FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC)

Monday, September 20, 2010

Hilton Washington D.C./Silver Springs
The Ballrooms
8727 Colesville Road
Silver Spring, Maryland

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBERS (Voting):

SANJAY KAUL, M.D.
Director, Fellowship Training Program in
Cardiovascular Disease
Cedars-Sinai Heart Institute
Professor, David Geffen School of Medicine at UCLA
Division of Cardiology at Cedar Sinai Medical Center

MORI J. KRANTZ, M.D., F.A.C.C., F.A.C.P.
Associate Professor
University of Colorado
Denver Health, Cardiology
Director, CV Prevention, & ECG Core Lab
Colorado Prevention Center, Community Health

DARREN McGUIRE, M.D., MHSc
Associate Professor
University of Texas Southwestern
Medical Center, Cardiology

JAMES D. NEATON, Ph.D.
Professor of Biostatistics
Coordinating Centers for Biometric Research
University of Minnesota School of Public Health

INDUSTRY REPRESENTATIVE (Nonvoting):

JONATHAN C. FOX, M.D., Ph.D., F.A.C.C.
Vice President, Clinical Therapeutic Area
Cardiovascular and Gastrointestinal Diseases
Research & Development, Clinical Development
AstraZeneca LP

TEMPORARY MEMBERS (Voting):

ALLAN COUKELL, Bsc. Pharm. (Acting Consumer Representative)
Director, Medical Safety Portfolio
Pew Health Group
The Pew Charitable Trusts

SCOTT EMERSON, M.D., Ph.D.
    Professor of Biostatistics
    Department of Biostatistics
    University of Washington

A. MICHAEL LINCOFF, M.D. (Chair)
    Vice Chairman, Department of Cardiovascular Medicine
    Director, C5Research (Cleveland Clinic Coordinating
    Center for Clinical Research)
    Professor of Medicine
    Cleveland Clinic

STEVEN NISSEN, M.D., MACC
    Professor of Medicine
    Cleveland Clinic Lerner School of Medicine
    at Case Western Reserve University
    Chairman, Department of Cardiovascular Medicine
    Cleveland Clinic Foundation

TOM SIMON (Patient Representative)
    Director, Interfaith Companion And
    Ride Express Inc. (I CARE)

FDA (Nonvoting):

ROBERT TEMPLE, M.D.
    Director of the Office of Medical Policy
    Director, Office of Drug Evaluation (ODE) I
    CDER, FDA

ELLIS F. UNGER, M.D.
    Deputy Director, Division of Cardiovascular and
    Renal Drug Products (DCRP)
    ODE I, CDER, FDA

NORMAN STOCKBRIDGE, M.D.
    Director, Division of Cardiovascular and Renal Drug
    Products (DCRP)
    ODE I, CDER, FDA

SPONSOR SPEAKERS:

STUART CONNOLLY, M.D.
    Population Health Research Institute (PHRI)
    Hamilton Health Sciences/McMaster University

CHRISTOPHER D. CORSICO, M.D., M.P.H.
    US Medical Director

Boehringer Ingelheim Pharmaceuticals, Inc.

PAUL REILLY, Ph.D.
    Clinical Director, Cardiovascular Medicine and
    Team Member Medicine
    Boehringer Ingelheim Pharmaceuticals, Inc.

JAMES REVKIN, M.D.
    Associate Clinical Professor
    Yale University School of Medicine
    Executive Director of Department of Clinical Research
    Cardiovascular and Metabolic Diseases
    Boehringer Ingelheim Pharmaceuticals, Inc.

SALIM YUSUF, M.D., Ph.D.
    Population Health Research Institute (PHRI)
    Hamilton Health Sciences/McMaster University

FDA SPEAKERS:

NHI BEASLEY, PharmD
    Clinical Reviewer
    Division of Cardiovascular and Renal Products

KEVIN KRUDYS, Ph.D.
    Pharmacometrics Reviewer
    Office of Clinical Pharmacology

RAJNIKANTH MADABUSHI, M.D., Ph.D.
    Medical Team Leader
    Cardiovascular and Renal Division

ALIZA THOMPSON, M.D.
    Clinical Team Leader
    Division of Cardiovascular and Renal Products

ADDITIONAL SPEAKERS:

ANUJA PATEL, M.P.H. (Designated Federal Official)
    Division of Advisory Committee and
    Consultant Management HFD-21
    CDER, FDA

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

2   (8:00 a.m.)

3   DR. LINCOFF: Good Morning. I'm Michael Lincoff

4   from the Cleveland Clinic and welcome you to the

5   Cardiovascular and Renal Drugs Advisory Committee meeting.

6   We'd like to start first with introductions, but before

7   that I'll just again remind everyone to please put your

8   cell phones on silent or off so we don't interrupt the

9   meeting.

10   Jonathon, if you'd start at your end and please

11   introduce yourself and go -- and your affiliations, please.

12   DR. FOX: My name is Jonathon Fox. I'm a

13   cardiologist in clinical development with AstraZeneca and

14   I'm the industry representative to the committee.

15   DR. NISSEN: Steven Nissen, cardiologist,

16   Cleveland Clinic.

17   DR. MCGUIRE: Darren McGuire, cardiologist, UT

18   Southwestern, Dallas.

19   DR. KRANTZ: Good morning, Mory Krantz,

20   cardiology, University of Colorado.

21   DR. KAUL: Good morning, Sanjay Kaul,

22   cardiologist, Cedar Sinai Medical Center in Los Angeles.

23   MR. SIMON: Tom Simon, patient advocate from

1   Atlanta, Georgia.

2   MS. PATEL: Anuja Patel, acting designated

3   federal official, FDA.

4   DR. COUKELL: Alan Coukell. I'm a pharmacist and

5   the Pew Charitable Trust and the acting consumer rep on the

6   committee.

7   DR. NEATON: Jim Neaton, a biostatistician from

8   the University of Minnesota.

9   DR. UNGER: Ellis Unger, deputy director, Office

10 of Drug Evaluation 1.

11   DR. STOCKBRIDGE: And I'm Norman Stockbridge, the

12 division director in cardio/renal.

13   DR. LINCOFF: Read the statement from the FDA.

14 For topics such as those being discussed at today's

15 meeting, there are often a variety of opinions, some of

16 which are quite strongly held. Our goal is that today's

17 meeting will be a fair and open forum for discussion of

18 these issues and that individuals can express their views

19 without interruption. Thus, as a gentle reminder,

20 individuals will be allowed to speak into the record only

21 if recognized by the chair. We look forward to a

22 productive meeting.

23   In the spirit of the Federal Advisory Committee

1   Act and the Government in the Sunshine Act, we ask that the

2   advisory committee members take care that their

3   conversations about the topic at hand take place in the

4   open forum in the meeting. We are aware that members of

5   the media are anxious to speak with the FDA about these

6   proceedings. However, the FDA will refrain from discussing

7   the details of this meeting with the media until its

8   conclusion. For the convenience of the media

9   representatives, I would like to identify the FDA press

10 contacts, Sandy Walsh and Karen Mahoney. If you are

11 present please stand.

12   Also, the committee is reminded to please refrain

13 from discussing the meeting topic during breaks or lunch.

14 Thank you.

15   MS. PATEL: The Food and Drug Administration is

16 convening today's meeting of the Cardiovascular Renal

17 Drug's Advisory Committee under the authority of the

18 Federal Advisory Committee Act (FACA) of 1972. With the

19 exception of the industry representative, all members and

20 temporary voting members of the committee are special

21 government employees (SGEs) or regular federal employees

22 from other agencies and are subject to federal conflict of

23 interest laws and regulations.

24   The following information on the status of the

1   committee's compliance with federal ethics and conflict of

2   interest laws covered by, but not limited to, those found

3   at 18 U.S.C. Section 208 and Section 712 of the Federal

4   Food, Drug, and Cosmetic Act (FD&C Act) is being provided

5   to participants in today's meeting and to the public. The

6   FDA has determined that members and temporary voting

7   members of this committee are in compliance with federal

8   ethics and conflict of interest laws.

9   Under 18 U.S.C. Section 208 Congress has

10   authorized FDA to grant waivers to special government

11   employees and regular federal employees who have potential

12   financial conflicts when it is determined that the agency's

13   need for a particular individual's services outweighs his

14   or her potential financial conflict of interest. Under

15   Section 712 of the FD&C Act, Congress has authorized FDA to

16   grant waivers to special government employees and regular

17   federal employees with potential financial conflicts when

18   necessary to afford the committee essential expertise.

19   Related to the discussions of today's meetings,

20   members and temporary voting members of this committee have

21   been screened for potential financial conflicts of interest

22   of their own as well as those imputed to them, including

23   those of their spouses or minor children and for purposes

24   of 18 U.S.C., Section 208, their employers. These

1 interests may include investments, consulting, expert

2 witness testimony, contracts, grants, CRADAs, teaching,

3 speaking, writing, patents and royalties and primary

4 employment.

5   Today's agenda involves discussions of new drug

6 application (NDA) 22-512, dabigatran etexilate mesylate

7 capsules, sponsored by Boehringer Ingelheim

8 Pharmaceuticals, Inc. for the proposed indication of

9 prevention of stroke in patients with atrial fibrillation,

10 abnormally rapid contractions of the atria, the upper

11 chambers of the heart.

12   This is a particular-matters meeting during which

13 specific matters related to dabigatran will be discussed.

14 Based on the agenda for today's meeting and all financial

15 interests reported by the committee members and temporary

16 voting members, no conflict of interest waivers have been

17 issued in connection with this meeting. To ensure

18 transparency, we encourage all standing committee members

19 and temporary voting members to disclose any public

20 statements that they have made concerning the product at

21 issue.

22   With respect to FDA's invited industry

23 representative, we would like to disclose that Dr. Jonathan

24 Fox is participating in this meeting as a nonvoting

1   industry representative acting on behalf of regulated

2   industry. Dr. Fox's role at this meeting is to represent

3   industry in general and not any particular company. Dr.

4   Fox is employed by AstraZeneca.

5   We would like to remind members and temporary

6   voting members that if the discussions involve any other

7   products or firms not already on the agenda for which an

8   FDA participant has a personal or imputed financial

9   interest, the participants need to exclude themselves from

10 such involvement and their exclusion will be noted for the

11 record. FDA encourages all other participants to advise

12 the committee of any financial relationships that they may

13 have with the firm at issue. Thank you.

14   DR. LINCOFF: We will start now with the opening

15 remarks by Dr. Stockbridge from the FDA.

16   DR. STOCKBRIDGE: Good morning and my thanks to

17 the committee for spending the day with us on the

18 particular matters relating to dabigatran. Like most of

19 the advisory committee meetings we hold, there's an

20 immediate issue. Often, as in this case, there's an

21 approval decision that we have to make. But often there's

22 also a more generic issue and there's certainly one here.

23 The dabigatran development program is of -- is kind of

24 interesting in that it employed several doses and gives you

1 some opportunity to explore the relationship between the

2 additional risk of bleeding events at high doses versus the

3 incremental reduction in cardiovascular events, in this

4 case, stroke also at higher doses, and I'm particularly

5 interested.

6   The main issue that I'm looking forward to having

7 a discussion on here relates to how you view that tradeoff.

8 So there's a fairly extensive set of questions that relate

9 to that matter, but certainly looking forward to other

10 aspects of this application and the discussion that

11 follows. Thank you.

12   DR. LINCOFF: Dr. Emerson, I -- since you walked

13 in would you take the opportunity to introduce yourself?

14   DR. EMERSON: Scott Emerson, professor of

15 biostatistics, University of Washington.

16   DR. LINCOFF: Dr. Temple, if you'd like --

17   DR. TEMPLE: Good morning, Bob Temple, director

18 of ODE I.

19   DR. LINCOFF: All right, so for the next

20 approximately 90 minutes we'll have the sponsor's

21 presentation. That's fairly long and that will leave us

22 with about 20 minutes for questions directed at the

23 sponsor. So given the time constraints, I ask the sponsor

24 to stay within that period.

1   DR. CORSICO: Good morning, Mr. Chairman, members

2 of the committees, representatives from the Food and Drug

3 Administration, colleagues and guests. My name is Chris

4 Corsico and I am the U.S. medical director for Boehringer

5 Ingelheim Pharmaceuticals. On behalf of Boehringer

6 Ingelheim, I'd like to thank the Food and Drug

7 Administration for the opportunity to present the results

8 of our dabigatran clinical development program for the

9 prevention of stroke with atrial fibrillation to this

10 committee.

11   Over the next 90 minutes my colleagues will

12 summarize the following. Dr. Stewart Connolly, the co-

13 principle investigator for our pivotal study, RE-LY, will

14 summarize the unmet medical need that continues to exist

15 despite the effectiveness of warfarin in this patient

16 population. He will also discuss the trial design and

17 summarize the efficacy results from the RE-LY study.

18   Dr. Paul Reilly, responsible for global

19 development of dabigatran in the stroke prevention

20 indication, will present an overview of the safety results

21 from RE-LY. Finally, Professor Salim Yusuf, the co-chair

22 for the RE-LY study, will summarize net clinical benefit

23 and risk benefit and provide conclusionary comments.

24   Prior to turning the podium over to Dr. Connolly,

1   please allow me to provide you with a brief overview of

2   dabigatran. Dabigatran is a reversible, direct thrombin

3   inhibitor. It is orally administered and dabigatran is

4   formed when the pro-drug dabigatran etexilate, depicted

5   here as the complete molecule in white and yellow,

6   undergoes esterase-catalyzed hydrolysis. The hydrolysis

7   occurs where the dash lines are. The yellow portions of

8   the molecule are cleaved, leaving the active mode

9   dabigatran, depicted here in white.

10   Following oral administration, dabigatran reaches

11 peak plasma concentrations in approximately two hours. It

12 reaches steady state in approximately three days after

13 twice daily dosing. As noted in our briefing document,

14 dabigatran has also been developed for the prevention of

15 venous thrombolumbolup disease in patients undergoing hip

16 and knee surgery. Although still under development in the

17 United States, dabigatran is approved outside the United

18 States in over 70 countries for the VTE indication. But

19 please allow me to return to the stroke prevention program.

20   Our stroke prevention program consisted of over

21 40 pharmacologic studies and drug-drug interaction studies

22 and three Phase 2 programs. As a result of our Phase 2

23 investigations, Boehringer Ingelheim was able to identify

24 two doses to carry forward into Phase 3 clinical

1   development. As noted in the briefing book, the focus of

2   today's meeting will be on that pivotal study, RE-LY.

3   Therefore, please allow me to provide you with a brief

4   overview of the RE-LY study.

5   RE-LY, or the Randomized Evaluation of Long-Term

6   Anticoagulation Therapy, was a study conducted in

7   coordination with independent academic coordinating

8   centers, as well as an independent data management and

9   trial center out of the Population Health Research

10 Institute in Hamilton, Ontario. RE-LY was designed as a

11 parallel group, non-inferiority trial. It compared two

12 blinded doses of dabigatran etexilate, 100 milligrams twice

13 a day and 150 milligrams twice a day to open-label

14 warfarin.

15   The study was conducted in 951 centers across 44

16 countries. Over 20,000 patients were screened and 18,113

17 were randomized. The median study duration was two years.

18 Given the nature of the study design, extensive measures

19 were implemented to mitigate bias. In his presentation,

20 Dr. Connolly will talk about the PROBE design as well as

21 blinded adjudication of endpoints, as well as the other

22 measures undertaken to mitigate this bias.

23   The results from the RE-LY program were

24 previously published in the New England Journal of

1 Medicine. Please allow me to summarize the results for

2 you. The 110-milligram dose of dabigatran etexilate

3 demonstrated non-inferiority to warfarin in reducing the

4 risk of stroke and systemic embolism and was superior to

5 warfarin with respect to the risk of bleeding. The

6 dabigatran etexilate 150-milligram dose was superior to

7 warfarin in reducing the risk of stroke and systemic

8 embolism and comparable to warfarin with respect to the

9 risk of major bleeding. Both doses of dabigatran reduced

10 the risk of intracranial hemorrhage compared to warfarin,

11 increased the incidence of GI bleeding, increased the

12 frequency of MI compared to warfarin and both doses

13 demonstrated a hepatic safety profile comparable to

14 warfarin.

15   As a result, Boehringer Ingelheim is seeking the

16 following proposed indication. Dabigatran etexilate is

17 indicated for the prevention of stroke and systemic

18 embolism in patients with atrial fibrillation. At this

19 time I'd like to acknowledge two external consultants that

20 are with us here today to help potentially address

21 questions this committee may have. The first is Dr. James

22 Lewis, a hepatologist from Georgetown University. The

23 second is Dr. Robert Makuch, a professor of biostatistics

24 from Yale University.

1   It is now my distinct pleasure to introduce Dr.

2   Connolly, the co-principle investigator for RE-LY. Thank

3   you for your attention.

4   DR. CONNOLLY: Good morning panel members, ladies

5   and gentlemen. My name is Stuart Connolly and I'm the head

6   of cardiology at McMaster University. I'm a cardiac

7   electric physiologist and as was said, I'm one of the co-

8   principle investigators of this study, of the RE-LY study.

9   This is my disclosure.

10   I'm going to begin by reviewing the unmet medical

11   need related to stroke prevention and atrial fibrillation.

12   Atrial fibrillation affects about 1 percent of the U.S.

13   population and is responsible for a substantial number of

14   strokes which occur, but there's a very important age

15   distribution. The incidence of atrial fibrillation

16   increases markedly with age, as shown by the yellow bars on

17   this diagram.

18   Essentially this is a disease of the elderly and

19   very elderly. What's even more striking about this

20   diagram, however, is the markedly -- even more increase in

21   the population attributable risk to atrial fibrillation for

22   stroke such that fully 25 percent of all strokes in the

23   very elderly are due to atrial fibrillation. Thus we have

24   a disease that effects an elderly population who in fact

1   are our most vulnerable patients.

2   Since the late 80s and early 90s we've know that

3   warfarin is a remarkable effective drug for reducing this

4   risk of stroke and atrial fibrillation. And this was

5   demonstrated by a series of randomized trials, some of

6   which were open and some of which were blinded, which

7   showed remarkable consistency in their effects, indicating

8   overall a reduction in the risk of stroke of about 60

9   percent. as shown by the summary statistic.

10   This remarkable efficacy has led guidelines to

11 consistently recommend warfarin since these trials were

12 published. And this slide shows the most current AHA/ACC

13 guidelines. Warfarin is indicated for patients who have

14 atrial fibrillation, but is only reserved for patients with

15 the highest risk of stroke, or a higher risk of stroke,

16 because of its inherent risk of hemorrhage. Patients with

17 no risk factors are recommended to receive aspirin and a

18 fairly large group of patients with intermediate risk are

19 recommended to receive either aspirin or warfarin depending

20 upon the physician's judgment of the risk/benefit ratio in

21 individual patients.

22   However, warfarin does have problems. I've

23 already alluded to the risk of hemorrhage with this drug,

24 but as well known, there are multiple drug and diet

1   interactions which leads to high variability within

2   patients and between patients in the anti-coagulate effect.

3   Coupled with this is a relatively narrow therapeutic range.

4   Thus, there is a need for lifelong monitoring of the INR in

5   order to achieve adequate anti-thrombotic therapy and

6   frequent dose adjustments are really part of this therapy.

7   The difficulties with warfarin have led -- or

8   have resulted in a relatively low uptake of this extremely

9   effective therapy. And many surveys have demonstrated that

10   there are many patients who are at high risk and who would

11   benefit from this, but who don't receive it. This is one

12   of those surveys from the U.S. done in Medicare patients

13   hospitalized with a diagnosis of atrial fibrillation and as

14   can be seen on this slide, only about half of patients were

15   discharged on warfarin, or if, as the investigators did,

16   one looks at ideal patients, only about 65 percent. Thus,

17   there's about a third of high-risk atrial fibrillation

18   patients who would be good candidates for warfarin who are

19   not receiving it.

20   If we look at this slide we see a bit more

21   information about exactly who doesn't receive warfarin.

22   And you can see that in this survey done also from

23   administrative databases in United Kingdom, that the

24   patients least likely to receive warfarin are again the

1 elderly and the extreme elderly who have very low rates of

2 uptake. So the most vulnerable patients in the population

3 and the population that is most in need of stroke

4 prevention is receiving it the least, probably least in

5 part due to the concern about hemorrhage in these elderly

6 patients.

7 The dilemma of anti-coagulate therapy with

8 warfarin is shown on this slide. To be effective you need

9 to stay in the therapeutic range. The slide shows

10 different levels of the INR on the X axis and on the Y axis

11 the odds ratio for outcome events. In blue we see the risk

12 of stroke, which increases markedly once the INR drops much

13 below two. Conversely, we see the risk of intracranial

14 hemorrhage start to rise at an INR of around four and gets

15 precipitously higher as the INR increases.

16 Thus, we need to maintain patients in the

17 therapeutic range once we get them on warfarin. How well

18 do we do with that has been summarized in this rather nice

19 meta-analysis which summarizes a whole variety of surveys

20 related to the United States practice, and you can see each

21 of the surveys summarized in a single box and whisker plot.

22 And we can see also the summary statistic at the bottom

23 showing that overall, based on all of these surveys, the

24 time to therapeutic range in the United States currently

1   are, at the time of this analysis, reflecting the previous

2   10 years or so, is around 55 percent. It's somewhat better

3   in -- it's quite a bit better, actually, in specialized,

4   anti-coagulation clinic practice, where it rises up to 63

5   percent, and it's somewhat worse in general clinical care

6   where it's down around 51 percent.

7   In clinical trials, we do better. We select the

8   sites. We select the patients and overall we're achieving

9   time to therapeutic range of about 65 percent. One has to

10 be careful comparing between these trials because they do

11 enroll different types of patients. And in particular they

12 enroll different numbers of warfarin-naïve patients, who

13 are known to be harder to control.

14   So to conclude the -- this part of my

15 presentation on unmet medical need, it's clear that

16 warfarin's a very effective treatment against stroke, but

17 has some serious limitations. Because of these, warfarin

18 use is relatively low, especially in the elderly. And even

19 when patients get on warfarin, it's difficult to manage

20 without and the time and range in the U.S. is only about 55

21 percent. Thus there is clearly a need for a better oral

22 anticoagulant.

23   I'll now discuss the rationale, the design and

24 the efficacy results of the RE-LY trial and the safety

1 results will be subsequently presented by Paul Reilly.

2 I'll begin by discussing dose selection and then the design

3 of the study. Selecting a dose of anti-thrombotic therapy

4 and atrial fibrillation can be challenging because of end

5 rates are relatively low especially for stroke and systemic

6 embolism. This slide shows the results of a Phase 2 dose

7 ranging study done with dabigatran in patients with atrial

8 fibrillation. A range of dose -- of total daily doses was

9 studied between 100 and 600 milligrams per day. And we

10 used either divided or twice daily dosing or single-day

11 dosing. In yellow we see the results for stroke and

12 systemic embolism and you can see a fairly clear pattern

13 here for this outcome.

14 With the rate of stroke dropping down from

15 relatively high rates at low doses and at once you hit a

16 dose of 300 milligrams per day or greater, the rate of

17 strokes seems to become quite acceptable. The results are

18 less clear for major hemorrhage, where we have a

19 surprisingly high rate on this lower dose, probably related

20 to small numbers of events. What's quite clear, however,

21 is that the 300-milligram, 600 total daily dose had a

22 higher bleeding rate and it was particularly high in

23 aspirin patients such that this dose was recommended to be

24 discontinued from the study by the DMC.

1   Thus, we were clearly looking at 300 milligrams

2   per day as the optimal dose and based on pharmacokinetic

3   principles and a desire to minimize peak to trough

4   differences, we wanted to use b.i.d. dosing. And so we

5   felt that the 150-milligrams b.i.d. dose was the dose that

6   was clearly indicated by this study. Now to validate that,

7   we looked at the effect of this dose on the aPTT

8   measurements and we saw that at trough we had quite a good

9   increase in the aPTT of 1.5 times baseline, suggesting or

10   indicating to us that we were probably at the higher end of

11   the concentration of the effect range that we wanted to be.

12   And because we wanted to take a second dose forward into

13   the Phase 3 study, we felt that is should be a lower dose.

14   And we looked at 110-milligrams b.i.d., modeled its effects

15   and these indicated that we would have adequate anti-

16   coagulant effect in vast majority of patients at trough and

17   therefore, these two dose, 110 milligrams b.i.d. and 150

18   milligrams b.i.d. were take forward into Phase 3.

19   The RE-LY trial had several unique features which

20   I will now describe. These were the non-inferiority design

21   blinded doses, open warfarin and multiple approaches to

22   minimize potential bias. First, the non-inferiority

23   margin. RE-LY was designed as a non-inferiority trial and

24   we based the non-inferiority margin on the standard

1   statistical reasoning that comes from looking at the upper

2   bound of the 95 percent confidence interval of the warfarin

3   versus control historical trials. We then reasoned that we

4   wanted to maintain, with high confidence, 50 percent of the

5   known benefit of warfarin. And this led us to a non-

6   inferiority margin of 1.46.

7   The FDA has argued that perhaps a margin of 1.38

8   would be more appropriate based on logarithmic scale for

9   the X axis and we will show data for both of these non-

10 inferiority margins. We controlled for multiplicity of

11 testing using the Hochberg procedure and superiority

12 testing was performed, as is typical in non-inferiority

13 trials once non-inferiority had been established.

14   There is a choice in warfarin-controlled trials

15 on whether to do blinded or open trials and most of the

16 previous warfarin trials in atrial fibrillation have been

17 open. There are some blinded trials and in fact the

18 Canadian atrial fibrillation study was one of the blinded

19 trials and I led that trial. However, in that trial we

20 made a decision to perform an open trial and there were

21 some advantages to the open trial, as I'm going to describe

22 in this slide. The main advantage is related to the fact

23 that dabigatran and warfarin are different drugs with

24 different pharmacokinetics and different pharmacodynamics,

1   which then lead to different ways of being used in clinical

2   practice.

3   By performing an open trial, we were able to use

4   the drugs in clinical practice the way physicians would

5   normally use them and the way they would be used in the

6   future. In particular, this meant that the INR control did

7   not have to be done under some remarkable constraints.

8   Investigators could manage the INR as they normally did or

9   they could refer the patient to an anticoagulation clinic,

10 which often happened, or they could use point-of-care

11 devices, as is done in some patients.

12   Also, if they wanted to temporarily discontinue

13 the drug for surgery, something that was quite common in

14 this study, they would do so using their standard approach

15 of bridging patients for surgery or procedures. On the

16 other hand, dabigatran management does not require ongoing

17 anticoagulant monitoring and this was not performed in this

18 study. Furthermore, because of the short half life of this

19 drug, it was possible to have shorter study medication

20 discontinuations for temporary procedures and less need for

21 bridging.

22   However, because it was an open design we needed

23 to institute serious measures to reduce the potential risk

24 of bias and we had two major approaches. One was the PROBE

1   design which -- and the other was multiple other safeguards

2   to protect against either differential or underreporting of

3   events. The PROBE design calls for objective and well-

4   defined outcome events and blinded adjudication of those

5   events. And I'll also describe the multiple safeguards in

6   a moment.

7   First, adjudication. We required that two

8   adjudicators who were blinded to treatment must agree on

9   each event. These adjudicators were trained neurologists

10 for strokes and cardiologist in general for other vascular

11 events. And we requested brain imaging on all strokes and

12 intracranial hemorrhages and we had that available in 95

13 percent of cases for further validation and objectivity of

14 the results. We also instituted several other techniques

15 to protect against underreporting of events and in

16 particular we had stroke and bleed questionnaires that were

17 administered to patients at every follow-up visit. And

18 these were searching for symptoms that might be assigned

19 about an event that might have been overlooked by the

20 investigator.

21   Questions such as have you noticed a black, tarry

22 stool, for example, for the bleeding questionnaire, if

23 there was a positive response to one of these

24 questionnaires and no event -- appropriate event had been

1 reported, then we would work with the sites to determine

2 whether or not event might have occurred and should be

3 reported. We also required that all TIAs be reported and

4 these were then adjudicated by neurologists to determine if

5 perhaps this should be reported as a stroke rather than a

6 TIA. And finally we did a fairly detailed analysis of all

7 hemoglobin drops looking for evidence of bias in the

8 reporting of events.

9   Another key feature of the RE-LY study was the

10 use of two blinded doses of dabigatran. This had two main

11 benefits for the validity and coherence of this trial. The

12 first benefit was that it allowed blinded dose evaluation

13 of dabigatran for both benefit and for risk. Secondly, it

14 allowed for replication of the results. We were able to

15 compare both doses of dabigatran to warfarin and we were

16 also able to compare the superiority of dabigatran 150

17 versus warfarin, which was pre-specified and versus

18 dabigatran 110, which was a post hoc analysis.

19   Now to the RE-LY study. This summarizes its

20 design. Patients were eligible for this study if they had

21 at least one risk factor for stroke with no

22 contraindications for anticoagulation. And as already

23 indicated, more than 18,000 patients were enrolled from

24 countries around the world. There were -- 50 percent of

1 patients were naïve to warfarin by our study definition of

2 less than 62 days of anticoagulation treatment ever in

3 their lives. And this was a key part of the protocol and

4 we went to some efforts to achieve an even balance of

5 patients, both warfarin-naïve and warfarin experienced.

6   The RE-LY study endpoints are listed in detail

7 here. I'll just draw your attention to the primary

8 efficacy outcome, which was a composite of stroke or

9 systemic embolic event, and the primary safety outcome,

10 which was major bleeding. We had a series of other --

11 secondary outcomes and draw your attention just to the net

12 clinical benefit outcome that was specified in the

13 protocol, which was at the bottom, and it was a composite

14 of all embolic and thrombotic events as well as major

15 bleeding.

16   Before I go into the results, just want to draw

17 your attention to a technical detail, which is that there

18 are going to be two different data sets discussed in the

19 various slides today. The first I'm showing is the --

20 essentially the intention to treat data set. It's all

21 randomized patients and includes all outcome events. The

22 second data set is called the safety data set or it's the

23 on-treatment data set. It includes only patients who were

24 administered at least one dose of study medication and only

1 includes outcome events up until the time from six days

2 after permanent study medication discontinuation. The

3 total patient years of follow-up in the safety data set is

4 about 10 to 12 percent less than for the intention to treat

5 data set.

6   And now the results. This shows the baseline

7 characteristics of the RE-LY population. It was a fairly

8 typical atrial fibrillation population with patients having

9 at least a single risk factor for stroke. In fact, the

10 average number of risk factors in the population was two,

11 as shown by a CHADS -- a mean CHADS score of 2.1. The

12 population was moderately elderly with an average age of

13 around 71 years. Twelve percent of patients had had a

14 prior stroke and as indicated previously, 50 percent of the

15 patients were warfarin-naïve at baseline.

16   This shows the main principle analysis of the RE-

17 LY study, the primary outcome of course being stroke and

18 systemic embolism. It shows the non-inferiority margin of

19 1.46 and next to it a non-inferiority margin of 1.38. Each

20 box and whisker plot shows the estimate of the treatment

21 effect of dabigatran versus warfarin for the two doses of

22 dabigatran and we show the statistics for non-inferiority

23 and superiority on the right. As you can see, the upper

24 bound of the 95 percent confidence interval for both doses

1   of dabigatran in comparison to warfarin falls well below

2   both the 1.46 non-inferiority margin and the 1.38 non-

3   inferiority margin and the p-values for non-inferiority are

4   highly statistically significant.

5   Furthermore, you can see that the upper bound of

6   the 95 percent confidence interval of dabigatran 150 versus

7   warfarin also falls well below the line of unity,

8   indicating superiority of this dose for the -- against

9   stroke and systemic embolism, once again with a p-value

10   that's highly statistically significant for superiority.

11   This shows the Kaplan-Meier curves for the

12   primary outcome for the three treatments and you can see

13   that the curve for dabigatran 150 separates early and

14   continuously from the other two curves. And there is a 35

15   percent relative reduction in the risk of stroke or

16   systemic embolism compared to warfarin with this dose. On

17   the other hand, for dabigatran 110 compared to warfarin,

18   the two curves mostly overlap. There is a point estimate

19   of 0.9, which is not statistically significant for

20   superiority although, of course, it is for non-inferiority.

21   Now this slide shows the events occurring on less

22   than six days post-study medication discontinuation. These

23   would be the events occurring in the so-called safety set

24   or the on-treatment analysis. We're showing this because

1   in a non-inferiority trial, of course, if you have very

2   high rates of medication discontinuation you can spuriously

3   achieve non-inferiority. And so we want to show you the

4   non-inferiority analysis for the on-treatment cohort and so

5   we see that here. What you can see for this on-treatment

6   analysis is, once again, both upper bounds of the 95

7   percent confidence intervals for the dabigatran/warfarin

8   comparisons are falling well below the line, the non-

9   inferiority margin. And if we look at the point estimates

10   for the hazard ratio we can see that they're actually more

11   in favor of dabigatran .85 for both doses of dabigatran in

12   comparison to warfarin.

13   Now the outcome of stroke is made up of both

14   ischemic stroke, which are thrombolic or thrombotic events,

15   and hemorrhagic stroke, which are bleeds into the brain

16   tissue and are something that we want to -- that are often

17   caused by the antithrombotic therapy itself. And so we'll

18   look at the outcome events for both the ischemic and the

19   hemorrhagic stroke strokes. And you can see for ischemic

20   stroke, as shown here, that a curve for dabigatran 150 once

21   again is separating very clearly from the warfarin curve

22   and you can see that there's a 25 percent reduction that is

23   statistically significant. On the other hand, once again,

24   we're seeing the curves for dabigatran 110 and warfarin

1 more or less overlapping with a slightly increased number

2 of strokes on -- ischemic strokes on dabigatran that is

3 still, I think, within the non-inferiority margin.

4 For hemorrhagic stroke, the results are truly

5 remarkable. You -- normally when we reduce embolic or

6 thrombotic strokes with an anti-thrombotic therapy, we

7 expect, in fact, to see an increase in the hemorrhagic

8 strokes as a result of that. But, in fact, in this case

9 we're seeing both types of stroke go in the correct

10 direction or in the favorable direction for patients. In

11 fact, the reduction in hemorrhagic stroke is even more

12 impressive than the reduction in ischemic stroke and it

13 occurs with both doses of dabigatran, not just with the

14 150-milligram dose. You can see that the curves separate

15 and dramatically separate throughout the course of the

16 study. And if we look at the hazard ratio's points

17 estimates we can see that there is more than a two-thirds

18 reduction in hemorrhagic stroke with both doses of

19 dabigatran.

20 There are just a bit of numbers to give you a bit

21 more of a flavor of what's going on here. I just want to

22 draw your attention to the actual make up of the reduction

23 of stroke for dabigatran 150. You can see we go from 186

24 event to 122 events. That's 64 events prevented. Thirty-

1   one of them are ischemic strokes prevented and 33 of them

2   are hemorrhagic strokes prevented. Thus, we're getting a

3   reduction of -- that's approximately equal for hemorrhagic

4   and ischemic strokes with dabigatran 150. If we look at

5   dabigatran 110, there's numerically somewhat more ischemic

6   strokes. There's 18 more ischemic strokes on 110 compared

7   to warfarin, but this is more than offset by 31 less

8   hemorrhagic strokes with dabigatran 110. And remember that

9   the hemorrhagic strokes are much more serious clinically.

10   The population in the RE-LY study consisted of a

11   considerable number of patients with a history of

12   myocardial infarction or documented coronary artery

13   disease, more than 20 percent of the patients. And we saw

14   a risk of myocardial infarction that is about in the same

15   range as has been seen in the -- many of the atrial

16   fibrillation trials, somewhat less than 1 percent per year.

17   We also saw that there was a higher rate in the dabigatran

18   arms compared to warfarin. This higher rate is shown here,

19   0.8 percent per year, 0.8 percent per year versus 0.6

20   percent per year. The rate was higher in both doses, but

21   was -- there was no dose response.

22   We've looked at a whole variety of analyses to

23   better understand this higher rate of myocardial infarction

24   and one of the analyses was to look for other types of

1 events that would go along with a myocardial infarction,

2 such as hospitalization for angina, CABG surgery, or

3 percutanious coronary procedure or cardiovascular death.

4 And what we see is that there's no big trend to an increase

5 for these other types of events related to coronary artery

6 disease. You can see here that, in fact, the risk of new

7 hospital angina is about the same for the three groups,

8 likewise for patients requiring CABG or PTCA, about the

9 same for the three groups. And in fact, there's a slight

10 trend towards a reduction in cardiovascular death.

11 When we have a reduction in stroke and in

12 hemorrhagic stroke, we expect that this should translate

13 into some benefits in mortality, notwithstanding the fact

14 that there are many competing causes of death in this

15 relatively elderly population. We do, in fact, see

16 numerically less deaths on both doses of dabigatran

17 compared to warfarin, as shown here, that radon warfarin is

18 4.1 percent per year, 3.6 percent on the higher dose of

19 dabigatran and 3.8 percent on the lower dose of dabigatran.

20 This difference is not statistically significant. However,

21 for vascular death, which is somewhat more specific, we see

22 a reduction from 2.7 percent per year to 2.3 percent per

23 year on dabigatran 150, which is nominally significant at

24 the $p=0.04$ level.

1   I mentioned before that an important feature of

2   the RE-LY study was the comparison of the two blinded doses

3   of dabigatran and I want to give you a bit of information

4   about that comparison. We did see a statistically

5   significant reduction in stroke with dabigatran 150

6   compared to 110 from 1.5 percent per year on 110 down to

7   1.1 percent per year on 150, highly statistically

8   significant. This is driven entirely by a reduction --

9   almost entirely by a reduction in ischemic stroke, which

10 goes from 1.3 percent per year down to 0.9 percent per

11 year, highly statistically significant. However, in both

12 doses, the risk of hemorrhagic stroke was uniquely low at

13 0.1 percent per year.

14   We've performed a considerable number of subgroup

15 analyses for the primary outcome of this trial. And to

16 summarize briefly what we found, the results of dabigatran

17 for both doses are highly consistent across all of the

18 subgroups which we've looked at and there are no

19 statistically significant interactions that we have

20 observed. Our primary subgroup analysis was that related

21 to warfarin-naïve and warfarin-experienced and we went to

22 great lengths to get even numbers of patients with these

23 two. And you can see here that the results are entirely

24 consistent across these groups, both for 110 and for 150.

1 Furthermore, when we look at age, there's no major

2 difference in response according to age for either dose,

3 gender, BMI or weight.

4   Sorry about this line. We have also looked at

5 the treatment effects according to ethnicity and according

6 to region and results are consistent across these

7 subgroups. Likewise, there's no difference in benefit

8 according to renal function. And there's no significant

9 interaction, although there might be a small trend for the

10 higher dose.

11   A final note on INR control. We measured the INR

12 control using a standard approach called the time in

13 therapeutic range and you can see the results for the RE-LY

14 study. Overall, we achieved a time in therapeutic range of

15 64 percent, which compares reasonably favorably with the

16 other recent trials of anticoagulation in atrial

17 fibrillation. I wanted to point out the fact, however,

18 that our trial was unique in having the highest percentage

19 of patients who were warfarin naïve, 50 percent. And we

20 achieved a time in therapeutic range in this hard to

21 control group of patients at 62 percent, whereas in

22 warfarin-experienced patients, we achieved 67 percent time

23 and range. Thus, we believe that we have excellent INR

24 control compared to both through clinical practice in the

1 United States and elsewhere and also compared to other

2 trials.

3   Thus, in conclusion, both doses of dabigatran are

4 non-inferior to warfarin for the prevention of stroke or

5 systemic embolism. And dabigatran 150 is superior to

6 warfarin and superior to dabigatran 110, also for the

7 prevention of stroke and systemic embolism. Both doses

8 markedly reduce hemorrhagic stroke. The effects are

9 consistent across all of the subgroups that we've looked

10 at. We do see a greater frequency of myocardial infarction

11 compared to warfarin, something that we still have yet to

12 fully understand. Dabigatran 150 also reduces vascular

13 death compared to warfarin. Thank you for your attention.

14   Sorry. Oh, you advanced it -- I was going to

15 introduce Paul Reilly, sorry. Thank you, Paul.

16   DR. NISSEN: Mike, you want to wait until after

17 both presentations for questions?

18   DR. LINCOFF: Yes, there'll be a period after the

19 -- all of the sponsor's presentations.

20   DR. NISSEN: Fine.

21   DR. REILLY: Thank you, Dr. Connolly. Good

22 morning advisory committee panelist, FDA, ladies and

23 gentlemen. My name's Paul Reilly. I've been working on

24 dabigatran for 10 years, the last eight as the coloncal

1 lead in the stroke prevention program. The safety

2 presentation today will cover four key safety areas, a

3 short overview of the patient experience in the development

4 program on dabigatran, and then I'll focus on the key

5 safety results from rely, namely the bleeding, the hepatic

6 safety and other adverse events.

7 The next slide shows you the overall treatment

8 exposure and clinical development of dabigatran. Eighty-

9 eight percent of the exposure came from the RE-LY study,

10 over 20,000 patient years of patient -- of experience.

11 Another 3,000 patient years comes from Phase 2 studies and

12 other indications as shown here on this slide. If we focus

13 on RE-LY, the study ran just over three years. The median

14 duration of a patient in the study was two years. Actual

15 time on drug was approximately 10 percent less than that as

16 shown in the table here, ranging from 21.4 months to 22.6

17 months on drug.

18 Patient disposition is shown in this consort

19 diagram. Over 20,000 patients enrolled, of which 18,113

20 were randomized. I draw the panel's attention to the

21 bottom row, where you can see that 96 percent of subjects

22 have completed the study according to plan, coming in for a

23 final visit during the study closeout period. The previous

24 row, the row above that, shows that approximately 680

1   subjects prematurely discontinued the study. This is

2   evenly balanced across the three treatment groups with

3   approximately a very rough average of about one year on

4   study for these patients.

5   In fact, we went to great lengths to collect data

6   and in any event, we collected vital status on all but 24

7   patients. That is, we have an overview accounting for 99.8

8   percent of the patients. The result -- the results on

9   major bleeding are shown here. Major bleeding is the

10 primary safety endpoint in RE-LY. It's pre-specified in

11 the protocol. The definition of major bleed that we used

12 was that defined by the International Society on Thrombosis

13 and Hemostasis. Note that the first two criteria,

14 hemoglobin drops and transfusions, require the presence of

15 bleeding to qualify as a major bleeding event. A

16 hemoglobin change or a transfusion in and of itself was not

17 a sufficient criterion for a major bleed. The other

18 components of the definition include systematic bleeding in

19 a critical area, a hypotension, bleeds necessitating

20 surgical intervention or fatal bleeds.

21   The results for major bleeding, the primary

22 efficacy safety endpoint, are summarized in this slide.

23 And this is the Kaplan-Meier curve for time to first major

24 bleed, the primary safety endpoint. Please note that this

1   is the randomized set, i.e. intention to treat and only

2   adjudicated events. The highest bleed rates are seen on

3   warfarin with a dose-related decrease of major bleeds with

4   the two dabigatran doses. The statistics for comparison of

5   each dose of warfarin are seen at the top of the slide.

6   The hazard ratio for 110 dabigatran is 0.8, a 20 percent

7   decrease in bleed rate, clearly statistically significant.

