Media Telephone Briefing
NHLBI Changes Intensive Blood Sugar Treatment Strategy in ACCORD Clinical Trial
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Unedited Transcript

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PRESENTATION

Moderator — Ladies and gentlemen thank you for standing by and welcome to the NHLBI Teleconference Call. At this time all participants are in a listen-only mode. Later we will conduct a question and answer session. Instructions will be given at that time. As a reminder, this conference is being recorded. I would now like to turn the conference over to our host, Dr. Elizabeth Nabel. Please go ahead.

D. Striar — Good morning, this is Diane Striar, Acting Communications Director for the National Heart, Lung and Blood Institute. Thank you for participating with in this briefing. We will start this morning with a statement from Dr. Elizabeth Nabel, Director of the National Hear, Lung and Blood Institute. Following Dr. Nabel's remarks, several representatives from the

leadership of the ACCORD Clinical Trial will make statements. ACCORD stands for Action to Control Cardiovascular Risk in Diabetes.

After the remarks we will field questions. The AT&T operator will provide instructions for asking questions. If you have not received the press release on ACCORD, it is now online at www.nhlbi.nih.gov. Prepared remarks from this morning will be posted online during the news conference. Dr. Nabel.

Dr. E. Nabel — Thank you and good morning. Today we're sharing with you a major finding and decision regarding the ACCORD trial. ACCORD is a large, important clinical trial designed to determine the best way to decrease the high rate of heart disease among adults with Type 2 diabetes who are especially high risk for heart attack and stroke. As you know, Type 2 diabetes is a complex metabolic disease that results in elevated blood sugar levels.

The ACCORD trial, which began in 2001, is testing three treatment approaches. One, intensive lowering of blood sugar levels compared to a standard blood sugar treatment; two, intensive lowering of blood pressure, compared to a standard blood pressure treatment; and three, treatment of blood lipids by a fibrate, plus a statin compared to a statin alone.

This morning we are announcing the outcome of one of the treatment strategies and a change in how the study will be conducted. After thoroughly reviewing the data collected to date, ACCORD investigators found that among those adults with Type 2 diabetes, who are at especially high risk of cardiovascular disease, a medical treatment strategy to intensively lower their blood sugar levels below the current guidelines, increase the risk of death compared to standard blood sugar lowering treatment.

Because of this finding, and at the recommendation of the study's Data and Safety Monitoring Board, the NHLBI is stopping the intensive blood sugar lowering treatment part of this study 18 months early. Although we have stopped this treatment, we will continue to care for all study participants.

Participants who were receiving the intensive blood sugar lowering treatment will now receive the standard blood sugar lowering treatment, which aims for blood sugar control, similar to that achieved in the general population of similar adults, treated for Type 2 diabetes, which is an A1C level of about 7.5%. As you know, A1C is a measure of blood sugar levels. The treatment approaches for testing blood pressure and lipid control will continue until the study ends as planned, in June 2009.

As always, our primary concern is to protect the safety of our study volunteers. We made the decision to stop the intensive treatment approach in the ACCORD study after a thorough review of the health risks to the study participants. We will continue to monitor the health of all study participants. We will seek to understand the underlying causes for this finding, and we will carry on the other important research within ACCORD.

These findings from ACCORD will inform treatment decisions for the millions of individuals with Type 2 diabetes who are at especially high risk for cardiovascular disease. It is important to note, however, that these results apply only to those individuals who are similar to the study participants.

All 10,251 participants had Type 2 diabetes on average for ten years when they enrolled in the study. In addition, the ACCORD participants had blood sugar levels that were higher than most Type 2 diabetic individuals in the United States today. That is on entry their A1C levels were about 8.2%.

To be eligible for the study, participants also had to have known heart disease or at least two risk factors in addition to diabetes, including high

blood pressure, high cholesterol, obesity and/or smoking. In other words, they had diabetes, plus other risk factors, which placed them at even higher risk for heart disease than if they had just diabetes alone. In this population of individuals with Type 2 diabetes, at especially high risk for heart disease, it has been observed that the risk of death is approximately 50 deaths for 1,000 individuals per year or about 5% per year.

All ACCORD participants were randomly assigned to either an intensive medical treatment strategy, with a goal to lower A1C levels to less than 6% or to a standard medical treatment strategy to lower A1C levels to 7% to 7.9%. A variety of FDA approved medications were used to try to reach the assigned blood sugar goal.

Now here is what the ACCORD researchers found. First, the median A1C level achieved in the intensive treatment group was 6.4%, while the median A1C level in the standard treatment group was 7.5%.

Second, in the standard treatment group, we observed 11 deaths per 1,000 individuals per year on average over the four years of follow-up. In the intensive treatment group, we observed 14 deaths per 1,000 individuals per year. First and foremost it is important to recognize that this death rate

is lower than what has been previously observed in individuals with Type 2 diabetes at especially high risk for heart disease.

Third, nonetheless in the intensive treatment group, there were 257 deaths and in the standard group 203 deaths. This is a different of 54 deaths or three per 1,000 participants per year over an average of four years of treatment. Because of this difference, the increased risk between the two groups outweighed the potential benefits of the intensive treatment strategy on non-fatal events.

Accordingly, the NHLBI has made the decision to stop this intensive treatment approach in the trial. This is an important finding, which shows that if you have Type 2 diabetes and are at especially high risk for heart disease, very intensive glucose lowering treatments aimed at normalizing blood glucose to an A1C of less than 6% may be detrimental.

These preliminary findings of the ACCORD trial are consistent with recommendations from the American Diabetes Association in three aspects. First and foremost, individuals with diabetes should not change their diabetes treatment without consulting first with their healthcare provider.

Second, we concur with the general recommendations of the ADA that advises people with diabetes to aim for an A1C level of less than 7%, understanding that treatment should be individualized.

Third, for this very special group of individuals with diabetes, as exemplified in the ACCORD population, which had an average age of 62 and had diabetes for an average of ten years, and had known heart disease or were at high risk, less stringent A1C goals are likely appropriate, with an aim for about 7%.

ACCORD researchers have extensively analyzed the data available to date and have not identified any specific cause for the higher death rate among the intensive blood sugar treatment group. We know that the higher death rate is not due to episodes of low blood sugar, known as hypoglycemia or due to any single drug, including rosiglitazone or any combination of drugs.

As I stated earlier, ACCORD researchers will continue to monitor participants and will conduct additional analyses to try and explain the findings, while continuing other important research studies, which are part of ACCORD.

Now I'd like to take a minute to describe how the decision to change the blood sugar treatment part of the study was made. The ACCORD Data and Safety Monitoring Board, or DSMB, is an independent group of ten experts who were appointed by the NHLBI to regularly examine study outcomes and safety data. The DSMB has expertise in diabetes, cardiovascular disease, statistics, ethics, epidemiology and clinical trials.

