 1   we set our confidence intervals. So typically

 2   we're setting 95 percent confidence intervals,

 3   but that's not cast in stone either, so you may

 4   have a broader 95 percent confidence boundary

 5   with a point estimate that's around one for the

 6   hazard ratio, and that's still not no

 7   information. There is some degree of

 8   probability with which you can rule out, let's

 9   say, the 33 percent increase. It's not

10   95 percent. You want to just comment on that?

11   DR. FLEMING: Yes. I agree with you

12   that there are obviously a continuum in terms of

13   the level of evidence that we have. My concern

14   is, in a setting where -- particularly if

15   there's a signal for a safety risk and that that

16   safety risk truly would meaningfully alter

17   benefit-to-risk, then I think it is important to

18   ensure that your confidence interval is ruling

19   out what would be unacceptable.

20   And to use -- let's say a 90 or an

21   80 percent confidence interval is essentially

22   saying I'm okay declaring safety when in fact

 1 I may be falsely declaring safety 10,

 2 20 percent of the time when this is an unsafe

 3 intervention.

 4   So I agree with you, Marv, that the

 5 point estimate and the confidence interval

 6 are important, and if you don't rule out

 7 something that's 1.33, in this example, you

 8 could still be contributing substantial

 9 information. But to use that as the basis

10 for saying that's all I have to do is in fact

11 in many settings at least an inadequate level

12 of assurance of safety.

13   DR. KONSTAM: I'll just end with a

14 comment: I think that all of that might be

15 considered relative to the potential benefit.

16   DR. FLEMING: Absolutely.

17   DR. KONSTAM: And relative to the

18 incremental value of that particular drug.

19   DR. FLEMING: In fact, the way you get

20 at that, Marv, is the actual margin you're

21 trying to rule out should be factoring that in.

22 So if you say I have substantial evidence of

 1   major effects on important clinical outcomes,

 2   then that could allow you to use a somewhat

 3   larger margin for other clinical outcomes.

 4   On the other hand, if you're

 5   looking at a symptom benefit and the risk

 6   that you're concerned about is irreversible

 7   morbidity or mortality, then you're not going

 8   to allow as much on that margin, so why what

 9   you're saying is intuitively correct is that

10   I don't have to rule out 1.33, I only have to

11   rule out 1.5 -- in a hypothetical setting

12   where I have major benefit on other

13   clinically important outcomes, and I just

14   have to know that it's not unacceptably

15   washed out by this other clinical outcome.

16   DR. BURMAN: Any other questions by

17   the panel? Yes?

18   DR. FRADKIN: You recommended that

19   each surrogate be validated for each class of

20   drugs for a disease, and I'm wondering in the

21   case of diabetes where there are already 10

22   different approved classes, that the surrogate

1   would say validate it for three classes of

2   drugs, would you then extrapolate from that, or

3   do you really feel that it has to be for every

4   single drug class?

5   DR. FLEMING: I think that's a

6   discussion that a lot of people should spend a

7   lot of time talking about. It's not something

8   that I alone would want to answer. Clearly, the

9   broader you are able to validate a surrogate

10 across classes of agents, the more confident you

11 would be. Yet if a new intervention has

12 plausible mechanisms that could lead to

13 unintended negative effects, then that goes out

14 the window.

15   So a lot depends on the degree to

16 which you can place confidence that the

17 unintended negative effects of this new class

18 should not be substantially more influential

19 than the unintended negative effects of the

20 classes that have already been studied.

21   DR. BURMAN: Yes.

22   DR. TEMPLE: I think I know what your

 1   answer will be from the last conversation. A

 2   lot of this is framed in terms of surrogates,

 3   and the whole conversation about this has had to

 4   do with surrogates, but in some sense, what

 5   you're saying from some of your examples like

 6   the COX-2 studies, we're not really talking

 7   about surrogates. We're talking about a benefit

 8   that is something short of mortality, where you

 9   want to know whether the drug has a bad effect

10   on something that's really important like

11   survival, stroke, or something like that.

12   So I take it you would agree that

13   all of the things you've said have to do with

14   determining how safe a drug is in the face of

15   a variety of possible benefits, one of which

16   might be a benefit based on a surrogate, but

17   another might be just a symptomatic

18   improvement, or the microvascular things that

19   most people here seem to be saying are

20   well-established. You'd still apply all this

21   thinking to ruling out a cardiovascular risk,

22   even in the face of a benefit.

1   DR. FLEMING: Yes, that's true.

2   DR. BURMAN: Yes?

3   MR. PROSCHAN: It seems to me that one

4   of the hardest things is determining the

5   non-inferiority margin, and I'm wondering

6   whether you think that the effect on the HbA1c

7   should be used in part -- you know, relative to

8   the comparator or the expected effect should be

9   part of the equation in terms of setting that

10 non-inferiority margin. And this is kind of a

11 scary thought, but what would you think about

12 the idea of setting that non-inferiority margin,

13 specifying a rule that says, if the difference

14 in HbA1c is this amount, here's the margin. If

15 it's that amount, here is the margin, and then

16 you know, actually looking at the difference in

17 HbA1c in your trial.

18   DR. FLEMING: It's an important

19 question. It's a very difficult one to answer.

20 It's easier for me to answer in a setting where

21 a great deal of thought has been given, and

22 Steve Nissen was actually the Chair of the

1   executive committee for this precision trial

2   that I've talked about. My role has been the

3   chair of the data monitoring committee, so he

4   can probably answer the question better than I

5   can.

6   But basically in that setting, a

7   careful discussion was given to what is the

8   effect, in this case, of the COX-2, what is

9   its effect? To what extent is it a unique

10   effect relative to what can already be

11   accomplished with other standard

12   interventions? To the extent that what you

13   are accomplishing can already be accomplished

14   by other interventions that don't provide the

15   risk, then your tolerance level for excess

16   risk would be less.

17   On the other hand, if you could

18   argue that the COX-2s provide more enhanced

19   analgesic effects than any other available

20   therapies, and provide a reduction in GI

21   ulceration risks that really matter to

22   patients, then that does influence the level

1   of excess risk that you might allow, what you

2   define to be the lowest level that would be

3   unacceptable.

4   In the case of HbA1c, where I've

5   had less opportunity to have the extensive

6   discussion as we did in the precision trial,

7   my sense is we would carefully look at what

8   is already known or expected for benefit, and

9   how much excess risk would need to occur that

10   would offset that benefit, and to what extent

11   are there already other available therapies

12   that provide that same benefit without the

13   excess risk. All of these are issues I think

14   would have to be thought through.

15   The temptation to avoid, though, is

16   to make that margin really big, so that we

17   can do a small trial.

18   DR. BURMAN: Last question.

19   Dr. Genuth?

20   DR. GENUTH: In your talk, you implied

21   or suggested that you would have a situation

22   where there's an early safety risk that might be

 1   counterbalanced --

 2   DR. FLEMING: Yes.

 3   DR. GENUTH: Outweighed by a

 4   longer-term benefit.

 5   DR. FLEMING: Yes.

 6   DR. GENUTH: Is there some way that if

 7   you suspect such a situation, that you can build

 8   your suspicion into the design of the trial?

 9   DR. FLEMING: Well, that's a great

10   question as well. The first point that I would

11   make is in such a scenario, the biggest mistake

12   we can make is to design the trial to be

13   short-term. The biggest mistake that we can

14   make is to have 10,000 people with six months

15   follow-up and that's it, because we're only able

16   to reliably understand short-term effects. So

17   where we anticipate that true benefit-to-risk

18   can't be adequately established by short-term

19   effects, the study should be designed

20   longer-term.

21   Now, in monitoring such studies,

22   they shouldn't be stopped early unless the

 1   effect is so profound short-term that the

 2   anticipated differences long-term, even if

 3   they would become apparent, wouldn't override

 4   the short-term. So for example right now in

 5   HIV/AIDS, we have used viral load all the

 6   time to assess how to approve therapies, but

 7   what that's meant is we don't know some

 8   fundamental things. When do you start an

 9   anti-retroviral therapy? Early versus late?

10   Both for prevention of transmission and for

11   therapeutic benefit for the patient.

12   So we're finally doing, now,

13   large-scale long-term randomized trials where

14   we fully expect that early anti-retroviral

15   use will look better short-term. But

16   longer-term could give a very different

17   profile because you're saving your silver

18   bullets, so to speak, to when you really need

19   them when you have lower CD4, higher viral

20   load.

21   So in our setting here, if we

22   believe that benefit-to-risk could be

1   unfavorable short-term based on some

2   unintended or unrecognized adverse mechanisms

3   on macrovascular complications that could in

4   fact be more favorable long-term, then your

5   safety assessments should be in fact set up

6   to be long-term to allow for that

7   understanding of benefit-to-risk over the

8   longer-term. This is a chronic setting.

9   What we care about isn't just

10 short-term. The design should allow for

11 that. And termination should only occur if

12 the early results are so profound that you

13 can argue they would be persuasive, you don't

14 need to know what that long-term result is.

15   DR. BURMAN: Thank you very much. I

16 think we have to move on to -- thank you very

17 much, Dr. Fleming.

18   Our next speaker before lunch, last

19 one before lunch, is Professor Rury Holman.

20   Welcome.

21   MR. HOLMAN: Thank you. And I

22 appreciate the opportunity to talk to the

 1   committee. I've been asked to reprise the UK

 2   Perspective Diabetes Study, and I'd just like to

 3   acknowledge the NIH and NHLBI support over many

 4   years, although it was largely on microvascular

 5   interest they had at that time, and to not only

 6   highlight some of the issues, but maybe correct

 7   a few misconceptions, and then put it in the

 8   setting for the discussion today.

 9   I appreciate our earlier speakers

10   who have covered and highlighted many of the

11   issues that are cogent to the UKPDS. Just

12   let me remind you of a few salient facts.

13   This is a cohort of newly

14   diagnosed -- whatever that means -- patients

15   with type 2 diabetes recruited over a 14-year

16   period. So we are seeing secular changes,

17   then followed for between 6 and 20 years, and

18   we have now just completed 10 years of

19   post-study follow-up -- that's a 30-year

20   segment of data for the first patient in.

21   We therefore will be in a unique

22   position to follow the natural history, to

 1   look at evolving trends in this condition,

 2   and to look at the inter-relationships of

 3   risk factors and some of the interventions

 4   over time.

