00001

CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Coverage Advisory Committee

August 30, 2006

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

00002

Panelists

Chairperson
Alan M. Garber, M.D., Ph.D.

Vice Chairperson
Alexander H. Krist, M.D.

Voting Members
Edgar Black, M.D.
Douglas D. Bradham, Dr.P.H.j
Margaret A. Piper, Ph.D., M.P.H.
James E. Puklin, M.D.
Jonathan P. Weiner, Ph.D.
A. Mark Fendrick, M.D.

HCFA Liaison
Steve Phurrough, M.D., M.P.A.

Consumer Representative
Charles J. Queenan, III

Industry Representative
Donald W. Rucker, M.D.

00003

Panelists (Continued)

Guest Panel Experts
Rodney A. Hayward, M.D.
Mark E. Molich, M.D.
Gayle E. Reiber, Ph.D., M.P.H.

Executive Secretary
Michelle Atkinson

00004

TABLE OF CONTENTS

00005

00006

PANEL PROCEEDINGS

(The meeting was called to order at 8:05 a.m., Thursday, May 18, 2006.)

MS. ATKINSON: Good morning and welcome, committee chairperson, members and guests. I am Michelle Atkinson, executive secretary for the Medicare Coverage Advisory Committee. The committee is here today to discuss the evidence, hear presentations and public comment, and recommendations regarding glycemic control and the use of glucose monitors by which sensors automatically monitor glucose levels and body fluids, and whether and how the frequency of outpatient glucose monitoring is related to glycemic control and clinical outcomes in various Medicare populations.

The following announcement addresses conflict of interests associated with this meeting and is made part of the public record. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interest. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest

00007

of fairness that all persons making statements or presentations also disclose any current or previous financial involvement in any company that manufactures. This includes direct financial investments, including fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presentations to hear today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn.
For the record, the voting members present for today's meeting are Alex Krist, Edgar Black, Douglas Bradham, Margaret Piper, James Puklin, Jonathan Weiner, and Mark Fendrick. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will

00008

participate in the voting today. The voting scores will be available on our web site following the meeting; two averages will be calculated, one for the voting members and one for the entire panel.
I ask that all panel members speak directly into the mikes, and you may have to move the mikes since we have to share. And lastly, please remember to discard your trash in the trash cans located outside the rooms. I would now like to turn the meeting over to Dr. Steve Phurrough.
DR. PHURROUGH: Good morning. I'm Steve Phurrough, I'm director of the Coverage and Analysis Group here. It is our group that is responsible for making decisions about the kinds of things that Medicare is going to pay for, and we are the sponsors of this particular advisory committee. I want to have a special welcome to those of you who have not been part of our advisory committees before. These are we think an extremely helpful forum to provide information to the public about the kinds of things that we are interested in.
Today's topic is certainly an appropriate, pertinent and timely topic. We are

00009

grateful to the Juvenile Diabetes Research Foundation for their assistance and suggestions for some of the discussions today, and we are looking forward to hearing your input.
I would like to thank the panel for their willingness to participate. Again, this is an extremely challenging meeting and they have spent significant amounts of time putting together their thoughts as well as reviewing significant amounts of material that we have provided for them.

There are two sort of broad goals today. One is to look at some of the newer technologies for type 1 diabetes, and two, to discuss the issues of application of principles attributed to type 1 to the older type 2 diabetic, which obviously in our Medicare population is the much larger population. The questions are designed to get at those two particular issues. The questions have been tinkered with over the last couple of weeks because we have had conversations with the panel to make those questions somewhat more direct, and somewhat simpler to provide a definitive answer to, so hopefully you have been able to see those as those

00010

have progressed over the last couple of weeks. We thank you for your attendance and we look forward to a good discussion. Dr. Garber.

DR. GARBER: Good morning, everyone. I would like to welcome everyone here and echo Steve's thanks to everybody for participating in today's meeting.

I will be very brief, but the main thing I want to say is that indeed, our agendas are also always packed and very tight, and this one, that's more true of this meeting than most others. It's going to be a real challenge to get through the agenda. It's a very important and interesting set of questions and we're going to have to keep things moving along. We always do strictly limit speakers' times to the amount of time they have been allotted. Today that is particularly true and we will cut you off in mid sentence, unfortunately, if the light turns red, if you use up your time. And I apologize in advance for that, but it is the only way that we can make sure that everyone gets their chance to speak, so purely in the interest of fairness, we will be doing that. Please don't take it personally, but you might want to keep track of

00011

the time when you're up here to speak.

There will be opportunities for committee members to question presenters during allotted times on the schedule. You will note that there is no scheduled break during the morning's proceedings so you will have to leave the room as the need arises, and I think the speakers and the committee members will understand that, so there may be a little going in and out here. Ordinarily we do have several scheduled breaks but today's agenda did not permit it.

I'm looking forward to a very interesting meeting. These are meaty questions, we have been presented with a lot of information

in written form and we're going to hear quite a bit today, so I look forward to a spirited discussion.
Now I would just like to go along the table and ask the committee members to please state your name, your affiliation, and any conflicts of interest that you might have for this topic.
DR. REIBER: My name is Gayle Reiber, I'm a VA career scientist and professor of health services and epidemiology at the University of

00012
Washington. I have no conflict of interest.
DR. MOLICH: Mark Molich, an endocrinologist at Northwestern University in Chicago. I have some conflicts in that I have received research support from Sanofi-Aventis and have done some consulting for Abbott Laboratories.
DR. HAYWARD: I am Rod Hayward, a general internist and the director of health services research at the Ann Arbor VA, and professor of public health and internal medicine at the University of Michigan. No financial conflicts.
DR. RUCKER: Don Rucker, MTC at Siemens Medical Solutions USA, which has an acquisition plan for Bayer Diagnostics, and I'm also on the clinical faculty at the University of Pennsylvania.
MR. QUEENAN: I'm Charlie Queenan, I'm an independent management consultant. I'm also a past board member of the Juvenile Diabetes Research Foundation but have no conflicts.
DR. FENDRICK: Good morning, I'm Mark Fendrick, general internist at the University of Michigan. I have received grant funding from many pharmaceutical companies in the field of diabetes

00013
mellitus implications; however, I don't have any conflicts in the area of glucose monitoring.
DR. WEINER: I'm Jonathan Weiner, professor at Johns Hopkins School of Public Health. I have not received any funding in this area for over ten years; however, I have received funding from companies that may or may not be involved in associated areas through the university.
DR. PUKLIN: My name is Jim Puklin, I'm a professor of ophthalmology at the Kresge Eye Institute of Wayne State University in Detroit, and I have no conflicts of interest.
DR. PIPER: Margaret Piper, with the Blue Cross and Blue Shield Association's Technology Evaluation Center. No conflicts of interest.

DR. BRADHAM: I'm Doug Bradham, a health economist and epidemiologist with the VA cooperative studies system and also an associate professor of epidemiology at the University of Maryland Baltimore School of Medicine. I have no personal conflicts of interest. I have received some funding for some research in diabetes in the past from the VA and also some other funding for

00014

research in MS from pharmaceutical companies.
DR. BLACK: My name is Edgar Black, I'm a member of the Technology Evaluation Center of the Blue Cross Blue Shield Association in Chicago. I previously have been involved in panels both at Blue Cross and Blue Shield in Rochester, New York, and at the Blue Cross Blue Shield Association that have discussed the topic of continuous glucose monitoring systems.
DR. KRIST: My name is Alex Krist, I'm a family physician at Virginia Commonwealth University and I have no financial conflicts of interest.
DR. GARBER: Alan Garber, general internist for the VA and Stanford University. I am not an endocrinologist although I do treat patients with diabetes, and I have no conflicts to disclose.
Okay. So, why don't we, let's go into the CMS presentation by Sandra Jones and Elizabeth Koller. Let me just point out to the people who will be speaking later, the next speaker's chair is right up there near the steps up to the podium.
MS. JONES: Good morning. I'm going to present the voting panel questions only, all of

00015

which are publicly available just outside this door, although I'm not sure how to get it to you here.
Moving on to the questions, question number one, we are asking people to rank stated complications one through eight according to their prevalence and severity in Medicare type 2 diabetics, with one being the least important and eight being the most important.
Question 2, we would like people to score one through five each of the six variables on the basis of effectiveness of continuous monitoring for type 1 diabetics, with five being the most important and one equaling the least important.
Question 3, rate one through five how confident you are that glycemic control prevents or delays chronic complications and death in patients who develop type 2 diabetes at age 65 or over, and that such is clinically and

statistically significant. Part B, rate one through five the importance of glycemic control relative to other therapies in preventing or delaying these complications and death in type 2 diabetics who develop this disorder at age 65 or

00016

later.
Question 4, rate one through five your confidence that glycemic control reverses or reduces progression of pre-existing chronic complications in a meaningful way in patients who had type 2 diabetes before age 65. And Part B of Question 4, rate one through five the importance of glycemic control relative to other therapies in reversing and delaying progression of pre-existing chronic complications and death in patients with type 2 diabetes prior to age 65.
Question 5, can hypoglycemia information for type 1 patients be generalized to Medicare-aged type 2 patients? Specifically, rate one through five how confident you are that hypoglycemic frequency and severity for a given level of glycemic control is similar in type 1 and type 2 diabetics.
Question 6, rate one through five your confidence that glucose monitoring improves glycemic control, hemoglobin A1c, and decreases the risk for hypoglycemia at a given level of hemoglobin A1c.
And Question 7, does increased glucose monitoring in type 2 patients improve clinical

00017

outcomes? Part A, rate one through five, how confident are you that increased frequency for outpatients with glucose monitoring translates to decreases in chronic complications in Medicare-aged type 2 diabetics. Part B, rate one through five how confident you are that the optimal frequency for glucose monitoring, that is the number of strips per week or quarts per day when continuous, in type 2 diabetics is known.
Thank you, and next, Dr. Koller will present as our lead medical officer.
DR. KOLLER: My name is Dr. Beth Koller and I will be presenting the background material for this session. Today we would like to examine the relationship between glycemic control and chronic diabetic complications, particularly cardiovascular complications. We will also break down for you the procedures being used, the frequency of chronic outpatient monitoring and the relationship between frequency of monitoring and chronic complications. The emphasis, as stated before, will be on type 2 diabetics who are 65 or older. We will review what's known about the

relationship between glycemic control and microvascular complications, and hypoglycemia. We

00018

will touch on the relative importance of non-glucose mediated therapies for complication prevention and management, and we will discuss whether there should be different hemoglobin A1c targets for different patient populations.
We will also discuss the role for glucose monitoring. If glucose control prevents complications and if glucose monitoring improves glycemic control, “how should this monitoring be accomplished?”. Our goals include review of what is known as well as identification of knowledge gaps, areas of ongoing research, and areas of future research.
Why are we even asking these questions?
These questions are being raised because there has been an evolution in glucose monitoring and because it's not clear if the DCCT data regarding glycemic control in young adults with type 1 diabetes is applicable to older type 1 patients or to patients with type 2 diabetes.
Over time there have been various methods for measuring glucose in an outpatient setting. Each system has its own positive and negative features. The first meters were pretty bulky, but they could provide real time

00019

measurements and did not require visual color matching skills. Later meters required less blood, but the strips were considerably more expensive. They cost anywhere from 25 cents to a dollar a piece and they could not be cut in half, something that had been previously used to save money.
Meters that measure interstitial fluid can now provide real-time continuous data, but these are relatively expensive with device costs between $3,000 and $4,000 and a q 3 day sensor cost of about $50. There have also been some concerns about the accuracy of computer systems, specifically overestimation of hypoglycemia and divergent readings when meters have been simultaneously placed on different parts of the body.
Meters that use transdermal electro-osmosis are less expensive, initially costing under a thousand dollars, but they have similar sensor costs, and they can also be affected by temperature and perspiration.
Now before we proceed, it's important that we define the Medicare population. Most Medicare beneficiaries have type 2 disease.
Dr. Lurvey will further discuss the Medicare

00020
population in his talk.
We will discuss a few of the
differences between type 1 and type 2 diabetes.
I'm sure these are quite well-known to the
diabetologists in the audience. Type 1 diabetes
is an autoimmune disease in which there is progressive islet cell
destruction that affects insulin and
sometimes glucagon secretion. Type 2 is a different entity. It's
polygenic.Insulin resistance is a key etiologic element linked to
hypertension and lipid problems.
Indeed, the hyperglycemia may really be a marker of
disease and not a central pathogenic feature.
The major complications for type 1
disease are microvascular disorders, and these are
retinopathy and nephropathy. Renal disease
previously reduced life expectancy by about 15
years. With longer survival, cardiovascular
disease has really become more prominent.
Nephropathy may portend cardiovascular problems.
Type 2 disease is distinct in
several ways. The hypoglycemia that occurs takes place
at 1/10 to 1/100 the frequency of that in
type 1 disease. The hypoglycemic risk is affected
by the dose of pharmacologic agent, by the type of
pharmacologic agent that is used and, but it's
especially affected by the coexistence of

00021
infirmity. The major chronic complication is
cardiovascular disease.
Several studies have delineated the
reduction in life expectancy from either the
“attained age” or from the “age of diabetic onset”.
With increased age, the survival gap between diabetic and
nondiabetic subjects narrows. If we look at this
in another way, there is a marked divergence in
longevity for those who developed diabetes between
25 and 44, versus those who were not diabetic.
For patients who develop diabetes after age 64,
the blue lines down here, you can see that the
divergence from those without diabetes was smaller and actually,
they start to
come together with longer duration of followup.
The major cause of death from
diabetes is cardiovascular disease. The solid
blue area here delineates ischemic heart disease,
40 percent; the broad blue striped area delineates
microvascular disease; and this small striped area
here delineates other heart disease. You will
note that renal disease doesn't even show up on
the pie chart.
Well, let's review some of the major studies.
The Diabetes Control and Complications Trial was
the pivotal study that was conducted in over 1,400

00022
type 1 diabetic patients with either no retinopathy or mild to moderate retinopathy. Patients received either conventional or intensive insulin treatment. Mean follow-up was six-and-a-half years and they were able to maintain a glycosylated hemoglobin unit difference between treatment group of about two percent units.
Well, what do the DCCT results reveal?
Well, the DCCT validated the use of glycosylated hemoglobin as the surrogate marker for stepped retinopathic risk in young type 1 patients using insulin. It should be noted here that blindness and renal failure were not endpoints in this study, that intensive treatment did not reverse pre-existing disease, and that treatment did not alter cardiovascular outcomes.
As one can see on this chart, three-step retinopathic progression was blunted in both the patients without preexisting retinal diseases and those who did have preexisting retinal disease, and this was statistically significant as indicated by the demarcation SS shown. More severe retinopathy was found only in these patients with pre-existing disease, and it too was blunted. But the treatment didn't have any effect on ophthalmologic

00023
complications such as macular edema, which would be important to our patient population.
The progression to microalbuminuria was blunted in patients without preexisting retinal disease, but there was no clear impact on more severe renal disease. Few patients in either this cohort here with mild or no retinal disease, or in those who had moderate retinal disease, developed creatinine clearance values less than 70.
Well, let's look at the relationship between retinopathic progression and glycemic control. It's not linear. The likelihood of retinal disease with a glycemic hemoglobin of 10.5 percent ~ 11 times that observed with glycemic hemoglobin of 5.5 percent. A one percent decrease in glycemic control provided a threefold greater blunting of retinopathic progression when glycemic hemoglobin started out at 10.5 percent than when the hemoglobin A1c started out at 6.5 percent.
In the same way, there were absolutely and relatively many more severe hypoglycemic events in patients with a glycemic hemoglobin of 5.5 percent than with a glycemic hemoglobin of

00024
10.5 percent. You can see the fourfold difference. A one percent decrease in glycemic

hemoglobin from 6.5 percent to 5.5 percent resulted in a tenfold increase in the number of severe hypoglycemic events as compared to a one percent change when we went from 10.5 percent to 9.5 percent.
When intensive treatment did not improve cardiovascular outcomes, the absence of a treatment effect was attributed in part to the relative youth of the population.
The next major study is the United Kingdom Prospective Diabetes Study, which was a pivotal study that was conducted in over 3,500 newly diagnosed middle-aged type 2 diabetic patients. Patients received either conventional or intensive therapy and the mean treatment was ten years, and the hemoglobin A1c was only a 0.9 percent difference between the two groups. The primary endpoints with the exception of hypoglycemia were all composite endpoints. There were additional secondary endpoints that were surrogate endpoints for end-organ damage.
The study was initially powered to detect a 40 percent change but after ten years of

00025

study, they did not see any differences so they repowered the study for detection of a 15 percent difference and more patients were recruited for the study. The study was actually notable for the fact that there was a statistically significant risk reduction for microvascular events, but it should be noted that this was primarily due to a decreased need for laser surgery; this was the major component of one of those composite endpoints. Visual acuity did not differ between the groups.
Despite the duration of the study and the temporal increases in hemoglobin A1c in both groups over time, proteinuria and serum creatinine did not become a problem for either group. Few patients went on to develop renal failure. Unlike the DCCT, neuropathy parameters, including impotence, did not differ by treatment group.
Despite the older-aged population, intensive treatment did not alter cardiovascular outcomes. The median complication-free interval was 14 years in the intensive group versus 12.7 years in the conventional group, and this was primarily eye-related disease. Expressed another way, the time to first complication was delayed, but only

00026

by a 15 months. Looked at even another way, to prevent any single endpoint complication, about 20 people would have to be treated and they would have to be treated for ten years.

What does this study say about the generalizability of the DCCT results? Well, hemoglobin A1c was validated as a surrogate marker for microvascular disease in middle-aged type 2 patients, but the relationship was much less robust than for type 1 patients. Furthermore, the relationship between hemoglobin A1c and microvascular disease is not easily expressed with a line or curve, nor is the relationship between hemoglobin A1c and hypoglycemia.

Well, let's take a look at the hypoglycemic events, and I direct you to the column in gold here, and as you can see, the hypoglycemic events were relatively uncommon. Even in the intensive group, we're talking less than two events per hundred patient years.

Well, do we actually have any data on the impact of intervention in older type 2 diabetic patients? Well, no, we don't. But we do have some modeling data. The authors used the

00027

DCCT rates for incidence (and we have to say that Kullberg, et al., suggested that these actually might be overestimates because there is a decrease in the incidence of retinopathy in older age groups) and the authors then used a type 2 cohort for their rates for progression.

Well, what did they find, or what did their model show? For 65-year-old patients, even with hemoglobin A1c of 10, there really was only a one percent risk of lifetime blindness. And if we go down to end-stage renal disease, in these older age groups the risk for end stage renal disease was even less. And if we look at it yet another way, 84 percent of the benefit of treatment could be achieved by treating only 17 percent of the population, and that would be these people down here, those would be the only ones. The majority of the benefit was achieved by treating the youngest patients with the poorest glycemic control. Modest glycemic control was sufficient to prevent microvascular complications in older patients with type 2 diabetes in this model.

Well, the VA further investigated the role of glycemic control in cardiovascular disease with a two-year pilot study of 154 men with

00028

type 2 diabetes. Unlike the UKPDS, they were able to maintain 2.1 percent unit difference between hemoglobin A1c for the two treatment groups. This study was focused on cardiovascular endpoints as well as hypoglycemia. As I indicated before, the VA study was able to achieve and maintain a hemoglobin A1c separation. The study was notable for the fact that there were 61 cardiovascular

events, including six deaths, and there actually was a trend toward more events in the intensive treatment group or the experimental group. Glucose control did not appear to enhance left ventricular function. Severe hypoglycemia was rare. There were three events per hundred patient years in the intensive treatment group and hypoglycemia did not appear to contribute, in any way, to these cardiovascular events. Well, we have to ask, is there a disconnect between glycemic control and cardiovascular disease? Can the absence of the link in this group be attributed to age alone? Do those with cardiovascular disease differ from those who do not have it? Well, I think that the Pittsburgh Epidemiology of Diabetes Study offers some interesting insights. This prospective

00029

cohort of over 600 type 1 patients was assessed for “hard” cardiovascular endpoints, including death, myocardial infarction, Q waves, revascularization, and stenosis by angiography. And the patients who had evidence of “hard” cardiovascular events (in this column) in comparison to those who did not, were more likely to have evidence of insulin resistance as indicated by high triglycerides, low HDL, higher blood pressure, increased waist-to-hip ratio, and a lower estimated glucose disposal rate. Glucose control was not the determining factor. Because of these lingering questions, there are several trials that are underway, including the NIH's Action to Control Cardiovascular Risk Trial and the Veterans’ Affair Diabetes Trial, and the Action in Diabetes and Vascular Disease Trial. We will hear from investigators from two of these studies later on today. Well, glycemic control has been linked to glucose monitoring, but what is the role for glucose monitoring in older patient populations if glycemic control does not substantially increase longevity, if it doesn't halt cardiovascular

00030

disease, and it doesn't reverse chronic diabetic complications that have already occurred. What is the role for glucose monitoring if only a minority of the vision loss that occurs in Type 2 patients is due to diabetic retinopathy and the vast majority are retinal lesions that can be treated regardless of hemoglobin A1c level? What's the role of monitoring if only ten percent, of type 2 diabetic patients develop diabetic nephropathy and if blood pressure control can retard most of the disease progression?

Well, that being said, there are many factors that do determine whether glucose monitoring can improve or affect glycemic control. Today here we're going to be focusing on monitoring regimens, in other words, the frequency and timing of monitoring. There are over 25 studies of glucose monitoring in type 2 diabetes, most of these are observational in nature. Many are based on pharmacy records of meter strip refills or they have employed a self-monitoring regimen in which monitoring was done only infrequently:1-4 times per month. Few trials have contemporaneous control groups, only 11 were randomized, and only one was blinded. Observational data can be important

00031

because large populations and people who would not typically enter a trial or qualify for a randomized study can be captured. That being said, we will look at some of the notable studies. Soumerai studied the impact of a policy change: that is providing free meters to patients. There was no improvement in glycemic control except in those patients who had really poor control, people with HbA`c levels of 11 percent. The difference between the poor glycemic control patients who initiated self-monitoring was only 0.6 percent better than those who did not use the meters. Karter, et al., have studied a large database, and what they observed was a dose-related response to the frequency of glucose monitoring: up to one strip per day in type 2 patients and three or more times a day in Type 1 patients. The greatest impact on hemoglobin A1c in type 2 patients was during the first six months. Using strip refill records, Evans,

00032

et al., found dose-related benefits on glycemic control from increased strip use in type 1 diabetics but not in type 2 patients using insulin; so it was different. In a cohort of over 3,000 patients, Martin, et al., found that those who self-monitored actually had higher hemoglobin A1c levels but lower rates of cardiovascular disease than those who did not self-monitor. It is not known whether the increased rate of medical visits resulted in more aggressive blood pressure control and lipid management. Unfortunately, observational data can be problematic because of hidden selection bias and because of its lack of blinding.

There are five randomized trials of glucose monitoring with more than 75 type 2 patients. Three of these studies were negative and two reported only modest benefits, a hemoglobin A1c reduction of about half a percent. These studies, however, were significantly flawed by either very high drop out rates or failure to perform intent-to-treat analyses. We will hear more about these studies a little later.

00033

There were six additional smaller studies, and all of these were negative. There are limited data on continuous glucose monitoring. The most recent published randomized data involves the use of intermittent continuous glucose monitoring in which the monitor was on for 72 hours. Studies of such monitoring in both insulin in children and adults, when compared to frequent finger sticks, revealed no benefit. There have not been any randomized trials of continuous glucose monitoring versus frequent finger sticks in older type 2 diabetic patients.

Well, because there are some outstanding questions about the role of glucose monitoring, there are ongoing studies such as the DiGEM study here, and we're going to hear more about this later.

Well, to recap, we're going to review the data on outpatient glucose monitoring. What devices should be used? How frequently and at what time should monitoring be done? Is the usefulness of monitoring dependent on a patient's capacity to affect changes in their treatment program based on the data they derive from the monitors? Does

00034

glucose monitoring improve clinical outcomes and is the benefit the same for all types of complications? If hemoglobin A1c is an imperfect surrogate marker for the prevention of complications in type 2 diabetic patients, what outcome measures should be used? Does glucose monitoring, in and of itself, prevent hypoglycemia? What is the role of glycemic control in preventing or reversing chronic complications? What is the relative importance of non-glucose mediated therapy, such as ACE inhibitors, for the prevention and treatment of chronic disease complications? If cardiovascular disease is a more serious clinical burden than microvascular disease in older diabetic patient populations, should that be the focus of our therapies? Does the benefit of intensive therapy outweigh the risk of hypoglycemia, particularly in patient groups such as the infirm? Should the limit targets differ by

patient population? In our discussion today, we would like to better define the gaps in the available knowledge and to identify other areas of research that would benefit the care of our Medicare population. Thank you.
DR. GARBER: Thank you. Arthur Lurvey

00035
will be the next speaker.
DR. LURVEY: My name is Arthur Lurvey, I'm an endocrinologist, a member of AACE, but the hat I wear today is that of a Medicare contractor medical director, or to be correct in Part A, intermediary medical director, but the same things I'd say would go for any position involving Medicare, and I'm going to go as fast as I can. This is some information about Medicare and diabetes that we were able to pull up from our own Medicare records, and you can see here basically in different colors the Medicare population by percentage and in the aged community this is typically the age for disabled, and you can see that the largest is 65 years or older with no diabetes, and with the blue and white spots, where 16 percent of the community has diabetes. Looking at, and this is estimated, self-reported data, so there's some biases here, patients don't even know if they have it, so it's one of the ways you can get a very large group of people to see what you have in your overall diabetic population. In the community of patients living with diabetes, you can see that percent which is type 1, 11.84 percent over 65, and 3.4

00036
percent less than 65, and that is within the usual textbook ranges concerning type 1 diabetes that you see when you're checking through articles. Over 65, you can see the community they're living in, it's not nursing homes, 10 percent, or 3 percent have diabetes.
We talk about insulin usage because many of the patients don't understand the difference between type 1 and type 2. If you look at it as a graph, you can see the percentage of people goes up in the Medicare population, particularly in the disabled population, who have the diabetes.
These are people in the nursing home population and as expected, there is a much higher percentage of patients with diabetes, and it peaks at the Medicare age, which is about 65 or more. Then it goes down as some of these patients expire, and the very old patients very often don't have diabetes.
Looking at the burden of cardiovascular disease with or without diabetes, and this is

again self-reported, so do you have heart disease, do you have hypertension, in the patient population for under and over 65, there is a

00037

strong correlation between cardiovascular disease burdens and the diagnosis of diabetes as self-described by patients.
The age of diabetes is diagnosed in the Medicare population. Again, because it's the Medicare population, understand that those are disabled and then those over 65, that the maximum diagnosis occurs in as many as 35 percent from age 65 to about 74, and this goes along with perhaps some of the benefits that we have in which patients are able to get on Medicare and be seen by doctors easier, and that may be one of the reasons that there is better diagnosis. And also as one ages and one gets a little more plump, one becomes diabetic.
The cumulative percentage of patients with diabetes we see here, and as you can see it tends to maximize, again, it goes up sharply at the Medicare age, and that is probably independent of simply getting Medicare. I think that's the age where both obesity and lifestyle and exercise change, and so type 2 would increase at that age.
And this is another slide showing the same thing, duration of diabetes in years for patients over 65. As you saw in the different age ranges, that

00038

starting with those who were living in the community, as one gets longer and longer aged diabetes, the maximum being less than five years.
But when we pick them up in Medicare, it appears the majority of patients have only had it about five years, and specifically type 2.
The type of treatments, and this again, are based on what patients report, but the vast majority of glaucoma, 60 percent are on oral agents, one or more, and approximately 20 percent in this group have no treatment, on diet alone, and 12 percent are on pills plus insulin.
Again, this is what patients report.
In other studies that I have seen that I did not annotate here, as many as four percent of the patients who are type 2 diabetic will be on insulin for the type 2 diabetes. The number of insulin doses is listed here and in the Medicare beneficiaries which are those under 65, they tend to use insulin, and those over 65 tend not to be.
And the largest number of doses is two per day, and I would imagine it's not that different from the general diabetic community, not those necessarily who are seen by endocrinologists but in the general community, if you rechart the

00039
Medicare population and look at patients treated by their family doctors, there are probably a large number of patients who are on insulin twice per day.
The relative testing of glucose frequency, you can see that there are some patients who are on oral and insulin that test more three times a day, approximately 25 percent of the patients who are on insulin with an oral medication are checking themselves three times or more a day, so a significant number of people are testing frequently.
As far as control, self-reporting, the majority of the patients, about half of them feel that they have good control, which we defined for them of having hemoglobin A1c less than 7.5 or (inaudible) less than 40. These people who are living alone and not in a nursing home, about half of them feel they are in good control most of the time, as you can see from this slide.
Okay. Here's a very quick look t additional information. About .2 percent of the Medicare diabetic population are currently on an insulin pump, subcutaneous pump. And less than 65, depending on which report we have, it's

00040
between 5 and 10 percent, greater than 65, slightly higher, and these are based on claims and survey data. So because of the change in the allowable reason of being on a pump in the Medicare Manual between 2000 and 2005, that concept changes between the surveys for the ones which were before 2004 and the one that was in 2005. During that period of the loosening up of the criteria, a lot of people would be on pumps.
So how does the insulin pump differ from other equipment, what are the implications to us, the Medicare contractors for Part A and Part B? Just for those of you who don't know, traditionally glucose monitors are reimbursed under two separate benefits. Typically they are DMERC equipment as well as diabetic supplies. In 1997, it was implemented that allowed coverage of glucose testing to non-insulin-dependent patients, that started in 1997, and there was a national coverage determination and if you look under Medicare coverage, you will find this in the manual, that there can be local coverages, each of the contractors can influence local coverage, controlling the number or the ways that you can be tested.

