FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE MEETING

DAY ONE

Silver Spring, Maryland

Tuesday, July 1, 2008

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P R O C E E D I N GS

(8:01 a.m.)

DR. BURMAN: Good morning. I'd like to welcome everyone this morning and start the meeting on time and introduce Paul Tran, who's going to have an introductory announcement.

MR. TRAN: Good morning. My name is Paul Tran. I'm the designated federal official for the EMDAC Advisory Committee. I just would like to remind everyone present to please silence your cell phone, BlackBerrys and other devices if you have not already done so. I would like to identify the FDA press contact, Ms. Susan Cruzan.

Stand, please.

Thank you.

DR. BURMAN: I'd like to welcome everyone and also start the introduction of the members and consultants around the table. If we could start on this end, please.

DR. PAN: Gerald Dal Pan, director, Office of Surveillance and Epidemiology at FDA.

DR. TEMPLE: I'm Bob Temple. I'm director of the Office of Medical Policy in CDER.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs at FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, director, Office of Drug Evaluation II.

DS. PARKS: Good morning. I'm Mary Parks. I'm director for the Division of Metabolism and Endocrine Products.

DR. JOFFE: Good morning. My name is Hylton Joffe. I'm the lead medical officer for the Diabetes Drug Group at FDA.

DR. HOLMBOE: I'm Eric Holmboe. I'm from the American Board of Internal Medicine.

DR. KONSTAM: Marv Konstam. I'm a cardiologist from Tufts University and NHLBI.

MR. LESAR: Timothy Lesar, director of Clinical Pharmacy Services, Albany Medical Center, Albany, New York.

MR. PROSCHAN: I'm Mike Proshan. I'm

a statistician with the National Institutes of Allergy and Infectious Diseases.

MS. FLEGAL: Katherine Flegal from the National Center for Health Statistics and the Centers for Disease Control and Prevention.

MR. BERSOT: Tom Bersot. I'm an associate investigator at the Gladstone Institute of Cardiovascular Disease at UCSF in San Francisco.

MS. HENDERSON: Jessica Henderson. I'm the consumer representative from Western Oregon University.

DR. BURMAN: Ken Burman, I'm the Chair of Endocrinology at the Washington Hospital Center, and Professor of the Department of Medicine at Georgetown University.

MR. TRAN: Paul Tran, the designated Federal Official for the EMDACS Advisory Committee.

DS. GOLDFINE: Allison Goldfine. I'm head of clinical research at the Johnson Diabetes Center in Boston.

MR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. FELNER: Eric Felner, Pediatric Endocrinologist at Emory University.

MS. DAY: Ruth Day, director of the Medical Cognition Laboratory, Duke University.

DR. ROSEN: Clifford Rosen. Endocrinologist, Maine Medical Center.

MS. KILLIAN: Rebecca Killian. I'm a Patient Representative from Bowie, Maryland.

DR. SAVAGE: Peter Savage. I'm a senior advisor to the director of the Diabetes Division at NIDDK.

DS. FRADKIN: Judy Fradkin, director of the Diabetes Division of NIDDK.

DR. GENUTH: Saul Genuth. Case Western Reserve University.

MR. VELTRI: Rick Veltri, industry representative, Schering-Plough Research Institute.

DR. BURMAN: Thank you all. I'd like

to welcome, especially the members of the committee, the visitors and guests, and especially thank the speakers for preparing their discussion for an active discussion this morning.

I'd like to read an announcement. For topics such as those being discussed at today's meetings, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive and active meeting.

In the spirit of the FDA Advisory Committee Act, the Federal Advisory Committee Act, and the Government in the Sunshine Act, we ask that the Advisory Committee Members take care that their conversations about the

topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

A press conference will be held in the Potomac Room immediately following the meeting today. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

MR. TRAN: I will now read the Conflict of Interest statement for this meeting.

The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members are Special Government Employees or Regular

Federal Employees from other Agencies, and are subject to Federal conflict of interest laws and regulation.

The following information on the status of the Committee's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

The FDA has determined that members and temporary voting members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special and regular government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of

interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this Committee have been screened for potential conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments; consulting; expert witness testimony; contract/grants/Cooperative Research and Development Agreements; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves discussions

of the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the Food, Drug, and Cosmetic Act to Dr. Thomas Bersot. Dr. Bersot owns stock in an affected firm worth between $25,001 and $50,000.

Limited waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the Food, Drug, and Cosmetic Act to Drs. Robert Califf and Steven Nissen.

Drs. Califf and Nissen will not be allowed to participate in the Committee's discussion, deliberations, or vote in the matters coming before the Committees.

Dr. Califf's limited waiver is for his employer's two studies on affected product. His institute receives more than $300,000 per year for both studies. His employer has another study on an affected product that is currently under negotiation.

Dr. Califf's waiver also covers his consulting job on an affected product for which he receives less than $10,000 per year, and another consulting job for an affected firm for which he receives between $10,000 and $50,000 per year.

Dr. Nissen's limited waiver entails his employer's three studies on affected products. His institute receives between $100,001 and $300,000 per year for two studies, and more than $300,000 per year for one study.

FDA has also decided to limit Dr. Saul Genuth's participation due to his past and current involvement with the Action to Control Cardiovascular Complications of

Diabetes (ACCORD) clinical trial. Dr. Genuth will be allowed to participate in the Committee's discussions, deliberations, but will be excluded from any vote with respect to the discussions on the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

With regard to the FDA's guest speakers, the Agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. David Nathan has acknowledged that he is the Principal Investigator for an investigator-initiated study funded by Sanofi-Aventis.

Dr. Hertzel Gerstein has acknowledged that he has research contracts

with GlaxoSmithKline, Sanofi-Aventis, King, and Merck. He lectures for GlaxoSmithKline, Sanofi-Aventis, Eli Lilly, Novo Nordisk, Merck, and Boehringer-Ingelheim. He is also a consultant for GlaxoSmithKline, Sanofi-Aventis, Eli Lilly, NovoNordisk, Merck, Boehringer-Ingelheim, Roche, and Medtronic.

Dr. Robert Ratner has acknowledged that he owns stock in Merck, Johnson & Johnson, and Abbott. He has research contracts with AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck, NovoNordisk, Pfizer, and Takeda. Dr. Ratner also serves on Advisory Boards for Amylin, AstraZeneca, Eli Lilly, GlaxoSmithKline, NovoNordisk, Sanofi-Aventis, and Takeda.

Professor Rury Holman has acknowledged that he has educational grants from Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, NovoNordisk, and Pfizer. He lectures for

Astellas, Bayer, Eli Lilly, GlaxoSmithKline, Merck, NovoNordisk, and Sanofi-Aventis. Professor Holman is also a scientific advisor to Amylin, Eli Lilly, GlaxoSmithKline, Merck and Novartis. Lastly, his employer is currently negotiating for studies of two affected products.

As guest speakers, Drs. Nathan, Gerstein, Ratner, and Professor Holman will not participate in Committee deliberations, nor will they vote.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the wavier documents, which are posted on the FDA's website, which can be found at www.fda.gov/ohrms/dockets/default.htm."

Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy

of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Enrico Veltri is serving as the industry representative, acting on behalf of all regulated industry. Dr. Veltri is an employee of Schering-Plough.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. BURMAN: Thank you. We will now

proceed with our first presentation from the FDA EMDAC division. I would like to remind public observers at this meeting, that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Joffe?

DR. JOFFE: Good morning, Dr. Burman, members of the Advisory Committee, and invited participants. FDA has convened this meeting to discuss a very important topic, specifically the role and nature of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for treatment of type 2 diabetes.

My name is Hylton Joffe, and I'm the lead medical officer for the Diabetes Drug Group for the FDA.

To help us work through this complex issue, we have an Advisory Committee that has been populated with experts in endocrinology, diabetes, cardiology,

statistics, and safety issues. We also are fortunate to have several thought leaders in the field who are here with us today who will be making presentations for most of the day.

