertainment of events.

 4   DR. EASTON: Sure. Yes, I think it is a good

 5 point and I think there is always some reassurance in

 6 knowing that the ascertainment was done.

 7   DR. RODEN: Perhaps another way of thinking about

 8 it, and maybe Lloyd knows the answer to this, is how the

 9 aspirin trials that were meta-analyzed were conducted. Were

10 they conducted in the same way? In other words, were

11 patients expected to remember at four-monthly intervals

12 whether they had a myocardial infarction or whether the

13 endpoints were recorded at that time? Because it seems to

14 me the key that we are going to come to, I think, is how

15 good this drug is compared to aspirin and compared to

16 placebo and that meta-analysis plays a key role. So if they

17 were not conducted in the same way at all, then that

18 argument holds less water.

19   DR. EASTON: Certainly the answer to that question

20 is the spectrum of techniques that were used in the 142

21 trials varied enormously, and I suspect there are people

22 sitting at your table that can answer the question because

23 their trials are in that analysis. But it is quite a range

24 of different techniques that were applied. I feel sure of

1 that.

2   DR. D'AGOSTINO: I think some of those trials

3 didn't even have the same endpoints as were ultimately

4 analyzed. They went back and sort of dredged them out. So,

5 I don't know how good that ascertainment is. But in this

6 question of ascertainment and four-month memory, I am at the

7 Framingham study and we wait two years to see people and ask

8 them what happened. You are scaring me that they will not

9 remember a hospitalization for a heart attack and so forth.

10 Do they do an EKG at the particular exams to pick up the

11 silent MIs? Remind me of how, in fact, they do make the

12 diagnosis. It is not just a self-report.

13   DR. EASTON: I can put up a slide, but the 3

14 criteria were typical ischemic chest pain of at least 20

15 minutes duration; enzyme changes, and I could specify those;

16 and EKG changes, and we can specify those. And they had to

17 have 2 out of the 3.

18   (Slide)

19   But if a patient complained and said they had some

20 chest pain a week ago, I think the issue of what an

21 investigator would have done under those circumstances -- I

22 can't answer that, except to say that I am sure most of the

23 ones who are concerned about the possibility of a myocardial

24 infarction got a cardiogram on those patients.

1   DR. D'AGOSTINO: They could have missed a silent

2   that wasn't too exciting.

3   DR. EASTON: Absolutely.

4   DR. PACKER: Ralph, we have had experience on a

5   personal level, and it is amazing how many non-fatal events

6   are missed when they are collected retrospectively.

7   DR. D'AGOSTINO: You know, when you get them at

8   the exam, if you do something systematic you have some hope.

9   If you are trying to elicit a comment and then react to it,

10 you are going to miss a lot. Right.

11   DR. EASTON: We know that is true in the stroke

12 field, that if you look at MRIs at the end of a trial you

13 find silent infarcts in a substantial number of patients,

14 and we simply had decided at the beginning of this trial

15 that we weren't going to seek out by those various

16 techniques all of those events. So, we know they are there.

17   DR. TEMPLE: This is true in every trial. If you

18 see people every two months you are going to miss the ones

19 they forget, or if you see them every six months. The

20 Physicians Health study requires that you write in and is,

21 yet, credible.

22   The main question here is whether there is bias.

23 it is inevitable that events are going to be missed,

24 probably in significant numbers. You miss them even by

 1 setting an enzyme elevation standard. The ones that are

 2 below that, there are probably some MIs where you didn't

 3 catch them. So, missing them is not the major problem;

 4 having bias is the major problem. That really is critical

 5 in this entire discussion. We are sort of discovering that

 6 you don't find all events in mortality trials. If that is

 7 really a worry, then the only acceptable trial is a

 8 mortality trial because you never miss that.

 9   DR. PACKER: I think these are two interrelated

10 issues. The first is the overall quality of the trial. The

11 extreme position, and no one would advocate such a trial,

12 would be to take patients who were going to be randomized

13 into a three-year trial and to give them three years of

14 study drug and ask them to come back in three years, and to

15 report everything that happened during that three-year

16 period of time. I am not proposing that example to suggest

17 that anyone follow it, but only to suggest that there is a

18 quality of trial issue in general when data are lost.

19   The second issue is whether there is base where

20 data are lost. I think it is hard to make a persuasive case

21 that one can always be reassured about that. I have the

22 inherent belief that there is no such thing as non-

23 informative dropouts. The dropouts are always informative

24 and the censoring process that occurs, if you stop

1 collecting data at the time of dropouts, always has a

2 potential bias.

3   DR. TEMPLE: To some extent, that is actually

4 assessable by looking at the people who leave and learning

5 about them. I am not sure everyone would agree with that.

6 There may be non-informative dropouts.

7   DR. MOYE: There are two issues here, it seems to

8 me. One is do patients remember non-fatal events when they

9 are asked about them. I would agree with Bob that that is

10 an issue that occurs in every trial. If the CAPRIE

11 investigators had, in fact, asked each single patient about

12 non-fatal events we would still have this issue. So, that

13 is endemic.

14   The other issue, which I think is more relevant

15 here, is that some patients were not asked, and I think that

16 goes directly to the quality of the lost to follow-up

17 ascertainment, and I think that is where we need to focus

18 our attention.

19   DR. EASTON: Of course, the primary purpose of the

20 visit -- as was pointed out, many of these patients were

21 being seen by a study investigator unrelated to their

22 private physician -- the whole focus of the visit when the

23 patient comes in is to ascertain what has happened to them

24 vis-a-vis trial events, drug effect, and so on in the last

 1   four months. I would expect that the probability that this

 2   history wasn't sought would be reasonably low or comparable

 3   to what occurs in other trials.

 4   DR. D'AGOSTINO: These aren't people who have

 5   never had an event. This is not a primary event; this is

 6   secondary. So, it must have had some meaning to it.

 7   Back to the comment that Bob raised, there are

 8   ways of looking at the bias. There are ways of modeling it

 9   to see what kind of an effect it does have on the study.

10   Some of the methods were mentioned, but there are particular

11   techniques for looking at the imputations. Some of the

12   stuff you were talking about yesterday in depression trials

13   when people have tried that, they have ended up saying that

14   you can't say anything about the trials because, no matter

15   how you model them, the dropout is so miserable. Maybe

16   here, you know, there is a way of doing it.

17   I think that it is not easy to say, just because

18   there is 1%, 5% of the individuals that have this

19   difficulty, what that 1% or 5% could actually impact on.

20   Did they do anything about it? Or, has this issue just been

21   raised so lately that all we know is that it is an issue,

22   and we don't have any analysis that has actually been done.

23   What is the status?

24   DR. LIPICKY: That last statement is the correct

1   statement. That is, nothing has really been done. The

2   first look at it has been submitted a few days ago.

3   DR. CALIFF: This is in the broken record category

4   but I think the generic loss in here is when you do a large

5   trial and aim at detecting endpoints, focusing resources on

6   measuring the major endpoints rather than multiple visits,

7   asking relatively meaningless questions in the last 15,000

8   patients of the trial would be a methodologic suggestion.

9   In other words, these patients who dropped out weren't

10   contacted, and if a lot more of the financial resources had

11   been put into finding those patients and getting a follow-

12   up, that would have been more valuable than maybe some of

13   the detailed measurements that we have been provided with

14   really aren't necessary in the last 10,000 patients in a

15   trial like this.

16   DR. THADANI: I think this is going to be a

17   problem in any large trial, especially when the patients are

18   dropping out and are not coming to the hospital visit, and a

19   person might contact them and ask how they feel and they say

20   fine. People might never ask them how they felt before.

21   One way around it is to just go by Q-wave infarctions, which

22   I think most people agree is a documented event like a

23   mortality or major stroke. That would probably be one way

24   in major trials one could avoid bias and you could put it in

1   a secondary endpoint rather than putting it in a primary

2   endpoint. I think it is a major dilemma, although Bob says

3   you miss events in both groups. But if you are looking at

4   drug efficacy where you are basing it on event rate and,

5   say, if 1000 patients never came back to the clinic how much

6   are you missing in each group is difficult. I realize it

7   could, hopefully, be equal in the two groups. But that

8   would be one way around looking at in a bit more objective

9   way, looking at the Q-wave ECG at some time point to

10 determine infarcts.

11   DR. PACKER: We are going to take a break. What I

12 would like to do when we reconvene is to spend just a few

13 minutes asking if there are any other questions related to

14 CAPRIE, and then go on with the remainder of the

15 presentation. We will reconvene in exactly 10 minutes.

16   (Brief recess)

17   DR. PACKER: Let's take a few more minutes for

18 general questions on any topic which has not yet been

19 covered on CAPRIE.

20   Ralph, if I could ask a question of you and maybe

21 I can first ask this of the CAPRIE investigators, the

22 interim monitoring of this trial prespecified, if I remember

23 correctly, three interim looks and then a fourth final

24 analysis. If I understand it correctly, a stopping

1 guideline was chosen in which 0.001 alpha was spent at each

2 interim look. I know this is an exceedingly statistically

3 naive question, but if you look three or four times and you

4 spend 0.001 each time, why is the final analysis done at

5 0.48?

6   DR. EASTON: it is so naive that I am going to ask

7 one of my colleagues to answer that for you.

8   DR. D'AGOSTINO: About three hours of mathematics

9 would show you that if you do that the total overall alpha

10 turns out to be --

11   DR. PACKER: It is not like taking 0.05 and

12 subtracting 0.001 four times? It is not like that?

13   DR. D'AGOSTINO: There is a little overlap. You

14 don't necessarily add them up.

15   DR. PACKER: Thank you.

16   DR. EASTON: I wanted to hear the answer.

17   (Laughter)

18   DR. PACKER: Other issues? Dan, you had a

19 pharmacology question?

20   DR. RODEN: I feel an urge to ask something that

21 has nothing to do with CAPRIE. It bothers me, and this is

22 just a statement without a requirement for a response, that

23 we have a drug whose mechanism of action is not completely

24 clear. At least, we are not sure what it is -- we are not

1   sure which compound it is or which of its metabolites is

2   doing what it is supposed to be doing. That is bothersome.

3   There is certainly a sense that biotransformation

4   is required for drug efficacy. I know you have done a lot

5   of _in vivo_ drug interaction studies. Have you done a study

6   with ketoconazole which, in my mind, is the way to test

7   whether the 3A4 pathway is not important? You know, there

8   are a number of the drugs on the market that didn't do that

9   and regretted it. I don't know whether that ought to be an

10 absolute requirement, but it seems in this case, Bob, that

11 you would like to know that.

12   DR. EASTON: The answer is no.

13   DR. RODEN: Because some of the _in vitro_ studies

14 that I saw somewhere in this stack suggested that 3A4 does

15 play a role to some extent. A pharmacokinetic argument

16 could be mounted that it is probably not very important, and

17 you guys can mount that if you want.

18   DR. THADANI: I was reading in the pharmacology

19 section. Is there any data on interaction with warfarin? I

20 realize heparin data look reasonable but I was wondering

21 about the warfarin data in a small number of patients. Do

22 you have any more on that?

23   DR. EASTON: Alison, can you speak to the issue of

24 interaction with warfarin? Dr. Pilgrim will comment.

 1   DR. PILGRIM: We actually do not have significant

 2   experience looking at co-administration of clopidogrel and

 3   warfarin. There was a clinical pharmacology study but for

 4   various methodological reasons the results were

 5   inconclusive. We did not allow concomitant use of warfarin

 6   during the CAPRIE study.

 7   DR. THADANI: Another relevant issue is that a lot

 8   of patients with these kind of disease processes are going

 9   to be on HMG coreductase, and there was some interaction

10   with some of them. I wasn't clear which ones.

11   DR. PILGRIM: We actually looked at HMG

12   coreductase inhibitors during CAPRIE and there was certainly

13   no evidence of any adverse interaction with clopidogrel,

14   wither in terms of efficacy or safety. About 30% of the

15   CAPRIE population took HMG coreductase inhibitors at some

16   point.

17   DR. THADANI: The last point is that there was a

18   lot about picking out this dose was based on what it did to

19   ADP, platelet aggregation and bleeding time. But looking at

20   the bleeding time, even on placebo some of the patients went

21   up from, you know, 120%. There is a lot of variation. It

22   depends on how deep a cut you make and the blade size. I am

23   told by my colleagues in hematology that bleeding time has

24   such a variation that, although it is reassuring that the

1 bleeding rate is not higher in the trials -- so the dose was

2 based more on platelet aggregation?

3   DR. PILGRIM: The primary marker that was used to

4 select the dose to put into CAPRIE was inhibition of ADP-

5 induced platelet aggregation. We also looked at bleeding

6 time in most of the clinical pharmacology studies, partly as

7 an efficacy measure but also from a safety point of view.

8   DR. CALIFF: I just want to verify -- I think I

9 have this right, about what was done. When we say

10 intention-to-treat in this analysis we are talking about all

11 patients as randomized, not all patients who got at least

12 one dose of the drugs?

13   DR. PILGRIM: It is all patients as randomized,

14 whether or not they took any study drug, although the number

15 that did not receive study drug was very, very small. I

16 think it was about 30 or 40 patients out of 20,000.

17   DR. DIMARCO: Relative to the warfarin question,

18 were there patients in the trial who had atrial

19 fibrillation, and if atrial fibrillation was an exclusion

20 what did you do when somebody developed atrial fibrillation

21 in the trial?

22   DR. PILGRIM: There were patients in the trial

23 with atrial fibrillation. I think we have that on a slide

24 so we can give you the precise figure.

1   (Slide)

2   If a patient had a clinical requirement for

3   warfarin, then the protocol required them to come out of the

4   trial. We didn't allow co-administration of clopidogrel and

5   warfarin. But because of the contraindication to warfarin

6   use it was quite a small proportion.

7   DR. PACKER: I have one question. I think that

8   you have done a wonderful job using due diligence on the

9   neutropenia issue because, obviously, it was identified

10 prospectively as something that you needed to look at

11 carefully.

12   At the present time, I think you would like your

13 labeling to say there is no neutropenia problem with

14 clopidogrel. Would that be a correct statement?

15   DR. PILGRIM: We don't believe that there is an

16 increased risk compared to aspirin, and aspirin is not known

17 to cause neutropenia. So, there were a very tiny number of

18 neutropenias occurring in the course of the trial but they

19 were pretty well balanced between the clopidogrel and the

20 aspirin group.

21   DR. PACKER: But you do also have data which is

22 provided in the document that white cell counts are

23 consistently lower on clopidogrel than on aspirin.

24   DR. PILGRIM: I think probably Dr. Beaumont can

1 comment on this in more detail, but there were very small,

2 probably not clinically significant, changes in mean white

3 cell count. They were seen early on in the trial but, in

4 fact, by the end of the CAPRIE there was virtually no

5 difference between the clopidogrel and aspirin groups in

6 terms of their mean values nor in the number of patients

7 having a clinically significant change.

8   DR. PACKER: This is really a point for Ray or

9 Bob. In the past, and I guess the example that comes to

10 mind is the example of ACE inhibitors, I remember when

11 enalapril came to the Committee, with captopril already on

12 the market, the Committee was specifically asked whether

13 they were convinced that enalapril was different than

14 captopril with respect to agranulocytosis.

15   The discussion that occurred at that point in time

16 was a discussion that can be summarized, I think, quite

17 simply that when you have very few events you have very wide

18 confidence intervals and, therefore, the conclusions that

19 you reach need to be appropriately cautious. That is the

20 reason why I believe it is still the case that the labeling

21 for enalapril said that although there was not a lot of

22 reason to think that agranulocytosis was a problem; that the

23 data that were available could not rule out the fact that it

24 was a problem because a similar problem had occurred with

1 another ACE inhibitor.

2   DR. LIPICKY: It wasn't quite that way but very

3 close. The problem was that with captopril at that time it

4 was clear that captopril induced agranulocytosis, and that

5 it induced agranulocytosis in a particular population where,

6 in fact, almost all the cases had occurred. That particular

7 population had not been studied by enalapril. Therefore,

8 that incidence of agranulocytosis could not be ruled out

9 because the population had never been studied. And the low

10 rate in the regular population was something that couldn't

11 be addressed by the sample size that was available.

12 Ticlopidine does not select out particular groups, and has a

13 particular rate in the exact patient population that was

14 studied. So, aspirin is not known to cause agranulocytosis.

15 So, the circumstances are a little bit different.

16   DR. TEMPLE: There isn't any doubt at all from

17 their data base that the drugs differ from ticlopidine. I

18 wouldn't say I have looked at the cases fully, and it may

19 not be known that aspirin causes agranulocytosis, but that

20 doesn't absolutely mean it doesn't.

21   Could you review at least a little of the cases in

22 which there were literally no, or under 450 neutrophils?

23   DR. EASTON: Yes.

24   DR. TEMPLE: Those are not things which are

1 supposed to occur in an ordinary population not given some

2 other drug to cause that. You know, a rate of 1/5000 or

3 something like that is higher than I would have thought was

4 the background rate, and it is higher than most people's

5 estimate of the background rate for the population.

6   DR. BEAUMONT: Before showing the data I would

7 like to briefly recall how we monitored them. It is because

8 ticlopidine is associated with a low but significant

9 incidence of these events of neutropenia that clopidogrel

10 included intensive hematological monitoring.

11   (Slide)

12   Initially blood count and platelet count was

13 performed weekly for 12 weeks. After 500 patients had been

14 enrolled, their hematologic data was reviewed, on a blinded

15 basis, and then the schedule was relaxed to what we call

16 schedule B of the protocol, which is every other week for

17 the first 12 weeks and then monthly. Then the steering

18 committee reviewed the data on the 5000 patients with 3

19 months of intensive monitoring and they were reassured that

20 there was not a clinically significant difference.

21 Monitoring was then reduced to schedule C, as per protocol.

22 That is a monthly blood count for 4 months and then followed

23 by every 4-month blood counts. By that time nearly 5000

24 patients, as you can see, had been enrolled and they

1 continued to be monitored with intensive monitoring. So,

2 indeed, clopidogrel collected a very extensive data base on

3 hematologic monitoring for both clopidogrel and aspirin.

4   (Slide)

5   Blood samples were then collected and analyzed

6 within 24 hours in one of three central laboratories, one in

7 North America, one in Europe and one in Australia. there

8 were alert values which were predefined, and when values

9 were below the threshold investigators had to obtain

10 confirmatory testing, to report the case urgently and to

11 follow them up. Sometimes below certain values, as you can

12 see, it was mandatory to discontinue study drug.

13   (Slide)

14   Here are the results: 26 cases were found to be

15 below 1200, 1.2 G/L, with clopidogrel versus 23 on aspirin,

16 of which 4 were below 450 with clopidogrel and 3 with

17 aspirin.

18   (Slide)

19   The timing of the occurrence of these events was

20 similar in both aspirin and clopidogrel groups. I will give

21 you details of 7 cases, 4 clopidogrel and 3 aspirin.

22   (Slide)

23   These are the 4 clopidogrel cases. You see the

24 gender and age of these patients. The time to onset was 1

1 month in 3 cases and 32 months in the other one. The lowest

2 count was zero in 2 cases, 290 in 1 and 340 in the 4th one.

3 Study drug was always discontinued, as per protocol. All

4 went back to normal. Treatment was resumed in one patient

5 and the reaction didn't recur. It was a negative re-

6 challenge. One of these cases appeared while on

7 chemotherapy for cancer.

8   (Slide)

9   Now let's compare it with the 3 aspirin cases

10 below 450. Here is the gender of the age; the time to

11 onset, 1.5 months, 4 months, 2.5 years. Here is the lowest

12 count. One of these patients was very low, zero.   One

13 study case actually appeared while off drug after 3 weeks of

14 discontinuation. In the other cases the drug was always

15 discontinued. Two went back to normal; 1 persisted after

16 discontinuation. Treatment was never resumed. There was

17 also one case which appeared while on chemotherapy for

18 cancer.

19   (Slide)

20   Finally, the last slide is to answer your question

21 of how it compares to ticlopidine. You have the analysis of

22 the two ticlopidine trials in which the monitoring was very

23 similar to the CAPRIE trial. The incidence with clopidogrel

24 is not different than that seen with aspirin. It is much

1 lower than with ticlopidine. You see 0.27% of neutropenia

2 below 1200 versus 2.4% with ticlopidine. With severe, below

3 450, 0.04% with clopidogrel compared with 0.8% with

4 ticlopidine. That is the data we have.

5   DR. DIMARCO: What happened to the patient whose

6 neutropenia persisted?

7   DR. BEAUMONT: The one patient in the aspirin

8 group was followed for one year and neutropenia persisted.

9   DR. DIMARCO: Oh, that was in the aspirin group?

10   DR. BEAUMONT: It was in the aspirin group. All

11 the neutropenia in the clopidogrel group recovered.

12   DR. LINDENFELD: Just a separate issue if you

13 could clarify for me, the numbers that you have shown us

14 today in terms of events are fairly different than the ones

15 that were published here. For instance, in the non-vascular

16 deaths there are 30 in each group that are different in MIs.

17 What is the difference there?

18   DR. BEAUMONT: You are referring to --

19   DR. LINDENFELD: The difference in other vascular

20 death. Today you have shown us about 30 in each group and

21 in your published report it is about 260. It was about the

22 same difference in each group.

23   DR. BEAUMONT: There is no difference between the

24 Lancet publication and our data base. I think you are

1 referring to the 226 cases of other deaths in each group

2 versus 260 which were all the vascular deaths in the trial.

