

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

86TH MEETING

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FRIDAY

OCTOBER 23, 1998

The Advisory Committee met in the Masur Auditorium in Building 10, National Institutes of Health, Bethesda, Maryland, at 9:00 a.m., Dr. Milton Packer, Chairperson, presiding.

Present:

MILTON PACKER, M.D., Chairperson
JOHN DiMARCO, M.D., Member
MARVIN KONSTAM, M.D., Member
JOANN LINDENFELD, M.D., Member
LEMUEL MOYE, M.D., Ph.D., Member
ILEANA PINA, M.D., Member
DAN RODEN, M.D.C.M., Member
UDHO THADANI, M.D., Member
JOAN C. STANDAERT, Executive Secretary

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P R O C E E D I N G S

9:07

1
2
3 CHAIRMAN PACKER: I'd like to open this
4 meeting this morning. The administrative structure
5 for this morning is slightly different than perhaps
6 what we generally have had in the Cardiac and Renal
7 Drugs Advisory Committee. Today, the Advisory
8 Committee is actually not advising the Division of
9 Cardiac and Renal Drugs. It is advising the GI
10 division.

11 And the procedure that govern today are
12 similar to the procedures that govern any other day
13 and we are being asked to advise the GI Division In a
14 course of assessments of Hirulog or bivalirudin. Is
15 that correct, bivalirudin? And I would say to the
16 Committee that if they choose they can use either name
17 if they find bivalirudin hard to say. And we will
18 have Joan read the conflict of interest statement this
19 morning.

20 MS. STANDAERT: The following announcement
21 addresses the issue of conflict of interest with
22 regard to this meeting and is made a part of the

1 record to preclude even the appearance of such at this
2 meeting.

3 Based on the submitted agenda and
4 information provided by the participants, the Agency
5 has determined that all reported interests in firms
6 regulated by the Center for Drug Evaluation and
7 Research present no potential for a conflict of
8 interest at this meeting with the following
9 exceptions.

10 In accordance with 18 USC section 208(b)3
11 and section 344(n)4 full waivers have been granted to
12 Dr. Ileana Pina, Dr. Lemuel Moye, Dr. Dan Roden, Dr.
13 Udho Thadani, Dr. Marvin Konstam, and Dr. Milton
14 Packer.

15 A copy of these waiver statements may be
16 obtained by submitting a written request to FDA's
17 Freedom of Information Office, Room 12A30 of the
18 Parklawn Building.

19 We would like to note that one of the
20 Committee participant's employer had a previous
21 involvement related to Hirulog, that we believe should
22 be disclosed. FDA believes that it is important to

1 acknowledge this involvement so that his participation
2 can be objectively evaluated.

3 In the past, Dr. Konstam's employer
4 studied Hirulog. Dr. Konstam has no involvement
5 whatsoever in the study.

6 In the event that the discussion any other
7 products or firms not already on the agenda in which
8 an FDA participant has had a financial interest, the
9 participants are aware to exclude themselves from
10 such involvement and their exclusion will be noted for
11 the record. With respect to all other participants we
12 ask in the interest of fairness that they address any
13 current or previous financial involvement with any
14 firm whose products they wish to comment upon.

15 It should be further noted that Dr. Robert
16 Califf has been excluded from the proceedings on
17 Hirulog.

18 CHAIRMAN PACKER: Thank you, Joan. We
19 generally reserve time for public comment. Is there
20 any public comment?

21 (No response.)

22 CHAIRMAN PACKER: There being no public

1 comment, the NDA being evaluated this morning is for
2 Hirulog, bivalirudin. The proposed indication is as
3 an anticoagulant for patients undergoing PTCA for the
4 treatment of unstable angina.

5 The sponsor is The Medicines Group. In
6 the last 24 hours the questions to the Committee has
7 undergone significant amount of revision so that the
8 questions which have been distributed up front do, in
9 fact, highlight many of the key issues that we will be
10 discussing today, but we will not be going through the
11 questions in the sequence in which the questions
12 distributed outside, in fact, outline.

13 We will discussing the essence of all of
14 the questions. We will be changing some of the
15 emphasis of the sequence and this has been already
16 discussed with the sponsor and Dr. Talarico. I think
17 everyone feels comfortable with the changes that have
18 been made.

19 We'll ask The Medicines Group to proceed
20 with their presentation. Dr. Meanwell, I think, will
21 begin the sponsor's presentation of the NDA.

22 DR. MEANWELL: Mr. Chairman, members of

1 the Advisory Group, members of the FDA, ladies and
2 gentlemen, we are here today to give you information
3 on bivalirudin, an intravenous direct thrombin
4 inhibitor which we believe can be used as an
5 anticoagulant in patients undergoing unstable angina
6 instead of heparin.

7 My name is Clive Meanwell. I'm the
8 President and Director of the program for bivalirudin.
9 The Medicines Company is a young company with the
10 mission of bringing drugs to patients which might not
11 otherwise get there, particularly drugs which are not
12 considered sufficiently large to warrant the attention
13 of larger pharmaceutical companies.

14 We acquired the drug bivalirudin from
15 Biogen in March of 1997 after Biogen decided to
16 discontinued their investment in this program for
17 business reasons

18 I'm joined today by Dr. John Bittl who was
19 the principal investigator in the phase III trial
20 program who will run through the pivotal trial data,
21 the data in PTCA. And then Professor Eric Topol from
22 the Cleveland clinic foundation who was involved in

1 the phase II program and continues to be involved in
2 this product.

3 Percutaneous transluminal coronary
4 angioplasty, PTCA is a common important intervention.
5 This year it is estimated that 700,000 PCIs
6 will be performed in the United States and in all
7 cases anticoagulation is considered essential in
8 practically all cases. The intravenous anticoagulant
9 of choice, because there is no alternative, is heparin
10 to be used during the procedure.

11 Now when heparin is used, the likelihood
12 of thrombosis or thrombo-occlusive events is reduced.
13 However, there is a trade-off between thrombosis and
14 hemorrhage in this setting.

15 Heparin use in PTCA is essentially a
16 balancing act. It is illustrated in the schematic on
17 the left of the slide showing the inverse relationship
18 between the risk of thrombosis along the bottom from
19 high, moving left, to low and risk of hemorrhage going
20 up as the risk of thrombosis comes down.

21 These combined risks usually present as
22 10 percent death of myocardial infarction or the need

1 for urgent revascularization during the first 7 days
2 after PTCA. Approximately seven to ten percent
3 clinically significant bleeding, including five
4 percent of patients requiring a transfusion of more
5 than two units of blood.

6 Now these limitations are essentially a
7 result pharmacological deficiencies of heparin
8 which have been studied extensively since 1996 when it
9 was first introduced.

10 Bivalirudin is a rationally-designed
11 inhibitor of thrombin, which was actually designed
12 that way to overcome some of the limitations of
13 heparin. It does so in the following ways. The mode
14 of action controls with heparin quite markedly.
15 Bivalirudin does not require cofactors, most notably
16 Antithrombin III, to exert its effect.

17 Bivalirudin is not inhibited by platelet
18 factor 4 or by other circulating plasmoproteins which
19 are often elevated in acute cardio syndromes. And
20 thirdly, at the molecular level, bivalirudin shows
21 reversible binding to thrombin.

22 These three features of the molecule tend

1 to provide more predictable linear relationships
2 between both plasma concentration and effect, a
3 feature which is not often seen with heparin.

4 Importantly, on the limited risk side,
5 bivalirudin is also able to inhibit both thrombin
6 which is bound to fibrin in a clot, as well as
7 thrombin which is circulated in fluid phase. And this
8 we believe underscores the ability to target anti-
9 thrombotic effect where it's needed with a lower
10 systemic or circulating anticoagulant burden.

11 Now this opens up the clinical thesis for
12 bivalirudin. But it is possible to achieve at least
13 similar or reduced thrombosis, at the same time reduce
14 the risk of hemorrhage. And we think this is an
15 important benefit. This clinical thesis has been
16 tested in a rather broad program of trials, and a
17 complete clinical data set has been submitted to the
18 FDA.

19 The data set includes approximately 6,000
20 patients, of whom 3,600 patients received bivalirudin
21 in trials of angiography, unstable angina, medically
22 managed and managed with intervention, PTCA, and

1 myocardial infarction. The others in this slide
2 refers to deep end thrombosis trials which were done
3 but which were not randomized and are not germane to
4 today's discussion we believe. The FDA do have the
5 data.

6 Now in every situation where bivalirudin
7 was studied, it showed consistent, reversible, dose-
8 dependent anticoagulant effect. In our view, the
9 question whether this drug anticoagulates is not the
10 issue. It seemed quite clear.

11 In every situation where bivalirudin was
12 tested against heparin in that clinical program, there
13 was evidence of similar or improved effect with
14 clinically striking reductions in hemorrhagic risk of
15 the patients.

16 And notwithstanding this broad experience,
17 our focus today is quite simply on the proposed
18 indication, which is that bivalirudin should be
19 considered for use as an anticoagulant in patients
20 during the procedure undergoing unstable -- undergoing
21 PTCA for unstable angina.

22 Now before we get on to the main

1 presentation, members of the panel, I'd like to make
2 it very clear, as we stated in all of the documents we
3 sent the FDA, that we understand fully that neither of
4 these two pivotal trials met the prime endpoint for
5 efficacy that was specified in the protocol.

6 Nevertheless, in view of the important
7 reduction, indeed striking reduction, in hemorrhagic
8 risk and the evidence which we believe supports that
9 bivalirudin is at least as good a heparin in all
10 patients. And we present these data in support of the
11 view that bivalirudin substantially improves the risk-
12 benefit ratio of patients undergoing PTCA for unstable
13 angina.

14 With that brief introduction, I would
15 propose to hand straight on to Dr. Bittl.

16 CHAIRMAN PACKER: If I could, I think that
17 you are not proposing to discuss any aspects of the
18 pharmacology, pharmacodynamics, or pharmacokinetics.
19 Is that correct? I know that information is
20 summarized in the briefing documents. I just want to
21 make sure -- and you need not present that. I just
22 want to make sure that the Committee does not have any

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1 questions about that before we proceed further.

2 DR. MEANWELL: Absolutely.

3 CHAIRMAN PACKER: Dan?

4 DR. RODEN: I don't have any questions at
5 this time.

6 CHAIRMAN PACKER: Then, let's proceed.

7 DR. MEANWELL: Thank you.

8 DR. BITTL: May I have the first slide,
9 please?

10 Mr. Chairman, panel members, ladies and
11 gentlemen, the goal of systemic anticoagulation during
12 coronary angioplasty is to inhibit thrombus formation
13 within a localized segment of the coronary artery
14 undergoing dilatation.

15 Heparin is the only anticoagulant used for
16 this purpose, but it has several limitations.
17 Ischemic complications and clinically significant
18 bleeding occur in five to ten percent of patients
19 undergoing coronary angioplasty.

20 Furthermore, there are no established, no
21 Phase III controlled trials establishing the effect of
22 heparin in this setting, although several

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1 retrospective case control studies suggest that
2 patients who have a high anticoagulant response to
3 heparin have lower event rates than those who had low
4 anticoagulant responses. It is possible that a direct
5 thrombin inhibitor such as bivalirudin will be safer
6 and more effective than heparin in patients undergoing
7 angioplasty for high-risk indications.

8 I will review the structure, the
9 execution, and results of two pivotal trials of
10 bivalirudin versus heparin in patients undergoing
11 angioplasty for unstable angina.

12 These two trials are unique for several
13 reasons. They have several unique characteristics.
14 Number one, both trials were carried out and governed
15 under a single protocol. And secondly, in contrast to
16 several other recently reported angioplasty trials
17 that studied an add-on to conventional therapy during
18 angioplasty -- that is, typically a platelet inhibitor
19 in addition to heparin and aspirin -- this trial looks
20 at a substitute or a possible alternative to heparin
21 in the form of a direct thrombin inhibitor,
22 bivalirudin.

1 Recall, again, that heparin is the only
2 anticoagulant we have at this time for patients
3 undergoing coronary angioplasty.

4 I think it's important at the outset to
5 discuss the rationale for these trials. The rationale
6 is based on the results of a large Phase II trial of
7 bivalirudin in patients undergoing angioplasty that
8 was chaired by Eric Topol and published in circulation
9 in 1993.

10 The rationale for the trial was also based
11 on a heparin registry study that we carried out
12 simultaneously when the Phase II trial was carried out
13 to identify the doses of heparin used, event rates,
14 and risk factors for ischemic events.

15 In the Phase II trial, which was a dose
16 escalation, open label study, six different doses of
17 bivalirudin were studied in patients undergoing
18 angioplasty. And from this trial we identified that
19 the highest dose should be used in the Phase III
20 study.

21 The heparin registry study actually was a
22 snapshot of angioplasty practice, as carried out in

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1 1992, involving 591 consecutive patients at nine large
2 interventional programs in North America. And in this
3 study we identified, at that time, that the average
4 heparin dose given to these patients was 178 units per
5 kilogram. The mean 24-hour total dose was 41,000
6 units of heparin given. The target ACT was 350
7 seconds.

8 With this protocol of anticoagulation,
9 ischemic event rates occurred in 15 percent of
10 patients, including death, myocardial infarction,
11 emergency revascularization, or abrupt vessel closure.
12 I should also point out that five percent of these
13 patients required transfusion.

14 One of the most important findings in this
15 paper was that we identified risk factors for
16 increased ischemic complications; that is, patients
17 undergoing angioplasty for the presenting syndrome of
18 unstable angina or post-infarction angina or an
19 increased risk for ischemic complications.

20 This confirmed the report of Serruys &
21 DeFeyter, a pooled analysis identifying, in
22 particular, the post-infarction patients as a high-

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1 risk subgroup for poor outcome after angioplasty. And
2 it also allowed us to test the hypothesis that a
3 direct thrombin inhibitor such as bivalirudin may be
4 superior to heparin in angioplasty for these patients.

5 In the protocol, we specified the
6 following primary objective, and I think it's
7 important to read verbatim at this point. The primary
8 objective of each of these two studies is to
9 demonstrate the safety and efficacy of bivalirudin in
10 patients undergoing angioplasty as a treatment for
11 unstable angina as compared with a controlled group of
12 similar patients receiving heparin during coronary
13 angioplasty.

14 I quote, "Efficacy will be determined by
15 using a composite endpoint called procedural failure,
16 and safety will be determined by the incidence of
17 clinically significant hemorrhage."

18 The specific endpoints used in the study
19 are shown here. The procedural endpoint was a
20 composite of in-hospital death, myocardial infarction,
21 revascularization, or abrupt vessel closure. In this
22 study, myocardial infarction was diagnosed in a

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1 classical sense, requiring the presence of two or
2 three criteria based on enzymes, ECG, and chest pain.

3 And so it's a little different than some
4 of the more recent studies that have classified
5 myocardial infarction predominantly on the basis of
6 enzyme rises.

7 In hospital, major hemorrhage was defined
8 as any intercranial bleeding, retroperitoneal
9 hemorrhage, or overt bleeding resulting in a fallen
10 hemoglobin of three grams per vessel liter or more;
11 that is, about a nine-point drop in hematocrit. Or
12 that requiring more than two units transfusion.

13 The protocol specified several secondary
14 analyses. The individual components of the composite
15 endpoint in hospital were to be analyzed. High-risk
16 subgroups were identified, and six-month rates of
17 death, myocardial infarction, or revascularization
18 were also analyzed.

19 All major endpoints were adjudicated by
20 committees consisting of senior cardiologists blinded
21 to treatment assignment. The angiographic core
22 laboratory reviewed the actual angioplasty films on 99

1 percent of the patients, and this was based in Boston
2 and adjudicated all the abrupt closure events.

3 The electrocardiographic core laboratory
4 was based in St. Louis and chaired by Dr. Bernard
5 Chaitman and adjudicated all of the myocardial
6 infarction events.

7 Creatinine kinase was measured in 99
8 percent of the patients eight hours and 16 hours after
9 the procedure. Those data, electrocardiograms, and
10 chest pain narratives were sent to the core laboratory
11 in St. Louis.

12 The Mortality and Morbidity
13 Classifications Committee consisted of five
14 investigators who were well-versed with the protocol
15 and reviewed all of the death cases. At the same
16 time, a Data Safety Monitoring Board monitored the
17 safety of the study with bimonthly meetings during the
18 course of the trials.

19 A single protocol governed the conduct of
20 these two trials, which may be considered replicates
21 of each other. In each trial, randomization of
22 patients to either bivalirudin or heparin was

1 stratified at each site according to whether the
2 patients presented with post-infarction angina or a
3 new onset of unstable angina. In this way, we were
4 assured of having an even balance of high-risk
5 patients in each treatment group.

6 The logistics of carrying out two trials
7 governed by a single protocol were relatively
8 straightforward under the guidelines recommended by
9 the FDA. The 121 sites in North America and Europe
10 who participated in these two studies were randomly
11 allocated to either Trial 1 or Trial 2.

12 And at each site, separate randomization
13 envelopes were available for the patients who
14 presented with either post-infarction angina or a new
15 onset angina.

16 The following sample size assumptions were
17 made and resulted in the requirement for 2,000
18 patients to be enrolled in each trial, for a total of
19 more than 4,000 patients. This was based on an alpha
20 of 1.05 with a power of .80.

21 These sample size assumptions were based
22 on the expected event rate in the heparin control

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1 group of 12 percent, which was conservative based on
2 what we observed in the heparin registry realizing
3 that the heparin registry actually observed a real-
4 life case mix of patients, and this was a clinical
5 trial. We downgraded the event rate to 12 percent for
6 procedural failure in this study.

7 The selection of doses for bivalirudin and
8 heparin, as I said earlier, were based on the results
9 of the Phase II trial and the heparin registry. The
10 goal was to achieve a target activated clotting time
11 of 350 seconds during the procedure, with overnight
12 anticoagulation for a total of 18 to 24 hours.

13 In the Phase II trial, there were six
14 different dose groups. One hundred patients in dose
15 groups 4 and 5 had very low event rates, and an
16 additional 12 patients were treated with bivalirudin
17 in doses that we ultimately used in this trial.

18 This is their anticoagulation profile.
19 Indeed, an ACT of 350 seconds was achieved during the
20 procedure and maintained during a four-hour infusion.
21 After the infusion was stopped, the activated clotting
22 time fell to a control and correlation with the plasma

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1 bivalirudin concentration.

2 This profile of anticoagulation is very
3 similar to the profile of anticoagulation achieved
4 with high dose heparin used for coronary angioplasty
5 in patients with unstable angina.

6 The actual dose regimens are shown on this
7 slide. At each institution, research pharmacists
8 prepared syringes containing either bivalirudin or
9 heparin and labeled them in such a way that the
10 technical nursing and physician staff performing the
11 procedure and providing after care could not identify
12 the contents of the syringes.

13 Five minutes before angioplasty was begun,
14 the patients received a bolus of study drug. In the
15 case of bivalirudin, this was a dose of one milligram
16 per kilogram; in the case of heparin, 175 units per
17 kilogram.

18 In order to ensure safety in this trial,
19 patients had ACT measurements made five minutes after
20 the administration of study drug to ensure that a
21 target ACT of 350 seconds was achieved. If this was
22 not achieved, the cardiologist had the option of

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1 administering a second bolus of heparin, 3,000 units,
2 or a dummy placebo injection of bivalirudin.

3 Anticoagulation was carried out for a
4 total of 18 to 24 hours, as specified by the protocol.
5 Four hours after the angioplasty was begun, the dose
6 of bivalirudin was reduced to about one-fifth the
7 bolus dose given on an hourly basis. And at the same
8 time, there was a bag switch for the heparin-treated
9 patients to maintain blinding. But the dose of
10 heparin was not changed from the usual post-
11 angioplasty dose of 1,000 units per hour.

12 Results of the study are shown here. The
13 patient disposition slide is here. More than 8,000
14 patients were screened in both Trial 1 and Trial 2 to
15 result in randomization of more than 2,000 patients in
16 each trial.

17 There was a small proportion of patients
18 who were randomized but not treated. These patients
19 were followed and had six-page case report forms
20 completed -- screening forms completed for them, as
21 specified by the protocol.

22 All of the analyses I present today will

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1 be on an intention-to-treat basis, and this cohort is
2 defined as any patient who received any amount of
3 study drug, whether or not they underwent angioplasty.
4 And in both studies, there were more than 2,000
5 patients available for analysis on the intent-to-treat
6 basis. Angioplasty was actually completed in the
7 majority of these patients.

8 The baseline clinical characteristics were
9 well masked between the treatment groups in the two
10 trials. The median age of the patients in the two
11 trials was 62 years. More than half the patients were
12 more than 60 years of age. More than 30 percent of
13 the patients were female and more than 20 percent had
14 diabetes. Most of the patients presented with a
15 rather severe or acute episode of unstable angina.
16 More than half of them had rest pain. We had missing
17 data on very few of the patients, less than .2
18 percent.

19 Baseline characteristics showed that about
20 10 percent of the patients had a history of prior
21 bypass surgery. Almost half of them had a history of
22 prior myocardial infarction.

1 The angiographic core laboratory
2 identified the lesion complexity of each dilated
3 lesion in these patients. And there were some
4 imbalances in lesion complexity in this study, but
5 they all tended to favor the heparin group.

6 There were statistically significantly
7 more patients with simple Type A lesions treated with
8 heparin than with bivalirudin, and there were
9 statistically significantly more patients with
10 moderately complex Type B lesions treated with
11 bivalirudin than with heparin. The Type C lesions
12 were a small fraction of the entire lesion profile and
13 were well balanced between the two treatment groups
14 across both trials.

15 Seventeen percent of the patients, or 741
16 patients, in the entire two studies had a recent
17 myocardial infarction. Twenty-five percent of the
18 patients were previously treated with heparin up to
19 the point of their angioplasty, which probably
20 reflects a very high-risk subgroup as well.

21 The primary efficacy endpoint is shown on
22 this slide. The procedural failure endpoint, as

1 defined by in-hospital death, myocardial infarction,
2 revascularization, or abrupt vessel closure, was
3 reduced in the patients treated with bivalirudin in
4 Trial 1 by 15 percent. There was a smaller reduction
5 in Trial 2.

6 One nice aspect of this model of two
7 trials governed by a single protocol is that we can
8 see whether small or large effects of bivalirudin are
9 consistent between the two trials throughout the
10 entire presentation today. And we can see that is
11 indeed the case. Even though the effects of
12 bivalirudin are small, they are consistent between the
13 two trials.

14 But the other important finding on this
15 slide is that the event rate in the control group did
16 not meet our expectations. We anticipated about a 12
17 percent event rate, and we observed about an 8 to 8.5
18 percent event rate.

19 Now, the protocol specified secondary
20 analyses based on the components of the composite
21 endpoint, and the clinically relevant components of
22 the composite endpoints are in-hospital death,

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1 myocardial infarction, or revascularization. And we
2 can see that in Trial 1 there's a 17 percent reduction
3 in this clinically important endpoint, and in Trial 2
4 a 14 percent reduction. Again, consistency between
5 Trial 1 and Trial 2 is seen here as well.

6 Are these effects sustained at six months
7 follow-up? The differences are small. But the
8 bivalirudin curve, shown in blue, remained one to two
9 percent points below those for heparin, all the way
10 through 180 days of follow-up for both Trial 1 and
11 Trial 2, suggesting that even though the effect is
12 small it is indeed durable.

13 Now, if there's a small benefit in terms
14 of a reduction in ischemic complications, does this
15 come at a cost of increased bleeding? And the answer
16 is no. The patients treated with bivalirudin had a
17 very substantial reduction in the rate of major
18 hemorrhage, 59 percent reduction in major hemorrhage
19 in Trial 1, 63 percent reduction in Trial 2.

20 These two trials were specified to have a
21 stratification of randomization based on high-risk
22 presentation of patients with post-infarction angina.

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1 This large subgroup is worthy of separate analysis
2 because of its size, as well as the fact that this
3 homogeneous subgroup is more likely to have thrombus-
4 containing lesions and may have a benefit from a
5 thrombin inhibitor that works in a direct manner
6 rather than with heparin.

7 Here we look at the post-infarction
8 patients in Trial 1 and Trial 2, and we look at the
9 differences in procedural failure, death MI,
10 revascularization, or the combination of death or
11 myocardial infarction. And we can see that there are
12 roughly 45 percent and 58 percent reductions in
13 procedural failure.

14 And again here, and this trial too was the
15 only one where we saw event rates in the heparin group
16 that approached or exceeded what we anticipated for
17 the entire study -- 13 percent. In Trial 1, it was a
18 little bit lower.

19 If we look at the clinically meaningful
20 endpoints of death, myocardial infarction, or
21 revascularization, we see even more striking
22 reductions in the patients who had been treated with

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1 bivalirudin. Are these effects sustained at six
2 months? Indeed, they are. We see it in Trial 1 and
3 in Trial 2, substantial long-lasting benefits in the
4 patients who are treated with bivalirudin.

5 The question is: did this come at the
6 expense of increase bleeding in this higher risk
7 subgroup of patients? And the answer, again, is no.
8 A very substantial reduction in major hemorrhage was
9 seen in the patients treated with bivalirudin. Sixty-
10 eight percent reduction in major hemorrhage in
11 Trial 1; 85 percent reduction in Trial 2. And to my
12 knowledge, this is the first time that I've witnessed
13 any kind of uncoupling of event rates that are based
14 on thrombosis versus those based on bleeding in the
15 investigation of a new antithrombotic approach in
16 coronary angioplasty.

17 In summary, neither trial reached the
18 prespecified primary objective of demonstrating a 33
19 percent relative reduction in protocol-defined
20 procedural failure. Both trials demonstrated
21 substantial relative reductions in protocol-defined
22 major hemorrhage. In all patients treated with

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1 bivalirudin as compared with heparin, in Trials 1 and
2 2, respectively, procedural failure rates were 15
3 percent and five percent lower.

4 Death, MI, and revascularization rates
5 were 14 and 17 percent lower, and major hemorrhage
6 rates were 59 and 63 percent lower. Procedural
7 failure rates in patients treated with heparin were
8 lower than foreseen in the study planning.

9 In the pre-stratified, post-MI patients
10 treated with bivalirudin compared with heparin, in
11 Trial 1 and Trial 2, procedural failure rates were 45
12 and 58 percent lower; death, MI, and
13 revascularization, 45 and 75 percent lower; and major
14 hemorrhage rates were 68 and 85 percent lower.

15 Similar clinical data were observed in
16 patients treated with heparin during the previous hour
17 -- another high-risk subgroup.

18 Thank you very much for your attention.
19 I could answer any pressing questions about protocol
20 design at this time. I do want to say that Eric Topol
21 is going to cover a discussion of endpoints, the
22 clinical efficacy of bivalirudin, the dosing of

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1 heparin and bivalirudin, and I'd like to avoid a lot
2 of overlap with his presentation. But as I said, if
3 there are issues regarding the conduct of the trial or
4 protocol design, I can answer those now.

5 CHAIRMAN PACKER: I'm sure we'll have a
6 number of questions, and we will -- if the question
7 that we ask is going to be addressed by Eric, just let
8 us know it's going to be addressed by Eric and we'll
9 be patient. Maybe.

10 (Laughter.)

11 CHAIRMAN PACKER: We're going to start
12 with Dan, who is our primary reviewer.

13 DR. RODEN: Thanks. I have a number of
14 questions I don't think Eric is going to talk about.
15 So I have some simple things first.

16 Were hematocrit values obtained on a
17 protocol basis in this trial?

18 DR. BITTL: Yes, they were.

19 DR. RODEN: At what points?

20 DR. BITTL: Baseline hematocrits were
21 obtained, and hematocrits and hemoglobins were
22 obtained on a routine basis immediately post-

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1 procedure. Also, all patients had blood samples sent
2 to a core laboratory in Indiana -- Scicor Laboratories
3 -- as well.

4 We can show you the actual time specified
5 for measurements of hematocrits on a flow sheet, if
6 you'd like to see that.

7 DR. RODEN: Sure. While you're thinking
8 about that, in the FDA reviewers' review, there was a
9 question of whether all patients were accounted for,
10 or whether the number of patients who were looked at
11 and then randomized in the post-MI stratum, and the
12 number of patients who were looked at and then
13 randomized in the non-post-MI stratum, all added up to
14 the same numbers. And the FDA reviewers thought not,
15 so I'd like somebody from the FDA to tell me whether
16 that has been resolved or not.

17 Are you going to talk about that?

18 DR. BITTL: We have a patient
19 accountability slide to review that.

20 DR. RODEN: So we need to touch on that
21 issue as well.

22 DR. BITTL: More than 16,000 patients were

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1 screened.

2 CHAIRMAN PACKER: For the tape, please
3 identify yourself.

4 AUDIENCE MEMBER: (Inaudible comment from
5 an unmiked location.)

6 CHAIRMAN PACKER: Okay. We can have --

7 DR. BITTL: That microphone is not on?

8 CHAIRMAN PACKER: -- Bill Kimball from
9 Quintiles review the patient accountability when that
10 slide comes up.

11 DR. RODEN: Okay. That means we're
12 waiting for another slide? Okay.

13 DR. BITTL: These are results for
14 hematocrit and hemoglobin, but the flow sheets for lab
15 testing specified by the protocol --

16 DR. RODEN: I mean, my question is pretty
17 straightforward. If you're going to use that as an
18 endpoint, you need to tell us that they were obtained
19 at this time, this time, this time, in every single
20 patient. And I just want to know what those times
21 were, and I want some assurance that that was done.

22 DR. BITTL: Yes. I know the CKs were

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1 specified at eight and 16 hours, 24 hours if they were
2 elevated, but the hematocrits were also specified at
3 baseline and on a daily basis in hospital.

4 DR. RODEN: I mean, were those done
5 locally, or were those done at a central lab? And I
6 mean --

7 DR. BITTL: They were done both locally
8 and at a central laboratory.

9 DR. RODEN: Okay. Now, I guess my other
10 question that I wanted to have some sense of, at this
11 point at least -- and I have a whole other list of
12 questions which I'm sure we'll get to -- is the slide
13 you showed of the bivalirudin concentrations and ACT
14 didn't have any confidence intervals or standard error
15 bars around it.

16 So I want some sense of what the
17 variability in anticoagulant effect with the regimen
18 of bivalirudin that was used versus the regimen of
19 heparin that was used.

20 DR. BITTL: The median ACT achieved in the
21 patients treated with bivalirudin in this study was
22 346 seconds. Obviously, the ACT values were not

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1 normally distributed so we used nonparametric methods.
2 The interquartile range was under 100 seconds. So the
3 25th/75th percentile for the ACTs on bivalirudin were
4 less than 100 seconds.

5 On heparin, interestingly, the median ACT
6 was 383, so less than 40 seconds longer. But the
7 interquartile range was quite a bit wider. So there
8 was much more variability in the heparin response than
9 in the bivalirudin response, even though both were
10 given on a weight-adjusted basis.

11 I should probably add it wasn't really our
12 goal to achieve identical ACTs in both treatment
13 groups. We didn't feel we needed to achieve such a
14 high ACT in the bivalirudin-treated patients. But we
15 did need to achieve one that was pretty similar to
16 heparin to maintain blinding. But there was much more
17 variability in the heparin-treated group than in the
18 bivalirudin-treated group.

19 DR. RODEN: So one issue that I'm going to
20 want somebody to address, perhaps not now, and perhaps
21 you're going to want to sort of put the slides
22 together and think about it, is there a relationship

1 between the extent of anticoagulation, particularly in
2 the heparin group or in the bivalirudin group, and
3 outcome under benefit or hemorrhage.

4 DR. BITTL: Yes. That's a very good
5 question, and Eric is going to cover that in quite a
6 bit of detail.

7 DR. RODEN: I think I'll just pass the
8 microphone down.

9 CHAIRMAN PACKER: Okay. Let's start at
10 here and go work our way up -- Marv, you have one,
11 too? Okay. Well, you have a question? Okay. So
12 we'll go Marv, Joann, Lem, Udho, and then we'll turn
13 to this side.

14 DR. KONSTAM: John, can you clarify the
15 major hemorrhage endpoint a little bit more? So if
16 you just have a three grams per deciliter drop in
17 hemoglobin, is that sufficient? Or do you have to
18 have evidence of overt hemorrhage simultaneously with
19 that?

20 DR. BITTL: You have to have evidence of
21 overt hemorrhage and a three gram hemoglobin drop, as
22 defined by the protocol. A three gram hemoglobin drop

1 alone did not qualify, unless the bleeding page of the
2 case report form also specified that the patient had,
3 you know, a growing bleed, most commonly.

4 I'd also like to put this into
5 perspective. What we call major bleeding in this
6 trial -- a three gram drop -- is actually considered
7 minor bleeding in most trials because most trials use
8 a five gram drop. By definition, you had to have some
9 form of overt bleeding, and it usually was a hematoma
10 at the catheterization site to qualify for major
11 bleeding, or a transfusion.

12 DR. KONSTAM: Okay. So this is a little
13 -- this is a -- what shall we say? A more aggressive
14 definition of --

15 DR. BITTL: A broad definition.

16 DR. KONSTAM: -- major hemorrhage than
17 other studies have used.

18 DR. BITTL: Yes, a broad definition.

19 DR. KONSTAM: And could that have been
20 made by an endpoint? So there was an endpoint
21 committee, and they could have identified it as a
22 major bleed. It wasn't necessarily an investigator-

1 driven observation?

2 DR. BITTL: That's a good question. The
3 bleeding events were actually investigator driven.
4 The flag was the change in the hemoglobin, and the CRO
5 then looked at the case report form to see if any of
6 the checkmarks were attached to boxes that referred to
7 overt bleeding.

8 DR. KONSTAM: Okay.

9 DR. BITTL: We assembled -- the committee
10 looked at several hundred bleeding events, and the
11 Data Safety Monitoring Board as well reviewed several
12 patients who had bleeding events. And the concordance
13 between the site reporting and the committee review
14 was very excellent, and so that effort was stopped and
15 we just relied on site reporting.

16 DR. KONSTAM: Okay. Now, the incidence in
17 the heparin group, in the two studies, I think was
18 10.7 percent and 7.9 percent. Can you comment from
19 your registry that you had previously how that
20 compares to what you observe in practice, or at least
21 in your registry?

22 DR. BITTL: The registry only collected

1 data on transfusions. 4.9 percent of the patients in
2 the registry required transfusions and had incomplete
3 data on hematocrits, unfortunately.

4 DR. KONSTAM: Because the numbers strike
5 me, I don't know others, as high in terms of the
6 incidence of what's being called major hemorrhage.
7 And I just wonder how that relates to what's out there
8 in terms of what's expected.