00041
The usual current coverage for insulin

is less than a hundred strips per month; for non, for insulin treated patients who are treating with insulin, they usually allow a hundred strips or lances per month covered by Medicare, and if they're non-insulin treated at all, it's 100 every three months. However, if there is any good clinical reason or documentation made, more will be allowed under any circumstance, so all it requires is documentation.
With respect to subcutaneous infusion pumps, this has broadened recently in the last couple of years and I will skip over this in the interest of time since this is pretty well known to most everybody in the audience who treats diabetic patients.
What are the costs? Glucose monitoring, Code A-4523, which is a DMERC equipment code, the allowed charges in 2003 approached a billion dollars. And of the population at the time of the diagnosis for using them, there were type 2 diabetics and 60 percent were not receiving insulin at that time.
What are some of the problem areas that we contractors and medical directors deal with,

00042

just so you understand? One, we are seeing in skilled nursing facilities relatively stable type 2 diabetic patients with multiple daily monitoring. However, there is no change in care, there is infrequently no slide in scale, frequently the information does not go to the doctor, some of these patients don't change for years but they are still tested two or three times a day with no apparent documentation of the information being used to change or adjust the treatment.
For home care, which is my area, they visit diabetic patients two or more times a day for testing insulin, their glucose could be 40 to 400 with no changes made in the results, there's no contact with the doctor, and as little as six units is given in the morning of insulin, with maybe five milligrams of lipocyte invasively in an insulin resistant patient.
That of course is very very heavily marketed in diabetic supplies to a patient. If you watch television, if you're one of the people who has insomnia and watches television late at night, almost any cable channel or even non-cable channel will be reminding you that, find out if

00043

Medicare will pay for your diabetic supplies, they will do so five years at a time, and this of course helps to keep you awake, but if you want to get to sleep I suggest reading the Federal

Register, that always works.
But glucose test strips, there have been various notes from the OIG about insulin and monitoring payments, marketing, that have come out in the past couple of years, noting that many times, several months of supplies have been sent to a patient, the patient doesn't understand how to use it or doesn't want to use it, and they tend to go past their useful life.
So without wanting to waste more of your time, we wanted to show you our demographics of data that we have. Often it was self-monitored, self-questioned by patients who are currently type 2 diabetics, as many as 16 to 40 percent may be taking insulin. The question is how often do they need the test, should they be tested, and what is the likelihood that the information gained will be used to improve their quality of life and their life expectancy, and that needs to be looked at. Thank you for your time.

00044

DR. GARBER: Thank you. We'll next move to scheduled presenters, Andy Karter, from Kaiser Permanente. Oh, I'm sorry, the TA, yeah, I got a little ahead of myself. Ethan Balk will be presenting.
DR. BALK: My name is Ethan Balk, I am with the Tufts New England Medical Center Evidence-Based Practice Center, and I and all the members of my team report no financial conflicts of interest.
We were asked to do a systematic review on these three questions, the relationship between hypoglycemic control and beneficial health outcomes for patients with type 2 diabetes, the effect of frequency of glucose monitoring on clinical outcomes in these patients, and the effect of frequency of glucose monitoring on glycemic control in hemoglobin A1c in these patients.
My talk today is going to focus just on the latter two questions, self-monitoring of blood glucose. And also, I want to note that in the original agenda I had more time, so I'm going to skip around a bit to try to compress things. But again, basically, I'm going to focus on

00045

self-monitoring blood glucose and it's effect on improved clinical effect, it's effect on changes in glucose control for hemoglobin A1c, and its effect on adverse events, trying to focus on severe hypoglycemia as the evidence allows.
I'm going to skip over this slide. So, our systematic review, we had a fairly stringent

eligibility criteria for this review. We would only review prospective studies, English language studies, both intensive glucose monitoring as an intervention and home self-monitoring for glucose as an intervention, and we focused as best the evidence would allow on type 2 diabetes in the adult population. The outcomes of interest were clinical events as listed here, and we stuck to these specific events and with this set of studies we were only interested in fairly large studies with over a hundred subjects with a relatively long follow-up duration of one year. For the other two outcomes, adverse events and hemoglobin A1c, we allowed smaller and shorter duration studies. For adverse events, we aimed to focus specifically on severe hypoglycemia, i.e., grades three and four, but in reality we ended up including studies that reported any evidence of

00046

hypoglycemic episodes.
The definitions of hypoglycemia vary from study to study and have varied over time. The general definition of grade three hypoglycemia is a hypoglycemia where the patient requires assistance from somebody for their care. Grade four hypoglycemia indicates that the patient became stuporous or went into a coma, depending on the definition that's used.
This is a graphic of the literature search that we did. Basically we searched MEDLINE and we also looked at review articles and other articles to find other citations. We found over 7,500 citations to screen through. We did that screen and we found 292 abstracts, citations that, some of the abstracts indicated that these studies pertained to patients managed with either intensive glycemic control or self-monitoring blood glucose. Most of these studies ended up not being eligible using our strict criteria and the majority of the studies were not eligible because either the sample size was too small, or they were of patients with type 1 diabetes, or the study design was not valid, most commonly retrospective or cross-sectional studies. So we ended up with

00047

22 studies that we reviewed. Notably, none of the studies focused on the populations of people 65 years or older, none of them did subanalyses in these populations.
My talk is going to focus on the studies focusing on the self-monitoring of blood glucose, and I will reiterate these numbers as I go along. Let me actually, in case I run out of time, I want to jump, if you will so allow me, to my conclusion, and then I will come back and

present the data. I want to make sure I don't run out of time before getting to the conclusion of the studies.
So again, we only studied the larger long-term studies; thus, there were a relatively small number of studies and a very small number of randomized controlled trials that we reviewed. In reference to the applicability of the studies to the Medicare population, we found that the minority of patients who were analyzed were over the age of 65 years or older, many of these studies included very few patients 65 years or older, occasionally no patients 65 years or older, and again, no analyses were specific to the older population.

00048

Across all the studies, there was a very wide range of duration of diabetes from new onset diabetes up to 20 years at baseline. The baseline hemoglobin A1c varied widely from about seven percent to about ten percent or so, and the treatment that was used varied considerably, including a large number of studies where none of the patients were using insulin, a large number of studies where all of the patients were using insulin, and everything in between.
Prevalence of cardiovascular disease and other comorbid conditions were generally very poorly described to the point where we really couldn't say much across the studies to describe these populations. Notably, only three of the studies, and they were cohort studies, meaning pre-post studies without a control group, there was only three of the 13 studies on self-managed blood glucose that were definitely conducted within the last decade, since 1995. There were six other studies that may have been conducted recently. The remaining studies were conducted either in the late '80s or early '90s. Two of the included studies for the self-management of blood glucose may have and actually probably did include

00049

patients with type 1 diabetes, confusing the issue a little bit from our perspective.
None of the studies that were eligible examined the relationship between self-monitoring of blood glucose and any of the clinical outcomes that we reviewed. For hypoglycemia, the adverse event of hypoglycemia as an outcome, there was only one study, which was an uncontrolled cohort study that was explicitly limited to patients with type 2 diabetes. Unfortunately from our perspective, the studies combined severe and non-severe hypoglycemia and so it was impossible to make any conclusion about the rates of, or the

risks of severe hypoglycemia. In all of the studies, there were no real data on the rate of severe hypoglycemia among patients with type 2 diabetes and there were no studies that compared self-monitoring of blood glucose to, quote-unquote, usual care or control group. For the hemoglobin A1c outcomes, overall they were inconclusive, without any specific or clinical significance of reduction in hemoglobin A1c with self-monitoring. There were five randomized trials. Two

00050

of them found a significant decrease in hemoglobin A1c, but the change was relatively small. The difference between the treatment group with self-monitoring and the control group without self-monitoring was only about a drop of about .25 to .5 percent units. Among the other three trials, and one non-randomized comparative study, there was a wide range of net differences between the self-monitoring group and the control group. Among the uncontrolled studies, there was also a fairly wide range of effect, with reductions of about 25 percent to 1.5 percent from the baseline. As a comparative among the controlled studies, the changes in hemoglobin A1c from baseline in the control group was on the order of about, a decrease of .5 percent also. So, in addition, there were a couple of studies that looked at the correlation between frequency of hemoglobin A1c testing, blood glucose monitoring, and achieved hemoglobin A1c, but we were unable to draw conclusions from those two studies. So, let me go back. I think I have stated these issues, that there were relatively few patients that would be Medicare eligible, and

00051

the standards varied considerably by stage and severity of disease, again with the hemoglobin A1c, a baseline between 7 and 10.5 percent, a wide range at baseline, a wide range of percentage of patients using insulin, and no data or little data on comorbid conditions. Again, there were no studies that met eligibility criteria that evaluated self-monitoring blood glucose to clinical outcomes. Again, there were three uncontrolled pre-post cohort studies that met eligibility regarding self-monitoring blood glucose and the risk of hypoglycemia. Only one of these studies, this top study, was definitely, only they definitely included only patients with type 2 diabetes; these other two studies probably

included patients with type 1 diabetes. And you can see that partly by the fact that the mean age of these two studies at 40 and 38 was considerably lower than the study with the mean age of 65. All of these studies included patients who all used insulin. The hemoglobin A1c varied a bit from 8 to 10 percent at baseline.
The self-monitoring blood glucose frequency regimen varied widely across these

00052

studies and across the other studies that I will be showing you. They range from, well, in one of the studies it was twice a day, one was four times a day, and one was about 15 times a week, and they all were fairly specific about what monitoring was done, how monitoring was done.
Another thing that we thought was important, and this will show up again in one of the later slides, is that there was a wide variation in what patients did with the information that they received from the self-monitoring. Most of the studies actually did not say what the patient's response or the clinician's response would be to the data that was being collected by the self-monitoring. One of these studies even commented that there was no specific training about what to do. The one study of type 1 diabetes, they did describe in at least a little bit of detail that the management of diabetes was altered on the --
DR. GARBER: Ethan, I'm going to have to ask you to wrap up.
DR. BALK: Okay. Let me just show you the results. These are the five randomized trials. Two of them are statistically

00053

significant, the other three are not significant. These are the non-randomized trials, the cohort studies. And this is the comparison between frequency of monitoring, hemoglobin A1c, two different studies, and this study found no significant association. This study claimed an association, although it's very problematic, especially with this one point here. And I think I'll end there.
DR. GARBER: Thank you. We now will go to Andy Karter from Kaiser Permanente. Just a reminder, please disclose any conflicts that you may have.
DR. KARTER: Andy Karter, no conflicts.
I'm going to be, for fear of running out of time, jumping around a little bit. I'm not going to talk about background, because you all have been reading about self-monitoring, but today I'm going to be presenting data from studies we have been

doing over the past ten years at Kaiser Permanente. We have a cohort of 210,000 patients with diabetes that we have been following. Our cohort was put in together in 1994 and we have been following them in an ongoing fashion since

00054

then. We are a managed care facility that serves about 35 percent in northern California, we have 3.3 million patients, and we annually refresh our diabetes registry and download all of their laboratory, pharmacy, outpatient, inpatient cost data.
This is the distribution of self-reported monitoring and frequency based on a 1994 to 1997 survey, and you can see that in type 1s and type 2s, the frequency is skewed toward the higher end, with the greatest being three times a day, and in black, the black being no monitoring, so type 1s are mostly monitoring quite frequently, whereas the type 2s on insulin are about two times a day, whereas the type 2s on oral agents or medical nutrition and therapy are monitoring less frequently. And these, if you compare this to American Diabetes Association guidelines, about 60 percent of type 1s are adherent to the guidelines and the monitoring frequency and 67 percent of type 2s.
On review of the literature, I find it puzzling because there's so much divergent evidence, and that's obviously why we're all sitting here today and based on what I see, and

00055

also trying to do this research myself, it becomes very evident that studying monitoring blood glucose and efficacy, effectiveness is very complex.
Now we standardly refer to, our gold standard for studying efficacy is randomized controlled trials. However, self-monitoring for glucose trials presents particular problems, and number one, double blinding is not possible.
Also, we see in many of the trials that concurrent trial interventions, like for example intensification of pharmacotherapy may wash out the SMBG efficacy, especially if there is a compensatory intensification in the control group.
Another thing that has been found in more recent years in terms of the clinical trial methodology is this issue of ignoring patient practices, and that can tend to bias as to the real roles of crossover of self-monitoring in the control group or non-intervention in the SMBG arm.
And another issue that we have is that the time frame for a randomized trial is often sufficient

to have patients start monitoring but it may not be sufficient to have them incorporate behavioral changes necessary in terms of those associated

00056

with supplementing monitoring.
Also, as you all know, trials are very expensive and it limits both sample size and follow-up time, and that's plagued a lot of our trials. If you review the literature, you'll see that there's very small sample size, and that may be accounting for a lot of underpowered studies, not accounting for the non-significance.
But on the observation studies, as you know, they have probably the most difficult time when it comes to dealing with bias, and there is non-random assignment of exposure, cross-sectional studies have the particular kind of the chicken and the egg problem of what comes first, the self-monitoring or the A1c.
And also, a lot of the studies have had problems with limited availability of confounding data. Now this is particularly important for studies of self-monitoring because there is an association with potential non-causative associations which, between self-monitoring and other health behaviors. People who monitor are likely to also take care of themselves in other ways that may impact glycemic control and is beneficial, and so some monitoring may be, there

00057

may be potentially a spurious relationship between self-monitoring and A1c. And so studies, we need to be able to adjust to that in our analysis of the net effect and any bias.
There are some examples from our data.
Looking at the frequency of insulin either among type 1 or type 2 treatment with insulin, you see that those that either use a pump or more frequent insulin injections are more likely to practice self-monitoring, and you can imagine that the more intense therapy is associated with better glycemic control. And so this could, because it's also associated with better monitoring, it acts as a very potent confounder, and so a study that couldn't adjust to this kind of thing could be biased.
But there is probably a more insidious bias that I think has plagued a lot of past observational studies, and that is the effect of initiating a self-monitoring practice may differ from the effect of changing the self-monitoring frequency in ongoing usage. And that has been called, recently it has been dubbed chronology bias, and clinical epidemiologists are now aware of this and have started to use what they call new

00058

user designs, and studied them separately from ongoing users or present users. And also, poorly controlled patients may be encouraged by the providers to increase the frequency or to initiate self-monitoring, so that is what we, we also call that confounding by indication, and that is a downward bias, and I'm going to show you an example. We studied a cohort of about 25,000 patients that had not used self-monitored blood glucose for a two-year period. And then we took this cohort and followed them forward for four years, and identified that over that four-year period many of them initiated self-monitoring, and then we went back to the baseline and compared whether or not they initiated self-monitoring. And you can see that for the red group, for those of you who can't see the legend, the red are the people who initiated, they had at baseline far worse glycemic control than the non-initiators. So that's kind of an example of how initiation of, or poor control may spur someone to start monitoring. Now you can imagine, if you did a cross-sectional study, what would you see? You would see that initiated self-monitoring, the A1c

00059

goes down, I mean it goes up two points, one to two points, and that's one of the problems with cross-sectional studies, as well as the prevalence studies, where you're not able to follow these individuals longitudinally and tease out whether or not, you know, what their purpose was in terms of initiation. Now ten years ago we started, we didn't understand some of these new user designs, but we thought we took care of it by what we called lagged cross-sectional studies, where we studied peoples monitoring behavior and then substituted modifying their behavior for A1c values, and we controlled for lots of those self-care behaviors that may confound the relationship. These are, at the bottom are confounders that we separated, age, sex, race, education, language, income, occupation, diabetes duration, and here's some modifiable behavior such as daily insulin injection, frequency, smoking, alcohol consumption, medication refill adherence, appointment no show rate, use of diet and exercise, and some other things I won't go over. But at any rate, we found a significant association between self-monitoring frequency and

00060

one year later A1c, and it was a graded response

that was highly significant in type 1, all subgroups, type 1, type 2, those that weren't being treated as well as medication therapy. And we saw this same, we took that data and then categorized individual's utilization of self-monitoring into whether or not they were being adherent based on ADA guidelines. And you can see that in all cases, adherence to ADA guidelines, that is the non-adherent, which is the green bar, and the dark blue which were the adherent, there was a significant drop of A1c in the following year. In summary, it was about, a one point lower A1c was associated with three times or greater monitoring in type 1s, about a .6 lower A1c in type 2s, both on oral or injected insulin, and there was a .4 drop in A1c associated with medical nutrition therapy, and there we used the guidelines -- we used the guidelines for every case but we said if they monitor at all, and so it was any monitoring versus no monitoring. But since then, we've come to understand more some of these issues about new use of designs and you know, prevalence versus incident, and so we just published, it came out

00061

this month in Diabetes, looking at separating out new users of self-monitoring blood glucose from ongoing users. And the first cohort was 16,000 subjects that had not practiced self-monitoring previously and did not, we restricted both these cohort studies, by the way, to people who did not switch diabetes therapy over our four-year longitudinal follow-up. And the reason is that switching therapies associated generally with an intensification of self-monitoring as well as hopefully improvement from glycemic control. However, it becomes closely retractable to analyzed data when you have a lot of switching of therapy, so we restricted, this was an artificial population but it made it a lot cleaner to look at the effect of self-monitoring. And we used, for this new user design, we used a pre-post control design, looking at patients that initiate versus the ones that continue not using. And then in the ongoing design, what we did was we did a fixed, we repeated it based on a time dependent adjustment, and what that means is we allowed individuals to make, we followed individuals' changes in their self-monitoring blood glucose over this four-year

00062

period, as well as their changes in their A1c and linked them together, so it wasn't just a baseline comparison, it was looking at all their data. Some individuals went up and down and back and

forth. And all these models were highly adjusted for a rich set of covariants that we talked about before, including lots of self-care behaviors that are potentially confounding.
Here's the data. This is the first cohort of the prevalent cohort, and you can see that on the Y axis, you're looking at the change in A1c as a function of the X axis, which is the change in strict use over time. So over the four years, for example, if someone increased their strips by one per day, you would see this much of a drop, like a .1 drop in A1c, so that's how these graphs work.
Now you can see here that medical nutritional therapy, there was absolutely no significant effect of changes in self-monitoring on changes in A1c. However, in oral agent only and insulin treated patients, there was a graded and significant effect, so that the more strips, for example, if they decreased four strips, their A1c would go up this much, this works in both

00063
directions, this is how much change there would be, it's a universe, so it could be a change, how much change there would be if they decreased this much, you would see their A1c go up that much, or if they increased strip use that much, their A1c would go down that much.
This is the new user cohort and here you can see there was a graded effect and it was highly significant for all groups. And this is the impact of initiating and this is how many strips they initiated per day, and you can see that the more strips they initiated, the better the improvement in A1c up to a point and then it levels off.
You can see insulin is rather spotty because most of the insulin users were already monitoring, it was hard to find a large enough cohort of non-self-monitoring insulin users, so it's a bit smaller sample size.
A one-strip change in self-monitoring blood glucose among ongoing users was associated with about a .16 and a .12 inverse change in A1c in oral agent only and insulin treated patients. Changes in self-monitoring blood glucose had no impact on A1c in medical nutrition therapy.

00064
However, in newly initiated self-monitoring, it was associated with a clinically and statistically significant dose response decrease in A1c in all subgroups.
Here's a few limitations. This was, I did not look specifically at the Medicare population, so these findings may differ in the

other group. As you all know, you have to make an extreme caution whether making causal inferences from observational studies, even longitudinal studies such as this.
And, let's see, self-monitoring blood glucose effectiveness likely varies widely depending on patients behavioral changes and provider response, and these are not measured. And these are somewhat conservative findings because subjects changing therapy during follow-up were excluded, and that's one of the pathways that may link self-monitoring with improved glycemic control.
So, just, I want to talk briefly about trying to understand the discrepancies in these cohort studies, why there was a substantial improvement, why you find strong impact in the new users, whereas in the ongoing users you only find

00065

it, it's often somewhat weaker, and not only in pharmacologically treated patients. This is, my hypothesis is that substantial initial motivation and educational benefits of starting self-monitoring, you know, there is, when you start monitoring, you get this motivational benefit and educational benefit. But once someone learns their profiles and they understand the responses, that practice is likely to have less of an impact on glycemic control unless the patients use the information to guide action, such as adjusting therapy, or to guide the provider in therapeutic decision making.
That may be why we see pretty much very similar dose response curves in the insulin users as we did on medical nutrition therapy. We only see, you see a substantial new user effect because they are gaining a lot of educational benefit; however, once they understand their profiles and impact, they may not, because of the poor behavioral changes made in response to their results.
DR. GARBER: Dr. Karter, we're running quite a bit behind schedule, so I'm going to need to ask you to wrap up in the next four to five

00066

minutes.
DR. KARTER: Okay.
Diabetes care is a complex intervention, of which self-monitoring blood glucose is only one facet. And we cannot expect an intervention dealing with a single facet of complex problems to be highly efficacious. Also, the effectiveness of new glucose monitoring programs is highly dependent on the ability of patients and providers to integrate the practices

into an overall program of self-care and therapeutic decision making.
This was one thing I wanted you to look at. There was a randomized trial published in Diabetes back in 2004 by Kwon, from Korea, and they showed that, they took a cohort of people who were already self-monitored and did a randomized trial and divided them into two groups, and with one they gave intermittent feedback on their self-monitoring, and this group showed a substantial improvement in their A1c based on that, and that shows how important the linkage between self-monitoring and some kind of behavioral action is.
In conclusion, I think evidence-based

00067

practice recommendations today are rarely based on observational study findings. Instead, they rely exclusively on randomized trials. However, there is at this point a shortage of good information from randomized trials, and I think that the similarity, the effect size reported by the meta-analyses of existing randomized trials, West and Sorrel are two of the most current meta-analyses, and these observational studies are compelling enough evidence to warrant the support of self-monitoring for motivated patients who are appropriately educated in its use.
And with this slide, I will end. Thank you.
DR. GARBER: Thank you very much.
Next, Alisha Wade.
DR. WADE: Good morning, everyone. My name is Alisha Wade. My current affiliation is Johns Hopkins, but I did this study while I was at the University of Oxford, and this is the study to which Dr. Koller referred to earlier, the Diabetes Glycemic Education and Monitoring Study, also known as DiGEM. It was conducted at the Department of Primary Health Care at the University of Oxford.

00068

The DiGEM study examined the effect of blood glucose self-monitoring, specifically in patients with non-insulin treated type 2 diabetes.
So as you've heard many times this morning, there have been many studies of blood glucose self-monitoring. There have been many observational studies we found when we reviewed the literature, and all of those studies by Blonde, Karter, Meng and Chan gave positive results, in which they found that there was an improvement in HbA1c in patients who monitored their blood sugar control. There were also eight uncontrolled intervention studies and Martin,

Banister and Ozmen found positive results. There were 17 randomized controlled studies in the literature, and studies by Rutten, Jaber, Kibriya, Brown, Schwedes, Oh, Guerci and Kwon found positive results.
There also were several systemic reviews of blood glucose self-monitoring in the literature. Faas in 1997 did a criteria-based literature review and his conclusion was the efficacy of this technology is still questionable. Indeed, he found that it was not possible to do a metaanalysis simply because the outcome measures

00069

indeed were so variable.
There was a second systematic review published in 2000 by Coster, in which he found no significant difference between groups. They compared blood glucose self-monitoring or urine self-monitoring with no self-monitoring, and also compared blood glucose self-monitoring to urine self-monitoring.
Now there were two more recently published systematic reviews which Dr. Karter just alluded to, one by Sarol in 2005 and one by Welschen, also in 2005. Both those systematic reviews did find a significant difference between groups.
I would caution that the major difference between the earlier systematic reviews and the more recent systematic reviews was the publication of what were probably to date the two largest randomized controlled trials, those by Schwedes and Guerci, and both of those studies found significant differences and may have helped Sarol and Welschen in the more recent systematic reviews.
So DiGEM, which as I said, is a study evaluating blood glucose self-monitoring in

00070

non-insulin treated type 2 diabetics, was first developed in 2001, and the rationale for developing the study is as we've heard this morning, that blood glucose self-monitoring results in a tremendous cost burden on the health system but the efficacy remains uncertain.
There are several deficiencies in existing research. First of all, most of these randomized controlled trials which have been brought up to date lack comparability between study groups. For example, the study by Schwedes, et al., which found significant differences in the group treated with glucose self-monitoring, actually used quite a different intervention in the group that was doing glucose self-monitoring, when compared to the control group.

Several of the previous studies have been underpowered, and hence the difficulties that Dr. Karter alluded to with the systematic reviews. There's also been an absence of theoretical basis for behavior changes, and I hate to keep quoting Dr. Karter, but I think the point that he made with regard to self-management of diabetes as part of glucose self-monitoring is a very important one. It's impossible to separate

00071

blood glucose self-monitoring from the general self-monitoring behaviors used in type 2 diabetes. Again, potential mediators which may actually result in the proved outcomes aren't clear. Is it simply the result of using blood glucose self-monitoring that results in better outcomes? Does the use of blood glucose self-monitoring change the way the patients perceive their diabetes? Does it change the way they approach the control of diabetes, or any interventions that could conceivably affect their overall outcomes?

And then lastly, there is a potential bias in the type of analysis used. In the two positive studies, the one by Schwedes and Guerci, they actually report with an intention to treat analysis. And in the study by Schwedes, which was the largest study to date, can actually show a positive result even with analysis with a modified intention to treat. They had a very high dropout rate, as Dr. Koller indicated, greater than 40 percent, and their final analysis is only based on the people who had remained in the study for at least two months. So it technically wasn't an intention to treat analysis.

00072

DiGEM is a multicenter trial currently being conducted in the United Kingdom. Patients are being enrolled from both Oxfordshire and Sheffield. The primary trial objective is to establish the effect of blood glucose self-monitoring, either alone or as a means combined with other self-monitoring behaviors, as a means to encourage self-monitoring behavior, as to whether or not there is an effect on HbA1c after one year.