8   For dabigatran 150, a hazard ratio of .93, a 7 percent drop

9   was not significant. So, we do show dose response for

10 these two blinded doses of dabigatran.

11   So a subset of major bleeds is life threatening

12 or fatal bleeds. This was also pre-specified in the

13 protocol. The definition is shown here. The two -- most

14 of the components come also from the major bleed

15 definition, but do note that there are two components

16 there, the drops of hemoglobin and transfusion, which

17 require a higher threshold to qualify as life-threatening

18 bleeds.

19   This is the Kaplan-Meier for life-threatening

20 bleeds. Again, clear dose response with the two blinded

21 doses of dabigatran, both doses resulting in significantly

22 less bleeding than warfarin. From statistics seen above

23 the curves, the hazard ratios are .67 and .80 for the low

24 and the high dose respectively. A 33 percent and a 20

1   percent decrease compared to warfarin. So, if we drill

2   down further we can focus on the most devastating subset of

3   major bleeds, namely, intracranial hemorrhage.

4   Intracranial hemorrhage, by our definition, is a composite

5   of intracerebral bleeding, subdural and subneractoid

6   hematoma. Again, the Kaplan-Meier for each of the three

7   treatment groups with -- shows substantial and significant

8   decreases in this outcome for dabigatran compared to

9   warfarin. As you can see from the statistics at the top,

10   there's a 59 percent to a 70 percent decrease in

11   intracranial hemorrhage for the high and low doses

12   respectively, both highly statistically significant. The

13   differences between he doses are smaller than the previous

14   slides but are still consistent with the dose response

15   effect that we have seen.

16   If we look at some of the criteria for the yearly

17   bleed rates in subcategories of major bleeding, we can see

18   some important differences across treatments. As shown

19   before graphically, the second line shows the major

20   bleeding event rates, which are lower for both the

21   dabigatran arms. Bleeding in a critical area is

22   significantly lower for both doses and as discussed before,

23   in particular the ICH rates are also materially lower than

24   with warfarin. However, for GI bleeds, in the second to

1 last row you can see that the rates for the dabigatran 150

2 in the second column are approximately 50 percent higher

3 than warfarin. This is statistically significant. The low

4 dose for GI bleeds is not statistically significant

5 compared to warfarin. In the last line we had fatal bleeds

6 on both doses relatively uncommon, but you can see that

7 both doses have numerically less fatal bleeds than

8 warfarin. And for the low dose this is statistically

9 significant.

10   So, if we now turn our attention to all bleeds,

11 that is, we pull together all the major bleeds and all the

12 minor bleeds in one Kaplan-Meier analysis, and again the

13 dose response emerges with lower rates versus warfarin.

14 And you can see that the hazard ratios for 110 versus

15 warfarin, .78, very close to the overall major bleed hazard

16 ratio of .80 and for 150 the hazard ratio is identical.

17 So, once again, in all of these blinded comparisons between

18 110 and 150, you see dose response, which is a remarkable

19 internal consistency supporting the robustness of the

20 results.

21   Subgroup analyses shown here in a Forest plot.

22 For almost all of these subgroups there are really no

23 obvious interactions similar to what was seen for the

24 primary efficacy endpoint. The dabigatran 110 and the

1 dabigatran 150 results are similar with a small shift to

2 the right for 150, reflecting somewhat higher bleed rates

3 for this dose. However, the subgroup analysis for age

4 highlighted here in yellow has a strong interaction with

5 treatment.

6   To make this more clear, I've blown this up on

7 the following slide. So you can see here that the age

8 subgroups are shown alone. For both doses the greatest

9 benefits versus warfarin are in the younger age group, with

10 diminishing advantages over warfarin as age increases. By

11 the time of age 75 or greater the bleed rates for warfarin

12 and dabigatran are similar. This systematic pattern is

13 clean -- is seen clearly with both blinded doses,

14 reinforcing its robustness.

15   So, one key aspect of this age-related increase

16 in major bleeds is that it is restricted to extracranial

17 bleeds, not intracranial. The intracranial bleeds are

18 rates -- by subgroup are shown on this slide. And you can

19 see from both the p-value for inter -- the p-values for

20 interactions and from the patterns on the box and whisker

21 plots that -- for the age subgroup that the reduction in

22 ICH is preserved in older patients. In fact, for age 75 or

23 older, this remains a large and significant benefit for

24 dabigatran versus warfarin on both doses. So the key

1 message here is that the age-related increase in the hazard

2 ratio for dabigatran versus warfarin is in fact due to

3 extracranial not intracranial bleeding. In fact, most of

4 the effect in this extracranial bleeding is due to the

5 increase in gastrointestinal bleeding.

6   So, summarizing the bleeding results, compared to

7 warfarin, dabigatran 110 significantly reduces major life

8 threatening and total bleeding. Dabigatran 150 reduces

9 life threatening and total bleeding. Dabigatran 150 also

10 significantly increases the risk of major GI bleeding.

11 Dabigatran 110 and 150 significantly and substantially

12 reduce intracranial hemorrhage.

13   So, the second topic for RE-LY safety is the

14 hepatic safety. So, due to the hepatictoxicity seen for an

15 earlier direct thrombin inhibitors, ximelagatran, we

16 undertook an extensive program of hepatic safety

17 monitoring. We undertook monthly monitoring in the first

18 year for the first 6,000 patients and thereafter three or

19 four monthly. And after pre-specified interim analysis for

20 hepatic safety by the DSMB, we reduced the overall LFT

21 monitoring in the trial to three to four months in the

22 remaining patients.

23   All hepatic abnormality were followed up

24 intensively with repeat testing, monitoring for symptoms

1   and abdominal imaging tests where possible to see a clear

2   diagnosis. The liver function test, all the data were

3   reviewed by the DSMB periodically and all together we had

4   approximately 250,000 liver function tests. The results of

5   the liver function testing are summarized in this slide.

6   So you can see for the first line, transaminase

7   is greater than three times the upper limit of normal.

8   This is a sensitive but non-specific marker for drug-

9   induced liver injury. Very consistent numbers across all

10 three treatment groups. No evidence of difference between

11 dabigatran and warfarin. A more specific marker,

12 transaminase is greater than 10 times the upper limit of

13 normal. Again, no signal for the dabigatran groups, if

14 anything, lower frequency.

15   The last line here is a component of the

16 potential Hy's law cases. These are a potentially serious

17 hepatotoxicity. This particular criterion involves a

18 transaminase elevation of greater than three times the

19 upper limit of normal followed in the subsequent 30 days by

20 a bilirubin elevation at least two times the upper limit of

21 normal. This sign, coupled with no alternative clinical

22 explanation or indication of obstructive process, would be

23 a sign for hepatotoxicity. You can see from these numbers

24 that the numerically less frequent in both dabigatran arms

1 versus warfarin, no indication based on the transaminase

2 measurements of any signal.

3   If we look at the hepatobiliary safety in terms

4 of adverse events reports, we see essentially the same

5 thing, very consistent, no treatment differences for

6 hepatobiliary AEs when you look at discontinuations due to

7 hepatobiliary AEs or fatal hepatobiliary AEs, no indication

8 of a treatment difference. So, based on liver function

9 testing summarized on the previous slide and the clinical

10 safety summarized on this slide, there is no evidence of a

11 signal for hepatotoxicity dabigatran compared to warfarin.

12   So, adverse events. This is a general overview

13 of adverse events. The adverse events occurred in 76 to

14 78.5 percent of patients. Slight excess on the both the

15 dabigatran arms compared to warfarin. Adverse events

16 leading to discontinuation, about 5 percent higher in both

17 dabigatran arms. Serious adverse events, actually lower on

18 dabigatran than on warfarin, fatal AEs balanced across

19 treatment groups. So if we look at a breakdown of serious

20 adverse events by preferred term, that's shown here. These

21 are the most frequent serious adverse events and there's

22 really no evidence of any treatment-related signal here.

23 This is typical of what you might expect in an elderly

24 atrial fibrillation population with concomitant

1　cardiovascular disease.

2　　　　If we'd look just at adverse events in general

3　and set a level of at least -- frequency of at least 5

4　percent, that is shown on this slide. Again, really no

5　indication of any treatment-related effect here with the

6　exception of dyspepsia highlighted in yellow where we have

7　about a 6 percent incidence on dabigatran compared to a 1.4

8　percent incidence on warfarin. No dose response, but

9　clearly statistically significant.

10　　　　So, permanent discontinuation of study

11　medication. There was a 4 to 5 percent increase in

12　permanent discontinuations on dabigatran compared to

13　warfarin, approximately 2 to 2.5 percent a year. If we

14　look at the reasons, we can see that despite the lower

15　frequency of outcomes in both dabigatran arms, the

16　discontinuation rates are higher, notably here for minor

17　bleeds. Also the discontinuations due to SAEs on

18　dabigatran were higher even though the SAE frequency was

19　lower.

20　　　　And this pattern repeats itself for adverse event

21　discontinuation and even voluntary discontinuations of

22　treatment by the patients. It does appear that the

23　investigators -- that the investigators or the patients

24　were not very comfortable with adverse or other new events

1 occurring in a new chemical entity and were more likely to

2 discontinue therapy despite the fact that the events

3 occurred with less frequency on dabigatran. I would also

4 remind the panel that 50 percent of the patients in this

5 study are warfarin experienced and the investigators are

6 very familiar with their adverse event profiles.

7 So, safety conclusions from RE-LY. The hepatic

8 safety profile is comparable to warfarin. Dabigatran did

9 increase the risk of dyspepsia. There was an increased

10 frequency of MI with dabigatran. The high dose of

11 dabigatran increased major GI bleeding. Dabigatran 110

12 reduces major bleeding and both doses of dabigatran reduced

13 intracranial, life threatening and total bleeding.

14 I thank the audience for their attention. I

15 would like to introduce Professor Salim Yusuf from McMaster

16 University who will give an overview of the benefit-risk

17 and the conclusions from the study.

18 DR. YUSUF: Good morning ladies and gentleman,

19 Mr. Chairman, respected members of the panel, FDA and

20 colleagues. I'm going to -- you've heard from Stuart

21 Connolly and Paul Reilly the key results on efficacy and

22 safety. What I'm going to try and do is to integrate the

23 information in the context of the field as a whole and use

24 it to discuss six issues that have come up during various

1 discussions and I dare say they will be part of today's

2 discussions by and large.

3   Now this is my disclosure, but my real disclosure

4 is that I'm one of the four people who led the study. I

5 was one of the co-chairs along with Lars Wallintin. The

6 other two are Stuart Connolly and Mike Ezekowitz, who are

7 joint PIs. Now I don't have to tell you that older

8 anticoagulants like warfarin are incredibly effective in

9 preventing strokes in atrial fibrillation. It's an

10 extremely effective drug. Now, this should have been --

11 should have caught on wildfire and used in practically

12 every patient with atrial fibrillation, especially given

13 how cheap it is. Yet, only 50 percent of people who should

14 get it get it and of those who take it, 50 percent stop.

15 And the reason is because it's cumbersome to use. It has a

16 side effect that's worrisome, increased bleeds, and the

17 most devastating of them all is intracranial bleeds.

18   There are multiple reasons why it's cumbersome,

19 which is interactions, adherents, need for monitoring and

20 all of this leads to in the long term poor compliance, sub-

21 optimal clinical and community effectiveness. So if you

22 could have a drug just as good, but safer or easier to use,

23 then I'd think we'd make a big step in the management of

24 these patients.

1   I will discuss six issues. The first, our key

2   design aspects and how those design aspects played out in

3   trying to minimize biases, because in an open study that's

4   always a question and it's something we need to focus on.

5   The results of 110 of dabigatran versus warfarin and 150

6   versus warfarin and versus 110, benefits by INR control,

7   safety overall very briefly and a discussion of why two

8   doses are in fact going to be useful to the clinician.

9   Now, the issue about open versus blind is not an

10   issue confined to just this study. This has been discussed

11   for several decades in the literature and in particular in

12   relationship to oral anticoagulants. For instance, in July

13   of 2005 there was a meeting organized by Duke University

14   which several people here participated, including the FDA.

15   And I quote from this and the discussion, open versus

16   double blind there may be advantages to using an open label

17   versus blinded design beyond the savings and trial cost and

18   complexity. In comparing a new antithrombotic therapy to

19   warfarin, which requires frequent monitoring and is

20   difficult to maintain in the therapeutic range, a blinded

21   trial design may not reflect the true, real life advantage

22   of new drugs that are easy to use or most stable, I would

23   say different pharmacokinetic properties.

24   The second thing is in the recommendation section

1 of the document on blinding it said there was a lack of

2 agreement on the balance of the benefits, i.e. controlling

3 bias -- that's obvious to all of us -- and its liabilities.

4 And it went on to say the clinical experts generally favor

5 the open-label design. There is the regulators present at

6 the meeting favored blinding and I have to say that the

7 clinical experts were people who were experienced in the

8 field of trials, like Rob Califf or Chris Granger and

9 people like that.

10   Now let's look at history. There has been six

11 trials of Vitamin K antagonist. And the reason I use

12 Vitamin K antagonist is that in different countries there

13 are other things used other than warfarin. So, I'm going

14 to use VKA, four were open or usual care and two were

15 placebo. I'm using the word "placebo" and not blind

16 because you can't be sure in these trials that placebo

17 meant blind; it could still be open. And here are the

18 results.

19   In the so-called placebo trials, there's a 60

20 percent reduction in strokes. In the open or usual care

21 studies there's about the same size reduction. So, no

22 obvious difference in the results of these two sets of

23 trials and the collectivity of these data, which is largely

24 weighted by this, is the basis of our management today of

1   these patients.

2   So we've accepted it. The community has accepted

3   it and obviously I don't think warfarin's ever gone through

4   regulatory approval. Has it, Paul? No. But, let's also

5   look at this. There are seven trials of Vitamin K

6   antagonist with anti-platelets. All were open. There's a

7   large trial of a new agent, idraparinux versus warfarin

8   open. The main trials post MI, WARIS-1, WARIS-2, ASPECT,

9   were open and a large trial of 2000 people in peripheral

10   artery disease was open. The exception to this is the

11   ximelagatran program where one trial was open and one trial

12   was placebo controlled. And on a superficial look, it

13   looks like they gave this different result and that's

14   something we look at in a minute.

15   Now all these trials that were open used one

16   strategy to minimize bias, that is, blinded adjudication.

17   When you read the reports, they do not describe any other

18   strategy to minimize bias. Maybe they did other things,

19   but we don't know.

20   Now let's look at the ximelagatran program. On

21   the left is SPOR TIF III, which is an open trial, SPOR TIF

22   V, a placebo trial. On strokes, systemic embolism, there

23   were 16 fewer, non-significantly so, strokes with

24   ximelagatran compared to warfarin, SPOR TIF V, 14 more,

1   almost exactly more, and if you do a test for interaction,

2   these are nominally significantly different results. If

3   you only focused on this you'd worry. Do open trials and

4   blinded trials give you different results? And that's

5   legitimate, but you shouldn't really choose one endpoint of

6   the multiple endpoints of the study. Look at the whole

7   thing in its totality. When you look at MIs, there are 11

8   more there. Exactly the same numbers here.

9   So if you said, well, maybe doing a blinded trial

10 is better than doing an open trial in terms of getting a

11 better result, but if you look at both of these together,

12 it's a wash, deaths minus one, minus seven, TIAs, really no

13 clear difference. But when you look at deaths, strokes,

14 systemic embolism and MI, you're minimizing the play of

15 chance because you got all these endpoints minus 20 here,

16 minus nine, at least directionally similar results. When

17 you look at bleeding, directionally similar results. So,

18 to me, when you look at all the endpoints in SPOR TIF III

19 versus V, there is no obvious evidence that there's

20 systematic biases one way or the other. Of course if you

21 focus on stroke alone, you'd worry.

22   Now are there downsides of doing a blinded study

23 versus an open study? You heard Stuart Connelly talk about

24 that it compromises the normal management of patients. You

1   saw that in the report of that meeting where it does. And

2   in the SPOR TIF III trial, about 18 percent and 14 percent

3   of the warfarin patients stopped the medications, an

4   absolute excess of 4 percent, but in the SPOR TIF V trial

5   these numbers were double. This means the proportion of

6   people who were adherent was reduced by one-third. And you

7   all know if you do a power calculation, a one-third

8   increase in non-adherence will lead to a substantial

9   compromise if your interest in superiority. But worse,

10   since the trials in these field are designed as non-

11   inferiority trials, it will spuriously make them non-

12   inferior. So, if you -- if open or blinded studies have

13   hurt adherence, you're actually going to get perhaps an

14   inferior trial.

15   Now there are obvious advantages of an open

16   design beyond complexity and cost because you could use

17   double-dummy if that was the only issue. But you're giving

18   the drugs differently when you start and stop. It's

19   different. The monitorings different, the safety

20   thresholds are different. The interactions are different

21   and in large prolonged trials of antithrombotic, about 40

22   percent of people in this field have looked at this across

23   all the trials, stopped the medication because of minor

24   bleeding on needing a procedure, two-thirds of it needing a

1 procedure, one-third of it for some reason and almost

2 always at that time, clinically it is important to know

3 what drug you are on because it impacts the timing of your

4 procedure. The bridging that you do, how long or short and

5 therefore, the likelihood of unblinding even in placebo-

6 controlled trials, so-called blind trials, is significantly

7 higher.

8   Now, let me just show you, this is not just

9 rhetoric; these are data. In RE-LY you'll see the

10 proportion of people who needed bridging when they stopped,

11 because a number of people with interruptions is about a

12 quarter, but the proportion of people who needed bridging

13 was much more in warfarin compared to the other -- the

14 dabigatran groups and the timing. And the duration was

15 much shorter here. Twice as many people needed it for two

16 days. Four times as many people needed it for more than

17 five days. You need to know which drug people are on in

18 order to use the bridging most appropriately.

19   So we deliberately chose a hybrid design. It was

20 not a default design. It was deliberate thought. It had

21 two components. It had an open component of warfarin

22 versus dabigatran, but various safeguards in advent of

23 adjudication to insure there was no ascertainment and

24 confirmation bias and a number of other checks, which I'll

1 show you as we go on. We had two blinded doses of

2 dabigatran. If you say, if you're so confident of an open

3 study, why would you do a blinded thing internally? Well,

4 we could legitimately, without compromising patient safety

5 and the quality of the trial, we could blind these two

6 doses and the management of these patients whether they're

7 on the high dose or the lose dose would be similar.

8   So where I can legitimately do a blinded study I

9 would prefer to do it. But where I can't do it or where it

10 compromises the integrity of the study, then I make a

11 judgment, or we make a judgment, and that's how the field

12 as a whole has behaved. And having two doses, which I

13 believe is very rare in large trials and is the only one in

14 atrial fibrillation, has advantages. It has methodological

15 advantages in that it allows us to check whether material

16 biases exist and most importantly, if the data follow a

17 coherent pattern, that pattern actually trumps p-values and

18 non-inferiority margins. Because that tells me the results

19 hold together in a biologically plausible manner and I'll

20 show you that's what this trial does.

21   Now, we put in a number of measures to avoid

22 biases. First, similar number of visits at which events

23 were ascertained. Second, we had a number of supplementary

24 steps, which I don't know of another trial of this field

1 doing. We had a stroke symptom questionnaire at every

2 visit, a bleed questionnaire at every visit. All

3 hospitalizations were checked to see if a stroke or bleed

4 occurred. We checked all AEs and SAEs, 130,000 of them to

5 see if there was a hint of a bleed or a stroke. We checked

6 all drops of hemoglobin to see if we missed a bleed. And

7 I'll show you in a minute, no matter which way you look at

8 the result, in four or five different ways, the results are

9 nearly identical. And that's what it is here.

10   So let's take the investigator reporter results.

11 This is dabigatran 110, 150, warfarin. You will see these

12 are the results. And just to take you easily through it,

13 let me say dabigatran 150 versus warfarin, there's about a

14 60 events difference here. After adjudication, there's

15 about a 60 events difference here so that the rejection

16 rate is no different across the three arms, the same if you

17 do the calculation across 110 versus warfarin. And not

18 surprisingly, the hazard ratios are the same here. Hazard

19 ratios are similar, if anything, slightly better. And then

20 if you look at disabling or fatal strokes, really bond

21 those strokes. People disable, they can't clothe

22 themselves or go to the washroom. You will see the results

23 still show similar directional results as all strokes.

24   Overnight, by reading the FDA document, I had

1   other data that would help us understand it. One is that

2   there was data you could derive from it on imaging.

3   Ninety-five percent plus of people had an image. So you

4   had a radiologist reading the images blind, didn't even

5   know perhaps that the patient was in a trial. And you will

6   see these are the numbers, 179 versus 115 and 163. And the

7   p-values for superiority, because I did it with my

8   calculator last night, is highly significant versus

9   warfarin. And when you look at fatal strokes, or strokes

10 caused or reported by the grim reaper, not the

11 investigator, you will see that there are two, that 23 with

12 150 dabigatran and 44 with warfarin, and that's also

13 nominally significant, about 2.6 standard deviations.

14   So no evidence of any hint of bias in the events

15 no matter which way you look at it. Now, as expected in a

16 good trial, pre-randomization factors and treatments were

17 balanced. Interestingly, and I didn't predict this, post-

18 randomization therapies that would affect stroke leads,

19 like anti-platelets, blood pressure lowering, statins and

20 rate-limiting drugs, was similar. I think that is

21 fortuitous, but that's nice. The second thing was, as I

22 said, we had exactly the same number of events in the -- I

23 mean, the follow-up visits in the three groups. What we

24 did find was a higher rate of discontinuation versus

1 warfarin whenever an event occurred.

2   This -- I don't know why it occurred, but it was

3 there also in the ximelagatran trial even in the blinded

4 part of it. So I think what it is, is when you've got a

5 new experimental drug and an old drug that you really know

6 works, you have no confidence in the old drug. It's a

7 nervousness. And the second thing which may be more real

8 is when you stop warfarin you don't have a whole lot more

9 options. If you still -- stop dabigatran, you can put them

10 on warfarin. And in fact, this -- disproportionately more

11 people went onto warfarin when it was stopped.

12   Now, there were other evidence suggesting lack of

13 biases. There was an unexpected pattern of bleeding. We

14 had to be incredibly clever to postulate. We'd get overall

15 lower bleeding, less intracranial bleeds, but more GI

16 bleeds. That simply isn't possible. At least none of us

17 are smart to have done it. But the other part of it was

18 within the blinded comparisons at dose relationship on GI

19 bleeding on other bleeding. Again, that's something we

20 couldn't have spuriously created out of 950 centers and

21 perhaps two, 3,000 investigators. There is -- we did not

22 expect a numerical excess in MIs. So that's telling you

23 that the reporting of the events, the conduct of the

24 trials, the analysis and hopefully, what we've reported

1 publically is as unbiased as is possible.

2   So, let me come to the second issue. In the

3 design we really felt having two doses would be useful. We

4 debated dose selecting ad nauseam for several meetings and

5 in the end we said, let's bite the bullet and study two

6 doses because the two doses will provide clinicians a very

7 important answer that allowed them to have a choice on

8 balancing efficacy and safety. But importantly, remember

9 our trial was designed as a non-inferiority trial and as

10 you know, non-inferiority trials, once you prove it you can

11 test superiority.

12   But what if we only had non-inferiority? You

13 always worry about certain methodological issues like

14 constancy. Is your population sensitive to change? One

15 way that has been written of the literature to overcome

16 this is -- because you can never prove constancy or lack of

17 constancy. It's really impossible. So, is to have two

18 doses and if the results are different in the two doses,

19 that methodological concern can be set aside. And that is

20 why we did it and ultimately we have a coherent patterns of

21 results and dose relationship of effects, which to me as a

22 clinical trialist is just as important as the p-values.

23 And the strength of the findings are, we have very clear

24 results on non-inferiority of each dose, not borderline,

1   but very clear. Superiority, the higher dose, very clear

2   versus warfarin with a zed statistic of 3.6 or thereabouts,

3   which to me indicates somewhere between two and three

4   trials that is nominally significant.

5   So the issues of you only have one trial really

6   should be viewed in the context how extreme this p-value

7   is. So a p-value of 0.05, well that's one thing. A p-

8   value this extreme is giving you much more robust results.

9   Again, internal coherence, there's a differentiation in the

10 two doses very clearly. I want to emphasize certain

11 aspects on key subgroups, consistency over time and the

12 coherence of evidence in a minute.

13   So these are the results you've seen. You will

14 see for non-inferiority, 1.38 was margin, stroke and

15 systemic embolism well away. Stroke alone well away.

16 Hemorrhagic strokes were showed superiority. Ischemic

17 strokes it borderlines non-disabling and disabling or

18 fatal. So it's extremely clear and if you had only the 110

19 dabigatran dose, while we'd be discussing it, we would all

20 agree it met the pre-specified criteria to claim non-

21 inferiority. And incidentally, it's just non non-

22 inferiority, substantial superiority on bleeding, which is

23 important.

24   What about 150 versus warfarin? And these p-

values are for superiority. You can see overall strokes
and systemic embolism, stroke alone, hemorrhagic stroke,
ischemic, non disabling, disabling and fatal. The worst
kinds of strokes, they're all highly significantly reduced
and the substantial degree, the relative risk is reduced by
about one-third. That is substantial.

And when you look at the two doses you all know
there's a clear difference in all of them except
hemorrhagic stroke. So there's nothing borderline about
the statistics and the robustness of this trial and we
should set aside the idea that there's only one trial.
It's one trial with an extremely clear result and compared
to anything published in the literature -- and I know there
are large trials going on -- compared to anything in the
literature, this is three times larger than the other
trial, which the active W study that Stuart Connolly led.
So we have very robust results.

Now, one of the points people say is, it's still
one trial. Show me replication. Well, one way is to look
at that subgroup where we were very interested to looking
at separately because we expected -- and we were proven
wrong -- we expected somewhat different results. We
expected quantitative interaction. So this is the group
who were warfarin-experienced versus warfarin-naïve. We

1 believed that the warfarin-experienced people would tend

2 towards non-inferiority. The warfarin-naïve would tend

3 towards superiority. Now, so we had equal numbers of

4 people recruited here from each country in these two -- and

5 these are almost like two independent strata, not that we

6 did stratified randomization, but you have proper subgroups

7 of 9,000 versus 9,000.

8   In both of these, we clearly show non-

9 inferiority. So this is well away from the 1.38 margin.

10 So, highly significant non-inferiority taking that alone or

11 that alone. And here again, two completely independent

12 populations which are somewhat different, again, internal

13 replication of the results. And the upper confidence

14 limits are away from one and the superiority p-values are

15 very clear.

16   Now other subgroups -- I'm not cherry picking the

17 subgroups and you will see, and I'll just focus on here, on

18 the superiority comparison, 150 versus warfarin age. Three

19 strata, the upper confidence limits are below one or just

20 touches one. Males versus females, again, well away from

21 it. This you've seen. Aspirin used, yes and no. Again,

22 clear results for each stroke, systemic embolism, previous

23 strokes you'll see and no previous strokes. CHADS scored

24 the consistency. Three different types of atrial

1 fibrillation. Within each, clear results and here there is

2 an interesting trend, which we shall discuss in a few

3 minutes.

4 The other thing is consistency over time. And I

5 must say unlike some of the previous situations I've been

6 on, I enjoyed reading the FDA document. I learned a lot

7 from it. One of the things I learned so much was to

8 plagiarize this slide. So with apologies, I've taken a

9 slide from the document and this is, I think, an analysis

10 done by Jim Hung and his colleagues where they looked at

11 the hazard ratio of one and its upper confidence limits and

12 when it crosses different boundaries.

13 So 1.38 is the boundary for non-inferiority. One

14 is obviously the confidence interval for superiority. Very

15 early in the trial you will see both doses crossed the non-

16 inferiority boundary and apart from one blip with 110, for

17 the rest of the trial for 70 to 80 percent of the trial,

18 they both remained below it. So, absolutely no doubt that

19 there's nothing blippy about these data. They're clear and

20 they remain clear throughout. For superiority, half way

21 into the study it -- the upper confidence limits was below

22 one for 150 and it remained so, and in fact, kept on

23 becoming wider over time. Again, so for 50 percent of the

24 trial you had clear superiority.

1   Now, the other thing that I find interesting and

2   persuasive is internal coherence within each randomized

3   subgroup -- randomized arm. In the dabigatran group you

4   will see once you strategized for age there's a dose

5   response of ischemic stroke versus concentrations of

6   dabigatran. As you increase it, the stroke rates goes

7   down. This is the oldest. This is the youngest. You have

8   to do this because age and renal function has an affect on

9   concentration. And on bleeding you're again seeing an

10   internal consistency. So we have external consistency

11   across doses, across strata and internal consistency here

12   within each arm giving you biologic possibility.

13   Let's look at the next issue of the effects by

14   INR. Now these are the data. As expected, people who are

15   warfarin-experienced had a better time in therapeutic

16   range. About 67 percent mean, 69 percent median and

17   various is with warfarin-inexperienced or naïve. It's

18   lower to start with, 62 percent, and in the median is 64

19   percent. And overall, it's 64 and 67 percent and once you

20   take into account the fact that half the people are

21   warfarin-naïve, this is the trial that I know of which has

22   amongst the best TTR control. So really our investigators

23   did a very good job.

24   And looking at it in another way, in the U.S.,

1   because ultimately this crowd, while it's very concerned

2   about the world, is more concerned understandably about the

3   U.S. And when you look at the U.S. you will see that the

4   median is 67 percent and above the median is here, but

5   compare performance in the trial and you will see in the

6   U.S., based on the meta-analysis of previous studies, TTR

7   as a whole is 55 percent. And even in specialized centers

8   with anticoagulant clinics it's only 63 percent. So

9   whether you take the trial as a whole, the U.S. by itself,

10 we achieved INR control that is better than average even in

11 specialized centers.

12   Now one of the things we tried to look at was is

13 there a relationship on efficacy and on safety by center

14 INR control? You all understand you can't use individual

15 patient INR control because you don't have a dabigatran

16 patient to compare it with because which patient do I

17 compare, good or bad?

18   The next best thing is to use center because it's

19 a pre-randomization variable. Having said that, centers

20 differ, so there's an ecological fallacy there. So this,

21 therefore, is a GUSTO kind of analysis that you have to

22 take into account. I don't know of a better way of doing

23 it, so we did it and you will see that for 110 versus

24 warfarin -- and I just want to say this is hazard ratio --

1 one is here, the red line. Above this means favors

2 warfarin. Below this means favors dabigatran. There's

3 really a flat line and the p-value for interaction is

4 there.

5   Interestingly, for 150 there seems to be a

6 relationship that when you get to about 90 or something

7 like that -- and there's nothing precise about where it

8 actually crosses -- there seems to be maybe warfarin will

9 do as well. Now I look at this to say, in my mind the real

10 slope is the average of these two. Why would I believe

11 this and not this or vice versa? So it's not surprising

12 that there would be a relationship between better INR

13 control, and the effects of warfarin versus the effects of

14 dabigatran should be independent. So there may be some

15 relationship. So I don't deny it that in some centers in

16 the United States or Canada or wherever, you can get very

17 good results with warfarin, but they're probably under 5

18 percent of the centers.

19   But what is interesting is this. This is

20 absolutely conclusive. The affects on lower ICH rates is

21 totally independent of INR control. And I think one of the

22 biggest benefits of this drug is that for equivalent levels

23 of anticoagulation, that is preventing ischemic events, is

24 avoiding the most dreaded fear of warfarin, that is the

1   excess of ICH. I mean, it's a devastating complication and

2   you'll see there's no interaction at all. So even if you

3   were a center that for some reason managed to get 100

4   percent ETR, you'll still get the benefits of the reduction

5   in ICH.

6   Very briefly, safety. Paul Reilly has summarized

7   it. Significantly less ICH and other life-threatening

8   bleed, but unexpectedly we didn't expect this, an increase

9   in GI bleed, which we can discuss if you'd like. And it's

10 in a dose-related manner, which gives it plausibility. I

11 believe it. Liver with happy, no obvious evidence of harm.

12 If anything, numerically fewer cases, but, you know,

13 warfarin's meant to be safe. I can't say there's a safer.

14 MI, there's a numerical increase and we've analyzed the

15 data -- which is unexpected -- we analyzed the data in many

16 ways and we can't find a coherent story. Dyspepsia's

17 increased with both doses, but what about one versus the

18 other dose? And we looked at this issue carefully.

19   So these are the data of 110 versus 150. You

20 will see there's a 28 percent highly significant reduction

21 in systemic -- stroke and systemic embolism. Good news.

22 There's also an increase in major bleeds and if you focus

23 on life threatening bleeds it is a little more extreme, but

24 it's about the same order, about 15 to 20 percent excess.

1 So the issue is how do you balance this benefit versus

2 this? Now statistically all we can do is to look at

3 average results or subgroups of the average results and we

4 don't have the luxury of a data analyst to say, well, there

5 is a patient with a high risk of stroke and low risk of

6 bleeding or this patient is very high risk of bleeding and

7 low risk of stroke.

8   So, I think in general, having the two doses will

9 say, having the low dose, we are sure it's as effective as

10 warfarin and safer that warfarin and it's safer than the

11 higher dose. The higher dose is more effective than

12 warfarin, no more unsafe than warfarin, perhaps safer. And

13 it's certainly more effective than 110. I, as a clinician,

14 having the two doses allows me the flexibility on what I

15 would do in individual patients.

16   Now, I tried as an analyst to try to work out

17 whether there's any group that I can find where I'm

18 convinced one dose is to be preferred over the other. What

19 I was convinced of was that dabigatran 150 had to be your

20 primary dose, the recommended primary dose. But some

21 things suggested to me that there were substantial clinical

22 advantages in having the low dose available and this is as

23 follows. The results -- so this is dabigatran 150 versus

24 110, favors 150, favors 110. This is the relationship.

1 The p-value for the regression slope is not significant,

2 but this curve is highly seductive to the eye.

3 If you look at major bleeds, this is independent.

4 So if you think of somewhere here, the balance of these two

5 could in some patients tip the wrong direction and I tried

6 -- we tried to model that statistically versus looking at

7 cardiovascular death, life-threatening bleeds, stroke and

8 systemic embolism. This p-value's a little more

9 tantalizing, but by no means convincing. But this is a

10 kind of slope. So the way I read these data are, on the

11 whole, I would prefer to use 150. But there are certain

12 people in whom it's equivocal which dose you use and a tiny

13 proportion of people, I think, the 110 has a role. And

14 I'll come to who it might be.

15 So the clinical impact of using dabigatran

16 instead of warfarin -- and I'm not doing imputed placebo

17 and those games because it's two sets of uncertainty you're

18 multiplying. Let's just take the data we have. And if you

19 use 110 b.i.d. instead of warfarin in 1,000 people for five

20 years will prevent 10 fewer strokes and systemic embolism.

21 This is entirely because of fewer hemorrhagic strokes and

22 will prevent 30 fewer life-threatening bleeds. That is 10

23 in addition to the hemorrhagic strokes. If you use 150

24 instead of warfarin we'll prevent 30 fewer strokes and

1   systemic embolism, approximately half from hemorrhagic

2   strokes and half from ischemic strokes. So it's got an

3   anti -- added antithrombotic effect and is safety -- an

4   added safety feature. And there are 17 fewer life

5   threatening bleeds. In the FDA document there are

6   different kinds of bleeds looked at. To me, fatal GUSTO,

7   everyone of them goes in favor of both doses in a dose

8   response way.

9   There seems to be more MI. We don't understand

10   it. That's the honest answer and we can discuss it and

11   show you a lot of analysis we looked at. But the net

12   effect in the end is what happens to death. And

13   cardiovascular mortality's lower and if you may wonder hey,

14   did non-cardiovascular mortality go the wrong way? It was

15   1.3 percent, 1.4 percent and 1.3 percent. So it's

16   identical. It's just noise. So the net benefit, if you

17   just take cardiovascular mortality, it's in favor --

18   clearly -- significantly in favor of the higher dose,

19   nearly significant with the lower dose.

20   So as a clinician, if this drug were available on

21   the -- to me in Canada, this is the way I'd like to treat

22   my patients. I would now say that -- leaving cost aside, I

23   would say 150 is the preferred dose in most patients. I

24   think 150 has a value. It should be used in -- it could be

1 considered if I'm very concerned about bleeding some

2 patients. Or if a patient is already declared they can't

3 tolerate 150. They've already bled on 150. My only choice

4 then is not to use it at all. So there the choice is not

5 between 150 and 110. The choice is 110 versus no

6 antithrombotic therapy.

7   That's a clinical choice and statistically I

8 think no matter how much we manipulate the data, the

9 average result doesn't tell us what we would do in an

10 individual circumstance. Same thing, the elderly might be

11 in this group. Say an 85-year-old person, you know, in a

12 nursing home. Well, you don't -- you want to minimize

13 troubles. So there is a value here and therefore, I

14 believe clinically with both doses enhance clinical

15 flexibility and enhance very importantly population

16 effectiveness.

17   Thank you very much. I think we and the team

18 would be happy to take questions or whatever the committee

19 wishes. Dance, not so.

20   DR. LINCOFF: Okay, so thank the sponsor for the

21 presentation. We now have a 30-minute period of questions

22 from the panel to the sponsor. When the sponsors address

23 the committee's questions, we'd appreciate it if the

24 responders identify their name and title and affiliation,

1 as we expect that different responders will respond to

2 different questions. If you indicate to me when you have

3 questions on the panel, we'll keep a list and deal with

4 that in sequence.

5   So, Dr. Nissen, you had the first question.

6   DR. NISSEN: I have a series of questions, but

7 let me just take, you know, a couple and then we'll see

8 what other people want to ask about. But, you know, for me

9 the elephant in the room here is this issue of

10 ascertainment bias. So I've got some questions for the

11 sponsor and maybe somebody could sort of take the

12 microphone.

13   But I'd like to understand exactly who was

14 blinded and who was unblinded. Did the sponsor have the

15 treatment codes? Did the CRO have the treatment codes?

16 Who did and did not have the treatment codes during the

17 course of the trial? Could someone help me with that?

18   DR. CONNOLLY: Stuart Connolly, McMaster

19 University. So the treatment codes were held by the

20 unblinded statistician at PHRI.

21   DR. NISSEN: Blinded --

22   DR. CONNOLLY: Let's get it right. By the

23 statistician who reported to the DNC.

24   DR. NISSEN: But not the sponsor?

1   DR. CONNOLLY: Not the sponsor.

2   DR. NISSEN: Okay, good. And in terms of

3 identification of events, I understand that you identified

4 events via the CRFs that were filled out by the

5 investigators. Were all hospitalizations reviewed or only

6 those hospitalizations where there was a -- in other words

7 was it the actual data from the hospitalization, the source

8 documents, were they reviewed or were the CRFs reviewed?

9   DR. CONNOLLY: No, the CRFs were reviewed. We

10 did not review all hospitalizations. There was, I think,

11 more than 10,000 hospitalizations. However, we did review

12 all CRFs, reviewed all free text on the CRF that gave

13 indications of the cause for hospitalization.

14   DR. NISSEN: You understand my concern is you

15 have the unblinded investigators that are deciding, you

16 know, what to put in on the CRFs and that worries me.

17   DR. YUSUF: Steve, let me help you here.

18   DR. LINCOFF: Dr. Yusuf, please just for the

19 record identify.

20   DR. YUSUF: Salim Yusuf. Steve, there is a

21 hospitalization CRF that collected all the major diagnosis,

22 obviously. And we asked for supporting documents. About

23 50 to 60 percent of the patients were reviewed. Is that

24 right Paul? At the sight? What proportion?

1   DR. REILLY: (Off microphone).

2   DR. YUSUF: Yeah, but the hospitalization form

3   collected all possible diagnosis. So, if anything there

4   hinted at a stroke or a bleed then we pursued it.

5   DR. NISSEN: Yeah, I understand, but it was an

6   unblinded investigator that was filling out the CRF. I'm

7   just trying to make sure I understand.

8   DR. YUSUF: And I think in the monitoring -- and

9   I don't know what proportion of the patients were actually

10   monitored. I know all the sites were monitored. The

11   monitors did not pick up any events that were not reported

12   and the FDA auditors, as far as I know, haven't picked up

13   anything in the sites they monitored.

14   DR. NISSEN: And then, one final question and

15   then I want to let somebody else take the mic, but if there

16   was accidental unblinding, which I understand occurred

17   about 20 percent of the time, what procedures were

18   followed? So at the adjudication committee, I understand

19   that often the source documents would refer to whether they

20   were taking an experimental drug or not, that sort of

21   thing. What did you do when there was accidental

22   unblinding of the adjudicators?

23   DR. CONNOLLY: Yeah, so we asked each adjudicator

24   to indicate when they were reviewing the blinded documents

whether there was -- they had been unblinded and they

responded on every adjudication CRF to that question. If

they indicated that they'd been unblinded than that

adjudication would not be used in the final assessment of

the events. The documents would then be reblinded or

further blinded to -- and then go out to other

adjudicators. So, yeah that's --

DR. NISSEN: Okay, that answers my question. I

will cease and I've got more questions later.

DR. LINCOFF: Dr. Kaul.

DR. KAUL: Thank you, Dr. Lincoff. Moving along

the same theme of ascertaining bias, ascertainment bias is

both inevitable and unavoidable in an open-label study.

And despite very persuasive presentation by Dr. Yusuf, I am

somewhat sensitized by the historical precedent of

Ximelagatran, and ascertainment error, especially if it is

not differential, it will bias the results towards the

null, which is the desired outcome of the non-inferiority

trial.

So in that regard, have you done sensitivity

analyses evaluating the impact of the source of potential,

unavoidable biases such as asymmetric rates of

discontinuation due to GI adverse effects in the dabigatran

group with crossover to warfarin treatment or interruptions

1   that were managed more frequently with bridging in the

2   warfarin treatment group? I understand some of it may be

3   captured in the on-treatment analysis, but I like to see if

4   you did sensitivity analysis where you took these patients

5   who had a discontinuation due to GI side effects or any

6   interruption.

7   DR. YUSUF: That's a good question. The -- there

8   are two sets of analyses that address it. One is the on-

9   treatment analysis and then the events after discontinuing

10 the medications and this -- okay, can you bring it up

11 please? That's the on-treatment analysis. You will see

12 the first line, stroke, systemic embolism, 183. This is

13 intend-to-treat there. But this is the on-treatment

14 analysis. If anything, the results are clearer here

15 because the relative reductions are -- the hazard ratios

16 are lower by about .1, which means .75 would go to .65 for

17 these.

18   So you'll see an on-treatment analysis reinforces

19 these and here, the intend-to-treat analysis -- actually

20 there are -- in this group there are more events. Here

21 it's purely a dilutional effect. And remember, here we're

22 looking at superiority in addition to non-inferiority. So

23 this would dilute it out. This, you're right, could tend

24 to take it to non-inferiority, but this -- but having all

these together helps us in understanding the data. The second analysis that we did is in the missingness of events and can we go to my slide? Do you have my imputation slide? As you know, there's a certain number of people who you -- we got vital status on practically everybody, but in about five, 600 divided by -- equally between three groups we -- they refused to come for visits so we had to follow them in other ways.