9 DR. BITTL: That's a good comment and a
10 very commonly-voiced one. And, again, Eric will
11 review the bleeding rates in this study, in the
12 heparin-treated patients, as well as in the
13 bivalirudin-treated patients, with several other
14 contemporary trials. They have the entire data sets
15 in Cleveland with hematocrits on all of these
16 patients. It's a fascinating analysis.

17 DR. KONSTAM: Okay. Well, my last
18 question just relates to the protocol, and
19 specifically the use of Hirulog versus heparin and the
20 fact that the Hirulog dose was decreased. At what
21 time was that, how many hours? I don't know.
22 Somewhere in the course of the protocol it was

1 decreased. It wasn't changed with heparin.

2 DR. BITTL: Right.

3 DR. KONSTAM: And then the other point is
4 that there was no PTT measurement with heparin, which
5 isn't the way you would normally use heparin. So I
6 just wonder whether you would comment on that and why
7 that was chosen as the protocol.

8 DR. BITTL: Yes. That's a good
9 observation. The dose of Hirulog was administered at
10 a rate of 2.5 milligrams per kilogram per hour for
11 four hours, and then reduced to .2 milligram per
12 kilogram for the remaining infusion period. If the
13 dose had remained at that high level. 2.5 milligram
14 per kilogram per hour, the ACT would have remained at
15 350 seconds for the entire 18- to 24-hour infusion.

16 On heparin, at 1,000 units per hour, the
17 ACT falls at a rate of about 25 to 50 seconds over a
18 period of three to six hours. In other words, the
19 contour or the profile of anticoagulation that I
20 showed for the 12 bivalirudin-treated patients,
21 reaching a peak of 350 and then falling to about 150
22 the next morning, actually matches what you see on

1 heparin.

2 The reason we didn't allow PTT or PT
3 measurements during infusion is because that would
4 allowing unblinding. A direct thrombin inhibitor
5 raises the protein, but heparin generally doesn't. So
6 if sites were allowed to monitor the coagulation
7 parameters during the infusion, they could have
8 conceivably become unblinded.

9 We did allow for a number of safety stop-
10 gap measures during the infusion. If there was any
11 oozing around the femoral sheaths, the cardiologist and
12 the nursing staff had the option of reducing the
13 infusion to 50 percent without pulling the patient out
14 of the study. That was specified by the protocol.

15 DR. KONSTAM: Well, I understand the
16 reason, but I guess we're going to come back to this.
17 And my concern is that that's not really the way
18 heparin is used. And I mean, I guess that's the
19 question that I'm going to have.

20 DR. BITTL: The trials were carried out
21 several years ago, but at that time heparin was used
22 in this way, four patients with unstable angina, and

1 it's still used in this way for patients who required
2 prolonged post angioplasty infusions of an
3 anticoagulant.

4 Secondly, there are many sites that don't
5 have 24 hour sheath pulling teams and so in that
6 setting heparin is still administered overnight.

7 CHAIRMAN PACKER: Marv, before you ask
8 questions because the issue that you're bringing up is
9 probably going to be mentioned again and again and
10 perhaps by others. Is the -- can you just clarify
11 this issue about the way that heparin was given in
12 this study so that we don't keep on coming back to it?
13 Is heparin given differently now than it was in this
14 trial and the second part of that is, is it given
15 differently now in association with 2B3A antagonists
16 than it was given in this trial because this trial was
17 done in let's say a slightly different era perhaps.

18 DR. BITTL: Right.

19 CHAIRMAN PACKER: And can you just clarify
20 all of this because I think Marv, that relates to not
21 only whether the heparin use here is conventional for
22 this patient population at that time, but would it be

1 conventional for a patient population at this time?

2 DR. BITTL: The heparin regimen that was
3 used in the trial actually was specified in the Fourth
4 American College of Chest Physicians Consensus Panel
5 for Anticoagulation for Angioplasty. For the highest
6 risk patients, the bolus of 175 units per kilogram and
7 then 1,000 units per hour of post procedure.

8 Since that time, angioplasty practice has
9 evolved quite substantially with the introduction of
10 stents and the much lower likelihood of acute vessel
11 closure and the introduction of glycol protein 2B3A
12 blockers heparin dosing has been reduced.

13 The other change that has come about is
14 that sheaths, the thermal sheaths are now commonly
15 removed the same day of the procedure, whereas in the
16 earlier era they were kept in overnight, especially in
17 high risk patients. So there have been changes.

18 The study still applies to a significant
19 proportion of patients undergoing angioplasty,
20 however, who cannot be treated with 2B3A blockers, who
21 may require prolonged post procedure infusions and in
22 all those hospitals that don't have night time sheath

1 pulling teams, these patients have to remain on
2 heparin as well. So I think it's still quite
3 applicable to a significant proportion of our
4 patients.

5 CHAIRMAN PACKER: Can you just help us out
6 here because many of us were on the Committee when
7 2B3A antagonists were evaluated. Who would not be a
8 candidate? In other words, what conditions still
9 exist for patients now that apply to the trial design
10 as it was conducted?

11 DR. BITTL: You're asking what are the
12 contraindications to 2B3A blockers?

13 CHAIRMAN PACKER: In general, who would
14 not receive the 2B3A antagonists and what proportion
15 of the patients does that comprise?

16 DR. BITTL: A significant proportion of
17 patients cannot be treated with 2B3A blockers because
18 they've had recent bleeding, CNS events, a stroke
19 within the previous two years, platelet counts under
20 100,000, previous treatment with warfarin. It
21 probably applies to about 50 percent of the patients
22 in some centers undergoing angioplasty.

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1 In the U.S., there's quite a bit of
2 variability and the use of 2B3A blockers in
3 angioplasty, a site like ours in Ocala, Florida that
4 treats a predominantly elderly population with a
5 higher prevalence of contraindications uses M6 in 25
6 percent of patients. Sites that treat younger
7 patients may use M6 in up to 80 percent of patients.

8 I know eptifibatide and tyrofiban are also
9 approved for the management of unstable angina
10 syndromes and these agents are used in angioplasty if
11 a patient has generally been pretreated with it. But
12 they pretty much have the same list of
13 contraindications.

14 I hope that answers your question.

15 DR. KONSTAM: I just want to nail down one
16 -- that was great --, one more point though. What
17 would you say in terms of typically if you were going
18 to use heparin for 24 hours, it wouldn't be common,
19 would it, to go the big bulk of that period of time
20 without measuring aPTT, would it or would it?

21 DR. BITTL: It turns out that you rarely
22 would administer heparin for 24 hours. It's often

1 given for a shorter period, about 18 hours, so an
2 angioplasty is done on Day 1 in the afternoon and then
3 sheaths are pulled the next morning.

4 If you measure aPTT within six hours of
5 the bolus like this, it's always off the scale. It's
6 higher than 100 or 110 seconds or 150 seconds, the
7 upper limit for the laboratory. So the practice is
8 not to measure aPTT until after six hours.

9 If it's measured around 12 hours the
10 result often comes back at the time when you're ready
11 to stop the infusion, so our practice at Brigham and
12 Women's Hospital and I was there in Boston using these
13 prolonged infusions was basically to use an overnight
14 infusion and only measure aPTT if there was any
15 bleeding complication. But the more common step was
16 to just stop the heparin infusion.

17 Certainly, I agree with you. If you're
18 going to use heparin for 24 hours or longer, you're
19 monitoring aPTTs very closely.

20 DR. KONSTAM: Thanks.

21 CHAIRMAN PACKER: Before we go on further
22 I just want to find out if anyone on the Committee, so

1 we can keep the questions organized, has any other
2 questions about the heparin dosing, the heparin
3 monitoring, the relevance of the heparin regimen used
4 in this study versus the heparin use in the present
5 era.

6 Udho?

7 DR. THADANI: I'm not sure whether you
8 took all comers with unstable angioplasty --

9 CHAIRMAN PACKER: No, no, no, Udho --

10 DR. THADANI: No, no, it is related to
11 heparin.

12 CHAIRMAN PACKER: Okay.

13 DR. THADANI: Did you take them straight
14 to the cath lab or they came from the coronary care
15 unit because they were already on heparin?

16 DR. BITTL: Only about 25 percent of the
17 patients in the study were previously treated with
18 heparin.

19 DR. THADANI: And then you gave them more
20 bolus before knowing the aPTT or ACT, then you did the
21 ACT and could have driven the ACT higher by giving the
22 bolus on patients who are already running an aPTT of

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1 say 80 or 90.

2 DR. BITTL: Well, the protocol is very
3 clear about how they handle the patients who are
4 previously on heparin. The protocol required that all
5 these patients had to be off heparin for one hour
6 before the procedure was started and an activated
7 clotting time at baseline was measured.

8 DR. THADANI: But that's not the current
9 practice for anybody with acute coronary syndrome who
10 is threatening to infarct to stop it and then redo it.
11 I'm surprised. Is that your practice in your
12 institution at the moment?

13 DR. BITTL: No, I agree with you. It's
14 not the practice to stop heparin in a patient who is
15 threatening to infarct. These patients had a broad
16 range of unstable syndromes and I would say that this
17 population ultimately was kind of a low risk
18 population, not really threatening to infarct. It is
19 very common practice to stop heparin when the patient
20 is on call to the laboratory. It happens in our
21 hospital in more than 90 percent of the patients.

22 DR. THADANI: And also, you know, I know

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1 you've got a good anticoagulant, but current practice
2 is, as you said, you do a procedure and the ACT comes
3 down to whatever, your requirements are -- I don't
4 know, is it 150 in your institution or something to
5 take the sheaths out? And if the patient is high
6 risk, we'll resume heparin and then the guidelines for
7 unstable angina would suggest any time you change the
8 dose of heparin, you must measure aPTT within six
9 hours.

10 DR. BITTL: Right.

11 DR. THADANI: And then also the guidelines
12 would suggest it's not an aPTT of 90, we're now down
13 to 70 in order to reduce the bleeding, so it's
14 unfortunate. I realize what happened three years ago
15 was 24 hour sheaths removal, but what has been done
16 has no application to current practice of medicine, so
17 my question to you, what's the relevance of this study
18 as we practice medicine today in acute coronary
19 syndrome and heparin regimen?

20 DR. BITTL: Well, I would say that the
21 guidelines for heparin dosing in other settings, such
22 as the medical management of unstable angina or in

1 deep venous thrombosis are different than the
2 guidelines for anticoagulation after angioplasty.
3 Anticoagulation for angioplasty is given very
4 intensively at the time of the procedure when the
5 patient is at high risk for abrupt vessel closure with
6 a rapid fall in PTT and ACT thereafter.

7 Many institutions do not monitor the PTT
8 while it's falling in a patient who is doing well
9 after angioplasty. Your other point is very
10 important. You raise the question about whether this
11 trial is of no significance to today's practice and I
12 would argue that in my practice in Ocala and in many
13 other practices that are very busy interventional
14 practices, we have patients every day who have to be
15 treated with prolonged infusions of heparin, are at
16 high risk for bleeding. Bleeding is still occurring
17 in 5 percent of our patients and it's quite a
18 significant problem. If we only had an alternative,
19 a safer alternative, I think our options would be
20 improved and our patients would be doing better.
21 We're stuck with heparin.

22 DR. THADANI: I'm not arguing with you.

1 What I'm saying in the cath lab, I agree with you, you
2 want to go ACT 250, 300, 350, whatever your comfort
3 level is. But most of the time at the present time
4 when I'm returning on the unit, patients come back,
5 sheath is removed and the heparin is restarted in some
6 of the high risk if you see a clot there. I'm not
7 denying that, but the convention is to repeat the aPTT
8 and keep it about 70.

9 DR. BITTL: Right.

10 DR. THADANI: For the fear of risk. So
11 it's unfortunate that historically you didn't study 24
12 hour infusion without monitoring and that could have
13 taken your risk of bleeding higher than you're
14 expected with current regimen. It may not be. I'm
15 not saying it is or not. It's unfortunate, the
16 practice of medicine has changed to the point or
17 evolved that what you are showing is probably not
18 relevant to the current practice of medicine so now
19 how do you compare what we do now to what the results
20 mean even in terms of bleeding.

21 DR. BITTL: I think Dr. Topol has this
22 comparison of bleeding rates for this trial. The EPIC

1 trial which was carried out at the same time where
2 sheaths were kept in overnight, as well as several
3 other trials and it may reassure you that the bleeding
4 rates were not out of line. I think it may reassure
5 you.

6 CHAIRMAN PACKER: Are there any other
7 questions on the heparin issue?

8 DR. RODEN: I didn't actually realize that
9 there were no ACT or PT data drawn for 24 hours.
10 Maybe I should have. So -- but there must have been
11 some patients at local sites who the investigators
12 felt an urge to look. So how often did people unblind
13 themselves by looking? Or how often did people get
14 ACTs outside the protocol?

15 DR. BITTL: I think ACTs were obtained
16 very rarely outside the protocol.

17 DR. RODEN: ACTs or PTs.

18 DR. BITTL: Yes. And I think -- and I
19 don't know how often PTTs were obtained outside the
20 protocol. In a patient who had a bleeding
21 complication, the operator had the -- or the
22 cardiologist had the option of stopping the infusion,

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1 measuring anticoagulation parameters and instituting
2 standard care. That was actually specified by the
3 protocol. How often PTTs were actually obtained
4 during the infusion, I'm not certain.

5 I can only speculate. I was pretty
6 closely involved in the protocol at our institution,
7 although not the investigator. I talked to a lot of
8 investigators. I had the feeling that blinding was
9 very well maintained.

10 CHAIRMAN PACKER: Where does the target
11 ACT of 350 come from?

12 DR. BITTL: It's an empiric observation
13 based on retrospective analyses. We can look at the
14 Narins results. The Narins paper is a paper that was
15 published from Duke that was a retrospective case
16 control analysis looking at the risk of a blood vessel
17 closure in patients undergoing angioplasty. And this
18 paper actually identified an inverse relationship
19 between the risk of abrupt vessel closure and ACT and
20 there seem to be no upper end for ACT that was
21 identified. In other words, there was no ACT that was
22 too high.

1 There's also a wonderful curve. And in
2 fact, at the time this was published it was actually
3 presented as an abstract at the American College of
4 Cardiology two years before and at the time there was
5 discussion about going for target ACTs of 400 seconds.

6 If I can actually slide Y-49 I can show
7 you as well that ACT results in this study show the
8 same pattern as the Narins paper.

9 CHAIRMAN PACKER: I guess you may be
10 giving me more information than I asked, but that's
11 okay.

12 DR. BITTL: I'm sorry. We looked at the
13 probability of abrupt vessel closure reported both by
14 the investigators and by the core lab so it's much
15 higher than just the core lab reporting in patients
16 treated with Hirulog and heparin in this study,
17 because on their initial 5 minute ACT. And the only
18 reason I show this is because this is identical to the
19 Narins relationship probability of abrupt closure and
20 ACT. Most of the patients in our study, obviously,
21 are clustered down here at just a few outliers, way up
22 here at these stratospheric ACTs, but there's really

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1 no significant break in the heparin relationship.

2 On the other hand, bivalirudin has this
3 very flat relationship. There may be questions whether
4 we use enough bivalirudin but I don't see any
5 significant relationship between abrupt closure and
6 ACT on bivalirudin in this analysis.

7 CHAIRMAN PACKER: It's funny, I actually
8 didn't -- you gave me more information than I wanted,
9 but now that you've shown it, can you keep that up for
10 a moment?

11 DR. BITTL: Sure.

12 (Laughter.)

13 CHAIRMAN PACKER: Can you explain that,
14 what you see there? It doesn't make a whole lot of
15 sense to me.

16 DR. BITTL: For the heparin treated
17 patients?

18 CHAIRMAN PACKER: No, heparin makes sense.

19 DR. BITTL: Oh, for bivalirudin?

20 CHAIRMAN PACKER: Yes.

21 DR. BITTL: Yes.

22 CHAIRMAN PACKER: The ACTs are flat. How

1 can that be?

2 DR. BITTL: No, actually, the ACTs range
3 between 200 and something like 900 seconds for the
4 bivalirudin treated patients.

5 I think we're at the upper end of the dose
6 response curve, to use that term loosely. It's a dose
7 effect curve for bivalirudin.

8 DR. THADANI: It's a random occurrence of
9 the acute closure has nothing to do with the ACTs.

10 DR. BITTL: That's another explanation.

11 DR. THADANI: If you put all the data
12 together, combine the whole thing, forget about which
13 drug you gave, you could conclude there's no
14 relationship whatsoever.

15 CHAIRMAN PACKER: No, no, no. Hold on.
16 Let's make sure that we're thinking clearly here
17 because these data are really interesting.

18 Why does -- why do you think that the
19 effect of Hirulog on the vessel closure does not
20 increase the effect increase as the ACT increases?

21 DR. BITTL: I think we're at the upper end
22 of the dose effect curve for Hirulog. I think we

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1 chose the right dose of bivalirudin for this study.
2 I don't think we under dosed, number one. Number two,
3 our current understanding of the mechanism of abrupt
4 closure is that this is a mechanical complication of
5 angioplasty and back in 1992 and 1993, we thought it
6 was almost entirely due to thrombosis, but endoscopic
7 studies and the use of stents have changed that
8 thinking completely and Eric will discuss this more
9 completely as well. I think using abrupt closure as
10 an end point in a thrombin inhibitor trial is probably
11 not appropriate, knowing what we know today.

12 CHAIRMAN PACKER: Okay, let me see if I
13 got this right. If you increased the dose of Hirulog,
14 you do not get an incremental effect because you may
15 be at the flat part of the upper end of the dose
16 response curve. But if you increased the dose of
17 heparin, you get an incremental effect. Why would
18 that be?

19 DR. BITTL: Well, --

20 CHAIRMAN PACKER: I understand that ACT
21 may not relate to abrupt vessel closure and that's one
22 hypothesis and okay, let's put that on the shelf. But

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1 why would the effect not be -- why would there be an
2 incremental effect as you increase the dose?

3 DR. BITTL: Of heparin?

4 CHAIRMAN PACKER: It seems to me that what
5 you are providing us perhaps not intentionally is
6 evidence that heparin has an effect on the process
7 which is not reflective as in its properties as an
8 anticoagulant.

9 DR. BITTL: That's a possibility, but as
10 you know, bivalirudin has a very specific
11 anticoagulant effect. It only does one thing. It
12 inhibits thrombin, where heparin has a broader range
13 of anticoagulant effects inhibiting other clotting
14 factors and it probably has IC-50s for each of these
15 actions at different doses.

16 CHAIRMAN PACKER: I guess I'm -- I use the
17 word anticoagulant too broadly. I guess what you're
18 suggesting, and in fact, I think you've confirmed the
19 suggestion, there's no way of confirming the
20 hypothesis that heparin has effects on the process
21 that leads to events or abrupt vessel closure which
22 are not reflected in the ACT. If that's correct then

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1 is a dosing regimen that is designed to compare two
2 treatment approaches based on ACT an appropriate way
3 of comparing the effects of a new agent versus an old
4 agent?

5 DR. BITTL: I think that's a good point.
6 I think the reason the monitoring of ACTs had to be
7 built into the protocol is to insure that we were
8 getting a safe heparin response. We certainly did not
9 want to be doing angioplasties with ACTs less than 200
10 because the heparin treated patients was such a low
11 heparin anticoagulation response would be in excess of
12 risk.

13 I think we put ourselves in a position
14 based on the questions that maybe there's a hint that
15 maybe we use too much heparin. But we certainly did
16 not want to be criticized for using too little. On
17 the other hand, we also wanted to be able to measure
18 and monitor the anticoagulation response during the
19 procedure.

20 CHAIRMAN PACKER: I only mention it
21 because and it really was not my original intent, but
22 these data really are interesting, that any time you

1 compare two treatments, that one would propose, have
2 a similar mechanism, one always has to be where
3 they're not similar, that in fact, they're different
4 and that there are properties frequently unmeasured
5 and not infrequently unknown, that in fact, may
6 account for differences in efficacy which are not
7 measured by the -- by anything in the trial and
8 consequently when one compares two things and claims
9 that they are similar one needs to be careful as to
10 the criteria one uses for the titration of the two
11 treatment regimens that was the basis for the study
12 design purporting to show similarity.

13 DR. BITTL: Dan?

14 DR. RODEN: I have a specific question
15 about how the data on this slide were generated. What
16 are each of those points?

17 DR. BITTL: Each point is the probability
18 of abrupt vessel closure for each patient in the
19 study, based on a logistic model.

20 DR. RODEN: So these are model data then.

21 DR. BITTL: Yes.

22 DR. RODEN: These are not real data?

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1 DR. BITTL: Right.

2 DR. RODEN: It's -- so each point is a
3 patient in the study, there are 2,000 heparin points
4 and 2,000 Hirulog points standing on top of each
5 other? And the probability is derived from some model
6 which is why those curves look so wonderfully
7 straight.

8 DR. THADANI: And was the real data --

9 DR. RODEN: A model is a model. It's not
10 the real world.

11 CHAIRMAN PACKER: Our whole world are
12 models.

13 (Laughter.)

14 CHAIRMAN PACKER: We always smooth our
15 lines in real life. The world is otherwise too
16 complicated.

17 DR. BITTL: I still would conclude that we
18 achieved similar ACT levels in both treatment groups
19 and yet we saw a substantial reduction in bleeding in
20 either a small trend or a small reduction in ischemic
21 end points for the entire cohort of patients, but a
22 striking reduction in ischemic complications for the

1 post infarct patients.

2 DR. THADANI: Do you have a real slide
3 where you can put your data points and what happened
4 in real situation on your logistic model?

5 DR. BITTL: If you look at a scattergram
6 you see what you get.

7 DR. THADANI: Is it all over the place or
8 is it --

9 DR. BITTL: It's all over the place. We
10 have bar graphs for each ACT category and the bar
11 graphs reflect what you saw there. If you use ACT
12 categories to find 50 second intervals for the Hirulog
13 treated patients it was flat. For the heparin treated
14 patients there was a decrease.

15 DR. THADANI: The other thing is initially
16 ACT has no value because by definition you're going to
17 give them extra bolus to take it up to 350 anyway. So
18 what one really wants to know when you started the
19 procedure at point zero, what the ACT value is and
20 then to see if the model is a flat line then probably.

21 But you're avoiding all the upper limit
22 from your logistic model which is driven if the values

1 are low, but in real situation you gave enough bolus
2 or drugs or whatever and pushed it up to 350, so it's
3 going to be a flat line. So I don't think model has
4 any value in predicting.

5 DR. BITTL: I think those are good
6 comments. I'm sorry I even asked for the slide. I
7 was hoping to show the Narins slide which was really
8 the basis on which we were refuting for ACTs of 350 to
9 400 seconds.

10 CHAIRMAN PACKER: Okay, we're still
11 proceeding this way. So Joann?

12 DR. LINDENFELD: A couple of quick
13 questions. Were all the ACTs measured in all the
14 cents with the hemochrome device or where other
15 devices used?

16 DR. BITTL: That's a good question. The
17 hemochrome device and the hematech device measure
18 different ACT levels at same levels of
19 anticoagulation. The sponsor, Biogen, provided
20 hemochrome devices to all 121 sites. So all the ACTs
21 were measured by the same device.

22 DR. LINDENFELD: And could you go over the

1 protocol for sheath removal?

2 DR. BITTL: Sheaths were removed two hours
3 after the stop of infusion of study drug the day after
4 angioplasty. It was recommended that 20 minutes of
5 manual compression or mechanical compression be
6 applied and longer compressions were recommended if
7 bleeding persisted, but it was the standard of care at
8 each institution that was actually applied.

9 DR. LINDENFELD: And again, we have -- do
10 we have any -- or I guess we don't have any ACT or PTT
11 levels prior to sheath removal or do we?

12 DR. BITTL: No. But it's interesting. We
13 do have a time analysis of bleeding events. There
14 were more hemorrhagic events in heparin treated
15 patients in the first four hours than in the
16 bivalirudin patients in the first 48 hours. So I mean
17 the bolus -- the bleeding events did not really relate
18 very strongly to sheath removal or even to the long
19 infusions.

20 CHAIRMAN PACKER: Do you have a picture of
21 that?

22 DR. BITTL: Somebody is going to show

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1 that. We'll hold.

2 DR. LINDENFELD: It would be unusual
3 practice to not have a PTT prior -- or an ACT prior to
4 sheath removal normally standard practice?

5 DR. BITTL: Uh-huh. The additional point
6 I want to make is that the dosing of study drug,
7 whether it be bivalirudin or heparin specifically the
8 heparin was given in response to initial ACT
9 measurements. The patient did not achieve a target
10 ACT. The cardiologist had the option of giving
11 additional heparin during the procedure at two time
12 points, 5 minutes and 45 minutes into the procedure.
13 So there was monitoring.

14 DR. LINDENFELD: No monitoring for sheath
15 removal. Just another question. I just want to know
16 if this is still a concern. Is there any concern at
17 all about anti-Hirulog antibodies and do we have any
18 data on retreatment with Hirulog?

19 DR. BITTL: I think Dr. Meanwell will
20 answer this question.

21 DR. MEANWELL: Yeah, I just want to
22 respond to that question. Four hundred seventy three

1 patients had -- were involved in Phase I and II
2 studies which repeat challenge was tested. There were
3 nine patients who had an initial antibody titer which
4 was then repeated to confirm false positive
5 denegatively. None of them were actually found
6 positive. Two additional patients of the 473 had
7 positive antibodies which were not retested, so we
8 can't refute or confirm that they had anti-bivalirudin
9 antibodies. In formal rechallenge tests there was no
10 evidence of bivalirudin neutralizing antibodies in any
11 patient.

12 CHAIRMAN PACKER: Lem?

13 DR. MOYE: I can understand how in a
14 randomized trial you would not be able to treat
15 everybody who is randomized, but I have a concern
16 about not analyzing everybody who is randomized.

17 Everything that I've read and all of the
18 biometrists and epidemiologists who have advised me
19 and everything that I think I know about this says
20 that intention to treat the intent occurs at the time
21 of randomization. It doesn't occur at some time after
22 randomization and the reason it is because you want to

1 avoid confusing or confounding therapy with a possible
2 effect of therapy. So when you remove patients from
3 the analysis because they've been randomized, but they
4 have not been treated, that leads to some concern that
5 you may be causing an influence on your results which
6 are due to some post randomization event.

7 So I'm not sure how you can say that the
8 analysis which excludes patients who are randomized is
9 really an intention to treat analysis that is commonly
10 used.

11 DR. MEANWELL: Perhaps I can respond to
12 that. First of all, the protocol specified this
13 analysis would be done up front and it is discussed
14 this would be the primary analysis of the trial. So
15 I just want to be very clear about that.

16 Secondly, this is an intervention trial.
17 It is perhaps a question of philosophical debate. I
18 don't know about what is and when did these conditions
19 have the intention to treat anybody. These patients
20 were referred in for the trial before their
21 angiography inclusion/exclusion criteria were clearly
22 known to be met in every case. It would be clinically

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1 unethcal, I believe, to consider treating a patient
2 with angioplasty if when you get into the cath lab
3 it's evident that they don't have a lesion that
4 warrants intervention or if they have a lesion which
5 warrants another type of intervention.

6 So I think in this trial, in order to try
7 and accommodate that and while recognizing the as
8 randomized point you make, but in this situation it
9 was considered impossible to declare there was an
10 intent to treat until the patient was on the table in
11 the cath lab with a lesion that was necessarily to be
12 intervened.

13 DR. DiMARCO: But that's the difference
14 between consent and randomization. So when did you
15 actually randomize? Did you randomize before any
16 catheter was placed and the lesion was identified? Or
17 did you randomize once a decision was made to go with
18 angioplasty and then what happened to those people?

19 DR. MEANWELL: Well, again, I think the
20 practical issues related to randomizing a patient when
21 they're actually on a cath lab table were clearly
22 problematic in a trial of this design and so they were

1 randomized before that.

2 CHAIRMAN PACKER: I just --

3 DR. MEANWELL: I'd also like to point out,
4 excuse me --

5 CHAIRMAN PACKER: No, I'm sorry. I just
6 wanted to make sure because I think both John and Lem
7 are saying the same thing. I don't think anyone on
8 the Committee is suggesting that one do angioplasty
9 and so on in someone whom angioplasty is not
10 indicated. I think what Lem would like to see are the
11 outcomes data and the patients who were randomized who
12 did not have angioplasty, but who were randomized.

13 DR. MEANWELL: Right.

14 CHAIRMAN PACKER: In other words, an
15 intention to treat analysis from the point of
16 randomization. One of the medical reviewers
17 specifically and I think the medical and statistical
18 reviewers specifically stated that the protocol said
19 that outcomes data would be collected in patients
20 randomized who did not have a procedure and what we
21 would like to know is were those data collected over
22 a comparable period of time and if they were, and I

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1 think this is what Lem is getting to, what would the
2 data look like, particularly in the post-MI subgroup.
3 And because I'm not certain they'd make any difference
4 in the overall population. If you analyze the data
5 from the point of randomization which would be the
6 true way of doing it according to the intention to
7 treat principal -- Lem, did I say that correct?

8 DR. MOYE: Absolutely.

9 DR. MEANWELL: I understand the question.
10 I understand the point well. The protocol require
11 that all patients would be screened and that any
12 patients who were screened and randomized but not
13 treated would have a pretreatment case record form of
14 six pages filled. I think Dr. Bittl mentioned that.

15 The 360 pages, let me just look at this.
16 In the two trials, the randomization numbers at the
17 top, total amount of patients actually treated so the
18 total number of patients not treated and this is the
19 overall population of two studies was about 360
20 patients, as you see.

21 The reasons they were not treated between
22 bivalirudin and heparin were essentially identical.

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1 The protocol did not provide for following these
2 patients in terms of their morbid or mortality
3 outcomes or their subsequent procedural outcomes.
4 That was not a provision of the protocol. It not
5 required in the record form.

6 I think what these data show you very
7 clearly is that there was no evidence of bias being
8 introduced between these two groups during the period
9 between randomization and treatment.

10 CHAIRMAN PACKER: I guess what they're
11 saying is they don't have the data.

12 DR. MEANWELL: That's correct. There are
13 not data on vessel closure or hemorrhage on those
14 patients, that is correct.

15 DR. MOYE: I also think that it is
16 potentially misleading to describe this model as an
17 intention to treat model. It's not how the term is
18 classically used or continues to be used. So if you
19 want to call it pseudo intention to treat or some
20 other moniker, then perhaps it's better described that
21 way.

22 DR. MEANWELL: I think our view is that

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1 it's clearly not as randomized. We agree to that. I
2 think the intention of the physician to treat these
3 patients was made in the cath lab, but surely there's
4 certainly a technical argument there that you make.

5 DR. MOYE: No, I think it's a little more
6 than technical because once you say intention to treat
7 at the time of randomization, you're essentially
8 saying that you are free to attribute the effect you
9 see to the therapy at randomization. As soon as you
10 allow post-randomization events to determine what
11 patients are going to be analyzed, you lose the
12 clarity of attribution.

13 DR. MEANWELL: I don't think there's any
14 evidence in these data that there was any loss of
15 clarity in those two groups and I think --

16 DR. MOYE: But you don't have the data.
17 We haven't seen it.

18 DR. MEANWELL: No, excuse me, I'm
19 referring to this slide, I'm sorry.

20 I think that our goal here is to follow
21 the protocol's intention and to analyze the data
22 exactly as the protocol requested. That's what's been

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1 done. These data are not available for outcomes in
2 these patients.

3 DR. KONSTAM: Can I just clarify? If all
4 -- correct me if I'm wrong, all patients who actually
5 receive drug were in the analysis?

6 DR. MEANWELL: Yes, they were.

7 DR. KONSTAM: So the patients who were
8 excluded were patients who would have been randomized
9 but then at the time of catheterization the
10 determination might have been, for example, not to do
11 an angioplasty in which case they did not receive
12 drug.

13 DR. MEANWELL: Yes.

14 DR. KONSTAM: But once they actually
15 receive drug even if for some reason after that there
16 was no angioplasty done, they still are in the
17 analysis.

18 DR. MEANWELL: That's absolutely correct.
19 Every patient who received any amount of study
20 indication is included in this analysis.

21 The protocol defined an evalutable
22 population as those people who completed the

1 procedure. Now again one can argue about whether this
2 is normal, but I think the design of the trial
3 required it, practically that these physicians knew
4 what they were doing when they made that intention to
5 treat this.

6 CHAIRMAN PACKER: Let me see -- I just
7 want to make sure that I understand the points because
8 it's not just a point for this study, it's a general
9 question that comes up. It's come up before. I just
10 want to make sure that we got it right because we have
11 to understand whether this is a small issue, big
12 issue, whatever. It's not -- this Committee in the
13 past has seen in trials, particularly angioplasty
14 trials. It's actually sort of not uncommon. We saw it
15 with -- in the integral and the NDA where there's a
16 randomization that occurs. The PTCA then occurs
17 subsequent to the randomization. The randomization
18 may occur before the patient is in the cath lab. Then
19 there is an angiogram perform. There is an intent to
20 do an PTCA, but a PTCA may not be done. And the drug
21 is administered at some point in time, maybe before,
22 maybe after the procedure and the events are collected

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1 afterwards.

2 In the past, this Committee has struggled
3 with what is a true intention to treat analysis. Is
4 it from the point of randomization or is it from the
5 point of PTCA, but what distinguishes this application
6 from the integral application is the fact that in the
7 integral application they actually collected the
8 events in the patients who were randomized, who did
9 not have PTCA, so that one could either gain assurance
10 or not gain assurance that there was a distortion of
11 the randomization philosophy or randomization process.

12 I guess what we're saying is that you
13 didn't collect the data in the patients who were
14 randomized and didn't get PTCA. That's not true,
15 Eric? You did.

16 DR. TOPOL: One point of clarification.
17 This is actually quite different. There were 170
18 patients in each group who didn't have an angioplasty,
19 did not have an angioplasty, who were on treatment,
20 who were included in the analysis.

21 Okay, so anybody here who had gotten --
22 who got randomized and got therapy, as Marv just

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1 reviewed. So it's not true that they had to have an
2 angioplasty to be included in the analysis.

3 CHAIRMAN PACKER: What determined when
4 they got into the analysis whether they got drug?

5 DR. TOPOL: Right, and that was the slide
6 that Clive just had up with why they could get dropped
7 from the analysis.

8 Now again, is this not a true --

9 CHAIRMAN PACKER: It's not a problem. I
10 stand corrected. I just want to say in the integral
11 NDA all the events from the point of randomization
12 were collected whether or not patients got drug. What
13 is different here is that the events were not
14 collected in the patients who were randomized who
15 didn't get drug. Is that a correct statement?

