

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

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

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

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

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

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

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

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1 indeed were so variable.
2 There was a second systematic review
3 published in 2000 by Coster, in which he found no
4 significant difference between groups. They
5 compared blood glucose self-monitoring or urine
6 self-monitoring with no self-monitoring, and also
7 compared blood glucose self-monitoring to urine
8 self-monitoring.
9 Now there were two more recently
10 published systematic reviews which Dr. Karter just
11 alluded to, one by Sarol in 2005 and one by
12 Welschen, also in 2005. Both those systematic
13 reviews did find a significant difference between
14 groups.
15 I would caution that the major
16 difference between the earlier systematic reviews
17 and the more recent systematic reviews was the
18 publication of what were probably to date the two
19 largest randomized controlled trials, those by
20 Schwedes and Guerci, and both of those studies
21 found significant differences and may have helped
22 Sarol and Welschen in the more recent systematic
23 reviews.
24 So DiGEM, which as I said, is a study
25 evaluating blood glucose self-monitoring in

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

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

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1 blood glucose self-monitoring from the general
2 self-monitoring behaviors used in type 2 diabetes.
3 Again, potential mediators which may
4 actually result in the proved outcomes aren't
5 clear. Is it simply the result of using blood
6 glucose self-monitoring that results in better
7 outcomes? Does the use of blood glucose
8 self-monitoring change the way the patients
9 perceive their diabetes? Does it change the way
10 they approach the control of diabetes, or any
11 interventions that could conceivably affect their
12 overall outcomes?
13 And then lastly, there is a potential
14 bias in the type of analysis used. In the two
15 positive studies, the one by Schwedes and Guerci,
16 they actually report with an intention to treat
17 analysis. And in the study by Schwedes, which was
18 the largest study to date, can actually show a
19 positive result even with analysis with a modified
20 intention to treat. They had a very high dropout
21 rate, as Dr. Koller indicated, greater than 40
22 percent, and their final analysis is only based on
23 the people who had remained in the study for at
24 least two months. So it technically wasn't an
25 intention to treat analysis.

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1 DiGEM is a multicenter trial currently
2 being conducted in the United Kingdom. Patients
3 are being enrolled from both Oxfordshire and
4 Sheffield. The primary trial objective is to
5 establish the effect of blood glucose
6 self-monitoring, either alone or as a means
7 combined with other self-monitoring behaviors, as
8 a means to encourage self-monitoring behavior, as
9 to whether or not there is an effect on HbA1c
10 after one year.
11 There are also several secondary trial
12 objectives, comparing treatment satisfaction,
13 well-being, health service use, self-management
14 behaviors, hypoglycemia, and beliefs about
15 diabetes across type boundaries. We're also going
16 to be looking at several subgroup comparisons. We
17 will be dividing our study population on the basis
18 of age, duration of diabetes, and baseline HbA1c,
19 to see whether or not any of these features affect

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

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

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

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

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

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

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1 psychological theory. And also, hopefully by
2 using the type of intervention we have, we hope to
3 be able to examine whether or not we could
4 effectively and potentially use blood glucose
5 self-monitoring as a treatment for glycemic
6 control.
7 We're going to hear presentations about
8 the advantage to diabetics and their beliefs about
9 the effects of their behaviors are on their
10 glycemic control at the beginning and at the end
11 of the study. So what we will hopefully determine
12 is whether or not the changes occurred, and if the
13 changes did occur, was that a result of the
14 changes in behavior. And we will also be doing an
15 intention to treat analysis with regard to the
16 study.
17 So with regard to the current status of
18 DiGEM, recruitment was carried out between 2003
19 and 2005. We recruited 453 patients, we are now
20 developing treatment targets, and we expect to
21 report our data probably midway through next year.
22 The study was actually funded by the
23 Health Technologies Assessment program of the
24 National Health Service of the United Kingdom, and
25 the blood glucose meters used in the study were

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1 provided by MediSense.
2 And I would just like to thank our
3 other study investigators, Dr. Andrew Farmer,
4 Professor Andrew Neil, Professor Rury Holman,
5 Professor David Mant, Ms. Sue Ziebland, Professor
6 Alistair Gray, Dr. Pat Yudkin, Professor Ann Marie
7 Kinmonth, and Dr. David French. Thank you.
8 DR. GARBER: Thank you very much. Next
9 will be Mayer Davidson.
10 DR. DAVIDSON: I'm Mayer Davidson. I
11 have no conflict of interest. And the first slide
12 I would show you, the primary area selected was
13 Seeking Diabetes Control, the use and abuse of
14 self-glucose monitoring. And what I might do, if
15 you can't find it, I brought it on a stick. Would
16 that be helpful? Let me go get that just in case.
17 (Pause.)
18 Here is the first slide. Now Dr.
19 Koller also talked about the relationship between
20 control of glycemia and microvascular disease, so
21 we're going to start with that as soon as it comes
22 up. Now the first slide after the opening slide
23 just states that the ADA goals of A1c are, or is
24 less than seven percent, and that's based on --
25 here it is.

00079

1 This is the relationship between

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

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1 look at Alc's, you have to look down here, and
2 again, this is the development of
3 microalbuminuria; patients at the beginning did
4 not have microalbuminuria, so what was their
5 chance of developing it. If you had an Alc in
6 this case that was less than eight, almost no
7 chance, but once you got over eight, the
8 development of microalbuminuria really took off.
9 This is the same data but looking at
10 patients starting out with microalbuminuria, what
11 were the chances of them going on to clinical
12 proteinuria, and this clear curve that you can
13 barely see is the result. And again, with an Alc
14 between six and seven, there is no development of
15 microalbuminuria to clinical proteinuria, seven to
16 eight a little bit, and really taking off above
17 eight.
18 Type 2 diabetes, you have the Kumamoto
19 study which is patterned after the DCCT.
20 Retinopathy, nephropathy, again, between six and
21 seven, no development of these complications or
22 progressions, over eight really taking off.
23 And finally, another study from Tanaka.
24 This is a little different. This is the
25 cumulative incidence, but it's the chance of

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

5 it really takes off.
6 So that's the relationship between
7 microvascular disease and Alc.
8 Now let's take a little different look
9 at the relationship between glycemia and
10 macrovascular disease. It's been known for a long
11 time that there's an association between glucose
12 levels and the development of CAD.
13 This is one of the earlier studies, the
14 Honolulu study, and over here we have fatal
15 coronary artery disease and total coronary artery
16 disease. This is the post-challenge glucose, so
17 this is the two-hour glucose tolerance test, and
18 the value of 40 to 114, the red, and the 115 to
19 133 stay in the normal range; 134 to 156 is
20 starting to get up into the ICT, but you can see
21 that even within normal ranges there are increases
22 in CAD, or coronary artery disease.
23 This is a metaanalysis looking at
24 95,000-plus patients and this is the relative rate
25 of getting CAD. This is the fasting glucose here,

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1 this is the two-hour glucose. This is normal so
2 for us Yankees, we have to convert this. This is
3 about 90, this is about 108, seven I think is
4 about 126, and you can see that there's an
5 increase after you get up into what we used to
6 call the normal range. Here's the values, it's
7 108 here, this is about 140. So the point is that
8 there's an increase in CVD in the normal range.
9 That's shown really well in this study.
10 This is actually called the EPIC study, this was a
11 cancer study, but they looked at the development
12 of myocardial infarction over a three-year period
13 in 4,662 men. They took as their baseline those
14 with Alc's less than five, and then they went up.
15 When you go to a baseline value between 5.0 and
16 5.4, there's a 250 percent increase in the
17 percentage chance of getting a heart attack, and
18 it goes up progressively from there. Since this
19 study was published, there's been another study
20 that show the same thing looking at 4.6 as the
21 baseline. The point is that within certainly the
22 normal range of glycemia, there are increases in
23 primary artery disease.
24 Now it's important to point out that
25 the changes of glucose that were shown on the

00083

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

8 Now in terms of lowering glycemia, as
9 has been pointed out in some of these studies,
10 there is no evidence in type 2 diabetes that a
11 lowering glycemia is beneficial, or has beneficial
12 effect on coronary artery disease, and there's two
13 metaanalyses where reviewers have said that. Now
14 having said that, type 1 diabetes (inaudible) and
15 initially as Dr. Koller has pointed out, in DCCT
16 there was not enough coronary artery disease to be
17 statistically significant, but the EDIC study has
18 shown that may not be true.
19 Now the EDIC study, what happened is as
20 follows. After DCCT ran out, they built extra
21 funding for EDIC, and they predefined their CVD
22 outcomes as non-fatal MI, stroke, death from CVD,
23 confirmed angina, or coronary revascularization,
24 and the results were published eight or nine
25 months ago.