And this slide, if you can put it up, and then there's another slide. So we had 199 person years in dabigatran 110 on 175 people that you'd say is duration of missingness. This is 235, 183. If we assume the warfarin event rates we would have three there, four there, three there. And since we know people who stopped coming, probably have stopped all their medication and they're different from the people who come, we can make another assumption of doubling the event rate in all of those. But it's still, you know, whatever you see. It's a dilutional effect.

But we said what about a crossover effect? In the warfarin group, for some reason the people who didn't come actually did very, very well and you have the doubled event rates only in the dabigatran group. And the next slide shows you the results. This is the observe results,

1   okay, which you've seen, that is, all the data. This is

2   the imputation of warfarin times two. So we're doubling

3   the event rate, but it's equally the same. You will see

4   .90, upper contents limits should be 1.11, not one. And

5   here you'll see it's still highly superior. Now you're

6   taking a worse where you're crossing over, warfarin no more

7   events. Here there are, you know, six or eight more

8   events. And you will see in all these cases you're

9   getting, still, consistent results. These are the only two

10 sets of analyses we've done that could address your

11 questions.

12   DR. KAUL: In your presentation you sort of

13 briefly alluded to this disconnect between 60 to 70 percent

14 reduction in critical bleeding events like intracranial

15 hemorrhage and yet, a 40 to 50 percent increase in GI

16 hemorrhage, and seems to me that the GI hemorrhage is

17 probably due to a local issue, probably some irritation, GI

18 toxicity from dabigatran.

19   Have you explored this further and then is there

20 any impact of other concomitant therapies on this adverse

21 event?

22   DR. REILLY: So -- Paul Reilly, BI. So Dr. Kaul,

23 if I understand your question, a little more exploration of

24 the site of GI bleeding? We did look at as many of these

1   major GI bleeds as possible. I recall, as they're looking

2   for the slide, approximately 463. We looked at the source

3   documents. About 20 percent of them had no investigations

4   whatsoever in terms of colonoscopy or

5   gastroesphagialduodenoscopy. There was another 20 percent

6   that were not evaluable, but basically what it did show was

7   that there was an excess of lower GI bleeds on dabigatran

8   compared to warfarin. The upper GI bleed rates were

9   similar across the three treatment groups.

10   DR. KAUL: Did you look at the -- what is the

11   impact of this drug on the gastric BH and things like that?

12   DR. REILLY: We have not looked at that.

13   DR. YUSUF: No, we don't. I mean, this came as a

14   surprise finding at the end of the study so we didn't

15   anticipate --

16   DR. REILLY: There were no pre-clinical findings

17   indicative of some toxicity in the GI tract.

18   DR. YUSUF: Just to add one other thing that you

19   asked about concomitant drugs, nothing seemed to budge it

20   once we looked at PPIs, aspirin, various other things. So,

21   yes, there's a dichotomy. Highly likely that this is local

22   because 66 percent of the dabigatran you can see normally

23   comes out in the feces as the activated form. Is that

24   right, as the activated form? So some local conversions

1 happening and may be -- I'm speculating. If you've got

2 tiny erosions or something, you're more likely to bleed.

3   DR. LINCOFF: Dr. Neaton.

4   DR. NEATON: Actually Salim, I think you actually

5 addressed my question, but would you mind putting back that

6 slide up on the number of patients whom -- for whom you did

7 not have the primary endpoint knowledge at the end of the

8 trial?

9   DR. YUSUF: Can you put that up, that imputations

10 slide we just showed?

11   DR. NEATON: So I was struck too that the vital

12 status follow-up was excellent, but I was not real clear at

13 the end of the trial what procedures were taken to verify

14 your primary endpoint status and for what percentage of

15 people that endpoint status was not known at the end of the

16 trial. I think that slide --

17   DR. YUSUF: This is that.

18   DR. NEATON: Yeah.

19   DR. YUSUF: See the number of vital status

20 follow-up was --

21   DR. NEATON: That was 24 or something. That was

22 clear from one of the other slides. But can we just put

23 that back up and --

24   DR. YUSUF: Sorry, this is not the number of

1 people. We had vital stats on most of these. These are

2 the people where we think the primary -- oh, you can't put

3 it up. Well, please put it up. Sorry. Okay --

4   DR. NEATON: So, is this the number of people

5 then, with the primary endpoint status unknown at the end

6 of follow-up?

7   DR. YUSUF: That's right.

8   DR. NEATON: The total sum of people?

9   DR. YUSUF: Yes.

10   DR. NEATON: And so -- can you just say a little

11 bit about what you did at the end of the trial to verify

12 that endpoint status was known? I mean, how did you know

13 that people did not experience a stroke? What procedures

14 did you take at the end of the trial to kind of verify that

15 during the course of -- apart -- I know you did the

16 questionnaires and you reviewed the hospitalizations, but

17 was there any assessment at the end of the trial for the

18 patients enrolled as to their, kind of, the endpoint

19 ascertainment?

20   DR. CONNOLLY: Well, most of these were patients

21 --

22   DR. LINCOFF: Please identify.

23   DR. CONNOLLY: Sorry. Stuart Connolly. Most of

24 these were patients either at sites that had been closed

1 down for cause or patients at sites where they had actually

2 withdrawn consent to be followed, and so we were under

3 significant constraints on what we could actually obtain.

4 We did get permission to obtain information on vital stats,

5 but we were not able to get the more detailed information.

6 But, of course, we reviewed all information we had on those

7 patients looking for evidence of stroke and we did attempt

8 to review their -- whatever records there were. We

9 reviewed their hospitalization forms looking for any clue

10 that there might have been a stroke, same thing with AEs,

11 and did a fairly thorough review of that sort.

12   DR. NEATON: So in your primary analysis, for the

13 time to event analysis, what was the nature of the

14 censoring done for the primary endpoint? Were people

15 followed through? Did you use a common closing date or did

16 you use the last visit the people were seen?

17   DR. CONNOLLY: I think I can answer that.

18 Essentially the closeout period began on December 15 and

19 ran until March 15. That's 2009 to 2010 and -- no, that's

20 2008 to 2009, excuse me. And patients were scheduled for

21 their final follow-up visit, which would have occurred

22 during that period. So these are scheduled and we counted

23 events up until the final visit of that patient and then

24 once they had their final visit, events -- that was their

1 final --

2   DR. NEATON: So can you give us some information

3 on what percentage of patients in each treatment group

4 attended the final visit?

5   DR. YUSUF: I think I'll answer that. I think,

6 Jim, there are --

7   DR. LINCOFF: Repeat in the mic.

8   DR. YUSUF: There are two parts to your question

9 and the people that we could physically see how did we

10 ascertain and the people that we couldn't physically see,

11 what did we do? So let me deal with the first one and the

12 people who came is -- about 96 percent actually physically

13 came to visit. The remaining 3, 4 percent is the numbers I

14 showed earlier. Can you put back the ones? Remember, they

15 were still in the trial half way.

16   So the average time of loss to follow is about

17 half of their expected time in the trial. So it's not as

18 if they were totally lost. We counted all events until we

19 were able to see them and whatever date they had the event

20 was the event. And the date they were lost to follow-up,

21 these refused consent. By and large they are refusing

22 consent. That was the censored date. There's about six,

23 seven different forms of censorship used and they give you

24 exactly the same results.

1   DR. NEATON: So let me just -- I'll say it back

2 to you and tell me if I'm right. And so that during the

3 last four months of the trial you aimed to see every single

4 patient at the clinic?

5   DR. YUSUF: Yeah.

6   DR. NEATON: And you saw 95 or 96 percent of

7 them? The ones you did not see represent -- are

8 represented in that slide?

9   DR. YUSUF: And, yes. And then many of them --

10   DR. NEATON: That's the sum total of the people

11 that were not seen?

12   DR. YUSUF: Okay, I think Paul tells me it's 90

13 percent. Okay, I'll explain to you. Sorry, I'm seeing

14 this for the first time.

15   DR. NEATON: Is it something you can show us or

16 --

17   DR. YUSUF: Yeah. I'll put it up.

18   DR. NEATON: There you go.

19   DR. YUSUF: No, you don't know. This is SA-5.

20 Okay. So nine -- so you have 87 percent of those was a

21 clinic visit. In a certain proportion there's home visits.

22 Nine percent of it telephone visits. So when you add those

23 up, that's where I get my 95 percent from. So, yup. So in

24 95 percent you could talk to a patient and say, did you

1 have a stroke or a bleed? And I think patients are pretty

2 reliable in telling you on a form whether they had a stroke

3 or a bleed. In five -- and in 3 percent of other visits, I

4 don't know what the other visits are. Paul, can you help

5 me? There were miscellaneous ways of doing it because

6 different IRBs gave us different permission on how to track

7 these patients depending on local circumstances.

8   Some of it could be through GPs. Some of this

9 could be newspaper obituary records. Some could be various

10 agencies that allow you to track people. Some of it could

11 be through social insurance numbers. So, it varies exactly

12 how we did and the 20, 23, 29 are people where we had

13 absolutely no information on them. And the previous slide

14 I showed you was the duration of missingness and therefore,

15 projected events.

16   DR. NEATON: Okay, so that -- maybe if this is a

17 piece of paper that we could -- I could take a look at. So

18 it looks to me like from -- this is the last visit within

19 that four-month window?

20   DR. YUSUF: Yes.

21   DR. NEATON: And so at your closeout of the

22 study, that you were able to kind of see or talk to over 95

23 percent of the patients?

24   DR. YUSUF: Yes. We'll get you that piece of

1 paper.

2   DR. LINCOFF: Dr. Emerson, you had a question

3 that can relate to this?

4   DR. EMERSON: Just a follow-up on this. That

5 last line is what's bothering me here because that last

6 line is suggesting that the other lines are all talking

7 about the last visit that you had rather than the last

8 visit you should have had. Is that true? So, every single

9 -- every patient on here is represented relative to the

10 time from randomization to the time at the study closeout

11 and that they would have -- be -- they would have had one

12 of those visits or be ostensibly dead.

13   DR. LINCOFF: So, I think --

14   DR. YUSUF: Could you give me time to clarify

15 this because we need to come to consensus because there

16 seems to be an honest difference of opinion on how to

17 answer that question. So give us time and we'll come back.

18   DR. EMERSON: The general question is, you took

19 -- you had a process at the end of closeout to see

20 everybody and I think ascertainment bias is an issue here

21 of concern. And so that what fraction of people by

22 treatment group did you actually talk to and verify that

23 they had not had a stroke at the end of the study and for

24 which fraction of people was that unknown? And if that

1   represents the earlier slide we saw, that's okay. But I

2   just -- that's what I'm trying to verify.

3   DR. YUSUF: Jim, the answer is 95 percent we

4   talked to one way or the other, either physically, by phone

5   or a home visit. In 5 percent we couldn't talk to them in

6   that -- in that period. They could have been seen three

7   months before that or six months before that. In that

8   period, in 5 percent we couldn't talk to them. And my

9   slide that I showed you earlier is taking the average time

10 that we couldn't talk to them about their stroke and then

11 doing imputations.

12   DR. EMERSON: But, if it's 5 percent Salim, then

13 those numbers in the earlier slide are too small.

14   DR. YUSUF: Well, this adds up to about 600

15 doesn't it? Six hundred -- oh 700, 680. So, 680. Jim,

16 what does that add up -- out of 18,000?

17   DR. LINCOFF: While your -- Dr. Temple.

18   DR. TEMPLE: I'm already doing it. That slide

19 seemed to add up to over 99 percent. Having some kind of

20 --

21   DR. YUSUF: Which one? The previous one?

22   DR. TEMPLE: The one you showed.

23   DR. YUSUF: Okay.

24   DR. TEMPLE: Look at it again. Except I don't

1 know what other visits means. But if you add each of those

2 numbers up it's almost 99 percent.

3 DR. LINCOFF: Yeah, I'm also -- I mean, do the

4 other visits mean visits outside the window of closeout? I

5 think part of the question here is although you account for

6 most of the visits, are you accounting for visits that have

7 occurred in close out?

8 DR. YUSUF: Okay, just being clarified is going

9 and visiting the patients in hospital. The patient is

10 admitted for something or in the nursing home, like an old-

11 age pensioner's home or whatever. So it's physically the

12 staff go out and visit them. That's what the other visits

13 means.

14 DR. TEMPLE: Well, if you add that to the

15 telephone, to the other, it adds up to over 99 percent. So

16 while you were explaining it, sort that all out.

17 DR. YUSUF: What you are saying is the answer is

18 better than I'm making it out to be.

19 DR. TEMPLE: Well, on its face, but we don't know

20 yet.

21 DR. LINCOFF: All right, so we'll ask the sponsor

22 after to recalculate or clarify and then after lunch

23 there'll be an opportunity to present that -- that

24 information.

1   Dr. Emerson do you have any other questions,

2   because you had asked?

3   DR. EMERSON: Yeah, a couple of questions. One

4   is, and you may have answered this, but in a sort of

5   offhand thing. The adjudication, what was the concordance

6   between the investigator and the adjudication committee?

7   And then the -- another way to sort of get at this also is,

8   do you have data on the disabling stroke or death from any

9   cause?

10   DR. CONNOLLY: So the -- is the slide I want to

11 see? No. I don't have the slide in front of me that would

12 address this. So the concordance was approximately 85, 86

13 percent on the primary -- on strokes. It was lower on non-

14 CNS systemic embolism because there was a high rate at

15 which investigators reported deep vein thrombosis to us.

16 And so the disagreement rate was closer to 50 percent on

17 those. And for major bleeds and most other events it was

18 in that 85 to 90 percent concordance rate. And it was

19 consistent across the treatment groups.

20   DR. LINCOFF: Are you addressing concordance

21 between investigator and CEC or among reviewers in the --

22   DR. CONNOLLY: No, I'm addressing the concordance

23 between the report of the investigator and the final

24 conclusion of the adjudication process.

1   DR. LINCOFF: Is that your question?

2   DR. EMERSON: The second question is do you have

3   data on the composite that would be disabling stroke or

4   death from any cause?

5   DR. CONNOLLY: Disabling stroke and -- you can.

6   Go ahead.

7   DR. YUSUF: We don't have a slide here that has

8   got that composite, but we have, as I showed you, disabling

9   of fatal strokes were reduced. And we know mortality was

10   reduced. We could do it, but it's not, as you know, a

11   simple arithmetic. We have to take out the people who had

12   both. So --

13   DR. CONNOLLY: Do you have a slide on stroke

14   severity?

15   DR. YUSUF: Yeah, which -- we have a slide on

16   stroke severity. That gives you fatal and severe strokes,

17   but the exact analysis you're asking, Dr. Emerson, I don't

18   have it with me. But my guess is, given that the

19   components that goes towards it were both lower with

20   treatment, I would expect the composite would be. But we

21   could run in it the next hour or so.

22   DR. LINCOFF: We'll ask the sponsor to please run

23   that in the next hour. Mr. Scott, you had a question? Oh,

24   I'm sorry. Mr. Simon, you had a question?

1   MR. SIMON: Yes, I'm the patient advocate so my

2   questions will come from that point of view. I have three.

3   Could you comment on the b.i.d. dosage? When the patient

4   takes it b.i.d., is it taken -- when is it taken? How is

5   it taken? Is it with or without food? And by missing a

6   dose, would that cause any severity in the dosage?

7   Also, the long-term effects, you mentioned that

8   your drug has been taken in Europe I believe it is. Could

9   you comment on that? Are there any long-term effects that

10   you're aware of now at this point in time, good or bad?

11   And then lastly, you mentioned the difficulty in monitoring

12   warfarin. How do you monitor your drug?

13   DR. REILLY: Paul Reilly, BI. If I under -- if I

14   heard you correctly, you had four questions. One is, how

15   is the b.i.d dosing given in terms of with food or water

16   and so forth? You're interested in a missed dose and the

17   consequences of it. You're interested in long-term

18   toxicity and monitoring. How do we monitor this drug?

19   So, b.i.d. dosing, the drug -- the patients were

20   instructed to take the drug with water, a reasonable volume

21   of water. They could also take the drug with food. So

22   with or without food, with fluid, there were no limitations

23   on that. In terms of a missed dose of the drug, the drug

24   has in these patients a half life in the range of 12 to 18

1 hours, so if you missed a dose, within the next 12 hours

2 your trough will drop below the normal range of therapeutic

3 concentrations for the drug. So, in contradistinction to

4 warfarin, which has a three- to five-day half life, so a

5 miss -- missing a couple of doses will have an impact on

6 whether you're protected.

7   Long-term toxicity, we have not seen anything

8 that you haven't seen here in the RE-LY trial. The RE-LY

9 trial represents a relatively long exposure. We have some

10 data on patients treated up to four years and there are no

11 other alarming safety signals.

12   And the last question you had was, how do we

13 monitor this drug? Obviously RE-LY was run without

14 monitoring dabigatran. It was a fixed dose and no attempt

15 was made to control the dosing using anti-coagulation

16 testing. However, you can monitor the ant-coagulant effect

17 of dabigatran by looking at tests such as aPTT, which I

18 think Dr. Connolly showed you is affected by dabigatran.

19 INR is less sensitive, not appropriate for dabigatran.

20   There are other more specific tests like Ecarin

21 clotting time and thrombin time, which are quite specific

22 and sensitive and have a linear relationship. However,

23 they're not that widely available and their methodologies

24 can vary.

1   DR. LINCOFF: All right, we're going to take a

2   break in a few minutes, but -- so we'll -- if unless

3   they're long, in which case we'll deal with them later.

4   Drs. Nissen and Mr. Coukell and Dr. McGuire and then if

5   there are any others, we will have opportunity this

6   afternoon to talk to the sponsor again.

7   DR. NISSEN: Maybe what I'll do is ask the

8   question and we can, after the break, can see these. There

9   are four Kaplan-Meier curves that I'd like to see here.

10   I'd like to see the time to event from myocardial

11   infarction, including silent MI. I'd like to see time to

12   event for the triple endpoint of MI, stroke and

13   cardiovascular death. I'd like to see the Kaplan-Meier

14   curve for time to permanent drug discontinuation and the

15   Kaplan-Meier curve for time to gastrointestinal bleed. And

16   again, so the sponsor understands what I'm trying to get

17   at, is this MI signal. I want to see if there are any

18   insights we can gain by looking at those actual time to

19   event curves and these others as well.

20   The question on the triple endpoint is that, you

21   know, we got to look at the totality of benefit versus

22   risk. And so conventionally in cardiovascular trials, you

23   know, cardiovascular death, MI and stroke is a pretty good

24   measure. I'd like to see how that comes out for the three

1 therapies.

2   DR. LINCOFF: Okay, just to clarify, right after

3 the break we're going to have the FDA presentation. After

4 lunch we'll have the opportunity for expanded questions to

5 either the sponsor or the FDA. So that would be the time

6 to have these extra materials that Dr. Neaton, Dr. Emerson

7 and Dr. Nissen have asked for. Mr. Coukell.

8   MR. COUKELL: Thank you. When you made the case

9 for having the availability of a lower dosage of

10 dabigatran, you made two arguments and one was that it

11 might be useful for patients who are intolerant to the

12 higher dosage, but what's the basis for saying that?

13 Because it looks like, setting aside GI bleeds, that

14 adverse events were essentially the same with the two

15 dosages.

16   And then secondly, Dr. Kaul asked about

17 concomitant medication and GI bleeds and you talked about

18 the location of the bleeds, but you didn't actually talk

19 about any analysis of the effect of concomitant meds.

20   DR. YUSUF: Let me answer the first one. You

21 answer the second one. The first one is, the basis of

22 suggesting is a clinical feel that when I use many drugs,

23 if I have a side effect, the alternative is to completely

24 stop it or to try a lower dose. For instance, whenever I

1 use an ACE inhibitor if a person has swelling, i.e. modest

2 angioedema, then I might try to use a lower dose.

3 Hypotension it is, but nobody I know for most indications

4 have taken -- people had a bleed in the randomized in the

5 lower dose versus non. It's a trial and feel kind of

6 approach. We do know that some of the side effects are

7 dose related. Like GI bleed is dose related. So it would

8 not be unreasonable to try the lower dose.

9   The other thing is often with a patient if you

10 want to get them back on the drug, you have to do something

11 different. You know, patients are -- would say look, I'm

12 not comfortable going on that drug at the same dose, versus

13 if you say, look, we have data that the lower dose has a

14 lower risk of bleeding. Would you mind trying it? Many

15 patients would be willing to try it. So, it's a clinical

16 statement. I don't think our trial can answer it and Paul

17 will answer whether there's a difference by concomitant

18 therapies and the rates of bleeds -- GI bleeds. My answer

19 is --

20   DR. REILLY: Paul Reilly, BI. So, aspirin will

21 elevate the rate of GI bleed across all treatment groups.

22 Doesn't seem to be any synergy. It's just an added effect

23 for all three. The other notable conmed is proton pump-

24 inhibitor usage. Patients who use pro -- who are using

1 proton pump inhibitors at baseline indicating some pre-

2 existent pathology, have about a three-fold increase risk

3 of GI bleed. Also, patients taking proton pump-inhibitors

4 during the study, for example, for dyspepsia, you will see

5 an elevated GI rate of bleed. But let's be clear, there's

6 no elevated GI bleed rate in the presence of dyspepsia.

7   DR. LINCOFF: Dr. McGuire.

8   DR. McGUIRE: I think a couple of very quick

9 questions. With regards to the myocardial infarction, the

10 clinical annotations around the time of the MI, do you have

11 information from the annotations about the dosing of drug

12 within the 12 to 24 hours antecedent to the MI getting to

13 the rebound speculation? Second question is, is there any

14 association with the hemorrhages both major and the GI

15 hemorrhages with myocardial infarction.

16   DR. YUSUF: Sorry, could you repeat the second

17 question because I was sort of thinking which slide to pull

18 up for the first one?

19   DR. MCGUIRE: Yeah, so the first ones about

20 aspirin -- I mean, study drug missed dosing antecedent to

21 the MI in the 12 to 24 hours. The second is the major

22 bleeding, is there an association with an MI occurring in

23 the clinical context of a major bleed in general and

24 specifically in a GI bleeding situation?

1   DR. YUSUF: I don't -- okay, Jim come up. This

2   -- is there a simpler version of this?

3   DR. REVKIN: Jim Revkin, cardiovascular medicine,

4   Boehringer Ingelheim. First if we can put up slide -- MI

5   slide 39 please. Slide up. So, we have limited

6   information on the drug dosing. Generally we've acquired

7   information on the drug at the last visit prior to the MI.

8   If you remember, most of these events occurred outside

9   hospitals and the patients, you know, there's limited

10   information on when the last dose was actually taken. So

11   in this slide you see the three different treatment groups

12   and then you see by days off study drug.

13   So if you look at the top yellow line there, you

14   can see the MI incidence greater than six days off drug

15   across the groups. And if we can have the next slide up,

16   which is 40. This shows a further breakout. If you look

17   at the second line from the bottom you can actually see

18   this imbalance still exists even greater than three months

19   off study drug. Now let's zoom in to the question you

20   asked about the period within one week or acutely off-study

21   drug. Perilously -- slide 42 up please.

22   DR. MCGUIRE: And for -- I've seen these data in

23   the briefing. I'm very specifically interested not in

24   those patients' off-study drug, but those who may be on

1 study drug but missed a dose within 12 to 24 hours.

2 DR. REVKIN: Yeah, we don't have that kind of

3 data. I should also mention that when -- the protocol

4 specified that when subjects became symptomatic they were

5 to discontinue study drug. So we have limited information,

6 but this also shows early on in terms of off-study drug.

7 Again, the numbers are pretty much balanced across the

8 treatment groups.

9 DR. LINCOFF: Wait one second. Dr. Neaton, you

10 had a clarifying question?

11 DR. NEATON: If I just ask for your definition of

12 MI. This is both silent and clinical MI. What did you do

13 with sudden deaths?

14 DR. REVKIN: So sudden deaths would be in the

15 category cardiovascular death.

16 DR. NEATON: They're not counted here; this is

17 clinical MI, fatal or non-fatal?

18 DR. REVKIN: That's correct, just --

19 DR. NEATON: And silent MI --

20 DR. REVKIN: Okay, let me clarify. You were

21 looking at clinical MI data. Let me bring up the slide 23.

22 Slide 23 up please. Slide 23 up, not 90. Twenty-three up.

23 So this shows the breakout by the MI category. So clinical

24 MIs would have been those for which one had two of three

1 criteria, chest pain symptoms, EKG symptoms and enzyme

2 levels. You can see the group of silent MIs as a subset,

3 the next line up from the bottom. And then the total MI

4 numbers are there. So in terms of sudden death, that was

5 categorized not as MI, but as cardiovascular deaths. And I

6 think if we can preview slide 90, MI slide 90.

7 　　　　　DR. NEATON: Just can I then, by your definition,

8 these are all non-fatal MIs?

9 　　　　　DR. REVKIN: Okay, the clinical MIs -- some of

10 the clinical MIs could -- so let me just explain. We had

11 no pre-specified definition of fatal MI. We went to

12 cardiovascular deaths and we could go back and find

13 subjects who had a recent prior MI to categorize that. If

14 we could put slide 90 up please. So here you see

15 cardiovascular deaths by two subcategories, sudden

16 arrhythmic and pump failure. And looking at the numbers,

17 you know, pump failure may have a small increase in

18 dabigatran group.

19 　　　　So if you look at the bottom section there with

20 recent MI, that's that category you were asking about that

21 may have had an associated MI. You can see it at the --

22 lowest dose actually was the highest frequency. The

23 numbers are quite small when you consider the number of

24 subjects in this study. And then we broke those up by

1 arrhythmic or pump failure deaths. And again the numbers

2 are pretty much balanced against, except for pump failure,

3 with MI somewhat higher in the lowest dose. So there

4 doesn't appear to be any dose effect.

5   DR. LINCOFF: Dr. McGuire, did that address the

6 questions that you had?

7   DR. MCGUIRE: No, but it sounds like probably the

8 first question isn't addressable. The second question is

9 the MI in the context of a bleed.

10   DR. YUSUF: While you bring that up, just to

11 address square on, because I think, Jim, the intention of

12 your question is is that a concomitant increase in fatal

13 MIs? And the closest we can come is this slide,

14 cardiovascular deaths, no excess, no major excess and

15 sudden arrhythmic deaths. Those are the numbers which is

16 what we epidemiologically worry is a fatal MI outside

17 hospital. So there isn't any evidence there.

18   And as we showed you earlier, ACS

19 hospitalizations, there wasn't an excess. And

20 revascularize -- cardio revascularization procedures, there

21 wasn't an excess. But I think this MI difference is

22 important to watch in future data.

23   DR. REVKIN: Jim Revkin again, cardiovascular

24 medicine. We can bring up slide 60 please to answer the

1 question in reference to bleeds. So here again you see the

2 three treatment groups, the clinical MI classes. And you

3 can see that there were a handful within one week prior to

4 the MI event of major bleeds prior to the MI. And one of

5 each of those in each of the groups were life-threatening

6 bleeds. So there's a higher numeric incidence of major

7 bleeds within one week prior to the MI event in the

8 dabigatran treatment groups compared to warfarin.

9   DR. LINCOFF: Okay, all right. We're running

10 about 10 minutes late, but we have time in the afternoon to

11 make it up, so this will be good. We will now take a short

12 15-minute break. Committee members, please remember that

13 there should be no discussion of the meeting topic during

14 the break amongst yourselves with any member of the

15 audience. We'll resume exactly at 10:30, when we'll start

16 the FDA presentation.

17   (A brief recess was taken.)

18   DR. LINCOFF: We're going to move on now with the

19 FDA presentation starting with the efficacy review by Dr.

20 Thompson.

21   DR. THOMPSON: Hi, can everyone hear me? I'll

22 take that as a yes. Thank you for coming. My name's Aliza

23 Thompson. I'm a medical officer in the Division of

24 Cardiovascular and Renal Products and I reviewed dabigatran

1 from an efficacy perspective. Over the course of the

2 presentation this morning, I'm going to focus on three

3 topics. I'm going to give you an overview of RE-LY's

4 design, talk about its efficacy findings and then focus in

5 on aspects of study conduct and design that could infect --

6 that could, excuse me, effect interpretation.

7   As you heard earlier this morning, atrial

8 fibrillation effects upwards of two million Americans and

9 stroke is a very important complication. In the late 1980s

10 and early 1990s, six trials established the efficacy of

11 warfarin in the prevention of strokes. And as you also

12 heard earlier this morning, these trials showed,

13 essentially very impressive findings for warfarin and

14 showed a 60 percent reduction in the risk of strokes

15 associated with the use of this therapy. In RE-LY -- RE-LY

16 was designed as a non-inferiority study against this

17 competitor and it was designed to show that upwards of 50

18 percent of warfarin's benefits or treatment effect on

19 stroke was preserved.

20   In RE-LY, over 18,000 subjects were randomized.

21 They were randomized into one of three treatment arms, open

22 label warfarin use and blinded use of one of two doses of

23 dabigatran. The primary endpoint in RE-LY was stroke and

24 systemic embolism. And the population that was enrolled

were patients with non-valvular atrial fibrillation with at
least one risk factor -- additional risk factor for stroke.
And as you also heard this morning, the trial enrolled both
warfarin-naïve and non-naïve patients.

Here in this slide you see the findings for the
primary endpoint, stroke and systemic embolism. As you
also heard earlier this morning, RE-LY established the non-
inferiority of both doses of dabigatran relative to
warfarin using both the sponsors pre-specified margin as
well as the FDA margin of 1.38. The trial also established
the statistical superiority of dabigatran 150 versus
warfarin and also the 150 dose over the 110 dose in the
prevention of stroke and systemic embolism.

As you may -- in this slide you see the
components of the composite endpoint. As you may remember,
if you've looked through the AC questions of -- you may
remember from hearing Norman's comments earlier this
morning, there's really two issues that we are interested
in. Or several issues, but I think two primary issues,
that we are interested in is the efficacy of dabigatran
relative to warfarin, as well as the efficacy of one dose
of dabigatran relative to the other. And so in this slide
I show you the components of the composite endpoint.

Just some points to bring up, again, points that

1   I think have also been made by the sponsor earlier this

2   morning, is that overall in the trial the rate of systemic

3   embolism was low and low across all treatment arms. Again,

4   if you look at the absolute incidence of both ischemic and

5   hemorrhagic strokes, the absolute number of both these

6   types of strokes was lower in the dabigatran 150 arm

7   relative to the warfarin arm. And if you look at the

8   dabigatran 110 arm relative to the warfarin arm, the

9   absolute incidence of hemorrhagic, but not ischemic strokes

10 appeared to be lower.

11   Shifting your eyes -- whoops -- shifting your

12 eyes down now to the lower table showing the hazard ratios,

13 a few points to make, one, that the finding for superiority

14 for the dabigatran 150 dose relative to warfarin is really

15 driven by effects on stroke and not systemic embolism. And

16 then shifting your eyes down to this lower table, I think

17 the notable findings are that the dabigatran 150 arm

18 appears to be having effects both on ischemic and

19 hemorrhagic strokes, whereas the dabigatran 110 arm is

20 primarily having effects on hemorrhagic strokes.

21   And as you can see that if you compare the hazard

22 ratio or look at the hazard ratio for the 110 versus

23 warfarin for ischemic stroke, the upper bound to the 95

24 confidence interval is approaching actually the FDA margin

1 for non-inferiority and crossing it.

2   As you heard this morning, in addition to the

3 primary endpoint, the RE-LY protocol specified two

4 secondary endpoints. That said, there was no statistical

5 analysis plan pre-specified to control for the type one

6 error rate in the analysis of these endpoints. And so in

7 this slide I just show you some of the endpoints that were

8 included in the composite. And I also show you MACE. I

9 think earlier today a question was asked about MACE.

10 Focusing on -- whoops -- I need to learn how to work this.

11 I apologize. Focusing on the upper table, which shows

12 annualized event rates, I think you see a few things. One,

13 in terms of pulmonary embolism overall in the trial, the

14 number of such events was low and appeared similar across

15 the treatment arms.

16   As you also or already heard this morning, there

17 was a numerical imbalance in the number of MIs with the

18 findings favoring, actually, the warfarin arm. If you

19 shift your eyes down to the lower part of this table, I

20 show you MACE and here defined as a composite of MI, stroke

21 and cardiovascular death. And what you'll see here -- and

22 then shifting your eyes lower to here, the actual hazard

23 ratios that are calculated is that at least for the 150 arm

24 relative to warfarin and looking at this particular

1 endpoint, there still appears to be net benefit. This is

2 not as clearly the case with the 110 dose. And again, if

3 you compare the 150 versus the 110 for this endpoint, the

4 150 dose looks to be better.

5   Another point that I want to make, again shifting

6 your eyes back up to this part of the table, is effects on

7 mortality. In RE-LY, mortality was adjudicated as vascular

8 or non-vascular and as you heard earlier this morning,

9 there was an imbalance in the number of all-cause mortality

10 and vascular mortality that appeared to favor the

11 dabigatran treatment arms. Earlier this morning, I think

12 you also heard about a nominal p-value. A p-value that

13 wasn't adjusted for the multiple endpoints that were

14 explored of the comparisons of one dose versus the other

15 and I believe that p-value for all-cause mortality was

16 about .052 and for vascular mortality .04.

17   A comment with regard to that mortality endpoint,

18 I think it's important to note that in addition to the

19 issue of the multiple comparisons when looking at the p-

20 value, you need to also keep in mind that the finding isn't

21 particularly robust. So, for example, the sponsor's

22 statistical analysis plan was actually finalized quite late

23 in the trial after essentially all the data had been

24 amassed. And if you include some deaths that were actually

1 censored by that plan, the p-value climbs slightly higher

2 to .06. If you also exclude those deaths that were

3 identified just via vital status queries alone, you get an

4 even higher p-value point -- an even higher p-value, a p-

5 value of .09. And finally, the last point I want to make

6 about the mortality effects is, as I'll show you later,

7 they're highly driven by subjects achieving very low levels

8 or poor levels of INR control in the warfarin treatment

9 arm.

10   So you've -- you're now probably pretty well

11 aware of the efficacy findings in RE-LY. And now I want to

12 focus on factors that could potentially affect your

13 interpretation of these efficacy findings, particularly the

14 comparison of dabigatran to warfarin. And the factors that

15 I'm going to discuss include subject follow up, the

16 adequacy of anticoagulation in the warfarin arm, potential

17 sources of bias in the setting of an open-label study, the

18 fact that this was a single trial, and there's lack of

19 replication. And by that I mean lack of replication of the

20 findings relative to warfarin. And then finally, the last

21 issue is again, the late date of finalization of the

22 statistical analysis plan, again, a plan that was finalized

23 after all the study data had essentially been amassed.

24   In the next few slides I'm going to focus on the

1 first three points. In this slide you see subject follow-
2 up. I think we are increasingly realizing that both the
3 amount of follow-up data on subjects, as well as the
4 quality of that data, have a strong impact on our
5 interpretation of efficacy findings. In RE-LY it was
6 specified that subjects who prematurely discontinued from
7 study medication, it was specified that these subjects were
8 to continue to be followed in the study. However, it was
9 also specified or allowed that these subjects could be
10 followed up via a revised follow-up schedule. It could be
11 negotiated with the investigator and follow-up visits could
12 also be made, not just in clinic, but also by telephone
13 contact.

14   I think it was noted earlier today that being
15 seen in clinic may be a little bit different than just
16 having a phone call at the end of the study and talking to
17 someone over the phone. And so in the analysis that -- the
18 analyses that we did, we attempted to look up -- to look at
19 follow up in part based on when a subject was last actually
20 seen in clinic. And to make that determination we looked
21 in the data for the last time vital signs were reported and
22 specifically a pulse. And so what you're seeing up here
23 for some of these analyses are based on the last reported
24 pulse for a patient. Whoops. Sorry.

1   If you go to the top figure, this shows follow-up

2 from the time course of follow-up for subjects over the

3 course of the trial. And I think what you note from that

4 top figure is that follow-up appears to be similar across

5 the three treatment arms. Shifting your eyes down to this

6 lower table, a few points. One, as you heard earlier this

7 morning, about 96 percent of subjects were reported to have

8 completed the trial. Of those who were reported to

9 complete the trial, approximately 19 percent in the

10 dabigatran arms and 15 percent in the warfarin arm stopped

11 study medication prematurely.

12   And then I'd just like to draw your attention to

13 this last line here. When we looked at subject follow-up,

14 one of the things we did is we looked to see the percent of

15 patients who had not been seen within six months of the

16 study closeout period. And to do this again, we used the

17 last time a pulse was reported for the patient. In doing

18 this type of analysis we saw that about 8 percent of

19 subjects were not seen in the clinic within about six

20 months of the study closeout period.

21   What to make of these data? Is this a reasonable

22 amount of follow up or not? I think it's important to

23 think of these data in the context of the efficacy findings

24 in RE-LY. I mean, if you think about the number of events

1   that you would need to reverse the efficacy findings, so,

2   for example, to reverse the finding for non-inferiority of

3   the 110 dose, you'd need around upwards of 40 additional

4   events. For the 150 arm to reverse non-inferior -- to

5   reverse the superiority finding, you'd need a little bit of

6   upwards of 30 events. And to reverse the non-inferiority

7   finding you'd need a little bit upwards of 90 events. And

8   I think -- at least I think that the efficacy findings

9   certainly for non-inferiority of the 150 dose would likely

10 be robust to this amount of missing data.

11   Another very important thing to think about

12 whenever you interpret the efficacy findings in a trial

13 comparing a new drug against warfarin is the efficacy of

14 warfarin and whether or not warfarin was given in such a

15 way in the trial so that you see or expect to see the

16 benefits of warfarin as established by the historical

17 trials. In this slide I show you the annualized incidence

18 rates in the historical trials for stroke and the warfarin

19 or Vitamin K antagonist arm and also in the recent RCTs.

20   A few things to just point out. If you look at

21 the historical rates for strokes in the placebo arm of

22 historical trials that established warfarin's efficacy,

23 they're all much higher than what we're seeing in RE-LY.

24 Another point to make is that if look across these studies

1 in the warfarin treatment arm, I think you're seeing pretty

2 low rates for strokes. And if you just compare these as

3 absolute numbers, I think they all look pretty similar.

4   That said, when you think about these numbers as

5 sort of relative differences, specifically focusing up

6 here, I think what you begin to realize is the differences

7 -- relative differences of this magnitude are what we try

8 to often rule out in non-inferiority studies. Another

9 thing to think about when you are trying to understand the

10 adequacy of anticoagulation in the warfarin arm is the time

11 in therapeutic range, something that's already been

12 discussed this morning.

13   And as pointed out this morning, the time in

14 therapeutic range in RE-LY was about 64 percent and that

15 range is perhaps not so dissimilar to what's been reported

16 in some other recent RCTs, but I think the question is

17 really what is achievable and also what is optimal? And to

18 just point out an example -- whoops. Sorry about that. If

19 you look at a recent trial of tecarfarin, which used a

20 central dose control center and pharmacogenomic information

21 to guide therapy, they actually achieved much higher levels

22 of control of the INR, again, raising the question of what

23 is sort of reasonable and what you really can get if you're

24 compulsive about it.

1   Another issue with time in therapeutic range is

2   that comparisons across studies are not necessarily

3   straightforward. I think for a range of reasons of the

4   correlation between the time in therapeutic range and

5   stroke rates is not perfect. So, for example, you see a

6   similar reported time in therapeutic range for the SPOR TIF

7   III and the SPOR TIF V trials. And yet you see markedly

8   different ischemic stroke rates reported in SPOR TIF III,

9   an open-label study with a stroke rate of 1.9 percent and

10   SPOR TIF -- sorry, excuse me, a blinded study. And in SPOR

11   TIF V, the open-label trial where you got a stroke rate of

12   1.1 percent.

13   Another important point to make is what TTR

14   reflects and what it doesn't reflect. Time in therapeutic

15   range reflects measured and reported INR values. And so

16   depending upon the adequacy of INR monitoring in a trial,

17   to the extent to which subjects assigned to warfarin

18   actually remained on warfarin during the course of the

19   study, it may or not actually be reflective of the degree

20   of anticoagulation in the warfarin arm. And so to develop

21   that point a little bit further in the context of RE-LY,

22   you know, as you heard earlier this morning, rates of

23   permanent discontinuation of warfarin in RE-LY, about 17.9

24   percent.

1   And I don't remember if this was presented

2   earlier or not, but about 52 percent of subjects who were

3   in the warfarin arm had an interruption in therapy during

4   the course of the trial. In terms of INR monitoring, about

5   2 percent of randomized and treated subjects lacked any

6   reported follow-up data on INR. That said, the majority

7   were on therapy for 30 days or less. And for subjects with

8   INR measurements that were taken and reported, about 30

9   percent had a least one measurement taken greater from --

10 greater than 60 days from the prior measurement. And about

11 16 percent had at least one measurement taken greater than

12 90 days.

13   I think, you know, certainly when we think about

14 the frequency with which you need to monitor INR with

15 warfarin, you give a lot of consideration to what the

16 values you're getting are. So, for example, in RE-LY,

17 subjects were supposed to have measurements taken once a

18 month, but if their INR was out of range they were supposed

19 to have more frequent monitoring. This slide attempts to

20 get at the issue of whether or not this was well done in

21 the trial. On the X axis what you're seeing is the total

22 number of days on warfarin divided by the number of INR

23 measurements for subjects. And here you see the vertical

24 line is drawn at 30, which would be about a month -- a

1 measurement once a month on average. And then on the Y

2 axis what you're seeing is the percent time in therapeutic

3 range, meant to be an indicator again of how well-

4 controlled a subject reportedly was. Is that clear? Okay.

5   What I want to do is draw your attention to two

6 areas. The first is this area and in this area you have

7 people who are reported to have very good time, very good

8 numbers for their time in therapeutic range. And yet

9 you'll notice some of these patients are monitored pretty

10 infrequently, which I think begs the question, is the

11 reported time in therapeutic range actually reflective of

12 what they really were in the study?

13   The other area of the graph that I want to call

14 your attention to is this area, because all these subjects

15 in this errand -- area and extending over this way of the

16 line are people who had reportedly pretty poor control, and

17 yet from what this graph is suggesting, they weren't

18 actually having very frequent measurements.

19   Finally, a last point in terms of INR control,

20 it's become pretty common practice in trials to look at

21 results of a new drug against warfarin after sub-setting

22 the population into subjects who achieved better in worser

23 levels of INR control in the study. And in this slide I

24 show you the findings for stroke and systemic embolism, the

1   primary endpoint as well as all-caused death. And I think

2   that it's worth noting that while dabigatran 150 is

3   certainly shown to be effective in comparisons against

4   those achieving lesser and greater levels of INR control,

5   the findings for superiority are heavily driven by this

6   subset of patients. Changing now to death, as you heard

7   earlier, there where findings of an imbalance that was

8   suggesting favorable effects in the dabigatran arm and you

9   just want to highlight here that this favorable finding for

10 mortality is entirely driven by those subjects at centers

11 achieving lower levels of INR control.

12   And with that I'd like to shift focus to

13 something that's also been discussed this morning, which is

14 RE-LY's open-label design. I think a lot of emphasis is

15 made when we talk about open-label trials, that the trial

16 was a PROBE study. And again a PROBE study is a

17 prospective, randomized, open-label, blinded endpoint

18 evaluation study. And the emphasis is often given to this

19 part. It's a blinded endpoint evaluation, meaning that

20 adjudicators looked at it blindedly.

