

When and How to Use Insulin Therapy in Type 2 Diabetes

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Good morning! It's really an honor to be here Dr. Bullock. Thank you for the invitation and I really am honored to be here with such an amazing and respected faculty that you have. Friends that I have worked with for years, Brenda Broussard, Terry Raymer, Steve Rith-Najarian who we have collaborated with. And then there are those that the whole country looks up to, including me, when you look for wisdom and leadership in the area of diabetes and health promotion, Yvette Roubideaux and my good friend Dorothy Gohdes and Kelly Acton. And I would like to also add my congratulations to Kelly, I know she is back in Washington already doing your work there, but for her award of the C. Everett Koop Medal for Health Promotion and Awareness that really one of the highest honors the ADA bestows. So just wanted to congratulate her and it's another reason and I hope all of you, or many of you will be in Orlando in June for the ADA meeting to see her receive that award.

Well, I get a chance today to talk with you and I hope you'll have questions and we will have some interaction here about one particular topic in diabetes, that's the use of insulin therapy. The When and the How and the Why, and I do work with lots of the insulin companies. They don't know personal compensation comes my way but we do lots of research studies to try to understand the new therapies. So I think whenever you talk about a therapy, be it one of the oral agents or the exciting incretin class or anything. You've got to start off with, what is my goal in the first place? Because that's the only way you know if you are achieving it. If you know what you're setting out to, and there is really not, it's hard to say, oh, every patient has to be treated the exact same way. But we still believe at the ITC, where I work day-to-day and representing the ADA, there are a lot of people who can get down around 7%.

The little asterisk says, it's not everyone, and there are exceptions today, we are learning from some of these trials and then what you say their pre-meal and their post-meal should be, is a little bit open to conjecture and your personal read of that patient.

Now when we summarized all the recent trials just to spend one more minute on this goal of around 7 and good glucose control as it's thrown out the window with all these recent trials, it calls some question. If you look at this summary of major trials and you say, does good blood sugar, around 7%, prevent eye, kidney and nerve disease? I think you would have to agree that all the arrows are pointing in the right direction. There really is little question from anywhere, anyone that is down around seven there is one result pending, the ACCORD Trial, which has thrown a little bit of a muck in a lot of this. They come up with contrary results, but their results on the eye findings, need for laser, preventing retinopathy will be presented in June. So another reason for you to come.

So which way that arrow will go, we will find out all of us together in June. I have this feeling where we will see, which way I go, but we will see. There was one study as you know, the ACCORD Trial said in a group of people, when we tried to get them to 6% and they already had heart disease, that didn't seem to benefit them. But I show you this one graphic, I know it

looks sort of like some spaghetti junction here, some highway, but I show it to you just because it was released yesterday. So I want you to have the latest from diabetes care, they are online, and what it says is, what did you take-away when you heard about the ACCORD Trial? And they said, oh, the intensive group had a higher mortality rate.

So everybody said, well that means low A1Cs cause mortality, because the intensive group was really pushed hard and the standard group was -- did a good job but not. So it turns out when you really look at the A1 data, it's actually just about the opposite. This orange line is the intensive therapy patients and what it says is, in the intensive group those who had lower A1Cs had a lower death rate, those in the intensive group who were not able to achieve a good A1C had a higher mortality rate. That as a whole the group may have had a higher mortality, but it was those who could not achieve the goal.

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And then others said, remember how the ACCORD Trial, we got people in control very quickly. People said, oh, Gosh! That's kind of crazy to really control them quickly. That must have been what caused the increased mortality in the intensive group as you treated them so aggressively. The faster they came down, they must have had a higher mortality rate. It turns out in the same paper. I didn't put the slides in. The same paper says, those who did not come down quickly in the first six months, other ones who had a higher mortality rate.

So we are learning still. So when studies come out, yes, you take the first look at them and then you dig a little deeper and try to say, well let's look at the subsets and the populations. See how it affects my practice. So steady increasing risk from 6 to 9, somewhere around seven. So just sort of by chance I think, some of these ADA standards where around 7 seems to be holding up. Other group said, oh, you're not aggressive enough, it should be 6.5. But the data says, right around 7 will prevent eye, kidney and -- well will minimize eye, kidney and nerve disease and won't do any harm to heart disease and may actually prevent some heart disease.