00084

1 This slide shows you that once the DCCT
2 stopped, we all know that the average Alc was
3 about seven percent in the intensively treated
4 group, and it stayed at about nine percent in the
5 control group. After the DCCT, there was a
6 convergence of the Alc levels, and so in six
7 months they were almost equal; certainly by here,
8 at two years they were equal, seven percent went
9 up to about eight, and nine percent went down to
10 about eight, and so for most of this period of
11 time, the Alc was no different than when it
12 started.
13 This is the cardiovascular incidence
14 from the beginning of EDIC and as I mentioned,
15 that was the end of the DCCT, and as you can see,
16 there is a divergence here with the intensively
17 treated patients here and the control patients in
18 the DCCT being here. The hemoglobin Alc's are not
19 different but there is a difference in the
20 incidence of cardiovascular disease. Now if you
21 look at this from the beginning of the DCCT, you
22 start to see the divergence maybe around 10, 11,
23 12 years, and at least statistical significance
24 here maybe at 15 to 20 years later after the
25 beginning of the DCCT.

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1 So now we turn to SMBG. This is a
2 slide that shows the rate of SMBG in type 1
3 patients and their Alcs. It's over a 21-day
4 period, and these are the number of SMBG's through
5 21 days and here's the Alc, and you can see a very
6 nice inverse relationship here.
7 A study was done, and this is just one
8 study, but there's been several like it, it was a
9 study done of type 2 patients, I think it was only
10 type 2, though it could have included some type 1,

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

00086

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

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

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

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1 percentage change, but there was no difference
2 among the groups.
3 Another randomized clinical trial,
4 smaller in number, baseline is very well defined
5 in both patients, and they both came down about
6 two percent, so obviously there was no difference
7 between the two groups.
8 Dr. Muchmore did one, again, small
9 numbers, and he had a baseline of 8.8 to 9.6.
10 There was a difference in their absolute change,
11 1.5 to 1.8, although they were not statistically
12 significant, probably because it was underpowered,
13 but again, the groups were not treated equally.
14 The patients who got SMBG were given extra dietary
15 help, they were taught carbohydrate counting and
16 they kept a food diary, and they went back and saw
17 their providers, whereas with the control
18 patients, none of that occurred.
19 And this study has also been mentioned,
20 by Dr. Schwedes. Higher numbers, the baseline is
21 comparable, and there was a two times higher
22 decrease in the SMBG group than the control group.
23 But again, the patients who got SMBG received
24 special dietary counseling, so again, you cannot
25 say that this is just due to the SMBG.

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

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

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1 take those numbers and he would use those to do a
2 nutritional counseling with the patients. The
3 patients who were not on SMBG were just getting
4 nutritional counseling. Here you see, there were
5 43 and 45 in each group, the number of visits to
6 the dietitian were no different in these two
7 groups, the baselines were comparable, and the
8 change was not statistically different, it went
9 down .8 in this group, the SMBG group, and coming
10 down .6 in the group that did not receive SMBG.
11 Now these 43 or 45 patients that took
12 SMBG were just a small group in the number of
13 patients that this nurse treated. We had 367
14 patients that she treated. On the year prior to
15 coming to see us in the nurse director care group,
16 their Alc was typically about 8.8. When they
17 finished that year, they were at about 8.6. They
18 didn't change much in the standard care. When she
19 was finished with them after one year, the average
20 Alc was down to 7.0 and their median came down to
21 6.7.
22 Now only 22 percent of those patients
23 were on insulin, all the rest of them were on
24 pills and so most of them, of course, did not have
25 SMBG, and therefore, I'm showing you here that you

00091

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

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

00092

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

00093

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

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

00094

1 the DCCT. It's obvious that the lower the A1c is,
2 the more likely you are to get hypoglycemia, and
3 that's what this shows, but notice here in type 1
4 patients, when you're at 20, 30, 40, 50
5 hypoglycemic events per patient year, and here's
6 the same study done in type 2 patients and here
7 we're at the nine, 10, 11, so there is at least a
8 five-fold difference in hypoglycemia.
9 And finally, there's information that
10 may be helpful for the panel's discussion later
11 on. It makes a difference at when the patient is
12 diagnosed to have diabetes. The age of diagnosis
13 is here, this is the duration of life after
14 diabetes, or after the diagnosis for male and
15 female. So if diagnosis age is 60, you are still
16 going to have on average 15 more years to live,
17 and if you're a female, you're going to have about
18 17 more years left. And a study that's coming out
19 in Diabetes Care in November shows you that there
20 is a difference. If you're over 65 and you had
21 diabetes diagnosed between 40 and 64, or if you're
22 over 65 with diabetes and you had the diabetes
23 diagnosed after the age of 65, there is no
24 difference in the coronary artery disease rates
25 but there's a tremendous difference in the

00095

1 microvascular disease. So the point I would make
2 here is that if a patient is diagnosed at 60 and
3 they've got 15 more years left, they have a lot of
4 time to get microvascular disease and
5 consequently, monitoring is important. Thank you
6 very much.
7 DR. GARBBER: Thank you very much. The
8 next speaker will be Dr. Denise Simons-Morton from
9 NIH.
10 DR. SIMONS-MORTON: I was nervous about
11 actually finding my slides. I am happy to present
12 ACCORD, The Action to Control Cardiovascular Risk
13 in Diabetes trial. I will be presenting the
14 design of the study because we have no data yet
15 for the study, the study is still ongoing. I have
16 no conflicts to report; however, I'm going to show
17 a slide that shows the contributors and
18 collaborators on this study.
19 We've heard some background, just one
20 slide on background, about 17 million people in
21 the U.S., or six percent of the population have
22 diabetes. The vast majority of those are type 2
23 diabetes. And as previously stated, diabetes
24 increases the risk of cardiovascular disease,
25 double to quadruple compared to people who don't

00096

1 have diabetes, and that cardiovascular disease is
2 the leading cause of death in diabetes.
3 You also saw some data that glycemia
4 level is directly associated with cardiovascular
5 disease rates in observational studies, and that's
6 even down to within the normal range. There is
7 some evidence from experimental randomized
8 controlled trials that reducing glycemia will
9 reduce CVD, but the evidence is borderline at
10 best, and the studies are inconsistent with each
11 other in terms of the findings. It's a very
12 important question. We also know that
13 hypertension and dyslipidemia are more common in
14 diabetic persons. However, optimal treatments for
15 these cardiovascular disease risk factors are
16 unknown, in diabetes as well as in non-diabetes,
17 as a matter of fact.
18 So, we designed ACCORD to test three
19 separate research questions addressing strategies
20 to reduce cardiovascular disease in diabetic
21 patients, a glycemia strategy, a blood pressure
22 strategy, and a blood lipids/lipoproteins
23 strategy. It's a multicenter randomized clinical
24 trial which includes 10,251 patients with type 2
25 diabetes who are at high risk for cardiovascular

00097

1 disease events.
2 Here are the eligibility criteria.
3 They had to have had stable type 2 diabetes for at
4 least three months. They had to have Alc ranges
5 which varied depending on whether they were on
6 more or less treatment; if they were on less
7 treatment, it could go up to 11 percent; if they
8 were on more treatment, it could go only to nine
9 percent, and so that depended on how many oral
10 agents and whether they were on insulin. So the
11 bottom range was 7.5 percent because we didn't
12 want to recruit anybody into the study, randomize
13 them into the standard control group, and have
14 their Alc get worse.
15 They had to be at high risk of
16 cardiovascular disease, either they had clinical
17 disease, for example had an MI in the past, or had
18 subclinical disease, for example as measured by
19 events, or they have two or more additional risk
20 factors like hypertension, dyslipidemia or
21 obesity. Regarding age, they could be 40 years or
22 older if they had cardiovascular disease history,
23 55 or older otherwise, if they didn't actually
24 have clinical cardiovascular disease. As we can
25 see from the baseline data, the mean age is in the