 5   Now we've heard, very nicely from

 6   Bob Ratner, about the microvascular

 7   component, and I think that really has taken

 8   as read -- the most significant risk factor

 9   is hypoglycemia. If you don't have

10   hypoglycemia, you don't have diabetes, you

11   don't get the microvascular problems, but

12   that is leveraged by blood pressure. And

13   after that, the issue I think is reasonably

14   solved.

15   What we didn't anticipate when we

16   first set up UKPDS was the true impact of

17   cardiovascular disease. The take-home

18   message is, though, as we continue to

19   decrease the impact of cardiovascular

20   disease, improve collateral therapies, and

21   extend lifetime, we extend the time for risk

22   of microvascular complications. So at

 1   smaller levels of A1c difference, may still

 2   be relevant, but we mustn't forget that in

 3   our headlong charge to reduce cardiovascular

 4   disease.

 5   So this paper, Paper 23, published

 6   just before we revealed the results of UKPDS,

 7   highlighted what Robert Turner coined the

 8   "deadly quintet" for CHD, showing, as we've

 9   seen earlier with data from David Nathan,

10   that HbA1c is a statistically independent and

11   potentially modifiable risk factor that

12   predicts bad outcomes. But of course, this

13   is epidemiology, and the true relationship is

14   to see if an intervention will reduce the

15   risk, hopefully in line with the expected

16   effect size -- it may be more, it may be

17   less.

18   And UKPDS set up the primary

19   question: if we minimize the difference in

20   glycemia and we used HbA1c as the overall

21   measure, would we reduce risk of outcomes?

22   And that was all outcomes, and they were

 1   pre-specified -- 21 particular endpoints.

 2   We heard a little bit earlier about

 3   the need to adjudicate. It's much more

 4   important that you count the things that

 5   matter, and preferably adjudicate them, than

 6   just rely on self-reported adverse events.

 7   And secondly, UKPDS said, does it

 8   matter how you reduce the A1c? Which is how

 9   we came to have a head-to-head between the

10   then-available therapies.

11   This is the slide you've seen in

12   part earlier, but this is the actual

13   incidence per 1,000 patient years. And this

14   is for microvascular disease. And again

15   remind you, UKPDS had microvascular disease

16   as a hard outcome. This is photocoagulation

17   for sight-threatening retinopathy, end stage

18   renal disease, or vitreous hemorrhage. This

19   is not albuminuria or any of the preceding

20   values.

21   And we can see quite nicely that if

22   you look at the updated mean data by Irene

 1   Stratton, so this is looking at the net

 2   impact over time of glucose exposure -- at

 3   near normal levels of A1c, there's very

 4   little risk of microvascular disease, but

 5   about a 15-fold increase over the range of

 6   A1cs that we typically saw in the study.

 7   And for myocardial infarction, even

 8   at the lower levels, there is already a

 9   substantial risk, reflecting the background

10   population and the increased risk for type 2

11   diabetes, but a fairly modest doubling or so

12   over the range of A1c.

13   So it seems to me a little

14   unrealistic that a drug to lower (?) A1c

15   would be a statin-like effect on myocardial

16   infarction, and we need to be reasonable in

17   our expectations.

18   We mustn't forget the microvascular

19   impact, though. These data from UKPDS 64 by

20   Amanda Adler (?) showed that the year-on-year

21   transition rates for no nephropathy to

22   microalbuminuria, from there to

 1   macroalbuminuria and end stage renal failure,

 2   are between 2 and 3 percent. But for each of

 3   these changes in microvascular state, the

 4   risk of death is tripled times 5 times 20.

 5   In fact, it's more likely you'll die than

 6   move to the next stage. So again,

 7   microvascular disease is important in the

 8   context of a cardiovascular risk.

 9   And these data from the now-iconic

10   graph from UKPDS show the impact of firstly

11   diet and lifestyle, and then the randomized

12   application of conventional therapy, or the

13   more intensive therapies. And a couple of

14   things here, during the study, these two

15   groups were referred to as usual therapy,

16   which meant diet until it was no longer

17   acceptable or glucose levels, and active

18   therapy with a pharmacologic agent. In no

19   real sense were these intensive, because as

20   we see here, the impact of these therapies

21   over time is only to track at a lower A1c

22   about .9 percent difference, the natural

 1   history in the diet treated group, and again,

 2   the available agents didn't show any real

 3   difference in their efficacy on glucose

 4   control.

 5   So just to make that point, this is

 6   the design of UKPDS. This is a patient

 7   randomized to sulphonylurea, they have a

 8   diet, an exercise entry, and then the

 9   sulphonylurea impact is seen here. Quite

10   impressive. But rescue therapy, when

11   metformin was added per protocol, was not

12   until a 270ml/dl, 15ml/L if glucose was

13   reached. We could never do this study again,

14   but it's a child of its time.

15   When I started this study, most

16   people didn't believe glucose was that

17   important for complications, some people

18   thought it was genetic. It was really just

19   symptom therapy in order to reduce the

20   glucose below a point the patients didn't

21   have glycogeria.

22   And of course now, this would be

1   unacceptable and so for trials, we can no

2   longer have this sort of data. However you

3   design it, you can only have relative small

4   differences, or for very short periods of

5   time.

6   The reason for that drop came out

7   of the UKPDS. When we first designed UKPDS,

8   it was on the back of my initial studies with

9   Robert Turner where we were really interested

10   in the insulin deficiency component of type 2

11   diabetes, and actually, we designed the trial

12   to look at the benefit of using insulin as

13   first-line therapy, which of course we had as

14   one of the randomized arms.

15   And here we see that the beta cell

16   function measured in the study both in the

17   non-overweight and overweight people is

18   around 50 percent of normal at the time of

19   diagnosis on average, and declines by about

20   4 percent a year. And whether we use

21   sulphonylurea, which initially boosts the

22   apparent beta cell efficacy in both groups of

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1 patients, once the effect is maximized, the

2 rate of decline is very similar, and even for

3 metformin, a small benefit initially is

4 followed by the same downward trend.

5   So long-term studies, we have this

6 real problem that we are tackling a

7 progressive disorder, and we have to have

8 rescue therapies -- these days earlier and

9 earlier. And of course, one of the benefits

10 of a particular treatment might be to stop

11 that process, which would make our lives

12 easier, although not necessarily change the

13 cardiovascular outcome.

14   So what were the results of the

15 study? Well, this monotherapy approach,

16 because for most patients, for most of the

17 study, they were on their first-line therapy,

18 it took all that time to achieve a net

19 0.9 percent difference, but over 10 years

20 median follow-up, the main composite endpoint

21 was significant.

22   That was what the study was powered

1 on. The enigmatic myocardial infarction

2 endpoint with a 16 percent risk reduction

3 just on the cusp, and we have never claimed

4 that significant, but of course it's

5 tantalizing. And many of the studies that

6 followed, particularly ACCORD, of course were

7 predicated on the process of could we prove

8 that myocardial infarction could be reduced

9 by reducing the A1c, but I think time has

10 moved on, because the guidelines after UKPDS

11 insist on reasonably low A1c levels are

12 optioned to do that nice scientific

13 separation as being minimized. As we've

14 heard, microvascular disease, no question.

15   Just a point about the separation.

16 We've seen this before from Bob Ratner, but

17 it takes here about two years before we see

18 separation in the curves. There's quite a

19 few endpoints here. Remember, these are hard

20 endpoints, not soft, but if I blow this up

21 you'll see actually there's an adverse effect

22 initially in the intensive group. We saw

 1   that in the Wellcome study in the late '70s

 2   in the Steno 1 study, an initial worsening of

 3   retinopathy before the longer-term benefit

 4   kicked in. Now many studies are using

 5   secondary intervention or secondary

 6   prevention like ACCORD, like many of the new

 7   studies, because we want high-risk patients.

 8   There's a slight concern that as we improve

 9   glucose controls, we may have to go through a

10   period of adverse effect before you might get

11   benefit. This is why we need long-term

12   outcome studies to truly evaluate the

13   risk/benefit ratio.

14   With myocardial infarction we've

15   seen the p-value. Here, we don't see

16   separation probably until close to three

17   years, although it is a systematic slight

18   widening over time. We can make no more

19   claim than that other than to say that for

20   this level of A1c difference which you might

21   achieve in a new study now, you would need to

22   go for that length of time before you might

 1   begin to see separation, so long-term

 2   studies. We're talking about six minimum

 3   years, in my view.

 4   Now we did look at a meta-analysis

 5   of A1c reduction. This is for type 2

 6   diabetes. Kumamoto actually did split their

 7   patients into secondary and primary

 8   prevention, and you can see for their primary

 9   prevention, they had an impressive result

10   compared to their secondary prevention

11   patients. These are the various components

12   of UKPDS and the Veterans Affair, which was

13   the wrong side net effect about a 19 percent

14   reduction for type 2.

15   Interesting, and we've seen a

16   little bit of this data already, in the

17   meta-analysis we did for the type 1 diabetic

18   patients, there is about a 62 percent risk

19   reduction here, reflecting maybe the

20   DCCT/EDIC result, and suggesting in these

21   patients with much fewer other risk factors

22   in play, the pure effect of glucose may be

1   easier to discern.

2   Coming back to UKPDS and Metformin,

3   and this is misconception number one, and I'm

4   afraid it was in your slide already, and that

5   is, the Metformin study was primarily part of

6   the UKPDS. Of the enrolled patients, those

7   that went into the main randomization were

8   stratified by ideal body weight. And of

9   those who were over 120 percent, they were

10   randomized to the intensive glucose policy

11   with sulphonylurea insulin or conventional,

12   but there was this additional possibility

13   only in overweight patients to have Metformin

14   pre-specified from the start, and reflecting

15   the regulatory environment in Europe at the

16   time -- and ethical approval.

17   So we actually have a sub-study in

18   terms of patients, but a primary

19   randomization of 753 patients, where we could

20   compare directly these two, and in fact we

21   compared intensive glucose as well.

22   And these are the results. The

1   actual A1c difference in these overweight

2   patients who were allocated Metformin as

3   opposed to conventional therapy was less than

4   the majority of the study which was

5   0.6 percent, but nonetheless, the risk

6   reductions were impressive.

7   For microvascular disease, it was a

8   similar effect size, 29 percent, though not

9   significant, and then this all cause

10 mortality, significant, over one-third

11 reduction, myocardial infarction, 39 percent.

12 Nearly a statin-like effect, you might think,

13 never replicated. And that's interesting. I

14 was taught you had to have two pivotal

15 studies in two reasonable populations to make

16 the effect.

17   In Europe, the regulators took this

18 and the label was improved. In fact, the

19 manufacturers of this agent have "saves

20 lives" stamped across their original

21 advertisement, so this is an issue which

22 really the jury is out. Another trial needs

 1   to be done.

