UNITED STATES OF AMERICA

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

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92nd MEETING

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THURSDAY
MAY 24, 2001

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The Committee met at 8:30 a.m. in the Jack Masur Auditorium, Building 10, Clinical Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland, Dr. Jeffrey Borer, Acting Chairman, presiding.

PRESENT:

JEFFREY BORER, M.D.	Acting Chairman
MICHAEL F. ARTMAN, M.D.	Member
RALPH D'AGOSTINO, PhD	Temporary Voting Member
ROBERT FENICHEL, M.D.	Temporary Voting Member
THOMAS FLEMING, PhD	Member
THOMAS GRABOYS, M.D.	Member
ALAN T. HIRSCH, M.D.	Member
MARVIN KONSTAM, M.D.	Temporary Voting Member
JOANN LINDENFELD, M.D.	Member
STEVEN NISSEN, M.D., FACC	Member
ILEANA PINA, M.D.	Member
JOAN C. STANDAERT	Executive Secretary

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Committee Reviewer: Dr. Thomas Fleming, PhD

FDA Invited Guests:

Dr. R. D'Agostino, Boston University

Dr. R. Fenichel, Washington, D.C.

Dr. M. Konstam, New England Medical Center

NIH Guest: Dr. B. Davis, University of Texas,
Director of ALLHAT Clinical Trials Center

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

2 (8:37 a.m.)

3 ACTING CHAIRMAN BORER: Good morning. I
4 would like to open the 92nd meeting of the
5 Cardiovascular and Renal Drugs Advisory Committee
6 today, Thursday, May 24th.
7 Before we open the meeting to public
8 comment, the Executive Secretary of the Committee will
9 read the conflict of interest statement.
10 MS. STANDAERT: The following announcement
11 addresses the issue of conflict of interest with
12 regard to this meeting and is made a part of the
13 record to preclude even the appearance of such at this
14 meeting.
15 Based on the submitted agenda for the
16 meeting and all financial interests reported by the
17 Committee participants, it has been determined that
18 all interests in firms regulated by the Center for
19 Drug Evaluation and Research present no potential for
20 an appearance of a conflict of interest at this
21 meeting, with the following exceptions.
22 In accordance with 18 U.S.C. 208(b)(3),
23 full waivers have been granted to Doctors Thomas
24 Fleming, Steve Nissen, Ralph D'Agostino, Robert
25 Fenichel, and Marvin Konstam, which permits them to

1 participate in all official matters concerning the
2 citizens' petition as it relates to Cardura and the
3 ALLHAT trial.
4 A copy of the waiver statement may be
5 obtained by submitting a written request to the
6 agency's Freedom of Information Office, Room 12A-30 of
7 the Parklawn Building.
8 In addition, Dr. Nissen's institution, the
9 Ohio State University's Cleveland Clinic, is involved
10 in unrelated studies sponsored by Pfizer. Dr. Nissen
11 has also presented lectures for Pfizer unrelated to
12 the product, competing products, or issues addressed
13 in the citizens' petition.
14 Dr. Fleming's institution, the University
15 of Washington's Department of Biostatistics, has
16 received an endowed student fellowship grant from
17 Pfizer.
18 Dr. Konstam's daughter has been offered a
19 summer internship from Pfizer to work on women's
20 health initiatives.
21 Although these interests do not constitute
22 financial interests in the particular matter within
23 the meaning of 18 U.S.C. 208, they could create the
24 appearance of a conflict. However, it has been
25 determined, notwithstanding these interests, that it

1 is in the agency's best interest to have Doctors
2 Fleming, Nissen and Konstam participate in the
3 Committee's discussions concerning the citizens'
4 petition as it relates to Cardura and the ALLHAT
5 trial.
6 In the event that the discussions involve
7 any other products or firms not already on the agenda
8 for which an FDA participant has a financial interest,
9 the participants are aware of the need to exclude
10 themselves from such involvement, and their exclusion
11 will be noted for the record.
12 With respect to FDA's invited guests, Dr.
13 Barry Davis has reported interests which we believe
14 should be made public to allow the participants to
15 objectively evaluate his comments.
16 Dr. Davis would like to disclose that he
17 serves as a consultant for Pfizer as a member of one
18 of their data safety monitoring boards, and for Tapp
19 Pharmaceuticals, a partnership of Abbott, on one of
20 their advisory committees.
21 With respect to all other participants, we
22 ask in the interest of fairness that they address any
23 current or previous financial involvement with any
24 firm whose products they may wish to comment upon.
25 That concludes the conflict of interest

1 statement.

2 I just also wish to make a correction to
3 those meeting dates which was distributed at the front
4 table. The meetings for the Cardiovascular and Renal
5 Drugs that have been proposed for the coming year are
6 August 9-10 and October 11-12, not the dates that were
7 indicated on that distribution. That is my final
8 statement. Thank you.

9 ACTING CHAIRMAN BORER: Thank you. This
10 morning the Cardio-Renal Advisory Committee is to
11 consider potential labeling changes for the drug
12 doxazosin, based on the currently available data from
13 the ALLHAT study.

14 It is a somewhat unusual circumstance for
15 us to be involved. As a result and because there are
16 so many people involved, I am going to have to be
17 certain that everyone understands that, if you are
18 going to speak, you are going to have to be recognized
19 by the Chair. We need to be sure that we can stay on
20 focus here.

21 For the Committee, during the initial
22 presentations, I hope we will limit our comments to
23 questions of clarification, but the questions from the
24 FDA should give us ample opportunity to discuss the
25 merits of the data and the inferences we can draw from

1 them.

2 The initial portion -- The meeting is open
3 for public comment, and we have two members of the
4 public who have requested time to speak, first Dr.
5 Sidney Wolfe who is the director of the Public Citizen
6 Health Research Group, and then Dr. Franz Messerli.
7 We will start with Dr. Wolfe.

8 DR. WOLFE: Thank you. In the spirit and,
9 I guess, law of full disclosure with respect to
10 financial conflict of interest, I would like to state
11 that we do not take any money from the pharmaceutical
12 industry and have not, and don't expect to.

13 You are being asked to recommend action to
14 the FDA based on a published analysis of the
15 Antihypertensive and Lipid Lowering treatment to
16 prevent Heart Attack Trial (ALLHAT). This trial
17 compared the alpha-blocker drug doxazosin (Cardura),
18 produced by Pfizer to the generically available and
19 much less expensive treatment chlorthalidone, a member
20 of the thiazide family of diuretics or "water pills"
21 for the control of high blood pressure.

22 I would just like to interject -- This is
23 not in the written statement -- that this trial was
24 designed to pick drugs that were typical of the
25 classes and findings, whether they were with respect

1 to diuretics or, in this case, alpha-blockers, I
2 believe, are applicable to the whole class. I think
3 that was the intention of the trial, not to come up
4 with conclusions that were limited only to
5 chlorthalidone but not to hyperchlorothiazide or,
6 conversely, only limited to doxazosin.
7 This analysis found that patients taking
8 Cardura were almost twice as likely as those on
9 chlorthalidone to be hospitalized for congestive heart
10 failure. The total incidence was actually twice as
11 high, had 25 percent more cardiovascular events, and
12 had a significantly elevated risk of stroke.
13 Patients who had originally been given
14 Cardura in the study greatly benefitted from being
15 taken off the drug in order to avoid the excess risks
16 of heart failure, stroke and other cardiovascular
17 events when the above results were made known in
18 January 2000.
19 Now almost 17 months later, thanks in part
20 to a massive misinformation and stonewalling campaign
21 by Pfizer, coupled with inadequate action by the FDA,
22 most of the hundreds of thousands of Americans still
23 using the drug have not had the advantage of stopping
24 Cardura and switching to other safer and usually less
25 expensive drugs such as diuretics and beta blockers.

1 Equally appalling is the likelihood that
2 many patients not previously on Cardura before the
3 results of ALLHAT were known have started using the
4 drug, despite the dire warnings of that study.
5 As physicians being asked by patients to
6 recommend drugs for the treatment of hypertension,
7 which affects me as well as the Advisory Committee and
8 many others, it would be highly unlikely for you or
9 for me, knowing what we now know, to recommend an
10 alpha blocker such as Cardura as a first choice drug.
11 The fact that it is still in the now
12 outdated JNC-6 listed as a first choice drug really
13 speaks to the fact that that has not been revisited
14 since this study came out. It is inevitable when the
15 next revision of JNC-6 occurs that this will no longer
16 be listed as a first choice drug.
17 More likely, we would relegate it to a
18 fourth or lower choice drug, only after adequate
19 trials of diuretics, beta blockers, or ACE inhibitors,
20 alone and in combination, had been tried without
21 success. If this is what we do for patients who
22 consult us, what can be done so that this evidence-
23 based prescribing decision will be made by other
24 physicians and their patients and that those already
25 on alpha blockers will be switched to other drugs?

1 The task at hand is for you to delineate
2 a series of actions which the FDA can take to maximize
3 the odds that few, if any, newly diagnosed
4 hypertensive patients are started on alpha blockers
5 such as Cardura and that most, if not all,
6 hypertensive patients now using such drugs are safely
7 switched to other agents.
8 One year ago in the May 2000 issue of our
9 monthly newsletter Worst Pills News, which is a
10 monthly update on our book Worst Pills, Best Pills, we
11 warned our 120,000 subscribers a year ago against the
12 use of Cardura and other alpha blockers, based on the
13 just published findings of the ALLHAT study.
14 The citizen petition that has been one of
15 the precipitating events for this hearing asks that:
16 (1) the FDA require Pfizer to notify all patients in
17 the U.S. who have taken or are taking Cardura to
18 control their blood pressure and that the FDA issue a
19 press release regarding the interim results of ALLHAT;
20 (2) that FDA require a boxed warning in the
21 professional product labeling or patient insert for
22 Cardura and its generic versions informing prescribers
23 of the ALLHAT interim results; and (3) that if deemed
24 necessary by the FDA, additional labeling changes for
25 Cardura that may include changes in approved uses,

1 warnings, precautions and contraindications.

2 We would add to that a number of things,

3 but one of which is that, although this arose in

4 litigation concerning doxazosin and Cardura, these

5 should be applicable to all the drugs in the class.

6 Public Citizen strongly supports the

7 fundamental intention of this petition to require

8 notification of physicians and patients of the ALLHAT

9 results, but although we support the principle behind

10 this petition, as it stands it will not achieve the

11 desired goal.

12 Therefore, we are urging the Committee to

13 make additional recommendations to the FDA such as a

14 mandatory FDA approved patient guide (Med Guide),

15 which FDA has the authority for, to be dispensed with

16 the drug. Before discussing the details of this and

17 other recommendations, we would like the Committee to

18 first consider Pfizer's role in stonewalling on the

19 ALLHAT results.

20 You have this in your file, and I will

21 just mention for about a minute some of the more

22 disturbing findings.

23 Pfizer contributed financially to the

24 ALLHAT study, ostensibly to answer an important

25 medical question: Which antihypertensive drugs are

1 the safest and most effective in producing clinically
2 meaningful outcomes for patients?
3 Pfizer did not like the answer, and the
4 petition's authors provide exquisite documentation of
5 corporate "damage control" to protect Cardura, one of
6 Pfizer's "Magnificent 7" drugs, a $800 million market.
7 The company's scripting of sales representatives'
8 elusive responses to ALLHAT questions, broken down by
9 which subspecialty the doctor was in, coupled with the
10 revelation that sales representatives were not
11 proactively discussing ALLHAT, is devoid of scientific
12 and medical ethics.
13 Because it is clear that Pfizer cannot be
14 relied upon to provide scientifically accurate, useful
15 information to patients or physicians, this Committee
16 and the FDA must take a much more proactive role to
17 ensure that medical professionals and the public
18 receive such drug information.
19 The first topic -- I'm just going through
20 the sequence of the possible ways -- and I say ways,
21 because I think all of them need to be used: FDA
22 press releases.
23 We support FDA's use of press releases or
24 public health advisories to inform the public
25 immediately about new drug safety warnings. However,

1 at the level of the individual patient, this method of
2 informing the public relies primarily on chance and is
3 available for only a short period of time. When you
4 take a look at how long articles, news articles,
5 appear after such a warning, not surprisingly, it
6 occurs for a while. It's a good first alert, but it
7 isn't sustained.
8 While serving as an initial alert, a
9 sustained effort to change the opinions of doctors and
10 patients must include permanent educational efforts
11 directed at both groups, as will be discussed.
12 Safety labeling changes: We agree with
13 the petitioners that a black box warning should be
14 required in the professional product labeling for
15 brand and generic versions of Cardura and, we would
16 add, all alpha blockers, alerting health professionals
17 of the ALLHAT results. However, we would like this
18 Committee to note that there is a growing body of
19 published evidence that safety labeling changes to a
20 drug's professional product labeling alone do not
21 protect a large proportion of patients from
22 preventable drug induced injury or death.
23 The concurrent use of the withdrawn
24 antihistamine terfenadine or Seldane with
25 contraindicated antibiotics and antifungal drugs

1 before and after safety labeling changes and the
2 issuing of "Dear Doctor" letters has been assessed in
3 several studies.
4 A retrospective review of computerized
5 pharmacy claims from a large New England health
6 insurer found that, despite significant declines
7 following reports of life threatening drug
8 interactions and additional warnings in the
9 professional product labeling, concurrent use of
10 terfenadine and contraindicated antibiotics and
11 antifungal drugs continued to occur.
12 In a couple of studies, about a third of
13 patients who were given, for the sake of the study,
14 prescriptions for both terfenadine and a
15 contraindicated drug had them filled, despite all of
16 this doctor and pharmacist directed publicity.
17 Using pharmacy claim data from 1988
18 through 1994 from state Medicaid programs in Michigan
19 and Ohio, it was found that the concomitant use of
20 ketoconazole and erythromycin with terfenadine had
21 fallen by 80 percent, but that means 20 percent still
22 doing it. IN a retrospective study of pharmacy
23 claims, it was found that co-prescription of
24 terfenadine with either erythromycin or ketoconazole
25 continued to occur after regulatory action.