21   As you heard this morning, or as one of the

22 questions raised this morning alluded to, if you actually

23 look at the blinding of the adjudication documents, there's

24 clear evidence that these documents contain text that could

1   have potentially unblinded adjudicators. In about 20

2   percent of the documents reviewed by the adjudication core

3   committee, they noted text that could have potentially

4   unblinded reviewers. And in my review of the CRFs that

5   were submitted, I found a similar number, about 17 percent.

6   I don't know whether or not I got the documents that were

7   supposed to be subsequently checked and had the blinding

8   information crossed off again or the first version of the

9   CRF. What I can tell you in my review is that even though

10   there were often phrases like these, "recruited in RE-LY

11   study on dabigatran," "Sunday to check INR," "consult with

12   physician regarding the Coumadin dose," even though there

13   are often phrases like this within the documents, many

14   times actually it was not noted or the adjudicator did not

15   comment that they had actually been unblinded. But

16   certainly there was phrasing contained within many of the

17   adjudication documents that could have had the potential to

18   unblind them.

19   Another issue I want to address is the measures

20   implemented in RE-LY in an attempt to mitigate bias in the

21   ascertainment of potential endpoint events. As you heard

22   earlier this morning, some of the methods used to capture

23   additional endpoint events included the screening of

24   investigated, reported reasons for hospitalization in

1 adverse events and also a questionnaire querying subjects

2 for signs and symptoms of strokes. And as I think also

3 noted this morning, all of these methods required that

4 investigators first report an event suggestive in order to

5 capture an event via this method. A question raised this

6 morning about the hospitalization CRF and what was actually

7 captured, thought maybe it'd be helpful to show you what

8 was captured in terms of information on hospitalization.

9   This is the CRF that the investigator filled out.

10 As you see, there's some tic -- tic boxes and also some

11 space for free text, again, all filled out by the unblinded

12 investigator. While I can understand how a review of all

13 hospitalization discharge summaries or records might help

14 you identify potential endpoint events, I'm not quite sure

15 how helpful this type of method is.

16   And then a last point before closing, as noted

17 earlier this morning, warfarin is a very difficult drug to

18 use. Yet despite this, if you look in RE-LY, rates of

19 permanent discontinuation of study drug were higher in the

20 dabigatran arm than in the warfarin arm, about 22 percent

21 in the dabigatran arms and about 18 percent in the warfarin

22 arm. If you look at the reasons for permanent

23 discontinuation of study medication shown in this slide,

24 and also this slide, which I'll come back to in a second, I

1 think the sense that you get is that patients who were

2 sicker on dabigatran tended to have their study medication

3 discontinued in the dabigatran arm more so than in the

4 warfarin arm.

5   So, to highlight a few, if you look at reasons --

6 serious AEs not related to outcome events, you get the

7 sense that there's a higher percent of subjects in the

8 dabigatran than warfarin arm continuing. If you look at

9 adverse events in general, I think you get that same sense.

10 And if you look at outcome events, again, you get that

11 sense as well.

12   And in the next slide I just want to show you in

13 particular the outcome events leading to the permanent

14 discontinuation of study drug. And what I want to

15 highlight is, if you had a stroke you tended to discontinue

16 more so in the dabigatran arm. If you had a TIA, again,

17 true. And if you had a minor bleed, again we see the same

18 pattern. What does this mean? What do we make of it? I

19 think, sort of, there's two key messages to take home from

20 this. One has to do with the way that we do analyses on

21 RE-LY, though there were some questions raised by the

22 committee about looking at on-treatment or as-treated

23 analyses.

24   I think that this fact or this observation that

1 patients who were sicker tended to discontinue from study

2 drug preferentially in the dabigatran arm raises some

3 concerns about looking at as-treated or on-treatment

4 analyses. Makes you really want to focus in on the ITT

5 analysis, though often in a non-inferiority study we like

6 to do these analyses as well. Another point that I think

7 it makes, and I think one of the key messages, is that

8 knowledge of treatment assignment in RE-LY clearly affected

9 how the patients were treated.

10   With that I'd like to close. So my conclusions,

11 I think that the analyses support that both doses reduce

12 the incidence of stroke and systemic embolism in patients

13 with non-valvular atrial fibrillation. I think that

14 dabigatran 150 is more effective than the 110 dose. I

15 think that the anticoagulation in the warfarin arm and

16 trial design and conduct were reasonable but not optimal.

17 And I think that superiority over warfarin was not

18 established. Thank you.

19   DR. LINCOFF: Dr. Beasley. We're going to have

20 the safety review now.

21   DR. BEASLEY: Now I have to handle two of these.

22 Good morning. My name is Nhi Beasley and I'm a clinical

23 reviewer at FDA. I will be presenting the main findings of

24 the -- my clinical safety review of dabigatran. These are

1 the three main topics that I will be discussing, major

2 bleed, potential drug-induced liver injury and myocardial

3 infarction.

4   These are the definitions of serious bleedings

5 that I will be referring to. The sponsor has already

6 defined major and life-threatening bleed shown here as LT

7 and ICH and they've also discussed all three of these

8 bleeds rather extensively. I just wanted to point out one

9 thing for clarification that I thought I heard the sponsor

10 say. According to the protocol, the definition of a major

11 bleed only required one of these criteria shown on the

12 left-hand side, bleeding with a hemoglobin reduction of

13 greater than 2 grams per deciliter or a bleeding -- bleed

14 leading to blood transfusion or a symptomatic bleeding in

15 critical area or organ. If there was either symptomatic

16 intracranial bleed, bleeding associated with hypotension

17 requiring IV inotropes or necessitated surgical

18 intervention, or if it was fatal, then the major bleed was

19 sub-classified as a life-threatening bleed.

20   For some historical perspective, the inclusion of

21 at least a five gram per deciliter drop in hemoglobin or

22 intracranial hemorrhage is the definition of a TIMI major

23 bleed. TIMI and GUSTO are major reperfusion and

24 thrombolytic trials for which we have a lot of information

1 on bleeding. Because the major bleeds in thrombolytic

2 trials are probably more serious than the major bleeds in

3 RE-LY, I also examined GUSTO severe bleed as defined by the

4 sponsor. GUSTO severe bleed was not an adjudicated bleed,

5 but it consisted of ICH or an adjudicated major bleed that

6 was associated with hypotension requiring IV inotropes or

7 necessitated surgical intervention. Note that the

8 definition of a GUSTO severe bleed is not reliant on a

9 reduction in hemoglobin or the need for a blood

10 transfusion. It was also not necessarily fatal.

11   This slide shows the overall relative risk of

12 serious bleeding. These are the four categories that I

13 just defined. This is investigator reported symptomatic

14 intracranial bleeds and this is hemorrhagic strokes which

15 were adjudicated. The first two figures show the overall

16 relative risk of serious bleeding on each dose of

17 dabigatran compared to warfarin and the last figure shows

18 the overall relative risk of serious bleeding on dabigatran

19 150 compared to dabigatran 110.

20   I have three points I want to make with this

21 slide. The first, there is a dose response and you've

22 already heard that from the sponsor. They've also already

23 told you that the bleeding on dabigatran 110 was 20 percent

24 less than the bleeding on warfarin. The bleeding on

1 dabigatran 150 is similar to the bleeding on warfarin and

2 there was a 16 percent higher increase in major bleeding on

3 dabigatran 150 compared to dabigatran 110.

4 The second point I want to make is that for all

5 of these serious bleeds, dabigatran 110 is always less than

6 warfarin. For dabigatran 150, major bleeding is similar to

7 warfarin, but for the other serious bleeds, dabigatran 150

8 was less than warfarin.

9 And the third point I want to make relates to the

10 severity of the bleed. As you seem to move from a more --

11 from maybe a less severe bleed to a more severe bleed, with

12 the one caveat the GUSTO severe did not necessarily include

13 a fatal bleed, it seems that there is a greater reduction

14 in bleeding on dabigatran compared to warfarin and this was

15 true for both doses of dabigatran.

16 Okay, so now I'd like to focus on GUSTO severe

17 bleeding in RE-LY. This is a Kaplan-Meier curve in a time

18 to event of GUSTO severe bleeding. Subjects without an

19 event were censored at the time of last information know

20 about bleeding. The red line indicates dabigatran 150.

21 The green line is -- I'm sorry. The red line is dabigatran

22 110. The green line is dabigatran 150 and the blue line is

23 warfarin. There is early separation between dabigatran 110

24 and warfarin. There is a dose response where there is a 42

1 percent higher increase in GUSTO severe bleeding on

2 dabigatran 150 compared to dabigatran 110. And there was a

3 dose response relative to warfarin. The event rates were

4 very low. Relative to major bleeding, GUSTO severe

5 bleeding was less than one-third of the total major bleeds.

6 Consistent with the relative risk, the absolute risk of

7 GUSTO severe bleeding was less on dabigatran compared to

8 warfarin, as shown by the annual event rates.

9   The next topic I'd like to talk about with

10 respect to major bleeding is an analysis of individual time

11 in therapeutic range. I understand and I note Dr. Yusuf's

12 problem of looking at individual time in therapeutic range.

13 There is no statistical test that I can use to compare --

14 oops, sorry. There is no statistical test that I can use

15 to compare worse control to better control because

16 dabigatran is -- people on dabigatran do not have an INR.

17   The clinical cut of 65 percent for worse control

18 or better control was somewhat arbitrarily chosen, but it

19 was between the mean and the median. If you remember, the

20 overall analysis showed that the point estimate for

21 dabigatran 110 versus warfarin was .8, which is shown by

22 this blue line. And the overall analysis for dabigatran

23 150 versus warfarin was .93, shown by this blue line in

24 this figure.

1   So there are two points I'd like to make with

2   this slide. The first relates to better control of

3   warfarin. So if you focus on the bottom box and whisker

4   plots on each of these figures, you will see that the

5   bleeding on dabigatran is similar to the bleeding on

6   warfarin in subjects that have better control. So if you

7   have a patient that is well controlled on warfarin, I

8   would not recommend switching to dabigatran, for the reason

9   of less bleed.

10   The second point I want to make relates to worse

11   control. Remember that that dash line indicates the point

12   estimate. You will see that the hazard ratio and

13   confidence interval is almost entirely to the left for each

14   dose of the point estimate. Now, worse control on warfarin

15   can either mean either over-anticoagulation or under-

16   anticoagulation. In RE-LY, worse control meant more

17   patients bled on warfarin.

18   The last point I'd like to discuss is mortality

19   in serious morbidity following a major bleed.

20   Approximately 25 percent of all major bleeds did not result

21   in hospitalizations. That tells me that not all major

22   bleeds were very serious. In addition, not all major

23   bleeds had long-term consequences. This table shows the

24   annual event rate for events occurring 30 days after a

1   major bleed for all-cause death, stroke or systemic embolic

2   event, disabling stoke and myocardial infarction. The

3   column to the right shows the annual event rates on

4   dabigatran 150 just for a reference. I could have put the

5   event rates for warfarin up there.

6   My point is, and which I think most of you

7   already realize, is that a subject that has a major bleed

8   is at risk for having more adverse events such as mortality

9   or more morbidity. What we can't know from these data are

10   the -- or are if the major bleed causes the events. These

11   are just associations.

12   So my conclusions on major bleeding is that there

13   is a dose response for dabigatran. Bleeding is less on

14   dabigatran 110 compared to warfarin irrespective of the

15   definition. Major bleeding is similar on dabigatran 150

16   compared to warfarin, but is less for other serious

17   definitions of bleeds. Risk of bleeding on dabigatran is

18   similar to warfarin in subjects with more time in

19   therapeutic range and risk of bleeding on warfarin is

20   driven by subjects with less time in therapeutic range.

21   So now I'd like to move to my analysis of

22   potential drug-induced liver injury or DILI. This slide

23   shows a stacked graph of subjects with abnormal liver test

24   results in the randomized -- in the randomized population.

1 The top of each of these bars indicates the subjects with

2 aminotransferases, which is ALT or AST, of greater than

3 three times the upper limit of normal and a total bilirubin

4 of greater than two times the upper limit of normal. There

5 was no time dependence for the peak bilirubin and

6 aminotransferase in these 55 subjects. So, if a subject

7 had a total bilirubin elevation prior to the

8 aminotransferase elevation, it was probably unlikely to be

9 hepatocellular injury. These subjects were further reduced

10 to look at significant total bilirubin elevations within 30

11 days the peak aminotransferase elevation. There were 13,

12 14, and 20 subjects in dabigatran 110, dabigatran 150 and

13 warfarin arms respectively.

14   These subjects were even further then reduced by

15 excluding subjects with a possible obstructive process or

16 cholestatic process. These subjects were called a

17 potential high subjects and there were 11, eight and 10

18 subjects respectively in this group. These numbers on its

19 face do not indicate a concern for drug-induced liver

20 injury. However, the question that was raised was why were

21 there so many cases on warfarin, which I will discuss in a

22 few more slides.

23   Now, since drug-induced liver injury is a

24 diagnosis of exclusion, all 55 cases were reviewed by

1 myself, Dr. Seeff and Dr. Senior to rule out other probably

2 causes. This slide shows the important results of review

3 of the 55 cases of interest. Dr. John Senior and Dr.

4 Leonard Seeff evaluated and scored all 55 cases for

5 clinical severity and probable cause. There was only one

6 subject on dabigatran 150 that had the highest severity

7 score, which meant that it was either fatal or required

8 liver transplantation due to liver failure. In this

9 particular case it was fatal. However, causality of DILI

10 was unlikely.

11   There was one probable case of DILI on dabigatran

12 110. Probable is defined as DILI more likely than all

13 other causes combined, only one other possible cause and in

14 this particular case it was heart failure. There were no

15 very likely or definite cases of DILI. The cases of

16 interest in the warfarin treatment arm of RE-LY were

17 approximately six-and-a-half-fold greater than that seen in

18 SPOR TIF V, which was a similar trial comparing

19 ximelagatran to warfarin. The reason for this difference

20 is not clear. The frequency of monitoring of liver test

21 seems similar. Background diseases seem similar with the

22 exception that there was more heart failure in SPOR TIF V,

23 which actually doesn't explain why you would see a greater

24 number of cases in RE-LY. Perhaps it's the longer duration

1   of RE-LY.   There were approximately 12,000

2   subject years per arm in RE-LY versus SPOR TIF V, which had

3   6,400 total subject years. Perhaps there were geographic

4   differences. SPOR TIF V was conducted in U.S. and Canada,

5   whereas RE-LY was an international study. I don't know.

6   What was reassuring is that all warfarin cases

7   had other probable causes. So my conclusions on dabigatran

8   drug-induced liver injury is that the randomized,

9   controlled, clinical data support a low potential for

10   serious DILI. I recommend no routine liver monitoring.

11   However, if a doctor -- a doctor should investigate

12   patients with symptoms of possible liver dysfunction or

13   abnormal tests to determine the probable cause, they

14   shouldn't assume that it's the drug.

15   Okay, now I'd like to move to my analysis of

16   myocardial infarction. This is the Kaplan-Meier curve for

17   the risk of MI -- risk of clinical MI. So I don't know if

18   it's going to get the sponsor out of creating a figure or

19   not for Dr. Nissen, but -- excuse me. I did include silent

20   and MI. The time to silent MI was an estimated time and

21   maybe the sponsor can talk about that a little bit more,

22   but the risk of MI was not statistically significant for

23   either doses of dabigatran relative to warfarin. The

24   number events were very low and the annual rate, as already

1 discussed, was .7 percent for each dabigatran arm

2 indicating that there was no dose response.

3 The annual event rate in the warfarin arm was .5

4 percent. This slide shows the imbalance in MI. And if you

5 take a look at the MI on drug, there's an imbalance on

6 drug, 56, 59 and 46 in each treatment arm respectively.

7 This imbalance persisted off drug, 13, 10 and eight at less

8 than six days off drug. At less than 30 days off drug it

9 was 15, 13 and 12. I think these numbers are too small to

10 come up with any conclusions about the risk of MI. What is

11 interesting is that more than 30 days off drug, which is

12 highly unlikely to be attributable to drug, the difference

13 is still apparent, 15, seven and eight.

14 So my assessment of MI, I could not find a clear

15 difference in baseline characteristics between the

16 treatment groups that might explain the imbalance in MIs.

17 Subjects were reasonably similar with respect to

18 hypertension, diabetes, coronary artery disease, prior MI,

19 age, total cholesterol and concomitant medications. MACE

20 event rate did not raise concerns. The annual event rate

21 was either lower or equal to the event rate with warfarin.

22 The risk relative to warfarin was not statistically

23 significant. If this is a real drug-related adverse event

24 then the trend shows that treating 1,000 subjects with

1 dabigatran for one year will cause two excess MIs compared

2 to treating with warfarin. I believe that the possible

3 risk of MIs should be weighed with the proven benefits of

4 stroke reduction.

5   DR. KRUDYS: Good morning, I'm Kevin Krudys. I'm

6 going to speak a little about exposure response analysis of

7 dabigatran in the RE-LY study. So these are the relevant

8 questions for the committee. You can see they're all

9 related to dose selection or dose response relationships in

10 the RE-LY study. More specifically, I'll focus on two key

11 points. First, the need to -- the possible need to study

12 higher dose of dabigatran based on exposure response

13 analysis, and second, I'll touch upon the need for lower

14 dose for patients who are older.

15   So first I want to step back and talk a little

16 bit about the value of doing this exposure-response

17 analysis. So by exposure I mean the concentration of the

18 drug and by response I mean the outcome. It could be

19 either safety or effectiveness. So fundamentally we know

20 that the concentration of the drug is what is driving the

21 effect. So it's important to look at this in clinical

22 trials. Second, as we know, the relationship between

23 concentration and response has been used to contribute to

24 the evidence of effectiveness in many studies.

1   So the idea behind this exposure-response

2 analysis is that if you give a fixed dose or two fixed

3 doses, as we gave in this trial, what you see is a range of

4 concentration values or exposure values. And if you take

5 those concentration values, what you can do is you could

6 explore different doses or try to find a -- best doses in

7 general or in special populations.

8   So for our exposure-response analysis we used

9 study-state of dabigatran concentrations obtained at the

10 month 1 visit in over 8,000 subjects receiving either the

11 110- or 150-milligram dose. So we pulled the data from

12 both treatment arms. For a marker of response we chose the

13 time to first event while patient was on study medication.

14 The analysis was time to event, one which accounted for

15 concentrations or exposure plus other relevant risk

16 factors, including medical history and patient

17 characteristics. For our marker of effectiveness we chose

18 ischemic stroke because that was the -- a major driver of

19 the primary endpoint.

20   For safety we chose the time to event for life-

21 threatening bleed because that was chosen as a more severe

22 marker of bleeding than major bleed, which is more on par

23 with ischemic stroke. So the motivation for this analysis

24 is shown here on this slide. So we see here is, for stroke

1   and SEE and life-threatening bleed are the hazard ratios

2   for the 110 dose and the 150 dose, where to the left of the

3   line favors dabigatran. So we saw for both stroke and

4   life-threatening bleed is a strong dose response, whereas

5   you go from the 110 dose to the 150 dose we see a reduction

6   in stroke and an increase in life-threatening bleeds.

7   And it's a bit surprising how we saw this steep

8   relationship when you consider that the 110 dose is pretty

9   close to the 150 milligram dose. So the 150 dose is a 40

10 percent increase over the 110 dose. So that raised the

11 question to us as to whether it's possible if you give the

12 higher dose, we see even a further reduction in stroke with

13 an acceptable level of life-threatening bleeds. So that

14 was the motivation for exploring this exposure-response

15 analysis.

16   So again, we had these two doses and a wide range

17 of concentration so we were able to establish exposure-

18 response relationship for ischemic stroke, which I show on

19 this slide here. So on the Y axis is the probability of

20 ischemic stoke per year. On the X axis is dabigatran

21 concentration. The solid line I show you the population

22 mean of relationship between probability of stroke and

23 concentration with a few broken lines showing a 95 percent

24 confidence interval. I also show two horizontal lines.

1   These represent the 10 to 90 percentile of concentrations

2   for both the 150 arm and the 110 arm. So two things that I

3   can note from these two vertical lines are, we see first

4   that there's a wide range of concentrations for both doses,

5   and second, there's substantial overlap between the two

6   doses. And again, this relationship, the solid line you

7   can count some other factors including age, weight, history

8   of stroke and diabetes. So we see is a higher

9   concentration as to probability of ischemic stroke is

10 decreasing, which is what we would expect.

11   Also, at the low concentrations the curve is

12 steeper than at higher concentrations where it seems to

13 flatten out a little bit more. So second, we looked at the

14 exposure-response analysis for probability of life-

15 threatening bleed versus concentration, which is shown

16 here. So now on the Y axis we have the probability of

17 life-threatening bleed per year and concentration again on

18 the X axis. The solid line again shows the population

19 mean, which was significant, and included other risk

20 factors including age, sex, history of stroke or TIA and

21 CAD. So again, as expected at higher concentrations, we

22 saw an increase in the probability of life-threatening

23 bleeds and throughout the entire course of concentrations

24 observed in the RE-LY trial.

1   So next up what we can do is combine these two

2   previous plots onto one, which I show here. So this

3   morning we saw a pretty similar plot from the sponsor

4   showing probability of events versus warfarin. So here I

5   show a similar plot for dabigatran. On the Y axis is the

6   probability of an event shown in percent. And over here I

7   have -- the blue line is for ischemic stroke and the red

8   broken line is for life-threatening bleed. So I stuck the

9   two previous plots and put them onto one.

10   So there are a few things I want to point out on

11   this plot. First, we can look at what happens for the 110-

12   milligram dose. This is for a patient at the mean

13   concentration shown by this solid line. So you can see

14   where this solid line will intersect with the probability

15   of life-threatening bleed and ischemic stroke.

16   Second, I show that the mean concentration for

17   the 150-milligram dose by the solid line here. It's pretty

18   close to the 110-milligram dose and we see how it

19   intersects with the two lines, the blue and red line. So

20   now what we can do is think about what would happen at

21   higher doses. We can explore what might happen at say,

22   220-milligram dose. So it's shown here. So the 220-

23   milligram dose is two times the 110 milligram dose. So we

24   expect the concentrations in this group to be two times

1   that of the 110-milligram dose. That's shown here by this

2   solid line. So we can project with this curve what we

3   expect might happen at higher doses. So, for example,

4   relative to the 150-milligram dose, we can expect about --

5   an increase in life-threatening bleeds of about 36 percent

6   and a decrease in ischemic stroke probability of about 8

7   percent. Again, these are in certain numbers, but we still

8   get an idea of what might happen at these higher doses.

9   Next we can extrapolate further to say what would

10 happen at a 300-milligram dose shown here by this solid

11 line, which is two times that of the 150-milligram dose.

12 Again, this is mean concentration that we expect at that

13 dose. So relative to the 150-milligram dose we can expect

14 about a 76 percent increase in life-threatening bleeds

15 compared to 150 and a decrease probability of 15 percent in

16 ischemic strokes. So now it's important to note that the

17 rate of bleeding is increasing faster than the rate of

18 stroke is decreasing. But the value of higher doses

19 depends on how the person would weigh bleeds versus

20 strokes. And we'll talk about that more in the next

21 presentation.

22   Next I want to switch gears and say a few words

23 about the need for the lower dose in older patients. Here

24 on the slide I show forest plots for the impact of age on

1 benefit risk. Where now I show on the left for stroke and

2 SEE and here I switched now to major bleed, which was

3 described earlier and which was a primary safety event in

4 the trial, so imputed major bleeds. First I show only that

5 for the 150-milligram dose broken up by age groups, so less

6 than 65, 65 to 75 and greater than 75. So I think that you

7 can see as you increase age the hazard ratio is increasing

8 for major bleed for the 150 milligram dose.

9   Next, if I superimpose the 110-milligram dose

10 group here, these are shown by the solid lines. So two

11 things you can observe are that for stroke we see -- for

12 the higher dose, 150, we see a benefit for all three age

13 groups. And for major bleed it's pretty similar throughout

14 the three age groups. I want to focus in on the group

15 that's greater than 75 years of age, shown in the red boxes

16 here. And to the right I show the event rate for the two

17 doses.

18   So we see for stroke, we see for the 110-

19 milligram arm there was an event rate in this population of

20 1.89 percent per year, which decreased to 1.43 percent per

21 year in the higher dose, which corresponds to about 25

22 percent decrease going from the 110- to the 150-dose. And

23 we also see for major bleed they're pretty similar, but for

24 the 150-milligram dose there is a higher -- hazard ratio is

higher. And we look at the event rates we see that the 110-milligram dose, the event rate per year was 4.44 percent, which increased to 5.12 percent in the 150-milligram dose, which corresponds to about a 15 percent increase in bleeding.

But we can't think about patient's age by itself because it's known that older patients tend to have compromised renal function. So here I show on this plot on the Y axis dabigatran concentrations versus creatinine clearance and the dots correspond to the mean concentrations for four different renal function categories. So what we see is as you decrease creatinine clearance, the concentration is increasing of dabigatran. So going from patients with normal renal function to moderate impairment we see about an increase of two fold, which is bigger than the change of the two doses, which is about 40 percent.

Next we can look at a similar plot for renal function cut into three categories again. On the left by creatinine clearance, here we see again stroke on the left, a major bleed on the right. So I start again showing the 150-milligram dose and skip ahead to the 110-dose as well, which is shown in the solid lines.

And here I want to focus in on those patients

1   with the poorest renal function. So what we see is, for

2   stroke, a hazard ratio is clearly better for the 150-

3   milligram arm, whereas for major bleeding we see they're

4   fairly consistent in that classification of renal function.

5   So in conclusion, higher dabigatran

6   concentrations result in lower probability of ischemic

7   stroke. Again, that's expected as well as higher

8   concentrations resulting in higher probability of life-

9   threatening bleed. But the value of higher doses or any

10 dose really depends on how one weighs bleeding events

11 versus strokes. Lastly, a lower dose of 110 in older

12 patients could compromise the effectiveness, without an

13 obvious advantage for major bleed.

14   DR. BEASLEY: Hi. I will now be presenting the

15 net benefit analyses that were conducted by both Dr.

16 Thompson and myself.

17   First, I just wanted to present a very simplified

18 overview of the Summary of Efficacy and Safety relative to

19 warfarin and RE-LY. There was a dose response demonstrated

20 on stroke and systemic embolic events and on major

21 bleeding. For strokes and systemic embolic events,

22 dabigatran 110 was not inferior to warfarin; dabigatran 150

23 was statistically superior to warfarin. On major bleeding,

24 dabigatran 110 was less than warfarin; dabigatran 150 was

1 no different than warfarin.

2 This slide explains the exploratory net benefit

3 analysis that we conducted. First, I want to say that the

4 analyses are problematic because a method is needed to

5 adjust for the clinical import of events. However, we are

6 stuck having to do something. The reasons for the analyses

7 are because I think it's important to understand the

8 relationship between risk and benefit on both the

9 regulatory decision level as well as in clinical practice.

10 This was our attempt to bring together safety and efficacy

11 findings to support a conclusion about the relative benefit

12 of each dose.

13 The weights given to events is important for

14 development programs for stroke prevention in general,

15 trying to decide which dose to carry forward into Phase 3

16 and, in this particular case, trying to decide which dose

17 or doses to approve. We do not believe, nor are we

18 endorsing, that these types of composite endpoints replace

19 the usual primary or secondary endpoints in stroke

20 prevention programs.

21 Okay, this slide shows the net benefit analyses

22 of various strokes and bleeds that we combined. This was a

23 time to first event analysis, and this shows the various

24 composites that we combined, ICH or stroke/SEE, GUSTO

1   severe bleeding or disabling stroke defined as an initial

2   rank and score of greater than or equal to 3, or a fatal

3   stroke; life-threatening bleed or stroke/SEE; and major

4   bleed or stroke/SEE. The analysis of major

5   bleed/stroke/SEE was primarily driven by the major bleeds

6   as there were more than double the number of major bleeds

7   as there were strokes in RE-LY.

8   This net benefit analyses, equally weighting

9   bleed with stroke, does not strongly favor one dose. What

10 it does seem to show is that the more serious bleeding,

11 such as ICH, there seems to be a benefit of the dabigatran

12 150 dose over dabigatran 110. But as you move to less

13 serious forms, less serious definitions of bleed, the

14 benefit of dabigatran 150 over 110 is less apparent. The

15 annual rate of these various composites are either equal to

16 or less on dabigatran 150 compared to dabigatran 110.

17   Okay, here's another way to look at the data.

18 This table shows the annual event rates for various

19 components of the composites that we looked at. If you

20 take, for example, life-threatening bleed, the annual event

21 rate is 1.2 percent on dabigatran 110. As you move to

22 dabigatran 150, the difference in percent per year is 0.3

23 percent.

24   Now let's take a look at stroke. The annual

1   event rate is 1.5 percent. As you move to dabigatran 150,

2   the reduction in stroke events is 0.4 percent. So the

3   reduction in stroke is greater than the increase in bleed.

4   Let's take a look at another bleed ICH. The

5   percent per year is 0.2 percent. As you move to dabigatran

6   150, the increase is 0.1 percent. If you look at disabling

7   stroke, the annual event rate is 0.9 percent. As you move

8   to dabigatran 150, the reduction is 0.3 percent. I know

9   these numbers are very small, but the data show that the

10   reduction in stroke is greater than the increase in bleeds,

11   and for this reason we believe that the data favor the 150

12   dose.

13   The elderly are at increased risk for bleeding as

14   well as for stroke. This analysis was a subgroup analysis

15   of approximately one-third of the subjects in RE-LY. The

16   elderly was defined as those greater than or equal to 75

17   years old.

18   These are the same composites that I discussed

19   earlier and these analyses show basically a similar pattern

20   as the overall analysis except that there are wider

21   confidence intervals. The rate of ICH or stroke or SEE was

22   lower on dabigatran 150 compared to dabigatran 110.

23   However, the rate of major bleed/stroke/SEE, again this is

24   driven by major bleeds, was higher on dabigatran 150

1 compared to dabigatran 110. Because of this analysis, we

2 do not believe, or we do not think that there is a clear

3 benefit of using dabigatran 110 in this age population.

4 The conclusions on the net benefit analyses are

5 that the annual rates of combined events tended to be lower

6 on dabigatran 150. The annual rates of individual events

7 suggested that there is a greater reduction in strokes

8 compared to the increase in bleeds as you move from the

9 lower dose to the higher dose.

10 I believe that the appropriate balance between

11 reduction in stroke risk and increase in bleeding risk

12 depends on the clinical import of each, and while the

13 elderly are at higher risk for bleeding they are also at

14 higher risk for stroke, and these analyses suggest that

15 there is no clear advantage for dabigatran 110.

16 DR. LINCOFF: So now we have a period of about 30

17 to 35 minutes for questions to the FDA, and we'll start

18 with Dr. McGuire and Dr. Kaul.

19 DR. MCGUIRE: Okay, a question for either Drs.

20 Thompson or Beasley. For the TTR stratified analyses, what

21 is the comparative group? Are you using all DE-treated

22 patients for each analysis or are you randomly matching

23 patients?

24 DR. THOMPSON: I'll speak for maybe efficacy --

1 oh, hi. Aliza Thompson.   I'll speak for maybe more the

2 efficacy analyses, and then Nhi may also want to make some

3 comments about safety.

4   I think we both ran the analyses both ways. And

5 as a whole, regardless of how you ran them, they sort of

6 came out the same way. So by both ways, I mean some of the

7 analyses, such as the one I presented, were center-level

8 analyses where you stratify those centers achieving higher

9 versus lesser levels of control, and then you look at the

10 -- you define your dabigatran population at that center and

11 also your warfarin population at that center.

12   We also did analyses where we just cut it and

13 compared to the population as a whole. We used different

14 cut points -- some pre-specified, like I think the 65 that

15 Nhi used, and some just based on the median or quartile.

16   So we did a lot of different ways, but I think

17 overall you get pretty much the same results.

18   DR. MCGUIRE: Okay, and just a quick follow-up.

19 Do you ever do propensity score, propensity-adjusted

20 analysis for --

21   DR. THOMPSON: I wish I were so smart. I don't

22 know. No, I've never done one.

23   DR. LINCOFF: Dr. Kaul.

1   DR. KAUL: Yes, I have two or three questions.

2   Slide 9 of Dr. Krudys's presentation, the benefit/risk with

3   concentration, a couple of clarifying questions. Did life-

4   threatening bleed include hemorrhagic strokes?

5   DR. KRUDYS: Me? Yes, it did.

6   DR. KAUL: Yes, and I was kind of somewhat

7   intrigued by your statement that since ischemic stroke was

8   the driver of benefit. My understanding of the data is the

9   otherwise -- that is, the hemorrhagic stroke that drives

10   the benefit. So that doesn't impact the outcome here.

11   The question I have for you is that for the 110-

12   mg dabigatran dose, there was a 0.2 percent per year stroke

13   benefit, which in my opinion was offset by a 0.2 increase

14   in MI. Why did you not construct a similar relationship

15   with the MI?

16   DR. KRUDYS: Probably because there are so few

17   events that it's hard to construct this kind of

18   relationship for such a few number of events for MI. For

19   stroke, we saw about 150 per arm, or 100 to 150 per the 110

20   and 150 arm.

21   DR. KAUL: See, in my opinion, the treatment

22   benefit of 110 mg on stroke would be washed out by the MI,

23   and I think it would be interesting to see if you had that

24   information.

1   DR. KRUDYS: There are just so few to identify

2   that relationship in this population.

3   DR. KAUL: Yes, I understand that.

4   The other question, if I can ask, is for Dr.

5   Thompson. I agree with your comment about the

6   ascertainment bias being still a potential problem, and

7   some of it may be partially addressed, although not to my

8   satisfaction, with the on-treatment or as-treated analysis.

9   I'm interested in the impact of ascertainment,

10 direct impact of ascertainment on the outcomes, and there

11 are two in my mind which are of concern to me, and both of

12 them are unavoidable ascertainment biases.

13   And let me re-ask the question to you that I

14 asked to the sponsor earlier. Have you done sensitivity

15 analyses where you look at the outcomes with or without

16 treatment, discontinuation due to GI-adverse events, with

17 or without interruption -- I know the frequency of

18 interruption was quite high -- and with or without both?

19   The related question to it is is there a

20 clustering of events around the time of discontinuation or

21 around the time of interruption?

22   DR. THOMPSON: Yes. So I have a backup slide,

23 but unfortunately I don't remember the number. So maybe

24 I'll go peek and see what number it is, and then we'll show

1   you.

2   DR. LINCOFF: In the meantime, Dr. Krantz, go

3   ahead.

4   DR. KRANTZ: Just a quick follow-on on this

5   ascertainment issue for Aliza, if she has the data. Was

6   there a differential amount of contact with and without the

7   necessary measurements that you would have for INR

8   checking, just so we get a sense of the number of patient

9   contacts we had beyond the study visits? So, in other

10   words, we had this new handout saying the last visit, but I

11   was wondering in aggregate were there more contacts with --

12   DR. THOMPSON: I'm sorry.

13   DR. KRANTZ: That's okay.

14   DR. THOMPSON: (Off microphone) be able to take

15   in multiple things at once, but I note that -- okay. So

16   maybe I'll answer the first question and then -- so first,

17   the disclaimers. I looked at efficacy. I didn't do any of

18   the safety analyses, so I can't directly address the

19   question that you asked about the GI bleeding events, but

20   just a few comments.

21   I think that the slide on permit discontinuation

22   of study medication, the reasons for that, highlighted that

23   there was a propensity to discontinue subjects in the

24   dabigatran arm if they were sick, or much more so than in

1 the warfarin arm. And my interpretation of that slide is

2 it makes me very wary to look at any analysis that censors

3 patients on the last day or shortly after they took study

4 medication. So this slide, it's one of the sponsor's

5 analyses, and it look at events in sort of the days

6 immediately after a subject discontinued the study

7 medication.

8   And I think a sense that you get from this, again

9 the numbers are very small, but that even in the immediate

10 days coming off study medication you're seeing slightly

11 more events. This slide is for stroke and SSE -- sorry,

12 stroke and systemic embolism in the dabigatran arms

13 relative to the warfarin arms. And I think again this is

14 this bias or this greater propensity to discontinue

15 subjects in the dabigatran arm than the warfarin arm.

16   I'd also just like to highlight in this slide

17 that if you compare permanent reasons for study medication

18 versus temporary reasons, you're not seeing this imbalance,

19 which I think drives the point home even further.

20   If you slip to the next slide, this shows these

21 same data, but again for bleeding. And I think that again

22 my take is you're seeing this similar relationship. You're

23 seeing more events reported in the immediate period after

24 coming off dabigatran than warfarin, but you don't see it

1 so much with temporary stopping of medication, which again

2 is I think a bias in the trial. I don't know if "bias" is

3 the right word, but essentially that knowing what group

4 your subject was in influenced how you treated these

5 subjects.

6   There may have been more to your question. Was

7 there something else?

8   DR. KAUL: If I may, with your permission, the

9 reason why I think the MI and exposure concentration

10 relationship is important, if you look at case fatality

11 rate of strokes and bleeding in MI, strokes, I think there

12 were 97 fatal strokes out of a total of about 500, which

13 gives it about a case fatality rate of about 18, 20

14 percent, and if you look at bleeding, there were 2, 2.5-

15 fold greater number of bleeding, but there were the same

16 number in terms of absolute number. There were about 93

17 total bleeding, which gives it a case fatality rate of 7 to

18 8 percent.

19   With MI, there are about 30 fatal MIs, and that

20 gives you a case fatality rate of about 12 percent. And

21 what is also interesting is that in the dabigatran 110-mg

22 dose arm the case fatality rate was higher compared to

23 warfarin, 17 percent versus 12 percent. The numbers are

24 small, but the risk ratio is about 1.4, which makes me

1   believe that the MIs that are occurring in association with

2   dabigatran 110 may be more severe and more fatal MIs, and

3   that's why I think it's important to explore that

4   relationship.

5   DR. LINCOFF: Dr. Krantz, do you want to clarify

6   your question now that she's --

7   DR. KRANTZ: Sure, and we can always withhold it

8   to the sponsor later. I just was trying to get a sense of

9   how many contact points in aggregate were there within each

10   group, be it the dabigatran or the warfarin.

11   DR. THOMPSON: Just to clarify, you mean how many

12   clinic visits they were seen in person, in one versus the

13   other arm? I'm not quite sure. I don't know that I

14   understand your question exactly.

15   DR. KRANTZ: Clinic visits as well as even

16   contacts, for example, by phone -- so to really get a

17   sense, for example, were there three-fold more contact

18   points between the investigator team either at McMaster or

19   at the site PI with the patients, just to give the

20   committee a feel for that, that type of --

21   DR. THOMPSON: And I don't remember the exact

22   numbers off the top of my head, but I think that my

23   recollection was that the numbers were actually similar

24   across the treatment arms, but I don't remember the exact

1 numbers.

2   DR. TEMPLE: Are you asking about INR visits too?

3 I mean there are undoubtedly more of those.

4   DR. KRANTZ: I think to get a holistic

5 perspective that would be useful as well.

6   DR. THOMPSON: Well, the INR, remember INR was

7 only being measured in the warfarin arm. This was an open-

8 label study with respect to warfarin.

9   DR. KRANTZ: Of course.

10   DR. THOMPSON: So I don't -- I guess I don't know

11 how to answer or make comparisons with dabigatran versus

12 the warfarin arm in terms of INR measurements, but maybe

13 I'm not understanding what you're asking.

14   DR. KRANTZ: It's really more of a contextual

15 flavor of the data. Maybe there are more phone calls as

16 well. I just didn't know how many points of contact were

17 recorded within each of the arms, be it part of routine

18 process of care or other.

19   DR. THOMPSON: That, I don't know.

20   DR. TEMPLE: I think you're wondering whether the

21 INR visits might have led to more capture of events, even

22 though those were not clinical visits in the usual sense.

23   DR. KRANTZ: Correct.

1   DR. TEMPLE: I don't know the answer.

2   DR. THOMPSON: Yes, I don't know the answer too,

3 though I'd like to point out I think the sponsor pointed

4 out that some of these patients were actually having their

5 INR measured in sort of centers that were devoted to that,

6 and so I don't know how much of a connect there was from

7 that to the other. Essentially, the CRS sort of tracked

8 patients and each time they came in asked about systems of

9 stroke or bleeding and asked if they had a stroke, where

10 it's pretty specified time points.

11   DR. LINCOFF: Dr. Nissen.

12   DR. NISSEN: I understand your analysis about how

13 the differential discontinuation rate might bias the on-

14 treatment analysis. I'm concerned about how it might bias

15 the ITT analysis, and let me ask a question.

16   You know, clinicians are pretty smart, and there

17 may have been harbinger events, maybe minor bleeding, other

18 things, that caused them to discontinue the drug, that had

19 it continued the patient would have had a serious major

20 bleed. So I'm really worried that it not just biases the

21 on-treatment, but it biases the ITT analysis, and I wonder

22 what your reaction to that is.

23   DR. THOMPSON: Yes. Yes, I share the same

24 concern. I think if you think about, or maybe if we could

1   go back to a slide in my presentation where I show the

2   reasons for permit discontinuation, I don't know that.

3   Certainly, your concern that more patients who had a stroke

4   reported prematurely discontinuing their study medication.

5   But what you're particularly concerned about are

6   those TIAs and minor bleeding. And you sort of have to

7   ask, yes, and what happened to those people, how well were

8   they followed after that? So I agree with you.

9   DR. NISSEN: So what I'm getting at is somebody

10 comes in and they are getting a lot of bleeding when they

11 brush their teeth or whatever, and somebody says, okay, I'm

12 going to stop your study drug. If they had continued the

13 study drug, they would have had a hemorrhagic stroke. So

14 this advantage on hemorrhagic stroke may in fact be an

15 artifact of the differential discontinuation, to some

16 extent.

17   DR. LINCOFF: Mr. Simon.

18   MR. SIMON: The sponsor as well as FDA have

19 mentioned that the 110-mg dose is less bleeding and more

20 stroke, and the 150-mg is more bleeding and less stroke.

21 Is it fair to ask you to comment on what a 130-mg dose

22 would do?

23   (Laughter)

24   MR. SIMON: Or maybe it's better to ask the

1 sponsor later.

2 DR. KRUDYS: Somewhere between, I guess. That's

3 the best answer based on the plot I showed. You saw the

4 two lines for the 110 and 150, where we saw at the 110, I

5 think, stroke was higher than bleed; at the 150 it was the

6 opposite. And between there, you kind of interpolate and

7 say it would be even closer to about being the same.

8 DR. LINCOFF: Dr. Emerson.

9 DR. EMERSON: In this non-inferiority study, and

10 since we're doing a lot about how everything is comparing

11 to warfarin, is the FDA real comfortable with the quality

12 of care on the warfarin? We've talked about what the

13 average time in the therapeutic range, but what about

14 outliers and things along those lines; is this any problem?

15 DR. THOMPSON: I think it's really hard to know

16 how you define the adequacy of the anticoagulation arm in

17 any of these trials that are being done, which is why I

18 tried to show you a few different ways to benchmark it. I

19 compared it to rates in other studies. I spoke about time

20 in therapeutic range and then tried to give you a sense of

21 the exposure to warfarin and also the frequency of

22 monitoring.