 2   And just to show you the

 3   Kaplan-Meier for that, this wasn't just a

 4   play of chance in the way the numbers fell.

 5   Separation was very early and widened over

 6   time, suggesting this might be a real effect,

 7   but clearly is not of a magnitude that

 8   relates to the A1c difference, and so this

 9   may be an off-target effect, and we can

10   speculate about what that might be of a

11   p-kinase, but it's a beneficial effect that

12   needs to be tested, as opposed to a harmful

13   effect, which we've discussed quite a lot

14   this morning.

15   I put this slide in because this is

16   the true sub-study where this is a post hoc

17   analysis of patients in whom once allocated

18   to sulfonylurea, were randomized later in the

19   study to additional metformin, at a blood

20   glucose fasting of 108mg/dl. So this was a

21   modification in a subset of patients. And

22   the worrying thing was that when we looked at

1   the comparison, there was almost a doubling

2   in risk for those who remained on

3   sulfonylurea to those who were randomized to

4   additional metformin.

5   These results have not been

6   replicated. No study is being done.

7   Trolling databases does not replicate this.

8   And the only point of reference I would give

9   you is in the study as a whole, patients who

10 were not part of this subgroup and who were

11 on sulfonylurea for the trial had a higher

12 rate overall.

13   So what we're seeing here is an

14 unusually low rate in this group, but then

15 those are the data, and we cannot

16 second-guess them. The purpose is to do

17 proper trials. We should do a large trial

18 and we should test this.

19   The blood pressure study, just to

20 point out, was introduced of necessity. In a

21 long-term trial, information comes along,

22 treatments change, guidelines change, and one

228

 1   thing the UKPDS demonstrated was a 45 percent

 2   increased risk of events in people who had

 3   hypertension in addition to their diabetes.

 4   We had no choice but to introduce a blood

 5   pressure study in a randomized factorial

 6   fashion if we wanted to see differential

 7   therapies in our open study randomized

 8   glucose groups. And this study differs from

 9   the glucose study.

10   Another misconception: This is a

11   treat-to-target multiple drug. The target

12   was 150/85 mmHy, and if the first drug didn't

13   make that goal, second, third, in a step-wise

14   protocol specified fashion, drugs were added.

15   In fact, over 30 percent of the patients were

16   on three or more drugs by three years. So

17   this is really quite a different approach to

18   treatment, and with that effect size

19   10/5mmHy, we saw significant and really very

20   impressive reductions in the risk for the

21   major outcomes pre-specified in the study.

22   And now of course, we cannot do a

229

 1 study without controlling this risk factor.

 2 And this is the two-by-two factorial. These

 3 are the randomized arms of the study, just

 4 showing that statistically in these 887

 5 patients who were in the two-by-two part of

 6 the study, a net improvement in those who had

 7 both tight glucose and tight blood pressure

 8 control in a stepwise fashion compared to

 9 those who had neither. It doesn't prove it,

10 but now Steno 2, and particularly the

11 extension, endorse the fact multiple risk

12 factor therapies have to be done. Any study

13 we do is going to be on a complex background.

14   So we did go on and do the

15 observation analyses. And we heard quite

16 nicely from Dr. Fleming the need to establish

17 what you might get for specific therapies,

18 and how that might play out on an

19 agent-by-agent basis. So again, these data

20 by Irene Stratton looked at the HbA1c

21 exposure over time against the hazard ratio

22 for coronary heart disease, and she

1   established that -- firstly, it was a

2   straight line relationship on this log linear

3   plot, no U-shaped curve, no suggestion that

4   there was a point where benefit might be

5   reduced as you went further down the curve,

6   and she established a 14 percent decrease was

7   the potential benefit for a 1 percent

8   decrement in A1c.

9   We've seen already that the study

10 had 16 percent for an 0.9 percent A1c

11 difference, so in line with the epidemiology,

12 and suggestive that another trial might buy a

13 result, and I believe ACCORD did most of

14 their power calculations based on these data.

15   For the blood pressure study, we

16 actually had a 14 percent decrease with 10mm

17 systolic blood pressure decrement, but the

18 effect of the trial was larger, and that's

19 where this issue of off-target effects,

20 multiple therapies, and non-glycemic

21 benefits -- or non-blood pressure benefits, I

22 beg your pardon -- might come into play. So

1   we were seeing more than we had expected, but

2   again, the relationship for blood pressure

3   established allowing us to make predictions

4   about the potential benefits of

5   interventions.

6   And for LDL-cholesterol, this is

7   not a published graph, but it is

8   demonstrating across the LDL-cholesterol

9   values observed during the study, again the

10   updated value, we would predict about a

11   29 percent decrease in risk for 1mmol of

12   decrement in LDL, and of course this is

13   almost precisely what HPS showed in the

14   diabetic gross subgroup, a 27 percent

15   decrease.

16   So we can, as it were, imagine the

17   sort of results we might see. We can plan

18   trials about potential benefits, and we can

19   also therefore look at multiple risk factors

20   in complex trial designs.

21   The problem is, it's all great

22   until the unexpected happens. Things come

1   along and they derail us. And the history of

2   the diabetologist is, we've had a bad run

3   with some agents -- with the best of

4   intentions. We've done a series of studies

5   and then found that we have had catastrophic,

6   usually cardiovascular or morbid results as a

7   result of off-target or unexpected issues.

8   And this really plays the fact that in a

9   gluocentric world, where we're looking at A1c

10 and microvascular, we cannot ignore the other

11 effects of these drugs, and cardiovascular

12 disease does need to be assessed where

13 appropriate in large-scale studies.

14   So what we've done here is tried to

15 capture in a model all the data that's in

16 UKPDS. This is a UKPDS outcomes model that

17 was put together with our group, but mainly

18 by Phillip Clarke and Alistair Gray who are

19 health economists, and what they tried to do

20 was see if we could look at the different

21 complications over time; that is not only the

22 macrovascular and microvascular, but the

1   sequences, and then assess these as quality

2   adjusted life expectancy, in order that you

3   can run trials in sillico, and you can, as it

4   were, optimize the designs and provide data

5   for the sort of calculations we saw in the

6   previous talk.

7   So this model, as it were, which is

8   used by a variety of groups now, including

9   mice (?) takes the data from the UKPDS which

10 is the best long-term natural history data we

11 have in that available, but could now be much

12 improved by using the other studies that are

13 here, and calculating for the major outcomes,

14 the determinants over time, and what is so

15 important in this is this is using time

16 varying covariants. So it's not just

17 baseline values.

18   The way the model works is to take

19 the information from a patient at any point

20 in their disease with or without

21 complications, and then on an annual event,

22 calculate their likelihood of having an

 1   outcome. You then update the covariates

 2   either on the natural history model that

 3   UKPDS provides or by imposing a trial design

 4   where you want to hold the difference, and

 5   then you rerun the model until at some point,

 6   all of the assimilated patients have died,

 7   and then you can do the calculation.

 8   Now, trials are no longer just

 9   glucose against two levels of glucose, they

10   are about managing on a background of varying

11   risk factors -- however you want to pull out

12   a net effect, so this sort of modeling allows

13   you to design trials perhaps more

14   efficiently.

15   But does it work? It predicts the

16   (inaudible) result, it predicts the HPS

17   result, but they are mainly just LDL

18   differences, of course, and quite simple.

19   But PROactive was an interesting

20   study. We've heard a lot about it but as a

21   study design, it's actually quite sensible.

22   In a high-risk group of people, in a usual

1 care setting, it's adding double blind

2 placebo control study on top of everything

3 else, and hopefully any differences are

4 protected by the randomization.

5 But this is a drug that has

6 multiple effects, and therefore, the question

7 is when in this principal secondary endpoint,

8 as it was referred to in the paper, they saw

9 a 16 percent risk reduction -- is this what

10 you might expect from the net changes in the

11 conventional risk factors or is this a magic

12 effect of the drug itself, in other words,

13 over and above what we have seen in the

14 physical measurements in the previous studies

15 with this agent?

16 So what we did was generate a

17 patient cohort who were matched precisely for

18 the published figures, including the measures

19 of dispersion for all of the risk factor data

20 that was available, both modifiable and

21 non-modifiable, and we achieved a population

22 which matched precisely, of course, by

1   definition, and then we applied these

2   changes. These were the within-trial

3   differences in A1c, blood pressure, and HDL,

4   and of course, they result in increase in

5   weight which was possibly adverse.

6   Now these actual differences we

7   could have culled from the literature because

8   many smaller-scale studies of this agent, if

9   you do a meta-analysis, would yield much the

10   same result. And when we ran the model, the

11   16 percent -- 2 to 28 percent result, the

12   model suggested 13 percent, which for

13   modeling is pretty close, and of course there

14   are other models, not just ours, that allow

15   you to do that.

16   This would suggest that the

17   secondary endpoint risk reduction fits with

18   the risk factor changes observed, leaving not

19   much opportunity for novel risk factors to

20   come into play.

21   For congestive heart failure, we

22   would actually have predicted an 11 percent

1   decrease. So in fact the 39 percent increase

2   reported in the primary study result is

3   perhaps more than it appears to be at first

4   glance, because the improvement in other risk

5   factors would have suggested an 11 percent

6   point estimate decrease.

7   So to conclude this part of this

8   talk, I think diabetes is a challenge for all

9   of us. It's a chronic condition, we've heard

10 that, and is incredibly complex. It's a

11 metabolic condition that requires long-term

12 trials to fully assess the outcomes, and we

13 need to improve therapies quite urgently,

14 firstly to arrest disease progression,

15 because it's on this background of relentless

16 need to keep increasing therapies that things

17 get complicated -- and if you have to give

18 multiple therapies for the same effect, that

19 can be beneficial, has been very successful

20 with blood pressure therapy, but also it

21 increases the chance for harm.

22   We have to not forget that the

1   reduction and prevention of microvascular

2   complications, particularly in patients who

3   have an extended lifetime as we reduce

4   macrovascular risk, cannot be ignored, but it

5   is this excess risk which remains the enigma.

6   We know that even when we reduce

7   the risk factor levels to those that are

8   optimal, the patients with diabetes still

9   remain at excess risk. And of course we are

10   now exploring that opportunities to look at

11   other therapies.