00098

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

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

00099

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

00100

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

5 Everybody is either in the intensive glycemc
6 control with the less than six target, or in the
7 standard glycemc control with Alc's in the
8 sevens, and that's 5,000 people in the intensive,
9 approximately, and 5,000 in the standard. The
10 outcomes in these two groups will be compared for
11 the primary analysis.
12 They also have to be in the blood
13 pressure or the lipid trial. If they are in the
14 blood pressure trial, they are randomly assigned
15 if their tested systolic blood pressure is below
16 120, versus standard. We have about 2,400 people
17 in each of those groups and the primary analysis
18 will be comparing the outcomes in those two
19 groups.
20 The lipids, they get fibrate plus
21 stain, or placebo plus statin, and there are about
22 2,800 people in each of the randomized arms of the
23 lipid trial.
24 The blood pressure and glycemia are
25 open labeled treatments, but there's people who,

00101

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

00102

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

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

00103

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

00104

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

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

00105

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

00106

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

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

00107

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

00108

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

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

00109

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

00110

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

20 alone, and then lower cholesterol was minuscule.
21 Okay, what's the truth?
22 That's a repeat of the other statement.
23 Metaanalysis. Lowering blood pressure requires
24 157 patient years needed to treat to be effective
25 in reducing cardiovascular events. Cholesterol,

00111

1 106, and glucose was not significant. So we have
2 the ADC completely backward to what is the most
3 important; cholesterol was the most important
4 here, blood pressure was the next most important
5 of the things looked at, and glucose, we just
6 don't know, period.
7 But what is the most important thing
8 for us to know about type 2 diabetes? What kills
9 most people with type 2 diabetes is vascular
10 disease, specifically heart disease, strokes, that
11 sort of thing. Here's the relative risk, lifetime
12 risk. End stage renal disease with age of onset
13 of 55, with a terrible Alc, the risk is down here.
14 The risk of cardiovascular death is up here, and
15 that's what we don't know yet.
16 We saw most of this data earlier, so I
17 will just briefly mention one thing, and that is
18 it really does make a difference when someone gets
19 the diagnosis of diabetes, not gets diabetes, it's
20 when they get the diagnosis of diabetes, the age
21 of that makes a big difference in lifetime risks.
22 You've heard about epidemiological
23 studies, so I'm sure that there is an association
24 between glucose and the cardiovascular problems,
25 and sometimes when you look at all of them, it's

00112

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

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

00113

1 really not very impressive in terms of their own
2 data in terms of cardiovascular events.
3 And you heard about the EDIC so I'm not
4 going to go through that group of slides either.
5 There is one that I promised that I
6 would mention, the Steno trial did show effect on
7 cardiovascular disease, cardiovascular events, but
8 it was probably, or may have been due to other
9 things that they were controlling. A fairly
10 good-sized study, fairly decent duration. They
11 looked at conventional treatment of glucose, blood
12 pressure and lipids to goal, and they found that
13 there was a 53 percent decrease in cardiovascular
14 risk, but intensive patients at goal for the three
15 things they were trying to treat, only 15 percent
16 had glucose goals met, 45 systolic blood pressure,
17 79 diastolic blood pressure, and total
18 cholesterol, even higher. So what really causes
19 the 53 percent decrease, we don't know.
20 One thing that is relevant, the UKPDS
21 also looked at blood pressure and the effect of
22 blood pressure control or treatment, it's
23 certainly not control. The blood pressure, if I
24 recall correctly, is 144 over 82 versus 154 over
25 87, but that little bit of control in blood

00114

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

00115

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

00116

1 have to use the same thing in both arms. Again,
2 optimize lipid and blood pressure treatments so
3 they are equal in both arms.
4 The enrollment information, duration of
5 diabetes 11.5 years, age 60, so they are now over
6 65 obviously, and they're obese, and a particular
7 reference to smoking, so I assume this means I
8 need to quit. One thing we were really concerned
9 about was this occurred in the UKPDS, after
10 initial control it was lost in the intensive
11 group, and it continued to rise in the standard
12 group, parallel really, so we did not want that
13 happening, so we did this to our control and we
14 have done pretty well.
15 Our goal was between eight and nine for
16 the standard, for reasons, some of which has been
17 mentioned earlier, and as low as we can get them
18 for the tough group in the intensive. We're now
19 running about six or seven in this group and the
20 control may be decreasing a little bit.
21 And I wanted to do this for a second.
22 Blood pressure control is exactly the same in both
23 groups. It started out pretty doggone good over
24 the three groups of patients, 131 over 77. And
25 over three years, this was the data we had

00117

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

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

00118

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

00119

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

5 macrovascular, health-related quality of life, I
6 think most people would agree with that statement,
7 but I would also suggest that people with diabetes
8 need better tools to achieve better control.
9 The DCCT was reported and published in
10 1993, and it's almost embarrassing when we look at
11 our type 1 population right now to see how far we
12 have come, or actually how far we haven't come,
13 when we see that somewhere between a quarter and a
14 third of patients with type 1 diabetes in the
15 United States are still on twice daily insulin.
16 Intensive management improves diabetes
17 outcomes. A1c is, as you have heard, a validated
18 surrogate for diabetes complications. Intensively
19 managed patients have a lower risk of developing
20 complications than patients on conventional
21 therapy who achieve equal A1c levels. Now this is
22 somewhat of a controversial statement but we can
23 talk about more about this later. Intensive
24 management requires frequent monitoring of blood
25 glucose levels, particularly in people on insulin.

00120

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

00121

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

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

00122

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

00123

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

11 far as glucose levels are concerned, is to avoid
12 severe hypoglycemia.
13 We downloaded this for everybody, and
14 this is what he looked like. And for this fellow
15 to be successful, even when the average is, he has
16 tremendous glycemc variability but he is able to
17 avoid hypoglycemia with his gastroparesis because
18 he is now intentionally keeping his blood sugars
19 as high as he can.
20 So let's think about this for a moment.
21 People with diabetes make up a significant portion
22 of those with end stage renal disease. In fact,
23 the incidence report of end stage renal disease by
24 primary diagnosis, for all the diabetes, it's over
25 200,000 cases, 10 percent are type 1 patients with

00124

1 a median age of 47 years, 90 percent are type 2
2 patients with a median age of 65 years, and almost
3 a quarter die in their first year. Sobering
4 statistics, and yet, 44.5 percent of all end stage
5 renal disease in the United States is from
6 diabetic nephropathy.
7 When you look at, these are incident
8 counts and adjusted rates by primary diagnosis,
9 what's fascinating is going all the way back to
10 1980 when you see the different etiologies of end
11 stage renal disease, there aren't a lot of
12 differences back in 1980. But as one goes through
13 the years and the decades, one can see that the
14 slope of the curve and the number of these
15 diagnoses continue to increase. Diabetes is far
16 outleading the pack and that's why it is such a
17 huge public health problem today.
18 Now what studies in end stage renal
19 disease patients illustrate the importance of
20 glucose control? Most of the data when one goes
21 looking at diabetic kidney disease and glucose
22 control is dealing with the (inaudible) stage, not
23 people with advanced nephropathy or in end stage
24 renal disease.
25 This is a recent study that was just

00125

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

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

00126

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

00127

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

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

00128

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

00129

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

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

00130

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

00131

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

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

00132

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

00133

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

00134

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

00135

1 significant source of morbidity in adults who have
2 diabetes at all. Dr. Hirsch referred to somebody
3 driving a car with a blood sugar of 40, that's
4 obviously very risky. However, elderly people are
5 at an increased risk of hypoglycemic events, and
6 unfortunately elderly people have a reduced
7 awareness of hypoglycemia, so that can be a
8 further counter-balance and further obstacle to
9 getting to your glycemic target because they don't
10 sense their blood sugar dropping.
11 We also think of glycemic variability,
12 because one thing that people were doing who were
13 trying to avoid hypoglycemia or trying to get as
14 close to target as close as possible, and Dr. Bode
15 showed that both people with type 1 and with type
16 2 experience tremendous variability in their
17 day-to-day lives, and these were people who were
18 monitoring their blood sugar quite intensively, up
19 to nine times a day.
20 So it's impressive that when we think
21 about a single point measurement and where we need
22 to go, and all of us argue that we need to go to a
23 target as well, even with very intensive
24 management, it is very difficult to get at the
25 target levels of glycemic level, and people with

00136

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

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

00137

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

00138

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

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

00139

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

00140

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

8 we need to bring these technologies to all people
9 with diabetes, young and old, and we need to do
10 more research. What we are looking for from this
11 panel and others is feedback on what are the
12 important outcome measures and how do we fund the
13 best studies to demonstrate these types of
14 outcomes. We are looking to fund studies in older
15 people, randomized studies, looking at not only
16 Alc and hypoglycemia, but looking at other
17 important aspects, and looking at the economic
18 impact of that. We know that diabetes is a major
19 economic drain on CMS. And those are my
20 presentations, thank you.

