[MUSIC PLAYING]

DR. RONALD CODARIO: So let's get started. Because it's a pretty dense talk today, no conflicts for me. All right, so endocrinology year in review, we've got a few diabetes topics and a few endocrine topics. And I tried to focus on what I felt were clinically-relevant, practice-changing updates in the last year for an internal medicine audience.

So as far as the diabetes topics, the first one's going to be metformin use in CKD, the FDA updates. Next, we'll talk about empagliflozin in cardiovascular risk reduction, another important FDA update. the LEADER trial in liraglutide, and then the last topic in diabetes, the so-called artificial pancreas. As far as endocrinology, we're going to go over the over-diagnosis of thyroid cancer and a big nomenclature change. I promise you'll understand that acronym by the end of the talk-- and finally, just a quick update on the T Trials, testosterone in older men.

All right, so metformin use in CKD. Now, if you plan on falling asleep, please just hang in there for the first 10 minutes. I really do feel like I've put the most important topic first. And the alternate title, I would say, for this would be, the FDA finally comes to its senses. What do I mean by that?

Well, let's take a look at the old recommendations versus the new recommendations. It's the old recommendations. Metformin is contraindicated in men with a creatinine above 1.5 and women with a creatinine above 1.4. This had most endocrinologists face palming on a daily basis.

Thankfully, the new recommendations are more enlightened. They recommend, first of all, checking GFR, not just creatinine. Then if the patient's GFR is above 45, you're good to go. That means max dose metformin.

If it's between 30 and 45, they don't recommend starting metformin. But if they're already on it, they recommend weighing the risks and the benefits. And I think a lot of experts would say, probably use half dose in this case. And if the GFR is less than 30, it's still contraindicated.

OK, so how about the updates with IV dye? Previously, you had to hold metformin for 48 hours. It didn't matter. Just hold metformin for 48 hours. Now, you only have to hold it in certain cases.

So the patient's GFR baseline is less than 60, or they have a history of liver disease, alcoholism, or CHF, or if they're getting intra-arterial dye, they recommend holding it. If they have none of those and the GFR is above 60, guess what? No need to hold metformin anymore-- fantastic.

OK, but let's back up a little bit. Why all the fuss? Why were we worried in the first place? Two words, lactic acidosis-- OK, so as we probably all know, lactic acidosis is already associated with a few conditions, CKD, CHF, COPD, chronic liver disease.

But it turns out that the fear of lactic acidosis with metformin is probably a misplaced fear of another biguanide, phenformin. So phenformin has potent inhibition of mitochondrial enzymes that leads to lactate release from the muscles. It has much higher rates of lactic acidosis than metformin, up to 20 times higher. It was, of course, taken off the market in 1976. But it remains sort of like that sibling that comes before everybody else in school and ruins it for the rest of the family.

Metformin I would say, in this regard, is in sharp contrast to phenformin. But I want to say this right at the outset, just so we don't get confused. Metformin itself does not generally cause renal disease. That's not the concern. It does not cause itself. The concern is when the patient already has renal disease, could you have a buildup of metformin that could lead to an elevated lactate?

And there are certain mechanisms that could lead to elevated lactate in metformin, increased intestinal production, inhibition of gluconeogenesis. They actually did a [INAUDIBLE] meta analysis about 50,000 patient years, and found that the incidence of lactic acidosis in metformin users is actually very low, about 0.08 per 1,000 patient years. But perhaps, more interesting is-- no.

All right, we seem to have paused here. Let me try this one. There it is. Perhaps, more interesting is that the rate is about the same in metformin non-users. And metformin levels actually tend to stay therapeutic in patients with CKD-- even advanced CKD-- and in patients who develop lactic acidosis. The metformin levels don't correlate with the lactate level, nor do they correlate with mortality.

And as I said earlier, lactic acidosis is just higher in certain conditions. And it turns out, diabetes is one of those conditions. So it sort of begs the question, in a lot of these cases of lactic acidosis in metformin users, is metformin just an innocent bystander?

OK, so how did the FDA sort of figure this out? How did they come to these conclusions, that actually we can probably use metformin in certain cases of CKD? What they did was they looked at real-world use of metformin. Now the funny thing about these studies, if you read between the lines, it seems like these studies were essentially meant to sort of admonish people for using metformin inappropriately.

But these brave trailblazers in metformin use wound up vindicating metformin in the end. So let's take a look at some of the data. So this is a small study from the UK, but pretty old, going all the way back to 1997, only 89 patients. But more than half of them had some contraindication to metformin. And that is in a context, in that population, of a very low background rate of lactic acidosis.

