We really have two sources of data to talk about rosiglitazone risk by itself. We have the integrated clinical trials summary that has been discussed extensively and we have DREAM.

Both of these studies are primarily placebo-controlled, and what I will be focusing on for the rosiglitazone meta-analysis are the placebo-controlled studies. The reason why we do that is because in the placebo-controlled study we can see most clearly what is the intrinsic risk, the add-on risk of rosiglitazone compared to its non-use, controlling for everything else.

[Slide]

So now, looking at the rosiglitazone meta-analysis, the details of that study have been described already but, most importantly, it was a post hoc adjudication of routine reported events. So, ascertainment may not have been what you would typically hope to see in a randomized clinical trial that was designed for cardiovascular outcomes.

In the DREAM study I think it is

particularly important to note that it was in pre-diabetic patients, patients where the risk of a coronary heart disease outcome was particularly low.

[Slide]

This slide shows a forest plot of placebo-controlled trials only, focusing on the serious ischemic heart disease risk. In her presentation, Joy Mele, our statistician, showed you similar forest plots for total ischemic heart disease, where she found an odds ratio of 1.4 for serious ischemic heart disease and for the unadjusted post hoc MACE outcome an odds ratio of 1.2. But in all of those, it was with all comparators. What I am showing you here is what happens when you take that total serious ischemic heart disease and you do it with placebo and you get an odds ratio of about 1.7, and it is statistically significant, and across these groups there is no heterogeneity. In other words, all of these meta-groups are describing a common risk.

Now, it is important to recognize that

these are placebo add-on studies. So, what we are seeing is that patients are on other treatments and we are adding placebo or adding rosiglitazone. We are seeing what the value is that rosiglitazone adds. So, what this analysis show us is that while rosiglitazone lowers hemoglobin A1c because, remember, all these studies came from the package of studies done by the sponsor to get approval of the drug, or afterwards to show that it is effective in treating diabetes, so while at the same time lowering hemoglobin A1c, we are increasing cardiovascular risk. So, the notion of using hemoglobin A1c and relying on it as a surrogate measure for future coronary heart disease benefits really must be called into question because you would have expected in this group, if I am lowering hemoglobin A1c that I am going to lower coronary heart disease risk as well, and that is not what we see.

[Slide]

Now, much time was spent in our statistician's talk about potential interaction. A

lot of time was spent looking at nitrates and ACE inhibitors. The interaction that I am presenting here on nitrates is from Joy Mele's presentation, and I want to call your attention to the fact that she did three analyses, one with total ischemic heart disease that included serious plus non-serious, then a second one that was serious. So, that means that it threw out the ones that were non-serious. Then, a third that was MACE.

It was only in the analysis of total ischemic heart disease that included both serious and non-serious that this interaction with ACE inhibitors was seen. As soon as we throw out the non-serious events, that is, the patients, whatever happened to them, were probably patients on nitrates because they had stable angina and they were having a recurrence of their angina or increased frequency of their angina but it is not serious enough to bring them into the hospital, because when we look at the serious or the MACE outcome this interaction isn't present.

The second thing I would like to point out

is that with ACE inhibitors there was no statistical evidence of an interaction between ACE inhibitor use and the outcome of ischemic heart disease risk, and that is what this p value for interaction tells us.

The third point I would like to make is that even if you want to assume that, yes indeed, there is an interaction, among the group that wasn't getting nitrates or wasn't getting ACE inhibitors there is still a 30 percent increase in risk. That is not trivial, especially when you consider that patients with diabetes have a two- to fourfold increased risk of cardiovascular disease. So, any increase in risk has this magnification effect that gets added on top of that.

Finally, in reference to the whole question of ACE inhibitors, I think it is important to realize that in the United States last year over 50 percent of patients treated with rosiglitazone were already on ACE inhibitors, and one could make the argument that all patients with diabetes should be on ACE inhibitors. So, even if there is an

interaction with ACE inhibitors, and I think there is a lot of contradictory evidence about whether there is or there isn't, it is still an important factor because diabetic patients eventually probably will be on an ACE inhibitor if they are not already on an ACE inhibitor.

[Slide]

Next I would like to turn to the DREAM study because I think there is a lot of information here that hasn't been discussed yet. Before turning to the question of the potential interaction with ACE inhibitors, I want to call your attention to what we see as the overarching message of DREAM, and that is that DREAM was conducted in pre-diabetic patients, patients at much lower risk for cardiovascular outcome than patients with well-established diabetes.

In this study, although we found that if you treated patients with rosiglitazone there was a delay in the onset of development of diabetes. In the face of that delay in the onset of diabetes, we still increase coronary heart disease risk. So,

that is a paradox and that paradox isn't explained and it hasn't been discussed up until now. It is the same paradox that we see in the rosiglitazone meta-analysis. How is it that you can lower hemoglobin A1c and increase coronary heart disease risk?

Now I want to talk a little bit about the interaction question in DREAM. A lot of time was spent talking about the fact that in the rosiglitazone plus ramipril, ACE inhibitor, arm we saw the increase in myocardial infarction and cardiovascular composites and congestive heart failure compared to patients treated with ACE inhibitor only. But we didn't see that in the rosiglitazone arm.

We have several questions relating to this. The first is it is well-established that rosiglitazone increases congestive heart failure. That is a well accepted fact. That being the case, why is it that in the rosiglitazone arm DREAM didn't capture it? It captures it in the arm with the ACE inhibitor but it doesn't capture it in the

arm where it is rosiglitazone only and we would have expected that it would because rosiglitazone causes heart failure.

Now, ramipril and ACE inhibitors are very effective therapy for congestive heart failure. So, you might expect that actually you would have seen it over here and maybe seen it less over here because you have the ACE inhibitor on board, which is a treatment for congestive heart failure.

So, this brings us to ask the question if we are not seeing congestive heart failure in the group over here that was not included in the ACE inhibitor randomization, could it be that we missed congestive heart failure, and could it be that we have also missed other coronary heart disease events? Or, if that is not the case, is there something different about this population within the randomization scheme than the group that was put here? In other words, could this simply be a play of chance? And, we think that when you compare these findings and this anomaly, this congestive heart failure anomaly, it raises a

broader question about whether what we are seeing is the play of chance rather than a true interaction with ACE inhibitors.

[Slide]

So, when we get to the question does rosiglitazone increase cardiovascular risk, we believe that the answer to that question is yes. The FDA meta-analysis has shown an increase of between 20 and 70 percent in ischemic heart disease risk within 6 to 12 months of rosiglitazone use compared to its non-use. This was especially noticeable in the placebo-controlled studies.

In DREAM we saw a risk increase of about 40 percent. This is in a relatively low risk population. Now, there is uncertainty about what the possible ACE inhibitor interaction findings mean, but overall cardiovascular risk was, nonetheless, increased.

Finally, ACE inhibitor use in patients taking rosiglitazone in 2006 was that over half the patients were using it. So, this really makes you wonder, well, if there is an interaction is that an

important consideration anyway because most of these patients are already on an ACE inhibitor and if they are not, they should be.

[Slide]

So, now we get to our second question, does rosiglitazone increase cardiovascular risk compared to pioglitazone? We have a pioglitazone meta-analysis that I will present results from. Takeda submitted these to FDA earlier in the year and they were reviewed by FDA and, as you heard earlier, they are in the process of reviewing the meta-analysis to sort of parallel the type of analysis that FDA did of GSK data.

We also have PROactive and then we have a third study called GLAI, which was a head-to-head clinical trial of rosiglitazone versus pioglitazone and it was done by Takeda to look at lipid effects of these two drugs.

[Slide]

Now, the pioglitazone meta-analysis of clinical trials included all randomized, double-blind, controlled trials that were in

Takeda's clinical trial database, excluding PROactive. So, there were about 10,000 pioglitazone-treated patients, about 11,000 person-years of exposure in the meta-analysis. It was submitted in 2006. FDA reviewed it and FDA did not re-analyze the data themselves but Takeda is doing a re-analysis for us now.

Takeda performed a prespecified patient-level time to event analysis that was stratified by category of study duration but it is not clear whether it was stratified by study itself. So, we don't know if randomization was preserved so we don't know whether it was truly a meta-analysis or a pooled analysis. I am going to call it a meta-analysis because that is what the company called it. The primary outcome was all deaths plus non-fatal MI plus non-fatal stroke. These were identified from standard adverse event reporting and these events were not adjudicated.

[Slide]

This slide is from the sponsor's submission to FDA. It shows the probability of

event on the Y axis, the time to event on the X axis, study time in weeks. The lower bar is pioglitazone use, the upper bar is comparator use. can see that for the outcome of all-cause mortality, MI and stroke the hazard ratio is 0.75. The confidence interval is going from 0.55 to 1.02.

[Slide]

Now, PROspective has also been discussed recently. It was a randomized, double-blind, add-on, placebo-controlled study. The primary outcome was all-cause mortality and a bunch of other things. You can see them here. The hazard ratio was reduced but they just barely missed getting traditional levels of statistical significance with an upper bound of the confidence interval of 1.02, but the majority of the data was below 1.

For the secondary outcome, all-cause mortality plus non-fatal MI plus non-fatal stroke, the hazard ratio was 0.84 and that was statistically significant.

[Slide]

This slide shows the meta-analysis results in the upper line, PROactive in the middle line and the combination of both in the lower line. Here we can see the hazard ratio of 0.75 and the confidence intervals that go up to 1.02, PROactive, 0.84 and overall 0.83. So, the conclusion from this is that while it may not prove definitively that pioglitazone reduces cardiovascular and coronary heart disease risk, certainly it is not increasing the risk and, if anything, it looks like it may be decreasing the risk.