So here is how I read it at the end of a post, post ACCORD as we like to call it around our place. Since we are the second largest site in ACCORD, we follow it closely. So some of the ADA goals and what did ACCORD tell us, I think it did say, we don't have to push for less than 6 and people around, should be around 7, but if you're pushing hard, if you're working with a team, if you're educating monitoring, and you can't get to less than 7, then okay, back off a little bit. Those are the people who had higher risk that you worked really hard on and they got stuck. Same thing with blood pressure. just released in the *New England Journal of Medicine*, this past week, it was on online for about a month. We don't have to push their blood pressure to less than 120, that was no benefit. 130 seems fine and if you work hard at 130 and you can't get there you are on your third, fourth blood pressure medicine, you can say this person is probably a 130 to 140 candidate. And LDLs of a 100 are still holding up, adding of fibrate to a statin didn't seem to add much, so that's not the topic today.

If you like to look at blood sugars, A1Cs by converting them to an average, feel free to do it, I kind of like it, others for some reason don't like this conversion. It's okay if you like it. My patients don't all get that percentage thing. A1C, let's see a percent of the red cell that's coated with glucose. So it doesn't make as much sense to them as poking their finger and getting a

number. So you can convert the A1C into a blood sugar. And remember A1cs, estimated average glucose don't tell the whole story. Please keep monitoring their blood sugars because these two green and yellow lines have the same A1D. The same estimated average glucose, but they are not the same, are they? I don't think their risk is the same, I don't think their quality of life is the same and you won't know it unless you actually get a few blood sugars. So use the two together. It's not one or the other which, I am afraid the world has kind of gone to.

And also keep moving. I mean I like the people at Kaiser because they are willing to put their data out there, good or bad, and that's what we need, and this was their early work. They were doing much better now that two-and-a-half years and then they went from diet and exercise to sulfonylurea, metformin, two-and-a-half more years when the A1C went up to 9, okay, I will add another one.

So by the time they got to insulin, it was eight or nine years, and that would be okay if it was an A1C of 7 up to 8 or 9, but it was an A1C of 8 to 9. And so what we think is, you can do this much faster, whether it's 3 months, 3 months, 3 months, or 6 months, 6 months, 6 months, or something about 9 months as some sort of gestation period. It seems to work here, for starting insulin.

So I don't think insulin is any better than the others, if you are at goal. But if you are not at goal, just keep moving and insulin will be part of it. So you may have seen this natural history curve before that we worked. I show it today only to say, in our current state of affairs; eventually most people with Type 2 do need insulin. Now I am not saying, that's a great thing, or I wish we had medications that changed that natural history and the beta cell didn't wear out and maybe we will over time know how to put those together.

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But right now the beta cell just wears out over time and Type 2 diabetes doesn't go to zero, so it's not their fault. It's not a bad person, they didn't do anything wrong. Sure we could all exercise more, we could all make some better choices in food but people will need insulin.

So the American Diabetes Association and European Association got some experts together and formed a consensus and here's an algorithm and for better for worse, algorithms are just road maps, or guides, or suggestions, and I would just take it as that. But we learn some things from this. Look at that far left. Metformin first and in most patients, that was a pretty bold thing. We used it first but they're saying right at diagnosis, and then that was people said, oh, I'm not so sure I want to do that. There are two reasons to think about it in particular. There is a study out, I didn't put the slide in, but just recently that said, the earlier you start it, the longer it works, the longer before you slip out of control. If you decide to do diet and exercise for two years and then start Metformin, Metformin works for about 6 to 12 months.

If you started early and the glucoses are lower and there is a little more reserve left, it works for 3 to 4 years. It really is -- the other reason is there is a lot of discussion lately about the next level over where you say basal insulin or sulfonylurea as a well-validated, well-tested. Does insulin cause cancer?

I'm going to throw in a slide to hear because I couldn't find any place else to really put it and just say the statement when the news broke back a year ago from the ADA, I think still holds up, the results are inconclusive and conflicting, interesting to think about, study more.