This topic has extreme importance. It can have far-reaching implications on new treatments for this very common condition. It may affect availability of such treatments or the timeliness of such treatments, and it may even impact on drugs that are already on the market.

What I'd like to do in the next 30 minutes or so is present the agenda for this meeting, give a very brief overview of type 2 diabetes, with the focus on those aspects that are directly relevant to the discussion at hand, discuss how FDA currently approaches drug approval for type 2 diabetes.

I'm then going to present some aspects that I would like the Advisory Committee to deliberate upon. This is just a starting point. We expect there will be many

more points that are brought up during discussions, and when the Committee hears presentations from our thought leaders. And then we'll end with questions to the panel.

Currently, all drugs that are approved for treating type 2 diabetes are indicated to improve glycemic control and are approved on the basis of HbA1c. FDA and leading medical organizations see value in glycemic control, and we'll come back to the basis for why we do this at all later in the talk.

There have been safety concerns that have been raised about some diabetes drugs such as muraglitazone and rosiglitazone, that have raised questions as to whether there should be more extensive cardiovascular assessment during the approval process.

So this Advisory Committee will explore this complex issue, and there are a lot of complex questions that will need to be

asked. For example, should a long-term cardiovascular trial be required for those therapies that have no evidence of a cardiovascular safety signal in the standard diabetes development program? Should such a trial be required to show cardiovascular benefit or rule out cardiovascular harm? This is a very critical aspect of this discussion at hand, and we're going to discuss this at length a little later in the talk.

This issue is frequently confused in academic publications and also in the press, and so we're hoping we can set things straight today.

We'll discuss challenges related to trial design, talk about timing relative to approval -- should these be changes if we decide to institute them, that take place pre-approval or post-approval, and then what do we do with currently marketed therapies for diabetes.

The presentations we will hear today are as follows: after my presentation, Dr. David Nathan will talk about diabetes and cardiovascular disease; Dr. Robert Ratner will talk about glycemic control and microvascular complications; Dr. Tom Fleming will talk about statistical considerations when evaluating benefit and risk in type 2 diabetes; Professor Rury Holman will talk about what we already know regarding clinical macrovascular outcomes with anti-diabetic drugs; Dr. Hertzel Gurstein will talk about recently completed studies and also ongoing studies and what they will teach us or have taught us about clinical macrovascular outcomes with anti-diabetic drugs; Dr. Steven Nissen will talk on the need for cardiovascular assessment during the approval process for these therapies; and we will end our presentations with Dr. Robert Califf, who will talk about challenges in designing a cardiovascular trial in type 2 diabetes.

As I'm sure everyone is aware, this is a two-day meeting. After my presentation, we'll hear presentations from the experts in the field. After each presentation, the panel will have an opportunity to question the presenters. After all presentations are done, there will be further opportunity for questioning of the presenters, and time permitting, the Committee can begin its discussion of this issue towards the end of the day.

Tomorrow, we'll start with the open public hearing, hear FDA comments from Dr. Mary Parks, then there will be a continued panel discussion -- this is the bulk of where the panel discussion and deliberations will take place, and we'll end with questions to the panel and a vote.

A brief blurb on type 2 diabetes. As I'm sure most people are aware in this room, diabetes is becoming -- growing to epidemic proportions due to the obesity

epidemic, widespread physical inactivity, the aging population.

There are more than 18 million people in the United States have this condition, it's associated with a two- to four-fold higher risk of cardiovascular disease compared to patients who do not have diabetes. Most of the deaths among patients with diabetes is due to cardiovascular disease and stroke, accounting for at least two thirds of such deaths, but it's also important to keep sight that cardiovascular disease is not the only important complication with diabetes.

Other macrovascular complications such as stroke and peripheral vascular disease, and importantly, microvascular complications -- retinopathy, affecting vision -- nephropathy, leading to end stage renal disease -- and neuropathy, leading to many debilitating conditions, from chronic pain to gastroparesis and autonomic

dysfunction.

Currently, we have 10 classes of therapies that are currently indicated to treat glycemic control in patients with type 2 diabetes. We think it's important to have a lot of therapies for this condition because it's a progressive condition. Patients may start on one medication at the beginning, but over time will need more treatments to help manage their condition. And we also think it's important to develop treatments that target different derangements in the condition.

With regard to macrovascular complications, in type 1 diabetes, it appears more clear that intensive glycemic control reduces macrovascular complications, and this is derived from observational follow-up from the landmark diabetes control and complications trial.

With type 2 diabetes, however, there's no conclusive evidence of

macrovascular risk reduction with any of the FDA-approved treatments in any of those 10 categories of drugs that I just showed you.

With these next two slides, I just want to touch very briefly on some cardiovascular findings with anti-diabetic drugs for type 2 diabetes. You'll hear a lot more about this from Professor Holman and Dr. Gerstein.

Earlier studies raised some interesting and somewhat unexpected findings with therapies for type 2 diabetes. For example, the UGDP reported that tolbutamide increased cardiovascular mortality compared to diet alone. These findings have been quite controversial, and I encourage the Committee to question our thought leaders about this if they would like to learn more.

Nonetheless, FDA has included a warning statement about this finding in all the labels for the sulfonylurea drugs. Tolbutamide was a first-generation

sulfonylurea.

With the UKPDS study, which you'll hear more from Professor Holman, in a self study that involved overweight patients who were given metformin as intensive therapy -- there were about 350 patients -- there was a reduction in diabetes-related death and all-cause mortality compared to conventional therapy. This finding has never been confirmed.

Interestingly, in the same study in patients who had inadequate control in sulfonylurea, they were randomized to either add on metformin or continue treatment with sulfonylurea -- the metformin add-on group had an increase in diabetes-related death -- another finding that hasn't been fully explained. Professor Holman may touch more on this during his talk.

This slide shows some of the recently completed or ongoing studies in patients with type 2 diabetes or pre-diabetes

that has cardiovascular assessments. And I'm going to focus on those studies that have a primary cardiovascular or mortality endpoint. As you can see, some of the trials have been in patients with type 2 diabetes, some are done in patients with pre-diabetes. Some of these trials have had results recently published, and Dr. Gerstein will talk on many of these trials during his presentation.

The first few studies on this slide actually are testing treatment regimens. So for example, ACCORD or ADVANCE or VADT are testing an intensive versus glycemic treatment regimen, and as I'm sure many people know, the ACCORD study was stopped prematurely because of excess deaths in the intensive treatment group.

ACCORD in all patients with longstanding diabetes and cardiovascular disease -- some of the types of patients that may be included in a cardiovascular trial of agents tested for type 2 diabetes -- and

we'll have to think how to use those results in the design of our clinical trial.

BARI 2D is testing an insulin sensitizing -- an insulin providing regimen. Of the results that have been presented so far -- for example, from ACCORD, ADVANCE, or VADT, the tested treatment regimen has failed to show a benefit on macrovascular events. There are few clinical trials on this slide that are testing specific type 2 diabetes drugs. PROactive is the only one that's been completed and published. This tested pioglitazone versus placebo as add-on to standard therapy in type 2 diabetes.

As you may hear from some of our thought leaders, there's been some controversy with that study. It failed on the primary cardiovascular endpoint, but won with a nominal p-value on a second endpoint that was added late in the game. Also, the pioglitazone group had some favorable changes in lipids and blood pressure and glycemia

that were more favorable with pioglitazone than with the placebo. Some say that may have biased results towards pioglitazone.

The other four studies are still ongoing. RECORD, as you call, published an interim analysis last year in response to the New England Journal meta-analysis -- that's testing rosiglitazone. ORIGIN is testing Vantis. NAVIGATOR is testing tagliamide and valsartin. And ACE is testing eckarbos (?).

As you can see from this slide, we have no evidence here that the treatment regimens that have been tested confer any benefit from the macrovascular endpoint, and we don't have any data on specific drugs and their effects on macrovascular disease -- or the beneficial effects on macrovascular disease.