16 DR. TOPOL: That's a correct statement.
17 The issue though in some angioplasty studies you had
18 to have an angioplasty in order to be part of the
19 analysis --

20 CHAIRMAN PACKER: No, no --

21 DR. TOPOL: This is not the case here.

22 CHAIRMAN PACKER: I understand.

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1 DR. TOPOL: The point that Lem is making
2 that as far as pure intention to treat on the basis of
3 randomization is absolutely true.

4 CHAIRMAN PACKER: Right.

5 DR. TOPOL: Which I think is quite
6 noteworthy is such a large proportion of patients who
7 didn't have an angioplasty are indeed included in the
8 analysis because they got any therapy.

9 CHAIRMAN PACKER: Then I want to modify
10 what I said. The deficit is still there which is the
11 lack of information on outcomes in the patients
12 randomized, whether or not they got -- they did not
13 get drug. In other words, we don't have any end point
14 data in the patients randomized who didn't get the
15 drug.

16 DR. KONSTAM: Can I just ask Lem on
17 practical grounds, could you -- I understand the point
18 completely, I mean from a theoretical perspective, but
19 could you create some kind of a construct in practical
20 terms in this protocol how a bias could have been
21 introduced as a result of dropping out those patients?

22 DR. MOYE: I'd have to a much better

1 specialist in procedures involving these invasive
2 procedures than I am to do that. But I would also say
3 the onus is not on me to do that.

4 DR. KONSTAM: Right.

5 DR. MOYE: The onus is to demonstrate
6 that, in fact, that did not happen which is an
7 incredible burden to bear. It's relieved -- and
8 again, I'm not criticizing the physicians who made
9 decisions to angioplasty or not. It's more an
10 analysis decision. Are you going to include the
11 events on patients who are randomized?

12 DR. KONSTAM: But one thing that's absent
13 that could be that sometimes is a concern is an impact
14 of therapy that creates some kind of bias that then if
15 for some reason you consider dropping those patients
16 out of the analysis you don't know that you haven't
17 introduced some kind of bias due to therapy.

18 Here, that's not possible because
19 everybody who actually received therapy was included
20 in the analysis.

21 DR. MOYE: Right, but the decision to
22 provide therapy or not was not a random one and that's

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1 the concern.

2 In a true randomized intention to treat,
3 the decision to provide therapy is random. It's
4 therapy or placebo based on the randomization
5 assigned. And the analysis is carried out -- that's
6 why you intend to treat. You don't know if you're
7 going to treat. You intend to treat.

8 DR. MEANWELL: I think that is why we
9 found the disposition of these patients and the
10 reasons being so clearly balanced reassuring in the
11 absence of the actual outcome statement.

12 DR. THADANI: And I think what will be
13 reassuring if we could show the outcome data is
14 similar. All you're showing is equal numbers did not
15 receive therapy for whatever reason. Normally, if you
16 randomize you collect some outcome which won't be
17 difficult. If you could say the outcome is similar,
18 then I think it would be very reassuring that there
19 was no bias created because the randomization just
20 fell through in some patients. I realize they didn't
21 get the drug. I think that's what Lem, that's what
22 you're asking, right, if there is outcome data, then

1 we would be more reassured.

2 CHAIRMAN PACKER: Let me just ask the
3 Committee, apparently the microphones are getting
4 echoes because we all have a tendency to speak across
5 them. So if -- I understand if we speak directly into
6 them we will eliminate the cross current. So I guess
7 I'll ask everyone to speak directly into microphone no
8 matter how difficult that might be.

9 (Laughter.)

10 CHAIRMAN PACKER: Lem, you're still on.

11 DR. MOYE: I think we've gone as far as we
12 can go with this issue.

13 CHAIRMAN PACKER: Okay, do you have any
14 other questions?

15 DR. MOYE: Not at this time.

16 CHAIRMAN PACKER: Udho?

17 DR. THADANI: Yes. Going off this point
18 now, most of the trials as Marv indicated are using
19 hemoglobin drop of 5 in all the thrombolytic and other
20 trials. Obviously, bleeding complication is low. I'm
21 not denying that, which is great.

22 If you took that out, I know it was

1 pre-specified for whatever reason. Maybe it was
2 pre-specified because you thought you may not be able
3 to show the difference, I don't know. But suppose you
4 took the group out who had hemoglobin drop 3 or more,
5 but did not require transfusion and reason to stop
6 treatment. Is there significant difference still
7 holds for other like patients who receive
8 transfusions? Because it's really driven quite a bit
9 by that because there was no other differences in
10 hemorrhage.

11 DR. MEANWELL: Let me give you a top line
12 answer on that. I think Dr. Topol will provide more
13 background on this.

14 DR. THADANI: Okay.

15 DR. MEANWELL: Whichever way you cut these
16 data, whether you look at 5 gram or 3 gram blood
17 drops, 3 gram drops for the transfusion or not; 3 gram
18 drops for the two unit transfusion or a less
19 significant transfusion there is consistently a 3:1
20 ratio of bleeds between the two treatment groups.

21 Just to go back to a point which was made
22 earlier by the Panel, I think it's important to

1 clarify. When you look at the data across ACT
2 populations in this 4,312 patients, if you look at,
3 for example, all the patients clustered around 350
4 seconds or greater, all of the patients cluster around
5 300 to 350, again, you always see for any given ACT
6 level a 3:1 ratio or more of bleeds between the two
7 treatment groups.

8 DR. THADANI: Another point which I may
9 raise, I know the trial was designed for superiority
10 claim which you are not able to show. How confident
11 -- I realize heparin is routinely used in the cath lab
12 setting. How confident do you feel there's no
13 inferiority compared to heparin? Is your sample size
14 enough or the trial is not powered that you can't be
15 sure that it is not going to be inferior to stand a
16 regimen of heparin.

17 Could you address that?

18 DR. MEANWELL: Yes, I think we should
19 address that with Dr. Topol's talk. Exactly, I think
20 that's a key point and if you would mind, I would hand
21 it over to him for that.

22 CHAIRMAN PACKER: Anything else? Okay,

1 let's see, John, questions?

2 DR. DiMARCO: I have four questions. One
3 is could you just repeat for me clearly the rationale
4 for not rebolusing with bivalirudin if you were really
5 trying to use a target ACT, if you didn't achieve it,
6 why didn't you give an extra dose of bivalirudin?

7 DR. MEANWELL: A couple of things might
8 help. First of all, it was not the intent of the
9 protocol to explicitly match the ACT to levels of
10 these two groups. I think that might not have been
11 quite understood earlier.

12 CHAIRMAN PACKER: Why not?

13 DR. MEANWELL: Because the intent of the
14 protocol was to test a single pre-determined dose of
15 bivalirudin against a standard of care titrated dose
16 of heparin. That was rather important because one is
17 seeking to support the view that the bivalirudin ACT
18 response is very predictable.

19 Had one allowed titration with anything
20 other than placebo, if you wish, then we would not
21 have been able to test that question.

22 CHAIRMAN PACKER: But I don't understand.

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1 Didn't you just confirm what John said? In other
2 words, I understand you fixed a dose of bivalirudin.
3 But you did match the heparin dose --

4 DR. MEANWELL: Yes --

5 CHAIRMAN PACKER: To the target ACT you
6 thought you would achieve with the dose of bivalirudin
7 that you used?

8 DR. MEANWELL: That's correct, Dr. Packer.
9 The Phase II protocol that's shown really fairly
10 squarely that you could achieve at 350 second ACT by
11 using this dose, you could nail that ACT basically.

12 Now the next question was if you compare
13 that to standard of care which is a carefully titrated
14 dose against ACT, and again, I also want to clear up,
15 these patients were monitored during the procedure.
16 They had a 5 minute and a 45 minute ACT measure. It
17 was a necessary part of the protocol. The difference
18 was the operator, okay, did not actually know whether
19 he was giving a placebo or more heparin at that time.
20 So the ACT would be measured. It would be called out.
21 The second bolus would be given and it was a blinded
22 titration of heparin. That was a deliberate and

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1 rather intricate important part of the protocol
2 design.

3 CHAIRMAN PACKER: John?

4 DR. DiMARCO: I still have some questions
5 there. Another thing is definition of post-MI. In
6 one of the medical reviewers' tables it looks like the
7 mean or the median was six days post-MI, but there
8 were a couple of patients who were over 2,000 days.

9 How did you define post-MI?

10 DR. MEANWELL: Again, I'll give a top line
11 answer. It's possible that Dr. Bittl may want to add
12 something. There are two parts in the case where
13 myocardial infarction history were recorded. One of
14 them is history of myocardial infarction which could
15 be some time ago, but the qualifying MI for that group
16 is an entirely different issue. The qualifying MI
17 which occurred in approximately 19 or 17 percent of
18 the cases, respectively, in the trials was driven by
19 patients having to meet the same criteria for an MI
20 within the last two weeks, but not nearer than four
21 hours ago so it's two weeks to four hours prior to
22 enrollment. They had recovered from an MI in terms of

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1 ischemia and that they could be randomized. So they
2 were recent MIs at that level of the trial.

3 DR. DiMARCO: So the outliers are really
4 violators or misclassified?

5 DR. MEANWELL: No sir. The outliers are
6 referring to patients who had a history of myocardial
7 infarction, maybe had an MI last year, but not --

8 DR. DiMARCO: I'm referring to page 28 of
9 the Medical Reviewers. There's a range of 0 to 5,846
10 days in the people who are classified as post-MI. So
11 that there's somebody who is 5,846 days out there,
12 classified as a post-MI patient.

13 DR. MEANWELL: I haven't had a detailed
14 review of that statement.

15 DR. DiMARCO: Your assumption is that
16 that's --

17 DR. MEANWELL: I think we would have to
18 clarify that for the reviewer and I regret if any of
19 our documents didn't convey the right message, but
20 this was a very tightly specified group of stratified
21 patients. There are certainly many other data in the
22 NDA related to long term histories of MI and from what

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1 I recall those numbers sound pretty familiar to me.

2 DR. DiMARCO: Could I --

3 DR. MEANWELL: Do you want to really nail
4 that point if we can't? A statistician would be happy
5 to help with that.

6 This is Mr. Kimball who is the lead
7 statistician on the project.

8 MR. KIMBALL: Hi. The issue that you're
9 raising here is the baseline characteristics summary
10 of data sets, most recent MI on this --

11 DR. DiMARCO: Do you have a copy of the
12 Medical Reviewers --

13 MR. KIMBALL: Yes, I do. I know what
14 you're referring to the post-MI patients where the
15 protocols specified that they would be post-MI within
16 two weeks. But yet on the baseline characteristics
17 summary it states that some patients, the maximum is
18 well above two weeks.

19 The reason for that, the post-MI
20 classification for patients is taken directly from the
21 randomization page of the case report form which
22 simply asks if the patient had an MI within the last

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1 two weeks, according to the protocol definitions of
2 either unstable angina or post-MI. So that is how
3 patients are classified in all these tables, whether
4 they're non-post MI or post-MI patients.

5 The baseline characteristic information
6 relative to data sets recent MI is taken from the
7 cardiovascular history page. In that page, we have a
8 few outliers which are well beyond two weeks. It is
9 unclear whether they were referring to their most
10 recent prior MI or the one that classified them for
11 the protocol, but the high majority of the patients
12 are well within those two weeks as expected. There's
13 a few outliers --

14 DR. DiMARCO: So there are just a few
15 outliers that were errors.

16 MR. KIMBALL: That's correct.

17 DR. DiMARCO: You're not sure what
18 happened to them?

19 MR. KIMBALL: That's correct.

20 DR. DiMARCO: The last thing in the
21 Medical Review they also mention a restenosis substudy
22 that you did in one of the trials.

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1 Can you comment -- and you didn't present
2 any data on that. Could you comment on that?

3 DR. MEANWELL: The restenosis substudy was
4 begun after the main work on the trial was completed.
5 It was an optional substudy, a few censuses took part,
6 I think 290 patients were -- it was published in
7 abstract. The data set were never actually available
8 to the sponsor and it wasn't considered an integral
9 part. We reported that in the FDA reports just for
10 completeness, but it was not a set of data that was
11 either sponsored or gathered.

12 The data that we think can overwhelm those
13 data entirely are the six month follow-up data that we
14 have on clinical end points. We think that's probably
15 more important than 290 patients out of 4,000 in a
16 substudy that was not completely organized with many
17 sides.

18 CHAIRMAN PACKER: Ileana?

19 DR. PINA: I have three questions and
20 maybe I still don't understand this blinding business
21 of the ACT. Wouldn't it lead to unblinding literally
22 of the investigator if he or she gets the first ACT

1 and it's right on the money at 350 and doesn't have to
2 rebolus? And do you know how many times they had to
3 rebolus on the group of the patients that were on
4 heparin?

5 DR. MEANWELL: The answer is yes to both
6 of those questions. Perhaps Dr. Bittl would like to
7 respond?

8 DR. BITTL: Sixty-three percent of the
9 patients treated with heparin achieved the target ACT
10 and did not require an additional bolus. The 37
11 percent of the patients did not achieve the target ACT
12 and received an additional bolus. I don't think this
13 resulted in unblinding of the investigator. Did not.

14 DR. PINA: My second question is there's
15 an amendment from the FDA reviewers' comments here.
16 There was an amendment that happened probably seven
17 months after the initiation of the trial that exclude
18 patients who had received dipyridamole on the day of
19 the angioplasty and it now became an exclusion
20 criteria. Did any patients get dipyridamole prior to
21 the seven months?

22 DR. BITTL: Yes. At that point in time

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1 the first stent was approved and released for use in
2 the United States. The Jan Turkle Rubin stent and
3 there were concerns about whether there would be
4 increased bleeding in patients who received
5 dipyridamole.

6 Less than 1 percent of patients received
7 dipyridamole in this study.

8 DR. PINA: And my third question, your
9 definition of procedural failure quote unquote and I'm
10 glad it's in quotes, also includes clinical
11 deterioration of cardiac origin and the patient status
12 which could come from another vessel closure, not
13 necessarily the one that the operator was working on.
14 Do you have any data on that?

15 DR. BITTL: Yes, the actual definition is
16 exactly as you stated it, plus requiring
17 revascularization. So for these slides here, I just
18 stated it as revascularization. So it's clinical
19 deterioration of -- or sudden cardiac deterioration
20 requiring revascularization.

21 DR. PINA: Related to the vessel that was
22 worked on?

1 DR. BITTL: Any vessel that caused this
2 that required revascularization either surgically or
3 with angioplasty would have qualified for this end
4 point.

5 DR. PINA: Thank you.

6 DR. MEANWELL: It is also important to add
7 that to help your question finally that the accounts
8 you're seeing here are people who had
9 revascularizations. I think your concern which is one
10 we share would be was there a subjective issue here
11 going on with regards to well I think this patient
12 really should have a revascularization and didn't get
13 one. All of the accounts you're seeing, people
14 actually had interventions here.

15 CHAIRMAN PACKER: Dr. Bittl, can you come
16 to the podium? I just want to see if we can clarify
17 this end point issue that Ileana brought up. This
18 Committee struggles a lot with end points its sponsors
19 bring to us because the -- it's not unusual for us to
20 have a different view of the end point than the
21 sponsor has and it's not unusual for us to have a
22 different view than the investigators had. Can you --

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1 we've been in particular confused by and have
2 struggled with composites that are combinations of
3 clinical end points and anatomical/physiologic
4 endpoints.

5 Can you review for us the thinking that
6 occurred when you put the protocol together as to why
7 this particular composite was chosen as opposed to
8 death-MI which would be a pure clinical composite?

9 DR. BITTL: Right. That's a good
10 question. At the time the trial was designed, the
11 thinking was consistent with, dealt with the path of
12 physiology of abrupt vessel closure as being caused by
13 thrombus. It was also apparent at the time through
14 analysis of the NHLBI registries that most of the
15 complications of coronary angioplasty were indeed
16 associated with abrupt vessel closure.

17 So we were testing a hypothesis that a
18 direct thrombin inhibitor, namely bivalirudin, would
19 be associated with lower incidence of ischemic
20 complications mediated by thrombus formation in the
21 treated coronary artery than would heparin and felt
22 that this may be the underlying pathophysiologic basis

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1 for death after the procedure, myocardial infarction,
2 the need for revascularization or abrupt vessel
3 closure itself, probably being the link between the
4 clinical end points and what occurs in the laboratory.

5 What we've learned since that time is, as
6 I stated earlier, that abrupt vessel closure is a
7 mechanical complication of dilating a lesion in an
8 artery and is probably best treated with the
9 mechanical solution, that is with a stent.

10 Angiographic studies -- angioscopic
11 studies have shown that in acute abrupt vessel closure
12 dissection flaps are seen in 80 percent of cases.
13 Thrombus itself, red thrombus or white thrombus is
14 seen in only a minority, 20 percent of cases as the
15 cause.

16 So we've learned a lot after the -- as the
17 trial was taking place and after it was completed and
18 the question about end points is excellent. We
19 probably would not use abrupt vessel closure as a
20 component of a composite endpoint today.

21 CHAIRMAN PACKER: See, this example is not
22 the only example of this Committee or the cardiology

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1 community has seen, but there's frequently a high
2 degree of enthusiasm on the part of both sponsors and
3 investigators to include nonclinical end points as
4 part of a composite. And almost entirely it is driven
5 by the desire to have more events so that the trials
6 can be quote reasonably sized.

7 The problem is that when one includes
8 nonclinical events, one is now making a judgment which
9 may or may not be valid that the nonclinical surrogate
10 that you are including in the composite is, in fact,
11 in the direct link of the pathophysiology to the
12 clinical end points which are in the composite.

13 This would not be the first example where
14 the knowledge base, after the trial was designed
15 advanced to the point where the linkage between the
16 physiologic end point and the clinical end point was
17 broken or disrupted significantly.

18 DR. BITTL: Right.

19 CHAIRMAN PACKER: And consequently one
20 kicks themselves all the time and very, very
21 frequently, I mean even in your own data base, the --
22 and the magnitude of the delta between the two groups

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1 is, in fact, greater if one analyzes only the clinical
2 composites, although the number of events is very
3 small than if one used the composite end point that
4 you designed maybe for precisely the reason that you
5 no longer believe in that physiologic surrogate at the
6 present time.

7 So I guess I welcome your comments that if
8 you had to do it all over again you wouldn't do it
9 this way.

10 DR. BITTL: Right. I think it's
11 reassuring, as you point out, that the end points that
12 really mean something are associated with largest
13 treatment effects of bivalirudin. You can look at
14 death and MI or death and MI revascularization and
15 that --

16 CHAIRMAN PACKER: The problem is that a
17 number of those events is so small.

18 DR. BITTL: Right.

19 CHAIRMAN PACKER: How many people actually
20 have a second angiogram in order to determine the
21 abrupt vessel closure?

22 DR. BITTL: I don't know the exact number.

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1 I -- I mean, it seems to me that about 80 percent of
2 the patients who have abrupt vessel closure had it
3 during the first procedure and that confirmed what we
4 had seen in the heparin registry and was reported in
5 several other studies.

6 Abrupt vessel closure tends to occur
7 during the procedure itself and in the vast majority
8 of patients and again, about 20 percent will occur
9 after the procedure has been completed.

10 I don't exactly know if it's 18 percent or
11 --

12 CHAIRMAN PACKER: I guess what I'm saying
13 is I guess it's possible. What I'm curious about is
14 how many people could have had the abrupt vessel
15 closure that you didn't know had abrupt vessel closure
16 because the second angiogram wasn't done.

17 DR. BITTL: Right.

18 CHAIRMAN PACKER: So that's my first
19 question.

20 DR. BITTL: Well, the answer to that is
21 there are patients who could have indeed had this end
22 point if another angiogram was not done, but if they

1 had a clinical complication from that, then that would
2 have been captured.

3 CHAIRMAN PACKER: And I assume that if
4 someone had an abrupt vessel closure and an MI they
5 were characterized here only once and --

6 DR. BITTL: Yes --

7 CHAIRMAN PACKER: And was the worse
8 classification used?

9 DR. BITTL: Yes, it's a hierarchical
10 classification.

11 CHAIRMAN PACKER: If a patient had an MI
12 and died, they were counted once?

13 DR. BITTL: As a death.

14 CHAIRMAN PACKER: As a death, so it's the
15 worst outcome.

16 So it's possible that there are patients
17 who had abrupt vessel closure who didn't have an MI,
18 didn't die, didn't have a vascularization procedure,
19 but we wouldn't know because the second angiogram
20 wasn't done?

21 DR. BITTL: That is possible.

22 CHAIRMAN PACKER: Can you tell me when the

1 events of MI and death were collected over what period
2 of time? My reading of the document leads a level of
3 uncertainty. I just want, if you could clarify that.
4 Over what period of time after randomization was death
5 and MI collected?

6 DR. BITTL: These events were collected
7 all the way out to 180 days.

8 CHAIRMAN PACKER: But in terms of primary
9 end point?

10 DR. BITTL: Through hospitalization which
11 extended out to 56 days for I think the longest
12 hospitalization.

13 CHAIRMAN PACKER: I'm worried about that
14 because that's not a finite period of time.
15 Hospitalization is a highly variable period of time
16 from patient to patient.

17 DR. BITTL: Right.

18 CHAIRMAN PACKER: Do you have any analysis
19 of death and MI over a fixed period of follow-up in
20 all patients?

21 DR. BITTL: I can give you the death rates
22 at 7 days, 9 in the bivalirudin group and 10 in the

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1 heparin group at 30 days, 9 and 10 at 30 days; 18 and
2 20 at six months for cardiovascular death in
3 bivalirudin and heparin treated patients respectively.

4 Dr. Topol will show the data.

5 CHAIRMAN PACKER: Rather than belabor this
6 because it is, it's such an important issue because
7 the lack of a constant duration of follow-up is a huge
8 potential confounding factor because the duration of
9 hospitalization might be determined by things other
10 than the event.

11 Let me give you a hypothetical example.
12 If heparin is as you are proposing responsible with
13 hemorrhage, it makes people bleed, and bleeding
14 prolongs the hospitalization, then patients in the
15 heparin group would have more events because they were
16 hospitalized for a longer period of time because they
17 bled more. That would have an enormous distorting
18 factor on the primary end point.

19 DR. MEANWELL: If I could respond to that?
20 At the risk of adding to the complexity, Dr. Packer,
21 I think it's slightly more complicated and that's
22 inasmuch as potentially in these designs every patient

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1 could be observed for different period of time to the
2 nearest minute, literally. So it is clearly a point
3 to consider.

4 Now in the protocol, the hospitalized
5 endpoint was in there because this was considered a
6 procedurally related patient care phenomenon, that if
7 a patient had an abrupt vessel closure while they were
8 in hospital perhaps -- that was usually in the cath
9 lab. Patients who went back to the ward after having
10 their procedure finished, the only way they could
11 really get back in the cath lab was if something
12 clinically went wrong. I mean, one wasn't running
13 angiograms routinely after all of these patients to
14 seek out a blood vessel closure which is angiographic
15 endpoint after all.

16 So the observation, once they were out of
17 the cath lab, they were essentially no observations of
18 the blood vessel closure as defined angiographically.
19 The patients were all observed for ischemic events,
20 for EKG changes, from heart attacks and so on. So I
21 think that is a limitation of using this kind of an
22 end point.

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1 Now I think it's overcome the minute you
2 look at actuarial data because there you can take 7
3 day, 30 day, 6 months and you can look at these curves
4 and see when you trace each patient out that kind of
5 takes that uncertainty away and gives you an
6 opportunity to look at patients observed or censored
7 if they've been removed from the trial at specific
8 time points. I think that's a very helpful analysis.

9 CHAIRMAN PACKER: I agree that that's --

10 DR. MEANWELL: But as a primary endpoint.
11 I think your point is well taken, that hospitalization
12 duration is a difficult endpoint to work with to say
13 the least.

14 CHAIRMAN PACKER: Because clearly if
15 someone bled and stayed in the hospital and because
16 they were still in the hospital or unrelated to
17 whether they were in the hospital or not, they just
18 had another ischemic event, whatever. They were taken
19 back and revascularized. They would be counted as the
20 primary endpoint here entirely because it occurred
21 during the time of hospitalization and that was much
22 more likely I imagine to occur in the heparin group

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1 than the Hirulog group because the heparin group bled
2 more than the Hirulog group.

3 DR. MEANWELL: Right. In actual fact, I
4 think the concern that that raises isn't perhaps as
5 great as you might imagine. The length of stay data,
6 you know across all of the populations don't show the
7 heparin treated patients staying in hospitals for days
8 and days. Again, back to your earlier point because
9 relatively few patients got a bleed. I mean 90
10 percent of patients didn't get a bleeder in this
11 trial.

12 Most of the observations of most of these
13 patients were of a very similar time period, about the
14 majority of patients have a similar period of
15 observation, but it's not an ideal way to do it.

16 CHAIRMAN PACKER: I think that, I guess,
17 Eric, you'll be showing some actuarial data so --
18 because in the absence of that I would state that this
19 primary end point is exceedingly hard to interpret not
20 only because of the inclusion of a nonclinical
21 physiologic component which now perhaps the community
22 no longer embraces as warmly, but also because of the

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1 potential for confounding for variable periods of
2 follow up.

3 DR. MEANWELL: Just to take this point a
4 step further then. These are the data for the
5 combined data set, both trials, looking at in hospital
6 events which were the primary events described by the
7 protocol, 5.4 versus 6.7. In hospital, approximately
8 68 percent of all events that would happen by 30 days
9 had occurred on the bivalirudin group, on the left,
10 compared to 74 percent of the heparin rates. So
11 there's some -- that might hint at some differences in
12 length of stay there. We have length of stay data
13 which show, in fact, it's not very different.

14 At seven days though, when you just take
15 that cut point and this is obviously taken from actual
16 analysis, you have a similar difference and also 30
17 days. So by the time all the 30-day observations are
18 made, you're still seeing real differences, well,
19 excuse me, I should say differences in death
20 myocardial infarction and revascularization.

21 CHAIRMAN PACKER: How many patients of the
22 4,312 that are up there had their status ascertained

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1 at the time points designated on that slide?

2 How many patients were lost to follow up?

3 DR. MEANWELL: No patients were lost from
4 the in-hospital end point. So that was the primary
5 one. And in the -- in terms of data lost at six
6 months which is probably the best, been the most
7 extreme number, I think 87 and 81, approximately,
8 around 80 patents, per se, in both groups in the
9 combined population did not have their outcome
10 accounted for at six months. But every patient had
11 their account, their outcome accounted for the primary
12 endpoint.

13 CHAIRMAN PACKER: So that the number of
14 patients lost to follow up was --

15 DR. MEANWELL: Out of 4,000 patients --

16 CHAIRMAN PACKER: About 4 percent?

17 DR. MEANWELL: It's 3 at six months.
18 Recalling that the protocol was not setting up the six
19 month endpoint as the primary endpoint.

20 CHAIRMAN PACKER: I guess if one took the
21 point of randomization and emphasized the number of
22 patients for whom there is no data from the point of

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1 randomization, would be larger than that.

2 DR. MEANWELL: I think one has to consider
3 the sensitivity of this and we can, if you wish.
4 We've looked at this, if that's of interest.

5 CHAIRMAN PACKER: Let me ask -- I think
6 it's one more question. The medical reviewer or the
7 statistical reviewer suggested that -- indicated that
8 there are a number of patients who had been
9 misrandomized. I guess I really didn't understand
10 what that meant, but that actually applied to some of
11 the patients who had events. Can you explain what
12 they're referring to when they referred to
13 misrandomized?

14 DR. MEANWELL: I'm going to call on the
15 statistical team to come and answer that question. We
16 received the reviewers comments a few days ago and
17 we've obviously had a chance to look at them and try
18 to understand how we miscommunicated these data or
19 didn't put them adequately in the documents. We don't
20 feel there's any discrepancy whatsoever and perhaps
21 Mr. Kimball can show us.

22 MR. KIMBALL: The issue of misrandomized

1 patients is one of stratifying groups, post-MI,
2 nonpost-MI patients. There were not patients that
3 were given a different treatment than what was
4 randomized. This is actually an issue --

5 CHAIRMAN PACKER: Okay, I understand.
6 What you're saying is that the -- there's a
7 discrepancy between the two aspects of the case report
8 form with respect to whether the stratification
9 procedure followed precisely to the way that the
10 history of MI was recorded and that happens all the
11 time. It's no big deal.

12 Maybe I should -- the medical reviewer
13 does say in reference to the data you have on this
14 table that there were at six months 37 deaths in the
15 Hirulog group and 26 deaths in the heparin group. Is
16 that correct?

17 DR. MEANWELL: That is a correct number.
18 There were at six months 20 and 18 cardiovascular
19 related deaths; at 30 days there were 9 and 10, and at
20 7 days there were 5 and 5 in the two groups
21 respectively.

22 CHAIRMAN PACKER: I guess it -- could you

1 show us the data you have on that slide, death and MI
2 as opposed to death, MI and revascularization? The
3 only reason is revascularization, I have no idea
4 whether to consider that the clinical component or
5 not, but I have no doubt that death and MI are a
6 clinical.

7 DR. MEANWELL: Yes. Death --

8 CHAIRMAN PACKER: Death alone and death
9 and MI at whatever time period you would like to show,
10 but I guess 7 days, 30 days and 6 months would be
11 good. So that what's good about that and let us
12 explain why we're asking for it so it doesn't appear
13 to be arbitrary. Those are clinically relevant events
14 unconfounded by the use of surrogates over a fixed
15 period of time which the primary endpoint did not
16 insure. And gives us a much better perspective, I
17 think, of how the clinical -- how the effect of
18 comparative effects of therapy might have occurred
19 over the way we normally see these analyses which are
20 clinically relevant end points over fixed periods of
21 time.

22 DR. MEANWELL: Dr. Packer, this is such an

1 important issue, the fact is this is embedded in Dr.
2 Topol's talk. I think our view is that you're right,
3 that death and MI really counts, that deaths matter.
4 The number of deaths in this study was rather low to
5 say the very least compared with other trials in this
6 area.

7 The data I think will be displayed by Dr.
8 Topol completely, including the death and MI as well.
9 Again, the top line here is that there were no
10 differences between death and MI at 7 days, at 30
11 days. There were differences at 6 months of 37 versus
12 26, as you mentioned. For cardiovascular causes
13 excluding --

14 CHAIRMAN PACKER: Oh yeah, no, no. We
15 understand there are no differences.

16 DR. MEANWELL: Right.

17 CHAIRMAN PACKER: You're asking us to look
18 at trends?

19 DR. MEANWELL: Yes.

20 CHAIRMAN PACKER: So we're asking you to
21 look at trends.

22 DR. MEANWELL: Absolutely, that's fair.

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1 (Laughter.)

2 DR. MEANWELL: Well, let's get on to that,
3 maybe. Shall we run through Dr. Topol's slides?

4 CHAIRMAN PACKER: Joann, you had one more
5 question.

6 DR. LINDENFELD: Just a couple of quick
7 ones. Where were the ACT sampled from? Was that
8 defined in the protocol? In other words, arterial
9 sheaths, venous sheath or intravenous?

10 DR. MEANWELL: I'll defer to Dr. Bittl for
11 that one.

12 DR. BITTL: I don't think it was specified
13 in the protocol whether it was arterial or venous
14 sheath.

15 DR. LINDENFELD: Because there is as much
16 as a 20 percent difference of venous and arterial. Is
17 that your understanding of the ACT levels?

18 DR. BITTL: If there is, I stand
19 corrected.

20 DR. LINDENFELD: I think there is. The
21 other question I have is could you tell us how many
22 patients in each group got nitroglycerine?

1 I think it's been reported that that
2 affects the heparin requirement. I don't know if it
3 affects Hirulog requirement. I just want to be sure
4 they're equal.

5 DR. BITTL: We may have a slide on how
6 many patients had nitroglycerine. In practice, its
7 effect as an anticoagulant is very small.

8 DR. LINDENFELD: I think it affects the
9 heparin requirement though on the ACT doesn't it?

10 DR. MEANWELL: It has been reported.

11 DR. LINDENFELD: I just want to be sure
12 they're equal.

13 And then the last question I have is can
14 you just tell us the length of hospitalization,
15 compare the two groups? I don't think we've seen that
16 yet.

17 DR. BITTL: An analysis of length of stay
18 was carried out in the two groups and it was -- I
19 remember correctly 4.4 and 4.2 days for heparin and
20 bivalirudin treated patients respectively.

21 CHAIRMAN PACKER: I'm sorry, one last
22 question. This is probably going to be answered best

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1 by the statistician.

2 What we've seen is an analysis of both the
3 post-MI and nonpost-MI subgroup combined which were
4 the two strata. That was the overall analysis and
5 we've seen the analysis of the post-MI strata alone
6 and the FDA has conducted an analysis of the
7 nonpost-MI strata alone, but -- each of these analyses
8 of the individual described alone are within strata
9 analyses. What I'd like to know is for the -- for any
10 end point you would like to show us, was there at any
11 time a significant interaction term, a p value for the
12 interaction between treatment and the effect within
13 the strata? In other words, what I don't want to see
14 is the within strata comparison. I want to see the p
15 value for the between strata comparison.

16 DR. MEANWELL: Yes, thank you. We'll
17 answer this with the statistician.

18 MR. KIMBALL: First of all, I want to make
19 clear that even though most of the narrative
20 presentations in the document submitted focused on the
21 all patients for the post-MI group, all analyses were
22 conducted on the nonpost-MI patients as well and

1 submitted in the tabular summaries.

2 Secondly, the issue of the interaction
3 which led, in part, to the analysis of the post-MI and
4 nonpost-MI groups is in one of the two individual
5 studies. There was a significant interaction between
6 treatment effects and post-MI status or nonpost-MI
7 status.

8 In the other study there was not a nominal
9 significant interaction, but in light of that
10 interaction, we did want to evaluate both studies for
11 the subgroup analysis.

12 CHAIRMAN PACKER: Was the p value for the
13 interaction in the combined analysis significant?

14 MR. KIMBALL: Yes, it was.

15 CHAIRMAN PACKER: For the combined
16 analysis?

17 MR. KIMBALL: For the combined analysis --

18 CHAIRMAN PACKER: Do you know what the p
19 value was?

20 MR. KIMBALL: The p value for that was,
21 yes, I do have that. The p value for the combined
22 analysis was .008 for the interaction.

1 CHAIRMAN PACKER: Okay, now I'll ask the
2 question, but I don't expect the answer until after
3 Eric is finished. Can you get us that p value for the
4 interaction between the post-MI and the nonpost-MI for
5 death in hospitalization at say 30 days?