3   DR. PACKER: For the sake of clarity, I think what

4 JoAnn is asking about is that the numbers in the Lancet

5 article in terms of primary endpoints are slightly different

6 than in your primary analysis. I think the document makes

7 clear the fact that the difference is related to the fact

8 that there was additional follow-up after the data base was

9 locked.

10   DR. BEAUMONT: That is correct. Out of the 56

11 patients lost to follow up in the data base, we retrieved 14

12 additional patients and they were, indeed, included in the

13 Lancet publication. Out of those 14 we retrieved, there was

14 1 event in the aspirin group and that was included in the

15 publication. That is the difference. It didn't change the

16 results.

17   DR. CALIFF: One other somewhat unrelated question

18 about outcome. Total hospitalizations in the two groups?

19 It is probably in the report we got but I couldn't find it.

20 There are different types of hospitalizations in different

21 tables, but just to get a flavor for it, do you have the

22 proportion of patients hospitalized at some time during the

23 follow-up in each group?

24   DR. BEAUMONT: I am not sure we have the data on

1   the number of hospitalizations at hand. We have to look for

2   that.

3   DR. PACKER: There appear to be no other

4   questions. Let's proceed to the presentations on issues of

5   heterogeneity and aspirin comparability. By the way, as

6   Lloyd is coming up, if anyone is trying to plan their

7   schedule for today, the intent of the meeting at the present

8   time is to try to complete all of the proceedings on

9   clopidogrel without a further break. We will see if we can

10   do that.

11   **Statistical Interpretation**

12   (Slide)

13   DR. FISHER: Dr. Packer, Cardiovascular and Renal

14   Drugs Advisory Committee members and FDA scientists, you

15   have heard about the primary results of the CAPRIE trial and

16   I will discuss two issues that have considerable

17   biostatistical content. First, I will address what might

18   have happened had there been a placebo arm in the trial.

19   Secondly, I will address the possibility of the treatment

20   effect difference by qualifying condition.

21   (Slide)

22   First I will address what might have happened had

23   there been a placebo arm in the trial. If you can change

24   gears here from the discussion of the CAPRIE trial where, of

1 course, we have been talking about the comparison with the

2 active comparator, to yesterday's discussions which revolved

3 around active control trials and whether, in fact, a drug

4 might have beaten placebo, that will be the issue that will

5 be addressed here.

6   I would suggest that they are two separate parts

7 to your deliberations. One, of course, is the approvability

8 which really relates to the thing I am discussing here,

9 except perhaps for Dr. Califf, based on yesterday's

10 conversations. The other issues, assuming the drug is

11 approvable, are what is appropriate for labeling vis-a-vis

12 aspirin, and that will be the main topic of part of the

13 considerations.

14   (Slide)

15   You have seen this slide before by Dr. Easton. It

16 is merely here to remind you about the antiplatelet

17 trialists' meta-analytic collaboration. The appendix to

18 that paper gives information on the results in many

19 different studies. This figure shows the uniformity of

20 effect of the odds ratios with respect to all the

21 antiplatelet therapy reported in their collaboration.

22   (Slide)

23   For the analysis that I did or the overall

24 comparison, I selected from the appendix all of the trials

1 that were unconfounded that had aspirin versus placebo arm.

2 I then examined them for heterogeneity and as, actually, has

3 been typical of almost all the analyses done in the meta-

4 analysis, if you express the results in terms of odds ratios

5 instead of absolute percents there is a great deal of

6 uniformity and certainly there was no evidence of

7 heterogeneity in this data set, with a p value for

8 heterogeneity of 0.994. So that is for the overall

9 comparison and I am sure you will want to discuss that, and

10 we can discuss that at the end of this section of my talk.

11   In addition, I will examine the possible

12 clopidogrel versus placebo effect in two of the three

13 clinical condition subgroups that were used for enrollment.

14 For the acute and prior MI, I have used the acute and prior

15 MI studies from the meta-analysis appendix for the

16 comparison in the MI subgroup; and the trials that they

17 present under prior stroke and TIA, the ischemic stroke

18 subgroup, the comparisons you will see use only those

19 particular parts of the meta-analysis. As you know, this

20 was published in the 1994 British Medical Journal.

21   (Slide)

22   I am going to be examining four endpoints. The

23 first endpoint is close but not identical to the primary

24 cluster within CAPRIE. I will look at all strokes from all

1 causes, not just ischemic strokes, MIs and vascular deaths.

2 The reason that I did not use the CAPRIE endpoint is that

3 the meta-analysis did not collect and present those data so

4 that was impossible for me to attempt. But this is as close

5 as I could get.

6   In addition, I will take the same combination

7 endpoint and include deaths from all causes. I will look

8 for deaths that were classified as vascular deaths, and the

9 meta-analysis actually took the same approach that was taken

10 in CAPRIE when they got their data. If they didn't know how

11 to classify something it went into this category. Then I

12 will look at all-cause mortality.

13   Equivalent events were used from both the meta-

14 analysis and the CAPRIE study for the data that I will be

15 presenting.

16   (Slide)

17   I will be talking about odds ratios because this

18 has been the tradition of the Oxford group. If relative

19 risks were used the presentation will change slightly. Time

20 to event analyses cannot be done unless one has the entirety

21 of the data sets in the trials, including the timing of

22 events, which again I did not have access to. However,

23 being randomized trials, the exposure is approximately equal

24 and, if anything, one would lose a little bit of power by

1 using the odds ratios.

2   But the underlying assumption used is that had

3 there been a placebo arm in the CAPRIE trial, the relative

4 comparison between aspirin and placebo within CAPRIE would

5 have been the same as for the controlled trials.

6   (Slide)

7   I am going to be presenting analyses graphically

8 for the study as a whole and for the MI and the stroke

9 subgroups. I did the analyses, and you have them in

10 briefing document that you received to prepare for this

11 meeting, for the geographical subdivision and those odds

12 ratio plots will be very similar to the group as a whole

13 but, of course, have wider confidence intervals because of

14 smaller numbers of events. So, there is more variability,

15 but in the interest of time I will be discussing these

16 three.

17   (Slide)

18   This is the first of a series of build-up plots.

19 I will spend a little more time to orient you to the

20 presentation. Over on the left-hand side of the slide are

21 the four different endpoints that I examined. When I get

22 done there will be a series of lines. The light blue lines

23 on each of the plots are the CAPRIE study so that they

24 compare clopidogrel versus aspirin. The vertical line at 1

 1 is an odds ratio of 1, representing precisely no treatment

 2 effect. Values to the left favor clopidogrel over aspirin;

 3 values to the right favor aspirin over clopidogrel in

 4 CAPRIE. As in the overall analysis that you saw, these are

 5 95% confidence intervals. As in the analysis that you saw,

 6 if this lies entirely to the left of this line there is a

 7 statistically significant difference, and there is a p value

 8 slightly less than 0.05 associated with the analog of the

 9 primary CAPRIE endpoint when all-cause mortality is used.

10 When vascular deaths are used and all-cause deaths are used

11 the point estimates are in favor of the clopidogrel over the

12 aspirin, although not statistically significantly so.

13   (Slide)

14   In this slide the pink bars now represent meta-

15 analytic trials of aspirin versus placebo for the same

16 endpoints. You can see that aspirin is an excellent drug in

17 an antiplatelet situation, as is well known. So it is a

18 very good comparator. Because of the large number of trials

19 that have been done and that are included in this meta-

20 analysis, the variability is small so that aspirin, compared

21 to placebo -- the estimated effect of these is larger than

22 clopidogrel compared to aspirin, although in each case

23 clopidogrel looks better than aspirin, which looks better

24 than placebo.

1   (Slide)

2   This final slide includes an estimate of the

3 clopidogrel versus placebo effect. The method that I used

4 fortunately was already presented yesterday. It was one

5 that was suggested by Dr. Rory Collins. I worked with the

6 logs of the odds ratios. I took into account the

7 variability for both parts of the components because to get

8 this estimate you multiply the odds ratios. The aspirin

9 effect cancels out and you end up with the odds ratio for

10 clopidogrel versus aspirin.

11   As you can see, for the overall population -- of

12 course, it is a mathematical necessity that if each of these

13 estimates is to the left of the line this will be further to

14 the left because you multiply the numbers, and we have an

15 estimated benefit of clopidogrel above aspirin and then an

16 estimated benefit of aspirin above placebo. So these white

17 lines give the estimated synthesized effect using the odds

18 ratios. The black bars in the middle, of course, show the

19 estimated superiority of clopidogrel versus placebo. On the

20 right we have the p values associated with these odds

21 ratios.

22   The first two combination endpoints have p values

23 of less than one in one million. I will discuss a little

24 bit later, and I am sure we will have a lot more discussion

1   after I get done how to interpret things. There were

2   statistically significant estimates in terms of preventing

3   death for both vascular deaths and all-cause mortality

4   because although the clopidogrel was not statistically

5   superior to aspirin, aspirin is known to be so effective

6   that the combination suggests very strongly that clopidogrel

7   compared to a placebo would have reduced both the vascular

8   mortality and the all-cause mortality. So these are the

9   results from the overall patient population. I will not

10 turn to the two subgroups.

11   (Slide)

12   These are the data for the MI subgroup, for the MI

13 qualifying condition. As you already know and as, when we

14 get to the heterogeneity part of the discussion, I am sure

15 will be discussed, there was a slight estimated benefit of

16 aspirin over clopidogrel in this one subgroup. The

17 estimates are not statistically significant because the 95%

18 confidence intervals overlap this line. Aspirin, as I

19 mentioned before, is a very effective drug in this setting.

20 So, the combined estimates are all in favor of clopidogrel

21 compared to placebo. For the two combination endpoints the

22 results are estimated to be statistically significant, with

23 a p of 0.0066 and 0.0053.

24   (Slide)

 1   This the same sort of analysis but shifted to the

 2   ischemic stroke qualifying condition. In each case

 3   clopidogrel was estimated to be superior to aspirin, except

 4   for the vascular deaths where basically it is a wash for the

 5   aspirin versus placebo data, with a slightly negative

 6   estimate for aspirin versus placebo. But when things are

 7   combined, in every instance clopidogrel was estimated to be

 8   superior to this putative placebo control. The p values for

 9   the two combination endpoints within this one subgroup are

10   significant, 0.0084 and 0.0022.

11   (Slide)

12   I wanted to talk some, and this will probably come

13   up again when we discuss interactions, about the peripheral

14   arterial disease subgroup. There is almost no controlled

15   aspirin-placebo data with this one subgroup. The combined

16   trials had a total of 17 events split between the two

17   treatment arms, and the confidence intervals are extremely

18   wide. I didn't bother to do the analyses and prepare a

19   slide but the intervals have this tremendous overlap. In

20   this case, the comparator does not have direct data. If one

21   is to look at this comparison and get a result, it would be

22   based on the overall consistency of the antiplatelet effect

23   in the meta-analysis, which is quite impressive but that is

24   a biological not a statistical issue.

1   Aspirin is very widely used for the prevention of

2 atherothrombotic events in patients with peripheral arterial

3 disease, correctly or incorrectly. It has a Grade A

4 recommendation from the Fourth Consensus Conference of the

5 American College of Chest Physicians.

6   Finally, within this one subgroup clopidogrel was

7 superior to aspirin in terms of the combination endpoint

8 alone. So, if you are willing to grant that aspirin is at

9 least not harmful within this subgroup, then one would

10 conclude that clopidogrel would be superior to placebo.

11   (Slide)

12   I wanted to talk about the weight of evidence

13 because you are being asked to approve a drug on one trial.

14 As you know, to approve a drug on one trial there really has

15 to be considerable weight of evidence. Remember, we are not

16 talking about the weight of evidence of clopidogrel versus

17 aspirin as the active control trial; we are talking about

18 what we might infer against placebo.

19   The usual FDA paradigm is that there will be two

20 well-controlled, randomized clinical trials, where the two-

21 sided p values are both statistically significantly positive

22 in favor of the new therapy. As Dr. Lipicky mentioned

23 yesterday, this corresponds to a p value of 0.00125, and let

24 me describe briefly how this arises since I have a feeling

1   this number may be worth putting in your memory banks for

2   future meetings; this may not be the last time you hear it.

3   For the moment, suppose that we wanted to do a

4   one-sided test because we want to show that the drug is

5   favorable, but we didn't want to weaken our strength of

6   evidence against the usual two-sided 0.05 level, then what

7   we would do is have a one-sided test but use a significance

8   level of 0.025. So, this is the probability, if two

9   treatments are identical, that a trial just by chance would

10 turn out to show superiority. If we have two separate

11 trials, then they would be statistically independent and the

12 probability that both of these one-sided trials turned out

13 to show superiority is the product of the two terms or the

14 square of 0.025. So, this would be the level of evidence

15 for a one-sided p value. If we convert that to a two-sided

16 p value we multiply by 2 and that is how this number arises.

17   So to get the same amount of evidence you would

18 like to have a p value at least as small as 0.00125. In the

19 overall clopidogrel analysis the p value was about 10^{-6}.

20 There is some uncertainty associated with this but I would

21 suggest that this satisfies it really rather handily.

22   (Slide)

23   Being a statistician, I do say I am not enamored

24 of historical controls. One thing I say to my classes when

1 I teach them, which I somewhat believe in, is that if it is

2 ethical to use a placebo it is unethical not to use a

3 placebo. But here we are in the modern era where we see

4 more and more active control trials, as was discussed

5 yesterday. Knowing this, the weight we attach to these

6 values involves a lot of judgment. We cannot take them

7 nominally. Somehow they have to be discounted. But I doubt

8 that any statistician will give you a strict formula for

9 discounting them. That is one of the reasons for

10 uncertainty.

11   But I would suggest that in this case there is so

12 much data on aspirin versus placebo that is uniform across

13 the data base in so many trials that this provides a fairly

14 robust sort of a basis and, in point of fact, rather handily

15 clopidogrel beats placebo with this level of evidence, and

16 that is very germane in your considerations of the

17 approvability of it.

18   (Slide)

19   Furthermore, as you saw, it was certainly better

20 than placebo for the overall group in the two combination

21 endpoints at a very strong level, but also for vascular

22 mortality and all-cause mortality, the estimated effects.

23 In the MI and the ischemic stroke subgroups it was estimated

24 to have a statistically significantly beneficial effect

1 compared to the two combined endpoints of all strokes,

2 myocardial infarction and vascular mortality, and all

3 strokes, myocardial infarction and all-cause mortality.

4   (Slide)

5   So, for this part of the talk I concluded that

6 clopidogrel meets the usual placebo standard and, then based

7 upon the things presented by Dr. Easton, is superior to

8 aspirin overall.

9   I have two parts to my talk. The second part is

10 on heterogeneity. But it might be good actually to invite

11 questions here for clarity to discuss the putative placebo

12 effect which are appropriate controlled trials, etc., and

13 then to move on to the other part.

14   DR. PACKER: Why don't we pause for questions?

15 Can we focus on the issue of a comparison to a putative

16 placebo? Ralph, do you want to begin the discussion?

17   DR. D'AGOSTINO: Yes, I would like to talk about

18 the p level for a moment and the computation. I think when

19 you run into looking at meta-analyses that the p values

20 aren't necessarily to be interpreted the same way you would

21 a p value, say, in a randomized trial. There is a lot of

22 sort of noise that enters that the meta-analyses, and they

23 tend to look sharp and to produce very small p values. But

24 I don't think that they necessarily translate to the same as

1 the usual clinical trial. That is number one issue that I

2 would like to hear you discuss.

3   Number two is that if you were talking about a

4 mortality trial and had a single trial with a very small p

5 value, I think I would have some sympathy to it. But here,

6 where you have endpoints that are not mortality and the

7 mortality is not really driving the analyses, I guess I

8 worry about this idea that you have a small p value and that

9 somehow or other that takes care of all problems of

10 representativeness, reproducibility of studies, and the sort

11 of usual considerations of why we want to see two trials.

12 Also, you know, if I had a trial that was sort of badly run

13 on a sympathetic population and I get a p value of 0.0001, I

14 don't think that is the same. I would call that maybe at

15 the 0.05 level but I would want to see another trial at the

16 0.05 level.

17   So, you know, you are using the p value from a

18 single comparison that I have problems with and then trying

19 to make that be the same as running a couple of trials, and

20 multiplying and adding some p values.

21   DR. FISHER: Well, I don't disagree, by and large,

22 with what you have said. I mean, there are a lot of issues

23 here. Strictly speaking, I didn't use the p values from the

24 meta-analyses per se; I used the variability but that

1 amounts to the same thing, of course, at the end of the day.

2   I think all of the issues in historical control

3 trials are present here, but I think this is really a very

4 nice example to follow yesterday's proceedings because there

5 is some aspirin-placebo data, and it has been examined in so

6 many different situations by so many people, and the people

7 at Oxford go to fairly extreme lengths to try, as best they

8 can, to ascertain data. But, undoubtedly, many of the

9 trials and the meta-analysis would be subject to the same

10 criticisms that you brought up in CAPRIE with respect to MIs

11 or strokes, and so on and so forth.

12   DR. D'AGOSTINO: That was going to be my next

13 point. The comparisons with the trials and the meta-

14 analysis, those weren't necessarily clinical trials with

15 these endpoints. They went back and gathered the endpoints.

16 It is the idea of using data that wasn't even, you know,

17 designed for particular endpoints. So, I don't have a

18 problem with sort of the direction in which we are going. I

19 think you do have an argument for it. But I have an awful

20 hard time buying the sort of particulars that this is a nice

21 comparison as if we had a clinical trial and can look at the

22 p values in the same way.

23   DR. FISHER: Well, I disagree with part of that.

24 You are saying as if we had a clinical trial. Well, these

1 were clinical trials.

2   DR. D'AGOSTINO: But with different endpoints.

3   DR. FISHER: There were different endpoints but

4 in terms of comparing it with CAPRIE, I think you would find

5 it really bizarre if I got up here and talked about totally

6 different endpoints.

7   DR. D'AGOSTINO: But in the meta-analysis some of

8 the trials weren't designed to look at vascular deaths.

9 They went back and asked the investigators if they could

10 tell them something about vascular deaths.

11   DR. FISHER: That is true, and there are a few

12 trials in the appendix where they could not ascertain some

13 things, and those trials I left out of each of the endpoint

14 analyses I ran because the data were unknown. So, I guess

15 there could be some bias there. Miraculously, trials that

16 didn't measure stroke were just the trials which went in the

17 opposite direction and aspirin was actually causing stroke,

18 for example, but that strikes me as a little implausible

19 biologically.

20   DR. D'AGOSTINO: That might be implausible but it

21 wouldn't be implausible that a trial that wasn't measuring

22 stroke and then later on tried to have follow-up on stroke

23 didn't do a very good job in the follow-up of stroke.

24   DR. FISHER: That is certainly possible. I mean,

1 you have heard how difficult it is to speak with absolute

2 certainty when we have the primary investigators here with

3 CAPRIE. We obviously have not invited everybody from all of

4 the 41 aspirin-placebo trials in the appendix.

5   I do take a little comfort, getting back to Dr.

6 Temple's suggestion, that the real issue is bias. It seems

7 to me that the ascertainment bias in relationship to therapy

8 would be less likely, although you are probably more likely

9 actually to miss some events. But that should decrease your

10 power.

11   DR. PACKER: Ralph, before we go on to anyone

12 else, I just want to understand. I think the point you are

13 making is that you do not have confidence in the p value

14 that Lloyd has calculated as the p value that might

15 represent a comparison of clopidogrel versus a putative

16 placebo.

17   DR. D'AGOSTINO: Right, exactly. We are going to

18 be asked questions about one trial versus two trials, and it

19 may or may not revolve around how we interpret the p values.

20   DR. FISHER: Milton, I will go further than that.

21 Lloyd doesn't have confidence in the p values to interpret

22 them as I would, you know, with a single trial with

23 concurrent controls.

24   DR. PACKER: I think what we are going to hear is

 1 how that uncertainty translates into an interpretation in a

 2 short time. Udho?

 3   DR. THADANI: Lloyd, nicely put. I think you

 4 emphasized that patients who were randomized to the stroke

 5 group had more significant difference. You did not comment

 6 too much on the patients with previous MI actually went the

 7 other way, in favor of aspirin. In your final figure on the

 8 p values, I presume you also included peripheral vascular

 9 disease to come to the p 0.001. Is that true?

10   DR. FISHER: Yes, I included the trials but that

11 is very little of the power because there was almost no

12 aspirin-placebo there. If you run it just ignoring the PAD

13 subgroup, you also get trials that are well below the 0.001

14 -- the p value is quite a bit below the 0.00125 level.

15   DR. THADANI: But in the present discussion the

16 drug under discussion is really highly significant in the

17 peripheral vascular group, not so in the MI group and

18 perhaps slightly in the stroke group.

19   DR. FISHER: But you are talking about compared to

20 aspirin, and you are getting into, it sounds to me, like an

21 interaction discussion. But compared to placebo --

22   DR. THADANI: But there is no data that aspirin

23 beat placebo in peripheral vascular disease. So you can't

24 impute that data. You might just say, well, we have no data

1   on that.

2   DR. FISHER: Right, and I didn't present an

3   analysis versus placebo precisely for that reason because

4   there is just virtually no data.

5   DR. THADANI: So your last data was just excluding

6   the peripheral vascular disease?

7   DR. FISHER: It included the little tiny bit of

8   data there was, but it was the other trials that were

9   clearly driving it because that was only 17 events. So, in

10 essence, you can think of it as not having peripheral

11 arterial disease data.