This study is actually out of our own institution-- 204 patients on metformin admitted to the hospital. 31% had at least one contraindication. And 41% were continued on metformin despite that. 14% had CKD. But 75% of these patients were continued on metformin.

And guess what? No lactic acidosis in these patients. OK, but those are kind of older studies. And that was before GFR was used commonly in clinical practice. So what if we used GFR instead? Maybe the picture looks a little bit better.

Well, there are a few studies that the FDA looked at. But really, the bottom line with these studies is that, when they looked at the numbers, using creatinine in low significantly underestimated renal impairment in these patients. In other words, even more patients than they thought had renal impairment and were on metformin.

This pair of studies, I love. I think it's particularly illustrative. So it's a 2007 study, Diabetes Registry in the UK. And it was almost 20,000 patients. And only about half of them were following the guidelines. Over a quarter had a GFR less than 60. And actually, the guidelines in the UK at that time were to hold metformin at a creatinine cut-off of 1.7.

They found that that equated to a GFR between 36 and 40, so pretty low GFR. Pair that study with an earlier study, but basically in the same population-- smaller study-- where they said about a quarter of the patients had contraindications with metformin. And only about 10% had it [INAUDIBLE]. Out of all of the patients in that study, 4,600 patient years, there was only one episode of lactic acidosis.

And it was in this poor old man, 72-year-old, but cardiogenic shock and renal failure after suffering an MI, who died on the same day. I can almost guarantee that metformin was not to blame in this case. I promise.

So how about the data on IV dye? There were a few studies, again, the FDA looked at. But I think this one is probably my favorite-- about 100 patients on metformin undergoing CT with contrast. Of the patients that had a GFR above 60, zero-- zero out of 77-- developed contrast-induced nephropathy. In patients with a lower GFR, one out of the 21 did develop contrast-induced nephropathy.

So if we put all this stuff together, there seems to be little to no increased risk of lactic acidosis in metformin patients who have CKD. And on top of that, there seems to be little to no risk of AKI with contrast, in general, but also in patients on metformin who have diabetes. And that's why the FDA decided to change their guidelines, let you use metformin down to a GFR of 45, and no need to hold it for contrast if the GFR is above 60.

But you may be asking yourself or saying to yourself, metformin is an old drug. It's a nasty drug, right? I don't care about metformin. Who cares? It's nasty. It's dirty. So why make the change at all? Isn't it just better to be safe than sorry?

Turns out, that's very wrongheaded. So, sorry if you were thinking that. But it's wrong. Because metformin is actually very beneficial not just in diabetic patients in general, but specifically in patients with CKD. Let's go all the way back to UKPDS where metformin in an overweight cohort showed a 36% reduction in all-cause mortality.

This was not true of insulin. It was not true of sulphonylureas. Now metformin was warned. It was given an explanation. And nevertheless, the effect persisted for 8.5 years after the trial. But that was in all comers. What about patients with CKD?

So this is a 2010 study, 20,000 patients with diabetes and cardiovascular disease, two year all-cause mortality. In patients with a GFR between 30 and 60 on metformin, all-cause mortality was reduced by 36%. How about older patients? I just got this today in my inbox, patients too old for metformin-- 23% reduction between 65 and 80, and above 80, no difference in mortality. So it's not dangerous.

How about in patients with CHF? A 40% reduction. How about this study? Over 50,000 patients followed for four years-- so I guess two times two, four times better than the other study. That's bad math, by the way.

Metformin as monotherapy-- and they looked at all-cause mortality and a few other outcomes. And they compared it to insulin and other orals. The GFR was above 60, improved all-cause mortality, 13% reduction. How about if it was lower? Same story.

How about if it was even lower than that, between 30 and 45? No difference in mortality, no difference in cardiovascular disease, no difference in acidosis or serious infection. And just to kind of drive this point home-- because this real-world data just keeps coming out and coming out on metformin.

This is just from this year. *Systematic Review* published in Annals, 17 studies, tens of thousands of patients. And they saw that metformin reduced all-cause mortality in patients with congestive heart failure and CKD, where they showed a 22% reduction. Patients with chronic liver disease, and hepatic impairment and cirrhosis-- regardless of the degree of cirrhosis, may be driven a little bit by NASH, but there were definitely some alcoholic and viral cirrhosis patients in there-- reduced CHF admissions in patients with CHF and CKD, and reduced hypoglycemia in patients with CKD.

So the bottom line, just so we're clear, is that metformin is safe. It's effective. It's inexpensive. It's lifesaving. It's the clear first choice in type 2 diabetes. And now, you can use it down to a GFR of 45. So metformin, at this time, is still the best.