[Slide]

This slide is comparing the results from the MACE analysis of the rosiglitazone integrated clinical trials meta-analysis that Joy Mele presented earlier. So, that is cardiovascular death, non-fatal MI and stroke. I am comparing those results with the result of the pioglitazone meta-analysis which differs slightly because it is all mortality, not just cardiovascular deaths but it is all deaths but otherwise non-fatal MI plus

stroke.

Plotting them together and doing a test for heterogeneity, which is basically my attempt to get at a test of difference, what we see here from this analysis is that there is in general a difference between the two drugs, at least if we compare one meta-analysis to another for outcomes that are fairly similar.

[Slide]

There was a head-to-head study done of rosiglitazone versus pioglitazone, submitted to FDA in February of 2005, a randomized, double-blind, 24-week study. The purpose of it was to assess the lipid effects of rosiglitazone and pioglitazone. Cardiovascular events were collected. They weren't adjudicated. However, the case report descriptions, in the words of the reviewing FDA medical officer, were very convincing. I looked at them myself and they are very convincing. The two groups were very balanced, as you would expect in a randomized study.

[Slide]

There were 366 patients in the rosiglitazone group, 369 patients in the pioglitazone group. You see the number of patient-years. There were 7 serious cardiac adverse events in the rosiglitazone group versus 2 in the pioglitazone group. Down here, in the footnote, you can see that there was a case of sudden death, 1 MI, 4 emergency CABGs and 1 case of unstable angina in the rosiglitazone group. There was 1 MI, 1 emergency CABG coronary artery bypass graft surgery in the pioglitazone group. This is the rate per 100 patient-years and the relative risk is 3.5 with a confidence interval that crosses 1 and a p value of 0.1. So, it doesn't achieve statistical significance but the compass needle is pointing in favor of pioglitazone and against rosiglitazone.

[Slide]

So, does cardiovascular risk with rosiglitazone differ from that with pioglitazone? We believe the answer to that question is yes. From DREAM, a relatively low risk population,

rosiglitazone increased the risk by about 40 percent compared with placebo. From PROactive, which was a very high risk population, pioglitazone decreased risk by about 15 percent compared with placebo. From the rosiglitazone meta-analysis, rosiglitazone increased the risk of serious ischemic heart disease by 40 percent compared with all comparators and by 70 percent compared with placebo. In the pioglitazone meta-analysis, pioglitazone decreased risk by about 25 percent compared with all comparators. From the head-to-head GLAI study, rosiglitazone increased risk by about 3.5-fold compared with pioglitazone.

[Slide]

Does cardiovascular risk with rosiglitazone differ from that of metformin and sulfonylurea? To examine this question we have ADOPT, RECORD and BARI 2D.

[Slide]

Now, ADOPT, as has previously been discussed, were recently diagnosed patients with type 2 diabetes, with a mean interval from

diagnosis of about one year. There were no prespecified cardiovascular outcomes. There was no cardiovascular adjudication and there was post hoc arbitration of congestive heart failure. So, by no stretch of the imagination was this a cardiovascular outcome trial.

[Slide]

ADOPT was not designed to assess cardiovascular risk. It had no established prespecified or audited procedures for capturing cardiovascular events such as MI, stroke or congestive heart failure so we really don't know what the completeness of ascertainment was. This lack of established procedures could cause problems relating to how events were captured, how they were classified, how they were coded and then how they were analyzed.

This slide shows pertinent adverse event data from ADOPT. The source of this was the publication in the *New England Journal of Medicine*. What I would like to call your attention to is that for congestive heart failure, once again, we

know that rosiglitazone causes congestive heart failure. But ADOPT did not clearly capture that, certainly not against metformin. We know that metformin doesn't increase congestive heart failure. Dr. Ratner, in his presentation earlier where he put up the nice 2X2 slide showing the different drugs and the different risk factors and the things that they cause, the complications that they cause--heart failure is one of the problems that you see with metformin. So, ADOPT didn't distinguish these two drugs with respect to congestive heart failure. It did distinguish them with respect to, in quotes, edema, twofold difference. So, this gets back to the question of how were events captured; how were they coded; and how much trust you can place in a study that isn't designed with cardiovascular outcomes in mind. And, ADOPT was not designed with that in mind.

Another anomaly with ADOPT is that the lowest rate for MI in ADOPT was found in the sulfonylurea group. This contradicts the UKPDS which found a difference between metformin and

sulfonylurea with respect to MI in overweight patients. It also contradicts the observational data that Dr. Gelperin presented just a few moment ago where, in carefully performed observational studies where there is linkage and capture of out of hospital deaths and total mortality, we see that sulfonylureas increase cardiovascular mortality and death compared to metformin, but we don't see that here.

So, at this point I would add that there is one other piece of evidence that really won't be presented in any detail today, but I and Dr. Paul Singh, from California, have just completed a study in California Medicaid data so it is an observational study. Just as the studies that were presented by GSK from Ingenix and PharMetrics, and just as the studies that Dr. Gelperin talked about, in our study, which had over 6,000 myocardial infarctions in a diabetic population of over two million diabetic patients we found that the relative risk of hospitalized myocardial infarction in rosiglitazone patients was increased with a

relative risk of 1.3. For pioglitazone the risk was 1.01. For metformin the risk was 0.85 and that was statistically significant, as was the rosiglitazone increase statistically significant, and for sulfonylureas the risk was increased 11 percent and that was also statistically significant.

So, from our Medicaid study we found that rosiglitazone increased the risk the most. Sulfonylurea increased the risk next. Pioglitazone did not increase risk and metformin decreased risk.

Finally, it should be noted that despite the very low statistical power that the ADOPT study has, for each of these outcomes the occurrence was greater in the rosiglitazone group than it was in the metformin or the sulfonylurea groups.

[Slide]

Dr. Gordon presented the BARI 2D study. This study is not designed to answer the questions that we are talking about today. It is not designed to answer questions about specific drugs. If you noticed in one of the slides that Dr.

Gordon put up, over 50 percent of the patients who had been randomized to insulin providing drugs were on both metformin and rosiglitazone. So, if metformin reduces risk, and the UKPDS suggests that, and rosiglitazone increases risk. If we don't see an increase in risk you have blending of effects. In other words, BARI 2D is not going to give us an answer to the specific question of what is the risk of rosiglitazone.

A further complication within BARI 2D is that assignment to either rosiglitazone or metformin is not blinded and it is not randomized. So, people now can select which drug they want to put patients on. The reason why we do randomized clinical trials in the first place is to get rid of the bias that might be introduced when you don't have blinding and you are not having random allocation.

The questions that BARI 2D is designed to answer it will answer. But it is not designed to answer a question about whether or not rosiglitazone increases cardiovascular risk. It

will not meaningfully inform that question. It has markedly low statistical power to answer drug specific questions. And, the finding of increased risk in the rosiglitazone integrated clinical trial summary that was presented by Dr. Mele earlier of rosiglitazone plus insulin in that meta-group may have implications for BARI 2D.

[Slide]

Now, the RECORD study has been previously discussed. I would like to just mention what our concerns are with that study. Its non-inferiority design has intrinsic limitations for safety studies. Suboptimal study execution related to adverse event identification or reporting could mask differences between groups. The non-inferiority margin of 20 percentB-a 20 percent margin for patients who have a 200-400 percent increase in cardiovascular risk, that is an enormous margin. No rationale or explanation was provided in the study of why a 20 percent increase was thought to be rational or reasonable. We don't think that it is.

The study was open-label. That means the potential for bias in the way we report the events are captured, and the way they are reported is magnified. The primary endpoint doesn't focus on the events that we are most interested in. This outcome of cardiovascular hospitalization could be driven exclusively or primarily by congestive heart failure and other things that don't relate specifically to coronary heart disease, which is what we are really concerned about today. Finally, it really does have very low to absent statistical power, as I will show you in the next slide.

[Slide]

This slide summarizes the power of ADOPT, BARI 2D and RECORD to exclude a 20 percent increase in coronary heart disease risk for rosiglitazone versus, in this case, metformin but for sulfonylureas the power calculations would be the same. What you see is that the statistical power is less than 10 percent. As I will show you in a few minutes, the whole point of statistical power is to avoid false-negative conclusions. What this

says is that we have no protection against that. There could be a risk that 20 percent in these studies won't be able to tell us with any degree of certainty that that risk isn't there.

So, none of these studies will really provide meaningful evidence about the comparative cardiovascular risk of rosiglitazone and metformin or rosiglitazone and sulfonylureas.

[Slide]

What is the problem? Why am I focusing on study power? Low power is equivalent to what is called high type II error, and type II error is the probability of concluding that the treatments are the same when they really differ. So, in this situation it would be saying rosiglitazone and some other drug have the same cardiovascular risk when actually rosiglitazone increases the risk.

So, the consequences of low power are that we will falsely conclude that the treatments are the same when important differences in risk exist. So, that is the false negative. That is the false-negative conclusion. This would promote a

false sense of security and complacency and it could lead to the failure to take appropriate measures to protect patients from unnecessary harm. What it really boils down to at the end of the day is that you could have a large study but if it is designed in a particular way that it has low statistical power, even though you think you have evidence, you really don't. It is the absence of evidence. It is the absence of evidence because it doesn't have the ability to actually see the problem if it is there, and the absence of evidence is not the same as evidence of absence.

[Slide]

So, does the cardiovascular risk of rosiglitazone differ from that of metformin or sulfonylurea? The data provide inadequate and insufficient evidence to conclude that rosiglitazone does not increase cardiovascular risk compared to metformin or sulfonylureas. It also provides inadequate, insufficient evidence to conclude that they are the same. Neither RECORD nor BARI 2D, in our view, will provide meaningful

answers to this question.