Next month you'll see a rather extensive review of this American Diabetes and American Cancer got together had some of the leading experts, we are going to put out a piece will come out in June summarizing the findings. But in a nutshell don't stop insulin because you're concerned about this. And the other thing we found is that Metformin looks to be protected for cancer. Metformin is now being used as an adjunct to chemotherapy in many cancers. Metformin is pretty amazing. So that algorithm that puts it first preserves glucose control probably reduces cancers. And there aren't cancers, the American Diabetes Association statement will not focus on insulin and cancer. It will just say- people with Type 2 diabetes do have some higher cancer rates. Whether it's the diabetes, the associated obesity, other factors but we haven't proven that it's one of their therapies that's causing it and the Metformin may actually prevent it or reduce it.

Now here's another algorithm and this is what we have used at the International Diabetes Center for a number of years, and it's very similar in some ways. Metformin is an early therapy. You see at the top we are so team-oriented that we just feel like we had to put the team there and say you need a team of people working together, or this isn't going to work. Then two drugs and we tried to explain why we might use them but the focus of today's discussion is when you come, when you've used Metformin and you've picked another agent, and now you are about to add the third oral agent.

My advice to you is to stop for a minute and think, do I want the third and fourth and fifth oral or non-insulin injectable, or is it time to think about some insulin a little sooner. Maybe it's not the first drug, but is it like at least by the third choice? And we put background insulin in the middle there and I am going to talk about these options that we have. A few basic principles you all know, but it's good to think about it and as you're seeing people in the office and do a double-check on this. Is about half their insulin as background? Is about half their insulin all added up with meals? That's what the normal pancreas does over a day, about half of your insulin in between meals and overnight to shut off that liver release of glucose and about half of it with the meals.

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Now we've got lots of choices. I won't spend a long time detailing these, but you can see we have got options today. There's a lot of work going on to make even faster acting insulins. We've learned that we don't even think our rapid acting insulins which we think have some advantage over regular are even fast enough in some patients, and so there is work going on in that field that next year maybe we can talk about as a new -- I don't know what they are going to be called. What do you think? Ultra-rapid or high-speed transit, I'm not sure; you'll have to have a naming contest here.

And we have some good long acting insulins. Here's where I wanted to put in one other little pitch for thinking about severe insulin resistance. Don't worry about those first four. There are some syndromes out there where people require thousands of units of insulin a day, thousands. But there are a lot of people and I have a feeling, you face it, I certainly do who

need 200, 300. And we're not sure how much more they need because we just get uncomfortable at some point to say, 200 is about my limit, others say, oh, 100 is about my limit or one syringe full is my limit. But there are differences and how much people need. Look at this dotted curve in the middle of Type 2 about 1.5 units per kilogram on average, the middle of that bell-shaped curve, 1.5. Well let's see, 220 pounds, a 100 kilograms, that's a 150 units in the middle but over to 200 and 250 on the right side of that bell-shaped curve. So don't be surprised if people need a lot of insulin, but what do you do when they get to 200 or 250, or 300 units? That's a lot.

And large doses of the U-100 our standard insulin; pens only give 60 at a time, so you are giving a lot. A syringe only holds a 100, so now you split it up into two or three shots. Big volumes, giving out once don't work the same. They are delayed and they are erratic. They cost a lot and people are worrying, this is a lot of insulin. I might get low. Actually, these people don't get that low. They are resistant not only to the action of insulin to lower their sugar. I mean if they don't get hypoglycemia that often either because they are resistant to that. But you worry about weight gain and then I think the bottom-line. I don't all of your patients say, every more unit you add, they feel like the diabetes is worse.

It's just something I'm doing wrong or I have worse diabetes now if I am on a 100 versus 50 units. It's not really true but I can appreciate it. If you add the third blood pressure medicine or the fourth, you feel like I've got worse hypertension. So I just show you this because there is now a U-500 insulin, five times as strong. I know you know about it, but look at the cost difference. If you just go to the far right for a 1000 units or 250 units a day, 250 units a day will cost you \$817 for some of the rapid acting insulins, \$367 for regular U-100, and \$232 for U-500. So it is cheaper per unit, but go over to the next column over. The U-500 comes in a 20 ml bottle of 10,000 units. So you go to the pharmacist and say, give me one vial of insulin and it costs \$310.