However there are some newer medications that are hot on metformin's tail. So let's talk about those-- empagliflozin. So this is a little bit of rehashing of what we went over last year. But there's a big update. In December of 2016, the FDA approved empagliflozin to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

The approval was based on only one study, EMPA-REG. And this was originally a post-marketing study to look at cardiovascular safety. But it turned out to be oh-so-much more. This was narrowly approved. But there were really no substantive criticisms of the study itself.

Really, it was just because it was-- as I said-- just one study. It's a fairly new class of agents. And the mechanism of the benefit is not 100% clear. Well, why is this important?

Well it was the first diabetes medication to show cardiovascular and all-cause mortality reduction in diabetes patients with cardiovascular disease in a randomized controlled trial. Was also the first diabetes medication approved by the FDA for this indication. And then, guess what? If you have a life-saving medication, even if it's a little expensive, it's more likely to be on formulary. I know it is up at the VA, which is very nice.

Well, let's back up a little bit. So SGLT2 inhibitors, that's the class that this medication is in. So let's talk about those briefly. There are three currently approved, cana, dapa, and empagliflozin. SGLT2 itself is a high-capacity, low-affinity sodium glucose co-transporter responsible for 90% of glucose re-absorption in the kidneys.

Of course, there's going to be a cartoon to see how it all works. But SGLT2 is actually up-regulated in diabetes. And when you inhibit it-- so blocking SGLT2-- it changes no glucose to yes glucose.

So you spill more glucose in the urine, which is good. Because that helps patients to lower their A1C, but also helps them to lose some weight. And actually, this class of agents has much lower rates of hypoglycemia than agents like sulphonylureas.

It's contraindicated in patients with type 1, anyone who's had DKA, anyone with a significantly impaired GFR, or anyone who starts out volume-depleted, because obviously, you're going to make more urine. If the patient's GFR is a little bit impaired, there's caution. But it's not contra-indicated.

The CHF caution is a little bit nuanced. Basically, it has a diuretic effect. So if they're on diuretics, you have to be careful. And you might need to adjust them. And then if patients are prone to UTIs or yeast infections, be careful, Because. more sugar in the urine will cause problems along those lines.

So just so we're on the same page, we're just going to quickly review the outcomes from that study. So top left is the primary outcome, major adverse cardiovascular events. That's a composite of CV death, nonfatal MI, and non-fatal stroke. The empagliflozin group had a 24% reduction for this.

How about death from cardiovascular cause? Top right, 38% reduction. How about death from any cause? Bottom left, 32% reduction. And then admission for CHF, 35% reduction.

Even more interesting, these groups started to diverge early, around three months. And the difference in the primary outcome was driven mainly by cardiovascular death, so preventing deaths here. So the number needed to treat to prevent one death was 39.

This is huge. This is robust. This is very good. And this is along the lines of other trusted classes like statins, and ACE inhibitors and things like that. But we have to ask ourselves the question, is this empagliflozin, or is this all SGLT2s?

We don't have the perfect answer right now, because CANVAS and DECLARE, the similar studies for canagliflozin and dapa aren't out yet. As I understand, preliminary results for CANVAS look non-inferior and not superior. But we'll see when all the data come out.

How about DKA? You may have heard about this with SGLT2 inhibitors. It turns out, a lot more in canagliflozin-- and again, mostly in type 1s, autoimmune diabetes. It may have just been because canagliflozin was and was approved earlier. But we don't know that for sure.

How about fractures? Again, it seems like kind of a risk with canagliflozin. Mechanism is not clear, not a lot of reports in the other SGLT2s.

How about AKI? Clear distinction here, the FDA recently strengthened its warning for AKI and canagliflozin and dapagliflozin. It tended to occur early, in the first month or so of therapy. So make sure, if you're on these agents, to check the GFR early.

But this is in sharp contrast to empagliflozin. And EMPA-REG actually improved renal outcomes by 39%. That was driven mainly by progression to macroalbuminuria. But perhaps, more relevant, there was no increased risk of AKI.

So to summarize this section, empagliflozin has a robust mortality and cardiovascular benefit in type 2 diabetes patients with established cardiovascular disease, and appears, at this time, to be sort of the leader of the pack. And that is the final leader pun that I will make. I promise. I'm going to move right into LEADER.

So LEADER, the Liraglutide Effect and Action in Diabetes, Evaluation of Cardiovascular Outcome Results-- man, the names of these trials get better and better every year. So this is obviously in liraglutide, which is a GLP-1 receptor agonist. The mechanism for those is that slow gastric emptying. They block glucagon. They suppress appetite. And they promote glucose-dependent insulin secretion.