1 The FDA reviewed reports of lactic
2 acidosis associated with the use of the diabetes drug
3 metformin (Glucophage) occurring from May 1995 through
4 June 1996, the drug's first year on the market in the
5 U.S. Of the 47 patients with a confirmed diagnosis of
6 the adverse drug reaction, 43 or 91 percent had one or
7 more risk factors for lactic acidosis that were listed
8 in the drug's professional product labeling at the
9 time of its approval.
10 Recently, the effect of the June 1998
11 regulatory actions in the form of a "Dear Doctor"
12 letter and additional safety labeling changes were
13 assessed on the contraindicated prescribing of
14 cisapride or Propulsid, which this Committee is very
15 familiar with. At one state Medicaid site surveyed
16 for the study, in the year prior to new warnings about
17 the drug, the use of cisapride was contraindicated in
18 60 percent of those for whom the drug was prescribed.
19 In the year after, the proportion of contraindicated
20 patients prescribed this drug had decreased to only 58
21 percent.
22 The authors of the study published
23 concluded: "The FDA's 1998 regulatory action
24 regarding cisapride use had no material effect on
25 contraindicated cisapride use. More effective ways to

1 communicate new information about drug safety are
2 needed."
3 We strongly agree with this conclusion,
4 particularly as it relates to providing effective
5 communication to patients. The FDA has had the
6 authority since June 1999 to mandate the distribution
7 of Medication Guides by pharmacists for five to ten
8 drugs per year that pose, quote, "a serious and
9 significant public health concern."
10 Cardura and the other alpha blockers
11 certainly fit this category when compared to
12 chlorthalidone for the treatment of hypertension.
13 So we get to this issue of medication
14 guides. The only way to ensure that patients using
15 Cardura are notified of the ALLHAT results is for the
16 FDA to require a Medication Guide for the drug that
17 reflects these results in non-technical language and
18 places the risks in a context that can be used by
19 patients.
20 Many people believe that, when you go to
21 a pharmacy to get a prescription filled, the piece of
22 paper you get is regulated. It is clearly
23 unregulated. It does not emanate from any FDA
24 approval process. It does not emanate from the
25 pharmaceutical company.

1 It emanates from a small number of
2 companies that generate through computer software
3 labeling for patients, which we have done a couple of
4 studies on two classes of drugs there and find there's
5 a lot of incomplete, misleading, out-of-date
6 information in them. So that's not what we are
7 talking about.
8 We are talking about an FDA approved
9 Medication Guide, which it has the authority to do.
10 It's interesting. Back about 20 years ago
11 when there was a lot of prescribing of progestins for
12 preventing miscarriage after the fall of the estrogens
13 -- those were prescribed. The required patient
14 labeling had an enormous effect not only on patient
15 behavior but on doctors, because the labeling which
16 patients were going to get, and the doctors knew this,
17 stated essentially this drug does not work to prevent
18 miscarriage; this drug may cause birth defects and so
19 forth.
20 The knowledge that the patient is going to
21 get something, as in the case of these drugs -- this
22 drug is the last recommended drug for hypertension,
23 and knowing that it was the first recommended drug by
24 a physician, I think, would have an enormous impact,
25 coupled with all of the other kinds of things we

1 discussed.

2 Additional labeling and Med Guide
3 requirements: Class labeling for the alpha blockers:
4 We also strongly suggest that the Advisory Committee
5 recommend to the FDA that the black box warning and
6 Med Guide developed for Cardura be the basis for a
7 warning for all alpha blockers -- also, the same is
8 true for the Med Guide -- marketed in the U.S.

9 This would include, in addition to Cardura
10 and its generic versions, prazosin or Minipress,
11 terozosin (Hytrin), and tamsulosin (Flomax).

12 Lastly, we also strongly suggest that the
13 Advisory Committee recommend to the FDA that all alpha
14 blockers approved by relegated, in labeling and
15 patient guides, to second, if not last or almost last,
16 line therapy for hypertension.

17 I have about two minutes left. I just
18 want to mention a couple of other things. One: In
19 looking again at the extraordinarily well done study
20 called ALLHAT, which I had not looked at for a few
21 months, I noticed that by the end of the four years of
22 the study, 47 percent of the patients originally
23 assigned to the doxazosin group, the alpha blocker
24 group, had received a step two or step three drug.

25 Since the analysis showing the very

1 striking differences in both heart failure and stroke
2 and a series of other cardiovascular diseases applied
3 to all the people in the trial, one conclusion from
4 that which I think will probably be discussed and
5 analyzed much further is that, not only are these
6 alpha blockers dangerous on their own, as in
7 comparison to chlorthalidone or possibly positively
8 dangers on their own, but even when they are used in
9 conjunction with other drugs which on their own, such
10 as beta blockers, have benefits, the net effects is
11 still a risk.
12 There will, hopefully, be before too long
13 a stratified analysis that looks at the comparison
14 between those that just at the end were taking
15 doxazosin compared with chlorthalidone and those who
16 at the end had been stepped up to other drugs.
17 Whether one wants to look at it that the alpha
18 blockers neutralize the beneficial effects of these
19 other step-up drugs or the other way around, the point
20 is that taken in combination with other drugs, which
21 would be a step use as opposed to a primary use for
22 alpha blockers, also seems to be dangerous.
23 I'd like to thank you for your time, and
24 hope that the Advisory Committee will seriously
25 consider the suggestions that we have made and the

1 suggestions that are in the petition.

2 I would be glad to try and answer any

3 questions.

4 ACTING CHAIRMAN BORER: Thank you very

5 much, Dr. Wolfe. Again, only if there are

6 clarifications here of statements. We don't really

7 want to get into a discussion of the merits of the

8 issue. I guess we are all set. Thank you very much.

9 The next speaker -- Oh, I'm sorry. I

10 announced that Dr. Messerli would be speaking, but

11 actually Edward Parr will be presenting Dr. Messerli's

12 comments.

13 MR. PARR: Good morning. I am an attorney

14 from New Orleans, and I am here today, actually, to

15 represent the petitioner. However, I have been asked

16 to read to you the comments which have been

17 voluntarily submitted to FDA in writing by Dr. Franz

18 Messerli of New Orleans.

19 Dr. Messerli is the Medical Director of

20 the Division of Research at the Alden-Oxner Foundation

21 Hospital, a practicing cardiologist at the Oxner

22 Clinic, a professor of cardiology at the Tulane

23 Medical School, and was a member of this Advisory

24 Committee from 1986 until 1990. His comments are as

25 follows:

1 To the Cardiovascular Drugs Advisory
2 Committee: The Food and Drug Administration has been
3 petitioned to revise the labeling of doxazosin. As a
4 former member of this Committee, I ask that you
5 consider the following comments as you formulate a
6 recommendation to the agency.
7 Congestive heart failure (CHF) is a common
8 outcome of hypertensive heart disease. In the
9 Framingham cohort more than 90 percent of patients
10 with CHF have a history of hypertension, and
11 longstanding hypertensive cardiovascular disease
12 invariably leads to CHF.
13 The prevention of CHF is, therefore, one
14 of the major therapeutic goals in the treatment of
15 hypertension. All major drug classes, diuretics, beta
16 blockers, ACE inhibitors and calcium antagonists, that
17 the Joint National Committee recommended for initial
18 therapy of hypertension have been shown to reduce the
19 risk of CHF when compared to placebo or active
20 therapy.
21 Until publication of the first results of
22 the ALLHAT study in March 2000, however, no such data
23 and no morbidity or mortality data were available for
24 the alpha blocker doxazosin, despite the fact that
25 this class of drugs has been promoted and used for the

1 treatment of hypertension for more than 20 years.

2 The data from the ALLHAT study published

3 over a year ago indicate the risk of CHF with

4 doxazosin is twice as high as in patients who are

5 treated with a simple diuretic. Similarly, in the V-

6 HEFT study, treatment with prazosin, another alpha

7 blocker, showed no benefit in patients with CHF.

8 In numerous drug company sponsored

9 symposia and journal supplements, alpha blockers have

10 been touted as being safer than other antihypertensive

11 drug classes, because alpha blockers not only lower

12 the pressure but had additional benefits in that they

13 improved insulin resistance and dyslipoproteinemia.

14 Physicians, therefore, have been under the

15 impression that these drugs were particular

16 efficacious for the prevention of hypertensive heart

17 disease, but data from the ALLHAT study attests to the

18 contrary.

19 This Committee will be asked to make a

20 recommendation to the FDA. I hope that you will agree

21 with me that changes to the labeling of doxazosin are

22 warranted.

23 Inasmuch as physicians have been subjected

24 to years of what, in retrospect, must be considered

25 misinformation, it seems only appropriate that they

1 now be made fully aware of the new findings through a
2 labeling change for doxazosin and possibly other alpha
3 blockers.
4 As I have stated in an invited editorial
5 in the Lancet, the revised labeling should state that
6 doxazosin, as opposed to other major drug classes,
7 should no longer be used as initial therapy for
8 hypertension and, in addition, doxazosin should be
9 contraindicated in patients with a history of CHF or
10 who are at risk for CHF. Sincerely yours, Franz H.
11 Messerli, M.D.
12 ACTING CHAIRMAN BORER: Thank you very
13 much, Mr. Parr. Again, are there any required
14 clarifications from the Committee? If not, thank you
15 very much.
16 Before we go on to the remainder of the
17 meeting, I received a communication from Dr. Philip
18 Hooper, Assistant Clinical Professor of Medicine,
19 University of Colorado Health Sciences Center, who
20 reports that he has recently published an hypothesis
21 on how Cardura might bring about an adverse event on
22 the heart. This is in a letter to the editor
23 published in the Journal of Human Hypertension 2001,
24 Volume 15, page 205. Copies of this are available at
25 the back desk.

1 Now we will move on to the presentation of
2 the petition and the information we will receive about
3 ALLHAT. Before we do, this Committee has been asked
4 by the FDA to provide an advisory opinion about
5 potential labeling changes for doxazosin. The
6 information that has been presented to us is unusual
7 for this Committee in that it really consists of a
8 published paper without the supporting data from a
9 trial that is still ongoing.
10 So the circumstances are somewhat unusual,
11 and I would like to take a minute to ask for a
12 statement about the specifics of the charge to us from
13 the FDA before we begin these proceedings.
14 Is Ray Lipicky here? Ray, can you make
15 some comments about specifically what kind of advice
16 you want, and how -- what form you want it in, and
17 what information you may have that would help us?
18 DR. LIPICKY: Well, I don't think this
19 meeting is different from other meetings in the sense
20 that what we want is an evaluation of the data that's
21 available, and whether or not you can draw
22 conclusions from the data that is available in order
23 to take some action.
24 As you know, we are sort of evidence
25 oriented, and we don't like to take actions when we

1 don't know what action we should take nor what the
2 basis for that action is.
3 So we've been asked to make a decision
4 from published materials. You have all of the
5 information that we have with one exception, which
6 I'll show, and we don't know anymore than you do. We
7 have not reviewed the subject, because it's not the
8 usual stuff that we have to review, and we will be
9 very interested in what you say.
10 The one thing that I can show for the sake
11 of orientation at the very beginning of the meeting is
12 data from the original doxazosin NDA which was
13 approved in 1990. This is the mean data from two
14 trials that were the major trials in that NDA.
15 I think you can easily see on the x-axis
16 the dose and on the y-axis the change from baseline
17 placebo corrected, and you see what the dose response
18 looks like. It looks like, when you get to 16
19 milligrams, it starts having -- it's going to take
20 off. So that anything below 16 milligrams is
21 basically not much drug.
22 Now as hard as we tried retrospectively
23 looking through the reviews of 1990, it isn't clear
24 that there are any dose limiting side effects. So
25 that it's unclear to us at the moment as to why the

1 dose wasn't -- a higher dose wasn't studied or how it
2 was settled that 16 milligrams was the top dose. But,
3 clearly, there is a dose response for both systolic
4 and diastolic blood pressure, and it does have
5 postural effects.
6 As best as we can tell from the reviews,
7 although the data that is presented in tables doesn't
8 support it, the principal concern was postural
9 hypotension, but the actual incidence of postural
10 hypotension didn't seem to be very dose dependent.
11 Now with that as a kind of background, I
12 think the process is, as usual, we have treated the
13 citizens' petition as sort of a sponsor. They are
14 hear. They will talk. They will interact, and they
15 will argue, the way in which it usually goes.
16 So that although it is unusual to have a
17 citizens' petition come to the FDA -- I mean come to
18 the Advisory Committee -- it seemed like this was
19 complicated enough that it was worthy of public
20 discussion with you.
21 Does that help you, Jeff?
22 ACTING CHAIRMAN BORER: I think so. Are
23 there, again, any clarification type questions from
24 members of the Committee? Thank you, Ray.
25 We will move on. This meeting -- Sorry,

1 Bob.

2 DR. TEMPLE: Just one point. We have

3 addressed in the document the use of published data

4 for which we don't have any back-up, and there's no

5 rule against it, for one thing.