[Slide]

This slide attempts to summarize in one place all the evidence that we have talked about today. On the X axis we have the hazard ratio, the odds ratio, the relative risk and it is on a log scale. Above the X axis we have the placebo or placebo add-on controls and below we have studies that are active controls.

If the point estimate is over on this side of 1 the risk is increased for that particular drug. If the point estimate is on this side the risk is decreased for that particular drug. The red are the studies comparing rosiglitazone, the yellow are the studies comparing pioglitazone.

What you can see is that in general the compass needles for rosiglitazone are all pointing south. That is, they are all pointing towards an increase in coronary heart disease risk. The compass needles for pioglitazone are all pointing north. That might not mean that pioglitazone protects against coronary heart disease. The

agency isn't prepared to make that statement, nor am I, but clearly it is not increasing the risk.

ADOPT and RECORD, because of their low power, really don't provide any real meaningful evidence on this but, as is shown here, the point estimates are on the risk increase side of the graph.

[Slide]

I would now like to turn to what is the population impact of cardiovascular risks and benefits of rosiglitazone use.

[Slide]

First I will focus on our estimations of potential cardiovascular harm from rosiglitazone use. To do the following analysis we used estimates of the relative risk obtained from the rosiglitazone meta-analyses and from DREAM. We used background rates for cardiovascular death, non-fatal MI and stroke from the published literature. To do this, I reviewed nearly 100 articles from the published literature to get a good estimate of the background rates in the

diabetic population. Although many of the articles reviewed didn't have relevant data, at least 40 did. Then we used national prescription data to estimate the person-years of rosiglitazone use in the population, and this is the time at-risk.

[Slide]

The analysis I will show you accounted for variability and levels of excess risk while focusing on what we believe is the range of most likely risk that we are talking about. Three different point estimates of relative risk were used. We used a relative risk estimate of 1.2, which as the MACE analysis from the rosiglitazone meta-analysis; another estimate of 1.4 from the rosiglitazone meta-analysis and DREAM for serious coronary heart disease in DREAM; and then 1.7 from the rosiglitazone meta-analysis of placebo-controlled data. We will show you information plus/minus one standard deviation because we think that this captures where most of the likelihood is for what the risks are. And we used the inter-quartile range for background event

rates in diabetic patients to try to further constrain what the range of most likely harm is that we are dealing with.

[Slide]

I will orient you to this slide. What this slide attempts to show is for varying background rates per 100 patient-years of the outcome of cardiac death plus non-fatal heart attack, going from a background rate of 1.2 up to 3.4. That represents the inter-quartile range from the literature, with a median value of 2.1. Given those background rates and the relative risksB-this slide is for 1.4 but we have similar slides at relative risk of 1.2 and another one at 1.7 and I will summarize everything on the next slideBwhat we do is we calculate. The blue dots represent the point estimate and the red line the plus/minus one standard deviation around that estimate for the number of excess cases of cardiac death and non-fatal MI that we think might have occurred in the U.S. based on a particular relative risk and these background rates. The next slide will

summarize these analyses in greater depth.

One thing to point out here is NNH. This is the median estimate at 1.4. What it says is that there are about 80,000 excess cases of cardiac death and MI attributable to rosiglitazone use over the seven and a half year period that this analysis covers. For that estimate the numbers range from about 30,000 up to about 140,000. The number needed to harm of 114, what that tells you is that at this point for every 114 patients that we treat with rosiglitazone for a year we produce one extra case of serious coronary heart disease.

[Slide]

This slide summarizes at a relative risk of 1.2 for the MACE analysis, 1.4 and 1.7 what the excess cases of cardiovascular death and non-fatal MI or cardiovascular death, non-fatal MI and stroke are for each of these scenarios.

What you can see is that combining all outcomes together we are talking about a range of between 66,000 and 200,000 or so for excess cases attributable to rosiglitazone over the period of

time that we are talking about.

What I would like to add is that while we haven't established that pioglitazone conclusively reduces coronary heart disease risk, if it does, if the slide I showed earlier where there is a 15 percent overall reduction in risk with pioglitazone, if that really is in fact true, then we have in addition an opportunity cost. That is, not only is there an excess cost of using rosiglitazone compared to not using it, but there is an additional cost incurred by using rosiglitazone instead of pioglitazone. If you did that, then these numbers, here, would be substantially increased. They would each go up by about 30 percent.

[Slide]

So, what are the benefits that we are interested in? How does rosiglitazone compare to pioglitazone? How does it compare to other oral diabetes agents? And, are there benefits unique to rosiglitazone?

Two recently published systematic reviews

help provide some information and insight on this question concerning major clinical outcomes. So, these are the real reasons why patients are treated for diabetes. This is what you are hoping to prevent, hoping to prevent cardiovascular death, MI and stroke and then so-called microvascular complications of diabetes, retinopathy, nephropathy and neuropathy. There is no evidence, none whatsoever, to support a benefit of rosiglitazone with these outcomes.

[Slide]

Now, for so-called intermediate outcomes, and these are more like surrogate endpoints. These aren't health outcomes. These are laboratory measures or other measures. For hemoglobin A1c, all of the drugs reduce hemoglobin A1c so there is no particular advantage to one drug or the other.

As has been alluded to earlier, the thiazolidinediones increase low density and high density cholesterol. You can see weight increase, heart failure unique to thiazolidinediones, hypoglycemia, bone fractures.

You can see then from this slide that there really are no what we would call unique intermediate outcome benefits to any of the thiazolidinediones and that includes rosiglitazone as well. So, we see that there are no major health benefits demonstrated for rosiglitazone, neither macrovascular benefits nor microvascular benefits. We also see no evidence that rosiglitazone confers any advantage over other oral anti-diabetes treatments for a variety of intermediate outcomes. Finally, rosiglitazone confers no unique advantage over pioglitazone and appears to be inferior to pioglitazone with respect to some intermediate outcomes.

I didn't present the results for that, but in the head-to-head studies both pioglitazone and rosiglitazone increase HDL cholesterol and LDL cholesterol. Rosiglitazone increases the LDL much, much more than pioglitazone and pioglitazone increases HDL much, much more than rosiglitazone. So, for cholesterol, in terms of raising it, pioglitazone is less damaging than rosiglitazone.

For triglycerides, rosiglitazone raises triglycerides and pioglitazone doesn't.

[Slide]

Now, for approval definitive proof, and I put that in quotes because many people within FDA, within the Office of New Drugs have insisted that definitive proof is what we need in order to take an action on a safety concern. Definitive proof of efficacy is obtained, and that is the p value less than 0.05. The health benefit, on the other hand, is assumed because it is not demonstrated and it is not proven. But the efficacy measures don't often translate into long-term benefits. When a postmarketing safety concern arises it is important to reassess that assumption of benefit. The benefit/risk assessment must be made at the population level. It is not something that gets made at the level of an individual patient but it is made at a population level.

In an actionable level the threshold for evidence for serious risk is not definitive proof. Definitive proof is rarely possible due to

statistical power considerations. In order to have definitive proof for a safety question you would need statistical power of at least 95 percent to minimize the false-negative conclusions. It is an unreasonably high threshold considering the obligation to protect the public from serious harm.

[Slide]

So, despite uncertainty, the analysis must take into account the potential consequences of risk, as well as the magnitude and certainty of the health benefit. Prior measures of efficacy are often inadequate to justify the serious risk so actual health benefits are necessary. It is important now to focus on coronary heart disease outcomes, not blood sugar. I showed previously that there is a dissociation with rosiglitazone between hemoglobin A1c and coronary heart disease risk. Hemoglobin A1c goes down, coronary heart disease risk goes up. So, we need health benefits.

For a health benefit to justify a serious risk, we believe that it must be clinically important and meaningful. It must be of comparable

or greater health value to patients, and occur with a greater frequency than the risk, and there must be definitive evidence or very strong evidence to support that benefit.

[Slide]

When one approaches a decision analysis of the benefits and risks the public health cost of a wrong decisionB-this is the public health cost now, not financial cost but public health cost-Bare not symmetric. There is absolutely no evidence of a major clinical health benefit with rosiglitazone. If rosiglitazone increases the cardiovascular risk a wrong decision will cost thousands of lives. If rosiglitazone doesn't increase cardiovascular risk the wrong decision causes no population harm because other therapies are available.

Now, the data on rosiglitazone cardiovascular risk, though not definitive, strongly suggests the following: It suggests that rosiglitazone cardiovascular risk is increased. Three studies suggest this, rosiglitazone meta-analysis, DREAM, and GLAI. The pioglitazone

cardiovascular risk is not increased and may be decreased compared to other therapies, including rosiglitazone. We have three studies for that, pioglitazone meta-analysis, PROactive and GLAI. Other studies, such as BARI 2D and RECORD, will not provide adequate evidence to refute these findings.

[Slide]

So, in conclusion, we believe that rosiglitazone increases cardiovascular risk compared to its non-use; that pioglitazone does not increase cardiovascular risk and may decrease that risk; that rosiglitazone has no unique short-term benefits related to glycemic control. Rosiglitazone also has no demonstrated long-term health benefits related to cardiovascular disease, diabetic retinopathy, nephropathy or neuropathy.

Given these conclusions, we ask the question are there definitively documented population-level health related benefits of rosiglitazone to justify its continued marketing? For that, we conclude the answer is no and that rosiglitazone should be removed from the market.