And people say, that's a lot. But that's 10,000 units. So cost per unit, so if you have people on 300, 400, 500 units this insulin is a lot cheaper and actually works a lot better because U-100 just gets lost. And I will show you, you have to be careful dosing it; they don't really have a U-500 syringe yet. So you use a U-100 and you say, but it's five times as much. So, you have to be careful when you do it. And the curve at the bottom is sort of the insulin curve. If you inject U-500, it looks a lot like NPH, but at least it works; whereas U-100 when you're up and it just doesn't seem to lower the blood sugar very much.

So the benefits are fewer injections that cost less, smaller volume at any one injection, but it can be confusing if you don't really explain how to draw up the units. And I will just show you this last curve it says, if you use it more like NPH, these are people who are on hundreds of units of insulin and it doesn't seem to be working.

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So you just give the U-500 if you're in 200 to 300 units twice a day before breakfast and dinner and let it work. If you're up to 400 to 500 to 600 units you give it at each meal and if you're up over a thousand units, you give it four times a day. And if you're up into tens of thousands you put it in a pump. So anyway, just a little diversion, but just to know that U-500 can help some patients who are taking a lot of insulin.

Now, let's come back to the basics of insulin of -- you see in our algorithm when I just blew up the bottom, a-third of it here. When you get to that third medication, just think about a background insulin, whether that be a Lantus or a Detemir or whether it be NPH, if that's more cost-effective. What I am going to show you is some of the materials out of our guides that we have, we have a guide for starting and adjusting insulin, we have one of that, let's talk about insulin.

Sometimes patients really need a little bit of a session and hand-holding to get through this whole barrier of starting insulin. It's a tough one, just to get their arms around to say, I really need this. So we have some guides for how to have that conversation and then how to look at patterns, and out of that we really just focus on three regimens. If you learn these three, you can cover I think 95% of your patients. Learn how to do a basal insulin or a background. We like the word background, in the scientific literature it's often basal, but we like background and meal time as opposed to basal/bolus. But I'll interchange them here because, scientific literatures still sort of uses basal/bolus.

Pre-mixed insulin or background and meal time. If you know how to do those three and which patient would fit best, you can really cover the needs of the people you'll see. So here is one principle again too -- well fix the fasting first, that often patients have high-fastings and they stay high through the day. Here is a patient with a high fasting, goes up, comes back down, goes up. So it's not going up, another 400 points during the day, or 300 points. But it's high and sort of stays there. So if you gave insulin to bring that fasting down, what you do is you just drop that whole curve down. So the after meal ones won't be perfect in this case, but it's pretty good. And that's really what those long acting insulins do. I know this is a cartoon but the studies really show about the same thing. The profile just drops. So if your meals aren't wildly out of range, things just drop down with a background insulin. So we usually keep the agents going through the day. Sometimes we cut the Sulfonylurea a little bit, and often we give it at night. That's how those initial studies were done, and so we give it in the evening.

But let me just show you one thing about long acting insulins, perfectly flat, right. If you put a glucose sensor in, that measures every minute, and you look at the blood sugars after giving -- in this case it was in the morning, a long acting insulin. Either one of the both excellent long acting insulins. Look at the curve from just the effects of that long acting insulin. There is a little dip there. Actually, I guess they gave this at 20:00, so I gave this at about 8 o'clock. There is a little dip, and so long-acting insulins are relatively flat, but if you give it at night, and you at night have a really excellent blood sugar leading into bed time and you are not one that wants to take a snack, because well, why I take a snack if I am trying to lose weight. You can get a little drop in the night time. It might be perfect for some, it might be too much for others, so just know that it can happen, even though we call it a flat insulin. In which case -- so I am just showing you this example, if you start at a 100 at bedtime, look where you would end up. I will go back, if I start at bedtime at 150, then over night at 2:00 a.m. or 4:00 a.m. I am right about at 100, that's good. But if I started at bedtime at a 100, I'd be right around 50 in some cases.

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So then you might say, well I will move it to the morning, which is good. Because you've got meals you are eating through the day. Now this has a little bit of glucose lowering additional

effect, you've got food that's balancing it, you're not eating extra just to match the insulin. So you can take this insulin once a day any time, night time, supper time, morning time, and that's okay. And as a matter of fact the morning time, when you do the different studies turned out to get a better A1C than taking it at night wherever they compared the two, head-to-head. So it is fine to take it at either time a day. It's just what's right for the patient, what's a more consistent time.