6 A set of criteria are listed that include

7 such things as whether you know the protocol, whether

8 you know the details of how the study was done, the

9 persuasiveness of the people who did it, obviously a

10 highly subjective matter, multiplicity -- that is,

11 findings at more than one site -- and things like

12 that.

13 So it's not impossible to believe data,

14 even though you don't have the back-up, and rely on

15 it.

16 ACTING CHAIRMAN BORER: An important

17 point, and thank you for the clarification.

18 Okay. This meeting, as we have heard, is

19 called in response to a citizen's petition, and the

20 citizen petitioners will present a summary of that

21 petition, which we have just received a copy of. It's

22 a big petition. So the summary will be very helpful.

23 That will be presented, I believe -- introduced by

24 Salvatore Graziano of the law firm of Milberg Weiss

25 Bershad Hynes & Lerach, if I pronounced it properly;

1 and comments will be made by Dr. Lawrence Krakoff of
2 Englewood Hospital, who I believe is the Associate
3 Editor of the American Journal of Hypertension.
4 Mr. Graziano.
5 MR. GRAZIANO: Good morning. I am not
6 going to spend much time up here. I'm going to turn
7 it to Dr. Krakoff as soon as possible.
8 I want to thank the Committee and tell
9 the Committee that we very much appreciate the
10 opportunity to address the Committee this morning.
11 We also did distribute our citizens'
12 petition, and the compendium is very thick. So I just
13 want to take a minute a highlight some things in the
14 compendium very quickly.
15 There are 26 exhibits of documents, and
16 Tab Number 26, the last one, is an affidavit by Dr.
17 Curt Furberg where he is supporting the request that
18 we are making today. He was the Chairman of the
19 ALLHAT study.
20 Tabs 15 and 16 are some internal Pfizer
21 documents that we received from litigation discovery
22 that show that awareness of ALLHAT is minimal. Tab 13
23 is another Pfizer internal document obtained from
24 discovery that shows that in Pfizer's opinion limited
25 media coverage of ALLHAT's adverse results were a good

1 thing and, therefore, they decided to keep it that way
2 and not issue any response to the ALLHAT findings,
3 because there wasn't very much media coverage out
4 there.
5 Tab 23 is another internal Pfizer document
6 where they internally comment amongst themselves that
7 they were able to get a change in a clinical alert
8 issued by the American College of Cardiology after the
9 ALLHAT adverse results were first released.
10 Tab 12 is a good look at Pfizer's internal
11 sales force response to ALLHAT which was a dedicated
12 effort to make sure that the sales of this drug,
13 Cardura, continued after the ALLHAT findings.
14 Now I would like to introduce Dr. Krakoff
15 who is really going to focus on the data, and I think
16 that is what the Committee is most interested in
17 hearing about this morning.
18 DR. KRAKOFF: Thank you very much to Mr.
19 Chairman and members of the Committee for allowing me
20 to have the time to review this very serious issue.
21 I will use Powerpoint slides, and I hope the machinery
22 works so that I can refer to these. I guess, as you
23 can't usually see these, I'll wait a minute or two, if
24 anyone would like to be sure they can see the
25 material.

1 As you are doing that, my titles are given
2 here. I am Executive Editor of The American Journal
3 of Hypertension, past President of the American
4 Society of Hypertension, and regarding conflicts of
5 interest, at present on review of my involvement, I
6 have had an advisory but intermittent advisory
7 committees for the past two years for Merck, Novartis,
8 Bristol-Myers Squibb.
9 In the past I have been involved with
10 Pfizer some years ago with the development of
11 Procardio XL and other members of the pharmaceutical
12 industry in the distant past.
13 I speak to you today from several
14 perspectives: As a clinician who treats hypertensive
15 patients on a regular basis, as a chief of a hospital,
16 community hospital, affiliated with a medical school
17 which has a medical residency and a medical staff of
18 about 170 for whom I am the responsible officer with
19 regard to quality of care, process improvement, and
20 increasingly the issues of safety that arise in the
21 hospital setting. So it is really with that
22 background that I would like to proceed.
23 In addition, I did serve as a writer for
24 one of the sections of the Joint National Committee's
25 sixth report.

1 This summarizes -- This is verbatim with
2 my emphasis from the current Cardura package insert,
3 and I am going to come back to this point about the
4 use of Cardura for the indication of prostatic --
5 benign prostatic hyperplasia and the emphasis on
6 monotherapy, because this condition, as I am sure you
7 well know, is treated by primary care physicians as
8 well as urologists who may not be fully aware of the
9 characteristics of the patients that they treat.
10 Then the second indication for Cardura,
11 which has, so far as I know, been in its insert and
12 information provided to the PDR, for example, since
13 its approval is that it may be used alone as
14 monotherapy or in combination with other drugs for the
15 treatment of hypertension. This is unchanged, as far
16 as I know, since the drug was approved.
17 Now as someone who does have some
18 background in pharmacology as well as clinical
19 medicine, and returning, actually, to ten years ago or
20 15, whenever I first became aware of doxazosin, these
21 are the properties that it has and has had.
22 It is an alpha adrenergic receptor blocker
23 at post-synaptic sites. The initial hemodynamic
24 effects are to reduce systemic vascular resistance,
25 and there are some effects on serum lipids that have

1 been characterized. They are small, but they seem to
2 be reproducible, particularly a slight reduction in
3 LDL cholesterol.
4 It's a once-a-day drug, and in this sense
5 it is different from other members of the class, and
6 it has been shown in more recent studies since it was
7 originally approved for hypertension to reduce
8 symptoms of benign prostatic hypertrophy.
9 Then there are some mechanistic studies
10 that suggested that it improves sensitivity to
11 insulin, which would be a valuable property, and
12 possibly some effects on platelets in at least one
13 study I could find, which might be considered
14 beneficial as well.
15 In other words, on the drawing board in
16 theory it looks like it ought to be a very effective
17 drug and possibly going back in time it looked better
18 than others with regard to treatment of hypertension,
19 either by itself or in appropriate combination.
20 I am going to provide background here
21 which I think we all are familiar with, but since I
22 can't be sure of that, I think it's best if I put the
23 treatment of hypertension in its current context.
24 Why do we treat hypertension? Not to
25 lower blood pressure, but to prevent cardiovascular

1 disease. This includes stroke and the fatal and
2 nonfatal debilitating stroke, fatal and nonfatal
3 myocardial infarction, prevention of progression to
4 heart failure, and increasingly, as we see from other
5 studies, the ability to prevent admissions to the
6 hospital for cardiac surgery or for coronary
7 revascularization.
8 Peripheral vascular disease possibly is a
9 target of antihypertensive treatment, but the data is
10 certainly less clear.
11 In reviewing the history of
12 antihypertensive drug treatment, the first studies
13 were done with diuretics, hydralazine, reserpine and
14 methyldopa, and showed in the VA studies that the
15 treatment of very severe hypertension within a year
16 and a half resulted in a reduction of cerebral
17 hemorrhage, aortic aneurysm, and the progression to
18 malignant hypertension.
19 The concept was proven, certainly, by 1972
20 or '73. From the next 20 years a number of studies
21 were conducted. They have been evaluated in meta
22 analyses in middle-age patients with diastolic
23 hypertension, mostly 90 to 110 range, and showed that
24 in these patients antihypertensive therapy
25 predominantly based with diuretics, methyl dopa,

1 reserpine, and then beta blockers could prevent stroke
2 unequivocally, monotonously similarly from study to
3 study, could attenuate coronary heart disease in
4 middle-age patients. Heart failure was less a target.
5 It was less obvious in these studies.
6 In this period the two crucial studies
7 were addressed to hypertension in the elderly with
8 predominant or isolated systolic hypertension, the
9 SHEP trial conducted in this country by the National
10 Heart, Lung and Blood Institute using chlorthalidone
11 as its base therapy, and then SYST-EUR conducted in
12 Europe using nitrendapine, a calcium channel blocker
13 not available here.
14 Both of these showed high effectiveness in
15 reducing endpoints compared to placebo for stroke,
16 coronary heart disease, and in SHEP the prevention of
17 heart failure.
18 So this is where we have been, and I think
19 this is universally accepted by the academic medical
20 community and those who are leaders in the field of
21 treatment of hypertension, that antihypertensive
22 therapy is unequivocally effective.
23 What has changed has been the recognition
24 that different drug classes are really not known, and
25 there are some clues that some might be better than

1 others. So there is a focus on strategies in recent
2 years.
3 There is a focus on the older patients who
4 were excluded from some of the other trials because
5 their blood pressure wasn't high enough, but their
6 risk for cardiovascular disease is increased due to
7 diabetes or their lipid status or already present
8 target organ damage.
9 Many of these patients don't have very
10 high blood pressures. So we assume that
11 antihypertensive is therapy, and then it becomes a
12 matter of strategy and practice. What is the best
13 practice, and that is where ALLHAT was designed in the
14 early Nineties, I believe. I don't know when the
15 first steps were taken to design it, but it was really
16 designed to compare in high risk patients, the kind
17 that doctors see every day -- primary care doctors
18 treat on an hour-to-hour basis -- and look at the
19 different drug classes, because there has been real
20 question: Are the diuretics really the best base to
21 start from?
22 The new classes have never really been
23 tested in practice settings or in small studies that
24 really weren't designed to settle these issues. Then
25 the alpha blocker, doxazosin, which is similar in

1 duration of action to once-a-day drug and has these
2 promising properties, was included in the ALLHAT study
3 to settle these issues.
4 I bring the risk issue in, because in the
5 ALLHAT study the average entry blood pressure of
6 145/83-84 in the two groups were remarkably low, lower
7 than were the entry blood pressures of any of the
8 previous antihypertensive therapy trials. This is a
9 high risk group with minimal elevation of blood
10 pressure.
11 A study from a clinician's perspective and
12 from the perspective of one who teaches evidence based
13 medicine on a weekly basis to residents and students
14 and, to some extent, attending staff, is impressive.
15 This is a big study, 15,000 in the chlorthalidone arm,
16 9,000 in the doxazosin arm, conducted in medical
17 practices and clinics of the United States, really a
18 remarkable achievement.
19 It is randomized perspective. It is
20 massed or blinded. It is multi-site, and to my
21 knowledge the statistical approach and interpretation
22 is excellent based upon what I can interpret from
23 reading the study and also the individuals involved
24 with it. High percentage of follow-up, which is
25 crucial for such studies, and it is designed to answer

1 important questions that clinicians have been asking
2 really since 1985.
3 The size and the power of this study
4 should allow it to answer questions that couldn't
5 possibly have been definitively answered in small,
6 uncontrolled or limited studies of 16 weeks or six
7 months or with, say, 500-600 patients.
8 So from my view, ALLHAT meets the criteria
9 from evidence based medicine as a superbly conducted
10 clinical trial, and this is based on what I have read.
11 It seems to me -- and this is an opinion -- it is very
12 unlikely that any similar study can ever be conducted
13 again in this country at least, and possibly nowhere
14 else.
15 These are the major results that may be
16 elaborated on later, but they are published in the
17 JAMA article that came out a year ago, and indicate
18 that for coronary heart disease similar outcomes. For
19 stroke, a small .6 percent absolute difference in the
20 rates that were reported.
21 If you calculate the number needed to
22 treat, this represents one stroke prevented for every
23 160 patients treated. This is almost identical to the
24 calculation of number needed to treat that was made
25 for the ancient classic British MRC trial of treatment

1 of mild hypertension, not terribly high statistical
2 significance. It makes a low .05, but the direction
3 is in the right way, if you accept this, and the
4 difference is clinical significance, particularly
5 compared with an old trial for stroke reduction.
6 The combined cardiovascular disease
7 endpoints are shown here, and this is a much more
8 impressive picture, because the absolute numbers are
9 much greater, and the difference between the two of
10 about 3.5 percent suggest that the number needed to
11 treat would be about, I guess, about 25-30 patients to
12 prevent an event.
13 The events that are most prominent are
14 those for congestive heart failure, which is now well
15 known, about a 40-50 percent reduction, highly
16 significant; and then coronary revascularization,
17 which is one percent, but one in 50 if you calculate
18 the number needed to treat.
19 Coronary revascularization in a community
20 hospital that has a growing cardiac program with
21 cardiac surgery and coronary intervention is a real
22 issue. Someone who is admitted for coronary
23 revascularization is a patient who is in big trouble
24 and in jeopardy, and something we want to avoid. I
25 think it's an appropriate endpoint to be included in