23 I walked away from it after thinking about it for

24 a long time, thinking, well, it looked reasonable. But was

1 it optimal? No, I wasn't convinced of that.

2   But I can't -- I mean what I would have loved is

3 if I could have added everything up and given them a score,

4 and I just don't know how to do that.

5   DR. EMERSON: But in terms of how far they were

6 outside of the therapeutic range?

7   DR. THOMPSON: Well, I don't know exactly what

8 you mean by that. I mean once the patient is -- you know,

9 do you care if it's an INR of 5 or 12? I mean clearly this

10 sometimes happens to patients, and I don't think that there

11 can be this expectation that no patient in the study will

12 ever have an INR outside of that far out.

13   I think it's just what you hope is that they're

14 being very compulsive and that their goal is not just to

15 get around the range which you need to get so that you show

16 that you were adequate, but that if they could be really

17 compulsive the idea would be that I think that they could

18 do better. I think they're just sort of targeting what

19 they need to get at.

20   DR. LINCOFF: Dr. Temple, you had a comment?

21   DR. TEMPLE: Yes. I don't want to comment on

22 whether this was a very well done or a not so well done

23 job, but we've had discussions with companies about this

24 question. After all, part of the trouble with warfarin is

1 that it's not that easy to use, and that means a lot of

2 strokes, and the strokes and bleeds occur because optimal

3 use isn't so easy to attain, and we saw that in here. In

4 the clinics, it did very, very well. It seemed to be about

5 as good as the test drug. And the ones that did very

6 badly, that's where a lot of the stuff came.

7 So we've actually had proposals from companies to

8 compare really compulsive use of warfarin with less

9 compulsive. You know, let them do what they're going to do

10 versus training the hell out of them and using genetic

11 predictors and all that.

12 So I think it's an open question about which

13 constitutes an interesting advantage because reality

14 matters too, but that's probably for a different day.

15 DR. LINCOFF: Dr. Fox.

16 DR. FOX: Yes, this is more of, I guess, a

17 process question for the agency in support of investigators

18 and sponsors everywhere. It has to do with telephone

19 versus in-person follow-up. What's the basis really for

20 the agency to imply that telephone follow-up is somehow

21 unacceptably inferior to live and in-person follow-up, as

22 long as it triggers the access to the appropriate

23 supporting documentation that can support conclusive

24 adjudication, which I think was done here?

1   DR. THOMPSON: Sorry. I think the question was

2   maybe not necessarily directed at me, but I can just tell

3   you maybe one concern. I think that the nature which you

4   elicit when you get someone on the phone, or talk to a

5   relative on the phone, can be very different than what you

6   elicit when the patient is sitting in the office and you

7   have a chance to examine them and really talk to them. I'm

8   not saying that you should disregard information you get

9   via phone, but I think that the nature of the data is just

10 different. So that's why I think it's important to look at

11 these two different ways when you look at the amount of

12 missing data in the trial.

13   Specifically for this type of study, if you

14 remember, there were certainly effects of dabigatran,

15 beneficial effects, relative to warfarin on the strokes we

16 most care about, disabling strokes and also the fatal

17 strokes. A lot of the effect is also driven by strokes

18 which are not that symptomatic. And remember, another

19 method that was used in this protocol in an attempt to

20 identify additional events were TIAs that were sent for

21 adjudication to determine if they were strokes.

22   One concern I have is that you don't see a person

23 in the office, but you talk to them a year later. Do you

24 really get that history about the TIA or the stroke event

1   that was potentially very mild?

2   But again, it's not to say that calling someone

3   on the phone and capturing them that way is not a good

4   thing. It is, but I think the quality of the data is a

5   little a little different.

6   DR. FOX: Well, as long as you don't see a big

7   discrepancy between treatment arms, it would seem to be

8   acceptable.

9   DR. THOMPSON: You know, how you impute for

10   missing data is always a hard thing.

11   DR. FOX: Sure.

12   DR. THOMPSON: Do you just assume it's evenly

13   distributed, or do you take a worst case and assume all the

14   events happened in one arm? I don't know.

15   DR. FOX: I guess the plea here is that the costs

16   of doing these kinds of trials have risen so dramatically

17   that if we're to be able to continue to do them, and to do

18   bigger ones, we kind of have to get out of the analog age

19   and go into the digital age, if you know what I mean.

20   DR. LINCOFF: Before I go to -- oh, I'm sorry,

21   Dr. Temple.

22   DR. TEMPLE: Well, you know, telephones are good

23   for vital stats, but unless you've got it very well

1 structured and organized it may or may not be a good way to

2 find out about all the events of interest.

3   But look, there have been trials done by mail. A

4 Physicians' Health Study was done entirely by mail. I

5 filled it out. But people would ask you whether you

6 remembered as well as you should if you're not preparing to

7 go see somebody, whether in the course of sitting down at

8 your table and filling out a form it's just as good as

9 seeing somebody. So those are all good questions. But I

10 do think if you really were going to do a telephone follow-

11 up or an email follow-up or something like that, you'd have

12 it structured and tested and you'd do a whole lot of things

13 that you wouldn't do when it's a fallback.

14   DR. FOX: No, I completely agree. There actually

15 are a lot of modern tools that are coming into play in

16 reality today, like, for example, issuing every patient a

17 small handheld electronic device so that when they

18 experience some kind of an event they push a button and it

19 triggers telephone follow-up or internet follow-up, what

20 have you.

21   I guess that's my plea is for the agency to keep

22 an open mind about as long as you say the follow-up is

23 structured, it's consistent, it's comprehensive as

24 possible, then it can take the place of.

1   DR. TEMPLE: You have to correct those for age,

2   I'll bet.

3   DR. LINCOFF: Before we go to another round from

4   some of the ones who have already a chance, I actually have

5   a few questions myself for Dr. Thompson regarding the

6   efficacy.

7   In your slide on interpreting the efficacy

8   findings relative to warfarin, you have factors to

9   consider, and you have a couple there that you really

10   haven't -- I mean it sort of casts aspersion without

11   discussing. So one of them was the late finalization of

12   the statistical analysis plan. So do you have any

13   indication that in doing so the sponsors, or whoever

14   finalized this, did so in light of knowing some of the

15   results? I realize this was an unblinded trial, but if

16   their codes were closed.

17   And moreover, do you have from prior experience

18   evidence that a plan that was done from prior trials, that

19   plans that were done late in the game had somehow been

20   influenced or were less reliable?

21   The other issue -- well, let me have you do that.

22   DR. THOMPSON: I think it's -- you know, I've

23   been at the agency now three years. Though I don't

24   necessarily, or I can't necessarily give you set examples,

1 what I would say as a general sense is that you just get a

2 little bit uneasy when things aren't finalized until later.

3 You sort of, not saying that someone knew something here

4 and changed something, but there is a sense of who knew

5 what and when.

6   And I think really the safest approach in

7 clinical trials is to finalize the statistical analysis

8 plan early, and I think the question is always, well, why

9 don't they? I mean, you know the design of the trial. You

10 know the endpoints you're looking at. Why don't you figure

11 out what you're going to censor at the start of the trial?

12 Why do you need to wait until all the study data have been

13 amassed?

14   DR. LINCOFF: So for this particular trial,

15 though, you don't have any indication that there was?

16   DR. THOMPSON: I would say that no, it's nothing.

17 No. I don't want to cast aspersions. It's more a general

18 concept. I think that it raises questions in general, in

19 all studies.

20   DR. LINCOFF: Okay.

21   DR. THOMPSON: We'd like to see it finalized

22 early.

23   DR. LINCOFF: Then the second thing is in your

24 conclusions your final point is superiority over warfarin

1 was not established, and you've certainly brought up the

2 various points, but yet you haven't really specifically

3 said why you made that conclusion, given that there was a

4 nominal superiority for the higher dose arm.

5   DR. THOMPSON: I think a lot of it does. It

6 relates to the adequacy of the anticoagulation in the

7 warfarin arm and what should be the standard. I think

8 there was reasonable control achieved, but not clearly

9 optimal control achieved.

10   I also think it deals with issues related to the

11 open label nature of the study and concern that that sort

12 of inflates the findings relative to warfarin.

13   DR. LINCOFF: So then as a reviewer, unless

14 you're going to make the statement that an open-label study

15 can never support superiority, is there a level of a p-

16 value or a level of superiority that you would consider

17 sufficient?

18   DR. THOMPSON: Yes, incredibly subjective, and I

19 don't know the answer to that question. My general sense

20 of the trial itself was that things were done reasonably

21 and adequately to establish efficacy, but just not there to

22 establish superiority, but I can't give you a single rule

23 or a single p-value.

24   DR. LINCOFF: Dr. Emerson, unless you have

1 something that's related to that.

2   DR. EMERSON: It's related to that.

3   DR. LINCOFF: Okay.

4   DR. EMERSON: To what extent is this the lack of

5 a confirmatory study that's making --

6   DR. THOMPSON: Thank you for bringing that up

7 too. I think that that also contributes as well.

8 Certainly, those who are in the field of atrial

9 fibrillation are very aware of the supportive trials where

10 one trial showed the efficacy of their drug, ximelagatran,

11 and the other trial failed to establish it, and what to

12 make of this discrepant experience. One was an open-label

13 study, one was blinded. I think the key message is that

14 when you don't have replication, that also adds a measure

15 of uncertainty.

16   DR. LINCOFF: All right. So we have --

17   DR. TEMPLE: This will be something I'm sure the

18 committee will want to discuss further. We have certainly

19 said that a p-value of in the neighborhood of 0.001 can

20 sometimes be the functional equivalent of a 2-study

21 finding. We've said that repeatedly, especially when

22 repetition is difficult.

23   I wanted to ask Aliza, though, I think some of

1 her reservations were about whether it's superior if you

2 use if you use Coumadin, right? Isn't that --

3   DR. THOMPSON: Yes, I think that that was --

4   DR. TEMPLE: And that's a philosophical question

5 that the committee needs to discuss.

6   DR. LINCOFF: All right. So we have 10 minutes

7 left, and I have on the list Drs. McGuire, Kaul, Neaton and

8 Nissen. So we'll limit to those four, and then if there

9 are any left afterward we can do those afterward.

10   And realize we have 10 minutes left. So if

11 they're going to be real long, maybe do them afterward.

12   So, Dr. McGuire.

13   DR. MCGUIRE: Okay. I have first a very quick.

14 In the net clinical benefit analysis, Dr. Beasley, have you

15 run these analyses with MI included, or could you, or has

16 the sponsor?

17   DR. BEASLEY: The quick answer is no.

18   DR. MCGUIRE: Okay. Then, Dr. Krudys, I have

19 some questions about your dose response relationships. I'm

20 struck by what my eyeball tells me is about a five-fold

21 variability within 90 percent confidence of the 150-dose

22 with regards to the steady state concentration achieved.

23 That seems awfully big to me in a drug that we're proposing

1 to use without any therapeutic monitoring. So can you put

2 this in the context of other anti-thrombotic therapies? Is

3 this a usual variability inter-patient, and also does this

4 speak toward possibly considering therapeutic monitoring of

5 some sort?

6   DR. KRUDYS: As relative to other drugs, I'm not

7 sure myself, but I can say for this drug there are certain

8 factors. Renal function, like I said, could change

9 concentrations two-fold. Drug interactions, we saw, could

10 change it 20 to 40 percent. So there are some factors that

11 will change concentrations quite a bit, but we didn't see a

12 need for a monitoring the concentration because we saw in a

13 study, favorable results in all subgroups. So it didn't

14 seem like we found something strong that we needed to

15 monitor concentrations and adjust in a certain subset of

16 the population.

17   DR. LINCOFF: Do you have a comment? To the

18 microphone, please, and please identify.

19   DR. MADABUSHI: This is Raj Madabushi. I'm a

20 team leader in the Office of Clinical Pharmacology.

21   One of the other drugs which we can compare is

22 warfarin, and there is a big distinction one has to make

23 here. Between-subject variability is one aspect, and

24 intra-subject variability is one aspect. And the reason

1 for us to have this monitoring with warfarin is the huge

2 intra-subject variability. It acts on two levels, on the

3 PD level, where you take green, leafy vegetables that are

4 going to change your INR response as well as it is a

5 cytosine-9 pathway, disposed, and it has polymorphisms.

6   Compared to that, if we compare dabigatran, it

7 has a high between-subject variability because this drug is

8 very poorly available and one can expect small changes of

9 low variability drugs to result in huge variability.

10 However, it has a predictable disposition. Once it gets

11 into the body, 85 percent of the drug is eliminated through

12 the renal route.

13   So that gives some reasonable comfort that the

14 between-subject variability is not as huge, and that gives

15 us comfort in not trying to go for a monitoring, what you

16 would be thinking.

17   DR. MCGUIRE: I think you've just made a very

18 cogent argument to monitor. If you have a predictor for an

19 individual subject, a dose has a wide variability, but

20 within that subject a constant one, why not monitor single

21 time at steady state to make sure you have the dose right

22 in that one individual?

23   DR. MADABUSHI: If one were to know what is an

24 appropriate cut point, then one could actually derive a

1 dose for that particular subgroup or for that particular

2 type of patient, and forget about it. So that would be

3 possible if we knew the appropriate cut point of something,

4 and then we can. Based on the baseline factors which may

5 affect his exposure, or her exposure, one could have done

6 that.

7   DR. MCGUIRE: Yes.

8   DR. LINCOFF: Dr. Kaul.

9   DR. KAUL: Yes, I have a question for Dr.

10 Thompson. You mentioned that the results with regards to

11 dabigatran 110 mg were not very robust, non-inferiority

12 results, and I assume that in reference to a margin of 1.46

13 or 1.38. So the question I have for you is that do you

14 think that the margin that was chosen for this study was,

15 in your clinical judgment, appropriate?

16   I mean the active clinical studies upon which

17 this margin is based were done almost two decades ago, and

18 since then the control of risk factors that can contribute

19 to incident stroke have, I would argue, been substantially

20 improved. And it's reasonable to assume that the act of

21 controlled treatment effect is likely not the same,

22 probably reduced. I understand that this is an infrequent

23 endpoint, and that would impact on the sample size, but

24 feasibility is not the only peak criteria to do a clinical

1 trial.

2   Do you think that a non-inferiority margin of

3 1.38 or 1.46 was clinically acceptable?

4   DR. THOMPSON: So, two comments. One, I just

5 want to correct something that I may have given the

6 impression of earlier, and I just want to clarify a little

7 bit. In talking about the robustness of the findings to

8 missing data, I think in terms of showing the non-

9 inferiority of the 150-dose and needed an additional 90

10 findings, 90 events, that it would be unlikely to reverse

11 the findings. Sort of, it's up to you to think about

12 whether or not they could have gotten another 30 or 40

13 events that would have reversed the superiority of the 150

14 and the non-inferiority of the 110. Some of you may

15 consider that the findings will probably be robust to that

16 as well.

17   But in terms of your next comment, which about

18 the constancy assumption, I very much agree with you that

19 times today are different from when these historical trials

20 were done. If you compare recent trials to the historical

21 trials, you'll note that as a whole we're studying sicker

22 patients. On the other hand, there have been tremendous

23 advances in therapies that treat these concomitant risk

24 factors, and in the end who knows exactly what the risk

1 reduction you'd expect to get with warfarin.

2   As I said in my review, I think nonetheless there

3 is likely to be substantial risk reduction, but I think it

4 does pose a challenge to the design of these non-

5 inferiority studies in defining the margin.

6   In terms of whether or not 50 percent is

7 acceptable, I don't know. I think this is debated

8 endlessly. I'm actually a nephrologist, and so I don't

9 know if I can. I may even know less than the rest of you,

10 but I think it's a hard issue.

11   DR. LINCOFF: Dr. Temple, you had a comment.

12   DR. TEMPLE: I think Aliza's last point is

13 critical. I don't think the constancy assumption is the

14 biggest trouble here. It's how to chose M2, the non-

15 inferiority margin you're going to rule out. We have a

16 long habit of using the neighborhood of 50 percent, but

17 when the effect is huge you could conceivably be more

18 demanding.

19   In infectious disease, we're typically more

20 demanding. We don't allow you to use 50 percent of the

21 effect. So that's a good question, but you do get sample

22 sizes that go through the roof.

23   DR. LINCOFF: Is it related?

1   DR. KAUL: Yes, I just wanted to respond. My

2   statement was in relationship to 110 mg of dabigatran. I'm

3   trying to convince myself whether 110 has a desirable

4   benefit/risk and so far I'm unable to do so.

5   DR. LINCOFF: Dr. Neaton.

6   DR. NEATON: I have a question about the

7   management of patients in the different groups when they

8   went off therapy, and I don't know whether Dr. Thompson can

9   look to this. I seem to recall reading something in the

10   briefing report. So dabigatran, when people discontinued,

11   did most of them go to warfarin? And when you discontinued

12   warfarin, was it an aspirin or what were the alternative

13   treatments that were used?

14   DR. THOMPSON: Yes, it's a little bit hard to

15   answer this question, and I may ask the sponsor if they

16   could chime in. When I looked at -- I wrote this down on

17   my folder. When I looked at what happened when patients

18   went off therapy, what the case report form captured was

19   not the specific agent that they went off to, but I think

20   it captured just whether or not they went off to an anti-

21   thrombotic agent. I think that that was the phrasing of

22   it. And when I looked at this, it was a little bit

23   confusing to me because I was trying to figure out what

24   exactly that would be in the warfarin arm. Right?

1   Nonetheless, when you look at this, my

2   recollection is that overall -- and the problem with this

3   statistic, I think, is it's not giving you the rights for

4   just those who were reported to have prematurely

5   discontinued, but overall. Clearly, it's a higher percent

6   in the dabigatran and the warfarin treatment arms. And I

7   can quickly look at what I wrote down in my notes, unless

8   the sponsor wants to chime in and give us that number.

9   DR. NEATON: I'm just trying to get at maybe

10   another cruder way of answering it. Is it fair to say that

11   dabigatran had --

12   DR. THOMPSON: They went on to warfarin.

13   DR. NEATON: -- an alternative?

14   DR. THOMPSON: Yes, exactly.

15   DR. NEATON: That the warfarin group did not

16   have.

17   DR. THOMPSON: That a significant number went on

18   to, if not warfarin, some Vitamin K antagonist -- yes, a

19   fair statement.

20   DR. LINCOFF: And that's something we can get

21   after the lunch break if we want details of that.

22   DR. NEATON: This is a fundamental point to a lot

23   of the questions that are being asked because we're

1 comparing here a strategy of using this new drug versus the

2 control, and I think you have to consider the whole

3 strategy, like the INR data that we've been looking at. I

4 mean, Bob, you had right. I look at that and say, well,

5 gee, this is just confirmation of what we've known for a

6 long time, that warfarin is a hard drug to use. So it's

7 kind of fundamental, I think, to understand what we're

8 comparing here.

9   DR. LINCOFF: Dr. Nissen.

10   DR. NISSEN: I have a comment and a question. A

11 comment is for my friend, Jonathan Fox. You know, I have

12 this clinic, and I wish I didn't have to go over to the

13 clinic and see all those patients face to face, and I could

14 just kind of email back and forth. You know.

15   (Laughter)

16   DR. NISSEN: But let me tell you that you can't

17 substitute with a phone call. I will tell you that I can't

18 tell you how many times you ask a patient, do you have such

19 and such a symptom and they say, no. And their daughter is

20 there and their daughter says now wait a minute, Grandpa,

21 you know, or whatever, you had this problem or that problem

22 or whatever. These are older people, and I think the

23 reliability of telephone follow-up in this setting is not

24 perfect. Is it better than nothing? Absolutely, but it's

1 not perfect.

2 Now the question is, for Dr. Thompson, to what

3 extent is your conclusion about the superiority claim

4 related to the overall benefit as measured by MACE? I

5 noticed that while there was a p-value of less than 0.01

6 for superiority for the pre-specified endpoint, for MACE,

7 it was 0.02, and that seems that's a long way from Dr.

8 Temple's 0.0125.

9 Did that factor into your thinking, the fact that

10 when you look at MACE there really isn't unequivocal,

11 highly statistically significant superiority?

12 DR. THOMPSON: I think one difficulty here in

13 terms of MACE and MI is whether or not you factor it into

14 your analysis depends upon whether or not you think the

15 finding is real or not. To be honest, at this point, it's

16 not clear to me what this finding is. So it actually

17 didn't play a major role when I looked at net benefit, or

18 not net benefit but essentially whether or not the

19 superiority claim should be granted

20 DR. LINCOFF: So that's all the time we have now

21 for questions. So I'd like to remind the sponsor that

22 unless somebody wants to say that they're no longer

23 interested, some of the open-ended issues that can be

24 addressed afterward include the Kaplan-Meier curves that

1   Dr. Nissen requested, the death and disabling stroke data,

2   the loss to follow-up clarification that Dr. Neaton had

3   asked for. And, Dr. Kaul, you had some specific requests

4   regarding discontinuation or outcomes after discontinuation

5   for gastrointestinal bleed, or do you think is that still

6   active?

7   DR. KAUL: Yes, I'd like to see the data. I'd

8   like to see the data stratified according to those who have

9   discontinued due to GI, those that were interrupted or both

10   of them. I'd just like to see and convince myself.

11   DR. LINCOFF: Then also, maybe a clarification of

12   what therapies, whatever data you have, happened after

13   discontinuation of study drug, and then so that would be an

14   opportunity for the sponsor to make some comments.

15   So we'll now break for lunch. We will reconvene

16   again in this room in one hour from now, at 1:10. Please

17   take any personal belongings you may want with you at this

18   time. Committee members, please remember that there should

19   be no discussion of the meeting during lunch amongst

20   yourselves, with the press or any member of the audience.

21   Thank you.

22   (Whereupon, at 12:11 p.m., a luncheon recess was

23   taken.)

24

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

1   A F T E R N O O N   S E S S I O N

2   (1:12 p.m.)

3   DR. LINCOFF: All right, welcome back. We

4   actually have no registered participants for the open

5   public hearing, so we'll close that part of the agenda and

6   move on straight to the Committee discussion now.

7   We'll start with responses from the sponsors, if

8   they'd like, to some of the questions that were raised. As

9   well, I had noticed at some points along in the discussion

10 there seemed to be some points that the sponsors or the

11 representatives had wanted to make as well. So this would

12 be an opportunity to do that.

13   DR. REILLY: Paul Reilly, BI. Our two other lead

14 speakers are in the back room, putting the slides on a

15 stick.

16   DR. LINCOFF: All right. Well, pending that

17 then, we'll have a period of committee discussion and then

18 we'll go into actually discussing in the context of the

19 questions which you've received. But first if there are

20 any of the members who want to have specific points,

21 independent of the questions?

22   Dr. Krantz.

23   DR. KRANTZ: This is Mori Krantz. I just had a

1 quick question. Maybe this is for the sponsor to pull up.

2 As I was looking at this MI data I was a little bit curious

3 about a study they had performed previously on patients

4 that were on a dual anti-therapy. I wondered if we could

5 see that data. I believe the study was called "RE-DEEM."

6 Does that sound familiar? Is that correct? The RE-DEEM

7 Trial?

8   DR. REVKIN: Jim Revkin, Cardiovascular Medicine,

9 BI.

10   Yes, this was a Phase 2 study which was primarily

11 a safety study. The primary safety endpoint was to look at

12 bleed events. It was conducted on about, I believe it was,

13 1,800. The treatment period was for six months, and these

14 were acute coronary syndrome patients. They were enrolled

15 within two weeks of an MI.

16   We can put the slide up, 20, from the RE-DEEM

17 deck. So here you see the treatment groups. You can note

18 the dose range is from 50 to 150 mg versus placebo, and as

19 you mentioned they were all on concomitant anti-platelet

20 therapy, and you can see the CB death rate at 2.4, 2.2,

21 2.5, 1.2 and 1.2. Again, the higher incidence of events

22 seems to be in the lower dose groups actually, 50 and 75,

23 which are nowhere near what we've been looking at.

24   Slide down. Does that answer your question?

1   DR. KRANTZ: Yes, thank you.

2   DR. LINCOFF: Dr. Coukell.

3   DR. COUKELL: Thank you. My question is for the

4   FDA; I suppose for Dr. Thompson. You spent some time

5   making the case that TTR in the RE-LY trial was good but

6   not as good as it could have been. Do you accept the

7   sponsor's contention that out there in the real world TTR

8   is much, much worse?

9   Then a follow-up either for the FDA or for the

10 sponsor, if that's correct, that half of the time that

11 patients aren't in the TTR and they're on warfarin are they

12 below the therapeutic range or above it? It seems to have

13 implications for how this drug might compare in the real

14 world.

15   DR. THOMPSON: Sure. Well, I think the sponsor

16 in terms of showing time in therapeutic range they showed

17 you a few things. One is they showed you just sort of

18 community practice in general, and then they also showed

19 you patients going to center where they're getting a more

20 supervised level of monitoring. And I think that the TTR

21 range in the study sort of fell within the range of maybe

22 what you're seeing at the centers, where they're getting

23 more, a higher level of monitoring.

24   Again, one of my thoughts about TTR is I think

1 it's limited as a metric, and one of the reasons it's

2 limited in these studies is because it's only capturing the

3 reported and measured values and it doesn't take account of

4 the fact if a patient is not being monitored well.

5   So I think again that TTR falls within some range

6 of reasonableness. I think it's maybe my point was more

7 that it's more probably akin to the real world in RE-LY

8 than maybe to something that potentially you could achieve

9 with more compulsive monitoring such as what's been

10 reported in at least some trials, and primarily I mean the

11 recent tecarfarin trial where they reported achieving

12 ranges upwards of 70 percent.

13   But you had an additional point maybe, sorry, a

14 question that I may not have answered?

15   DR. COUKELL: You may have answered it

16 indirectly. I mean my question was if the patients in the

17 community on warfarin are only in the TTR half the time

18 where are they the rest of the time? But I think you

19 already gave --

20   DR. THOMPSON: Do you mean where they tend to be?

21 I mean I can tell you where they tend to fall in RE-LY.

22 You mean above or below the range? Is that your question?

23   In RE-LY, where they tended to fall was they

24 tended to be below an INR 2. So if you look at it when

1   they're outside that range of 65 percent I think I focused

2   on, I think it's about 22 percent of the time, or the vast

3   majority of the time they're too low. It's the minority of

4   time, at least in RE-LY, that they were too high.

5   DR. COUKELL: But you're really saying that RE-LY

6   is the real world; it's not better than the real world.

7   DR. THOMPSON: Yes. Well, I would say I don't

8   know if it's exactly real world. I think it's more akin to

9   the real world than optimal or what is potentially

10   achievable if you really tried hard.

11   DR. LINCOFF: Dr. McGuire.

12   DR. MCGUIRE: Yes, I just wondered if I could get

13   a comment from the sponsors, if either or both of these

14   doses are approved, how aspirin use will be handled for the

15   prescription of this compound, knowing that a large

16   proportion of patients to be treated with this compound

17   potentially would need, or have an indication for,

18   concomitant aspirin therapy.

19   DR. YUSUF: Is it possible to clarify the

20   question you've asked both to FDA and the sponsor, for

21   which Stuart has an answer regarding the TTR, and then

22   we'll address the question that you also asked, Dr. Krantz?

23   DR. LINCOFF: Yes, that would be fine.

1   DR. YUSUF: Go on, Stuart.

2   DR. CONNOLLY: Well, the question was how does

3   the INR control in RE-LY compare to the INR control in the

4   community, and my perspective is somewhat different. I

5   think that what's going on in the community and that was

6   shown, that survey, where the majority of patients are

7   being treated in non-specialist practice, achieving INR

8   control in the range of around 50 to 60 percent, and

9   specialist practice, doing somewhat better in the range of

10   60, let's say 65 percent, is actually the truth.

11   To say that, yes, optimal INR control could be

12   achieved, but that would be having to change the whole

13   medical care system that currently exists. To try, if we

14   wanted, to have patients above 70 percent consistently

15   across the United States or Canada, that would be a massive

16   undertaking that would require a huge expenditure. So I

17   mean the reality is that INR control is far from perfect

18   because it's very challenging and because there are

19   difficulties in implementing very high technology services.

20   You have to recall that in RE-LY we specifically

21   chose 50 percent of our patients who we knew would be

22   difficult to control. These are warfarin-naïve patients

23   who come into the study, and we showed in spite of our best

24   efforts that they were more difficult to control and had

1 poor INR control.

2   So we actually achieved 67 percent time in

3 therapeutic range in the experienced patients and we think

4 that's a very good reflection of what could be achieved in

5 good specialist care centers in the U.S. We're mostly

6 treating experienced patients.

7   DR. LINCOFF: Dr. Neaton.

8   DR. NEATON: Could I just ask a follow-up

9 question on that? Do you know what the TTR was from the

10 meta-analysis of trials for warfarin?

11   DR. CONNOLLY: The meta-analysis of trials for

12 warfarin?

13   DR. NEATON: That you used kind of as a

14 foundation.

15   DR. CONNOLLY: Yes, that's a question that I've

16 thought about because I actually wrote a review article not

17 too long ago. The reality is that those trials were done

18 before we had INR. In fact, ours was the only trial that

19 actually started using INR at that time. So, yes, they

20 were using PT ratios. It appears from reading the papers

21 closely that the INR control was less good than it is

22 currently today and certainly than it was in our trial.

23   DR. LINCOFF: Dr. Fox.

1   DR. FOX: Yes, I have a question around renal

2   function. It wasn't really clear from the FDA's packet.

3   There was some recommendation from the clinical

4   pharmacology reviewer about what to do with patients with

5   severe renal insufficiency, but if I read the documents

6   correctly it seems that there are little to no data at all

7   in patients with creatinine clearance estimated less than

8   30 mils per minute. I wonder if the sponsor can comment

9   what their recommendation should be around what physicians

10 should do for patients with severe renal insufficiency.

11   DR. REILLY: Paul Reilly, BI. It was an

12 exclusion criterion in the trial because 80 percent of the

13 drug is excreted renally and currently in the proposed

14 label it's a contraindication.

15   DR. MADABUSHI: This is Raj Madabushi. For the

16 severe renal function impairment, and maybe some of the

17 team members and Dr. Temple may add, there was a discussion

18 internally, that these people would be progressing either

19 in the severe renal impairment arm. A substantial fraction

20 of patients would be severely renally impaired.

21   Now it is true that it was an exclusion

22 criterion, and we ended up with roughly around 35 subjects

23 on each of the treatment arms. What we tried to do was the

24 drug is predominantly renally cleared and since renal

1 function is a predictor of the time course of dabigatran,

2 we tried to use the PK parameters to come up with a dosing

3 regimen such as 75 mg QD which will provide an exposure at

4 steady state, reasonably comparable to the experience that

5 we have with 110 as well as 150 mg QD in normal subjects.

6 So that was the strategy which we used.

7 　　　　And this also addresses to what Dr. McGuire asked

8 in the morning, what can we do about a drug which has high

9 between-subject variability, but not much within-subject

10 variability? So this was the strategy we used.

11 　　　　DR. LINCOFF: I realize I had moved on before you

12 had an opportunity to answer Dr. McGuire's question, so if

13 you know.

14 　　　　DR. REILLY: Was that the one on aspirin?

15 　　　　DR. MCGUIRE: If I can ask, can we see the

16 stratified analysis, efficacy and bleeding by aspirin

17 background therapy while you respond? My point is the same

18 things that clinically dictate prescription for aspirin

19 predict bleeding, and so whether the deltas in the bleeding

20 between those with and without aspirin are different

21 between those in the study groups on aspirin.

22 　　　　DR. REILLY: So, to answer the first question,

23 Dr. McGuire, we would have a precaution or warning

24 statement in the label concerning the elevated risk of

1 aspirin use. I think they're going to show the aspirin use

2 and efficacy first, and then we'll go to safety, but the

3 basic answer is you see about a 1.5 to 2 percent increase,

4 essentially a doubling of bleed risk with aspirin, but

5 across all groups, warfarin and dabigatran.

6   DR. MCGUIRE: But that's counter to clinical

7 guidelines and evidence for Coumadin where aspirin is a 2B

8 indication concomitantly with warfarin, for patients with

9 arthroscleratic disease, and we wouldn't caution or

10 contraindicate aspirin in that group.

11   DR. YUSUF: I'm sorry, can I just show you the

12 efficacy and then discuss this issue? Can we put the slide

13 up, please?

14   Somewhere there, that is aspirin user baseline.

15 You will see for the 150 -- both, aspirin yes, aspirin no

16 -- the results are consistent and the upper confidence

17 limit is well away from 1. So the drug works compared to

18 as warfarin is superior with and without aspirin, and the

19 lower dose is non-inferior. And the upper confidence

20 limits, I can't read it, but it's probably around 1.3 or

21 something like that.

22   Now on the bleeding, I'm sorry, it is commonly

23 used. I mean people use anticoagulants, either IV or oral,

24 on top of aspirin. It's not uncommon to clinically use it.

1 And on safety, while the absolute rates of bleeding were

2 higher against a background of aspirin, the relative

3 differences were similar.

4   And Paul, do you want to deal with that?

5   DR. REILLY: Yes. Slide BL-22. Thank you.

6 Slide up, please.

7   BL-42, slide up, yes. So I don't have the risk

8 ratios calculated with and without aspirin, but you can see

9 here aspirin use was extensive in the trial, 35 percent of

10 patients had coronary disease. The elevation of bleeding

11 risk is quite similar across all treatment groups, about a

12 2 percent, 1.5 to 2 percent absolute increase, be it

13 warfarin or dabigatran.

14   And you see essentially the same thing with

15 clopidogrel and the combination with aspirin.

16   DR. YUSUF: I mean the same ordered results exist

17 if you take people who are not on aspirin relative to each

18 of the three drugs, three dosings, so lowest with 110,

19 approximately similar with 150 and warfarin, but the

20 absolute rates are about half. Is that right?

21 Approximately, or two-thirds or something like that, but

22 the structure is the same.

23   DR. MCGUIRE: Based on those data, what is the

24 premise for caution or precaution? Because I think what

1 you've just shown me is that it's comparable to Coumadin

2 for both bleeding and efficacy, and we use them commonly

3 together.

4   DR. YUSUF: I don't know what the label proposal

5 is, but I would say as a clinician I would use it on top of

6 aspirin.

7   DR. REILLY: There is a cautionary statement in

8 the Coumadin label concerning aspirin use increasing the

9 risk of bleeding. I would expect we would have such a

10 similar statement.

11   DR. LINCOFF: Okay, Dr. Kaul.

12   DR. KAUL: I have a general question regarding

13 CHAD score. Dr. Connolly, do you use CHAD score in your

14 clinical practice? What is the predictive value of CHAD

15 score?

16   DR. CONNOLLY: Yes, I do use clinical CHAD score

17 in my clinical practice. As everyone knows, it gives a

18 point each for congestive heart failure, age over 75,

19 diabetes, hypertension, and stroke gets 2 points.

20   And it does have predictive value. It's been

21 studied. Brian Gage studied it, and others. Although its

22 predictive value is not great, the receiver/operator curves

23 do separate from unity, and it is a reasonable score.

1   No better score has been devised that has a

2   greater predictive value, and indeed there has been a new

3   score suggested, the CHAD VASc score. I haven't really

4   entirely gotten my head around whether it's better. I know

5   that its predictive value is no better from a statistical

6   point of view.

7   So I do use it. Most clinicians do as well.

8   DR. KAUL: The reason why I'm asking is that if

9   you at the data, with a CHAD score of 1 or under, you would

10   have predicted a stroke and systemic embolism rate of about

11   2 percent per year, and what you're getting is half of

12   that. And the bleeding -- or you're getting 1 percent per

13   year. And the bleeding, major bleeding event rate is about

14   3 percent per year.

15   DR. CONNOLLY: Sorry, where are you getting these

16   numbers from?

17   DR. KAUL: This is from the subgroup analysis, 1

18   percent per year is a CHAD score of 1 or less than one.

19   I've lumped zero and 1 together. So the point I'm making

20   is that there is increasing evidence that people with a

21   CHAD score of zero and 1 have the bleeding liability for

22   warfarin and perhaps not as much benefit, and the chest

23   guidelines seem to sort of favor aspirin over warfarin in

24   people with a CHAD score of zero and 1. So do you think in

1 hindsight it was fair to include a CHAD score of zero and 1

2 in the study?

3   DR. CONNOLLY: Well, you know the patients who

4 have a CHAD score -- a CHAD score of zero in our study, by

5 the way, was a relatively small number of patients who had

6 other risk factors such as peripheral vascular disease. So

7 they weren't without risk.

8   And patients who have a CHAD score of 1, under

9 current guidelines in the U.S., physicians are really given

10 the instruction to use their judgment and to weigh the

11 risk/benefit of each individual patient, both for stroke or

12 bleeding, and then to decide whether aspirin or warfarin is

13 the appropriate therapy. I think this is in general how we

14 see these risk scores being used.

15   Physicians do have to face each individual

16 patient and understand that patient's particular risk

17 strata, and each patient is different for both stroke and

18 bleeding, and also understand the patient's preferences.

19 Some patients, in general patients fear stroke much more

20 than bleed. But I'm sure you've experienced, as have I,

21 patients who come in and say, you know, Doctor, my husband

22 bled terribly once, and I'll never take warfarin again.

23   So people have different values that are very

24 important to take into account, and physicians are able to

1   make those decisions.

2   DR. KAUL: The bleeding advantage with the 110 mg

3   of dabigatran was only observed in those with a CHAD score

4   of less than 1, but not in those with a CHAD score of 2 or

5   greater. So that's the reason why I'm asking.

6   DR. CONNOLLY: Bleeding events by CHAD score,

7   yes. I think that the first thing is would you put the

8   slide up because I think that it shows the data I believe

9   that you're referring to. This shows the major bleeding

10 events by CHAD score for dabigatran 110 versus warfarin.

11 It's based on the intention-to-treat set.

12   I think the key thing in all of these subgroup

13 analyses is we have to remember that when you cut a

14 population into smaller groups it increases the potential

15 for the play of chance, and we really need to be looking at

16 the interaction p-values as our first step in understand

17 these subgroup analyses. And when you look down, you can

18 see that the p-value has not anywhere suggested that there

19 is an important interaction. So I would think we should be

20 very cautious in trying to over-interpret this.

21   DR. LINCOFF: Dr. McGuire.

22   DR. MCGUIRE: Yes, just a quick point of

23 clarification. The CHAD scoring projects if untreated, and

24 so if you have a 2 percent risk untreated then a drug like

1 warfarin reduces risk by 60 percent. You would expect,

2 with spot-on, that they're actually achieving efficacy

3 across all groups.

4   DR. LINCOFF: Is the sponsor prepared to show the

5 slides on the information that was requested before the

6 lunch break?

7   DR. YUSUF: Okay. Thank you. With your

8 permission, we'll show these slides, but there were a

9 couple of issues that came up in the discussion. If you

10 don't mind, we'd like an opportunity to respond.

11   Okay. So can we get the slide up, please? Okay,

12 the next one. All right, this is what Dr. Nissen asked

13 about the Kaplan-Meier curves. It's hard for me to say

14 anything -- what do you call -- insightful here.

15   The next slide. Next slide. Okay. Sorry, I

16 have the controls. This is, I think, a request on GI

17 bleeds. So you will see the 150 and warfarin are

18 superimposable. No, sorry, 110 and warfarin are

19 superimposable. Thank you, Stuart. And the 150 is higher,

20 and it's higher throughout. So that's -- sorry, it's the

21 other.

22   DR. CONNOLLY: That's 150 at the top.

23   DR. YUSUF: Yes, 150 is the top. Okay, then

24 permanent discontinuation, it was early that we had this

1 permanent discontinuation, in the first six, three months

2 or so, and then it's pretty parallel throughout. So

3 there's some discomfort or side effect early, and it

4 stopped.

5   If you look at in the people, and use of open-

6 label anticoagulant certainly is higher in the two

7 dabigatran doses compared to warfarin. That's not

8 surprising because people know they're on warfarin.

9   But if you look at the absolute difference, say

10 at 12 months, it's about 5 percent, which reflects the same

11 number of people are going off. So it's at that point you

12 add the number of the people on dabigatran plus open-label

13 warfarin, and study warfarin plus open-label warfarin,

14 you'll end up with the same number of people. So overall,

15 the proportion of people on an anticoagulant is the same,

16 so this cannot create a benefit in favor of dabigatran

17 because of that.

18   The next slide. Oh, sorry, it's me. Okay, the

19 patient disposition, the question Jim Neaton asked, there

20 are 200 -- I mean, Jim, just before I preface it, there are

21 different ways to approach it and there are two other

22 backups if you want, but they essentially give you the same

23 answer because it's how you define that point. So this is

24 one approach that I was able to calculate from tables.

1   So there are 203 people -- 230 from 242 -- with

2   no final visit or telephone call, or any of that kind of

3   thing. Now these people, some of them had strokes before.

4   So they've already informed the analyses. Some of them

5   came from centers that were close. In a sense, that is

6   unbiased as vis-à-vis the randomization. So if you take,

7   add these two, it's about 30-30-30, about 100 there, just

8   under 100 there. Then the remaining is 171, 199, 211.

9   This is close to the analysis I showed, but I did some

10 imputation earlier in my presentation.

11   Of these, we tracked the people wherever

12 possible, by various means, and we got the vital status in

13 these people. So the vital status missing is in between.

14 And the majority of places we weren't able to track them

15 was truly we exhausted everything we could or we were told

16 by the REB, or the rules in that country by GCP, you're not

17 allowed to follow these people once they've said you can't

18 follow them.

19   Yes?

20   DR. NEATON: Can I just ask, is that vital status

21 known or is it -- because in an earlier slide you showed

22 there were, I think, only like 24 people with unknown vital

23 status.

24   DR. YUSUF: Okay.

1   DR. NEATON: So this is really vital status here,

2   not end-point status?

3   DR. YUSUF: It is vital status. So death is

4   known. So the difference between this 171 -- see, these

5   are the people I would say after they were followed we

6   didn't know whether they had a stroke. So, in any

7   imputation, use this as your denominator because here all

8   -- I mean we may have captured fatal stroke, but quite

9   honestly in these people we just had death without a whole

10 lot of details. Well, you never know. We probably did.

11 We didn't have much.

12   So this is the number to use in any imputation,

13 and that was the implication I showed you earlier, using

14 the warfarin rates, twice the warfarin rates, and a

15 crossover kind of analysis where there are no events, and

16 warfarin in eight events in the other two, and they don't

17 change the results materially.

18   There's a number of different imputations the

19 company has made, but it essentially confirms that

20 imputation on a doubling of event rate in the dabi groups

21 and completely no events in the warfarin group. That's

22 really either the non-inferiority of 110 or the superiority

23 of 150.

24   Is there another slide there? I think this was

1 also requested by Steve. You wanted to see. Well, this is

2 really the basis of that stuff, Steve, the hazard ratio,

3 you know, the Kaplan-Meier. These are the numbers. It

4 doesn't say anything more than that.

5   DR. LINCOFF: I think Dr. Emerson had actually

6 asked about that.

7   DR. YUSUF: Oh, did you? Sorry.

8   DR. EMERSON: Leave it up there for just a

9 second.