After stating this, I would like to say that the future studies in progress will not change our state of knowledge. The poor design and low power of RECORD and the low power of BARI 2D mean that a very high risk of a false-negative conclusion exists. Waiting for these studies will ensure additional 1,600 to 2,500 adverse cardiovascular events per month. And, waiting for these studies does not seem to make sense to us.

Now, senior officials within FDA have maintained that you can't withdraw rosiglitazone based on a meta-analysis. That ignores any consideration of whether rosiglitazone has demonstrated health benefits. We would also like to point out that it ignores the fact that earlier this year FDA withdrew Zelnorm, a drug for irritable bowel syndrome on the market, based solely on a meta-analysis. Now, we have much more data here than a single meta-analysis. We have not only the rosiglitazone meta-analysis, we have a meta-analysis of pioglitazone. We have DREAM. We have GLAI and we have PROactive.

So, this is an unprecedented wealth of data and all of it is consistent. The compass needles for every rosiglitazone study points south in that rosiglitazone increases coronary heart disease risk. For pioglitazone every compass needles points north and suggests that it doesn't increase coronary heart disease risk.

Since 1980 FDA has withdrawn over 30 drugs from the market. Almost all of these drugs were withdrawn based solely on MedWatch adverse event case reports. For those of you who aren't familiar with that, those are the things that physicians, patients and pharmacists send in to FDA saying they have seen an adverse event. In the hierarchy of evidence, MedWatch case reports are considered the lowest form of evidence. They have the lowest quality, the lowest weight, the lowest degree of certitude. Yet, with 30 drugs being withdrawn from the market, that level of evidence was sufficient to pull drugs off the market to protect the public from harm.

I would also like to point out that in

2000 FDA withdrew Resulin, triglitazone, the very first thiazolidinedione so it is in the same class as pioglitazone and rosiglitazone. Triglitazone was withdrawn from the market because we had 80 case reports of acute liver failure with the drug. And, when that was compared with pioglitazone and rosiglitazone that same signal wasn't seen. At the time that triglitazone was withdrawn from the market the rationale given by FDA was that resulin, triglitazone, as an outmoded drug compared to pioglitazone or rosiglitazone. I think that the same could be said about rosiglitazone today, being compared to pioglitazone. Thank you.

DR. ROSEN: Dr. Meyer?

Conclusions and Summary

DR. MEYER: In the interest of time, I will make my comments from the chair rather than from the podium.

Over the course of this morning the committee has heard a lot of data and some opinions, and you have much to consider. The last talk summarized the opinions of a senior member of

the Office of Surveillance and Epidemiology based on his consideration of the various data sets relevant to Avandia, including those earlier discussed by Drs. Mahoney and Mele.

I think it is important that the committee understand there is a fundamental disagreement within CDER on the scientific conclusions that should be drawn from the information available. Of course, if there were unanimous opinion we need not have convened an advisory committee.

I do agree with the last talk, as do my Office of New Drug colleagues, that we need not have definitive proof of harm to act. Avandia, like other oral diabetic therapies, is approved only for glycemic control as no oral agent, as you have heard, including Avandia, has been proven to have a positive effect on long-term macrovascular risk. In other words, we use hemoglobin A1c for these drug approvals as a direct endpoint of glycemic control, not for its potential surrogacy.

FDA is not at all sanguine about a drug for type 2 diabetes posing a potential

cardiovascular ischemic risk. If the evidence does reasonably establish an elevated cardiovascular ischemic risk for Avandia, and the evidence reasonably establishes that this risk is not found with comparator drugs, that would raise a profound concern for us, irrespective of any statistical significance.

Speaking for myself, I must say that I don't have a particular opinion at this moment on the correct regulatory action that should be taken with regard to Avandia. I do, however, have a profound interest in the FDA making all of its decisions based on good, rigorous, fair and evaluation of all the available data that is properly and dispassionately weighed.

In anticipation of this afternoon's discussion, we have set forth for you three types of evidence that you need to consider in weighing the questions. The first are the meta-analyses. The most robust signal of potential cardiovascular ischemic risk with rosiglitazone comes from a meta-analysis of the registration trials. The

studies in this meta-analysis were mostly six months in duration, and the large majority were placebo-controlled. These trials have all the limitations of the large randomized, controlled trial databases or large randomized, controlled trials that you have just heard about. They have all those limitations and more because they are just small registration trials that do not generally have any kind of prespecified safety outcomes.

I would point out that the pioglitazone pooled analysis, referred to prominently in the last talk, was largely a pooling of active-control trials so it was very different from that which was comprising the Avandia meta-analysis. In fact, I would remind you that when the active-control trials in the Avandia meta-analysis were separately looked at they showed no signal of risk.

The second set of data that you need to consider this afternoon are the individual randomized, controlled trials. Given the limitations of meta-analytic techniques, it is

important to place the evidence from the Avandia meta-analysis into context with the other available data, especially those from long-term randomized trials such as DREAM, ACCORD and RECORD. These trials, which have their own merits and limitations, do not show a worrisome signal, at least not relative to the likely therapeutic choices. For example, while some FDA, and outside of FDA, have expressed the opinion that RECORD will not have adequate statistical power to refute the meta-analytic signal, considering the results in the interim analysis many, myself included, find the data quite informative to date. As an example, for the composite endpoint of death, MI and stroke a values grouping of cardiovascular outcomes in clinical trials, the point estimate for the hazard ratio with rosiglitazone in RECORD is 0.96, with the upper bound of the confidence interval being 1.24 and the lower bound 0.74.

While this may not prove the meta-analysis is wrong, RECORD already has far more outcome events than all the studies that made up the

meta-analysis and on the MACE endpoint RECORD already excludes a 25 percent increase in risk.

The third set of data you will need to consider are the observational studies. In weighing all the evidence we should not dismiss these out of hand. Many of these studies have not shown an elevated risk for rosiglitazone compared to other treatments.

That said, I fully acknowledge the limitations of pharmacoepidemiologic approaches to this question, just as I acknowledge the limitations of the meta-analyses data set, meta-analytic techniques and, in fact, the limitations of randomized, controlled trials. Clearly, given the variety of data and findings, the issue of rosiglitazone's cardiovascular ischemic risk is a challenging issue, yet it is also a crucially important public health issue to sort out.

In that light, I would like to place the discussion points and questions for you into clinical context. First, I would like to point out

that while the last talk posed the question whether rosiglitazone carries a cardiovascular risk in comparison to placebo, an absolute risk, if you will, patients with type 2 diabetes needing additional treatment to control their blood sugar don't have the choice between a drug and placebo. They and their doctors must choose between one drug and another. Understanding this important clinical reality leads one to accept that active-control trial data are of considerable clinical relevance to the overall evaluation of risk with rosiglitazone.

Secondly, while cardiovascular ischemic effects of any drug used to treat type 2 diabetes mellitus are important to consider, so are the risks of uncontrolled diabetes and the total pattern of risks with the available therapies. Choice of an appropriate therapy for an individual patient and, indeed, assessment of risk and benefits for a population are not unidimensional. This is not just about cardiovascular ischemic risk. In fact, simply having drug choices is

worthwhile for a disease where multiple drug treatment is common and patients do not uniformly either respond to or tolerate any given agent.

The last presentation made much of the comparison of rosiglitazone and pioglitazone solely based on the considerations of a putative difference in cardiovascular ischemic risk. It is worth noting that other important differences in the safety profile of these drugs exist. For instance, pioglitazone's labeling mentions positive carcinogenicity studies in animals, specifically bladder cancers in rats given the drug at the same level of exposure as those used clinically.

While we don't know, and I would stress that we don't know that there is a clinical correlate to this animal finding, at least some evidence from clinical trials also cited and available in the labeling raised the possibility that there might be a human risk, and that continues to be evaluated in postmarketing studies.

As another example of the differences in safety profiles of the drug choices, sulfonylurea

drugs, which have long carried a warning about their potential to increase cardiovascular deaths, also carry significant precautions about their potential for causing profound hypoglycemia. In this regard, it is important that any consideration of relative risk for rosiglitazone be done in the full context of the risks and established benefits, or lack thereof, of the other options for treating type 2 diabetes mellitus.

On behalf of the staff of the Office of New Drugs, I thank you all for serving on this advisory committee today, and for your careful review of the large amount of data sent to you previously, and for your close attention to the presentations today. I look forward to a rigorous scientific and thoughtful discussion of the issues and questions this afternoon.

I also wish to thank all of my FDA colleagues, those in the Office of New Drugs, those in the Office of Surveillance and Epidemiology and those in the Office of Biostatistics for their tireless efforts on these important matters. As

Dr. Parks alluded to earlier, many, many person-hours have gone into this and many personal lives have gone on hold in the last few weeks to come to this meeting today. Truly, I would consider all of us in FDA to be public health advocates. Thank you.

DR. ROSEN: Thank you, Dr. Meyer. We will finish with Dr. Dal Pan.

Conclusions and Summary

DR. DAL PAN: In the interest of time, I will just stay at my chair. My remarks are short and I would like to just provide some follow-up to what Dr. Graham said in his talk about the risks and benefits of rosiglitazone.

As you have heard this morning, there has been a vast amount of data that have been examined to answer this question. Unfortunately, none of the completed clinical trials was designed specifically to examine the risk of myocardial infarction and myocardial ischemia with rosiglitazone so we must use the available data as best we can to address the issue.

I concur with the overall approach that Dr. Graham has taken to address the issue. The talks you heard earlier in the morning were rally by specialists in each area of type of analysis. You have heard about meta-analysis. You heard about controlled clinical trials. You heard about observational studies. What Dr. Graham did was to take some of those data and answer some clinical type of questions that are relevant to the issue at hand. While I may disagree with him on some minor technical issues and the strength of any one given piece of evidence or other, he and I have both concluded that when we look at the data the balance of the benefits and risks of rosiglitazone is not favorable for rosiglitazone.