21 DR. GARBER: Thank you. We will now
22 turn to the scheduled public presenters, and first
23 up is Kevin Peterson. For this segment, each
24 presenter has exactly six minutes to speak. Is
25 Dr. Peterson here? And if Dr. Walter will be

00141

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

00142

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

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

00143

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

00144

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

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

00145

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

00146

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

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

00147

1 from Medtronic for studies related to CGM.
2 To give you some background, I'm based
3 at the Joslin Diabetes Center in Boston. Our
4 clinic population includes 592 patients with type
5 1 diabetes who are covered by Medicare, so we do
6 have considerable experience with some of the
7 clinical issues that these patients grapple with.
8 And the issue that I'm going to raise here, that
9 even though these patients generally aren't on the
10 radar screen in terms of most Medicare coverage
11 decisions, they have specific needs that need to
12 be addressed and managed in your decisions.
13 In the course of my clinical
14 activities, I have been involved in a trial
15 involving CGM, so I have an appreciation of some
16 of the clinical utility that one can get from this
17 technology. To give you some background on some
18 of the specific challenges one faces with type 1
19 diabetes patients who are elderly, one of the main
20 issues that these people grapple with and
21 particularly as they get older is, more
22 significant than others, is hypoglycemia, which
23 obviously in this population, you have a lot of
24 significant other burdens.
25 And what's clear from some studies is

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

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

00149

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

00150

1 hypoglycemia.
2 The issue here is that because these
3 people recognize the value of staying at a level
4 that's much closer to the level (inaudible).
5 So I think the issue here, as pointed
6 out in some of the other speakers, is that the
7 data that is accumulating certainly indicates that
8 CGM shows promise in showing reductions in
9 duration of hypoglycemia for patients in that
10 range. I have seen only one study which actually
11 addressed individuals who covered into the
12 Medicare population group, but I think clearly
13 based on this evidence, there is the need for
14 research studies to address the issue for elderly
15 patients with type 1 diabetes. My hope is that if
16 the data does show a comparative benefit, that my
17 patients will be able to get CGM, and I thank you
18 for considering this issue. Those are my
19 comments. Thank you very much.
20 DR. GARBER: Thank you very much.
21 Next, Dr. Richard Bergenstal.
22 DR. BERGENSTAL: Good morning, rapidly

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

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1 multispecialty clinic with 300 primary care
2 physicians, so we have a lot of experience working
3 with primary care, and our center has done studies
4 with Abbott, Lifescan, Roche, DexCom, and
5 Medtronic, and so I'm heavily conflicted but not
6 biased, the only bias being what's actually best
7 for the patients we take care of with type 1 and
8 type 2 diabetes.
9 We're convinced that the evolving
10 models must include some sort of team care and
11 that the patients with diabetes have to be
12 educated and use, in this case the glucose
13 monitoring data, or the data that we're getting is
14 not terribly helpful. So one should look at that
15 in some way to link the use of monitoring to
16 actual education about the data and putting it in
17 perspective. You have seen plenty of the data by
18 this point in the morning.
19 Our center is one of the few that did
20 both the DCCT and is now doing the ACCORD trial,
21 and we would love the ACCORD trial to look like
22 the DCCT in terms of separation that would move
23 both curves down about two percent, and that's
24 what our goal is in that study, and we're learning
25 a lot. And we learned that there is hypoglycemia

00152

1 in Type 2 when you start to get to an Alc of six
2 percent. If you want to have an Alc of eight
3 percent, or 8.5, don't bother to monitor at all.
4 If you want to get to an Alc near normal, glucose
5 monitoring appears to be essential, as it was in
6 the DCCT, that study was about monitoring and
7 feedback and we believe that ACCORD will be
8 similar, and we believe that was partly what did
9 not happen in UKPDS enough, was the monitoring and
10 the feedback, and aggressive adjustment of
11 medications.
12 So the Alc, as our excellent presenters
13 have said, the glucose control is much more than
14 an Alc, and we await more definitive data, but are
15 pretty convinced at this point that the red curve
16 is much more detrimental than the green, even
17 though the Alc may be similar. You will not know
18 this without either frequent point monitoring or
19 better yet, continuous glucose monitoring, and you
20 have heard the references.
21 We're not doing a very good job, as
22 we've heard to date, and some very recent data
23 says maybe we're coming up to the 50-50 point, but
24 that's just an Alc less than seven, as has been
25 pointed out. I'm convinced that we need better

00153

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

00154

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

00155

1 I'll spend just the remaining minute on

2 looking at an algorithm, not saying that a
3 specific one may be better than another, but just
4 saying it's all about moving, and moving means by
5 nine months you should either be on insulin or
6 less than seven, but you are only going to move if
7 you have data to respond to. And people, I would
8 agree, on diet therapy alone, maybe they don't
9 need to monitor after six months, but if you look
10 at the current ADA guidelines, there is no such
11 patient. You are started on that form on the day
12 you're diagnosed, so all patients should be doing
13 some monitoring.
14 And the other thing I would just throw
15 out to the panel is, there is probably more of a
16 difference between type 1 and type 2 than what I
17 believe is the middle ground, to say more type 2
18 is trying to get specific, you've had it for 10 or
19 15 years, and it acts a lot more like type 1 in
20 terms of needing basal bolus, intensive insulin
21 therapy, they don't have quite as much
22 hypoglycemia. But when you're trying for an Alc
23 of less than six or near normal, monitoring is
24 critical, and we look forward to testing some of
25 these concepts in the ACCORD trial to really

00156

1 verify that. Thank you.
2 DR. GARBER: Thank you. Dr. Clark.
3 DR. CLARK: I'm Dr. Nathaniel Clark,
4 I'm the vice president for clinical affairs and
5 new strategies for the American Diabetes
6 Association. The American Diabetes Association
7 would like to comment briefly on the three
8 questions that are covered in the published
9 questions for this committee meeting.
10 Question 1: What is the relationship
11 between increased glycemic control and the
12 reduction in microvascular or macrovascular
13 complications? The two major studies which are
14 generally used as evidence of this relationship
15 are the DCCT and the UKPDS, as you've heard this
16 morning. Both of these trials produced
17 unequivocal evidence that there was improvement in
18 glycemic control and resulted in statistically and
19 clinically significant reduction in microvascular
20 complications. Neither of these trials produced
21 specific data regarding those over the age of 65.
22 While the original data from the DCCT
23 only suggested there was a relationship in regard
24 to macrovascular disease, as was pointed out, the
25 (inaudible) has now produced quite convincing

00157

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

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

13 In setting specific goals for glycemc
14 control as measured by Alc levels, the ADA
15 suggests that the patient's Alc goals need to be
16 individualized and a number of factors be
17 considered, including the age of the patient, the
18 clinical status of the patient, and the patient's
19 history of hypoglycemia.

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

00158

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

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

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

00159

1 that's utilized to determine if the patient is
2 achieving glycemc targets is the use of the Alc
3 with regularly scheduled visits, there is the
4 potential that getting the person to target will
5 take an excessive period of time and all the
6 potential risks of poorly controlled glucose
7 levels will persist too long.

8 Next on the continuum would be a
9 patient with type 2 diabetes on insulin alone. In
10 this group, again, Question 1 is predominant,
11 although if a patient is on an oral medication
12 with a tendency towards hypoglycemia, Question 3
13 would also be operative.
14 Next on the continuum would be a
15 patient with type 2 diabetes on oral insulin, and
16 once or twice daily insulin. Again, in this
17 patient, Question 1 is predominant, although
18 Question 3 becomes a more important reason to
19 test.
20 Next on the continuum would be a
21 patient with type 1 diabetes on fixed doses of
22 insulin. In this patient, Questions 1 and 3 are
23 predominant.
24 The last two groups on the continuum
25 would be the patient with type 1 or type 2

00160

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

00161

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

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

00162

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

00163

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

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

00164

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

00165

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

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

00166

1 think it is reasonable that you have a coherent
2 and logical plan for the use of these devices. I
3 thank you very much.
4 DR. GARBER: Thank you. The next
5 speaker will be Paula Yutzy.
6 MS. YUTZY: Good morning. I am a
7 diabetes educator and I run the diabetes center
8 here at Mercy Medical Center in Baltimore. I am
9 also a consultant to (inaudible) and Abbott
10 Diabetes Care.
11 Members of the committee, I thank you
12 for the opportunity to testify before you. The
13 focus of this committee is sizable, and is of
14 personal interest and concern to me. I provide
15 care to hundreds of Medicare beneficiaries each
16 year here in Maryland. These are the only
17 patients that I manage who can consistently afford
18 to manage their diabetes by regular blood glucose
19 monitoring. They're my Medicare patients.
20 In the mid 1990s I dedicated many hours
21 to inform members of Congress, Speaker Newt
22 Gingrich, President Clinton, of the need for
23 Medicare to cover blood glucose monitoring for all
24 people with diabetes. It's extremely discouraging
25 that CMS has asked this committee to question the

