MARY KORYTKOWSKI: Thanks for inviting me to be part of this. Usually I think people expect me to talk only about diabetes when I come up here but today's going to be a bit of a smorgasbord. That was the only way I could really keep up with all the updates there have been in the past year, some of which are hot off the press.

These are my disclosures. OK, so this is the smorgasbord. I'm going to talk a bit about the latest in testosterone therapy for men, this has been a controversial issue now for several years. And I don't think I can talk about hormone replacement therapy for men without giving you an update on hormone replacement therapy for women. There have been changes to metformin labeling in 2016. This is the most widely prescribed drug for treating diabetes and some of the limitations on its use have now been removed.

And there is very recent information on updates and diabetes technology. And even though this isn't all from 2016, I do want to talk a little bit about the new insulins that are available for treating diabetes and making that list of insulin products that are available to us even wider.

So let's start with men's health. I don't know that all men think about being Superman but some do with testosterone. And that's what I'm going to really address is testosterone therapy in the aging male because we know that testosterone deficiency and symptoms of low testosterone increase as men get older.

Testosterone is approved for low testosterone due to medical conditions such as testicular diseases, pituitary and hypothalamic disorders. But just the low testosterone alone is not an indication for treatment. Despite this, there have been over 1.3 million prescriptions in 2009 to 2.3 million prescriptions in 2013 for testosterone therapy in men. And these are the legitimate prescriptions, we don't even know what people are getting online.

The use of testosterone is quadrupled. In part, marketing is the reason for this. I mean, we've all seen the commercials on television. And 25% of prescriptions for testosterone are given without any measure of circulating testosterone levels, so it's just being based on symptoms. So hopefully, that won't happen after today with this group here.

So we know that testosterone levels decrease in levels of sex hormone binding globulin, which bind. The majority of circulating testosterone increase with aging. So the amount of free testosterone he has the possibility to decrease over time. The proportion of men, because testosterone levels decrease with aging, the proportion of men with levels below 325 increases with age. But when you read any guideline for how to treat men with hypogonadism, it's hard to find the number at which to treat.

The lower the number, the more likely it is that they have hypogonadism. But when you start getting into levels between 300 and 400, it's a great zone, particularly between 300 and 350. Above 350 may not be so much of a gray zone. It again depends on what you read but about 10% of men between ages 40 and 50 will have a testosterone level less than 325. And 50% of men above the age of 80.

So testosterone therapy is not indicated for treating just a low testosterone, you need symptoms as well. And the symptoms that are most suggestive of antigen deficiency include a decrease in libido, energy, or mood, a decrease in morning erections low bone mineral density, or overt osteoporosis, gynecomastia, and anemia. These are the most telling. A lot of other things are suggested as well. But they're not really specific. Certainly, lots of people have changes in energy and mood as they get older. And so that really can be used alone.

So the candidates for testosterone replacement are men who have symptoms of low testosterone, along with at least two measures of early morning testosterone, preferably measured by liquid chromatography mass spectrometry of less than 300. Less than 200 would be even more confirmatory that this is true hypogonadism.

Now, the guidelines actually say to get three measures but it's very difficult to get men in for two morning measures so many of us use just two morning measures. If you feel that you want to correct for the total t by getting a free testosterone, it's best not to use an analog essay. It's best to actually order a bio of available testosterone or to order a free testosterone by equilibrium dialysis. The radio amino acids for free testosterone are not at all reliable.

If you can actually do these calculations yourself, there are sites available on the web. I've included one here, which is the society for andrology medicine. And that's a fairly reliable calculator. You need an SHGB and albumin as well as the total testosterone to plug into that. But most of the guidelines use the total testosterone for guiding whether or not a man needs testosterone therapy.

The cases where you might get into confusing territory is in the setting of obesity, where total testosterone levels tend to be low and in diabetes. So there have been two studies in 2016 that I wanted to bring to your attention. One is the study, which is the European male aging study, which investigated the prevalence of low testosterone levels in men over four years and looked to see who would develop a low testosterone over a period of four years.