Let me tell you just a little bit about how I get there. I recognize that there is uncertainty in the data we have looked at concerning the myocardial ischemic risk of rosiglitazone. There are recognized limitations of meta-analyses. However, data from FDA's meta-analysis points to an increased risk of

ischemic myocardial events in patients taking rosiglitazone. The effect is most pronounced when rosiglitazone is compared to placebo and is even more pronounced in certain subgroups, such as those on concomitant insulin therapy.

When we look then to compare rosiglitazone to non-thiazolidinedione active comparators, a comparison that I believe is important, the data are less clear on myocardial ischemia. They are less robust. However, the available data do point to an increased risk and, moreover, don't point to any convincing evidence that such a risk does not exist. I have noted in a memorandum that you have in the background material that I don't think the ongoing RECORD study will adequately address this issue, and the reasons are explained in that memorandum.

Finally, we have tried to compare the risk of ischemic cardiac disease of rosiglitazone to that of pioglitazone, the other marketed thiazolidinedione. It is important to note, first of all, that both agents can cause heart failure

but that is not the issue at hand here. It is also important to note that the data on pioglitazone have not been as carefully reviewed by FDA as the data on rosiglitazone have been, and some of these data have been received only recently so it is imperative that FDA actually review these data with the same degree of scrutiny with which we have been reviewing the rosiglitazone data.

With the exception of the GLAI study that Dr. Graham spoke about and which was a direct comparison of rosiglitazone to pioglitazone, all the other comparisons we have of these two agents are indirect. So, such an approach must be viewed with some caution. But, nonetheless, pioglitazone appears to be neutral with regard to cardiovascular risk in a way that, in my view, rosiglitazone does not appear to be neutral. However, I agree with Dr. Meyer that pioglitazone, like other agents, has its own side effects.

My conclusion about this is based on an overall public health approach, not a statistical approach, and in reaching this conclusion I am

aware of the growing burden of diabetes, especially type 2 diabetes, in the United States. I am also aware of the need for better treatments for diabetes. Finally, I am aware of the need for good glycemic control in patients with type 2 diabetes, and specifically that for most patients with diabetes no treatment is not an option. However, when I look at the data before me I see data that point to a meaningful risk of myocardial ischemia that is not offset by data that can convincingly refute that risk.

While rosiglitazone does provide glycemic control which is important in the treatment of diabetes, it seems to have no unique qualities in that area. Data that demonstrate that rosiglitazone favorably impacts the long-term micro- and macrovascular complications of type 2 diabetes don't exist. It is imputed more by the hemoglobin A1c. Given this information, I believe that the balance of benefits and risks do not favor rosiglitazone. I note that there will be a lot of new data coming in. I am sure a lot of other

people will be looking at this issue and a lot of data will be coming in and so we will have to look at that as well.

Finally, you may wonder if I am interested in the deliberations of this committee meeting given that I have arrived at a conclusion. Let me say emphatically that I am very interested in your deliberations. Your opinions are important to me and are important to FDA since FDA has not reached a final position yet and many individual staff at FDA have not reached their own conclusions. So, I will be listening very carefully to your deliberations and when we go back to continue this work I will keep them in mind.

I would also like to thank all of my colleagues at FDA, thank the advisory committee members and a special thanks to the Drug Safety and Risk Management Committee members who are here at today's meeting as the first of three days of advisory committee meetings so you have a long way ahead of you. So, thank you, and I hope you endure.

DR. ROSEN: Thank you, Dr. Dal Pan. We are going to break for lunch but, before I do that, I just want to tell you that we are really tight on time and we have a lot of work to do. So, our plan is to start at 1:45 with the open public hearing. That is 1:45 for the open public hearing and following that will be our deliberations.

[Whereupon, at 1:10 p.m., the proceedings were recessed for lunch, to reconvene at 1:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. ROSEN: We are about ready to start the open public hearing pretty much on time. There is some housekeeping that I will go over as we move along in the advisory committee meeting, but for right now we have a special presentation of an award to one of our advisory committee members. So, Dr. Parks?

DR. PARKS: Thank you, Dr. Rosen. It is common practice for the review divisions to acknowledge members of the advisory committee who have served their time and they are now retiring from the advisory committee as full-time members. They certainly will be retained for consulting purposes with future advisory committee meetings.

Today we have with us Dr. Morris Schambelan and he is Chief of Endocrinology and Professor of Medicine at the University of California San Francisco. He has been with the advisory committee since 2003 and has presided over numerous advisory committee meetings, ranging from discussion on the draft guidance for obesity and

weight loss drugs, also discussion of several Rx to OTC switches of drugs that involve our Division, and has contributed significantly. We are most grateful for his presence today to discuss yet another very difficult safety issue, but we very much look forward to his continued guidance in this area.

With that, I actually would like to turn this over to Miss Kathy Miller who has a plaque to offer to Dr. Schambelan. Again, Dr. Schambelan, from the FDA thank you very much.

DR. SCHAMBELAN: Thank you, Mary. Does that mean I can leave now?

DR. PARKS: That is up to Dr. Rosen.

Open Public Hearing

DR. ROSEN: Welcome to the open public hearing. I just need to read a brief statement about the procedure. Both the FDA and the public believe in a transparent process for information gathering and decision-making. You have already seen that this morning. To ensure such transparency at the open public hearing session of

the advisory committee, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with a sponsor, its product or, if known, direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration. That

said, in many instances and for many topics there will be a variety of opinions. One of the goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully, treated with dignity, courtesy and respect. Therefore, please speak only when recognized by me. Thank you for your cooperation, and I would add that we really have to stick to the seven minute time limit for each speaker. We have 16 scheduled speakers. You know who they are, and they will be called by number. I can't identify you by name initially. But I would like to start by speaker number one.

MS. BRASHERS-KRUG: Good afternoon, Dr. Rosen and members of the committee. My name is Gail Brashers-Krug and I represent *Voice of the Diabetic* magazine, the nation's only magazine targeted to diabetics who are experiencing complications of their disease such as blindness, kidney failure, heart disease and neuropathy. *Voice of the Diabetic* provides helpful information to 320,000 readers about techniques and

technologies for maintaining good diabetes control despite their complications.

My purpose here today is to remind you that whatever you recommend, your most important consideration must be the people who are living with this disease all day, every day, struggling to maintain good control despite the ravages that diabetes has already wrought on their bodies.

Rosiglitazone helps millions of people control their diabetes and helps delay or even prevent the onset of additional complications. Any recommendation that you may make today that limits the availability of rosiglitazone is quite likely to result in more diabetic complications.

As you consider the scientific data, the public health considerations, the costs, the benefits of any recommendations, I ask that you keep foremost in your mind the actual diabetics who lie at the end of this process.

To that end, I would like to introduce you to some of those actual diabetics virtually, some *Voice of the Diabetic* readers who are living with

diabetic complications and taking rosiglitazone.

Let me start with Dan. Dan is an accountant. He is a 64-year old type 2 diabetic. He has hypertension and last year he had to have two toes amputated as a result of his diabetes. He also suffers from peripheral neuropathy which causes constant pain and numbness in his feet and his fingers. Dan takes two different oral diabetes medications, including rosiglitazone, and he injects Byetta. He also takes medications for his hypertension, high cholesterol, neuropathy and arthritis, a total of 18 pills a day plus the two Byetta injections. Dan needs to exercise regularly for his diabetes and for heart health, but exercise is really hard for him. He has a hard time walking due to his missing toes, the neuropathy in his feet and the arthritis in his joints.

Then there is Cheryl. Cheryl is a 42-year mother of two and a type 2 diabetic. As a result of her diabetes, Cheryl is legally blind and her kidneys have failed. She is on dialysis three times a week while she awaits a kidney transplant.

Cheryl is on three different oral medicines, plus occasional insulin to control her diabetes. She also takes medicine for her kidney failure and for hypertension.

If I can, I would like to give you a little glimpse into Cheryl's daily diabetes routine so that you can see a little bit of what it is like to live with diabetes and these kinds of complications. Every morning when Cheryl wakes up she tests her blood sugar. She can't do that with the regular blood glucose meter that you buy at CVS or Wal-Mart because she is blind and she can't read the numbers of the display. She uses a talking blood glucose meter. After she tests her blood sugar, Cheryl has to take a whole bunch or morning pills. Again, she can't see the pills and she can't see the prescription labels because she is blind. So, she has developed a non-visual labeling system for all of her medications to tell her when to take them and what time, how much and which pill she is taking.

After she takes her medicines and gets her

children dressed, and fed and off to school, she makes her own breakfast. This is no small task for a diabetic who is also on dialysis because she has to balance the diabetic diet with the extensive dietary and fluid restrictions required by dialysis. She can't have a cup of coffee, no caffeine; can't have a banana, too much potassium; can't have bacon, too much sodium; can't have raisin bran, too much phosphorus. Of course, as a diabetic she had to count the carbohydrates in her food based on the nutrition labels that, again, she can't see. So, she uses magnifiers to read the labels and then marks all her boxes and cans with Braille labels and other tactile markings devices to help her figure out the carb count of her food.

Now, once she has negotiated the difficult task of actually figuring out a breakfast that she can eat and what the carb count is, she has to give herself her mealtime insulin. Again, she cannot see an insulin syringe so she has to use a pre-filled insulin pen that has tactile and auditory cues to help her know how much she is

dosing. She does this every mealtime and she also has to check her blood sugar every two hours after meals and whenever she exercises.