What I'd now like to do is turn to our current FDA approval process. As I mentioned at the opening slide, all treatments for type 2 diabetes are indicated

to improve glycemic control, and FDA sees a lot of value in this. There is value in controlling symptoms in hypoglycemia such as polyurea, polydipsea (?), and this isn't at all unusual. Some surrogates we rely on -- when you lower the surrogate, you don't have any immediate symptomatic benefit.

This is a situation where lowering glycemic -- or improving glycemic control can have symptomatic benefit. We use HbA1c as our primary efficacy endpoint. It correlates with mean glucose over the preceding several months. And lowering HbA1c has been shown to reduce the risk of onset and progression of microvascular complications.

The package inserts for drugs developed for this treatment are very explicit about what the basis of approval is. We're in the process of streamlining our indication, which now reads, "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with

type 2 diabetes." If they have data in children, certainly it would change -- it would have adults and children, or patients with diabetes. We also add in a disclaimer saying that, "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Drug X or any other anti-diabetic drug." And we don't mention any improvement in long-term sequelae of diabetes with any of these therapies.

I now want to touch on the Phase 2, 3 development program in type 2 diabetes. Phase 2 is when we typically do dose-finding, although we also encourage dose-finding to continue in Phase 3. The Phase 2 program typically consists of usually one or two 12-week trials. We recommend two 12-week trials because using one trial may lead to spurious results or may have inherent biases that we don't detect.

And what we do is we randomize patients to one of several doses of

investigational agent or placebo, treat them for 12 weeks, look at the change in HbA1c from baseline to endpoint relative to the change of placebo, because a lot of placebo-treated patients in these trials have improvement in their A1c as well. It's the nature of being in a clinical trial.

Patients that are enrolled in such a trial typically are treatment-naïve. They might be washed off of a single anti-diabetic agent. Sometimes, drug companies have been using patients who are on a stable dose of metformin. We get a little weary when you have patients on background therapy, because if there is any unanticipated interaction between the background therapy and your tested treatment, you then are going to base those results on dose selection for your entire Phase 3 program, and you may have issues in doing that.

For Phase 3, these typically consist of several six-month randomized,

double-blind, controlled trials that have 6- or 18-month extensions. These can be placebo-controlled or active-controlled. An active-controlled trial could be a superiority trial. Occasionally, it's a non-inferiority trial as well. And the margin for non-inferiority is based on the known efficacy of the comparator. These six-month core trials are done in monotherapy, and then they're also done as add on to other commonly used anti-diabetic drugs.

Now, one other important issue with diabetes which I've alluded to before is that it's a progressive disease, and so that limits how long one can investigate a single agent in the treatment. Another issue relates to the placebo arms of these trials, and it raises ethical issues in terms of how long we can leave patients on placebo and have them exposed to prolonged hyperglycemia.

A typical Phase 3 monotherapy

program looks like this. It looks very similar to what you saw earlier except now we're typically six months -- one or two doses of the investigational agent versus placebo, and enrolls the same patient population as I mentioned in Phase 2.

Now, a point worth making is that in these monotherapy trials, these patients are generally at very low cardiovascular risk. They're very early in their disease process. Therefore, you're not expecting many cardiovascular events in these monotherapy trials.

Add-on trials are performed as follows. These enroll patients who have inadequate glycemic control, typically defined as an A1c of 7 to 10 percent despite stable maximal or near-maximal doses of a background anti-diabetic drug such as metformin or sulfonylurea or thiazolidinedione. These patients are then randomized to either add on investigational

agent or add on placebo. The dose of the background therapy is kept constant. Again, 24 weeks of HbA1c is the endpoint of interest.

What I'm discussing today, incidentally, is in our draft guidance which was published earlier this year and it's available on our website and was included in your background package.

So a typical Phase 3 program will have a placebo-controlled monotherapy trial, it will have an add-on to metformin trial, it will have an add-on to sulfonylurea trial, and an add-on to thiazolidinedione. And then there are several other trials that are thrown in the mix.

We could have active-controlled monotherapy trials, add on to DPP4 inhibitors now that cetaglyptin (?) has been around for a while, add-on to insulin, and also add on to dual agents, so someone who's failed, for example, metformin and sulfonylurea -- can

get randomized to add-on investigational agent or add-on placebo.

The extension trials are an interesting issue. So after these six-month core studies, patients typically enter extension trials. Now if you have an active-controlled six-month study, investigational agent versus metformin, for example, those treatment arms can continue in the extension. The issues come with these placebo-controlled trials. Again, there are ethical issues that arise related to prolonged hyperglycemia and leaving patients on the placebo for long periods of time.

So what usually happens in the placebo-controlled trials is that the placebo arm switches over, either to another anti-diabetic agent or to one or several of the doses of the investigational agent being tested. So either to one of the approved diabetes agents or to one or more doses of the investigational agent being tested.

The problem, though, with these uncontrolled extensions, it's very difficult to evaluate efficacy and safety, and so we ask sponsors if they are going to use uncontrolled extensions, how they are going to interpret those results. Sometimes they do things like adjusting for subject exposure, but again, this is not going to give you the same type of data as in a randomized control trial.

For efficacy, as I mentioned, HbA1c is the primary endpoint of interest. We do sensitivity analyses and subgroup analyses such as based on baseline HbA1c, age, body mass index, to test the robustness of the results. We also look at key secondary endpoints -- fasting plasma glucose, responder analyses -- for example, the proportion of patients achieving HbA1c below clinical practice guidelines, changes in body weight -- and then some endpoints related to the mechanism of action of the drug -- if it

works on postprandial glucoses, we look there, if it has an effect on insulin sensitivity, there will be some measures of insulin sensitivity.

For safety, we do a very thorough review. We look at all the deaths, we look at serious adverse events, which has a regulatory definition -- including things like life-threatening conditions, hospitalization. We look at discontinuations from the trial and why do people discontinue. We look at many other types of adverse events -- common adverse events, adverse events of interest -- for example, hyperglycemia.

Some of these adverse events are specific to the drug being studied. For example if it's a biologic, it might have immunogenicity concerns. Or if there's approved drugs in the class, we may know some of the safety concerns and look for those in this development program.

We do extensive analyses with laboratory data. We look at summary data, ranges of data. We look at shifts from normal to abnormal. We look at the proportion of patients with markedly abnormal labs. We do the same for vital signs, and we do analyses of electrocardiograms. And this is just some of the safety analyses we do. We do many more.

We look at inadvertent pregnancies. We look at early phase studies where oftentimes very high doses of the agent is given to see what happens with overdose. We do look at thorough QTC studies. There's a lot of things we look at, and then we tie that all in with the non-clinical data.

How do we analyze the safety data? Well, one way is to look at the individual trial data and compare findings in the active treatment group versus the control group. We also do a pooled analysis where we group data from similar trials. That certainly has to

make sense to group some of the data depending on what the analyses are you're trying to do, but this helps improve power for analyzing some of the more infrequent events such as death.

What hasn't routinely been performed but is certainly open for discussion today is whether we could go one step further and use meta-analyses, because the current Phase 2, 3 program has multiple studies that form the basis for the approval of the drug, and if we saw a signal with pooled analyses, we could then go on and test that more with a meta-analysis.

Some caveats with the safety analyses. Multiplicity. You're looking at a lot of associations. Some of those are going to be positive just by chance. Studies, as I've mentioned, are rarely powered for safety, so assessing infrequent events like deaths or myocardial ischemia can be inconclusive. And usually the events are not

adjudicated, so at the end of the day, sometimes we scratch our head with an episode of chest pain and say, well, is that a serious cardiac event or is that gastro esophageal reflux disease?

With regard to sample sizes for direct development, currently, the International Conference of Harmonization has published a guideline on sample sizes recommended for drugs developed for chronic, non-life-threatening conditions. At least 1,500 subjects total, at least 300 to 600 subjects exposed for six months; at least 100 subjects were exposed for at least a year.