They studied over 3,000 men and they measured testosterone at the beginning of the study and at follow up. They defined a low testosterone as a level of greater than 317. So you're going to see numbers that range anywhere from 275 to about 350 in this talk because different studies use different levels to define low testosterone. So they considered a testosterone level of less than 317, in combination with at least three sexual symptoms, to be present in 2.1% of men. These were men between the ages of 40 and 79. And of course, they noticed an increase in this as men got older.

They found that this was associated with a lower hemoglobin, lower bone mineral density, lower mid upper arm circumference, so some muscle wasting, and decrease in physical performance that was measured using standardized methods.

More severe degrees of hypogonadism were noted in men that they defined as a testosterone level less than 230. And this was also associated with insulin resistance. So they felt that their data actually supported the concept that a low testosterone level does occur but it occurs in a very small percentage of middle aged and older men.

And It was the most frequently found in men above the age of 70 and those with chronic illnesses, many of which have been identified as being contraindications for testosterone therapy but whether these contraindications are absolute or relative is really not known because most of the testosterone trials have excluded men with disorders like congestive heart failure or lower urinary tract symptoms or prostates disorders from their trials.

So this European male aging study did not address whether testosterone replacement therapy improved any of the physical manifestations that they found. So really they just defined that the prevalence was actually low. Now, when looking at the benefits and risks of testosterone replacement therapy that are purported, and this is excluding what you see on television commercials, would be an increase in muscle mass, decrease in fat mass, improved physical and sexual functioning, and improved energy.

But the reason for caution is that there's concern for risks with this, just like there was concern for risks of estrogen therapy in women. One study, a randomized study, with testosterone therapy in older men was stopped early because of an increase in adverse cardiovascular events. This was published in the *New England Journal* a couple of years ago. But in looking at that study, those men were treated to super physiologic testosterone levels, so it was really hard to apply that to everyone.

Concerns have been raised by some other studies that it increases the risk of cardiovascular events but the data is very mixed and not all the studies have measured testosterone levels during therapy. There's also the concern of polycythemia. and certainly a CBC has to be measured during therapy, and an increase in risk for prostate cancer.

So the most recent study is the testosterone treatment trial in older men. This was an FDA mandated study based on all the confounding evidence and confounding definitions of low testosterone that exist in the literature and they asked for seven different studies of testosterone therapy and older men. In this report in *The New England Journal,* actually reported on three of these studies, the others are still ongoing, but they randomized men aged 65 and above with a total testosterone, confirmed on one occasion, total testosterone of less than 275 and symptoms suggesting hypogonadism.

Two, testosterone therapy with testosterone gel or placebo for 12 months. Some of the symptoms were those that were described for hypogonadism of a low libido, decreased morning erections, loss of body hair, low BMD, or gynecomastia. And each subject participated in one or more of these seven trials. So the data analysis, I don't know that this clears it up completely, some of the data is reassuring but I will show you that. But the three that I'll report on are the sexual function trial, the physical function, and the vitality trial.

These are the clinical characteristics of the study population. You can see that there's approximately 400 men in each of the arms that receive placebo or testosterone, this is participating in all three trials. I don't know that you can say that these are going to be widely applicable. 51,000 men were screened for this study. About 24,000 met enough sufficient criteria to come in to have a testosterone level measured. Of those 24,000, only 14% met the criteria of a testosterone level of less than 275 with symptoms of hypogonadism to participate in the trial.

So they did use that strict criteria, which really is supportive. I didn't really compare the math completely to what was in the European male aging study but it's actually getting to be fairly close to the fact that the actual prevalence of this is low. Other criteria for this study, including having a partner who was willing to participate in sexual activity with the person participating in the trial. So the screening also probably excluded people for that reason, some of whom were widowers or single.

The average age was, the men had to be above age 65. The average age was about 72 in each group. With class one obesity, they did not exclude people with diabetes from this study. So over a third of the participants had diabetes. More than 2/3 had high blood pressure about 15% had a history of an MI. And you can see that their testosterone levels were low to begin with, with a mean level of about 235 in both groups.