The study itself was all the stuff that we like, multi-centered, placebo-controlled, double blind, randomized, all that good stuff. The primary outcome was essentially the same as in EMPA-REG, composite of cardiovascular death, non-fatal MI, non-fatal stroke. It was over 9,000 patients, about a four-year median follow up, duration of diabetes pretty long, 13 years, A1C 8.7s, pretty typical for these kind of studies.

But 81% of patients had cardiovascular disease. 72% had CKD. And about 16% had both. We have to compare everything to EMPA-REG now, because that's the standard. So in EMPA-REG, essentially, 100% of cardiovascular disease, but much fewer had CKD for obvious reasons, harder to use, the SGLT2s, and advanced CKD.

All right, so let's real quickly review the inclusion criteria. So obviously, they had to have elevated A1C, 7 or more. They could be treatment-naive or previously treated. It didn't matter. That would be at least 50 with at least one cardiovascular condition, CAD, CVA, PVD, CKD stage 3 or worse, CHF, or more than 60 with one risk factor, as listed here.

Exclusion criteria, nothing surprising here, type 1 if they were already on a GLP-1 receptor agonist or similar agent, if they had a family or personal history of MEN2 or medullary thyroid cancer. That's based mainly on animal studies where there were some c-cell hyperplasia with these agents. And if had a heart attack or stroke like right before the study, they were excluded.

All right, so since I'm a huge fan of delayed gratification, we'll go over the non-cardiovascular outcomes first. So microvascular, improvement there. 16% reduction overall driven mainly by nephropathy, again, driven mainly by progression to macroalbuminuria. No significant differences in pancreatitis, all cancer, or pancreatic cancer, which is big. Because there's sort of a not-well-founded fear of pancreatitis and pancreatic cancer in these agents.

Small difference in A1C, but remember, at follow-up in both groups, doctors could do, essentially, whatever they want to get the A1C to goals. You wouldn't expect a huge difference. Weight loss-- which is nice, nothing to sneeze at-- 2.3 kilos, and minimal changes in blood pressure and pulse.

Adverse events, look out for gallstone disease. Because it was higher in the liraglutide group. And some of those events were severe. Hypoglycemia is the opposite story, a lot less hypoglycemia and a lot less severe hypoglycemia in the liraglutide group.

And then discontinuation of the agent from adverse events, this is not a huge surprise. We know that the GLP-1 analogs cause nausea, vomiting, abdominal discomfort, decreased appetite. And so, a few more people dropped out in that group.

All right, so onto the good bits, the cardiovascular outcomes-- so again, primary outcome, as we already discussed, composite of CV death, non-fatal MI, non-fatal stroke. Liraglutide showed a 13% reduction-- not bad. How about death from cardiovascular causes? 22%-- not bad. How about death from any cause? 15%-- again, not bad.

But if you're remembering back a few slides, you're probably saying to yourself, well, but empagliflozin was about twice as good, which is true. But the leader investigators had an answer to your terrible thought. They said, although the magnitude of the effect was smaller, the consistency was so much better in LEADER.

What did they mean by that? I'll tell you what they meant. So basically, they looked at all these outcomes individually and tried to convince us that liraglutide was just so much more consistent. So let's look at them together.

Fatal or non-fatal MI, excluding silent, mm, turns out, they're both pretty good. How about just nonfatal MI excluding silent? Still about the same. All right, how about silent MI? Ah, finally, liraglutide did better.

How about hospitalization for unstable angina? Neither one of them was really all that better than placebo. Well, how about coronary revascularization? No difference.

All right, how about a fatal or non-fatal stroke? Here we go. Liraglutide did better. How about just non-fatal stroke? Yes, OK. And how about TIA. Nope.

But if you look at it, so much more red on the empagliflozin side, right? What's up with that? So that's what they were talking about, more consistency.

But I will caution you. Considered separately, absolutely none of these outcomes in either study was statistically significant. All of these pluses were trends, so to speak. So it depends if you believe in trends or if you think the trends are simply alternative facts.

All right, so we'll ask ourselves the same question we asked with empagliflozin. Is this liraglutide, or is it a class effect? Has every GLP-1 been studied exactly the same way? No, but a few have, or they have been studied in similar ways.

So there was the ELIXA trial on lixisenatide, patients with diabetes and recent acute coronary syndrome. Not inferior-- it's not dangerous, but not superior. Then there was sustained in semaglutide once a week. So that's fun.