Diabetes, we've moved beyond those numbers. So our minimum pre-approval sample size for type 2 diabetes -- we're talking a minimum of 2,500 patients for Phase 2/3, 1,300 to 1,500 exposed for at least a year, 300 to 500 patients exposed for at least 18 months, and these are minimums.

Certainly if specific safety

concerns arise, larger sample sizes may be required.

I just wanted to touch briefly on the rule of three as it relates to our current sample sizes. To get a sense of how rare an event -- how certain we can be about a rare event occurring with the drug -- for example, if you look at 2,500 which is our current sample size, if we expose 2,500 patients to a study drug and we see no cases of Event A -- say, severe hepatic toxicity, then we've ruled out incident rates for that event of 0.12 percent or higher with 95 percent certainty, and this shows you how those numbers break down with larger sample sizes.

What are the challenges in doing clinical trials in type 2 diabetes? One, there's -- as mentioned before, there's worsening glycemia over time if therapy's not altered, so these patients need more and more therapies over time. We have to protect

patients from prolonged hyperglycemia. We do that by limiting the HbA1c entry criteria for the studies.

We limit the duration of the placebo-controlled portions of the trials, and we have predefined glycemic risk criteria that will prompt either discontinuation from the trial or add-on a rescue glycemic therapy. These criteria are typically based on fasting plasma glucose and on HbA1c. But as I've been trying to get at, the progressive nature of diabetes results in multiple drugs being added, and if we're trying to tease apart the effects of the efficacy and safety of one of those drugs from a multi-drug regimen, that becomes a very difficult thing to do.

What we'd like the Advisory Committee to think about during the open deliberations are some of the questions on the next few slides. We'd like you to think about what changes you'd recommend to the

current Phase 2/3 trials for diabetes that would enhance detection of a cardiovascular safety signal prior to drug approval. Things like an independent, blinded cardiovascular adjudication -- the meta-analysis that I mentioned before -- do we want to make changes to sample sizes or durations of exposures? And these are just a few of the examples. I'm sure folks in the room will come up with many other useful suggestions.

Now, this is a critical issue that I wanted to spend some time on. I warned about this at the beginning of the talk, and this is what the intent of a long-term cardiovascular trial should be. Some have questioned whether we should have a long-term cardiovascular trial that shows cardiovascular benefit in a drug for type 2 diabetes.

However, there's a caveat with that. We don't have conclusive evidence of cardiovascular benefit for any of the

treatments available for type 2 Diabetes in any of those 10 classes. So setting this as a requirement now would set a very high hurdle, effect the availability of new drugs, and may very well not be possible.

We think the other question to ask is whether a long-term cardiovascular trial should rule out an unacceptable increase in cardiovascular risk, a so-called non-inferiority study. If that's the case, then important discussions at hand include how much harm do we accept; in other words, how much harm do we need to rule out. What should the non-inferiority margin be?

Other questions for the committee to consider: In the absence of a concerning safety signal in a standard diabetes program, should we require that the drug company of that agent conduct a long-term cardiovascular trial? If yes, when should it be conducted -- pre-approval or post-approval, and what do we do about marketed therapies,

which as I've mentioned, none of them have shown conclusive evidence of macrovascular benefit, and very few have been tested to show cardiovascular harm?

Here are some of the aspects that are related to the large clinical trial that could be discussion points for the Committee over the next few days. I've touched on the benefit versus ruled out harm issues. What should the patient population be in these trials? What should the comparators be? What should the primary endpoint be? What should the HbA1c target be?

As you'll hear from Dr. Gerstein, the results of ACCORD call into question normalizing HbA1c in patients with longstanding diabetes and cardiovascular disease. How do we define and manage deteriorating glycemic control? How do we manage other cardiovascular risk factors? How comparable do the cardiovascular risk factors and glycemic control need to be

between the treatment groups? And how big a trial and how long a trial would we need?

I want to just touch very briefly on each of those questions in the last few minutes of my talk. So with regard to patient population, do we want to enroll patients with pre-diabetes, new-onset diabetes, longstanding diabetes, patients who have had a recent acute coronary syndrome?

Certainly picking the population is going to affect generalizability of results, and also can affect statistical power if you pick a population that has low number of events of interest.

I just wanted to show two patient populations on this slide to give thought to this. The DREAM study enrolled patients with pre-diabetes and no cardiovascular disease, followed patients for a median of three years, and these patients had only a 1 percent event rate for major cardiovascular endpoints, an endpoint that's typically used

in these cardiovascular trials.

This 5,000-some patient trial with only 1 percent event rate would be underpowered if cardiovascular events were the primary endpoint to this study.

What about new-onset diabetes? We've spoken about how diabetes progresses. Someone might say, well, why don't we just enroll patients with new-onset diabetes, and that way, they should be able to get by with just a single agent over a multi-year trial.

Well, in ADOPT, which took patients with new-onset diabetes, followed for four to six years, up to 25 percent developed inadequate glycemic control over the course of the study. Here, inadequate glycemic control was defined as a fasting plasma glucose that exceeded 180mg per deciliter on two occasions at least six weeks apart.

Is that too loose? Is that too stringent? It would depend on many factors, such as the duration of the trial, and again,

how long we feel it's ethical to have patients exposed to prolonged hyperglycemia.

What should the comparator be? Drug X versus placebo? Drug X versus placebo as add-on to standard therapy? Drug X versus Drug Y as add-on to standard therapy? And if we're adding on to standard therapy, how should standard therapy be defined? How should deteriorating glycemia be defined and managed? And if we're comparing drug to placebo, we could expect that deteriorating glycemia will be different in the two groups.

How should we handle that?

Again, diabetes progresses. Multiple agents are likely to be added over the course of the trial. How are we going to tease apart the effects of a single drug from a multidrug regimen? If we do the cardiovascular trial, we want to rule out harm in a so-called non-inferiority trial. How much do we need to know about the cardiovascular effects of the comparator?

With endpoints, what should the primary endpoint be? Do we want an all-course mortality trial? Do we want a composite endpoint such as cardiovascular death or all-cause mortality or nonfatal myocardial infarction, nonfatal stroke?

Should we throw in other events -- worsening angina, coronary revascularization, lower extremity amputations? Regardless of what we do -- and this applies both to the primary endpoint and all other aspects of the trial -- we'll need to have these things predefined up front. They'll need to be justified, accurately captured, and analyzed.

These are the treatment goals from the American Diabetes Association 2008 Clinical Practice Guidelines, which shows some of the goals for other cardiovascular risk factors in diabetes such as blood pressure and cholesterol, aspirin therapy. How should these be managed in these

cardiovascular trials? Should all investigators be encouraged to manage these factors to current guidelines which may not necessarily ensure comparability across treatment groups, as I alluded to with the PROactive trial? Or should there be algorithms post-randomization, with the intent of equalizing these risk factors across treatment groups. What are the statistical ramifications of doing something like that?

And lastly, I'd like to close on the sample sizes for these trials. So these are sample sizes provided by Miss Joy Mele from FDA, and these show you sample sizes for a cardiovascular trial when you want to rule out cardiovascular harm. On the left, we have annual event rates for the drug and comparator. And on the right, we have total sample size to rule out an increased risk of -- for example, it has a ratio of 1.2, 1.3, or 1.4 with the drug, which are typical

hazard ratios which have been used in the past. As you can see, if you want to have a very narrow non-inferiority margin, sample sizes go up.

Also, depending on the annual event rate -- as your annual event rate goes up, sample sizes go down.

What's interesting is if your drug is slightly worse than comparator, sample sizes can become unimaginable.

So these are the questions that we're going to propose to the Committee. We'd like to throw them out now so you can ponder them while you hear the further discussions today. We can assume that if an anti-diabetic therapy has a concerning cardiovascular safety signal during a standard Phase 2/3 development program, in those situations, of course, we would conduct a long-term cardiovascular trial. But what about those drugs and biologics for type 2 diabetes that do not have such a signal in

the standard program? Should we require a long-term cardiovascular trial for those treatments? And this is where a yes/no vote is requested. If yes, we'd like you to discuss when such a study should be conducted. Should it be conducted pre-approval or post-approval? If it's going to be conducted post-approval, when should it be initiated? Can it be initiated once approval has taken place, or should it be up and running even prior to approval?