And of course the men, the group that was randomized to receive the testosterone gel did have an increase in their testosterone levels to the mid-normal range for what would be considered normal for men between the ages of 19 and 40. And stayed fairly constant over the 12 months of the trial.

Some of the measures they had, so this first measure is changes in sexual activity. And you can see that there was a significant improvement in those receiving testosterone with the waning of the effect towards the end of the year but still remaining statistically significant from those randomized to receive placebo.

Vitality, which was measured by scores in questionnaires that the participants filled out really did not improve, It was really fatigue scales is what was used. So the results of the study were that testosterone therapy did increase sexual activity, sexual desire, and erectile function. They also measured physical activity. And to measure physical activity, they did a six minute walking distance and they combined the men from all three trials into this analysis. They looked at it separately, just for the physical functioning study and then compared all the men. And when they compared all the men in each of the groups, there was an improvement in the groups receiving testosterone therapy.

No change in vitality, but there was better moods in lower severity of depressive symptoms. They actually, this is really not their primary outcome, but then they just asked about men's perceptions as to whether they felt better or not. And the men were blinded to what they were receiving. The dark bars here are the men who received the testosterone, the white bars are the men who received placebo. And it goes from much better, to much worse.

And you can see that the testosterone men are in the positive side of things with more of them feeling much better. Quite a few without change in most of these measures. For overall health, sexual desire, walking ability, and energy level.

The other thing that was looked at, again, this was just a one year trial, but in terms of looking at changes in PSA, there was a higher number of higher percentage of men in the testosterone group that had an increase in PSA of at least one nanogram per deciliter but the risk of prostate cancer was very low. This is the prostate score remained the same, this is a symptom score. It was the same in both groups. As would be expected, those that were randomized to receive testosterone were more likely to develop an elevation in their hemoglobin.

As far as cardiovascular events, there was really no difference in any of the groups. And in terms of serious adverse events, there was really no difference in either of the groups. Again, emphasizing that this is a one year study.

So the implications of this study is that there were modest benefits in sexual function that waned in the later part of the trial but definitely were still there. There were small gains in physical performance, vitality, mood, and depression. But there was wide variability in men in both the testosterone group as well as in the placebo group. So the study was not large enough, or long enough to address the risks of testosterone therapy. And the strict criteria that was used for study entry limits the generalizability, such as being able to generalize this to younger men who might be reporting symptoms of hypogonadism at lower levels of testosterone but still what might be considered subnormal for their age.

So I just will leave you with this take home message that in the absence of pituitary or testicular disease, testosterone replacement therapy can be considered in men with symptoms of hypogonadism, with confirmed morning testosterone levels, at least two measures, between 200 and 300, and only after discussion with the patients of the potential benefits and risks.

But given the number of testosterone prescriptions we see, it seems like many men are very willing to accept the risks that go along with testosterone therapy.

So now, I'm going to turn to women's health and the whole issue of the estrogen question, which has really remained. And one thing that has really surprised me is that we went through an era where we were probably over-prescribing estrogen. And we were using it for cardiovascular protection and we were using it for osteoporosis and then realized it was really not for everyone.

The Women's Health Initiative came out where the study was done with conjugated equine estrogens and medroxyprogesterone acetate, which are probably not the optimal forms of estrogen replacement therapy for a woman. But everyone became afraid of estrogen therapy and many women were taken off of it. Some women who were taken off of it against their will, even knowing the risks of a higher risk for cardiovascular events, only in that first year after randomisation in the group receiving combined hormone replacement therapy looked for other methods to treat their uncomfortable menopausal symptoms.

So women spend over a third of their lives in menopause. And certainly, you don't have to go through how many women there are that are in menopause. But some women experience significant symptoms such as, hot flashes, sleep disturbances, mood changes, as well as cognitive effects, which can have their ability to contribute to work and to keep up with activities with their family.

We really went through an era where, even women with these severe menopausal symptoms, and not all menopausal women get these symptoms, but we were actually denying hormone replacement therapy to these women because of the results of the Women's Health Initiative. And what I was going to say earlier is when I talked to our fellows in endocrinology, many of them have never written a prescription for estrogen therapy. And it's almost like teaching them a whole new area of medicine for how to go about prescribing and monitoring therapy over time.