12   We heard that it may be (inaudible)

13   stress, may be insulin resistance, may be

14   inflammatory disease, may be endothelial

15   changes. In one of the targets at the moment

16   is the postprandial glucose rise, not

17   well-captured. UKPDS didn't have a measure

18   of it. We are doing two studies, one with a

19   postprandial glucose regulator, one with an

20   alpha glucosidese inhibitor, in large-scale

21   pragmatic trials, specifically to address

22   that, so it may be there are opportunities to

1   look at macrovascular risk reduction still

2   with a glucose difference, but specifically

3   targeted at one part of the daily profile.

4   Because of the complexity, and we

5   heard very elegantly just before me, we need

6   innovative and probably adaptive study

7   designs. If you're going to follow somebody

8   for 6 or 10 years, things will change, and we

9   must allow for the study to be flexible over

10   that period without compromising its outcome.

11   And of course, the off-target

12   outcomes that do no harm or capture the

13   unexpected benefit remain one of the

14   interesting issues that I hope will be

15   discussed later today.

16   I just pointed out that lifetime

17   models can help optimize trial designs in

18   this complexity, and with the statistical

19   expertise that's now available, it may be

20   that we are able to design more efficient

21   designs for the results we need to identify.

22   So large-scale pragmatic trials in a usual

 1   care setting I think should be commenced with

 2   all new agents as early as possible if we are

 3   to not only understand in a cohort of

 4   patients that represent those in whom will

 5   receive the treatment eventually, but also

 6   allow the opportunity in a large-scale study

 7   to investigate the relationship for the new

 8   agent with others -- setting up very

 9   specific, tightly controlled, closely

10   recruited patients for very tight

11   inclusion/exclusion criteria is fine for the

12   early studies where you need to establish the

13   parameters.

14   But in clinical practice, these

15   drugs get used in the vast majority of

16   patients. And we do need to go to studies

17   where we catch that information proactively.

18   We don't restrict entry just because we're

19   concerned that there may be an issue. If

20   there's a good signal beforehand, fair

21   enough. But if not, we should have as open

22   design as possible. And then of course, the

 1 crucial issue is monitoring that data in a

 2 timely fashion in order that we don't put

 3 people in excess harm for longer than

 4 necessary.

 5   Thank you.

 6   DR. BURMAN: Thank you, Dr. Holman.

 7   Questions from the panel?

 8   MR. PROSCHAN: You mentioned that

 9 randomization in UKPDS was pre-planned, the

10 obese patients. Why were those sample sizes so

11 different?

12   DR. HOLMAN: Okay, firstly,

13 randomization is one of those things that's too

14 important to leave to chance, so it's very

15 important that you actually get this right.

16 This is a child of its time. This is the

17 second-ever large-scale trial undertaken in

18 type 2 diabetes. And what I can tell you that

19 the pilot power calculations were looking at a

20 possible effect size of 50 percent, you can

21 understand why we were in the infancy then. As

22 we moved to the main trial, and we got

1   substantive funding, then of course we looked at

2   a much more sensible effect size, but this idea

3   of doing analyses on subsets of patients and

4   doing a power calculation for those, that just

5   wasn't done at those times, so we really just

6   left with the values that we had. The

7   proportion of patients in each group were

8   pre-established, but the numbers and the

9   potential power were not calculated from the

10   subgroups.

11   MR. PROSCHAN: But it looks like those

12   proportions were not one-half is what I'm

13   saying. It looks like it was not --

14   DR. HOLMAN: So nice piece of history

15   for the UKPDS. Because of the UGDP and the loss

16   of tolbutamide, there was a similar concern in

17   the States, though not so much in Europe, that

18   sulphonylureas were harmful, and of course the

19   study showed that not to be the case. So we had

20   a first and a second generation sulphonylurea

21   which was called propinmide and glitaneride.

22   And so we allocated 40 percent of the patients

1   to sulphonylurea, and lesser numbers to insulin

2   and then to metformin, and that was if we had to

3   drop the first-generation sulphonylurea, if it

4   had been toxic, we would still have a reasonable

5   number on the second generation. So that's why

6   it's an unequal split.

7   DR. TEMPLE: Is the pragmatic trial

8   that you think every new drug should get

9   designed primarily to show benefit, like say the

10 pioglitazone trial, or one to rule out risk?

11 There's a lot of questions that would follow

12 that, but at some point, if you actually show

13 benefit from lowering HbA1c more, no one will

14 let you do those trials. So which are you

15 talking about?

16   DR. HOLMAN: I think it's where the

17 tension of this whole discussion is going, and

18 if an agent is primarily reducing A1c and you

19 want to show it does that more effectively or

20 more efficiently than perhaps another agent,

21 that's one particular design of trial, but we

22 have to be concerned about off-target effects.

1   So that's why you need some long-term follow-up.

2   If you believe the agent has some

3   additional benefit over and above glucose,

4   which is going to perhaps improve your

5   cardiovascular effect, then you're going to

6   have that as the primary outcome probably,

7   looking to see if there is superiority. So I

8   think it depends on what we feel that agent

9   would achieve, but to put a new agent into a

10   patient for maybe 20 or 30 years without

11   having some sense of potential off-target

12   effects and a monitoring, I think, is no

13   longer acceptable. So it's horses for

14   courses is what you're trying to evaluate for

15   that agent.

16   DR. TEMPLE: But you're talking

17   particularly about adverse off-target.

18   DR. HOLMAN: I'm talking about both.

19   I think if you're going to use an agent for that

20   length of time and you have a mechanism which,

21   you know, does offer potential off-target or

22   pleiotropic effects, then you might want to

1   include those in the analysis plan. If it's a

2   specifically glucose-lowering agent, and there

3   are some very specific examples around, then

4   really you're just concerned about probably the

5   durability question is can you achieve A1c at a

6   target for longer without the complexity of

7   adding other agents? But you still need to

8   ensure that there isn't some unanticipated or

9   possibly beneficial effect.

10   DR. TEMPLE: I'm sure this will get

11   more discussion.

12   DR. BURMAN: Thank you. Dr. Rosen?

13   DR. ROSEN: One of your conclusions

14   was that modeling might help from UKPDS, and I'm

15   curious as to what happened with the modeling

16   for congestive heart failure, where you actually

17   predicted a decrease and you saw this increase.

18   Can you illuminate this for us a little more?

19   Is that based on the fact that there wasn't

20   experience with the TZDs in the UKPDS that was

21   the shortfall of the model prediction?

22   DR. HOLMAN: Yes, for the -- there

1   were no TZDs in the UKPDS. They weren't

2   licensed until the year after we published. And

3   the relationship with weight -- really, we see

4   CHF with increased weight gain, so the model

5   allows for the increased weight gain on TZDs,

6   but the effect in the trial, as you see, was

7   much larger than our model predicts. So this is

8   an example where modeling might give you a level

9   of comfort about a particular outcome, and if

10   you saw something going outside that prediction,

11   then the DSMV or those managing the trial, may

12   want to look in more detail at that aspect.

13   DR. BURMAN: Dr. Day?

14   DR. DAY: Concerning the modeling

15   studies, when there is a discrepancy between

16   what the model predicts and what some of the

17   outcomes are, is there anything consistent going

18   on? Is it structural properties of the models,

19   are there parameter weights or anything of the

20   sort? Can you comment on that? I'm

21   particularly interested in the use of the model

22   to test other things that aren't often tested,

1   such as other health conditions -- you're

2   matching your simulated patients for various

3   variables, but you could use those in an

4   experimental way perhaps if the models are

5   working well. So can you comment on model

6   predictability, and when there is a mismatch,

7   and is there anything consistent going on?

8   DR. HOLMAN: Modeling is a complex

9   area. In fact, with the ADA, we published

10 guidelines on what good models should do. So I

11 think the value of models is they allow you on a

12 common baseline to evaluate different

13 interventions, even complex ones. Models, when

14 used, have to be validated, and so you step

15 forward slowly in time taking datasets from

16 either registries or for trials, and if you can

17 match them, then you have a confidence, so we

18 are fairly happy that our model is validated in

19 some areas, not others. And that's how you move

20 forward.

21   As the data come together, as I'm

22 saying to this group, is we have the

 1   opportunity now with suddenly a large number

 2   of outcome trials, to take this sort of

 3   approach, refine it, and maybe get more

 4   accurate predictions, which might save time

 5   in the long-term. They're not a substitute

 6   for trials.

 7   DR. BURMAN: Thank you. I had a

 8   question. I think you showed a slide that

 9   wasn't in the packet regarding the effect of

10   sulphonylurea alone versus sulphonylurea plus

11   metformin in cardiovascular events, and you had

12   three bars on that graph. What was your

13   conclusion from those studies, because I think

14   it was slightly different from what I had

15   gleaned from the publication.

16   DR. HOLMAN: So in the publication, as

17   a post hoc analysis, we looked here at the trial

18   which is on the right-hand side, at the effect

19   of patients who, in a modified protocol, had to

20   stay on the sulphonylurea alone, if their

21   glucose rose above 108mg/dl fasting, or were

22   randomized to have additional metformin. And

1   the concern was that in the group that got the

2   additional metformin, there was an apparent

3   twofold increase in risk which was statistically

4   significant.

5   In the remainder of the trial,

6   patients who were not part of this sub-study,

7   who remained on sulphonylurea throughout the

8   trial, their event rate, if anything, was a

9   little higher. It wasn't significantly

10 different in this group.

11   So this is not special (inaudible),

12 it's just saying we have weighed the control

13 group in this comparison quite correctly

14 being those who remained on the original

15 therapy compared to those who got dual

16 therapy, there's an apparent doubling, or it

17 may just be that in this group, there's an

18 unusually low number of events.

19   The health warning is, these are

20 too small a number of events to draw a major

21 conclusion, and the real result to this is

22 you should do this trial properly, because

 1   now there is genuine uncertainty about the

 2   benefit of these two treatments together.

 3   Sadly, that's never been done.

 4   DR. BURMAN: Thank you. Other

 5   questions or comments from the panel? No?

 6   Dr. Parks, do you have any further

 7   comments before we break for lunch? Any

 8   other comments?

 9   Okay, then what we'll do now is

10   break for lunch. We'll reconvene again in

11   this room in approximately one hour, at 1:30,

12   an hour and 15 minutes.

13   Please take any personal belongings

14   you may want with you at this time. The

15   ballroom will be secured by the FDA staff

16   during the lunch break.

17   You will not be allowed back into

18   the room until we convene.

19   And panel members, please remember

20   that there should be no discussion of the

21   meeting during lunch amongst yourselves or

22   with other members of the audience.

1   Thank you.

2   (Whereupon, at approximately

3   12:14 p.m., a luncheon recess was

4   taken.)