6 MR. KIMBALL: Yes, we can do that.

7 CHAIRMAN PACKER: Okay.

8 DR. DiMARCO: I have one more question.
9 I still am quite sure when was the randomization
10 envelope opened?

11 DR. BITTL: It was very clear from the
12 protocol that patients could not be randomized in the
13 cardiac catheterization laboratory or after receiving
14 any medications that may result in sedation.
15 Randomization could only take place after the patient
16 was identified as a patient with unstable angina,
17 post-infarction angina and a candidate for
18 angioplasty.

19 DR. DiMARCO: How did you know they were
20 a candidate for angioplasty before the angiograms?

21 DR. BITTL: They all had to have
22 diagnostic angiograms done before randomization could

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1 be completed. Some of the diagnostic angiograms were
2 done at referring institutions. Patients were then
3 sent to the treating institution, evaluated for
4 enrollment in the study, consented and then randomized
5 and then taken to the cath lab and that probably
6 accounts for the fact that about 330 patients were
7 treated, but did not undergo angioplasty as specified
8 by the protocol. However, all their outcomes are
9 presented today.

10 It's a fact of life in doing an
11 interventional trial. You try to identify patients as
12 candidates for an intervention based on diagnostic
13 angiograms and most of the time they're accurate and
14 they are consistent, but when the patient actually
15 enters the cath lab and has the set up shots taken for
16 the actual intervention you may find left main disease
17 that was previously missed. You may find that lesions
18 that were previously severe are now not significant
19 and so on. So there's a variety of reasons why
20 patients may be found out to be candidates.

21 DR. DiMARCO: So all these patients had
22 prior angiograms before the day of this procedure?

1 DR. BITTL: They could have had the
2 angiogram done on the day of the procedure, but
3 according to the protocol they could not have been
4 consented if they were treated with sedatives.

5 DR. DiMARCO: I'm not talking about
6 consent. I'm talking about randomized. I mean they
7 could have been consented and then you randomized
8 after you got the shots.

9 DR. BITTL: Right. But not in the cath
10 lab.

11 DR. RODEN: The consent procedure didn't
12 take place in the cath lab.

13 DR. BITTL: Pardon me?

14 DR. RODEN: The consent procedure. We
15 understand the consent procedure didn't take place in
16 the cath lab, but John, I still haven't heard a
17 question to -- an answer to John's question. When was
18 the envelope opened?

19 DR. BITTL: Generally, the envelope was
20 opened actually when the patient was in the cath lab.

21 And in some cases, just for logistic
22 reasons the envelope was opened before the set up

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1 shots for intervention were completed. Patients
2 received some study drug, but did not undergo
3 angioplasty, but you're right. The envelopes were
4 opened when the patient was in the cath lab.

5 DR. LINDENFELD: Then did they get a bolus
6 of heparin before the actual angiogram, prior to
7 randomization?

8 DR. TOPOL: No.

9 DR. LINDENFELD: No?

10 DR. TOPOL: Heparin isn't used for
11 diagnostic angiography.

12 DR. RODEN: Even in patients with unstable
13 angina?

14 DR. TOPOL: That's right.

15 CHAIRMAN PACKER: Wait, I'm sorry.
16 Heparin is not used --

17 DR. TOPOL: If patients are coming in with
18 unstable angina on a heparin drip, they may have that
19 maintained, but to do --

20 CHAIRMAN PACKER: No, no, no. All the
21 patients had unstable angina so my -- the large
22 majority of patients in this trial came into this

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1 trial on heparin, right?

2 DR. BITTL: No, about 35 percent came into
3 this trial on heparin.

4 CHAIRMAN PACKER: Why did patients with
5 unstable angina not get heparin?

6 DR. BITTL: There were about 30 percent of
7 the patients had new angina after a prior angioplasty
8 and therefore had restenosis. Many of these patients
9 are not treated with heparin. They were -- some
10 patients who had a slight worsening of their angina
11 from say Class 1 to Class 2 and many of those patients
12 were not treated with heparin.

13 DR. RODEN: I have two questions, one
14 question and then a sort of comment that I hope Eric
15 will be able to answer over his talk.

16 The first question is I still haven't
17 heard an answer to Ileana's question and that is I
18 want to know what happens in the following scenario.
19 A patient comes to the lab. They are entered into the
20 study. I didn't say they were randomized or whatever,
21 and an ACT is obtained at 5 minutes. That number is
22 available to the investigators, is that correct?

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1 DR. BITTL: Yes.

2 DR. RODEN: The five minute ACT is
3 available to the investigator.

4 DR. BITTL: Right. But I want to clarify.
5 I think in the study we would have called that the
6 baseline of ACT --

7 DR. RODEN: But they received a study drug
8 and then the 5 minute ACT is obtained.

9 DR. BITTL: Okay.

10 DR. RODEN: That number is called out and
11 somebody says give them more or don't give them more
12 or whatever. And then a 30 minute ACT is obtained.

13 DR. BITTL: Forty-five minutes.

14 DR. RODEN: Forty-five minute ACT is
15 obtained. Now, couldn't an investigator make some
16 inference as to which arm the patient was randomized
17 in by comparing the ACT, by knowing what happened at
18 5 minutes and what happened at 45 minutes and seeing
19 that there was no change or the ACT went down despite
20 a "bolus".

21 DR. BITTL: I imagine that could have
22 happened. Only 40 percent of the patients in the

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1 entire cohort had the second ACT measured because 60
2 percent of the patients had procedures that were over
3 by 45 minutes.

4 DR. RODEN: Okay. So that was --

5 DR. BITTL: I think there were a couple
6 other confounding factors that prevented unblinding
7 based on ACT measurements and one is the fact that
8 patients at 37 percent of the heparin patients
9 received a bolus, an additional bolus.

10 Here, the ACTs at baseline for the two
11 study groups at 5 minutes and at 45 minutes and I
12 think like all investigators, they may try to have
13 second guess what drug the patient was on, but I don't
14 think they could have.

15 DR. RODEN: And those are statistically
16 significantly different, right, at 5 minutes?

17 DR. BITTL: Yes, they are, using
18 nonparametric analysis.

19 DR. RODEN: Okay. So my comment that I
20 want Eric to think about is suppose heparin doesn't do
21 very much in this situation, nor does bivalirudin in
22 terms of efficacy, because we don't have placebo

1 controlled data. What you're showing us, I think,
2 then is that the higher the ACT the greater the
3 bleeding complications. Is that a scenario?

4 I guess now it's time for Eric to talk.

5 CHAIRMAN PACKER: No, it's not.

6 DR. TOPOL: I'd be happy to address that.

7 CHAIRMAN PACKER: Eric, before you even
8 start --

9 (Laughter.)

10 CHAIRMAN PACKER: We just have one more
11 question. Marv?

12 DR. KONSTAM: I'm a little confused now
13 about the population and I'm going to make a statement
14 and maybe Eric or John can disagree with it. Heparin
15 is standard -- the administration of heparin is
16 standard practice in unstable angina. I believe in
17 the studies that we've seen before this Committee
18 where there's for treatment of unstable angina,
19 heparin or something trying to be as good as heparin
20 is always administered.

21 I know in our practice we routinely use
22 heparin for patients who we call unstable angina. So

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1 I'm not sure why there is such a low use of heparin on
2 the way in and I just wonder whether it's different
3 from what is conventionally called unstable angina.

4 DR. BITTL: That's a good point and I'm
5 glad you asked it. I think what the protocol and the
6 case report form specified was to identify those
7 patients who are on heparin within one hour before the
8 procedure. So it's possible that we miss patients who
9 were treated with heparin and the heparin was stopped
10 more than one hour before the procedure and as you
11 know, procedures don't always occur at a scheduled
12 time. So the protocol specifically gathered
13 information on those who had heparin within one hour
14 before the procedure.

15 Number two, getting to the description of
16 the population, I think, is another important point.
17 The symptoms of unstable angina is a very
18 heterogeneous syndrome consisting of patients with a
19 broad range of risks and presentations, depending on
20 whether they have nuance angina, crescendo angina or
21 at rest angina and even in the public health document
22 on unstable angina, hospitalization is not even

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1 recommended for all patients who fall under this very
2 broad diagnosis and for those who are hospitalized
3 with high risk features, obviously, heparin is
4 recommended.

5 I think there were some patients who met
6 a very broad definition of unstable angina in this
7 protocol who did not feel, did not receive heparin.

8 DR. TOPOL: And I also want to add onto
9 that, Marv that many patients who have presented de
10 novo with unstable angina would go right to the cath
11 lab without getting any prior heparin and only get
12 heparin if they're going to have an intervention or be
13 treated on a medical basis. So sometimes that
14 decision to start heparin is waited until there's a
15 decision about whether intervention is going to be
16 performed.

17 DR. KONSTAM: You know, but I would still
18 say and it's my impression that there's sort of a
19 definition creep that occurs where you have the
20 diagnosis of unstable angina as a requirement for
21 entry as opposed to, for example, a trial where
22 patients with stable or unstable angina are permitted

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1 in and then are stratified. I dare say that the
2 breakdown between those two would be different than
3 what you'd get if you require somebody saying the
4 patient has unstable angina in order to get in. I
5 think at the very least, this is a very broad
6 definition of unstable angina that you're using here.

7 DR. BITTL: I think the implication is
8 that there are some patients in this trial who aren't
9 very sick. They weren't pretreated with heparin and
10 maybe that was one explanation that the event rating
11 the control group was lower than we anticipated.

12 CHAIRMAN PACKER: Just so I understand.
13 Marv, I just want to clarify the point you're making.
14 If a patient had a routine angioplasty done and after
15 the angioplasty had chest pain, may not even have left
16 the cath lab, but let's assume they go out in the
17 hallway and maybe they're on their way to a room and
18 they get chest pain. Maybe they could come. Is that
19 a patient that would have, in fact, been the candidate
20 for the study?

21 DR. BITTL: No. Patients who had recently
22 angioplasty were excluded from this study. I think it

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1 was a two month interval that was required after a
2 prior angioplasty for a patient to be a candidate for
3 this study. It was an exclusion criterion. Recent
4 angioplasty was an exclusion criterion.

5 CHAIRMAN PACKER: I guess if a patient had
6 a little bit of chest pain on exertion a month ago and
7 had a little bit more a week ago, but no pain at rest,
8 would they be a candidate for this study?

9 DR. BITTL: Yes. They didn't even have to
10 have the second episode a week ago. If they had new
11 angina one month before consenting and enrollment,
12 they would be candidates.

13 CHAIRMAN PACKER: Maybe I can -- because
14 Marv, we wouldn't treat patients who had chest pain
15 within the -- new chest pain within the last month
16 with heparin. Then my question is one is this really
17 unstable angina and second, is how many patients were
18 like that in the trial?

19 DR. BITTL: I think the general guideline
20 that we use for classifying these patients with
21 unstable angina came from Dr. Braunweld's paper in
22 1989 and circulation and it was -- it involved

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1 patients who had rest, pain, nuance angina or
2 crescendo angina within one month. So it is a broad
3 definition.

4 Fifty-four percent of the patients in the
5 study had rest pain and we could look at a cross table
6 analysis to see how many of those were treated with
7 heparin.

8 CHAIRMAN PACKER: It would be, I think,
9 informative if an analysis were done of the patients
10 entering this trial that met with a conventional, I
11 have no idea how to define that, criteria for unstable
12 angina at either -- either determined by -- well, they
13 don't actually have that information in the precise
14 way.

15 Maybe by using the definition of rest pain
16 and I'm not certain that's the best definition, but
17 it's one that occurs to me. I don't know if anyone
18 has done that analysis.

19 It could be an analysis that would be more
20 sensitive to a treatment effect, than the more broad
21 based definition you're using.

22 DR. BITTL: I think it's a good point and

1 we did specify an analysis looking at the patients
2 that you probably are trying to define here and that
3 is those who are pre-treated with heparin. This was
4 a specified secondary analysis and in study 1 there
5 was a treatment effect in terms of reduced ischemic
6 complications that was statistically significant. And
7 in Study 2, there was a large effect not quite
8 statistically significant.

9 CHAIRMAN PACKER: It may be yet another
10 example of the kind of trouble you get into when you
11 try to make recruitment easier, but the treatment
12 effect weaker.

13 DR. BITTL: Yes, right. I think Eric will
14 show those results.

15 CHAIRMAN PACKER: Ileana?

16 DR. PINA: I may show my heart failure
17 ignorance here but aren't there HCPR guidelines that
18 specifically risk stratify unstable angina and the
19 high likelihood of disease, and I think the guidelines
20 probably came out while the study was on-going because
21 I think that, Eric, you should know those guidelines
22 -- you were on the Committee. They are what 2 to 3

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1 years old? But there are pretty clear cut ways to
2 differentiate people who are at high risk and lower
3 risk so I think Milt's point is well taken.

4 DR. TOPOL: I think it's an excellent
5 point and the post-MI group was the one who has the
6 most evidence for being the highest risk in all
7 studies converging at that point.

8 CHAIRMAN PACKER: Okay, Eric, I think
9 we're ready.

10 (Laughter.)

11 DR. TOPOL: Thank you. Well, I'm pleased
12 to have a chance to try to address many of these
13 issues which in fact the last two hours have been the
14 subject of discussion and, hopefully, I can help round
15 out that with additional data, not only from the trial
16 itself from what has happened since this trial was
17 performed and published.

18 First, I'd like to discuss the issues that
19 have been raised that we think are central and
20 important and these are the five, before summing up
21 what the data, I think, shows us with respect to
22 bivalirudin.

1 The endpoint 1 is the one I'd first like to turn to
2 because I think justifiably this is a source of
3 significant concern and that is that we have learned
4 considerable amount in interventional cardiology over
5 the last decade in doing controlled trials and
6 certainly our view of what is an appropriate endpoint
7 has changed and perhaps one can say matured and
8 refined over time.

9 Clearly, this endpoint of procedural
10 failure we would not deem acceptable in 1998 because
11 as Dr. Packer has pointed out, it represents a mosaic
12 of both clinical as well as anatomical angiographic
13 features and included such things as clinical
14 deterioration and also abrupt vessel closure. As
15 you'll see, that could have been impending, that could
16 have been actual. It might not have always been
17 defined by the second catheterization. Many of those
18 points which take the procedural failure question as
19 an endpoint and really subject to consternation.

20 Secondly, that this trial was indeed
21 conceived back in 1992, so fully six years ago and as
22 I mentioned much has changed and many trials over

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1 10,000 patients have been performed in the setting of
2 interventional cardiology.

3 Our focus has indeed shifter to that of
4 death or myocardial infarction. That is the central
5 endpoint for ischemic heart disease rather than this
6 hodgepodge or composite endpoint when many additional
7 things are added in.

8 So if we just look at the patients who
9 were the most uniform and the highest risk in the
10 current set of trials, those patients with
11 post-myocardial infarction, unstable angina, you see
12 that the difference for the composite and death, MI,
13 revascularization which was a three-fold difference or
14 for death or MI which was more than a fourfold
15 difference of benefit or for death alone which was a
16 significant difference, if we looked at each of these
17 endpoints there's considerable evidence of efficacy.
18 Whereas if we look at established abrupt vessel
19 closure or impending abrupt vessel closure which are
20 endpoints that could have led to this procedural
21 failure definition, you see there's lack of a real
22 effect and this, of course, is also accentuated by

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1 what we know is underlying this, that patients with
2 abrupt vessel closure have a tear in the artery
3 induced by the balloon or catheterization induced
4 trauma of the target vessel and it's very hard to deal
5 with that in terms of a drug therapy when there's an
6 overriding mechanical problem.

7 So I think it's clear today that our focus
8 would be on either death or myocardial infarction --

9 CHAIRMAN PACKER: Eric, could you --
10 because there's a little bit of confusion and sorry to
11 interrupt, where did the data you are showing coming
12 from?

13 DR. TOPOL: This is the post-MI subset of
14 the combined trials, a total of 741 patients in the
15 two trials. This is the stratified post-MI group and
16 in light of the recent discussion which is
17 appropriate, how sick were these unstable angina
18 patients? This by all the evidence we have and
19 included as Ileana has mentioned to the AHCPR
20 guidelines who are the sickest group of patients of
21 unstable angina, it would be the post-MI patients.

22 Now let's talk about the dose of

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1 bivalirudin because this has also come under
2 discussion. Back in 1990 in Ann Arbor, we embarked on
3 a very -- in retrospect -- frightening experience.
4 And that was when we put the first patients in this
5 cohort because up until this point from 1977 for 13
6 years there had never been a patient, to our
7 knowledge, that knowingly did not receive heparin in
8 undergoing coronary intervention. So this was the
9 first study ever to take away anticoagulation with an
10 investigational agent.

11 So when we did this dose escalation with
12 low -- with what proved to be lower doses of
13 bivalirudin, we were looking to see what would be a
14 threshold dose in which we would achieve at least an
15 activated clotting time of over 300 seconds. Indeed,
16 it was only until we got to .45 milligram per kilogram
17 bolus in this infusion, this latter half, that we were
18 getting in the majority of patients, at least a
19 threshold of 300 seconds. In fact, many
20 interventional cardiologists who were not routinely at
21 this looking at ACTs, this was not widely available as
22 far as bedside or cath lab monitoring, would not have

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1 known what would be the appropriate threshold. I'm
2 not sure if we still know that today.

3 So this group of patients were in jeopardy
4 and in fact, as you see in this next slide who were
5 underdosed with respect to anticoagulation. You see
6 that the rate of abrupt vessel closure acknowledging
7 the limitations of this particular surrogate, you'll
8 see the instance of death and MIs in subsequent slides
9 in this Phase II effort of 291 patients, dose
10 escalation, and unsuccessful angioplasty. And it was
11 only when the doses of bivalirudin anticoagulation
12 were in this higher end and ultimately the dose that
13 was used in the large Phase III trials that we could
14 get abrupt vessel closure or successful angioplasty
15 which here was zero into an appropriate acceptable
16 range.

17 Now this is just review of a slide you
18 just saw, but I think it's an important one because
19 what you can tell is that the ACT, this box and
20 whisker plot, started out here in the mid-100 range
21 and very quickly after bivalirudin was near, beyond
22 350 seconds with this dose and at 45 minutes with just

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1 a constant infusion and in many patients, of course,
2 a placebo, dummy syringe, but no further additional
3 bivalirudin and then the tailing off of the effect at
4 the time when the perivascular sheaths were
5 discontinued.

6 This was looked at in a substantial cohort
7 of patients, over 2,000 patients in which there was
8 systematic study of the ACT through a uniform device
9 in the cardiac catheterization laboratories.

10 Now let's talk about the dose of heparin
11 because there's been very considerable concern is this
12 the appropriate dose and what does this dose translate
13 to in terms of 1998 or contemporary standard.

14 Well, to address this because we shared
15 the concerns about what this -- whether this higher
16 dose used in the current trials under review was too
17 high. So we looked at eight large double blind PTCA
18 trials that were conducted between 1993 and 1998,
19 predominantly in North America. In fact, all except
20 for one trial. These are trials that we had the
21 entire data base available so we could look at any end
22 point we wanted to look at, rather than just that

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1 which was reported, a total of over 16,000 patients
2 over 6,700 patients who received heparin and as I
3 mentioned with common data fields, that is, having the
4 actual data bases to work with.

5 Now these trials that were used in this
6 analysis, most of the ones that have been conducted in
7 the last five years included the CAPTURE, EPIC,
8 EPILOG, EPILOG-STENT, EPISTENT, IMPACT-II, RAPPORT and
9 then the two trials under discussion today. All these
10 patients were being enrolled with coronary artery
11 disease, of course, some with unstable angina, some
12 with acute myocardial infarction.

13 Now this is an important slide because it
14 sums up a lot of information regarding the heparin use
15 in the other trials and what you can see in these
16 other trials, uniformly, the dose of bolus heparin was
17 considerably lower. It was 100 units per kilogram
18 throughout these studies in the placebo, heparin
19 control arm of these studies whereas, as you recall,
20 was 175 units per kilogram here.

21 Now also the ACT target specified was
22 different in the various studies. In some, it was a

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1 low of the most recent EPISTENT of 250 and in others
2 300 to 350 and in the bivalirudin trials it was 350
3 was the desired target.

4 You see here, the bar graphs with standard
5 deviations, the actual mean cumulative heparin given
6 during the procedure or related to the procedure. And
7 indeed, the bivalirudin heparin study is at the higher
8 end of this and so also I would like to point out that
9 this dose of 175 units per kilogram was the upper
10 limit specified by a consensus conference as published
11 in Chest, a Thrombosis Consensus Conference, and as
12 Dr. Bittl pointed out, it was the desire in this trial
13 not to use too low a dose of heparin to be perceived
14 as somehow handicapping or reducing the likelihood of
15 showing heparin's true potency.

16 Now as we look here, it's really quite
17 striking to see the hemorrhage incidents and to
18 address some concerns that some of the panelists have
19 mentioned. We look at either three to five grams
20 which heretofore before this trial, many of the
21 studies have just been reporting over 5 grams drop in
22 hemoglobin. Transfusion of greater than 2 units,

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1 hemorrhagic stroke or retroperitoneal hemorrhage shown
2 in the dark blue and the light blue are lesser but
3 still important amounts of hemoglobin decrements in
4 these patients.

5 In the reference trials, the six trials of
6 over 4,000 patients, here you see the results in the
7 heparin arms over 4 percent for very significant major
8 bleeding where in the heparin, even though it was
9 administered at a higher dose, it was lesser of
10 serious hemorrhage and somewhat more in this
11 intermediate bleeding complication, three to five
12 grams. But here with bivalirudin in these trials, you
13 see a very step-wide market reduction in both
14 categories, whether it be severe, major hemorrhage or
15 this 3 to 5 grams of hemoglobin decrement.

16 Now if we take out the patients who had
17 bypass surgery which is probably worth doing to look
18 at this because you don't want to have that as a
19 confounding variable, you see that there's very much
20 a facsimile of the incidents of the severe hemorrhage
21 across these trials, so it doesn't appear that the
22 bolus of heparin influenced the incidents of severe

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1 hemorrhage. And there was very little effect on this
2 lesser rate of hemoglobin drop and again, you see a
3 marked benefit or difference favoring bivalirudin
4 relative to all these other 6500 patients in the other
5 trials.

6 Now, you may say well, these trials
7 differed somewhat. Someone had different inclusion
8 criteria. They had different heparin. Let's look at
9 the trials one by one. Let's look at the point
10 estimates and the 95 percent confidence intervals.

11 Here's the bivalirudin and this is stroke,
12 hemorrhagic stroke, retroperitoneal hemorrhage,
13 hemoglobin greater than 5 grams reduction or
14 transfusion greater than two units. This is serious
15 major hemorrhage, no matter how one would like to
16 categorize this.

17 This is significantly lower than any other
18 trial with a singular exception of EPISTENT which used
19 a 250 second target. And so every other study, the
20 heparin control arm comes out significantly higher
21 than the bivalirudin.

22 So that hopefully takes us through the

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1 dose of heparin and while many of us thought that as
2 a peer reviewer of this manuscript when it was being
3 considered for publication in New England Journal, I
4 raise this as a major concern, that the heparin dose
5 may have been too high. But now with these data for
6 multiple trials more recently I would say there's no
7 evidence of that and the fact is quite in keeping with
8 the other trials or the dose of 100 units per kilogram
9 bolus was utilized. And the differences in post cath
10 infusion really show no difference of heparin, no
11 difference in the incidence of hemorrhagic events from
12 these other trials.

13 Now let's just discuss briefly bivalirudin
14 clinical effects because it's more than just an
15 angioplasty story, that is, a much broader experience
16 with this drug in comparative randomized trials,
17 comparative and randomized.

18 So here, I'd like to review the data that
19 David Kong and his colleagues at Duke University
20 Medical Center have generated, part of which have been
21 presented at the last European Society in Vienna in
22 August and moreover, will be presented at the AHA.

1 This is a metanalysis of the trials done with
2 bivalirudin. The first two studies, the one I had
3 just reviewed earlier, the first study of bivalirudin
4 of any anticoagulant except as an alternative to
5 heparin, this 291 Phase II study and then TIMI-7,
6 unstable angina trial of 410 patients. Then, there
7 are four other studies where there were randomized
8 versus heparin. One, of course, you're familiar with,
9 the one that we're discussing in angioplasty, but
10 there was another unstable angina trial. There was a
11 trial with thrombolysis known as HERO Streptokinase
12 study and there was another trial in Canada by Pierre
13 Theroux and colleagues, a randomized trial of
14 streptokinase as well. So the total experience of
15 bivalirudin with respect to clinical effects is much
16 broader than just angioplasty.

17 Now this was a formal metanalysis that has
18 any patients treated with any amount of drug and if
19 you would like further details, David Kong is here and
20 certainly can review them. Using this empirical base,
21 random effects model, these endpoints, death, MI,
22 death or MI, the endpoints that we would prefer to

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1 look in contemporary trials and of course major
2 hemorrhage as just reviewed are provided.

3 Now let's first look at the trials which
4 there is not a heparin comparator, but rather there
5 are data available for insufficient, inadequate
6 anticoagulation, so here, as defined by the ACT, aPTT
7 is not at least twofold greater than baseline or is
8 twofold and is not. So we have adequate levels of
9 bivalirudin versus inadequate levels as you saw in
10 that early Phase II angioplasty trial and in the
11 unstable angina TIMI-7 trial.

12 If you look at these patients in the
13 incidents of death or MI, you see and this is
14 important because in our Phase II study we had a 4
15 percent incidence of death or MI versus 1.4 percent at
16 those low doses of bivalirudin. Ten percent versus
17 3.2 percent in the TIMI-7. Overall, a 70 percent
18 reduction, 7.1 to 2.6 which is quite statistically
19 significant, as you see.

20 Now perhaps even more worthwhile to look
21 at are the other comparative trials and you have asked
22 earlier with respect to the Day 7 death or MI or Day

1 30 or subsequent, these data summate the TIMI-8
2 unstable angina trial, the current trial of
3 angioplasty, the Theroux trial of thrombolysis and
4 also the HERO thrombolysis, all bivalirudin versus
5 heparin. Just as in the prior slide and in all the
6 slides in which comparisons are done, those patients
7 with bivalirudin at adequate doses are always on the
8 side, this is with a logarithmic plot of a favorable
9 odds ratio. Here, at 25 percent reduction from 3.4
10 overall to 3.1 which is not statistically significant
11 at this early time frame of seven days. However, if
12 we look at 4 to 6 weeks you see that it now is
13 statistically significant. This is the incidence for
14 unstable angina, medically treated unstable angina,
15 12.3 versus 4.4. This is the incidence in the current
16 angioplasty trials, 5.3 versus 4.3 per death or MI and
17 this is thrombolysis 15 versus 9.9 percent. Overall,
18 a 27 percent reduction, which is statistically
19 significant.

20 Now at the same time hemorrhage, this
21 metanalysis affords the opportunity to look beyond the
22 instrumented patients in the angioplasty trials. And

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1 what you can see is in medically treated patients, be
2 it with thrombolysis or with unstable angina always
3 the major hemorrhage, the definition that I've been
4 using is always on this side of bivalirudin being
5 better than heparin. And you see the incidents, it's
6 a 60 percent reduction from 10.5 to 5.4 percent with
7 respect to enhanced safety, avoidance of significant
8 hemorrhage across all these trials.

9 Now the last review, the issue of
10 bivalirudin safety. This has been touched on by a
11 number of questions that have come up earlier this
12 morning. I want to go back to this slide because I
13 think it's really quite remarkable that when you have
14 data from so many thousands of patients in different
15 trials and up through 1998 in terms of enrollment, and
16 to see this outlier here of significant hemorrhage
17 being so low with this as an endpoint, not three
18 grams, but five gram, transfusion, retroperoneal
19 hemorrhage or hemorrhagic stroke relative to all these
20 other trials, so you can look at it individually. I
21 don't think there could be any question regarding the
22 safety enhancement of bivalirudin relative to

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1 contemporary practice and contemporary trials,
2 standards of anticoagulation with angioplasty. But,
3 if there is still question we can turn to a large
4 administrative data base that is the Lewin group in
5 collaboration with our group at Cleveland Clinic with
6 Mike Lauer and Shelly Sap have looked at a recent data
7 base, HCIA data base of 37,000 patients undergoing
8 angioplasty from October 1995 to September 1997, so
9 about as proximal a look as we can get and the
10 patients' characteristics that we looked at, their
11 demographics which are, of course, much less available
12 in an administrative data base were quite similar to
13 those of the demographics in the current trial. Now
14 the first point is that the heparin in this HCA, this
15 recent contemporary 37,000 patients use and of course
16 instrumentation of patients, led to any transfusion,
17 7 percent; and transfusion greater than 2 units in
18 nearly 6 percent. This is very similar, these
19 numbers, to the incidents of hemorrhage, transfusion
20 or greater than two units transfusion, any transfusion
21 in the current trials. And of course, here's the
22 incidence with the bivalirudin.

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1 It's also interesting to note because
2 administrative data bases are great for such things as
3 cost, that the patients who had a bleeding
4 complication had a significant financial liability
5 attached to that, approximately an average of \$15,000
6 in addition to a doubling of the length of stay. So
7 these bleeding complications, at least as categorized
8 here with transfusion are quite meaningful.

9 So I want to sum up a few last points,
10 that there is very strong evidence of a net clinical
11 benefit for bivalirudin. It is not inferior, no
12 matter how you look at it in any study, any
13 comparative trial it never comes on the side of
14 inferiority. It is superior in this important post-MI
15 group, the highest risk group which was stratified and
16 in which all the data in unstable angina point to as
17 the highest risk group going into a trial with
18 unstable angina and I want to just touch on with one
19 last point on the remarkable safety of this new or
20 novel anticoagulant.

21 Not inferior, death, MI is a relevant
22 endpoint, but another key issue is how was MI defined

1 in this study? It was defined with -- raising the bar
2 considerably and Barry Chaitman who ran the ECG core
3 lab can help on this, but the way that a patient had
4 to have an MI was 30 minutes of chest pain or more,
5 ECG changes of a Q-wave or left bundle or new bundle
6 branch block by the Minnesota code, not even ST
7 changes, T-wave changes, but Q-wave or bundle branch
8 block and enzyme changes of CPK going up twofold with
9 MB positive, had to have two out of three of those
10 features.

11 This is very different than the MIs we
12 look at today. In fact, all the 2B3A trials had a
13 much lower threshold. So this is looking at big MIs
14 and death composite. Here, death, MI,
15 revascularization. But the odds ratio tells us 11 to
16 17 percent reduction, not inferior. In the post-MI
17 patients, it's really quite remarkable. Here, we
18 finally have a group of patients with external
19 validation of heightened risk, internal validation of
20 heightened risk and accentuation of the benefit.

21 Let's forget about procedural failure.
22 We've really critiqued this endpoint as unacceptable

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1 in modern standards. But look at each endpoint and
2 the key message here is that each endpoint be it
3 death, MI, revascularization, a threefold difference,
4 death or MI, a fourfold difference, a significant
5 reduction in mortality alone, MI alone,
6 revascularization alone.

7 The directionality, the consistency in
8 this high risk subset is quite noteworthy, while at
9 the same time, as Dr. Bittl highlighted, an emphasis
10 of accentuation of the reduction in hemorrhage, a very
11 striking reduction in major hemorrhage incidents. And
12 this is the post-MI benefit at 6 months. So not only
13 is this benefit here, immediately after the procedure
14 in terms of death, MI, revascularization, but here you
15 look at over the course of six months, there's never
16 a time when this benefit is not sustained. It's a
17 highly durable benefit in the post-MI subgroup
18 throughout the entire temporal observation window of
19 the trial.

20 The last point about hemorrhage and this
21 has already been discussed, well, is this a
22 significant hemorrhage that was reduced in these

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1 trials? Here's major hemorrhage with a 5 grams drop
2 in hemoglobin, the difference 62 percent. Well, you
3 don't want 5 grams, just two units of transfusion,
4 major hemorrhage, 65 percent reduction. Well, don't
5 want that. Major hemorrhage with 3 grams, 60 percent
6 reduction. No matter how you slice and dice these
7 data, the reduction in hemorrhagic events is
8 remarkable and the safety of this agent is really
9 noteworthy.

10 Now this is a complex plot for those not
11 initiated to this -- not just the -- it's just not a
12 blobogram in one dimension, but a blobogram in two
13 dimensions, but it really summates this data very
14 nicely, because what you see here is heparin center,
15 the comparator. And these are the data that we're
16 looking at for the current angioplasty trials. And so
17 we look in two different dimensions. Here, we look at
18 death, MI, revascularization, a relevant contemporary
19 endpoint. Here, we look at major bleeding as been
20 defined on the previous slides. And so for all
21 patients in these trials you see where the odds ratio
22 is for two dimensions and you see the 95 percent

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1 confidence intervals in two dimensions. So a
2 significant reduction in hemorrhage in all patients
3 and a trend in the reduction of death, MI,
4 revascularization for all patients. These are the
5 post-MI patients and these patients have a significant
6 reduction in death, MI or revascularization as I've
7 shown you and for each endpoint specifically,
8 including mortality and they have a reduction in the
9 major bleeding.

10 So the clinical thesis that Dr. Meanwell
11 introduced earlier this morning, seems like a long
12 time ago, but earlier this morning, what this shows is
13 can there be a drug that can uncouple the bleeding
14 risk with the clinical benefit and this is the first
15 agent that we're familiar with that has achieved that
16 goal because we see in this quadrant now, in this 2 by
17 2 plot of this double blobogram, if you will, we have
18 an agent that is capable of reducing the clinical
19 endpoints, the clinical outcomes while at the same
20 time reducing significantly, even more substantially,
21 their risk of major hemorrhagic events. So I think
22 that this really has been instructive. This trial,

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1 these data were, of course, the trial can see the 1992
2 data generated, 1993, 1994, but even five years later
3 there's marked clinical relevance to these data.
4 We've learned a considerable amount about
5 interventional cardiology over this period of time.
6 And I think through thorough review of this trial, I
7 just want to make one last point about this trial. We
8 can criticize and say well, it was an intention to
9 treat, but in fact, it was specified in the protocol
10 how the data would be analyzed and this protocol was
11 indeed reviewed before any patients were put in it.

12 As far as the largest trial ever performed
13 of interventional cardiology to date, this is it.

14 As far as the largest screening, over
15 16,000 patients were screened. No other trial in
16 interventional cardiology has gone through a screening
17 procedure and of course, these patients were carefully
18 followed. So I think just the robustness, the
19 largeness of the trial can increase the confidence of
20 a lot of these findings and I think for that it makes
21 an significant contribution.