So the treatments were really never taken off the market. They've been there, but we just haven't used them. And the Women's Health Initiative actually took women who were well above 10 years post-menopause, some of whom had cardiovascular disease to begin with, and so we've taken the results from this older subgroup and applied them to all women. And it really has not been fair to women. And what's happened is women are also going to the internet and the drugstore and using all kinds of unapproved over-the-counter therapies.

So a few years ago, this whole concept of well, is starting estrogen replacement therapy in the early menopausal years different from starting hormone replacement therapy in the late post-menopausal years? And that's the result of the elite trial, which has now been published. And they really paid attention to the cardiovascular effects of postmenopausal hormone replacement therapy because that was the issue that caused this sort of withdrawal of enthusiasm about these types of drugs.

The design was that women were randomized to estradiol, one milligram a day, or placebo. If they had not had a hysterectomy, they were also given a topical progesterone cream to use for 12 days out of the month. The early menopause group were women who had experienced menopause within the preceding 10 years and the late menopause group were over 10 years post-menopause.

And these are the clinical characteristics of this study population. So more women in the late menopause group and well over 100 in each group. The early menopause group being much younger than the late menopause group, with 3 and 1/2 years on average post-menopause in the early group, about 14 years in the late group. The BMI was in the overweight category but not the obese category. About 20% of women had high blood pressure and the LDL cholesterol, the mean LDL cholesterol, was about 134.

So I'm showing you the results of the positive aspect of the study here. So just to walk you through this, this blue solid line is the late menopause group before and after estrogen therapy. So there was no progression of carotid intima-medial thickness, which is a surrogate marker of underlying cardiovascular disease. It's not an event study, this is just a measure. And these are women studied for six years.

The early menopause group, at baseline, the thickness of the carotid intima was actually lower than it was of the late menopause group.

The early menopause group with estradiol, this is progression. This is progression in the late menopause group. And this is the late menopause group placebo, this is the late menopause group estradiol. This is the early menopause group with estradiol.

And there was less progression of the carotid intima-medial thickness in the group receiving estrogen compared to placebo, only in the early group. So the results of this study suggest that the greater increase in thickness in the placebo group was suggested that there might be some protection of estrogen therapy in the early menopause group. And there was no effect, adverse or beneficial, in late menopause group.

So this could be of benefit in the early period post-menopause. They also obtain coronary artery calcium scores in these subjects and those did not change in either group. They remain stable. There was no worsening of coronary artery calcium scores but there was also no improvement in either group. So the relevance to cardiovascular outcomes isn't entirely clear. But there was certainly no increase in cardiovascular events in either group, including the late menopause group that could be compared to what was observed in the Women's Health Initiative. Although, the type of hormone replacement therapy used was much different.

So I'm going to move now on to metformin labeling. This will be very quick. But earlier this year the FDA came out with a revised guidelines regarding the use of metformin in patients with impaired renal function. We've always used an EGFR of 60 as the criteria at which we allowed metformin to be used. And with a EGFR of less than 60 being one we were at least recommending that it be changed. Although, many of us were using this with a lot of comfort in people with EGFR's between 50 and 60.

But this was a group at Yale, Sylvio Inzucchi and Dr. Lipska, who actually led this movement with the FDA asking for a call to change the labeling criteria. And this summarizes the change in labeling criteria. So this is pretty standard. That an EGFR be obtained before starting metformin. Before beginning metformin and then more frequently in those at risk for renal impairment, such as with increasing age. That it remains contraindicated in those with an EGFR of less than 30. That starting metformin in people with an EGFR of 30 to 45 is not recommended, but that metformin does not necessarily have to be discontinued if they're already on it.

If they're EGFR, is less than 45, we'll usually reduce the dose to a maximum dose of 1,000 milligrams. And certainly monitor their renal function more carefully. And as is previously recommended, that metformin be held before patients undergo radio iodide contrast studies because of the risk for kidney disease induced by the iodine contrast material.