What dose do you use? Well, the companies I can't fault them, keep it simple. They just say 10 units for everybody and we just felt like, oh, it doesn't seem to make scientific sets, if somebody weighs 150 pounds, they take 10, if they weigh 300 pounds, they take 10 units. If their sugars are 400, they take 10 units, if their sugars are 150, they take 10 units. So we try to do a little differently. If your A1C is under 9.1 units per kilogram, that's about 10 units. Alright, if you weigh 200 points, 220 pounds that's 10 units. But if your A1C is over 9, we give 20 units or 0.2 units per kilo.

You need much more than this in everybody, but at least you're starting where you're going to get a few more people, a little closure to goal, a little more less frustrated that they take the insulin and say, oh, this is junk, it didn't do anything. I took your 10 units and my sugar went from 380 to 365. Thank you very much. So at least this gets you started with some success without fear of hypoglycemia. So you'll see all of our guidelines sort of use this principle, where is your A1C when you see them and what's the units per kilogram. Just gets you a good start.

And again usually maintaining the other drugs. And I know I have here DPP-4 and GLP 1 agonists, not officially approved but amazingly effective to use, a long acting insulin with these other agents that cover real-time.

So you take it at night, you monitor particularly in the morning because that's where you can see the effect of the basal insulin. It's working all day, but it's hard to see it with other insulins or other meals during the day or other medicines. So the morning is the one place that's sort of isolated to see, is it the right dose or not? I advice you to do an occasional one before and after supper as well because I actually like to know how much is dropping over night. To me the perfect dose of a background insulin or a basal insulin is one that keeps your sugar, whatever it is at night, the same the next morning. I mean nobody really gets that concept, they just think I keep moving up to the Lantus till my mornings are 100 or 120.

But let's say you're 200 at night, you're 300 at night. If you're 300 at night, you need 80 units to get you to start at 100. So what if you don't have that big meal and what if you go to bed at a 100 at night, what are you going to be the next morning? If you are using the insulin to drop it 300 points over night, you should be working on the blood sugars during the day. It's not really the Lantus that should the savior to dropping it, the basal insulin should maintain it the same. You should go to bed with a good sugar and wake up with a good sugar. So it's a concept that isn't well appreciated. So we like to increase that bedtime insulin but when you get to around 0.5 units per kilogram, or 0.7, 50, 70, stop for a minute and just think, now wait a minute, this is a lot of insulin.

Let me look at before and after dinner. I'll bet you'll see before dinner it's a 180 and after dinner it's 260, and you're putting in more-and-more Lantus to try to bring that 260 down. Why not

give 10 units of rapid acting at dinner and that would be probably equal to 30 more units of Lantus at night or Levemir at night, so just a concept to think about.

Now let's say you had a patient with a profile like this. Again high-fastings but maybe a typical American diet, at least at the dinner time, then more eating, and so you say I am going to fix to fasting because I heard that, I like that. So boom, you put it in, you drop everything down.

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Well, you did help the fasting but you really didn't cover those extra carbs at breakfast or that bigger meal at dinner. So you're going to get an improved A1C by fixing that fasting, by getting their basal, but you're not going to get to goal. You're going to be 8% still or something, because you haven't covered at least in this case two meals. So you might think, this is a pretty good profile for something like a premixed insulin that at least two of the meals have some rapid acting insulin in and it covers it with two shots a day. So look at those profiles, look at your patient and see, if that can work. How do you dose a premixed insulin? Guess what, it's about the same. 0.1 unit per kilogram, we do it twice a day. So 0.1 unit per kilogram premixed in the morning, 0.1 per unit kilogram premixed in the evening or 0.2 and 0.2.

Now you'd say, ooh, that's twice the amount of insulin. But it's sort of intentional because the basal really isn't intended to cover everywhere. It didn't cover the background and what's the background, that's half of your insulin needs, when you use a premixed insulin, you are saying I am using insulin that's covering all day, meals and background. So I need a little more, I am depending less on my oral agents and the pancreas must be worn out a little more. So these doses are just amazingly safe and really effective start. We haven't seen it get people in trouble. You still need to titrate up but it gets you a really good start.