This group is responsible for providing recommendations to the NHLBI on starting, continuing or stopping the study or portions of the study. The DSMB carefully considers the safety and efficacy of the study treatments and monitors the overall conduct of the study. Importantly, the DSMBs recommendations are based on safeguarding the interests of the study participants.

Since the study began in 2001, the DSMB has met regularly, generally every six months, to monitor study conduct and to review the ACCORD data. In its regular review of the study data, the ACCORD DSMB noted an unexpected higher total death rate from any cause among participants who had been randomly assigned to the intensive blood sugar treatment group compared to those assigned to the standard blood sugar treatment group, the difference of 54 deaths, which I described a moment ago.

Although there appeared to be some benefit of an overall lower death rate in both group, the DSMB recommended stopping the intensive treatment, because the difference in deaths between the intensive and standard treatment groups existed. That is, the harm of the very intensive treatment outweighed the potential benefit.

The NHLBI accepted the DSMBs recommendation to stop the intensive treatment group and the NHLBI decided to continue treating all ACCORD participants at the standard treatment approach, as well as to continue the blood pressure and lipid treatment parts of the study. We will continue to monitor all study participants for an additional 18 months, as planned, until the study ends in June 2009.

As I emphasized earlier, on the whole, the death rates in both blood sugar treatment groups were lower than those seen in similar populations. That is, although the death rate was higher in the intensive treatment group than the standard group, it was still lower than death rates reported in other studies of Type 2 diabetes in similar adults.

As people with diabetes learn the results of the ACCORD trial, we advise them to consult with their healthcare professional before making any changes to their treatment. This an important message that we will repeat

multiple times today. The NHLBI felt it was important to inform study participants and the diabetes community soon after reaching this decision.

Accordingly, letters were sent to all study participants by their clinical site principal investigators on Monday February 4th, with recommendations regarding further follow-up care. Investigators have begun to prepare a report of these initial findings, which they will submit for publication in a peer-review medical journal. We anticipate that these findings will be published shortly.

So to summarize then, ACCORD is the first major clinical trail to study whether lowering a raised blood sugar level, to a level similar to that seen in people without diabetes, reduces the risk of cardiovascular disease. We now have one part of the answer to this question. The study will continue to examine other ways to lower the risk of cardiovascular disease, in high-risk adults, with Type 2 diabetes, using blood pressure and lipid lowering approaches.

Our message to individual's with Type 2 diabetes that are at especially high risk for heart disease is to target your A1C level to about 7%, and not to more intensive levels. No one with diabetes should change their treatment without consulting with their healthcare professional first. And

we concur with the ADA recommendation that treatments must be individualized.

We now are fortunate to have several experts with us today, who have contributed enormously to this research and who will provide additional detail about the ACCORD study and these important initial findings. I am going to introduce them to you and then several will be making comments.

First, Dr. William Friedewald is Clinical Professor of Public Health and Medicine at Columbia University and Chairman of the ACCORD Steering Committee.

Dr. Hertzel Gerstein is professor at McMaster University and Hamilton Health Sciences in Ontario, where he holds the Population Health Institute Chair in Diabetes Research. Dr. Gerstein is principal investigator of one of the seven ACCORD Clinical Center Networks and led the group that designed the blood sugar treatment approaches.

Dr. Judith Fradkin is the Director of the Division of Diabetes, Endocrinology and Metabolic Diseases at the National Institute for Diabetes and Digestive and Kidney Diseases, here at the NIH and is the key person from NIDDK involved in ACCORD over its duration.

Also with us, to answer your questions, are Dr. John Buse, Professor of Medicine and Chief of Endocrinology at the University of North Carolina, School of Medicine and Vice Chair of the ACCORD Steering Committee. Dr. Buse also serves as President of Medicine and Science of the American Diabetes Association.

We also have Dr. Robert Byington, Professor in the Department of Epidemiology and Prevention, in the Division of Public Health Sciences at Wake Forest University, School of Medicine, who lead the ACCORD Coordinating Center.

And also Dr. Denise Simons-Morton, Project Officer for ACCORD at NHLBI and a member of the ACCORD Steering Committee.

Dr. Friedewald will start. Dr. Friedewald.

Dr. W. Friedewald Thank you, Betsy. As Dr. Nabel has just described, ACCORD first began recruiting participants in 2001. We have been treating and following our study participants for an average of about four years, ranging individually from two to seven years.

At the same time that we began to observe the troubling mortality differences described by Dr. Nabel, we were also noticing a light trend toward beneficial effects of the intensive blood sugar lowering. The primary outcome for our study is a combination of heart attacks, stroke and cardiovascular death. And we were seeing about 10% fewer, non-fatal cardiovascular events, such as heart attacks, in the intensive treatment group compared to the standard treatment group. However, it appeared that if a heart attack did occur, it was more likely to be fatal. In addition, the intensive treatment group had more unexpected sudden deaths, even without a clear heart attack.

The ACCORD researchers undertook extensive analyses to try and understand potential causes of this mortality difference. Our analyses have not identified to date, any specific cause for the increased deaths among the intensive treatment group. However, the magnitude of the difference in the death rate, with only a small improvement in non-fatal events, indicated that in the interest of safety of the participants, the intensive blood sugar treatment part of the ACCORD study should be changed, and all participants treated according to the standard blood sugar group.

As we examined the data, we sought to identify any drugs, or combinations of drugs that might explain this higher mortality rate in our intensively treated group. However, with our analyses so far, we haven not been able to find conclusive evidence that any medication or combination of medications is responsible for the increased risk.

Because of the recent concerns raised with regard to rosiglitazone, also known as AVANDIA, one of the drugs we use in ACCORD, we specifically analyzed the data to try and determine whether there was any link between this particular medication and the increased deaths we were seeing in the ACCORD Intensive Treatment Group. At this time we have found no link, and thus the use of rosiglitazone does not seem to explain the increased mortality.

Based on other studies, it is possible that the intensive blood sugar lowering therapy benefits patients in other ways, such as by lowering the risk of other complications of diabetes, such as eye and kidney diseases. We will continue to analyze all of the effects of the intensive treatment group, based on the data gathered to date, and on future assessments of the participants in the intensive group, even though they will now be treated to standard blood sugar lowering goals.

In addition to actively monitoring ACCORD participants, we will conduct additional analyses to try and explain the findings. Meanwhile, we are preparing a report, as Dr. Nabel mentioned, of our current findings for publication in a peer-reviewed medical journal in the near future.

In a moment, Dr. Gerstein will provide more details on how the blood sugar treatment part of the study was conducted and how ACCORD will continue over the next 18 months.

Before I close, however, I want to reiterate Dr. Nabel's comments and assure everyone, especially our study volunteers that our first priority is to the safety of our participants. On Monday, our 77 clinical centers across the United States and Canada, sent letters to each study participant, explaining this important finding and describing the changes in the ACCORD study. For the participants in the standard treatment group, their care will continue without changes.