12   DR. TEMPLE: The meta-analysis, as I remember it,

13 made a point of saying that whether you looked at trials in

14 people who had stroke or trials in people who had MI, the

15 reduction in new stroke events or MI events was more or less

16 the same, which partly goes to the question Ralph raised

17 because, presumably, ascertainment in a post-stroke trial is

18 better for stroke. But one of the points that the aspirin

19 trialists made is that it didn't matter very much.

20   One other question, not ignoring at all the

21 arguments that say those p values are not p values as we

22 usually mean them, what would happen if you took a more

23 conservative estimate of the effect of aspirin and ran the

24 same things using, not the mean effect plus whatever

1   variance there is, but the 95% lower bound for the effect of

2   aspirin? In other words, a more cautious estimate of what

3   the aspirin effect is. I wonder if you have done anything

4   like that.

5   DR. FISHER: I am trying to remember the results,

6   but in my report I included some estimates using different

7   bounds for the aspirin of the percentage of effect

8   preserved. In general, it was quite good. But to give you

9   a specific number --

10   DR. TEMPLE: The confidence intervals for aspirin

11 are fairly narrow so maybe it won't make much difference.

12 That would be a sort of more conservative use of that

13 historical control.

14   DR. FISHER: We are sitting here in a situation

15 overall where we are arguing about whether -- for this one

16 trial, and I don't want to put words in your mouth, but we

17 are arguing about whether it has really been shown that

18 clopidogrel is better than aspirin, or whether there are

19 enough caveats that it is just very close. But I haven't

20 heard anybody suggest that clopidogrel is a lot worse than

21 aspirin. So, with the aspirin being that good and

22 clopidogrel, if anything, beating aspirin, when you look at

23 those tables clopidogrel basically preserved the whole

24 effect.

 1   DR. LIPICKY: Listening to you talk, I have sort

 2   of been developing an intuition in my head that says that

 3   when you look at p values you shouldn't start to think that

 4   one value was different from another unless it changes by a

 5   factor of 10. So, 0.1 is different from 0.01 and 0.01 is

 6   different from 0.001, etc., and that things in between

 7   probably aren't different in terms of looking for power or

 8   saying that you really found a difference. Do you want to

 9   comment on my intuition that you have developed just now?

10   DR. FISHER: Well, actually, statisticians have

11   all sorts of guidelines but this is a historic moment. They

12   have put some confidence intervals in front of me using an

13   alternative approach at the lower endpoints, and for the

14   combination endpoints overall the p value is 10^{-7}, 10^{-8}, and

15   for all-cause deaths 0.023 and for vascular deaths 0.0068.

16   I say this is a historic moment; the first

17   suggested guideline here. I haven't thought about this

18   enough that I am willing that is a good or bad thing. And

19   part of the reason I am doing that, if that is a precedent,

20   this is really a very unusual situation to have this much

21   control data. There are going to be a lot of situations in

22   cardiovascular medicine, let's say, where somebody does a

23   mortality trial and they are significant at the 0.03 level.

24   If you go very conservatively for the upper endpoint of the

1 confidence interval, you get into a situation where if that

2 same drug was developed again it would have a relatively low

3 probability of being able to establish itself against

4 itself, never mind another drug.

5   And I was disappointed yesterday. I didn't

6 comment because I knew I would be speaking today on active

7 control trial for a sponsor and I didn't want to embarrass

8 the FDA by getting up and making comments in the general

9 session. But I think we have some very difficult tradeoffs,

10 some very, very difficult tradeoffs on rules that allow the

11 possibility of mediocre drugs or possibly adverse drugs

12 getting through and entirely just killing off drug

13 development in certain areas because nothing can be done.

14 It would be so prohibitively expensive you couldn't possibly

15 recruit the money. I was sorry the discussion didn't

16 advance further yesterday.

17   So, to adopt the ten rule as going in that

18 direction, that is quite a strong rule of thumb. We know we

19 can't take them at face value when we are using historical

20 controls to begin with. They are slightly to greatly

21 different populations, etc., etc., etc. And I think we do

22 need to come up with some rules of thumb. It would be nice

23 to have a rule of thumb. I am just not willing to accept a

24 numerical value. In this situation, of course, we could

1 adopt that rule but I think that will be a fairly rare

2 event.

3   DR. KONSTAM: I would like Lloyd's comments on

4 this and also maybe Rob and Ralph would like to comment. At

5 a previous meeting of this Committee we had, in my mind, a

6 somewhat analogous situation of enoxaparin versus heparin

7 with historical data and an active control trial. At that

8 meeting, the merits of a Baysian analysis were put forward

9 as an alternative to the traditional approach of seeing the

10 strength at which the null hypothesis is rejected.

11   In this question of how strong the finding is

12 compared to the standard of two placebo-controlled trials,

13 does it merit that type of an approach? Was that done here?

14 I would just like you and anybody else to comment.

15   DR. FISHER: Just precisely what was the approach

16 when you say that type of approach?

17   DR. KONSTAM: A Baysian approach.

18   DR. FISHER: This is one of my favorite subjects

19 actually, but I am a little conscious of time because I

20 think the most interesting discussion is interaction. Let

21 me give you a 30-second thing. I am not a fan of true

22 Baysian analysis, and I had an article published last year

23 in Controlled Clinical Trials, so that you all should run

24 out and read --

1   (Laughter)

2   But there are now analyses that I called stylized

3   Baysian analyses where they really don't take expert

4   opinion. They take very pessimistic sorts of prior

5   distributions, for those of you who understand what is being

6   said and to me, that is frequentness in nature and we have

7   to look at the operating characteristics and may very well

8   be appropriate. So, I will move on.

9   DR. CALIFF: Two weekends ago I had to sit through

10   two hours with several of us, Lloyd and others, yelling at

11   each other, calling each other dirty names and whether they

12   were Baysian or frequentist statistics. I am glad you held

13   it to 30 seconds.

14   DR. FISHER: And I am thankful Frank Harold is not

15   in the audience.

16   DR. CALIFF: Right. But no matter how you think

17   about it, Baysian or non-Baysian, what we are talking about

18   here for is a probabilistic statement. Your definition of a

19   p value is slightly different than what I recall the p value

20   to be. I doubt if there are many people in the audience who

21   have any idea what a p value actually is, but could you say

22   again in the context -- when you put up that 0.00125, can

23   you translate that into something that a mortal human being,

24   non-statistician can understand?

1   DR. FISHER: Well, if there is no therapeutic

2   difference, only 1.25% of the time would an outcome this

3   extreme appear by chance.

4   DR. CALIFF: Okay, because what you initially said

5   was would a positive outcome occur. I think it may have

6   just been --

7   DR. FISHER: No, no, it is a positive outcome that

8   is statistically significant using that level.

9   DR. CALIFF: Using that level.

10   DR. FISHER: But it is a false-positive outcome,

11   of course --

12   DR. RODEN: It is one-eighth of a percent, Lloyd.

13   I hate to correct a statistician's math.

14   DR. FISHER: Yes.

15   DR. CALIFF: I want to ask a couple of questions

16   because, I mean, by definition what we are saying is that

17   our guidelines on the Committee are that approximately we

18   would recommend for approval a drug knowing that there is

19   roughly less than 1/1000 chance, or close to 1/1000 chance

20   that the results that we were approving this on are

21   something more extreme could have occurred by chance alone.

22   My question first to Ray or Bob is that is sort of

23   extreme mentality of having to be that sure. What is the

24   basis for that?

1   DR. LIPICKY: Let me respond first and then I am

2   sure Bob will give you another, similar response. What

3   Lloyd is saying is that that has been the usual paradigm for

4   decision making, and that, in fact, most scientific evidence

5   is evaluated the same way. One finds something once and it

6   becomes replicated, and it is that replication problem that,

7   in fact, puts it into that realm. That is the usual

8   paradigm that has been established.

9   The problem perhaps that you are addressing is,

10 because sometimes you can't repeat a trial, what is the

11 strength of evidence from the single trial that you can use

12 to make a similar decision? But what Lloyd laid out is what

13 the usual decision making is. It is not something new or

14 different or extraordinary.

15   DR. TEMPLE: As usual, none of these things are

16 completely simple. What Lloyd described is the statistical

17 equivalent of two trials, and only two trials, each of which

18 is significant at exactly 0.05. If it is less than that,

19 then the evidence is stronger. If what you are saying is

20 that that is a pretty high standard, I think a lot of people

21 would agree with you.

22   It often doesn't come out that way though.

23 Sometimes there are two trials that make it and a couple of

24 other trials that don't. So the true overall p value for

 1 those things is much fuzzier. What we have said recently,

 2 and this is available on our web site if you wanted to read

 3 it, is that sometimes a single trial can be persuasive. We

 4 didn't put a particular p value on it. Ray has from time to

 5 time done that. But what we have said is that if one study

 6 is very strong it can be persuasive, the idea being that you

 7 are very likely to believe it could be replicated. We all

 8 know of examples, not many but some, of very extreme p

 9 values in a single trial that weren't replicated. So, doing

10 that is not without risk. But it is also true that

11 sometimes you can have a couple of studies that are so-so

12 and you are not 100 percent sure you can replicate them

13 either. So, there is always some degree of uncertainty.

14   Of course, the discussion here is when you show a

15 significance against a trial and you have beaten an active

16 control but you are pretty sure on historical grounds that

17 it is better than placebo, does that sort of strengthen the

18 study in much the same way that a second study would? Well,

19 that is a novel discussion that hasn't really gone on but,

20 as somebody pointed out, that is not too different to what

21 the thinking was --

22   DR. FISHER: I would suggest, and this is just a

23 suggestion that at least for the Cardiorenal Division for

24 serious irreversible endpoints there needs to be more

1   guidance on conceptual things.

2   DR. CALIFF: There are two aspects to this that I

3   want to pursue for just a second. For the two trials, I

4   mean, to me it really is extreme because you are not only

5   asking for replication in a probabilistic sense but you both

6   trials have to be below the 0.05 threshold, which is fairly

7   arbitrary, and if you do that then you end up with this

8   extreme of less than 1/1000 probability.

9   DR. LIPICKY: Who said extreme? Only you are

10 saying that is extreme. I haven't heard anyone else say

11 that.

12   DR. CALIFF: Okay. Well, it would be interesting

13 to pursue that. The reason I am doing it is that a single

14 trial, to come up with that kind of a p value, would be a

15 remarkable trial and, yet, I think most of us thing that

16 something has to be --

17   DR. LIPICKY: But perhaps a more interesting

18 discussion would be whether, in fact, you should evaluate

19 things in terms of orders of magnitude of p value. The

20 question is how do you know that when you are different from

21 a p of 0.05 -- does it really take 0.005, and so on?

22   DR. CALIFF: So I guess one thing that I would

23 just argue about is that two trials at 0.05 is pretty

24 persuasive if they are done independently.

1   DR. LIPICKY: Absolutely.

2   DR. PACKER: Could I put a bookmark here? This is

3   an issue which is of importance to future trial designs, but

4   I think what I hear everyone saying is that a decision of

5   this Committee based on one trial needs to be based on

6   evidence which is more persuasive than a decision which is

7   based on two or more trials; and there are many factors that

8   go into the decision of persuasiveness other than a p value.

9   I think everyone would agree with that. It is not just the

10   p value; it is the concordance of data; it is the quality of

11   the trial. There are many aspects of the trial which are

12   important and, in fact, I would probably venture to say that

13   those non-p value aspects of the trial are frequently the

14   rate-limiting step as opposed to the precise p value which

15   would or would not need to be achieved.

16   So with that in mind, and I think there would be

17   concordance of that on the Committee, I would like to go to

18   Ralph and then go on with the rest of the presentation.

19   DR. D'AGOSTINO: I don't have anything more. I

20   was just going to try to remind the Committee of what I was

21   saying. I don't think we can put a lot of weigh in the p

22   values that are presented here. They are small, but how

23   small they are I don't think we can actually say that.

24   Other considerations have to loom in terms of a decision of

1 whether or not we think we have enough material here.

2   I also have to squeeze this out here, you are

3 looking at two positive trials but I have seen many

4 submissions with six or seven trials and two are positive,

5 some are supportive. I mean, if you started multiplying all

6 those p values together, who knows what you would get. It

7 is the replication, the scientific integrity, the different

8 populations, the different investigators.

9   DR. CALIFF: We are coming to the same

10 conclusions.

11   DR. PACKER: I think we are all saying exactly the

12 same thing, and I think Ray is also in agreement with the

13 fact that there are both p value and non-p value components

14 to the concept of persuasiveness. I guess, Ray, you would

15 agree that even a p value of 0.00001 would not be persuasive

16 if there were other problems with that trial.

17   DR. LIPICKY: Correct. It might make you feel

18 warm and fuzzy though.

19   (Laughter)

20   DR. RODEN: I have tried to learn from yesterday.

21 Lloyd, have you computed a guaranteed drug effect the way

22 Bob Fenichel suggested one should, or one should think about

23 for clopidogrel versus placebo?

24   DR. FISHER: No, I haven't done that calculation.

 1   DR. RODEN: Bob, have you? Is it going to be

 2 greater than zero?

 3   DR. FISHER: Yes.

 4   DR. RODEN: Okay.

 5   DR. FISHER: I mean, it will definitely be

 6 positive.

 7   DR. TEMPLE: Bob's analysis mostly related to when

 8 you achieved equivalence. It is arguably a much easier case

 9 when you are actually better.

10   DR. PACKER: With the indulgence of the Committee,

11 and I think we need to do this, let me ask the sponsor to

12 confine all of the remaining presentation to the issue of

13 heterogeneity. That is the only thing we have not

14 discussed, which means that I would ask you to have both

15 your statistical and clinical presentations confined to the

16 issue of heterogeneity. Cut everything else out. The issue

17 of heterogeneity pertains to one of the questions to the

18 Committee. In fact, it pertains to a whole host of

19 questions to the Committee, and relates to the fact that

20 there is a p value associated with the strata that were

21 involved in this trial. So, Lloyd and Dr. Pilgrim, I would

22 ask you to complete both presentations without interruption

23 by the Committee in the next 15 minutes.

24   **Statistical Interpretation-Heterogeneity**

 1   DR. FISHER: It might stretch to 20, 22 or

 2   something.

 3   (Slide)

 4   The second part of my talk is precisely what was

 5   requested.

 6   (Slide)

 7   The investigators planned a very large number of

 8   analysis, both in the protocol and also Dr. Gent is here who

 9   has discussed this with me. There were at least 17 analyses

10   planned, and the clinical qualifying conditions subgroup

11   analysis was one of many.

12   The primary preplanned subgroup analysis was by

13   geographic area to show consistency, although there was

14   definitely a plan to look at things by clinical qualifying

15   condition. I have no doubt that if there had been a

16   difference by geographical area we would have a debate about

17   the differences in therapy and care in different areas.

18   So, any remotely reasonable multiple comparison

19   adjustment of the 0.043 value for treatment by qualifying

20   condition subgroup interaction would remove the statistical

21   significance of the qualifying medical condition by

22   treatment interaction. This is not to say that the effect

23   could not be real but merely to put the nominal statistical

24   p value into a proper perspective.

1   The issues of addressing subset analysis, and in

2   particular the multiple comparisons involved, have been

3   addressed before. The best known is the Oxford group

4   looking at astrological signs and finding an effect. In

5   another content Robert Temple said, quote, it is also a fact

6   of life that every time you change one subset you find out

7   that you were probably wrong, end of quote. Still, although

8   the inference depends on the large number of subsets

9   examined, a lower standard might be argued for labeling

10   concerns, and here the biological understanding may also be

11   important to interpretation.

12   (Slide)

13   The psychology of looking at data of small under-

14   powered subgroups is very interesting, and I would suggest

15   that the focus is primarily here on, because the estimated

16   negative effect compared to aspirin not to placebo, I must

17   mention, which we already covered but compared to aspirin --

18   the numerically negative effect.

19   I did a quick computation to see whether in a

20   study this size with subgroups there might be one or more of

21   the subgroups which would have a negative estimate on the

22   true effects on the size observed, and the probability of

23   that was 35%. So, it is not particularly surprising that

24   there is a subgroup around, if you have these subgroups,

1 with a negative estimate.

2   This, of course, again, does not say that it is a

3 real finding but it is to point out that it is not an

4 unexpected finding either even when there is a true positive

5 value within each of the subgroups.

6   (Slide)

7   Statisticians and often clinicians distinguish

8 between different types of treatment interactions. A

9 quantitative interaction is an interaction where in each of

10 the subgroups you have directionally the same true effect

11 but possibly of a different magnitude. For most purposes,

12 this is usually of clinical concern because the reason you

13 want to give a drug is that you want to help the patient and

14 if a drug helps the patient compared to something else in

15 each subgroup, then it makes sense to give the drug even

16 though some patients will benefit more than others, and

17 every clinician knows that there are certain patient

18 characteristics where some drugs tend to be more effective

19 than in other patients.

20   My working assumption here, to be perfectly frank,

21 is that this is virtually always true if you have a large

22 enough data set. The drugs are beneficial but within

23 subsets you may get different magnitudes of effect.

24   A much more important issue, and one which we are

1 considering here, is a qualitative interaction. An

2 interaction is called qualitative if you have opposite

3 effects in the subgroups, if it is positive in one subgroup

4 and negative in another subgroup. That means, say,

5 clopidogrel compared to aspirin, again not compared to

6 placebo but aspirin, if it is better than aspirin in one

7 subgroup and worse than aspirin in another.

8   (Slide)

9   So, in looking for qualitative interactions there

10 are statistical tests. There is a test by Gail and Simon.

11 This test was not statistical significant, with a p value of

12 0.7. Nevertheless, I do have to say you don't have a lot of

13 power for looking at interactions, depending upon what is

14 going on.

15   My conclusion is that from a statistical point of

16 view there is certainly not compelling evidence there is an

17 interaction. I wouldn't say there is absolutely compelling

18 evidence there is not qualitative interaction. I think in

19 issues like this, this is where your biological medical

20 understanding becomes very important in trying to put this

21 into context. In my opinion, I doubt very much that it is.

22 I would suggest for a lot of reasons, including things like

23 shrinkage estimators -- I guess Lem has already gone, but

24 things like shrinkage estimators would indicate it is

 1 probably not there. But if there is an interaction, it is

 2 probably more likely to be quantitative than qualitative.

 3   (Slide)

 4   So just to summarize this, the statistics are

 5 suggestive at best, and not conclusive, because of the large

 6 multiple comparison issue. The review mentioned that the p

 7 value for the interaction was about the same as the p value

 8 for the primary predefined treatment effect and suggested,

 9 as I recall, that this indicated the same level of evidence.

10 That, of course, is just not true. There are reasons that

11 we predefine primary endpoints because, given a lot of

12 multiple comparisons, we can always find something going on

13 in general. So we have to somehow take that into account.

14 Again, I am not saying that proves there is no interaction

15 but I am saying it is not statistically compelling and I

16 found that statement not a very appropriate statement in the

17 review, actually, because there was a predefined primary

18 analysis. This is a number of things that were done, and

19 Dr. Gent has told me, in fact, that they didn't even plan an

20 interaction test. They were just going to look at the

21 treatment effect in the group, and when they saw the

22 estimates they said, well, maybe we ought to do an

23 interaction test and then they did it with the p of 0.046

24 value that you observe. Even if there is interaction, it

1 could certainly be quantitative and not qualitative.

2 Finally, it is not particularly surprising that one of the

3 subgroups has an estimated negative effect.

4   With that, I will turn the microphone over to Dr.

5 Pilgrim to discuss the biological-medical part of the issue.

6 **Clinical Interpretation**

7   DR. PILGRIM: Thank you. I will try and confine

8 myself to analyses related to heterogeneity or which affects

9 the interpretation of heterogeneity. I am afraid even with

10 computerized slides we can't quite go fast enough to exclude

11 all the issues I was going to cover but I will deal just

12 with focusing on those issues.

13   (Slide)

14   That is the first of the clinical issues, does the

15 observed variation in treatment effects across the

16 qualifying conditions make clinical sense?

17   Dr. Easton told you about the overall results of

18 the CAPRIE study, and Dr. Fisher has just commented in the

19 statistical interpretation.

20   (Slide)

21   In dealing with the subgroup differences I would

22 like to look at the CAPRIE results in more detail, and I am

23 going to use a number of post hoc analyses, many of which

24 were suggested to us by a consultant panel which, at the

1   Agency's suggestion, we had look at this issue.

2   I would like to look at the CAPRIE results with

3   regard to the sort of types of events prevented by

4   clopidogrel, and then look at the background characteristics

5   of the population in more detail to see how this affects

6   one's understanding of how clopidogrel is comparing with

7   aspirin. I hope that by looking at the data from these two

8   different perspectives it will help us in judging whether

9   the treatment differences are actually clinically credible.

10   (Slide)

11   This was the overall Kaplan-Meier curve of the

12 primary efficacy analysis, the combined endpoint of ischemic

13 stroke, myocardial infarction and vascular death. This is

14 the analysis for which CAPRIE was designed and powered. It

15 was not powered to make individual comparisons within

16 subgroups.

17   This analysis included the first event experienced

18 by each patient, whatever type of event that was. And

19 clopidogrel was superior to aspirin on this composite

20 endpoint. However, does clopidogrel have a beneficial

21 effect on each individual type of event?