10   DR. YUSUF: Okay. Can we go back and show that

11 again? I can't go backwards here. That last slide.

12   DR. EMERSON: Okay. Thank you.

13   DR. YUSUF: Thank you. Yes, one of the points I

14 would like to make on that slide -- can I have that slide

15 back, please, if I may -- is this last line where you put

16 everything into the mix, and here there is net clinical

17 benefit in superiority over warfarin. And here, remember

18 with the lower dose the goal is to show non-inferiority.

19   I don't know what boundary to use, but let's use

20 1.38. This 1.16 is well away from that. So, to the

21 question that Dr. Kaul asked earlier, I don't see net

22 clinical benefit confirmed with 110. He's right.

23 We don't have superiority on net clinical benefit with 110,

1   but we do have non-inferiority, with the caveat I don't

2   know what boundary to use for this endpoint. I think those

3   are the points.

4   The other thing we wanted to make was the INR

5   data and the efficacy. Is that possible? That is the one

6   thing that we wanted to share. Stuart, do you want to do

7   that? And I wanted to briefly mention bias issue at the

8   end, but you go ahead.

9   DR. CONNOLLY: I mean I already addressed the INR

10 issue just a little bit, so I'll be very brief, but I think

11 there are a couple of key messages that we want to show.

12   Okay. So, slide up. Just to remind ourselves

13 that these are the -- Salim showed this slide already, but

14 it just reminds us that in the RE-LY study we did choose

15 excellent centers to participate. These were not just the

16 average centers, and yet we still have a fairly, a

17 substantial number of patients that are being treated in

18 centers that are unable to achieve the excellent INR

19 control that we'd all like them to have. I think that this

20 represents still better than the average INR control in the

21 community, and it is really, I think, reality.

22   Next slide, please. Yes, put this up. So I mean

23 I take the liberty of just showing this slide, which comes

24 from the paper that we recently wrote in the New England

1 Journal, and it just cautions us about over-interpreting

2 the different quartile analysis. This is looking at the

3 baseline characteristics of all the patients in the four

4 quartiles of INR control, and I just draw your attention to

5 the p-values on the right. For virtually every clinical

6 characteristic, there are highly significant differences

7 between these quartiles. So this analysis has many co-

8 variants that go well beyond the INR control itself, and so

9 we have to be very careful in interpreting this.

10   I would say, however, that this type of center

11 control analysis is better than just taking all of the good

12 warfarin patients and comparing it to the average

13 dabigatran patient, which is clearly biased and non-

14 randomized.

15   Next slide. Now this is the analysis that is

16 done by a center, and it is for the primary outcome -- a

17 stroke or systemic embolism. The key message here again is

18 that in subgroup analysis really the question is, is there

19 evidence that the effects are not consistent?

20   And when we do the analysis with the four

21 quartiles and we look at the interaction p-values for both

22 dabigatran 110 versus warfarin, dabigatran 150 versus

23 warfarin, certainly for dabigatran 110 versus warfarin

24 there is no suggestion that there is any change. The

1   interaction p-values are shown here, 0.90 for dabigatran

2   110 versus warfarin, 0.20 for dabigatran 150.

3   What we see for dabigatran 110 and warfarin is

4   both of them are actually getting better as you get into

5   better quartiles, again pointing out that there are

6   probably other co-variants at work here. For dabigatran

7   150 the event rates for the primary are relatively steady

8   across the quartiles, and the p-value becomes a little bit

9   more interesting, but not statistically significant.

10   Next slide.

11   DR. NEATON: Just to be sure that we've seen a

12   number, and I apologize I didn't read your paper, so I

13   wasn't sure when the last one came.

14   DR. CONNOLLY: It just came out.

15   DR. NEATON: But this analysis takes all the

16   sites and looks at the TTR level for those assigned

17   warfarin within the sites and rank-orders them.

18   DR. CONNOLLY: Yes.

19   DR. NEATON: And then it basically compares

20   treatment versus control within site?

21   DR. CONNOLLY: Yes.

22   DR. NEATON: Okay.

23   DR. CONNOLLY: Actually, yes. It's a co-variant

1 analysis. It takes all the patients at the sites in the

2 lowest quartile.

3 DR. NEATON: There's no question about the

4 comparability of the treatment versus the control within

5 site?

6 DR. CONNOLLY: Yes.

7 DR. NEATON: But there is the post-hoc

8 classification that you've sorted people by TTR, and, for

9 all that matters, maybe it's reflecting something else?

10 DR. CONNOLLY: Right. This is not a pre-

11 randomization variable.

12 DR. NEATON: No.

13 DR. CONNOLLY: It's a post-randomization variable

14 that is focused on the warfarin patients, not on the

15 dabigatran patients.

16 DR. NEATON: But the previous tables you showed

17 from your paper, where all the differences were by the

18 quartile, that's an individual patient analysis, right?

19 DR. CONNOLLY: That's the patients, yes. We took

20 all the patients that were at the lowest quartile sites,

21 yes.

22 DR. LINCOFF: It has to be by site, because there

23 is no way to make a comparative patient.

1   DR. NEATON: No, I agree. This is the preferred

2   analysis, and so I mean there's no question for all the

3   reasons you've mentioned.

4   DR. CONNOLLY: Right, and it's still not a

5   perfect analysis by any means. Well, I just want to show

6   this one last slide which I personally -- next slide,

7   please -- which I personally find really highly convincing,

8   and this is for intracranial hemorrhage which was not a

9   rare event in this study. In warfarin, the rate of

10   intracranial hemorrhage reached about 2 percent by the end

11   of the follow-up, the cumulative risk.

12   This shows the effect across the four quartiles

13   for intracranial hemorrhage, and you can see we're not

14   really worried now about the interaction p-values here

15   because it's very clear that even in the best controlled

16   center, where the mean INR is in fact close to 80, this is

17   the minimum value at those centers. So a lot of patients

18   were well above that.

19   You can see that there is a very large and

20   substantial reduction in the risk of intracranial bleeding.

21   That is a consistent finding in virtually every subgroup

22   we've looked at in this study and in these, across

23   difference of INR control. Thank you.

24   DR. YUSUF: I want to add one point to Stuart's

1 before I just talk about bias, just to tell you we had

2 175,000 INRs in these 6,000 patients, now because some of

3 them stopped. This is an average of 1.4 INRs per month,

4 which is likely better than the usual practice in North

5 America.

6   The second point we want to say is our center

7 under Jack Hirsh is considered one of the better centers in

8 thrombosis, yet our INRs are about 67 percent. And Stuart

9 just finished a randomized trial of computerized algorithms

10 to improve INR versus usual care, and it didn't budge at

11 all. So while we can hope for better INRs, and it's a

12 desirable goal, it's a monumental task to achieve it.

13   Now I just wanted to talk about bias. Clearly

14 regarding, there's management bias, and nothing we've seen

15 shows a difference in favor that would favor dabigatran, no

16 more anti-thrombotic, no more blood pressure lowering, no

17 more statins, all of that. On the endpoints, there are two

18 levels of potential bias. One is when you know of an event

19 do you more often classify it one way or the other, you

20 know, in one group or another? Everything we've looked at

21 doesn't show that because fatal strokes, disabling strokes

22 and image-confirmed strokes are all reduced, so once you

23 know an event.

24   Of course, one could say what if there's a

1 differential way of you detecting events? Fair question.

2 That's where we looked at 125,000 SAEs and AEs. So we did

3 a number of things, so not just the hospitalization alone.

4 I don't disagree that the hospitalization by itself is not

5 very good at picking it up. But we had every visit, a

6 stroke questionnaire. Do you have weakness? Four

7 questions, a bleeding questionnaire.

8   So in 18,000 people times 12 visits we had these

9 questionnaires addressed. So that was an added search.

10 Then 125,000 SAEs and AEs, which is free text, were

11 scanned. So if they forgot to report it, that was another

12 way. And the FDA knows that we found very few events by

13 that massive effort. So every possible way that we can

14 humanly think that we may have missed an event, we looked

15 for it, and it doesn't change the results.

16   And hemoglobin drops, we looked at 95,000

17 hemoglobins by central laboratories and looked for drops

18 there. If there were drops greater than a certain amount,

19 we went back and queried the site: Is there a bleed? Then

20 the monitors visited the sites. In, I don't know what

21 proportion, but in a fairly high proportion of cases they

22 looked at the source document verifications, and again they

23 didn't find anything. And obviously, in a smaller random

24 subset the FDA auditors visited the sites, and they didn't

1 find anything.

2 So in every search that we've done, that we may

3 have missed events really didn't turn up anything that was

4 different. And when we did pick up an event it was a very

5 low rate, and it was non-differential. Like the stroke we

6 picked up was in the warfarin group. Two strokes, I think.

7 One stroke and one systemic embolism, that was in the

8 warfarin by the SAE scan. It wasn't in the dabigatran

9 group. So while we can be concerned about bias, and we

10 were too, every search doesn't show anything.

11 DR. LINCOFF: Are there any other comments from

12 the sponsor before we move on to the panel discussion?

13 Okay. Are there any others before we move on to

14 the questions? Dr. McGuire.

15 DR. MCGUIRE: Just one quick clarification. The

16 sponsor is proposing a lower dose for those 80 years and

17 older, and all day we've seen age stratifications by a 75-

18 year cut point. Have we seen any data about 80 years and

19 older?

20 DR. YUSUF: Yes. Can you bring up the two slides

21 in my presentation? Not that one, my presentation.

22 I think it's better to look at it as a continuous

23 variable because you're using information just below 80 and

24 over 80 to inform what happens there. So I showed that.

1 The honest answer, it's a very hard one. You have to

2 stretch your imagination a bit to believe there is

3 something magic happening there.

4   Yes, just before that. That's it. Can you bring

5 that up, please? So this slide is 150 versus 110. It's

6 not warfarin versus warfarin. Okay. That would be if you

7 want me to show that, I have a slide on that. But this is

8 looking at the hazard ratio. As people are getting older,

9 the relative benefit of 150 over 110 is diminishing. At

10 least to the eye, there is a trend, but a purist would say

11 your p-value or interaction is insignificant. And I just

12 show you the data. You decide whether you believe it or

13 not. For major bleeds, we're not seeing -- the relative

14 advantage of the lower dose is constant in a very close to

15 no slope at all, compared to 150, 150 having more events

16 than 110.

17   The next slide therefore integrates these things.

18 Can I have the next slide, please? Yes. This is like a

19 net clinical benefit. It's one of the many analyses the

20 FDA did, and here we took that and did it by the relative

21 doses -- cardiovascular debt, life-threatening bleeds,

22 strokes and systemic embolism. I acknowledge MI is not

23 there, but we weren't smart enough to think of it. But

24 when you look at that -- but it won't change very much. It

1   just adds 0.1 percent to it, and you will see there is that

2   slope, interesting p-value, by no means significant.

3   So as a clinician, I would say on average in this

4   older age group, and I don't want to put a precision around

5   80, the two drugs are equivalent in its net benefit, are

6   likely equivalent. I want to use the word "likely" because

7   this is not significant.

8   And in different patients, depending on their

9   risk tolerance to bleeding with a stroke or depending on

10 whether they've already had a bleed or depending on whether

11 they already had a stroke, I think different clinicians

12 might legitimately make different conclusions. So I hope

13 that has addressed your question.

14   Mr. Chairman, with your position, there was one

15 little point I wanted to make which is not related to that,

16 if I may.

17   DR. LINCOFF: Okay.

18   DR. YUSUF: Thank you, and this was related to

19 the presentation by the FDA where they said only 33 events

20 are needed to nullify the superiority in the higher dose,

21 150. Well, the word "only" has to be put in the context of

22 probabilistic calculations, given that we have 70 fewer

23 primary endpoints, given that what is the probability of 33

24 excess just in one direction. I'm not a facile

1 statistician to calculate it here, but my guess is it will

2 be incredibly low, that probability.

3   So in your deliberations either somebody can

4 quickly calculate what that probability is. My guess is it

5 will be under 1 in 10,000 or more extreme, or I think one

6 just needs to take that in consideration.

7   DR. LINCOFF: Dr. Thompson, I understand you have

8 some comments.

9   DR. THOMPSON: I think I need to be very careful

10 with my phrasing. I'm not paying attention to when I'm

11 inserting "only" and other things, but I actually wanted to

12 put this slide as a follow-up.

13   Similar to this, the PROBE concept where the

14 question becomes yes, the trial is designed, there's

15 adjudication, it's supposed to be blinded, and you asked

16 the question to what extent were things blinded. I think

17 that it's also important when you look at some of the

18 measures that they took to mitigate bias, such as trying to

19 get additional information that could suggest a potential

20 stroke event and then following up those patients the

21 extent to which they have missing data.

22   So this is actually one of the sponsor's tables

23 and shows again at each clinic visit, in addition to asking

24 whether or not someone had a stroke, they asked additional

1   questions about whether or not a patient had signs or

2   symptoms of stroke. As I understand, at the end of the

3   trial they went back and tried to follow up on these

4   patients who had reported these problems, and one of the

5   issues you see that they ran into is that they couldn't

6   actually get follow-up on everyone.

7   And I'm not arguing that they got more or less

8   follow-up on one arm than the other, but I think that what

9   you become aware of is there is some amount of missing

10 information, and this is missing information on people who

11 did have potentially signs or symptoms that are suggestive.

12 How you impute, how you consider this or calculate it, I

13 don't know, but I just thought it was appropriate to show

14 as well.

15   DR. LINCOFF: All right. So now we're going to

16 move on.

17   DR. REILLY: Mr. Chair, could I respond? I think

18 I might be able to elaborate a little bit. So Dr. Thompson

19 just showed the stroke and symptom questionnaire. We also

20 had a bleeding questionnaire. We actually followed that

21 one up during the study, and it did result in new events.

22   Slide up, please. This shows in fact the second

23 to last line there, that we did find three new strokes as a

24 result of this survey. So it did pick up a few new events,

1 and they were balanced across treatment groups. I think

2 the commentary on missing still stands.

3   DR. YUSUF: I think the point the previous good

4 doctor said, I'm sorry I don't know your name -- can you

5 put that slide up -- is that despite all our efforts, in

6 some people we couldn't follow through. Completely accept

7 it. Also the point you made, it's not differential. We

8 accept it.

9   But please note of the people -- can you put the

10 slide up? Please note in the people we followed through

11 the catch rate is so low, so that if you take this as your

12 average rate that you'd pick up, maybe you'll pick up one

13 more event in these, each of these. So it's not that here

14 this becomes a denominator, but the numerator would be. So

15 these are the people you'd search.

16   So here are the people we were able to search,

17 and there. We knew of the stroke already in many people,

18 and the additional strokes we picked up were one, one, one.

19 So whether you use the 41 or the difference between 41 and

20 29, here I don't know. But not all of these will be

21 strokes. Maybe some small percent of it would be. I'm

22 sure that would happen.

23   But the likelihood is that, first, it's not

24 differential. Second is one more event in each of these

1 three groups isn't going to change the results, or two more

2 isn't. In fact, as I showed you, eight more, here and

3 here, versus zero there isn't going to change it.

4   DR. LINCOFF: Okay. So now what we'll do is

5 we'll go on to the questions. There are a total of six

6 questions, of which only one actually requires a vote, a

7 formal vote, and we'll talk about the instructions for that

8 at that point. But we'll work through our structured

9 discussion based upon these questions.

10   So the Advisory Committee is asked to opine on

11 the approvability of dabigatran, a direct thrombin

12 inhibitor, to reduce the risk of stroke and non-CNS

13 systemic embolus in patients with non-valvular atrial

14 fibrillation. The support for this claim comes primarily

15 from RE-LY in which 18,113 subjects with persistent,

16 paroxysmal or permanent atrial fibrillation, about one-

17 third each, were randomized to open-label warfarin or 1 of

18 2 blinded doses of dabigatran. The trial was event-driven

19 and ran about three years. Important results are as

20 follows, and we all have this table, plus it has of course

21 been presented.

22   All right, so please comment on the adequacy of

23 the design of RE-LY. First, was it reasonable to use open-

24 label, investigator-adjusted warfarin as a comparator for

1   assessing the effects of dabigatran?

2   DR. NISSEN: You know, interesting choice of

3   words, Norman. The question is "reasonable." Let me say

4   that it was reasonable but not optimal, and I want to be

5   really clear here. There is a reason why we do double-

6   blind studies. If you could eliminate all bias in open-

7   label studies, then we'd just do open-label studies. They

8   are a whole lot easier to do. So you have to assume that

9   no matter how good the intentions are of the people

10   involved, and I do think that there was a lot of effort put

11   in to try to do a good open-label trial, it is still an

12   open-label trial. And an open-label trial, by definition,

13   has inherent biases. So the issue that we'll have to think

14   through here is how much.

15   Now there was a concept I wanted to put on the

16   table for the other members of the committee that I think

17   might be useful for future studies. I think this is a

18   precedent-setting application in many ways. I would argue

19   that if you allow an open-label design, that the allowable

20   upper 95 percent confidence limit for the hazard ratio

21   ought to be lowered, that for an open-label trial it ought

22   not to be 1.38 or 1.46. You have to assume that there are

23   some biases involved.

24   And I would argue that you give sponsors, future

1   sponsors, a choice of doing a blinded trial with an upper

2   confidence interval in the range of 1.38 or perhaps an

3   open-label trial of 1.25 or 1.20. So you can kind of pick

4   your poison here. But you can't be entirely comfortable

5   with any open-label trial involving a drug of this

6   importance, that's going to be taken by this number of

7   people, given the fact that there may be biases we can't

8   even measure or understand in trials. There's a reason why

9   historically we've always done double-blind studies, and

10   that reason is a good reason.

11   DR. LINCOFF: Dr. Neaton.

12   DR. NEATON: Well, I'll throw out a slightly

13   alternative point of view. So I mean you're right. I mean

14   we use blinding to minimize bias, and we have to assess

15   kind of in the absence of blinding the potential for that.

16   I think about maybe 60 or 70 years ago, I think Bradford

17   Hill said, for precision, you shouldn't throw common sense

18   out the window. This design, I think, really brings that

19   to a head.

20   Think about what we would be looking at, had this

21   been a blinded trial. When I try to visualize that, I

22   think this actually is far more informative to clinical

23   practice in terms of what this drug really can do under

24   real-life circumstances than a very artificial trial that

1   would be set up, that would require to do it double-blind.

2   So I'm not convinced it wasn't optimal in this particular

3   situation.

4   But having said that, there is clearly, I agree

5   with you, that we need to pay attention to the potential

6   biases and come back and talk about that when it comes time

7   for the vote.

8   DR. LINCOFF: Dr. Emerson.

9   DR. EMERSON: I'll just concur with what Jim just

10 said. I worry that since one of the advantages of the drug

11 is that you don't need to do the more intense monitoring,

12 in the double-blind we might not have gotten that answer.

13   I always prefer a double-blind trial, but I also

14 recognize that even in double-blind trials we have

15 ascertainment bias due to the safety profile and the other

16 things that go on. So in this particular case, I'm not

17 convinced that there is a very large step between

18 ascertainment bias that might have come up in a double-

19 blind trial and that that came in this open-label.

20   DR. LINCOFF: Dr. Kaul.

21   DR. KAUL: Yes, I agree with the two previous

22 perspectives. I think it's reasonable, given the logistic

23 challenge of the design. If I understand correctly, the

24 largest double-blind trial with warfarin was SPOR TIF V,

1 and it enrolled 3,900 patients. So reconciling feasibility

2 and minimizing bias is an important challenge for

3 consideration.

4 So while I'm willing to give them the advantages

5 of this approach, I'll have to agree with Dr. Nissen, that

6 I would have opted for a tighter margin. There are certain

7 biases that are unavoidable, and it's hard to predict what

8 the direction of that bias is. You can only say that if

9 you know the bias is differential or non-differential. I

10 would assume the worst case scenario, to say that the bias

11 would have shifted it towards the null and biased it

12 towards non-inferiority. So I would have picked a tighter

13 margin.

14 DR. LINCOFF: I'll take the opportunity to make

15 my own comment. I also would like to actually come down on

16 the side of this being the optimal trial design. I mean I

17 don't think we settled in this case for a trial design

18 based upon the feasibility or the logistics. I think that

19 given that when you're testing therapies, that part of the

20 potential advantage is the mode in which it's given, the

21 mode in which it's monitored, the way in this case,

22 bridging, et cetera.

23 The only way to effectively test and evaluate the

24 real advantages is to be able to treat patients

1 differently, aside from, based upon the treatment that

2 they're actually receiving, the randomized treatment.

3 Although you give up the precision that would be involved

4 in removing that level of bias, the advantages I think

5 outweigh the disadvantages, particularly if adjustments are

6 made, both statistically and in the conduct of the trial,

7 to minimize the ascertainment bias. So also as a clinician

8 I think that that would be a stronger trial design for this

9 particular type of therapy.

10   And I'll remind, at least from the experience

11 that I recall, that in trials where warfarin has been

12 blinded and there has been a generally central control of

13 the INRs and often the adjustment of the dosing, there's

14 often been very good control of the INR ranges, but it has

15 not been what reflects reality. Again, part of the value

16 of this therapy is it probably is more effective because it

17 is more often on target.

18   I mean we have seen the data here that very good

19 warfarin control gets very good results, but I think we

20 also all believe that it's very difficult to achieve that

21 uniformity in medical practice. That would be something

22 you would be less likely to achieve in a blinded trial if

23 there was central control of the warfarin.

24   DR. TEMPLE: Is the thing that people worry most

1   about ascertainment bias or, oh, I don't know, behavior

2   bias, getting people out of the study, not keeping them in

3   is hard, or is all of the above? And if it's the first,

4   surely what the endpoint is must matter. You have to be

5   less worried about mortality than you are about other

6   stuff.

7   One of the big trials of TPA against

8   streptokinase was the GUSTO trial, was open-label. We got

9   a lot of -- we, being CBER, so I had nothing to do with it

10   -- we got a lot of harassment from Congress actually

11   because they thought that the choice of secondary therapy

12   might be different. Maybe you're more inclined to do a

13   CABG in one group than the other, and things like that. So

14   that's another thing to worry about, the behavioral part.

15   DR. LINCOFF: Just because Congress worries about

16   it, I don't know that we need to.

17   (Laughter)

18   DR. TEMPLE: Actually, it was quite a sensible

19   worry, I thought.

20   DR. LINCOFF: Dr. Emerson.

21   DR. EMERSON: So I guess to answer your question

22   I worried about the ascertainment bias, and that was one of

23   the questions that I wanted to see the harder endpoints, as

24   the concept of what would come up there. So a lot of my

1   feeling comfortable with this is outcome-dependent, that in

2   this particular trial they got away with it.

3   But things that would have scared me are if I had

4   seen instead there was a greater tendency for the warfarin

5   patients to drop the treatment. That would have been an

6   indication that the investigators were biased towards

7   believing that the new drug really worked, whereas I

8   thought there was -- I'm guessing here. But the fact that

9   they were more willing to drop the new treatment suggested

10   that there wasn't the a priori bias that this was going to

11   be the clear homerun or things like that.

12   So I think those come in there, but again you'll

13   never remove with a double-blind study the possibility that

14   the ancillary treatments might be different because of

15   secondary outcomes.

16   DR. LINCOFF: Dr. Nissen.

17   DR. NISSEN: I worried about both sources of

18   bias, both ascertainment and differential management. I do

19   think that there is evidence that there was differential

20   management, and the reason I say that is that there was a

21   much greater likelihood that people who were in the

22   dabigatran arm would be discontinued from therapy. So

23   people were making decisions based upon some notion about

24   what they expected, and that's what bias is all about.

1   I will come back to what I said before. I do not

2   think it is an optimal design. I think it is a reasonable

3   design, and I think that overall the importance of blinding

4   is so great in trials that it has to trump these other

5   real-world advantages. Just as a matter of principle, I

6   don't like it.

7   You know, we had another experience with this.

8   You may remember because you were at the table on July

9   15th, where we saw an open-label trial that literally blew

10   up when it was subject to more careful examination. So for

11   lots of reasons, lots of reasons, I really don't think that

12   one can say that it is optimal. What I said here was that

13   it was reasonable, and I think "reasonable" is the correct

14   word. You chose that word very carefully.

15   But I do think there ought to be a penalty to be

16   paid for running this trial open-label because we really

17   want trials to be blinded whenever possible, and I don't

18   think we want to encourage open-label designs.

19   DR. TEMPLE: Maybe you should have to show

20   superiority. Just kidding.

21   Well, this has come up before in other

22   discussions, and one of the remedies to ascertain bias that

23   has been suggested was send everything over to the

24   Committee. Don't make them take a very complex judgment.

1 Just send it over and the blinded adjudication people will

2 do it. And I must say that seems to me a lesson that we've

3 learned and would probably endorse if anybody did want to

4 do an unblinded study.

5   The other thing that struck me here is -- I'd be

6 interested in what people think -- some of the concerns

7 about dropping people, keeping them in and all that stuff

8 maybe can be partly resolved by looking at both the on-

9 treatment, the 30 days plus off-treatment and the true ITT

10 because if you count everybody, then if you got rid of them

11 early, you can't have made them not count. So I wondered

12 what you thought about that.

13   I guess one of the things that struck me here is

14 that all those analyses sort of show the same thing. Do

15 people think that helps? Usually, in a different showing

16 trial, we liked ITT.

17   DR. LINCOFF: I think part of it is that most of

18 the patients in the dabigatran group who discontinued, or

19 many of them, if we saw the exact numbers I'm not sure, but

20 went on to warfarin. So had this even been a blinded trial

21 and patients went off the blinded drug, most of them would

22 have gone on to warfarin perhaps. You might have seen very

23 similar, but just you would have called your

24 discontinuation rates the same because in warfarin it would

1 have been warfarin to warfarin, but discontinued, blinded.

2   DR. NEATON: I think you go back to your first

3 question. I think you're concerned about both types of

4 biases, both the ascertainment of endpoints and potential

5 behavior of different concomitant treatments. I actually

6 think it is -- well, I found it reassuring that the on-

7 treatment and the intention-to-treat analysis pretty much

8 told me the same thing for the reason that Mike just said.

9 It seemed to me from reading this what was probably

10 happening is the people who were stopping, when they

11 stopped the study drug, they went on warfarin. For the

12 warfarin group, there wasn't an alternative or it was going

13 to be something lesser. That's the nature of the world.

14   So it becomes important, not only because of the

15 non-inferiority design but to better understand the

16 consequences of the strategy that were really being

17 compared here, which was study drug until you had what

18 looked like a GI bleed or couldn't tolerate the treatment,

19 and then you went on to warfarin.

20   DR. LINCOFF: Dr. Fox.

21   DR. FOX: Yes, just a comment really in support

22 of the agency in fact. You know, the agency, I think, made

23 it very clear to the sponsor at the outset and along the

24 way that they preferred a double-blind design. The sponsor

1 chose to conduct the trial a bit differently for the

2 reasons that have been discussed at some length. It

3 doesn't seem that they were punished in any way upon filing

4 and review. In fact the review, to me, seemed quite

5 balanced and fair and quite thorough. That's the only kind

6 of residual issue I wanted to bring up.

7 We have been kind of focused more on the efficacy

8 and the ascertainment bias, potential ascertainment bias

9 around efficacy endpoints, but I'd like to throw out there

10 that had there been. While there doesn't seem to be a

11 major safety issue at hand here other than bleeding risk,

12 which is the obvious safety-related endpoint for this class

13 of drugs, but had there been some sort off-target or some

14 other kind of other organ toxicity involved that might have

15 been influenced by differential rates of discontinuation

16 and drop-in and drop-out and that sort of thing, we might

17 have been facing a bit more difficult discussion today.

18 DR. LINCOFF: Mr. Simon.

19 MR. SIMON: As a patient having been on warfarin

20 for about 14 years, from the blinded standpoint as opposed

21 to open-label, I believe, of course I know a lot more now

22 than I would have when I started. But from this

23 standpoint, I would have been more readily or more ready to

24 jump to warfarin if I had the slightest problem, if I had

1   events that took place on the study drug. So that's the

2   only comment I had, that I'd be ready almost and willing to

3   jump to warfarin.

4   DR. LINCOFF: Dr. Emerson.

5   DR. EMERSON: So one thing that you do have to

6   worry is another scenario that could happen is what if in

7   fact we had the entirely wrong patient population and this

8   was a population that warfarin did no good but did cause

9   intracerebral hemorrhage, and that the major effect of the

10   drug was just to delay the time that they got onto warfarin

11   to decrease those bleeds.

12   (Laughter)

13   DR. EMERSON: I mean this is something that's

14   compatible if you have enough people dropping off and

15   moving on to warfarin. So it's something that you'd always

16   have to entertain, and that could happen in a double-blind

17   study as well.

18   DR. LINCOFF: Dr. Nissen.

19   DR. NISSEN: One more comment about the

20   crossovers, and I just have to remind everybody that in a

21   non-inferiority study crossovers tend to bias toward the

22   null hypothesis. So the idea that somehow that's

23   reassuring, that they were crossed over to warfarin, isn't

24   reassuring. In a non-inferiority design, you really want

1   to minimize crossovers. Now I'm comfortable here because

2   the numbers of crossovers were very modest.

3   Let me just see if I can be really clear. As an

4   open-label trial goes, this one was executed well, but it's

5   not necessarily the most desirable approach, and I'm sure

6   that's why the agency counseled against it, because you

7   can't know going into a study that you're going to be as

8   successful as they happened to be here at minimizing bias.

9   I think they were reasonably successful although not

10   perfect.

11   And that's the problem. If once we open

12   Pandora's Box here, you may get a lot of open-label trials

13   in the future that won't be as clean, and sponsors need to

14   know that you're going to look at them very, very carefully

15   before you're going to declare something to be non-inferior

16   based upon open-label.

17   DR. TEMPLE: Just regarding crossovers, our non-

18   inferiority guidance doesn't absolutely say the preferred

19   analysis is on treatment, but it comes moderately close,

20   and we definitely ask for that analysis, and we look at

21   them both together. Usually, in different showing trials

22   we like the more conservative intent to treat, but it turns

23   out in these settings it's a good idea to look at all of

24   them, isn't it? Yes.

1   DR. LINCOFF: Dr. Neaton, you had a comment.

2   DR. NEATON: I just was going to say in terms to

3 Steve, I mean it's not so much in my mind. What is

4 reassuring is the on-treatment and the intention-to-treat

5 line up. The fact that they kind of crossed over to

6 warfarin, of course, that's kind of the part that you have

7 to build that into your thinking in interpreting the

8 intention-to-treat analysis.

9   DR. LINCOFF: Dr. Kaul.

10   DR. KAUL: I was just going to say I am reassured

11 by more robust outcomes, including mortality outcomes which

12 are relatively insensitive to ascertainment bias, going in

13 the right direction.

14   DR. LINCOFF: Dr. McGuire.

15   DR. MCGUIRE: Just three quick points. I think

16 we'd have a very different conversation if we had this

17 before we saw the data, but, you know, the data stand on

18 their own. And the sponsor took a big risk, but it seems

19 to have worked out well.

20   Two other quick comments. I think we're being

21 overly optimistic if we think we can do better than a 65

22 percent TTR. In clinical practice, that's just not

23 achievable. We've tried forever to do it, using all kinds

24 of mechanisms, including dedicated clinics. So I think

1   this is real-world comparison, and it shows us a

2   comparative strategy.

3   And then the third point is the open-label nature

4   perhaps contributed to, or allowed, the second dose of

5   dabigatran to be studied. So we have clinically a lot more

6   information with regards to the continuum of dose response

7   than we may have had in a two-arm trial limited by cost, to

8   do a blinded study. So there are some certain benefits,

9   both clinically and scientifically, to doing this type of

10 trial.

11   DR. LINCOFF: Dr. Krantz.

12   DR. KRANTZ: Darren, just in follow-up, what do

13 you think about this whole idea of comparative

14 effectiveness research? I mean is that the purview here?

15   I mean something I sort of worry about, the

16 slippery slope that we're going to be looking at. Rather

17 than efficacy studies, we're going to be moving towards

18 strategic studies, and you can see how things may change.

19 When you mentioned that, it's a strategic study design. I

20 wondered if you had any thoughts.

21   DR. MCGUIRE: Well, I think in a drug that is as

22 effective as Coumadin -- we have very few in the world that

23 give you a 60 percent relative risk reduction -- I have

24 much less concern that we'll walk backwards in non-

1 inferiority analyses, I think. And I think the net

2 clinical benefit analyses for comparative effectiveness is

3 quite helpful, not to replace but to augment the efficacy

4 data.

5   DR. LINCOFF: Dr. Nissen, did you have --

6   DR. NEATON: I really didn't. I think it's a

7 false dichotomy to suggest that doing an open-label design

8 allowed you to study two different doses of the drug. I

9 mean you can do a blinded design and blind all three dose

10 regimens. I don't think you've gained an advantage in

11 terms of the numbers of arms by making it open-label.

12 Either design can study three doses.

13   DR. LINCOFF: Okay. So we'll move on to the next

14 question, which is 1.2, were reasonable doses of dabigatran

15 selected for the study in RE-LY?

16   Dr. Nissen.

17   DR. NEATON: You know, I really like the fact

18 that they studied more than one dose. I've got to tell you

19 so often we're sitting here, looking at data, particularly

20 for anticoagulants where you've got a tradeoff between

21 efficacy and safety on the bleeding side. By giving us the

22 anchor of showing us two different doses, that were

23 sufficiently different that there were at least some

24 differences in outcome, they gave us a lot more

1   information. So I think they got this one right, and I

2   think these were reasonable doses.

3   Look, after seeing the phase two data I'm not

4   sure exactly how they came up with the two doses because

5   it's pretty dirty data, but they gave us two doses. I

6   think that was like throwing a dart at a dartboard, but

7   they gave us two doses that gave us somewhat different

8   results. And that, to me, is informative about making

9   decisions here, and frankly I think it's one of the biggest

10 strengths of this study was the fact they had the courage

11 to study two different doses.

12   DR. LINCOFF: Dr. Krantz.

13   DR. KRANTZ: I thought the PETRO data were pretty

14 convincing clinically, and then the way they looked at sort

15 of the trough versus effectiveness curves. It seemed very

16 reasoned in terms of how they picked the doses. So I think

17 I agree with Steve.

18   DR. LINCOFF: From my standpoint, I too agree. I

19 think there was some concern, I think, in some of the

20 background material about whether or not the doses were

21 enough different, but I think that they were very

22 rationally designed based upon what is a somewhat narrow

23 window, based upon the exposure data. And I think they

24 nicely bracketed the window, and clearly having this very

1 demonstrable dose response, I think, is very convincing of

2 the activity of the drug.

3   Dr. McGuire.

4   DR. MCGUIRE: You know, I think the doses were

5 well chosen, but I'm still quite concerned about the wide

6 variance of response PK, and so we have some PD data as

7 well suggesting that it may not just be a dose that needs

8 to be chosen but a titrated strategy. And I know that

9 wasn't studied in this trial, but there remains some

10 concern about, even within a given dose, the wide variation

11 with a lot of overlap between the two doses in the PK data.

12   DR. LINCOFF: Well, perhaps the applicability of

13 monitoring would come up later when we discuss whether or

14 not one or two doses should be approved.

15   If there are no more comments on that, we'll move

16 on to the next, which is 1.3.

17   DR. TEMPLE: Can I just mention something? Those

18 doses of 110 and 150 in the long tradition of cardiorenal,

19 we would laugh at that. We'd say, come on, you need at

20 least an order of magnitude. I mean I can hear Ravafiki

21 (ph) saying that. So it's amazing to me that they saw as

22 much as difference as they did with doses that close. We

23 usually counsel if you're going to do it spread them out,

24 for goodness sake, but they were right.

1   DR. LINCOFF: You wouldn't have counseled that

2   for warfarin, would you, 5 milligrams and 50?

3   DR. TEMPLE: No, that's the point. There were

4   some very steep parts of some dose response curves, right.

5   DR. LINCOFF: Do I see any other comments on

6   this?

7   Okay. The third: How should endpoint events

8   that occurred after discontinuation of study drug or

9   following crossover from dabigatran to warfarin be counted

10   in this open-label, non-inferiority study? Now we did

11   address this to some extent in the previous comments, but

12   if anybody wants to deal with this directly.

13   Dr. Emerson.

14   DR. EMERSON: Well, I guess I always go on the

15   idea that once you randomized you should have a firm point

16   that's the same for everybody that you answer, and I don't

17   like saying that just because somebody discontinues their

18   study drug that all effect is worn off or that there isn't

19   an aspect there. So my basic approach is always to say

20   that they should be counted in the primary analysis, and

21   then obviously the whole study can go to pieces if you find

22   out that it's not robust to doing the other, what I regard

23   as more mechanistic, sorts of analyses.

24   DR. LINCOFF: Dr. Nissen.

1   DR. NISSEN: Yes, I do think we need -- it's good

2   to do a sensitivity analysis where crossovers are excluded

3   just because of the fact that crossovers are going to tend

4   to bias toward the null hypothesis. I think that's a

5   reasonable sensitivity analysis to perform. Even though

6   the analysis is always going to be ITT as primary, that

7   would be a useful analysis to have.

8   DR. LINCOFF: Dr. Neaton.

9   DR. NEATON: I agree with the two previous

10   comments. I just want to say it's so nice to see a trial

11   where you actually can do the intention-to-treat analysis,

12   and so it's good to be able to do them both.

13   DR. TEMPLE: It's worth mentioning that when

14   we're looking at safety studies, which are in a sense like

15   non-inferiority studies, we strongly advise people that the

16   initial analysis should be the on-treatment analysis, and

17   Dr. Nissen is running a study in which that very approach

18   is taken because you don't want to bias toward the null

19   when you're looking for bad news.

20   DR. LINCOFF: Okay, and finally 1.4, are there

21   other aspects of the study design that importantly affect

22   the interpretation of the study?

23   Dr. Kaul.

24   DR. KAUL: I'm not sure whether it importantly

1 affects it, but I find it unusual when you use the same

2 endpoint for both efficacy and safety analysis. My

3 understanding was that the hemorrhagic strokes were counted

4 towards efficacy and, if I understand correctly, also

5 towards bleeding. So I mean if the drug favors both they

6 got lucky because the drug favored both. You're having

7 your cake and eating it too.

8   DR. LINCOFF: I think in general at this point

9 the sponsor's comment should probably be confined to

10 providing data or if we have specific questions.

11   Any other points on this?

12   All right. I've been asked to provide a chair

13 summary for each of these questions. So correct me if I'm

14 wrong, but for this question 1, I think I can summarize as

15 follows. With regard to the first point, I think most felt

16 that it was a reasonable approach to have used an open-

17 label study although with the caveats, particularly for

18 future development efforts, that this is a risky design and

19 that one needs to be extremely careful about both the

20 design and the execution.

21   And in the end, the data itself will sort of

22 define how acceptable the results are in light of an open-

23 label design, but that there are some advantages,

24 particularly given the types of agents that were being

1 tested and the treatment regimens associated with them.

2 The doses, perhaps surprisingly, were felt to be a good

3 choice and a good feature in terms of interpreting the

4 study.

5   Endpoint events are ideally, at least from the

6 pure sense, assessed as intention-to-treat. But for the

7 issue of non-inferiority and the fact that much of this is

8 oriented around safety, at least a key secondary analysis

9 is the on-treatment design, and that in general there

10 weren't huge other issues felt to influence the

11 interpretation of the study.

12   All right, question 2, please comment on the

13 adequacy of the conduct of RE-LY, and then 2.1 first,

14 disregarding other factors potentially confounding such

15 comparisons, was the time in the therapeutic range on

16 warfarin in RE-LY good enough so the warfarin group is an

17 appropriate comparator to show effectiveness of dabigatran

18 and/or to show superiority of dabigatran to warfarin?

19   So in this case I think I interpret this that

20 we're being asked to comment on how we feel the control

21 therapy was, and this is our opportunity to make a comment

22 regarding whether or not we think that this trial has

23 demonstrated superiority.

24   Dr. Nissen.

1   DR. NISSEN: I hate silence. I think that they

2   did as good a job as anybody has done in any contemporary

3   trials. Now it's disappointing that no one can seem to do

4   any better with warfarin, but 65 percent is kind of where

5   most of these studies end up. I think it was reasonable.

6   There are probably people who, with specialized

7   clinics and very intense follow-up, are able to do better,

8   but we also have to consider the real-world implications of

9   this. You know, if you're a cowboy in Montana and you have

10   to go in and get your INR checked every week, you're not

11   likely to be very happy when you're out on the range.

12   There is a practical limit on how often you can get INRs in

13   order to keep people in range. Coumadin is just a tough

14   drug to use. I think they did an adequate job to show

15   effectiveness.

16   I am concerned about the superiority question and

17   not so much because of how warfarin was used, but because

18   of the inherent biases in an open-label design and the fact

19   that the p-value for MACE is not as robust, mainly because

20   MI seems to go in the wrong direction. The issue on

21   superiority for me is not so much how they used warfarin,

22   but other areas of trial conduct. So I think warfarin use

23   was quite reasonable in this trial, not perfect, but good

24   enough.

1   DR. LINCOFF: From my standpoint, I actually

2   think that the warfarin control was fairly optimal, and I

3   say "optimal" not because of how high it was, but the fact

4   at how well it models the upper end of clinical practice.

5   In fact, had this been artificially high -- we always, in

6   trials, want our comparative arm to be excellent medical

7   care because comparing to mediocre medical care doesn't

8   really tell us as much as it would have. But comparing to

9   unrealistically high medical care I think is also a

10 deficit, and it would have been a lost opportunity, a lost

11 opportunity to bring a therapeutic that really does improve

12 outcome in patients really being treated, even in patients

13 being treated at the upper end of what's generally

14 clinically available. So I think it actually would have

15 been unfortunate had there been a greater degree of

16 warfarin control than there is in the good real world.

17   I want to throw my vote to the issue of

18 superiority. I actually think that the data demonstrate

19 superiority for the 150 dose. I think the number of events

20 that would have been required to remove, to lose

21 superiority, statistical significance for superiority is

22 too many to believe would have happened, regardless of

23 ascertainment bias.

24   I'm also much less impressed with the myocardial

1   infarction. I don't know if it's true, and I believe, and

2   I'm a cardiologist, so obviously I'm worried about

3   myocardial infarction. But I much more importantly fear

4   stroke than a myocardial infarction. So I think the issue

5   is not myocardial infarction; the issue is stroke.

6   There could be a caveat until further data comes

7   out that this drug may not protect us from myocardial

8   infarction as well as warfarin, but I think the data are

9   fairly convincing that there's also superiority over

10   warfarin.

11   Any other comments here? Yes.

12   MR. SIMON: From a patient standpoint, after

13   knowing what I know now, which is a lot more than what

14   other patients know, I would have no problem taking

15   dabigatran, the 150 mg.

16   DR. LINCOFF: Dr. Emerson.

17   DR. EMERSON: So there are two parts to this

18   question, neither of which do I have the clinical

19   perspective to answer, but one is whether they applied

20   warfarin therapy appropriately for what warfarin therapy

21   should be, and the second is that they applied it in the

22   correct patients. When asking, I haven't heard anybody say

23   it was the incorrect way to do warfarin therapy. It seemed

24   to be the right therapeutic range, and so on. And the only

1   question I heard about the patient population was the CHAD

2   0/1 group, and that that was one-third of the patient

3   population.