00167

1 relevance of glucose control and its measurement
2 in the management of all types of diabetes. I now
3 fear, based on the questions CMS is asking us for,
4 that CMS contemplates turning back the clock and
5 taking blood glucose testing out of some, if not
6 all, of my patients' hands.
7 As a person with type 2 diabetes and as
8 a certified diabetes educator, and as someone who
9 is not that far from joining the Medicare program,
10 I applaud the committee's effort with respect to
11 its charge to identify where the current data is
12 deficient and where additional research is
13 warranted. There is no question that we need more
14 work to identify how best to control the raging
15 diabetic epidemic. CMS can help. However, the
16 overall tenor of the questions being explored
17 today is troubling.
18 It is not difficult to infer that some
19 of the questions published prior to today's

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

00168

1 disservice to the nearly seven million people with
2 Medicare who have diabetes. And because Medicare
3 is an important bellweather for the private sector
4 coverage, any move to reduce coverage could have a
5 chilling effect on people with diabetes with all
6 insurance coverage in the nation's health care
7 system.
8 Instead, I hope that the committee
9 questions were asked to help determine how to
10 optimize current coverage. The fact is diabetes
11 is one of, if not the single most self-managed
12 disease in existence. It will be troubling if the
13 committee suggests that self-management through
14 regular blood glucose monitoring and the use of
15 A1c is somehow inappropriate for any of the
16 Medicare population.
17 Let me give you an example. Everyone
18 understands driving. In order to drive safely and
19 avoid tickets, you have to be taught how to drive
20 and you have to learn the rules of the road -
21 diabetes education. You must have a speedometer -
22 blood glucose monitoring. And you have to know
23 how to use it. When you have diabetes, you no
24 longer have cruise control, you need to look at
25 the speedometer, look frequently to stay within

00169

1 the speed limit. As a person with type 2
2 diabetes, I frequently check before meals and
3 again two hours after meals to see exactly what
4 happens to my blood glucose as a result of the
5 food that I ate, and with that information I can
6 learn to make better choices.
7 Diabetes is a disease of choices, when
8 to take medications, when to do exercise, how much
9 exercise to do, when to eat, what to eat, how much
10 to eat. By checking the blood glucose several
11 times a day, I can make those choices that improve
12 my blood glucose control and that prevent the
13 complications for me in the future. But I'm a
14 certified diabetes educator. I know these things.
15 Patients who come to me have to learn them.
16 Diabetes education and blood glucose
17 monitoring are the most important tools in the
18 management of diabetes. It is my hope and a
19 strong recommendation that the committee will take
20 this opportunity to examine the substantial
21 impediments that exist related to patient
22 utilization of diabetes self-management training,

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

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1 are what prevent Medicare beneficiaries from
2 achieving the glycemic control that will block the
3 progression to complications.
4 It's true that diabetes outcomes are
5 not what they need to be. Our nation experiences
6 far too many preventable and controllable diabetes
7 complications like heart attacks, strokes,
8 blindness, amputation, and kidney disease. These
9 are complications that science has proven are
10 related directly to poor glycemic control. If
11 this committee puts forth any recommendation that
12 restricts methods to control or manage the blood
13 sugars of a person with diabetes, the incidence
14 and prevalence of these disastrous outcomes will
15 increase, the associated costs to the Medicare
16 system will prove staggering, and far exceed the
17 cost of preventing and controlling the
18 complications.
19 In closing, I would like to remind
20 members of this committee of the substantial
21 medical opinions supporting the use of blood
22 glucose monitoring as a necessary tool in the
23 control of diabetes that you've heard today. More
24 importantly, I want to remind the committee of the
25 statutory requirements on Medicare Part B, to

00171

1 cover blood testing for Medicare enrollees with
2 diabetes, without regard to whether the individual
3 has type 1 or type 2 diabetes or to the
4 individual's use of insulin. I strongly encourage
5 this committee to review the steps Medicare
6 programs should take to improve the outcomes of
7 the millions of Medicare seniors with diabetes and
8 pre-diabetes. Thank you very much for your time
9 and consideration.
10 DR. GARBER: Thank you. Next, John
11 Mastrotatoro.
12 DR. MASTROTATORO: Thank you, Alan. In
13 the interest of time, I will introduce myself as
14 John M. I'm a biomedical engineer by training
15 with 17 years of experience in developing
16 continuous glucose monitoring systems, and as an
17 employee of Medtronic I do have a conflict of
18 interest, since we currently have out for approval
19 several continuous monitoring systems which I will
20 be discussing. I'm also going to provide some
21 clinical evidence which demonstrates the utility
22 of continuous glucose monitoring systems in
23 improving diabetes management by reducing Alc and
24 also reducing hypoglycemia.
25 Shown here are three systems that have

00172

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

00173

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

00174

1 actions to correct those blood sugars, and

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

00175

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

00176

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

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

00177

1 daily injection patients using finger stick
2 testing to either maintain that therapy or move to
3 a sensor-augmented pump, and this trial is
4 scheduled to start very shortly.
5 DR. GARBER: Thank you.
6 DR. MASTROTATORO: In summary,
7 continuous glucose monitoring technology is
8 evolving. The early results are promising. Our
9 initial focus has been in type 1 diabetes patients
10 but type 2 patients requiring MDI also seem likely
11 to benefit, and significant research is ongoing to
12 determine the full implications of this technology
13 for patients with diabetes, including Medicare
14 beneficiaries. Thank you.
15 DR. GARBER: Thank you. Next, Steve
16 Edelman.
17 DR. EDELMAN: I would like to introduce
18 myself and then talk about my conflicts. I'm a
19 professor of medicine at the University of
20 California San Diego, I work for the Veterans
21 Healthcare System. I'm also a founder and
22 director of a patient organization called Taking
23 Control of Your Diabetes, and I've also lived with
24 diabetes since 1970. I'm not an expert in
25 everything, but I am qualified to talk about

00178

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

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

00179

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

00180

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

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

00181

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

00182

1 number and the slope of the line, and they were
2 two-thirds type 1, one-third insulin-required
3 type 2. And this was only a nine-day study. I
4 want to point out that for the first three days,
5 both groups were blinded, and the group that was
6 unblinded right here only saw data for six days,
7 and that's important when I show you the results
8 of this study. These patients just were
9 free-living patients doing their usual things.
10 So this was recently presented to the
11 American Diabetes Association, it was the first
12 randomized trial, and you can see that there was a
13 23 percent improvement in the blood sugar for the

14 240 to 400 grams, a 26 percent improvement in the
15 81 to 140 grams, and a 21 percent reduction in the
16 hypoglycemic readings. Now remember --
17 DR. GARBER: Dr. Edelman, your time is
18 up.
19 DR. EDELMAN: -- they were only on it
20 for six days.
21 And the last study looks at the Alc
22 reduction, and basically it is a study looking at
23 patients with different Alc's that are put on
24 continuous monitor, and there's another study
25 repeated after the MiniMed study showing that the

00183

1 overall reduction for those patients of greater
2 than a one percent drop in Alc, and a trend to
3 reduce hypoglycemia during that period.
4 So in conclusion, I would just like the
5 committee to really think about the fact that
6 although the studies aren't perfect, they're not
7 focusing on this population, it's technology
8 that's needed right now for the Medicare
9 population with type 1 and insulin-controlled
10 type 2 diabetes. Thank you very much.
11 DR. GARBER: Thank you. Dr. Bruce
12 Bode.
13 DR. BODE: Thank you. I appreciate the
14 opportunity to be here. I am a consultant for
15 Johnson & Johnson, who is paying my travel here.
16 I represent our group, Atlanta Diabetes
17 Associates, and we take care of about 12 to 15,000
18 patients with diabetes per year in the greater
19 Atlanta area. And we do have a conflict of
20 interest, we do work and have done clinical
21 research for Abbott, BD, DexCom, Johnson &
22 Johnson, Medtronic, Roche, and other companies
23 also.
24 But what I'm going to really get into
25 is we always look at our data, we always look at