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 1   A F T E R N O O N   S E S S I O N

 2   (1:27 p.m.)

 3   DR. BURMAN: We'll get started in

 4   about a minute or so. Everybody take their

 5   seats, please.

 6   Good afternoon. Why don't we get

 7   started on the afternoon session. Just a

 8   quick announcement. My understanding is

 9   Dr. Nathan and Dr. Gerstein won't be able to

10   attend the conference tomorrow, so if there

11   are any specific questions that you have for

12   them, it would be wise for you to ask them

13   later today.

14   We're going to start the afternoon

15   with Dr. Gerstein from McMaster University.

16   Thank you.

17   DR. GERSTEIN: Thank you very much.

18   And I'd also like to thank the FDA Advisory

19   Committee for asking me to be here and share

20   some of my insights. And I also am quite

21   honored to be asked to speak with such an

22   illustrious group of people.

1   I'm going to be discussing

2   macrovascular outcomes with anti-diabetic

3   drugs, and specifically talk about the

4   ongoing studies, as well as some of the

5   studies that have already reported briefly.

6   I think it's important for us to step back a

7   little bit and think about diabetes and what

8   diabetes means. You've already heard a

9   number of presentations today stressing the

10   point that diabetes increases the risk of

11   microvascular and macrovascular outcomes.

12   I would suggest that that is

13   actually too small a way to look at diabetes.

14   Diabetes is a huge, growing public health

15   problem that affects more than 10 percent of

16   people. And diabetes is, as we've already

17   heard, defined on the basis of hyperglycemia.

18   And diabetes increases the risk of a host of

19   problems that cannot be easily classified

20   into microvascular or macrovascular.

21   And on the slide, we see here the

22   chronic consequences of diabetes. And

 1   diabetes is an independent risk factor for

 2   all of these things. So it is today the

 3   single-most important cause of adult onset

 4   blindness. And eye disease is still an

 5   important part of diabetes.

 6   It is the single-most important

 7   cause of end stage renal disease. It causes

 8   significant neurologic disease, including

 9   nerve pain and foot pain, which can be quite

10   debilitating. And ulceration. It is the

11   single-most common cause of below-knee

12   amputations in Western societies. Yes, it

13   increases the risk of ischemic heart disease,

14   stroke, and peripheral vascular disease. And

15   the rest of my presentation will be based on

16   that.

17   But it also now is emerging as an

18   important and serious risk factor for

19   cirrhosis, secondary to non-alcoholic

20   steatohepatitis -- cognitive decline and

21   Alzheimer's disease now -- it's clear that

22   diabetes increases the risk about 50 percent.

1   It's increasing the risk of depression. It

2   increases the risk of hip fractures. Not

3   necessarily low bone density, but certainly

4   hip fractures. Imbalance and frailty.

5   Connective tissue disorders. Sexual

6   dysfunction and erectile dysfunction.

7   Infertility. And studies show that today

8   people with type 2 diabetes have about a 10

9   to 15 year earlier death on average.

10   So diabetes cannot be thought of as

11   just micro- or macrovascular disease. It is

12   a risk factor for many of the ills that

13   affect people in our society today. And when

14   we're thinking about outcomes to measure in

15   studies, we need to keep track of these, in

16   addition to the macrovascular outcomes.

17   Now, the nature of this meeting is

18   focusing on macrovascular outcomes, and the

19   rest of my presentation will focus on

20   macrovascular outcomes, with that caveat in

21   mind. So I'm going to discuss first the

22   relationship between diabetes and

1   cardiovascular disease, just to remind you of

2   the nature of the size of the relationship.

3   And then discuss the link between glucose and

4   cardiovascular disease, and then the

5   glucose-lowering trials and trials with other

6   drugs that may not be looking at

7   glucose-lowering, per se.

8   So what about the relationship

9   between diabetes and cardiovascular disease?

10 Even today, it is clear that diabetes is an

11 independent risk factor for cardiovascular

12 disease. So a recent meta-analysis of

13 450,000 people in studies done all around the

14 world published this result, which shows very

15 clearly that after adjusting for age, men

16 with diabetes are twofold more likely to have

17 fatal coronary heart disease compared to men

18 without diabetes.

19   And women with diabetes are

20 3.7-fold more likely to have fatal coronary

21 heart disease compared to women without

22 diabetes.

1   In addition, after adjusting for

2   all the other risk factors for cardiovascular

3   disease, there is clearly still a three-fold

4   higher risk compared to non-diabetes in

5   women, and a two-fold higher risk compared to

6   non-diabetes in men. So diabetes is an

7   independent risk factor for cardiovascular

8   disease.

9   Diabetes is defined on the basis of

10   hyperglycemia, that you've already heard.

11   And after adjusting for all the other things

12   associated with hyperglycemia that can be

13   clinically measured, it still is a risk

14   factor. So there is something about the

15   hyperglycemia that is adding risk to

16   diabetes. Adding cardiovascular risk to

17   people with diabetes that is not explained by

18   the other risk factors that also are higher

19   in people with diabetes. And I think that

20   needs to be kept in mind when we think

21   through this.

22   What about glycemia? What is the

 1   relationship between glycemia and

 2   cardiovascular disease in people with

 3   diabetes and in people without diabetes? And

 4   probably the best way to assess this is with

 5   a meta-analysis. And this meta-analysis was

 6   published in 2004. And this was a

 7   meta-analysis of prospective studies, cohort

 8   studies, or cohort analyses of trials.

 9   So prospective epidemiologic

10   studies that looked at the relationship

11   between A1c as a measure of

12   cardiovascular -- as a measure of

13   glycemia -- and cardiovascular risk, defined

14   here as coronary heart disease and/or stroke.

15   And you can see the list of studies

16   here. And these are the things that were

17   controlled for in these various analyses.

18   Some controlled for age and smoking, et

19   cetera. And when you look at the

20   meta-analyzed odds ratio, when you

21   meta-analyze all these studies, you see that

22   for every one percent higher A1c in these

 1   studies, there is an 18 percent higher risk

 2   of coronary heart disease and/or stroke.

 3   And probably this represents the

 4   best estimate of the relationship between A1c

 5   and cardiovascular disease in people with

 6   established diabetes.

 7   What about in people without

 8   diabetes? Very briefly to allude to that, as

 9   was referred to by Dr. Nathan, there was a

10   whole issue of the Journal of Chronic Disease

11   in 1979 that was not able to assess a

12   relationship or discern a relationship

13   between glucose and cardiovascular disease in

14   people without diabetes.

15   And in 1999, we published this

16   meta-analysis of all of -- the

17   meta-regression analysis of all of the

18   prospective studies that have been published

19   to that date, and showed if you go down to

20   glucose levels as low as 72 -- both two hour

21   glucose levels and fasting glucose

22   levels -- there is a graded progressive

1   relationship between glucose levels above 72

2   subsequent to cardiovascular events, and

3   there's no clear threshold that the diabetes

4   line -- and this type of data for both

5   two-hour or fasting glucose level supported

6   the notion that we introduced and coined the

7   term dysglycemia in the literature to show

8   that there is a progressive relationship, or

9   to reflect a progressive relationship between

10   glucose and cardiovascular events, starting

11   from normal levels going right up into the

12   diabetes range.

13   And subsequent to this, there have

14   been other papers that have subsequently

15   supported that, such as this meta-analysis of

16   1.2 million person years of data from the

17   Asia Pacific Collaboration using fasting

18   plasma glucose. And showed that for every

19   1 mmol/L, which is 18 mg per deciliter, rise

20   of fasting plasma glucose above 4.5, which is

21   about 80 or so, there's a 21 percent higher

22   risk of stroke. And for every 18 mg per

1   deciliter rise above normal, there's a

2   23 percent higher risk of ischemic heart

3   disease, and a 19 percent higher risk of

4   cardiovascular death.

5   And when one looks at two-hour

6   post-load glucose levels going down to

7   normal, this data from the Whitehall study

8   with 30 years follow-up shows a similar

9   thing. That as the glucose levels rise above

10 85, for every 18 mg/dl or 1 mmol/L rise above

11 85, there is a 22 percent higher risk of

12 coronary heart disease death. And after

13 adjusting for everything, there's still a

14 12 percent higher risk of coronary heart

15 disease death, with no clear threshold at the

16 diabetes sort of cutoff, which would be at

17 726. (?)

18   So it's clear from this in a

19 cartoon that I'll show next that there is a

20 graded relationship between glucose, however

21 it's measured, and cardiovascular disease.

22 And this relationship seems to extend down to

1   normal levels. And the relationship on a log

2   scale is certainly less steep.

3   It's not nearly as steep as the

4   relationship between glucose and eye disease

5   on a log scale. So this cartoon is on a log

6   scale. So curvilinear lines become linear

7   and the point -- this is not to scale,

8   obviously. But the notion is there seems to

9   be a steep relationship between eye disease

10   and perhaps kidney disease and glucose levels

11   starting around the diabetes threshold. And

12   for cardiovascular disease, and probably many

13   of the other consequences, the relationship

14   is shallower but seems to extend right down

15   to lower levels.

16   So starting from there, I think

17   then the next question is does glucose

18   lowering reduce cardiovascular disease

19   outcomes? And to first recapitulate a slide

20   that was shown -- actually, another version

21   of the slide was shown by David Nathan. In

22   type 1 diabetes, there seems to be fairly

1   strong evidence that that is indeed the case.

2   So this is the primary outcome for

3   the DCCT/EDIC analysis. And in that

4   analysis, which David described nicely, the

5   primary cardiovascular composite was more

6   than MI or stroke or cardiovascular death.

7   It included a number of other things as part

8   of the primary cardiovascular composite.

9   And this was the primary outcome,

10   which showed that intensified insulin therapy

11   targeting normal glucose levels for six

12   years -- the active treatment trial part

13   ended at six years -- led to a 42 percent

14   reduction in the primary cardiovascular

15   composite at about 18 years. And you can see

16   that the curves start to diverge at perhaps 3

17   or 4 years in these low-risk patients, and

18   then they go after that -- despite no

19   contrast after 6-1/2 years.

20   And in this particular study, which

21   I think shows for type 1 diabetes there is

22   evidence to support glucose lowering as a

1   cardiovascular protective therapy, post hoc

2   analysis showed that if you adjust for the

3   difference in A1c achieved during the trial,

4   you eliminated the difference in

5   cardiovascular events, suggesting the

6   hypothesis that the effect was due in large

7   part to the contrast in A1c that was achieved

8   by this trial by insulin.