There are also several secondary trial objectives, comparing treatment satisfaction, well-being, health service use, self-management behaviors, hypoglycemia, and beliefs about diabetes across type boundaries. We're also going to be looking at several subgroup comparisons. We will be dividing our study population on the basis of age, duration of diabetes, and baseline HbA1c, to see whether or not any of these features affect

blood glucose self-monitoring and HbA1c. First, as again Dr. Karter alluded to, it is a randomized controlled pragmatic track. We're going to have three trial lines. First will be the control group. I'm only going to discuss what the intervention entails, I will be happy to

00073

answer questions further. First is going to be a control group. That control group will have standardized usual care. They will have three monthly visits from the study nurse, and then their HbA1c is going to be taken every three months and they will get feedback from the study nurse as to whether or not their glycemic control is adequate or whether they may be able to make efforts to improve it. All patients, regardless of which study group they are in will receive a talk about goal setting and how they may improve their glycemic control by modifying their diet, their exercise, or the medication that they're on. In the second less intensive modified group, there was the same standardized usual care intervention, but in addition to meeting with the study nurse every three months, they're going to be given blood glucose self-monitoring and asked to monitor their blood sugar three times a week on any three days a week. Now we chose this particular frequency of glucose self-monitoring because, again, as the literature says and was reviewed, the diabetes literature suggests what the appropriate frequency

00074

of glucose self-monitoring is. In this population, which is not using insulin, we felt that measuring blood glucose twice a week or three days a week would give us enough information in regard to what their baseline control was. And we also asked them in addition to testing fasting blood sugars, to test their blood sugars after meals, with the intention of hoping that we would get some guidance as to what influence various meal compositions, for example, might have on their blood sugar. And then the third and more intensive monitoring group would have an intervention similar to that of the second monitoring group. But in addition, we asked them to test their blood glucose after exercise to see what the effect of the exercise would be on their blood sugar. We also asked them to test if, for example, they did not take their medication, to see what effect that might have on their blood sugar. And we have actively encouraged them to use the results of their blood glucose self-monitoring to feed back

into their day-to-day activities, so hopefully there will be some connections between what blood sugars they had and what behaviors they would be

00075

carrying out, and therefore, receiving some kind of positive, or possibly negative feedback with regard to their self-monitoring behaviors.
So in terms of the population, this study was restricted to patients with type 2 diabetes. We also restricted the population to patients aged 25 or older at diagnosis, because we wanted to be sure that we were picking up patients with type 2 diabetes. There is no upper age limit with regard to the study and really, the only restriction was that patients had to be independent in activities of daily living, because we felt this would be necessary to help the patients manage their behavior, doing their exercise, changing their diet which might influence their overall control. And we also wanted patients to manage their lifestyle or oral hypoglycemic agents.
Patients who had used blood glucose self-monitoring at least twice a week in the preceding three months were excluded from the trials, and the reason for this is we wanted patients who were as naive as possible to blood glucose self-monitoring to be enrolled. As was also alluded to previously, patients who already

00076

may have been exposed to glucose self-monitoring probably had predetermined ideas about its use, they may well have been enthusiastic about continuing their monitoring. So we wanted patients who really had no idea about the technology to come forward so we could really examine what the initiation of monitoring and continuing monitoring over the course of the year, how it affected their readings. Again, patients who had a limited mobility or significant comorbidity were excluded, again, because we felt they may be unable to modify their lifestyle regimen. And lastly, we excluded patients who had a HbA1c of less than 6.2, and the reason for this is that we were looking actually targeting changes in HbA1c scores as evidence of glycemic control, and we felt that we were limiting a significant effect in patients who had glycemic control and a low HbA1c.
So, how did DiGEM address the existing questions or issues in the literature? DiGEM is powered to detect an absolute difference of HbA1c of 0.5 percent with 80 percent power. Our intervention is based, which I will skip over because of time, but is actually based on

00077

psychological theory. And also, hopefully by using the type of intervention we have, we hope to be able to examine whether or not we could effectively and potentially use blood glucose self-monitoring as a treatment for glycemic control.

We're going to hear presentations about the advantage to diabetics and their beliefs about the effects of their behaviors are on their glycemic control at the beginning and at the end of the study. So what we will hopefully determine is whether or not the changes occurred, and if the changes did occur, was that a result of the changes in behavior. And we will also be doing an intention to treat analysis with regard to the study.

So with regard to the current status of DiGEM, recruitment was carried out between 2003 and 2005. We recruited 453 patients, we are now developing treatment targets, and we expect to report our data probably midway through next year.

The study was actually funded by the Health Technologies Assessment program of the National Health Service of the United Kingdom, and the blood glucose meters used in the study were

00078

provided by MediSense.

And I would just like to thank our other study investigators, Dr. Andrew Farmer, Professor Andrew Neil, Professor Rury Holman, Professor David Mant, Ms. Sue Ziebland, Professor Alistair Gray, Dr. Pat Yudkin, Professor Ann Marie Kinmonth, and Dr. David French. Thank you.

DR. GARBER: Thank you very much. Next will be Mayer Davidson.

DR. DAVIDSON: I'm Mayer Davidson. I have no conflict of interest. And the first slide I would show you, the primary area selected was Seeking Diabetes Control, the use and abuse of self-glucose monitoring. And what I might do, if you can't find it, I brought it on a stick. Would that be helpful? Let me go get that just in case.

(Pause.)

Here is the first slide. Now Dr. Koller also talked about the relationship between control of glycemia and microvascular disease, so we're going to start with that as soon as it comes up. Now the first slide after the opening slide just states that the ADA goals of A1c are, or is less than seven percent, and that's based on -- here it is.

00079

This is the relationship between

glycemia and microvascular disease. You've heard about the DCCT trial. This is the time since inception running out to about nine years, and this is the relative rates now, not the absolute rates, of retinopathy. And you can see that with an A1c of seven percent, there is no development and no progression of established retinopathy in the patients participating in the study. If you have an A1c of eight percent, the first four or five years there was no increase and then it was a moderate increase. With nine, 10 and 11 percent, it really went up. And based on what I'm going to be saying from that slide, if the A1c is very high, it goes up very quickly, the retinopathy. This is the other complications, neuropathy and two forms of nephropathy, and you can see the same thing. If we did not see an A1c above seven percent, there is no progression or development of those complications. Once you get above seven, then you see they really take off. This is just the average A1c from this study. This is a retrospective study done where we looked at microalbuminuria over a six-year period, and these are hemoglobin A1; to

00080

look at A1c's, you have to look down here, and again, this is the development of microalbuminuria; patients at the beginning did not have microalbuminuria, so what was their chance of developing it. If you had an A1c in this case that was less than eight, almost no chance, but once you got over eight, the development of microalbuminuria really took off. This is the same data but looking at patients starting out with microalbuminuria, what were the chances of them going on to clinical proteinuria, and this clear curve that you can barely see is the result. And again, with an A1c between six and seven, there is no development of microalbuminuria to clinical proteinuria, seven to eight a little bit, and really taking off above eight.
Type 2 diabetes, you have the Kumamoto study which is patterned after the DCCT. Retinopathy, nephropathy, again, between six and seven, no development of these complications or progressions, over eight really taking off.
And finally, another study from Tanaka. This is a little different. This is the cumulative incidence, but it's the chance of

00081

getting microalbuminuria over a six-year period looking at the mean A1c, and again, if it's under seven, don't worry about it; between seven and eight, just a few percent; but after eight, again,

it really takes off.
So that's the relationship between microvascular disease and A1c.
Now let's take a little different look at the relationship between glycemia and macrovascular disease. It's been known for a long time that there's an association between glucose levels and the development of CAD.
This is one of the earlier studies, the Honolulu study, and over here we have fatal coronary artery disease and total coronary artery disease. This is the post-challenge glucose, so this is the two-hour glucose tolerance test, and the value of 40 to 114, the red, and the 115 to 133 stay in the normal range; 134 to 156 is starting to get up into the ICT, but you can see that even within normal ranges there are increases in CAD, or coronary artery disease.
This is a metaanalysis looking at 95,000-plus patients and this is the relative rate of getting CAD. This is the fasting glucose here,

00082

this is the two-hour glucose. This is normal so for us Yankees, we have to convert this. This is about 90, this is about 108, seven I think is about 126, and you can see that there's an increase after you get up into what we used to call the normal range. Here's the values, it's 108 here, this is about 140. So the point is that there's an increase in CVD in the normal range.
That's shown really well in this study.
This is actually called the EPIC study, this was a cancer study, but they looked at the development of myocardial infarction over a three-year period in 4,662 men. They took as their baseline those with A1c's less than five, and then they went up. When you go to a baseline value between 5.0 and 5.4, there's a 250 percent increase in the percentage chance of getting a heart attack, and it goes up progressively from there. Since this study was published, there's been another study that show the same thing looking at 4.6 as the baseline. The point is that within certainly the normal range of glycemia, there are increases in primary artery disease.
Now it's important to point out that the changes of glucose that were shown on the

00083

previous slides are not independent predictors of CVD. If you take the other risk factors into consideration and take them into account, then there is no increase in CVD, and there are three studies now that have shown that. On the other hand, certainly IGT is a predictor of subsequent development of type 2 diabetes.

Now in terms of lowering glycemia, as has been pointed out in some of these studies, there is no evidence in type 2 diabetes that a lowering glycemia is beneficial, or has beneficial effect on coronary artery disease, and there's two metaanalyses where reviewers have said that. Now having said that, type 1 diabetes (inaudible) and initially as Dr. Koller has pointed out, in DCCT there was not enough coronary artery disease to be statistically significant, but the EDIC study has shown that may not be true.

Now the EDIC study, what happened is as follows. After DCCT ran out, they built extra funding for EDIC, and they predefined their CVD outcomes as non-fatal MI, stroke, death from CVD, confirmed angina, or coronary revascularization, and the results were published eight or nine months ago.

00084

This slide shows you that once the DCCT stopped, we all know that the average A1c was about seven percent in the intensively treated group, and it stayed at about nine percent in the control group. After the DCCT, there was a convergence of the A1c levels, and so in six months they were almost equal; certainly by here, at two years they were equal, seven percent went up to about eight, and nine percent went down to about eight, and so for most of this period of time, the A1c was no different than when it started.

This is the cardiovascular incidence from the beginning of EDIC and as I mentioned, that was the end of the DCCT, and as you can see, there is a divergence here with the intensively treated patients here and the control patients in the DCCT being here. The hemoglobin A1c's are not different but there is a difference in the incidence of cardiovascular disease. Now if you look at this from the beginning of the DCCT, you start to see the divergence maybe around 10, 11, 12 years, and at least statistical significance here maybe at 15 to 20 years later after the beginning of the DCCT.

00085

So now we turn to SMBG. This is a slide that shows the rate of SMBG in type 1 patients and their A1cs. It's over a 21-day period, and these are the number of SMBG's through 21 days and here's the A1c, and you can see a very nice inverse relationship here.

A study was done, and this is just one study, but there's been several like it, it was a study done of type 2 patients, I think it was only type 2, though it could have included some type 1,

and half of those patients were given self-management skills, what to do with the results, and the other half were just told to measure their glucose. In those that were given self-management skills, the A1c's came down. Those that were just told to test more often, there was no change in A1c.
So the point is that, as was pointed out by previous speakers, you need to do something with that information in order to get the benefit from SMBG. Dr. Karter related a lot to you about the retrospective and observational studies. From here on, we'll be talking about SMBG in type 2 patients not on insulin.
And there are, I could find at least 14

00086

negative observational retrospective studies in the literature showing that measuring your glucose or SMBG in patients on pills or diet alone did not make any difference in their glycemic outcome.
There were some positive ones, and Dr. Karter talked to us about his studies, and there are at least two of them, they are retrospective studies looking at a large database, and they showed changes, as he showed you, about A1c's coming down.
However, as he pointed out, there is a potential issue here with healthy lifestyle behavior, and he actually has shown this, because in one of these studies they did a questionnaire and if the patient did not answer the questionnaire, they actually called them on the telephone. And the results of that showed that the patients who were selected by their physicians or themselves with the SMBG had better self-care practices and healthier lifestyle behaviors by these questionnaires or telephone interviews. So my point here is that there is a self selection, that patients more likely to accept SMBG are probably more likely to have healthier behaviors and that may account for their positive findings.

00087

Here's another observational study that was published, and this is, the problem here is that a therapy decision scheme was applied only to the patients who did SMBG, patients in the control group received no particular instruction, so the problem we see here is that the two groups were not treated equally.
Here's the third one, and I think Dr. Wade or somebody talked about the Soumerai one. Free glucose meters were given to those who wanted to use them, and they only had positive results in those who, one, had very high A1c levels, and also were receiving sulfonylurea

agents; all the other patients, there was no positive changes. And again, probably self selection in the poorly controlled patients that accounted for those results.
Here's another one, and we have heard talked about the very few randomized clinical studies that are in the literature. Fontbonne, he had 68 SMBG patients, and he compared SMBG, urine testing, and the control group getting neither. The baseline A1c's were fairly comparable. There were modest, at best, changes in the A1c levels, and the ones getting neither actually had the best

00088

percentage change, but there was no difference among the groups.
Another randomized clinical trial, smaller in number, baseline is very well defined in both patients, and they both came down about two percent, so obviously there was no difference between the two groups.
Dr. Muchmore did one, again, small numbers, and he had a baseline of 8.8 to 9.6. There was a difference in their absolute change, 1.5 to 1.8, although they were not statistically significant, probably because it was underpowered, but again, the groups were not treated equally. The patients who got SMBG were given extra dietary help, they were taught carbohydrate counting and they kept a food diary, and they went back and saw their providers, whereas with the control patients, none of that occurred.
And this study has also been mentioned, by Dr. Schwedes. Higher numbers, the baseline is comparable, and there was a two times higher decrease in the SMBG group than the control group. But again, the patients who got SMBG received special dietary counseling, so again, you cannot say that this is just due to the SMBG.

00089

This one was also mentioned, very large groups in each one, or a large number of patients in each group, and there was a statistical significance, but almost half of the SMBG patients dropped out, 48 percent, and 40 percent of the control group dropped, out and so that put some doubt on the validity of those results.
Now here's the one blinded study, and I agree it's very difficult to do blinded studies, but we were able to carry one out. That's because we have a unique system, we have a trained nurse who follows protocols that I've written, and I just talk to her over the phone once a week, but she makes the clinical decisions. We then did a study in which patients were randomized either to take some pills again, to see the dietitian with

SMBG, or just to see the dietitian. The nurse treated all the patients and she did not know which patients were on SMBG. The patients were scheduled to see the dietitian five times during the six-month study. They were asked to test six times a week, before and after breakfast twice, lunch twice and supper twice.
About half of them did, 45 percent total compliance, and then the dietitian would

00090

take those numbers and he would use those to do a nutritional counseling with the patients. The patients who were not on SMBG were just getting nutritional counseling. Here you see, there were 43 and 45 in each group, the number of visits to the dietitian were no different in these two groups, the baselines were comparable, and the change was not statistically different, it went down .8 in this group, the SMBG group, and coming down .6 in the group that did not receive SMBG.
Now these 43 or 45 patients that took SMBG were just a small group in the number of patients that this nurse treated. We had 367 patients that she treated. On the year prior to coming to see us in the nurse director care group, their A1c was typically about 8.8. When they finished that year, they were at about 8.6. They didn't change much in the standard care. When she was finished with them after one year, the average A1c was down to 7.0 and their median came down to 6.7.
Now only 22 percent of those patients were on insulin, all the rest of them were on pills and so most of them, of course, did not have SMBG, and therefore, I'm showing you here that you

00091

can do fairly well without SMBG. When they started in that year before seeing the nurse, 17 percent met the ADA goal of seven percent, 28 percent met it afterwards, and she was able to bring that up to 60 percent meeting the ADA goal at the end of one year.
Now we talked about the two metaanalyses, Dr. Wade did. There was a modest .39 percent reduction. She said that there was a lot of clinical heterogeneity, and in practice she did not do any evaluations, but as the editor I forced her to do it, and it came down to minus .39. And she did point out that there was this study by Sarol, and Sarol did not talk about any of the clinical heterogeneity studies and came out with a rather modest .31 percent.
So that's the data as I could see it in the literature and in our study on SMBG.
Now why doesn't it make any difference?

The value of SMBG in insulin-requiring patients is easy, because they could do something about it, they could change the timing of their meals, they could change what they eat in their meals, or their exercise pattern, the doctor could use all these values to adjust the doses. And again, as

00092

pointed out, it also serves as motivation and education.
But now patients not on insulin, it does serve as motivation and education, but most people measure only in the fasting state, and if it's going to motivate you, you've got to see the highest numbers; if it's going to educate you, you really need to see the post-prandial numbers. But even if you do see the post-prandial numbers, it has a limited effect on glycemic outcome. There are only certain things you can do, there is only one medication that you can change that's going to make any difference, and that's repaglinide, you can change the dose of that, but that only has about one percent of the market, so that's not going to have any effect.
I guess you could delay your meal, eat less carbohydrates, and that's nearly impossible.
The long-term pattern to adjust medication, you really don't need to do that in our type 2 patients, and that's because the fasting glucose really is fairly stable in patients who are on oral agents.
And here is a study looking at two fasting glucoses from day to day where you see a

00093

very tight correlation, and here's another study showing it one week apart. Although it's spread out here and they are very high, clinically that doesn't make any difference, because obviously your decision's going to be the same whether they're 280 or they're 200. So if you use the fasting sugar, at least in our study, in our program, and monitor the glucose of the oral agents on the fasting glucose, you can do just as well.
And this is very expensive. In 2002, this is the Medicare B fee-for-service number of what it cost for ICD-9 code 250.00, and the cost for reagent strips, lancets, devices, meters, batteries, et cetera, was almost half a billion dollars. And this is a minimum cost, because it only includes Medicare B, it doesn't include HMO Medicare, and it certainly, from the payer's point of view, it doesn't include all the other patients who are not in Medicare.
And finally, two quick other things.
Dr. Koller asked me to give you the data on A1c's

between type 1s and type 2s. This is a study looking at two groups with insulin, but the curves here are the same kind of curves that you get from

00094

the DCCT. It's obvious that the lower the A1c is, the more likely you are to get hypoglycemia, and that's what this shows, but notice here in type 1 patients, when you're at 20, 30, 40, 50 hypoglycemic events per patient year, and here's the same study done in type 2 patients and here we're at the nine, 10, 11, so there is at least a five-fold difference in hypoglycemia.

And finally, there's information that may be helpful for the panel's discussion later on. It makes a difference at when the patient is diagnosed to have diabetes. The age of diagnosis is here, this is the duration of life after diabetes, or after the diagnosis for male and female. So if diagnosis age is 60, you are still going to have on average 15 more years to live, and if you're a female, you're going to have about 17 more years left. And a study that's coming out in Diabetes Care in November shows you that there is a difference. If you're over 65 and you had diabetes diagnosed between 40 and 64, or if you're over 65 with diabetes and you had the diabetes diagnosed after the age of 65, there is no difference in the coronary artery disease rates but there's a tremendous difference in the

00095

microvascular disease. So the point I would make here is that if a patient is diagnosed at 60 and they've got 15 more years left, they have a lot of time to get microvascular disease and consequently, monitoring is important. Thank you very much.

DR. GARBER: Thank you very much. The next speaker will be Dr. Denise Simons-Morton from NIH.

DR. SIMONS-MORTON: I was nervous about actually finding my slides. I am happy to present ACCORD, The Action to Control Cardiovascular Risk in Diabetes trial. I will be presenting the design of the study because we have no data yet for the study, the study is still ongoing. I have no conflicts to report; however, I'm going to show a slide that shows the contributors and collaborators on this study.

We've heard some background, just one slide on background, about 17 million people in the U.S., or six percent of the population have diabetes. The vast majority of those are type 2 diabetes. And as previously stated, diabetes increases the risk of cardiovascular disease, double to quadruple compared to people who don't

00096

have diabetes, and that cardiovascular disease is the leading cause of death in diabetes. You also saw some data that glycemia level is directly associated with cardiovascular disease rates in observational studies, and that's even down to within the normal range. There is some evidence from experimental randomized controlled trials that reducing glycemia will reduce CVD, but the evidence is borderline at best, and the studies are inconsistent with each other in terms of the findings. It's a very important question. We also know that hypertension and dyslipidemia are more common in diabetic persons. However, optimal treatments for these cardiovascular disease risk factors are unknown, in diabetes as well as in non-diabetes, as a matter of fact.

So, we designed ACCORD to test three separate research questions addressing strategies to reduce cardiovascular disease in diabetic patients, a glycemia strategy, a blood pressure strategy, and a blood lipids/lipoproteins strategy. It's a multicenter randomized clinical trial which includes 10,251 patients with type 2 diabetes who are at high risk for cardiovascular

00097

disease events.

Here are the eligibility criteria. They had to have had stable type 2 diabetes for at least three months. They had to have A1c ranges which varied depending on whether they were on more or less treatment; if they were on less treatment, it could go up to 11 percent; if they were on more treatment, it could go only to nine percent, and so that depended on how many oral agents and whether they were on insulin. So the bottom range was 7.5 percent because we didn't want to recruit anybody into the study, randomize them into the standard control group, and have their A1c get worse.

They had to be at high risk of cardiovascular disease, either they had clinical disease, for example had an MI in the past, or had subclinical disease, for example as measured by events, or they have two or more additional risk factors like hypertension, dyslipidemia or obesity. Regarding age, they could be 40 years or older if they had cardiovascular disease history, 55 or older otherwise, if they didn't actually have clinical cardiovascular disease. As we can see from the baseline data, the mean age is in the

00098

lower 60s, so we will have a fair proportion, I

think, who are over 65. They also have to be eligible for either a lipid or blood pressure trial and we have additional eligibility criteria, but in the interest of time I'm not going to show you those, but those are based on blood pressure values or HDL and LDL values, as well as whether they've had, for example liver disease or kidney disease that might preclude some of the medications.
They were excluded if they had a cardiovascular event or procedure such as CABG or PCI with stenting, angioplasty, or hospitalization in the past three months, so if they had cardiovascular disease (inaudible). If they had a history of hypoglycemia, coma or seizure in the last 12 months, they were excluded. If they had a serum creatinine greater than 1.5 milligrams per deciliter, they were excluded, because of possible effects on renal disease. They were excluded if they had symptomatic heart failure or history of New York Heart Association class III or IV heart failure. They were excluded if they had transaminase greater than two times the upper limit of normal, known liver disease, or factors

00099

likely to limit adherence.
So, what are the questions we're testing, glycemia, blood pressure and lipids questions? The glycemia question is to ask whether intensive control of hemoglobin A1c with a target of less than 6.0 percent versus a standard control with a range of 7.0 to 7.9 percent would give you expectations, and I will tell you a lot more about this question.
The blood pressure question is testing, intensive control, targeting systolic blood pressure less than 120, versus standard control targeting systolic blood pressure less than 140. I'm not going to focus my talk on this, but we can talk about that and I would answer any questions if you want.
And the lipid question, we're testing fibrates in order to increase HDL and lower triglycerides, and statins to lower LDL, HDL being the bad cholesterol and LDL being the bad cholesterol, versus just statins to lower LDL-C alone, so it's a combined therapy versus statins alone. I'm not going to tell you much more about this either, in the interest of time.
So here's the design. It's a double

00100

two-by-two factorial design. If they meet eligibility criteria, they're randomized into one of these eight sets, and it shows the final sample size numbers. So let me just explain this.

Everybody is either in the intensive glycemic control with the less than six target, or in the standard glycemic control with A1c's in the sevens, and that's 5,000 people in the intensive, approximately, and 5,000 in the standard. The outcomes in these two groups will be compared for the primary analysis.
They also have to be in the blood pressure or the lipid trial. If they are in the blood pressure trial, they are randomly assigned if their tested systolic blood pressure is below 120, versus standard. We have about 2,400 people in each of those groups and the primary analysis will be comparing the outcomes in those two groups.
The lipids, they get fibrate plus stain, or placebo plus statin, and there are about 2,800 people in each of the randomized arms of the lipid trial.
The blood pressure and glycemia are open labeled treatments, but there's people who,

00101

the outcomes are blinded to treatment assignment, which I show on this slide. The primary outcome is a composite outcome, nonfatal MI, nonfatal stroke, or cardiovascular disease death. It is the same outcome for all three questions, glycemia, blood pressure and lipids, and those outcomes are adjudicated by a blinded committee, the committee does not know to which group a patient is assigned.
We have 89 percent power to detect a 15 percent effect in the glycemia trial. For the blood pressure, 94 percent power to detect a 20 percent effect. And for the lipid trial, 87 percent power to detect a 20 percent. We intentionally designed it to be able to detect a smaller effect in the glycemia trial because we wanted to make sure that we detected a significant effect if it should occur; however, we think that all of these effect sizes are clinically relevant.
We're also looking at other cardiovascular outcomes. These include each component of the primary outcome and expanded outcomes including revascularization or treatments like coronary bypass surgery or angioplasty, and also heart failure hospitalization. We're looking

00102

at total mortality, at microvascular outcomes including nephropathy, diabetic eye disease, and neuropathy, and our outcome here is designed to pretty much mimic what we see in other microvascular outcomes. We are taking retinal photographs in the substudy to look at retinopathy. We also have a substudy analyzing

health-related quality of life and cost effectiveness, and cognitive functioning, and an even smaller group of people where we do brain MRI. All of these will be analyzed by randomized groups, the same as the primary outcomes.
So, how are we actually testing, what intervention are we doing to test our glycemia research question, which is, in middle aged or older people with type 2 diabetes at high risk for cardiovascular disease event, does targeting A1c less than 6.0 percent safely reduce cardiovascular events more than targeting A1c of 7.0 to 7.9 percent?
This is a strategy question, we are not testing individual drugs. We are testing strategies that can be delivered in clinical practice. So, compared with the standard group, the intensive group has, as we said, a lower A1c

00103

goal, 6.0, less than six, versus in the sevens. But how do you get that goal? They will have more clinic visits with more adjustment of therapy. They receive point of care A1c measures right there in the clinic, so the therapy can begin without waiting for lab results to come back, we can call them on the phone or have them come in again. There is a greater use of multiple medications and combination medications in the intensive group versus the standard arm. They are more likely to need insulin to reach the goal, and highly relevant to this meeting, self-monitoring blood glucose therapy with greater frequency in the intensive versus the standard group, up to eight times a day in the intensive group, and more likely one or two times a day or maybe seven times a week, they don't necessarily have to do it every day.
The key, and relevant to what a couple other speakers said, is that the results of this therapy are used by the patient and the physician to modify lifestyle and medications in order to reach the goal. So for example, behavioral strategies and sliding scale insulin may be used as a result of the A1c values, or not A1c, the

00104

SMBG values as a result of the monitoring. So we think this is an integral part of the intervention, and it's not only important for adjusting the therapy but also for helping prevent hypoglycemic events when people can see that their SMBG values are low and if they're dangerously low, then the lifestyle, their eating patterns, the insulin patterns, et cetera, can be modified to prevent hypoglycemia.
So we're going to actually randomize

comparisons between SMBG-guided therapy, because the amount of monitoring is greater than the standard group, and we can do this in a randomized comparison. But it's not the only thing that's different, all this other stuff is different too, including the medications.
Speaking of medications, here's the ACCORD formulary of medications. It's just like we would use in clinical practice, we have metformin, we had secretagogues, we have THZDs and we have a variety of insulins, and the clinicians in ACCORD can choose among this formulary for their particular patients to select the appropriate therapy in order to reach the A1c six percent goal, and combination therapies that may

00105

not be used in clinical practice today are being used in ACCORD.
Background treatments, the other aspects of diabetes and cardiovascular disease care are given in accordance with current practice guidelines and the study gives recommendations to the physicians who are providing this care. We also deliver lifestyle therapy as an integral part of glycemic treatment and cardiovascular disease risk reduction, and that's delivered by ACCORD clinicians. So we provide medical nutrition therapy, physical activity counseling, and weight management approaches. We think it's critical to tend to lifestyle care in order to get to the goals that are targeted.
We have an external monitoring committee and an independent DSMB safety monitor appointed by the National Heart, Lung and Blood Institute. They monitor a variety of different things. I put a list here, but let me just point out a couple of things. They look at the A1c achieved group-specific levels and between-group difference in the levels. In order to get to the research question, we have to make sure that the intensive and standard groups actually do have a

00106

difference and they closely look at these A1c values.
They also monitor severe hypoglycemia events, in large part because of this benefit question. If we link cardiovascular disease events but have a whole lot of severe hypoglycemia, that would be really important to know, or maybe that won't happen, and that would be important to know also.
They also monitor a bunch of other things, including SAEs and whether they're caused by the SCA and its effect on the primary outcomes to determine whether it is efficacious or may be

going the wrong way, and this can be caught in the study early. There are no SAEs right now, everything is going just fine.
Here's our time line. We are right here in 2006. We did the vanguard to see if we could actually, the clinicians could actually achieve the targeted goals for blood pressure, lipids and glycemia, and recruitment. That was successful, and we started a main trial, we finished recruitment, the follow-up is going to end in 2009. There is a four, eight to four-year range in terms of following participants, the