And then the last point for deliberation -- we're not asking for a vote, but we would like the Committee to discuss these -- and this relates to currently marketed therapies. So as I mentioned a few times in my talk, none of the marketed therapies for type 2 diabetes have established conclusive evidence of macrovascular benefit.

Also, most of these marketed therapies have not been tested for lack of

cardiovascular harm.

So if you feel a cardiovascular trial should be a requirement in type 2 diabetes, how should that requirement apply to existing therapies?

Thank you for your attention.

DR. BURMAN: Thank you very much. We will now proceed with our guest speakers' presentations. I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Nathan?

DR. NATHAN: Thank you. I'd like to thank the FDA for inviting me to join this discussion of this obviously very important question. I'm also pleased to be included with such a distinguished panel of experts in the area.

One of the reasons I'm being effusive about complimenting my fellow

speakers as I'm about to give their talks and mine if they'll forgive me.

I was asked to talk about actually the natural history of cardiovascular disease and diabetes. I found that's somewhat ironic talking about the natural history here at the FDA. Everything is treated history or clinical course. So the general topic is the role of cardiovascular assessment, obviously, in the approval process of diabetes medications.

I've chosen to maybe change that a little bit to a diabetes, hyperglycemia and cardiovascular disease, one in the same. It seems to me that we have gotten to a point where, predominantly for safety reasons that Dr. Joffe has reviewed, there's concern as to whether -- or there is interest in whether diabetes medicines should be judged in some way according to the outcomes of another disease, which is cardiovascular disease, as I will discuss, a tightly affiliated disease

with diabetes, but not the same, I don't think.

So I'm going to address whether in fact diabetes and heart disease are the same, what their common origins are, the common soil that many have been investigating, and we'll discuss those issues. And again, I apologize to my fellow speakers. I suspect there will be some redundancy during the day, and I will start with that.

So let's start with the basics. I mean, what is diabetes? This is the definition that one finds in the World Book Encyclopedia, the millennium version, and it says, "Diabetes mellitus is a chronic disease characterized by abnormal metabolism of glucose, blood sugar, as well as other nutrients such as protein and fat, and accompanied by the risk of long-term complications specific to diabetes that affect the eye, kidney, and nervous system."

So this has a very nice circular

definition, as most definitions are supposed to be in some way, referring to diabetes being a disease that's related to diabetes complications. It's kind of you know it when you see it. It doesn't reflect or refer to cardiovascular disease. So this seems to me to be defensible, since I wrote it, actually.

I was actually asked by the World Book in 1999 to write the new millennium definition. They said I had 342 words, because it had to be exactly the same number of words, so I crafted it to be 342, and they said they were going to give me 27 volumes of the World Book Encyclopedia for free if I did it, or I could have the disc.

So I was no dummy. I took the disc and I wrote the thing, and then about two days later I saw in Barnes and Noble it was remaindered for $1.99, the disc.

In any case, the nosology of diabetes is related to hyperglycemia, as I see it -- I'm going to defend this -- as it

relates to complications that are relatively specific to diabetes, and not cardiovascular disease necessarily.

The relationship between glycemia and the long-term complications I think had been suspected and proposed for decades, obviously, but didn't come into focus until the measurement of chronic glycemia became refined with the development of the HbA1c assay in the late '70s and '80s, and here's just an earlyish paper from my group looking at the relationship between retinopathy and the prevalence of retinopathy according to A1c. The assay we used then is the same assay we use now, so this actually is the currently used HbA1c assay. It's identical to it.

And again, one sees this relationship -- this is prevalence -- between the prevalence of retinopathy and a rise in the A1c levels on the X axis.

The same kind of relationship has

been used to actually define the glycemic cut points. That is where we actually define diabetes. So this is from the 1997 Expert Committee Report that the ADA sponsored, which looks at where one defines diabetes based on glycemia. And here you see three different epidemiologic studies. Most of this is also prevalent so that one of these studies had some longitudinal data in it.

And what one sees is that lower levels of glycemia -- and this is rather small, the fasting glucose 2RA1c, but there seems to be an inflection point for all of these, below which diabetic complications don't occur. Therefore, conversely, diabetes is defined generally as some level of glycemia above that where you start to see, in this case, retinopathy.

An easily quantifiable complication that is fairly unique although not absolutely unique, but pretty unique to diabetes. And these are numbers that actually I think were

picked out in the paper or noted in the paper. You can look at where the inflection is, and it turns out to be an A1c of about 6. The two-hour glucose level, as you all know, is one of greater than 200 after a glucose tolerance test, and fasting is currently the consensus is greater than equal to 126mg per deciliter, but all of this reflects a relationship between glycemia and what is again described as a relatively specific complication of diabetes.

So the model here in terms of diagnostic criteria is that the diagnosis, the diagnostic cut-offs, are predicated on glucose levels associated with risk for diabetic complications. Again, a kind of circular argument. And the notion is that although risk increases with rising glycemia, here, there is a threshold below which diabetic complications do not occur.

Now, where one draws the line and whether this is absolutely true has come into

increasing question of late, in part because of one study from the Diabetes Prevention Program study, and lots of other studies, frankly.

There was another epidemiologic study recently published that shows the same thing. And what it shows is that either we've drawn the line slightly incorrectly, or this notion that diabetic complications really start at a very specific glucose level, glycemic level, may be incorrect. It's probably actually where one draws the line, because as you see on the previous slide, there really is a little bit of noise down here, but it's really pretty low in terms of prevalence in this lower part of the graph.

But the new studies that have come out, or relatively newer studies that have come out, have shown in fact, from the diabetes prevention program, which started with a population of persons with imperative

glucose tolerance plus some abnormality in fasting glucose, but who had never had diabetes, never had diabetes, that in that population, when we look at photographs of their eyes, about 8 percent of them had evidence of what was considered a characteristic of typical diabetic retinopathy.

Again, so these are patients who had not had diabetes in the past. We followed them for six or seven years. At this point in the study, had never developed diabetes. Some of them had reverted to normal glycemia, in fact, out of the impaired glycemia group, and yet they had about 8 percent of -- 8 percent of them had some evidence of retinopathy.

Of note, within about two to three years when we had taken these photographs, from two to three years on average, in the patients who had developed diabetes during the study, in fact their risk of

micro-aneurisms had gone up by about 1-1/2-fold. So about 12 percent, 13 percent of them had microvascular complications at this point.

So this is probably a pretty good and sensitive measure of "diabetes" or the effect of hypoglycemia on the organs.

So that's the associational, the epidemiologic data linking glycemia with complications. Do we have more causal data? Do we have actually control trial data? And the answer is, obviously, yes. Again, I don't want to step on Dr. Ratner's talk, but in the Diabetes Control and Complications trial, a DCCT study which is co-chaired by Dr. Genuth, a member of the panel, and myself, we know back from more than a decade ago, of course, that if you separate A1c in this controlled clinical trial by about 2 percent, one gets rather remarkable effects on diabetic complications, including retinopathy, neuropathy, and nephropathy. So

this was evident to us in 1993.

Lower glycemia in the setting of type 1 diabetes, and one has this effect. So the reason I'm bringing up type 1 diabetes and the DCCT in particular, is that it represents still kind of the clearest example of the effects of glycemia on complications. The second reason I bring it up is that I am under a lifelong contract with NIDDK to talk about it once a day, so I've fulfilled my obligation today.

So this is in addition to the associational data, this is the control clinical trial. This is kind of moving towards a Cox's postulates of the relationship between glycemia complication in this disease we're calling diabetes.

So intensive therapy of type 1 diabetes, DCCT, the Stockholm Study as well, by Pere Rouchard, which everyone forgets about, but a very important clinical trial that really looked just like the DCCT,

demonstrated this causal relationship.

Lower glycemia -- not only is glycemia is associated with complications, but you lower glycemia and you increase the complications.