Participants in the intensive treatment group will be transitioned to the standard treatment after consulting with their ACCORD clinician. They will be called by their study doctor in the next few days, so they can discuss without delay, any concerns or questions they may have.

Although the ACCORD findings are extremely important, most individuals with Type 2 diabetes are not treated to blood sugar levels as low as those tested in the intensive treatment group in the study. In addition, these results only apply to patients like the ACCORD participants, who were selected to have cardiovascular disease or two additional risk factors for cardiovascular disease, in addition to their diabetes.

To reach the levels of blood sugar achieved by our intensive group required consistent hard work on the part of these participants, with frequent blood sugar monitoring, multiple medications and frequent contact with our ACCORD clinical staff diabetes experts. However, for this special group of individuals with diabetes, as exemplified in the ACCORD population, which had an average age of 62, had diabetes for an average of ten years, and had know heart disease or were at high risk, less stringent A1C goals are likely appropriate, with an aim for around 7%. No one with diabetes should change their treatment without consulting with their healthcare professional, first.

Finally, I would also like to reiterate that even with the higher death rate in our intensive group compared to our standard group, this rate is still lower

than that seen in similar populations in other studies and it is lower among individuals with Type 2 diabetes in the general community.

I would now like to turn to my colleague, Dr. Hertzel Gerstein, who leads the ACCORD Clinical Center Network in Canada and the ACCORD blood sugar working group. Hertzel will describe the blood sugar treatments used in the ACCORD trial. Hertzel.

Dr. H. Gerstein Thank you, Bill. Before we go into more detail regarding the blood sugar treatment approach in ACCORD, I'd like to take a few minutes to describe why we tested an intensive blood sugar lowering approach. Adults with Type 2 diabetes are two to four times more likely to have a heart attack, stroke or to die from cardiovascular disease than people without diabetes. This likelihood is even higher if an individual with Type 2 diabetes is middle-aged or older, has had a heart attack or stroke in the past and has other risk factors for cardiovascular disease. Other risk factors include high blood pressure, high cholesterol, being overweight or obese or being a smoker.

A large body of research has shown that higher glucose levels predict a higher likelihood of fatal and non-fatal cardiovascular events. Other studies have shown that lowering blood sugar levels can significantly

lower the risk of certain complications of diabetes, such as eye, nerve and kidney diseases.

In addition, a major study in people with Type 1 diabetes, which is a different from of diabetes that used to be called juvenile diabetes, suggests that intensive blood sugar lowering strategies reduce the risk of cardiovascular disease and death. Furthermore, a study in people with more recent onset of Type 2 diabetes in ACCORD participants showed a trend toward fewer heart attacks. This body of research strongly suggests that lowering glucose levels to levels typically observed in people without diabetes could reduce the risk of cardiovascular disease in people with established Type 2 diabetes.

But, until ACCORD, no major clinical trial had studied whether lowering a raised blood sugar level, to a level similar to that seen in people without diabetes, reduces the risk of cardiovascular disease in people with Type 2 diabetes. In addition, no clinical trial has studied the effects of intensive blood sugar lowering in people with longstanding Type 2 diabetes, who already had cardiovascular disease, or who have multiple risk factors for cardiovascular disease in addition to diabetes.

So one of the key questions that ACCORD was designed to answer, is whether intensively lowering blood sugar levels could reduce the risk of

heart attack and stroke. Drs. Nabel and Friedewald have described the basic design of the study and the characteristics of the study participants.

The two blood sugar lowering approaches studied by researchers in 77 centers in the United States and Canada used lifestyle approaches focused on modifying diet and physical activity, together with glucose lowering drugs. All of the drugs were FDA-approved and are commonly used for glucose control in the general diabetes population.

The choice of drugs was based on the doctor's medical judgment that took the clinical characteristics of the participant into consideration, while maximizing safety and glucose lowering effectiveness. Thus, the treatments used in ACCORD were similar to those used by practicing physicians who treat patients in the community.

Drugs representing all of the types of glucose lowering therapies available when ACCORD began in 2001 were used. And a few more drugs were added as they became available. The same menu of medications were used in both treatment groups, although in different combinations and doses.

The medications included Metformin; Thiazolidinediones, or TZDs, such as Rosiglitazone or Pioglitazone, injectable insulin's, Sulfonylureas, such as Glimepiride, Glipizide, Glyburide and Gliclazide, Acrabose, and Exenatide. Although the same drugs were used by both treatment strategy groups, more drug combinations and higher doses were prescribed to participants assigned to the intensive glucose lowering group than the standard group, in order to reach their targeted A1C goal.

Participants in the intensive treatment group were seen approximately every two months at an ACCORD Clinical Center, and participants in the standard group were seen approximately every four months. At each visit, clinical staff reviewed the participant's health status, discussed with the participant any side effects of drugs, adjusted medication doses as needed, tested the participant's blood sugar and performed other measures as appropriate.

Volunteer participants in both groups also received most drugs free. They received state-of-the-art medical care, with access to diet and physical activity counseling, experts in diabetes care and the latest information related to diabetes. They were also provided with free glucose monitoring equipment, so that they could check their own blood sugar levels and make adjustments at home, to achieve the goals to which they had been

assigned. It is our view that the high standard of care received by all participants, contributed to the lower death rates in both groups, compared to the rates seen in the general community.

On average, the volunteer participants in both treatment strategy groups achieved a stable level of glucose within six to nine months after being enrolled. The average blood sugar levels for both groups were lower than when they entered the study. The intensive treatment group achieved lower average A1C values than the standard treatment group participants.

Half of the participants in the intensive group achieved an A1C of less than 6.4%. In the standard treatment group, half of the participants achieved an A1C of less than 7.5%. Both groups have maintained stable glucose control throughout the study, which to date has been an average of about four years.

Now I'd like to turn to Dr. Judy Fradkin from the NIHs National Institute of Diabetes and Digestive and Kidney Diseases.

Dr. J. Fradkin Thank you, Hertzel. I've been asked to address the implications of these new findings from the ACCORD study for diabetes patients. I will focus

my remarks on Type 2 diabetes, the form of diabetes being studied in ACCORD.

Type 2 diabetes is by far the most common form of diabetes in the United States. It accounts for about 95% of the nearly 21 million diabetes cases in the country. Type 2 diabetes is most common in adults age 40 and older. It is strongly associated with obesity, inactivity, a family history of diabetes and racial or ethnic background. Minority groups are at particularly high risk.