So this has really opened the door for us to feel very comfortable about continuing metformin. And we know that EGFR's decline with age, just because age is a major contributor to any of the formulas for calculating EGFR. So this should make you all more comfortable about continuing to use this in your patients. It's such a valuable drug. And the risk for lactic acidosis is very, very, very low.

What about advances in technology? So this is a picture of a man in one of the earlier studies wearing quote, "the bionic pancreas." This is a fairly complicated device but it consists of an insulin pump that is delivering insulin. As a basal rate, he would still need to program in any meal related boluses. Here is a glucose sensor that is inserted under the skin and is measuring interstitial glucose levels and is feeding this material back to the pump, where you really can't see it so well in this screen. But there is a readout of what is happening with his glucose levels on a moment to moment basis. So he can see if it's trending upward or downward.

This is the most advanced portion of the bionic pancreas. The whole thing isn't approved yet. But in this particular study, they also included a pump with a glucagon infusion. Normal physiology is insulin levels rise following a meal, glucagon levels drop. And as insulin levels drop, glucagon levels go up, in order to cause the liver to make more glucose. So we can maintain a normal glucose level in between meals and when we're sleeping overnight.

So this is sort of a bi-hormonal bionic pancreas. And that is not what's been approved. But two things about diabetes technology, so this is the email I received on September 27th. That the endocrine society will publish, it will be published next month in the *Journal of Clinical Endocrinology and Metabolism.* But they gathered a consensus panel to review the literature about continuous glucose monitoring. And their recommendation is that continuous glucose monitoring be considered the standard of care for patients with type 1 diabetes and some people with insulin treated type 2 diabetes.

They give its strongest recommendation. They say that it can be used on a short term, intermittent basis, for patients who are above target. We do use these glucose monitoring devices to identify people who have mismatches between their a1c in home glucose monitoring. They also recommend insulin pump therapy over multiple daily injections for people not meeting their goals for a1c and who are able and willing to use the device.

If there is frequent hypoglycemia and glycemic variability, glycemic variability is an area of research that hasn't really come up with any finite answers. But there are many people who still develop complications even with a normal or near normal a1c. And it's thought that glycemic variability is the contributor to that.

That insulin pump therapy is important for those who require flexibility in their insulin dosing or are feeling like this would be a better way for them to care for their diabetes. Or for some patients with type 2 diabetes. And, of course, the recommendation is that we should all know how to use these devices. But there is some technological complexity with the use of these devices that extends beyond what we have with multiple daily injections.

The very next day, after I received the email about the recommending CGM is the standard of care, the email came out that the FDA has approved the first artificial pancreas system as one of the most significant advances in type 1 diabetes. I'm not sure that it's the most significant. Inventing insulin back in 1922, or discovering insulin, was certainly one of the most significant.

And this is really not a tremendous breakthrough. But what it does offer is it closes the loop a bit. And this will be without glucagon, this is still going to be the insulin pump together with the continuous glucose sensor. But now, when the glucoses from the sensor feed into the pump, the pump will make decisions about how much insulin to deliver as a basal rate. They still need to program in their pre-meal boluses. It would only bolus after the fact if they started eating and we actually prefer that people bolus before they start eating, to have some insulin on board beforehand.

But it is an automated system, so that we set basal rates for patients on the pump and we try to look at their CGM's or their home glucose monitoring to adjust basal rates. This is basically the diabetologist version of the self-driving car.

This morning, I was seeing patients. I Actually have a patient who works at Google and he is so technologically advanced with everything in his life, but he won't use the bolus wizard on his pump. The bolus wizard, he likes to give all manual boluses because he doesn't trust the bolus wizard.

And so I said to him, I said, well, then you're probably somebody who doesn't support the self-driving car. And he said, oh no. I'd buy a self-driving car. He would trust that more than the bolus wizard on this pump. Although, we do try to encourage most of our patients to use the bolus wizard because it takes some of the work out of managing their diabetes.