1 a clinical trial at this point in time in this
2 country.
3 Was ALLHAT predictable? This is an
4 interesting thing. First of all, it wasn't obviously
5 predictable, because it would be unethical to do a
6 study in which it was clearly thought that one drug
7 would be worse than the others.
8 The previous studies of doxazosin were
9 small. They were narrowly focused, often on very low
10 risk patients, and I think they couldn't possibly
11 reveal real clinical differences, even summed up
12 together to predict that ALLHAT would have the results
13 it had. And, certainly, no, because the pharmacologic
14 profile for doxazosin certainly promised equal or
15 greater benefit compared to the diuretic, especially
16 if one looks at the small but statistically
17 significant effects on serum lipids.
18 So to my mind, when I heard about ALLHAT,
19 I was surprised. The results were unexpected, and I
20 think should be treated as any other unexpected and
21 harmful publication of harmful effect that wasn't, at
22 least in my mind, fully explained by the known actions
23 of the drug.
24 We have a treatment of hypertension that's
25 highly effective, a low dose diuretic therapy,

1 possibly other agents. But this was a surprise and,
2 I think, had to be treated as such, in a powerful
3 large study.
4 What happened to the message? After
5 presentation at the American College of Cardiology,
6 there was a publication that I became aware of in the
7 JAMA of 2000. No one sent it to me. Actually, I
8 picked it up from a copy of the JAMA that had been
9 mailed to me as usual, and I read it in the journal.
10 I began to analyze it and look at it very
11 carefully because of some writing that I am doing in
12 preparing some chapters for books on treatment of
13 hypertension and cardiovascular disease.
14 There were notices on these websites. I
15 don't know if they were reached or looked at. My
16 impression, and it's only that, is from colleagues,
17 that they didn't see these or were not aware of it.
18 Then there's Dr. Messerli's comment in the
19 Lancet which you heard, and then there is an article
20 by Dr. Witt in the Cleveland Clinic Journal
21 summarizing, basically describing the results of
22 ALLHAT.
23 I actually personally made an inquiry to
24 the Chair -- one of the Chairs of the Joint National
25 Committee asking would there be a response on the part

1 of the JNC, and as I have been involved with the
2 writing of the adverse drug portion, I thought this
3 was something we really should do. But I was told
4 that there wasn't any immediate plan to do that.
5 Then, as you are aware, there was no
6 information forthcoming from the Food and Drug
7 Administration or from the manufacturer by way of
8 Letter to Doctors or any change in labeling to the
9 present time.
10 I think there is -- One of the things
11 that, I think, bothers clinicians when something
12 appears that is unexpected is can I understand it?
13 What's the mechanism? It's puzzling that there isn't
14 an obvious mechanism for the differences, and I am
15 just going to briefly touch on these, not because they
16 are convincing but because they have come up in
17 discussion.
18 Do the differences in systolic pressure
19 between the groups explain the differences in outcome?
20 If so, the small difference of systolic blood pressure
21 of 3 millimeters of mercury or so between the groups
22 was not known to the treating doctors. They couldn't
23 detect it, because you cannot measure from visit to
24 visit a difference of 3 millimeters of systolic blood
25 pressure in any patient.

1 It is a variable pressure, and the most
2 you can probably pick up is 10-15 millimeters of
3 difference from visit to visit. So the doctors can't
4 detect this.
5 Are there differences in compliance? I'm
6 not sure why there should be, but if so, then failure
7 to comply is something that really concerns us, and
8 any drug that shows that it can't be complied with is
9 a less good drug to treat hypertension. So this, in
10 and of itself, is a worry.
11 If the explanation is unmasking of latent
12 congestive heart failure who are people at entry
13 because somehow they were withdrawn from effective
14 treatment, how would the doctors know this? How would
15 a primary care physician know this? How would a
16 urologist know this?
17 This is another safety issue, as far as I
18 am concerned. You need to know a lot more about
19 treating the hypertensive patient than is normally
20 done in the usual work-up that is advised by our same
21 guidelines.
22 Tachyphylaxis or tolerance appeared with
23 prazosin in heart failure studies years ago, and if
24 that is the basis for this explanation, then again
25 this indicates that doxazosin is ineffective in a

1 target population where it ought to be beneficial.

2 Recent changes in the strategy for

3 treatment of hypertension, I think, have to be

4 emphasized here. The JNC-6, now three or four years

5 old, is not about to be immediately changed based on

6 what I have been told. JNC-7 is not in press. There

7 isn't any JNC-7 at present.

8 There is greater emphasis on drug

9 treatment of higher risk patients, stages 2-3 of B,

10 and all of C in the JNC classification. These are in

11 general. There's emphasis on treating older patients

12 with drugs, those who have other risk factors, and

13 target organ damage, in other words, those like the

14 ALLHAT recruitment cohort.

15 Goals to treat hypertension have dropped.

16 There's emphasis on greater reduction of blood

17 pressure to less than 140 systolic, more use of drugs

18 to lower drug pressure, and in target groups such as

19 diabetics. The aim is to get near to normal, and this

20 is not universally accepted, but there's certainly --

21 This is in print and recommended by many in the field.

22 So the overall attempt is to increase the

23 fraction of hypertensive who are on treatment to start

24 at lower pressures than ever before and get to even

25 lower blood pressures on treatment. It's an

1 aggressive approach.

2 The consequences of this will be, one
3 hopes, in a sense, more intensive drug treatment with
4 those who have minimal hypertension, slight
5 elevations, but who are at high risk for other
6 reasons, and it is not at all clear for these patients
7 that small differences in blood pressure between
8 treatments are really going to be the basis of
9 outcome.

10 Instead, if it looks like that the either
11 beneficial or adverse effects of drugs in treating
12 these kinds of hypertensive patients will emerge, the
13 other actions of the drugs will, in fact, determine
14 the event rate, the outcomes. And as we have seen
15 from the HOPE trial with ramipril and, I think, with
16 doxazosin with the ALLHAT study, this is exactly, I
17 think, where the other actions of the drug, known or
18 unknown, that affect cardiovascular disease emerge.

19 So from my view as a clinician and one
20 responsible for the training and supervision of other
21 doctors, I think there must be a warning. It is
22 certainly not too late, because Cardura is widely
23 available, and it's still recommended that it be used
24 alone in the package insert.

25 So I don't think that it is at all too

1 late to issue a warning, and I am convinced, based on
2 a polling of my own staff within the past few days,
3 that many physicians are not aware of ALLHAT, are not
4 aware of the potential danger of doxazosin where it
5 might be dangerous.
6 So I would request that all providers be
7 sent a letter with a summary of the ALLHAT results
8 indicating that the use of doxazosin alone is only to
9 be considered as an add-on -- that is, a Step 2 or 3
10 drug -- in selected individual cases, indicating that
11 there is a risk of congestive heart failure and
12 possibly other cardiovascular disease endpoints in
13 predisposed patients as defined by ALLHAT entry
14 characteristics, and then leave it to the doctors as
15 to if they need to know more about the patients for
16 considering this choice.
17 I think, certainly, the labeling ought to
18 be changed, because -- and it should include that in
19 a large and well conducted, randomized clinical trial,
20 that use of doxazosin was associated with a
21 significantly worse outcome compared to the diuretic
22 treatment.
23 I would personally favor prohibiting
24 monotherapy with doxazosin in any high risk patient,
25 irrespective of blood pressure, and this undoubtedly

1 will include some of those who have benign prostatic
2 hypertrophy, and emphasizing the need for knowing more
3 about these patients before considering doxazosin as
4 part of the treatment.
5 I conclude with: This is a safety issue,
6 and I ask you to do the right thing. Thank you.
7 ACTING CHAIRMAN BORER: Thank you very
8 much, Dr. Krakoff. Once again, do we have questions
9 about Dr. Krakoff's statements for clarification
10 purposes? Ileana?
11 DR. PINA: Thank you for your
12 presentation. I don't have any data in front of me
13 about those early trials like the VA cooperative trial
14 back in the late Sixties and some of the trials in the
15 Seventies.
16 What was the age group in that era of
17 trials? You said that a lot of the older patients
18 were excluded. Is there an age difference in all
19 these trials that we are looking at?
20 DR. KRAKOFF: I don't remember the exact
21 age of the VA initial study, which really was a study
22 of about 200 patients. Most were middle-aged. I
23 don't recall the exact age range.
24 In the large HGFP trial conducted in this
25 country, the age range actually, I think, was from the

1 mid-thirties to 70. Below age 50, actually, no
2 benefit of antihypertensive treatment could be shown.
3 The design of that study was usual care versus special
4 clinics, so aggressive antihypertensive therapy versus
5 relatively little antihypertensive therapy.
6 For those patients age 50 to 70, there was
7 an unequivocal, clear difference in the outcomes. So
8 the average age, I think, was in the late fifties or
9 early sixties, and this is also true of the British
10 MRC trial that I mentioned.
11 Older patients are excluded for many
12 reasons, not necessarily because they were older, in
13 some cases I think above age 75 or 80. I don't
14 remember the details of each one, but largely because
15 of concurrent disease or risk factors. So that it's
16 not just the age alone, but rather the mix of patients
17 who were kept out of the trials.
18 DR. KONSTAM: That was a great
19 presentation. Could we ask you to reflect a little
20 bit more deeply on this 3 millimeter mercury thing,
21 because the way you indicated it, if I interpret your
22 remarks, was that, okay, but if that's the reason,
23 then it doesn't matter because the doctor can't
24 distinguish the 3 millimeters of mercury anyway.
25 I guess I would challenge that in the

1 sense that the 3 millimeters isn't 3 millimeters of
2 mercury across 9,000 patients. It's an average. So
3 there's some patients who are substantially out of
4 control contributing to that mean 3 millimeters of
5 mercury.
6 Then thinking about that and reflecting
7 on, you know, Ray's comments about the fact that I
8 guess the dose was capped at 8 milligrams, 16
9 milligrams seems more effective. So could you go with
10 that? I mean, is it really clear that if you didn't
11 go ahead and get the blood pressure down a little bit
12 that some of these things wouldn't have gone away?
13 DR. KRAKOFF: Well, I think that's a
14 central question in a sense, and it can be interpreted
15 different ways, and there are different points of view
16 about these small differences in systolic blood
17 pressure. How many had large reductions in pressure,
18 and how many had modest reductions in blood pressure?
19 The physicians in the study and the nurse
20 clinicians who conducted the study were given the same
21 instructions across the whole study. They were
22 blinded, and they went by the blood pressures and
23 their titrations.
24 So does this mean that it's more difficult
25 in the clinic setting actually to know whether there

1 is control with one drug versus another, as one
2 possibility, or -- I mean, it's very difficult to
3 explain, because these are group differences across
4 9,000 plus 15,000, and it tells us nothing about the
5 composition of the changes within the groups.
6 That might be interesting, but for the
7 clinician it's not going to show up on their screen.
8 The dosage issue -- This is an impression.
9 I don't have data on the use of Cardura by physicians.
10 My impression is that there are very few physicians
11 who used anything above 4 milligrams of Cardura before
12 they added or changed, and 8 milligrams which even
13 then is somewhat unusual for treating hypertension,
14 and that many physicians -- looking at charts,
15 including my own -- would just simply figure that if
16 you didn't get much of a response by the time you got
17 to 4 to 8 milligrams once a day, you were going to add
18 or switch.
19 DR. KONSTAM: Okay, but just to follow on
20 that: But then the message might be different,
21 because if the underlying premise of ALLHAT is that at
22 comparable reduction in blood pressure, you know, what
23 is the differential effects on endpoints? And if
24 there was not comparable effect on blood pressure,
25 well, maybe the message would then have to be, well,

1 you need to do a better job to control blood pressure,
2 as opposed to saying that at comparable reductions in
3 blood pressure, there are differences in these
4 different drugs.
5 DR. KRAKOFF: I am not sure that the
6 question was asked exactly that way. I think it was
7 thought, and the designers would have to speak to
8 this, that this is a trial of reduction of
9 cardiovascular risk. In a target population defined
10 as high risk, the question is does one treatment do a
11 better job than another as a starting point of the
12 four drugs that were at the start of the race, as it
13 were.
14 I don't think the question could be asked
15 with precision, can you really do this at equal -- to
16 get everybody to the same blood pressure level? One,
17 the variance of individual blood pressures makes that
18 almost impossible to do. You know, blood pressures
19 measure much less accurately than many other things
20 such as serum cholesterol, for example.
21 So I think the issue was -- and ALLHAT is
22 a study in practices -- what is the best way within a
23 high risk group who are defined as hypertensive in a
24 certain way, including being on treatment -- the best
25 way to reduce cardiovascular disease, and hope that