00184

1 what our patients provide us, we look at it, and I
2 want to talk about just glucose monitoring because
3 that's what this conference is about. Obviously,
4 it's very common that the more you monitor, the
5 better you do. Patients and health care providers
6 are able to make changes either in their behavior
7 or medication management to try to normalize
8 glucose.
9 Clearly glucose monitoring is a tool,
10 and as we measure our performance and control our
11 Alc's, earlier studies essentially appear to be
12 very true to this, what's controversial is type 2
13 diabetics, especially not treated with insulin.
14 We looked at that in our group and we went on the
15 course of developing a non-linear mathematical
16 model for Alc as a function of number of blood

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

00185

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

00186

1 testing falls off. This is a database of over 500
2 patients. And again, you can see what appears to
3 be a significant decline in Alc over time.
4 And so when you look at this, you can
5 just look at the mean curves themselves for
6 insulin pumps to subcutaneous insulin to no
7 insulin at all. When we did our statistical
8 analysis on this, we broke these into quintiles,
9 we compared the two lower quintiles to the two
10 upper quintiles. For insulin pumps, out of 417
11 patients, 6.4 tests versus 5.6 tests, the Alc
12 difference was 7.7 to 6.8, highly significant.
13 For subcutaneous insulin, it was .8 tests a day
14 versus 3.8 tests a day, the significance there was
15 8.4 to 7.8 Alc drop, highly significant. And for
16 no insulin it was .4 versus 1.9, and again, a
17 significant drop in Alc from 7.5 to 6.7. And you
18 can look at it in bar graph form too, seeing the
19 same data.

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

00187

1 Obviously, glucose monitoring,
2 hypothesis two, may be an indicator more of
3 compliance, and obviously some people will have
4 low Alc's regardless of how much they monitor and
5 whether they monitor or not because they're very
6 insulin-sensitive or have endogenous insulin.
7 What we have to really do is look at
8 the non-insulin people, you've got to look at this
9 lower quadrant that are running in the six range,
10 and what's happening to these people, are they
11 early in their course of their disease, have they
12 had good ito cell function, have they controlled
13 their weight loss, exercise or whatever.
14 And there has been a study of glucose
15 monitoring, we are very actively involved in
16 studies with type 1 and type 2 in this subject,
17 and there is no question, the more you monitor,
18 the more you come to range. So if your Alc is
19 six, you might raise it up to 6.3, 6.4, and if Alc
20 is eight or nine, you might drop it a point or
21 more.
22 There is a study that was done for
23 type 2, average age 74 years old. They were on
24 oral sulfonylureas, 55 percent were on metformin,
25 the average Alc was 6.2 percent. They used CGMS

00188

1 retrospective 72 hours, repeated a month apart,
2 and looked at the data. And you can see here, out
3 of the 188 hours of CGMS monitoring of 25
4 patients, they had 103 episodes of significant
5 hypoglycemia, defined as less than 50, and mild
6 hypoglycemia is defined as 60 to 65. When you
7 also look at the overall data, 96 percent of these
8 patients had at least one episode of significant
9 hypoglycemia defined as less than 50.
10 So obviously, this is a major problem.
11 People, even Medicare patients who are normal, you
12 can't just take away --
13 DR. GARBBER: Time.
14 DR. BODE: In summary, all treatment
15 regimens show a significant association, it's not
16 a cause, between high glucose monitoring and low
17 Alc. We as practitioners, whether you're a
18 practicing health care provider, whether an
19 educator, an endocrinologist or a physician in
20 general practice, obviously the more you test, it
21 appears the better you do. It's a tool to use to
22 get Alc's to normal. And I appreciate your time.

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

00189

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

00190

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

00191

1 little bit with that. Certainly if you look at
2 the curves and look at the reduction, you get much
3 more reduction in risk way out at the far end at
4 the highest levels, so you reduce risks for these
5 complications from 11 to nine much more so than
6 you do from nine to seven, and certainly much more
7 so than from seven to five. So I think you get
8 much more bang for your buck at the high end. But
9 as was mentioned earlier, whether there is a
10 breakpoint or not, I think is a matter of debate.
11 Certainly the risk reductions that you get at
12 substantially below eight, or below seven, it
13 becomes relatively small, with increasing amounts
14 of effort as well as increasing amounts of
15 hypoglycemia.

16 DR. FENDRICK: So the first question
17 was, the studies show that where Alc reductions
18 actually occurred, tended to be very small in the
19 randomized trials, and I'm just wondering when you
20 see a statistically significant reduction of .5
21 percent, is that something to get excited about?

22 DR. HAYWARD: One of the difficulties
23 when you look at an average in a clinical trial is
24 that that is not the amount of benefit going from
25 the mean of the control group to the mean of the

00192

1 intervention group. Because of that, because of
2 the (inaudible) as the speakers suggested, because
3 most of those very highly sloped things are the
4 first part of a multi-step process when you find
5 no disease to early disease, and the same
6 relationship goes when going from no disease to
7 moderate disease. Something that wasn't
8 mentioned, when the person already has advanced
9 disease, there is very little association, so once
10 the person has severe disease like severe
11 neuropathy or severe kidney disease, Alc is no
12 longer a major progression indicator to end stage
13 disease in most of these studies.

14 But the multiplicative aspect of it
15 makes those even more dramatic, so what you can
16 find is going from a mean of eight percent to
17 seven percent looks important, and then when you
18 actually look, almost all the events are occurring
19 in the mean of eight percent, who have values up
20 to nine. And often, if 75 to 85 percent of the
21 events are occurring in the 15 percent with the
22 worst control, you might be misunderstanding those
23 studies completely by just looking at the average.
24 In addition, those people that start in
25 those studies with values of 11 didn't get a .5 or

00193

1 a one percent reduction. Most often there is an

2 interaction between the two, so the people at 11
3 often came down to nine and got a lot of benefit,
4 the person who started at eight might have gotten
5 less of a reduction, so I think that you really
6 can't say how important .5 is unless you know that
7 individual overall risk, and whether going from a
8 high level to a moderate level, it's a very
9 complex function.
10 DR. GARBER: Alex?
11 DR. KRIST: I agree with what you're
12 saying, but I want to add to Mark's question just
13 to make it a little more concrete, because I think
14 what he's telling me is he's looking at some of
15 the RCTs on the self-monitoring glycemc controls
16 with a reduction of .5 percent. And I agree with
17 you that the benefits occur more likely in the
18 extremes, but in those randomized control trials
19 on the individual Alc's, you're going to have
20 those extremes as well that are going to
21 contribute to that average reduction of .5
22 percent, you'll have those people at 9 and 10
23 percent coming down to 7 percent.
24 But when I was looking at this, kind of
25 taking that same logic that Mark was taking,

00194

1 what's the clinically significant reduction, if we
2 just focus on that when looking at the evidence,
3 and I look at something like a reduction of .9
4 percent, 7.9 with intervention was controlled to 7
5 in the intervention group. Are there examples,
6 just looking at the VA CSDM where there was a two
7 percent reduction in hemoglobin Alc, and then I
8 don't remember what it was in the others, but are
9 there studies that anyone here knows about? I can
10 ask the presenters as well, if there's studies
11 where there are improvements in clinical outcomes
12 between an intensive and a control group, and
13 there's a lower reduction on the order of .5
14 percent?
15 DR. HAYWARD: What we know from our RCT
16 is that in ten years of follow-up in people with
17 reasonable, not even high blood pressure control,
18 there are no clinically meaningful benefits from
19 going from eight percent to seven percent,
20 including the DCCT. What people forget is that
21 all the eyecare benefit with retinopathy occurred
22 in the 30 percent of people with baseline
23 retinopathy, there was no significant difference
24 in the others.
25 So we're all going to come to the

00195

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

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

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

00196

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

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

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

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

00197

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

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

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

00198

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

00199

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

11 no retinopathy, because you have these progression
12 steps. Once you have moderate control, going from
13 no retinopathy, to the laser therapy, if you have,
14 unless you have poor blood pressure control, is a
15 long process. And so you'd have to think the
16 70-year-old would get different if they had
17 moderate proliferative retinopathy or severe
18 background retinopathy, as compared with somebody
19 with normal, that was the only point I was making.
20 DR. PUKLIN: But what do you do with a
21 type 2 diabetic who is recently diagnosed at the
22 age of 70 with moderate background retinopathy?
23 DR. HAYWARD: That person has a chance
24 of getting benefit from tight control. If they
25 have normalized at that point, their chance of