22   (Slide)

23   Here are three separate analyses. Each one

24 compares the number of patients on clopidogrel and on

1 aspirin who experienced one of the event types at any time

2 during the study. For the ischemic stroke and myocardial

3 infarction analyses, that included fatal and non-fatal

4 events. For the vascular death analysis, it includes fatal

5 ischemic stroke, fatal myocardial infarction and other

6 vascular deaths. Thus, it gives a measure of overall

7 vascular mortality. Patients were included in each analysis

8 for which they experience an event. Thus, a patient having

9 both a stroke and an MI would appear in both the first two

10 analyses. A patient having a fatal MI would appear in the

11 MI analysis and the vascular death analysis.

12   As you can see, clopidogrel has a beneficial

13 effect compared to aspirin, a positive risk reduction, for

14 all three types of events considered separately, with by far

15 the greatest benefit being seen in the reduction of fatal

16 and non-fatal myocardial infarctions overall in 19.2%

17 relative risk reduction, and the risk reduction which was by

18 itself statistically significant. I think I would like you

19 to bear that effect in the prevention of MI in mind as we

20 look at the patient population in more detail.

21   (Slide)

22   How did patients qualify for CAPRIE? For ischemic

23 and myocardial infarction subgroups there were time windows

24 specified between the qualifying event and the time of

1 randomization. The time windows were defined for good

2 methodological reasons. They captured patients at or

3 shortly after their hospitalization for the qualifying

4 event, thus, ensuring that that event had been properly

5 documented, and they captured a population which was at high

6 risk of further events so giving good statistical power to

7 the study.

8   There wasn't any need for time window for

9 peripheral arterial disease because the disease is a chronic

10 one in which one can confirm the diagnosis at any time.

11 Patients tend to have a relatively constant event rate.

12   However, the time windows that were set for

13 ischemic stroke and myocardial infarction are relatively

14 arbitrary. They don't mark abrupt changes in the natural

15 history of the disease, and that is particularly important

16 in interpreting CAPRIE because atherosclerosis in more than

17 one vascular territory wasn't an exclusion criterion. Since

18 atherosclerosis is usually a generalized disease, it meant

19 that many patients who were entered in CAPRIE had

20 symptomatic disease in more than one vascular bed.

21   (Slide)

22   The next few slides present an analysis of the

23 CAPRIE population, the overall population taking into

24 account the full clinical range of manifestations of their

1 underlying atherosclerosis. About 40% of the total

2 population had symptomatic cerebral vascular disease that

3 could be the ischemic stroke that led to qualification but

4 it could be an ischemic stroke in the other two subgroups,

5 or it could be history, for example, of transient ischemic

6 attacks.

7   (Slide)

8   Over half of the CAPRIE population had symptomatic

9 coronary disease. Again, it could be the qualifying MI but

10 it could be a past MI or a history of stable or unstable

11 angina or a coronary revascularization procedure.

12   (Slide)

13   And 38% of the population had a history of

14 peripheral arterial disease which either led to

15 qualification for the study or was part of the medical

16 history in the other two subgroups.

17   (Slide)

18   So, if you look at the overlap in these groups,

19 something over a quarter of the CAPRIE population had

20 symptomatic disease in more than one vascular bed, and many

21 more are likely to have had asymptomatic but clinically

22 significant disease in more than one territory.

23   (Slide)

24   Dr. Easton showed you this analysis of the primary

1 outcome cluster by qualifying condition subgroup. This is

2 the analysis in which we observed quantitative heterogeneity

3 of treatment effects. As Dr. Fisher discussed, there are

4 statistical limitations to this observation and I would

5 suggest that because of the allocation of a patient to a

6 qualifying condition subgroup was in many respects an

7 arbitrary one, it also limited clinical relevance.

8   (Slide)

9   Since ischemic stroke and myocardial infarction

10 are normally reliably recorded in a patient's past medical

11 history, it is possible to group together all the patients

12 who have had either an ischemic stroke or an MI at any time

13 and disregard the trial entry time windows. On this slide

14 we have added that analysis, and these are the bars shown in

15 green, for patients with any history of ischemic stroke, any

16 history of MI and any history of peripheral arterial

17 disease.

18   When you take this broader view of the patient

19 population and their medical history into account, we see

20 convergence of the treatment effects with clopidogrel

21 showing a positive risk reduction over aspirin in each type

22 of patient. This analysis is still relatively restricted in

23 that it takes only the index event types rather than the

24 broader symptoms of, for example, coronary disease.

1   (Slide)

2   As you have seen, there is considerable overlap in

3   symptomatic atherosclerosis across the whole population.

4   What we have also done is look at the relative effects of

5   clopidogrel and aspirin in patients who have only isolated

6   disease -- they appear on the outside part of the diagram --

7   any history of coronary disease, and that is the broadest

8   definition of coronary disease including angina and

9   revascularization, cerebrovascular disease or peripheral

10   arterial disease, and also looked at what happens in this

11   overlap group where they have very severe disease with

12   symptoms in at least two vascular territories.

13   (Slide)

14   This isn't an issue which the CAPRIE trial was

15   designed to look at and, as with any post hoc analysis, you

16   have to be very cautious about it. But we did it because we

17   thought it might provide useful clinical insights into what

18   is happening with clopidogrel compared to aspirin.

19   It certainly suggests the possibility that the

20   benefits of clopidogrel over aspirin are more apparent when

21   you have patients with more extensive or severe disease as

22   we move from the patients with only disease in one territory

23   to the ones with any history, and then the overlap group

24   where the relative risk reduction appears to be greater than

1 | was seen in the overall population.

2 | (Slide)

3 | So fro ma clinical viewpoint, we conclude that the

4 | qualifying condition entry criteria in CAPRIE were driven

5 | more by trial design and recruitment considerations than by

6 | clinically significant distinctions, and that the qualifying

7 | condition subgroups do overlap substantially in terms of

8 | their overall medical history. When you take this overlap

9 | into account the treatment effects converge.

10 | (Slide)

11 | Furthermore, the benefit of clopidogrel over

12 | aspirin is apparent in each individual component of the

13 | composite endpoint, with the greatest effect being in the

14 | reduction of fatal and non-fatal myocardial infarction.

15 | Since those entering the trial with an MI are clearly at

16 | risk of further myocardial infarction, it is clinically

17 | compelling to expect that group to benefit from clopidogrel.

18 | I would suggest that the observed subgroup differences are,

19 | thus, not supported by a broader look at the CAPRIE data

20 | base. Thank you.

21 | DR. PACKER: Thank you. What I would like to do

22 | is open up the discussion on the issue of heterogeneity and

23 | ask Ralph to initiate that discussion.

24 | DR. D'AGOSTINO: I sit here with fear and

 1 trembling because what I am going to say I am going to say

 2 so quickly that people will ignore me. I think that in this

 3 particular trial, and in trials in general, it is nice to

 4 look at subgroups but I think the heterogeneity that they

 5 have seen here is well explained by chance. I mean, I think

 6 the discussion that happened it could happen with a 35%

 7 probability is clearly consistent with this happening, and a

 8 very comforting large probability. If you look at the

 9 discussion that we have just had or that was just given,

10 where you look at individuals with existing MIs as opposed

11 to MIs within 35 days, you see a consistent response. So my

12 feeling on this is that the heterogeneity is a statistical

13 artifact that we shouldn't spend time with. I think that

14 when you take the MIs even as defined and you look at the

15 placebo comparison, which I think is our bottom line, it is

16 pretty striking that it is significantly better than the

17 placebo.

18   DR. PACKER: Any other discussion from any other

19 member of the Committee? Udho?

20   DR. THADANI: Just a question. You raised the

21 issue that patients with a recent MI were not probably a

22 high risk group, while other groups were higher. I would

23 have thought, as a clinician, that a guy who has an infarct

24 in 1 day to 35 days -- the event rate is very high in those

1 patients. So, to me, that is one of the highest risk groups

2 for cardiovascular morbidity and mortality. I realize

3 stroke patients are risky too. I realize there are always

4 problems in subgroup analyses, as you have alluded to. It

5 is a risky business but compared to aspirin in that group, I

6 realize it could just be chance, is going up in that

7 direction so if one treated all those patients it is just a

8 bit uncomfortable that you may not be doing them any good in

9 the acute phase post-MI. I realize it probably is a post

10 hoc analysis. So, to me, that is one of the highest risk

11 groups, not a low risk group. If you look at the event rate

12 at 6 months you are talking about 12%, 13% problems. So I

13 am not sure -- that last conclusion, I could probably say

14 other groups are probably more high risk than that group.

15   DR. FENICHEL: I don't think one has to speculate

16 about that. In the trial there were approximately 900 --

17 the 3 groups, I will remind you, were almost exactly equal

18 and there were about 900 events in the stroke group. There

19 were fewer than 600 events in the MI group, and there were

20 fewer than 500 events in the PAD group. That was the extent

21 of risk in the 3 different groups.

22   DR. PACKER: Before concluding the discussion, let

23 me ask Ralph just a general question, maybe not so pertinent

24 to CAPRIE but a general question about trial design and

1 analysis. I believe this is true, that the qualifying

2 condition in CAPRIE was not as much subgroup analysis as it

3 was a part of the design of a stratified trial. I don't

4 know if that is the case and I wanted to ask that. Were

5 there separate randomization codes that were assigned to

6 patients based on their qualifying condition?

7   DR. PILGRIM: Yes, there were, and patients tended

8 to be entered into one clinical center only in one of the

9 subgroups because they were being entered by cardiologists

10 or neurologists or peripheral vascular surgeons.

11   DR. PACKER: So, in essence, this is not as if

12 everyone enrolled a relatively uniform population and

13 someone went back and asked whether patients who were over

14 the age of 75 responded differently than those who were

15 younger. This is a situation where the qualifying condition

16 was actually part of the initial stratification procedure,

17 which then led to a separate process of randomization to

18 either clopidogrel or aspirin within each of the strata.

19 Furthermore, the follow-up in the individual strata was not

20 precisely identical and that was as defined by the steering

21 committee. When the end date of follow-up was specified, it

22 was specified somewhat differently for purely

23 administratively things in the three strata. So, in some

24 ways this is not so much a retrospective or prospective

1 subgroup analysis as it is an analysis of strata within a

2 stratified trial.

3   To a non-statistician, what we have heard the

4 statisticians tell us in the past is that when you do a

5 stratified trial and you look at an overall p value, the p

6 value has meaning primarily if there is no heterogeneity

7 amongst the strata. So my question to you is if there is

8 now a finding, at least of the p value, of heterogeneity

9 amongst the strata? Do we take from that the play of chance

10 as we would if this were one of 20 subgroup analyses, or

11 does this have more meaning for us because it was part of an

12 initial stratification procedure, with literally separate

13 groups being studied as if it were three separate trials in

14 an umbrella study?

15   DR. D'AGOSTINO: I don't read it as three separate

16 trials. If it were thought that there were levels of

17 severity or levels of initial condition that would impact on

18 the outcomes, producing different types of outcomes, then I

19 think it is compelling. I don't read the design that way.

20 I don't read any of the material that was presented that

21 that is what was going on. Oftentimes when I stratify in

22 this case that you are talking about, I worry about it

23 because I might have different levels of severity and I

24 might, in fact, say that might in fact say that most

1   severity isn't going to produce anything; it is only going

2   to be in the really severe individuals. I am not

3   anticipating that, or at least I don't read anything that

4   anticipates that. Here, I thought it was a way of getting

5   at patients and then you sort of have follow-ups according

6   to those patients but you aren't expecting differential

7   outcomes.

8   DR. CALIFF: But it might be worthwhile to hear

9   Dr. Gent. If it were really just another subgroup why would

10 you randomize separately in each group? I mean, we have had

11 long discussions about this, as you know, and we were taught

12 to never do that unless you have a good reason to think that

13 there may be something different about those patients in the

14 different strata that would change the result of the trial.

15 So, I am just surprised that you don't at least give it some

16 credit for being a little different than just another

17 subgroup.

18   DR. FISHER: They actually stratified by center.

19 The enrollment, because of the type of referral and what was

20 being studied, was by center. So, if you stratify by center

21 you, de facto, stratify by qualifying condition.

22   DR. CALIFF: Okay, so it is not an intent to

23 stratify --

24   DR. FISHER: Dr. Gent should speak to that. I

1   wasn't there.

2   DR. GENT: The key intent was to stratify within

3   clinical centers, a standard procedure in these things. It

4   just happens that, you know, the PAD patients are going to

5   come in from the vascular surgeon group; the stroke patients

6   are going to come in from neurologists. So, it just works

7   out that we stratified by center and automatically you are

8   going to stratify by qualifying conditions.

9   DR. CALIFF: And that is true 100 percent of the

10 time? You never had an MI patient enrolled in a site that

11 also enrolled cardiovascular patients?

12   DR. GENT: Yes, we had it three times in Europe

13 and it was severely reprimanded. So, the intention was to

14 keep it pure within the center. It was a center

15 randomization.

16   DR. D'AGOSTINO: You do have to go back and look

17 at the conditions, like MIs and stroke. What about previous

18 MIs and how they impacted?

19   DR. PACKER: One second. So, Ralph, I just want

20 to make sure, again, that the issue is broader than CAPRIE.

21 The expectations of the investigators here are key to your

22 interpretation of the p value?

23   DR. D'AGOSTINO: The way I am reading the material

24 that was sent, and I don't see anything in the FDA's review

1 of it that says differently, that there was not the

2 compulsion to think of these individual groups as producing

3 different outcomes, and they were a convenience, and

4 evidently it was convenience by the centers that led to the

5 stratification that way. If there was an anticipation of a

6 different outcome if, as Rob says, you really are

7 stratifying because there is potential difference, then I

8 think it would be much more worthwhile and much more

9 important to consider it.

10   DR. PACKER: I understand, but just to follow

11 through on that, and I don't want to belabor the point, how

12 would investigators know to anticipate unless they had done

13 the trial?

14   DR. D'AGOSTINO: From having run preliminary

15 previous trials. I mean, most of the trials that I am

16 involved in have fed from other trials. You don't design a

17 trial with a blank sheet of paper. You have other things

18 that you anticipate.

19   DR. CALIFF: One could imagine in this scenario

20 where the aspirin overview is not very impressive for

21 peripheral vascular disease that you might, as an

22 investigator, even think your drug was particularly good or

23 maybe you would worry it would be like aspirin. If you had

24 specified that, and had that as a reason to stratify, then I

1   think what you say makes a lot of sense, and that wasn't

2   done in this case.

3   DR. TEMPLE: In a trial this size you probably

4   don't have to stratify by condition to get relatively equal

5   numbers of people in each group. There is almost no risk of

6   a severe imbalance.

7   But I guess I would say that there are some

8   preliminary grounds to at least consider the possibility

9   that response would be different in these groups. It is

10 fairly striking in the aspirin overview that with 500

11 patients in each group there isn't a dime's worth of

12 difference between aspirin and placebo in the subgroup with

13 peripheral artery disease. That doesn't make any particular

14 sense but we don't always know why things happened before

15 the explanation arises. So it isn't absolutely crazy to

16 look for those groups.

17   I guess what struck me about these results is that

18 although there is the striking difference between the

19 diagnostic groups, within those groups the results don't

20 make any sense so that, for example, the greatest effect is

21 on MIs. Well, how does that fit with the fact that the

22 people who had an MI initially are the ones that don't seem

23 to have a greater benefit with clopidogrel than aspirin? It

24 doesn't really make sense. Not only that, within the

1 peripheral artery disease group it is the people who also

2 had MI by history who had the greatest benefit. That

3 doesn't make any sense either.

4   All of which, I guess, makes me think that the

5 most likely explanation is chance because it doesn't sort of

6 add up once you look at the other pieces.

7   DR. RODEN: Just to continue that thought for a

8 second, the other possibility is that those were actually

9 not the same disease. I mean, we have been told that

10 atherosclerosis is a generalized disease and we are not

11 allowed to think of it as different in different beds, and

12 what I think this may be telling us is that it is different

13 in different beds; that the aspirin data don't support any

14 effect in peripheral arterial disease, whereas, these data

15 do. So, I mean, this may be important when it comes down to

16 sort of thinking whether these two drugs are identical or

17 not.

18   DR. FENICHEL: To the extent that it is pertinent

19 as to what the investigators contemplated when the trial was

20 designed, the evidence that I see in the protocol is that

21 there was a prespecified intent to check for homogeneity

22 among the three diagnostic groups but, at the same time,

23 there was no special intent to follow that up because the

24 strong expectation was that homogeneity would be found as,

1 of course, it was not at a level of significance, which may

2 or may not be moving. There is a piece of the protocol

3 which says that there is no prior evidence to suggest that

4 over a long period of time the relative efficacy of

5 clopidogrel and aspirin should differ among the separate

6 diagnostic groups and, thus, the primary analysis will

7 combine the treatment effect estimates for stroke,

8 myocardial infarction and peripheral arterial disease

9 patients. The consistency of these treatment effects across

10 the three clinical disorders will be investigated. That is

11 essentially all that is said about it in the protocol. The

12 further investigation along the three strata of the clinical

13 diagnostic groups was not, I think, really seriously

14 contemplated.

15   DR. KONSTAM: I just want to make a clinically

16 related point. I happen to agree with everything that has

17 been said that, to my reading, this is likely a play of

18 chance in terms of heterogeneity.

19   But there is another issue, other than the

20 etiologic group per se, and that is the temporal issue.

21 That is, the patients entered into the MI group did not only

22 have a prior MI, they had a recent prior MI, to be

23 distinguished from the patients, for example, who had

24 peripheral vascular disease who also had a history of an MI.

1 I just want to throw that out as another factor that may be

2 in play here. The distribution of clinically relevant

3 events occurring within a few months following a recent MI

4 may, in fact, be very different to the distribution of

5 events who happened to have had an MI a year or more ago in

6 terms of arrhythmic events, for example; certainly in terms

7 of what we know about the value of anticoagulation post-MI.

8 We really know about it in terms of the period after the MI,

9 not two, three or four years after. So I just want to throw

10 that out, that there is something more here than just MI

11 versus no MI. It is also recent MI, which is a little

12 different.

13   DR. PILGRIM: Could I possibly pick up on that

14 point? We did look for any interaction between time between

15 MI that led to qualification and time of randomization into

16 CAPRIE, and there was no significant effect across a 35-day

17 time window. Remember, the MI group looks less beneficial

18 because of the other vascular deaths category, and the small

19 excess on clopidogrel doesn't appear until some months into

20 the trial. So, I think everything suggests that that MI

21 group should behave like the 2100-something patients in the

22 other two subgroups that had an MI in the past.

23   DR. PACKER: Could I appear one final question?

24 This Committee has emphasized earlier today its preference

1 for a more general endpoint, for example, the endpoint of

2 stroke, MI or death from any cause, which is one of your

3 prespecified secondary endpoints. It would be interesting

4 to know whether this endpoint, which had some advocates on

5 this Committee earlier today -- whether there was

6 heterogeneity amongst the three qualifying groups for that

7 more general endpoint.

8   DR. PILGRIM: We didn't test for heterogeneity on

9 any of the secondary endpoints. There are a number of

10 secondary endpoint clusters.

11   DR. FENICHEL: We looked at that a little bit and

12 I don't think we actually did look for heterogeneity per se,

13 although Dr. Hung may want to comment on this, but

14 numerically results were pretty similar to the results using

15 the protocol-specified endpoint of vascular death. For

16 example, if we look at the endpoint of any stroke, not just

17 ischemic stroke, MI and any death, the relative risk

18 reduction in the stroke group was 5.5%; the relative risk

19 reduction in the PAD group was 18%, which was quite

20 impressive just as it was in the overall thing; and the

21 relative risk increase in the MI was 3%, which is not that

22 different from 4%.

23   So, if I may say with regard to your point about

24 this statement that the value for heterogeneity was

 1 comparable to the overall p value, we really made two

 2 statements. One was the significant was comparable, and I

 3 think Rob's point is well taken, that we really didn't think

 4 about this as one of multiple, potentially tantalizing

 5 results which should, therefore, be subject to some kind of

 6 multiplicity correction. On the other hand, Jim and I said

 7 the overall robustness of the finding was comparable to that

 8 of the overall finding in the trial. I think that is still

 9 a fair comment.

10   We tried in multiple analyses to make this result

11 go away by other co-factor analyses, by looking at different

12 versions of the endpoint, and some of these analyses were

13 confirmatory in the sense that they really could have been

14 different and weren't. Some of them were not confirmatory

15 really because they were highly correlated with the original

16 thing and so they really don't add anything. It would be

17 implausible that one would not be the same as the other.

18 That is really in the same way that we regarded the primary

19 result of 0.045 to be stronger than its apparent p value.

20 So that was the sense of that comment.

21   DR. FISHER: Can I make one quick comment for the

22 Committee? If a finding is a chance finding, you should not

23 be able to explain it away because it is a chance finding

24 and not related to the other characteristics. So there is a

1 robustness but it is not surprising either way.

2   DR. PACKER: I think the intent of the question

3 was simply to say that if the p value for heterogeneity

4 became more interesting if one generalized the endpoints, it

5 would be of a greater level of concern. I guess, on a

6 personal level, I would like the FDA to reassure itself

7 about the fact that the heterogeneity does not become more

8 striking if one generalizes to a more general endpoint.

9   DR. D'AGOSTINO: It becomes less so.

10   DR. PACKER: It becomes less so?

11   DR. D'AGOSTINO: According to the numbers. Who

12 knows what the p value is, but numerically --

13   DR. PACKER: It becomes less so.

14   DR. FENICHEL: You would expect it to become less

15 so, just as the primary result from the trial becomes less

16 impressive if one includes, you know, auto accidents and

17 what-not. As you include noise deaths the biological effect

18 becomes less visible.