1 the groups -- You know, perhaps it was a thought, they
2 will come out very close to being similar. They can't
3 be identical, but then who does best?
4 ACTING CHAIRMAN BORER: Yes, Steve?
5 DR. NISSEN: I wonder if you could help
6 me. I can't find anywhere in here, what was the mean
7 dose of doxazosin used, and what was the mean dose of
8 chlorthalidone used?
9 ACTING CHAIRMAN BORER: Excuse me. Before
10 you answer that, Dr. Krakoff, I think that the people
11 who actually did the study probably would be in a
12 better position than Dr. Krakoff to respond to those
13 specific questions. So maybe we could hold that stuff
14 until we get the NIH presentation. But are there
15 particular issues that anyone -- particular questions
16 of clarification that we want to direct to Dr.
17 Krakoff? Bob?
18 DR. TEMPLE: Larry, I think I might
19 understand your view of this. But can you say
20 something about the distinction between initial
21 therapy, which after all was what was studied, and the
22 use as an add-on.
23 Whether you think the results reflect,
24 well, the absence of a benefit or something else
25 adverse really matters a lot. So my question is what

1 do you think the best explanation here might be? Is
2 it the absence of a favorable effect in heart failure,
3 which you could also deduce from V-HEFT, I suppose,
4 for the class, in which case adding the therapy on
5 might not be a worrisome thing, or do you think it's
6 more likely that something harmful is going on here?
7 I admit, you don't have full data. I'm
8 asking for impression.
9 DR. KRAKOFF: Well, I would like to, I
10 think, read that letter that was sent by someone who
11 offers a hypothesis about what might account for a
12 possible harmful effect of doxazosin.
13 What I said was -- and this is really a
14 speculation. The outcomes speaks for itself. These
15 patients were started with one drug class, and then
16 other drugs were added along the way. The duration of
17 their initial exposure to whatever they were assigned
18 to is something that people who have the actual data
19 can speak to.
20 I would have to suggest that in a high
21 risk, hypertensive population there is an underlying,
22 as I suggested, latent heart failure component who
23 people are unaware of it. If they were aware of it,
24 they would have been kept out of the study, and that
25 the treatment perhaps exposed those individuals

1 because of the ineffectiveness, the tolerance issue or
2 tachyphylaxis issue for doxazosin.
3 That is the best hypothesis I can offer.
4 As I said, this is an unexpected finding, and to me it
5 has to be -- and it resulted in a lot of disease, and
6 I think that's the way it should be seen.
7 ACTING CHAIRMAN BORER: Okay. Maybe we
8 can move on to the NIH presentation of ALLHAT, because
9 I think we are beginning to get into the questions
10 now, and first we ought to hear the data.
11 The presentation will be by Dr. Jeffrey
12 Cutler, the Director of Clinical Application and
13 Prevention Program at the NHLBI.
14 DR. CUTLER: Thank you. As the Chairman
15 just said, you've already heard quite a lot about the
16 ALLHAT data, and certainly the Committee has an
17 opportunity to read a lot. So I'll try to concisely
18 summarize the data that was associated with the
19 termination of the doxazosin arm early last year.
20 There are only two of my slides that are
21 not strictly represented in what's in the paper. Just
22 by way of introduction, I am a physician at the
23 National Heart, Lung and Blood Institute. I have been
24 there since 1981, mostly involved in management and
25 oversight of randomized clinical trials,

1 cardiovascular disease, particularly hypertension.

2 I'll just wait a second for the slides to

3 start. I apologize for turning the Committee around

4 again.

5 As already stated, these data were first

6 presented at the American College of Cardiology a year

7 ago March, and then published in April in the JAMA.

8 The remainder of the trial is continuing through next

9 year.

10 The close-out process for the remainder of

11 the trial begins in October, and in the process of

12 closing -- of continuing the trial and closing it

13 down, there is additional accumulation of late

14 reported events that occurred before the February 15,

15 2000, cutoff for this portion of the trial.

16 The members of the Steering Committee at

17 the time the results were reported are shown here.

18 The numbers in parentheses simply represent which of

19 the nine ALLHAT regions the particular member of the

20 Steering Committee is responsible for in terms of

21 field monitoring and such.

22 Patients were recruited, treated and

23 followed at 625 clinical sites which were located in

24 47 U.S. states, the Caribbean, Puerto Rico, and U.S.

25 Virgin Islands and eastern Canada.

1 The settings are quite diverse, ranging
2 from a few academic centers all the way to some rural
3 general practices, including some 60-plus VA medical
4 centers, and all of this necessitated -- All of this
5 diversity of the sites necessitated following a large
6 simple trial model.
7 For example, the follow-up form -- The
8 routine follow-up form has only four pages of data.
9 This approach to the trial -- This practiced based
10 approach was required in order to enroll the sample
11 size that was aimed at as 40,000 patients, in the
12 implementation was actually 42,500, older hypertensive
13 patients with at least one additional cardiovascular
14 risk factor.
15 The trial was designed to compare diuretic
16 based regimen with each of three other regiments based
17 on representatives of three other drug classes, and
18 I'll show you that in a minute, for their effects
19 primarily on coronary heart disease. It was a double
20 blind, active controlled trial.
21 This shows the specific arms, the four
22 randomized groups, which included chlorthalidone as
23 the control group at a dose of 12.5-25 milligrams per
24 day, amlodipine, lisinopril and doxazosin, as you've
25 heard, dose of 2-8 milligrams per day. One of the

1 titrations in the chlorthalidone group was actually a
2 sham titration from 12.5 to 12.5, and then the third
3 dose being 25.
4 The planned follow-up period was four to
5 eight years with an average of six. The design also
6 includes a sub-randomization to a lipid lowering trial
7 which was pravastatin versus usual care with an all-
8 cause mortality endpoint. There were about 10,500
9 patients in that portion of the trial, and I won't say
10 anymore about that today.
11 Among a list of hypothesized secondary
12 outcome questions, the four listed here are, of
13 course, total mortality plus the three main
14 cardiovascular secondary outcomes, the most inclusive
15 of which was combined cardiovascular disease which
16 included an expanded coronary endpoint that
17 encompassed revascularization and angina, stroke,
18 lower extremity arterial disease involving
19 hospitalization or revascularization, angina treated
20 either in hospital or as an outpatient, and heart
21 failure, fatal, hospitalized or treated as an
22 outpatient.
23 In terms of blood pressure eligibility,
24 just to summarize this somewhat complicated slide,
25 most patients came in with previous treatment for two

1 months or greater and under eligibility criteria that
2 had no lower level of blood pressure and had a maximum
3 level at the screening visit of 160/110 on one to two
4 drugs.
5 The aim here was to get patients in who
6 would be relatively easy to control to maximize the
7 separation of the three arms in terms of drug regiment
8 required. If patients were newly treated or
9 untreated, they basically fell within JNC Stages 1 and
10 Two.
11 Among a variety of exclusion criteria, I
12 just wanted to mention specifically that symptomatic
13 heart failure or, if known -- not symptomatically
14 sought but, if known, low ejection fraction were
15 reasons for exclusion.
16 Summarizing some of the main baseline
17 characteristics, a longer table is in the paper: First
18 of all, the sample size. The chlorthalidone arm was
19 allocated 70 percent more patients in order to
20 optimize power in a four-arm trial. In terms of
21 baseline blood pressure, it was given those
22 eligibility criteria in the fact that 90 percent of
23 the patients came in on previous treatment. They were
24 relatively low, 146/84. Average age, in the mid-
25 sixties.

1 About one-third of the patients were
2 black. The intent of the trial was to try to over-
3 recruit blacks into this hypertension treatment trial.
4 About half women, and about a third, importantly,
5 diabetics, an increasingly important high risk group.
6 With regard to maintenance on assigned
7 drug, this slide summarizes the data. Toward the
8 later part of follow-up for the diuretic group, about
9 86 percent of those coming in for visits were
10 maintained on the assigned drug, and for doxazosin
11 group it was about ten percent lower. This was in
12 spite of greater use of step-up treatment in the
13 doxazosin group.
14 The blood pressure data have been
15 mentioned. Diastolics, as shown in the paper, were
16 identical in the two groups, and the systolic blood
17 pressure during the first 12 to 18 months was about 3
18 millimeters higher in the doxazosin group, and for the
19 remainder of the trial was about 2 millimeters higher.
20 Other intermediate endpoints that were
21 measured were biochemical. The expected more
22 favorable effect on serum cholesterol was seen in the
23 doxazosin group, about a five percent difference.
24 Cholesterol declined in both groups, partly because
25 about one-eighth of the cohort were actually

1 randomized to Pravastatin. So that affected the mean
2 levels.
3 Fasting serum glucose: A slight rise in
4 the chlorthalidone group, which tended to come back
5 toward baseline, and a slight fall in the doxazosin
6 group. This difference is about three or four
7 percent.
8 Now going to the endpoints and the
9 decision to terminate the arm, this decision was made
10 in January by the Institute following external
11 reviews, and it was based on two criteria. The crux
12 of the rationale: First of all, there was a futility
13 criteria written into the stopping guidelines, and if
14 there was, certainly, a comparison for the primary
15 coronary outcome met that criterion in that the
16 conditional power for finding a protocol specified 16
17 percent difference was about one percent at the time
18 it was stopped.
19 The second part of the rationale was this
20 25 percent higher rate of a pre-specified secondary
21 endpoint, combined cardiovascular disease. So now
22 I'll elaborate a bit on both of these aspects.
23 First for the primary endpoint, the curves
24 pretty much stayed on top of each other throughout
25 follow-up. Relative risk, relative hazard was

1 estimated as 1.03, and there was a little bit of a
2 separation during years two and three, but they came
3 back together. If you need a reason for those minor
4 fluctuations, it could represent the increasing
5 crossover, particularly from doxazosin to diuretic
6 that occurred later on follow-up.
7 The expanded coronary endpoint that
8 include hospitalized angina and coronary
9 revascularization did show a marginal difference, a
10 ten percent higher rate in the doxazosin group with a
11 P equal to .05. That's in the paper.
12 This is the combined cardiovascular
13 disease endpoint. As I mentioned, it was
14 prespecified. It had a p-value corresponding to about
15 10 or 11 zeroes. So this is a compressed p-value.
16 And as was mentioned, the absolute difference here was
17 about one percent per year, relative risk 1.25.
18 One of the major components of combined
19 cardiovascular disease but also prespecified as a
20 secondary endpoint was stroke, about a 19 percent
21 higher rate in the doxazosin group, separated early
22 and stayed -- appeared to continue to separate through
23 follow-up, p-value of .04.
24 Now from meta analyses of trials of blood
25 pressure lowering in a general hypertensive

1 population, not high risk as in this trial, a 3
2 millimeters difference in systolic blood pressure
3 could be expected to produce about a 10-15 percent
4 effect on stroke risk. So this is certainly within
5 the range of what might be expected from the blood
6 pressure difference that was seen based on external
7 evidence.
8 The combined cardiovascular disease
9 endpoint was, as you know, substantially driven by
10 heart failure. These are the curves. They separated
11 early, but also did continue to slowly separate
12 throughout follow-up, twice the risk in the congestive
13 heart failure in the doxazosin group.
14 This difference was first noted during
15 monitoring after the Data Monitoring Board asked us to
16 disaggregate the combined cardiovascular disease
17 endpoint. It was also seen for hospitalized and fatal
18 heart failure looked at separately, with a relative
19 risk of about 1.8.
20 Now with due regard for heart failure
21 being a softer than certain other cardiovascular
22 endpoints, at the request of the Data Monitoring Board
23 we did conduct further analyses and attempt to
24 validate the endpoint.
25 Remembering that ALLHAT is a large simple

1 trial, did not have routine central adjudication of
2 major endpoints, there was a ten percent sample of
3 coronary events and strokes reviewed centrally. Heart
4 failure initially was not reviewed centrally, but a
5 sample was selected after this difference began to
6 emerge and reviewed blindly by the Trial Endpoints
7 Committee based on the hospital discharge data of
8 those events.
9 That review showed that, by and large, the
10 investigators were using the prespecified heart
11 failure criteria in their diagnoses.
12 A second thing that was looked at had to
13 do with -- Sorry, forgot to advance the slide. The
14 first point, I just made. The second point is that,
15 based on a 50 percent sample of discharge summaries we
16 reviewed at the coordinating center for ejection
17 fraction data, and where those data were given in the
18 discharge summary, two-thirds of participants
19 diagnosed with heart failure in both groups had
20 ejection fractions of 40 percent or less.
21 What was also looked at was drug treatment
22 following the heart failure diagnosis based on routine
23 follow-up forms and, by and large, the frequency of
24 use of open-label diuretics, ACE inhibitors and beta
25 blockers post-diagnosis were consistent with practice

1 and recommendations in the community. So the docs
2 were treating this as if it were real heart failure.
3 Finally and probably most importantly,
4 following the diagnosis of heart failure in the
5 hospital, subsequent mortality, case fatality rates,
6 as it were, for these participants was high. It was
7 20 percent over a three-year period, and it was
8 similar in both groups.
9 This plot just subtracts out of the
10 combined cardiovascular disease the heart failure,
11 just to show you that indeed for the residual part of
12 that endpoint -- and this is not a prespecified
13 analysis, clearly, but there was a significant effect,
14 a significant difference, once you exclude heart
15 failure.
16 Then for completeness, all-cause
17 mortality: There was no difference. This is pretty
18 much tracking together throughout follow-up. In terms
19 of why the cardiovascular difference, morbidity
20 difference was not translated into mortality
21 difference. I guess I can only say that perhaps
22 follow-up did not go long enough to see that.
23 Numerically, the trend in favor of the
24 diuretic for cardiovascular mortality was
25 approximately offset by a trend in favor of the alpha

1 blocker in terms of cancer mortality. But that's what
2 the data show. We haven't published class-specific
3 mortality yet, but that's the description.
4 So in conclusion, this tracks what we said
5 in the paper with regard to the overall results. In
6 patients such as in ALLHAT who are older patients with
7 additional risk factors, it appears that
8 chlorthalidone is superior for first line treatment of
9 hypertension because of greater drug compliance,
10 better hypertension control, and occurrence of some
11 chiefly heart failure and stroke cardiovascular
12 events.
13 There was no evidence of a differential
14 effect on major CHD, though angina related events,
15 including revascularization, tended to be more
16 frequent in the doxazosin group. Thank you. I'll be
17 glad to answer questions.
18 ACTING CHAIRMAN BORER: Thank you very
19 much, Dr. Cutler. That was really an extraordinarily
20 clear presentation of the data, and it is very
21 helpful.
22 I want to begin by asking a question that
23 may not be relevant to our deliberations today, but I
24 didn't quite understand it. Perhaps you can tell me
25 something about it.