So then you look at it and you say, well, that one works there and the other one works the other place, but occasionally do a bedtime or before lunch, I am a big monitoring fan, but I wouldn't advise you to jump in and do those too fast right-away, because they're kind of confusing. Because when you're doing these two, you know what to adjust. If it's high at dinner you need more in the morning, it was high in the morning, you need more at dinner, and the in between ones kind of get in your way. But eventually after you've titrated it up you do want to go back and look at those, you'd be sure you're not causing a low in between, and that this regime it just isn't going to work. But let this titrate a little bit based on these two and then come back and do a bedtime or before a lunch. So premix can work, you do have to have a little more strict eating regimen because when you take that premixed insulin in the morning, you've got not only your meal covered but you've got some in between, and if you decide, oh, I don't think I have lunch today, well the insulin doesn't know that, it's still working away.

So it does put you under a little bit of constraint, but it's a good insulin I found for like emergency room. When somebody comes in newly diagnosed and they show up and I don't know why but 90% of new diagnosis happens on Friday afternoon. And what is it about that? Why is everyone diagnosed on Friday afternoon or Saturday? But so in the ER, we give them kits of the premixed insulin with a little glucose meter and it's a good insulin because you take it twice a day, and it covers the whole day. It may not be perfect, but it knocks out those very high sugars and then you can see them in your office and decide, is that what I want, or do I want a basal or basal/bolus. But you get started in a safe and effective way.

And I will just show you one other study, just where they used twice a day, premixed insulin and they gave the patient a little card to take home of how to adjust it themselves. Boy, they did pretty well, look at that. I mean from 9.8 to 7. - what is it 3 or 4, 7.4 and the profiles came down, so it can work as well.

If you are on mixed insulin, twice a day, premixed and you say, it was okay, but now my patient -- it's just not working well enough or the patient wants more flexibility in their schedule. They'd like to skip lunch on occasion, they'd like to have dinner sometimes at 6 o'clock and sometimes at 8 o'clock at night, this insulin might not.

I want to switch them to a background and mealtime insulin. Just add up all the premixed insulin, divide it by two, give half of it as the long acting and half of it split up with the meals, and it will work. If your sugars are pretty good on the premix and you still want to switch, then add it all up and subtract about 10%, some will say, 15% and then split it 50-50.

If your sugars aren't very good, you really don't have to add it up and subtract anything. Just switch. So anyways, just a way to keep you. Now here's our last patient or another patient anyway. You'll probably have some others, I hope for us to tackle.

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But now it's up in the 200s and the meals go pretty high with every meal. So now you follow our same principle and you fix the fasting and you really still are pretty high. I mean you did fix the fasting, that will help the A1C a couple of percentage points but you're still up at 9% or 8.5%.

So this person really does need a little help at each meal as well as the background. So you do really have to fix that fasting, but this one needs some help and they are probably going to need, I mean it looks pretty intimidating, it doesn't look all those syringes, those daggers in the drops. But it actually is the most flexible regimen, I mean people see this and I say, I am doing you a favor by giving you four shots, and they say, oh yeah, great favor, you know thank you! You know friends like you need.

But you really the background insulin if you have the dose right, you take this background insulin and it's right if you can eat breakfast, take some insulin and then if you skip lunch, the background doesn't pull you down, or doesn't left you drift up too high, it just stays the same. So if lunch instead of usually at 11:30 is at 1:30, you will be okay. Whenever you eat those meals, you take your rapid acting insulin and so you can move the meals around, most of us just are not exactly on the clock with our meals. We have busy schedules.

So this really gives people flexibility. We don't advice skipping meals and this and that, but if it happens, or certainly delaying meals, so this regimen really does allow for that, or if you are flying back and forth in different time zones and really don't know where you are, it's all right. When I eat, I take some insulin, when I don't, it really works for travelers too.

So, the same principle, just to keep it as straightforward as we can, .1 units for the background and .1 units split up for all the meals. So, it just works our .2 and .2. So you can just use this

and get people started, if you don't have a dietitian, to help look with you to count the carbohydrates, you can make it just 30% at breakfast, 30% at lunch, and 40% at dinner, if you can really ask about carbs and say, I have a habit of my biggest meal at lunch, you can go 30, 40, 30. You could move a little more insulin there. So you don't need the sulfonylureas when you are doing this. So stop those agents.