9   That's sort of type 1 diabetes.

10   What about type 2 diabetes, which clearly

11   affects 90 percent of people with diabetes?

12   So I'm going to talk about trials of glucose

13   lowering first, and then I'll talk about

14   trials of glucose-lowering drugs. And I'll

15   make the distinction.

16   These are the trials in which

17   different levels of glucose are trying to be

18   achieved in some way or another to try to

19   prevent cardiovascular disease. And just to

20   start off at the bottom to orient you, here

21   is a spectrum of dysglycemia, starting from

22   perfectly normal glucose levels going up into

 1   the diabetes range. As the glucose levels

 2   rise, the glucose levels are first

 3   high-normal and then high. Then they go into

 4   the impaired fasting glucose and/or impaired

 5   glucose tolerance range. And then they

 6   develop frank type 2 diabetes.

 7   And as I've already showed, as

 8   glucose levels rise above normal, the risk of

 9   cardiovascular disease rises and is clearly

10   there. And this also may include many of the

11   other consequences I showed you. So

12   cognitive decline, perhaps sexual dysfunction

13   and other things may track with this. But

14   then as you get close to the diabetes

15   threshold, the risk of eye, and kidney, and

16   perhaps nerve disease starts to rise as well.

17   And this is obviously a cartoon, but sort of

18   reflects where we are.

19   Three trials -- the ACCORD trial,

20   the VA diabetes trial, and the ADVANCE trial

21   have recently been reported. And they are

22   examining people with well-established

1   diabetes, more than five years' duration in

2   this sort of 5- to 15-year duration of

3   diabetes. And they've assessed all of them

4   in one way or another, whether a strategy of

5   more-intensive glucose lowering using a menu

6   of drugs -- a different menu of drugs -- but

7   a menu of drugs achieves lower cardiovascular

8   events than a strategy of less-intensive

9   glucose lowering using the similar menu of

10 drugs.

11   And so those are those two trials.

12 This trial, the origin trial, is ongoing.

13 And this trial is assessing whether a

14 strategy of trying to normalize the fasting

15 glucose levels with insulin glargine reduces

16 cardiovascular events more than usual care.

17 So but it is also attempting to lower glucose

18 level in an open type design.

19   So I'm going to talk about these

20 three trials mainly. And I'll first go over

21 briefly the ACCORD findings. So the ACCORD

22 study had 10,251 people in it. This was a

 1   study conducted -- NIH sponsored study in the

 2   United States and Canada -- and asked whether

 3   in middle-aged or older adults with

 4   established type 2 diabetes who were at high

 5   risk for cardiovascular events because they

 6   either had existing cardiovascular disease or

 7   because they had additional risk factors for

 8   cardiovascular disease in addition to

 9   diabetes -- in those people, does a

10   therapeutic strategy targeting an A1c less

11   than 6 percent reduce cardiovascular events

12   more than one targeting 7 to 7.9 percent,

13   about 7.5 percent?

14   And people had an average age of

15   62, diabetes of 10 years' duration.

16   35 percent had previous cardiovascular

17   disease. The average BMI was 32. And the

18   mean A1c -- these were poorly controlled

19   people with diabetes -- the mean A1c was

20   8.3 percent. The median was 8.1 percent.

21   And 35 percent were on insulin therapies. So

22   these were advanced diabetes.

1   And as was already shown, there was

2   a very clear contrast achieved in A1c levels

3   between these two groups. So within -- they

4   came in with a median A1c of 8.1 percent.

5   The standard group within four months

6   achieved 7.5 percent and stayed there for

7   almost the whole duration that was analyzed.

8   And the intensive group within four

9   months had gone down to 6.7 percent. And by

10   eight months was 6.5 percent, and then

11   6.4 percent. And stayed around there for the

12   duration. And the data that were presented

13   are those that were published in the New

14   England Journal of Medicine three weeks ago.

15   These were the results in that

16   publication. And as you know, the

17   Independent Data Safety Board recommended,

18   because of excess mortality in that trial,

19   that the intensive intervention arm

20   participants stop getting that intervention.

21   And they have subsequently been transitioned

22   to the standard arm. But these were the

 1   findings that drove that. So in the

 2   intensive arm, the mortality rate was

 3   5 percent versus 4 percent in the standard

 4   arm for an increased risk of 22 percent and a

 5   p-value .04. The study obviously did not go

 6   to its planned completion at this point. And

 7   at the time that the study stopped, there was

 8   a trend towards a reduction in the primary

 9   outcome, which was the classic MI stroke

10   cardiovascular stroke outcome of 6.9 percent

11   in the intensive versus 7.2 percent in the

12   standard for a non-significant hazard of .9,

13   or a 10 percent reduction.

14   Other secondary outcomes in

15   addition to mortality, non-fatal MI, there

16   was a 24 percent significant reduction in

17   non-fatal MI. Cardiovascular death, there

18   was a 35 percent increase in cardiovascular

19   death. And then heart failure and non-fatal

20   stroke had really nothing either way on

21   either direction.

22   The next slide will show the

 1   mortality event curves. And I think the

 2   thing to point out here is the time when the

 3   events began to accrue within the two groups.

 4   And you can see the mortality rates in the

 5   standard group are 1.14 percent per year. In

 6   the intensive group, 1.41 percent per year.

 7   Certainly it looks from this curve like the

 8   curve separated at about two to three years

 9   at some point. And that persisted

10   subsequently.

11   The primary outcome curves, you

12   see, were not statistically significant. As

13   I pointed out, 2.1 percent per year versus

14   2.29 percent per year. And obviously, this

15   is a trend only. If there is any effect on

16   the primary outcome, it's clearly not going

17   to occur within the first three years. And

18   the data that we're presented with ACCORD

19   represent a median of 3.5 years of follow-up

20   data.

21   So at this point in time, we know

22   that a strategy of intensive therapy

1   targeting A1c less than 6 percent does cause

2   an increased mortality on a median of 3.5

3   years of follow-up.

4   What about the ADVANCE trial? The

5   ADVANCE trial had 11,140 patients with

6   well-established type 2 diabetes once again.

7   The average age was 55. High cardiovascular

8   risk patients. They had a median duration of

9   diabetes -- I think it was seven years, as I

10   recall. And I'll show you that later. And

11   they asked whether sulfonylurea as initial

12   therapy plus any added treatment that

13   targeted A1c less than 6.5 percent can reduce

14   cardiovascular events more than usual care as

15   it is given within any of the investigators'

16   sites.

17   And the primary outcome was a

18   composite of either micro- or macrovascular

19   events. And this was the difference in A1c

20   that was achieved. There was about a

21   .6 percent difference in the standard group

22   versus the intensive group. Point out that

1   it took three years to achieve that

2   difference. And the study was a five-year

3   median duration follow-up.

4   Bob Ratner has already showed you

5   this slide, that the primary outcome showed a

6   significant 10 percent reduction in micro- or

7   macrovascular events, with the action being

8   in the microvascular event domain and not in

9   the macrovascular event domain. So there was

10   a 6 percent non-significant reduction, but a

11   14 percent significant reduction in

12   microvascular events.

13   When one looks at the macrovascular

14   events in more detail, stroke and non-fatal

15   MI were fairly neutral, as was cardiovascular

16   deaths, which trended to the left of the

17   line. Again, those are the point estimates,

18   and it's non-significant.

19   One can think of the events in many

20   ways as confirming the results of the UKPDS

21   that Professor Holman showed earlier on, but

22   not telling us a lot about macrovascular

1   outcomes. And certainly, the ADVANCE

2   intervention does not suggest a benefit from

3   macrovascular outcomes.

4   So just to come back to this slide

5   that I showed earlier on, there's ACCORD and

6   ADVANCE. The VA diabetes trial also was

7   presented. And that has not yet been

8   published. And I'll show you in the summary

9   slide some of the results from the VA

10   diabetes trial, which was a much smaller

11   trial with a lot less power, looking at 1,700

12   people to see whether a more-intense versus a

13   less-intense glucose lowering strategy made a

14   difference. And then I'll show you some of

15   the characteristics of origin as well.

16   So this slide kind of compares and

17   contrasts these four trials. And I think I

18   should probably start by focusing on the VA

19   study since that's the one I didn't show data

20   from. The VA diabetes trial, 1791 patients.

21   Diabetes for 11-1/2 years, high

22   cardiovascular risk, 6.3 years' duration.

1   The A1c fell from 9.5 percent at

2   baseline to 6.9 versus 8.4. And multiple

3   polypharmacy was tested. The ADVANCE trial,

4   diabetes for eight years. Long duration

5   again. Study duration five years, 6.4 versus

6   7 was the A1c contrast, and it was testing

7   sulfonylurea plus multiple therapies.

8   I showed you ACCORD. Study

9   duration at the time it was presented, 3.5

10 years. Diabetes for 10 years, so all

11 well-established, long-term diabetes, 8.1 to

12 6.4 versus 7.5. Multiple treatments were

13 tested.

14   And origin is still ongoing.

15 12,000 people. Participants have either

16 diabetes or IFG or IGT, so they have early

17 dysglycemia. Much earlier than the other

18 trials. It's an ongoing study, and the

19 intervention is largely mediated normal

20 glycemia versus usual care.

21   What about the results of those

22 trials? Well, here, they're summarized here.

1   So ACCORD, for the cardiovascular primary

2   outcome, non-significant, 10 percent

3   reduction, myocardial infarction, 24 percent

4   significant reduction of secondary outcome.

5   Mortality, secondary outcome

6   22 percent harm. ADVANCE, primary outcome

7   6 percent non-significant, MI 2 percent

8   non-significant, mortality 7 percent

9   non-significant.

10   VADT, I don't have the mortality.

11   I don't know if they were presented. I don't

12   recall them being presented in the

13   presentation. A 13 percent non-significant

14   reduction. And remember, a much smaller

15   study with much less power to look at.

16   And obviously, the results for

17   ORIGIN aren't known. So those are the trials

18   of glucose lowering therapies or approaches.

19   What about glucose lowering drugs? And this

20   is kind of an important distinction. Because

21   when one is giving a drug to prevent

22   cardiovascular events, the question will

 1   always be is it the drug that's doing it or

 2   is it what the drug is doing to the glucose

 3   or the LDL or the blood pressure, or any

 4   other risk factor that's doing it, or both?

 5   And often it will probably be a combination.

 6   So here are the glucose-lowering

 7   drug studies -- trials -- that are ongoing.