4   Again, the thing that we always have to entertain

5   is since the major effect seems to really be the bleeds are

6   we just removing the ill effects of inappropriately applied

7   therapies. I don't think that's true, but I'd just be

8   interested to hear confirmation on that.

9   DR. LINCOFF: Dr. Temple.

10   DR. TEMPLE: What do we think the effect of

11   warfarin on MIs is?

12   I mean there's actually a study to see how good

13   it is in people who have a stroke, not atrial fibrillation

14   stroke. It's not close to aspirin. The war study showed

15   that pretty well. So I'm not too surprised that the MI

16   component didn't come out one way or the other because I'm

17   not sure how effective warfarin is on that in the absence

18   of embolic phenomena.

19   DR. LINCOFF: Mid-dose warfarin plus aspirin

20   compared to aspirin alone after acute coronary syndromes

21   has been -- actually its biggest difference has been on the

22   stroke component of the composite endpoint, but there have

23   also been at least trends toward reduction of myocardial

24   infarction is my understanding.

1   DR. TEMPLE: Yes, but trends isn't the same as a

2   70 percent reduction. I mean that could be why MACE isn't

3   as strong as the other things because those are not the

4   things that anticoagulants do in people with fibrillation.

5   DR. LINCOFF: Dr. Kaul.

6   DR. KAUL: Dr. Temple, are you asking the

7   question what would be the impact of dabigatran on MIs if

8   we had a different comparator like a placebo and see what

9   happened?

10   DR. TEMPLE: No. I was just not too surprised

11   that MACE wasn't as strong as the other finding because one

12   of the components of MACE isn't, as far as I know, markedly

13   affected by either of these drugs. So I expected it to be

14   sort of even and not move very much.

15   DR. KAUL: But if warfarin decreases the MI

16   frequency, post-MI, and if dabigatran were to be compared

17   to the right control, then you would see an amplification

18   of this MI signal, wouldn't you?

19   DR. TEMPLE: Yes. I mean I can see a study on

20   MIs directly. It probably would have to be considerably

21   larger than this because the effect is probably smaller.

22   We're talking about a 70 percent, 60 percent reduction in

23   these things.

24   One of the components of MACE is not something we

1   expect to be markedly affected by this. That's what I'm

2   asking about. I didn't think it was.

3   DR. LINCOFF: Dr. McGuire.

4   DR. MCGUIRE: Yes, just coming back to the

5   specifics, this question is asking specifically is the TTR

6   percent adequate, not were these things demonstrated. So I

7   would say there may be reasons to believe these things were

8   or were not demonstrated, but I would say the TTR was

9   reflective of clinical practice at the upper end and was

10   adequate for both of these considerations.

11   DR. LINCOFF: But do you care to comment on the

12   second part of that question? Do you believe it shows

13   superiority of dabigatran?

14   DR. MCGUIRE: Well, that's a different question

15   altogether. This is asking about the adequacy of the TTR.

16   If superiority was not shown, in my mind it's not because

17   the TTR wasn't adequate. Does that make sense?

18   DR. LINCOFF: Yes.

19   Dr. Nissen.

20   DR. NISSEN: Yes, this superiority question is

21   really an important one, and let me see if I can explain,

22   Bob, where I'm coming from here.

23   First of all, I would encourage the agency to

1 look at MI across the entire development program. We saw

2 another trial shown here that wasn't really presented, but

3 where the MIs were sort of going in the wrong direction as

4 well. I think if you look at this and there's a consistent

5 pattern of more MIs in comparison to warfarin, that is

6 informative about whether or not there is some potential

7 difference between warfarin and dabigatran.

8   The other issue on superiority is GI bleeding,

9 which we haven't talked very much about, but there clearly

10 is a higher risk in GI bleeding. Now would I equate a GI

11 bleed with a GI bleed with a stroke? No, but it's not an

12 event of zero importance. It can result in hospitalization

13 and consumption of health care resources and lots of other

14 things. So the fact that there were -- and then the last

15 thing, of course, is the open-label design which tends to

16 undermine confidence in the lack of all the biases we've

17 talked about.

18   So what undermines the superiority claim is a

19 whole series of issues here that I think make it very hard

20 for me to conclude decisively that we have a superior drug.

21 Even though it may well be non-inferior, I'm not sure it's

22 superior.

23   DR. TEMPLE: Can I ask people about that? I mean

24 we don't usually, sort of, give ratings from 1 to 10. This

1   one is 8, this one is 6, stuff like that. But we're going

2   to show the data if it's approved and you recommend, all

3   things being considered subsequently.

4   So the data will show what -- I mean if you show

5   the data and put a p-value next to it, what is that? Isn't

6   that a superiority claim, sort of? I mean it would also

7   show the excess bleeding. It would show all of those

8   things in labeling. We always do.

9   Pasaril (ph) was not given a superiority claim,

10 but there's a result that shows there were fewer of these

11 events. So people can read those things, and people are

12 allowed to put them in their ads and stuff.

13   So what reservations are you talking about?, a

14 statement that says, "by the way, I don't believe this?"

15   (Laughter)

16   DR. TEMPLE: Where do we go with these concerns?

17   DR. NISSEN: Isn't this really question 3?

18   DR. TEMPLE: Maybe it is.

19   DR. LINCOFF: Yes, it does come up again in

20 question 3.

21   Dr. Kaul.

22   DR. KAUL: Effectiveness of 110 mg of dabigatran,

23 I have some issues with it, but the way I interpret non-

1 inferiority is while, okay, you met the non-inferiority

2 criteria, but does it offer ancillary advantages, usually

3 in terms of safety, in terms of convenience, in terms of

4 cost. Okay. I know we're not allowed to consider cost

5 here, so safety and convenience.

6   Convenience -- it's a b.i.d. dosage, but you

7 don't have to monitor. Okay.

8   Safety -- yes, if you eliminate the hemorrhagic

9 stroke, because it's always counted towards the evaluation

10 of non-inferiority/effectiveness, I'm not quite sure

11 whether we'll see a slam-dunk advantage in favor of safety

12 in bleeding. But then that's counterbalanced by the

13 increased signal for myocardial infarction. I agree with

14 you. If you don't believe it, you dismiss it. But it's

15 hard for me to kind of dismiss this MI. So I'm not quite

16 sure the 110 mg of dabigatran makes it slam-dunk.

17   With regards to the 150 mg of dabigatran, I'm

18 more easily persuaded to an inference of non-inferiority

19 with respect to the 150 mg of dabigatran. There are some

20 issues with regards to superiority. I don't know whether

21 we are coming back to it or not.

22   DR. LINCOFF: Let's come back to that because it

23 is more explicitly in question 3.

24   Okay. The next part of question 2 is, was

1 follow-up for endpoint events adequate in all treatment

2 groups?

3   Dr. Neaton.

4   DR. NEATON: I think that while it could have

5 been better, I think the response the sponsor gave us after

6 lunch has clarified some things in my mind, at least in

7 terms of the numbers involved. It does seem to me very

8 implausible, given the number of people with unknown end-

9 point status, unless there were major differences in risk

10 across the treatment groups, that it would kind of change

11 the results very much. So I think the follow-up in a trial

12 of this size was adequate, and that would be my simple

13 answer.

14   DR. LINCOFF: I'm sorry, Dr. Coukell. You had, I

15 guess, wanted to speak.

16   DR. COUKELL: It's fine. I can defer to question

17 3.

18   DR. LINCOFF: Okay. All right. This is 2.3, was

19 follow-up for adverse events, particularly hepatotoxicity

20 and bleeding, adequate in all treatment groups?

21   Dr. Emerson.

22   DR. EMERSON: So, hepatotoxicity, I think yes.

23 The bleeding, I'm not certain only because I don't know how

1 well the surveillance was against the GI bleeds and as that

2 turns out to be something that is potentially plausible

3 mechanistically. Ninety percent of the administered pro-

4 drug is excreted in the feces, and what I believe I heard

5 them say was that roughly two-thirds of that is as active

6 form and so on. Now to talk about clinical bleeding, it's

7 probably okay; subclinical bleeding, I don't know.

8 DR. LINCOFF: That if a tree falls in the forest

9 and no one hears, does it matter?

10 DR. EMERSON: That's the subclinical versus

11 clinical question.

12 DR. LINCOFF: Dr. Temple, you have your light on.

13 DR. TEMPLE: No.

14 DR. LINCOFF: Okay. Anybody else want to comment

15 on this?

16 DR. COUKELL: With regard to hepatotoxicity, I'm

17 convinced by the follow-up or the monitoring they've done,

18 but it is two years in 12,000 patients and there is

19 apparently a class effect or an effect in other drugs in

20 this class on liver function. So I think the labeling, we

21 have to trade it off against a drug that whatever its

22 downside the profile is well characterized.

23 So it seems to me the labeling would have to talk

1   about this effect in other drugs in the class, so that

2   clinicians, once it's out in practice, are alert to that

3   possibility, at a minimum.

4   DR. LINCOFF: I would want to -- I mean I might

5   question that. A class relates these are thrombin

6   inhibitors. But do we know what it is structurally or what

7   determines hepatotoxicity? Is there any reason to believe

8   that in that regard these drugs function as a class?

9   ximelagatran versus?

10   DR. TEMPLE: None that I know of. And for what

11   it's worth, experience with other hepatotoxins show members

12   of the same class do sometimes and don't sometimes. But I

13   mean nonsteroidal anti-inflammatory drugs are highly

14   hepatotoxic; the rest of them are not. That's been true

15   for most. So the structural thing that makes you

16   hepatotoxic isn't necessarily the same thing that

17   determines your pharmacologic effect.

18   DR. LINCOFF: Dr. Nissen.

19   DR. NISSEN: Yes, there is a puzzling aspect of

20   the data which is the surprisingly high rate of Hy's Rules

21   in the warfarin. Having served on the ximelagatran panel,

22   we saw a very different pattern. So because the numbers of

23   events are very small, there is at least some uncertainty

24   left here. I think we have to acknowledge that.

1   I mean is it possible that some kind of spurious

2   result in the warfarin arm here has colored these results?

3   I think it's very unlikely. There's no signal there at

4   all, but I can't explain all those Hy's Rule cases in the

5   warfarin arm. I just can't get it. It's really way out of

6   ordinary from what you'd expect.

7   DR. LINCOFF: I would like to though, on that

8   point, point out that again there was a much broader

9   representation from different countries in this trial than

10   in the supportive trial. So I think that that -- not to

11   say that there's -- I mean there's lots of other reasons

12   why all the patients may have had higher rates of Hy's Law.

13   DR. TEMPLE: Nhi may need to comment, but I don't

14   think there were so many, if any, cases of Hy's Law. That

15   includes ruling out obstructive reasons. It's not just

16   transaminase plus bilirubin and no other. No hepatitis;

17   you've screened it out.

18   I'm not sure there were any we thought were.

19   But, Nhi, do you want to correct me? Is that right? She

20   says that's right.

21   DR. BEASLEY: There was only one probable case.

22   The numbers that I showed up there were potential.

23   DR. LINCOFF: Dr. Kaul.

24   DR. KAUL: Yes, with regards to GI

1 hepatotoxicity, since we really don't understand what the

2 mechanism is and since it was an unanticipated finding, I

3 agree with Dr. Emerson. There was no a priori surveillance

4 here. So we don't know whether it requires a permissive

5 environment or whether it's contributory or whether it says

6 something else that we haven't looked at. So I remain

7 potentially concerned that the follow-up might not be

8 sufficient.

9   With regards to hepatotoxicity, I guess one could

10 make an argument that two years may not be sufficient, but

11 if there is a follow-up study that will be monitoring these

12 adverse events I'll be a little bit more reassured.

13   DR. LINCOFF: Dr. Krantz.

14   DR. KRANTZ: I'm just going to agree with Dr.

15 Kaul. I think for me one of the puzzling aspects was this

16 higher risk of gastritis symptoms which correlated with a

17 three to four-fold increase in GI bleeding. Yet, if I

18 recall Salim Yusuf's presentation, it was lower GI bleeds

19 that they were documenting. So I think there really is a

20 lot of unanswered questions here remaining for this

21 medication in that respect.

22   DR. LINCOFF: I've noticed the sponsors. At this

23 point again, it should be confined to if there are specific

24 data that we're either interpreting wrong.

1   DR. CONNOLLY: No, I mean I just wanted to

2   clarify that there is a follow-up study ongoing. So 6,000

3   patients who were enrolled in RE-LY and randomized to

4   dabigatran were offered the opportunity to go in the RE-LY-

5   ABLE study that began when they finished their final

6   follow-up visit. They remained on their randomized doses,

7   and they remained double-blind, and they're now approaching

8   the end of the second year of follow-up, and this is

9   planned to continue another year. It's being monitored by

10 DSMB, and we will have further information on

11 hepatotoxicity from those patients.

12   DR. LINCOFF: Dr. Yusuf.

13   DR. YUSUF: Again, I'd like to present some data

14 that reflects on some of the discussion. One of the points

15 that Dr. Nissen said was to look at MI systematically

16 across different trials. We've done it.

17   DR. LINCOFF: Okay.

18   DR. YUSUF: I'm sure we all acknowledge you

19 shouldn't look at non-fatal MI without looking at

20 cardiovascular debts. And when you look at them together,

21 even in the RE-DEEM study, the two doses that we're

22 interested in, there isn't an excess, 110 and 150.

23   And I believe we saw some data in the DVT trials.

24 Again, there isn't an excess. So we're puzzled. There

1 isn't a clear signal that cumulates across. We need to add

2 non-fatal and cardiovascular debt.

3 DR. LINCOFF: Sorry. Are you saying it's not,

4 isn't or is?

5 DR. YUSUF: Isn't. Isn't.

6 And the second point I just want to make is a

7 point that Dr. Emerson made, and Dr. Nissen was interested

8 in. It's whether the open nature of the trial led to an

9 imbalance in the stoppage of dabigatran, higher rate,

10 compared to warfarin.

11 This is best addressed, not from the RE-LY study,

12 but from the ximelagatran trial which was SPOR TIF V and

13 SPOR TIF III. SPOR TIF V was blinded. There are two.

14 Actually in both trials, in the open and the blinded trial,

15 there was a 5 percent excess, almost identical to this

16 study, excessive stopping in the ximelagatran compared to

17 the warfarin group. So the blinded and open didn't make a

18 difference.

19 The last point I want to say is whatever penalty

20 you choose in the future, for future trials, that's fine,

21 for your non-inferiority margin. But I'd like to point out

22 that the non-inferiority margin achieved in this trial was

23 1.1 which is below Dr. Nissen's suggestions of 1.25 or 1.2.

24 DR. LINCOFF: Thank you. Then the last point

1   here, are there other aspects of the study conduct that

2   importantly affect interpretation of the study? So then

3   summarizing 2, I think with regard to the warfarin control

4   I think the consensus was that it was acceptable, perhaps

5   even good, and that at least that factor didn't affect the

6   decision of whether or not there was superiority of

7   dabigatran to warfarin. Follow-up endpoints in general for

8   endpoints was adequate, and the loss data was unlikely to

9   have meaningfully affected the results.

10   Follow-up for hepatotoxicity was adequate and

11   fairly convincing that there's no signal there. It's

12   unclear for some subclinical bleeding or the mechanism of

13   the observed increase in gastrointestinal bleeding,

14   although that was not prospectively anticipated, and it's

15   not surprising that that data are not available.

16   Moving on to question 3, please comment on

17   effectiveness. Is dabigatran effective in reducing the

18   combined risk of stroke and systemic embolus? If so, 3.1,

19   do both stroke and non-CNS systemic embolus contribute to

20   the effect?

21   Let's not go to sleep yet. Dr. Nissen.

22   DR. NISSEN: The answer is it is. And, you know,

23   Dr. Yusuf made my point before I could make it, which is

24   that even if I penalize the trial for the open-label design

1 and lower the acceptable upper confidence interval here it

2 is better than any reasonable upper confidence level that

3 you might select. I mean you could even be very rigorous

4 and select 1.2, and it makes it, so for me.

5   But the reason I'm saying that though is that you

6 may face in the future another drug that comes along where

7 the margin is much closer. And if the trial is open-label,

8 if this trial had come very close to 1.38 and had been an

9 open-label trial, I would not have been able to vote for

10 the effectiveness. I'm able to vote for effectiveness here

11 because it achieved such a high level of demonstration of

12 non-inferiority, that any reasonable upper confidence

13 interval would have been achieved.

14   So I agree with Dr. Yusuf, but that does not mean

15 that you won't face this issue for other drugs and have to

16 decide whether an open-label design. The biases require

17 you to lower the acceptable upper confidence interval.

18   DR. LINCOFF: I'll try to address the issue of

19 both stroke and non-CNS systemic embolus. Obviously, the

20 rates of non-CNS systemic embolus were very low, and they

21 were essentially the same. I think part of that reflects a

22 difficulty in adequately making that diagnosis as well as

23 the rarity of the events. So I think this is primarily a

24 stroke phenomenon, although there's nothing to suggest that

1 there was an adverse effect on other embolus.

2   I also agree with Dr. Nissen, that effectiveness

3 is shown here, because of these data.

4   Dr. McGuire.

5   DR. MCGUIRE: I would just comment. As you

6 mentioned, it's a very low event rate contributing to the

7 composite, and also it was the one adjudicated event that

8 was discordant in its rate of adjudication by Coumadin

9 dosing, where some unblinding. In such few events,

10 unblinding could have contributed. I think 21 out of 27

11 events were confirmed, if I recall, in the warfarin arm

12 versus only about 50 percent of the dabigatran arm. So

13 there were differential adjudication proportions, which

14 only raises a small signal. I don't think it detracts from

15 the overall effectiveness for the stroke though.

16   DR. LINCOFF: Any other comments on this point?

17 Okay, 3.2, this is key, is effectiveness demonstrated at

18 both doses?

19   Dr. Emerson.

20   DR. EMERSON: Well, I think so in terms of the

21 non-inferiority versus warfarin. I think it's just well

22 away from the margins or any margins that I would put on

23 this.

1   DR. LINCOFF: Dr. Nissen.

2   DR. NISSEN: Yes, and again I know that the

3   primary reviewer was not comfortable with a 110-mg dose. I

4   am comfortable. And I do think that no matter how you look

5   at this there is a safe margin from what was a reasonable

6   upper confidence interval for the hazard ratio for non-

7   inferiority, even at the 110-mg dose.

8   And I want to just speak to a minute to the

9   clinical implications here because I think they're very

10   important.

11   DR. LINCOFF: Dr. Nissen, just one second?

12   DR. NISSEN: Yes.

13   DR. LINCOFF: Question 6 is all oriented around

14   the dose.

15   DR. NISSEN: Okay.

16   DR. LINCOFF: Not that I want to cut off, but I

17   think it would be most relevant there because that's the

18   key question.

19   DR. NISSEN: All right. Well, I will save it.

20   DR. LINCOFF: Okay.

21   DR. NISSEN: Okay.

22   DR. LINCOFF: I think this is specifically just

23   are we seeing efficacy in both doses because that's really

1 the reason, my understanding of why the FDA wants us here,

2 is to discuss the different doses.

3   Are the data sufficient to conclude that the 150-

4 mg dose is superior to the 110-mg dose for reducing the

5 risk of stroke and non-CNS systemic embolus?

6   DR. TEMPLE: Can I just ask Sanjay how he feels

7 about that because he was sort of expressing the contrary?

8   DR. KAUL: Well, you know, like I said, you can't

9 have it both ways. I mean if you want to count to

10 endpoints, count it towards one, efficacy or safety.

11   And if you look at the ischemic stroke event rate

12 with 110 mg of dabigatran, the hazard ratio by my

13 calculation is 1.12 with the upper boundary going to 1.42,

14 and I would argue that it does not meet the FDA's non-

15 inferiority criteria of 1.38.

16   DR. TEMPLE: So that's just looking at?

17   DR. KAUL: Just at the ischemic stroke.

18   DR. TEMPLE: At ischemic strokes.

19   DR. KAUL: Right. So we've got to make up our

20 minds. You know. I was critical of the WATCHMAN study

21 because they did exactly the same thing. They used

22 hemorrhagic stroke towards efficacy and safety assessment.

23   And there's a point to be made that you can use

1 that, but here, when you look at the pure ischemic stroke

2 event rate, it doesn't meet the more robust FDA-suggested

3 non-inferiority criteria. Then when you look at the

4 hemorrhagic endpoints, I would argue that there's some

5 counterbalancing by the MI signal. So I am not convinced

6 in my mind that the dabigatran 110 mg makes it by the type

7 of analyses that I did.

8   DR. LINCOFF: Dr. Emerson.

9   DR. EMERSON: I guess, so I take the view of I

10 like it both in the same endpoint because the whole

11 question is can you remove one without introducing the

12 other. That's where I -- but this is what I've also been

13 hinting at all along, is saying the major effect appears to

14 be in the bleed. It's really that this is a safer way to

15 treat it, more than it is more effective on the ischemic

16 stroke. It seems it's more a benefit on the hemorrhagic.

17   DR. LINCOFF: Dr. Temple.

18   DR. TEMPLE: Well, if I understand it -- Aliza

19 needs to correct me if I'm wrong -- the non-inferiority

20 margin was based on the sum of the two kinds of strokes

21 because that's what the past studies did. So they're

22 supposed to be allowed to use that.

23   DR. KAUL: Can I seek some clarification in

24 regards to that because I'm not quite sure whether each of

1 the five or six trials that went into the pooled estimate

2 looked at the same endpoint because I thought it was a

3 mixture? Some had ischemic stroke only; others had

4 ischemic and hemorrhagic stroke only. So I think that

5 would be important to clarify that.

6 　　　　　DR. LINCOFF: Yes, I understand you have some --

7 　　　　　DR. CONNOLLY: I can clarify that.

8 　　　　　DR. LINCOFF: You are PI on one of the studies.

9 　　　　　DR. CONNOLLY: Yes, I was PI on one of the

10 studies, and I've been involved in a lot of this area. In

11 fact, the composite of hemorrhagic and ischemic stroke was

12 the primary outcome of all of these studies.

13 　　　　　DR. KAUL: If I can respond to Dr. Emerson's

14 statement, non-inferiority, the way I interpret non-

15 inferiority, is essentially focusing on the efficacy

16 endpoints. Then once that criteria has been met, then we

17 should look at safety assessment. I personally look for

18 superiority with respect to safety.

19 　　　　　And I think there's been a debate amongst the

20 cardiovascular community, particularly the acute coronary

21 syndrome trials that the Chairman has been involved in --

22 REPLACE-2 and ACUITY and HORIZONS. Do you consider mixing

23 efficacy and safety for non-inferiority assessment, or do

24 you like to separate them?

1   DR. LINCOFF: You can rightfully criticize trials

2   like that where a bleeding endpoint is combined with an

3   ischemic endpoint, but this is different. I mean these are

4   strokes. You wouldn't, for example, differentiate a

5   hemorrhagic myocardial infarction, which occurs rarely,

6   from a non-hemorrhagic, I mean.

7   So I agree with Dr. Emerson, that this is an

8   appropriate combined endpoint. And the fact that it is a

9   component of bleeding, albeit a small component of

10   bleeding, numerically the overall bleeding endpoints were

11   not driven by the hemorrhagic stroke. So it's not like we

12   were driving both endpoints by the same.

13   I think that the neurologic deficit that results,

14   if anything, with a hemorrhagic stroke is greater than that

15   of many ischemic strokes. So I think that's an appropriate

16   combination. Had you seen a markedly different ischemic

17   stroke rate, and I agree the protection wasn't as good, but

18   I don't think it's fair to expect a non-inferiority margin

19   to be significant for a component of a composite endpoint.

20   DR. KAUL: Well, those are very precise reasons

21   we should a priori define that.

22   DR. LINCOFF: Dr. Emerson.

23   DR. EMERSON: Just commenting on the non-

24   inferiority, I mean we can do non-inferiority against any

1   sort of endpoint. I mean frequently we apply the non-

2   inferiority on some major top-line endpoint to then prove

3   superiority on some sort of a safety endpoint of things,

4   and we separate it. But in this case it just seems clear

5   to me that truly its effectiveness rather than efficacy

6   really that we're really trying to go at here, and that

7   combining them is the most appropriate thing.

8   DR. LINCOFF: Dr. Nissen.

9   DR. NISSEN: Sanjay, we could do it your way.

10 What we could do is look at efficacy for ischemic and

11 hemorrhagic stroke and then take the hemorrhagic stroke out

12 of the safety endpoint.

13   I mean I think you make a good point about not

14 double-counting, and I get it, and I do get it. But even

15 if you do that, it really doesn't change the overall

16 impression.

17   I can't see splitting out the two types of stroke

18 from the efficacy analysis. I presume this was agreed to

19 in advance, that it would be all stroke, both ischemic and

20 hemorrhagic. So that 1.38 or 1.46 was based upon an

21 understanding of what would be counted in the endpoint, and

22 they met that non-inferiority margin by a considerable

23 amount for both the 150 and the 110, albeit with some

24 issues about trial design.

1   DR. LINCOFF: Dr. Neaton.

2   DR. NEATON: I took the question to be

3 effectiveness too and for that reason you want to look at

4 the entire range of endpoints that were looked at here. I

5 think one of the nice things in this trial is you have a

6 range of both the stroke endpoints, the mortality,

7 cardiovascular and the bleeding endpoints. And it seems

8 pretty consistent to me that at both doses you're clearly

9 not inferior, and so that if you believe warfarin is

10 effective these doses are effective.

11   Just to follow up on what Steve said, I do agree,

12 Sanjay, that if I were to look at this I'd take it out of

13 the bleeding endpoint and leave the stroke the way it is.

14   DR. KAUL: But then you have to factor in the MI

15 signal as well.

16   DR. NEATON: The MI signal is more complicated,

17 and I guess Salim said that when you throw in

18 cardiovascular. It doesn't make any sense to me to look at

19 the MIs that we saw earlier without factoring in at least

20 the arrhythmic deaths or the other cardiovascular deaths.

21 They have to be factored into this. Otherwise, we're

22 talking about people that survived to get to the hospital,

23 to get a diagnosis, and there are a lot of people that just

24 drop dead. So that has to be factored into this at some

1 point.

2   DR. LINCOFF: Dr. Emerson.

3   DR. EMERSON: So I'm not doing this with as much

4 certainty, but the concept of the overall mortality being

5 tied in there and the fact that signal is still in the

6 direction, though not quite as convincingly, I think is

7 also just speaking to the overall effectiveness, and that's

8 sort of how I deal with the MIs.

9   DR. LINCOFF: Dr. Temple, it looked like you had

10 --

11   DR. TEMPLE: Not that we couldn't reconsider it

12 if people thought we should, but in all of the anti-

13 platelet drugs and things like that hemorrhagic and

14 thrombotic strokes are always counted as part of MACE just

15 because nobody feels -- I mean we've always thought you

16 couldn't really tell them apart very well anyway. There's

17 a very well established pattern of doing that.

18   DR. KAUL: But there, the hemorrhagic stroke

19 rates are very, very low. It's a very small component of

20 the overall stroke. This is a different population. This

21 is atrial fibrillation on a blood thinner. So the relative

22 proportion is quite high.

23   DR. LINCOFF: Well, in fibrinolytic trials, it

24 was often disabling stroke, both hemorrhagic which was the

1   majority of them, but also some ischemic strokes. So I

2   mean there is precedent even in cardiovascular trials.

3   DR. EMERSON: And I'll also note there's just a

4   huge competing risk here that my a priori belief would be

5   that we are sometimes swapping ischemic strokes for

6   hemorrhagic strokes in the exact same patients, and there

7   are no data that we will ever have that can answer that

8   question.

9   DR. LINCOFF: I think that's an advantage here

10   because it speaks again to the dose response. I mean what

11   looks like a fairly striking difference in ischemic stroke

12   I think speaks to the activity of the drug. The fact that

13   we could do that and still maintain the safety reduction in

14   hemorrhagic I think is a benefit.

15   And that speaks to the next question, which is: Are

16   the data sufficient to conclude that the 150-mg dose is

17   superior to warfarin?

18   DR. KRANTZ: I think it was pretty compelling, at

19   least for ischemic stroke. And I think even the trend that

20   the FDA showed: Theoretically, if you increase the dose

21   further, would that dose response be augmented further? So

22   I think the data was pretty good.

23   DR. LINCOFF: I may have skipped 3, so we'll come

24   back to 3. But 4, so this is really where I guess it was

1 intended to comment on the superiority, which we have

2 discussed a bit in the past.

3   Dr. Nissen, you had a comment?

4   DR. NISSEN: No.

5   DR. LINCOFF: Okay. All right, then jumping back

6 to 3.3, which I inadvertently skipped, are the data

7 sufficient to conclude that the 150-mg dose is superior to

8 the 110-mg dose for reducing the risk of stroke and non-CNS

9 systemic embolus?

10   DR. KRANTZ: That was the question I was

11 addressing, just to clarify.

12   DR. NEATON: I mean I think the data are less

13 compelling for the comparison of the two doses as opposed

14 to the comparison of the high dose versus warfarin, which I

15 guess is the next part of the question. So I would say no,

16 it's not compelling for high dose versus low dose for the

17 primary endpoint.

18   DR. LINCOFF: So can you say why? I mean the

19 numbers were, the p-values were, and this is the blinded

20 comparison. So what is it about this that -- can you

21 explain why you feel that way?

22   DR. NEATON: Again, I'm looking at the overall

23 kind of effectiveness question. If you look at the

1 bleeding, the stroke, I mean compared to warfarin the high

2 dose is clearly superior than balancing kind of against the

3 low dose. I think there's the potential that both doses

4 could have efficacy in some populations, and so I guess I

5 buy the argument that the two doses are both effective and

6 have some utility.

7   DR. LINCOFF: But I have to push you on this

8 because the question is phrased "for reducing the risk of

9 stroke and non-CNS systemic embolus." So they're really

10 trying to get purely on efficacy here.

11   You've got a p-value that is. So if you don't --

12 we will talk later about the balance, which is the whole

13 point of question 6.

14   Dr. Emerson.

15   DR. EMERSON: So if I remember correctly, this

16 one was not pre-specified?

17   DR. LINCOFF: I thought it was, which is the

18 reason for the blinding.

19   DR. NEATON: It was presented as a post hoc.

20   DR. EMERSON: It was presented as a post-hoc

21 analysis, and so this is where the scientific theory and

22 statistical theory meet game theory. The concept of

23 throwing in an extra dose and realizing that yes, I am

1 drawing a whole lot from the dose response, and I'm liking

2 that, and so I have to say that since I'm putting some sort

3 of weight in it I say there must be some part of me that's

4 saying it's sufficient to conclude that.

5 But recognizing that had it not been

6 statistically significant and just the estimate being the

7 in right direction, a lot of us might have tried to look at

8 that and say, oh, but there's a suggestion in the right

9 way, and it's 50-50 that they would have been in that if

10 they were exactly equal.

11 So I'm just trying to give an unqualified maybe,

12 to say I am putting some weight in that, but that there is

13 an aspect on the post-hoc analysis that should be taken

14 into account here.

15 DR. LINCOFF: Dr. Fox.

16 DR. FOX: Yes, I think the agency and the panel

17 have poked and prodded the deficiencies, real or perceived,

18 in the open-label design enough to cast any doubt they want

19 to on the reliability of the statistical analysis. And in

20 the end, what we've got here is a comparison of two blinded

21 arms, in terms of compared to each other.

22 It's not like the sponsor is trying to pull out

23 in a post-hoc way or at the last minute a comparison of a

24 test article to an active or inactive comparator on some

1 other endpoint, like ingrown toenails or sudden cardiac

2 death, but in fact just saying is there a dose response is

3 the way I interpret this question. It's got a p-value of

4 0.04, and I would say yes.

5   DR. LINCOFF: Dr. Nissen.

6   DR. NISSEN: I'm not so sure, and again I'm

7 looking at Table 2 on page 11 of the FDA briefing document.

8 What you see there is this analysis of net benefit, and I

9 would encourage everybody to look at it. Intracranial

10 hemorrhage or stroke/SEE, the 150 versus 110, which is the

11 way the question is asked here, is a hazard ratio of 0.79

12 with a p-value of 0.3. Now a p-value of 0.3 in a single

13 trial, even blinded, doesn't generally meet the standards

14 for proof of superiority, and so unless I'm

15 misunderstanding something here, the way the question is

16 worded --

17   DR. STOCKBRIDGE: The question has only to do

18 with the effectiveness endpoint. It has nothing to do with

19 the overall approvability of that dose.

20   DR. NISSEN: Yes, but I understand. But isn't

21 that p-value 0.3?

22   DR. THOMPSON: Well, the ICH is not stroke,

23 right?

24   DR. NISSEN: I see. Okay, I see.

1   DR. STOCKBRIDGE: Right. The p-value that's

2   appropriate is the one that Jonathan cited, 0.004.

3   DR. NISSEN: I see. Okay. Sorry. I'm sorry, I

4   misread the table.

5   DR. TEMPLE: Could I mention one other thing?

6   We're currently trying to write a guidance on multiplicity,

7   and one of the hairiest things is when you have multiple

8   pathways. That is this was a non-inferiority trial, but of

9   course they wanted to be able to test for victory. So that

10   takes them down one pathway at the high dose, but they're

11   also interested in non-inferiority on two different doses.

12   Dealing with the total multiplicity of additional

13   endpoints there is murder. We don't know what to tell

14   people yet. We're working on it. So maybe that's why some

15   of these things didn't get into being secondary endpoints.

16   I don't have an easy remedy, but it's very rugged.

17   DR. MCGUIRE: In that light, what is the upper

18   confidence limit of that comparison for the primary

19   outcome? I don't have that data right in front of me.

20   DR. LINCOFF: Any other comments on this one?

21   Okay, and I believe we've covered 3.4. There were no other

22   comments, but if there are, this is the last chance. So

23   are the data sufficient to conclude 150 mg is superior to

24   warfarin?

1   Dr. Fox.

2   DR. FOX: And I would basically say what I said

3   on the last comparison and just substitute the data for

4   this one, and a p-value of 0.01

5   DR. LINCOFF: So can you, for those of us whose

6   short-term memory, is that a yes or a no?

7   DR. FOX: That's yes.

8   DR. TEMPLE: But again, this refers to the

9   effectiveness endpoint. Superior, you know, where in the

10   sky it fits; that's not what the question is about. It's

11   on this reducing the stroke, risk of stroke and non-CNS.

12   DR. LINCOFF: Dr. Krantz, you had a comment.

13   DR. KRANTZ: Does this relate to a label

14   indication or does this relate solely, Dr. Temple said, to

15   a trial of his own?

16   DR. TEMPLE: Well, we haven't figured all that

17   out, but it's not -- we don't usually rate drugs as best,

18   next best, stuff like that, but you show the results of the

19   trial.

20   If you showed the results of this trial there

21   would be an appropriate p-value next to the relevant

22   comparisons. And I don't know if we use the word

23   "superior" at all, but there it sits, and anybody can see

1 it. That's what you would do. I mean unless you want to

2 leave it out. I don't know how you could do that.

3   DR. LINCOFF: Dr. Nissen.

4   DR. NISSEN: Yes, but, you know, you can put in

5 the label here that it's superior. You can use language

6 like that, and you've done that before. I've sat on panels

7 where we were asked to opine whether a superior result was

8 shown. I can remember a blood pressure study where we

9 compared 2 ARBs, 1 of which had about 2 mm greater blood

10 pressure lowering. We were asked whether it was superior

11 or not, and we ultimately opined that it was -- 2 trials,

12 both graded better than 0.5.

13   So I don't want to dodge the question. I guess

14 that's the concern I have. And I want to reiterate my

15 concerns that the superior -- I'm uncomfortable with using

16 words like "superiority" in an open-label trial where there

17 are other issues, and that's where I'm sort of drawing a

18 line.

19   You can put the data in the label, and you will.

20 But the question is do you call it superior or not and I'm

21 suggesting that it's not the right thing to do, at least

22 not yet.

23   DR. TEMPLE: Okay. I'm not sure we usually do,

24 but we will certainly think about that.

1   DR. KRANTZ: I don't mean to beat a dead horse,

2   but I think that depending on how you slice the data,

3   whether you take the median time in therapeutic range,

4   depending on how you look at it. You can cross the

5   confidence intervals and it's no longer superior, depending

6   on which analysis you do.

7   So I think, for me, what Dr. Nissen said holds

8   true, that with an open-label design there are a lot of

9   advantages but there's a price to be paid. And I think I

10 would be a little bit uncomfortable as well with the

11 superiority claim.

12   DR. LINCOFF: Dr. Emerson.

13   DR. EMERSON: So I guess I'd come down on the

14 side of saying it is superior, and the reason is that

15 clearly in this patient population, assuming that it's

16 appropriate. And I haven't really heard any strong

17 testimony that the physicians were not treating the

18 patients appropriately with warfarin, and nobody has really

19 come up with saying this isn't the right population. So

20 clearly in this it appears to me that this is doing better

21 than warfarin on that endpoint.

22   Now I still worry about the open-label study, but

23 I feel comfortable with all-cause mortality and the

24 disabling stroke composite as being not subject to a strong

1 ascertainment bias. That hits a p-value of about a two-

2 sided p-value of 0.02, a one-sided p-value of 0.01. With

3 all the other stars aligning, that sort of relieves my

4 pivotal trial type of worry. So I guess I come down on the

5 superior.

6   DR. LINCOFF: Dr. Neaton.

7   DR. NEATON: For the primary endpoint here, I

8 think this one is clearly superior in my mind. I mean the

9 magnitude of the effect, the fact that it kind of holds for

10 each component as well as the non-fatal strokes and the

11 fatal strokes. It seems to kind of all be very consistent,

12 and it's a substantial effect as opposed to the treatment

13 difference we were talking about a moment ago, between the

14 two doses.

15   DR. LINCOFF: Mr. Simon.

16   MR. SIMON: As a patient, I'd be willing, or I

17 would like to take dabigatran -- make sure I say that right

18 -- versus warfarin. Then I would call it superior.

19   The one thing is, and maybe I missed this, if

20 there is no monitoring, how is a physician going to monitor

21 the patient with regard to if it's doing its job?

22   DR. LINCOFF: Well, I'll add my vote as a

23 cardiologist to the two statisticians. I think this shows

24 superiority. I don't think we want to be in a position

1 where we say that no open-label trial can establish

2 superiority. I think we want to look at the design of the

3 individual trials and the strength of the statistics and

4 the strength of the treatment effect, and I think this one

5 is very strong.

6   And as was point out by our statistical

7 colleagues, all the stars line up in the same direction,

8 and the hardest endpoints that are least likely to be

9 subject to ascertainment bias show superiority. So I think

10 you look at this and you would prefer to have this drug to

11 warfarin.

12   So, as a summary then, I think we can conclude

13 then that both stroke and non-CNS systemic embolus do

14 contribute, although the effect of the embolus is

15 relatively minor. Effectiveness was, in terms of non-

16 inferiority, seemed to be clearly demonstrated with both

17 doses, although with some caveat from at least some of the

18 advisor regarding the ischemic stroke in the lower dose,

19 not a consistent belief that the 150 was clearly superior

20 to the 110 and clearly some disagreement in terms of

21 whether or not superiority could be declared relative to

22 warfarin for the 150.

23   Moving on to question 4, please comment on

24 safety. 4.1, what, if anything, should the labeling say

1   about the risk of hepatotoxicity?

2   Dr. McGuire.

3   DR. MCGUIRE: I'll make it simple; nothing.

4   DR. LINCOFF: Dr. Emerson.

5   DR. EMERSON: You could throw in that it hasn't

6   been evaluated in a long-term situation.

7   DR. LINCOFF: Dr. Kaul.

8   DR. KAUL: I agree. There is no short-term

9   signal for hepatotoxicity detected. However, there are

10   follow-up studies.

11   DR. LINCOFF: Okay, I think we can move on then.

12   4.2: Is the risk of bleeding lower on dabigatran 110 mg

13   than on warfarin? If so, what classes of bleeding do you

14   consider in reaching the conclusion?

15   And I believe they mean by this which definition,

16   not which organ site. Is that correct?

17   Okay. And also was dabigatran superior when INR

18   control was good on warfarin?

19   And I'm sorry if I missed Dr. Fox and Dr. Nissen

20   on the previous question, by all means.

21   DR. NISSEN: I just wanted to comment that

22   idiosyncratic liver injury tends to show up fairly early

23   on, and so I'm less troubled by the lack of long-term

1 follow-up data. If you understand the history of

2 idiosyncratic liver injury, if you haven't seen it in two

3 years, can you guys think of any drugs where it shows up

4 that late? It just tends not to. So I think that's, to

5 me, a bit reassuring.

6 　　　　　DR. TEMPLE: Well, there have been drugs that

7 cause cirrhosis which took five or six months or something

8 like that, but the acute injury is always early, with a

9 rare late one occasionally.

10 　　　　　DR. LINCOFF: All right. So then to this

11 question of bleeding, so do we believe the risk of bleeding

12 was reduced or was lower on dabigatran 110?

13 　　　　　Dr. Kaul.

14 　　　　　DR. KAUL: The answers are yes, yes and no.

15 　　　　　Yes, it's lower on dabigatran 110 mg, all classes

16 of bleeding. Was dabigatran superior when INR control was

17 good? No.

18 　　　　　DR. LINCOFF: Dr. Emerson.

19 　　　　　DR. EMERSON: Just on that last aspect, I didn't

20 see an analysis that I believe is specifically going after

21 when INR control was good in the sense that you were, but

22 certainly at centers that have good INR control and may

23 also have a lot of other good treatment of the patients, it

1   looked that it was not as beneficial.

2   DR. LINCOFF: Okay, 4.3, is the risk of bleeding

3   similar on dabigatran 150 mg and warfarin?

4   Dr. McGuire.

5   DR. MCGUIRE: I was just going to comment.

6   There's nowhere in here where we're going to discuss the

7   110-mg dose, and 4.2 seems to be the last chance to do

8   that.

9   DR. LINCOFF: Well, the last, 6, I think is

10   really oriented in fact. 6.4 I think is really -- 6.5,

11   what doses should be approved? So save that for the climax

12   of the whole.

13   Dr. Krantz, do you have a comment?

14   DR. KRANTZ: I just thought for the primary major

15   bleeding it was slightly better but didn't reach

16   statistical significance. So I guess that would be my

17   answer.

18   DR. LINCOFF: Dr. McGuire.

19   DR. MCGUIRE: Okay, I will make a comment. I

20   agree with Sanjay, that it was, the bleeding risk was

21   lower. And I make very little out of the stratified

22   analysis by TTR. It's post randomization differential

23   distribution to patients, and I just have no use for those

1   analyses at all.

2   DR. LINCOFF: Are there any other major safety

3   issues in 4.4?

4   All right, so again, the summary. So I think the

5   consensus was little, if anything, should be said about

6   hepatotoxicity, at most that we don't have long-term data,

7   but maybe not even that, that the risk of bleeding was

8   convincingly lower with 110. And the questionable

9   influence or the questionable legitimacy of the post-hoc

10   analysis by INR control, some felt it was a good indicator,

11   others felt that it's probably not valid. The bleeding

12   seems to be similar with 150, and there's no other major

13   safety issues.