00107

average is going to be about 5.5 years. And then we should know the results and publish the results in 2010.
This shows the ACCORD clinical centers, network centers and sites in the United States and Canada. We have a coordinating center at Wake Forest, the project office at NHLBI. We have a distribution center, central laboratory, central DCT reading center, and probably other things that I've missed.
I just want to acknowledge the cooperation and support of several sister institutes, the NIH and Centers for Disease Control, as well as contributions from a variety of different drug and pharmaceutical companies, almost all the drugs are donated.
So, ACCORD is a large complex study addressing fundamental clinical questions about diabetes management, what are appropriate targets for treating glycemia, blood pressure, and lipids to reduce cardiovascular disease, which is the dominant cause of morbidity and mortality in diabetes. And so we'll know the results in 2010.
Thanks.
DR. GARBER: Thank you very much. The

00108

next speaker will be Bill Duckworth, from the VA.
DR. DUCKWORTH: Well, I'm Bill Duckworth, and this never works. Conflicts of interest, our study and diabetes trial is being supported by a number of companies just as the ACCORD trial is, specifically Aventis, Novo Nordisk, Roche Diagnostics, Coast, I think that's it. For the sake of completeness at this monitoring session, I was formerly a consultant for Roche Diagnostics, I'm not now. And my biggest conflict of interest I'll save for last, the fact that I have children at both the University of Arizona and Arizona State University, and that's a conflict. I tried not to say that loudly.
Okay. Here is the name of the trial

and two of the people, the two co-chairs, me and Carlos Abrarra. Tom Moritz was the statistician and he prepared a number of these slides, which I will mention briefly as we go.
The rationale for this is very very simple. We're going to look at the effect of glucose control on cardiovascular disease, and the reason we're doing it is because we don't know the relationship, the true relationship between

00109

glucose control and cardiovascular disease. It's a reasonably sized study, 20 centers, 1,700-plus, specifically 1,792 patients.
And I'm going to read this carefully because it has some meaty things in it, important things. It's a prospective, randomized study of intensive versus standard glycemic treatment on cardiovascular events, hard endpoints, in patients with type 2 diabetes and sub-optimal response to maximum oral agents or insulin. So basically, the purpose was to get glucose under control, and we were probably stupid for doing this, but we did this so we're stuck with it.
Of extreme importance, and I'll try to show you some of the reasons for this, but of extreme importance is that both groups are treated identically with all other known cardiovascular risk factors, blood pressure and lipids, diet and lifestyle, they all get identical instruction on diet and lifestyle changes and they all are intensively treated for what we can do something about, to prevent other things from interfering with the examination of glycemic control alone.
Now there are a number of, you have been hearing a lot about this this morning, so

00110

I'll go through some of these slides rather quickly, because some of them you've seen or at least you've seen their details, but epidemiological and observational studies reveal associations about benefits of glucose control on cardiovascular events, but say nothing about cause and effect. Interventional studies have not been definitive, but there are known and proven important effects of blood pressure control in type 2 diabetes with regard to both micro and macrovascular complications.
This is some interesting data that has popped up a few years ago. It was a survey of 900 physicians, 700 primary care, 100 endocrinologists and 100 cardiologists. They gave their opinions about what was most important for preventing cardiovascular disease in type 2 diabetes.
Controlling blood glucose was the most important, a smaller number believed blood pressure control

alone, and then lower cholesterol was minuscule.
Okay, what's the truth?
That's a repeat of the other statement.
Metaanalysis. Lowering blood pressure requires
157 patient years needed to treat to be effective
in reducing cardiovascular events. Cholesterol,

00111

106, and glucose was not significant. So we have
the ADC completely backward to what is the most
important; cholesterol was the most important
here, blood pressure was the next most important
of the things looked at, and glucose, we just
don't know, period.
But what is the most important thing
for us to know about type 2 diabetes? What kills
most people with type 2 diabetes is vascular
disease, specifically heart disease, strokes, that
sort of thing. Here's the relative risk, lifetime
risk. End stage renal disease with age of onset
of 55, with a terrible A1c, the risk is down here.
The risk of cardiovascular death is up here, and
that's what we don't know yet.
We saw most of this data earlier, so I
will just briefly mention one thing, and that is
it really does make a difference when someone gets
the diagnosis of diabetes, not gets diabetes, it's
when they get the diagnosis of diabetes, the age
of that makes a big difference in lifetime risks.
You've heard about epidemiological
studies, so I'm sure that there is an association
between glucose and the cardiovascular problems,
and sometimes when you look at all of them, it's

00112

about 50-50, so we've confused the issue even
more. Here's our epidemiological data of the
subjects that were entered into the study and
their baseline results. What correlates with
cardiovascular disease? Age, no surprise there.
Duration of diabetes, no surprise there. Insulin
use, known for a long time, not sure exactly what
that means. What about A1c at entry? No
difference in the two groups with or without
cardiovascular disease whatsoever.
I'm sorry that I'm sort of wandering
around here. Glucose lowering trial we've heard
about, so I'm not going to go into those anymore
except, not all of them have been significant in
terms of the longer time trials, and one of them
was actually trending the wrong way, as you know.
There was one that was significant which I will
talk very briefly about in a minute. We've heard
all this so I'll just keep going.
I don't think this has been shown
exactly this way, but here's the data from UKPDS
in terms of the risk of increase in A1c on

microvascular events and on cardiovascular events, totally different curves, flattening out here. There is some increase in this range but it's

00113

really not very impressive in terms of their own data in terms of cardiovascular events. And you heard about the EDIC so I'm not going to go through that group of slides either. There is one that I promised that I would mention, the Steno trial did show effect on cardiovascular disease, cardiovascular events, but it was probably, or may have been due to other things that they were controlling. A fairly good-sized study, fairly decent duration. They looked at conventional treatment of glucose, blood pressure and lipids to goal, and they found that there was a 53 percent decrease in cardiovascular risk, but intensive patients at goal for the three things they were trying to treat, only 15 percent had glucose goals met, 45 systolic blood pressure, 79 diastolic blood pressure, and total cholesterol, even higher. So what really causes the 53 percent decrease, we don't know. One thing that is relevant, the UKPDS also looked at blood pressure and the effect of blood pressure control or treatment, it's certainly not control. The blood pressure, if I recall correctly, is 144 over 82 versus 154 over 87, but that little bit of control in blood

00114

pressure resulted in a decrease of any diabetes-related influence, twice as much as glucose did, diabetes-related deaths, which glucose control didn't do anything to, stroke -- let's see. Three times more in terms of diabetes-related death. Stroke was, glucose control didn't do anything for. And microvascular influence, 50 percent more than glucose control. So blood pressure control is absolutely essential to prevent cardiovascular events. Primary outcomes in this study, which is now in its sixth year, a year and a half to go basically, major cardiovascular events, cardiovascular death, MI, stroke, congestive heart failure, and many of these patients will advance to neuropathy or infection, and interventions for coronary artery disease or peripheral vascular disease. Secondary outcomes, angina, TIAs, critical limb ischemia, total mortality, retinopathy, nephropathy, neuropathy, quality of life, cognitive function, and cost effectiveness, a pretty large basket to fill. Eligibility, which I mentioned briefly before, veterans, this is a VA study, with type 2 diabetes; A1c better than 7.5 at entry; either on

00115
insulin or maximum dose of some oral agent, or both; male or female; no maximal age limit, and it's greater than 40, or 41 or greater; and no major cardiovascular event in the last, pretend there's a six there, past six months. Really complicated design, take a group of patients, randomize them half to one treatment and half to the other, that's it. That's what we're studying. So we're not going to have trouble, I hope, with too complicated a study for you to interpret ultimately. Something that we thought was very important, there are independent effects of certain drugs on cardiovascular events and it's probably more than we actually know about right now, so we had to make sure as best we could that patients in both groups were treated as nearly identically as possible with one aspect of the control than the other. So everybody is on, or potentially on the same drugs in a specific order of administration, particularly setting it up so insulin is used as early as possible, because there is an association with insulin and cardiovascular disease for whatever reason. And then after we get the basic scheme set, then we

00116
have to use the same thing in both arms. Again, optimize lipid and blood pressure treatments so they are equal in both arms. The enrollment information, duration of diabetes 11.5 years, age 60, so they are now over 65 obviously, and they're obese, and a particular reference to smoking, so I assume this means I need to quit. One thing we were really concerned about was this occurred in the UKPDS, after initial control it was lost in the intensive group, and it continued to rise in the standard group, parallel really, so we did not want that happening, so we did this to our control and we have done pretty well. Our goal was between eight and nine for the standard, for reasons, some of which has been mentioned earlier, and as low as we can get them for the tough group in the intensive. We're now running about six or seven in this group and the control may be decreasing a little bit. And I wanted to do this for a second. Blood pressure control is exactly the same in both groups. It started out pretty doggone good over the three groups of patients, 131 over 77. And over three years, this was the data we had

00117
available, 127 over 72, which is also pretty good.

Lipids, again, pretty good at baseline, all things considered, and again, improvement in everything over time, including the HDL. Most patients were on aspirin, 90 percent roughly. Most were on lipid treatment, 80 percent on statins, this is now higher because we have been pushing the statins after the recent studies.
Those are the conclusions. ADA goals for A1c, blood pressure, triglycerides, and LDL cholesterol can be achieved in a difficult group, and the risks/benefits of intensive glycemic control in an older high-risk cohort are not known but can be established. Thank you.
DR. GARBER: Thank you, and I hope you feel better. Next speaker will be Irl Hirsch.
DR. HIRSCH: Thank you, and good morning. First, my conflicts of interest. My travel from Seattle was funded by the JDRF. I consult with Abbott Diabetes Care, Johnson & Johnson, and Roche. I also have research grants from Medtronic Diabetes, American Diabetes Association, and have one forthcoming from the JDRF. I actually have a much larger conflict of interest that I want to share with you. I have

00118

had type 1 diabetes for 42 years, and looking around the audience, watching everybody checking their blood sugar and looking at their sensors, I know I'm not alone this morning.
Very briefly, aa little bit about me, I run a large diabetes clinic in Seattle at the University of Washington. A quarter of our patients are Medicare patients, 50 percent of our clinic patients are type 1, and we're going to focus on type 1 diabetes in my discussion. My personal clinic population of about five to 600 patients, 80 percent are type 1. I'm the medical director of the center, I'm on the board of directors of the ADA. I'm a member of the American Board of Internal Medicine, that means I write the diabetes questions for the ABIM. I have received awards from both the ADA and AACE.
What I want to talk about, however, is the importance of glycemic control for all people with diabetes, including Medicare patients who are elderly, who have end stage renal disease. And I also want to touch on the importance of continuous glucose monitoring, CGM, to improve glycemic control in Medicare patients, and what additional research is required.

00119

So let's talk about, first, the importance of glycemic control. You've seen the data. Metabolic control matters for all people with diabetes. Yes, we have microvascular,

macrovascular, health-related quality of life, I think most people would agree with that statement, but I would also suggest that people with diabetes need better tools to achieve better control. The DCCT was reported and published in 1993, and it's almost embarrassing when we look at our type 1 population right now to see how far we have come, or actually how far we haven't come, when we see that somewhere between a quarter and a third of patients with type 1 diabetes in the United States are still on twice daily insulin. Intensive management improves diabetes outcomes. A1c is, as you have heard, a validated surrogate for diabetes complications. Intensively managed patients have a lower risk of developing complications than patients on conventional therapy who achieve equal A1c levels. Now this is somewhat of a controversial statement but we can talk about more about this later. Intensive management requires frequent monitoring of blood glucose levels, particularly in people on insulin.

00120

With greater insulin deficiency, there is more glycemic variability and risk for hypoglycemia, a very important concept, more variability with less insulin, this is for both type 1 and type 2 diabetes.
And there is an entire debate right now about glycemic variability, but the research does support that it appears to fuel vascular complications by increasing oxidative stress, and you will hear more about this in the next presentation by Dr. Kowalski.
So glycemic control is critical for Medicare patients. Tight glycemic control is standard for all patients with diabetes, including the elderly. The ADA, as you've heard, recommends an A1c of less than seven percent for all patients, but you have to read the fine print. The ADA standard of care, as I look at it, is talking about the populations of patients. For individual patients, if you read what the standard says, as close to normal as possible as long as it is safe, and of course the main inhibiting factor here is hypoglycemia. So I want to make sure that the ADA is not misquoted. Yes, for the population the current standard is less than seven, but

00121

that's for a population.
The American Association of Clinical Endocrinologists actually recommends a lower target of 6.5 percent or less for the population. And then the American Geriatrics Society Panel for Improving Care for Elders with Diabetes, they recommend an A1c of less than seven percent for

patients with good functional status, and less than eight percent for frail older adults and high risk patients. These are the current recommendations.
Research shows that better control measured by a lower A1c in the elderly prevents progression of retinopathy; results in better cognitive function, we haven't talked much about that this morning; prevents prolonged hospitalization with exacerbated congestive heart failure, this is actually a research interest of mine; increases survival for those on dialysis, you'll see more about that in a moment; decreases post-operative morbidity. However, tighter control must be balanced, and that's the key word, balanced with increased risk of hypoglycemia, particularly in the elderly, as we think about the elderly patient on insulin, the elderly patient

00122

with type 1 diabetes.
Let me give you an example. This is a Medicare-aged type 1 patient. This was my very first patient when I arrived from St. Louis to Seattle in the summer of 1990. She's now 78 years old. She was diagnosed with her diabetes in 1956 and I saw her in July of 1990 after an episode of severe hypoglycemia which was associated with a cardiac arrest. At that time she was on one injection of insulin a day, she was not doing any glucose testing as her insurance at the time would not provide her with the strips. Since then she's had bypass surgery, she's had a thyroidectomy for thyroid cancer, she's had bone fracture, she's had treatment for peripheral retinopathy, and she's had cataract removal. However, she is active, she walks her dog daily, she's on multiple injections of glargine/lispro, she lives alone, and she has not had any further severe hypoglycemia since receiving the multiple injections of glargine and lispro, but I think the other issues is she's checking her glucose five to six times per day, which means every six months I have to fill out the Medicare paper work saying why she needs to do this, and I'm happy to do that.

00123

This is type 1 care in another Medicare population group, a kidney transplant patient, this is another patient I follow. He's 36 years old, type 1 diabetes, had a kidney transplant. He has a peripheral retinopathy, he's already had a lower extremity amputation, he's already had a mild myocardial infarction, and he's 36 years old, and yes, he has gastroparesis. He's tested four to six times per day. His major problem has been in the past hypoglycemia awareness, so his goal as

far as glucose levels are concerned, is to avoid severe hypoglycemia.
We downloaded this for everybody, and this is what he looked like. And for this fellow to be successful, even when the average is, he has tremendous glycemic variability but he is able to avoid hypoglycemia with his gastroparesis because he is now intentionally keeping his blood sugars as high as he can.
So let's think about this for a moment.
People with diabetes make up a significant portion of those with end stage renal disease. In fact, the incidence report of end stage renal disease by primary diagnosis, for all the diabetes, it's over 200,000 cases, 10 percent are type 1 patients with

00124

a median age of 47 years, 90 percent are type 2 patients with a median age of 65 years, and almost a quarter die in their first year. Sobering statistics, and yet, 44.5 percent of all end stage renal disease in the United States is from diabetic nephropathy.
When you look at, these are incident counts and adjusted rates by primary diagnosis, what's fascinating is going all the way back to 1980 when you see the different etiologies of end stage renal disease, there aren't a lot of differences back in 1980. But as one goes through the years and the decades, one can see that the slope of the curve and the number of these diagnoses continue to increase. Diabetes is far outleading the pack and that's why it is such a huge public health problem today.
Now what studies in end stage renal disease patients illustrate the importance of glucose control? Most of the data when one goes looking at diabetic kidney disease and glucose control is dealing with the (inaudible) stage, not people with advanced nephropathy or in end stage renal disease.
This is a recent study that was just

00125

published this summer in Diabetes Care. 114 end stage renal disease patients, most of them with type 2 diabetes. Their mean age was 60 years, duration of diabetes 45 months. And the groups were divided into good A1c, which they said was less than 6.5 percent, fair was between 6.5 and eight, and poor control, which is an A1c above eight. The clinical characteristics of the three groups were identical except for the A1c. Now what one sees is that those people with the highest A1c, above eight percent, have the worst survival rates, survival curve. The lower A1c groups had better survival curves over the course

of almost 90 months. So the conclusion was that in diabetic chronic kidney disease patients on regular hemodialysis, poor glycemic control is an independent predictor of prognosis. This was not an intention to treat analysis, but it was still, I think, an important observational study. What about the potential of continuous glucose monitoring? I recently, if one goes on line and looks at all the different sites, this is what the patients are talking about. Let's think about this for a moment. Let's go back to our patient that I

00126

showed you who was trying to avoid severe hypoglycemia because of his hypoglycemia, he had a transplant, he had gastroparesis. This was him two years ago. The same patient at the time had an A1c of 6.4, he was having repeated severe hypoglycemia, and CGMS, retrospective CGMS was performed on this patient on a morning that he awoke with an extremely high blood glucose. So he gave himself insulin at six in the morning and he saw that by eight o'clock his glucose was 125, so he thought it was safe to drive to work. Well, was he? Take a look. Here he is at 8:15, his glucose level was 125. At 8:20 he goes west on Interstate 90 to Seattle, and here he is. Right here when he gets to Mercer Island, he's down in the 40s. Do you know how many people take that route to Mercer Island? I hope you didn't this day, because you're driving next to somebody with a glucose level in the 40s, and he had no idea. He had no idea after he checked his glucose level here that his glycemic slope was coming down about as fast as you can see physiologically, and he had no idea that he was driving on the Interstate west towards Seattle, and his glucose level was

00127

actually down here. He just didn't know. So glucose trends lead to better diabetes management decisions, and this is what we are learning now with the introduction of CGM. With severe insulin deficiency, one needs more, not less data, to understand the concept of glycemic trending. Finger stick testing provides a point-in-time data while continuous monitoring supplies directional and trend information on blood glucose levels. Knowing whether the glucose is trending up or down gives meaning to the numbers. Looking at cross-section periods of time, this sort of makes sense. If one is about to sit down and eat and the glucose level is 120, you're going to do something different with the insulin if you're going down quickly compared to

going up quickly. And doing four tests a day, the formula at that time, we just don't know that information. So we get more informed and effective treatment decisions.
CGM holds promise in improving glycemic control, and there have been several studies published. The first one was presented last year at the ADA from Medtronic. The Medtronic Guardian RT showed a statistically significant drop in A1c

00128

compared to the control group, significant drops in times below 70 and above 190, and significant drops in the number and time spent hypoglycemic.
Another study published earlier this year from DexCom showed that subjects blinded, which was a control group, and unblinded, which was a display group, to continuous glucose monitoring, as far as hypoglycemia was concerned, as assessed by two different thresholds -- I can see my time is blinking, so I will go quickly here, you can see that when patients are knowing their glucose levels, they have less time spent in the high range and more time spent in the target range.
This is a Medicare patient of mine who is in a study with Medtronic MiniMed called the Star 1 study. He's a 72-year-old man. This is what he looked like on his first week on the continuous glucose sensors, not very good, his A1c was in the high sevens. This was him a couple of weeks later, knowing an event and acting on it as it is happening.
So we need more research, we need studies, because studies today have not included significant numbers of Medicare patients and

00129

additional research is needed to determine the value of CGM to Medicare patients to reduce A1c, the ability to decrease hypoglycemia and related adverse events, ER visits, falls, better wound healing, cognitive function, quality of life, there are many more.
So, a sensor-augmented pump at least in my opinion is the next logical step. CGM could be combined with existing pump technology to provide a platform for an external artificial pancreas, that's what we are looking for. And given the increased life expectancy for both the general population and those with type 1 diabetes, Medicare recipients should have access to these newer technologies as we prove the effectiveness from clinical trials.
Now, there are three major barriers.
First, the access to improved tools to reach glycemic targets, we've heard about these tools,

we don't all have access to these. We need access to providers and health care teams knowledgeable enough as to the special needs of both type 1 diabetes and the elderly.
What's really key here is the medical students. Our medical students in Seattle get one

00130

afternoon on diabetes as medical students. There is no way we can treat a complicated disease such as type 1 diabetes, or for that matter even type 2 diabetes, if the training isn't provided.
And finally, we don't have good systems. This was mentioned earlier today. We actually showed a study at a recent meeting, this was a type 2 study, a randomized controlled trial, where one year into the trial, we could reduce A1c by 1.1 percent when the participant was downloading their meter into the software on line, and having physical interaction with the nurse in our clinic. Those types of systems don't exist with the way we take care of patients today.
So our conclusion is, metabolic control matters. Mother Nature keeps score. All patients with diabetes benefit from improved glycemic control, it reduces long-term complications from hyperglycemia. It limits short-term risks from hypoglycemia. CGM shows particular promise for certain groups of Medicare patients who are particularly challenging to manage, type 1 over 65 and ESRD patients who are so tough because so many of them have vascular diseases. CGM offers additional data, including trend data, which can

00131

help reduce hypoglycemia while helping to avoid hypoglycemia. We need additional studies, especially for this population. Thank you all very much for your time.
DR. GARBER: Thank you. Our next speaker will be Aaron Kowalski.
DR. KOWALSKI: My name is Aaron Kowalski, and I will be presenting on behalf of the Juvenile Diabetes Research Foundation today.
I have no conflicts other than, like Irl, I do have diabetes as does my brother, and I'll start right off.
The Juvenile Diabetes Research Foundation has a mission to cure diabetes and its complications. We are the leading charitable organization funding type 1 diabetes research and this year it will be at least $140 million, looking at both diabetic complications and biological indications. It was founded by and is largely run by people who have a direct connection to type 1 diabetes.
I want to take a step back from some of

the, we did hear of the specific studies, and just get to sort of the heart of the issue from our perspective at the JDRF. The bottom line is,

00132

people with diabetes now are struggling to maintain glycemic control, and the leading organizations stress, the ADA, AACE, American Geriatrics Society, that glycemic control is critical, and I will probably take issue with some of the points that people made with the DCC trial. With all due respect to Dr. Koller, I think the bottom line from my perspective, and I run the JDRF strategic research project, but I also ran the JDRF study section on diabetic complications, is that the closer one person gets with either type of diabetes to a non-diabetic level of glycemic control, the risk of diabetic complications becomes closer and nearer that that similar person would have diabetes.
And as Dr. Hirsch pointed out, I think we also have to note that these levels of A1c's that we're shooting for as our targets are actually hyperglycemic. A person with an A1c, and I'm speaking to the panel here, who has an A1c of seven is actually walking around with a mean blood glucose of probably 20, which gets to the level of you on the panel who don't have diabetes.
When we get to some of the issues of why aren't we seeing dramatic decreases in

00133

diabetic complications when we're decreasing from eight to 7.5, these people are still severely hyperglycemic.
Here's another interesting point. I was recently at the DMICC meeting at NIH. CMS was present, FDA, many of the institutes at the NIH. As Dr. Hirsch pointed out, it's a bit depressing that even many years after the DCCT, we are not improving the Hemoglobin A1c scores for all patients with diabetes across the United States. And a number of people presented at this meeting, CDC did, Kaiser did, the Veterans Administration did. A1c levels have plateaued over the last 20 years and most people are not hitting target levels. So if we're setting the A1c target level at seven, which again, I won't say is hyperglycemic, the majority of people in the United States aren't there, in fact the average is in the eights, so there is still plenty of room for improvement.
Again, we can debate the UKPDS and the DCCT, but the keystone message as we look at this data is the closer you are to a non-diabetes level of glycemic control, you are at significantly reduced risk of developing diabetic complications.