Now, this is classic sort of pattern control, each one regulates the next level. But should you do a post-meal blood sugar? People say, well Gosh, when you are doing Intensive Insulin Therapy, I thought you do before and after meals. We do that in most all of our Type 1s, not every day, people don't do seven tests everyday but we like to get some post-meals and see how that mealtime insulin is working.

Do we need to do it in our Type 2s? Well we decided to do a study of a large number of Type 2s and just do before the meals. And just regulate it without knowing what the post-meals are and assuming if it's good by lunch, it couldn't have been too terrible after because I got it down by the next meal. Now, that may be faulty reasoning but we decided to try that, and then we decided to study two other questions. Do you need to do the posts, and do you need to adjust your meal insulin based on how many carbs? Like we do a lot of Type 1 diabetes, I am taking two units of insulin for any carb choice or 15 grams, and that works well in Type 1. Do we have to do it in Type 2? So we tested that. And it was interesting, whether you counted the carbs or you just said, I took a simple dose each day, a standard dose, 7 units of breakfast and 8 at lunch and 10 at supper and both worked amazingly well with no post-meal testing and whether you counted carbs or not, it worked.

So, this was not an indictment that carb counting is bad, it just says whatever you can use either method and try it out with a patient, if they like to count carbs, I think it gives them some more control over there, a sense of control of their insulin and their food. But if they don't want count carbs or it seems too overwhelming, we did a really decent job of getting them down into mid 6s, certainly under 7 by just looking at their blood sugars once a week and saying what were the patterns.

(00:40:01)

Oh I look mostly high at supper; I'll take a little more at lunch. So it really that concept of pattern control, really does work. So we've looked at the insulin's background, mealtime, pre-mixed background and mealtime, when you are doing this adding mealtime insulin on, remember you don't have to go from a background, one shot to four shots.

You can say I am going to add one shot of rapid acting insulin at my main meal. So they transitioned from one shot to two shots, and they get used to that, and they cover their main meal, and may be that's all they need for a while, because that's where they were having problems. And then may be later they say, I better add it at dinner and breakfast, because breakfast is kind of escaping too, and then may be eventually it gets to all meals. But you don't have to go from one to four, you can go to two shots, you can go to a third and that works for some too.

So, which one of these regimens is really the best? I mean I showed you studies to say each of them can work. So my friends over in England did a really nice study. They said, "Well, we

are going to try three different regimens, and we are going to just test. If you started this way, several years later who did the best?" So they picked three regimens.

Now unfortunately they didn't listen to my advice; they wouldn't be the first. But they did the study where they picked three regimens, and we were hoping, oh great, they are going to do premixed and they are going to do basal/bolus, and they are going to do basal, but they did premixed and they did basal, but then the middle one was rapid acting at each meal.

So it was a little bit of a regimen that not many of us use that much to start right off with three shots at meals but -- so they did those three, and they said the first year we are just going to start one of those three regimens, and we are going to see how they do. And then after the first year if they are not in control, we are going to start to intensify it, because that's what we would do.

We would add rapid acting to the background and to the three shots a day with the meals will add the background and the premixed will add another little shot of rapid acting, so we are going to intensify. So how do they after year one? . Well, everybody came down, the basal, in the red, didn't come down quite as much, but none of them were to goal. None of them were after a year where we wanted to be, under 7, they actually were trying to get them under 6.5 or down to 6.5.

So no regimen was optimal at one year, so they intensified. And this is what we are looking at, because most studies, everybody works real hard and they see these amazing results for three months. And you say, well that's good but I wonder how these patients would do two and three and four years later.

So they wanted to look three years later. And just summarizing it, what they basically showed is that the starting with basal and then adding rapid acting as needed, three years later was really the best approach because the A1C achieved those little pluses was the same for starting with mealtime insulin or basal, the amount of glucose monitoring level drop was the same. But look at there, there were fewer hypoglycemic episodes in the basal people after three years. There was less weight gain in the basal. There was less waist circumference. So that there really was almost no downside, but the benefits of starting the basal even though on that first year, their A1C drop wasn't quite as much, it was a good start, and then you add the mealtime.

So anyway they just sort of showed that, when you do a randomized trial, starting basal and building up, seems in a long run to be a good approach. So in our little guide to starting and adjusting, we summarize what I showed you, but you can see it in one slide here, it's really the same principles of starting insulin. We have little tips for meals with each of the ones if you are interested to look at, how you might teach food to match the different regimens.