22 The last point I want to make is why do we

1 need this agent today? We have heparin. Well, we
2 need this agent because in the last few years there
3 has been a significant change in how we deal with
4 patients in the cath lab. Instead of them just coming
5 to the cath lab on aspirin, today, it's much more
6 common when they come in with dual antiplatelet
7 therapy, aspirin, anticlopadine or aspirin and
8 clopidrogel. And in the cath lab they're much more
9 likely to get a 2B3 inhibitor. So the chance of
10 hemorrhagic risk is much higher than ever before and
11 that's why anything that we can come with which will
12 reduce the hazard is something that's worth very
13 serious consideration.

14 Thank you.

15 CHAIRMAN PACKER: We are going to open
16 this up for discussion. Let me just, I guess, make
17 one point. We frequently have this great difficulty
18 in the Committee with analyses that have been
19 pre-specified in the protocol which we would like to
20 give a lot of credit for, but which we disagree with
21 and so that it's really a balancing act. The extreme
22 positive would be to pre-specify analysis that

1 everyone agrees is the right analysis. A strange set
2 of circumstances occurs when you pre-specify analysis
3 that people think is silly.

4 That is not necessarily what was done
5 here, but pre-specifying something is not the whole
6 game. Pre-specifying something that people feel can
7 withstand scrutiny in the test of time is really where
8 things are at. One should get a significant amount of
9 credit for pre-specification, but if the pre-specified
10 -- I mean one could pre-specify as you might imagine
11 using your imagination. A whole host of analyses that
12 no one would want to do, but one wouldn't want get a
13 whole lot of credit for pre-specifying them.

14 Dan?

15 DR. RODEN: I'm not sure what that comment
16 was all about. Eric, after listening to that I'm not
17 sure whether you're making an argument that this is a
18 safer drug or a more effective drug. I thought the
19 argument, I thought we had decided that we weren't
20 going to make a big deal out of the efficacy, that it
21 was similar.

22 So can I go back to your slide 22?

1 DR. TOPOL: Can I comment on that before
2 you do?

3 DR. RODEN: Well, as we do.

4 DR. TOPOL: Okay. We'll wait to go
5 through the slide, but I think the point here is that
6 we are handcuffed because we can't do a placebo
7 controlled trial in coronary intervention and many of
8 us who had the misfortune of having a patient undergo
9 coronary intervention without heparin inadvertently
10 and I've been asked to review many cases,
11 medical/legal cases where patients had a problem
12 without heparin.

13 So part of the problem as far as efficacy,
14 if this could be -- if a placebo controlled trial
15 could be done that would, of course, be a pretty easy
16 thing to demonstrate the efficacy across all patients,
17 not just unstable angina. But that is a difficult
18 situation which we cannot do.

19 DR. RODEN: No, I'm just -- the reason I
20 wanted to look at this slide again was that this was
21 the one that showed efficacy, the one previously the
22 p value was .09 and then we came to this one with a p

1 value of .02 showing superiority of bivalirudin over
2 heparin.

3 DR. TOPOL: Yes.

4 DR. RODEN: But isn't that result driven
5 by a very, very large trial in which there is no
6 statistically significant difference, not even close
7 and two smaller trials, albeit in somewhat different
8 populations, which have striking differences. So I'm
9 not sure that it is fair to combine them in this way
10 and I wanted to make that point because this went by
11 pretty quickly.

12 DR. TOPOL: I didn't mean it to go by
13 quickly. I guess one point I'd like to make, I'm glad
14 to have this chance to review this slide because I
15 think there's a couple of points in that we're looking
16 at bivalirudin versus an active control, heparin. And
17 of course, always, whenever you do that bivalirudin
18 comes out on this side. And many times this group has
19 looked at data without inactive controls such as
20 clopidrogel, such as enoxaparin, such as many things
21 that this particular group has reviewed.

22 We don't have a placebo controlled trial.

1 Heparin has never been validated in any trial, but
2 that's what we're forced to compare with. But the
3 point that it always comes in on this side I would
4 submit to you that even in this large trial where
5 there was only a one percent absolute difference is
6 noteworthy.

7 DR. RODEN: I think it's noteworthy, but
8 I'm going to defer to Lem with the statistical
9 question. I'm going to ask Lem a statistical question
10 and that is we heard yesterday and we've heard from
11 Tom Fleming and we've heard over the past several
12 meetings the considerations that we have to go into to
13 think about active control trials and one of the
14 points that was made yesterday was in order to
15 evaluate an active control trial outcome and I
16 recognize that the safety issue may be tangential to
17 this, that there were three criteria and if I remember
18 them correctly it was that the comparator be highly
19 effective, that the comparator's efficacy be known
20 with tight confidence intervals and the conditions
21 under which the comparator, those data were derived
22 for the comparator be very similar to the conditions

1 under which the current active control trial is being
2 conducted.

3 So can you -- I recognize that there is a
4 tremendous reluctance to concede that heparin should
5 not be used in unstable angina. I think I said that
6 right, you don't want to -- you want everybody to get
7 heparin.

8 DR. TOPOL: Well, undergoing intervention.

9 DR. RODEN: Undergoing intervention.

10 DR. TOPOL: I think that what we had done
11 back in Ann Arbor, in those early days of doing
12 insufficient anticoagulation reinforces -- I still
13 feel terrible about what those patients went through,
14 taking away their anticoagulation. I would never
15 submit a patient to that again and I think all the
16 other experiences we had anecdotal, doing inadvertent
17 coronary interventions on no anticoagulation make that
18 an unacceptable alternative.

19 DR. RODEN: I mean does that apply to
20 every single patient who has an intervention?

21 DR. TOPOL: Yes.

22 DR. RODEN: Are there not data that

1 patients who have an angioplasty for stable angina,
2 that is very difficult to show that there's a benefit
3 of heparin.

4 DR. TOPOL: In the cath lab, I think it's
5 across the board.

6 DR. RODEN: In the cath lab.

7 DR. TOPOL: That when you have equipment
8 in the coronary artery and no anticoagulation, it's a
9 setup for serious following events.

10 DR. RODEN: But there are data that
11 suggest that in that latter situation that I just
12 described to you that heparin can be stopped
13 essentially immediately.

14 DR. TOPOL: Yes, after the procedure.
15 Doesn't have to be continued for four hours or 24
16 hours or whatever.

17 DR. RODEN: So there are perhaps shades of
18 gray in the extent to which one would be aggressive or
19 not, recognizing that when there's hardware in the
20 coronary that there probably ought to be heparin or
21 something like heparin on board.

22 DR. TOPOL: Yes, exactly.

1 DR. RODEN: So can you make a comment with
2 respect to the criteria that I just outlined? To Lem
3 or -- I actually want Eric to think about, to make the
4 comment about the clinical data that tell us how
5 effective heparin is, how confident we are about that
6 efficacy and under what conditions those were -- those
7 data were generated.

8 Is that a fair question to ask?

9 CHAIRMAN PACKER: Let's take this in two
10 steps. One is a clinical component, one is a
11 statistical component. Eric, you want to address the
12 clinical part and then Lem will have you address the
13 statistical part.

14 DR. TOPOL: I guess on the clinical side,
15 the way -- I was not involved in these angioplasty
16 trials, only in the Phase II, so in many respects
17 trying to come from the outside, trying to integrate
18 the information with our knowledge of the trial since
19 that point. If bivalirudin had come out on the wrong
20 side, on the odds ratio for the various endpoints, I
21 would have been concerned that this is not -- what
22 about the efficacy of this agent? But on the other

1 hand --

2 DR. RODEN: Let me just make it clear,
3 that it always comes out on what you call the right
4 side, but the question is if we're going to argue
5 about efficacy and I'm not sure want to be arguing
6 about efficacy or not. Dr. Meanwell wanted us not to
7 discuss this, but let's talk about efficacy for a
8 second. If you're going to talk about efficacy, then
9 what you want to know is how confident are you that
10 heparin works because bivalirudin being a little bit
11 better than heparin and it's always just a little bit
12 better than heparin, maybe heparin is not any good at
13 all. And so in that case you're making the
14 comparison to something that isn't -- whose efficacy
15 is either unestablished or you don't have much
16 confidence in how effective it is. So my question is
17 not whether it's on one side or the other. I don't
18 want to talk about bivalirudin. I want you to talk
19 about heparin and how confident are you about heparin
20 in the patient populations that were studied here and
21 there is a concern about how sick or not sick this
22 particular population was.

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1 DR. TOPOL: As far as heparin, I think
2 we've only learned about heparin through these types
3 of comparative trials. We've never, of course, had
4 such a trial nor could that trial be done in the field
5 of interventional cardiology. But I think it's clear
6 that if we look across all these different trials, as
7 I tried to present that there's little variability in
8 the rate of hemorrhagic events, irrespective of the
9 dose and so as far as efficacy in terms of we can look
10 at the endpoints of efficacy across the various trials
11 too, but I think it's fair to say we believe that the
12 anticoagulation provided by heparin is the fundamental
13 anchor here, that it's needed, that we have to have
14 some anticoagulation. The dose has never been
15 adequately ascertained of heparin. That's why I think
16 it's quite meaningful to look at a whole lot of
17 different doses and different trials including this
18 large data base, a patient's slice of life of PTC in
19 the U.S.

20 But I think the points about it never
21 having validation in a clinical trial, no question.
22 If you were to -- and I have many times talked about

1 lowering a dose of heparin in trials and even to do
2 that when we did, for example, of the trials of EPILOG
3 and EPISTENT where we used 70 units per kilogram
4 instead of 100 units per kilogram. We had to go
5 through a pile of studies just to get the buy in of
6 the cardiologist that it was okay to go 30 percent
7 reduction and no one has gone in a prospective trial
8 below 7 units per kilogram. It's felt to be
9 prohibitive. So there's a strong acceptance that some
10 level of heparin is necessary, but the actual, the
11 right dose has never been adequately defined and the
12 drag of heparin across various doses in terms of a
13 bleeding risk is quite obvious.

14 DR. RODEN: Let me just, I guess you've
15 answered my next question, which was are there any
16 data on how long heparin should be continued and how -
17 - because again, they're sort of -- the 24 hours that
18 were done here may be -- may have been too long it
19 seems to me for some of the subsets or some of the
20 large subsets that were included in this study.

21 I wanted to just to ask you one question
22 about the last comment you made about the scenario,

1 the current scenario of patients coming to the lab on
2 aspirin, clopidrogel or ticlopidine and the 2B3A
3 receptor blocker. Are there data on -- are there any
4 sort of data at all on what the performance of
5 bivalirudin would be in that setting?

6 DR. TOPOL: It's interesting that you
7 bring it up. We've been lobbying Dr. Talarico to
8 release the bivalirudin so we could do such a study,
9 but we haven't been successful. I've written her and
10 I haven't received a reply from my letter for quite
11 some time. But we would like to get the answer to
12 your question, but we haven't yet been able to do the
13 pilot study, and of course a large trial that we plan
14 to do to answer that very question. We think that in
15 the late 1990s in the 2000 of interventional
16 cardiology that very question is going to become
17 central.

18 DR. RODEN: One last question which I
19 meant to remind myself to ask and maybe this is more
20 for Dr. Meanwell or someone else.

21 Are there trials right now ongoing of
22 bivalirudin?

1 DR. TOPOL: There are none. We would like
2 to, but we haven't been able to get the bivalirudin
3 available for the additional studies. It's been very
4 difficult. We've been working on this for well over
5 a year. Maybe Dr. Talarico can help us. I don't
6 know.

7 CHAIRMAN PACKER: Why don't we go on to
8 the statistical question. This sounds like more of a
9 political question than --

10 (Laughter.)

11 CHAIRMAN PACKER: We don't do very well
12 with politics, so we'll skip that one. Lem, the
13 concept of noninferiority is a complex one and we have
14 been about this for quite some time not just at this
15 meeting, not just at yesterday's general discussion,
16 but at many other applications. In the discussion
17 that took place with clopidrogel and where their major
18 data base was a comparative trial versus aspirin, the
19 sponsor took great pains to demonstrate that -- took
20 great pains to create a putative placebo group because
21 there were data that were available of aspirin versus
22 placebo and then there was a point estimate from

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1 clopidrogel versus aspirin, so one could then derive
2 an estimate even though a direct comparison had never
3 been done of clopidrogel versus placebo. And the
4 Committee was persuaded that by following such a
5 procedure, one could be highly confident that
6 clopidrogel was effective.

7 Is that the -- and that is similar to the
8 comments that were made yesterday by Tom Fleming,
9 because what Tom simply said was these are the things
10 that you need to know in order to construct the
11 putative placebo concept that had been constructed for
12 the clopidrogel NDA.

13 So the question that I think Dan is asking
14 you is in the absence of that, because that can't be
15 created here, what -- how does one -- first of all,
16 can one and if one can, how does one get some sense of
17 noninferiority if one cannot construct a putative
18 placebo group?

19 DR. MOYE: That's a very difficult
20 position to be in and unfortunately that's precisely
21 the position we find ourselves in this morning.

22 As you point out, the three criteria that

1 Tom mentioned yesterday are sufficient to build this
2 putative placebo from which you can deduce an efficacy
3 of your new intervention. We don't have those
4 criteria. We don't have the data necessary to fulfill
5 those criteria today. And so we have no objective
6 information that we can fall back on to demonstrate,
7 to formulate an efficacy for heparin. And so we're in
8 a very tough position.

9 One thing that one might do is pretend
10 that heparin is like placebo and if that were the case
11 you would have to show superiority today of Hirulog,
12 but, in essence, that was not the case.

13 Now, if you still want to go by the weight
14 of clinical impression that heparin is active, that
15 heparin would be placebo, then has noninferiority been
16 demonstrated here? Well, in order to have
17 noninferiority you have to have two things. You have
18 to have a clinical trial which does not reject the
19 null hypothesis, no problem here, but you also have to
20 deal with the issue of power.

21 Now the investigators dealt with power
22 here from the standpoint of trying to demonstrate

1 superiority. They said prospectively that they had --
2 this trial was designed for 80 percent power to
3 demonstrate a 30 percent decrease in events, in the
4 primary endpoint. Well, nonrejection of that does not
5 imply noninferiority. It does not imply equivalence
6 because all you really said was that the difference
7 between the two is less than 33 percent. Well, is
8 that equivalence? I don't think so. I think
9 equivalence usually has a much tighter criteria, not
10 of 33 percent, but -- or maybe on the order of ten
11 percent, 5 percent. It depends on what set it
12 prospectively.

13 Now Eric has observed accurately that the
14 point estimates all fall on the correct side of the
15 null line and if that were the issue there would be no
16 problem. But the issue is not what happens in the
17 sample. The issue is what are the implications for
18 the population and it turns out it's very likely that
19 in the population there might be a harmful effect of
20 Hirulog, but that the population would spin you a
21 sample of 2100 in which you got the results that we
22 see. And so we have inadequate power here in order to

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1 demonstrate, convincingly, noninferiority. I
2 therefore would conclude that this experiment was
3 unfortunately not positive. Unfortunately, it's not
4 negative because we don't have adequate power. It is
5 uninformative.

6 (Laughter.)

7 CHAIRMAN PACKER: Let's stay on this for
8 a moment because I think I understood most of what you
9 said, but I don't think I understood the last part so
10 well. Without having to take the time to clarify
11 that, this is a generic question. And we have not
12 dealt with this question in this Committee in any
13 systematic fashion.

14 If you went to Eric and said do a trial of
15 a new drug, forget about Hirulog, just a new drug
16 versus heparin and let's assume that this drug were
17 cheaper, had less hemorrhage, had every advantage over
18 heparin.

19 Other than efficacy, let's say the sponsor
20 knew 100 percent -- I wouldn't know how they would
21 know 100 percent, that it was just as effective as
22 heparin. How would the sponsor -- but heparin has

1 never been evaluated, but heparin is the standard.
2 How does the sponsor ever get a drug like that
3 approved?

4 DR. MOYE: Let me describe how you might
5 do it, perform, design a trial. What you would have
6 to do is demonstrate convincingly that in the
7 population from what you choose your sample that
8 heparin and your new drug are essentially identical in
9 terms of efficacy.

10 CHAIRMAN PACKER: How do you do that?

11 DR. MOYE: Well, you do that to -- you do
12 that by getting a large enough sample to be able to
13 resolve relatively small differences in averages.
14 So you first have to reach some consensus as what
15 equivalence means. And equivalence may mean that you
16 want to be able to show that there is no more than a
17 10 percent absolute difference in event rate. That
18 will -- statisticians from the sponsor will tell us
19 that leads to a very large sample size on the order of
20 perhaps about 13,000 or 14,000, about 5 or 6 times as
21 large as the study that we have.

22 If that study is executed and per protocol

1 all endpoints are ascertained on everybody. You
2 involve the protocol right down the line, if you do
3 not reject the null hypothesis then you are allowed to
4 embrace the concept that the difference between the
5 two -- there may be a difference, but the difference
6 is very small.

7 Essentially small enough to be considered
8 clinically equivalent. If you've demonstrated that,
9 and you also simultaneously show that the number of --
10 that the incidents of side effects is much lower on
11 the intervention drug than on -- than heparin, and I
12 think you're very close to the mark.

13 CHAIRMAN PACKER: So apparently, based on
14 what you've just said the number that drives the
15 process is the degree to which you would risk being
16 wrong. In other words, how much of lower can an
17 effective new drug be compared with heparin. In this
18 case, it's 10 percent.

19 DR. MOYE: That's right.

20 CHAIRMAN PACKER: And that number would
21 probably be driven more by clinical considerations
22 than statistical considerations, but once you got that

1 number from the clinicians, in other words, what risk
2 they would be willing to take --

3 DR. MOYE: That's right.

4 CHAIRMAN PACKER: You would then -- that
5 would directly lead to a calculation as to what sample
6 size one would need in order to gain confidence that
7 you weren't making that much of a mistake. Is that a
8 correct statement?

9 DR. MOYE: That's right.

10 CHAIRMAN PACKER: Okay, now the way that
11 that -- this comes up in heart failure trials all the
12 time because ACE inhibitors are out there and people
13 sometimes think they might have a better ACE inhibitor
14 or who knows what and the -- at least the Cardiorenal
15 Division has provided a sense that they would like a
16 high degree of assurance that least, say, two thirds
17 of the effect that's seen with an ACE inhibitor, would
18 be seen with a new agent.

19 You wouldn't lose more than a third. No
20 one has ever undertaken that challenge because even
21 that difference leads to sample sizes which are huge,
22 primarily because the ACE inhibitor data base itself

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1 has wide confidence intervals in it and that's part of
2 the problem. But this is a generic issue of
3 significant magnitude because I don't think we'd want
4 to inhibit the development of better drugs that are
5 safer or have some ease of administration advantage or
6 have some -- maybe even cost advantage.

7 I mean we can go through all of the
8 nonefficacy issues related to the choice of an agent.
9 We wouldn't want to discourage people from doing that,
10 but one has this consideration of how do you know what
11 is the equivalent and it's particularly difficult
12 since it's hard to match confidence intervals when the
13 confidence interval of the agent that you are
14 comparing against hasn't been established.

15 DR. MOYE: Right.

16 DR. TOPOL: Is that fair?

17 DR. MOYE: That's fair.

18 CHAIRMAN PACKER: Can we have more comment
19 from the Committee on this issue because this is
20 really important.

21 DR. RODEN: Milton sort of said it right
22 and maybe we can get an estimate from somebody of --

1 given the numbers in these two large trials, can
2 anybody make an estimate of how much of the heparin
3 effect, if there is one is preserved by bivalirudin?
4 Is there any way of doing the number? Is it a third
5 or two thirds or nine tenths or is there none at all,
6 so we don't know that either. We don't know what the
7 heparin does, so we don't know --

8 DR. KONSTAM: May be can ask the question
9 another way. Within the data set that we have, is
10 there a way of estimating within 95 percent confidence
11 limits how much worse bivalirudin could be than
12 heparin in terms of one of the major endpoints.

13 DR. MOYE: I couldn't do it on the fly,
14 but there's a way to do it.

15 DR. KONSTAM: Right. Can the sponsors
16 speak to this?

17 CHAIRMAN PACKER: Let us make sure we're
18 not confusing two separate, but very related concepts.
19 The first is how much worse it could be. I think that
20 actually can be addressed.

21 DR. KONSTAM: Right.

22 CHAIRMAN PACKER: The other issue which is

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1 the issue which was -- is related, but not by any
2 means the same is how much of a -- how much of the
3 efficacy of heparin might be lost here and the answer
4 is that's not addressable because there is no heparin
5 versus placebo data base to construct confidence
6 intervals. I think that's fair.

7 DR. MOYE: If you remember, the
8 clopidrogel example is noteworthy for two things.
9 Number one, the very large data base they have for
10 aspirin versus placebo, but also the size of CAPRI was
11 in a number of patients randomized was huge. They had
12 over 20,000 patients. And so they wound up
13 demonstrating something like an 8 percent efficacy
14 that we might debate, but that certain is a large
15 enough sample size for you to presume the true
16 difference in the population to an event rate between
17 aspirin and clopidrogel was very small.

18 CHAIRMAN PACKER: In that trial, of
19 course, the Committee was persuaded that 8 percent
20 difference one, was real, but more demonstrated the
21 ability of clopidrogel to beat placebo than the
22 ability of clopidrogel to beat aspirin.

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1 DR. MOYE: Precisely.

2 CHAIRMAN PACKER: That we were not.

3 DR. MOYE: That's right.

4 CHAIRMAN PACKER: We did not consider the
5 8 percent to be persuasive by the two trial criteria,
6 but we felt that it was extremely persuasive of
7 comparing clopidrogel versus a putative placebo. We
8 thought that was compelling.

9 DR. MOYE: Right.

10 CHAIRMAN PACKER: Could we ask the
11 statistician -- where did he go? Could we get some
12 guidance here because these are very important issues
13 and it is worth spending a few minutes because it's
14 not just an issue with this drug. It is a generic
15 issue to development of any new agent that is -- I
16 mean we could take the position here that we would
17 only approve agents that are substitute for old agents
18 if the old agents were known, had been established to
19 be effective.

20 Okay? And that -- because the way that
21 one reaches that conclusion, mathematically is
22 straightforward and Tom and Lem have outlined in broad

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1 strokes the criteria one would use.

2 There does not appear, however, to be --
3 one can't get from A to B with agents that the
4 community uses, but which haven't been compared with
5 placebo and I'm just wondering whether we are truly
6 stymied here or whether there's any other approach
7 that could be used, conceptually or mathematically, to
8 get from A to B, because it's a way of -- we don't
9 want to send the wrong signal to those responsible for
10 drug development.

11 We want to send a reasonable signal to
12 those responsible for drug development, and we have to
13 understand that for us to sit here and say go away,
14 don't come back, I don't think that's reasonable. I
15 think what we have to do is fashion a reasoned
16 approach to solving a very difficult problem, but we
17 have to provide some reasoned guidance here. And it
18 could be that the reasoned guidance is that you need
19 very large numbers, but I would like to understand why
20 we need those large numbers and what the goal of
21 achieving them are. In other words, how do we resolve
22 this dilemma?

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1 Now this has a clinical component and a
2 mathematical component, so Eric, I'll assume you'll
3 deal with the former.

4 DR. TOPOL: I won't do the mathematical
5 cohort, although I would bring up one issue about that
6 in a second.

7 What I first think it would be worthwhile
8 considering is this TIMI-7 trial. The TIMI-7 trial,
9 as you recall, was a placebo control study; that is,
10 we have an incidence in the unstable angina patients,
11 they weren't instrumented. So that's why they didn't
12 have to get heparin, but at least to look at the
13 efficacy of the drug.

14 So if we can look at the TIMI-7 data, if
15 we can get into it here, I think -- because I showed
16 that as part of David Kong's metanalysis, but I think
17 -- it's coming? We just want data. Next one. What
18 this shows is just death or MI.

19 This is unstable angina in patients with
20 very substantial, this is what, I think 400, I forget
21 the total number of patients. It's 410 patients. So
22 of course not as large as the overall trials in

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1 angioplasty, but the same disease state with a placebo
2 or inactive control next to a 0.00 dose. So you see
3 a very pronounced benefit, death and MI. I think this
4 is one answer to your point.

5 CHAIRMAN PACKER: Can you hold on? This
6 a is very important study because it's -- forget about
7 the heparin comparison issue. There's no heparin
8 issue here.

9 DR. TOPOL: Right.

10 CHAIRMAN PACKER: We have spent virtually
11 no time on this trial and the reason is it's not part
12 of the indication being sought.

13 DR. TOPOL: Right.

14 CHAIRMAN PACKER: But let's see if we can
15 get a little bit more information about this study
16 because it may or may not help the Committee
17 understand how to get from A to B.

18 Can you tell us what the primary end point
19 of this study was and what pre-specified analyses were
20 utilized in this trial?

21 DR. MEANWELL: Thank you. Okay, I'd like
22 to have slide Y03, please.

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1 Okay, this is the TIMI-7 study, Dr.
2 Packer. The objectives are to compare the safety and
3 efficacy of one expected to be inactive dose of
4 bivalirudin with three expected to be active doses,
5 those -- the expectation was based upon Phase I and
6 other Phase II data in unstable angina which
7 established a null-effect dose level and effect dose
8 level.

9 CHAIRMAN PACKER: They actually said that
10 in the protocol, one inactive and three active?

11 DR. MEANWELL: I would have to check the
12 exact wording, Dr. Packer, but I'm quite sure that
13 there was very clear realization that .02 was not
14 going to move the dials in terms of ACT or aPTT, but
15 I would have to literally read the protocol again to
16 confirm the words.

17 CHAIRMAN PACKER: Let me just say it is
18 very reasonable to do parallel dose response curves
19 where you don't have a placebo where you think that
20 you might be evaluating the subtherapeutic dose
21 because one, it might not be subtherapeutic and two,
22 it sometimes makes trials difficult to do do-able.

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1 DR. MEANWELL: Let me suggest why this is
2 helpful, this trial. Because we look at the next
3 slide. This is the design of the study. Unstable
4 angina managed medically, I want to be clear. These
5 were not intervened. They all got aspirin and in the
6 four dose groups patients were randomized 2:1:1:1 in
7 the so-called inactive dose level and fairly
8 reasonable doses as you're seeing from Dr. Topol's
9 previous slides. Those doses do move the dials. I'm
10 going to show that in a moment. All patients got 72
11 hours infusion intravenously as management of their
12 unstable angina.

13 Now these data are quite important because
14 on the left you see the plasma concentrations of
15 bivalirudin against those and you can see that the
16 yellow line which is the so-called inactive dose was
17 almost immeasurable, unmeasurable in terms of plasma
18 concentrations of drug, where there was a really
19 rather striking and clear dose response relationship
20 between the so-called active levels of dose.

21 Now on the right, you see the aPTT in the
22 three groups above and in the so-called non-active

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1 group and I think it's important to point out that the
2 small rise in aPTT in the yellow line is essentially
3 not -- not clinically important, but it's certainly,
4 there are three rises in the top three groups. Now to
5 be very explicit, this trial had predefined structure
6 and objectives which looked at a variety of ischemic
7 endpoints, including angina. You may remember another
8 -- what we might today call soft endpoints. And there
9 was no evidence of any dose response relationship
10 across those three doses for things like recurrent
11 angina, ischemia, revisits to hospital and so on.

12 And so I would say right away that this
13 trial did not nail the point on a dose response curve.
14 All it really could do was say an inactive dose versus
15 something which is moving the aPTT significantly.

16 And therefore, and this was not a pre-
17 specified analysis in the protocol. I want to be
18 clear about that too. When you take the event rates
19 in hospital and at six weeks and compare the three
20 active groups against the so-called inactive group,
21 those are the data that we're looking at here. No one
22 is going to stand here and pretend this was all pre-

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1 specified. It was not. But I think that importantly
2 here, these are large effects and in a sense, this is
3 probably the last ever placebo controlled trial one is
4 going to see unstable angina, I suspect. I'm not a
5 cardiologist myself, but these are fairly striking
6 data for the value of moving the aPTT upwards in these
7 patients.

8 Now these were pre-specified components in
9 the protocol. Nobody went back and redefined death or
10 MI. They were all in the protocol, measured according
11 to protocol, but like we saw in the other trials,
12 there was a lot of other softer endpoints on top which
13 were really not very predictive of anything. So we
14 feel that this trial, although it's not directly on
15 the indication which is why we didn't want to dwell on
16 it a lot is very helpful in understanding whether
17 bivalirudin has clinical effect or not.

18 It doesn't nail the dosing in PTCA or
19 anything like that but I think it assures one that
20 anticoagulation matters in unstable angina.

21 CHAIRMAN PACKER: One understands that
22 this is a retrospective analysis --

1 DR. MEANWELL: Well, I want to be clear --

2 CHAIRMAN PACKER: Of a retrospectively
3 defined endpoint. It's okay. It's okay.

4 DR. MEANWELL: Well yeah, no. But the
5 endpoints were not retrospective. These were
6 components of a broader sent of endpoints.

7 CHAIRMAN PACKER: Why was there -- I'm
8 curious. Why was there a 2:1:1:1 randomization?

9 DR. MEANWELL: You know, I'm going to ask
10 Dr. Adelman who, if you don't mind, Bert. Dr. Adelman
11 was very instrumental in this program, but Dr. Adelman
12 is the head of medical and regulatory at Biogen and
13 was around at the time these trials were done.

14 Bert?

15 DR. ADELMAN: This was as Clive described
16 an early dose ranging, dose escalation study in
17 unstable angina. We used an extremely low dose of
18 Hirulog that we knew would have a perceptible, but
19 very small effect on the aPTT. That was acceptable to
20 the investigators. They would not accept a placebo
21 arm.

22 The apparently unbalanced enrollment

1 reflected the initial intention of evaluation which
2 would compare each individual dose to the lowest, the
3 .02 dose, hoping to actually identify a statistically
4 meaningful step up in efficacy across those doses.

5 CHAIRMAN PACKER: Which I understand was
6 not observed.

7 DR. ADELMAN: That's right.

8 CHAIRMAN PACKER: But I guess -- I think
9 you answered the question I was pursuing which is the
10 .02 dose there was always conceptually viewed as being
11 a -- I hate to say inactive because I don't want to
12 get into the philosophical issues.

13 DR. ADELMAN: Right. It was a compromise
14 with the investigators that --

15 CHAIRMAN PACKER: This was your placebo
16 surrogate trial?

17 DR. ADELMAN: That's right.

18 DR. THADANI: I think this is on the FDA
19 clinical review, page 8. Since it was a dose response
20 study and you did not really find a difference between
21 doses it reads that there was no statistical
22 difference among groups in efficacy. If you look all

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1 across groups. Then you're doing another analysis.
2 Now you're saying you're going to combine all the
3 doses and show a difference. The question to you is
4 what's the relevance of that since the primary defined
5 data base was really negative. You couldn't find a
6 dose response in efficacy terms.

7 DR. MEANWELL: I think --

8 DR. THADANI: I think you're combining the
9 data, but your primary endpoint was to look at a dose
10 response relationship in efficacy which you're not
11 able to show and then there's a fall back and combine
12 the whole data group.

13 Another data is useful, I'm not saying
14 that, but there are some problems to use that.

15 DR. MEANWELL: I think we agree and that
16 is why we didn't shall we say grandstand these kind of
17 data. I think we have to be very cautious with these
18 sorts of data, but I think Dr. Packer's question was
19 what else can one bring to bear on this issue which
20 could be helpful clinically? I think we want to --
21 we're just trying to respond to that question.

22 DR. THADANI: Perhaps one of the ways you

1 could turn around the data is say since we know that
2 we have no idea how heparin works or doesn't work,
3 suppose you did not have -- I'm just asking Lem.
4 Suppose you know that we don't know the placebo or
5 what, it doesn't work, but it's in the guidelines and
6 everybody is using it. So you say turn around, forget
7 about efficacy. If we can show you a good
8 anticoagulant which has less bleeding complication,
9 Lem, would that be acceptable or in the absence of
10 data on the comparative we have no idea if it works
11 would that be not acceptable statistically in absence
12 of inferiority claim which has been shown here.

13 DR. MEANWELL: Perhaps we get -- I'm going
14 to ask Dr. Gary Koch, a consultant statistician to
15 help with this issue, but before going out to that I
16 think we should just establish that the reason heparin
17 is in the ACCP Fourth Consensus Guidelines written by,
18 among others, Dr. Bittl, Dr. Weiss and Dr. Popner who
19 is now in Boston, the reason it's in there is not
20 because it was fashionable, although it was just a
21 standard of care, actually. There are several case
22 control studies, retrospective, the studies of Dr.

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1 Narins from the Duke Group, the studies of Dr. McGarry
2 and Dr. Ferguson in which all showed quite a
3 compelling relationship for heparin between the dose
4 response in terms of ACT or aPTT and the likelihood of
5 having an ischemic event of similar abrupt vessel
6 closure in angioplasty.

7 Now these are case controlled studies and
8 one has to be cautious, but that that was sufficient
9 evidence to guide a group of consensus experts to
10 recommend the use of heparin for the procedure of
11 angioplasty. And I think that frankly is the main
12 clinical basis that the panel can work with on does
13 heparin work and the main thing we can do for you is
14 provide you with as much evidence as we can that
15 against a putative placebo, as in this trial, and
16 against a putative placebo in Dr. Topol's dose
17 escalation trial and I'm going to use the word
18 putative very carefully, that there really was a
19 substantial, indeed 60 percent of clinical endpoints.

20 DR. THADANI: But the guidelines which are
21 written are really for unstable angina.

22 DR. MEANWELL: Excuse me --

1 DR. THADANI: They're not written for PTCA
2 or angioplasty. The guidelines really are to use
3 heparin up to 48, 72 hours, at least in that
4 guideline.

5 DR. MEANWELL: I would just like to
6 clarify this point.

7 CHAIRMAN PACKER: Do yourself a favor. It
8 makes no difference at all what the guidelines say.

9 DR. THADANI: Right.

10 CHAIRMAN PACKER: They are totally
11 irrelevant to our process of thinking. Sorry, Marv.
12 Wait a minute. This is really important. This is
13 really important. And I don't -- I really don't want
14 hypoglycemia to influence the process of thinking
15 here.

16 (Laughter.)

17 CHAIRMAN PACKER: And there is a general
18 nodding of the heads that people are getting a little
19 hungry. We have to think this thing through. It
20 doesn't matter what conclusion we've reached, but we
21 have to make sure we've thought it through.

22 Eric, I want you to also think it through

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1 with us and be prepared after the break to discuss a
2 study we previously saw which was a tyrofiban and
3 heparin comparison which may or may not be at all
4 relevant here, but we're thinking this through. We're
5 going to take a break and we're going to think about
6 this and we are going to come back at ten minutes
7 after one. We are going to come back at quarter after
8 one.