00134

So we need to get lower. And when we talk about people who are older and can you realize a benefit of improving your glycemic control in a short amount of time, the answer is yes, that improved glycemic control can be seen in reductions of complications fairly quickly.
We spend a lot of research funding into the diabetic complications. What is important to realize here when we think about distinguishing type 1 and type 2 diabetes, the bottom line is, the molecular pathways that are stimulated in diabetes are stimulated by hypoglycemia, and they're very similar or identical in type 1 or type 2. And there are three main pathways, and these stimulate the majority of microvascular complications and actually probably do stimulate the macrovascular complications of diabetes at a longer time frame.
So why aren't we getting to better target glycemic control levels? One, obviously for people with type 1, but also for people with type 2 diabetes, is hypoglycemia, it's a counter-balance. There is much literature here about the nature of the obstacle of hypoglycemia in achieving target glycemic control levels, it's a

00135

significant source of morbidity in adults who have diabetes at all. Dr. Hirsch referred to somebody driving a car with a blood sugar of 40, that's obviously very risky. However, elderly people are at an increased risk of hypoglycemic events, and unfortunately elderly people have a reduced awareness of hypoglycemia, so that can be a further counter-balance and further obstacle to getting to your glycemic target because they don't sense their blood sugar dropping.
We also think of glycemic variability, because one thing that people were doing who were trying to avoid hypoglycemia or trying to get as close to target as close as possible, and Dr. Bode showed that both people with type 1 and with type 2 experience tremendous variability in their day-to-day lives, and these were people who were monitoring their blood sugar quite intensively, up to nine times a day.
So it's impressive that when we think about a single point measurement and where we need to go, and all of us argue that we need to go to a target as well, even with very intensive management, it is very difficult to get at the target levels of glycemic level, and people with

00136

type 1 and type 2 are spending a lot of time on

the target. Intensive management probably reduces the risk of developing diabetic complications both through reducing mean blood glucose levels, but also probably through reducing the swings in blood glucose.
And Dr. Hirsch and Michael Brownlee wrote a review about this, and some interesting data has come out recently that shows older people with type 2 diabetes who have elevated A1c's, but when they compare people with significant variability to those with less variability, those with more variability stimulate those diabetic complication pathways that lead to the oxidative stress that we believe causes diabetic complications.
This is a reiteration of a lot of what Dr. Hirsch pointed out, but again, I think we really have to be careful when we're interpreting this data, that you look at the A1c level and you look also and compare it to a person without diabetes, it's clear that, the literature is overwhelming that lower A1c leads to less microvascular complications, amputations, strokes, and fewer heart attacks. And these benefits are

00137

seen, again, reiterating what Dr. Hirsch said, in all people with diabetes, including the elderly.
And we reference some papers here, and this was the same graph that you saw Dr. Hirsch present.
It has been pointed out, the literature is sparse in people who are over 65, and I won't argue that we need more studies, but I think it's very suggestive. This is in renal disease, increased survival, and again, it's a base, but what's significant for somebody with diabetes is how much can we push? I won't argue with anybody who, you know, with this increased survival, it is significant for any one single person who lives longer on dialysis.
Post-operative morbidity, we've been talking a lot today about the traditional macrovascular complications of diabetes. There are also, hypoglycemia is very important here in the operating situation, coming out of an operation, and we know that hypoglycemia affects macrophagic function, for example, preventing infective complications, and glycemic control levels lead to better post-operative morbidity.
Dr. Hirsch pointed out this study in people with congestive heart failure, again, a

00138

retrospective study, but again, shows that people who are under better glycemic control do better in this situation.
One of the things that I often heard

while working in the area of diabetic complications was, well, you don't see a regression in diabetic complications with tight glycemic control. Now here is a reduction in progression, but again, tight glycemic control right now, we're talking about A1c around seven, we're seeing some studies now shooting for lower than six, because truly the normal range is topping out at six.
Here is a study that looked at people without, not on insulin, but older, and looking at their glycemic control. And it showed you could slow the rate of the progression of diabetic retinopathy through this tighter control, control of diabetes mellitus being the most important factor associated with the progression.
Cognitive functions, when we think about the utilization of newer technologies in people who are older with diabetes, well, cognitive function is obviously important. There is interesting literature suggesting that good

00139

glycemic control improves cognitive function in these people. We often at the JDRF, when we think of our younger patients with type 1 diabetes, we think of the cognitive function associated with hypoglycemia, but there is probably damage done with hyperglycemia in the brain as well.
So I will argue that we need to step beyond single point measurements to more intensive management with continuous sensors. The bottom line is, to get better glycemic control and to get to near normal glycemic control levels, you can't do it with just finger sticks alone. I was there for urine testing and then the advent of blood glucose testing. We need more and more testing to get to target levels and now we need to take it to the next level, which is continuous sensing.
The preliminary data is very, very suggestive, it's not there yet for the Medicare population, but we at the JDRF are looking at one-week sensor studies. Dr. Hirsch referred to some of the preliminary data that we've seen, talked about the benefits of seeing trends, if you're going up or down is much more important than just seeing a single point measurement. I can give you the example of my brother, who pulled

00140

off on the side of the highway after just, as Dr. Hirsch pointed out, testing and getting into a car with normal reading, and then it was dropping rapidly and he didn't know it.
Ultimately we need to close the loop to get the really normal blood sugar levels. I think the first step will be continuous monitoring, but

we need to bring these technologies to all people with diabetes, young and old, and we need to do more research. What we are looking for from this panel and others is feedback on what are the important outcome measures and how do we fund the best studies to demonstrate these types of outcomes. We are looking to fund studies in older people, randomized studies, looking at not only A1c and hypoglycemia, but looking at other important aspects, and looking at the economic impact of that. We know that diabetes is a major economic drain on CMS. And those are my presentations, thank you.
DR. GARBER: Thank you. We will now turn to the scheduled public presenters, and first up is Kevin Peterson. For this segment, each presenter has exactly six minutes to speak. Is Dr. Peterson here? And if Dr. Walter will be

00141
prepared by sitting in the next speaker chair, please.
DR. PETERSON: I would like to thank the committee on behalf of the American Academy of Family Physicians for the opportunity to talk. I have no conflicts of interest related to self-monitored glucose testing. I don't have any slides so you can turn that off. Understanding that I have six minutes, I'm not going to distract you with some slides, actually.
I represent over 97,000 physicians providing most of the care to most of the people with diabetes in this country. I don't mind telling you that family care physicians provide more outpatient visits for people with diabetes than all of the other specialties in the country combined. So the primary care physicians are really the ones in the trenches and they provide first contact to people that have any illness that walks in the door. Diabetes is a temporal kind of disease in this country, it's the seventh most common disease that walks in the door, but to put it in perspective, it only makes up about four percent of what we see. For better or worse, I wish we could see these patients longer, but for

00142
better or worse, the average visit is about 12 minutes of face-to-face time.
Now because of time constraints, I don't have slides, I want to just talk you through this. The evidence has been summarized so I'm going to speak to you as a generalist. I'm going to try to use some broad and some common terms, and give you the perspective in this country, from the trenches of a generalist.
First I would like to, on behalf of the

Academy, I would like to applaud the evidence-based medicine analysis given by Dr. (Inaudible) from Tufts. I think the Academy has gone on record as fully supporting an evidence-based approach and seeing that as really the best way to prevent harm to patients by avoiding some of the natural and inherent bias associated with expert opinion.
Three are 30 questions that we are asked to address and rather than taking 10 seconds for each one, I'm going to just kind of touch on some of the major points. First of all, kind of the major issue, what are the clinical outcomes associated with glucose monitoring? Well, in the trenches and in real life I would say most common,

00143

that depends. Self-monitored glucose testing in itself doesn't change blood glucose at all, it doesn't change A1c at all. Medication, lifestyle, weight loss, those lower blood sugar. Glucose monitoring is a tool, it's not a treatment. And I guess if I was going to use a simplistic analysis, I'd say if you had bad carpentry, you really can't blame the tools.
There are a lot of reasons that A1c's aren't what they should be. There are a lot of things that go into an A1c such as pancreatic function and resistance, and how about access to medications. The effect of A1c, if I can check my blood sugar but can't afford the medication, my A1c won't change. So to me, I think we need to change the paradigm a little bit and say that blood glucose, testing levels of blood glucose will help promote more appropriate therapy, it helps promote the correct choice of therapy, and it helps avoid hypoglycemia and contributes to patient safety.
Well, what do I mean by that? Well, without glucose management, therapy can't really be satisfactorily targeted. Do all people need to self-monitor? Well, I suppose if you've got

00144

well-controlled blood glucose, you're on metformin, maybe you don't have to check very much, but that's a really small percentage, so in order to really target the medications that are appropriate, you do need to self-monitor blood glucose.
Should targets be individual? Well, of course they should. Targets need to be individualized according to comorbidities and whether a person is vulnerable. A hypoglycemic event in a ten-year-old child is very different than a hypoglycemic event in an 80-year-old woman living alone. Should we target a life expectancy?

Does it have an infection point then? I think so, but I don't think that anybody knows. There's like strong opinions on both sides of that issue. Lower targets? With lower targets there is certainly a higher risk for hypoglycemia, and people with higher A1c's may rarely need monitoring, but again, we might want to prevent having high A1c's. So as targets decrease, just as, in order to provide better safety issues, we need to continue to monitor blood glucose. You know, I'm not sure of how many of you have sat in front of somebody and talked to

00145

them and had them describe a hypoglycemic event while driving, but you will sit there glued to your chair, and the only defense against hypoglycemia that I can see is self-monitored blood glucose.
So, I've got what, two minutes? What's the optimal therapy? Well, we can get into a whole lot of detail, they want these, and are these associated outcomes, and yes, I suppose they are tentatively tied to cardiovascular, or to mortality, and they seem to be unequivocally tied to morbidity. And it's, I think that the ACCORD study will give us a much better answer, but you know, if you use kind of, again, a kind of common sense perspective, if it takes eight to 15 years for complications to develop, then when a person is 65 years or older when they are diagnosed, they may have already had the disease for five or ten years, and again, it's highly likely that they will be at risk for developing some of the complications or the morbidities of diabetes.
DR. GARBER: Dr. Peterson, your time is up.
DR. PETERSON: Can I sum up? Can I just say, is it important for people over 65,

00146

absolutely, it's absolutely important for the appropriate medication. It's absolutely important for, depending on what a person's current A1c is, it depends on what a target A1c will be. There may be subgroups that it's not necessary, pretty small subgroups. Blood glucose monitoring provides for better education, better safety, provides for better lifestyle modifications, more appropriate therapy, and if those elements are compromised and that will lead to higher A1cs. You know, in a situation where Medicare is now reimbursing primary care physicians based on the percentage of patients with a lower A1c, it really seems, it seems antithetical to now say well, maybe a higher A1c doesn't make a difference, so we won't provide the tools to help us get those

numbers down.
DR. GARBER: Thank you. Next,
Dr. Wolpert.
DR. WOLPERT: I'm going to be focusing
on a quite a bit narrower perspective with the
risks of hypoglycemia in the Medicare population
with type 1 diabetes. First, some disclaimers. I
am on the advisory board for Abbott Diabetes Care
and Lifescan, and I've also received grant support

00147
from Medtronic for studies related to CGM.
To give you some background, I'm based
at the Joslin Diabetes Center in Boston. Our
clinic population includes 592 patients with type
1 diabetes who are covered by Medicare, so we do
have considerable experience with some of the
clinical issues that these patients grapple with.
And the issue that I'm going to raise here, that
even though these patients generally aren't on the
radar screen in terms of most Medicare coverage
decisions, they have specific needs that need to
be addressed and managed in your decisions.
In the course of my clinical
activities, I have been involved in a trial
involving CGM, so I have an appreciation of some
of the clinical utility that one can get from this
technology. To give you some background on some
of the specific challenges one faces with type 1
diabetes patients who are elderly, one of the main
issues that these people grapple with and
particularly as they get older is, more
significant than others, is hypoglycemia, which
obviously in this population, you have a lot of
significant other burdens.
And what's clear from some studies is

00148
that a lot of other related issues involving these
elderly patients are affected by this. For
example, there is a study that shows for patients
who are elderly and develop severe hypoglycemia
are three times as likely to end up having to go
to an ER or to get EMT attention because they
don't have family members who can assist them as
readily.
There is also a lot of data in
relationship to hypoglycemia and elderly patients
and how this impacts on accidents and falls. As
you know, this is one of the main expenditures for
the Medicare population. As you know, Medicare
spends anywhere from $17,000 to $18,000 for each
hip fracture. And a study from our registry also
indicates that in individuals who have insulin-
treated diabetes, they are twice as likely to end
up with a fracture as similar patients who don't
have diabetes. Added to that is the fact that

people with diabetes or related comorbidities often will not be as agile, will not be able to respond as readily to other risk factors. So the picture I'm trying to present to you is that this is a major issue in the Medicare population. What we know from clinical practice, I

00149

can tell you that these patients are among the most brittle people with type 1 diabetes that one encounters. Many of them receive insulin or other therapy, they may have high insulin antibody levels, and sometimes these insulin kinetics and clinically their diabetes is very difficult to manage. And CGM obviously offers a tool which will help us define what the glycemic protocols are, and it will help the patient actually act more effectively to keep their glucose in range. One of the main issues one runs into with the elderly population generally in hypoglycemia risk is the fact that it's been shown in plan studies that in nondiabetic elderly patients that when you lower the glucose level, there is actually an (inaudible) tremulousness, sweats, et cetera, but what they found in these studies in nondiabetics who are elderly, they only started developing symptoms when they were 55. (Inaudible) what's thought to happen is that people who have a hypoglycemic episode, they will then have attenuation of their symptoms; because they have an attenuation of symptoms, they will likely have further hypoglycemic episodes, so you have a vicious cycle of how do you handle the

00150

hypoglycemia. The issue here is that because these people recognize the value of staying at a level that's much closer to the level (inaudible). So I think the issue here, as pointed out in some of the other speakers, is that the data that is accumulating certainly indicates that CGM shows promise in showing reductions in duration of hypoglycemia for patients in that range. I have seen only one study which actually addressed individuals who covered into the Medicare population group, but I think clearly based on this evidence, there is the need for research studies to address the issue for elderly patients with type 1 diabetes. My hope is that if the data does show a comparative benefit, that my patients will be able to get CGM, and I thank you for considering this issue. Those are my comments. Thank you very much.

DR. GARBER: Thank you very much.

Next, Dr. Richard Bergenstal.

DR. BERGENSTAL: Good morning, rapidly

approaching afternoon. It's a pleasure to have a chance to talk to you. I just want to put in context, our diabetes center is part of a

00151

multispecialty clinic with 300 primary care physicians, so we have a lot of experience working with primary care, and our center has done studies with Abbott, Lifescan, Roche, DexCom, and Medtronic, and so I'm heavily conflicted but not biased, the only bias being what's actually best for the patients we take care of with type 1 and type 2 diabetes.

We're convinced that the evolving models must include some sort of team care and that the patients with diabetes have to be educated and use, in this case the glucose monitoring data, or the data that we're getting is not terribly helpful. So one should look at that in some way to link the use of monitoring to actual education about the data and putting it in perspective. You have seen plenty of the data by this point in the morning.

Our center is one of the few that did both the DCCT and is now doing the ACCORD trial, and we would love the ACCORD trial to look like the DCCT in terms of separation that would move both curves down about two percent, and that's what our goal is in that study, and we're learning a lot. And we learned that there is hypoglycemia

00152

in Type 2 when you start to get to an A1c of six percent. If you want to have an A1c of eight percent, or 8.5, don't bother to monitor at all. If you want to get to an A1c near normal, glucose monitoring appears to be essential, as it was in the DCCT, that study was about monitoring and feedback and we believe that ACCORD will be similar, and we believe that was partly what did not happen in UKPDS enough, was the monitoring and the feedback, and aggressive adjustment of medications.

So the A1c, as our excellent presenters have said, the glucose control is much more than an A1c, and we await more definitive data, but are pretty convinced at this point that the red curve is much more detrimental than the green, even though the A1c may be similar. You will not know this without either frequent point monitoring or better yet, continuous glucose monitoring, and you have heard the references.

We're not doing a very good job, as we've heard to date, and some very recent data says maybe we're coming up to the 50-50 point, but that's just an A1c less than seven, as has been pointed out. I'm convinced that we need better

00153
systems and that's what most of our work today is focusing on, better systems of care from point of care to teams, to support for the primary care 12-minute visit. It has to, we have to have someone looking at the glucose monitoring data with the patients who are teaching them how to look at it.
So in type 1 diabetes and type 2 on insulin, there is no question that it's critical. You have heard over and over again of these studies summarizing the non-insulin users, a .4 percent reduction in A1c, a .4 reduction in A1c in two meta-analyses that included the same and slightly different studies again.
The Schwedes study I thought was very interesting and important, not so much for difference in nutrition, but difference in, the intensive group actually asked the patients to reflect on their glucose monitoring data. If every patient took a Sunday evening and looked at their number and did something about them for the next week, we would see I think dramatically different results.
Dr. Karter's nice data says if you actually follow some guidelines, you do better.

00154
And I'll just tell you briefly about a consensus conference we had, and this was an international one, and so we got 1,500 of them together, leading experts, and did the same thing we're doing today, and had some of the very same presenters. And we concluded that people should monitor with the current data we have available to us today, more if you're not at target and more if you're on insulin, less if you're on target and not on insulin. And our findings are available to the panel obviously to look at, the September of 2005 American Journal of Medicine it was published. So we think that all people, after we reviewed all the data, this international group, should monitor proportionately to your therapy and to the goals you're trying to achieve.
And Dr. Karter presented his own data better than I can summarize for him, so I'll just agree that with the current data we have available, as imperfect as it is, we have to make day-to-day clinical decisions, and we're convinced that glucose monitoring is part of it and convinced that knowing your data even more frequently with continuous monitoring will take us one step further.

00155
I'll spend just the remaining minute on

looking at an algorithm, not saying that a specific one may be better than another, but just saying it's all about moving, and moving means by nine months you should either be on insulin or less than seven, but you are only going to move if you have data to respond to. And people, I would agree, on diet therapy alone, maybe they don't need to monitor after six months, but if you look at the current ADA guidelines, there is no such patient. You are started on that form on the day you're diagnosed, so all patients should be doing some monitoring.

And the other thing I would just throw out to the panel is, there is probably more of a difference between type 1 and type 2 than what I believe is the middle ground, to say more type 2 is trying to get specific, you've had it for 10 or 15 years, and it acts a lot more like type 1 in terms of needing basal bolus, intensive insulin therapy, they don't have quite as much hypoglycemia. But when you're trying for an A1c of less than six or near normal, monitoring is critical, and we look forward to testing some of these concepts in the ACCORD trial to really

00156

verify that. Thank you.

DR. GARBER: Thank you. Dr. Clark.

DR. CLARK: I'm Dr. Nathaniel Clark, I'm the vice president for clinical affairs and new strategies for the American Diabetes Association. The American Diabetes Association would like to comment briefly on the three questions that are covered in the published questions for this committee meeting.

Question 1: What is the relationship between increased glycemic control and the reduction in microvascular or macrovascular complications? The two major studies which are generally used as evidence of this relationship are the DCCT and the UKPDS, as you've heard this morning. Both of these trials produced unequivocal evidence that there was improvement in glycemic control and resulted in statistically and clinically significant reduction in microvascular complications. Neither of these trials produced specific data regarding those over the age of 65. While the original data from the DCCT only suggested there was a relationship in regard to macrovascular disease, as was pointed out, the (inaudible) has now produced quite convincing

00157

evidence of this relationship. While there are no trial data of significance in those over 65 to document the relationship between improved glycemic control and a reduction in microvascular/

macrovascular complications, it is widely accepted by the diabetes community that such relationship exists regardless of age. Clearly, the duration of diabetes or hypoglycemia is a key determinant of the risk of complications and the patient's expected life expectancy is a key to determining the potential benefit of maximizing blood glucose control.

In setting specific goals for glycemic control as measured by A1c levels, the ADA suggests that the patient's A1c goals need to be individualized and a number of factors be considered, including the age of the patient, the clinical status of the patient, and the patient's history of hypoglycemia.

Question 2, what is the relationship between blood glucose testing known commonly as self-monitoring of blood glucose and the attainment of glycemic targets? SMBG is felt to be an important component of a treatment plan of patients with diabetes when properly performed.

00158

SMBG permits patients with diabetes to determine their blood glucose levels. Indications of frequency for monitoring will vary considerably depending on the clinical situation of each patient and the purpose for which SMBG is being used.

It has been suggested that SMBG could answer three potential questions: One, is my current treatment program working in regard to achieving a glycemic target? Two, what insulin dose should I take prior to a meal or snack? And three, if my blood glucose level is in the hypoglycemic range, then what action needs to be taken. In considering these three questions, it has been suggested there is a continuum in regard to who needs to test and how often they need to test.

At one end of the continuum in regard to who needs to test and how often, it would be the patient with type 2 diabetes whose treatment is diet and exercise alone. For these patients, Question 1 is the most significant question; by monitoring blood glucose level periodically the patient is able to tell whether their current treatment is working or not. If the only test

00159

that's utilized to determine if the patient is achieving glycemic targets is the use of the A1c with regularly scheduled visits, there is the potential that getting the person to target will take an excessive period of time and all the potential risks of poorly controlled glucose levels will persist too long.

Next on the continuum would be a patient with type 2 diabetes on insulin alone. In this group, again, Question 1 is predominant, although if a patient is on an oral medication with a tendency towards hypoglycemia, Question 3 would also be operative.
Next on the continuum would be a patient with type 2 diabetes on oral insulin, and once or twice daily insulin. Again, in this patient, Question 1 is predominant, although Question 3 becomes a more important reason to test.
Next on the continuum would be a patient with type 1 diabetes on fixed doses of insulin. In this patient, Questions 1 and 3 are predominant.
The last two groups on the continuum would be the patient with type 1 or type 2

00160

diabetes on a basal bolus insulin regimen. In these two final groups, while Questions 1 and 3 continue to be extremely important, Question 2, the use of blood glucose monitoring to determine a dosage also becomes extremely important. On a basal bolus insulin regimen, boluses are taken before each meal and snack, and are determined based on what is the blood glucose level at the time, as well as the amount of carbohydrates to be consumed, and any change anticipated in the physical activity level. Without blood glucose testing, which is generally performed at a minimum of four times per day, the basal bolus regimen cannot be successfully implemented.
In summary, the need for blood glucose testing and frequency should be based on the treatment modality employed in the blood glucose target. We have stated in our guidelines that the SMBG should be carried out three or more times daily for patients with multiple insulin injections, and for patients who do less frequent injections or oral agents, or medical nutrition therapy alone, SMBG is useful in achieving glycemic goals.
The question posed to the meeting

00161

involving the evidence base for the value of blood glucose testing in and of itself in either effective glycemic control or complication risk, we are not aware of any definitive data to answer these questions. SMBG testing was a central component of both the DCCT and the UKPDS trials. Both of these trials had positive results. It is assumed that in the absence of blood glucose testing and glycemic control, the positive results obtained could not have been obtained, or would

have been obtained with significantly higher rates of hypoglycemia. Thank you very much.
DR. GARBER: Thank you. Next will be Dr. Richard Hellman.
DR. HELLMAN: It is a pleasure to be here and to follow such excellent speakers. On behalf of the American Association of Clinical Endocrinologists, as clinical endocrinologists and our millions of patients that we see in consultation, my biases are probably on the basis of those patients. I have done research for Medtronic, Adventist, Pfizer, and I'm on the advisory board of Abbott.
I think there is little question that glycemic control is established as absolutely

00162

essential, and I wanted to point your attention to a work we did in 1997 in diabetes care where we did a 14-year cohort study showing that patients with an A1c median of 7.3 for the 14 years had improved outcomes when measured by death rates and kidney failure rates. The important subset, however, was that this data was also noted in a cohort of patients over 60 years of age at the start of the 14-year study. There is no question that glycemic thresholds are not really relevant, the closer to normal you can get, the better off you are to be clinically safe and the data from the UKPDS shows that.
Probably not well-known is when we did the cardiovascular subset of the mortality settings, the cardiac mortality was strikingly different than our type 2 patients, and in contrast to our other overall studies, we looked at this 14-year study to show significant differences. As it was for the patients over 60 years of age, the cardiac mortality differences were apparent very, very early. This was actually underreporting, because since it was derived from actual mortality data from CDC, we probably underreported it.

00163

There is no question that probably the most important issue is probably the safety issue, and it is the safety issue that I would like to confine some of my comments to. There is little question that, you cannot really ask someone to get very close to a normal range without some sort of a safety net, without something to suggest where they are, and all the major studies have tried to do this for safety and ethical reasons, which of course was considered in our study, which uses four times daily.
JCAHO considers insulin one of the high alert medications, because insulin causes an

enormous amount of morbidity due to hypoglycemia, and from recent studies in the European literature, we know that the most frequent cause of hypoglycemia in the elderly was in oral hypoglycemic agents, and it is for that reason that our AACE guidelines state that blood glucose levels should be obtained before insulin is given, because that will bolster your therapy if you have an unexpected result.
There is another reason why our guidelines say that the SMBG frequency should be individualized for the needs of the patient. For

00164

instance, if the patient is 75 years of age, is on intensive insulin therapy, which is sometimes required because the doses may be quite low, they should get four tests daily at a minimum, and it is a minimum. And it is very important to go back to the earlier statement, which is that oral medication, drug interactions, or the underlying comorbidity of the patient may greatly influence what their relative risk is for hypoglycemia.
In general, the more rapid we have feedback, the safer this is for people, and certainly I think it is a safety issue, but it is also a public health issue. Do you want an elderly patient on an oral agent to be driving a car while hypoglycemic? I think it offers enormous promise and I think that although the story is not settled on it, it is very clearly something that is of potential great benefit because it may have both quality and safety, and the limitation would be what we know yet and what we will soon learn.
There are two caveats I have. The first is that if you perform glucose monitoring and you don't link the result with a process that improves the care, you have done very little. And

00165

that probably is where Medicare itself is having problems, because what we're seeing is what the state of quality of care is in many parts of America, and it is substandard, and that is troubling because it should not deter us from what the main focus is. A standard of care should be to demonstrate how it is to be used, whether it be the patient or others, they have to have a plan. Not only do they have to have a plan, it needs to make sense. It is not enough for a busy practitioner to slap a sliding scale insulin regimen, see where you register on this chart, and say you're done. If it's a bad plan, it means that mistakes will occur regularly as a consequence of it.
I think there is no question that

glucose monitoring is an essential component, it is not an option, and it is both a safety issue and even a public health issue, and I think that without doing it, or withholding it from those who are too poor to pay for it by themselves, essentially and unwittingly results in discrimination against the poor. I think the interstitial use of sensor story has not yet unfolded and I think it may be remarkable, and we

00166

think it is reasonable that you have a coherent and logical plan for the use of these devices. I thank you very much.

DR. GARBER: Thank you. The next speaker will be Paula Yutzy.

MS. YUTZY: Good morning. I am a diabetes educator and I run the diabetes center here at Mercy Medical Center in Baltimore. I am also a consultant to (inaudible) and Abbott Diabetes Care.

Members of the committee, I thank you for the opportunity to testify before you. The focus of this committee is sizable, and is of personal interest and concern to me. I provide care to hundreds of Medicare beneficiaries each year here in Maryland. These are the only patients that I manage who can consistently afford to manage their diabetes by regular blood glucose monitoring. They're my Medicare patients.

In the mid 1990s I dedicated many hours to inform members of Congress, Speaker Newt Gingrich, President Clinton, of the need for Medicare to cover blood glucose monitoring for all people with diabetes. It's extremely discouraging that CMS has asked this committee to question the

00167

relevance of glucose control and its measurement in the management of all types of diabetes. I now fear, based on the questions CMS is asking us for, that CMS contemplates turning back the clock and taking blood glucose testing out of some, if not all, of my patients' hands.

As a person with type 2 diabetes and as a certified diabetes educator, and as someone who is not that far from joining the Medicare program, I applaud the committee's effort with respect to its charge to identify where the current data is deficient and where additional research is warranted. There is no question that we need more work to identify how best to control the raging diabetic epidemic. CMS can help. However, the overall tenor of the questions being explored today is troubling.

It is not difficult to infer that some of the questions published prior to today's

hearing that CMS has asked the committee to look at, much of which, this Medicare coverage is legally mandated, congressionally authorized. If this is the case and the committee were to consider recommending reductions to Medicare coverage for diabetes care, this would do a great

00168

disservice to the nearly seven million people with Medicare who have diabetes. And because Medicare is an important bellweather for the private sector coverage, any move to reduce coverage could have a chilling effect on people with diabetes with all insurance coverage in the nation's health care system.

Instead, I hope that the committee questions were asked to help determine how to optimize current coverage. The fact is diabetes is one of, if not the single most self-managed disease in existence. It will be troubling if the committee suggests that self-management through regular blood glucose monitoring and the use of A1c is somehow inappropriate for any of the Medicare population.

Let me give you an example. Everyone understands driving. In order to drive safely and avoid tickets, you have to be taught how to drive and you have to learn the rules of the road - diabetes education. You must have a speedometer - blood glucose monitoring. And you have to know how to use it. When you have diabetes, you no longer have cruise control, you need to look at the speedometer, look frequently to stay within

00169

the speed limit. As a person with type 2 diabetes, I frequently check before meals and again two hours after meals to see exactly what happens to my blood glucose as a result of the food that I ate, and with that information I can learn to make better choices.

Diabetes is a disease of choices, when to take medications, when to do exercise, how much exercise to do, when to eat, what to eat, how much to eat. By checking the blood glucose several times a day, I can make those choices that improve my blood glucose control and that prevent the complications for me in the future. But I'm a certified diabetes educator. I know these things. Patients who come to me have to learn them. Diabetes education and blood glucose monitoring are the most important tools in the management of diabetes. It is my hope and a strong recommendation that the committee will take this opportunity to examine the substantial impediments that exist related to patient utilization of diabetes self-management training,

medical nutrition therapy, better team and specialty care, and regular A1c testing. These tools, in addition to blood glucose monitoring,

00170

are what prevent Medicare beneficiaries from achieving the glycemic control that will block the progression to complications.

It's true that diabetes outcomes are not what they need to be. Our nation experiences far too many preventable and controllable diabetes complications like heart attacks, strokes, blindness, amputation, and kidney disease. These are complications that science has proven are related directly to poor glycemic control. If this committee puts forth any recommendation that restricts methods to control or manage the blood sugars of a person with diabetes, the incidence and prevalence of these disastrous outcomes will increase, the associated costs to the Medicare system will prove staggering, and far exceed the cost of preventing and controlling the complications.

In closing, I would like to remind members of this committee of the substantial medical opinions supporting the use of blood glucose monitoring as a necessary tool in the control of diabetes that you've heard today. More importantly, I want to remind the committee of the statutory requirements on Medicare Part B, to

00171

cover blood testing for Medicare enrollees with diabetes, without regard to whether the individual has type 1 or type 2 diabetes or to the individual's use of insulin. I strongly encourage this committee to review the steps Medicare programs should take to improve the outcomes of the millions of Medicare seniors with diabetes and pre-diabetes. Thank you very much for your time and consideration.

DR. GARBER: Thank you. Next, John Mastrotatoro.

DR. MASTROTATORO: Thank you, Alan. In the interest of time, I will introduce myself as John M. I'm a biomedical engineer by training with 17 years of experience in developing continuous glucose monitoring systems, and as an employee of Medtronic I do have a conflict of interest, since we currently have out for approval several continuous monitoring systems which I will be discussing. I'm also going to provide some clinical evidence which demonstrates the utility of continuous glucose monitoring systems in improving diabetes management by reducing A1c and also reducing hypoglycemia.