And if you look at the primary outcome-- which, again, is the same-- a nice reduction, 24%. Then when they looked at deaths from cardiovascular cause, unfortunately, not as good as liraglutide. So bottom line, although the effect was not as robust as with empagliflozin, this would be the second diabetes medication to show mortality and cardiovascular benefit in type 2 diabetes patients with cardiovascular disease or risk factors in a randomized controlled trial. But I think we're going to be hearing a lot more about this and the class going forward.

All right, so let's move on to our fourth and final topic in diabetes, the so-called artificial pancreas. There's a lot of excitement about this, probably because people are just sick of me personally and want me to be replaced by a robot. I can only assume that's what it is.

Oh, by the way, OK, disclaimer, I'm going to use a brand name, not because I'm endorsing any particular brand, but because it just doesn't make sense. There's no real generic name for it. So I have to tell you what it is. But I promise I'll try to be fair and balanced.

The one that's approved is the Medtronic MiniMed 670G. And I'll explain what I mean by, "quote unquote." This is a hybrid closed-loop insulin delivery system. Basically, a continuous glucose monitor transmits glucose readings to the pump. And the pump delivers insulin based on a proprietary algorithm.

But at this time, it's delivering basal insulin only, meaning boluses are still manual. So it doesn't fully replace human input. So it's the "artificial pancreas." It is approved for patients with type 1 diabetes, diabetes for 14 years of age or older.

And I don't mean to pooh-pooh it. It is a significant upgrade from prior models. So before, they responded mainly to hypoglycemia or only to hypoglycemia. Threshold suspension means if it dropped below a certain level, insulin delivery stopped.

Predictive is a little bit more clever. There was a trend downward. It would modify or stop insulin delivery. This one is more like a thermostat or-- I don't know-- cruise control, however you want to think about it. It responds to both low and high blood sugars in a predictive way.

So what's the data for this? How was this approved? So there was this one trial, 124 patients with type 1 diabetes, wide age range, 14 to 75, mean around 40. If you look at the data-- so here's how they set it up.

First, they had them on standard pump for two weeks, kind of a run-in period. Then they had them on the closed loop. If you compare the numbers, you can see reduced hypoglycemia, reduced hyperglycemia, and reduced glycemic variability, meaning they spent more time in the goal range for the closed-loop portion.

There was no severe hypos, no DKA in either group. There were a couple severe hyperglycemia episodes. But that was basically pump infusion set problems, which just happens with pumps.

And there was an improvement in A1C, which I thought was kind of impressive, because it's a short study. And these people were already pretty well controlled to begin with. And you got a 0.5% drop without any increase in severe hypoglycemia. So I like that.

There were four serious adverse events. But they were in no way related to diabetes or to the pumps themselves.

And of course, there are some limitations to this study. It's kind of small. There's really no control group, the big imbalance between the study periods, relatively short. And again, patients were relatively healthy. But it's kind of a low bar for approval here, because this is not a new indication for insulin. But I think we're going to be seeing a lot more of this in the future.

Now I felt the need to, even though these aren't available yet, to kind of review some of the data from the competitors. This is from last year's ADA. Because there are a few competitors, like this one, Dana Diabecare R.

It's a similar kind of closed-loop insulin delivery system without bolusing. And this was a fun study, 24 in-patients. 12 got sub-q injections, as we would normally do, and 12 were just hooked up to this insulin delivery system. And they had a blinded 72-hour CGM. And the patients on the artificial pancreas spent more time at goal, which they define as 100 to 180, less time above goal. And there was no difference in hypoglycemia.

And they didn't have to fuss or fight with it at all. They just slapped in on them. And they were done. So that's exciting, I guess. If you do inpatient diabetes, it's exciting.

And then there's the iLet. This one has a few different iterations. Here's the dual-chamber one.

So this is unique. It has insulin and glucagon together. People are calling it the bionic pancreas for some reason. It's a fun name, so we'll go with it.

And they compared it to a standard pump for 11 days-- better mean glucose and less time spent in hypoglycemia. Now this one is going to take longer to be approved, because it is a new indication for glucagon. But they have an insulin-only one.

And they actually compared it to the bi-hormonal one and to standard pump. And this clever little study with 20 patients, 6 three-day arms, random order crossover. And they had really tight targets for the bi-hormonal. You can see their 1 went all the way down to 100. And there were no differences in hypoglycemia.

And the bi-hormonal was able to achieve much lower mean glucose. So that's kind of fun. So when you insert a glucagon algorithm, you're able to get much tighter control without increasing hypoglycemia, which is difficult.