 8   So the same format as the previous slide.

 9   There's the spectrum of dysglycemia.

10   Diabetes at the top, IFG, IGT high glucose

11   there. And I'll go over them briefly. I'll

12   spend a few minutes showing data once again

13   from PROactive and RECORD briefly. And I'll

14   just now allude to the other trial.

15   So there are four trials that have

16   been or are being conducted in people with

17   established type 2 diabetes. Again, a fairly

18   established duration. And I'll show you

19   PROactive and RECORD. BARI 2D is asking the

20   question of whether lowering glucose with

21   insulin-providing therapy, such as

22   sulfonylurea or insulin, has a different

1   effect on cardiovascular events than lowering

2   glucose with insulin-sensitizing

3   therapies -- metformin, rosiglitazone, et

4   cetera.

5   The HEART 2D study which was just

6   presented at the ADA was asking whether

7   targeting prandial glucose levels with bolus

8   insulin reduces events more than targeting

9   basal insulin -- basal glucose levels with

10   basal insulin, or fasting glucose levels with

11   basal insulin -- has an effect on

12   cardiovascular events. And this study was

13   neutral. It did not show any effect. And I

14   won't say more about the HEART 2D study.

15   There are two studies that are

16   ongoing right now in people with impaired

17   fasting glucose and/or impaired glucose

18   tolerance. Navigator is looking at whether

19   or not giving the drug Nateglinide, which is

20   a rapid-acting glucose-lowering glinide

21   reduces cardiovascular events more than

22   giving a placebo in people who are at high

1   risk for cardiovascular disease but have IGT.

2   The ACE trial, which is being led by

3   Professor Holman, is asking whether Acerbose

4   versus placebo reduces cardiovascular events

5   in patients with IGT but who are at high risk

6   for cardiovascular events.

7   So these are the spectrum of

8   glucose-lowering drug studies that are

9   actually ongoing. And I'll just spend a few

10   minutes just revising or viewing the results

11   from PROactive and then RECORD, since they've

12   been published. PROactive, again, as you

13   recall, was a study of 5,000 patients with

14   well-established type 2 diabetes whose A1c

15   was greater than 6.5. And they were

16   randomized to max dose Pioglitazone first as

17   placebo, with a composite primary outcome

18   that was prestated. And this was a short

19   trial, 2.9 years of follow-up.

20   And this was the primary outcome

21   from the PROactive trial. And the primary

22   outcome showed a non-significant 10 percent

 1   reduction. And it's appropriate to point out

 2   that the curves cross. So earlier in the

 3   study, there was a trend towards worsening

 4   events in the one group. At the end, there

 5   was a trend towards less events in the

 6   Pioglitazone group.

 7   And the other important point to

 8   point out in this study is the fact that

 9   Pioglitazone is a drug that lowers glucose

10   level. And this was a randomized double

11   blind placebo-controlled trial, but clearly

12   there was a lower glucose level. There was a

13   HbA1c contrast of .6 percent. The

14   investigators were told to intervene whenever

15   they could to keep glucose levels as low as

16   possible. And they did. But there was a

17   contrast. And you'd expect there would be

18   when there is an additional glucose-lowering

19   drug being added.

20   There was also a blood pressure

21   contrast. And it's well-established that

22   glitazones lower blood pressure. Of course,

 1   there was a systolic blood pressure contrast.

 2   And there was a slight LDL contrast and a HDL

 3   contrast, et cetera, as is pointed out.

 4   And this is always going to

 5   happen -- when you give drugs to see whether

 6   one prevents events, you're going to look at

 7   the chemical effect of the drug, plus

 8   whatever the drug does to the risk factors.

 9   And it seems a little bit silly and

10   artificial to try to design a trial where

11   you're going to prevent any of the risk

12   factors from changing and just have the drug

13   versus placebo.

14   Because, A, you're going to

15   threaten the blind, and, B, it'll be a very

16   artificial thing that one's doing. And it

17   won't reflect when one is doing real life

18   studies in patients, or one is doing real

19   life prescribing after the trial is over.

20   Because when the trial is over, you're

21   actually dealing with things as they come up

22   when you prescribe drugs.

1   What about the RECORD study?

2   RECORD was a non-inferiority trial, which was

3   designed to see whether adding rosiglitazone

4   to either metformin or sulfonylurea has any

5   difference in cardiovascular events compared

6   to adding metformin and sulfonylurea

7   together. That's essentially what was asked.

8   So is rosi plus either metformin or

9   sulfonylurea non-inferior to sulfonylurea

10   plus metformin regarding cardiovascular

11   disease?

12   This is 4,000 people, A1c 7 to

13   9 percent on maximum metformin or

14   sulfonylurea at baseline. And they are

15   randomized to that therapy.

16   Addition of rosi or not. And the

17   study -- an interim analysis was published at

18   3.75 years. And this is what it showed. It

19   showed that for the primary outcome of

20   cardiovascular hospitalization or

21   cardiovascular death, there was no signal at

22   all, 1.08 with a p of .43. For

 1   cardiovascular death, there was a

 2   non-significant 17 percent reduction -- not

 3   significant for any death. There was a

 4   non-significant 7 percent reduction

 5   non-significant. Acute MI, 16 percent

 6   non-significant increase. MI stroke

 7   cardiovascular death of 3 percent

 8   non-significant reduction. But clearly for

 9   heart failure, which is known for the

10   glitazones, there was an increase.

11   And so right now at this point in

12   time, the results of all the trials that have

13   been published so far, or they're ongoing,

14   are not clearly telling us whether any of the

15   glucose-lowering drugs or the

16   glucose-lowering therapies clearly reduce

17   and/or safely reduce cardiovascular events or

18   not. And some of these things are still up

19   for grabs. And the answers to these

20   questions are still unknown.

21   So in conclusion, diabetes and

22   non-diabetic dysglycemia are present for

 1   decades. And they will be present for

 2   decades. And there are strong risk factors

 3   for cardiovascular disease in people who have

 4   these. A key determinant of this risk is the

 5   elevated glucose. Whether elevated glucose

 6   is a marker for an unmeasured issue is

 7   obviously possible, but clearly it is a key

 8   determinant of this risk.

 9   Despite trends that have been out

10   there, reported trials of intensive

11   glucose-lowering strategies using

12   combinations of drugs have not detected

13   cardiovascular benefits in people with

14   advanced well-established diabetes. If there

15   is a benefit in such people, it will be

16   modest initially.

17   So the initial benefit will be

18   modest, and it will require five or more

19   years to clearly emerge. And I think we see

20   that more and more that for glucose lowering

21   or glucose type trials, one will need more

22   than five years. Remember, the UKPDS had a

1 median follow-up of 10 years. And so I think

2 that's becoming very clear.

3   Trials of anti-diabetic agents or

4 strategies need to be long enough, at least

5 five years, and large enough to allow any

6 beneficial effect to emerge or to establish

7 non-inferiority. And as already Dr. Fleming

8 said, if you do a million person trial for

9 two days, you'll have the right number of

10 events, but you'll learn nothing about

11 whether that intervention does anything. All

12 you're going to get is side effects. You're

13 not going to get any benefits. You're just

14 going to see side effects. You need a long

15 enough trial for any benefits to start to

16 work for the underlying biology to be

17 changed.

18   Short trials may miss benefits.

19 And it'll only detect adverse effects. And

20 this is being seen, for instance, in the DCCT

21 trial, which everybody in the world clearly

22 acknowledges that intensified insulin therapy

 1   for type 1 diabetes prevents retinopathy.

 2   But had the DCCT been stopped at two years,

 3   we would have concluded that it actually

 4   increases retinopathy and it causes

 5   significant hypoglycemia. And our whole view

 6   of type 1 diabetes would have changed

 7   completely.

 8   So one needs to have long enough

 9   trials to answer this question. Whether

10   glucose lowering or prevention of its rise by

11   an anti-diabetic agent as opposed to a

12   strategy by an anti-diabetic agent reduces

13   cardiovascular disease in people with early

14   diabetes or pre-diabetes remains unknown, and

15   is being tested in a number of studies right

16   now. And whether most specific anti-diabetic

17   agents reduce cardiovascular disease or other

18   clinical outcomes remains unknown.

19   So there's two components of this.

20   The first one is we don't know what happens

21   even if we did a glucose-lowering strategy in

22   people with early diabetes or early

 1   dysglycemia. Maybe as you get advanced in

 2   the course, you're going to have less of an

 3   effect of glucose-lowering agents. But we

 4   also don't know what the specific

 5   agents -- whether any specific anti-diabetic

 6   agent has a benefit.

 7   If such an agent is effective, it

 8   may either be due to the agent and/or its

 9   effects on glucose or blood pressure, or

10   whatever. The only anti-diabetic agent shown

11   to reduce cardiovascular disease in a 10-year

12   trial is metformin, and it needs to be

13   replicated, as Rury Holman said. It is

14   clearly not replicated yet, but it is the

15   only one so far.

16   And finally, diabetes increases the

17   risk of many serious diseases.

18   Cardiovascular disease is not the only

19   clinically important outcome. Anti-diabetic

20   agents that will make a difference are those

21   that will be proven to reduce clinically

22   important outcomes and not just glucose

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 1   levels. And these outcomes may include

 2   cardiovascular disease, but do not

 3   necessarily have to include cardiovascular

 4   disease.

 5   Thank you for your attention.

 6   DR. BURMAN: Thank you very much.

 7   This discussion is open for questions.

 8   DR. KONSTAM: Thanks very much. I

 9   want to pick your brain a little bit about

10   ACCORD. And actually thinking about it, I sort

11   of want to raise the thought that, you know, you

12   set up this nice dichotomy between drug versus

13   strategy, but I'm thinking there may be, in

14   fact, three elements. You know, one is drug,

15   one is level of blood sugar, and then three is

16   strategy. Because your strategy to lower blood

17   sugar may have some adverse effects,

18   particularly in the short-term. Maybe more than

19   just two elements, per se.

20   Because I wonder about ACCORD. And

21   I'll sort of pick two findings. You know,

22   suggested findings to get your thoughts. One

1 is that looking at the curves for the primary

2 endpoint, it looks like there's absolutely

3 nothing going on for quite a while, and then

4 they begin to separate.

5   And I wonder whether that actually

6 is an emergence of an natural history effect

7 in arthrosclerosis, perhaps, or something.

8   And the other interesting thing

9 that you didn't show is the subgroup

10 findings. Specifically vis-a-vis patients

11 who started out with HbA1cs above and below

12 8. And there really seems to be something

13 going on there. And I just wonder if you

14 could sort of expand what you really think is

15 going on with ACCORD with those points.