19   DR. CALIFF: This is a somewhat different but

20 related question. It is on Table X and, again, it has with

21 dancing around 0.05 for the overall result, not the general

22 magnitude of the effect. Bob, your adjustment for all

23 covariants except anchovies, which I thought was an

24 impressive analysis -- generally when you adjust for the

1   kitchen sink the p value gets smaller, I thought, in

2   randomized studies. In this case the result goes a little

3   bit the other way. Am I wrong? Does it matter?

4   DR. D'AGOSTINO: Yes and no, but, you know, if you

5   randomize beautifully and so forth, hopefully, it wouldn't

6   go away at all by taking care of all these other factors.

7   DR. TEMPLE: But the direction isn't uniformly to

8   make the p value smaller.

9   DR. D'AGOSTINO: No, not at all.

10   DR. PACKER: We are going to, at this particular

11   point in time, to ask the sponsor if there is any pressing

12   information that they would like to convey to us because you

13   can rest assured that we have seen the remainder of your

14   slides and they are entirely consistent with the information

15   you have sent to us.

16   DR. EASTON: You have our slides. I think you can

17   link through the presentation at this time.

18   DR. PACKER: Thank you. One brief comment before

19   going to the questions, are there any comments from the FDA

20   medical reviewers or statistical reviewer that they would

21   like to put forward to the Committee before we go to the

22   questions? If not, we will ask the Committee one last time

23   if they have any questions to the sponsor or to anyone else

24   about any remaining issues which have not been covered.

1   DR. THADANI: I have one short question. I think

2 in the morning we raised the issue of total mortality and

3 vascular mortality. If one looks at the total mortality the

4 p value becomes non-significant. Am I correct? If you

5 include infarction, stroke and total mortality, then there

6 is no difference between aspirin and clopidogrel. Is that a

7 true statement?

8   DR. FENICHEL: The analyses that we have, stroke,

9 MI, amputation or vascular death, vascular death by itself,

10 any stroke, MI and any death, is that what you wanted?

11   DR. THADANI: Yes.

12   DR. FENICHEL: Any stroke, MI, any death, the risk

13 reduction is 6.9% and I know that for this whole cluster of

14 analyses, they are all from slightly below to well below

15 significance with everything going in the same and positive

16 direction.

17   DR. TEMPLE: One of them might be 0.52 and then

18 you can debate whether 0.52 is different.

19   DR. FENICHEL: Actually, the best of them was 0.08

20 of the list of five analysis in my Table IV, and then one of

21 them was just any death, where there was still a benefit but

22 it was only a 2.2% risk reduction, and that came out 0.71 so

23 that was nothing at all, but it was going in the right

24 direction.

 1   DR. TEMPLE: Do you know a p value for the all-

 2   stroke, all-death, all-MI?

 3   DR. FENICHEL: I don't, no. I am sure the firm

 4   does.

 5   **Committee Consideration of Questions**

 6   DR. PACKER: Let's proceed to the questions. I

 7   think the courses of the discussion already this morning has

 8   facilitated greatly our consideration of the questions and,

 9   although it may appear to some that the list of questions

10   before the Committee is intimidatingly long, it is unlikely

11   that we will need to address each of the questions and each

12   of the sub-questions in the specific detail in which they

13   may otherwise have had to be considered had the discussion

14   gone in a different direction.

15   Let me simply say for purposes of introduction

16   that the FDA reminds us that, "for clopidogrel to be

17   approved, the demonstration that it is superior to placebo

18   must be as convincing as those which, in other clinical

19   settings, have usually been provided by two or more

20   successful clinical trials. Recent discussions have

21   emphasized that the expectation of two successful trials is

22   not absolute, but that is only because a single trial can

23   sometimes provide evidence of similar strength."

24   Also, "before permitting comparative claims in any

1 drug's labeling, FDA has generally insisted on the

2 evidentiary equivalent of two or more successful trials.

3 Additionally, FDA has required that the comparator regimen

4 has not been handicapped by inadequate dosage or other

5 unfair burden."

6 With these reminders to the Committee, let us turn

7 to the first question. The first several questions are

8 concerned with the comparison of clopidogrel and aspirin,

9 and do not relate to the relative comparison of clopidogrel

10 to placebo. So, let me remind the Committee that the first

11 question deals primarily with the results of CAPRIE.

12 The question is, in the overall CAPRIE population,

13 clopidogrel appeared to be superior to aspirin. This

14 finding has one of five choices available. The intent here

15 is to pick one or to pick a choice between two choices, I

16 guess.

17 Let me ask the Committee, given the question of

18 the integrity of follow-up to answer the question first with

19 the assumption that the FDA is satisfied that the integrity

20 of follow-up is adequate; is non-biased or non-informative.

21 So, for purposes of the initial vote of the Committee, let

22 me ask the Committee to assume that the integrity of data is

23 not a problem. So, we are asking the members to choose one

24 conclusion that describes, in their view, the results of

 1 CAPRIE.

 2   Dan, let me turn to you as the primary reviewer

 3 and ask what your view is, 1(A) through 1(E), as to how you

 4 think the CAPRIE study could be viewed.

 5   DR. RODEN: Thank you. After all the paperwork

 6 and seeing the data, I think I am swayed more by the issues

 7 of total mortality as opposed to the prespecified endpoints.

 8 of the five options, I lean towards 1(A). I think that

 9 overall clopidogrel is the same as or perhaps marginally

10 superior to aspirin. I certainly don't think it is worse.

11 So, of the answers given, 1(A), 1(B) or 1(C), I lean toward

12 1(A).

13   DR. PACKER: Let me just clarify the intent of the

14 question, and maybe those who created the questions can

15 assist in this process. I think they would like to have the

16 questions reflect your spectrum of views. What you are

17 saying for 1(A) is that you can reach no conclusion at all

18 about this, which I don't think is what you are saying.

19   DR. RODEN: No, that is not what I am saying. See,

20 the answer I want to see isn't here. So I would choose

21 1(F), and the answer is that -- well, of the answers given,

22 I will take 1(B) then, probably attributable to the play of

23 chance.

24   DR. FENICHEL: May I explain this format, which is

1 something of an experiment?

2   DR. RODEN: If you tell us how we are supposed to

3 vote --

4   DR. FENICHEL: I am trying, and I want to do this

5 as early as possible in the game so we will not be telling

6 you how to choose your vote but how to vote.

7   The idea was in some of these questions that if

8 one believes that the overall CAPRIE population is so

9 disparate that the effects were of significant opposite

10 sense in subgroups, then it is pretty silly to talk about

11 the overall population, whether it is good in the overall

12 population or not because, plainly, that could depend in a

13 given patient and we would be going off in a whole different

14 direction. So that would be the 1(A) option. Heterogeneity

15 is so important that it is a silly question.

16   1(B) says, look, I don't care. It came out

17 positive or it came out negative in the other group. I

18 don't believe any of it. If you did it again I have no idea

19 where it would come out. It wouldn't matter if they did

20 100,000 patients, we don't know what would happen.

21   1(C) is sort of a typical p of 0.2 trial, where

22 perhaps there is some biological basis. You think if they

23 did it again and did it bigger, yes, it probably would come

24 out. It is too bad that they didn't do it bigger.

1   1(D) is your typical successful trial and 1(E) is

2   the single trial that blows you away.

3   DR. TEMPLE: Can I add one thing? This part is

4   not asking about the question -- this is important --

5   whether clopidogrel has been documented for labeling and

6   other purposes to be better than aspirin. That is not the

7   question. That comes later. This is an attempt to get a

8   view of this particular trial and what it shows.

9   DR. PACKER: Let me see if I understand. The idea

10   is to get a sense as to what the Committee's view of CAPRIE

11   per se is, and whether we would rank it as being, one, non-

12   meaningful which means that we can't interpret it; two, that

13   whatever was found was due to the play of chance; three, it

14   is going in the right direction but is not as persuasive as

15   a typical successful trial. The others you can read for

16   yourself. In other words, this is really an evaluation of

17   CAPRIE but not a conclusion about the comparison of

18   clopidogrel and aspirin. I understand those are related

19   issues, but this is not the question being asked.

20   DR. TEMPLE: If this were a placebo-controlled

21   trial and you beat it at this level of significance, with

22   this kind of quality and with the other concerns, what would

23   you think of it?

24   DR. RODEN: If I get it explained to me again I

1 will change my mind again I suppose, but I think I

2 understand what the question is now and, having understood

3 the question, my answer is (C). And I don't want it

4 explained to me again!

5   (Laughter)

6   DR. PACKER: It is interesting, Dan, as we

7 continue to explain it your answer moves down the list!

8   (Laughter)

9   So, Dan has voted for (C). Marv, (A) through (E),

10 please pick one.

11   DR. KONSTAM: I am also going to vote 1(C). I

12 interpret it as a positive trial but the results are made

13 marginal, to me, in part by the fact that the p value is

14 close, the fact that when you look at some of the secondary

15 endpoints the p value falls above 0.05, and the

16 heterogeneity, although I think it is probably a play of

17 chance, adds an element of doubt in my mind. So I consider

18 it a plausible finding but weaker than that of a typical

19 successful trial. 1(C).

20   DR. DIMARCO: I will go for 1(D) for the endpoints

21 the investigator specified, but since I think total

22 mortality is more important it is probably 1(D -), or 1(C

23 +), either way you want to look at it.

24   DR. PACKER: Those are perfectly reasonable

1 responses. You know, these are arbitrary subdivisions.

2 JoAnn?

3   DR. LINDENFELD: I would say 1(C) too, I think,

4 because of the total mortality issue and also this is a p

5 value that is significant but a very small clinical effect.

6   DR. PINA: I am also going to vote for 1(C) for

7 very similar reasons to what Marv said. Even though the

8 heterogeneity may be chance, it plants a seed of doubt in my

9 mind, and I also have an interest in the total mortality

10 and, as you know, I continue to be concerned about the early

11 myocardial infarction group.

12   DR. CALIFF: Yes, I would also go with 1(C). If

13 this were one of two trials it would be phenomenal. As a

14 single trial it is right on the border but it is still a

15 successful trial, a little bit weaker than what one would

16 hope for.

17   DR. THADANI: I would go for 1(C). I already said

18 the p value is marginal and if you include the total

19 mortality there is not much difference. I am really

20 concerned -- the patients with a recent MI worries me a bit.

21 So I would say 1(C).

22   DR. PACKER: I would also vote for 1(C). I guess

23 my primary reason for concern is the cause specificity of

24 the endpoint. I think I would be a little bit more

1   comfortable if the endpoint were more general, and it is

2   just a borderline significance.

3   DR. D'AGOSTINO: Do I vote?

4   DR. PACKER: Yes, you do.

5   DR. D'AGOSTINO: I would go for the 1(D -). I

6   think if we had two trials like this we would look very

7   favorably on this one, here. So I would put it in 1(D).

8   DR. PACKER: We have two semi-absentee ballots,

9   one from Dr. Moye voting 1(C) and one from Dr. Graboys

10 voting 1(D). So, I believe there are two or three votes for

11 (D) and the remaining are for (C).

12   Before going on to question two, there is the

13 question about the integrity of the follow-up, and I would

14 assume, without taking any votes, that if there were

15 concerns about that that were not adequately addressed by

16 the FDA that none of what we vote would matter.

17   DR. CALIFF: One nuance of that is if the modeling

18 or whatever is done to deal with it, lost-to-follow-up

19 pushes the p value above 0.05 for the estimated p value.

20   DR. PACKER: Also, it is hard to know what models

21 might be appropriate here. Ralph, do you want to address

22 that in any way?

23   DR. D'AGOSTINO: I have no real notion of the sort

24 of lost-to-follow-up in terms of how it will affect the

1 numbers here, but I think once they start getting in some of

2 the data they will have a sense of the notion of the

3 randomness or the informed bias. There are techniques that

4 can do it, and if these results turn out not to be robust

5 the application of some of those techniques start driving

6 the p value, not to 0.06 but if they start driving it to

7 0.20 or something like that, I can't imagine that happening

8 but if things like that happen I certainly would drop my

9 vote in the (A) or (B) category. I think that is very

10 important.

11   Let me also just throw in too that I think our

12 discussion of the mortality and the overall mortality, I

13 voted for this trial as a (D). If they were to go to a

14 second trial, I think all the discussion about overall

15 mortality as part of that endpoint is extremely important,

16 and putting in vascular deaths -- I wouldn't want to see a

17 complete replication of this trial.

18   DR. PACKER: Thank you. That is actually very

19 helpful. The second question deals specifically with the

20 issue of homogeneity in CAPRIE. The Committee is being

21 asked what it thinks about this as being an issue or not.

22 We have the already familiar choices: play of chance; a

23 plausible finding; persuasive or very persuasive, I guess

24 would be the way of thinking about this.

1   Dan, let me ask you to choose one.

2   DR. RODEN: Of the options offered, I am inclined

3   to 2(B).

4   DR. PACKER: (B). Marv?

5   DR. KONSTAM: I think it is play of chance, 2(A).

6   DR. DIMARCO: I would go with 2(B). I can't think

7   of an explanation for it but I don't think that you could

8   never find an explanation.

9   DR. LINDENFELD: I think probably 2(A).

10   DR. PACKER: Hold on, I am sorry. It was (B),

11   Marv? (A). John?

12   DR. KONSTAM: (B).

13   DR. PACKER: JoAnn?

14   DR. LINDENFELD: (A).

15   DR. PACKER: Ileana?

16   DR. PINA: 2(B).

17   DR. CALIFF: I am really torn about this, but I

18   would go for 2(A -). I think it is very much likely due to

19   the play of chance, but the fact that it was a

20   stratification variable in a sense makes me lean a little

21   bit more towards 2(B) but a lot of subgroups were looked at

22   and this happens all the time.

23   DR. THADANI: I will go for 2(B). Although it

24   could be a play of chance, I think the fact there were

1 separate groups from the start worries me somewhat so I will

2 vote 2(B).

3   DR. D'AGOSTINO: 2(A).

4   DR. PACKER: Okay. The vote of Dr. Moye is (A).

5 The vote for Dr. Graboys is (C). My own vote is (B). It is

6 approximately evenly split between (A) and (B), which I

7 think sort of reflects the Committee's sense that it is

8 either (A -) or (B +). There is some level of concern but

9 we could also accept the high probability that this is due

10 to the play of chance. I think that would be an accurate

11 assessment of the Committee's view.

12   The next series of questions deals with subgroups.

13 Bob, let me ask you, do you want us to deal with these

14 questions, given the fact that our sense of confidence in

15 the presence of homogeneity was voted the way it just was?

16   DR. FENICHEL; I think not.

17   DR. PACKER: Having said that, let us now go to

18 question five. Question five: To draw a regulatory

19 conclusion about clopidogrel and placebo -- let me

20 emphasize, this is now a shift in emphasis -- one must

21 somehow combine the CAPRIE data with the accumulated data

22 from trials that compared aspirin to placebo. There are

23 obviously pitfalls to doing so. All those have already been

24 discussed and mentioned. The FDA would like to know if we

1 are willing to engage in such a process. I guess the answer

2 here is yes or no. So, we are being asked whether we are

3 willing to reach conclusions about whether clopidogrel would

4 have beaten placebo based on what we know in CAPRIE and what

5 we know in the meta-analysis aspirin trials. So, Dan, are

6 you willing to keep going?

7   DR. RODEN: yes.

8   DR. PACKER: Marv?

9   DR. KONSTAM: Yes.

10   DR. DIMARCO: Yes.

11   DR. LINDENFELD: Yes.

12   DR. PINA: Yes.

13   DR. CALIFF: Yes.

14   DR. THADANI: Yes.

15   DR. D'AGOSTINO: Yes.

16   DR. PACKER: Yes. Having said that, we will keep

17 going. In the overall analysis of the pooled aspirin-

18 placebo trials whose patients were similar to CAPRIE,

19 aspirin was superior to placebo. That is what the meta-

20 analysis has concluded. The question is do we agree with

21 that meta-analysis or how would we judge our comfort with

22 that conclusion. We have again the usual spectrum of

23 responses, from we don't believe it at all to the

24 possibility that we find it entirely persuasive. Dan?

1   DR. RODEN: Well, I think it is a sort of (C +) or

2   (D -) and I will say (C). This is aspirin versus placebo.

3   DR. PACKER: This is aspirin versus placebo.

4   DR. RODEN: I mean, the numbers are larger and the

5   trials are multiple, on the other hand, it is a meta-

6   analysis. That is why I say (C).

7   DR. PACKER: It is a meta-analysis which includes

8   many individual positive trials. Marv?

9   DR. KONSTAM: I vote 6(E). I have no statistical

10   basis for doing it, based on what I hear, but I just must

11   say that looking at the entire meta-analysis, and something

12   that has been discussed before this Committee at a previous

13   meeting a year ago, I am very, very impressed by the overall

14   efficacy of aspirin on the basis of the meta-analysis, and I

15   am going to vote 6(E).

16   DR. DIMARCO: I think the Committee, in its

17   wisdom, voted 6(E) last year and I will stick with that.

18   DR. LINDENFELD: I agree, 6(E).

19   DR. PINA: 6(E).

20   DR. CALIFF: Yes, I would say if you don't believe

21   this, what could you possibly believe about efficacy about a

22   therapy? (E).

23   DR. THADANI: 6(D).

24   DR. PACKER: (D)?

1   DR. THADANI: (D), as in David.

2   DR. D'AGOSTINO: (E), as in Edward.

3   DR. PACKER: Dr. Graboys is (C) and Dr. Moye does

4   not vote because he was not willing to engage in the

5   process. And my vote is (E).

6   Question number seven is a relevant issue because

7   it deals with one of the deficiencies, potential

8   deficiencies of the meta-analysis on aspirin, which is the

9   lack of a great deal of information about the effect on

10 vascular events in patients who entered the aspirin trials

11 who had peripheral arterial disease as their qualifying

12 condition. In that meta-analysis aspirin was not

13 distinguishable from placebo. The Committee is asked as to

14 whether we believe that lack of distinguishability from

15 placebo to either be, (A), due to inadequate sample size.

16 That means that we believe that an effect would have been

17 observed if there had been more events. (B), a plausible

18 finding, but weakened by the fact that there is an

19 inadequate sample size. Those are the only two options

20 available to the Committee.

21   So the question is how concerned are you about the

22 fact that there are no data about the effect of aspirin in

23 peripheral arterial disease? Does it just make sense and

24 you think that there just isn't enough data? Or, do you

1 think that it is actually a reason to think that aspirin

2 does not work in patients with peripheral arterial disease?

3   DR. RODEN: (B).

4   DR. KONSTAM: Yes, I agree. (B). I don't know

5 what the basis of the plausibility is but I think it is

6 possible. I also just want to say, you know, I don't think

7 atherosclerosis is a single disease. So, I guess on that

8 basis I would say it is plausible.

9   DR. DIMARCO: I will say (B). I think it is hard

10 to take an observed fact and say it is not plausible.

11   DR. LINDENFELD: I will say (B) too.

12   DR. PINA: (B) for me.

13   DR. CALIFF: (A -) for me. It is plausible but

14 very, very, very weakened by an inadequate sample size in

15 the overall weight of the evidence in the aspirin overview.

16   DR. THADANI: I vote (B) again. The small sample

17 size is worrisome. So (B) for me.

18   DR. D'AGOSTINO: I am voting (A), not because it

19 isn't plausible but because I just have no way of

20 interpreting it with the sample size.

21   DR. PACKER: I will vote (B) as well.

22   Let me clarify something. I said something in

23 error and I truly apologize for this. The vote for the

24 unwillingness to merge the data came from Dr. Graboys and

1 not from Dr. Moye. I apologize for that. I have a whole

2 host of little pieces of paper and I got them confused. Dr.

3 Moye's vote is actually (C). He really basically abstains

4 on the vote. My vote is (B) and Dr. Graboys didn't want to

5 vote because he wasn't merging the data so it is an

6 abstention.

7   Questions that remain to the Committee attempt to

8 ask the Committee to bring all of the available information

9 together to make recommendations that would lead to a

10 decision by the Agency.

11   The first question, which is number eight, what

12 are the populations, if any, in whom there is persuasive

13 evidence of clopidogrel's superiority to placebo?

14   The Committee has already voted on how it feels

15 about CAPRIE, and the Committee has voted on how it feels

16 about the comparisons of aspirin versus placebo. So, this

17 question deals with the extrapolation of how clopidogrel

18 would fare over placebo, were there a placebo in the

19 controlled trials.

20   Clopidogrel seemed to be superior to aspirin;

21 aspirin seemed to be superior to placebo. The conclusion,

22 therefore, that is posed is that clopidogrel might be

23 considered to be superior to placebo in all patients similar

24 to those enrolled in CAPRIE. It is A over B, B over C; A

 1   must be greater than C. The question is, do we think that,

 2   given our view about CAPRIE and our views about the aspirin

 3   data base, how would we judge the efficacy of clopidogrel

 4   over placebo? Dan?

 5   DR. RODEN: I am sitting here reading the options.

 6   Well, without reading the options, my view is that

 7   clopidogrel clearly is superior to placebo. Whether that is

 8   (E), about as persuasive as a typical successful trial, or

 9   (F), as persuasive as a package of two or more, I am not

10   sure. I think I lean towards (E +), (F -). (E).

11   DR. PACKER: (E). One vote for (E). Marv?

12   DR. KONSTAM: I guess I am at about an (E +). You

13   know, I think that logically, based on what I have said

14   before in terms of the aspirin data, if one were to believe

15   that the CAPRIE data prove that clopidogrel is no worse than

16   aspirin, I think then one would have to be pushed all the

17   way to (F). I have trouble quite getting there because it

18   is a single trial, because of uncertainty in my own mind

19   about how to analyze this difficult problem of an active

20   control statistically, and for those reasons I am not quite

21   there. I am definitely at (E) and I guess I am at about an

22   (E +).