For type 2 diabetes, we have Dr. Holman here so I'm not going to talk much about the UKPDS because I'll get it wrong because I usually do, but in any case, it looked in type 2 diabetes just as we were doing in the type 1 diabetes in the DCCT, they created a 1 percent separation in A1c, a little bit different than in the DCCT, also because it demonstrated most importantly that type 2 diabetes is not a stable metabolic disorder, but it gets progressively worse over time.

But nevertheless, without going through the details, the UKPDS and another study, the Kumamoto study in particular, showed that in fact, again, lower glycemia and you reduce the long-term complications of

diabetes, and these were the microvascular complications as in the DCCT.

The relationship or the association that's been demonstrated at both of these studies is that higher -- and it's this kind of monotonic, (inaudible) linear relationship, so a (inaudible) relationship for the DCCT, and you see that the higher the -- the current mean A1c means the average A1c up to the point that the patient was censored or developed the complication, and here you see this relationship between A1c and retinopathy for the DCCT with this 43 percent reduction in risk.

For every 10 percent reduction decrease in A1c, 10 to 9, 9 to 8.1, 8.1 to 7.3, and a similar type of relationship demonstrated in the UKPDS. Again, these are now associations derived from experiments through controlled clinical trials.

All right. So here, we have a point at which it appears that -- again where

you draw the line is of some question -- but a point at which complications start developing, where you go from end type 2 diabetes from IGT or IFG to calling it diabetes -- and in addition, once you have diabetes, there's this relationship between complications and hyperglycemia. Ergo, glycemia is important in diabetes and it's important, in particular, with regard to microvascular complications.

So the apparent glycemic thresholds for the development of complications define the diagnostic cut point for diabetes. Glycemia in the diabetic range is associated with risk for developing complications, and treatments that lower glycemia reduce the risk for development and progression of those microvascular diabetic complications. So nowhere in here have I talked about heart disease yet, cardiovascular disease, which as Dr. Joffe pointed out is arguably the most important complications, because it's what's

associated in type 2 diabetes, but certainly the majority of mortality and a substantial fraction of the morbidity.

So where do we go from here? Well, here I say that on the basis of the intimate association between glycemia, and in particular measures of chronic glycemia, with diabetes complications based on epidemiology and clinical trials, the effectiveness of medications to lower A1c has been used as a metric in considering new diabetes medications, as Dr. Joffe has already mentioned.

However, as he has also mentioned, recent experience has suggested that some anti-diabetic medications may worsen CVD risk, and that as well as the misunderstandings or the kind of conflation of cardiovascular disease as a diabetes complication have I think led us to where we are now.

So again, re-framing what Dr. Joffe

has said much more eloquently than here, some have questioned whether the FDA posture of approving diabetes medications on the basis of their effects on glycemia, a surrogate, is adequate. And then the question, again restating what Dr. Joffe has said, should the effects of diabetes medications on CVD be required during the approval process in some way based on toxicity or benefits?

So again, how did we confuse these diabetes complications -- eyes, kidneys, and nerves -- with heart disease? And it starts in a major way, I think, back in 1999, when the American Heart Association published this pamphlet, a joint editorial statement, on diabetes mellitus, and finally recognizing it a little bit late as a major risk factor for cardiovascular disease. And in that statement, they concluded that thus, diabetes must take its place alongside the other major risk factors as important causes of CVD.

In fact, from the point of view of

cardiovascular medicine, it may be appropriate to say -- and the yellow is mine but the quotes are theirs -- "diabetes is a cardiovascular disease."

So here, the cardiologists kind of subsuming diabetes under their wing. This led to, I think it's fair to say, some panic in the endocrine community. We had already seen lipids and blood pressure stolen from us by the cardiologists, and now the one disease that they had refused to touch because it was too much of a pain, frankly, now they were co-opting it as well and we would be left -- I don't know -- doing research, I guess.

So the origin of this kind of signal event was in fact the paper I think published by Steve Haffner -- the Finnish study in which he was the lead author, a non-Finn, the lead author of this, in which as you all know at this point, that what he demonstrated -- what this study demonstrated

was that diabetes seemed to have the same impact in terms of risk factor as having had a previous major cardiovascular event.

So if you looked in patients with no prior MI, the yellow being the diabetic population, the green being the non-diabetics, at first, the seven-year incidence of major cardiovascular events, MICVA or mortality, was substantiality higher by four- or five-fold in the diabetics than the non-diabetics, but if you looked at those with prior MI, again, a kind of two- to three-fold increase in the diabetics than the non-diabetics, but in fact, the diabetic patients without prior MI had the same risk of seven year incident risk of an event as did the non-diabetics with a prior MI.

And that's where this common kind of idea that diabetes is essentially the cardiovascular risk equivalent of having had a prior MI.

So this is kind of the birth, I

think, of most of the major concern that we're looking at. Of course, the data are far older than that. We can go back 40, 50 years to the Framingham Study, which clearly delineated the relative increased risk especially in women -- diabetic women compared to non-diabetic women, but in men as well, of course -- of the effect of diabetes on cardiovascular disease.

So in type 2 diabetes, the confusion is heightened a bit by the fact that diabetes, type 2 diabetes in particular, is accompanied by these numerous risk factors for cardiovascular disease. So if we look at cardiovascular disease, of course the generic, non-specific effects of age and smoking have an effect, but then a lot of the other major Framingham risk factors -- hypertension, obesity -- and this is a more late-coming risk factor -- dyslipidemia -- you know, contribute to CVD, and all of these in yellow

are increased in prevalence and in severity in type 2 diabetes.

And it leaves the question, of course, is what does hyperglycemia itself contribute? And hyperglycemia can contribute through the development of renal disease, again a diabetes-specific complication, which really heightens the risk for cardiovascular disease as much if not more than any one of these others, and then there is autonomic neuropathy, cardiovascular autonomic neuropathy, increasing potentially the risk of especially cardiovascular mortality, (inaudible) glycated lipoproteins -- I mean, how hypoglycemia specifically contributes in this isn't so clear.

What is clear is that even if you subtract out all of those other co-morbid, or those other risk factors, that hyperglycemia appears to still play a role. It's not the most powerful role of all, perhaps, but it still persists as a risk factor for

cardiovascular disease.

So the question is really, how does it contribute? So I'm born and bred in Brooklyn so I remember the "Honeymooners," how sweet it is, and the question is whether in fact or to what extent the hyperglycemia itself contributes to the cardiovascular disease as opposed to the other risk factors that accompany type 2 diabetes so often.

So association of glycemia with CVD. Hardly anyone's old enough to remember, but there was something called an International Collaboration Publication in 1979 that looked at dozens of papers that had attempted to link glycemia itself with cardiovascular disease, and which concluded that they couldn't divine -- they could not demonstrate an association between glycemia and cardiovascular disease for a whole variety of reasons in retrospect -- for the most part, probably because the measurement of glycemia was really so inept. Again

before the HbA1c measurement came along.

So early studies could not demonstrate or establish a relationship, again owing in part to poor measures of chronic glycemia. In 1992 using Framingham data, we were able to establish a significant relationship between glycemia measured with A1c. We went to Framingham and basically offered to do A1cs in them for free in whatever was the surviving population.

Previously, they had had a measurement of glycemia which some of you may recall was called a casual glucose measurement, which was basically whenever they came in, they grabbed a glucose and that was the level that they had. And we were able to look at the relationship between A1c and prevalent CVD in the predominantly non-diabetic Framingham population. And subsequently, as you know, there have been a dozen studies at least, and much more impressive, frankly, than this initial

Framingham Study that have shown the same.

What we showed in Framingham, we had about -- of the original 5,200 or so Framingham patients recruited in 1948, there were only about 2,400 who were surviving. Of the 2,400, about 1,200 of them live in Florida now. And so we were able to look at 44 percent of the survivors. We measured the A1c in 1986 to '89 and then looked at the prevalence, the prevalence of CVD major risk factors controlled for all the Framingham other risk factors, and were still able to demonstrate this rather powerful effect of glycemia on the prevalence of complications, of cardiovascular disease complications.