16   DR. GERSTEIN: I think a couple of

17 things. Certainly, the subgroup findings from

18 ACCORD did suggest that there may be a

19 benefit -- a bigger benefit in people who had

20 better -- less-advanced diabetes at

21 randomization. Their A1c was less than

22 8 percent. There seemed to be a benefit in the

 1   primary outcome on ACCORD compared to people

 2   whose A1cs were greater than 8 percent. And

 3   that was a heterogeneous finding. So in other

 4   words, that was a significant difference in

 5   subgroups.

 6   That was not apparent in the

 7   mortality outcome. However, there was a lot

 8   less power to detect heterogeneity and the

 9   mortality outcome because there were a lot

10   lower events in the mortality outcome.

11   So after the fact, one can always

12   come to any conclusion that one wants. But

13   if you sort of -- there is some evidence from

14   ACCORD to suggest that what I said may be

15   true. There may get to a point in diabetes

16   that once you've had diabetes for a long

17   enough period of time, it may take a long

18   time or it may be impossible to reduce any of

19   the glucose-related effects of it. We don't

20   know that.

21   And that's why I think it's

22   important that we focus on the earlier

 1   spectrum of dysglycemia as part of our

 2   ongoing trials.

 3   The second question related to

 4   whether or not it takes a while for any

 5   glucometabolic intervention to emerge. And I

 6   think the trends that we see in the ACCORD

 7   event curve suggest that it may. They're not

 8   significant, and so perhaps those curves will

 9   collapse afterwards. Perhaps it's the play

10   of chance. However, it is certainly possible

11   that they won't, and they may continue to

12   diverge. And I think that drives my

13   conclusion, that when we do -- and you see

14   that also in the proactive study, by the way.

15   That those curves are trending in a

16   direction. And perhaps if that study had

17   gone another one or two years, you would have

18   seen a much bigger effect.

19   I think it does take time. When

20   we're using any cardiovascular intervention,

21   especially one that doesn't have a dynamic

22   effect, you're changing underlying biology.

1   You're asking the blood vessels to remodel.

2   You're doing other things, and it makes sense

3   that it's going to take a while for a benefit

4   to emerge, if there is a benefit.

5   DR. KONSTAM: I guess my main question

6   is how much of a thorn in the side is ACCORD of

7   the theory that the more we lower blood sugar

8   within that range, the more benefit we will get.

9   You know, how worried do we have to be about

10 ACCORD that that's just wrong?

11   DR. GERSTEIN: I think ACCORD provides

12 important information that we didn't know. What

13 we learned from ACCORD is that in patients like

14 ACCORD, an aggressive strategy to profoundly

15 intensively lower A1c targeting less than

16 6 percent has -- at least in that 3-1/2-year

17 window -- has a mortality signal. And I think

18 that's an important one. Obviously, other

19 studies need to look at it. And it tells me as

20 a clinician that that information has to be

21 taken into account. When you're looking at your

22 patient in front of you with an A1c of

 1 8.5 percent, thinking am I going to try to get

 2 this person's A1c down to normal, little yellow

 3 flag. Wait a second.

 4   There's the ACCORD trial. It

 5 doesn't tell us what would happen if we were

 6 targeting less than 7 percent. It doesn't

 7 tell us anything about preventing A1c from

 8 rising. If somebody's A1cs are 7 percent,

 9 should we make it go up to 7.5 percent?

10   Clearly, that's not information

11 that comes out of the ACCORD study. And the

12 farther you go from the actual findings in

13 ACCORD, the more speculative the conclusions

14 come. And I'm trying to stay as close as

15 possible to the data when I say that. And

16 acknowledging the limitations. And there's a

17 lot more information to come even from

18 ACCORD, because the study is continuing.

19 There's a blood pressure, a lipid

20 intervention, plus other analyses of a legacy

21 effect and other things that may emerge. I

22 think we need to wait and see.

1   But it certainly raises a yellow

2   flag. And it tells us that when we have

3   data, things are not nearly as simple as they

4   are when we don't have data.

5   DR. BURMAN: Thank you. Other

6   questions? Dr. Genuth.

7   DR. GENUTH: In the DCCT, the first

8   observed effect of intensive treatment was a

9   worsening of retinopathy, which is correct. And

10   that had already been seen in several European

11   studies, trials, and case reports. But it's

12   very interesting to note that those people who

13   suffered early worsening in retinopathy were as

14   likely, and in fact, even more likely, to

15   ultimately have a beneficial effect of that same

16   intensive treatment by the seven year end of the

17   trial as were the people who didn't suffer early

18   worsening.

19   And I think that may have

20   applications to the cardiovascular disease

21   situation, in that it may suggest that there

22   are different biological effects which we

 1   don't yet understand that made things worse

 2   for retinopathy, and a different biological

 3   effect that ultimately made retinopathy

 4   better.

 5   So in ACCORD, for example, we may

 6   be seeing that kind of thing in that early

 7   mortality may result from intensive treatment

 8   by one mechanism, and ultimately with further

 9   follow-up, we may see a beneficial effect,

10   which just underlines the same point that

11   everybody has made. You need long-term

12   follow-up in all trials, as long as we can do

13   them safely for long-term.

14   DR. BURMAN: Dr. Savage.

15   DR. SAVAGE: One thing I'd like to

16   hear your comment on is that several people have

17   mentioned the issue of whether you could

18   intervene early on diabetes and get a different

19   outcome, versus the type of trial that ACCORD

20   and ADVANCE, so forth, where you have people

21   with 10 years or so duration. But there's a

22   major difference between getting normal or

1   near-normal gycosylated hemoglobin in those two

2   groups of people. In the early onset patients,

3   maybe one drug, an oral agent, can normalize the

4   glucose with minimal risk of major oscillations

5   of the glucose or hypoglycemia. These very

6   complex regimens inevitably have a component of

7   hypoglycemic risk.

8   So could you comment on that?

9   DR. GERSTEIN: Clearly, you're

10   100 percent right. When you're intervening on

11   people that have more-advanced diabetes, there's

12   going to be more adverse consequences of that

13   intervention. Which means more drugs are going

14   to be used. There'll be more hypoglycemia, et

15   cetera. Now, in the end, the question is

16   whether the benefits as my colleague in front of

17   me said -- is whether the benefits outweigh the

18   risk.

19   So in the DCCT, the risk of severe

20   hypoglycemia was 27-fold higher than in the

21   intensive group compared to the standard

22   group. However, the whole world acknowledges

1   that the benefits of intensified insulin

2   therapy in type 1 diabetes clearly outweigh

3   the risk. And the challenges being in the

4   DCCT to find therapies in type 1

5   diabetes -- to find therapies that minimize

6   the risk while maintaining the benefit.

7   I think the same type of thing

8   applies to type 2 diabetes. As we're using

9   multiple therapies -- or if we try to use

10 multiple therapies, we're going to have

11 adverse events. There's no question.

12   And you'll never be able to know

13 what adverse event is attributed to what drug

14 or whether it's a strategy, et cetera. It

15 becomes a lot simpler when one is looking at

16 earlier on in the course of diabetes. You

17 can get better glucose control with one or

18 two agents, a lower dose of insulin, less

19 hypoglycemia, because there's beta-cell

20 function, which is defending the body against

21 hypoglycemia. There's alpha-cell defending

22 it, et cetera.

1   So it just makes it harder to make

2   the inference. I think the ACCORD, and the

3   ADVANCE study and the VA study, those had to

4   be done. Right now as a result of their

5   findings, the focus on other trials is

6   probably going to shift somewhat.

7   I'm not sure if I totally answered

8   your question, Peter, but there's no real

9   answer to that question.

10   DR. SAVAGE: One quick follow-up.

11   Everybody is now talking about individualizing

12   care.

13   And I think most of us know there

14   are some individuals -- people who are

15   alcoholics -- there are certain people that

16   you obviously don't want to intensify glucose

17   control in. But I'm not at all clear that

18   the recommendations that are being given out

19   are specific enough for people to make a

20   choice in the real-world setting as to who

21   are the people that they would be

22   particularly worried about and who are the

 1   ones that might be less of a risk. Do you

 2   want to comment on that?

 3   DR. GERSTEIN: I think it's difficult

 4   to do that -- to ever take the results of any

 5   clinical trial and apply them directly to the

 6   patient in front of you.

 7   I think it's always -- actually, I

 8   think it's impossible.

 9   Clinical trials, and all the

10   evidence that we generate, don't tell you how

11   to manage patients.

12   All they do is they inform the

13   clinical management of patients so that you

14   can look at the person in front of you, take

15   the results from the trial, and say, all

16   right, what do I know from the trials? What

17   does this person tell me about there? What's

18   their other risk profile? And make an

19   individualized decision.

20   I would say the same thing about I

21   don't think you should give statins

22   indiscriminately who walks into your door, or

 1   ACE inhibitors, or anything else, because

 2   then that's cookbook medicine, and then you

 3   don't need physicians. And clearly,

 4   everybody does not respond the same way to

 5   therapies. So I think that as we get more

 6   data we can sort of get a sense of which

 7   patients are going to respond better or not.

 8   So I think that's probably the best

 9   answer to the question. We cannot blanketly

10   apply any finding to all of our patients. We

11   just have to individualize it.

12   DR. BURMAN: Yes, please.

13   MS. FLEGAL: Yes, I'd like your

14   thoughts on two things. One is in ACCORD,

15   they're really not able to accomplish the goal

16   of the intensive therapy. Is it marginal return

17   from additional therapy, just not enough to

18   lower below six? And the other is kind of a

19   different topic, but it reminds me of the

20   obesity paradox literature a little bit where

21   obesity increases incidents. But sometimes it

22   improves mortality. Is there any distinction

1   between incident CVD and mortality from CVD

2   that's involved with some of these findings?

3   DR. GERSTEIN: The first part of the

4   question is ACCORD achieved A1c levels in these

5   participants that had not been achieved in any

6   other clinical trial. And the A1c levels that

7   were achieved were deemed -- people did not

8   think they could be achieved. They didn't go

9   down to 6 percent, but we learned something from

10   that. And the most important thing in any trial

11   is the contrast between the two groups. So

12   there was a contrast of 1.1 percent between the

13   two groups.

14   So I think for the period of time

15   that it was happening, the question was being

16   asked, but the second question about the

17   obesity paradox is hard to answer because

18   that's based on epidemiology.

19   And you know, the whole question

20   of, you know -- I'm not sure that I really

21   have an answer for that question. Because

22   you're saying is it possible that glucose may