Shown here are three systems that have

00172

been developed. The first one on the left is called the CGMS system. This system was approved back in 1999, and it's a system that's used in an analogous fashion to a cardiac holter monitor in that while the patient wears it at home, they're blinded to the glucose information. After wearing it for a few days, they can return to the physician's office where continuous glucose sensor information can be downloaded, analyzed and reviewed with the patient.
In the middle we have the Guardian platform of products, and these systems provide real-time continuous glucose information to people with diabetes, and also have alerts to alert them if their blood sugars reach a threshold which they decide upon for both hyper and hypoglycemia.
Finally, on the right is our latest system. This is an integrated device where we have taken the continuous monitoring features of the Guardian platform and mated it with an external insulin pump.
Just to give you a brief overview of continuous glucose monitoring technologies, typically there's a sensor that's used that is inserted underneath the skin to make the

00173

continuous measure. It is connected to a device which operates the sensor and transmits the data to a receiving monitor which is then used to display the glucose information and again, it could also be applicable to alarms to alert the patient of high or low blood sugar events.
This slide illustrates the benefits that you can achieve with continuous glucose monitoring. On the left is shown intermittent finger sticks, and unfortunately those intermittent values, even if collected at four times per day, can miss some of the glycemic excursions that are present and are observed when you have a continuous sensor profile. With the retrospective CGMS product, a physician can look at a complete picture of the glycemic excursions over time and make an informed, better informed treatment decision about how to optimize the patient's diabetes management.
Adding the benefit of review of information, the Guardian platforms and other devices that give real-time glucose values, you can now have the device alert the patient to glucose levels that are deviating beyond their target range so that they can take immediate

00174

actions to correct those blood sugars, and

therefore reduce long-term hypoglycemia, and also minimize hypoglycemia. So by having the continuous information, you are able to both reduce HbA1c and at the same time minimize hypoglycemia.
Since sensors are measuring blood sugars typically in the interstitial fluid, one of the questions that often comes up is how do the interstitial glucose values compare to blood glucose, and typically and on average they are very similar. There can be slight time differences between the two environments, especially when blood sugars are changing rapidly. However, in general the accuracy between the two systems is pretty good and in fact, typical averages are between 15 and 20 percent errors, or lower. And if you look at reproducibility of two sensors run simultaneously, you can see that they pretty much mimic one another. I think the most important thing, once you get accuracies below 20 percent with these systems, it's not the point in time glucose values the systems provide, but rather the trend information that's very important, and that's the utility for having the

00175

real-time alerts for hypo and hyperglycemia.
Here are some of the studies that have been published which look at the ability of continuous glucose monitoring to reduce HbA1c. A lot of the studies were based upon the original CGM system. The one at the top, though, is a randomized control trial in people using the real-time Guardian platform and it demonstrated a reduction in HbA1c of 1.1 percent when using continuous glucose monitoring and there was a statistically significant reduction with continuous monitoring versus finger sticks alone.
Likewise for hypoglycemia, there have been many publications and in one that was, again, using the Guardian real-time system, we found a statistically significant reduction in the duration and magnitude of hypoglycemia when using real-time continuous monitoring versus finger sticks alone.
What I'm going to talk about now is some of the planned clinical trials and ongoing clinical trials which use the latest technology, which is the combined insulin pump and continuous glucose monitoring device. In an early feasibility study that was conducted in children

00176

with diabetes, even after one month's use, we already saw a tendency toward reduced HbA1c and reduced average blood sugar levels. This led to a progression of clinical trials and a roadmap that

we've laid out. The first study shown here, again a randomized control trial using a Guardian type platform without the combined pump system, and then all of these three STAR trials involved a sensor augmented pump. In the first trial, the STAR 1 trial, this is for all insulin pump patients who are randomized to either use the pump with finger stick monitoring or the sensor augmented pump. This study was recently completed and we're currently analyzing the data from this trial. The STAR 2 trial was an observational study to understand what it takes to help educate and get a patient up and running on the real-time paradigm system when they started with just using MDI and finger stick testing, what does it take to convert someone from that over to a pump and continuous monitoring. And this is leading up to our largest STAR 3 trial where we will be randomizing multiple

00177

daily injection patients using finger stick testing to either maintain that therapy or move to a sensor-augmented pump, and this trial is scheduled to start very shortly.

DR. GARBER: Thank you.

DR. MASTROTATORO: In summary, continuous glucose monitoring technology is evolving. The early results are promising. Our initial focus has been in type 1 diabetes patients but type 2 patients requiring MDI also seem likely to benefit, and significant research is ongoing to determine the full implications of this technology for patients with diabetes, including Medicare beneficiaries. Thank you.

DR. GARBER: Thank you. Next, Steve Edelman.

DR. EDELMAN: I would like to introduce myself and then talk about my conflicts. I'm a professor of medicine at the University of California San Diego, I work for the Veterans Healthcare System. I'm also a founder and director of a patient organization called Taking Control of Your Diabetes, and I've also lived with diabetes since 1970. I'm not an expert in everything, but I am qualified to talk about

00178

continue glucose monitoring and its current need. Most of my patients are type 1 or insulin requiring type 2 diabetics. I did come here on my own time, my flight was paid for by DexCom. I'm not doing any current studies but I have in the past with all three of the CGM companies, and I have no stock options or any kind of financial

interest in any of these companies.
Now the most important thing I can tell you today, and I'm going to start with my conclusions in case I run out of time, we know that a majority of people in this country are still having a hard time getting their A1c down. It's not anyone's fault, not any one person, but the system, it's a tough disease to treat. We know that reducing the A1c reduces complications, there's no question about that, so I won't waste any time on that.
The second thing is, as people get their A1c closer and closer to normal, or closer to the goals that every major organization supports, the incidence of hypoglycemia goes up, and not only do we die from hypoglycemia, unfortunately I have had several patients pass away, it's called the dead in bed syndrome, and if

00179

you talk to any diabetes specialist here, they will tell you their own sad stories of their patients. But it's a disability, and it's also fear of hypoglycemia among not only the patients but also in their families. So as we try to reduce these goals, hypoglycemia is going to be more common.
And the third big point is that unfortunately when you get type 1 diabetes, you still get older, and many type 1's are approaching Medicare age, and many type 2's require insulin. These are the groups that are primarily the best candidates for this technology. They're getting older. And although there are not a lot of studies in this age group, the disease doesn't change just because you go from 64 to 65, and I'm much closer to the Medicare age than I was at the time that I was diagnosed, and that's important. Don't turn your back on the technology now because the perfect studies have not been done, and that's one of my major points.
Now, why do we need CGM? I think you've heard from everyone here that blood glucose monitoring is fantastic, it's needed for almost all type 2's, for some type 1's for glycemic

00180

control without fluctuations, without hypoglycemia, fine. But for a certain subset of the population, CGM is vital. I mean, a patient wants to sit down to test his or her blood sugar before a meal, they need to figure out how much they're going to eat, how high their blood sugar is, how much they think they should exercise, concomitant illness, stress, but one thing we don't have is the trend blood sugar for that person. And as one speaker showed you in that

slide, a 125 may not mean things are just perfect, but this is knowledge that really has helped a tremendous amount of people, it's here now, and I think what I would like the committee to consider is what persons in the Medicare population would be the best candidates for this. It's obviously not for everybody.
Now what I would like to do is just show you two studies that represent conceptually what CGM can do. And while I'll show you the two studies from DexCom, the studies have been validated with the Navigator system. So, here is what the applicator looks like, the plastic shield comes off, the needle is inserted, goes down, and at that point the needle is inserted with a little

00181

sensor in the inside of the needle. Then the needle comes out, so the only thing left inside the body is a soft flexible wire, this stays on the skin and is about the size of a quarter. This is the size of the monitor, it looks like a pager. All the companies have their own, there are certain differences, but the concept is the same, you can see the blood sugar, over the last hour, you can look back over the last three hours, or when you wake up in the morning you can see the last nine hours and see what the heck happened overnight. You can put in your own high and low alarms, and that's a key, you can put it at any level you like. And that protects against hypoglycemia, even if you have a fear of overdosing, you're protected because you have that alarm.
Let me show you two studies, they're very impressive studies. This one was prospective and randomized, it was a short study, but it was a group of 91 patients, the control group was blinded to CGM, they relied only on SMBG, and they tested on average seven-and-a-half times a day. This group was allowed to see their CGM device, there wasn't any information, just showed their

00182

number and the slope of the line, and they were two-thirds type 1, one-third insulin-required type 2. And this was only a nine-day study. I want to point out that for the first three days, both groups were blinded, and the group that was unblinded right here only saw data for six days, and that's important when I show you the results of this study. These patients just were free-living patients doing their usual things.
So this was recently presented to the American Diabetes Association, it was the first randomized trial, and you can see that there was a 23 percent improvement in the blood sugar for the

240 to 400 grams, a 26 percent improvement in the 81 to 140 grams, and a 21 percent reduction in the hypoglycemic readings. Now remember --

DR. GARBER: Dr. Edelman, your time is up.

DR. EDELMAN: -- they were only on it for six days.

And the last study looks at the A1c reduction, and basically it is a study looking at patients with different A1c's that are put on continuous monitor, and there's another study repeated after the MiniMed study showing that the

00183

overall reduction for those patients of greater than a one percent drop in A1c, and a trend to reduce hypoglycemia during that period.

So in conclusion, I would just like the committee to really think about the fact that although the studies aren't perfect, they're not focusing on this population, it's technology that's needed right now for the Medicare population with type 1 and insulin-controlled type 2 diabetes. Thank you very much.

DR. GARBER: Thank you. Dr. Bruce Bode.

DR. BODE: Thank you. I appreciate the opportunity to be here. I am a consultant for Johnson & Johnson, who is paying my travel here. I represent our group, Atlanta Diabetes Associates, and we take care of about 12 to 15,000 patients with diabetes per year in the greater Atlanta area. And we do have a conflict of interest, we do work and have done clinical research for Abbott, BD, DexCom, Johnson & Johnson, Medtronic, Roche, and other companies also.

But what I'm going to really get into is we always look at our data, we always look at

00184

what our patients provide us, we look at it, and I want to talk about just glucose monitoring because that's what this conference is about. Obviously, it's very common that the more you monitor, the better you do. Patients and health care providers are able to make changes either in their behavior or medication management to try to normalize glucose.

Clearly glucose monitoring is a tool, and as we measure our performance and control our A1c's, earlier studies essentially appear to be very true to this, what's controversial is type 2 diabetics, especially not treated with insulin. We looked at that in our group and we went on the course of developing a non-linear mathematical model for A1c as a function of number of blood

glucose tests per day, and we looked at this model and looked at it specifically for people not on insulin, people on subcutaneous insulin only, as well as people on insulin pump. And these studies unfortunately were retrospective, the data was collected all from meter download data, so nothing made up. We looked at download data only. We also looked at A1c done on the date of download, so it's all

00185

based on data that's true that we have in our database. Our curve fitting was a weighted, non-linear, least squares method. The data was ranked by blood glucose and divided into quintiles. T-tests were performed on the first and second versus the fourth and fifth quintiles, and I'll go through that with you. First I will just show you the results. Just eyeballing it, obviously you can see in the insulin pump group which represents about 400 pumpers, you can see there are very few people who test less than once a day, but as you increase your testing, the A1c falls. The red is the mean and the yellow curves are standard error curves. After the insulin pumpers, we then looked at subcutaneous insulin, this encompasses both type 1 and type 2, and again, the same curve. You see you have more people down under one test a day, going up to four tests a day, you can see the reduction in A1c of less than seven, but again, you see the standard error curve. We then looked at people with diet control or oral agent control only. You can see you have a lot of people that are not testing, it goes to two tests a day and the frequency of

00186

testing falls off. This is a database of over 500 patients. And again, you can see what appears to be a significant decline in A1c over time. And so when you look at this, you can just look at the mean curves themselves for insulin pumps to subcutaneous insulin to no insulin at all. When we did our statistical analysis on this, we broke these into quintiles, we compared the two lower quintiles to the two upper quintiles. For insulin pumps, out of 417 patients, 6.4 tests versus 5.6 tests, the A1c difference was 7.7 to 6.8, highly significant. For subcutaneous insulin, it was .8 tests a day versus 3.8 tests a day, the significance there was 8.4 to 7.8 A1c drop, highly significant. And for no insulin it was .4 versus 1.9, and again, a significant drop in A1c from 7.5 to 6.7. And you can look at it in bar graph form too, seeing the same data.

Obviously, you can talk a lot about reasons for this. Clearly, if your glucose is high and you're taking insulin, you can take a corrective treatment. You can also do the same thing with behavior including exercise, you can also do it with your medications.

00187

Obviously, glucose monitoring, hypothesis two, may be an indicator more of compliance, and obviously some people will have low A1c's regardless of how much they monitor and whether they monitor or not because they're very insulin-sensitive or have endogenous insulin. What we have to really do is look at the non-insulin people, you've got to look at this lower quadrant that are running in the six range, and what's happening to these people, are they early in their course of their disease, have they had good ito cell function, have they controlled their weight loss, exercise or whatever. And there has been a study of glucose monitoring, we are very actively involved in studies with type 1 and type 2 in this subject, and there is no question, the more you monitor, the more you come to range. So if your A1c is six, you might raise it up to 6.3, 6.4, and if A1c is eight or nine, you might drop it a point or more.

There is a study that was done for type 2, average age 74 years old. They were on oral sulfonylureas, 55 percent were on metformin, the average A1c was 6.2 percent. They used CGMS

00188

retrospective 72 hours, repeated a month apart, and looked at the data. And you can see here, out of the 188 hours of CGMS monitoring of 25 patients, they had 103 episodes of significant hypoglycemia, defined as less than 50, and mild hypoglycemia is defined as 60 to 65. When you also look at the overall data, 96 percent of these patients had at least one episode of significant hypoglycemia defined as less than 50. So obviously, this is a major problem. People, even Medicare patients who are normal, you can't just take away --

DR. GARBER: Time.

DR. BODE: In summary, all treatment regimens show a significant association, it's not a cause, between high glucose monitoring and low A1c. We as practitioners, whether you're a practicing health care provider, whether an educator, an endocrinologist or a physician in general practice, obviously the more you test, it appears the better you do. It's a tool to use to get A1c's to normal. And I appreciate your time.

Thank you.
DR. GARBER: Thank you. That completes the scheduled presentations. I would like to just

00189
ask the committee, we currently have one speaker signed up as an open public speaker, which will be a four-minute presentation. Does anybody have an objection to doing that before lunch. I have to make sure the speaker is here. Cynthia Wright, are you in the room?
MS. WRIGHT: No, we can forgo that.
DR. GARBER: Okay. Is there anybody else who did not sign up who wishes to speak briefly? Okay. We will break for lunch, and we're going to start promptly at one, even if people aren't here.
(Luncheon recess.)
DR. GARBER: I think that we have a quorum here, and this is actually the committee deliberation segment of the meeting anyhow, so we're going to open panel deliberations. The first question is, does everybody have a set of the questions in front of them, in blue. If you have them in front of you, you might want to just remind yourselves about the questions and, first of all, I would like to ask if there are any general questions. This would be, if there were more speakers in the room, we could ask them questions now, but we should have

00190
opportunities throughout the afternoon, but then we will go through question by question and you may have specific inquiries to other speakers at that time. Mark, did you have a question or comment?
DR. FENDRICK: Are we open to deliberation?
DR. GARBER: Yes.
DR. FENDRICK: I would like to, if it's okay, ask our guest panelist experts a specific question I have. Thinking about this in the chain of logic, it appears that the A1c terminology could be considered a severity marker to the A1c in your diagnosis. For instance, this term control that was talked about in a variety of contexts, at least to me, is not what the A1c is, but how the A1c changes. And one of, if not two of the questions ask specifically about clinically meaningful health outcomes. And I'd like to ask the three experts to my right, or anyone else, what should we consider a clinically meaningful A1c reduction? And particularly, does an A1c dropping from 11 to nine, or nine to seven, or seven to five mean the same thing?
DR. MOLICH: I guess I can start a

00191
little bit with that. Certainly if you look at the curves and look at the reduction, you get much more reduction in risk way out at the far end at the highest levels, so you reduce risks for these complications from 11 to nine much more so than you do from nine to seven, and certainly much more so than from seven to five. So I think you get much more bang for your buck at the high end. But as was mentioned earlier, whether there is a breakpoint or not, I think is a matter of debate. Certainly the risk reductions that you get at substantially below eight, or below seven, it becomes relatively small, with increasing amounts of effort as well as increasing amounts of hypoglycemia.
DR. FENDRICK: So the first question was, the studies show that where A1c reductions actually occurred, tended to be very small in the randomized trials, and I'm just wondering when you see a statistically significant reduction of .5 percent, is that something to get excited about?
DR. HAYWARD: One of the difficulties when you look at an average in a clinical trial is that that is not the amount of benefit going from the mean of the control group to the mean of the

00192
intervention group. Because of that, because of the (inaudible) as the speakers suggested, because most of those very highly sloped things are the first part of a multi-step process when you find no disease to early disease, and the same relationship goes when going from no disease to moderate disease. Something that wasn't mentioned, when the person already has advanced disease, there is very little association, so once the person has severe disease like severe neuropathy or severe kidney disease, A1c is no longer a major progression indicator to end stage disease in most of these studies.
But the multiplicative aspect of it makes those even more dramatic, so what you can find is going from a mean of eight percent to seven percent looks important, and then when you actually look, almost all the events are occurring in the mean of eight percent, who have values up to nine. And often, if 75 to 85 percent of the events are occurring in the 15 percent with the worst control, you might be misunderstanding those studies completely by just looking at the average.
In addition, those people that start in those studies with values of 11 didn't get a .5 or

00193
a one percent reduction. Most often there is an

interaction between the two, so the people at 11 often came down to nine and got a lot of benefit, the person who started at eight might have gotten less of a reduction, so I think that you really can't say how important .5 is unless you know that individual overall risk, and whether going from a high level to a moderate level, it's a very complex function.

DR. GARBER: Alex?

DR. KRIST: I agree with what you're saying, but I want to add to Mark's question just to make it a little more concrete, because I think what he's telling me is he's looking at some of the RCTs on the self-monitoring glycemic controls with a reduction of .5 percent. And I agree with you that the benefits occur more likely in the extremes, but in those randomized control trials on the individual A1c's, you're going to have those extremes as well that are going to contribute to that average reduction of .5 percent, you'll have those people at 9 and 10 percent coming down to 7 percent.

But when I was looking at this, kind of taking that same logic that Mark was taking,

00194

what's the clinically significant reduction, if we just focus on that when looking at the evidence, and I look at something like a reduction of .9 percent, 7.9 with intervention was controlled to 7 in the intervention group. Are there examples, just looking at the VA CSDM where there was a two percent reduction in hemoglobin A1c, and then I don't remember what it was in the others, but are there studies that anyone here knows about? I can ask the presenters as well, if there's studies where there are improvements in clinical outcomes between an intensive and a control group, and there's a lower reduction on the order of .5 percent?

DR. HAYWARD: What we know from our RCT is that in ten years of follow-up in people with reasonable, not even high blood pressure control, there are no clinically meaningful benefits from going from eight percent to seven percent, including the DCCT. What people forget is that all the eyecare benefit with retinopathy occurred in the 30 percent of people with baseline retinopathy, there was no significant difference in the others.

So we're all going to come to the

00195

estimating, which is the other problem that you have. If somebody has early microvascular disease, they get much more benefit from tight control than someone who is 65 without it. So if

you have a 70-year-old with early microvascular disease, they're going to get substantial benefit or at least a chance of substantial benefit from tight control than somebody who is 70 who doesn't have early microvascular disease, who has almost no chance of getting benefit from microvascular. And I keep saying microvascular because I believe the macrovascular jury is out, and that could change a lot of things if a year or two from now the VA or ACCORD study suggest that there is a macrovascular association.

DR. GARBER: I have a question for Mark, or maybe for Rod or anybody else. In a post hoc analysis of the DCCT, I think it was by Davidson and Brownlee, they looked at subgroups of attained hemoglobin A1c, and in addition to non-linearity where the benefits occurred, as we've heard about, i.e., very much concentrated on people with high hemoglobin A1c's, there was another fact, which was that the lowest hemoglobin A1c group data seemed to reflect the highest

00196

incidence of hypoglycemic events, and that was skewed dramatically as you went up in the glycemic hemoglobin level. So not only does this reinforce the idea that most of the benefit is concentrated in the high hemoglobin A1c group, but the risk is much much smaller in that group from intensive therapy. The question I have is, have there been similar studies to UKPDS looking at what they looked at for the type 2 population? That wasn't meant to be a conversation stopper.

DR. MOLICH: I'm not exactly sure what your question is.

DR. GARBER: Well, this very clearly shows in the DCCT population that there was much greater benefit and lower risk if you treated a high hemoglobin A1c, and if you instituted intensive therapy. The question is, in UKPDS, are there studies showing the same phenomenon, that most of the benefit is concentrated at the higher levels?

DR. HAYWARD: The bottom line is true of almost all types of studies. The incidence of serious hypoglycemia was so that it didn't really have much power to talk about unusual hypoglycemia. If you're talking about symptoms,

00197

I'm not aware, but there really weren't many serious hypoglycemic events in the UKPDS, and so it was not the important outcome that it was in the DCCT.

DR. REIBER: And then in the UKPDS data, there is an analysis projecting out quality of life and it compared individuals with the tight

control to the comparison group, and there was only a very modest benefit in terms of improved quality of life.
DR. MOLICH: As long as we're going into this in more detail, UKPDS and others, that was a study where people were just diagnosed with diabetes and then followed over the course of time, and one of the things that came out of that study was that people needed more and more therapy over time in an effort to keep A1c levels as close to normal as they could be, and in fact A1c levels still went up despite add-on therapy.
And I think one of the things that hasn't been brought out in this conversation is that type 2 diabetes is a progressive disease, it gets worse over time, and I would expect this diabetes to get worse and worse and worse over time, it's variable from one person to another,

00198
but it does get worse. And so that ultimately, most, or many of these patients will end up on insulin who have type 2 diabetes, and there is no particular reason for that process to halt at the age of 65.
And in fact, those people, as they get older, more and more will need insulin, and in fact some of those patients start to act like type 1 patients as they get very minimal doses of insulin until they require basal bolus insulin just like a type 1 patient will after a long period of time. So we shouldn't think of this as a static picture but as a progressive picture, so you shouldn't just look at them as early patients, but think about these patients as they continue to progress over time.
DR. GARBER: Yes.
DR. PUKLIN: I would just like to ask Dr. Hayward, I wanted to ask you, perhaps I misunderstood you, when you were referring to the DCCT and the A1c level, did I --
DR. HAYWARD: I was referring to the UKPDS with the comments about the relative progression from baseline retinopathy.
DR. PUKLIN: So the comment was, I

00199
think, that patients who are younger who get effective metabolic management early on would do better and develop less changes than a 70-year-old diabetic who is recently diagnosed and put on tight metabolic management going forward; is that what I heard you say?
DR. HAYWARD: I think the comment, if somebody has early retinopathy, their chance of benefitting from tight control over short periods of time is much higher than if they start out with

no retinopathy, because you have these progression steps. Once you have moderate control, going from no retinopathy, to the laser therapy, if you have, unless you have poor blood pressure control, is a long process. And so you'd have to think the 70-year-old would get different if they had moderate proliferative retinopathy or severe background retinopathy, as compared with somebody with normal, that was the only point I was making.
DR. PUKLIN: But what do you do with a type 2 diabetic who is recently diagnosed at the age of 70 with moderate background retinopathy?
DR. HAYWARD: That person has a chance of getting benefit from tight control. If they have normalized at that point, their chance of

00200

getting benefit from tight control is almost zero.
DR. PUKLIN: If they have normalized, but that's an usual scenario at the age of 70. Aren't most people who are diagnosed with that disease at that age, don't they have frequently some sort of diabetic retinopathy?
DR. HAYWARD: No, most don't. But if you look at it cross-sectionally, most 70-year-olds who have had it for 15 years will, but the recently diagnosed, the vast majority would not.
DR. GARBER: Any other general questions before we proceed to the voting questions? All right. We can have discussion of each question one by one. Don, did you want to make a comment?
DR. RUCKER: Yeah, I had one question maybe for Dr. Lurvey, if he's here. You know, it looks to me like we have had a lot of discussion about what seems to be a fairly motivated group of human beings, someone who's getting frequent blood strip testing. But it looks like from those comments that there's also, Medicare is also paying for a lot of folks who are just, you know, where there is no real intent to do tight control, that the system's being game, what I got from the

00201

one presentation.
And I was just curious if that was in fact, if we're talking about two separate populations here, if there's a whole group of people who are getting frequent tests that aren't in fact, you know, getting any kind of management.
DR. LURVEY: The population that I described tend to be institutionalized people or people in home health, who are senior seniors, and having reviewed a large number of those charts for utilization problems, we would note that these individuals all have type 2, all are on what anybody in this room would call very, very sparing

therapy, with maybe one oral agent not at maximum dose. As an endocrinologist, I can assure you that there are five, six, seven agents available, but if they are on insulin, the majority of the insulin is at minimal dose, like split ten units of mixed insulin.
But the most important part is, it's written down there's a blood glucose but nothing is done about it. There's no documentation, the doctor is called, there's no change from month to month in the treatment. If it's 350, there is no examination of why that happened, or if it's 62,

00202

why it happened that way. And those particular types of individual circumstances have been denied, because the tests have not been used for any reason.
We acknowledge in our policies that a normal test gives information, important information when people want to know have they reached a certain level, and as was spoken earlier, for any indication like a change in recent hospitalization, a change in any situation, frequent testing above the limits that are normally done are always good.
DR. RUCKER: Even, there was a comment that $450 million, did that sort of fit into it?
DR. LURVEY: That wasn't -- someone else made that comment, I think in 2002. I said that the total cost for strips that we found through our medical records was just under a billion dollars for diabetic strips in the year 2003, and it's probably hit a billion by now.
DR. RUCKER: Do you have any sense of what percentage of that is spent on people who are managed in sort of like the way that you're describing?
DR. LURVEY: No. The only information

00203

we had was total expenditures and so there was no way we could look behind it, but thank you for asking.
DR. KOLLER: I can answer part of that question. CMS conducts surveys on its various populations. They do look at skilled nursing facilities, and they look at community dwellers who are 65 or older, and the disabled population which is 64 and under. And we don't have all of the information that you're asking for, but what we do know is that those people who are 65 and older are testing only, I would say about, there is a slide actually in Dr. Lurvey's materials, that about 40 percent of patients are testing, and the numbers are not particularly different by therapy. They're a little bit higher if you're on

insulin or insulin and an oral agent, but there are a substantial number of patients who simply aren't testing at all dwelling in the community, and they are somewhat similar figures for the others, but I don't know that precisely.
DR. GARBER: Mark.
DR. FENDRICK: This may be a question for Steve, but it looks like I'm treading on thin ice. I was moved by the comments about this idea

00204
of potential benefit for glucose monitoring, but at the same time it is very clear that there are probably some people who are Medicare beneficiaries who do not receive any or minimal benefit and are putting themselves at high risk for hypoglycemia or other types of things by doing certain types of treatment patterns.
Given that we now have for the first time Medicare pharmacy claims data, and we've heard an argument that maybe, particularly the intensive glucose monitoring may be most beneficial to individuals on insulin, is there any chance ever to think about decisions to consider certain interventions based on other patterns of care, in other words, if the monitoring can be very useful in individuals on insulin, are we making a recommendation that would be minimally wasteful for people who are not on insulin, if you think about that, or is that crossing the boundary?
DR. PHURROUGH: It's not uncommon that we do, when we do national coverage determinations, that we select populations that we believe benefit from a technology and exclude populations that we believe do not benefit from

00205
the technology based upon the evidence presented to us. In making those decisions, we do have to be cognizant of other guidance that we get from Congress, so there are specific rules that they tell us to follow, and we will follow those rules.
And to clarify one of the comments from one of our speakers earlier, we currently do not have in place a national coverage determination to look at whether we should modify the use of glucose testing or not. The purpose of this meeting was to address the issues involved in treatment of diabetics in our population, with glucose monitoring being one of those issues.
Is there an ability within the current law that says cover glucose strips for type 1 and type 2 diabetics for the Agency to have nationally, or the DMERCs at a lower level to modify volumes abuse, yes. Is there ability to prohibit use of glucose strips, that would be a

challenge.
DR. FENDRICK: Thanks.
DR. GARBER: Maybe we could use that to segue into our voting questions, and I would ask Steve if he wants to make any comment before we begin that discussion.