14   Dr. Nissen, you wanted to add?

15   DR. NISSEN: Let me just raise one little, small

16   one that always has to worry a little bit, and that is this

17   is a drug with relatively short duration of action and with

18   a signal on dyspepsia.

19   And we know that patients in clinical trials tend

20   to be considerably more adherent than they're likely to be

21   in the real world. We have to have at least some worry in

22   the backs of our minds that you put somebody on the drug,

23   they get some GI distress, they're not in a clinical trial,

24   they're not quite as motivated, and they just don't take

1 some doses because it hurts their stomach when they do. So

2 just keep in mind that this dyspepsia problem could

3 translate into lower adherence rates, longer term, and that

4 could be a safety issue down the road.

5   Now is it a huge issue? Probably not, but it

6 ought to at least be something that we ought to be aware

7 of.

8   DR. LINCOFF: Dr. Kaul, you had a comment?

9   DR. KAUL: Yes, I was going to raise this issue

10 of the MI signal. You know, I still -- it keeps on nagging

11 me. Is there any biologically plausible -- I know what Dr.

12 Nissen is going to say if I ask this question.

13   (Laughter)

14   DR. KAUL: Is there any biologically plausible

15 mechanism by which dabigatran may increase urethral-

16 thrombotic events or thrombotic events? I think I read

17 somewhere that the urinary thromboxane levels were

18 increased in patients that were on dabigatran.

19   And I know that there is this inconsistent

20 relationship between the monovalent direct thrombin

21 inhibitors and increase in MI, and the inconsistency may

22 perhaps be due to variable use of aspirin. For example, in

23 the SPOR TIF studies the aspirin use was excluded, whereas

24 in the ESTEEM study the aspirin use was allowed. So have

1   you sort of connected the dots?

2   DR. LINCOFF: Yes, please, Dr. Yusuf.

3   DR. YUSUF: I have a sub-study that John

4   Eikelboom has done on urinary thromboxane. There is no

5   increase. It's a fairly large study.

6   How big was it, Stuart? About several hundred?

7   DR. CONNOLLY: Four hundred.

8   DR. YUSUF: Four hundred people. There's no

9   excess. The other thing is we really worried -- oh, here

10   are the data. Can we put that? No, this is not it. This

11   is not it. Okay, this is from something else.

12   The other thing is there are three, two or three

13   possibilities. First is the MI signal may be real or

14   spurious. So if it is real, it could be that it truly

15   causes MI. Had we not had -- was this no anti-thrombotic

16   therapy or it could be that it's not as effective as

17   warfarin, so that it's not a causing; it's just not as

18   effective.

19   For what it's worth, and the reason I'm saying

20   "for what it's worth," the old trials do not report MI

21   systematically. So it's missing, and so the aspirin trials

22   also did not report it systematically. But from where it

23   is available and then you do like an imputed analysis, it

1 suggests that warfarin is about 40 percent, 30 to 40

2 percent effective, wide confidence interval, versus no

3 anti-thrombotic therapy in reducing MI -- by no means

4 convincing to anybody, but that's the point estimate.

5   If you look at, then impute, what dabigatran

6 would do, it's about a 20 percent reduction versus no anti-

7 thrombotic and about 15 percent versus aspirin. So that

8 indirect imputation is not suggesting a harm, if there is a

9 real signal. It's suggesting perhaps lesser benefit, if

10 you assume warfarin has a benefit which is reasonable if

11 you take the post-MI trial. But any of the data are so

12 sparse.

13   DR. LINCOFF: All right, question 5, this is a

14 one-vote question. So the instructions for this: We will

15 be using the electronic voting system for this meeting.

16 Each of you have three voting buttons on your microphone,

17 yes, no and abstain. Wait for the buttons to start

18 flashing, then please press the button that corresponds to

19 your vote. The vote will then be displayed on your screen.

20 I will read the vote from the screen into the record.

21   Next, we will go around the room, and each

22 individual who voted will state their name and vote into

23 the record as well as the reason why they voted as they

24 did. Since there will be the opportunity to discuss your

1 votes, we can have a brief discussion if anybody has points

2 to make, but please at this point let's wait until after we

3 actually do the vote, on why you would vote yes or no. But

4 if there are any other clarifying points of discussion that

5 people want to have, otherwise, we can go.

6   All right. So then we'll now begin the voting

7 process. Please press the button on your microphone that

8 corresponds to your vote, and the question is: Should

9 dabigatran be approved for the reduction of stroke and non-

10 CNS systemic embolism in patients with non-valvular atrial

11 fibrillation, yes, no or abstain?

12   (Voting)

13   DR. LINCOFF: I think we're still missing one

14 vote.

15   All right, so the voting results are yes, 9; no,

16 0; and abstain, 0. So everyone has voted. The vote is now

17 complete. Now that the vote is complete we'll go around

18 the table and everyone who voted state their name, their

19 vote and the reason they voted into the record. And if

20 your reasons are exactly the same as the person before you,

21 by all means you can say as much.

22   So why don't we start actually at this end of the

23 table, Dr. Emerson?

24   DR. EMERSON: So, Scott Emerson. I voted yes. I

1 was sort of hoping that somebody else would say it, so I

2 could just say I agreed.

3   (Laughter)

4   DR. EMERSON: Basically, it's for the reasons I

5 think they've demonstrated that it's superior to warfarin.

6 I guess I'll put it to the test of if I had to take it, one

7 or the other, I'd probably go with this.

8   DR. NEATON: Jim Neaton, University of Minnesota.

9 I voted yes because clearly warfarin is very effective.

10 They've shown really tight confidence bounds relative to

11 warfarin and superiority I believe for the higher dose

12 across a range of endpoints that are really hard.

13   DR. COUKELL: Allan Coukell. I voted yes for the

14 reasons that have been stated.

15   And on the question of superiority, I didn't

16 weigh in earlier. I might just say now that I concur with

17 Dr. Nissen, that we have an open-label trial here and do we

18 have reason to believe that the fact that it was open-label

19 changed the way patients were managed, and we do in that

20 patients were, it seems, more likely to be discontinued due

21 to adverse events on the investigational drug.

22   What impact did that have? We don't know. But

23 it does suggest that the fact that it was open-label did

24 change the way patients were managed.

1   DR. LINCOFF: Michael Lincoff. I voted yes for

2   the reasons that have been described. I think it's very

3   clearly non-inferior, with hard clinical endpoints. I

4   believe the higher dose is superior, but regardless of

5   whether superiority was demonstrated I think it's very

6   clearly non-inferior, with an advantage and with regard to

7   key endpoints like intracranial hemorrhage.

8   MR. SIMON: Tom Simon. I voted yes. Ditto for

9   the reasons, as well as I'm the patient, and I would take

10   the drug.

11   DR. KAUL: Sanjay Kaul. I voted yes. I think a

12   desirable benefit risk profile has been demonstrated, more

13   convincingly for the higher dose than for the lower dose.

14   DR. KRANTZ: Hi, I'm Mori Krantz, University of

15   Colorado in Denver, and I voted yes for this drug. I think

16   what really was so exciting about this product was the fact

17   that it looked like it has a tendency to lower stroke more.

18   I was concerned that the differences were small.

19   The absolute reductions were maybe a few tenths of a

20   percentage point, which means you need to treat hundreds of

21   patients to be different than Coumadin. And if you had

22   optimal control, there was no difference.

23   But I think really what it boiled down to in my

24   mind is that a stroke is very different from an MI, as our

1 chairman said, and I think that's truly a catastrophic

2 event with family being impacted severely as well.

3 　　　　　DR. MCGUIRE: Darren McGuire. I voted yes and

4 for the reasons already stated.

5 　　　　　DR. NISSEN: I voted yes, and I just want to

6 explain a couple of things.

7 　　　　　DR. LINCOFF: First, identify for the record.

8 　　　　　DR. NISSEN: Oh, Steve Nissen, Cleveland Clinic.

9 I voted yes for a couple reasons, and one is that no matter

10 how I penalize the trial for the open-label design you

11 can't make this non-inferiority go away. And I probably

12 assign the greatest penalty to the open-label of anybody

13 around the table, and no matter how you do that, by any

14 reasonable measure, this is a drug that is non-inferior.

15 　　　　　Even if you penalize for the MI, if you believe

16 the MI risk, and you look at the MACE endpoint, the MACE

17 endpoint is going the right direction. The p-value is only

18 0.02, but it's going in the right direction. So there's no

19 way, no matter how you look at this, that non-inferiority

20 can be eliminated, and so it is clearly non-inferior to

21 warfarin.

22 　　　　　And I think one other issue on approvability is

23 the fact that we'll talk about a little bit later.

24 Warfarin has its own warts here that we didn't talk about

1 at all, that I think we do need to talk about as we discuss

2 the relative benefits of the doses.

3 DR. LINCOFF: Okay. Now we move on to question 6

4 which is perhaps one of the main reasons we're here. Now

5 you have questions ahead of time, but this has been

6 simplified somewhat. We're not going to have a formal

7 quality-adjusted life-year analysis as was suggested in the

8 questions, but instead focus mainly on discussing the

9 questions.

10 So the Division would like the Committee to

11 discuss doses that should be approved -- 110 mg, 150 mg or

12 both -- which is largely determined by the tradeoffs

13 between prevention of cardiovascular events and causation

14 of bleeding events.

15 Before suggesting how to weigh various clinical

16 events, please consider the following issues with regard to

17 hemorrhagic events, 6.1. Ethicists sometimes attach

18 additional importance to adverse consequences of an

19 intervention. Is a bleed caused by dabigatran adequately

20 characterized by its actual clinical consequences --

21 hospitalization, other interventions, maybe later clinical

22 events -- or is it worse than that because the intervention

23 you chose to use caused it?

24 Dr. Emerson.

1   DR. EMERSON: SO if only the word "unnecessarily"

2   was in there, I'd have a real easy time answering it, but

3   that isn't really the key point. It's that there are

4   always tradeoffs with anything we do. Whereas I do believe

5   that if somebody is given a treatment unnecessarily that

6   causes problems, that is worse than the clinical event they

7   might have had otherwise, but in situations like this,

8   where there's just a cost/benefit tradeoff, I don't think

9   it's any worse than the clinical outcomes

10   DR. LINCOFF: Dr. McGuire.

11   DR. MCGUIRE: You know, my mentor, Rob Califf,

12 always said that instead of ascribing to first do no harm,

13 we should ascribe to do more good than harm on average. In

14 cardiology, we've gotten accustomed a bit to causing events

15 when we know on average we're saving more events -- bypass

16 surgery, percutaneous coronary interventions, thrombolytic

17 therapy. And I don't put so much differential weight on

18 these outcomes, whether we prescribe them or not.

19   DR. LINCOFF: For my part, I would add that I

20 agree with that entirely. I think that's the crux.

21 However, in terms of influencing clinical practice, there's

22 no question that an event you caused may have more impact

23 on a physician's behavior -- the physician who causes an

24 intracranial hemorrhage with fibrinolytic therapy and then

1 refrains or is gun-shy about using. So I think that there

2 is a true psychological advantage to not causing

3 catastrophic events, and I think that's part of the reason

4 patients refuse warfarin and physicians are reluctant to

5 use it.

6   So even though an event is an event, and a body

7 count is a body count, if you caused it, it may have more

8 impact on clinical practice.

9   Dr. Nissen.

10   DR. NISSEN: That is exactly the reason why

11 warfarin is underutilized -- is that I think in the mind of

12 clinicians, if they give a patient warfarin and they have

13 an intracranial hemorrhage, they feel terrible. If they

14 don't give them warfarin and they have a stroke, they were

15 unlucky.

16   Part of what we're dealing with here is a disease

17 that's devastating, stroke in atrial fibrillation patients,

18 for which we are not giving adequate preventive treatment.

19 I think that's why options are so important here. But you

20 know, I think we have to get it out of our heads. It's no

21 different if you have a hemorrhagic stroke or an

22 intracranial bleed. The consequences are the same, whether

23 you have it on a drug or if you have the hemorrhage stroke

24 or ischemic stroke not on a drug.

1   DR. LINCOFF: And I think that's an important

2   distinction as we talk about whether retain both dosages

3   because part of the physician motivation for maybe using a

4   lower dose may not be right from a scientific standpoint,

5   and we'll get to that, but I think this is an important

6   issue.

7   Dr. McGuire.

8   DR. MCGUIRE: Yes, and I'll extend the comments I

9   had earlier, or will fit in here, about the differential

10   dosing. You know, the risk of getting two doses on the

11   market will perpetuate this risk/treatment effect paradigm

12   that was presented as a clinical unmet need. That is the

13   higher the risk patient, the less likely they are presently

14   on-drug.

15   And we heard about this at the rivaroxaban review

16   when the orthopedist wanted a half-dose approved because

17   then they could check the box that they're using

18   prophylaxis but still prevent the bleeding complications,

19   and that clinical inertia is in existence. So I think

20   there's a real disincentive to approve two doses,

21   especially when the second dose is going to be

22   prospectively advocated for the highest risk patient

23   population when the data that have been presented,

24   especially the net clinical benefit data, don't strongly

1   support this incremental bleeding risk out of context of

2   clinical efficacy, even in the elderly.

3   DR. LINCOFF: Dr. Fox, then Dr. Nissen.

4   DR. FOX: Going back to the early part of the

5   sponsor's presentation, they talked about the unmet medical

6   need, and part of that equation was very clearly stated as

7   bleeding risk associated with the use of warfarin for all

8   the reasons that have been discussed. And a lot of it is

9   patients at increased risk because of other comorbidities,

10 and some of it is the difficulty in controlling INR and so

11 forth. But if we accept that that is still part of the

12 equation, then why would we recommend a new therapy where

13 the bleeding risk is about the same versus trying to

14 subdivide the patient population to those that might do

15 better on a higher dose versus those that might do better

16 on a lower dose?

17   Now we'll come on to that, I think it's important

18 to recognize that it's not all about efficacy. There is

19 some safety consideration as well.

20   DR. LINCOFF: Dr. Nissen.

21   DR. NISSEN: There is a risk here, and let me see

22 if I can articulate that, and here's the risk. Because

23 physicians psychologically feel differently about events

24 that they caused than events they failed to prevent, there

1   is a risk here that physicians will choose the 110-mg dose

2   over the 150-mg dose because they don't want to cause a

3   problem.

4   So we all believe the 150-mg dose is probably

5   optimal for most people, and so how you label this drug if

6   both doses are approved has to be clear -- that there is, I

7   think, the clearest evidence of benefit at the higher dose.

8   And I worry that the preferred dose in clinical practice

9   could be a dose that has less clear advantages simply

10 because of the way this question was worded. We do feel

11 differently about events when we cause them.

12   So this is something that has given me a lot of

13 angst in deciding what to recommend about the two different

14 doses.

15   DR. LINCOFF: Dr. Neaton.

16   DR. NEATON: Can I just ask you, Steve? So I

17 mean it sounds like you guys on that side of the table

18 don't trust physicians very much in terms of making

19 judgments.

20   (Laughter)

21   DR. NEATON: The low dose is clearly -- if you

22 believe warfarin has 60 percent efficacy, the low dose is

23 clearly efficacious. So why shouldn't there be that choice

1 out there for people to make, considering the range of

2 data?

3   DR. NISSEN: Oh, I wasn't telling you there

4 shouldn't be a choice, but what I am telling you is that

5 how it's worded in the label will have an effect on what

6 dose becomes the preferred dose.

7   And I'm not at all convinced that the preferred

8 dose for most patients, I think, is 150 mg. If we're going

9 to have 110 mg, I want to have it for those patients where

10 the clinical considerations of bleeding are heightened and

11 where they might get nothing at all if you didn't have the

12 110-mg dose, if you follow where I'm coming from.

13   DR. LINCOFF: Dr. Fox.

14   DR. FOX: Yes, I just want to reinforce, I think,

15 what Steve is saying and what I'm saying are compatible,

16 that I'm kind of driving the committee to consider the

17 utility of two doses, but it has to be captured adequately

18 in labeling as to who those patients are that would, where

19 the benefit/risk is the balance has shifted.

20   DR. LINCOFF: I would take an actually somewhat

21 more extreme view. Yes, we have a 60 percent benefit with

22 warfarin, but we now have a dose that looks like it's

23 better. Medical practice and medical research are designed

24 to keep things getting better. I think if we have evidence

1 that there is a better medication, at a better dose, that

2 we shouldn't be advocating that it's okay to use the old

3 standard, a dose that's equivalent to that of warfarin,

4 unless we truly believe that the excess liability, in this

5 case bleeding, that we take on by getting that progress and

6 reducing stroke even further, unless we believe that's

7 outweighed.

8   And we'll get to this more when we actually talk

9 about should both doses be approved. But I think it is

10 least reasonable to argue that once we know that there is a

11 therapy now, 150, that reduces stroke even further, it's

12 not acceptable to bring out a new drug or a new dose that

13 only achieves the previous standard, unless you clearly

14 believe that the bleeding outweighs that potential benefit.

15   DR. NEATON: But just to follow up, so in the

16 opening presentation I think what I heard was that 50

17 percent of the people that should be getting warfarin

18 aren't even getting it, for reasons of concern and for

19 reasons of convenience and drug interactions and everything

20 else. So if a lower dose in these patients who are

21 presumed to be at higher risk was going to be more often

22 used, isn't that a good thing, given the data we have here?

23   DR. LINCOFF: If you had convincing data that

24 would be used more frequently. But there are a lot of

1 reasons why warfarin isn't used, and a lot of it is

2 difficulty in giving the drug, and also it's the

3 intracranial hemorrhage which was equally reduced in the

4 high dose, 150, as it was in the low dose. So we don't

5 really know that 150 would not be used more frequently than

6 warfarin.

7   Dr. Emerson.

8   DR. EMERSON: And so here I guess is where it's

9 so much easier to deal with superiority than it is non-

10 inferiority, and particularly non-inferiority on an open-

11 label study, that you realize that lots of things can go

12 wrong along the way as to non-inferiority.

13   A really great thing is if I could just sell

14 distilled water because it does better than warfarin in

15 terms of bleeding, and that we were in a situation that

16 we're not really able to rely as much on the true non-

17 inferiority comparison, I can make an awful lot of money

18 with that distilled water. And we have to avoid that

19 aspect.

20   I think what I personally feel most comfortable

21 about on this is the superiority aspect of this drug and

22 that the questions on the other aspects would make me not

23 want to have a lower dose that would be pushing people into

24 the less appropriate therapy.

1   DR. LINCOFF: Dr. Kaul.

2   DR. KAUL: Oh, I just wanted to put some data

3   behind the statements that you made, with which I

4   completely concur with. You know, hemorrhagic stroke

5   reduction benefit is equivalent with both doses. There is

6   a 69 percent reduction with the lower dose and 75 percent

7   reduction with the higher dose.

8   However, when you look at the ischemic stroke,

9   that's where they dichotomize. There's a 12 percent

10 increase with the lower dose in ischemic stroke compared to

11 a 25 percent reduction with the higher dose. So that's how

12 I arrived at my math, that the benefit/risk profile of the

13 higher dose is much more convincing than the lower dose.

14   DR. LINCOFF: Okay, let's go on to 6.2: Subjects

15 with important bleeding events are at higher risk for

16 subsequent serious clinical events such as death or

17 myocardial infarction. Is bleeding a marker of sick

18 patients or is the hemorrhage causing later outcome events?

19   This could have been a question in many different

20 drug reviews over the last few years.

21   Dr. Emerson.

22   DR. EMERSON: I guess my first answer is that

23 precisely 14 angels can dance on the head of a pin.

1   (Laughter)

2   DR. EMERSON: This is an unanswerable question.

3   While in my mind I most often regard that most of these

4   things are bleeding, are markers of sicker patients, in the

5   absence of being able to show in a randomized trial that I

6   am able to cause the later outcome events, that's still not

7   really speaking to that the intermediate outcome of the

8   hemorrhage is what's causing that. So I guess I'm going to

9   say that does this really matter?

10   DR. LINCOFF: I think the tobacco companies have

11   been trying to answer this question too -- causation or

12   association. Anybody else want to contribute to this?

13   Dr. Kaul.

14   DR. KAUL: I agree. I mean it's hard to tease

15   out whether this is the chicken or the egg, but one way to

16   look at these endpoints of different clinical relevance is

17   look at mortality. Of course, the leap of faith here is

18   that they are causally linked.

19   In the RE-LY program, the case fatality rate with

20   bleeding was about 2.5 or lower than the case fatality rate

21   with stroke. So if you want to give it a relative utility

22   ranking weight, that's basically what you would give, 2.5

23   to 1. And with regards to myocardial infarction, it was

24   about 12 percent. So it's right in between.

1   So stroke supersedes MI, supersedes major

2   bleeding as defined in this trial. Someone can argue that

3   the major bleeding that was defined in this trial was

4   probably of liberal criteria.

5   DR. EMERSON: But that still doesn't answer the

6   question of are those just better markers of the sicker

7   patients. So when you realize that there's I believe it's

8   something like 30 percent mortality, 6 months after a hip

9   fracture, whereas I don't really believe that breaking a

10 hip is causing them to die. If I go out and break that --

11 well, I don't know this -- and hemorrhage, and I don't know

12 how to cause that hemorrhage and be able to answer this

13 question.

14   DR. LINCOFF: Dr. McGuire.

15   DR. MCGUIRE: You know, I think both of these are

16 true, and there's actually a third relevant possibility,

17 that the bleeding may precipitate discontinuation of an

18 otherwise effective therapy. So risk may be incremented

19 subsequently, not due directly to the risk of the patient

20 or the bleeding event, but because of the clinical result,

21 response.

22   DR. LINCOFF: Dr. Nissen.

23   DR. NISSEN: Yes, I agree with Dr. McGuire.

24   Let me tell you what happens down in clinical

1 practice because it happens to me all the time. I have a

2 patient I put on Coumadin to prevent stroke in atrial

3 fibrillation. They get a little nuisance bleeding, and

4 then they go to their family practitioner who says just

5 stop your warfarin, and then they have something really

6 terrible happen to them. So that's the problem, that there

7 is a failure.

8   I mean I don't want to say you can't trust

9 physicians to do this, but reality is we haven't done very

10 well. I mean that's the bottom line -- is that an awful

11 lot of people that should be treated are not getting

12 treated, and we have to understand why that is and how we

13 can close that treatment gap with newer therapies.

14   DR. LINCOFF: I think perhaps a fair summary of

15 this, or point with this, is that there are potential

16 mechanisms where it could be causative -- discontinuation

17 of anti-thrombotics, inflammatory blood transfusions,

18 whatever -- but it's impossible to differentiate.

19   Number 3, in RE-LY, subjects who experienced a

20 bleed were generally followed for later outcome events.

21 Does this type of follow-up capture most of the long-term

22 consequences of the bleed? Perhaps if I may clarify this,

23 my understanding of this question is we often talk about

24 the late consequences after a bleed, of death or ischemic

1 events, but yet these patients were actually followed for

2 late events. So do we need to talk about late consequences

3 if we're actually counting the late consequences? Do we

4 need to give a bleed a particular consequence beyond its

5 immediate event because of what might later happen, if

6 we're actually checking to see if it later did happen?

7   Is that, Norman, what I'm --

8   DR. STOCKBRIDGE: Yes, that's exactly right.

9   DR. LINCOFF: Stay with me a little longer.

10 We're almost done.

11   DR. EMERSON: I think I'm always in favor of

12 following of these adverse outcomes to find out whether I

13 care about it, and that's again looking at the mortality,

14 looking at the additional stroke outcomes or whatever is

15 most important. So I think that does capture.

16   DR. LINCOFF: So, given the structure of this

17 trial, where there is long-term follow-up, do we need to

18 look at these bleeding events as anything more than face

19 value bleeding events, given that we're going to look later

20 to see if they have consequences?

21   All right, if the sponsor has --

22   DR. CONNOLLY: I have a bit of data to share with

23 you. We did look at the relative risk of death within the

1 trial for patients who had events compared to patients who

2 did not have that event, for a variety of events, and we

3 adjusted that for a variety of baseline risk factors,

4 trying to adjust for the fact that some patients were more

5 likely to have events. Patients who were at higher risk

6 are the ones who have events.

7   The results show that if you've had an ischemic

8 stroke your chance of dying in the trial was seven-fold

9 higher than if you haven't had an ischemic stroke. If

10 you've had a non-intracranial major hemorrhage, your risk

11 of dying is five-fold higher than if you haven't had one of

12 those events. For subdural hemorrhage, it's about seven-

13 fold higher. For myocardial infarction, it's about seven-

14 fold higher. And for the intracerebral bleeds, not the

15 subdurals, but the intracerebral bleeds, it's about 30-fold

16 higher.

17   DR. LINCOFF: All right, the next slide then.

18 All right, 6.4, which events should be considered in

19 assessing the risks and benefits of the two dabigatran

20 doses? What weights should be assigned to them? So I

21 assume by "which events" at least you're asking which of

22 the different bleeding definitions and how would you weigh

23 them.

24   Dr. Nissen.

1   DR. NISSEN: That's a not answerable question,

2   but obviously, you know, it's a little bit you kind of know

3   when you see it. Obviously, at the top of the scale is

4   intracranial hemorrhage, and then the kind of major bleeds

5   come at lower seriousness.

6   But we should also keep in mind that even GI

7   bleed can result in pretty severe consequences. Dr.

8   McGuire made the point very nicely that if you have a bleed

9   it tends to be a harbinger of a lot of bad things happening

10   to you subsequently. But there is a hierarchy, and I think

11   Mike Lincoff made another point which is that if you ask

12   patients what they think they would rather have an MI than

13   a stroke.

14   I think I'd rather have an MI than a stroke. I

15   mean stroke is the worst outcome for people, and a

16   myocardial infarction. So there is a hierarchy of adverse

17   events. When we do clinical trials and we look at these

18   composite sorts of endpoints, it's just almost impossible

19   to properly weigh all of those. So we do our best, but

20   they are not all the same.

21   DR. LINCOFF: Well, for my part actually I think

22   this is addressable, and in part it's addressable because

23   the efficacy endpoint is so unequivocal.

24   I agree that with myocardial infarction, when

1   you're trying to weigh saving a periprocedural MI, it's

2   hard to decide what threshold of bleeding you're going to

3   consider an equivalent or a comparable.

4   But when you're talking about a stroke, which is

5   not only irreversible but in general so debilitating, I

6   think that a bleeding event, because we're not -- I don't

7   think we're that interested in what the bleeding event

8   portends because we're counting the portends, but we're

9   interested in the actual event itself.

10   And I think either an intracranial hemorrhage or

11   a life-threatening bleed, a bleed that if you weren't

12   intervened upon aggressively you might have died. So you

13   had a potentially terrible hospital experience. I think we

14   can take the very highest of the bleeds, and those are the

15   only ones that should be weighed in my mind, in

16   consideration against an efficacy endpoint such as stroke.

17   So my vote would be in this that although all

18   bleeding is important, we're counting the deaths at the

19   end, we're counting consequences. And so we should only

20   count the bleeds themselves for their face value, and that

21   would be the very important bleeds.

22   Dr. Kaul.

23   DR. KAUL: I thought the question was which

24   events. So are you sort of separating bleeding from

1 stroke, or are you counting them?

2   DR. LINCOFF: Well, I know we had this

3 controversy about whether or not intracranial hemorrhage

4 should be counted twice, and so either way. I mean

5 obviously I am counting it as a bleed in this case, but

6 obviously from the standpoint of formal.

7   DR. KAUL: When I said that stroke has the number

8 one weight in my hierarchy, I'm counting the intracranial

9 hemorrhage toward stroke. Otherwise, I agree with you.

10 Stroke should be more important than bleed, MI should be

11 more important than bleeding, excluding the intracranial

12 hemorrhage.

13   DR. LINCOFF: I wouldn't save a major bleed to

14 have -- I wouldn't risk a stroke to save a major bleed.

15   Okay, this is where the rubber meets the road.

16 What doses, or dose, of dabigatran should be approved? If

17 you recommend more than one, how would you recommend

18 physicians be advised to select a dose?

19   Now we've not been asked to formally vote on

20 this, but as many who would like to weigh in on this I

21 think it would be illustrative, and explain your reasons.

22 So we can either go by hands, or we can go around the room,

23 depending upon how enthusiastic people are to respond here.

24   Steve, do you want to start?

1   DR. NISSEN: This is the question I thought the

2   longest and the hardest about as I was reading the briefing

3   documents. You know, I completely understand why the

4   primary reviewer was concerned about approving the 110-mg

5   dose.

6   You know, Sanjay, you made the point very well,

7   that on ischemic stroke the point estimate is actually

8   greater than one compared to warfarin. But what I think we

9   have to factor in here, this is where clinical judgment

10   becomes a very important factor, and the reality is there

11   are a lot of people out there that are getting nothing,

12   maybe aspirin, but maybe nothing at all. And there are

13   people that have been treated with Coumadin, with warfarin

14   and that had a bleed of some sort, and they're not going to

15   get any therapy at all. So I think we need clinically to

16   have both doses available, but I don't want the use to end

17   up being a predominantly lower dose because I do think the

18   evidence is much stronger for benefit to risk with the 150-

19   mg dose.

20   So I would do in the labeling is I would say that

21   the primary approved dose is 150 mg, that 110 mg is made

22   available as an alternative for those patients deemed at

23   high risk of bleeding. I wouldn't put an age criterion.

24   If you want to mention, for example, that it can be

1 considered in people that have had prior bleeding or have

2 had bleeding on the 150-mg dose, there's lots of ways you

3 can say it, but the key message should be that the primary

4 benefit is from the 150-mg dose.

5   Now the reason I want the 110-mg dose is that I

6 think if you don't have a 110-mg dose we're not going to

7 end up having this therapy lead to more patients being

8 treated, and I want more patients treated because stroke is

9 such a devastating complication. The way you get more

10 patients treated is you provide physicians with a lower

11 dose alternative that for people that they're afraid to

12 give fully anticoagulation to, which is either warfarin or

13 the 150-mg dose, that they have an alternative.

14   And I think it's the right thing to do. Even

15 though statistically and otherwise the evidence of benefit

16 isn't as clear-cut, I do think there is a clinical

17 advantage that tends to dominate my thinking about this.

18 So I do recommend both doses be approved.

19   DR. LINCOFF: Anybody else want to weigh in?

20   Actually, Dr. Fox, if you'd like to.

21   DR. FOX: Yes, I'd reinforce what Dr. Nissen

22 said. I think the emphasis should be put on the 150-mg

23 dose for the reasons he stated, and others have also

24 pointed out about the superiority and the more clear

1 clinical benefit.

2   I sort of listened to him talk about it. I

3 remember patients that have come into my clinic in the

4 past, and they've run into problems with, sort of, full-

5 dose warfarin, and so they're being maintained at really a

6 sub-therapeutic INR. It's kind of those people who

7 probably would do better on 110 than on a sub-therapeutic

8 dose of warfarin.

9   So I don't know exactly how the agency and the

10 sponsor will land on this one in terms of getting the right

11 kind of language in the label, but emphasis should be on

12 the 150.

13   DR. LINCOFF: Dr. McGuire, did you?

14   DR. MCGUIRE: Yes, as I kind of suggested

15 earlier, I'm going to support only the 150-mg dose. I have

16 great reservations that the clinical practice will adopt a

17 lower risk, if available. I've not yet met a clinician

18 who's read a product label. And we can be as sophisticated

19 as we want in the product label, but clinicians are going

20 to practice according to their concern about bleeding, as

21 we are presently with Coumadin.

22   So I don't see compelling, I know it's

23 theoretical, about the incremental risk of bleeding over

24 efficacy for the elderly. The 80-year-old cut point is

1   somewhat arbitrary, although it makes sense. But I don't

2   see a signal.

3   You know, there is some deterioration of the

4   point estimate of efficacy in the greater-than-75 group,

5   from CE Slide 39, but with an absolute risk in that cohort

6   a slightly lower relatively risk reduction still is a

7   larger absolute risk reduction in a drug that is

8   approaching superiority against Coumadin. So I'm afraid

9   we'll take a step back, accepting non-inferiority and lower

10   bleeding risk for a drug that may actually improve, be

11   superior to Coumadin, at the higher dose.

12   DR. LINCOFF: Dr. Krantz.

13   DR. KRANTZ: I'm going to weigh in on the two

14   doses. I agree with Darren, but at the same time I think

15   that we need choices. I think as long as there's a strong

16   sort of push for the higher dose, I think ultimately this

17   will work out okay.

18   DR. LINCOFF: Dr. Kaul.

19   DR. KAUL: I agree with Dr. McGuire. I think

20   that 150 mg is the right dose to approve. I see clear-cut

21   advantages, but I don't see much of a liability in any of

22   the subgroups that were evaluated. So 150 mg is what I

23   support.

24   DR. LINCOFF: Mr. Simon.

1   MR. SIMON: I hope I can say this correctly.

2   Going back to what the sponsor said, I think I'm, since I'm

3   64 years old, I'm in the elderly group, not the super

4   elderly yet. So I would go for the 150 mg. However, the

5   order I got I might tend to go with the 110 mg because

6   again sometimes a patient, you know too much. I would not

7   go on warfarin at 80 years old. At 80 years old, I think I

8   would go on this drug.

9   DR. LINCOFF: So do I interpret that as both

10   doses approved?

11   MR. SIMON: That's correct.

12   DR. LINCOFF: As we go around the table, I

13   actually would vote to approve the 150 for the reasons that

14   Darren McGuire has really, I think, brought out. I too am

15   afraid that it would become too much of a default to move

16   to the 110 regardless of how much you move, you try to put

17   things in the label.

18   And I'm unconvinced that the data are very firm

19   that there is an important advantage with regard to

20   bleeding. That is the bleeding endpoints that I think are

21   important and can be potentially weighed against the risk

22   of stroke with the 110 as compared to the 150, so that my

23   vote would be for the 150 only.

24   DR. COUKELL: I hear the concern that Dr. McGuire

1 is raising, and I agree that it's a huge concern. At the

2 same time, it seems to me that there may be a small

3 population of patients in whom you just don't want to be

4 aggressive. And as Dr. Yusuf pointed out this morning,

5 there may also be folks that the only way you can get them

6 to try this drug again is to reduce the dose. So I would

7 opt for approving both, but with really strong labeling and

8 guidelines and so on that pushes it towards the 150 for the

9 vast majority.

10   DR. LINCOFF: Dr. Neaton.

11   DR. NEATON: I'd like to see both doses approved

12 for reasons stated earlier. There's a clearer bleeding

13 disadvantage to the high dose, for including what you

14 consider to be an important intracranial hemorrhages and

15 the life-threatening hemorrhages. And I just think I don't

16 buy the age 80 cutoff, but I think in general there's

17 probably a risk of bleeding that potentially could be

18 clinically assessed, for which the dose might be useful.

19   DR. LINCOFF: Dr. Emerson.

20   DR. EMERSON: I'm for the one dose for the same

21 reasons all the other one-dosers.

22   DR. LINCOFF: All right. Just to summarize the

23 straw poll. I realize it carries no, but there were four

24 for the single dose, the 150, and six, it looks like, one,

1 two, three, four, five, six for both doses, because the

2 non-voting members --

3   SPEAKER: (Off microphone).

4   DR. LINCOFF: That's right, absolutely. So

5 that's the straw poll. We have one left. Do you want it

6 now or do you want to --

7   DR. STOCKBRIDGE: Just a word?

8   DR. LINCOFF: Okay, sure.

9   DR. STOCKBRIDGE: Dr. Temple and I have just been

10 discussing the possibility that for the weak at heart we

11 should approve a 145-mg dose.

12   (Laughter)

13   DR. LINCOFF: Which brings us to the next

14 question: Has the dose-response relationship with

15 dabigatran been adequately defined? If not, what dose

16 would you like to see in future study?

17   Dr. Fox.

18   DR. FOX: I would say that a dose-response

19 relationship has been described. It's certainly better

20 than no dose-effect relationship. I think several of the

21 panelists have already come at this from a couple different

22 angles -- both scientific, or medically, and statistically.

23 It provided certain comforts or insights to several of the

1   panelists around believing the effectiveness part of the

2   equation, trying to understand how bleeding risk might

3   relate to exposure. It informed an exposure effect model

4   that I found to be insightful by the agency.

5   So I'm not sure that additional doses need to be

6   studied in this core population, but for either special

7   populations or additional indications it might certainly be

8   indicated.

9   DR. LINCOFF: Dr. McGuire.

10   DR. MCGUIRE: Yes, I'll go back to some earlier

11 comments. I think there are compelling data to suggest

12 there may be differential treatment effects based on

13 underlying bleeding risk, and I think they're compelling

14 not so they have been defined, but not optimized.

15   And getting back to my earlier comment about

16 steady state analysis of PK and/or PD measurements, that I

17 think a very informative trial would be a fixed dose versus

18 dose titrated to PK or PD data. In our clinical zeal to

19 get away from therapeutic monitoring this domain, the

20 burden of INRs is substantial. So we're all as clinicians

21 very keen, and patients as well, to get away from having to

22 be monitored. But especially if there is such

23 predictability for intra-subject variability, a single

24 steady-state analysis may actually prove to titrate drugs.

1 So that not only would we have a 150 and/or a 110, but we

2 may have a whole spectrum of therapeutic options, like

3 Coumadin, where we can personalize the anticoagulant

4 strategy to optimize risk and benefit.

5 　　　　　DR. LINCOFF: You'd have the 145 that they had.

6 　　　　　DR. MCGUIRE: I was going to go with 137.5.

7 　　　　　(Laughter)

8 　　　　　DR. LINCOFF: Dr. Nissen.

9 　　　　　DR. NISSEN: Yes, I think we have to compliment

10 the academic investigators and the sponsor for doing this

11 trial in this way, with two different doses. I mean look,

12 in anticoagulants we often don't get this, and I found

13 having the two doses and the data to be very informative.

14 　　　　　Now do we know everything we ever would want to

15 know? No, we don't. You can't study an infinite variety

16 of doses. At least we got two here and not one, and I

17 think it helps us considerably.

18 　　　　　I do think Dr. McGuire has an interesting point.

19 It would be interesting to use an ECT and maybe try to

20 understand a little bit better what's going on. But keep

21 in mind, if you want to do that, you know we don't really

22 know enough to design such a trial, and analyzing the data

23 when you have a continuous dose variation could be

1   extremely difficult.

2   So I'm not sure how much more data we're likely

3   to get, even within any reasonable timeframe, but the fact

4   that we have two doses is to the benefit of everybody, and

5   the sponsor and the academic investigators should be

6   complimented for giving us two doses to look at.

7   DR. LINCOFF: Dr. Emerson.

8   DR. EMERSON: So I guess I would be truly more

9   interested in looking at different populations than at the

10 dose in this one population. And I'll note that there was

11 some suggestion that weight had more of an effect on the

12 distribution of the drug, and such things like that.

13   All of that having been said, there's

14 practicality that comes in this too. The second that

15 you're going to start saying that the pharmacy has to stock

16 17 different doses there, that's as good as saying it's

17 also not going to be used.

18   So what I think is within the usual limits of how

19 we do such things I think the dose-response relationship

20 has been adequately defined in the general population, and

21 then in terms of finding out how it behaves in more special

22 populations may be warranted, but probably at these doses

23 is the adequate.

24   DR. LINCOFF: Dr. Kaul.

1   DR. KAUL: I just had a comment about Dr.

2   McGuire's suggestion of using PK/PD monitoring. PK

3   monitoring is impractical, and PD monitoring, I'm not quite

4   sure how reliable that is going to be with ECT assay which

5   is probably the best correlated assay. And I have

6   difficulty using platelet function assay in tailoring my

7   therapy, leave alone ECT which is a black box to many of

8   us.

9   DR. LINCOFF: Actually, for my part, I interpret

10   this a little differently. You know, the FDA, in their

11   presentation, put the little question marks around the 300

12   dose. So I wondered if this was referring to the idea of

13   testing a dose outside the range.

14   For my point, I think that the exposure,

15   response-exposure bleeding are a little scary in terms of

16   how little additional benefit one could expect to achieve

17   with regard to stroke while at the same time be coming on

18   the fairly steep part of the bleeding curve. And I realize

19   I said I don't care about bleeding, but obviously there's a

20   limit to that as well, and I think you may lose your

21   advantage with intracranial hemorrhage. So I would have a

22   little bit of difficulty participating in, or running a,

23   trial that was looking at much higher doses, but for my

24   part.

1   DR. TEMPLE: We're sort of schizy on the dose

2   modification thing. We modify doses for abnormalities of

3   renal function just by thinking what the blood level will

4   be based on our knowledge of how excretions in pyridine.

5   We don't retest it to see if the drug still works there.

6   We just adjust the dose, and we increasingly are doing that

7   for liver function too.

8   So I mean it seems to me one possibility is to

9   try to pin down the sources of this variability and think

10 about whether what has sometimes been called PK-modified

11 dosing might be of some value, if we could account for

12 enough of the variability, which I don't know whether we

13 can.

14   DR. LINCOFF: But is that right? I know we do

15 that with certain drugs, and I don't know if it's

16 appropriate to mention them, but the drugs that it was

17 purely modeling that created these renally-impaired doses,

18 but we've never shown that their efficacy is preserved at

19 those lower doses. That's different from taking different

20 dosing recommendations and then testing a response

21 variable, like APTT, as we do say with some of the direct

22 thrombin inhibitors intravenously in patients with hepatic

23 failure.

24   DR. TEMPLE: But the trouble is there are so

1   many, you can't do it. You finish various -- you finish

2   renal function, hepatic function. Then you start getting

3   into your drug-drug interactions. If you were to test in

4   an 18,000-patient study, each of those, I mean you'd be

5   over in two minutes. So we do adjust the dose based on the

6   reasonable assumption that the blood level has something to

7   do with the effect of a drug. But I think there's always

8   nervousness when you do that and don't actually get the

9   data. And we don't always behave the same either.

10   DR. LINCOFF: Well, if there are no other

11 comments, then I think we've completed the questions.

12   Dr. Stockbridge or Dr. Temple, do you have a

13 final?

14   DR. STOCKBRIDGE: Yes, I want to thank everybody

15 for participating in this today. It's been a very useful

16 conversation, and gives us something to think about in

17 terms of how to label this and encourage its appropriate

18 use. Thanks.

19   DR. TEMPLE: Just one thought I had, you know, we

20 have these things called MedGuides that advise patients on

21 what to do. One of the uses, potential uses of a MedGuide,

22 one of them is to help them understand the risk-benefit.

23 The other is to make sure they do what they need to, to

24 avoid damage. A third, almost never used, is to remind

1 them that it's very important to not stop the drug

2 frivolously and keep taking it, that it's really worth it.

3 This might be the sort of case where a MedGuide with that

4 direction ought to be: "Do not stop this by yourself."

5 There are other drugs where we've had that same thought.

6   Also, your discussion made me want to put in the

7 label for the drug, to doctors, that under-treatment is

8 your fault too.

9   (Laughter)

10   DR. LINCOFF: Thank you to all of the committee

11 members for a very interesting discussion. After

12 adjournment, we ask that the committee members please place

13 your name badges in the box located on the reception table

14 immediately outside of the room. I don't know if this is

15 recycling or they don't want us walking around with FDA

16 badges. Thank you very much.

17   (Whereupon, at 4:08 p.m., the meeting was

18 adjourned.)

19

20

21

22

23

24