00200

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

00201

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

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

00202

1 why it happened that way. And those particular
2 types of individual circumstances have been
3 denied, because the tests have not been used for
4 any reason.
5 We acknowledge in our policies that a
6 normal test gives information, important
7 information when people want to know have they
8 reached a certain level, and as was spoken
9 earlier, for any indication like a change in
10 recent hospitalization, a change in any situation,
11 frequent testing above the limits that are
12 normally done are always good.
13 DR. RUCKER: Even, there was a comment
14 that \$450 million, did that sort of fit into it?
15 DR. LURVEY: That wasn't -- someone
16 else made that comment, I think in 2002. I said
17 that the total cost for strips that we found
18 through our medical records was just under a
19 billion dollars for diabetic strips in the year
20 2003, and it's probably hit a billion by now.
21 DR. RUCKER: Do you have any sense of
22 what percentage of that is spent on people who are
23 managed in sort of like the way that you're
24 describing?
25 DR. LURVEY: No. The only information

00203

1 we had was total expenditures and so there was no
2 way we could look behind it, but thank you for
3 asking.
4 DR. KOLLER: I can answer part of that
5 question. CMS conducts surveys on its various
6 populations. They do look at skilled
7 nursing facilities, and they look at community
8 dwellers who are 65 or older, and the disabled
9 population which is 64 and under. And we don't
10 have all of the information that you're asking for,
11 but what we do know is that those people who are
12 65 and older are testing only, I would say about,
13 there is a slide actually in Dr. Lurvey's materials,
14 that about 40 percent of patients are testing, and
15 the numbers are not particularly different by
16 therapy. They're a little bit higher if you're on

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

00204

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

00205

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

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

00206

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

00207

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

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

00208

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

00209

1 terms of fatal and non-fatal cardiovascular
2 disease including CHF secondary to ischemic
3 disease and non-hemorrhagic stroke, for 65 to 74
4 it would be 135 per 1,000, and for 75-plus it
5 would be (inaudible) per 1,000.
6 In terms of retinopathy resulting in
7 legal blindness, that would be about one in 6,000.
8 In terms of other retinopathy, that
9 would be about 21 per hundred in the group from 65
10 to 74, and (inaudible) in the group 75-plus.
11 In terms of nephropathy resulting in
12 dialysis or transplantation, this is now per
13 hundred thousand, and that would be 405 in the
14 group from 65 to 74, and 383 for the group that's
15 75 and above.
16 In terms of other nephropathy including
17 micro or macrovascular disease, about five per
18 thousand.
19 Amputation, that would be about 6.6 per
20 thousand in the 65 to 74, and 7.9 in the group
21 75-plus.
22 And then in terms of abnormal
23 neuropathy testing, that would be about 40 percent
24 -- excuse me. That would be about 16.8 in the
25 group 65 to 74, and 29.3 in the group 75-plus.

00210

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

00211

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

00212

1 DR. GARBER: Okay, discussion of that

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

00213

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

00214

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

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

00215

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

00216

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

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

00217

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

00218

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

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

00219

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

00220

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

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

00221

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

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

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

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

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

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

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

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

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

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1 unimportant.
2 Any discussion on that question?
3 Please go ahead and vote.
4 (Members voted and staff collected
5 ballots.)
6 DR. GARBER: Question 4A, how confident
7 are you that glycemic control reverses or reduces
8 progression or pre-existing chronic complications
9 in a clinically meaningful way in patients who had
10 type 2 diabetes prior to age 65? So the only
11 difference here is pre-existing diabetes versus
12 new onslaught. Any discussion on this question?
13 (Negative response.)
14 DR. GARBER: Okay. Please go ahead and
15 vote on 4A.
16 (Members voted and staff collected the
17 votes.)
18 DR. GARBER: Question 4B, how important
19 statistically and clinically is glycemic control
20 relative to other therapeutic modalities in the
21 reversal and delayed progression of pre-existing
22 chronic complications, especially cardiovascular
23 events and death, in patients with type 2 diabetes
24 prior to 65?
25 So this is people with pre-existing

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

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1 important. So if you think it's very important
2 for delaying progression, even if it doesn't work
3 for reversal, you might give that a somewhat
4 important rating. It doesn't have to do
5 everything.
6 DR. PUKLIN: But it's and, it's not
7 and/or, and all these questions have the concept
8 of reversal --
9 DR. GARBER: I think that should be
10 and/or, is what Steve was saying.
11 DR. BRADHAM: Should we add and/or?
12 DR. GARBER: Yeah, change it to and/or.
13 DR. PUKLIN: And what about the last
14 question? Then I need my answer slip.
15 DR. GARBER: Well, Question 3A is an
16 or, and 4A is an or. This is only 3B and 4B. Is
17 there anybody that needs to change their vote on
18 3B?
19 (Negative response.)
20 (Members voted and staff collected the
21 votes.)
22 DR. GARBER: Okay. Is everyone ready
23 for Question 5? Question 5 is, can the
24 information on hypoglycemia in type 1 patients be
25 generalized to Medicare-aged type 2 patients?

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

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1 is can the information on hypoglycemia be

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

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

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

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

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

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

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

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

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1 MR. QUEENAN: That would be fine.
2 DR. GARBER: So the question is, do you
3 want to break up the voting that way or just leave
4 it all together? So, discussion from the
5 committee?
6 (No response.)
7 DR. GARBER: Do you want to just vote
8 on whether to break it up? Okay. All those in
9 favor of breaking it up into two subgroups, using
10 and not using insulin, raise your hand.
11 (Panelists raised hands.)
12 DR. GARBER: Those who want to keep it
13 as one?
14 (Panelists raised hands.)
15 DR. GARBER: Okay, the splitters have
16 it this time. So what I would like you to do is
17 break up your answers to the question, very
18 confident to very unconfident, first would be with
19 insulin use, and the second would be non-insulin
20 use. Maggie?
21 DR. PIPER: Well, another way to do it
22 would be to leave the question as is and then
23 follow up with another question, or is that
24 implied in the question?
25 DR. GARBER: I think that is intended.

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

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

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

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

11 actually doing something about it, and in some
12 cases the difficulty in studies is interpreting
13 the results. So I guess just to clarify, are we
14 assuming that all variability as to whether or not
15 someone reacts to a measurement is imbedded in
16 this question? In other words, did it help or
17 could it help.
18 DR. GARBER: I think this really says
19 did it help, that is to say it may provide better
20 information, but it doesn't mean it changed the
21 management.
22 MR. QUEENAN: So then, the
23 interpretation could be in effect one-directional,
24 that if you add testing or more testing, that it
25 may or may not improve outcome, but it doesn't

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1 necessarily address what would happen if you were
2 to take testing away, what that would do to
3 outcomes. At that point I can't do that, I would
4 be deprived of the ability to do that to improve
5 management.
6 DR. GARBER: Alex, did you want to make
7 a comment?
8 DR. KRIST: Well, I just wanted to make
9 sure I understood the distinction so when we talk
10 about clinically meaningful, because I'm trying to
11 differentiate Question 6 from 7. I mean, 7 is,
12 does it decrease chronic complications. When I'm
13 reading 6 and it says clinically meaningful, I'm
14 thinking about clinically meaningful meaning
15 controlling blood sugar, focusing on that as
16 opposed to decreased long-term complications like
17 morbidity and mortality. Just to differentiate,
18 am I right on that or am I misunderstanding that?
19 I wanted to make sure we're all in agreement.
20 DR. GARBER: Well, they are not totally
21 unrelated. If you think that there's a, you would
22 have to explain, let's say that hemoglobin A1c
23 falls by .1 percent with no change, no decrease in
24 hypoglycemic episodes. Whether that, you would
25 consider that to be clinically meaningful, one

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1 thing would be your assessment of whether that
2 translates into long-term outcomes. So they're
3 not totally unrelated, the question is whether
4 there's a clinically meaningful change in glycemic
5 control, so you have to decide what makes it
6 clinically meaningful.
7 DR. KRIST: Then how is 7 different
8 when I get to 7?
9 DR. GARBER: You could say that
10 presumably it's not due to glycemic control, like
11 if your patient has lost weight, et cetera, you
12 might have a different answer to 7, regardless
13 of 6. So, is everybody ready to vote on