00206

DR. PHURROUGH: For those of you who have not been at these meetings before, when we get to the voting time, it becomes somewhat of an interesting spectacle from our end, watching you to try to write down all the numbers, because everyone is holding up cards. You won't get to do that today, we're going, because there is a lot of numbers to write down, the panelists have ballots, they're going to write the numbers down, they're going to be taken up, and then you will see the results posted on the screen shortly after that, the totals will be posted on the screen. And then the individual totals for the entire panel will be posted on our web site tomorrow. So stay in your seats, be comfortable, you don't have to jump up and down to see who's holding up a five or a one.
DR. GARBER: And although I know we will be making every attempt to do this real time, I know that based on past experience, if there is this many questions and this many votes to be compiled, it's going to take a little while. So I know they have to go through some steps to get the numbers compiled and displayed as quickly as possible, but we will presumably be moving on from one question to another as they compile the voting

00207

themselves.
So let's open then with Question 1, this has been modified from the question that was originally distributed, we have columns for relative prevalence and clinical severity, and we're being asked to rate the following complications according to their burden, prevalence times severity, in Medicare patients with type 2 diabetes, rank each of them. So you're going to use a one to eight ranking for prevalence and clinical severity. So, this is probably pretty clear to you, but if you think there's something that's highly prevalent, but has relatively minor health effect, you would give the prevalence a low number, meaning a high ranking, and the clinical severity, you would give --
DR. KRIST: I think you reversed them.
DR. GARBER: Right, sorry. Eight is what we call highest, okay. Let's just reverse what I said, but it's clear that you understand better than I do. What I was trying to get across, if you give it the highest, you could give

it a very high ranking on prevalence but a very low ranking on severity. Conversely, if something has very serious health consequences but it's

00208

unusual, you would reverse the rankings. Any questions about Question 1, and then we will open it to discussion, or any questions about how we do the voting? Maggie.
DR. MOLICH: So is this just our guess, or are these when the numbers are actually known?
DR. GARBER: There are some estimates in the readings we were given, if you want to take a minute. This is an open book test, but it's not a take-home exam.
DR. HAYWARD: Although I would interpret it as absolute risk increase rather than relative.
DR. GARBER: The relative refers to your ranking, I believe, your ranking on that basis.
DR. REIBER: If anyone needs them, I looked them all up on the CDC web site, so just ask me.
DR. GARBER: Well, we could start with a discussion which might enlighten everybody what the CDC web site says. Jonathan.
DR. WEINER: If one were to look them up on the CDC web site, what would you find?
DR. REIBER: I'm glad you asked. In

00209

terms of fatal and non-fatal cardiovascular disease including CHF secondary to ischemic disease and non-hemorrhagic stroke, for 65 to 74 it would be 135 per 1,000, and for 75-plus it would be (inaudible) per 1,000.
In terms of retinopathy resulting in legal blindness, that would be about one in 6,000.
In terms of other retinopathy, that would be about 21 per hundred in the group from 65 to 74, and (inaudible) in the group 75-plus.
In terms of nephropathy resulting in dialysis or transplantation, this is now per hundred thousand, and that would be 405 in the group from 65 to 74, and 383 for the group that's 75 and above.
In terms of other nephropathy including micro or macrovascular disease, about five per thousand.
Amputation, that would be about 6.6 per thousand in the 65 to 74, and 7.9 in the group 75-plus.
And then in terms of abnormal neuropathy testing, that would be about 40 percent -- excuse me. That would be about 16.8 in the group 65 to 74, and 29.3 in the group 75-plus.

00210

DR. PUKLIN: Per thousand or percent?
DR. REIBER: No. The only one that was per hundred thousand is the end-stage renal disease, everything else is per thousand, and then was per hundred, and that was other retinopathy.
DR. PUKLIN: How about all cause of mortality?
DR. REIBER: I can't give you that one.
DR. GARBER: Of course the relevant question here is all cause mortality among diabetics, what the incidence is.
(Members voted and staff collected the votes.)
MR. QUEENAN: While they're collecting those, did you review the protocol for the questions that appear below.
DR. GARBER: Yes, we're just going to have discussion, we intended to use these discussion questions in part to make sure that you considered these things as you voted, so one of them is, to this particular question, do the kinds of chronic diabetes-associated complications that occur with type 2 differ qualitatively and quantitatively from those that occur with type 1 diabetes, and are there any other important

00211

chronic complications in type 2 diabetics over the age of 65.
MR. QUEENAN: So just to be clear, this question as it's worded relates solely to type 2, but the discussion question compares the two.
DR. GARBER: Right. We had decided in the conference call in the interest of time not to go point by point through the discussion questions unless they came up, but anybody who wants to discuss one of these should say so. Maggie.
DR. PIPER: One of the discussion questions is should other outcomes be considered. Do you want to talk about that now?
DR. GARBER: Yes.
DR. PIPER: They mentioned something about overall quality of life. Is that something we ought to consider, in the context of an overall assessment with validated instruments?
DR. GARBER: So what you're asking is, should one of the outcomes considered be sort of a global quality of life rather than solely being one that's a complication?
DR. PIPER: Right. We have some that are very fractured, but on the other hand, quality of life is hard to do.

00212

DR. GARBER: Okay, discussion of that

point? That's certainly a valid consideration.
DR. REIBER: From a patient's perspective, it is a very important consequence, I applaud you for that.
DR. GARBER: If people would like to add to that, let me make sure Steve agrees, it's not exactly a parameter, but if you want to add an extra row for, let's just say a global quality of life measure without necessarily specifying them any further. We all know there are many that exist.
MR. QUEENAN: Wouldn't it be just as well to get the sense of the panel that that's a good idea to add that, but it's not in the request.
DR. GARBER: Well, there's sort of mechanical problems that we're not set up for, doing this one to five scale on Question 2 to do it. But what would be most useful to you, Steve? The suggestion is to either get the sense of the panel whether a global quality of life would be an important outcome to follow qualitatively, or we could ask them to score that just like the other ones.

00213

DR. KRIST: We could add this to Question 2, but that's also a bullet for Question 1, are there other important complications.
DR. GARBER: Yeah, but you already voted on Question 1. Charlie, is that what you meant, for Question 1, to ask the sense of the panel?
MR. QUEENAN: Yes. I mean, I though we voted on Question 1.
DR. GARBER: Which did you mean, two?
MR. QUEENAN: That's fine.
DR. GARBER: So we can make that, if people agree with me, just put a line at the bottom, I don't have the same form as you, I think. I do now. So stick in Q of L under Question 2.
DR. KRIST: Well, I mean, we're adding other outcomes for Question 2. I mean, there's a host of other outcomes to add to this, you can add all the outcomes looked at in UKPDS or DCCT, or get into cardiovascular disease with continuous monitoring, I'm sure there are various complications that aren't listed here as well, so that gets more complicated. I think our purpose

00214

is more to give guidance for those who are funding future research on these monitors, so we might not have to vote on that, but we're able to say our comments and what we think would be important

outcomes. This list is not all-inclusive for all the outcomes I would want to see for the effectiveness of continuous monitoring.
DR. MOLICH: I think what we're talking about in Question 2 would be more like surrogate outcomes for the clinical outcomes, and these other things are much more short term, and I think that quality of life could very well fit into the short-term as well as the long-term process. I think they're different categories.
DR. BLACK: Alan, again, I agree with those comments, but I think that the presentations this morning, thinking about the use of these devices is if it is early in the stage of disease or is it more with chronic, the way I read this question is where in the care of the patient with ongoing diabetes, which of these measures should it be. And I actually think it would be helpful just to clarify what we're talking about, I presume we're talking about essentially monitoring in the ongoing care of the patient with diabetes,

00215

rather than anything that might be done for a newly diagnosed diabetic.
DR. GARBER: Maggie.
DR. PIPER: Since we're talking about outcomes, I just want to point out something that has concerned me, and it changes if A1c is one outcome. But one question I had in relation to continuous monitoring is how have daily changes in -- well, that's not, I guess, how do you get from daily changes (inaudible) to overall changes in hemoglobin A1c, and how do you assess what is clinically meaningful versus what is there on paper but may have no relation to symptoms, and that's something that we haven't really touched on.
DR. GARBER: Well, I'm not sure this is exactly your point, but some of the presentations show that if you took spot measurements of glucose with continuous measurement, you might see a lot of variability, and similarly, hemoglobin A1c is not a particularly good measure of variance, it's more like an integral measure of average blood glucose, but you could have people with similar hemoglobin A1c that have a very different pattern of blood sugar. Is that part of what you're

00216

getting at?
DR. PIPER: Yeah, that is what I'm getting at, but how do you go from those measurements to, you know, clinically significant exclusions? And I think there is a body of data that might have been clinically validating a biomarker, but what are the limits that are

important and where does it become important, and how is that related to overt symptoms of, for example, hypoglycemia, either minor symptoms or the more severe symptoms, and I'm not sure that our answering these questions is going to highlight the need for that kind of information.
DR. GARBER: Well, that can be a discussion point. As I understand it, these are not intended, no one of these questions is intended to be all-encompassing. We're really being asked to rate how important these measures are, but that doesn't mean they have to be comprehensive, and you're saying that there are other --
DR. PIPER: Well, I'm just saying these are all good, and yes, I understand they're not all-inclusive. I'm just pointing out a gap that I have noticed, that I think is important, and I'm

00217

not sure if it's being brought out by just voting on these.
DR. PUKLIN: Are you asking to include things such as the continuous subcutaneous glucose monitoring and other data points for glucose parameters as opposed to A1c?
DR. PIPER: I'm suggesting an item for other data, which is not really what we're voting on, but there are some other things.
DR. GARBER: Well, I think the transcript will mark your point, no matter what, and we can say that there are other aspects that need to be determined, maybe if you're going to assess continuous glucose monitoring, you may need better measuring than we have today that are surrogates for things such as A1c.
DR. PIPER: Or daily glucose levels.
DR. GARBER: Right. Are people ready to vote on that? As I hear the sense of the panel, and let me just make sure this is truly a consensus. There will be a voting rating on quality of life in addition to the ones listed here, and it was noted that these mesures are not fully comprehensive, and others may need to be developed.

00218

MR. QUEENAN: Just to follow up on the discussion there, it might be possible to include as an additional voting item without at this time trying to define it too precisely, (inaudible), but again, giving CMS the sense of the committee to say that's another element that would be noted, so we can, the suggestion, and I'm not sure, but the suggestion would be to add that as a global comment as well.
DR. PIPER: Or even to qualify the

clinical significance.
MR. QUEENAN: Well, I think, yes.
DR. GARBER: Right. Ed.
DR. BLACK: Well, I also wondered what folks think about something about compliance. I keep thinking that this is going to be a comparative study of either no monitoring or one type of monitoring or another, if you keep the issue about compliance, both compliance with detection regimen, but also compliance with the diabetic treatment regimen. And again, because the hypothesis might be that the reason A1c gets better is because of sort of some increased attention to numbers, changing diets, maybe again, trying to figure out the linkage, so I think that

00219

would sort of be another possible outcome, something about measures of compliance.
DR. RUCKER: Wouldn't that be included in A1c measurements? Wouldn't measures of compliance go with the A1c?
DR. BLACK: I guess it may be or it may not be, and it sort of relates to are there changes made in the medication regimen that drive changes from A1c or do patients -- I mean, I understand if A1c changes, that's one of the main drivers of that change, and this may be getting too deep.
DR. MOLICH: I think maybe as it's being used, at least currently in clinical practice in that these continuous glucose monitoring devices are not for the non-compliant patient; the non-compliant patient's home glucose monitoring is not going to be continuous monitoring. This is for really the patient who is already doing three, four, five, six times a day and is still having periods of hypoglycemia, and so that this is a way of getting to those unexplained values for the crashes from hypoglycemia all the time, and you get better indication by looking at these trends before the

00220

points have already been measured. And so that the changes that occur will be to regimen based upon these trends that really weren't apparent when he was testing four or five times a day. So this is not going to assess compliance. These patients are already compliant. This is to go ahead and do this next step.
DR. GARBER: I suggest we go ahead and vote now. We have had a fairly long discussion on this and we do have five more questions after number two. So, if there are any suggestions about stuff to add, how about if the record reflects the suggestion that compliance be added,

but we'll just limit the voting to these?
MR. QUEENAN: So we are voting on global quality of life?
DR. GARBER: Yes.
DR. PUKLIN: I thought it was stressed in one of the presentations that measuring blood glucose multiple times a day or through a continuous feedback mechanism is one way you could get to the effectiveness of glucose monitoring based on the three-month A1c. So I think the concept of some sort of glycemic measurement on a frequent basis is an effective way to get to the

00221

point that everything we're discussing now. You can't get the A1c levels, as I recall, without assessing the right population, right?
DR. MOLICH: Right, but it's not a closed-door system, it's an open-door system. Let's make sure everybody understands that.
DR. GARBER: Okay.
(Members voted and staff collected the votes.)
DR. GARBER: Are people ready to move on to Question 3A, which is, this is a whole new section on the relationship of glycemic control and outcomes in type 2 diabetes.
DR. HAYWARD: There's two ways I could interpret what it means by glycemic control and I ask you for some guidance. One is tight glycemic control, you know, because there is that distribution, and the other is given the distribution of people with onset of diabetes after age 65, that distribution amongst that category of patient, and the answer may or may not be different, but I think I want to be voting on the same conceptual relationship. Most people with onset after 65 have very mild diabetes as opposed to a 70-year-old who's had it for 15 years

00222

who may have severe diabetes. So the intent of the question is which of those, tight glycemic control or given the amount, because I think everyone here would agree there is benefit regardless of your age in going from 11 to nine, I mean, people at 11 feel terrible.
DR. GARBER: Well, I think the reference is to the DCCT and the UKPDS when they talk about tight control.
DR. BRADHAM: So the implication is that the target is in the seven range, or eight range? There was a good bit of information this morning that suggested maybe six should be the range, and that's where some of the current trials are targeted, and is your question relevant, or is it important to understand what the target is to

answer that question?
(Dr. Garber and Dr. Phurrough conferred off microphone.)
DR. GARBER: As Steve says, the targets are to be the targets in the trial, so we're talking about the lower range. Mark?
DR. FENDRICK: But Rod's question gets this idea of control meaning where you set it and you say seven, or were you ten and became seven.

00223
And the speakers, because I'm not an endocrinologist, used control both to talk about absolute numbers of where you were as well as change. And Rod's question very much articulated, the question pertains to the average Medicare beneficiary who is an instant diabetic, he's saying that patient will not have very severe disease and is likely to have a lowish A1c. Is that controlled or not?
DR. GARBER: My interpretation, and Steve, you can correct me if CMS has something different in mind, but this is about what the target hemoglobin A1c starting point is, it's what the target is. So I just want to direct your attention to discussion points which apply to Questions 3 and 4 and appear on the next page, so things to think about as you address each of the questions. And Mark, you were trying to get at at least one of these, what change in hemoglobin A1c is needed to delay or reverse complications? Jonathan?
DR. WEINER: One thing that's clear from many of the speakers is that a lot of people feel that a cardiovascular event is different than some of these other chronic diseases, but the way

00224
the question is worded says especially cardiovascular. So I think if you were to poll us about cardiovascular and then poll us about the others, it might be a different response. So are we to answer it based on factors we think is the most assured, so in other words, if we have some that we're confident on but some we're not confident on, do we vote the high or the low? Do you see my point?
DR. GARBER: Yeah. I'm cringing a little bit because the most precise and clear way to deal with your question is to vote separately on different complications which, if it's the committee's pleasure, we could try to do it, but otherwise you would have to give an overall assessment.
DR. KRIST: We could divide it into micro and macrovascular.
DR. GARBER: I think cardiovascular and

non-cardiovascular would be cleaner, but it's up to the committee. Would you rather vote separately on cardiovascular and non-cardiovascular, or would you rather answer them overall?
DR. KRIST: Although another way to

00225

maybe separate out some of this is in part A and past B of the questions, because the part B, not exactly, but one is treatment and one is the complications.
DR. GARBER: How many people would rather break this up into two, say cardiovascular and non-cardiovascular, this is 3A, and then how many would prefer to leave it as it is? First, how many are in favor of breaking this up and going to separate votes.
(Panelists raised hands.)
DR. GARBER: Five? Okay. And how many would rather leave it as it is?
(Panelists raised hands.)
DR. GARBER: Six. So just vote how you feel. Let me just add, I think those of you who wanted to break it up, after you turn in your vote, or you can state right now what your reasons are for voting for wanting to distinguish them, or how your answer would differ for cardiovascular or non-cardiovascular. Does anybody want to speak to that point? Jonathan?
DR. WEINER: I would rather hear from the experts, but I think it's very clear that there is a lot of questions about cardiovascular,

00226

but it's also clear that when it says especially cardiovascular in the question, that I would be more confident in my question if it didn't say especially. But I think it's fine, we had a vote and the experts tended to vote one way, and I heard them.
DR. GARBER: Okay. Any further discussion on 3A? Are you ready to vote on that?
(Members voted and staff collected the votes.)
DR. GARBER: Question 3B is, how important statistically and clinically is glycemic control relative to other therapeutic modalities such as lipid control and blood pressure control in the prevention and delay of chronic diabetic complications, especially cardiovascular events and death, in patients who develop type 2 diabetes at age 65 or older?
Let me just point out something that's probably obvious to you. The ratings here, the words describing the ratings are different from most of the other questions. This one ranges from

very important to very unimportant. This is not about your confidence, this is how important it is, so five is very important, one is very

00227

unimportant.
Any discussion on that question?
Please go ahead and vote.
(Members voted and staff collected ballots.)
DR. GARBER: Question 4A, how confident are you that glycemic control reverses or reduces progression or pre-existing chronic complications in a clinically meaningful way in patients who had type 2 diabetes prior to age 65? So the only difference here is pre-existing diabetes versus new onslaught. Any discussion on this question?
(Negative response.)
DR. GARBER: Okay. Please go ahead and vote on 4A.
(Members voted and staff collected the votes.)
DR. GARBER: Question 4B, how important statistically and clinically is glycemic control relative to other therapeutic modalities in the reversal and delayed progression of pre-existing chronic complications, especially cardiovascular events and death, in patients with type 2 diabetes prior to 65?
So this is people with pre-existing

00228

diabetes and also with pre-existing chronic complications. Any questions? And this is a rating of importance, five being very important, one being very unimportant. Any discussion on this question?
DR. PUKLIN: I may have missed a point here, but help me, everybody, if I have. I think all the evidence indicated that no tight management, either from the DCCT or the British study, or any study that's going on, nothing reverses established complications in diabetics for micro or macrovascular disease. So in that regard, you would have to find that there is no confidence in that. But tight management does retard the rate of progression of a lot of these clinical features, certainly in the younger population, and there's some evidence that it may ultimately be doing that in the elderly population. So this question, by lumping together the concept of reversal or delayed progression, kind of forces certain answers upon us in my opinion. Am I correct?
DR. GARBER: Yeah. If you think that it's important for the rate of progression and not reversal, you could still rate it as relatively

00229
important. So if you think it's very important for delaying progression, even if it doesn't work for reversal, you might give that a somewhat important rating. It doesn't have to do everything.
DR. PUKLIN: But it's and, it's not and/or, and all these questions have the concept of reversal --
DR. GARBER: I think that should be and/or, is what Steve was saying.
DR. BRADHAM: Should we add and/or?
DR. GARBER: Yeah, change it to and/or.
DR. PUKLIN: And what about the last question? Then I need my answer slip.
DR. GARBER: Well, Question 3A is an or, and 4A is an or. This is only 3B and 4B. Is there anybody that needs to change their vote on 3B?
(Negative response.)
(Members voted and staff collected the votes.)
DR. GARBER: Okay. Is everyone ready for Question 5? Question 5 is, can the information on hypoglycemia in type 1 patients be generalized to Medicare-aged type 2 patients?

00230
More specifically, how confident are you that hypoglycemic risks, meaning frequency and severity, for a given level of glycemic control is similar for patients with type 1 diabetes and type 2 diabetes, with the definition of hypoglycemia at the bottom there, less than 30 milligrams per deciliter or requiring third-party intervention. And note the discussion questions below there.
MR. QUEENAN: Alan, I have two questions. For the first discussion question, you know, we mentioned that we would discuss this today, but the frequency of hypoglycemia might differ by the class of therapeutic agent, so do we want to put that on the table for some discussion as to whether we want to consider differentiating that, acknowledging that it may be a little complicated?
DR. GARBER: Yeah.
MR. QUEENAN: So that's my first point. But secondly, and related to that, in looking at the definition of hypoglycemia that's on here, that's a very stringent definition of hypoglycemia, and the question that we're voting on is actually a two-part question. The first one

00231
is can the information on hypoglycemia be

generalized, and it seems to me that that information has to stand on its own in terms of whatever definition you use in a particular setting has to be what we evaluated. And secondly, when you talk about whether hypoglycemic risks for a given glycemic control are similar for type 1 and type 2, the question is asking us to consider frequency and severity. So it seems to me, again, there might be, I don't understand why we're putting that definition in here as a caveat to the voting question.

DR. GARBER: I think that it's in the context of asking for more specificity where CMS came up with this. That sounds like a very (inaudible) definition of hypoglycemia. But let me just ask you, Charlie, your first comment maybe could be combined a little bit with the second, and that is to say, would one useful distinction be, rather than type 1 versus type 2, would be whether they were receiving insulin or not? Is that what you were sort of driving at?

MR. QUEENAN: Certainly within the subset of type 2, yes, whether they are on insulin. But I think we could also say whether

00232

they are on oral hypoglycemic agents and I think there was some hypoglycemia observed in those patients.

DR. GARBER: Yeah. Anyway, I think we have a lot of variables floating around here. There was the age of the population, there's type 1 versus type 2, there's the therapy, and presumably there is also the therapeutic goal, i.e., whether you are trying to go for a very low blood sugar or low hemoglobin A1c, that might be a very different situation. So I think what you raised in the question was the best way to talk about generalizability to the Medicare population, which information applies to the population of interest to us. And so if you were suggesting at first, maybe we might want to hear from some people here. Mark, did you want to say something?

DR. MOLICH: There clearly is a gradation of frequency of hypoglycemia in type 2 patients depending upon the therapy that you're doing, and also in the glycemic targets in general with type 2 patients on insulin, or with hypoglycemia in type 1. But on the other hand, in the type 2 patient who is over 65, it may be more fragile or more modest, but a hypoglycemia that

00233

might make them a little bit light-headed, may be far more dangerous than the same development that might give you a light-headed 18-year-old who will bounce off the floor, while the 70-year-old will

fracture a hip. So I think that we have to think about the entire situation.
DR. GARBER: Well, Charlie's, I think suggestion, or what you were floating, I think, is the idea of should we maybe break this up into different classes, whatever they might be, or should we leave this just one overall question.
MR. QUEENAN: I was just raising the question, which is to differentiate between insulin and non-insulin, if we had to simplify, if it's not more beneficially broken apart further than that, but that would make sense to me.
DR. GARBER: So, let me just make sure how I understand this would affect the wording of the question. Maybe it should be, can the information on hypoglycemia for type 1 patients who are already on insulin be generalized to Medicare-aged type 2 patients, and then with two subgroups, one subgroup being using insulin and the other group not using insulin. Charlie, is that how you would break up the question?

00234
MR. QUEENAN: That would be fine.
DR. GARBER: So the question is, do you want to break up the voting that way or just leave it all together? So, discussion from the committee?
(No response.)
DR. GARBER: Do you want to just vote on whether to break it up? Okay. All those in favor of breaking it up into two subgroups, using and not using insulin, raise your hand.
(Panelists raised hands.)
DR. GARBER: Those who want to keep it as one?
(Panelists raised hands.)
DR. GARBER: Okay, the splitters have it this time. So what I would like you to do is break up your answers to the question, very confident to very unconfident, first would be with insulin use, and the second would be non-insulin use. Maggie?
DR. PIPER: Well, another way to do it would be to leave the question as is and then follow up with another question, or is that implied in the question?
DR. GARBER: I think that is intended.

00235
Mark?
DR. MOLICH: It's not intended. You said the risk of hypoglycemia. Is that the risk of becoming hypoglycemic? Those are different questions.
DR. GARBER: Well, frequency and severity are both, that is the probability of it

occurring as well as severity, should it occur.
DR. PIPER: But is that severity in terms of numbers or severity in terms of some kind of event?
DR. GARBER: It's the latter. Severity is what Mark was just citing, a 70-year-old falls and breaks his hip, versus the 18-year-old jumping off the floor and getting right back up. The prevalence means the probability, or the frequency that the event will occur, that the hypoglycemia will occur. You're now voting splitting the two on the question as I rephrased it, insulin and non-insulin, the first one is insulin users, the second one is non-insulin users.
(Members voted and staff collected the votes.)
DR. GARBER: Are people ready to tackle Question 6? This is really a one-part question,

00236

to start out with anyhow. Question 6, how confident are you that glucose monitoring improves by a clinically meaningful degree glycemic control and decreases the risk for hypoglycemia at a given level of hemoglobin A1c? The idea here, this includes the trade-off between the risk of hypoglycemia and tightened glucose control. And this question has a large number of discussion questions, so please take a few moments to review the discussion questions.
DR. FENDRICK: Is your interpretation, Steve, we talked about this on the conference call, so if we believe that it improves glycemic control but did not lower the rate of hypoglycemia, or vice versa, your interpretation is that we should vote on the positive, but I want to hear from Steve that that's -- this is one that should probably be split, because you could directly address how you feel about hypoglycemia and you could also address how you feel about A1c, to get rid of any of this confusion about saying they might be equal. They might be different.
DR. HAYWARD: (Inaudible.)
DR. FENDRICK: You're agreeing, I just want Steve to confirm that.

00237

DR. PHURROUGH: Yes, net health outcomes.
DR. FENDRICK: Then that's what it should read, which is what you proposed.
DR. GARBER: Okay. So, is there further discussion on this question?
MR. QUEENAN: I guess I want to raise one point, since the discussion questions refer to changes in medical management, and we've heard a lot today about the linkage between measuring and

actually doing something about it, and in some cases the difficulty in studies is interpreting the results. So I guess just to clarify, are we assuming that all variability as to whether or not someone reacts to a measurement is imbedded in this question? In other words, did it help or could it help.

DR. GARBER: I think this really says did it help, that is to say it may provide better information, but it doesn't mean it changed the management.

MR. QUEENAN: So then, the interpretation could be in effect one-directional, that if you add testing or more testing, that it may or may not improve outcome, but it doesn't

00238

necessarily address what would happen if you were to take testing away, what that would do to outcomes. At that point I can't do that, I would be deprived of the ability to do that to improve management.

DR. GARBER: Alex, did you want to make a comment?

DR. KRIST: Well, I just wanted to make sure I understood the distinction so when we talk about clinically meaningful, because I'm trying to differentiate Question 6 from 7. I mean, 7 is, does it decrease chronic complications. When I'm reading 6 and it says clinically meaningful, I'm thinking about clinically meaningful meaning controlling blood sugar, focusing on that as opposed to decreased long-term complications like morbidity and mortality. Just to differentiate, am I right on that or am I misunderstanding that? I wanted to make sure we're all in agreement.

DR. GARBER: Well, they are not totally unrelated. If you think that there's a, you would have to explain, let's say that hemoglobin A1c falls by .1 percent with no change, no decrease in hypoglycemic episodes. Whether that, you would consider that to be clinically meaningful, one

00239

thing would be your assessment of whether that translates into long-term outcomes. So they're not totally unrelated, the question is whether there's a clinically meaningful change in glycemic control, so you have to decide what makes it clinically meaningful.

DR. KRIST: Then how is 7 different when I get to 7?