So this is our -- we published this in Diabetes, I think, and here you see in women and in men, this relationship between rising A1c and CVD. And please note that here, that these first, second, third, and fourth quartiles are for the most part in the non-diabetic range. It isn't until you get

to the 4th quartile, greater than 5.92, that you start getting into the diabetic range. And on the very bottom of this slide, you can see that the diagnosed diabetes in these groups were really quite tiny until you got to the 4th quartile, about 25 percent.

In fact, when we subtracted all of those patients who were known to have diabetes, it didn't change this result at all, so the relationship between glycemia here in this first demonstration, appeared to be mostly in the sub-diabetic range of glycemia. Sub-diabetic range of glycemic using A1cs -- one sees an increasing risk as one of those from the kind of the referent quartile, first quartile, up and up, and you see the risk of cardiovascular disease increases.

Now, this kind of study has been done much better -- of course, you have this initial foray, so this is now 12, 14 years later -- and here's the epic Norfolk Study

which looks at more than 4,000 men, more than six years of follow-up, and here we see incident cardiovascular disease of much greater interest.

And here you see the same kind of risk profile -- in the sub-diabetic range here of A1c, there is an increasing risk for cardiovascular disease of all sorts, and here you see I've put roughly in triangles were the diagnosed diabetic patients, were with relative risks of kind of about four- to fivefold, not that different than the Framingham Study which showed two- to sevenfold increases in risk with men and women.

So, again, we're looking at sub-diabetic hyperglycemia, to some extent. Once you develop diabetes, type 2 diabetes in this case, the risk jumps substantially, but even in the sub-diabetic range, there seems to be an association. We have gone back and further looked, since the Framingham Study,

again, most of the population was gone, we went back and looked at their children, the Framingham Offspring Study. Now, these folks are already in their sixties, so they're no longer that young. But when we did this, which was several cycles ago, I published this in 1998, we took that population.

And this -- you see we divided glucose tolerance. Here, we divided by fasting glucose, but I can show you exactly the same relationship. In fact, it may be even a little bit stronger if you look at A1c as the way we divide them. And we look at normal glucose tolerance quartile or quintile, one, two, three, four, five, and then we looked at IGT and diabetes, and we looked at it. We didn't have enough incident events, although we're looking at those now, of course -- about 10 years ago, we didn't have enough incident events of cardiovascular disease, but we started looking at the risk factors.

How did glycemia correlate, for the most part, in the sub-diabetic range, with the risk factors for heart disease? And whatever one we look at -- I'm only giving you a couple of examples, this is hypertension -- one sees the p-value trend here is less than .001, and one sees a smooth and continuous relationship across the entire range of glycemia with regard to -- in this case, hypertension, .001. If you look at the low HDLs, it's the same thing. If you look at high triglycerides, it's the same thing. If you look at insulin resistance, it's the same thing.

And so for all of these, we see a smooth and continuous relationship in the sub-diabetic range. And these patients, now we've ruled out diabetes because you've done glucose tolerance tests as well as A1cs and fasting blood tests as well. We also looked at some of the bio -- you know, at that point. What were they -- I mean, looking at

Fibrinogen factor seven. These are not the most up to date biochemical markers of arthrosclerosis but looking at these -- and they also all had the same kind of p-value for trend.

And subsequently there's a cottage industry in looking at this in metabolic syndrome across glycemia in both, again, the sub-diabetic range going right into the diabetic range. So this provides a slightly different model. The one that I presented initially -- again, depending on where you put your cut point, but the bottom line is that diabetes itself has a threshold of hyperglycemia below which you don't get complications -- once you reach that level, there's a relationship, but for CVD, it's starting to look like it's a continuous relationship with hyperglycemia.

And even when you control for these other risk factors -- hypertension, dyslipidemia, et cetera -- that relationship

appears still to persist. But it looks like instead of a categorical kind of definition of where the disease starts, it's more of a continuum.

Okay, so that's the associational or the epidemiologic data that relates hyperglycemia with CVD in the same way as I talked about hyperglycemia and the more diabetes-specific microvascular complications.

Are there any data that suggest that there's causal relationship here? And for that I need to turn back to the DCCT/EDIC. In 2005 we published this kind of long-awaited analysis. We had to follow our population for 18 years to demonstrate it, but what we demonstrated was that if you looked at the original intensive treatment group, compared it to the original conventional treatment group, again a separation of A1c of about 2 percent, keeping in mind that after the initial DCCT ended,

1993, A1cs came together, so this really is related to an initial period of glycemic separation.

You get this fairly profound effect on cardiovascular disease. This is major outcomes non-fatal and fatal MI stroke and MI. And you see a 57 percent reduction. The absolute event rates are tiny for a cardiologist, they'd look at this and go, yeah, these are pretty young, healthy people and they were. Nevertheless, we're demonstrating an effect of glycemia on cardiovascular disease in type 1 diabetes.

Now, why have we been able to see this type 1 diabetes but we haven't yet been able to show it, as I'll review briefly, in type 2 diabetes? Well, here's type 2 diabetes with all of its multiple risk factors, all of which are increased prevalence, type 1 diabetes -- I'll just push this button here -- type 2 to type 1, and the only risk factor that really is present here

is hyperglycemia. That doesn't mean that type 1 diabetic patients don't get hypertensive over time like everyone else, if they get renal disease in particular, but by and large, the dyslipidemia they have is rather subtle -- compared to type 2, there would be a prevalence of obesity. Back then, certainly it was much lower, the country was much thinner.

Now that's changing a bit. We see many of our type 1s have the same prevalence of obesity as the general population, but in any case, back in the DCCT days, when we started, most of these patients were not hypertensive. We screened against hypertension actually. They weren't obese, they weren't that insulin-resistant, they didn't have a profound dyslipidemia.

So this is an example of really pure glycemia as it affects cardiovascular disease. Different than type 2 where you have this morass of other risk factors, the

treatment of which -- and those risk factors may actually interfere with our ability to see an effect of glucose control on CVD.

The bottom line is that with type 2 different than type 1 -- and the following speakers will go, I'm sure, into many of these studies in much greater detail -- but no control clinical trials have been able to demonstrate a benefit of intensive therapy and at lowering glycemia on CVD events, everything from the UGDP, UPKDS, ACCORD, ADVANCE, PROactive, VADT, the interim report of RECORD, none of them have suggested a benefit to date -- again buried in the setting of type 2 diabetes with multiple risk factors.

Some trials, as has been noted -- and that's why we're here -- have suggested harm with specific drugs or regimens. UGDP was tolbutamide, UKPDS as was already mentioned is this funny combination of sulfonylurea and metformin in one substudy

but not in the rest of the study where people were changed to combination therapy, the ACCORD regimen, as Dr. Gerstein will be talking about.

And then some trials have suggested benefit. UKPDS and metform was kind of this borderline which has not been repeated. A PROactive study, again highly contentious study for many of us who are clinical trialists, it made us a little bit nauseated to read it, but pioglitzone with this principal, secondary, late chosen outcome, pioglitzone may have helped there.

So where do we go from here? Well, the question is, I think, really whether there is this common soil, whether there is a common origin in some way between type 2 diabetes and CVD that is related to glycemia, because what we're talking about is glycemic medications -- the medications chosen to treat glycemia, and the question has been whether there are common antecedent risk

factors that underline both of them -- demographic, clinical, biochemical, or genetic -- and if common soil is present, are there treatments that modify both?

Are there treatments that modify such factors that might ameliorate both diabetes and CVD, and should we expect medications that affect glycemia to therefore affect CVD? So the common soil -- I mean, you've seen this probably more elegantly than here -- the common soil, for example, obesity, increased fat mass with all of the adipal kinds that have been implicated now in inflammation and hemoreologic (?) abnormalities that underlie maybe diabetes and CVD or in some resistance, another way of looking at it.