As Dr. Nabel noted earlier, Type 2 diabetes is a complex metabolic disease that results in elevated blood glucose levels. It usually begins as insulin resistance, a disorder in which cells in fat, liver and muscle do not respond to or use insulin properly. As the need insulin rises, the pancreas gradually loses its ability to secrete enough insulin to meet the body's needs. At diagnosis, many patients do not need medication and most patients do well with oral medications, such as Metformin. Over time, however, they have a progressive loss in insulin production and they need additional medications to control their diabetes.

Eventually, especially if not well controlled, Type 2 diabetes causes damage to the eyes, nerves, kidneys, heart and blood vessels. Many people with diabetes also have high blood pressure and lipid or cholesterol

problems, conditions that further add to their risk for cardiovascular disease. About 65% of people with diabetes die from heart disease or stroke. Diabetes is increasingly important as a cause of cardiovascular disease in the United States.

I would now like to briefly review how ACCORD is different from earlier studies. One crucial way in which ACCORD differed from earlier clinical studies is that it studied the effects of lowering glucose to near-normal level, a lower level than that targeted in earlier studies. ACCORD also differed in another critical way from earlier studies aimed at preventing complications through intensive glucose control.

At enrollment, ACCORD patients were older; they were on average 62 years old. They had lived with diabetes for a longer time, an average of ten years, and they at especially high risk for cardiovascular disease.

In contrast, participants in the earlier studies of intensive glucose control were younger, had recently been diagnosed with diabetes and were not at a similar high risk for cardiovascular disease. It is not yet known whether controlling glucose to near-normal level will prevent heart disease and extend life in other groups, such as younger people with diabetes, those

earlier in the course of the disease and in whom glucose is easier to control and those without established cardiovascular disease.

So what have we learned from ACCORD so far? These new findings give us important information. They show that a medical strategy to intensively lower blood glucose to a goal of near-normal, or non-diabetic levels, increases the risk of death and outweighs the potential benefits of such therapy for this specific group of patients, those with established or longstanding Type 2 diabetes, who have cardiovascular disease, are at especially high risk for it.

In this group of patients and with the treatments that are currently available to us, clinicians should be wary of striving for intensive glucose control to near-normal levels. The ACCORD trial tells that patients with diabetes and a high likelihood of established hear disease, should not aim for near-normal levels of blood glucose, level that are rarely achieved with current medical care in comparable patients.

We've learned that a one-size approach does not fit all in treating diabetes. And the ACCORD findings reinforce this message. The National Diabetes Education Program, which is sponsored by the National Institutes of Health and Centers for Disease Control and Prevention, promotes the

American Diabetes Association's guidelines for diabetes care. Under these guidelines, the A1C goal for most patients with diabetes is less than 7%. The guidelines also state that treatment should be tailored to individual needs. For example, a less stringent A1C goal should be considered for people with severe or frequent hypoglycemia or those with a limited life expectancy.

In tailoring therapy to determine an individual patient's A1C goal, physicians should now consider whether the patient has established cardiovascular disease or additional cardiovascular risk factors. I want to stress that ACCORD is studying the effects of intensive glucose control in Type 2 diabetes. We cannot extrapolate its results to patients with Type 1 diabetes, which is a different form of diabetes.

Dr. E. Nabel Thank you very much, Judy. And thank you to all of our speakers this morning.

In summary, we have discontinued the intensive blood sugar treatment strategy in the ACCORD trial and will now treat all of the ACCORD participants according to the standard blood sugar treatment strategy. The ACCORD blood pressure and lipid trials are continuing.

The findings we're reporting to you today are extremely important for the care of individuals with diabetes around the world. They indicate that in older individuals with diabetes, who also have existing heart disease, or two or more heart disease risk factors, such as high blood pressure, elevated blood cholesterol, obesity or overweight and smoking, care should be taken not to intensively lower than blood sugar levels to a near-normal level, using combinations of medications available today.

Now we will move on, and we're very pleased to take your questions. Before so, I want to just highlight a couple of things. First of all, the press release, a question and answer sheet and these prepared remarks have been posted that the NHLBI Web site at www.nhlbi.nih.gov. A transcript of this teleconference will be posted in the next two days. And in addition, a recording of this press conference will be available within about 30 minutes after the end of the conference, and I'll give you that phone number at the very end.

So, operator, if we could move now to our questions. I would just ask that you identify yourself and your organization.

Moderator — Thank you. Our first question is from the line of Jacob Goldstein from *Wall Street Journal*; your line is open, sir, please go ahead.

J. Goldstein Thank you. Can you talk a little bit more about the risk of death in comparable populations, in other studies and in why the intensive treatment group in this study had a lower risk of death? And also, if you've calculated the P value for the difference between the intensive treatment group and the standard treatment group in this study, what is that value?

Dr. E. Nabel I'm going to ask Dr. Gerstein and Dr. Buse to address your comments in just a moment.

These findings are initial. I just want to emphasize that the analyses are continuing, and details regarding the data will be reviewed by the study PIs and prepared for a peer reviewed publication. So at this point, we are not in a position to release details regarding key values or other analyses.

Dr. Gerstein and Dr. Buse, could you respond?

Dr. H. Gerstein The answer to the question is that a large epidemiologic studies, which have followed people with Type 2 diabetes, of a similar age, and with risk factors — similar cardiovascular type risk factors — have reported total mortality rates in the order of 4% to 6% per year, depending on the study, and there have been a number of these that have been reported.

Now these are community-based studies that are out in the general population of people and they reflect whatever care these individuals are providing. Within the ACCORD trial, people received state-of-the-art medical care. They had frequent contact with healthcare providers and experts in diabetes, and they had access to all of the medications, essentially, available to deal with diabetes. And we feel that it is this expert care that they were able to have that led all of the participants in ACCORD to have a much lower rate than is seen in the general population of people with diabetes in similar risk factors.

Dr. J. Buse The only thing I would add to Hertzel's answer is also remember the ACCORD study also involves a blood pressure and cholesterol randomization. So all of the patients, or the patients in general, had excellent care of other cardiovascular risk factors, as well. And that likely contributes to the general low mortality rate in the study.

J. Goldstein Thank you.

Moderator Our next question comes from the line of Julie Steenhuysen from Reuters; your line is open, please go ahead.

J. Steenhuysen Hello, thanks for taking my call. Can you hear me?

Dr. E. Nabel Yes, we can.

J. Steenhuysen Great. A couple of things. I'm really curious if you can tell us how many of the deaths that you've noted were actually cardiovascular related. Were they heart attack, stroke or can you tease that out a bit more for us? And also, does this raise new questions about a surrogate end point of lowering blood sugar, or is this population too specific to start questioning the merits of intensive blood sugar lowering as a surrogate end point? Thank you.

Dr. E. Nabel Thank you for your question. I'm going to ask Dr. Friedewald to address your two questions.

Dr. W. Friedewald Yes, as expected in a population like this, the mortality mainly was from cardiovascular disease, and roughly about half of the deaths were cardiovascular, as expected.