9 (Laughter.)

10 CHAIRMAN PACKER: We've got to, because
11 otherwise we will be here forever today.

12 (Whereupon, at 12:45 p.m., the meeting was
13 recessed, to reconvene at 1:20 p.m., Friday, October
14 23, 1998.)

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A F T E R N O O N S E S S I O N

1:20 P.M.

1
2
3 CHAIRMAN PACKER: Before we took a lunch
4 break, we were struggling with the concept of how to
5 evaluate a drug against a standard which has not been
6 shown to be better than placebo. We're still
7 struggling. What's that? We're still struggling with
8 that.

9 So before we took a break I asked Eric to
10 review for us any pertinent data that might pertain to
11 our consideration of this dilemma. And Eric, I'll ask
12 you to come forward now and bring to bear any
13 information you think might be relevant on this
14 dilemma because it's a very, very important dilemma
15 for us.

16 DR. TOPOL: Thanks very much, Milt. I
17 think the first point to underscore is that the
18 heparin effect, while not validated in the placebo
19 controlled trials and comes from an era in medicine
20 which is not evidence based, we have to look at what
21 are the best data in the literature, carefully done,
22 large experience and this comes from the Duke

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1 University Med. Center. The first author is Narins.
2 It was published and in circulation in 1996. It's
3 from a very large consecutive series of patients. I
4 think actually over 1,000 patients undergoing PTCA at
5 Duke.

6 And what they did was look at the
7 hemachron device in the cath lab, the initial ACT from
8 all heparin treated patients and what was the
9 relationship between the initial ACT and the instance
10 of abrupt vessel closure in the lab. What was seen is
11 that this -- in patients who were inadequately
12 anticoagulated with heparin, this at the lower end was
13 in excess of 12 percent and these are actual data at
14 the upper and lower limits.

15 As the dose of heparin was increased and
16 the ACT correspondingly raised, 350, 400 seconds, you
17 see this declining curve. This is not from a model.
18 These are actual data plotted from the Duke
19 experience.

20 So what this conveys and there are two
21 other studies in the literature. There are only three
22 in total about this is that there is a very strong

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1 relationship between the anticoagulation effect of
2 heparin and the outcomes measured by an abrupt vessel
3 closure. Now if we can look at the other two studies
4 such as the McGarry Ferguson study. Can you put that
5 up next, please?

6 DR. RODEN: Eric, before you leave that,
7 I thought we told earlier that the probability of
8 abrupt closure, that's a mechanical thing, that has
9 nothing to do with clot formation in the artery?

10 DR. TOPOL: No, no. I want to be clear.
11 It has something to do, abrupt vessel closure. I
12 tried to say that we shouldn't use it as a primary
13 end point in the trials because it's influenced by
14 things beyond anticoagulation. But when there's an
15 adequate basal anticoagulation, it's hard to
16 incrementally show abrupt vessel closure effects
17 because there is a mechanical underlying issue as
18 well. So not to -- I mean those are slightly
19 different descriptions.

20 This is a study from the Texas Heart
21 Institute or the group of McGarry and Ferguson and
22 what it looks at is outcome relationship to the

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1 elevation in PTT of angioplasty patients and a total
2 of about 330 patients. This was published in the
3 American Heart Journal and you see the difference in
4 ischemic events. Point 8 percent in the PTT that was
5 in the range of 76 to 150 whereas the ischemic events
6 of 9.2 percent, 34 to 75 PTT range.

7 There was one other study if we can pull
8 that up. In all these studies, I should emphasize
9 there is also a relationship of bleeding, that is PTT
10 went up, the ACT went up, but also the bleeding
11 incidents went up, so that uncoupling effect very
12 quite disparate from the bivalirudin evidence we've
13 been reviewing today was apparent. But this is also
14 from that group. It's a whole different series.

15 It's a cumulative 503 patients,
16 consecutive patients from the institution at Texas.
17 And what it shows is that the patients who had any
18 complications, death, MI, urgent revascularization or
19 closure, you see the differences between the ACT. So
20 the patients who are complication free had a very
21 significant difference in their clotting,
22 anticoagulation parameters.

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1 Now what I would like to do is to turn to
2 the pool and analysis of the PTCA trials and these are
3 the -- remember the A trials that I reviewed earlier
4 just before we broke up for lunch. And here, this is
5 interesting because remember, we had the data bases
6 for all these trials. So instead of using the
7 definitions that were different, intertrial for MI,
8 for example, we have the same definition of MI. The
9 same definition of all cause mortality and the same
10 definition of urgent revascularization out to 7 days
11 because we had the actual time movie event in all the
12 data bases.

13 So in this -- this is now the compilation
14 of over -- or nearly 9,000 patients, six referenced
15 heparin trials, that is heparin control arm trials
16 I've already reviewed today, EPIC, EPILOG, EPISTENT,
17 etcetera. The incidence of death, MI,
18 revascularization with heparin in these trials was
19 just over 10 percent using uniform definitions in the
20 current trial and this argues to the overall risk of
21 this population that was discussed this morning was
22 less, actually in heparin over 2,000 patients. But it

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1 was over 8 percent.

2 In the patients who received bivalirudin,
3 this was lowered quite substantially. This is a
4 highly significant reduction in death, MI,
5 revascularization, over 8 percent, just over 6
6 percent, over 20 percent reduction.

7 So the point being is if we accept some
8 level of anticoagulation is necessary and heparin is
9 a standard anticoagulant, any way that we look at
10 these data it suggests that there is at least as good,
11 if not better clinical outcomes. Now we're not
12 talking about hemorrhagic complications. We're
13 talking about death, MI, revascularization with the
14 use of bivalirudin as compared to all the data that's
15 available that we can get our hands on with respect to
16 heparin. And it's more than just getting our hands
17 on. It's actually having the data bases to look at
18 it.

19 CHAIRMAN PACKER: Eric, I am not certain
20 I guess how helpful these are. Maybe I can ask you to
21 help us with one thing. This committee, I was not on
22 it at the time so I really need a refresher. I don't

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1 even need a refresher. I need information.

2 It evaluated another NDA that sought a
3 claim against heparin or had a data base against
4 heparin which was enoxaparin which was evaluated in an
5 NDA against heparin.

6 Can you familiarize us with the
7 indication, the endpoint and the result? I think it
8 was one trial.

9 DR. TOPOL: Yes.

10 CHAIRMAN PACKER: That was a typical
11 trial.

12 DR. TOPOL: I'm glad you mentioned that
13 because I think it does have some relevance to the
14 discussion today. There was one trial, not two
15 trials, the ESSENCE trial of 3,000 approximate
16 patients and unfractionated heparin was compared to
17 low molecule weight heparin, namely enoxaparin. The
18 point there was well, how do we know that heparin is
19 necessary, a similar thing we're confronting today.

20 The only difference was that there were
21 some trials, small, five small trials of placebo
22 versus heparin that were used as a basis of a

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1 foundation that there's advantage of heparin over
2 placebo. That difference which that metanalysis was
3 published in JAMA was not statistically significant.
4 There was a trend. The actual p value on all the
5 trials combined was .06, but it was used -- a value
6 for placebo was imputed to say that enoxaparin is
7 better than the would be placebo in one trial and that
8 led to the Committee, the panel at the time within the
9 last year, recommending an enoxaparin for superiority
10 over placebo or what would have been placebo in the
11 indication of unstable angina.

12 CHAIRMAN PACKER: Maybe we can just
13 clearly identify similarities or differences between
14 that NDA and this NDA, just so we make sure that our
15 frame of reference is the same and the logic of
16 thinking is reasonable.

17 In the enoxaparin NDA, there was a data
18 base. It may not have been the world's best data
19 base, but there was a data base that compared heparin
20 to placebo in the indication being sought and the
21 trial that was put forward as the pivotal trial for
22 the NDA was a trial in which enoxaparin was

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1 statistically better than heparin?

2 DR. TOPOL: Yes.

3 CHAIRMAN PACKER: For which endpoint?

4 DR. TOPOL: For the composite of death,
5 MI, revascularization, refractory angina at 14 days.

6 CHAIRMAN PACKER: Okay, so a four
7 component endpoint all of which were clinically
8 relevant at a pre-specified time which was 14 days
9 with a statistically significant greater effect of
10 enoxaparin versus heparin with a data base where --
11 although not the world's best data base, that showed
12 that heparin was better than placebo, a data base
13 which allowed the creation of a confidence interval --

14 DR. TOPOL: Right.

15 CHAIRMAN PACKER: That could be used to
16 show that enoxaparin might be better than an putative
17 placebo. Is that correct?

18 DR. TOPOL: Yes.

19 CHAIRMAN PACKER: Is that -- I just want
20 to make sure. I wasn't on the Committee, that is, the
21 stepwise thinking at the time? I just want to make
22 sure that we're faithful to the integrity of the

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1 process?

2 DR. THADANI: You are right there. Plus,
3 it was written in the guidelines that heparin has to
4 be used in --

5 CHAIRMAN PACKER: I don't care. I don't
6 care.

7 DR. THADANI: So you're right. The claim
8 was confirmed in the trial, otherwise, it would not
9 have been approved.

10 CHAIRMAN PACKER: Apparently the answer is
11 yes.

12 DR. TOPOL: Yes.

13 (Laughter.)

14 CHAIRMAN PACKER: Just so that we
15 understand, in the overall patient data base that
16 exists here for this NDA that sequence of events is
17 missing. In other words, I just want to make sure
18 that we understand the distinction between that NDA
19 and this NDA. In this NDA there -- it is hard to find
20 data in PTCA patients which are heparin controlled,
21 even if they're fairly -- I understand the heparin
22 controlled data and unstable angina was not

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1 definitive, but it allowed for the creation of point
2 estimates that allowed for the creation of a putative
3 placebo and the drug, the new drug beat the comparator
4 at a pre -- on a clinical endpoint that was
5 pre-specified at a pre-specified time in a trial of
6 sufficient size.

7 In this case there is no data base
8 comparing heparin to placebo on PTCA with unstable
9 angina. The trials which are being put forward have
10 physiologic components without a fixed time point and
11 the -- and regardless of how one does the analysis in
12 the individual trials the new drug doesn't beat
13 heparin.

14 DR. TOPOL: Well, let me make a few points
15 about this.

16 CHAIRMAN PACKER: Right.

17 DR. TOPOL: First of all, I think this
18 precedent thing is useful to discuss, although clearly
19 we don't, we're not dealing here as lawyers. We're
20 doctors and we're trying to advance the therapy for
21 patients. And so we don't always use a particular
22 trial as precedent, but I think there are some

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1 interesting parallels.

2 Firstly, that indeed the data that existed
3 for heparin versus placebo and unstable angina were
4 quite insufficient. They're very small studies, very
5 inconclusive, but you can derive a point estimate, in
6 fact impute one. In fact, we can do that actually for
7 heparin and PTCA. We can do lots of different point
8 estimates for what it might be if we could do a
9 placebo. But that's the point. We can't do a placebo
10 because what you saw in the low doses of bivalirudin
11 in the Phase II was an unacceptable incidents, 10
12 percent incidents of death or MI which we just can't
13 live with this. No one who does in the practice of
14 interventional cardiology on this planet will do a
15 procedure with no anticoagulation. That is a problem,
16 interestingly, today, for example, in patients with
17 heparin induced thrombocytopenia which are not so
18 uncommon where we don't have an anticoagulant which we
19 can use in its place and it's very difficult to
20 approach these patients when they need coronary
21 intervention.

22 So we have a problem where the best data

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1 we can use to simulate and as a proxy, if you will,
2 for placebo is to look at the low end of these curves,
3 such as the Narins study. And we can come up with an
4 imputed -- what the placebo would look like if we had
5 used a placebo.

6 CHAIRMAN PACKER: Let me just see if we
7 can get there. If and I think I can ask you this
8 question straight forward. If, in fact, you are
9 confident that enoxoparin is better than heparin and
10 I have no -- you can tell us what's happening in
11 community in terms of the acceptance, but in patients
12 with unstable angina should be on enoxaparin as
13 opposed to heparin because the results of the ESSENCE
14 trial. Would they be switched to a drug like this if
15 they had PTCA?

16 DR. TOPOL: Well, the problem with
17 enoxaparin, since you bring it up is that in the cath
18 lab you cannot measure any anticoagulation parameters.
19 It doesn't change the ACT. It doesn't change the PTT,
20 so today in this era we don't an anti 10A assay. So
21 you can't work with enoxoparin in the cath lab.
22 That's the problem. We have no anticoagulant that

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1 raises the ACT in the cath lab besides heparin that's
2 available to clinicians today.

3 DR. THADANI: That's true, Milton, because
4 the patients who went to cath lab in a sense were
5 allowed open label heparin according to the required
6 intervention to drive the ACT perhaps 250, 300, but
7 enoxaparin data base all comers with unstable angina
8 as opposed to patients going to PCT directly.

9 CHAIRMAN PACKER: Eric, TIMI-7 is unstable
10 angina. A number of times you referred to the point
11 that you felt on the basis of the .2 milligram --

12 DR. TOPOL: .02.

13 CHAIRMAN PACKER: Sorry, .02 milligram
14 group that it's unacceptable to do angioplasty in the
15 absence of anticoagulation, but how does that come out
16 of TIMI-7?

17 DR. TOPOL: Oh no, no. Let me try to get
18 this -- this is an important distinction.

19 First of all, the TIMI trial of unstable
20 angina was not connected to any intervention. That
21 was a medical therapy trial.

22 CHAIRMAN PACKER: I understand, right.

1 DR. TOPOL: And at that time when that
2 trial was done, that was before all the recent trials
3 were active comparisons. No longer would an unstable
4 angina trial have a placebo control, but in that era
5 it was marginally acceptable medical therapy and the
6 .02 which led to undetectable levels of bivalirudin in
7 the plasma was achieved. But that's different because
8 those patients didn't undergo coronary intervention
9 and in the few patients that did have to go into
10 coronary intervention that basically escaped the
11 protocol because they broke through ischemia and
12 indeed got heparin at the time of their interventional
13 procedure.

14 CHAIRMAN PACKER: You made a comment a few
15 minutes ago that if we wanted to create an imputed
16 placebo we could do that --

17 DR. TOPOL: Right.

18 CHAIRMAN PACKER: And you've alluded to
19 this a couple of times that you wouldn't do an
20 intervention with anticoagulation, so how do you know
21 that and what would we do to input the placebo effect?

22 DR. TOPOL: Right, I guess it would be

1 good, Gary, if you could address this because I think
2 there's some important concepts to try to develop.

3 DR. KOCH: Gary Koch. I'm a statistical
4 consultant to the Medicine Company. The way in which
5 we've tried to shed some light on this particular
6 question is to simply revisit the event rates for
7 death, MI, and revascularization in the hospital.
8 This event rate, basically, was for the combined
9 studies of 5.7 percent in the bivalirudin group and
10 6.7 percent in the heparin group. And each of those
11 rates is based on about 2,000 patients which leads to
12 a standard error of about a half a percent or producing
13 a two sided confidence interval, plus or minus one
14 percent. So for bivalirudin, the confidence interval
15 for this event rate would be from 4.7 percent to 6.7
16 percent and for heparin it would be 5.6 percent to 7.7
17 percent. Both of these upper limits are below 8
18 percent and so one can argue hypothetically that as
19 long as the placebo event rate was in excess of 8
20 percent as an absolute number, then both heparin and
21 bivalirudin would have been significantly better than
22 placebo.

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1 DR. KONSTAM: Sorry, could you just tell
2 us those confidence limits again?

3 DR. KOCH: The confidence limit for
4 bivalirudin was 4.7 percent to 6.7 percent. This
5 corresponds to plus or minus one percent, about a
6 point estimate of 5.7.

7 DR. KONSTAM: Right.

8 DR. KOCH: And basically it's coming from
9 two standard errors where the standard error is a half
10 of a percent and that half of a percent is coming from
11 the rate being based on 2,000 patients.

12 And in the heparin group the point
13 estimate is 6.7 percent. The confidence interval is
14 5.6 to 7.7. Again, basically, plus or minus one
15 percent or two standard errors being that plus or
16 minus one percent where the standard error is a half
17 of a percent.

18 Now both of these upper limits of
19 confidence intervals are below 8 percent. So if the
20 true value was 8 percent, both regimens in this study
21 would have been significantly better than 8 percent.
22 Alternatively, had we had 2,000 placebo patients in

1 this study and their rate had been 9 percent with a
2 plus or minus 1 percent confidence interval or 8 to 10
3 percent, then again you would have had nonoverlapping
4 confidence intervals indicating the significant
5 advantage of both heparin and bivalirudin relative to
6 that placebo.

7 So what the clinicians have to do is to
8 argue that had placebo been in this study its event
9 rate would be above 9 percent.

10 CHAIRMAN PACKER: Is there any evidence
11 that exists that the heparin lower 95 percent lower
12 confidence interval would be 8 percent?

13 DR. TOPOL: Yes. Yes. I reviewed that
14 data, that is the data --

15 CHAIRMAN PACKER: I'm sorry --

16 DR. TOPOL: For placebo.

17 CHAIRMAN PACKER: Placebo.

18 DR. TOPOL: The best we have are, I guess
19 three points of evidence. One is in the Narins study
20 with inadequate anticoagulation which is probably
21 still better than placebo, the incidence was 12
22 percent of closure, the extrapolated clinical event

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1 rate would be considerably higher, in fact, was
2 reported being much higher than 10 percent in that
3 paper. That's one point.

4 The second point is when we had inadequate
5 bivalirudin in the early studies, we saw an instance
6 of 10 percent --

7 DR. KONSTAM: Which studies?

8 DR. TOPOL: Phase II, the 291 patients,
9 dose escalating study of bivalirudin. The incidents
10 of death or MI in the insufficient anticoagulation
11 patients which are again, somewhere intermediate, best
12 case scenario for placebo, there's some activity of
13 anticoagulation there. The incidence of death or MI
14 was 10 percent.

15 DR. KONSTAM: Could you show these data?

16 DR. TOPOL: I did earlier. The third
17 point is that Dr. Bittl, myself and so many others in
18 the field of interventional cardiology can recall
19 patients in whom for one reason or another heparin was
20 inadvertently omitted, that the case was begun, a clot
21 formed in the vessel. It was recalled that what is --
22 how much heparin was given and indeed none and these

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1 are not cases that we like to remember.

2 That would suggest, perhaps in our own
3 experience that the incidence of complications could
4 approach 100 percent. We would never do a procedure
5 without some anticoagulation present.

6 DR. KONSTAM: I know you showed it before,
7 but now we have some guidance about what we should be
8 looking for.

9 DR. TOPOL: First, it's the Narins study
10 again, the curve.

11 CHAIRMAN PACKER: The problem with Narins
12 is that the endpoint is different.

13 DR. TOPOL: In the paper, they present
14 death, MI.

15 CHAIRMAN PACKER: Oh, they do?

16 DR. TOPOL: Yes.

17 CHAIRMAN PACKER: Okay.

18 DR. KONSTAM: It is figure 7.

19 DR. TOPOL: John's right. It's on the
20 slides that you have, the handout. You have the
21 copies of the slide.

22 The point that Gary Koch has underscored

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1 is that if the imputed rate of placebo was 9 percent
2 in 2,000 patients, then both heparin and bivalirudin
3 would be significantly reduced in terms of death, MI
4 or revascularization.

5 Since we will never have those data in our
6 lifetime, that is interventional cardiology procedure
7 without any anticoagulation and we're trying to
8 advance this field, I don't know what other way to do
9 but to impute some value. That seems like a very
10 reasonable, conservative estimate of what placebo
11 would yield. This is the Narins data that show abrupt
12 closure of over 12 percent and in the paper the
13 incidence of death and myocardial infarction is
14 considerably higher than that.

15 DR. KONSTAM: It is? The death, MI,
16 revascularization is higher than that?

17 DR. TOPOL: Yes.

18 DR. THADANI: Eric, you also showed a
19 slide on the clinical result related to dose in PTCA
20 on the Hirulog different boluses.

21 DR. TOPOL: Yes.

22 DR. THADANI: In which you pointed out

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1 there was no incidents when one milligram bolus was
2 given. Yet the sample size was only 12. If you just
3 had one patient showing a problem it would have taken
4 you to 8 percent. Two patients could have taken you
5 to 20 percent. I think that gives you really kind of
6 misleading information, at least if you're basing it
7 on the pilot. I'm looking at 54438. If you want to
8 show the slide again --

9 DR. TOPOL: Yes. I think we should do
10 that. First of all, your point is well taken about 12
11 patients in that last dose group and of course that
12 was what we now have 2,000 plus patients in a
13 randomized trial. But at that time that was an
14 inadequate sample.

15 Let's just review these data because they
16 are relevant. This is at 291 patient dose escalating
17 study of bivalirudin where we started clearly with too
18 low a dose of anticoagulation necessary to
19 successfully perform PTCA. So let's go to the next
20 slide.

21 This was published back in Circulation in
22 1993. All these patients received aspirin. These

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1 were just elected angioplasty. There was nothing
2 unstable about them. These were just, again, this is
3 the best case scenario because these are not patients
4 who are particularly prone to events. And we -- these
5 are the doses and the number of patients and you're
6 bringing up there are only 12 patients. In this case
7 group, very good, but the point is, of course, there's
8 thousands of patients now.

9 Next slide. The point, of course, is that
10 we had insufficient ACTs. Actually, it would be nice
11 to have the ACT, but here you just have the threshold,
12 proportion of patients with 300 or 350. And in these
13 first three groups, this was grossly insufficient,
14 number of patients who had adequate anticoagulation.
15 A proxy for placebo, if you will, best that we have
16 because it's the only study that intentionally started
17 with very low doses of anticoagulation.

18 Next. And here you see the abrupt vessel
19 closure. In three of these groups it was well over 10
20 absolute percent and these are the failed PTCAs, that
21 is unsuccessful procedures. Of course, zero in this
22 last group of 12, again your point is so what? But

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1 the point of course is that even in these other two
2 groups of sufficient anticoagulation, above the
3 threshold established by the Narins study, there was
4 a much lower rate, significantly lower rate I should
5 add, compared to these insufficient inadequate
6 anticoagulation patients.

7 Is there one other slide? Okay.

8 DR. THADANI: So you're running still at
9 about 9 percent unsuccessful, plus the problematic --
10 even at the .55. Forget about the 1 --

11 DR. TOPOL: But the main point is the
12 closure of patients that have events. The
13 unsuccessful patients don't necessarily have events,
14 but the closure patients all had myocardial infarction
15 or had an urgent procedure or death and these patients
16 are much less.

17 DR. THADANI: In column 1 it seems like
18 closure rate is again lower than that compared to
19 column 2 and 3. I think that's the problem you run
20 into with these dose response studies. Sample size is
21 not large enough.

22 Can you say there are statistical

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1 differences in this population?

2 DR. TOPOL: Using the 300 second
3 threshold, there was statistically significant
4 differences.

5 DR. THADANI: No, in each dose group?

6 DR. TOPOL: No, no, there's insufficient
7 numbers in each dose group and I would argue in a
8 general way that there's never been an inadequate dose
9 finding study that I know of in medicine to meet my
10 standards. And this one doesn't, is no exception.

11 CHAIRMAN PACKER: It is not a requirement
12 to evaluate the response for each cell to be placebo.

13 DR. TOPOL: Right.

14 CHAIRMAN PACKER: And that would be an
15 inefficient way of evaluating dose response
16 characteristics. And we would not wish that upon
17 anyone, let alone apply that retrospectively to any
18 data base.

19 Let me see if we can -- but I will tell
20 you the only thing that bothers me about this is that
21 it's on the surrogate. I think that data from the NIH
22 experience on death and MI is more interesting. And

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1 I think that's an MI.

2 DR. TOPOL: Right. I did show that.

3 CHAIRMAN PACKER: Yes, you did.

4 DR. TOPOL: And it was a difference in
5 death and MI in the insufficient anticoagulation.
6 Sixty percent, right, reduction.

7 CHAIRMAN PACKER: Okay, do we have any
8 other questions for Eric before we go on to the formal
9 questions? We'll start from our primary reviewer.
10 We'll go down. I'll ask everyone to try to highlight
11 the issues that they think will be pertinent to their
12 evaluation of the questions.

13 Dan? Marv?

14 DR. KONSTAM: Eric, in your comparator
15 trials, CAPTURE, EPIC, EPILOG, etcetera, can you
16 remind us where you try to build a case that in the --
17 and the comparator arms that you're showing us in
18 there are the pure heparin. There's no concomitant
19 therapy in those arms?

20 DR. TOPOL: Exactly, Marv. In these
21 studies, the arms we've selected for the sake of
22 comparison are the anticoagulant pure, no 2B3A arms

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1 are put in. We've looked at that, but that's not
2 relevant to today's discussion.

3 DR. KONSTAM: Now what about the duration
4 of heparin therapy in each of those trials to bring it
5 to what we have in this today?

6 DR. TOPOL: In the capture trial it was 24
7 hours or more, so it's simulated.

8 DR. KONSTAM: Twenty-four hours or more.

9 DR. TOPOL: And RAPPORT it was 24 hours or
10 more. In the EPIC trial, it was 24 hours or more and
11 in the other three trials, IMPACT II, EPISTENT and
12 EPILOG it was -- heparin was either discontinued, the
13 only treatment given at the time of the bolus or at
14 some point before 24 hours.

15 And in the current trial, 15 hours was the
16 actual duration of therapy of heparin.

17 DR. KONSTAM: Well, wait a minute. In
18 terms of actual duration of therapy, what I'm trying
19 to get at is you're building a case that heparin in
20 all of these trials looks worse than bivalirudin in
21 terms of major hemorrhage and what I'm -- the question
22 I'm wondering about is trying to compare it to today's

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1 heparin comparator dose.

2 DR. TOPOL: Yes.

3 DR. KONSTAM: How does it compare in terms
4 of duration of actual, actual duration of heparin
5 therapy?

6 DR. TOPOL: If we could put that slide up
7 of the separate studies with the hemorrhagic risk?

8 DR. KONSTAM: It's your slide 25.

9 DR. TOPOL: It would be helpful, but I
10 guess while we're trying to find it, the point I want
11 to emphasis is that you bring up that prolonged use of
12 heparin enhances or unfortunately potentiates bleeding
13 complications, no question.

14 DR. KONSTAM: Right.

15 DR. TOPOL: And in the trials that I just
16 mentioned, such a RAPPORT or CAPTURE, EPIC, the
17 bleeding complications were considerably higher. But
18 of note, the studies that had the short, for example,
19 EPISTENT or EPILOG, one shot of heparin, no more,
20 they're still in EPILOG, there was a significant
21 difference in bleeding complications favoring
22 bivalirudin and so the detailed --

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1 DR. KONSTAM: Yes.

2 DR. TOPOL: So if we can just show that,
3 I can review that. The separate studies, that's it.

4 The RAPPORT study, the heparin was given
5 like in the current study, that is, 24 hours or more
6 because these are acute MI patients.

7 In EPIC, they're given 24 hours. In
8 CAPTURE, it was 24 hours of heparin. And in the other
9 studies, a large proportion of patients only had one
10 dose of heparin and no sustained heparin. But here's
11 bivalirudin. And so it's significantly less in any of
12 the other studies with the sole exception of EPISTENT.

13 DR. KONSTAM: Well, I guess the problem
14 that I'm going to face, and other Panels as well is
15 you know whether or not heparin, as it's given in the
16 present trials really simulates real life and so that,
17 as a potential explanation for why bivalirudin beat it
18 and so I'm trying to look for some comfort that it if
19 it were given real, in a real life way, it would still
20 work and I guess -- so you're saying a couple of the
21 studies really should support that. So to do that, I
22 guess you have to match, try to match the duration of

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1 heparin therapy to the bivalirudin group.

2 DR. TOPOL: Before we did this analysis,
3 I shared your concern that if a large dose of heparin
4 had been used in this study that perhaps that bleeding
5 rate wasn't going to be consistent with more
6 contemporary studies, but actually interestingly this
7 is really quite a surprise that the incidence induced
8 bleeds is very -- it actually quite respectable
9 compared to all the other trials as well. And of
10 course with it being much larger, pretty narrow
11 confidence intervals for serious bleeding.

12 DR. KONSTAM: That's why I'm trying to
13 learn something more about the duration of heparin
14 therapy in all of the other trials. That's really why
15 I'm asking that question.

16 DR. TOPOL: Right.

17 DR. KONSTAM: The other question I had was
18 someone had said that they were going to show us the
19 time distribution of the hemorrhagic events in the two
20 treatment arms. I don't think we've seen that.

21 DR. BITTL: Slide Y-56, please. The case
22 report forms were very good about capturing the time

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1 of hemorrhagic and ischemic events and this is the
2 distribution overtime and hemorrhagic events and the
3 patients treated with heparin in purple and
4 bivalirudin in blue. And the point I tried to make
5 earlier is that a number of hemorrhagic events in the
6 heparin treated patients in the first four hours of
7 therapy exceeded the number of hemorrhagic events in
8 the bivalirudin treated patients in the first 48
9 hours. So the duration of heparin infusion in this
10 study didn't have much of an effect or as great an
11 effect as the type of anticoagulant used.

12 You can also see what happens after two or
13 three days in patients treated with bivalirudin as
14 they're switched over to prolonged heparin infusions
15 monitored by PTTs. They start to have bleeds.

16 DR. KONSTAM: Thanks for showing these
17 data. I mean I guess I hear what you're saying about
18 a significant number of the bleeds occurring early,
19 but there are also a significant number of bleeds
20 occurring later within the first day. What really
21 drives the curve way above the Hirulog curve is really
22 going on during the whole course of that first day and

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1 into the second day. Would you agree?

2 DR. BITTL: Right. There are still many
3 patients in contemporary interventional practice who
4 require heparin overnight.

5 DR. KONSTAM: Well, we can debate that
6 point, but the other point of concern that we raised
7 earlier is whether heparin during the course of that
8 24 hours was really given as it would be given vis-a-
9 vis monitoring PTT and I know we discussed that, but
10 I think there's still some concern about that.

11 DR. BITTL: It's still the way we give it.
12 And the comparator here is bivalirudin given as a
13 constant infusion as well.

14 DR. THADANI: Looking on that slide, you
15 know, I sympathize with you. There are less bleeding
16 complications in the earlier part, but you gave a lot
17 of boluses of heparin in the cath lab to drive your
18 ACT above 350 in some patients and some might have
19 gone 4. We see patients coming from the cath lab into
20 the unit, some of them are running aPTTs of 170 and
21 they bleed and at the moment, at least the current
22 practice after you remove the sheath you measure aPTT

1 at least every six hours. I raise that issue and
2 perhaps I could argue the way the protocol is
3 designed, you're driving the event rate very high by
4 just doing that and not measuring which is normally
5 done in practice.

6 So the question really to you is this
7 bleeding event rate which is lower is driven by the
8 protocol design, that you drove a protocol and you're
9 going to show that because you never gave boluses of
10 Hirulog to keep the ACT, once it starts declining you
11 get a lower dose, it never came up and down. So it
12 was just protocol design that you're going to show
13 this anywhere that you're going to go on bleeding and
14 that's what we are left with now because efficacy did
15 not, unfortunately, show a difference?

16 DR. BITTL: I understand your concern that
17 the protocol may have been flawed, but I would argue
18 that heparin is flawed. It's a double edged sword.
19 You have to drive the ACT up to a minimum level of 350
20 to 400 seconds to avoid the ischemic complications,
21 but you run the risk of bleeding.

22 DR. THADANI: I'm not denying that heparin

1 is a very difficult drug to use. I'm not saying that.
2 But at the moment, at least, we do every six hours,
3 especially if you remove the sheath at two to four
4 hours, so that I'm driving it too high because you
5 know now we are targeting 70, as I said, rather than
6 90 in unstable angina patients. To ask another
7 question is there any data now with the newer regimen
8 we're targeting with a bleeding lower rate? I know
9 Eric showed in all the data base, I'm just --

10 DR. BITTL: Using the insurance data base,
11 bleeding rates are exactly the same as we reported in
12 this study. And I'd also remind you that every
13 bivalirudin study that we discussed today, every one
14 ever done shows that bleeding actually is favorably
15 affected by the use of bivalirudin compared with
16 heparin. You can say that perhaps we had a flawed
17 protocol. I wouldn't agree with that, but we didn't
18 just review one protocol today. We reviewed protocols
19 in unstable angina and acute myocardial infarction and
20 all of them show the same finding. Bivalirudin
21 reduces bleeding.

22 DR. THADANI: Why the bleeding is going

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1 higher later on in this slide after one day it creeps
2 up on your drug?

3 DR. BITTL: Pardon me?

4 DR. THADANI: What's the reason that
5 bleeding events are going up on Hirulog in this
6 diagram after say 10 hours when the actual ACT is
7 declining and bleeding complications are going up?

8 DR. BITTL: It may have been the timing of
9 bleeding was probably established when the hematocrit
10 was drawn.

11 DR. THADANI: So it's protocol driven to
12 some extent.

13 DR. BITTL: Whatever occurred first. The
14 bleeding event met our criteria for defining major
15 bleeding. The first component of that that was
16 identified in terms of time set the time for that
17 bleeding event.

18 These are cumulative curves.

19 CHAIRMAN PACKER: Marv, anything else?

20 DR. KONSTAM: I keep staring at this
21 curve. It's a beautiful curve. I mean I challenge
22 what you said, John. I don't think I look at this

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1 curve and say you know what, we really sort of can
2 explain this within the first four hours. To me, it
3 says just the opposite. To me it says really most of
4 the difference, most of the effect we're seeing after
5 the change in the Hirulog infusion rate and during a
6 period of time that you're administering heparin at
7 some unknown PTT in a period. You can infer whatever
8 you think about what effect heparin is having, but
9 nevertheless, it's occurring during that period of
10 time.

11 DR. BITTL: I guess my only point there
12 were so few bleeding events in the bivalirudin treated
13 group in 48 hours that number of events matched what
14 we saw in the heparin group in the first four hours.
15 I mean you see such a striking separation of the
16 curves, even early on. I know there's concern about
17 the duration of the heparin infusion and so on. But
18 the separation doesn't occur at Day 1. It occurs by
19 four hours.

20 CHAIRMAN PACKER: Okay. Let's keep going.
21 Joann?

22 DR. LINDENFELD: Just one question. Given

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1 that we're being asked to approve this drug because
2 it's safer, do we have reason to believe that these
3 antithrombin drugs, in general, are safer than
4 heparin? Is this something consistent across this
5 drug class? That there's less bleeding? That hasn't
6 been my impression.