And these lead to insulin resistance. For example, IGT and then in the setting of insulin deficiency, progressive metabolic abnormalities lead to diabetes and dyslipidemia and hypertension that can lead

to an endothelial, inflammation, and thrombosis. So again, common soil here, and those can lead to CVD.

So there you go as a common skein of risk factors, of metabolic changes that can lead to both diseases, but it gets much more complicated than that since all of these have bi-directional relationships. The more you look, the more you find that it is not clear that there is one pathogenetic stream that leads to both of these. It turns out to be quite complicated.

Some examples. I mean, I'll just give you two very quick ones. The insulin resistance one, I'm not going to play out because you've all seen it. I mean, that insulin resistance is associated with metabolic syndrome, and then furthermore, type 2 diabetes is absolutely clear, it's been established over more than 20 years -- that it's associated with CVD has also been established in numerous

examinations, more recently inflammation. So I'll pick one surrogate marker of inflammation, it's not everyone's favorite but it's one of the earlier ones, CRP. So here we see the Reykjavik Heart Study looking at the relationship between CRP.

And here is the odds ratio for an MI. And the higher the CRP -- and this is just one of dozens of studies that have shown this -- higher CRP, even when controlled for other inflammatory markers, even when controlled for other risk factors, seems to be associated with an increase in MI risk, cardiovascular disease risk, the same thing for diabetes.

The higher your CRP level -- okay, so again, is a marker of inflammation being the common soil that underlies them both, and this is the MONICA study looking at 4,000 patients over seven years, incidence of diabetes adjusting for all of the -- you know, age, BMI, smoking, blood

pressure -- the odds ratio for incident diabetes by quartile of CRP goes up. The Rotterdam study, same kind of thing. This is when it's just adjusted for age and sex. Here if you adjust for age, sex, BMI, blood pressure, stolic, diastolic, HDL levels, again associated with diabetes.

So just one example of this common soil. So if we treated inflammation, would we both treat diabetes as well as heart disease? Would that be a legitimate reason to look at both heart disease outcomes as well as diabetes outcomes? However, if we think about cultivating that common soil, there are no good examples of CVD interventions that improve glycemia. I mean, some of them have weak effects -- in fact, though, the DREAM study failed to demonstrate the putative benefit of ACE-inhibitors, and several very commonly used classes of drugs for CVD actually worsened glycemia.

Beta-blockers for example, worsened

glycemia. The TINSIL study is an ongoing study sponsored by NIDDK, I think, yes? Shaking your head? Sponsored by NIDDK, that is looking at the effectiveness, potential effectiveness of an anti-inflammatory agent or drug that fits into that class of drugs on diabetes.

What about more specific examples? Lifestyle interventions, so lifestyle interventions we think of, although the data are not very strong at this point, but we certainly all think that if we could reverse those pernicious lifestyle factors that lead to both an increase in diabetes and CVD, that it might have a benefit. So the ongoing Look:AHEAD study is particularly important here. So Look:AHEAD is a study of persons with type 2 diabetes where the major outcome is cardiovascular disease.

It is mid-term about now. It's got another five years to go or so, but already, they've published one year of data and sure

enough, lifestyle intervention aimed at weight loss and increasing activity, which most of us kind of assume, oh, it's got to be good for you, but this is a study that's looking specifically to determine whether it's good.

So first thing is that it lowers A1c in the first year, and it also lowers the use of medications, anti-hypertensive and hypolipidemic agents, it lowers blood pressure, diastolic blood pressure -- LDL was not changed very much -- HDLs are raised significantly more. These are all relatively small changes, but statistically significant, triglycerides, lowered more significantly, and microalbuminuria levels are lowered. So an example of, again, an intervention that may affect both CVD and diabetes, and we can see even early on that there may be some effects that would benefit both.

What about glycemic medication therapy? I'm going to leave this to the

following speakers, but looking at the chronic effect of chronic glycemic control, we've got ACCORD, ADVANCE, all those other trials that I mentioned, that have studied in the aggregate about 30,000 patients and have not been able to demonstrate an effect of glycemic control on cardiovascular disease.

But as I noted at the recent ADA meeting where I was chairing the advanced study, the problem is that this is all terribly confounded, because all of these regimens end up using different profiles of drugs in the intensive treatment group versus the conventional; therefore, you have this almost by design a confounding of the effective lowered glycemia with the medications used to achieve those levels.

And it's really going to be, I think, impossible, frankly, to disentangle those two issues over time. What about this issue about toxic drugs? And again, I'm going to just mention as Dr. Joffe's already

mentioned them, and other speakers will talk about them, but for the question as to whether specific diabetes medications are cardio-toxic, we've been living with this since the UGDP. So this is actually not new. This is actually a very old question that has just resurfaced now.

The issue about the tolbutamide, the 1 percent CVD mortality associated with it. Biguanides we talked about in UKPDS, questionable finding with sulfonylureas, rosiglitazone, Dr. Nissen is here and will talk, I'm sure, more about this, and then of course the most recent, the ACCORD intensive regimen, where this excess number of deaths in the intensive treatment group forced the early termination of the glycemic part of that study.

Conversely, are there beneficial interventions? Well, there's a list of medications that may be beneficial, none of which have been established. The use of

insulin with intensive therapy acutely in the DIGAMI and Leuven Studies, this is looking in the acute treatment post MI or in the surgical ICU setting. Metformin with sulfonylurea may be bad, metformin without sulfonylurea may be good UKPBS. Acarbose and the STOP-NIDDM study looking at the prevention of going from pre-diabetes to diabetes. And then this question about pioglitazone as I've mentioned already.

So, conclusions. Back to the basics, back to definitions where I started. I'm going to give you my opinion here. Obviously just my opinion because I can't stay for the entire two full days, but going back to the basics. Diabetes and its long-term specific complications and hyperglycemia are tightly linked -- the specific complications.

The rationale for decreasing glycemia is primarily based on its demonstrated effect on diabetes-specific

complications. Somewhere in this entire discussion, we've lost that. The reason we did this was for DCCT, UKPDS, other studies demonstrated I think unquestionable beneficial effects of lowering glycemia on those complications, not on cardiovascular disease.

Cardiovascular disease, the issue that we've seen now has been an adverse effect of some of these medications. Although hyperglycemia is associated with CVD, no studies of type 2 diabetes have demonstrated a benefit of lowering glycemia on CVD. And again, my opinion, approval of diabetes medications on the basis of lowering glycemia seems merited -- assuming they are safe. No one has said that we should just adopt medications that improve your eyes but kill you.

That's just nothing -- none of us that that was what we were looking for. And I think the issue summarizing how many

patients we'd need to study to look for safety in this would basically slow down the development of good glucose lowering medications infinitely. I think that would be, frankly, a mistake. The potential adverse or beneficial effects, especially on CVD of such medications, should obviously be taken into account but should not be the primary basis of approving or not approving glucose lowering drugs.

Thanks for your attention.

DR. BURMAN: Thank you very much. Any questions from the panelists?

MS. FLEGAL: I have two questions. One is, your graph showed that for retinopathy, a threshold effect and that there would be no particular impact below a certain value then increasing impact above that. For cardiovascular complications, you showed a different effect in people without diabetes, where risk increased at lower levels of HbA1c, but what do you think the upper portion of that

curve is like?

One graph almost suggests that it goes up and then flattens. So you do align with kind of going up and up and up. Do you think it flattens out or goes up beyond that part? Or do we know? And then sort of a related question, could you just comment on the implications of that relationship for the benefits or the implications for lowering glucose levels below the diabetic level for people in terms of CVD prevention.

DR. NATHAN: So in terms of what the graph looks like at the high level, much of the data we have is looking at dysglycemia states as categories, so looking at for example, IFG versus IGT versus diabetes. And then there's another set of data, some of which I showed you, that looks at A1c as a continuum, just looking at what happens, and the graph I showed you for A1c really looks pretty much as I showed it.

There's a discernible increase in risk as your A1c gets higher. This is for