I'm sorry; I didn't fully understand your second question. Could you repeat it?

J. Steenhuysen Well, we're seeing a lot, in the broader cardiovascular area, we're seeing a lot of debate right now about surrogate end points. And I'm wondering, the assumption was that lower would be better in this study, you didn't find that, and that's somewhat of a surprise. I think we were a bit surprised in the VYTORIN study as well. And I'm wondering what does this say about making assumptions on end points, as surrogates for actual studies that show reduction in death?

Dr. W. Friedewald That answer is obvious, I think, and that is if you can you want to study the important events, which are the clinical events, which is what we did. Surrogates are only as good to the limit that they are true surrogates for the clinical event and to make assumptions frequently because the disease used a smaller sample size to study surrogate end points. But, in fact, if we can, we want to study the clinical end point, and that's why we studied this in ACCORD and that's why we had to have 10,251 patients, because when you study these kinds of clinical events, although they're much higher than the general population, they still aren't that common, and that's why you need as much population.

Dr. E. Nabel I think it's also important to remember that this was a medical treatment strategy, to lower A1C levels to near normal levels in the population. So the A1C level, in and of itself was not a surrogate end point. And, in fact,

the primary outcome for the study is a combination of heart attack, stroke and cardiovascular death. So the clinical end points really were the primary outcome.

J. Steenhuysen Okay. Thank you very much.

Moderator Our next question is from the line of Steve Sternberg from *USA Today*; your line is up, please go ahead.

S. Sternberg Thank you very much. Could you specify the causes of death? Could you also tell us what percent of patients in the intensive arm were getting rosiglitazone and what percentage of patients in the standard treatment were getting rosiglitazone? And I also wanted to ask you about an ethical question, and that is that rosiglitazone now has two black box warnings attached to it. Back in May, concerns were raised, as you know, about its affect in heart attacks. I wonder what you think about the difficulty in teasing out what this study means and how rosiglitazone may have contributed to that confusion.

Dr. E. Nabel I'm going to ask our Chair and Vice Chair of the ACCORD Steering Committee to address those questions, Dr. Friedewald and Dr. Buse.

Dr. W. Friedewald Let me start out and maybe John can follow up with the black boxes after that. Let me make it clear that this was a treatment strategy, so that both groups, as you commented, received rosiglitazone. More rosiglitazone was used in the intensive treatment group compared to the standard treatment group.

So when we tried to understand whether rosiglitazone was responsible for this increase in mortality we couldn't rely on randomization. We had to do what we call an epidemiological analysis. And by that I mean we had to then to look at people who were assigned to rosiglitazone and compare their mortality experience to those who were not on Rosiglitazone and there are problems with those kinds of analyses, but we do them routinely.

When we did that in ACCORD, what we observed was that there was no increased mortality in the group assigned to rosiglitazone compared to those who were not. So it did not explain, at least as far as the analyses we were able to do, did not explain the increased mortality.

John, do you want to respond?

Dr. J. Buse Yes, the only thing I would add, just to clarify, no patients were assigned to Rosiglitazone. They were assigned to an intensive strategy versus a

standard strategy and the investigators were free to use whatever combination of drugs they wanted, to achieve those targets in the two different arms.

With regard to the black box warnings and … analyses over the last six months to a year with rosiglitazone, this has been reviewed repeatedly by the investigators, by the DSMV, by the institute, by the project office, by the statisticians, by basically everybody involved in ACCORD. This was discussed with every participant in ACCORD. Some patients did switch from rosiglitazone to pioglitazone or from rosiglitazone to other medications over the last six months. But I don't think there's a direct relevance of the black box warnings and … in ACCORD.

Dr. E. Nabel Dr. Simons-Morton.

Dr. Simons-Morton Yes, thank you. I'm the ACCORD Project Officer at NHLBI. I would like to add that we actually convened a special urgent meeting of our Data and Safety Monitoring Board and the information about rosiglitazone came out and we asked the DSMB to analyze the publications that had come out in the *New England Journal of Medicine* and subsequent publications, and also at the same time, to look at analyses within ACCORD of the ACCORD data and ACCORD participants. And we did

post a public statement about that, which is still available on our Web site. And at that time, and still today, we could find no link between the use of rosiglitazone and the mortality findings or any other adverse outcome in the trial.

S. Sternberg Thank you very much.

Moderator Our next question comes from the line of Richard Knox with National Public Radio; your line is open, please go ahead.

R. Knox Thank you. Just a follow-up on Steve's question, can you tell us what proportion of patients in the standard and intensive groups did receive rosiglitazone?

Dr. Simons-Morton It's actually quite a difficult question to answer, because the treatments changed over time, and so we've been treating these patients for an average of four years and some people were put on rosiglitazone and then taken off and other additional medications were added over time. So it's not an easy question to answer. It's a question of were they ever on rosiglitazone, were they on rosiglitazone at their latest visit, etc, etc. And we really would prefer that that level of detail to be available for the peer reviews publication.

R. Knox So one way to look at it would be the number of patient's days on rosiglitazone in each group.

Dr. Simons-Morton Thank you for that excellent suggestion. We'll take that under consideration.

R. Knox You haven't done that, I take it.

Dr. Simons-Morton I don't believe the coordinating center has done that particular analysis.

R. Knox Okay. Thanks.

Moderator The next question comes from the line of Gina Kolata from the *New York Times*; your line is open, please go ahead.

G. Kolata Hello, thank you for taking my question. I was wondering if you could tell us a little bit about how difficult it was to achieve this very intensive blood sugar control, how many drugs on average were they taking or what kinds of doses. And what was it like for the patients to undergo that sort of intensive control?

And also, I was wondering if you could tell us how big a surprise was this for you? I know every time you end a study early, it's got to be a surprise.

But in terms of the things that have happened in diabetes, was this truly a major shock, or had you thought maybe something like this might happen?

Dr. E. Nabel Let me address your last question first, and then I'll ask Dr. Gerstein to address your first question. Clearly we did not anticipate the findings, and in that sense, we were surprised. But now knowing the findings, we took the important step of stopping the intensive treatment arm, due to safety concerns. We've recommitted ourselves to continuing to monitor the study participants and in addition, the study investigators will continue to explore potential reasons for the findings while continuing with the other important research studies within ACCORD.

We felt at the onset, that this was one of the most important questions, what is the best treatment for individuals with Type 2 diabetes who are very high risk for heart disease. And we are still committed to finding the answer to that question. I'll ask Dr. Gerstein to address the other.

Dr. W. Friedewald Could I follow on that?

Dr. E. Nabel Yes, please.

Dr. W. Friedewald It's one of the reasons we do this research, as you understand, obviously. We obviously were surprised. We were hoping for a positive outcome, but the reason we do this research is we don't know that, and that's why we had to do this stuff.