Then they actually have a glucagon-only pump, which, again, this is really interesting. And what they did to study this one, just got 22 people. They served as their own controls.

And they could be taking whatever. They were type 1s with hypoglycemia unawareness. They could be on multiple daily injections, pump, didn't matter. They just had a period where they weren't using this-- they were using placebo-- and a period where they were on the glucagon pump.

And it managed to reduce both daytime and nighttime hypoglycemia with no increase in mean glucose and no excess adverse events. Part of why I think this is fun, too, is it could have application in other disorders, like post-gastric bypass hypoglycemia, where they don't need insulin at all, or congenital hyperinsulinsim or things like that.

But I guess the bottom line for this section is kind of short. But there's just much more to come for these. So be on the lookout. And remember, these ones not yet available.

All right, so that wraps up our year in diabetes. But we still have a couple of endocrine hot bangers waiting for us. All right, so the over-diagnosis of thyroid cancer, this is our first topic in the endocrine section. I'm going to have to define this for you the best way that I can.

What do I mean by over-diagnosis? Increased incidence of indolent neoplasms from intensive surveillance without a clear clinical benefit. Sot the International Agency for Research on Cancer looked into this-- some clever statistics here.

And they estimated based on age-specific curves before and after the advent of thyroid ultrasound for clinical use. And they said that around 470,000 women and 90,000 men were over-diagnosed with thyroid cancer in 12 high-income countries, including the US, in a 20-year period with the mortality rates remaining, essentially, the same. There was no clear evidence of new risk factors and no increased exposure to known risk factors.

For women, in the most recent time period, they said that over-diagnosis accounted for 90% of thyroid cancer in South Korea, 70% to 80% of the US, Italy, France, and Australia, and 50% in some of the other countries. For men, same time period, 70% were thought to be over-diagnosed in France, Italy, and South Korea, 45% in Australia and the US, and 25% everywhere else. Let's take a look at this in graphical form.

So you can see here that black line at the top, the one that's just steadily rising from like the 1980s onward, is the incidence of thyroid cancer. And this sluggish blue thing at the bottom here, that's mortality in thyroid cancer. It didn't change. So what happens between here and here?

Well, here's what we think. I think a lot of it had to do with increased surveillance, which had to do with the advent of neck ultrasound, but also had to do with more CAT scans and MRIs. And actually, 70% to 90% of thyroid cancers in places like the United States, Western Europe and Australia are thought to be identified incidentally, meaning, you would have never known it hadn't you not got to study for something else and found it on there.

Wait. Again, let's back up. You may be asking yourself, what's the big deal? It's cancer. We found it, and we fixed it, hooray, right? Well, it turns out, it's more of a problem than we might think. Because most of these incidentally-discovered cancers were small, low-risk papillary cancers.

And they actually did a study on this in Japan. They diagnosed papillary cancer by biopsy when they were less than a centimeter, so micro-papillaries. They just followed them for like five or six years, didn't treat them at all. Only 3.5% had any sort of even remote progression. There are absolutely no deaths in that time period in over 1,200 patients.

Well, what happens in real life-- what was happening-- vast majority of these patients were getting their whole thyroid removed right out of the gate. And a lot of them were also getting radical lymph nodes dissection and radioactive iodine, which is just not indicated for this in any way, shape, or form. And we have to remember that these treatments don't come without complications. And some of them can be pretty nasty, vocal cord paralysis, hyperparathyroidism, which is a pain to treat, hemorrhage, sialadenitiis, loss of taste, secondary malignancy, things like that.

All right, so now that we are sort of aware of this problem, what can we do about it? I have bad news for you. In order to understand that, I have to take you through historical perspective on thyroid cancer pathology. If that doesn't put you to sleep, I don't know what will. But I promise, there will be pictures.

So in the 1950s, when America was great, thyroid cancer was much simpler, as were a lot of other things, I presume. Differentiated thyroid cancer, which is papillary and follicular. Papillary is the one with those finger-like projections. There you go. And follicular had the nice little follicles that you could tell it was cancer, because it busted through the capsule, invaded stuff.

All right, but then in the '60s, things got more complicated. And that included thyroid cancer. They discovered a mixed type called follicular variant papillary thyroid carcinoma. It had a follicular growth pattern. But it had nuclear features of papillary. So let's do another picture.

From the left there is normal. And on the right with the red arrow, these are nuclei that are typical papillary nuclei. They're big. They overlap.

They are opaque, because the chromatin is on the periphery. And probably it's hard to see this, but sometimes there's grooves in nuclei. So they just look weird.