1 In the paper there was a mention of the
2 DSMB, and then there was a discussion of independent
3 reviews. But a clear distinction between them wasn't
4 made, and other information we received -- I believe
5 I'm correct here -- that the DSMB did not vote to stop
6 the trial, and then a second independent committee was
7 empaneled, and did.
8 Do I have that right?
9 DR. CUTLER: That is correct. The DSMB,
10 more or less, split down the middle with regard to
11 continuation or stopping, which, in our view, just
12 sort of presented the Institute with an untenable
13 situation and, I think, has some precedence, and we
14 constituted a separate and, I think, very well
15 qualified review committee who took another look at
16 the data and made the recommendation.
17 ACTING CHAIRMAN BORER: I'm not suggesting
18 that it's -- I'm just asking for clarification. Can
19 you tell us anything about the specifics of the
20 differences between the first committee and the second
21 committee? I don't know if the composition was any
22 different in terms of expertise or such, but in terms
23 of the points that were made or the points that were
24 discussed, or is that something that really is not
25 something we can hear about?

1 DR. CUTLER: The data that they were shown
2 with regard to these two arms was identical, and the
3 attempt was made to focus the committee strictly on
4 the comparison of those two arms rather than broader
5 considerations of the trial, which is, of course, the
6 charge to the DSMB itself.
7 ACTING CHAIRMAN BORER: Ileana?
8 DR. PINA: Maybe I missed this, and I
9 haven't seen it in the ALLHAT protocol that we have
10 been supplied. The definition of heart failure was
11 similar to the definition of heart failure in SHEP.
12 DR. CUTLER: Yes.
13 DR. PINA: What was the definition of
14 heart failure, and what was included to make a
15 diagnosis? I see here in one of your slides that the
16 validation was similar to what the guidelines were for
17 the diagnosis.
18 DR. CUTLER: I have a slide with the
19 criteria. I can get it up for you.
20 DR. PINA: I would like to see that.
21 DR. CUTLER: Okay. If I could have the
22 back-up carousel.
23 ACTING CHAIRMAN BORER: While we are
24 waiting for that, Tom, you had a question. Why don't
25 we do that, and then we'll get back to Ileana.

1 DR. CUTLER: It will be Slide 35 in that
2 carousel.
3 DR. FLEMING: I don't know how far we'll
4 get with my questions before you turn back to this,
5 but I had two questions that are fundamental design
6 questions, the second relating to the dosing schedule
7 that you chose for the alpha blocker.
8 The first question relates to the overall
9 choice of a superiority rather than non-inferiority
10 analysis. This is an active controlled trial with the
11 diuretic as the active comparator, which, for example,
12 in SHEP, had been documented to have a favorable
13 effect on stroke, on major CHD events, and on heart
14 failure.
15 Recognizing that the active comparator
16 provided those benefits, nevertheless, the study was
17 designed not to show non-inferiority of these other
18 regimens, i.e., that they aren't meaningfully worse,
19 but to actually require them to be superior, so that
20 quality, in essence, was viewed as an unacceptable
21 result. I would like to get some sense about that.
22 That's the first question.
23 The second question is: With doxazosin
24 what was the rationale for the choice of a strategy of
25 titrating on a monthly rather than two-week interval

1 and going to an age rather than 16 milligram max?

2 DR. CUTLER: Okay. On the overall design,

3 the focus on a coronary disease endpoint and on a

4 difference hypothesis really grew out of the earlier

5 trial literature where meta analyses both of trials

6 and epidemiology suggested that diuretic based

7 treatment or, if you will, diuretic and sometimes beta

8 blocker based treatment was not achieving the expected

9 coronary benefit that would be expected by the degree

10 of blood pressure lowering, and there were certainly

11 claims made, based on intermediate effects of each of

12 the newer classes of drugs, that they may indeed

13 provide a greater benefit not only from the blood

14 pressure lowering effect but also for these ancillary

15 effects.

16 So it seemed reasonable to formulate the

17 hypotheses as potentially providing a better outcome

18 for coronary disease. If you want more of a

19 statistical answer, I would be glad to call upon my

20 colleagues, director of Center, Dr. Davis, who is

21 here.

22 DR. FLEMING: Well, let me probe your

23 clinical answer first. Basically, what you are saying

24 is there were plausible mechanisms of action that made

25 it reasonable to anticipate that effects could be

1 better than with diuretics. Well, that does, in fact,
2 argue that superiority is a possibility.
3 DR. CUTLER: Yes.
4 DR. FLEMING: The null hypothesis, though,
5 ought to be based on what is minimally acceptable.
6 Even if one thinks that an experimental agent may be
7 better, if in fact it's the same -- and that, in fact,
8 is an adequate conclusion -- then a superiority design
9 isn't the appropriate design. It should be a non-
10 inferiority design.
11 So I am interpreting from this design that
12 there are other features of the experimental
13 interventions that required a superiority conclusion
14 for this to be an acceptable benefit-to-risk profile.
15 DR. CUTLER: Well, I'm not familiar with
16 the logic that somehow a null result is unacceptable
17 in a superiority trial. It's acceptable. It's what
18 you see, what the data show. I'm not sure why that is
19 considered unacceptable.
20 DR. FLEMING: Well, the study should be
21 designed to, in essence, address an alternative
22 hypothesis which, in fact, you would like to be able
23 to establish by ruling out a null hypothesis, that
24 null hypothesis generally being what you would
25 consider to be an inadequate level of benefit.

1 So typically, if you would argue it's okay
2 to be the same, then you would set that up as ruling
3 out that you are meaningfully worse. If you set it up
4 to be a superiority trial where you are then trying to
5 rule out equality, then by logic that's saying
6 equality isn't an acceptable level of benefit. That's
7 the logic with hypothesis testing.
8 So I am assuming, when the team set this
9 up as a superiority trial, there was a rationale given
10 by the team that equality of these efficacy effects
11 would not have been an acceptable conclusion.
12 DR. CUTLER: Well, I don't remember that
13 logical line of argument being pursued.
14 DR. FLEMING: If I could just pursue this
15 one more step, then why was it that the team gave as
16 its rationale for stopping the trial that the
17 probability of being able to prove benefit was now
18 only one percent, conditionally given current results?
19 That's a conclusion that has a logical basis, if you
20 are saying I am only accepting this experimental
21 therapy if it is better.
22 DR. CUTLER; I don't think the trial would
23 have been stopped solely on the basis of futility. It
24 was a combination of futility and the secondary
25 endpoint.

1 DR. FLEMING: But I'm trying to get to
2 that very essence of the point. It seems to me the
3 team is saying with the logic it is using that, if
4 there's only a one percent chance to prove
5 superiority, therefore, this futility has been
6 established.
7 It must be then that equality isn't
8 adequate. It has to be better, and you have ruled out
9 a reasonable chance that it could be better. Hence,
10 there is the basis for stopping the intervention.
11 DR. CUTLER: Well, I guess I'm being
12 dense. I don't follow the twists and turns of your
13 argument.
14 ACTING CHAIRMAN BORER: Can we have the
15 microphone on at the table, please?
16 DR. DAVIS: As I said, the coordinating
17 center came on board when most of the trial had been
18 designed, but I think that the key question that
19 you're asking, Tom, is they wanted to prove
20 superiority in some sense was in the background
21 because of the believability of the trial, at least
22 three newer agents which had been touted as being
23 better than chlorthalidone, and it wasn't a question
24 of wanting to show non-inferiority but actually
25 superiority for this to be believable.

1 The reason -- As Jeff has said, the
2 futility was only one portion of this. But it wasn't
3 only looking at the futility under just the null or --
4 and it wasn't the present level. It was the protocol
5 level, and we looked at even other levels. It was
6 just -- Probability was extremely low.
7 DR. FLEMING; Let me try to answer my
8 question and see if, in fact, this is what the team is
9 saying it's trying to tell us with this decision to
10 stop this alpha blocker arm.
11 Given other features of the profile beyond
12 the primary endpoint, the primary endpoint being fatal
13 CHD and non-fatal MI, the team is saying to us a
14 combination of two observations. First of all, there
15 is an excess of other clinically important events,
16 most notably heart failure. Heart failure was twice
17 as frequent.
18 There are other features such as cost that
19 come into play. When you think about these other
20 features, then it's not acceptable relative to the
21 primary endpoint to be the same. You need to be
22 better, and there was only a one percent chance that
23 you could be better. Hence, you put all of those
24 features together -- the rationale for stopping. Is
25 that the essence of the logic?

1 DR. DAVIS: Yes.

2 ACTING CHAIRMAN BORER: Before we go on to
3 the 8 milligram, 16 milligram and titration schedule
4 question, let's get back to Ileana's question and get
5 that answered. Then we have Steve and Marvin and
6 probably several others, and Tom's.

7 DR. CUTLER: Well, let me first say that
8 I'm not an expert on the dose response of this drug.
9 Is this the next one you wanted me to go to?

10 ACTING CHAIRMAN BORER: No. Let's talk
11 about the definition of heart failure.

12 DR. CUTLER: Basically, it required at
13 least one finding under Category A and one finding
14 under Category B.

15 ACTING CHAIRMAN BORER: Were these the
16 criteria that were used for the nonhospital based
17 patients as well as the hospital based patients?

18 DR. CUTLER: Yes, except that we have no
19 documentation in terms of how the diagnosis was
20 reached from the nonhospitalized cases.

21 DR. PINA: Let me continue along that same
22 line. You said one from each category to make the
23 diagnosis.

24 DR. CUTLER: Yes.

25 DR. PINA: At entry, patients were

1 excluded if an ejection fraction was known to be less
2 than 40 percent, and yet two-thirds of the patients
3 who ended up with heart failure, in fact, had ejection
4 fractions of less than 40 percent.
5 So I gather that there was no urge to find
6 out ejection fraction about a lot of these patients
7 when they were entered, and they were assumed to be
8 okay.
9 Another very interesting point, to me, in
10 the heart failure incidence here is the large number
11 of women that are included in this trial. Do you have
12 a breakdown of the percentage of women versus men who
13 ended up with heart failure in the doxazosin group?
14 DR. CUTLER: Yes. We have the subgroup
15 findings. They are in the paper, but I can show you
16 a slide.
17 DR. PINA: Is this appropriate, Jeff, to
18 continue at this point since, even from Framingham, we
19 know that, you know, in a large population of heart
20 failure individuals, the women are more likely to have
21 hypertension as a background for their heart failure.
22 Do you have that slide?
23 DR. CUTLER: Yes. I have the relative
24 risks. I don't have the rates, but it's Slide 24 in
25 this current carousel. It's actually broken down

1 concurrently by ethnicity and gender.

2 So basically, the fourth, fifth and sixth

3 set of bars are the men in respective ethnic groups,

4 and the next three are the women in respective ethnic

5 groups, pretty similar relative risks.

6 DR. PINA: Thank you.

7 ACTING CHAIRMAN BORER: Why don't we go on

8 to Steve's question, and then we'll go to Marvin and

9 Tom again.

10 DR. NISSEN: I'd like to get a very good

11 sense of what the exposure was to doxazosin, and what

12 the exposure was to chlorthalidone. I mean various

13 measures like the mean dose and so on.

14 The reason I'm asking the question is I

15 want to try to understand whether there was some

16 relationship to the amount of drug the patient was

17 exposed to and the differences that were seen. I know

18 that may not have been prespecified, but it's a big

19 study. So there's a lot of opportunity to look at

20 this.

21 Was the difference the greatest in those

22 patients that got exposed to the most of these drugs

23 or the least of these drugs.