Dr. H. Gerstein The answer to the question related to the difficulty in the work that had to be done to achieve this is very important. So I want to start off by saying that the average A1C level of participants in the ACCORD trial at the time that they started was 8.2%, which suggests that their glucose control was not good and was higher than it typically is in the United States.

We set ourselves a very challenging goal of trying to get the A1C level down as efficiently and as safely as possible, and it does require a lot of work. Participants around ACCORD used at least two drugs in addition to diets and lifestyle approaches and other drugs were added, as they were needed. Many patients needed to use insulin in addition to pills, in all sort of combinations.

Patients had to have frequent contact with the sites, coming for a visit, at least every two months, but subsequently having phone contact and interactions on a very regular and frequent basis, and participants, volunteers checked their glucose levels at home and were taught how to

make adjustments to their own medications, in order to facilitate achieving these values. So this is no easy task for people to do, and they did it with the support of sites and doctors and the nurses who were involved.

G. Kolata — So what was the difference between doing the very intensive when the life of a patient, if you were trying to do the intensive control as compared to trying to do the less intense control?

Dr. H. Gerstein — So imagine that you're a patient with diabetes and you're in the intensive group and you need to prick your finger and write down your blood sugar level, about three to five times a day. That means you have to interrupt your routine. You may have to take three or four injections of insulin during the day, in addition to two pills at breakfast, two at lunch and maybe two or three at supper, in addition to what other drugs you may be taking for blood pressure or for asthma or whatever other problems that you may have. You need to see if your numbers are high that you need to do something about it, speak to your sites, etc.

If you were in the standard group, then the amount of work that you had to do was considerably less. You would have to check your blood sugar perhaps once or twice a day, depending on what medications you were on. See the site every three to four months and not be concerned if the blood

sugar levels were in the level that they'd been, even before people got involved with the study. So it is really a different amount of work that both the patients, and you would have to do with the patients, as well as the site would have to do.

G. Kolata — I'm sorry to keep going on about this, but I just want to sort of understand what the difference was for the patients. Were people in the intensive group also at risk or were they complaining as they were passing out, having their blood overshooting it, getting their blood sugar too low and did that happen in the standard group?

Dr. H. Gerstein — Patients in both the intensive group and the standard group would tell us that they found the experience and they continue to find the experience enjoyable, in terms of the frequent interaction with the staff and the amount of access and medical therapy that they were receiving. People in both the intensive and the standard group did have occasional episodes of hypoglycemia that required adjustments in therapies and this, as you can imagine was also followed.

So both groups did have this and both groups will continue to be followed, in order to see in the end whether or not the other parts of the trial, the

blood pressure, the lipid parts of the trial are affecting cardiovascular events.

Dr. E. Nabel Dr. Buse.

Dr. J. Buse Yes, just to add a little bit, something that I think is important with regards to the approach between the two groups. As you heard, the average A1C in the standard group was 7.5%, pretty much right in the middle of the range we were looking for. So most patients in that group were giving pats and rubs that they had achieved the target for the ACCORD study. In the intensive group, the average was around 6.4%, not under 6%, which was the target. So there was this sort of constant pushing, can we do this with diet, can we change your medication here, maybe if you monitored a little bit more here.

So it was a more demanding process, certainly, for the patients in the intensive group. And really all of the ACCORD participants need to be congratulated for a heroic effort. I mean doing much better than average in the United States in glucose control, over a prolonged period of time, with all kinds of stuff in the press leading to concerns and that sort of thing, they really did an amazing job.

G. Kolata Thank you.

Moderator Our next question comes from the line of Randolph Schmid from *Associated Press*; your line is open, please go ahead.

R. Schmid Yes, I'm curious. There's a paper coming out in the *New England Journal of Medicine*, which talks about a similar study and they found lower deaths in the intensive blood sugar lowering group. I'm wondering if you're familiar with that paper and if how it compares with what you've found.

Dr. E. Nabel Yes, we understand that that paper is under embargo until 5 p.m. today. However, the group has published a design paper that appeared in 2003, an outcome paper, excuse me, that was published in 2003, which we've had a chance to look at. And if you look at the levels, A1C levels that are achieved in their intensive treatment arm, it roughly is equivalent to what was achieved in our standard treatment arm. And there may be individuals here that would like to comment further. John.

Dr. J. Buse I think the major difference between that study and ACCORD is that that study, the people that were in the intensive arm, all got as intense blood sugar lowering as they could do at the time, intensive blood pressure lowering and intensive cholesterol lowering. In fact, in the 2003 report,

the A1C level achieved was around 7.8% or 7.9%, so higher than the standard patients in our study, but they were all managed to blood pressure and cholesterol. And I think, really, the importance of that study was the demonstration that taking care of blood sugar, blood pressure and cholesterol together does seem to reduce cardiovascular influence.

Dr. E. Nabel And to build upon that, let's not lose sight of the fact that while much of our discussion this morning is about blood sugar levels, that equally important parts of the ACCORD trial are blood pressure and lipid management as well. And certainly we want to emphasize and this is in full agreement with the ADA recommendations. That treatment for individuals with diabetes should pay attention to all cardiovascular risk factors, including cholesterol lowering and blood pressure lowering, where appropriate.

So again, as the ACCORD study unfolds, and certainly over the next 18 months, we will actively continue the blood pressure and lipid randomization arm. And at the end of the study we are confident that we will have very interesting information about the integration of blood glucose, blood pressure and lipid treatment in individuals with Type 2 diabetes.

R. Schmid Thank you.

Moderator Our next question comes from the line of Ron Winslow from the *Wall Street Journal*; your line is open, please go ahead.

R. Winslow Thank you very much. Actually you were just speaking exactly to my question. And in evaluating this mortality increase or increased risk of mortality, how did you look at this other background therapy, with lipids and blood pressure? I'm assuming you've ruled out some association. But how did you connect with the levels that people achieved in that part of the strategy, with what was happening with glucose and was there any impact at all?

Dr. E. Nabel I'll provide just a general comment and the Dr. Byington, who directs the Coordinating Center, will provide more information.

Obviously, when we examined the safety data, we looked at all components of the trial. And we looked very carefully to see whether we would need to discontinue either the blood pressure or the lipid arm of the trial and the safety data suggested that we did not need to do that.

Again, all of the details regarding this will be in the peer review manuscripts, so I don't want to jump the gun here too much, especially since the analysis are still being prepared by the study investigators. But I think Dr. Byington will have more to add on that.

Dr. R. Byington Hello, yes, I can add a little bit more to that. Dr. Nabel just mentioned how we can't say too much, because of the ongoing work that we're doing now for publication in the next few weeks or so, we're trying to put together a paper. But also, in addition, we're working towards continuing to follow our patients and treat our patients in the blood pressure and the lipid trials, so I can't give you any details about exactly what was going on in that.