All they have to do is put in the number of carbohydrates, all they have to do, is put in the number of carbohydrates they're going to eat, the sensor will have informed their pump what their glucose level is at the time, and the pump will calculate what their dose should be. Based on what's entered in terms of what their insulin to carbohydrate ratio should be, what their goal range is, and what their correction ratio is.

So this is supposedly going to be available to us in December of this year. I think those of us who are going to use these devices are going to require education about how to use these. I haven't personally used one of these myself. The device that was available before this just had a suspend feature to it, for two hours if the blood glucose went below the desired level. But this advances that even a little further.

And this is what happens. So this was actually just published in JAMA in September of this year, sort of preceding the announcement by the FDA. They studied 124 patients in order to bring this to approval. The age range of the people who participated in this study was between 18 and age 70. The oldest participant was age 70, and they wore the device for three months in a free living situation.

But before they had three months in a free living situation, they actually had two weeks of intense training. One of the weeks was in a hotel, where they were under constant surveillance. But if I think back to even the early days of the insulin pumps, when we started using a lot of insulin pumps, we used to hospitalize everyone for several days, until we all felt more comfortable with the pumps.

But just to take you through this. This is what a continuous glucose monitoring printout looks like. You just see this line here in the middle is the average glucose over the course of the day. And then the borders of this line are the variation in the glucose.

So the gray part of this curve is the variability before being on this, quote, "bionic pancreas." The sort of pinker, pink shaded area, is the variability after they were on this bionic device for three months. So the variability was lower, there was an improvement in a1c. The number went from about a mean of 7.2, I think, to 6.6%. Frequency of hypoglycemia was lower and it worked for adolescent patients as well as for the adult patients.

Dr. Drash who was at Children's Hospital of Pittsburgh years ago, is the person who really made a case for including adolescents in all these studies. When the diabetes control and complications trial was recruiting years ago, many people didn't want to include adolescents because they thought they would mess the whole thing up, that they wouldn't do what was supposed to be told. But because of Dr. Drash, adolescents were included in this study. And their a1c was a couple of tenths of a percent above that of the adults, but it was really important to know that we could pursue tight control in the adolescent population, as well.

Now, I just want to introduce you to the new insulins. And not only are we getting new insulins, we are getting new concentrated insulins. So up until recently, every insulin we had was called a u100 insulin, meaning that there were hundreds units in every one ml of insulin. The only one that was different was the u500 regular insulin, where there were 500 units in each one ml. and when we prescribe the u500 insulin, we had to be very careful about prescribing it to be sure the patient understood how to do it.

So if they drew up to five units on a u100 insulin syringe, that was really 25 units of insulin. And if we wanted them to take 25 units, we didn't want them pulling the syringe up to 25 units because that would have been 125 units of insulin. But now, we have u200 insulins, u200 lispro, which is one of the rapid acting analogs, a u300 glargine, which is a concentrated lantus. We have a u100 and u200 degludec. And soon, this will be available in December of this year, we're going to have a pegylated lispro.

Hopefully, people will realize that the pegylated lispro is different from the lispro because this is the rapid acting insulin that will be taken before meals. And this is the long acting insulin that would be taken once or twice a day, similar to what glargine would be. People don't really use the term bio-similar per se, but it's kind of similar.

So here's the concentrated insulin. So we talked about what it is for the u100. And this is a picture of the u300 300 insulin. It's just a third the volume of what someone would get if they used the u100. Where this was important for us is really with volumetric dosing. And with the prevalence of insulin resistance has actually increased, the percentage of people needing u500 insulin has actually increased with the increase in prevalence of obesity.

And so we were almost having patients where we were no longer dosing insulin in units but almost dosing it in ml's. If somebody was on 200 or 300 or 400 or 500 units of insulin per day, and that's a lot to give subcutaneously, especially when it's being given two, three or four times a day. So by decreasing the volume, you really alter the pharmacokinetics of the insulin preparation. So that's the point of this slide.