7 DR. MEANWELL: We would like to answer
8 that question by referring to Dr. Jeff Weitz because
9 I think there are frankly no clinical thrombin
10 inhibitors between one another and in different sets
11 of trials and I think one has to be very cautious
12 about clinical assertions, but I think Dr. Weitz is
13 very familiar with --

14 DR. LINDENFELD: But my impression is in
15 other studies and we have the people here who can
16 answer that, I think, GUSTO-II and TIMI-9, that the
17 bleeding complications were actually slightly greater
18 or equivalent between heparin and bivalirudin?

19 DR. TOPOL: No, you're right, Joann. In
20 fact, the other trials of hirudin have actually shown
21 higher bleeding. So that's why this really separates
22 from that. GUSTO-II and TIMI-9 and the OASIS recently

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1 reported trial, all did show higher bleeding
2 complications relative to the heparin control arm.

3 So this bivalirudin PTCA trial is a
4 standout, and of course, as John mentioned and
5 emphasized, it wasn't just in the PTCA trials. It was
6 in the MI trials as well as the unstable angina
7 trials, less bleeding. That is different than at
8 least how hirudin has performed.

9 Also, I should add that in the low
10 molecular weight heparin studies there have been no
11 reductions in bleeding, but on the other hand at least
12 minor complication increase in bleeding complications.
13 So this, of the various new anticoagulants, whether it
14 be low molecular weight heparin, hirudin and
15 bivalirudin, bivalirudin is a stand alone in terms of
16 lessening the bleeding risk.

17 DR. KONSTAM: How do you explain that
18 mechanistically?

19 DR. TOPOL: That's a good question for Dr.
20 Weitz.

21 (Laughter.)

22 DR. WEITZ: Jeff Weitz. I can just give

1 you a hypothetical reason why they may be different.

2 CHAIRMAN PACKER: Just give us the reason,
3 no data.

4 (Laughter.)

5 DR. WEITZ: The reason might be that we
6 have -- the interaction of bivalirudin with thrombin,
7 as you know, it's a bivalent inhibitor and the amino
8 terminal, the amino moiety interacts with the active
9 site of thrombin and then you've got the hirudin
10 peptide, the hirudin-like peptide which interacts with
11 the substrate binding site on thrombin.

12 But the difference between bivalirudin and
13 hirudin is that with hirudin, this is a very stable
14 complex which is very, very slow to associate. So you
15 really have a noncompetitive inhibitor. But with
16 bivalirudin, what happens is once this complex forms,
17 thrombin cleaves the chain, the bivalirudin molecule
18 here and releases the active site moiety. So you get
19 only transient inactivation of the active site. And
20 that's shown, the impact of this is shown on the next
21 slide.

22 Here's an example where we're looking at

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1 clot induced fibrinopeptide agent regeneration in
2 plasma as an index of clot bound thrombin activity and
3 you can see if you put hirudin into the system you
4 totally inhibit thrombin activity for the duration of
5 the experiment. But if you put in bivalirudin, what
6 happens is you get a transient inactivation of
7 thrombin activity.

8 You get inhibition and then you would get
9 some activity coming back and that's due to cleavage
10 of the bivalirudin within that complex.

11 So I think that what you have is you have
12 a -- with hirudin you have a noncompetitive inhibitor.
13 With bivalirudin you have a noncompetitive inhibitor
14 which becomes a competitive inhibitor after a short
15 period of time and once you get the act of site coming
16 back you have a chance to get some hemostatic
17 activity.

18 DR. THADANI: This would be true if you
19 did not give a constant infusion.

20 What would happen on a constant infusion,
21 would it stay flat?

22 DR. WEITZ: Right. So I take your point

1 is that you've got a constant infusion so you've
2 always got new drug coming on, but remember too though
3 that when you have -- you have some thrombin that will
4 have just the hirudin peptide piece still attached to
5 it. Now that thrombin may have a lower affinity for
6 new Hirulog, but it may also be able to interact with
7 the substrate.

8 So I take your point.

9 CHAIRMAN PACKER: I have one last
10 question. Can you tell me the death rate -- the
11 number of deaths at 6 months in the two treatment
12 groups combined analysis in the new non-MI, nonpost-MI
13 population?

14 Let me clarify that, combined analysis six
15 months we have seen the post-MI death rate. What I'd
16 like to see is the nonpost-MI death rate.

17 DR. WEITZ: Can you give me a minute to
18 get that data?

19 CHAIRMAN PACKER: Okay, while you're
20 getting it, let me ask the FDA reviewers, medical and
21 statistical reviewer, whether they have any additional
22 comments, questions or insights to the Committee

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1 before we go through the questions?

2 Have we covered all the major issues and
3 topics that were important during the course of the
4 review?

5 Good. Is there anything else or any other
6 concerns that you have that have not been explored
7 during today's meeting?

8 And from the statistical point of view?
9 Can you come to the microphone, please?

10 DR. RASHID: Now we cannot push for
11 equivalence or non-inferiority at this point, because
12 the trial was not designed for equivalence or non-
13 inferiority. That's the concern. If we go for
14 equivalence, we need to specify the equivalence range,
15 like delta, or non-inferiority of any delta. And
16 delta has to be estimated from previous trials, not
17 from the concurrent trials.

18 CHAIRMAN PACKER: We have, in fact, hit
19 upon that.

20 Do we have any information on mortality,
21 the nonpost-MI patient population at 6 months or
22 whatever?

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1 DR. MEANWELL: We do, but we don't have it
2 by, immediately by cardiovascular and
3 noncardiovascular --

4 CHAIRMAN PACKER: All deaths is great.

5 DR. MEANWELL: There were 31 deaths on
6 bivalirudin and 18 deaths on heparin in that group.

7 CHAIRMAN PACKER: 31 and 18?

8 DR. MEANWELL: Yes.

9 CHAIRMAN PACKER: Going against
10 bivalirudin?

11 DR. MEANWELL: Yes. And if we look at the
12 cardiovascular level, approximately 9 of the
13 bivalirudin deaths were not cardiovascular deaths,
14 they were related to things like cancer, suicide and
15 so on.

16 CHAIRMAN PACKER: The only reason I ask
17 that is because in the documents provided to the
18 Committee there was a 37 versus 26 difference overall
19 and in the data that I think Eric showed, someone
20 showed, the delta was in favor of Hirulog at six
21 months in the post-MI population.

22 DR. MEANWELL: Correct.

1 CHAIRMAN PACKER: I could only then assume
2 that if one took that and subtracted it from the
3 overall, that the difference in the overall would be,
4 in fact, more striking in the non-post MI population.

5 DR. MEANWELL: That's correct.

6 CHAIRMAN PACKER: So the numbers are 31 on
7 Hirulog, 18 on heparin.

8 DR. MEANWELL: That's the total numbers,
9 yes.

10 CHAIRMAN PACKER: Okay. Those are deaths
11 at six months. All right.

12 Okay, we're going to go to the questions
13 as I said at the very beginning of the meeting. The
14 questions have been revised, so it would not be useful
15 for those who are in the audience to look at the
16 questions that they have.

17 (Laughter.)

18 CHAIRMAN PACKER: I assume that you
19 usually find it useful.

20 (Laughter.)

21 CHAIRMAN PACKER: We will make sure that
22 we read all the questions. They're not that

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1 dissimilar to the questions. The order is a little
2 bit different and the emphasis is somewhat different.

3 DR. RODEN: And the handwriting is much
4 more difficult to read.

5 CHAIRMAN PACKER: Thank you.

6 DR. RODEN: You're welcome.

7 CHAIRMAN PACKER: Really?

8 DR. RODEN: Yes.

9 CHAIRMAN PACKER: Okay. Then I'll read it
10 for you too then.

11 Okay, Question 1, which is very similar to
12 Question 1 which exists right now. A composite
13 endpoint of death MI, revascularization and coronary
14 patency during hospitalization was used for the
15 assessment of efficacy in the studies presented by the
16 sponsor. Is this an appropriate endpoint? If not,
17 what endpoint would be appropriate.

18 Dan?

19 DR. RODEN: We can talk about this for the
20 next day or two. Death and MI are clearly appropriate
21 endpoints. Revascularization, I think is probably
22 close but more subjective. Coronary patency, I'm more

1 troubled by. And the issue of the endpoints we talked
2 about ad nauseam here. So pretty close.

3 CHAIRMAN PACKER: I think we -- I don't
4 think there should be too much disagreement here. The
5 sponsors' consultants have already, I think,
6 eloquently said that death and MI is what they would
7 do these days and that it's worth emphasizing because
8 those are the clinically relevant endpoints. They've
9 always been the most insightful and least biased of
10 all the endpoints that we see and I was personally
11 gratified to hear that if you had to do it all over
12 again that's what you would go with and not with the
13 surrogates.

14 I'm not exactly certain what to do with
15 revascularization, but that's for discussion for
16 another day.

17 DR. THADANI: Milton, on that perhaps only
18 comment I would make is if it's emergent
19 revascularization. Say a patient occludes, is having
20 osteolivation and infarcting in front of you, so
21 either putting a stent or taking him to the CABG is a
22 clinical endpoint because he is complaining of chest

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1 pains. I think that would be reasonable in acute
2 setting rather than an elective.

3 CHAIRMAN PACKER: I think it also is worth
4 emphasizing that this endpoint probably should be
5 prospectively measured over a fixed or I shouldn't say
6 necessarily fixed, but pre-specified time that is
7 unlikely to be biased by treatment. In other words,
8 the present protocol that use hospitalization,
9 endpoints during hospitalization is a nonideal way of
10 defining a time period of relevance and in the past
11 this Committee has actually seen much more definite
12 time intervals that are least likely to be biased by
13 treatment.

14 Question 2. Has heparin been shown to be
15 effective in this or any other endpoint in PTCA
16 patients with unstable angina. If so, at what dose?
17 And if so, what pharmacological property or action of
18 heparin may contribute to such efficacy?

19 DR. RODEN: I think the answer to the
20 first question is no. And so the answer to the second
21 and third question is I don't know what dose and I'm
22 glad I don't have to answer the third question because

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1 I'm not a hematologist.

2 CHAIRMAN PACKER: Okay. Anyone have any
3 comments other than that?

4 Okay, Question 3. Trials submitted by the
5 sponsor which show no statistical significance, no
6 statistically significant difference between heparin
7 and bivalirudin on the primary endpoint are the
8 primary trials being submitted as part of this NDA?
9 Can these data provide useful information as to what
10 bivalirudin might do if it had been compared with
11 placebo which is our usual way of thinking through the
12 process?

13 DR. RODEN: This sort of data, I think,
14 could provide useful information if one had an
15 estimate, if one could power the trial to clearly be
16 able to draw the conclusion that there is no
17 difference between heparin and Hirulog and then one
18 has to make some assumption about what would have
19 happened had we been able to answer Question 2.

20 As submitted, I don't think we can say
21 based on the trials that we've seen what Hirulog would
22 have done in comparison to placebo. We can have

1 feelings about what it would have done, but I don't
2 think we can have data.

3 CHAIRMAN PACKER: Okay, this is an
4 important question. I just want to see what the
5 feelings of the Committee are on this issue.

6 This issue integrates a number of issues
7 relevant to noninferiority which were discussed and I
8 just want to make sure that in fact it might be useful
9 prior to going further because the other questions
10 provide other ways of thinking and other options that
11 we reach consensus on Question 3.

12 Question 3 is do the trials submitted by
13 the sponsor that show no statistical significance, are
14 they helpful? Dan has said they are not helpful.
15 Does anyone disagree with that?

16 CHAIRMAN PACKER: Okay. Question 4. A
17 subgroup analysis submitted by the sponsor showed a
18 statistically significant difference in favor of
19 bivalirudin in patients with a recent MI. This
20 post-MI stratum was, in fact, the MI condition of
21 patients was part of a prespecified statistical plan
22 that determined the stratification of patients into

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1 separate groups that were randomized separately. This
2 post-MI stratum, however, comprised only 15 percent of
3 the population and the effect, this effect was not
4 present in a second study, but it was present in a
5 combined analysis of the two trials. Does this
6 finding support the efficacy of this agent for the
7 proposed indication?

8 DR. RODEN: The answer to the question is
9 yes. It supports it. Does it provide strong support?
10 No. Does it provide a comfort level of some sort? I
11 think it does. Is it a basis for approval all by
12 itself? No.

13 CHAIRMAN PACKER: The last question
14 actually comes up a little bit later.

15 DR. RODEN: This particular one.

16 CHAIRMAN PACKER: This particular one.
17 Okay. Dan has said that it provides some level of
18 support, but does not find it to be in and of itself
19 persuasive.

20 Udho?

21 DR. THADANI: Why you say so? I realize
22 they randomized the patients so that they would have

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1 high risk patients in both groups. Then your primary
2 analysis is negative, then you're doing a subgroup
3 analysis and realizing the randomization might be
4 taken into account and in one study we have 13 or 14
5 percent of the patient population is there, there's a
6 difference and yet the higher percentage, 19 percent
7 in the second study shows no difference. Then you
8 combine again to show a difference. I'm not sure how
9 much -- I think there is something there, but I'm not
10 sure how comfortable one feels if you are to do
11 another trial, whether you're going to maintain the
12 differences.

13 So I think I've got some more reservations
14 than you have in saying yes.

15 CHAIRMAN PACKER: Marv?

16 DR. KONSTAM: To me, it's essentially
17 hypothesis generating. I mean I think it's
18 intriguing. It's nice to see it going positive. It
19 was -- there was a prespecified stratification, but
20 this was not a prespecified analysis that is
21 separating this group out for that purpose. So it's
22 significant only in one of the two, so I think it's

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1 very interesting, but hypothesis-generating to me, I
2 think.

3 CHAIRMAN PACKER: I'm not certain, Marv,
4 it sounds like your comments are essentially similar
5 to Dan's. But I mean, no, it's -- okay, a little
6 comfortable. It's interesting, which I guess is the
7 same as being a little comfortable.

8 DR. KONSTAM: Well, I'm not sure what the
9 question is asking. I mean does it support? I mean
10 does it support at the level of hypothesis generation?

11 CHAIRMAN PACKER: Okay, that's fine. Does
12 anyone disagree with that?

13 (No response.)

14 CHAIRMAN PACKER: Question 5. The sponsor
15 provides a metanalysis comparing high dose and low
16 dose bivalirudin across various trials in patients
17 with an acute coronary syndrome. These trials are not
18 necessarily restricted to studies of patients with
19 PTCA. It includes patients with unstable angina. One
20 of those trials was TIMI-7 or 8. 7? 7. 7? 7. That
21 a retrospective analysis of low dose which hardly
22 affected ACT versus the higher doses that affected ACT

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1 had a lower, the higher doses had a lower risk of
2 death in MI with nominal p values less than .05. It's
3 hard to call them real values because it wasn't a
4 prespecified analysis. Do these data provide evidence
5 to support the efficacy of bivalirudin for the
6 indication being sought?

7 Dan?

8 DR. RODEN: Not much. I mean I think that
9 the metanalysis really was driven by these very large
10 numbers in the two pivotal trials and the other trials
11 are, as you point out, different endpoints and while
12 they might provide perhaps I shouldn't say it again,
13 it's sort of a bit of a comfort level that everything
14 is going in the right direction, I think they really
15 don't do much beyond that.

16 CHAIRMAN PACKER: Let me just make sure
17 that the metanalysis being referred to is high dose
18 versus low dose, not Hirulog versus heparin.

19 DR. RODEN: I don't care to change my
20 comments.

21 CHAIRMAN PACKER: Okay. Other discussion?

22 DR. THADANI: Also, I think perhaps it's

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1 worth mentioning the TIMI-7 was not related to this
2 trial in any way, that unstable angina had nothing to
3 do with angioplasty.

4 CHAIRMAN PACKER: Is unstable angina
5 without angioplasty really that much different than
6 unstable angina with angioplasty?

7 DR. THADANI: Sure, it's totally different
8 because what you are suggesting from this trial that
9 every patient with unstable angina has to be taken to
10 the cath lab which is really not true, unstable angina
11 is mixture of different people. Some have vascular
12 pressure some don't, some are high risk, some are low
13 risk, so I think you can't lump them to acute
14 intervention trials, having a totally different --
15 you're dealing with apples and oranges here.

16 CHAIRMAN PACKER: Okay. Does anyone
17 disagree?

18 Question 6. Do you disagree? Oh.
19 Question No. 6, the sponsor provides a metanalysis
20 comparing bivalirudin and heparin -- this is different
21 than Question 5 -- across various trials in patients
22 with an acute coronary syndrome, many of which did not

1 have PTCA, but most did have PTCA because it
2 corresponds to the largely, the biggest contributor to
3 those trials are the trials, two major trials which
4 are part of the NDA. So this is actually more in line
5 with the issue, Dan, that you raised originally. Do
6 these data provide evidence to support the efficacy of
7 the drug for the indication being sought?

8 DR. RODEN: I'd have the same comment as
9 before, that it's all reassuring that there's not much
10 of a signal that anything is going in the wrong
11 direction, but really, the two trials that we're
12 talking about today are so huge compared to everything
13 else that they -- and that's what we're considering
14 today. So a little level of comfort.

15 CHAIRMAN PACKER: Anyone disagree?
16 Question 7. The sponsor provides data on the late
17 assessment, 3 to 6 months post-PTCA of patients
18 enrolled in the two major trials. The data indicate
19 no difference in clinical events or angiographic
20 patency. Do these -- I don't know if we've actually
21 seen the angiographic, late angiographic patency. I'm
22 not even certain that there were data. It's really

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1 clinical events. Do these data influence your views
2 regarding the efficacy of bivalirudin? Dan?

3 DR. RODEN: We really didn't talk about
4 this issue much, I'm not sure six months is the right
5 time to look. We've had, just to sort of go back to
6 recent past history. We had this discussion over the
7 2B3A receptor blockers a lot when the right time to
8 look is and I think six hours is too early, and six
9 months might be too late. So they don't influence me
10 much because I think that's sort of a late, late time
11 point which I'm not sure is really relevant to our
12 discussion today.

13 DR. THADANI: I agree with Dan that six
14 months probably is a late point, but we have data and
15 I think what worries me a little bit that the deaths
16 are going in the wrong direction of six months. I
17 know the trial is not designed to do that and there's
18 some question on six months is almost 40 something and
19 20
20 -- I can't remember offhand, so it just worries me a
21 bit. If your therapy is going to be effective, you
22 might think there's some maintain effect, because you

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1 collect the data. You're going to live with it. You
2 can't just ignore it. It's there. Whatever the
3 reasoning, it just -- since the trial is not superior
4 we are not sure about inferiority. I think this just
5 worries me. And I want to Lem to comment on this a
6 bit more.

7 DR. LINDENFELD: On the other hand, Udho,
8 those curves stay parallel from the beginning out and
9 that gives me a little bit of reassurance that we
10 haven't lost the early benefit. So I'd interpret that
11 just a little bit differently, although I am concerned
12 about the deaths. We don't see loss of early benefit,
13 so I felt better about that.

14 CHAIRMAN PACKER: It should be emphasized
15 that the lack of a p value during long term follow up
16 when a significant p value has been seen early is not
17 so unusual and I think Joann's point is the most
18 important to underscore which is the maintenance of an
19 effect as opposed to the achievement of a p value at
20 the end of follow up. It's more that the curves
21 continue to maintain their separation. I understand
22 that's more of a visual impression than the

1 statistical concept, but in many ways the collection
2 of long-term follow-up is a conceptual issue as
3 opposed to a pure mathematical one.

4 Lem, are you okay with that? Okay.

5 Question 8. Was there a difference in the
6 risk of major hemorrhage in patients assigned to
7 bivalirudin as compared to those assigned to heparin?
8 And if so, could this difference be accounted for by
9 the difference in ACT achieved in the two groups or
10 the difference in the dosing regimens achieved in the
11 two groups? Or dosing strategies.

12 DR. RODEN: Yes and yes.

13 CHAIRMAN PACKER: Okay. While we still
14 have you on the telephone --

15 (Laughter.)

16 CHAIRMAN PACKER: -- do you think that the
17 difference in dosing strategies is sufficient to raise
18 significant doubts about the finding of a true
19 difference in hemorrhagic risk between the two agents
20 being compared in the two major trials?

21 DR. RODEN: I answered that last question
22 sort of -- perhaps a bit facetiously because this is

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1 the issue around which the discussion and the decision
2 that we're going to make in a couple of minutes
3 hinges, it seems to me. The -- I don't think anyone
4 is arguing that the efficacy of bivalirudin is so much
5 more astounding than that of heparin. In fact, in the
6 two pivotal trials, the efficacy endpoint was missed
7 in both.

8 So the real question is do you believe, do
9 I believe, that the difference in the bleeding
10 incidence in those trials is sufficiently compelling
11 to make me think that the drug should be proved just
12 to jump ahead for a second? So without thinking about
13 that for a second, just -- I'm not going to be sucked
14 into that. But the -- it is I think relatively clear
15 even from the discussion that we heard from the
16 sponsor that this regimen of heparin is relatively
17 aggressive and I think we all have that sense. To
18 what extent that aggressive nature contributes to the
19 difference is uncertain. It indubitably contributes
20 some.

21 And so one is left with an uncertainty of
22 how much of a difference in the safety profile is it

1 due to a protocol issue as opposed to how much is due
2 to a true difference between the drugs and I think
3 that's all I can say.

4 CHAIRMAN PACKER: Let us -- what I want to
5 do, this is not a small point. This is a very, very
6 important point. I really would like to have
7 individual members of the Committee talk about this
8 because there's nothing minor about the answer to this
9 question. And we've been sort of picking on the right
10 side of the panel all day and so John, what do you
11 think about this question? Is there a difference and
12 if there is a difference, to what degree are you
13 concerned that the difference that you see is -- does
14 not reflect something other than a true biological --
15 a difference in the pharmacological, inherent
16 pharmacological properties of the two drugs, but is
17 sufficiently confounded by difference in dosing
18 strategies as to make conclusions regarding the
19 relative incidence of major hemorrhage difficult to
20 maintain?

21 DR. RODEN: Yes, I think that as I look at
22 the data I think that we can see that clearly there

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1 were less serious hemorrhagic complications in the
2 bivalirudin group as defined in this protocol. I
3 think that clearly I agree that this -- and if we look
4 at the comparison of the other studies, this was an
5 aggressive heparinization protocol, probably more
6 aggressive than is used now in most laboratories in
7 the majority of patients.

8 There seems to be an increase in bleeding
9 hemorrhagic complications with more aggressive
10 anticoagulation protocols and there was some imbalance
11 in the way the two protocols were sort of designed.
12 So I think that I am -- there's no question that in
13 these studies there were fewer hemorrhagic
14 complications with bivalirudin, but would that occur
15 in another study that were done with a less aggressive
16 heparin protocol with the added caveat that we're not
17 quite sure how much anticoagulation is needed with
18 heparin. I can't be sure, so I can't be certain that
19 it's superior -- if a trial were designed today using
20 a different heparin protocol.

21 CHAIRMAN PACKER: Ileana?

22 DR. PINA: I want to add to what John said

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1 that I understand that the sponsor did not want to be
2 blamed for under heparinization. But I am also
3 uncomfortable with the degree of heparinization and
4 may not be consistent with what's being used today
5 clinically.

6 CHAIRMAN PACKER: Marv? Coming back.
7 Joann?

8 DR. LINDENFELD: I think there's a real
9 difference here. I'm persuaded. I just think the
10 problem how much is that real difference. It's very,
11 very large in these studies, but with a less
12 aggressive protocol it may not be large enough that
13 we'd be nearly as impressed, so I guess I would just
14 shade slightly different than what John said. I think
15 there is a real difference. I suspect it's not nearly
16 as large in today's world or in today's dosing as it
17 was in this study.

18 CHAIRMAN PACKER: Lem? We'll come back to
19 Marv.

20 DR. MOYE: It's certainly plausible that
21 the effect on hemorrhagic complications is ACT
22 mediated. Now one way to be sure, not a perfect way,

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1 but one way to get at this would be to try to estimate
2 an ACT adjusted therapy effect where ACT is put into
3 a Cox model which is a time dependent covariant model.

4 Now this is not a perfect solution, but it
5 does give us a pseudo objective way of parsing out the
6 ACT effect from the therapy effect. That is to say,
7 you remove the relationship. You identify the
8 relationship between ACT and therapy. You also
9 identify simultaneously the relationship between ACT
10 and events, remove those relationships and examine
11 what's left.

12 CHAIRMAN PACKER: Hasn't the sponsor
13 actually presented that analysis? I remember in the
14 briefing document and I am flipping through the pages,
15 perhaps aimlessly, but I remember that there was a
16 bleeding, an analysis of major hemorrhage that
17 controlled for ACT as a cofactor and if someone can
18 help me identify what table that is. It's not a table
19 that was seen today. It's in this book? Really? No,
20 no, that's not it. It's a simple table. No, that's
21 not it, either.

22 DR. MOYE: Page 48.

1 CHAIRMAN PACKER: Which book? Green or
2 black. The black book, page 48. Is that what --
3 that's it. Page 48. This is Table 3.8 and this comes
4 from the sponsor's briefing document.

5 DR. BITTL: If I may, there's a figure
6 that has perhaps the same type of analysis that looks
7 at the incidence of major hemorrhage as a function of
8 categories of ACT values achieved for patients on
9 heparin in gray and bivalirudin in this blue. I think
10 it was less than one percent of patients, actually,
11 had their 5 second ACT or 5 minute ACT under 200
12 seconds, so you can pretty much ignore this group
13 here, but I guess the message here is it really didn't
14 matter what your ACT was during the procedure on
15 bivalirudin. The highest ACTs achieved on bivalirudin
16 were associated with lower hemorrhagic complication
17 rates than the lowest ACTs achieved on heparin.

18 DR. KONSTAM: So this is procedural ACT.
19 What's the time that this was taken?

20 DR. BITTL: This is the 5 minute ACT,
21 after the bolus. Only about 40 percent of the
22 patients had a 45 minute ACT obtained.

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1 DR. KONSTAM: I'm sorry, what percent had
2 a 45 minute?

3 DR. BITTL: About 40 percent of patients
4 had the 45 minute ACT measurement made. The other 60
5 percent of patients had a faster procedure and they
6 were out of the lab before 45 minutes had elapsed.

7 DR. KONSTAM: So for the majority of
8 patients this was the only ACT?

9 DR. BITTL: Excuse me?

10 DR. KONSTAM: In the majority of patients,
11 this was the only ACT measured.

12 DR. DiMARCO: But all the patients under
13 350 got a bolus.

14 DR. BITTL: That was an option of the
15 investigator, to give an additional bolus. In actual
16 practice, many of them did. On heparin, they got an
17 additional bolus.

18 DR. THADANI: But on that slide you did
19 not do an extra bolus of your Hirulog, right?

20 DR. BITTL: The additional bolus --

21 DR. THADANI: The way the protocol was
22 written, you only gave a bolus of heparin and a

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1 placebo imputed for the other one. So you could have
2 driven the event rate lower just by keeping it, not
3 going up.

4 DR. BITTL: That's possible, but I still
5 submit that the differences are so striking across a
6 range of ACTs of 150 seconds with the patients on
7 bivalirudin with ACTs around 400 seconds, still have
8 60 percent lower rates of bleeding than patients at
9 the lower range of heparin.

10 DR. THADANI: I'm not denying that. What
11 I'm having problems sometimes, we had given extra --
12 everybody doesn't bleed with the same ACT because the
13 event rate, even at the same is about 8 or 10 percent.
14 That means other 50, 60 whatever percentage don't
15 bleed. Had you given a higher dose, could you have
16 driven the event rate higher?

17 DR. BITTL: I deal with additional boluses
18 of heparin in the cath lab every day and the 3,000
19 unit of bolus of heparin will raise your ACT 25 to 50
20 seconds. So we might take a third of the heparin
21 treated patients on the previous slide and take them
22 from an ACT of 300 to 350, but we're not going to send

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1 them up to 800 with that additional bolus.

2 DR. THADANI: But this is a total event
3 rate, right?

4 DR. BITTL: That is the hemorrhagic rate
5 in the first 24 hours.

6 DR. THADANI: But that also is driven by
7 more aggressive, perhaps heparin regimen throughout
8 the 24 hours because you have no control of aPTT and
9 after the cath lab, you have no idea what the aPTT was
10 running. So as a composite of earlier aggressive,
11 plus whatever the treatment strategy later on.

12 DR. BITTL: Correct. The point is that
13 the ability of the procedural ACT to predict
14 hemorrhagic events provides a very consistent message.
15 It's lower in bivalirudin treatment than with heparin
16 treatment.

17 CHAIRMAN PACKER: I just want to make sure
18 we have clarification.

19 Lem, the only reason this is being shown
20 at this point in time is because you thought an
21 analysis that factored in ACT might be useful. I have
22 -- I don't know whether this is the kind of analysis

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1 you would or would not do, but my question to you is
2 still the question that is being asked of each member
3 of the Committee which is that do you think that the
4 difference that -- the observed difference in
5 hemorrhage is a true difference or do you have
6 sufficient concerns that it might be confounded by
7 differences in dosing strategy to make a definitive
8 conclusion difficult?

9 DR. MOYE: This slide gets us most of the
10 way there. My concern about a non-ACT moderated
11 effect is amplified by this slide.

12 CHAIRMAN PACKER: Okay, let me just see.
13 John is shaking his head, so let's clarify.

14 DR. DiMARCO: I just think the fact that
15 you have this five minute ACT and you then rebolus
16 with heparin and then you don't know what the
17 subsequent ACT is, only tells you about five minutes,
18 so that in fact, I would have expected all the heparin
19 groups to normalize out the same because they all got
20 rebolus and they just don't have subsequent data. So
21 the fact that the heparin is -- I mean the only two
22 groups you can compare probably is the initial -- is

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1 the group of heparin who didn't get a bolus, versus
2 the bivalirudin who were over 350 at the start who
3 were at least over 350. And so you have two groups
4 that are initially over 350 and then there is a
5 difference so that you probably could look at it that
6 way.

7 CHAIRMAN PACKER: Okay. I just want to
8 make sure. I understand what you're saying. This
9 slide that we saw, I guess most of the people who had
10 ACTs that were more than 350. I'm not certain I'm
11 going to -- that what I'm about to say helps the
12 process, but didn't get a bolus and they had a big
13 difference in hemorrhagic risk. The patients who --
14 I guess I was struck by the fact that I actually
15 expected the hemorrhagic risk with heparin to be
16 related to the ACT and that wasn't seen here probably
17 because the bolus issue.

18 DR. DiMARCO: I think the striking this is
19 that even if the ACT was over 350 on bivalirudin, they
20 had a lower complication rate.

21 CHAIRMAN PACKER: Right. I see. Okay,
22 I'm sorry, Lem. We are taking votes here. So we just

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1 have to make sure we've got your feelings accurately
2 portrayed.

3 Your sense here is that -- just so we make
4 sure that we've got everyone's vote accurate. John,
5 Ileana and Dan all said that the difference in dosing
6 strategies were that dosing strategies were
7 sufficiently different, that they have concerns as to
8 whether one could reach a conclusion that there's a
9 true difference in hemorrhagic risk. Is that accurate
10 across the three?

11 Joann said that she was actually more
12 comfortable that the difference was a true difference.
13 Is that right, Joann?

14 DR. LINDENFELD: Yes.

15 CHAIRMAN PACKER: Lem, your vote on this?

16 DR. MOYE: I would say that the difference
17 between the effect mediated on ACT is related to the
18 dosing of the different, two different therapies.

19 CHAIRMAN PACKER: And not due to
20 differences in the two therapies?

21 DR. MOYE: Right.

22 CHAIRMAN PACKER: Udho?

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1 DR. THADANI: I think there might be real
2 difference, but I'm concerned it could be protocol
3 driven, so I have again concern that it could be
4 protocol related the way the heparin was used to drive
5 the ACT up and not being monitored later on in the
6 later phase.

7 CHAIRMAN PACKER: Marvin?

8 DR. KONSTAM: Yes. I actually would like
9 to refrain the question slightly because I think
10 clearly what we're doing is comparing two different
11 drugs with different pharmacodynamics and we're
12 comparing them at the regimens that were performed.
13 And so the differences were real, but they're
14 obviously going to be influenced by the regimen that's
15 administered. So the question really to me is whether
16 the heparin regimen is the appropriate heparin regimen
17 and if it were a different regimen would we have seen
18 something else? Well, I think if it were a different
19 regimen we would have seen something else. If we give
20 less heparin we're probably going to see less
21 hemorrhagic effect, although we may also see less
22 benefit and we just don't know that.

1 So to me, the problem here really is that
2 this is a more aggressive heparin regimen than what
3 was typically given clinically at the time this study
4 was done. And to me it isn't standard practice to go
5 24 hours on heparin without monitoring PTT. And so
6 that's one set of problems.

7 The other set of problems that compounds
8 that is that standard therapy has now changed since
9 the time of that study which really would give us
10 another set of problems because most typically
11 patients post PTCA are not get on heparin for 24
12 hours.

13 So those are the issues and I think
14 framing it that way, I guess I say yes, it's a real
15 difference, the difference, I'm sure, is related to
16 the particular regimens and I'm concerned that the
17 regimen of heparin is not necessarily the most
18 clinically appropriate regimen.

19 CHAIRMAN PACKER: Okay, I guess I would
20 right now, if I understand it correctly based on what
21 everyone has said, although there are slight
22 difference in the words used that there is -- Joann,

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1 I'm not even certain you disagree even though your
2 comfort level is higher, that the consensus of this
3 Committee is that they are not -- they believe that
4 the dosing regimen is strategy used to dose heparin
5 here may provide a sufficient confounding factor to
6 make conclusions about the relative incidents of major
7 hemorrhage difficult to sustain either in terms of its
8 existence or its magnitude.

9 DR. THADANI: What was your words
10 regarding that?

11 CHAIRMAN PACKER: I agree with that.
12 Okay. Let me just ask one question. Is anyone
13 concerned about a similar issue which is the lack of
14 information with 2B3A antagonists? We talk about this
15 all the time. Remember, we emphasized yesterday that
16 one data that was clinically relevant in which there
17 was an experience, an interpretable experience -- who
18 knows what that means -- with drugs that are assumed
19 to be useful in the condition being studied in 2B3A
20 antagonists are deemed to be useful in this condition.
21 There are no data in cases receiving 2B3A antagonists.
22 To what degree does the Committee believe that that's

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1 a limitation of the present data base?

2 Dan, why don't you --

3 DR. RODEN: If you want to repeat that
4 question? I defy you to repeat that question.

5 CHAIRMAN PACKER: I have no problem
6 repeating the question, not exactly the same way. Do
7 you think the lack of data on 2B3A antagonists in this
8 NDA is a problem?