But I can assure you that we did actually look at any possible interactions between our two treatment groups, intensive or standard glycemia treatment groups, in terms of what was also going on in the blood pressure trial and also what was going on in the lipid trial. And we did not see anything that caused us any concern, so that's why the recommendation has been made to continue those two trials.

R. Winslow Thank you.

Moderator — Our next question comes from the line of Matthew Herper from *Forbes Magazine*; please go ahead.

M. Herper — Hello. I just was hoping that you could all revisit and I'd particularly like to hear what Dr. Buse thinks. But about the issue of A1C as a surrogate marker, given a trial where an overly aggressive treatment strategy led to an imbalance in mortality, don't you have to wonder about how to value and use the surrogate marker, both in treating and evaluating new drugs, and if not, why not? I'd kind of like some more clarity on that.

Dr. J. Buse — Yes, so the notion of a surrogate marker basically is as suspect, that it is a way of determining future risk, based on something that you can measure today. And hemoglobin A1C has been shown to do that for micro-vascular complications in clinical trials and trends towards being useful in that regard, with regards to cardiovascular disease. But in ACCORD hemoglobin A1C is not being used as a surrogate marker, it's a target. If the question that you're asking is really about the utility of hemoglobin A1C as a surrogate marker for relevant outcomes in patients with Type 2 diabetes, I think that's still an arguable point, and not something that ACCORD addresses directly. But it is an issue about which there has been a great deal of discussion over the last six months in the context of drug studies.

Dr. H. Gerstein May I add to that? When used as a target in other studies, for instance in people with Type 1 diabetes, it has been very clearly shown that targeting a particular hemoglobin A1C level or an A1C level, a low A1C level, does reduce the risk of heart attacks and strokes and cardiovascular events. And in Type 2 diabetes, it has been shown that targeting that A1C level reduces the risk of eye disease and nerve disease and kidney disease in the past.

So we are continuing to learn more about this and these findings. And in addition to other trials that are still continuing and will be completed within the next two years or so, will tell us a lot more about the optimal way and the safest and effective way of reducing cardiovascular events and mortality in people with Type 2 diabetes.

Moderator Does that answer your question Mr. Herper?

M. Herper Sort of. I'm having a little trouble seeing how — I mean obviously this wasn't a study designed to evaluate a surrogate marker. But I'm trying to understand how the surrogate marker isn't — how the use of the surrogate marker isn't affected by such a negative result in using it as a treatment.

Dr. J. Buse So maybe one thing that would clarify things a little bit about the utility of hemoglobin A1C as a surrogate marker and what ACCORD needs in that regard, in general it doesn't appear that hemoglobin A1C explains the problem with excess mortality in the ACCORD study. There's a lot more analyses that need to be done in that regard. But I just think that in many ways the ACCORD study is irrelevant to the issue of, is hemoglobin A1C a valid surrogate marker.

Dr. E. Nabel One more comment and then we would be more than happy to follow-up with you after the call.

Dr. Simons-Morton I just have something to add, ACCORD, obviously because it was testing a strategy of treatments, a therapeutic strategy that could lifestyle and multiple medications, as they would be use in actual clinical practice, ACCORD was not designed to answer the question about the effectiveness of any individual drug on, for example, like drug companies do when they're trying to get a drug approved. It's a different kind of question; it's more of a practical, in practice question. And I think that maybe thinking of it that way might help the issue of surrogates. We weren't intending to answer the question about whether A1C was a surrogate.

Dr. E. Nabel Again, the point that we wanted to mimic real life treatments to achieve certain targets was really the emphasis of the study, using combinations of FDA approved medications. Thank you for your question, we'd be happy to follow up with you after the call, if you would like to discuss it further.

M. Herper Yes, that would be great.

Moderator Our next question comes from the line of Avery Comarow from *US News & World Reports*; please go ahead, your line is open.

A. Comarow Thank you for taking these questions. I have a few, if you don't mind. Following up on Ron Winslow's question about the blood pressure and lipid groups, was there any major difference in the number of excess deaths across these two arms, the blood pressure group and the lipid group? And within the groups, were there clear indications in the intensive blood pressure group and the standard blood pressure group and intensive lipid group and the standard blood pressure group. That's number one. Do you want to deal with that and then I can ask a couple of others?

Dr. E. Nabel Sure. We aren't going to be able to provide details at this time, because that will really be the subject of the manuscript, which is being prepared

and needs to be peer-reviewed. Let me just reiterate that we looked very carefully at the data with the safety of the study participants paramount in our mind. If there had been safety concerns, we would have discontinued one or both of those arms.

A. Comarow Yes, I understand, but in terms, this is in detail, it seems to me, if you saw numbers that were clearly tilted toward blood pressure or toward lipids, that would have jumped out at you, wouldn't it?

Dr. E. Nabel Well remember that the blood pressure and lipid arms are blinded. So those components have not been unblinded to the study investigators yet. And I'll let Dr. Byington follow up.

Dr. R. Byington And just to follow-up on what I said earlier, those two trials are still ongoing. So that's one of the reasons why we can't give you any specific numbers right now, because that would be a clue as to what's going on in terms of those trials, information that you'll be getting in 18 months.

A. Comarow But I understand that which patients were intensive and which were in stand groups treatment groups were blinded, are you saying that the investigators who analyze the data won't even know until unblinding,

which patients, all patients were getting blood pressure and lipid treatment, isn't that distinction unblinded now?

Dr. W. Friedewald This is a factorial trial, as we've tried to explain. So what we are talking about today are randomization between the two glycemia approaches. There was also a separate randomization for blood pressure and a separate randomization for the lipid trial. Among the people sitting around here at the table now, there are only a handful that know those data; Dr. Gerstein and Dr. Buse do not know those data, because they are blinded with regard to the outcomes.

They clearly know which group people are in, but they don't know the group data and they don't know the interactions. So you'll have to wait, we'll all have to wait 18 months to have those revealed.

A. Comarow Okay. Now my next question has to do with one of your answers in the FAQ that you posted online, that only about half of excess deaths were from cardiovascular causes, and the others were from causes, such as cancer. I'm sure that nobody has any answer right now for why there might be excess cancer related deaths. But if the non-cardiovascular causes of death were removed, would you have still been as concerned, in other words if there were not 50 some excess deaths, but more like 25?

Dr. Simons-Morton Actually, the Q&A document does say about half of the deaths were from cardiovascular diseases. That was true for both the intensive and the standard glycemia groups. The excess deaths were in total mortality and also in combined cardiovascular causes. The majority of the excess deaths were in cardiovascular causes. Does that make it clearer?

A. Comarow No.

Dr. W. Friedewald Basically there is no difference in terms of the distribution between the intensive and the standard group, in terms of the causes of death.

A. Comarow Okay, that I understand. And I have one very small question, regarding the lipid group. All of the other arms had specific targets for blood sugar and blood pressure; I didn't see anything in the protocol that set any kind of target figures for lipids.