23   DR. DIMARCO: I will go with (F).

24   DR. LINDENFELD: Yes, I think (F). I think that

 1 clopidogrel certainly appears unlikely to be worse than

 2 aspirin. So I would go with (F).

 3   DR. PINA: (D), to me, sounds a little bit more

 4 credible. I am still confused by the peripheral vascular

 5 disease group and by that myocardial infarction group. I

 6 would say (D), maybe (D +).

 7   DR. FENICHEL: Milton, it seems to me if that is

 8 your reasoning, then I would think that you would choose (A)

 9 and then express your feelings about the specific groups,

10 one or more of questions 9, 10 and 11. The purpose of (A) is

11 to say you can't combine them because you have good things

12 here and bad things there, and so let's go down to the other

13 more group-specific questions.

14   DR. PACKER: That is an important point. If one

15 looks at the questions for 9, 10 and 11, we would

16 effectively skip those questions if you vote (E) or (F). If

17 you believe that going through questions 9, 10 and 11 is

18 important, then you would vote something other than (E) or

19 (F).

20   DR. FENICHEL: I mis-spoke a minute ago and this

21 may have confused members of the panel and of the audience.

22 The people worried about heterogeneity should be going for

23 (B), as in boy.

24   DR. CALIFF: Well, people that are really, really,

1 really worried about heterogeneity -- I mean, I am worried

2 about heterogeneity but I would go with (F) here, and I am

3 going with (F) here because it seems like basically we have

4 a single trial but it is a huge trial, and it either

5 marginally beat or almost beat aspirin and aspirin is better

6 than placebo. And I think the majority feeling was that

7 subgroup analysis of the aspirin meta-analysis is not a big

8 deal.

9   DR. D'AGOSTINO: Can I make a comment here?

10   DR. PACKER: Yes, Ralph, given the fact that there

11 probably wasn't a lot of discussion of this before the vote,

12 we should have some discussion on this.

13   DR. D'AGOSTINO: Yes, this is not saying CAPRIE,

14 you know, with the two positives basically; this is saying

15 clopidogrel with placebo. If you take each of the endpoints

16 and you start looking how it does placebo and the subgroups

17 you get quite a striking consistency.

18   DR. TEMPLE: And no heterogeneity.

19   DR. D'AGOSTINO: And no heterogeneity. The

20 heterogeneity is in the CAPRIE. It is not in the meta-

21 analysis comparison.

22   DR. CALIFF: So that was my feeling. It is a very

23 persuasive argument, it seems, that clopidogrel is better

24 than placebo in all the groups, even if you think there is

 1 heterogeneity versus aspirin with these tiny, little p

 2 values. We said we can't say exactly what the p value is

 3 but it is an order of magnitude different p value for

 4 clopidogrel versus placebo if you accept that you can do

 5 this.

 6   I would like to add that if we say we can't do

 7 this, then future development of therapies where you can't

 8 get a placebo is sort of out the window because there is no

 9 other data base as good as the aspirin meta-analysis to use

10 as a historical control. So, I think we would need to

11 suggest an alternative for how to develop drugs if we reject

12 this.

13   DR. LIPICKY: Can I enter into this for just a

14 second? I am getting confused now. I thought that you had

15 already decided about whether or not CAPRIE had a finding,

16 and that the discussions about whether you are going to use

17 the placebo group and all that sort of stuff -- and, in

18 fact, there was a finding with respect to placebo. And

19 questions 8, 9 and 10 deal essentially with who these

20 findings apply to.

21   Question eight says you said something about the

22 study. Is that for patients like were entered in CAPRIE?

23 That would mean MIs, stroke and PAD. Depending on how you

24 answer that, question nine then deals with each of the

1 subgroups sort of. So the discussion about endpoints and

2 things like that is not the appropriate -- this doesn't seem

3 like the appropriate place to be doing that because you

4 already said that CAPRIE found something with respect to

5 placebo.

6   DR. PACKER: No, we didn't. We did not conclude

7 that.

8   DR. LIPICKY: Oh.

9   DR. PACKER: We can go back to what the vote on

10 question one was.

11   DR. LIPICKY: No, no, no. That was compared to

12 aspirin.

13   DR. PACKER: Right. The question was whether

14 CAPRIE found something compared to aspirin.

15   DR. LIPICKY: No. I said you had already answered

16 in question six --

17   DR. PACKER: That is aspirin versus placebo.

18   DR. LIPICKY: Oh, I am terribly sorry.

19   DR. PACKER: I assume that what we are looking for

20 here is a conclusion of clopidogrel versus placebo, a

21 question this Committee has not addressed to date.

22   DR. CALIFF: Then I vote (F) because it seems that

23 clopidogrel beats placebo in all three subgroups. Even if

24 you think there is heterogeneity of clopidogrel versus

1 aspirin, it still beats placebo for all three subgroups.

2   DR. PACKER: Let me just ask, for those of you who

3 had voted (E), which is a comparison of clopidogrel versus

4 placebo, and until this point in time most of you have voted

5 (E) or (F) with some variation between the two, would anyone

6 change their mind based on the discussion and interaction

7 that has taken place?

8   DR. RODEN: (E +).

9   DR. PACKER: Okay. Udho?

10   DR. THADANI: I will vote (E).

11   DR. D'AGOSTINO: (E) also.

12   DR. PACKER: I would vote (E). Dr. Moye votes

13 (D).

14   DR. CALIFF: So what people are saying is that

15 they feel that the evidence presented here -- this is just

16 with regard if you said it for all three. So we need to go

17 through it.

18   DR. PACKER: What we are saying is that based on

19 the vote on question eight, I can't see any reason to go

20 through questions 9 and 10 and 11. Is that a correct

21 statement?

22   DR. FENICHEL: No, I don't think it is, Milton.

23 The 8(F) option says this is the same strength of evidence

24 that we normally use for approval, and only a small minority

1 of the members of the Committee voted for that. It is

2 possible that members of the Committee would choose an

3 analogous option in the group-specific questions. So, it

4 might be worthwhile to go through those questions, although

5 it would be very fast.

6   DR. CALIFF: Milton, this is critical because the

7 vote on question eight says the majority would not say that

8 this meets the two-trial standard for beating placebo.

9   DR. RODEN: I just want to say that, you know, we

10 are sort of in uncharted water here and the two-trial

11 standard is one that I am not sure we necessarily have to

12 adhere to. We are asked for sort of qualitative answers to

13 these questions, and just because I voted 8(E +) doesn't

14 necessarily mean I think we ought to have two p 0.05 trials.

15 Because we are really being asked about active controls and

16 we are being asked about a single trial. These are sort of

17 new issues.

18   DR. TEMPLE: You are being given thorough

19 discretion on this. This doesn't say to use two separate

20 trials; it says is it about as persuasive as the usual

21 standard for approval. You are being asked to make a

22 judgment, and the judgment you made was almost. That is

23 what your (E +) sounds like.

24   DR. LIPICKY: In fact, there is a question here

1 | that asks do you think it should be approved. This is only

2 | attempting to sound out the persuasiveness that you would

3 | attribute to each of the components that you are eventually

4 | going to say approve or don't approve on the basis of.

5 | DR. TEMPLE: But having said that, if you say that

6 | even though it is clearly less than the usual standard, I

7 | might not do that. You need to know that. We haven't

8 | abruptly lowered the effectiveness standard. So consider

9 | these things together. These are organized to try to find

10 | out your reasoning, and some kinds of things you could tell

11 | us we might not do. If you said there were no adequate and

12 | well-controlled studies but we would like you to approve it,

13 | we wouldn't do that because that would be a violation of

14 | law. If you say this is less thana the usual standard -- I

15 | am not saying we couldn't, but we would have to think

16 | strongly about why we should honor that request.

17 | DR. CALIFF: I would like to urge that we talk

18 | about this a little bit.

19 | DR. PACKER: Why don't we go through it? Let me

20 | recommend the following, which I think might be a useful way

21 | of doing it. We should go through 9, 10 and 11 and then,

22 | depending on the answers to those, we might want to revisit

23 | number 8.

24 | DR. FENICHEL: Milton, if you had the same answer

 1 to each of 9, 10 and 11 --

 2   DR. PACKER: No, no, depending on the answers.

 3   DR. FENICHEL: -- and did not revisit 8, then we

 4 would take you have all just changed your minds.

 5   DR. PACKER: I understand.

 6   DR. TEMPLE: Milton, it is hard to see how 9, 10

 7 and 11 are going to get you the discussion you want of this

 8 point. Do you really think people are going to be persuaded

 9 that one of those subgroups is the answer? Is that a

10 plausible outcome of the discussion?

11   DR. PACKER: Bob, I think that although I cannot

12 totally understand the rationale for going through 9, 10 and

13 11, the Committee seems to want to do so.

14   (Laughter)

15   DR. LINDENFELD: Can we vote on whether we want

16 to?

17   DR. PACKER: No one cares one way or another?

18   DR. RODEN: Milton, can I change my vote from 8(E)

19 to 8(F -) instead of 8(E +)?

20   DR. PACKER: Rob, maybe you can explain why you

21 think going through 9, 10 and 11 is important.

22   DR. CALIFF: No, no, I am actually more interested

23 in the discussion that is really behind question 8 than I am

24 in 9, 10 and 11. The one reason that it might be worth

1 going through 9, 10 and 11 is if some members felt that

2 there was an (E) answer to 8 but for some components there

3 was an (F) answer; if they really believe that for

4 peripheral vascular disease clopidogrel meets the two-trial

5 equivalence standard. Because what the majority have voted

6 here I think is an incredibly difficult barrier under 8 for

7 any new therapy to be approved where there is already an

8 effective treatment. I mean, if you got a treatment that

9 has a dramatic reduction in the primary endpoint already on

10 the market, and then you had to come through and do better

11 than this, that is a remarkable barrier to have to get

12 through.

13   DR. TEMPLE: We knew this was a hard question. We

14 knew there was only one study, and we knew that it wasn't

15 all-cause mortality, and we knew that it was close to the

16 usual margin p value. The questions, and all that, are set

17 up to evaluate the question of whether an active control

18 trial that has that result, which the Committee thought was

19 somewhere between not so persuasive and persuasive, is

20 enhanced enough to be persuasive by the existence of the

21 aspirin data.

22   That really is the question, and it is very much a

23 judgment call. There isn't a way that we could think of to

24 add up p values and reach an answer. So, it is very much a

 1 judgment. But, I don't want to be coy about this, that

 2 judgment has something to do with whether we can approve it.

 3 You know, that is why we call on experts on things like

 4 this.

 5   DR. D'AGOSTINO: My voting (E) as opposed to (F),

 6 and I am also willing to change I guess, is not the aspirin

 7 comparison so much but the CAPRIE study. I just think that

 8 that study has questions about it so that I would like to

 9 see a replication. I am not asking that they ever do a

10 placebo. I mean, they can go right back to the meta-

11 analysis and make their comparisons, but I would like to see

12 the positive control study redone, and I would like to hear

13 some discussion on that.

14   DR. PACKER: Rob, before we go further, let me

15 just ask, it sounds to me -- and this is to Bob Fenichel --

16 that what you want to hear from the Committee, given the

17 fact that the Committee has voted to varying degrees between

18 (E) and (F) on question 8, as to whether individual

19 qualifying condition would be viewed by some as meeting one

20 or two trials. Is that fair? The strength of evidence for

21 individual conditions is one or two trials because we have

22 already said that from a global perspective it is (E) or

23 (F).

24   DR. FENICHEL: I am not sure I can add much to

 1   what bob Temple just said, which is that any answer short of

 2   (F) says this product overall does not meet the usual

 3   regulatory standard. I don't want to comment on the value

 4   of that judgment but, if that is so, then when we get to the

 5   question which asks whether it should be approved -- so,

 6   first of all, consistent with regulatory history and perhaps

 7   with the law, one would have to say no. And if one decided,

 8   well, we need not to be consistent; let the Agency sort this

 9   out and we voted yes, then we go to the next question which

10   asks in what population is this as convincingly as the usual

11   regulatory standard, etc. shown to be superior to placebo?

12   And there is not an option there in no population because,

13   once again, if there is no population in whom it is

14   convincingly superior to placebo it doesn't make any sense

15   to approve it. It is approved for use in no one. Well,

16   that doesn't make any sense.

17   So, there is a difficult situation here and I

18   guess in expressing an interest in questions 9, 10 and 11 I

19   am looking at what, at least as the questions are written,

20   the only remaining option, perhaps finding members of the

21   Committee who somehow think it ought to be approved and have

22   a reason, consistent with regulatory history, which is not

23   expressed in their answer to question 8.

24   DR. PACKER: I guess what the Committee is being

1 told is that if we believe that there is a difference

2 between (E) and (F) in terms of strength of evidence, and

3 whether that distinction is being made for all patients or

4 for individual groups of patients, that has different

5 regulatory implications. So, the Agency would want to know

6 whether globally or individually the strength of evidence

7 meets one or two trials. The Committee should remember that

8 in question 8, when they went through it, the majority of

9 the Committee voted (E), which was as persuasive as the

10 findings of a typical successful trial.

11   DR. FENICHEL: Yes, I think that what Ralph said

12 just a minute ago is very clear and correct on that tack.

13 What Ralph said was that this is pretty convincing but not

14 convincing enough; I want them to do another one. So, that

15 is a useful, behavioral definition of saying this is about

16 as strong as one trial because, by and large, when people do

17 one trial in an ordinary clinical setting we say that is

18 nice; it is probably true, but you should do another one.

19 Well, is that what you are saying here by voting (E)?

20   DR. LIPICKY: But you do have to be sure, and I

21 think Ralph said it, that this is with respect to the

22 clopidogrel versus placebo comparison, and not the

23 clopidogrel versus aspirin comparison. Is that what you

24 were talking about, Dr. D'Agostino?

1   DR. D'AGOSTINO: Exactly, and that CAPRIE

2   reproduction leads to the placebo comparison. You know, I

3   would just like to hear some discussion because Rob is

4   evidently saying even though we may have problems with the

5   positive control trial, when you go to the placebo those

6   diminish or fall away. I would like to know how that works

7   out.

8   DR. LIPICKY: I have just one question that I

9   would like to ask you about that then. Why would the

10 clopidogrel versus placebo comparison be a better one if you

11 had two CAPRIEs? How does that strengthen your ability to

12 make the placebo comparison?

13   DR. D'AGOSTINO: If I had overall mortality --

14   DR. LIPICKY: No, no, no. No, you have the data

15 you got. Or do you want a different trial, different

16 endpoints?

17   DR. D'AGOSTINO: Why would the second trial help

18 me with the placebo comparison?

19   DR. LIPICKY: Yes.

20   DR. D'AGOSTINO: If you are following the idea of

21 the positive control trial you want to have a strong sense

22 of the comparison of the two positive agents, and then make

23 the comparison of the positive agents with the placebo. I

24 don't have, at this point, a strong sense of the two

1 positive agents being compared to each other. Why shouldn't

2 I want two trials at that level, I guess is the question I

3 would ask.

4   DR. PACKER: Before we go any further with the

5 questions we need to discuss this and clarify all of the

6 issues related to this in a little bit more detail because I

7 don't think it is the intent of the Committee to provide

8 misleading recommendations, and we do need to understand

9 what is being asked. So, let us spend just a few minutes

10 clarifying the intent and mechanisms of the questions. Rob?

11   DR. CALIFF: Let me try then. I think what we

12 have is a positive controlled trial in a condition in which

13 you can't give a placebo. We have the best systematic

14 overview of previous trials of the positive control

15 demonstrating one of the biggest treatment effects of

16 anything that we do in medicine. Now we have another active

17 agent being compared to it, and you come out with a p value

18 right around 0.05 for the new one compared to the already

19 dramatically effective treatment. And we are talking about

20 real outcomes here in a 20,000 patient trial.

21   Now, where we deal with diabetes, depression and

22 other life-threatening illness we have no outcome data and

23 drugs are being approved every day in the same context. You

24 know, I am delighted that we are advocating large trials and

1 definitive answers, but this is so far out of bounds

2 compared with standards for other areas of medicine and what

3 is being done, it just seems to me that asking for another

4 trial, when you have already done a 20,000-patient trial

5 with the best data you could possibly have in a positive

6 control situation, is just too much.

7   DR. PACKER: I guess I don't read the question as

8 being a direct question that asks us whether we need another

9 trial. I think the question that is actually being asked is

10 whether we find the present data as persuasive as one or two

11 trials, and it is possible -- I think this is more to the

12 point that you are making -- that we could find it as

13 persuasive as one trial and that would be persuasive enough.

14 We could, in fact, make such a recommendation.

15   DR. CALIFF: I am also hearing Bob saying pretty

16 clearly that if we say it is persuasive as one trial we are

17 saying it doesn't meet the usual regulatory standard.

18   DR. PACKER: Bob, can you help us clarify this?

19   DR. TEMPLE: As I said, it is on our web site, we

20 have tried to explain why under some circumstances a single

21 trial without further evidence on the same point can be

22 persuasive. The usual reasons are that it is a well-

23 designed trial -- you assume all that -- and it has a

24 relatively extreme result, the timolol trial, the BHAT

 1 trial, some of the ISIS trials. That is the usual reason.

 2 In that sort of setting, what you are saying is, well, the p

 3 value is so extreme I am very confident that it is a

 4 replicable finding.

 5   In this case, anybody can look at CAPRIE and say,

 6 well, it doesn't meet that test for statistical extremity by

 7 itself; it is right at the margin. Everybody found it sort

 8 of right at the margin for a single reasonable trial. But

 9 what is unusual here is to have a data base about the active

10 control that tells you something about the active control.

11 I guess I should remind everybody of the discussion

12 yesterday. I would find it hard to be persuaded by a trial

13 that showed equivalence to aspirin, even though I believed

14 the meta-analysis, because there are plenty of little

15 aspirin trials which have not shown much. So an equivalence

16 trial would not necessarily be persuasive in this setting.

17   But the construct of the question is, with a

18 finding that you are at or close to significantly better

19 than aspirin, and knowing what aspirin ordinarily does, does

20 that become a level of persuasiveness that we ordinarily use

21 for approval, which is usually -- usually -- a replicated

22 trial or a single trial that is particularly persuasive?

23 That is the form of the question I think.

24   DR. KONSTAM: Let me take a stab at this. The

 1 thing that is keeping me from getting all the way to 8(F)

 2 really is an uncertainty about how to draw a conclusion with

 3 an active control and a historical data base around that

 4 active control. Now, we have heard Dr. Fisher say that it

 5 is statistically overwhelming, that that is there. You

 6 know, that it is equivalent or better than two placebo-

 7 controlled trials. The problem I have is that I haven't

 8 heard anybody agree with that on a statistical basis and the

 9 problem is that we don't have a methodology to go forward,

10 to really reliably statistically reach, in my mind, 8(F).

11 That is, let's say we repeated CAPRIE and found exactly the

12 same or worse -- you know, based on the confidence limits

13 the point estimate could come out a little bit worse than

14 aspirin. I don't have the methodology, or I haven't heard

15 it, that would push me over that limit.

16   The question to me is how do we go forward? To

17 me, although I don't reach the same level of statistical

18 certainty that I would if I had two placebo-controlled,

19 randomized trials, because I haven't heard that advice, I

20 think I am sort of with Rob on this. How do we handle it?

21 Do we slightly reduce the standard of evidence under those

22 circumstances because we are never going to get there

23 because we haven't agreed on a methodology that would permit

24 us to get there? So I guess that is the closest I get to

1   say that perhaps 8(E +) might, in fact, translate into the

2   potential approvability.

3   DR. PACKER: I want to go back to what Ralph said

4   because it really helps in the flow of the thought process

5   here. What Bob is saying that this isn't your usual

6   equivalence trial with wide confidence intervals. This is

7   an equivalence trial in which there is a p value which is

8   just around 0.05. The question is, does that bring you

9   further in the process than if these two were right on top

10 of each other?

11   DR. TEMPLE: Yes, but, in addition, you don't have

12 to rely as much as usual on aspirin having done its usual

13 thing because you actually have a comparison in which

14 superiority is almost or is shown. So, it is not the usual

15 equivalence trial; it is a little different. That is what

16 makes this thinking process hard. Whether it is different

17 enough is sort of what we are being asked.

18   Ralph's answer was very clear. He says no; I want

19 another trial. That is a perfectly coherent answer. That

20 is what this was designed to elicit.

21   DR. D'AGOSTINO: I guess though it is this word

22 "persuasively." I don't think it is two trials, but that is

23 not necessarily the question that you asked --

24   DR. TEMPLE: No, it is not two trials.

 1   DR. D'AGOSTINO: -- and is there enough evidence

 2   here to make us say that it should be approved? If it has

 3   to be the equivalent to two trials, I have a difficulty with

 4   that.

 5   DR. TEMPLE: It depends on what equivalence means.

 6   The timolol post-infarction trial wasn't two trials; it was

 7   one trial. But the p values were relatively extreme and

 8   people found it -- of course, this was a long time ago, but

 9   people found it very persuasive, and there are many other

10   examples of that. You know, there is only one post-

11   infarction trial for each of the drugs that has been

12   approved. None of the beta-blocker trials have ever been

13   replicated. There is only one trial for each of them, 100

14   percent of them; never replicated. In fact, hardly any

15   mortality studies have ever been replicated. Apparently,

16   people found those persuasive as single trials because the p

17   value was extreme or some reason like that. It doesn't have

18   to be two trials, but we like to think that the standard of

19   evidence is similar but derived from a different way.