9 DR. RODEN: Oh, in this NDA. I see what
10 you're saying. Well, it is a problem, particularly
11 since -- I mean that group of drugs are becoming
12 widely used. I guess I would just leave it at that.
13 I'm not sure it's a fatal flaw, but it's a concern, I
14 guess.

15 DR. KONSTAM: You know, it is a concern,
16 given change in practice patterns. I actually would
17 like to ask the sponsor's opinion on this because it
18 occurs to me that if Hirulog has a specific effect on
19 thrombin induced platelet effects, what the potential
20 interaction would be with the addition of a 2B3A
21 antagonist, as opposed to heparin which does not
22 influence thrombin effects on the platelets as much.

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1 DR. TOPOL: I would like to speak to that
2 because that's what I tried to underscore this
3 morning. And that is that we need a safer background
4 therapy and if it hasn't been convincing enough that
5 this is safer, that is to start with heparin, not just
6 -- and I really object to the way this has been
7 discussed on the safety side because every study in
8 the contemporary era through 1998, not just the
9 current study, we show significant, significant
10 reduction in bleeding hemorrhage. I don't understand
11 why there's all this discussion about whether safety
12 was demonstrated. The point is that 2B3A addition
13 which is done ad hoc in the middle of many coronary
14 interventions today add a 2B3A inhibitor, you'd like
15 to have it on a safer background, one in which there's
16 lesser risk of hemorrhage. That's the whole issue.
17 We can't do the study. We have wanted to do it for
18 over a year, but we haven't been able to get access to
19 the agent.

20 As far as the anti-thrombin effect, would
21 that be different than heparin? The anticoagulant,
22 you could argue that an ACT on Hirulog is different

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1 than an ACT on heparin. So we could even get it down
2 to that level. We don't know until we can get to test
3 it and we haven't been able to test it. But that's
4 the whole issue. We'll have an opportunity if the
5 drug is out there to have a safer background therapy
6 for anticoagulation during coronary intervention.

7 DR. THADANI: Milton, perhaps one of the
8 comments could be the currently approved 2B3As have
9 been used on top of IB heparin. We have no data
10 whatsoever here. So if you're going to use the 2B3As
11 they are on top of IB heparin, so I think you'll have
12 to obtain data whether it's determined or not. I
13 think all we could say is there no data to make
14 conclusion one way or another. That has to be studied
15 to evaluate whether it's going to be more effective or
16 less effective. We've already learned with Tyrol 5N
17 when given alone it was not effective, although the
18 trial was prematurely terminated so I don't think we
19 have data to give one way or another. There's just
20 lack of data. So the question of concomitant use
21 would be -- it doesn't, shouldn't even arise because
22 we have no data.

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1 CHAIRMAN PACKER: Okay, let's go on to the
2 final question. The final --

3 DR. DiMARCO: Can I just interrupt for one
4 second?

5 CHAIRMAN PACKER: Sure.

6 DR. DiMARCO: And this is a question for
7 Lem. On page 59 of the sponsor's booklet, the last
8 five lines at the bottom of the page, they state they
9 did a post-in hoc noninferiority, I assume it's an
10 analysis, giving confidence limits there.

11 Could you interpret that paragraph for me?
12 Does that mean that at most there's an 11 percent loss
13 of efficacy with this compound as comparison to
14 heparin?

15 And do you agree with the appropriateness
16 of such an analysis?

17 DR. MOYE: I am not even with you yet.
18 What page is this?

19 DR. DiMARCO: 59. Black book.

20 CHAIRMAN PACKER: Lem?

21 DR. MOYE: I'm reading.

22 CHAIRMAN PACKER: These are the confidence

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1 intervals of a metanalysis? Right, it's a metanalysis
2 of the pivotal trial --

3 DR. KONSTAM: Could you clarify 11
4 percent? I'm not sure what -- 11 percent of what?
5 What's the 11 percent?

6 DR. KOCH: Do you have the table to
7 display? Basically -- I'm Gary Koch again. To
8 address the comparative efficacy of the two regimens,
9 the pooled studies had an analysis that produced a
10 confidence interval on the odds ratio. And basically
11 that confidence interval describes the similarity of
12 the efficacy for the original primary endpoint or
13 various revisions.

14 My understanding is that an upper
15 confidence limit on the primary end point was
16 something like 1.11, although the upper limit may be
17 somewhat less for other endpoints. 1.07 for the
18 endpoint of -- so for the endpoint that had more
19 discussion, death, revascularization or MI, the upper
20 limit was 1.07.

21 DR. DiMARCO: I guess my question is that
22 sort of the equivalent of an equivalency trial?

1 That's what I'm asking.

2 DR. KOCH: You still have the outside
3 issue that the Committee has been concerned about
4 which is how would either of the regimens done against
5 placebo. All this analysis does is to identify how
6 similar the efficacy of the two regimens are and
7 basically the two regimens are quite similar when you
8 put the two pivotals together and essentially if you
9 believe that heparin has some efficacy, then this
10 quantifies the degree to which bivalirudin would have
11 similar efficacy. It would be within an odds ratio of
12 1.11 for the original procedural failure endpoint.
13 1.07 for death, MI or revascularization. Death or MI,
14 the limits are wider, but there were, of course, were
15 fewer events there.

16 CHAIRMAN PACKER: Could you keep it up?
17 It's just that we may want to discuss it a little bit
18 more. Let me see if I -- we can just define this a
19 little bit more.

20 Let's take the last column. The last one
21 is the one that I guess everyone would feel represents
22 the hardest clinical endpoint which is death and MI.

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1 And understandably a number of events -- also, the
2 confidence intervals are wider so that the point
3 estimate here is an 11 percent difference. More
4 importantly, the 95 percent confidence intervals mean
5 that Hirulog could be 40 percent better or 31 percent
6 worse, as much as 40 percent better or as bad as 31
7 percent worse.

8 DR. KOCH: And these events are
9 sufficiently low rate, that although the interval
10 formally is on an odds ratio, you could think of it as
11 being on a relative risk.

12 CHAIRMAN PACKER: That's fine.

13 DR. KOCH: So the risk ratio is below
14 1.31.

15 CHAIRMAN PACKER: Right. Does that mean,
16 Gary, that if heparin were -- I want to go someplace
17 -- you can just focus on the --

18 DR. KOCH: Why is it so dark?

19 DR. THADANI: He's trying to plot the
20 non-MI patients where the intervals are wider. It
21 goes up to 1.85.

22 (Laughter.)

1 DR. KOCH: Just leave it there.

2 CHAIRMAN PACKER: It's good to shed some
3 light on this.

4 (Laughter.)

5 CHAIRMAN PACKER: Does that mean if
6 heparin were -- I'm trying to figure out how one uses
7 this. If one knew that heparin was 50 percent better
8 than placebo and I'm making that number up. I don't
9 have any idea where I'm getting it from. How do these
10 data help you determine if Hirulog is better than
11 placebo? I guess they just don't --

12 DR. KOCH: If heparin is better than
13 placebo, since these data indicate a trend for
14 bivalirudin to be better than heparin, they would
15 confirm that bivalirudin was better than placebo as
16 well.

17 CHAIRMAN PACKER: But no. If the
18 confidence interval is at .6 to 1.3, would mean that
19 -- if the heparin confidence intervals --

20 DR. KOCH: The heparin confidence interval
21 would have to have something like an upper limit of .8
22 if you were multiplying upper limits together. That's

1 probably a bit stringent to multiply two upper limits
2 together, but as long as the upper limit for heparin
3 versus placebo was no worse than say .8, then if you
4 multiplied the .8 by 1.3 maybe you get 1.04. So drop
5 the .8 to about .75. So if your upper confidence
6 limit for how well heparin beats placebo is .75 or
7 thereabouts, then multiplying the two upper limits
8 together, which is actually much more stringent than
9 what would happen if you actually looked at the ratio
10 of the two risk ratios and put a confidence limit on
11 that. That's going to actually be the right way to do
12 it and in that case probably .8, .85 would work.

13 DR. THADANI: Before you leave there, I
14 agree with you, but then you show nonpost-MI versus
15 post-MI and the majority of the population is driven
16 by nonpost-MI and it's going in the wrong direction.
17 The ratio is 1.21. I believe in the totality of the
18 data, but here there's some -- a concern one might
19 have that the majority of the population, driven by
20 nonpost-MI is going in the wrong direction.

21 DR. KOCH: Yes, but see -- again, you're
22 reacting too much to the point estimate. The

1 confidence intervals for nonpost-MI are basically from
2 the .8 region up to 1.3 and of course that's
3 counterbalanced by --

4 DR. THADANI: It was 1.85 and in the last
5 column you could go 80 percent higher.

6 DR. KOCH: Yes, but if you're arguing that
7 you believe that, then you have to also admit that you
8 believe what's going on in the post-MI. And in the
9 post-MI you're seeing significant benefit. So we're
10 not trying to argue the subgroups of this point here.

11 DR. THADANI: No, the sample size is much
12 smaller in post-MI. I'm not saying which is right or
13 wrong, but if you look at that it's just a bit in the
14 wrong direction and in the nonpost-MI, although
15 overall, there's no difference.

16 DR. KOCH: All I'm saying is you have to
17 take a position one way or the other. You either have
18 to say the difference between nonpost-MI and post-MI
19 is real in which case you then have to say that the
20 significance for post-MI is true. Or you say the
21 difference between nonpost-MI and post-MI is random in
22 which case you emphasize what's in the all patients

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1 column. You can't have it both ways.

2 DR. THADANI: I know. I'm just raising an
3 issue. Overall, there's no difference and one is
4 going in the wrong direction. That's the subgroup
5 analysis problem.

6 DR. KOCH: All we're indicating here is
7 that if you put a confidence interval comparing the
8 two regimens then basically for the original primary
9 endpoint the upper limit is 1.11 and for the death, MI
10 or revascularization it's 1.07. So these two regimens
11 on an all patients basis are very, very close to one
12 another and there is some tendency that the one
13 regimen does noticeably better in post-MI, but that
14 could be random. Correspondingly, they're pretty much
15 sitting on top of each other if you're nonpost-MI.

16 CHAIRMAN PACKER: Any other discussion of
17 the data here? Lem?

18 DR. MOYE: Just one thing. These are
19 certainly interesting conjectures. And there is no
20 doubt that in the sample the event rates for the
21 heparin group and for those patients randomized to
22 Hirulog are pretty close. But the issue is not so

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1 much what happens in the sample. The issue is what's
2 the truth likely to be in the population. The
3 resolving power of this study says that we can only be
4 sure that the difference between the two therapies
5 isn't as large as 33 percent and that's all we can say
6 because we don't have the resolving ability because
7 even though as hurtful as it is to say -- right, even
8 though they did a lot of work in bringing together two
9 trials of over 2,000 patients, many more patients are
10 needed to have a finer resolving ability. So we
11 really can't say what's going on in the population in
12 terms of equivalence from this relatively small
13 sample. So the answer to John's question, I don't
14 think that this substitutes for a noninferiority
15 study.

16 CHAIRMAN PACKER: I guess, Lem, I guess
17 the major concern I had about this without a whole lot
18 of knowledge of the issue of noninferiority was that
19 these were events during the hospitalization.

20 DR. MOYE: Right.

21 CHAIRMAN PACKER: And we've already gone
22 through the concern about the fact that that creates

1 potential for confounding due to varying time
2 intervals of follow up, but what I think you're saying
3 is even if they were to show us this for a fixed
4 period of follow up, that wouldn't be persuasive to
5 you. Is that correct?

6 In other words, if they were to show this
7 at 7 days or 30 days or whatever time period would be
8 relevant and take out the surrogates that would not --
9 I guess --

10 DR. MOYE: It still would not be
11 persuasive.

12 CHAIRMAN PACKER: That would not be
13 persuasive?

14 DR. MOYE: Right.

15 CHAIRMAN PACKER: Okay. No. 9, actually,
16 I had forgotten. Did the data reveal any other safety
17 issues with bivalirudin that should be discussed?
18 Dan?

19 DR. RODEN: No.

20 CHAIRMAN PACKER: Dr. Talarico?

21 DR. TALARICO: I'd like to go back if we
22 can to question 2 and 3 and I would like a more

1 individual answer to each of these questions because
2 we have to face the question is heparin effective in
3 this indication that this is one of the basic points.

4 So if we could go back to question 2, has heparin
5 been shown to be effective on these or any other
6 endpoint in PTCA patients with unstable angina. Can
7 I have the answer to this question.

8 CHAIRMAN PACKER: Everyone said no.

9 DR. TALARICO: So it was unanimously no.

10 CHAIRMAN PACKER: But that's not
11 necessarily the only way of phrasing this question.

12 DR. TALARICO: Right.

13 CHAIRMAN PACKER: Which is what Question
14 10 is all about.

15 DR. TALARICO: Okay, all right.

16 CHAIRMAN PACKER: Question 10 is phrased
17 in a way which I guess is typical of questions
18 concerning approval. Given the totality of the data,
19 do you recommend the approval of bivalirudin for use
20 as an anticoagulant in patients undergoing PTCA who
21 have unstable angina? And this allows you to
22 integrate everything that you know. And I want to

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1 hold the question there. There are a number of
2 subquestions that may or may not be relevant based on
3 the answer to Question 10.

4 Dan, we'll begin with you. We'll have a
5 discussion of this after Dan leads off the discussion
6 and then we will have a vote.

7 DR. RODEN: I'll make a couple of comments
8 first. And that is that it seems to me that we're
9 never asked on this Panel to answer simple questions.
10 And I have struggled with this for the last week or
11 two since I got all these data. And I have sort of
12 yo-yo'd through the day today.

13 We do operate under a series of rules for
14 drug approvals and I guess if it were straight forward
15 to work up a drug for this kind of indication, then
16 we'd work it up and we wouldn't have this difficulty
17 because of the undoubted, but unquantified efficacy of
18 heparin in this setting.

19 Milton referred to the fact that we had
20 looked at enoxaparin, recently and you did point out
21 that there were some differences, notably that
22 enoxaparin was shown to be superior to heparin in that

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1 big trial.

2 So what we have is the awkward situation
3 of a sponsor coming to us with two pivotal trials well
4 designed. The easiest metanalysis in the world
5 because they're identical protocols so there's no
6 problem performing a metanalysis combining the two and
7 there's no question that the primary endpoint was
8 missed.

9 On the other hand -- so on the face of it
10 you'd say well, go away. But there is this intriguing
11 safety issue and it really does look like the
12 incidence of bleeding is half or lower compared to the
13 heparin regimen and so the next question one has to
14 ask oneself is it conceivable -- is that a real
15 difference or is that driven by the doses that were
16 used in this protocol.

17 We've already answered that question and
18 we think that part of it might be real and part of
19 might be driven by the protocol. And we just don't
20 know how much of which. I don't want to deny patients
21 who are undergoing PTCA and apparently safer, albeit
22 perhaps equally effective therapy. On the other hand

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1 the data, as presented right now don't allow me to go
2 forward with the recommendation for approval. I wish
3 the Agency would support the pleas of the
4 investigators to perform the appropriate studies for
5 the year 1999 and forward. So that's my conclusion.

6 CHAIRMAN PACKER: I don't want to get into
7 what may or may not be the reasons that additional
8 studies have -- who knows? It doesn't matter.

9 The most important, I think for all the
10 reasons that you've mentioned at the present time your
11 comfort level is that the totality data are
12 insufficient to recommend approval. We want to open
13 this for discussion, but since you're asking about
14 additional trials, I just want to ask, maybe Eric
15 would be the best one to ask.

16 Eric, the post-MI subgroup here is very
17 intriguing. And there may, in fact, be a difference
18 in efficacy, not just in terms of safety. Wouldn't
19 you want to know that?

20 DR. TOPOL: I think we do know that. That
21 in fact, the post-MI patients have heightened efficacy
22 about bivalirudin compared with heparin. That subset

1 of patients was identified by the registry that was
2 done, that was antecedent to this trial, pivotal
3 trial, showing that they were the ones the patient
4 posed the highest risk and they have, concordant with
5 all the other studies and we see reduction in
6 mortality, alone; reduction in death or MI, alone; MI,
7 revascularization. I don't know what more -- and an
8 80 percent reduction in hemorrhagic complications.

9 CHAIRMAN PACKER: So you don't even think
10 that that question is worth answering again?

11 DR. TOPOL: That question is resolved.

12 CHAIRMAN PACKER: That question is
13 resolved?

14 DR. TOPOL: That is relative to heparin,
15 bivalirudin in post-MI patients. It's highly
16 significant advantage, both with respect to ischemic
17 complications and bleeding.

18 CHAIRMAN PACKER: Eric, just to -- I just
19 want to say that our answer to Question 4 would
20 suggest the Committee disagrees with that.

21 DR. TOPOL: Yes, I have several
22 disagreements. That's one of them. But I think the

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1 one that we missed here is that the safety here --
2 well, totality of evidence, you know of all these
3 terms, these questions we saw for the first time this
4 morning, not conventional protocol by the way. But
5 the totality of evidence is across several trials, not
6 just bivalirudin versus heparin. We have MI, unstable
7 angina trials that were reviewed, but across all other
8 interventional cardiology trials. It's very unusual
9 to have the data bases to look at all these trials.
10 And to discuss it, there's not evidence of safety
11 advantage here. It's uncontrovertible. All the
12 studies. And what really is amazing is
13 anticoagulation for interventional cardiology will
14 stop here. This is it. There will never be another
15 trial if the rigidity and the lack of thinking,
16 flexibility is going to be somehow -- if you're not
17 going to say is this 4,000 patient trial or 4,000 with
18 over 6,000 patient data base with a 16,000
19 interventional cardiology data base, that's not
20 enough? What's going to be enough?

21 CHAIRMAN PACKER: Eric, we're not in the
22 position, nor would it be useful or desirable to

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1 debate that specific issue. Let me -- I do think we
2 do need to address the issue that you're asking. But
3 that is not the question that is before us. The
4 question that's before us is the approval based on the
5 present data base? We need to have a discussion after
6 the vote on this question on the issue that you're
7 talking about.

8 Okay, let's go through this and we'll
9 start the same way we started before.

10 John?

11 DR. DiMARCO: Maybe because I'm mostly a
12 clinical electrophysiologist I have a lower standard
13 for useful drugs.

14 (Laughter.)

15 DR. DiMARCO: I didn't see any evidence
16 that it's killed people and I actually would -- you
17 know, if I looked at this let me start with the
18 premise that I think I can accept that heparin is more
19 effective than placebo and I will accept that no one
20 will ever test that hypothesis. So I think that I'll
21 just take that as a given.

22 It looks to me that I see no evidence that

1 bivalirudin is much worse than heparin and possibly
2 some evidence that there may be some subgroups in whom
3 it's an advantage even though it's not very
4 convincing.

5 In terms of the safety, I see no evidence
6 that it's worse than heparin and again, some evidence
7 that requires some manipulation of data bases that it
8 may be safer and I am driven by the fact that there's
9 really no alternative to heparin. So I would vote for
10 approval.

11 CHAIRMAN PACKER: Ileana?

12 DR. PINA: I think that the way the
13 question is written, it's written for approval as an
14 anticoagulant in patients. It doesn't say superior to
15 heparin. It doesn't say inferior to heparin.

16 CHAIRMAN PACKER: No. It in fact -- none
17 of the subquestions even raise the possibility of
18 inferior. It's just is it approvable for the
19 indication being sought?

20 DR. PINA: Right. That's what I'm saying
21 and you know I think we have proof that it is an
22 anticoagulant and I think very interesting data about

1 the post-MI group, even though I share everybody's
2 concern about the smallness of the group, it was 15
3 percent and one trial, not both, but I think that
4 based exactly on what John said, I would vote for
5 approval.

6 CHAIRMAN PACKER: Marv?

7 DR. KONSTAM: I'm going to vote no and I'm
8 doing it reluctantly because I believe that this is an
9 effective anticoagulant and I believe that it probably
10 is safe and effective, but I don't think that it shows
11 that at the standard that I become used to expect on
12 this Committee.

13 I think that this was a program designed
14 to show that the agent was superior to heparin and
15 efficacy. It failed at doing that. So then what else
16 can we get out of it? Well, we would like to say at
17 least that it's equivalent. Statistically, it doesn't
18 quite make it. I believe that it's probably
19 equivalent or better, but belief just doesn't quite
20 get me there and this wasn't a program designed to
21 show its equivalence. I think such a program could be
22 designed.

1 In terms of the safety, I guess you can't
2 look at the safety and efficacy separately. You have
3 to look at safety in dose that you're sure is
4 equivalent or better. Even if we could get to that,
5 I'm still personally -- I do believe that as Eric
6 obviously feels very strongly and I agree with him
7 that in these protocols, Hirulog beat heparin in terms
8 of safety. There's no doubt about that. The concern
9 I have is that the regimen used in this protocol and
10 the way it was administered is different from the way
11 -- certainly the way we're going to use heparin and
12 PTCA today. It's just different. So I don't know
13 whether, if we saw a regimen of heparin that was more
14 standard, I'm not sure we would see that safety
15 benefit.

16 And so that leaves me with an encouraging
17 data set which does not quite meet the standard of
18 approval that I think we've been used to on this
19 Committee.

20 CHAIRMAN PACKER: Joann?

21 DR. LINDENFELD: Well, we've been through
22 all those questions and I think I understand the

1 statistics and I think this is one time when I just
2 wouldn't go with the statistics.

3 I think it's unlikely this drug is worse
4 than heparin. We have some data to suggest that it
5 might be a little bit better. It might be equal. I
6 just doubt very much that it's worse. And I agree
7 that the anticoagulation protocols may have affected
8 the difference, but I don't think that's the whole
9 difference. I think this is the safer drug. And I'm
10 impressed by the very low incidence of bleeding and
11 bleeding is a huge problem in those patients. And
12 this is a low incidence of bleeding with this drug.

13 So while some of the difference may be the
14 protocol, I doubt very much it is and I would vote to
15 approve this drug. I think we ought to have it to use
16 and to test with the 2B3A inhibitors and see. I think
17 this represents really a markedly improved safety.

18 CHAIRMAN PACKER: Lem?

19 DR. MOYE: We are in a position on this
20 Committee to demand that our decisions be evidenced
21 based. Now to some degree we are handicapped. We are
22 handcuffed by the absence of this policy, maybe 20 or

1 25 years ago. In fact, if they had such a policy
2 then, we would not be in a position now of -- or in
3 this quandary of trying to decide whether heparin is
4 superior to placebo or not. We'd have the answer to
5 that question.

6 Given the situation that -- given the
7 conditions today, we -- and given the fact that we do
8 not have this evidence of superiority of heparin, I
9 think in no way excuses us from demanding that our
10 decision today be evidence based. There is a model,
11 a workable model to demonstrate and workable I mean in
12 the design of an experiment, a workable model to
13 demonstrate that Hirulog is both safe and effective
14 compared to heparin. Unfortunately, the investigators
15 were not able to achieve that. They believed, I
16 think, that Hirulog would be shown to be superior to
17 heparin. The design of the trial to me, has the look
18 and feel of a superiority trial. They're looking for
19 33 percent efficacy. I'm surprised and chagrined to
20 see that they did not achieve that. And I think that
21 an attempt to look at that trial as being if it's not
22 positive, then it's negative and it shows equivalence

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1 is misleading. In fact, the trial is patently
2 noninformative. And I think that the finding of
3 improvement in the incidence of major bleeding is
4 important and it's promising. It does not meet the
5 standard of demonstrating safety and efficacy.

6 And I would resist the notion that since
7 we've made mistakes in the past by not demanding
8 efficacy data in an unblinded trial for heparin, that
9 we have to repeat that mistake by not demanding
10 evidence of superiority or at least firm evidence of
11 equivalence for Hirulog. So I would vote no approval.

12 CHAIRMAN PACKER: Udho?

13 DR. THADANI: I think looking at the
14 totality of the data I think there's a good
15 anticoagulant. I have not the problem with that.
16 Perhaps it might even have lesser bleeding, but since
17 I'm on the Committee and I have to weigh it on the
18 evidence shown I concur with a lot of Lem's comments
19 that the superiority claim was not met and if I'm
20 driven by Lem's comment also, there's no data that is
21 not going to be inferior equivalent. So if I put the
22 efficacy in it, realizing that perhaps it might be --

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1 it's probably safe, but that also could be somewhat
2 protocol driven, even if it was not. If indication is
3 PTCA in patients with unstable angina, I'm having a
4 hard time. If you are to ask me just to prove it's an
5 anticoagulant that would be a different issue, so I'm
6 going to vote no.

7 CHAIRMAN PACKER: You know, the Chairman's
8 vote never, hardly ever makes any difference on this
9 Committee because I guess I've established the policy
10 a long time ago that I was going to vote last and by
11 the time I get a chance to vote the evidence of what
12 the vote is going to be has already been fairly
13 determined and I usually don't get a chance to
14 actually make much of a difference. But I guess as I
15 tally the votes, this is the very first time I can
16 think of that my vote actually matters.

17 (Laughter.)

18 CHAIRMAN PACKER: And with that in mind,
19 sitting here and thinking about how I have thought
20 about these data from the moment I picked up this
21 package and the fact is that my gut feeling is as a
22 clinician, is that this drug probably works and it

1 probably works as an anticoagulant to do good things
2 for patients who have unstable angina in PTCA.

3 And when I look at the totality of data
4 that's my sense of what's going on. When I look at
5 the data base I think well, gee, what is this data
6 base? We have two trials designed to meet its primary
7 endpoint which didn't meet a primary endpoint, that
8 had a primary endpoint that the investigators don't
9 like anymore. Didn't necessarily have a total
10 ascertainment of events. There are lots and lots of
11 problems with these trials that we have discussed
12 today and I guess I'm personally convinced that there
13 probably is a difference in hemorrhagic risk, but I
14 don't know what the magnitude of that difference is
15 because I don't know if the heparin regimen is
16 clinically relevant in the present era.

17 My vote today is really primarily
18 determined by my concern about the way we make
19 decisions and I guess my own personal feeling is that
20 we are likely to see a whole host of applications that
21 come to us with claims of equivalence and that we need
22 to set a certain kind of standard as to what, how we

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1 would conclude that equivalence has been demonstrated.
2 And this comes close, but for me it's not sufficient.
3 It comes close, but I vote no.

4 Okay, we need to talk about other studies
5 that would be required. Any comments?

6 Marv?

7 DR. KONSTAM: Two things come immediately
8 to mind. One is to design an equivalence trial such
9 as Lem is discussing and really nail down that this is
10 at least as good as heparin. That's one way and the
11 other one is the post-MI which I think is a very neat
12 story if it proves way in a prospectively designed
13 trial, specifically done to address that. And those
14 are the two things that seem to come to mind.

15 CHAIRMAN PACKER: Comments? I guess what
16 you're talking about, Marv, is potentially a post-MI
17 trial using a more conventional heparin regimen versus
18 the proposed regimen of dosing of Hirulog and this
19 information, this suggestion is actually consistent
20 with the suggestion of the medical reviewer who also
21 suggested a post-MI confirmatory trial, to confirm the
22 subgroup analysis.

1 Any comments?

2 DR. THADANI: I think looking at the data
3 base that's the most driven and all those post-doc
4 analysts, maybe they'll get over the small sample size
5 if the true data is accurate, although it was
6 randomized, but randomization was to balance it, not
7 to prove the hypothesis, I think, is a hypothesis that
8 needs proving.

9 But that will be a very narrow indication
10 because post-infarct angina occurs in a small number
11 of patients. If they want a larger population which
12 I think they might win because safety is there, if
13 they were to do a trial designed with a larger sample
14 size, they might, then the Committee might feel more
15 comfortable that the indication they're getting is
16 real, so I won't say that they can't do a large trial.
17 The question is what sample size and that will be the
18 way to do it.

19 CHAIRMAN PACKER: Ileana?

20 DR. PINA: I'm intrigued by Eric's comment
21 that you can't get the drug to do an appropriate study
22 that you want to do. Why is that? Maybe I'm showing

1 naivete here.

2 DR. TOPOL: We've been trying to sort of
3 large scale trial as a sparing of 2B3A inhibition
4 because of working with a more efficacious safety
5 background. That 5,000 patient trial entitled CACHET
6 requires a pilot study and we haven't been able to get
7 the drug released for that pilot study, so it's as
8 simple as that.

9 But as far as additional studies, I mean
10 the complexities as far as heparin dose, what to do
11 with 2B3A inhibition, there are so many tiers of
12 complexity. I think the field of anticoagulation
13 interventional cardiology just hit the wall.

14 CHAIRMAN PACKER: They used to say that
15 about heart failure too.

16 DR. TOPOL: Yes.

17 CHAIRMAN PACKER: Can we clarify the
18 issue, Dr. Talarico? Do you want to comment?

19 DR. TALARICO: This is my question No. 2
20 where the Committee decided that the heparin was shown
21 to be noneffective.

22 CHAIRMAN PACKER: No, no, no. That is not

1 what the Committee said.

2 DR. TALARICO: That's what I asked again
3 and you said it was --

4 CHAIRMAN PACKER: The Committee simply
5 said that they did not think that the heparin had been
6 shown to be effective, which is a true statement.

7 DR. TALARICO: Okay, so no one accepted
8 the demonstration of the recommendation that would a
9 placebo have been --

10 CHAIRMAN PACKER: No, no, we're not saying
11 that placebo controlled trials should be done.

12 DR. TALARICO: No, I'm not saying that.

13 CHAIRMAN PACKER: We're simply saying that
14 heparin is the one -- one could in fact design trials
15 to either be better than heparin or define the
16 confidence intervals for equivalence to heparin much
17 better than has been done at this point in time.

18 DR. TALARICO: So the prospect that
19 heparin beats placebo is just on fate?

20 CHAIRMAN PACKER: The concept that heparin
21 is an effective agent is part of clinical practice and
22 not part of the clinical trials literature.

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1 DR. MEANWELL: Then I'd like clarification
2 from the Panel about two things. Number one, what is
3 the confidence interval for death, myocardial
4 infarction and revascularization you would look for
5 which is smaller than 1.07, I presume. And secondly,
6 are you looking in these trials, probably several
7 people in the audience have interest in this for a
8 death, MI endpoint in an intervention trial. If
9 that's the case, then we're going to be going for
10 10,000, 20,000 patients. It's just a straight
11 question.

12 The second question is -- which I think
13 everybody needs to know is what do you recommend is
14 the appropriate dose of heparin in PTCA to test
15 against, bearing in mind the high risk patients needs
16 more heparin?

17 CHAIRMAN PACKER: I don't know if anyone
18 wants to take that.

19 Lem?

20 DR. MOYE: I think I'll take the first
21 question. The first question I can address. I think
22 that the CAPRI model serves us well. I think in CAPRI

1 they were looking for equivalence between clopidogrel
2 and aspirin and therefore were interested in
3 demonstrating an efficacy on the order of about 10 or
4 12 percent. They were not able to demonstrate that,
5 but the sample size was large enough that they could
6 have resolved a small difference and therefore
7 conclude that clopidogrel was essentially equivalent
8 to aspirin.

9 Here, we cannot exclude just small
10 differences. We also have large differences which are
11 likely to have occurred in the population.

12 DR. MEANWELL: Then what was the 95
13 percent confidence interval on the CAPRI trial, do you
14 remember?

15 DR. MOYE: I am afraid I do not. That, I
16 don't know.

17 DR. MEANWELL: I'm not sure it was much
18 above, much below 1.07. That's my point.

19 DR. MOYE: But it's based on a larger
20 number of patients and in fact, it's not just an issue
21 of confidence interval. It's an issue of what you
22 believe is happening in the population and

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1 unfortunately this trial was not able to exclude large
2 differences in the population.

3 CHAIRMAN PACKER: Let me try and see if I
4 -- I think that I've gotten this from trying to get a
5 sense of everyone's opinion.

6 You have an extremely encouraging result
7 in the post-MI population. And my sense is that
8 you've got a point estimate of an effect that you are
9 likely to see if you were going to compare Hirulog to
10 heparin, it's a very intriguing result. It's a result
11 on a clinically relevant endpoint which is death plus
12 myocardial infarction.

13 You could beat heparin on that patient
14 population at an apparently extremely low risk of
15 hemorrhage easily determined because that was your --
16 not only most effective subgroup, but may be your
17 safest subgroup. A confirmatory trial in post-MI
18 patients, my sense is that Committee, this Committee
19 would find that to be persuasive. And I do not think
20 that such a trial need be large because in fact your
21 whole post-MI analysis, combined analysis is based, if
22 I remember correctly on 700 patients. And if your

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1 confidence intervals are as narrow as you claim them
2 to be, it would not be a major burden on anyone to do
3 a confirmatory trial in post-MI trial in patients in
4 700 or 1000 patients to show that you truly do have a
5 superior effect on clinical events because that's what
6 you suggest from your post-MI data base.

7 My personal feeling is that that doesn't
8 set the field of anticoagulation back. That sets --
9 if you confirm that, you set a standard for how these
10 kind of agents should be evaluated. You have a very
11 interesting intriguing hypothesis and you probably
12 should pursue confirmation of it.

13 Marv?

14 DR. KONSTAM: I just want to add to that
15 that you know to the extent that the finding of the MI
16 population is real and it may well be, it may be
17 telling us that in fact the key is a more unstable
18 population. I don't really believe this is an
19 unstable angina population. And so I think one could
20 take a chance that what this MI signal is telling us
21 is that this is going to be more effective than
22 heparin in the more unstable patients and redesign the

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1 trial with a slightly expanded population compared to
2 what Milt is saying and just say a real unstable
3 angina group, post-MI or more rigorously defined
4 population of unstable angina in order to achieve a
5 broader indication, but that would be taking some
6 chance.

7 CHAIRMAN PACKER: Udho?

8 DR. THADANI: Milton, I think I concur
9 with that because post-MI, you could take unstable
10 angina with ST depression which is again a very high
11 risk group. Thrombosis plays a major role in a lot of
12 those patients, so you could combine those two groups.
13 I will suggest in addition to death and MI to include
14 urgent revascularization because patient's arteries
15 are completely closing off or he goes back into the
16 unit and gets an ST elevation so I think you could, as
17 long as not elected PTCA or CABG, I think you can use
18 the event driven patients having tests and you're
19 forced to do it. So I think you could add that as an
20 end point too. So you could have three rather than
21 putting all revascularizations in this situation.

22 CHAIRMAN PACKER: Any other comments?

1 Okay, we are adjourned.

2 (Whereupon at 3:39 p.m., the meeting was
3 concluded.)

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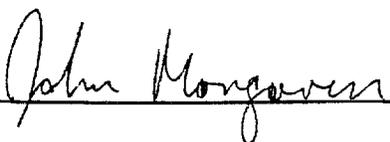
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