Dr. E. Nabel I think your question really addresses the design of the randomization, it was between a fibrate plus statin versus a statin alone, and Dr. Byington can address that.

Dr. R. Byington Sure. As Dr. Friedewald indicated before, that ACCORD is a factorial trail, which basically means we have three concurrent trials going on at the same time, the glycemia trial that we're talking about today, the blood pressure trial and the lipid trial. In both the glycemia trial and the blood pressure trial, we had strategies in terms of intensive versus standard treatments to try to reach certain goals.

In the lipid trial, it's basically like the typical blinded randomized clinical trial where we randomize half of the people to one treatment, and specifically phenol fibrates and the other group gets just placebo. So we're not targeting any kinds of LDL levels. All of this is being done in the context of good LDL controls, so everybody in the trial is getting the standard.

The notion behind the lipid trial is that people with diabetes are more likely to experience lipid abnormalities, specifically elevated triglyceride levels and lower HDLs. So that's why we're specifically testing in this trial phenol fibrate versus placebo, rather than the typical LDL change, things that we usually do.

A. Comarow Well you're also testing, both groups got a statin, was there any stipulation as to the statin or the dose?

Dr. W. Friedewald Yes there is, everybody is on, I can't remember off the stop of my head, everybody is on Simvastatin. But I can't remember the — and we're trying to titrate it so that everybody is getting their LDLs to a level less than 100, which they're actually achieving, which is along the guidelines promulgated by NIH and AHA.

A. Comarow Thank you.

Dr. E. Nabel I think Dr. Buse is reminding us that they're receiving Simvastatin in 20 milligrams

Dr. J. Buse Except for … cardiovascular disease or who's LDL isn't less than 100, then they go to 40 ….

A. Comarow Thank you.

Moderator Our next question comes from the line of Michelle Cortez from Bloomberg News; please go ahead.

M. Cortez Thanks for taking my question. You guys gave us the mortality rates in this group, in patients who weren't in the ACCORD 4% to 6%, have you

crunched out the actual mortality rate in these two separate groups, it looks like it would be less than one percent. I'm wondering if you could give that to us, and also tell us, I know you don't want to give P values, but if that difference was indeed statistically significant and not a result of chance. That's my first question.

And then the second one is, does this study give us any kind of insight at all in terms of treatment going forward, like should we not go with combination drugs or is there something that looks better than another kind of a treatment, you know there's always this concern, as the diabetes get worse and you add on more and more, should we not be doing that or any kind of guidance at all to doctors and patients? Thanks.

Dr. E. Nabel Well as you'll recall, we indicated that the mortality in the intensive treatment arm was 14 per thousand individuals per year on an average of four years of follow-up and in the standard treatment arm, 11 deaths per thousand individuals per year for an average of four years of follow-up. In addition, in our prepared comments, we do have a number of recommendations that we are providing to individuals, and I'll just reiterate those very quickly.

First and foremost, individuals with diabetes should not change their diabetes treatment without first consulting with their healthcare provider. Second, we believe that the preliminary results of the ACCORD trial are still very consistent with the ADA general recommendation about individualized care and advising people with diabetes to aim for an A1C of less than 7%.

We do think, however, for this very special group of individuals with diabetes, who had an average age of 62, who had diabetes for an average duration of ten years or either had known heart disease or were at very high risk, that left stringent A1C goals might be appropriate, with an aim for more about 7%. And at this time, with the information we have at hand, these would be the recommendations that we would like to provide individuals and their caretakers.

Dr. H. Gerstein — I just want to add a few things to remember — that this trial tested two different degrees of glucose lowering in people who had high glucose levels at the start. So they came in with an average A1C of 8.2%. And the two treatment strategies, one of them tried to drive that level right down to below 6% and the other one tried to drive that level down to about 7.5%. And this tells us nothing, for instance.

And to get into the trial, you had to have an A1C above 7.5% to even start and the average was 8.2%. So this doesn't tell us anything about what one should do with people whose A1C levels are already 7.5% etc. In other words, if they start a study with reasonable A1C levels or lower, it certainly doesn't mean that one should make it go higher.

We don't know anything about what we should do with people who are newly diagnosed with diabetes or who have A1C levels that are in the high 6% etc, at the time. This tells us that if it's particularly high, driving it down with a comprehensive approach that uses lifestyle, diet, as well as all the drugs available in our armamentarium today, increases mortality compared to driving it down more modestly to a level typical of what people have in the United States today.

Dr. E. Nabel Thank you. We'll take one last question.

Moderator Your last question comes from the line of Alice Dembner from the *Boston Globe*; your line is open, please go ahead.

A. Dembner Yes, thank you very much. My question was whether you could go over in a bit more detail, what things beside rosiglitazone you actually looked at and ruled out as a cause of the increased deaths.

Dr. E. Nabel Again, all of that detail will be in the peer-reviewed publication. We can provide just a higher overview, this morning, but again, that detail will be in the publication. Dr. Byington.

Dr. R. Byington Yes, I can tell that as Dr. Nabel has indicated earlier, that we looked at almost the gamut of materials that we had used in our armamentarium. We looked at them individually, we looked at them in combinations and we didn't see anything specific. But as far as the specific details of what we actually found, that will be found in the publication.

A. Dembner So you looked at every drug that was used, is that what you're saying?

Dr. R. Byington Almost every class of drug that we happened to have in the trial.

A. Dembner And you looked at the glucose levels and were there other things that you also looked at?

Dr. R. Byington Well we looked at race and ethnicity and gender; the basic demographic characteristics.

Dr. H. Gerstein Let me just add that these are interim analysis and these are being announced because of safety. That first of all more data is being collected. These patients continue to be followed, and they're going to continue to be followed for another 18 months, because of the important blood pressure and lipid trial. And second, many more analysis need to be done to explore these and to try to come up with other possible explanations for this. We can only say what analyses are being done to date, and to date nothing has emerged. But this is going to continue to be done and will be looked at exhaustively.

We also looked at as was said earlier, other things that could possibly be related to this, such as hypoglycemia, etc.

Dr. E. Nabel Yes, we did. Again, just to reiterate, we're making the announcement today for safety reasons. And again, we anticipate the publication will be peer-reviewed and available within a short period of time.

I do want to thank all of you who have called in today. We are very, very appreciative of the vital role that all of you play in communicating this important health information to the public.

A recording of this press conference will be available at the following phone number, within about 30 minutes or so, and that number is 1-800-475-6701 and the access code is 909685.

If you have any additional questions or would like follow-up, please contact the NHLBI press office at 301-496-4236. And again, the press release, question and answer sheet and the prepared remarks have been posted at the NHLBI Web site www.nhlbi.nih.gov. And a transcript of the teleconference will be posted within the next few days.

Thank you all again, very much.