If it is a Monday, Wednesday or Friday, then Cheryl spends the rest of her evening at the dialysis center where she is hooked up to a hemodialysis machine for three to four hours. Of course, because she is blind she cannot drive there so she has to arrange rides to and from. When she gets home, physically drained and exhausted from her dialysis, Cheryl usually has time to kiss her sons good night before checking her blood sugar again with her talking meter, taking her nighttime pills and going to bed.

As you can see, maintaining good diabetes control in the face of complications is extremely challenging. Cheryl's and Dan's daily diabetes to-do lists may have 20, 30 or more items on them. What is more, having complications doesn't just make good diabetes control more difficult for Cheryl and Dan, it makes it even more critical because once a diabetic develops one complication,

like blindness or neuropathy, he or she stands a greatly increased risk of developing a second or a third or a fourth.

So, on behalf of *Voice of the Diabetic* magazine, I am here to ask that you keep Cheryl and Dan and the millions of other diabetics who are living with complications at the forefront of your minds as you consider your recommendations. And, as you weigh the risks and benefits, please consider them the risks to Cheryl, the benefits to Dan. Rosiglitazone is an essential part of their diabetes control regimen, as it is for millions of Americans, and anything that makes rosiglitazone unavailable to any group of patients, like Cheryl or Dan, is likely to have the immediate effect of worsening their diabetes. Worsening diabetes means that they will very likely develop more complications and so will millions of diabetics who don't have complications.

So, I ask you, please, to keep your eyes on the prize, improved outcomes for diabetics with complications like Dan and Cheryl. Thank you very

much.

DR. ROSEN: Thank you, and thank you for staying on time. Speakers two and three are doing a joint presentation, I believe.

DR. DIAMOND: Thank you. My name is George Diamond, and I thank the committee and the FDA for the opportunity to present some alternative interpretations of the evidence.

When my colleague, Dr. Sanjay Kaul and I first took note of the meta-analysis by Nissen and Wolski, we were struck by the number of zeroes in the tabulated data, specifically in table 3. We wished to illustrate how this might impact the conclusions of the analysis under a number of alternative methodologic assumptions. The results will be posted, by the way, on the *Annals of Internal Medicine* website on August 6th.

Here is the pooled data from all 42 trials with respect to myocardial infarction. The event rates are very small, well under 1 percent, and the difference between the treatment and control groups is smaller still. Most of these trials reported no

events at all in the treatment or control groups.

This slide, which looks something like a three-dimensional game of sudoku, breaks up the pooled 2X2 data matrix on the previous slide into 42 separate 2X2 tables, 6 across times 7 down, with respect to myocardial infarction, one for each of the trials. The number of patients in each cell is represented by the height of the bar. The black squares represent the 4 trials that were excluded because no events were observed in both the treatment and control groups, leaving 38 trials for analysis. Note that most trials were relatively small in size.

This is a similar summary of the trials with respect to cardiovascular death. Here 19 trials were excluded because no events were observed in both groups. Note the number of holes, the sparsity of the data.

Here are the results of the analysis by Nissen and Wolski, along with the conventional meta-analytic power plots that were not reported in the *New England Journal* paper. Although the odds

ratios are both increased, the one for myocardial infarction significantly so, the confidence intervals for the individual studies and the meta-analytic results are rather wide.

In addition to the excluded trials, a large number of the included trials exhibited zero events in one or the other treatment arm. There were 26 such instances out of the 38 trials analyzed for infarction, 20 in the control group and 6 in the treatment group, represented here as gold squares. There were 17 such instances out of 23 trials analyzed for cardiovascular death, 15 in the control group and 2 in the treatment group.

How might all these zeroes have affected the analysis? We can answer this question by inspecting the equation used to calculate Peto's odds ratio. The term O minus E in the numerator represents the difference between the observed and expected cell counts in the treatment group. The number of zero cells affects the calculation of this term and, therefore, the result in odds ratio.

The table below the equation shows that

the zero cell counts in the control group inflate the odds ratio, while zero cell counts in the treatment group deflate the odds ratio. Because there were more zeroes in the control group by a ratio of 20:6 for infarction and 15:2 for death, the calculation of Peto's odds ratio was inflated in Nissen's and Wolski's analysis.

We can mitigate this problem by applying one or another continuity correction to the data, effectively filling in zeroes. One can apply such corrections by adding some small value, one-half or something proportional to the sample size to all cells of the trial exhibiting no events at all, or to trials exhibiting zeroes in only one study arm. We, therefore, performed a variety of alternative analyses on the Nissen and Wolski data using different meta-analytic models and different corrections.

This slide summarizes our results. A minus sign indicates analyses that excluded the zero event trials; a plus sign, analyses that included these trials by applying one of the two

continuity corrections. The point estimates of the odds ratios are represented by the vertical black bars and the 95 percent confidence intervals by the horizontal colored bars. Statistical significance is indicated if the horizontal bar does not cross the vertical line at unity. Peto's model, the one used by Nissen and Wolski, produces the highest values for both death or MI and the only statistically significant result for MI alone. These additional analyses emphasize the degree of uncertainty in these assessments. None establish or exclude the possibility of increased risk.

So, what does it all mean? This slide quantifies the cumulative probability of harm, increase in risk, on the Y axis based on the odds ratio distributions on the previous slide as a function of varying risk thresholds along the X axis. The yellow curve is for the uncorrected Peto model used by Nissen and Wolski which produces the highest odds ratios. The green curve is for an alternative corrected model. The difference between the curves illustrates the wide range of

values that we observed. For both death and MI the probability of at least a 10 percent increase in risk is around 95 percent for both death and MI, using the uncorrected data, but in the range of 55 percent for MI and 40 percent for death using corrected data. These values are lower than those implied by Nissen's and Wolski's point estimates reporting a 43 percent in MI and a 64 percent increase in cardiovascular death.

The authors reported a number of limitations involving their analysis and our analyses are subject to the very same limitations. However, we have highlighted two additional limitations not considered by them, the sensitivity of their conclusions to alternative meta-analysis and the implements of continuity corrections on the quantitative assessment of risk. Although we have not investigated the entire spectrum of alternative analytic methods, those we have conducted serve to temper Nissen's and Wolski's assessment of risk.

My colleague, Dr. Sanjay Kaul, will summarize the application of these same methods to

the analysis of clinically relevant subgroups. Thank you.

DR. ROSEN: Number three is speaking. Seven minutes, remember.

DR. KAUL: I would like to thank the FDA committee for the opportunity to share our interpretation of the evidence.

Of the three key questions relating to the Nissen and Wolski meta-analysis, Dr. Diamond addressed the first. The other two will be the focus of my presentation. Is there sufficient heterogeneity to preclude pooling? If so, what is the impact of continuity corrections on clinically relevant heterogeneous groups? Second, are the risk estimates consistent with other studies?

The authors justified pooling the studies on the basis of lack of statistical heterogeneity as assessed by the conventional Cochran's Q test. This test has limited ability to detect variability across studies with sparse data. Even if studies are statistically homogeneous, there may be clinical heterogeneity. For example, there is

clinical heterogeneity in patient populations. Alternative patient populations such as diabetics and non-diabetics or those with congestive heart failure may not be poolable. Alternative trial designs may not be poolable, small trials, short-term follow-up and large trials and longer-term follow-up and, as has been stated earlier this morning, it might not be unreasonable to question whether short-term trials may reliably predict long-term outcomes. Alternative treatment comparator groups may not be poolable. There were seven treatment comparison groups involving two different doses of rosiglitazone. So, absence of statistical heterogeneity does not imply absence of clinical heterogeneity and perhaps both are equally important when considering pooling.

We will now examine the impact of continuity corrections on these clinically heterogeneous subgroups. We will start off with the myocardial infarction, the subgroup analysis of uncorrected odds ratio for the risk of MI in small trials combined, and the individual data for the

two large trials are shown. Although the point estimates are elevated, the confidence interval overlaps unity, suggesting risk differences are not statistically significant. The overall pooled estimate of the smaller and larger trials combined indicate a statistically significant increase in risk, which was the primary result reported by Nissen and Wolski.

These are the corrected data using the Mantel-Haenszel model with continuity correction and we see that it lowers the pooled risk estimates such that the overall pooled estimate is now no longer statistically significant, thereby exposing the fragility of the data. Similar observations are made with the analysis of cardiovascular death. The corrected pooled estimates, although still elevated, are substantially lower with confidence interval overlapping unity.

The subgroup analysis for uncorrected data and corrected data are shown with regards to subgroup of patients with and without diabetes and difference treatment comparison groups. The point

estimates enumerated on the slide are the highest for the incident group and for the group that included patients with heart failure and patients with psoriasis and Alzheimer's disease, non-diabetics. The point estimates of corrected analyses were consistently lower than the uncorrected analyses. None of the subgroups showed increased risks that were statistically significant.

Similar observations are made with subgroup analysis for cardiovascular death with regards to uncorrected as well as corrected analyses. None of these analyses-Band I emphasize, none of these analyses conclusively adjudicate the association between rosiglitazone and the risk for myocardial infarction or cardiovascular death in particular subgroup of patients.

Are the risk estimates consistent with other studies? Several additional analyses have assessed cardiovascular risk associated with rosiglitazone. We heard this morning that the integrated clinical trial analysis conducted by the

sponsor included about 28 of the 42 trials included in the Nissen and Wolski analysis. An exact logistic regression model was used for pooling the data, thereby excluding the zero total events as in the Peto method. The results indicate a 30 percent statistically significant increase in the risk of all myocardial ischemic events with rosiglitazone. In light of the alternative analyses that we have just shown you, what might the impact be on the results?