All right, so what happened with this mix type over the years? Well, in the '70s, there's sort of wider acceptance that it existed. But then they also started to think, huh, I think this is more like papillary cancer than anything else. OK.

And then in the '80s, they discovered a fully encapsulated form of follicular-variant papillary thyroid cancer. So here it is encapsulated follicular-variant PTC. On the left is normal. On the right is the cancer. And right in the middle there is the capsule.

It turns out this is about 20% of thyroid cancers. But this is where the record scratch noise should be going off in your head. It certainly did in mine. Because this is where a lot of the problems started. And I'll explain why.

So if you're assuming that this behaves like papillary, you're assuming that it can metastasize to the lymph nodes. But if you're assuming it behaves more like follicular and it was completely encapsulated without any sort of invasion, that's totally benign. We call those follicular adenomas. They are not cancer. So which one is it, and maybe, are there different types?

Unfortunately, in the early 2000s, there was a lot of overlap that conflated invasive encapsulated follicular variant PTC with the noninvasive type. And they are actually very different. But they assumed at the time that the nodal metastatic rate would be the same. So they were treated the same.

So in 2000, people actually recognized this. And they had their first attempt at renaming this cancer. But they decided to call it a well-differentiated tumor of uncertain malignant potential. So obviously, it still scared the crap out of people. And it didn't catch on.

In 2006, we had even more information to tell us that the invasive type behaved more like papillary. Whereas, the noninvasive type behaved more like a follicular adenoma, it was, essentially, benign. And then in the 2010s, thanks to work at our very own institution and other places, they showed that the molecular profile of these noninvasive encapsulated follicular-variant PTCs was more like follicular adenoma than anything else, lack of b-raf mutation, high prevalence of ras mutations.

So finally, this year, we've got a new name for this type of thyroid neoplasm, noninvasive follicular thyroid neoplasm with papillary-like nuclear features, commonly abbreviated NIFTP, not with all the extra parentheses. Do I have thyroid cancer or dyslexia is sort of the question I asked when I first heard this name.

But there's a good reason they called it that, a very good reason, actually. And this is fantastic work spearheaded by our very own Yuri Nikiforov. So if you see him in the hallways, please congratulate him and shake his hand.

So what they did was-- this was a whole bunch of pathologists and really smart people-- found 109 noninvasive capsulated follicular-variant PTCs that were not treated except for lobectomy. And there was zero recurrence despite only having a lobectomy for 13 years. They got no radioactive iodine, no completion thyroidectomy.

Versus 101 invasive ones-- 12% recurrence rate at 3.5 years, which is basically the same as PTC. And the reason the nomenclature is so long is they really, scrupulously avoided the term carcinoma, which is leading to full-blown hysteria and over-treatment despite what everyone is saying. And that led to about 45,000 patients per year worldwide being over-treated. So this is a big step forward.

But what else can we do about this over-diagnosis of thyroid cancer problem? Well, first of all, let's stop getting thyroid ultrasound for hypothyroidism. It's generally not indicated. Don't biopsy sub-centimeter nodules. This is ATA guidelines most recent update.

On ultrasound-- and this is maybe for us more than you guys-- but recognize the difference between irregular borders, which are clear and distinct but irregular-- that's a bad sign-- versus hazy borders. That means you just can't see the border. That's a nothing sign.

Consider lobectomy if you think you might have a NIFTP on your hands, meaning you do a biopsy, you have a ras mutation, and the ultrasound appears just looks like a nice encapsulated little egg. If you find micro papillary when you take out a lobe, guess what? Cured.

Re-review the path for those patients that you think might actually have NIFTP but were already treated. In other words, if they had encapsulated follicular variant, have that pathway reviewed. And if it's noninvasive encapsulated follicular variant, stop surveillance. Stop suppressing their TSH. Stop all of it.

And then, of course, in general-- and I think this is maybe the most important one-- just consider your patient's age and their co-morbidities before you embark down this whole nodule thyroid cancer route. Because if they're 35, and super healthy, and very attractive-- like me-- maybe you do want to treat them for thyroid cancer.

But if they're like 85, and they have really bad heart failure, and renal failure, they're not going to die of thyroid cancer. And if you don't care about patients at all, Dr. Nikiforov still has an answer for you. He says, avoidance of RAI alone, let's say, between $5,000 and $8,500 per patient based on US costs, and decreased long-term surveillance would account for another substantial proportion in cost reductions. So I guess the bottom line here, there are many reasons to sort of take a moment and kind of rethink your strategy with thyroid cancer and thyroid nodules, in general. But now we have more ammunition for that cause.