20   DR. PACKER: I want general comment but, Ralph, if

21   a second trial were done comparing clopidogrel with aspirin,

22   and it was another 20,000-patient trial with just as many

23   events, and the p value was 0.2, I would be interested in

24   knowing what we have learned by doing that second trial.

1   DR. D'AGOSTINO: A p value of 0.2? Well, you

2   would have some of the discussion we had yesterday in terms

3   of how does that then relate to the placebo. I mean, if it

4   turns out that the value of 0.2 was tremendously negative

5   you would come out to the conclusion, when you start making

6   comparisons with the placebo, that it is not significantly

7   different.

8   DR. PACKER: I am sorry, 0.2 in the right

9   direction.

10   DR. D'AGOSTINO: In the right direction?

11   DR. PACKER: In the right direction.

12   DR. D'AGOSTINO: Then, yes, I think you might have

13   some more discussion again that we had yesterday and how

14   that then relates to the placebo data base. You would have

15   a replication of seeing those confidence intervals with the

16   placebo comparison worked out. We were saying earlier that

17   we think that the deaths should be all-cause mortality with

18   some individuals, not myself, saying that they think this

19   heterogeneity is a problem. By us jumping to say that this

20   is two studies, we are saying we don't care about any of

21   those questions with the additional comparison, and that is

22   the type of thing that I want to hear. Are we really not

23   interested? Even though it is only 0.045 and it could

24   change to 0.6 if we add the overall mortality, are we really

1 not that concerned about the positive comparisons? Do we

2 have enough information to say that we are only interested

3 in the positive comparison with the placebo? And I don't

4 think it is the two trials. It doesn't mean I am not

5 persuaded in terms of the approval. I mean, this is saying

6 have I produced two trials? No, I don't think you have.

7   DR. TEMPLE: It doesn't ask if there are two

8 trials. It asks whether the strength of evidence is

9 comparable to what you would ordinarily have in two trials,

10 and there is judgment in that.

11   DR. D'AGOSTINO: Yes.

12   DR. LIPICKY: I guess I want to pick on Ralph some

13 more too. Dr. Fisher calculated a p value for the

14 comparison of clopidogrel and placebo. As I recall it, it

15 had six zeroes -- 10^{-11} for the placebo versus clopidogrel

16 comparison. The usual regulatory standard, which is an

17 extreme one the way it is presented, is two zeros before the

18 one. So, there is 10^9 difference here, which is a pretty

19 impressive difference to me, but are you telling me -- and I

20 recognize he had no way to calculate the p value and all

21 that sort of stuff, and that you shouldn't interpret these p

22 values in the same way, but 10^9 is a pretty big number to

23 me. Are you telling me I should ignore that? Is that what

24 you are really saying?

1   DR. D'AGOSTINO: Far from it. I think that is a

2 very exciting result. The question is do I believe I would

3 get it again. No, I think you should definitely be

4 impressed by it, but I don't know if you should be impressed

5 by all those zeroes. I think once you go into the meta-

6 analysis and you start using those data bases you start

7 getting data that would not really support that you can use

8 those p values in the same fashion. That data has been used

9 a hundred times. It has been used for lots of different

10 endpoints and so forth. There are all the questions about

11 data dredging surfacing there, and I just don't think you

12 can use those p values as absolute numbers.

13   DR. LIPICKY: I understand that, but I guess what

14 I fail to see is why another trial that would get a p of

15 0.045 would help me decide that 10^9 is a number I trust a

16 lot or I don't trust a lot.

17   DR. D'AGOSTINO: It is the replication of the

18 positive controlled trial that I am talking about, and then

19 I can go on to the placebo comparison.

20   DR. TEMPLE: In one case you have a direct measure

21 and in another you are having to deduce some things. It is

22 not the same but the question is how strong it is.

23   DR. PACKER: Ralph, I am sorry, to a non-

24 statisticians it is not the reproducibility of the p value

1 that matters, it is the reproducibility of the finding.

2   DR. D'AGOSTINO: Of the finding.

3   DR. PACKER: So, one is not trying to necessarily

4 reproduce a value of 10^{-11}, the point is trying to reproduce

5 the fact that there is a finding.

6   DR. D'AGOSTINO: If another CAPRIE trial were run,

7 with the same sample size and so forth -- I don't think it

8 necessarily needs the same sample size but if another one

9 were run with a positive outcome, the comparison with the

10 placebo would probably be as striking. But that is not the

11 p value matching but the replication of the CAPRIE trial

12 that I am talking about.

13   DR. PACKER: I am sorry, I am still confused. I

14 understand that there is some uncertainty about how to do a

15 p value, or what the magnitude of the p value is, and

16 whether or not the p value is 10^{-11} or 10^{-5} or whatever,

17 doesn't that p value tell us that if you were going to do it

18 again you would find the same delta versus placebo?

19   DR. D'AGOSTINO: No. No, because the p value can

20 be a function of sample size. I mean, you would get the

21 same p value for different deltas depending on the sample

22 size. So, it is not reproducing the same --

23   DR. PACKER: I am sorry, if you did the trial

24 again, wouldn't you then conclude the same thing about the

1 superiority of clopidogrel versus placebo?

2   DR. D'AGOSTINO: Well, if you did you would have

3 resolved my dilemma. What if you did another trial and it

4 actually turned out to be that the aspirin was significantly

5 better, overwhelmingly better, then what would you do with

6 that result? If you reproduce the trial and you get exactly

7 the same result, fine. What if you didn't get exactly the

8 same result? That is the question I am raising. How do you

9 know you are going to get exactly the same result?

10   DR. RODEN: So, if Bob will interpret a vote of

11 8(E) as a requirement for a second trial, then I will change

12 my vote to 8(F). That is a preface to a comment, and that

13 is, I guess we are being asked not how much we believe -- at

14 least my view is that we are not being asked how much we

15 believe in the reproducibility of CAPRIE necessarily but of

16 the subsequent result that clopidogrel beats placebo by

17 many, many zeroes. If CAPRIE-II were conducted and then an

18 analysis of clopidogrel versus placebo were reconducted, how

19 likely is it that clopidogrel would beat placebo by many,

20 many zeroes? I think that is what we are being asked to

21 vote on. And my impression is it would.

22   DR. PACKER: Let me just clarify. If you turn

23 these questions backwards, then no one will have learned

24 anything bout how the Committee thinks. So, the intent here

1 is not to say I am worried about the implications of my

2 answer so I am going to change my vote. The question that

3 is important here is to follow the questions through because

4 one then establishes a line of thinking, and you can then

5 vote anything you want regardless, but one has to understand

6 what the process of thinking is. So, please don't change

7 your vote based on what you are afraid is going to happen.

8   DR. RODEN: No, but I think it is important that

9 Ralph's answer and Ralph's vote and my answer and my vote

10 will come out to the same number but we actually have quite

11 different reasons, and maybe just saying them out loud and

12 having the Agency hear them is enough. I am not going to

13 change my vote just for the heck of it, but I just want to

14 make sure that the interpretation is correct.

15   DR. LIPICKY: This is not quite right. The

16 question is really saying do you think if you did the CAPRIE

17 trial again, that the comparison to placebo would change

18 from 10^{-11} to something like 0.1? Okay? That is really what

19 the question is asking.

20   DR. TEMPLE: Milton, I don't think it is quite as

21 specific as that. It is asking for a gestalt judgment on

22 the strength of the evidence. If you get down too much to p

23 values you do something that is probably not appropriate

24 under the circumstances. It is really asking is this the

 1 strength of evidence typical of what you have, or something

 2 less than that. I hear Ralph saying very clearly saying,

 3 no, it is not enough. I am not convinced enough that this

 4 is the usual standard of evidence. And you can elaborate on

 5 that and say it is because he is not sure it would be

 6 replicated if he found it, and that is fairly clear. But it

 7 is that. It is true, we don't want you changing votes on

 8 practical grounds, but the implication of your view of the

 9 strength of the evidence has something to do with whether a

10 drug is approvable or not. You can't hide that.

11   DR. FENICHEL: I would like to expand on some of

12 the implications of what Ralph has said, I guess a couple of

13 things about possible outcomes. Let us imagine that the

14 finding in CAPRIE-I is a correct finding; that the effect

15 size was correctly estimated and so on. It is more likely

16 than not that the p value in the second trial will be higher

17 because this trial would not have come here if the p value

18 had been -- you know, if it had very bad luck. So, what we

19 might expect is that it will be 0.1 or 0.2 or something like

20 that.

21   The thing about a 0.1 or 0.2 p value in CAPRIE-II

22 is that it strengthens the overall finding. It sounds

23 worse, but the fact is once again you have shown with

24 strength which is even less than this but still it is

1 different from losing. So, now we move from 10^{-11} to a new

2 estimate, which I am sure Lloyd can provide, and the

3 question is, what is the standard to which that calculation

4 is being held? At what point are you going to say that is

5 enough? I find it very difficult to understand what

6 threshold is being applied here.

7   DR. CALIFF: To keep trying to push this as far as

8 I can, you know, the question specifically says a plausible

9 conclusion, supported about as persuasively as the findings

10 of a package of two or more typical trials. This is a group

11 that has approved drugs for the treatment of angina in wimpy

12 populations where there are really no patients at high risk

13 enrolled in the studies because treadmill time is improved.

14 Here, we have a 20,000-patient trial, really bad outcomes,

15 death, stroke, heart attack involved; the world's best data

16 base on the positive control. And we are saying that the

17 best estimate of 10^{-9} is not as good as two angina trials

18 that have the typical successful package.

19   DR. PACKER: I know we are not saying that, and I

20 don't think anyone at the FDA thinks that we are saying

21 that.

22   DR. CALIFF: Okay. If we vote (E), what are we

23 saying?

24   DR. FISHER: Milton, can I make one comment on

1   methodology?

2   DR. PACKER: Sure.

3   DR. FISHER: Think of it this way, suppose you had

4   two equivalence trials that were both equivalent, not

5   statistically significant but equivalent, and in each one of

6   those you did the same comparison, and both of those were

7   like 0.04 or maybe 10^{-4}. That would be replication. Right?

8   You can obviously divide this up at random and, actually,

9   that will happen. The question then is, one implication of

10 what you are saying is if you go this way the sponsor should

11 not go for superiority. They should go for two equivalence

12 trials and, in fact, they can probably reduce their total

13 sample size because the aspirin data base is so strong, and

14 then try to market it by doing their own meta-analysis, and

15 get people to speak around the country and avoid the

16 marketing laws, and so on.

17   I think that is one way to think about this, or

18 any other trial. If you divide it up into parts and did the

19 placebo comparison, not the aspirin comparison, you know,

20 how would you feel? Would you rather have two equivalence

21 trials here than this trial?

22   DR. PACKER: I think that is an interesting

23 question. Ralph, can I ask you to respond to that?

24   DR. D'AGOSTINO: Yes. I mean, again, I am looking

1 at this as two or more typical successful trials. I am not

2 thinking of deceit. I am thinking of the question that is

3 written down before me, and it is not two or more typical

4 successful trials. You say I am making myself clear but I

5 am not because it is not a question of what I am going to

6 say on the approval; it is a question of is it like two or

7 more typical successful trials?

8   DR. TEMPLE: As persuasive.

9   DR. D'AGOSTINO: I don't think it is as persuasive

10 as typical trials.

11   DR. TEMPLE: I think that is very clear.

12   DR. D'AGOSTINO: You know, if the company were to

13 pick up and want to run a suboptimal study to make the

14 comparison, they run into the situation where the confidence

15 intervals work against them and, in fact, it doesn't come

16 out so good for the drug. I mean, that is one of the

17 problems of under-powered studies. It isn't necessarily

18 going to work the way it was described.

19   DR. LINDENFELD: I would just say I think we all

20 agree on the strength of the aspirin-placebo data, but it

21 seems extremely unlikely that if the p were repeated it

22 would not turn out to favor aspirin over placebo.

23   DR. PACKER: Clopidogrel?

24   DR. LINDENFELD: Clopidogrel over aspirin, right.

1   DR. PACKER: Clopidogrel over placebo?

2   DR. LINDENFELD: No, I am sorry. If CAPRIE were

3   repeated I think it is extremely unlikely to come out the

4   opposite way where we would be concerned the results would

5   be opposite.

6   DR. PACKER: Let me just take that thought, and it

7   might be worth thinking about this question in a slightly

8   different way but, Ralph, taking what JoAnn said and trying

9   to, I guess, get a global perspective here --

10   DR. D'AGOSTINO: Well, I think if we expand

11   "persuasively" -- I am stuck on "persuasively." If you

12   broaden that in the sense of what do you think the trial is

13   going to look like, or put the approval point in here, is

14   there enough for approval if they want to interpret it as

15   two or more successful trials, that is one way of doing it.

16   I think, you know, is there enough evidence to convince you

17   that you will see the same, and so forth -- do I think I

18   will see the same doesn't mean will I see the same if I run

19   two trials. I can think of what is going to happen, but am

20   I persuaded that I am going to see the same two trials?

21   DR. TEMPLE: Is it as persuasive as two trials at

22   conventional levels of significance? You know, 0.05.

23   DR. D'AGOSTINO: Well, it is the same question

24   though. The answer is I don't think it is as persuasive as

1 two trials. That doesn't mean that, in my mind, it

2 shouldn't move on to approval. I think it is a different

3 question.

4   DR. PACKER: If they did CAPRIE-II and it is a

5 very large CAPRIE-II, 80,000-patient trial --

6   (Laughter)

7   -- the p value is 0.9. The confidence intervals

8 are extremely small. And as John mentioned earlier, it

9 would, in fact, have the ironic -- it wouldn't be ironic but

10 understandable fact of increasing one's confidence that

11 clopidogrel would beat placebo. Would that be a correct

12 statement?

13   DR. D'AGOSTINO: Depending on how that 0.9 went.

14   DR. PACKER: No, I am just saying they are right

15 on top of each other. Let's assume that the odds ratio --

16   DR. D'AGOSTINO: But then I have addressed the

17 questions of homogeneity and addressed the questions of the

18 endpoint including the mortality. I mean, we were saying in

19 earlier discussions that we wouldn't ask them to repeat the

20 trial exactly the same way. We would have addressed some of

21 those questions along the way, and I think then the

22 comparison between the two drugs would look great and the

23 comparison with placebo would look phenomenal. I don't know

24 if it is going to turn out that way. If it turns out that

1 aspirin is the only thing that works and this whole trial is

2 presented to us because it is positive and then it turns out

3 that everything falls apart.

4   DR. TEMPLE: I am probably going to be repeating

5 myself, but ordinarily historically and because of the way

6 we read the law, we have said findings ought to be

7 reproducible. Also, over the years in a variety of settings

8 we have said that a very impressive single study can

9 sometimes do the work of replication. I guess you could say

10 that is partly practical, partly a sense of urgency because

11 some of the findings were important, but also because in

12 general they were statistically powerful. So we have said,

13 and probably the law is going to be changed to allow us

14 specifically to rely on a single study when we think it is

15 the right to do and when it is persuasive.

16   The question here is -- and I have to say this,

17 the fact that everybody is finding it difficult doesn't

18 bother or embarrass me at all. We have never really put

19 this question in a formal way. It has never been discussed

20 publicly, to my best knowledge. So this is very new

21 territory. That said, however, the question that is being

22 asked is something become persuasive because you have beaten

23 an active control which is incredibly well documented to be

24 better than nothing, even though the beating of the active

1 control is not all that persuasive by itself and is only at

2 the margin. That is sort of the question. Does the

3 conglomerate of that add up to a very persuasive finding?

4 That is really it in a nutshell, and I don't think it is

5 going to be determined by the exact p value.

6   DR. D'AGOSTINO: And I don't think it is going to

7 be determined by the statement of two trials.

8   DR. TEMPLE: That was an attempt to describe the

9 usual standard. Maybe that was inadvisable, I don't know.

10   DR. PACKER: Bob, without even putting this to a

11 vote, my sense is that the Committee believes that the data

12 demonstrating a superiority of clopidogrel over a putative

13 placebo is persuasive.

14   DR. TEMPLE: Many do; some don't.

15   DR. PACKER: No, no, but they have reservations

16 about CAPRIE, the endpoints, the various elements that have

17 already been mentioned earlier today, and it would be,

18 therefore, difficult to balance those concerns as to whether

19 one actually considered this to be one- or two-trial level

20 of persuasiveness.

21   DR. TEMPLE: Well, you have sort of said the

22 opposite thing. When you started you said the Committee

23 seemed to find it persuasive, and then you described some

24 reservations that some members make it seem not so

1 persuasive. Well, that is the question. I want to observe

2 that the trip from 0.045 to 0.6 or something, when you add

3 in all cause-mortality -- I guess I would be interested in

4 just how awful that is. That is not surprising. That

5 always happens when you add in other deaths. It didn't go

6 to 0.5 or something. But you are right, you have put the

7 question how persuasive this is. We are all sorry that it

8 is a hard question. It is an unfamiliar question. I think

9 that is what has got everybody nervous. We don't usually

10 ask this. We don't usually ask ourselves this.

11   DR. LIPICKY: It seems like you could even take

12 the p of 0.045 to 0.1 and not destroy the argument with

13 respect to is it better than placebo. So, you have very

14 clearly elucidated all of the considerations with respect to

15 comparison with aspirin. Okay? That has been very clearly

16 heard, and so on and so forth. But the comparison to

17 placebo seems like a different problem and, indeed, it seems

18 like the p value is not the thing to focus on. It just

19 happens to be a ready number. I must admit, I am impressed

20 by the 13 zeroes before the 1.

21   DR. DIMARCO: But for this question, I don't think

22 clopidogrel has to beat aspirin at all. As Ray says, it

23 just has to not be a lot worse than aspirin. So it doesn't

24 matter if there are many zeroes, there are enough zeroes. I

1   think that is what is important.

2   DR. RODEN: Can you confidence intervals from the

3   CAPRIE data that, were CAPRIE-II to be performed, it would

4   show that aspirin beat clopidogrel by 30%? What are the

5   chances of that happening?

6   DR. FISHER: That can be done, as Milton

7   mentioned. You have to know the size of the study because

8   the variability is very important.

9   DR. RODEN: Twenty thousand patients.

10   DR. FISHER: I am not bright enough to do it in my

11 head standing here. It can obviously be done.

12   DR. RODEN: But that is what John just asked.

13 That is the point. The concern that Ralph has is that

14 CAPRIE-II, were it to be performed, would show that aspirin

15 beats the heck out of clopidogrel.

16   DR. D'AGOSTINO: No, the concern I have is that

17 the question says is it like two or more typical successful

18 trials, and the answer is no. That does not say what I

19 anticipate the second one will look like.

20   DR. FENICHEL: I think that question can be

21 answered very roughly, and Lloyd and the other statisticians

22 will have to forgive me but here we are, with an 8% or so

23 relative risk reduction, which we know is almost exactly two

24 standard deviations significant. Well, that means that if

1 you said, well, how likely is it that the real situation is

2 that aspirin is not 8% worse but really 8% better, well, now

3 you are four standard deviations out and that is something

4 on the order of 10^{-3} or so, and that wouldn't be enough, I

5 don't think, to overwhelm the aspirin data. So, aspirin has

6 to be something like 15% better -- I think that is about

7 right. So, that is on the order of six standard deviations

8 out and that, as I say, is not tabulated. I happened to use

9 standard deviations yesterday and I needed to use an

10 approximately to figure it out, and it is around 10^{-10} which

11 -- surprise, surprise -- is just about the same number of

12 zeroes that Lloyd computed.

13   DR. PACKER: Let me try to take question 8 and

14 reframe it in accordance with what we have heard, and then

15 let's vote on it.

16   Under an ideal circumstance, if a placebo were

17 possible, the sponsor would be encouraged by the Agency to

18 do a comparison of clopidogrel versus placebo and could

19 have, therefore, come in with a variety of trials, maybe one

20 or two, in which clopidogrel beat placebo. Imagine for a

21 moment that they have come in with a package in which

22 clopidogrel beats placebo in a direct head-to-head

23 comparison in two trials. Now imagine a package where

24 clopidogrel beats placebo in one trial. Now imagine this

1 package. Which of those scenarios does this package

2 resemble? That is the question. That is the question that

3 is being asked.

4   DR. THADANI: Is there going to be consistency of

5 data across the board?

6   DR. PACKER: No, no, no. You have the data as it

7 is.

8   DR. THADANI: I realize that.

9   DR. PACKER: As you know, any time you see two

10 trials with p less than 0.05 --

11   DR. THADANI: I will go with one trial.

12   DR. PACKER: -- nothing is perfect but you do

13 have two trials with p less than 0.05, because that is what

14 the Agency is asking the Committee to convey a sense of.

15 There is no placebo-controlled trial. The sponsor has not

16 come in with two trials in which clopidogrel beat placebo.

17 It hasn't come in with one trial in which clopidogrel beat

18 placebo, but there is an overwhelming data base that says

19 aspirin beats placebo and they have come in with

20 clopidogrel, with all the caveats about what CAPRIE is.

21 Based on our interpretation of CAPRIE and the existing meta-

22 analyses with aspirin, which do we think the present data

23 base resembles? Does it resemble the equivalent of two

24 trials in which clopidogrel beats placebo; one trial in

1   which clopidogrel beats placebo; or neither of those

2   scenarios? Rob?

3   DR. CALIFF: I would say this is overwhelmingly

4   more impressive than two typical placebo-controlled trials

5   that this group sees.