Next, the interim analysis of the RECORD trial that has the largest number of myocardial infarction events revealed insufficient data to determine if there was an increase in MI, probably due to lower power related to unexpectedly lower event rates and incomplete follow-up.

A large observational study, the balanced cohort study commissioned by the sponsor, showed no significant differences in the risk of MI between rosiglitazone and comparator groups. A recently published review of 18 studies among patients with diabetes found a tendency towards increased risk of

MI with rosiglitazone, but the differences were not reported to be statistically significant.

Thus, in our opinion, the risk for myocardial infarction for diabetic patients taking rosiglitazone is uncertain. Neither increased nor decreased risk is established.

In conclusion, the risk estimates are sensitive to the meta-analytic method. They are sensitive to the continuity correction, to subgroup analysis and, if present, the magnitude of harm is small. Clearly, more data are needed to adjudicate the uncertain association between rosiglitazone and cardiovascular risk. We believe that only prospective clinical trials, designed for the specific purpose of establishing the cardiovascular benefit or risk of rosiglitazone will resolve the controversy about its safety. Concurrently, meta-analytic approaches for assessment of sparse data, especially safety signals, should be refined and standardized.

Finally, we need to be aware of the limitations of meta-analysis and maintain a healthy

skepticism about its reproducibility and applicability. Thank you very much.

DR. ROSEN: Thank you.

DR. EGILMAN: I AM Dave Egilman. I am a clinical associate professor at Brown. We are talking about if we knew then, when this drug was approved, what we know now, would we have approved it? That, I think, is the question. And, that is the major bias because the context of the talk is not money alone. The context of the talk is explaining why the safety division is interested in coming to one conclusion with the same data and the division that approved the drug initially has a slightly different opinion about the data. That can be seen consistently in other areas of research where companies who sponsor research results get favorable results and independent studies come out with opposite results.

Primum non nocere is my bias. That is the first one. I have served as a litigation expert but not against GSK, not in this. And I am from Brown. Brown receives a lot of money or has

received a lot of money from GSK and wants as much money as it can get from anybody, at any time, anywhere. It has no ethical principles at all, which is the same as everybody else. Everybody takes tobacco money. Everybody is laughing. There is no university, "no, we won't take tobacco money." So, everybody will take money and Brown wants money. In this case it is even more relevant because it is Brown that did study 329. The result of that study was accusations of fraud by Spitzes which resulted in the GSK data being put on the web, allowing this meta-analysis to be done.

One other irony, of course, is that the defense that the meta-analysis is no good because the individual studies are no good. Well, it is a little bit akin to the orphan telling the judge to let him off because he killed his parents. You know, who was responsible for those studies? Who is responsible for assuring the safety of the drug before it is marketed? It is actually not the FDA. It is the manufacturer of the product that has the responsibility to assure safety. So, there should

be no uneasiness here or queaziness about the data because it is not the FDA's job to make the data. It is not any of your job to make the data. It is the company's job to assure the safety of its drugs.

Now, on surrogates, he died with a normal A1c. Yes, apparently there are thousands of such graves, hundreds perhaps or thousands. But those are not the only graves. You can't read the bottom, but it is just like the patients who died without joint pain from heart attacks, taking Vioxx. It is just like patients who took nifedipine and died with normal blood pressures because we thought we were smart and we thought that lowering blood pressure would reduce MIs. Aha, no, heart rate turns out to be maybe more important and we killed some people with nifedipine but they died with normal blood pressures. And, the Seldane patients too. Now this one, they died without a runny nose. That is also an important contribution.

Is this a hint? Resulin, all these drugs,

all the same class were approved and removed. The other three were removed before they even got to this step. There is something maybe we should think about in this class. This could be a clue. Maybe we ought to look at some other endpoints here, like the real endpoints. The reason we treat people is not to have them die with normal blood pressures and normal glucoses. It is to have them not die.

Now, this the FDA calls a warning. This is the table in the current package insert. The table has CHF on it so it obviously only refers to CHF and there is no statistical significance here. There are ten events and five events, and they think doctors are going to look at this, with no language, and know that there is a risk of MIs and ischemic events? Come on! This table actually is an anti-warning because you look at this table and you say, hey, everybody else isn't at risk.

By the way, not only do I not think it is a warning, look at how GSK does in its PAIRS. Oh, it doesn't tell anybody, any patients, in their

information that there is a risk of ischemic events. Nowhere, nohow, not in CHF, nowhere. And this was mentioned at the congressional hearings and it still hasn't been changed. So, GSK doesn't think it is a warning either.

So, what is it? Oh, it is something you need to cover your behind when you get out of the shower, when you have made a mistake. You can't read what is on the towel but it is blah, blah, CHF. For those of you familiar with the Ginger cartoon, that is what doctors read when they see this warning. It is not enough. A black box is not enough.

But let's skip ahead. We have heard a little mention of what is going on in Europe and England but not enough. Why? For years now in England and Europe there is a contraindication for use in combination with insulin. But here we have an uninformed consent trial you heard about where they are using it with insulin. Contraindication in the United States is if you are allergic, that is the contraindication. In the United Kingdom any

form of heart failure--contraindicated. Not here. Just if you are allergic. I don't think that means having CHF. In fact, here we say here is the use. It is indicated for use in combination with insulin. So, in England it is a contraindication. It must be a genetic thing. It is. Okay? The regulators in England genetically have larger cojones.

Last but not least, a black box is not enough. There are two studies looking at black boxes. Seven and a half thousand patients received a prescription violating a black box warning in one trial. FDA doesn't study this. They should, but other people have. When they came out with a regulatory action regarding cisapride it had no material effect on contraindicated use. If this were an NDA it would be rejected. You would say go finish those studies. Show me that this early data is not real. Thank you.

DR. ROSEN: Thank you.

DR. EGILMAN: One quick one, the correction of zeroes is like--

DR. ROSEN: You are out of time. We are on to the next speaker, please.

MR. FERNANDES: Good afternoon. My name is Raul Fernandes and I join you today as both a heart patient and a diabetes patient. I also join you as vice president of Mended Hearts, a nationwide non-profit organization dedicated to inspiring hope in heart patients and their families. Our organization has been around for more than 56 years and with 19,000 members. We are one of the nation's largest networks of heart patients.

In that regard, Mended Hearts has worked with a number of pharmaceutical companies on unbanded educational initiatives to advance our mission, including GlaxoSmithKline. However, it is on behalf of heart patients that I am here today. We feel very strongly as an organization that the safety and medical value of drugs and treatments are matters that should be discussed in appropriate medical and scientific forums such as this where reason and expertise shall prevail.

Additionally, we feel that decisions to

use medications should be made between the patient and his or her healthcare provider with as many options available as possible. As a patient with both heart disease and diabetes, I can personally testify from my own experience that it is vital that patients have as many tools in the toolkit as possible. I thank you for your time today.

DR. ROSEN: Thank you very much. Number six?

DR. HELLMAN: Thank you. My name is Dr. Richard Hellman. I am president of the American Association of Clinical Endocrinologists. I also sit on two advisory panels for the National Quality Forum, one on diabetes and the other one on safety and therapeutic drug administration.

In terms of conflicts of interest, while on QD panels and as president of my association, I will not be personally benefitting from any monies I receive. All that will go to charity. I also am the director of a not-for-profit medical research foundation which is small, and I have not received any income from that in 14 years, which shows what

kind of business acumen I have. I did actually do a talk earlier this year before I became president, and that was it, that was a drug company sponsored one.

I would like to talk about the topic at hand. One of the reasons I think why, in an editorial I wrote in *Endocrine Practice*, which is attached to the handout, entitled, "The Perfect Storm." Why we had such chaos following, I think, the excellent article of Dr. Nissen, was the fact that it raised a question, raised multiple questions and among the questions not only was the accuracy of the data, which has been discussed, but why were there not adequate epidemiologic studies? Whey were there relatively few comparative studies? You know, physicians rarely have clear-cut comparative studies that fit clinical needs, head-to-head comparisons. And, why were all these clinical trials we have discussed inadequately powered? A more important question is, is this unique to this drug? Sadly, I think it is not. I think this is a system problem that we

have which really will bite us again if we do not look at the more general issues of the shortcomings of the post-approval drug safety surveillance.

I think it is very clear that when you look at it, any time you enlarge the pool from the margin that is relatively healthy populations in the RCTs you see patients who are more at risk. But we do not capture the data. Perhaps 1/100 adverse drug events actually get sent forward, if that, and the high risk populations are routinely not discussed. So, we get into this shocking discovery each time of the special risks that a drug has for the new population. And, the longer duration of drug exposure has its problem. More important too I think is how this is used. How an excellent drug is translated. It may be so variable as to undermine the signal and the outcomes that we are looking for.

I think the funding is a major issue in terms of what the FDA has on its plate. I think that your post-approval drug safety budget is terrible. It is seriously under-funded. I don't

think PDU is going to fix it. I think the NIH, ARC and others really should be contributing more but I have seen their budgets too.

The truth of the matter is that it is very hard for a company, that has spent half a billion dollars putting together a project, to really look at the safety issues with the same look as someone who has no connection whatsoever.

As far as the NIH funding, this is a nation that doesn't deal with infrastructure. I consider NIH infrastructure. I think the issue of drug safety isn't given at all. Just because they are good people doesn't mean it gets there. We don't have good educational resources. There are very few. Tell me the last time you saw someone actually putting a line item in a budget on drug safety, and inadequate information systems, electronic, are widespread.