DR. GARBER: You could say that presumably it's not due to glycemic control, like if your patient has lost weight, et cetera, you might have a different answer to 7, regardless of 6. So, is everybody ready to vote on

Question 6? Let me know. Go ahead, Edgar.
DR. BLACK: I just wondered whether it's worth having any discussion about the second bullet point, whether particularly our diabetes experts have some comments about that, the use of monitoring in someone who is newly diagnosed versus someone with chronic disease. Again, not for changing voting, but as a discussion and for the record.
DR. REIBER: There is a star here that indicates that we're excluding newly diagnosed in this question, because I think we saw the evidence

00240

this morning how important it is for newly diagnosed individuals to get both education and how to use the blood, monitor the blood glucose.
DR. GARBER: I think that, but if people, maybe the experts want to address the answer to the question, that is the discussion question for excluding newly diagnosed from the voting column, so if anybody has any comments, please feel free. Are there established benefits for increased glucose monitoring for six months, so yes, we've not seen any data on that. Any other comments on that? Okay, Dr. Davidson.
DR. DAVIDSON: It will be a short comment. (Inaudible.) I'm not sure it's monitoring per se that leads to tremendous improvement. What happens is (inaudible).
DR. REIBER: Isn't that the same as what we want to do when we give them information on what their lifestyle choices will do to their blood glucose? It continues to teach them how to deal with blood glucose, so just that self-awareness is critical.
DR. GARBER: Any other discussion? Mark.
DR. MOLICH: The other thing, as I

00241

mentioned before, is patients get worse over time, so periodic monitoring is certainly worthwhile to give them an idea of what's happening to their diabetes. If they're under control, if their blood sugar, A1c is under seven, that means they only have to measure their A1c so many times a week.
SPEAKER: At the risk of taking the opposite position, I just want to point out that the new guidelines for type 1 and type 2 strongly suggest that these moments are absolutely critical, and the frequency (inaudible) may be much greater than the possibility of (inaudible) type 1 or 2 is critical during that time. So I would say that that's one of the stronger (inaudible) very special to get very good control,

monitoring.
DR. GARBER: Thank you. I just want to remind you all that you are being asked to vote on the frequency of monitoring to give these confidence ratings. That includes diet therapy all the way to using insulin for type 2, and then type 1 separately.
DR. FENDRICK: I presume the fifth option is not applicable for type 2 diet and

00242

non-insulin?
DR. GARBER: Yeah. That's right. If there's no further discussion, please go ahead and vote.
(Members voted and staff collected the votes.)
DR. GARBER: You're almost at the end of the marathon, so we'll see if you have that last wind. Question 7, does increased glucose monitoring in type 2 patients improve clinical outcomes? More specifically, how confident are you that, 7A, an increased frequency of outpatient glucose monitoring translates to decreases in chronic complications, specifically here, cardiovascular morbidity and mortality, in Medicare-aged patients with type 2 diabetes? And then the second, 7B is whether the optimal frequency is known. Any discussion on 7A? Mark.
DR. MOLICH: An increase implies a process; where are we starting from? And it does make a difference whether they're on insulin, not on insulin, and the presumption is that whatever the increased frequency may be, that that information will be utilized by the patient and the caregiver to change care when indicated; is

00243

that the implication?
DR. GARBER: I think in theory what would happen is what would happen in practice. And with regard to whether they're on insulin or not, I think once again that if it's really important to draw the distinction, we could break this up into two separate questions.
DR. MOLICH: What's the starting point, increase from what?
DR. HAYWARD: Also, I'm having difficulty deciding what 7 adds to Question 6, so the purpose, after answering 6, what am I answering in 7 that would give something different than averaging my answers to 6?
DR. GARBER: Well, if you think that the only measurement by which this increases frequency, if you think the only measurement for glycemic control is frequent measures based on hypoglycemia is --

DR. HAYWARD: But what's the difference if we said high clinical significance in 6, so what's the difference?
DR. GARBER: Let me just add, by the way, what we learned from several of these centers is that the important thing is really the whole

00244

diabetes management program, of which this is an element. So if you think it's an essential element to the program, increasing the frequency, and it doesn't specify what the baseline is or the targets are, but if you think it's an essential element and that increasing frequency will improve it, then you should say that you're confident, or whatever your response would be. I don't know how to answer this question about frequency, or about baseline frequency. Steve, do you want to give that a shot?
DR. PHURROUGH: The intention was, whether correct or not, was that it increased from whatever is currently being performed to whatever the next level is, so twice a week to once a day, once a day to four times a day, recognizing that that is fairly indistinct, but in fact we did not intentionally want to specify what you were going from and to.
DR. HAYWARD: Would it be fair then to summarize the question as how often would a clinician in regular practice increase the intensity to lead to clinical benefits, would that be the nature of the question?
DR. PHURROUGH: I think that's a decent

00245

assumption.
DR. GARBER: Mark, did you want to make a comment?
DR. MOLICH: This is really a vague question. If a patient is doing well with an A1c of 6.0 and has glycemic control, I'd say great and wouldn't change anything at all, so it very much depends on the clinical situation. I would vote to stay with 6 and delete 7 also.
DR. GARBER: Well, 7B is a very different question.
DR. MOLICH: Not really.
DR. GARBER: Well, you might still think you can't answer it, but it's a different question. 7B, part of what you're saying is that you might say that the optimal frequency varies with the patient or some sort of algorithm, and this is a general question about what we know about how often it should be done.
DR. MOLICH: But didn't we apply that to 6 when we said how many times we were going to testing, one time, two times, four times?

DR. GARBER: No, no. I mean, if you're highly confident, basically if you're not confident that glucose monitoring improves

00246

glycemic control with a particular frequency, the answer may or may not be due to your concern about what the optimal frequency is, so there is a difference.
DR. HAYWARD: I withdraw my objection to 7B. 7B is my rating of how confident I am of my rating on 6.
DR. GARBER: That's a fair interpretation. So first of all, we have heard one, I guess not quite a motion, but a suggestion that we strike 7A. So, the committee can choose not to vote on 7A, so let me see a show of hands of the people who do not want to vote on 7A.
(Panelists raised hands.)
DR. GARBER: Those who do.
(Panelists raised hands.)
DR. GARBER: Okay, so it's six to four for voting. So, has everybody voted on 7A? Vote now if you haven't already, please.
(Members voted and staff collected the ballots.)
DR. GARBER: Okay. 7B, further discussion of 7B?
DR. REIBER: Accepting Rod's comment.
DR. GARBER: You just told us how you

00247

were going to vote.
DR. WEINER: I view it a little bit differently from my perception of health plans and Medicare and Medicaid, so this might be time for a plug. We're scientists and well-intentioned advocates here, but when you translate it for insurance plans or for Medicare or Medicaid, or are people planning to do the right thing for what needs to be, I think of the gentleman from Minnesota that had the algorithm, taking the science and trying to translate it, the previous matrix needs to be filled in for the clinician, for the payer, and so that's why I look at this question a little bit different. I don't know if that's what you wanted right now.
DR. GARBER: Yes, Jonathan, I think that's a perfect segue and Steve may have some comments and questions for the group, but any further questions?
(Negative response.)
DR. GARBER: Has everyone voted on 7B?
(Members voted and staff collected the votes.)
DR. GARBER: Well, this is a shockingly needy performance, but this issue of research

00248

guidance is very important, and we need to know some of these research challenges to be able to help us assist CMS in making their decisions. Steve, did you want to add some things?

DR. PHURROUGH: Yes. I would like to spend a few minutes, since we have an hour and a half left in the day, what I would like to hear both from the panel and from the audience is sort of a twofold question. What are those questions that we need to answer? We talked to some of the speakers, most of the speakers talked about that, but in a type 1 continuous monitoring pump setting, what are those questions that need to be focused on? And then for the type 2 patients, particularly the older Medicare patients, there's a different set of questions, and what's the best way to answer those questions. That's sort of the first set.

And then the second set is, what can CMS do to help with that? What role should CMS assume in not just its typical role of attempting to ensure the patients get what they need, but more in the role of fostering, answering some of the questions that are left to be answered. So let me throw that out, and perhaps

00249

it's just a summary of things we've already heard, but since we have a good number of people, it would be helpful for us to hear what you as a panel have digested along with what we've heard today.

DR. PIPER: Just to repeat what I was talking about earlier regarding continuous glucose monitoring, and I think there is a strong need to go beyond reporting numbers of daily sticks, and numbers and graphs, and to really get to clinically meaningful outcomes such as falls or other measures of hypoglycemia.

DR. PHURROUGH: And I was going to ask that question, particularly of those who have presented that information or made some point, are there measures of glucose excursion that are validated or, let's just ask that question, what are the measures of glucose excursion that are validated, and if the answer to that is none, what are those that are being utilized in research, or should be utilized in research? Number of times below 200, number of times below 50, do we need a continuous monitor, whatever? What kind of specificity do we have in this data?

SPEAKER: Well, I could just add a

00250

little bit about the strips that are used, we talk

about standard deviations. To get an average of 124 at breakfast is fine (inaudible) 220 or 230, so you're not bouncing around too much. But when you see patients, you get a third of the numbers above 230, so that is a number we use all the time in research looking at this. And although the organizations don't have the exact postprandial goals, I think that everyone agrees that 200 is a good general baseline, above 200 is too high whether before or after eating. And then of course with hypoglycemia, below 60 is the standard, I'm not sure where you all got 30, but certainly below 60 with or without symptoms is a real cut point for measuring.
DR. PHURROUGH: You're writing a protocol and in the protocol you're going to write down, here are our outcomes, so we need a very short phrase, here's what we're going to measure, the number of times or the ratio of, or --
SPEAKER: Well, you could say the percent of time patients are in the hyper and hypoglycemia range, what is the percentage of time blood sugars are above or below the percent of numbers above or below these two numbers, the hypo

00251

and the hyper range.
And the third one is the ability to see where, if you have a study that's at least three months, you're obviously going to (inaudible) so that's the gold standard.
DR. GARBER: I think one of the issues is that a standard deviation is simple to measure, but what this points out is why that is not that meaningful by itself. A standard deviation is not that difficult to measure, but if you go 70 points below --
SPEAKER: Then you would have a mean plus or minus a standard deviation.
DR. GARBER: But the point is that wouldn't be helpful, if you have measures where you could have percent of time with comparable health risks, and you may be coming up with sort of a second measure only in more detail where you define severe hypoglycemia, moderate hypoglycemia, and then come up with a hyperglycemia which could be a totally different size range.
DR. PIPER: The question has to be in relation to clinically significant events and whether the data is there, that's kind of what I was getting at.

00252

DR. RUCKER: Well, one question that you may want to comment on, I think it was in one of our questions around, for example, the wound healing. In terms of Medicare policy, it may be

interested to look at the effects of glucose monitoring on some of these patients. I mean, our discussion today has really been about chronic things, but it may be that there is an economic impact on Medicare just the way some of these things, and I don't know if that's within the purview of the group here. I think that in terms of wound healing, the last set of subquestions sort of got at that, and I don't know that we were shown that today or in the materials.
DR. PHURROUGH: I would like to not go there, Don. I want to keep it honest here. One of the reasons that we've heard today about the need for continuous glucose monitoring is to prevent these hypoglycemic and hyperglycemic events, and my question is what should we do to determine whether that is in fact a benefit from this continuous glucose monitoring. You've got to have a trial and the trial has to measure something. What is that measurement that is the outcome, the number of times below 60, the number

00253

of times above 200, the square root of the sum of the participle? What are you going to put in the trial to measure?
DR. HAYWARD: This literature is very complex and I think the answer to what you really want is not determined. Ultimately you would want to know how dispersion is done in a prospective study before complications affects these. I think you're going to want to confer with the investigators from the DCCT and look at dispersion to get the best answer, and not from me.
But you want to be very careful. A lot of the work that's being mentioned by several members of the audience here are confusing an outcome, ridding us of diabetes, that is due to a history of poor glycemic control with an assessment of variability of control in somebody who does not yet have complications but may have them in the future. The DCCT had a devil of a time applying that dispersion or variation when it was associated with outcomes. I think they have the best studies and the best look at this, but there is no doubt that people that have the most dispersion and variation have the worst outcomes. And it's not clear that those studies

00254

are, at least epidemiologically they are invalid for answering that question. So I don't think anyone knows, and in fact there's a lot more doubt in the epidemiological literature that dispersal is as important as many people believe in their heart. I think it's good theory but there's something else going on.

I would really recommend, rather than trying to get the answer here, to talk to those investigators that have done the most detailed work.
SPEAKER: I need to jump in here and disagree because it's not that complicated. You can be a numbers person and really confuse the issue. We know what normal people do throughout the day, we know that they hardly ever get below 70 and they hardly ever get above 140. We know that high A1c's can be damaging. There have been studies to show, and I showed one today, that a certain subset of the population can lower A1c. The hard numbers that you're looking for are right there in front of you, low blood sugar. There is nothing more complex than that. And yeah, we can argue, and I agree with you that --
DR. HAYWARD: I just repeat that those

00255

studies are --
SPEAKER: I didn't interrupt you.
DR. HAYWARD: -- not really epidemiologically valid because those people already have brittle diabetes, and you want people before they develop brittle diabetes.
SPEAKER: I disagree a hundred percent on that. So what I'm saying is that the outcomes are quite simple, it's the number of times that people spend outside the normal range. You can play with these numbers all you want to make it really complicated, but it's not that complicated when it comes down to practicality.
DR. PHURROUGH: And since those numbers are not yet, that particular, that is not a validated measure, then I think any of these trials we're looking at for continuous glucose monitoring needs in some manner or fashion, if it's going to measure that, to validate that as an appropriate surrogate outcome for the hard outcomes that are a problem, falls, break your hip, run into your neighbor backing out of the driveway.
SPEAKER: If I could make a couple of comments. (Inaudible, not speaking into

00256

microphone.) -- looking at their blueprint measurement and looking at dispersion or instability, and I think you'll find real differences between that versus CGM. And the third thing is the suggestion which, I think what you have to do is to do a study in which you're doing preprandial or usual monitoring, and compare it to continuous and see if there is a difference in outcomes. There has been a study published in a small number of patients showing there was a

difference in that, but future studies need to show that.
DR. PHURROUGH: So, did I understand that you are not sure that dispersion is something that's necessarily needed to be measured in CGM studies, that we can just use the standard A1c and other outcomes?
SPEAKER: The data are that dispersion in in vitro systems do set off a string of metabolic abnormalities, stress, a whole bunch of things related to surrogates in vitro. I don't think it's been shown in vivo that it makes any difference, but I think as Dr. Hayward said, it has never been shown in vivo, so this may be a way to get at it.

00257
DR. PHURROUGH: Back to my question. We've heard a lot today that the benefit of CGM is to avoid these dispersions. Is that in fact something that needs to be measured, that's Maggie's question, is it something that needs to be measured and what is a validated measure to use?
SPEAKER: I would say yes to the first one, and you could use (inaudible) or could use the number of times they spin low and the number of times they spin high, but I'm not a statistician.
SPEAKER: I think part of the reason why it's so difficult to answer your excellent question is what Dr. Garber was talking about, which is the asymmetry of the numbers in terms of their clinical significance. If we look at the results with A1c, a straight mathematical model is not a very difficult thing to construct. I know in diabetes care (inaudible) of using a mathematical model to express some of the advantages of continuous glucose monitoring. But there are models, they are very valid, and I think they are fairly reasonable and it's a good way of measuring the percentage of time below the target,

00258
but the area above that is also, I think we do need to look at it.
However, on the issue of safety, it's a whole different matter. If all you do is look at the percentage of time the person spends under 60 or 70 milligrams percent, that really is clinically not terribly as important as the number of minutes or the number of times that a person's glucose is so low that they are incapacitated because their cognitive function is zilch, and at different times it has great importance. A moderate episode of hypoglycemia when a person is traveling down the freeway is very, very different

than in the evening, and likewise at night. Some of the others that are reported are scary. I think technology for this entire area is in flux, so there's some of these data reported in ones less active than others, there are conditions where this trait is not going to be accurate as well. But from the point of view of what I would suggest is, I would suggest that there should be a separate measure that relates to the safety issue, and in that case we should have a disproportionate emphasis on the hypoglycemia as it results to safety, which is powerfully

00259

different for different age groups and for different ways of measuring. That is something that has not yet been constructed and we would be happy to work with you on it, I think it's important.
But in addition, you have several benefits. One is the ability to lower the A1c, the other is the ability to avoid hypoglycemia. And the others are significant safety issues, and that is separate and I would say it is a third separate measure that you should consider, and one of the enormous potential advantages of this is it could help us in areas where we would otherwise not be able to do it because if someone is disabled, they cannot check their own.
DR. PHURROUGH: I want to quickly summarize this and then move to type 2 continuous monitoring. What is a potential to happen in the Medicare world is that we have no national decisions around monitoring, continuous monitoring, it's done at contractor discretion currently, and there's the potential for our contractors to do some local decisions that may not be consistent across the country, and there's the potential for our DMERCs to make broader

00260

decisions on the DNE aspects of it that may in fact not make many of you comfortable. I have no prediction as to whether that's going to occur or not, but those kinds of things happen.
So if someone then comes to me and says we don't like what's occurring with our local contractors or our DMERCs, we want you to make a national decision. So when you come to me to say I want you to make a national decision, you're going to have to come to me with some of this evidence that we're talking about. So it's not necessarily I'm the one who needs to know what measure is an appropriate measure in determining whether continuous glucose monitoring is worthy of coverage or not, it's your issue. So you need to have this discussion so that you as researchers

are able to produce evidence that allows experts to become comfortable that in fact it does make a difference in a patient's life and, therefore, we have the evidence that says if we're asked nationally to make that decision, we can rationally make that decision. So I'm trying to stimulate a discussion that you need to have within your field to answer those questions that you as clinicians need to answer.

00261

DR. MOLICH: I agree with Dr. Hellman that a reduction in A1c of .4 percent is at the same time occurring as with a reduction in hypoglycemia, so the overall feeling is that it affects the benefits-risk ratio. And I think a reasonable study that the manufacturers may want to do is to have a study that randomizes patients to improve the hemoglobin A1c level with or without CGMS, but then looking at hypoglycemia (inaudible) trying to reduce frequency because for all of us clinicians, as we try to get better data, what we're really looking at is hypoglycemia and to try to get better control. So you look at control of hypoglycemia, that is an outcome.
SPEAKER: (Inaudible, not speaking into microphone) bringing their mean down, so I think this discussion is actually looking to a composite of A1c and hypoglycemia.
Now getting to your question, and so until we actually get to more use of the actual technology, only then will we be able to sort of validate what these discussions mean. The American Diabetes Association has come out with a guideline working with a 30 percent reduction in hypoglycemic events, and that is what they were

00262

specifically referring to as meaningful for new technology.
DR. FENDRICK: I want to ask a quick question. What we've seen before in Medicare coverage decisions is that when you're basing your decision on individual relative risk reductions like the likelihood a person might have a slightly lower risk of hypoglycemia, but at the same time there's a widespread availability and the potential media frenzy, like we saw in the New York Times yesterday about glucose monitoring, that so many more people will start doing this that don't need it. Then your absolute numbers of hypoglycemia will go up significantly, because although you get a small reduction per person, because I assume the rate of hypoglycemia even with tighter control is not zero. So there is the potential to have this population effect that actually does greater harm than good. Are you

following me?
DR. MOLICH: Not quite. It's a widespread use of this technique that's going to occur?
DR. FENDRICK: Well, that's because they're promoting the use of this unproven

00263

technology outside of diabetes. Alan, are you following what my point is on this?
DR. GARBER: I am, but I'm not sure that it's going to work out the way you're stating.
DR. FENDRICK: I actually think because we have not been convinced about the value of going from seven to six, that we know that the attempt, I think we heard from all the experts, the more people try to go from seven to six, while the clinical benefits may be small, the likelihood of hypoglycemia may be large.
DR. PHURROUGH: A lot of people are not attempting tight control because they think they have to stick their finger too many times a day. If they don't have to stick their finger too many times a day when they have a continuous monitor, then there will be more people trying tight control and, therefore, more hypoglycemia, I think is your argument.
DR. FENDRICK: You've heard that before, okay.
DR. GARBER: Yes, Bob.
SPEAKER: The research that we're going forward with in a prospective fashion is to take

00264

advantage of the technology that for the first time provides us with information we've never had. So even if it sounds redundant, it's different, because we want to understand excursions or dispersions and what the impact is. The anecdotal data which you saw some of is very striking in that you can take wide excursions and move them into normal range, and for the people who study complications who tell us that glucose on an electronic basis in an elevated fashion is toxic to tissue, to get rid of that is a wonderful idea. You started your question and asked what was the statistical outcome measuring. I don't know the final answer but you would like to know everything you possibly could, whether it be error, the percent in the abnormal range, and if you can change that, whether it's in somebody who started with a hemoglobin A1c of seven but now they never have excursions beyond whatever normal range is, we may not be able to live long enough to reproduce the DCCT forever, but if I had the disease or you had the disease, you would

certainly prefer the normal range over glucose toxicity if you had a choice. So I think some of those questions are

00265

unanswered and what we need to do, perhaps is not necessarily vote on the correct answer to the one measure that we should engage in, but understand where this new technology is taking us and sort of work together on what measures we could be bringing to bear to answer the real question.

DR. PHURROUGH: The whole goal of this conversation is to stimulate that thinking and to recognize that our interest is that you're going to come to us potentially and ask us to do something on a coverage basis, and we're going to want to see what the evidence is, and so you have to know what you will need.

Let's talk type 2 for just a minute. What questions should we as CMS be insisting that you as diabetologists answer in the type 2 Medicare population?

DR. HAYWARD: Just to reiterate, I think we're close to accepting that as an outcome, so I think he's right, we need more research, but improving variance is only interesting now to test the hypothesis, and I think that CMS should not be making decisions on coverage based upon that outcome, you know, A1c, hypoglycemia, quality of life. So I think the answer is in the research

00266

realm and, you know, years from now they might show that improving that is a good enough outcome, but that intermediate outcome, I think people will attempt to say that's worth this intervention. And I think there is no quality epidemiologic data that's using it as an outcome, it didn't show up in our list of outcomes for these studies, and I think rightfully so.

MR. BOYER: My name is Tom Boyer, I've worked in the diabetes field for 23 years and actually lobbied on behalf of the American Diabetes Association about 10 to 12 years ago. I would like to share with the committee a couple of thoughts as a person with type 1 diabetes. Number one, I hope that any barrier or any guideline you use to determine the efficacy of continuous glucose monitoring is not restricted in nature and that it is consistent with what you use to examine other benefits that are out there. Because I just have to say, if this was a tool that was used to fight cancer or some other disease where outcomes were actually improving right now, CMS would probably cover it in a heartbeat.

It's very disturbing to hear the tenor

00267

of the conversation right now, at least on the staff side, and as a person who lives out there, it's improving people's lives, and it's really frustrating to me. I have been in this place for 23 years and never before in my life have I actually heard the DCCT challenged the way in which I heard it challenged this morning, and that's really frustrating and of concern to me. The second thing that I would like to share with the group is, I'm concerned with the focus on glucose monitoring and not necessarily A1c control. If you look at the measures that exist in the Medicare program today of the people over age 65, most people are not having A1c tests done per recommendations by ADA, by NCQA, or by any other reasonable standard or measure that's out there.

There are some rather significant impediments that exist that are preventing people in the Medicare program to take care of themselves and my hope is that in the future that this committee will address those impediments and make some recommendations both to Congress, to the Secretary of HHS, and to others in the community about what we can do collectively to help those

00268

folks. Because if we don't, based on the data that just came out from CDC this week that we are going to have 40 million people living with type 2 diabetes within our lifetime in America, we're going to have a rather substantial problem in the Medicare program. This is not just about one benefit, this is about continuity of care for people with diabetes. And with that, I will turn the microphone back over, and I would hope that the research would examine what those folks need over the days ahead. Thanks.

DR. PHURROUGH: Question. For our type 2 older Medicare population, what questions do you think are left to be answered, what do we need to encourage from our viewpoint from the diabetic community? We voted on some things, I don't know what all the answers to those were, but what should we be focusing on in our operation?

DR. HAYWARD: Just in terms of the last questions, I strongly encourage those people interested in continuous glucose monitoring to select cohorts of older patients who are the most likely to benefit, and demonstrate it. These are really dramatic improvements. You don't need a big study. We're not talking about asking for,

00269

you know, $15 million studies. If you look at

brittle older type 2 diabetics, if this adds information, it should be fairly easy to demonstrate that in a clinical trial, and I can do the power calculation for people.
But although it may seem logical that more information does good, we know from lots of industries that more information can do harm. If you monitor INRs too frequently, you will make worse decisions than if you monitor them less frequently; you can overcorrect. You give fighter pilots too much information, they make worse decisions and can make a lot of mistakes in combat. These things that seem logical are not always logical.
If these are beneficial, do those studies, select your patients better, and, you know, I'm all for it. I have a nephew with type 1 diabetes; one of my closest colleagues, Will Manning, has type 1 diabetes; we've written half these papers together. You know, my father, my grandmother and two of my sisters have diabetes. But I think we underestimate how much you can do harm from untested anecdotal evidence. And we've done it many times in medicine, you know, from

00270

hormone replacement therapy to Vioxx, where everyone was sure that it was malpractice not to do that. So do the studies, and we just do not have any high quality evidence now.
DR. RUCKER: I think if you look at the numbers that I think Gayle cited on the cardiac things, the big issues to me for Medicare, the core, it sounds like they answered sort of the monster questions that had to do with cardiac disease, how much of it has to do with blood sugar control, how much is done by blood pressure or lipid control. And I think one of the big issues is just to factor the timetable, having that information, into these decisions about type 2, because it looks, just from reading and doing the math, that's the biggest point of impact in terms of life years.
DR. KRIST: I was going to make a similar comment, and that is with all the studies going on right now, I think they're going to be very helpful, I think cardiovascular disease seems to be a big area we have to look into, and tied in with that, we should take a look at opportunity costs. So when there's an older diabetic type 2, is there an opportunity cost to lower his A1c's

00271

along with hypertension and other things, so this is something we should look at as well.
DR. BLACK: We've talked a lot about the need for clinical trials, but I think there

are also some questions that would be in our interest to learn just from descriptive studies. I was impressed by the results of, the preliminary results we saw from the VA diabetes trial and what seems to be their sense of keeping A1c's in what I think most people would say is a very good target range, so maybe some descriptive studies of what is it taking, you know, what medications, what severity, what level of monitoring. Again, I think the idea that it isn't just testing but how it's used, and it's a team approach, so sharing information about how close was that study to actually attaining good control of diabetes, and what is the role of self-monitoring blood glucose in achieving those target ranges.
SPEAKER: Since the ACCORD trial has been brought up, what CMS might do is think about helping the ACCORD trial to look at continuous glucose monitoring in that population, because it actually is a perfect study. There is a group that's intensively trying to get these very good

00272

controls, and some are making it and others aren't, or having difficulty running up against hypoglycemia or not achieving goal. Could this therapy actually improve those patients' ability to get there, and although the studies have already been done, this may add another element, but it may be a very good way to look at this.
SPEAKER: I wanted to underscore what Rod Hayward said. I think the issue of (inaudible) beyond the capability of someone comprehending, it is highly likely that the new technology will spawn certain solutions which will cause errors just by the complexity or the way in which they come to fruition, and there may be winners and losers, and not all the products that are being proposed will probably be ones that achieve long-term preference.
Having said that, I'm reminded of the fact that the reason why we don't have a DCCT for type 2 diabetes to my understanding was primarily the cost, the estimate was that the proposed expense was something a little bit too much for NIH to deal with. And that is actually one of the reasons why a lot of the data that ultimately used and not necessarily from RCTs, the staggering cost

00273

of doing multiple studies, resulted in mixed populations. There is, it would be unfortunate here if the payment issues kind of stood the science on its head.
And the last thing I wanted to comment on is that we had made a decision when we started our study, which I shared some data on, that given

that the information suggested that a multiple target approach was more likely to be effective, we were willing to sacrifice the fact that we couldn't figure out which was more important, whether it be hypertension control or cholesterol control or sustenance management, or glucose control, but doing them simultaneously, although not comprehensive, was appropriate. And it may be a less important question as to whether hypertension is more important than glucose, and it may well be in many groups, and whether or not we can get the best possible outcomes for patients.

DR. PHURROUGH: All right. Well, I think we've had some good discussion on that. I appreciate your input. Panel, any last comments before we let you head your way?

(Negative response.)

00274

DR. PHURROUGH: Thank you very much for your attendance and your input and spending the time reading the vast amount of work that's here. Thank you to the audience, those who presented and attended, and you can look at our web site sometime tomorrow for all the results. Thank you very much.

(Whereupon, the committee adjourned at 3:09 p.m.)