24 DR. CUTLER: That last question is one of

25 the topics of a manuscript we are coming close to

1 closure on, but not quite at the point of publicly
2 reporting the conclusions.
3 The first part of it, which is a
4 description of the dose exposure, I don't have the
5 data in mind, but my recollection is that the majority
6 of patients in the dox group ended upon the 8
7 milligram dose. Barry, do you want to add to that?
8 DR. DAVIS: I'd say it's a majority, about
9 a third in the chlorthalidone group and, I think, 38
10 percent of the doxazosin group.
11 DR. CUTLER: Thirty-eight percent on 8
12 milligrams?
13 DR. NISSEN: So what was the mean dose?
14 DR. DAVIS: I'm sorry. I read the wrong
15 page. Forty-nine percent in the doxazosin group and
16 46 percent in the chlorthalidone group.
17 DR. CUTLER: On the higher dose, the
18 highest dose.
19 DR. NISSEN: So what was the mean
20 exposure? What was the mean dose? Do we not know?
21 We must know that.
22 DR. DAVIS: We haven't really done a
23 formal calculation of that.
24 DR. NISSEN: It's really not known?
25 DR. LIPICKY: It's not known to us, you,

1 now. It's not known. So if you need that
2 information, you don't have it.
3 ACTING CHAIRMAN BORER: Marvin, you had
4 your hand up there?
5 DR. KONSTAM: Yes. I've got a couple of
6 questions. One is: Could you just help us again
7 reconcile the different points about mortality? I
8 guess, so you find that in the patients who present
9 with heart failure, they go on to have a higher
10 mortality, and yet the overall mortality curves for
11 the two groups is absolutely superimposable.
12 So how do you explain that?
13 DR. CUTLER: Well, I think we are both
14 overstating it to say they are absolutely
15 superimposable, but they are certainly not
16 statistically different.
17 DR. KONSTAM: Well, they look
18 superimposable.
19 DR. CUTLER: Do you want the slide up
20 again? It's in the paper. I mean, I think it
21 basically has to do with the proportion of deaths that
22 were attributable to heart failure, which was, you
23 know, modest. I mean, there were a lot of deaths, a
24 lot of causes of death. I can't tell you the exact
25 proportion. Barry, do you have that? But it was a

1 relatively modest proportion of deaths, and it's not
2 enough to affect, with a play of chance, the overall
3 mortality.
4 DR. KONSTAM: I mean, just to reflect in
5 terms of heart failure studies, I think it's a little
6 unusual, and also to have what appears to be a pretty
7 substantial early effect on heart failure
8 hospitalizations. I mean, I just wonder if you could
9 -- Maybe you don't have an answer, but what do you
10 think is going on there? I mean, you have this very
11 early effect, and what is that? I mean, is that some
12 harmful effect of doxazosin or is that, well, that
13 chlorthalidone actually treats heart failure, and
14 you're not giving it. I mean, can you comment on
15 that?
16 DR. CUTLER: Well, I think it's got to be
17 predominantly that chlorthalidone is an effective drug
18 both for preventing and treating heart failure. It
19 was a very effective drug in SHEP at preventing heart
20 failure, 50 percent reduction.
21 You know, coincidentally, you see the same
22 relative risk of chlorthalidone versus placebo in SHEP
23 and chlorthalidone versus doxazosin in ALLHAT.
24 DR. KONSTAM: Well, it's going to be an
25 important issue for us to grapple with, is which one

1 of these things is going on. Okay.

2 I want to ask just about blood pressure.

3 ACTING CHAIRMAN BORER: Just before you

4 do, Joann, you had a follow-on on the heart failure?

5 DR. LINDENFELD: Yes. I want to just

6 follow up to what Marv said. Can you tell us how many

7 patients were withdrawn from antihypertensive therapy,

8 and how many were started de novo in the study, what

9 percentage in each group?

10 Then in follow-up to that and just this

11 question about withdrawing potentially effective

12 failure for heart failure, was there a difference in

13 the incidence of heart failure in those two groups --

14 that is, the groups that had to be withdrawn?

15 I'm concerned, because there's a very

16 early difference here.

17 DR. CUTLER: About 90 percent came in on

18 treatment. Actually, the relative risk for heart

19 failure in those who came in untreated and those who

20 came in on treatment is essentially the same. We have

21 those numbers.

22 ACTING CHAIRMAN BORER: Do we know what

23 the distribution of treatments was from which people

24 were withdrawn who had heart failure?

25 DR. CUTLER: No, we don't.

1 ACTING CHAIRMAN BORER: Marvin, you had
2 another question?
3 DR. KONSTAM: Yes. With regard to blood
4 pressure, you had target blood pressures for the
5 treatment algorithm. Correct? I mean, you were
6 shooting for a certain blood pressure goal.
7 DR. CUTLER: Yes.
8 DR. KONSTAM: Can you comment on then why
9 do you think there was a 3 millimeter difference
10 between the two groups at the end?
11 DR. CUTLER: Well, of course, as a double
12 blind trial the clinicians were titrating without
13 regard to the base drug. They were also somewhat
14 constrained, though in the end no constrained, as to
15 what drugs they could choose to add. The protocol
16 steered them toward the drugs that were supplied by
17 the study, and were not any of the study drug classes.
18 They did have both a systolic and
19 diastolic goal. By and large, they were achieving the
20 diastolic goal equally in all classes. I think it's
21 true that physicians are still not well oriented
22 toward achieving systolic blood pressure goals. It's
23 sort of been an increasing emphasis and acceptance of
24 that.
25 So those are all factors, and I can't --

1 I don't think I can go any further than that.

2 DR. KONSTAM: All right. This is my last

3 question. Have you looked at al at blood pressure

4 effects relative to events? That is to say, you know,

5 what are the various blood pressure effects in

6 patients who did and did not have stroke, for example,

7 and heart failure, for that matter, but as another way

8 of getting at is the difference in the events

9 explainable on the basis of the blood pressure?

10 DR. CUTLER: That's another analysis

11 that's part of this manuscript I mentioned. I think

12 that those kind of analyses have their limitations, as

13 you well know, but we are doing them.

14 DR. KONSTAM: So you don't have any

15 answers today. Right?

16 DR. CUTLER: I don't.

17 ACTING CHAIRMAN BORER: Ralph, you had a

18 comment?

19 DR. D'AGOSTINO: I've got a couple of

20 questions, if it's all right.

21 If I read the paper correctly, at the time

22 the analysis was done, you didn't have follow-up on

23 all individuals, but you had follow-up on about 90

24 percent of the individuals. I've been in the setting

25 in data safety monitoring committees where we see big

1 differences, and if you sort of wait a while, they go
2 away.
3 Some of the differences in this graph that
4 we are showing and we're saying there's a big
5 difference at the beginning is obviously tied in with
6 the scale. So my question, my first question, is:
7 Did you redo the analysis with a better follow-up, a
8 more complete follow-up, and did that have any effect
9 on the results?
10 DR. CUTLER: You mean subsequent to the
11 publication?
12 DR. D'AGOSTINO: Right.
13 DR. CUTLER: Yes. We do look at that from
14 time to time, but we haven't -- Everything we've
15 looked at is completely consistent with the original
16 analysis.
17 DR. D'AGOSTINO: Did you do an analysis on
18 those who were actually taking the drug? I agree to
19 the intent-to-treat analysis, but sometimes you might
20 want to chase down and see what were they actually
21 doing.
22 DR. CUTLER: Yes. That's also part of
23 this paper that I've been mentioning.
24 DR. D'AGOSTINO: And just one other
25 question now. We have lots of different arms in the

1 study. There are a number of different drugs being
2 looked at, and I realize that there's a sort of
3 confidentiality. But I'm trying to get a setting of
4 sort of should I be surprised -- Even though it's
5 upsetting, should I be surprised by one event being
6 significant, driven very much by the CHF, when I don't
7 know anything about all the others, all the other
8 comparisons that were going on.
9 Then also, if I do some subtractions and
10 I'll leave it to you to respond to it -- But if I do
11 some subtractions, I get the overall CVD rate. That
12 shows a higher rate for the Cardura, and then I
13 subtract out the CHF and I subtract out the stroke,
14 and then suddenly I'm in the other direction. Is
15 there something else -- Is there some other event like
16 PAD where maybe the direction was the other way?
17 I'm just trying to get a sense of how do
18 I look at this striking one result and understand how
19 to put it in context of all the possible results that
20 could have come out of -- all the possible differences
21 that could have come out of comparing the two drugs.
22 DR. CUTLER: No. The PAD data are in the
23 paper, and also I have a slide, if you want to see it.
24 But, no, all of the components went in the same
25 direction, and I guess the subtraction you get into,

1 the accounting rules as to whether -- what's a first
2 event and multiple events in the same patient. So
3 it's a little hard to sort it out in that way.
4 The answer to your question about on
5 treatment analysis: We also are doing that with this
6 paper that's forthcoming.
7 ACTING CHAIRMAN BORER: Alan.
8 DR. HIRSCH: A very nice presentation. I
9 remain concerned about the definition of heart
10 failure, just like everyone else, because that seems
11 to drive the analysis. As a clinician, though I am
12 cognizant that one has to have simple rules for these
13 definitions in a practice based trial, I want to make
14 sure I know how they were applied.
15 If I were a patient in the trial and I
16 were going to have this heart failure definition
17 applied to me, did I have to have both an A category
18 and a B category as a new finding? Alternatively, if
19 I were in my doctor's practice with ankle edema and I
20 complained, or orthopnea, did that become a heart
21 failure definition? That's my first question. I'll
22 follow that up.
23 DR. CUTLER: I believe the instructions
24 were that they had to be new findings.
25 DR. HIRSCH: Both new?

1 DR. CUTLER: Yes.

2 DR. HIRSCH: So two new findings. That's
3 helpful.

4 Then you made the comment that, since we
5 did a post hoc adjudication of the heart failure
6 outcome, that this was largely consistent with the
7 physician's diagnosis, and I would like you to define
8 "largely consistent."

9 DR. CUTLER: In about two-thirds of the
10 cases, and most of the remainder were not because
11 there was evidence in the discharge summary that
12 contradicted the diagnosis, but because there just was
13 not sufficient data.

14 DR. HIRSCH; And how was that handled? In
15 other words, if one deleted that one-third.

16 DR. CUTLER: The central adjudication,
17 both for the heart failure and for the primary outcome
18 and for stroke, was not used to change the diagnosis.
19 These were quality control reviews. The local
20 physician's diagnosis was maintained.

21 ACTING CHAIRMAN BORER: Ray.

22 DR. LIPICKY: This wasn't the question I
23 wanted to ask, but based on what you just said, does
24 that mean that two-thirds of the data that say it's
25 congestive heart failure are okay, and one-third is

1 not, but you accept it all?

2 DR. CUTLER: We accept it all.

3 DR. LIPICKY: Okay, fine. I had three

4 questions to ask. I'm sorry. You disagree with that?

5 DR. DAVIS: Clarification. That was for

6 the quality control. Don't say that was for the whole

7 thing.

8 DR. LIPICKY: But what I hear is that you

9 knew that a third of the data couldn't be confirmed by

10 anything you read about the patient.

11 DR. CUTLER: You can't extrapolate from

12 the sample very accurately to the whole dataset, and

13 it may very well be appropriate to do central review

14 of a larger sample.

15 DR. LIPICKY: So the driving force of the

16 whole business, you don't need to be certain of. All

17 you need is the number? Is that right?

18 DR. CUTLER: I didn't understand that

19 question.

20 DR. LIPICKY: Well, you don't need to know

21 what you are talking about. You just need to know how

22 many of what you don't know you're talking about you

23 have.

24 DR. CUTLER: Well, that sounds like a

25 rhetorical question.

1 DR. LIPICKY: Well, yes, it was. But my
2 three questions were: In the publication it says that
3 patients who were randomized to chlorthalidone were on
4 chlorthalidone or a diuretic, as if they may not have
5 been on chlorthalidone.
6 Then it says patients were randomized to
7 doxazosin or an alpha blocker, as though they may not
8 be an alpha blocker. That's when the time in study --
9 the table of time in study in the publications, and
10 the slide you showed said doxazosin and
11 chlorthalidone. I would just like you to clarify
12 that. What did the publication mean when it said
13 chlorthalidone or a diuretic and doxazosin or an alpha
14 blocker?
15 DR. CUTLER: In each of those categories
16 of maintenance on assigned treatment, there was a
17 small percentage who were, in fact, on an open-label
18 drug of the same class. It's a small percent, but
19 that's the way we presented the data.
20 DR. LIPICKY: Okay. So it is that it was
21 chlorthalidone or something that people thought was
22 like chlorthalidone?
23 DR. CUTLER: Yes.
24 DR. LIPICKY: Okay. Then the second and
25 third questions might take a little longer to answer.