All right, so one last topic. And I hope this is a fun one, because it was for me-- the T Trials. These are the testosterone trials in older men. And the data keep trickling out. So this is sort of an update from this year.

But let me give you the background a little bit. So in 2003, the Institute of Medicine said, hey, you're using a lot of testosterone in older dudes. We should probably figure out if it works. So we embarked on this journey.

We found 790 men, who were older than 65, who had a testosterone less than 275 and symptoms of hypoandrogenism. Now this is going to sound basic to you. But actually, this is fantastic that they defined what they meant by a low testosterone in the study.

Shockingly a lot of studies in testosterone don't do this. So this is great. They used testosterone gel versus placebo. Again, this might sound sort of basic, but a lot of studies don't have a placebo group, so A-plus.

They looked at a bunch of different things. They had sort of three different wings, the sexual function, physical function, vitality, which, again, is great that they're being so thorough. And they actually had a treatment target, which again, thank you, wonderful. Lots of the other studies didn't do that.

And they wanted to treat to bid normal, for many just 19 to 40, which they considered the median to be about 500, and the range between 300 and 700 total testosterone. Sounds about right to me and to most people, I would say. So what did testosterone do for these older gentleman?

Well, it significantly increased sexual activity-- all right-- significantly improve sexual desire-- thumbs up-- improved erectile function-- great. It even improved six-minute walking distance. I love it. And a couple of bonuses, slightly decreased the severity of depression and improved mood-- wow, great.

And there were no difference in adverse events-- sounds like a win to me. And as I've sort of telegraphed here, I feel like the design of these trials was just perfect, much to their credit. Much to their detriment, it was a perfectly-designed study. So what do I mean by that?

So what's the T? What's the truth for the T Trials? Let's take a closer look at the numbers.

So first of all, 51,000 patients enrolled. Only about 1.5% met the criteria. That's where we came up with the 790 men. Some highlights from the exclusion criteria, conditions known to cause hypogonadism. I'm not sure why you would exclude those people. A systolic blood pressure over 160, also known as the blood pressure all my patients have until I recheck it, even the ones without hypertension.

But, OK, OK, well, let's look at the actual benefits. Let's look at the benefits. So you see there in red, that's testosterone towering over placebo in blue. But if you look at the last three months, that effect started to converge a little bit. That's a little disconcerting. This is sexual activity.

All right, how about that walking speed? That was good, right? It's actually pretty tight for nine months. It did start to diverge in the last three. But then I actually did a little math. How much faster were these guys going, on average? 0.31 miles per hour in a six-minute challenge, so not great.

But, OK, all right, let's look at some hard outcomes-- pun completely intended. And you can see here, testosterone's in gray. Placebo's in white. Now look at those bars.

Those gray bars are doing great. They're towering over the white bars. They're doing such a better job.

But look at the scale. This is average frequency. And it's actually average daily frequency. And probably why they chose daily is because, if they picked monthly, you would not be able to perceive the differences with the naked eye on the bars.

So let's look at a few of the choice selections here. Orgasm, 1.5 more orgasms per month in the testosterone group, sexual interaction with partner-- interaction, not intercourse-- one more per month, and then, of course, intercourse, 0.6 more intercourses per month, so not exactly the robust benefit that the headlines gave us.

And then on top of it-- and this is a direct quote from this study-- "the number of participants was too few to draw conclusions about the risks of testosterone treatment." So the bottom line is, although the headline may be that testosterone is effective and safe in older men, if you look at the numbers, the details tell us a different story. Testosterone in older men, based on these numbers, has a modest effect on sexual activity, though statistically significant.

And we can draw, unfortunately, absolutely no conclusions about the safety of testosterone from these studies. Rest assured, however, that the people that are making money off of these testosterone products will continue to take advantage of the most fragile thing in the universe, masculinity. That's me in the middle there in the off season.

All right, so that's it. That's the end of our talk. Let's review what we talked about today. So go out and buy metformin if your patient's GFR is greater than 45-- not available at Nordstrom. Strongly consider empagliflozin and liraglutide in your patients with type 2 diabetes and cardiovascular disease. Or wait another 20 more years, just like we did with metformin.

Diabetologists haven't been replaced with robots yet. Noninvasive encapsulated follicular-variant PTC was cured, in that it was never cancer. And finally, definitely prescribe testosterone to your older male patients lest they miss out on 0.6 intercources.

All right, and as always, more to come on all of these topics in the future. And certainly, I'm sure you can find my references online. Because these are going to be very difficult to read. But I hope that we left time for some questions. Thank you.