6   DR. PACKER: That question is being asked.

7   Regardless of what the answer is -- the question that is

8   being asked is which of those scenarios does this resemble?

9   So, because the Agency normally asks sponsors to meet that

10 level of evidence, the sponsor says, and we agree with the

11 sponsor, it couldn't do that so it did something a little

12 bit different. So, we need to decide whether what they did

13 is similar to had they come in with two placebo-controlled

14 trials in which there was superiority, or one, or neither.

15 Ray?

16   DR. LIPICKY: I don't want to introduce another

17 thinking process here, but the decision making on

18 approvability is an evidence-based thing but it is not as

19 rigid as it sounds. I am sure that given the right

20 circumstances two trials with a p of 0.06 would be fine.

21 Okay? So, there isn't some numerical value here that

22 suddenly meets a threshold. It really is the strength of

23 evidence business, and the two typical trials with a p of

24 0.05 is a kind of shape of the thing that might be warm and

1 fuzzy but you don't know much more than that. That is kind

2 of its shape. Okay?

3   DR. PACKER: I understand. So, imagine the

4 scenario where the sponsor had done something different.

5 They had actually done comparison versus placebo, and

6 imagine a scenario where they came in with two positive

7 trials like that, one positive trial like that, and then

8 imagine the data base. Are you persuaded by this data base

9 as much as had the sponsor come in with two positive trials

10 against placebo, one positive trial against placebo, or none

11 of the above? That is the question.

12   DR. RODEN: Bob keeps on talking about this is

13 judgment, and the judgment is yes.

14   DR. TEMPLE: Of course it is judgment.

15   DR. RODEN: So my answer is two. Say the options

16 again -- one trial, two trials or no trial?

17   DR. PACKER: Is this as good as two trials, as one

18 trial or some other choice?

19   DR. RODEN: Well, you know, I said before that

20 this is a new paradigm. That is why it is getting a little

21 fuzzy. Of course, that is why the Agency is bringing it to

22 us. So, the answer to your question is two trials.

23   DR. PACKER: That is why we get paid $100 a day.

24   (Laughter)

1   DR. RODEN: That is why I put my flight off, so I

2   could get my full honorarium for the day today! I get $150.

3   DR. PACKER: You get $150? Joan, we have to talk!

4   DR. THADANI: Why should the conclusion change?

5   Basically, the majority of the people voted on 8(E) earlier

6   on. I am just asking. And the way you are proposing really

7   should not change my view because the data, given as it is,

8   meets one large placebo-controlled trial. Why should one be

9   changing the vote? I don't understand that.

10   DR. PACKER: Let me say that I think that the

11   question now is clearer than the way the question was asked

12   before.

13   DR. D'AGOSTINO: It is still one trial --

14   DR. TEMPLE: We know that. We know it is only one

15   trial.

16   DR. D'AGOSTINO: Exactly. The question is, is

17   there enough for approval?

18   DR. PACKER: No, no, this is an intellectual

19   exercise only. Let us try to do this because it is supposed

20   to be instructive, and Dan says he is as persuaded by the

21   data base as if the sponsor had come in and beaten placebo

22   twice. Is that correct?

23   DR. RODEN: Right.

24   DR. PACKER: Good. Marv?

1   DR. KONSTAM: I am going to say two trials also.

2   You know, I think that my uncertainty before in getting

3   there, as I said, really was a lack of clarity from a

4   statistical base as to how to draw this conclusion, and

5   listening carefully and thinking about it and putting

6   clinical judgment into it and putting the persuasiveness of

7   the aspirin data into it, I am going to turn around and say

8   I think that it is equivalent to two trials.

9   DR. DIMARCO: I already said two trials.

10   DR. LINDENFELD: Yes, two trials. You would love

11 to see two trials right now with today's medications in all

12 patients but I think this is so close that I will take two

13 trials.

14   DR. PINA: Based on your clarification, I would

15 say two trials.

16   DR. CALIFF: Two trials.

17   DR. THADANI: I vote still for one trial.

18   DR. D'AGOSTINO: One trial.

19   DR. PACKER: My vote is two trials. We can't

20 impute votes.

21   DR. D'AGOSTINO: Based on the historical data set

22 that we know is full of later follow-ups and so on, we are

23 so overwhelmed by it. Can we encourage drug companies to

24 gather historical data sets so that the p values are smaller

1 and smaller?

2   DR. TEMPLE: This is a complicated question.

3 Beating an active control is not an easy thing to do. Very

4 few drugs can ever show superiority to an active drug. Many

5 try; very few do. It is not "nothin'" to do that or get

6 close to doing it. I guess the vote is that they almost

7 did. So, that does have implications.

8   If this had just been an equivalence trial,

9 despite the aspirin data base, I would find it very hard to

10 be persuaded by it for the reasons we went through yesterday

11 but, arguably, this is different and I think that is what

12 people have said.

13   DR. PACKER: Let me ask, is there a need to go

14 through 9, 10 and 11 now because the Committee has said that

15 this is now as persuasive as if the company had come in with

16 two trials that beat clopidogrel (sic), and the Committee

17 has said that although it doesn't know what to do with the

18 heterogeneity issue, it hasn't necessarily identified it as

19 a major point of concern.

20   DR. FENICHEL: It is not necessary, Milton. I

21 think the residual heterogeneity issue will come out in the

22 answer to question 14.

23   DR. PACKER: If that is the case, we are

24 sprinting. Question 12, the intent of question 12 is to

1 determine whether the results of CAPRIE are generalizable

2 beyond the patients who were enrolled in CAPRIE. That is,

3 there is a possibility that the sponsor might wish labeling

4 in which all patients with symptomatic atherosclerosis would

5 have an indication for this agent. In fact, that might not

6 necessarily be so farfetched.

7   Could we get some clarification from the sponsor

8 as to what they are actually seeking? As I saw in the

9 proposed package insert, the proposed package insert

10 suggested that what you would like is an indication for

11 patients with a history of symptomatic atherosclerosis. Let

12 me ask the sponsor to clarify if someone with a history of a

13 myocardial infarction two years ago -- would you like

14 patients with an MI two years ago to have an indication for

15 treatment with clopidogrel?

16   DR. EASTON: Yes.

17   DR. PACKER: That is what they are asking.

18   DR. TEMPLE: Are we surprised that they are asking

19 this?

20   DR. FENICHEL: Milton, there is a reason why we

21 direct the questions to the Committee.

22   DR. PACKER: Yes, I understand.

23   DR. TEMPLE: We presume the broadest claim would

24 be not unwelcome.

1   DR. PACKER: I guess I am just saying that they

2 actually are seeking a broad claim in their proposed package

3 insert.

4   DR. FENICHEL: We are shocked; shocked!

5   DR. PACKER: And that would be indicated by the

6 patients specifically enrolled. So, the question that we

7 are being asked is are we comfortable with the extension of

8 the CAPRIE data base to patients not enrolled in CAPRIE?

9 That is the question being asked. The question, therefore,

10 is how comfortable are we, and (A) means please go away;

11 don't ask for this broader claim, or (D), you are as

12 persuaded by this as you would be if they had, in fact,

13 studied these additional patients in two trials and won.

14 So, then the question of generalizability is beyond the

15 patient population enrolled in CAPRIE.

16   DR. RODEN: I think this sort of centers on

17 whether you think atherosclerosis is a uniform disease or

18 not, and we will come back to that I suppose before we are

19 finished today. But I don't think it is and, therefore, a

20 generalizable claim like this I don't think I can support.

21 So, the way I would answer that I guess is somewhere between

22 (B) and (C), and I think (B) actually.

23   DR. PACKER: So, one vote for (B). Marv?

24   DR. KONSTAM: I don't find this question lends

 1 itself well to this format. If I have to vote I will say

 2 (C). I think the spirit of my answer is going to be that I

 3 don't really believe that we have enough to say all

 4 atherosclerosis is the same, and I personally would stop

 5 short of permitting a claim involving patients that are

 6 totally unrepresented, at least in terms of enrollment

 7 criteria, in the trial. For example, a patient who had an

 8 MI four years ago. So I would stop short from a broad

 9 agreement that all patients with atherosclerosis would

10 benefit.

11   DR. PACKER: Let me just remind the Committee that

12 there is a similarity between question 12 and 14. Question

13 14 actually asks the Committee to specifically advise the

14 Agency about the wording of labeling.

15   DR. FENICHEL: Milton, let me make a distinction.

16 It seems to me that 14 in its way is much cruder than 12; 14

17 says is it now appropriate to recommend in labeling -- well,

18 as regards 12, 14 says is it now appropriate to recommend in

19 labeling that the drug be used in patients with

20 atherosclerosis possibly just to remote MI. Now, obviously

21 if one says yes to that component of 14, then one must be

22 voting for 12(D) here. But if one would say no to 14, there

23 is still stuff in 12 which is of interest. For example,

24 what would it take to expand the claim? If one believes

1 that the claim is so weak in generalized all atherosclerosis

2 that it is now possible to do a placebo-controlled trial in

3 that are, and I am not sure that that is wrong, then one

4 might ask, well, do they have to do one? Do they have to do

5 two? How good would it have to be to combine with this and

6 convince one the broader claim could offered? So, there is

7 stuff in 12 not covered in 14.

8   DR. PACKER: Okay, 12 is really asking us to give

9 a sense of our comfort level; 14 is a more specific

10 recommendation. So, I think you have already addressed

11 that, Dan.

12   DR. KONSTAM: Are we talking about 14?

13   DR. PACKER: No, 12.

14   DR. KONSTAM: I already said I wouldn't generalize

15 to all atherosclerosis.

16   DR. PACKER: So it is really between (B) and (C).

17   DR. KONSTAM: I will say (C).

18   DR. PACKER: (C). John?

19   DR. DIMARCO: I will go with 12(B).

20   DR. LINDENFELD: I think (B) too. I wouldn't be

21 willing to generalize to a much lower risk group.

22   DR. PINA: I would also not be willing to

23 generalize. I would go with (B).

24   DR. CALIFF: I think I would go with (C). My

1 intent with that is that there would need to be one more

2 trial, but I would not be in favor of requiring two more

3 trials in that general population.

4   DR. THADANI: I will go for (B).

5   DR. D'AGOSTINO: (B).

6   DR. PACKER: My answer is (B) as well. Dr. Moye

7 also votes (B).

8   Question 13, should clopidogrel be approved for

9 the prevention of atherothrombotic events, acute MI, stroke

10 and vascular deaths, in some patient population at high

11 risk? And 14 allows us to define that more specifically.

12 So, 13 is a general concept that you would find the drug

13 approvable for some patient population, albeit small or big.

14 So, it is general approvability and we will refine that in

15 the subsequent questions. Dan, 13?

16   DR. RODEN: Yes.

17   DR. KONSTAM: Yes.

18   DR. DIMARCO: Yes.

19   DR. LINDENFELD: Yes.

20   DR. PINA: Yes.

21   DR. CALIFF: Yes.

22   DR. THADANI: Yes.

23   DR. D'AGOSTINO: Yes.

24   DR. PACKER: Yes. And Dr. Moye votes no and Dr.

 1 Graboys says yes.

 2   DR. CALIFF: Did Dr. Moye give a rationale?

 3   DR. PACKER: Yes, he did. Let me try to read that

 4 when we go to question 14. So, for approvability it is 10

 5 yes and 1 no.

 6   Having voted yes, if the FDA decides to accept

 7 that recommendation should the labeling and advertising the

 8 patients in whom clopidogrel is indicated -- I am sorry, how

 9 should the labeling do that? It obviously should. How

10 specific? You have a whole host of choices here. So, the

11 question is, now that you have recommended approval, who

12 should the drug be indicated in?

13   DR. RODEN: I don't think you can do anything but

14 be consistent and rely on the data that has been presented

15 so far. So, 14(B), it seems to me, is the only rational

16 answer. The subsets are sort of peculiar because the MI

17 subset that doesn't show the benefit is the ones that

18 aspirin shows the greatest benefit; in the PAD group where

19 clopidogrel shows the greatest benefit is the one where

20 aspirin may not do very much. So, in the end it is not

21 possible to identify a particular group within CAPRIE that

22 benefits a lot more compared to the placebo than another

23 group. So I think 14(B) is my answer.

24   DR. KONSTAM: 14(B).

1   DR. DIMARCO: (B).

2   DR. LINDENFELD: (B).

3   DR. PINA: I am going to say 14(C).

4   DR. CALIFF: (B).

5   DR. THADANI: I know we are imputing the results

6   compared to aspirin here and one of the worries is that it

7   is a subgroup. I realize there are problems but it just

8   worries me that it was inferior to aspirin in that group.

9   So, I have some reservations there so I am going to vote

10   14(C).

11   DR. D'AGOSTINO: (B).

12   DR. PACKER: I vote (B). Dr. Graboys votes (C)

13   and Dr. Moye would say that the drug should not be approved.

14   I will just read it because his rationale is that the low

15   efficacy and high, although marginal, p value make it, in

16   his opinion, a weak study and he is concerned about the

17   patients lost to follow-up and the small difference on the

18   primary outcome. So, that is 3 (C)s and 7 (B)s.

19   We have reached the final question. Bob Fenichel,

20   let me ask a question. There are five choices here. There

21   could be a sixth choice, which is that there should be no

22   mention of a comparison to aspirin.

23   DR. FENICHEL: Well, it is customary in labeling

24   to describe the clinical trials, or at least the major

1 clinical trials supporting approval. So, it would be odd to

2 produce this labeling without mentioning, on the one hand,

3 the aspirin trialists' collaborative data and, on the other,

4 without mentioning CAPRIE. One could say almost all of the

5 clinical efficacy data regarding clopidogrel rests upon

6 CAPRIE in which it was tried against aspirin, and stop. It

7 seems tantalizing and odd to do that in labeling.

8   DR. PACKER: One could also, as a sixth

9 possibility -- I just want to make sure we go through this

10 question once -- conclude that the labeling would say that

11 clopidogrel was not superior to aspirin.

12   DR. FENICHEL: That is certainly a possibility,

13 and I should have thought of it and put it in just by way of

14 completeness, yes.

15   DR. PACKER: It is the more conservative side of

16 (E).

17   DR. FENICHEL: It is not very different from

18 15(E), but it is even perhaps more negative than 15(E). So,

19 that is a possibility.

20   DR. TEMPLE: But 15(E) was in that direction, to

21 give the data but explain that you can't reach a conclusion

22 from that that superiority has been established. So, some

23 version of that is what is being asked.

24   DR. FENICHEL: I am not sure you have to have an

1   option. I think maybe we can fiddle with (E) depending on

2   the discussion, if that is the way things go.

3   DR. PACKER: So, the question is how comfortable

4   the Committee is with the various options presented to it

5   for labeling. You can read the options on your own. Dan,

6   which option would you prefer and why?

7   DR. RODEN: Well, I think it has to be in patients

8   meeting the enrollment criteria of CAPRIE because we just

9   voted on that. So, it would be (C) or (D) or (E). Then the

10 question is whether we get excited about the subgroups. I

11 think the subgroups are important, and my own view -- and

12 maybe this comes back to the things that Ralph was arguing

13 for -- is that I am clearly convinced that clopidogrel would

14 beat placebo. I am not all that convinced that clopidogrel

15 would necessarily beat aspirin. And that is sort of what we

16 are being asked here. So, of these choices, I really think

17 15(E) is the most reasonable. Somewhere there needs to be a

18 sort of cautionary note that this is not the drug that

19 should supplant the generalized use of aspirin, and 15(E)

20 comes closest to that in my mind.

21   DR. PACKER: Let me just clarify, please not only

22 vote on the choice but if you think the choice should in

23 some way be modified, please explain how you would modify

24 it.

 1   DR. RODEN: I think, and I am not sure when along

 2   the line of this afternoon's discussion it should have been

 3   brought up, I do think that we have decided that clopidogrel

 4   would clearly beat placebo. I am not so convinced that

 5   clopidogrel beats aspirin at all. That is one trial with a

 6   significance value of equals 0.045. So, I would prefer to

 7   see labeling that says something like in a large trial -- I

 8   mean, it is possible to do that in the labeling -- in a

 9   large trial clopidogrel was marginally superior or roughly

10   equivalent to aspirin, and there was heterogeneity among

11   subgroups. So, 15(E) comes closest.

12   I guess I have a concern that, you know, we do

13   believe in aspirin I suppose in the cardiovascular community

14   and one of the attractive things about aspirin is cost.

15   There is a statement at the bottom of the first page of the

16   questions that we are not supposed to talk about that too

17   much, but there is a danger in advocating a non-aspirin

18   therapy because it may lead to less compliance for example.

19   That is sort of an aside. I think the labeling can deal

20   with that.

21   DR. PACKER: Dan, let me just clarify, I think

22   what I heard you say was that you would actually want the

23   labeling not to reflect a statement of superiority, but (E)

24   actually does reflect that statement. It says clopidogrel

1 was superior, and gives the caveats.

2   DR. RODEN: Well, I was looking at Bob Fenichel

3 and he was nodding when I said they can fiddle with the

4 labeling to say something like in one trial, you know, it

5 was marginally superior, something like that because I think

6 that is sort of what we are looking for.

7   DR. FENICHEL: Let's not wordsmith here. I get

8 the tone.

9   DR. PACKER: Okay. Marv?

10   DR. KONSTAM: My answer isn't on this list. It is

11 somewhere between (B) and (C). I think in patient meeting

12 the enrollment requirements of CAPRIE clopidogrel was

13 significantly superior to aspirin in preventing

14 atherosclerotic events, but I think it does need to be

15 qualified, one, by the fact that that finding has never been

16 replicated and, two, by a comment about the heterogeneity.

17 However, I would stop short of the comment made in (C) which

18 says to me, essentially, that it is no better in MI. The

19 reason I would stop short of that is that I think the spirit

20 of the Committee and my own opinion is that the

21 heterogeneity was, in fact, a play of chance. Therefore,

22 somehow I would like it reflected in the wording that our

23 best guess is that clopidogrel beats aspirin in patients

24 like those enrolled in CAPRIE. There was heterogeneity and

1 we are not sure what that means, rather than saying there

2 was heterogeneity and, therefore, it doesn't beat it in MI.

3 I am not sure if I have made myself clear.

4   DR. PACKER: Dr. DiMarco votes (E).

5   DR. LINDENFELD: I would be more comfortable with

6 something that said in patients meeting the enrollment

7 criteria of CAPRIE clopidogrel was at least as effective as

8 aspirin or as effective. I don't think I found data to say

9 that it is clearly superior to aspirin.

10   DR. PACKER: I know your microphone wasn't

11 working.

12   DR. LINDENFELD: I would feel much more

13 comfortable with a statement that said that clopidogrel was

14 as effective as aspirin, but I don't think I have found data

15 to say that it is clearly superior, and I would be a little

16 uncomfortable sort of even putting that in.

17   DR. PINA: I would go for (E) with the following

18 recommendations: before the word "superior" I would use

19 either the word "somewhat" or "marginally." At the end of

20 the word "replicated" I would add a statement, and in

21 patients whose sole indication of risk was a recent history

22 of MI it seemed to be a bit inferior to aspirin.

23   DR. CALIFF: I would also go for (E) but I would

24 strongly urge not using the word "superior." I would

1 describe the results of the study and point out the

2 heterogeneity. This is a phenomenal clinical trial that

3 really finds a marginal result in the direct comparison, for

4 which we would normally require more evidence. I am

5 concerned that if the word "superior" is used that gives

6 license -- that is a pretty strong word even if we modify it

7 with the other phrases. I would rather describe the results

8 of the trial and say a p value of 0.045 was reached, or

9 something to that effect.

10   DR. THADANI: I will go with (E) or (E -). But I

11 have a couple of comments. I think the value is marginal

12 and if you include total mortality the deaths are further

13 higher. Also, I think given the data base, I realize

14 heterogeneity might be chance but in acute post-MI visit at

15 35 days it went the wrong way. I think I would urge the

16 company, if they feel so confident, to repeat the trial in

17 post-MI patients who are a high risk group and show the

18 effect of aspirin, it would be very useful. So those are a

19 couple of my comments.

20   DR. PACKER: Okay. Ralph?

21   DR. D'AGOSTINO: I also vote for (E). I don't

22 know if you can avoid the term "superior" but I would

23 emphasize the one trial and marginally superior. If you can

24 remove that and put something like the p value that is

1   understandable, that is a better way. I wouldn't want to

2   give the message that this is a trial and we don't need two

3   here.

4   DR. PACKER: My own view is that I guess I would

5   favor (E) or a more conservative version of (E). I would

6   also like to avoid the term "superior." I think a simpler

7   statement of the results of the trial would probably be

8   sufficient, and with caveats. I think the word "superior"

9   probably sends the wrong message.

10   Dr. Graboys votes (C) and I think that the sense

11 of the Committee, Bob, is that we think that the data are

12 persuasive for the comparison of clopidogrel versus placebo

13 and, therefore, we would recommend approval. I think that

14 given our concern about the selection of endpoints, some

15 concerns about the follow-up and certainly concerns about

16 the marginality of the p value, we are very reluctant to

17 conclude that clopidogrel is superior to aspirin. I think

18 you can wordsmith this any way you feel comfortable doing.

19   Are there any other questions from either Dr.

20 Fenichel, Dr. Temple or Dr. Lipicky?

21   DR. LIPICKY: No.

22   DR. TEMPLE: No, we thank you. This was a very

23 enlightening discussion.

24   DR. PACKER: We are adjourned.

1   (Whereupon, at 3:20 p.m., the Committee adjourned)