1 But I guess, since there is no information available,
2 I'd like to get a feeling for why the DSMB, which sort
3 of looked after the data for a long time, came to one
4 conclusion -- maybe it was a hung vote or maybe it was
5 50/50 -- but did not come to the conclusion that
6 something should be done, and that what the reasons
7 were; because we have no feeling for that.
8 We don't know what directions things were
9 going in. We don't know how any of the other groups
10 were faring and what they thought of the reasons.
11 Then why an independent group apparently quite clearly
12 came to a very different decision.
13 Can you give some feeling for how that
14 happened or what the thought processes were? Then I
15 have one other question after that.
16 DR. CUTLER: Well, as you might imagine,
17 that's very hard to summarize.
18 DR. LIPICKY: That's okay. If you can't,
19 you can't.
20 DR. CUTLER: No, no. I'll say a few
21 things. You know, I think there was still on one or
22 two members some discomfort still with the heart
23 failure diagnosis, as has been evidenced by some of
24 the questions we've heard here.
25 In fact, I think everybody who first sees

1 these data are skeptical. They know that there are
2 some -- that alpha blockers cause in some patients
3 peripheral edema and so forth, and that this is just
4 some sort of an artifact.
5 So we looked at everything within the
6 study dataset that we could to shore up our confidence
7 in this data, and some members of the Board ended up
8 with more confidence than others. I think probably
9 there was also some feeling that with 60 percent of
10 the information time in, even with as low conditional
11 power as we had, that there's always some reluctance
12 to stop a trial, and there are different orientations
13 in terms of what threshold it requires to make that
14 judgment, but depending on people's background and
15 experience.
16 DR. LIPICKY: Well, I understand, but
17 could you put that in the context that the
18 presentations -- the early presentations were, and
19 that is this is a cut and dried circumstance. You
20 ought to damn well know what the conclusion is. How
21 could those boards vary so much?
22 DR. CUTLER: I wouldn't put it that way.
23 You know, I'm the one who is up here at the podium,
24 and I'm reflecting my orientation to the chain of
25 events and the data. You know, I can't represent

1 everybody's orientation.

2 DR. LIPICKY; Then my third question, may

3 I?

4 ACTING CHAIRMAN BORER: Yes.

5 DR. LIPICKY; Okay, I'm sorry. Give us

6 some insight into why you thought that you could pick

7 a member of a class and draw class conclusions, when

8 in fact it's pretty clear to me that members of a

9 class behave differently. So I'd like to get your

10 feeling for what your rationale was for thinking that

11 you were going to be studying class effects.

12 You might add to that why dose didn't

13 matter.

14 DR. CUTLER: Well, at the end of the day,

15 of course, everybody has to make their inferences as

16 to whether these are single drug findings or class

17 findings. But, certainly, every --

18 DR. LIPICKY; But you designed the study

19 as a class study.

20 DR. CUTLER I hadn't finished yet. I

21 mean, you know, if you're going to do a trial

22 addressing this kind of question, you can only do it

23 with a single drug; and your decision is basically

24 don't do it all or do it with a drug that you feel is

25 typical of a class. So we chose the latter.

1 DR. LIPICKY: But fully well knowing that
2 like, say, beta blockers in heart failure -- they can
3 take beta blockers that have beta blockade and alpha
4 blockade and just pure beta blockers and all that sort
5 of stuff, and that they have a completely different
6 clinical outcome when you study them. So that it
7 doesn't matter --
8 DR. CUTLER: I'm not sure that's the case,
9 but that's --
10 DR. LIPICKY; Well, take businolol and any
11 other beta blocker you want to name.
12 DR. CUTLER: Well, I'm -- I don't know if
13 we want to divert to that discussion.
14 ACTING CHAIRMAN BORER: We'll get back to
15 the issue of the extrapolability of the data from one
16 drug to a class.
17 DR. LIPICKY: I just wanted to get a
18 feeling for the thought process in the design, is all
19 I was looking for.
20 ACTING CHAIRMAN BORER: I think we sort of
21 have that. But you mentioned a dose issue, and Tom
22 raised the question initially, and maybe we could get
23 back to Tom's question now. Maybe, Tom, you want to
24 restate it.
25 DR. FLEMING: Well, I'd like to concur

1 with one of those who said this is an extremely
2 important, very informative trial in addressing
3 relative safety and efficacy issues in a real world
4 setting.
5 In that context, one would wish to choose
6 a dose and schedule for each of these regimens that
7 best matches what would be a real world delivery. It
8 has been stated that we may have given doxazosin a
9 less than optimal opportunity by having a maximal dose
10 of eight rather than 16. I'm sure the team gave this
11 great thought.
12 Could you give us a sense for why it was
13 viewed that the most relevant, appropriate answer is
14 the one that is achieved from a maximal of 8 rather
15 than 16?
16 DR. CUTLER: The aim, as was discussed
17 earlier, was to have as close as possible to
18 equivalent blood pressure control in these arms, so
19 that one would be in a position to test the effect on
20 clinical endpoints of ancillary properties of the
21 drug, and the doses were chosen by our Steering
22 Committee to aim for that outcome.
23 Other arms in the study also didn't
24 necessarily go to maximum dose.
25 ACTING CHAIRMAN BORER: That's not

1 actually my reading of the paper or the protocol.
2 Amlodipine, you allowed up to 10 milligrams per day,
3 which is the maximally labeled dose. Lisinopril was
4 40 milligrams a day, which isn't the maximally labeled
5 dose, but if you read the label, the label makes the
6 point that there is no evidence that you get anymore
7 benefit above 40. I don't know the evidence one way
8 or the other, but both chlorthalidone and doxazosin
9 were limited to half the top labeled dose.
10 So I think, you know, we need a better
11 answer than that to Tom's question.
12 DR. CUTLER: Well, I'm giving you the best
13 answer I can. As I said, the aim was to achieve blood
14 pressure levels that were roughly equivalent across
15 the arms, and the doses were -- we were advised to use
16 by our leadership group was the doses we chose.
17 ACTING CHAIRMAN BORER: Steve?
18 DR. NISSEN: Yes. I want to come back to
19 the issue of dose response curve and see if the sense
20 of the study group was the same as mine, namely that:
21 Is it not correct that the dose response curve to
22 diuretics is very, very flat as compared to other
23 drugs or would you not agree with that?
24 In other words, when you double the dose
25 of chlorthalidone, very little incremental effect, as

1 opposed to some of the other agents used. Is that
2 your feeling also?
3 DR. CUTLER: Well, I think that's true.
4 I think that, if you look at clinical endpoints,
5 there's some evidence that higher dose diuretic --
6 that there is better benefit for stroke, although
7 probably not for coronary disease. So that's not the
8 blood pressure answer, but the clinical endpoint
9 answer. I guess that's my response.
10 ACTING CHAIRMAN BORER: Bob?
11 DR. TEMPLE: You can think of a lot of
12 good reasons for limiting the dose of chlorthalidone
13 to 25, because larger doses don't work, and they
14 probably are lethal.
15 I have a question about the follow-up
16 treatment. Jeff, you've suggested at a number of
17 places that the protocol specified follow-up
18 treatments were apparently not considered sufficient,
19 and so the people ignored that and used whatever they
20 wanted.
21 Can you elaborate on that? The follow-up
22 treatments that I remember were reserpine, an alpha
23 agonist, and one more, but I can't remember what it
24 was.
25 DR. CUTLER: The most common step-up drug

1 was a beta blocker, atenolol, most commonly used. I
2 didn't mean to imply that investigators ignored the
3 protocol. In fact, you can see from the paper that
4 they very commonly used the actual -- the drugs
5 specified in the protocol.
6 All I was saying was that they didn't
7 universally use the drugs specified.
8 DR. TEMPLE: Okay. But that leads me to
9 my question in some ways. I imagine many people who
10 start with a -- This may relate more to the trial than
11 to the immediate question here. But I imagine most
12 people who didn't get a satisfactory response to an
13 ACE inhibitor would add a diuretic.
14 Well, they weren't really allowed to do
15 that here. So that's a little peculiar, especially if
16 the goal is to see how things work in practice. Do
17 you have any sense of whether the limited options
18 available as follow-up therapy might have had anything
19 to do with the inability of the groups to get equal
20 control of systolic pressure, because it was a sort of
21 odd constraint? I mean, it wouldn't be what you would
22 do in practice.
23 DR. CUTLER: It was a constraint imposed
24 by the decision to do a double-blind trial, and all
25 trial designs have tradeoffs, and that was a tradeoff

1 we chose.

2 DR. TEMPLE: Yes. I'm not criticizing, but

3 it's sort of a peculiarity.

4 ACTING CHAIRMAN BORER: Joann?

5 DR. LINDENFELD: Just quickly for my

6 education, was there a time specified for the drugs to

7 be taken and the blood pressure than to be checked

8 with each of the different groups?

9 Then I guess I would also ask, is there a

10 difference -- Today we are just comparing the two

11 drugs. Is there a difference in the peak onset of

12 action? What I'm getting at here is have we measured

13 the difference in blood pressure between these two

14 drugs adequately or could there be a greater

15 difference because of differences in onset of action?

16 DR. CUTLER: Certainly, the diurnal

17 pattern was not a focus in this study. Drugs were

18 specified to be taken in the morning, and they were

19 all once-a-day drugs, and blood pressure was -- The

20 clinic visits were scheduled at the physician and

21 patient's convenience. They may not have all been in

22 the morning.

23 DR. LINDENFELD: Just in terms of the

24 systematic problem, most of my patients on morning

25 diuretics ask to come to the clinic in the afternoon.

1 You know, I think there just could be a difference in
2 how we evaluate blood pressures.
3 ACTING CHAIRMAN BORER: Alan?
4 DR. HIRSCH: Well, sort of following up
5 from Dr. Temple's question, I would again want to
6 think in real life of how I might have responded as
7 the patient in the trial, and again I want to flatter
8 the trial design as being real world, and I'm not
9 particularly worried in its generalizability, because
10 this is how life is practiced. But I'm trying to look
11 for confounding variables to explain the outcome,
12 obviously.
13 So if I were a patient enrolled in ALLHAT
14 with a left ventricular systolic dysfunction, as
15 undoubtedly some patients were, and if I were
16 randomized to doxazosin and, although the primary
17 physician may not have noted it, my systolic blood
18 pressure were not quite as well controlled, the
19 secondary then use of beta blockers does become
20 important in unmasking one or two of those clinical
21 outcomes that would have created the CHF diagnosis.
22 Can you remind me of what the relative
23 rate was of secondary use of beta blockers in the two
24 arms, whether the committee had considered whether
25 that by itself might have provoked this CHF outcome

1 difference?

2 DR. CUTLER: It's in the manuscript on

3 page 1970, middle column, middle paragraph. Let's

4 see. At one year, beta blocker was 18 percent in the

5 chlorthalidone arm and 20 percent the doxazosin arm.

6 Corresponding percentages at three years were 25

7 percent, chlorthalidone, and 29 percent.

8 DR. HIRSCH: Small differences of use, but

9 I don't know whether these could be extrapolated to an

10 outcome difference, and I guess I'm speculating on

11 that for the panel.

12 ACTING CHAIRMAN BORER: Dr. Fenichel.

13 DR. FENICHEL: Yes. I just wanted to

14 clarify something that came out of Bob Temple's

15 comment, and that is there is a difference between

16 speaking about a difference in systolic blood pressure

17 control and a difference in systolic blood pressure

18 outcome.

19 The definition of control was that the

20 systolic blood pressure be below 140, and the

21 definition of control for diastolic was that it be

22 below 90. If those numbers -- If the number 140, in

23 particular, had not been prophetically chosen, it

24 might well be that one would have equal control and

25 yet a different result, which is to say perhaps

1 everyone was below 140 indeed, because the physicians
2 were on the ball, but some were running at 139 and
3 some were running at 135.
4 Some of the comments here are hard to
5 interpret, because I think the two terms are being
6 used interchangeably, and they are not.
7 ACTING CHAIRMAN BORER: Tom, you wanted to
8 follow up on the response to your comment?
9 DR. FLEMING: Yes. I'm just thinking
10 through the response that you had given for the
11 selected dosing and regiment, that actually involves
12 both, the titration as well as the maximal. In
13 essence, if I interpreted your answer, you said the
14 selection of the specific schedule of monthly
15 titration intervals to a maximum of 8 was based purely
16 on the expectation that this would give us comparable
17 blood pressure control to the other regiments. Is
18 that correct?
19 DR. CUTLER: Not purely. Basically, the
20 charge to the protocol writing committee was that that
21 was the goal. But I guess one of the factors was the
22 number of titration steps and keeping that the same in
23 all arms to maintain the blind and to keep the
24 implementation as simple as possible.
25 I must say, you know, the option of

1 pushing to 16 milligram doxazosin dose was not
2 seriously advocated by anybody on the protocol writing
3 committee. So --
4 DR. FLEMING: Were there any issues of
5 safety that anticipated safety differences at 16
6 versus 8 that weighed in this in any way?
7 DR. CUTLER: Not to my recollection, but
8 it's a long time ago.
9 DR. FLEMING: And, I guess, one last
10 question: Given that you have now seen the results
11 for relative systolic blood pressures, is it your
12 judgment that the choice of the specific schedule was
13 appropriate or would you now say that it was intended
14 to deliver comparable blood pressure control, but we
15 may well, in retrospect, now have judged that we
16 should have allowed to have a more rapid titration or
17 a higher maximal dose?
18 DR. CUTLER: I think it would have been
19 appropriate to give it serious consideration. Whether
20 it would have been doable and practical in the context
21 of this protocol, I can't be sure.
22 ACTING CHAIRMAN BORER: Ray, you had your
23 hand up there. Joann?
24 DR. LINDENFELD: Just a quick question.
25 Was the incidence of new diabetes any different