This is what you have. This is the Swiss cheese model of safety with one piece of Swiss cheese, and that is poor FDA. Imperfect people make imperfect barriers. I think we are all

imperfect to some degree. The truth is it is impossible to have one barrier in complex systems and be sure that you actually got it right.

In addition, one of the issues of the cardiovascular benefits had to do with the fact that we tend to focus on the issue at hand, what we see clearly. That is why the problem with hyperglycemia in acute care went on for years before people realized its significance. Our scope of awareness is often focused on what we know and if we are focused and we are stressed because we now are stressing the system because we want to do it on the cheap, this is what happens to our scope of awareness and you can imagine what happens next.

I think the data collection is inadequate. These issues are incredibly important and I think at this point one of the things we have forgotten is that the cognitive issues today are so large as to really seriously interfere with the patients. They don't know what they are doing. Drug reconciliation is not being done and people are not sufficiently knowledgeable. There is much on our

plate.

I think the proposed solutions include making it a collective responsibility. We all have skin in this game really, the patients, the scientists, the government, the industry. We all have skin in it and it shouldn't be just industry. It shouldn't be just the ticket for the pharmaceutical company. Government and foundations need to ante up, so to speak, to put our money where our mouth is. And, I think physician groups such as ours, patient groups and health groups of all sorts, I think we need to be involved together because another way of looking at this is the Swiss cheese model again, and I would maintain that this is really from the work of Prof. James Reason, modified for this topic, that if the FDA was more robust, better funded in this area and stronger, but the NIH was active in getting the best scientists to do the studies, and physician organizations like ours were involved, allied health organizations and patient organizations we will have a much better chance of making this the

last debacle that we have to deal with of this sort. Thank you very much.

DR. ROSEN: Thank you. We all know the next speaker.

DR. WOLFE: I am Sidney Wolfe, of the Health Research Group of Public Citizens. I do not have any financial conflicts of interest.

This is the question that I will spend most of this talk on, the benefit/risk ratio, as many people have alluded to, beyond just the cardiovascular risk.

The onus presented today concerning the increased risk of ischemic heart disease, including myocardial infarction, appears to justify the removal of this drug from the market. But due to the ubiquitous nature of PPAR-gamma receptor sites in so many it is hardly surprising that there are many other significant kinds of damage this drug is causing to patients.

Before the drug ever went into the mouth of anyone, in the 1999 FDA pharmacology review of the animal toxicity which noted left atrial

thrombosis and cardiac hypertrophy, the reviewer said, quote, it is not possible to anticipate potential human toxicities. He further stated, these findings appear as a long-term clinical concern. The final recommendation was, quote, pharmacology recommends not to approve rosiglitazone for the proposed indication for long-term use. This is 1999.

This is sort of the basis of the concerns in terms of cardiac toxicity. The upper panel, if you look in the upper right, shows that in these dogs the dose was only 1.2 times the human dose. In the lower what you can see is in males statistically significant increased cardiac weights by 26 weeks at this 1.2 times the human dose.

In a paper presented last year by former FDA pharmacologist, Dr. Jeri El-Hage, looking at this class specifically, the gamma PPAR agonists, she said, quote, fluid accumulation in all species, mouse, rat, dog, rabbit, monkey, humanB-fluid accumulation leads to weight gain, edema, cardiac hypertrophy with result in heart failure in all

species. Drug-induced heart failure and death were observed with chronic treatment greater than six months in animals and man, and in people the longer a patient was on a PPAR gamma, the lower the dose needed to produce edema or congestive heart failure.

This a jut released study by your consultant here, Dr. Curt Furberg and his colleagues, showing in a meta-analysis for congestive heart failure of two studies, one with rosiglitazone, one of pioglitazone, a statistically significant increase in heart failure across the board. There is no dispute about that I believe.

Finally, in FDA adverse reaction reports filed since the marketing began through the end of last year, there were 698 cases of heart failure reported with Avandia compared with 39 with the older diabetes drug glucotrol. Adjusting for differences in the number of prescriptions for the two drugs, the rate of heart failure reports for Avandia compared with glucotrol was 15.2 times higher.

Liver toxicity. This is too much data but it couldn't be reduced, but what this slide shows is that highly significant increases in ALT were shown, again at this dose that is slightly higher than the human dose, in dogs at 26 weeks. These are eight published cases of well documented liver toxicity in patients using rosiglitazone. The exposures had been from 2 weeks to 15 months, and for 7 patients for whom there are follow-up data 5 recovered within 2 weeks to 4 months, 2 of them died. Bilirubin levels in these patients, consistent with similar hepatocellular toxicity seen with triglitazone, ranged from 2.9 to 22.3, total bilirubin, with an average of 10.5.

Finally, again in FDA adverse reaction reports filed since marketing began through the end of last year, there were 594 cases of hepatic toxicity, including 122 cases of liver failure, reported with Avandia compared with 53 cases of toxicity and only 7 cases of failure with glucotrol. Again adjusting for differences in the number of prescriptions for the two drugs,

increased adjusted rate of reports for Avandia compared to glucotrol was 9.5 and for liver failure 14.8. And, these are just some reports of deaths also with the heart failure.

This is a recently published study showing significantly increased fractures in women specifically. The left bar is rosiglitazone, in the middle is metformin and the right one is glyburide. That is total on the left, lower limb and upper limb on the right. These are just the data from which those slides were taken.

Pre-approval evidence of anemia from clinical trials showed 1.9 percent of patients receiving Avandia as monotherapy as opposed to 0.7 on placebo and severe, severe anemia as in hematocrit under 28 for women, under 31 for men was shown in 9/2,000 patients on rosiglitazone, none given placebo. But more commonly less severe anemia was seen in 7.1 percent of people getting rosiglitazone plus metformin, and only 2.2 percent getting placebo plus metformin. Again, with the red line there you can see a much higher rate of

reports of anemia in patients using Avandia as opposed to patients using glucotrol.

In the next slide, macular edema, although the major worry as far as vision is visual deterioration from diabetic retinopathy, in this case, based on cardiovascular problems you have macular edema, usually reversible but causing some visual impairment in the interim.

I don't have time to go through this. This is a very thoughtful editorial by David Nathan, in the *New England Journal*, pointing out we really haven't had any advance in terms of glycemic control for about 50 years, 50 years being the sulfonylureas and metformin, and the new drugs are more expensive, in some cases with the same adverse effects but in some cases new adverse effects.

Labeling changes are not enough. We have seen this with triglitazone and I don't think we need to see it now. If there is any doubt, particularly because there are alternatives, it should to off the market.

Finally, the same question, does the

risk/benefit profile merit leaving it on the market? No, there is no evidence of any unique beneficial clinical outcome for Avandia and growing evidence of multiple organ system damage. If the drug were up for approval today--

DR. ROSEN: Thank you. Speaker number eight?

MR. PETERSON: Good afternoon. Thank you for the opportunity to talk with you. I am Mike Peterson, from the Assistant Secretary of Defense Health Affairs Office, Strike Care Management Activity.

When the May, 2000 article in the *New England Journal of Medicine* came out DOD expressed immediate interest in determining very quickly, if we could, if our beneficiaries were at similar risk as expressed in the article. We also wanted to ask could we begin to answer questions such as these with some of the data that we had been collecting for years and years. Basically, we wanted to determine whether or not there was evidence of an increased incidence of select cardiovascular events

and we looked at specifically MI and CHF among our military health system beneficiaries with filled scripts for Avandia compared to those with filled scripts for other anti-diabetic medications.

Our methodsB-we have in the military healthcare system 9.1 million beneficiaries. We focused on our HMO-like benefit beneficiaries known as Tricare Prime. They do not include, for the most part, people 65 and older who are not eligible for that benefit so our study was limited to those under 65 years of age. The primary reason we focused on that group was because the data that we have for them is virtually 100 percent complete. The focus of our study, our method was a cross-sectional analysis of data for four years, from fiscal year 2003 to 2006.

We have three data sources that we used, the first one of which is to establish demographics of this population. The second one is to look at our clinical administrative data from inpatient and outpatient and counter claims, and I would point out it is not clinical data. Thirdly, we looked at

our pharmacy prescription fill data. This is a system that is rather unique. It allows us to track real-time pharmacy fill records regardless of the source of the prescription, whether it is the military or civilian sources.

We linked these three basic groups of data by identifiers. We used a case definition for type 2 diabetics based on ICD-9 coding and we then grouped individual drugs into therapeutic classes of anti-diabetic drugs. I would point out right up front that our drug categories are not mutually exclusive for this study. We used the data of earliest diagnosis for acute myocardial infarction and for CHF to identify our incident cases.

I think that is rather difficult to read from here. This is basically tale 1 of two tables in the study. Table 1 just discusses the demographics of our population. We had approximately 232,000 individuals for this four-year period of time that had been diagnosed as type 2 diabetics, about a 55-45 percent female to male split and, as you would expect, increasing

percentages as age increased in terms of this diagnosis.

In terms of the results on table 2, LT. COL. Baker from the same office will go ahead and present the results.

LT. COL. BAKER: On table 2 we see that we were able to do incidence rates per 10,000. The TZDs fall in the middle between the biguanides on the bottom at 33/ 10,000, with insulin on top at 51.67/10,000. Also, with the CHF you will see that the range is also with the biguanides on the bottom and insulin on the top, with the TZDs and sulfonylureas falling in the middle of that range.

So, this is a summary of the two tables. We have roughly 232,000 Prime enrollees that we were able to track in this four-year period. Fifty-four percent of them were female; 70 percent of the population fell between 45 and 64. You can see the BENCAT, or the beneficiary category that they have there.

In table 2 the annual incidence rate was averaged because it was roughly the same each year