And the food part is important because remember in ACCORD study, where people said, I think they had a lot of hypoglycemia in that intensive group. I think this is kind of a dangerous regimen or approach to intensify, what was the intensification -- what was the main cause of hypoglycemia, it was people who delayed or missed a meal, or ate too few carbohydrates.

(00:45:03)

It emphasize to us that part of insulin therapy is having some counseling about food and nutrition, and it's not just all in the injections. You do have to understand how insulin works and how food matches it, and that was an important learning.

So don't forget about the glucose monitoring. It's a key part of any regulating of insulin in showing that it works and reinforcing it. Look at the patterns. I am a big believer and just looking at the numbers. I love to print out the numbers and just look at a quick graphic. I sometimes take some heat for this I know, because a lot of the nurses and dietitians do a great service by spending time in the log book and then that's good.

What happened yesterday and then let's look at did you walk a block or two blocks and was it two spoonfuls or three. So it's valuable to go through the detail but sometimes you also need to step back and just look at a picture and say, when you look at this, all their blood sugar is for a month, displayed in one picture. Can you sort of guess where we have to start? I mean, all I want where the picture is, well you know in the evening out there, those are the highest. I think we better focus there, but I am going to circle the lows first so that I anything I focus on, one, I want to be sure I am not increasing those lows. So with a quick picture we can have a dialogue about what the next step should be.

Alright, so this isn't coming to every Type 2 immediately, but you just need to know there is exciting technologies that you do know about that are out there and certainly in Type 1 diabetes and we will see over time what the role is in Type 2 diabetes, pumps, and patch pumps, and sensors, and we just wish all the sensors didn't have different reports, we sort of taken back. Here is our analogy, you see if you think it works, because we use all of these and every report is different and it was like, uh, so we say, the EKG people figure it out.

There are eight to twelve companies that make EKGs but they don't all report a different read and printout. This Philips(ph) shows you the waves this way but this – so why can't we all just get one refill(ph). We have been working hard figuring out a report, a graphic that all the meters go into. We take numbers like this and turn them into a curve that you can understand. So we are hoping that will gain some traction over time. So there is one view, so we all can start to look at it together. So let me end there, and see maybe if there is a question or two or -

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[Applause]

Okay, so the question is, is there any literature about seeing a patient for the first time, their A1C is above 9, just starting right on insulin? I didn't spend a long time on the details of our algorithm but you might have seen going in from the side was we worked down the algorithm, but on the side is, we use a little higher number 10 or some use 11, but if it's really high, just start right on insulin. If it's around 9, probably start on two oral agents versus one. If it's really high, A1Cs of 10 or 11 just starting on insulin, you can back off later. So there is more work saying that that really does work. It's just at what point is it necessary. So somewhere up around that 10% range, you are going to be much better to start insulin even if it's temporary.

For targets for blood sugars and – yeah, well I started off with saying that targets are important because you've got to be on the same page. So we generally still like around 7.0 and less, I have some contraindication to it.

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Hypoglycemic unawareness, or there is no data that says, if you shoot for around 7.0, and you're making progress towards that goal that you're doing any harm. It's only when you are shooting for 6.0 and you keep adding the forth, the fifth and the sixth medication that you sort of say, there is something different about this person. So around 7.0, is what I would advice unless if had a hypoglycemic unawareness, or they had a few severe reactions, then I go between 7.0 and 8.0. And we are trying to find what other categories or that between 7.0 and 8.0, we just don't have a lot of them. One study said, if you had diabetes more than 20 years, that maybe instead of under 7.0, between 7.0 and 8.0, but two of the other studies didn't find that, but one did. So do we go with that, well at least it makes us think.

If you've had a previous heart attack, one study said, that would put you at risk going under seven, two other studies said, no, you have a benefit. So my main advice is get people early, then there is no question that under 7.0 is beneficial. Twenty years later, we are not quite sure if we are trying to rescue people's blood sugars. Then certainly don't shoot for 6.0. So around 7.0 for most, between 7.0 and 8.0, and 8.0 for those that you can't get there despite fairly intense efforts. Good, well thank you very much and I will be around a little bit.

Total Duration: 52 Minutes.

[End of transcript.]