U500 is now available in a pen device. The cost of the pen device is really the same as the cost of the vial and it'll really decrease the dosing errors that came that he had to be done with the math that was done for making sure people were giving the right dose. Especially when they came into the hospital setting. So the pen is newly available, just within the past couple of months. And the person just dials in the dose. Five units of u500, would be five units of u100. It would be the same, using the pen device.

These are the pharmacokinetics of the u300 glargine versus the u100 glargine. The nice thing about u300 glargine being introduced to the market is, I felt it made the company much more honest about the effects of glargine, about the pharmacokinetics of glargine. If you all remember the advertising that came out when glargine was first introduced, it was like the 24-hour sign. You know, it's always on board. But those of us who use this a lot and treat a lot of people, particularly with type 1 diabetes, we really felt that this was not lasting the full 24 hours. And so this is just a comparison of the insulin levels and this would really be the insulin effect, using a euglycemic clamp study, with the amount of glucose that has to be infuse in order to maintain a normal glucose level here.

And here, you can see that the glargine insulin is much more effective during that first 12 to 18 hours, than it is during that next 6 to 12 hours. Both measured by insulin levels and insulin effect, where the u300 gives the more consistent 24-hour pharmacokinetic profile with a flatter curve.

Insulin degludec is another long acting insulin that we actually were anticipating it's approval about two to three years ago. But then the FDA asked for more cardiovascular outcome study. When this was first being tested, it was being tested as being able to give this every two to three days. But they found that that really wasn't effective. So it's a daily insulin but the half life is up to 36 hours. So if somebody misses a dose at 8 AM, they can take it at 3 o'clock that day without really experiencing any difference in their glycemic control.

This is the u100 formulation at different dosing levels. It's a relatively flat profile, which is really different from insulin levemir, which at sort of higher doses, insulin levemir becomes more like a long acting NPH. and it's available in the u100 and u200 formulations.

And then this is the pegylated lispro, which is just comparing the pegylated lispro here in the solid line to glargine insulin with similar doses. This is a one time dosing study and people with type 1 diabetes. And here, they're looking, it's really an insulin effect, looking at glucose infusion rates over a period of 24 hours. And you can see, they're fairly close to each other, at least in terms of the pharmacokinetics profile.

So what's so great about these new insulins and why should we know about them? There's two points here. One is that there are now about 26 million people, here in the United States alone, who have diabetes. The majority have type 2 but a significant percentage have type 1. And among the patients with type 2, a significant percentage are using insulin therapy. And these people are as diverse as we are from each other in this room. And there's no one insulin preparation that fits all. So it's nice to have some other tools available to us to use if we're having difficulty getting somebody under control with one insulin.

If you look at the studies of these drugs, most of the new studies, they rate themselves. They're usually non-inferiority studies or they look at frequency of hypoglycemia. They usually seem to have lower rates of hypoglycemia compared to whatever they are compared for, whether it's NPH or degludec compared to glargine.

I think the issue is, really, just what's best for the patient? The downside of these drugs is that they are very expensive and we are having difficulty getting them covered by some of the insurance companies. And so that seems to be the rate limiting step to us having a lot of experience, even on the diabetology side, with these agents.

There were coupons available, not all the insurance companies take coupons. So I have to say, I personally, don't even have extensive experience with them but we've had successes with some patients who we've had difficulty getting under control with some of the agents that we've had around for a while. So I don't want to overplay the differences but if you're having difficulty, sometimes it's worth trying something else.

So just want to summarize with back to the beginning. The testosterone trial, really, is the first study demonstrating the benefit of testosterone replacement therapy in older men. That showed no increase in cardiovascular events with testosterone therapy.

The elite trial showed that estrogen therapy can be used in post-menopausal women, particularly in the early post-menopausal years without adverse cardiovascular effects. And this was a six year trial.

As far as diabetes, the door has opened for us a little bit about being able to continue metformin in our patients. CGM devices are becoming more the standard of care, for selected people with type 1 diabetes,

The bionic pancreas, or I guess, advanced pump in CGM techniques are becoming a reality for us. It means that we're having to learn a lot more in the technology world. And the introduction of a new insulin products with different insulin concentrations expands the number of choices that are available to us for treating people with insulin treated diabetes.