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

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

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

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

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

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

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

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

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

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

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

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

00248

1 guidance is very important, and we need to know
2 some of these research challenges to be able to
3 help us assist CMS in making their decisions.
4 Steve, did you want to add some things?
5 DR. PHURROUGH: Yes. I would like to
6 spend a few minutes, since we have an hour and a
7 half left in the day, what I would like to hear
8 both from the panel and from the audience is sort
9 of a twofold question. What are those questions
10 that we need to answer? We talked to some of the
11 speakers, most of the speakers talked about that,
12 but in a type 1 continuous monitoring pump
13 setting, what are those questions that need to be
14 focused on? And then for the type 2 patients,
15 particularly the older Medicare patients, there's
16 a different set of questions, and what's the best
17 way to answer those questions. That's sort of the
18 first set.
19 And then the second set is, what can
20 CMS do to help with that? What role should CMS
21 assume in not just its typical role of attempting
22 to ensure the patients get what they need, but
23 more in the role of fostering, answering some of
24 the questions that are left to be answered.
25 So let me throw that out, and perhaps

00249

1 it's just a summary of things we've already heard,
2 but since we have a good number of people, it
3 would be helpful for us to hear what you as a
4 panel have digested along with what we've heard
5 today.
6 DR. PIPER: Just to repeat what I was
7 talking about earlier regarding continuous glucose
8 monitoring, and I think there is a strong need to
9 go beyond reporting numbers of daily sticks, and
10 numbers and graphs, and to really get to
11 clinically meaningful outcomes such as falls or
12 other measures of hypoglycemia.
13 DR. PHURROUGH: And I was going to ask
14 that question, particularly of those who have
15 presented that information or made some point, are
16 there measures of glucose excursion that are
17 validated or, let's just ask that question, what
18 are the measures of glucose excursion that are
19 validated, and if the answer to that is none, what
20 are those that are being utilized in research, or
21 should be utilized in research? Number of times
22 below 200, number of times below 50, do we need a
23 continuous monitor, whatever? What kind of
24 specificity do we have in this data?
25 SPEAKER: Well, I could just add a

00250

1 little bit about the strips that are used, we talk

2 about standard deviations. To get an average of
3 124 at breakfast is fine (inaudible) 220 or 230,
4 so you're not bouncing around too much. But when
5 you see patients, you get a third of the numbers
6 above 230, so that is a number we use all the time
7 in research looking at this. And although the
8 organizations don't have the exact postprandial
9 goals, I think that everyone agrees that 200 is a
10 good general baseline, above 200 is too high
11 whether before or after eating. And then of
12 course with hypoglycemia, below 60 is the
13 standard, I'm not sure where you all got 30, but
14 certainly below 60 with or without symptoms is a
15 real cut point for measuring.
16 DR. PHURROUGH: You're writing a
17 protocol and in the protocol you're going to write
18 down, here are our outcomes, so we need a very
19 short phrase, here's what we're going to measure,
20 the number of times or the ratio of, or --
21 SPEAKER: Well, you could say the
22 percent of time patients are in the hyper and
23 hypoglycemia range, what is the percentage of time
24 blood sugars are above or below the percent of
25 numbers above or below these two numbers, the hypo

00251

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

00252

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

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

00253

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

00254

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

8 I would really recommend, rather than
9 trying to get the answer here, to talk to those
10 investigators that have done the most detailed
11 work.
12 SPEAKER: I need to jump in here and
13 disagree because it's not that complicated. You
14 can be a numbers person and really confuse the
15 issue. We know what normal people do throughout
16 the day, we know that they hardly ever get below
17 70 and they hardly ever get above 140. We know
18 that high Alc's can be damaging. There have been
19 studies to show, and I showed one today, that a
20 certain subset of the population can lower Alc.
21 The hard numbers that you're looking for are right
22 there in front of you, low blood sugar. There is
23 nothing more complex than that. And yeah, we can
24 argue, and I agree with you that --
25 DR. HAYWARD: I just repeat that those

00255

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

00256

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

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

00257

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

00258

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

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

00259

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

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

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

00261

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

00262

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

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

00263

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

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

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

00265

1 unanswered and what we need to do, perhaps is not
2 necessarily vote on the correct answer to the one
3 measure that we should engage in, but understand
4 where this new technology is taking us and sort of
5 work together on what measures we could be
6 bringing to bear to answer the real question.
7 DR. PHURROUGH: The whole goal of this
8 conversation is to stimulate that thinking and to
9 recognize that our interest is that you're going
10 to come to us potentially and ask us to do
11 something on a coverage basis, and we're going to
12 want to see what the evidence is, and so you have
13 to know what you will need.
14 Let's talk type 2 for just a minute.
15 What questions should we as CMS be insisting that
16 you as diabetologists answer in the type 2
17 Medicare population?
18 DR. HAYWARD: Just to reiterate, I
19 think we're close to accepting that as an outcome,
20 so I think he's right, we need more research, but
21 improving variance is only interesting now to test
22 the hypothesis, and I think that CMS should not be
23 making decisions on coverage based upon that
24 outcome, you know, Alc, hypoglycemia, quality of
25 life. So I think the answer is in the research

00266

1 realm and, you know, years from now they might
2 show that improving that is a good enough outcome,
3 but that intermediate outcome, I think people will
4 attempt to say that's worth this intervention.
5 And I think there is no quality epidemiologic data
6 that's using it as an outcome, it didn't show up
7 in our list of outcomes for these studies, and I
8 think rightfully so.
9 MR. BOYER: My name is Tom Boyer, I've
10 worked in the diabetes field for 23 years and
11 actually lobbied on behalf of the American
12 Diabetes Association about 10 to 12 years ago.
13 I would like to share with the
14 committee a couple of thoughts as a person with
15 type 1 diabetes. Number one, I hope that any
16 barrier or any guideline you use to determine the
17 efficacy of continuous glucose monitoring is not
18 restricted in nature and that it is consistent
19 with what you use to examine other benefits that
20 are out there. Because I just have to say, if
21 this was a tool that was used to fight cancer or
22 some other disease where outcomes were actually
23 improving right now, CMS would probably cover it
24 in a heartbeat.
25 It's very disturbing to hear the tenor

00267

1 of the conversation right now, at least on the
2 staff side, and as a person who lives out there,
3 it's improving people's lives, and it's really
4 frustrating to me. I have been in this place for
5 23 years and never before in my life have I
6 actually heard the DCCT challenged the way in
7 which I heard it challenged this morning, and
8 that's really frustrating and of concern to me.
9 The second thing that I would like to
10 share with the group is, I'm concerned with the
11 focus on glucose monitoring and not necessarily
12 Alc control. If you look at the measures that
13 exist in the Medicare program today of the people
14 over age 65, most people are not having Alc tests
15 done per recommendations by ADA, by NCQA, or by
16 any other reasonable standard or measure that's
17 out there.
18 There are some rather significant
19 impediments that exist that are preventing people
20 in the Medicare program to take care of themselves
21 and my hope is that in the future that this
22 committee will address those impediments and make
23 some recommendations both to Congress, to the
24 Secretary of HHS, and to others in the community
25 about what we can do collectively to help those

00268

1 folks. Because if we don't, based on the data
2 that just came out from CDC this week that we are
3 going to have 40 million people living with type 2
4 diabetes within our lifetime in America, we're
5 going to have a rather substantial problem in the
6 Medicare program. This is not just about one
7 benefit, this is about continuity of care for
8 people with diabetes. And with that, I will turn
9 the microphone back over, and I would hope that
10 the research would examine what those folks need
11 over the days ahead. Thanks.
12 DR. PHURROUGH: Question. For our type
13 2 older Medicare population, what questions do you
14 think are left to be answered, what do we need to
15 encourage from our viewpoint from the diabetic
16 community? We voted on some things, I don't know
17 what all the answers to those were, but what
18 should we be focusing on in our operation?
19 DR. HAYWARD: Just in terms of the last
20 questions, I strongly encourage those people
21 interested in continuous glucose monitoring to
22 select cohorts of older patients who are the most
23 likely to benefit, and demonstrate it. These are
24 really dramatic improvements. You don't need a
25 big study. We're not talking about asking for,

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

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

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

00271

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

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

00272

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

00273

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

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

21 DR. PHURROUGH: All right. Well, I
22 think we've had some good discussion on that. I
23 appreciate your input. Panel, any last comments
24 before we let you head your way?
25 (Negative response.)

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1 DR. PHURROUGH: Thank you very much for
2 your attendance and your input and spending the
3 time reading the vast amount of work that's here.
4 Thank you to the audience, those who presented and
5 attended, and you can look at our web site
6 sometime tomorrow for all the results. Thank you
7 very much.
8 (Whereupon, the committee adjourned at
9 3:09 p.m.)

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