Computational Systems Biology
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Lecture - 54
Guest Lecture: Quantitative Systems Pharmacology

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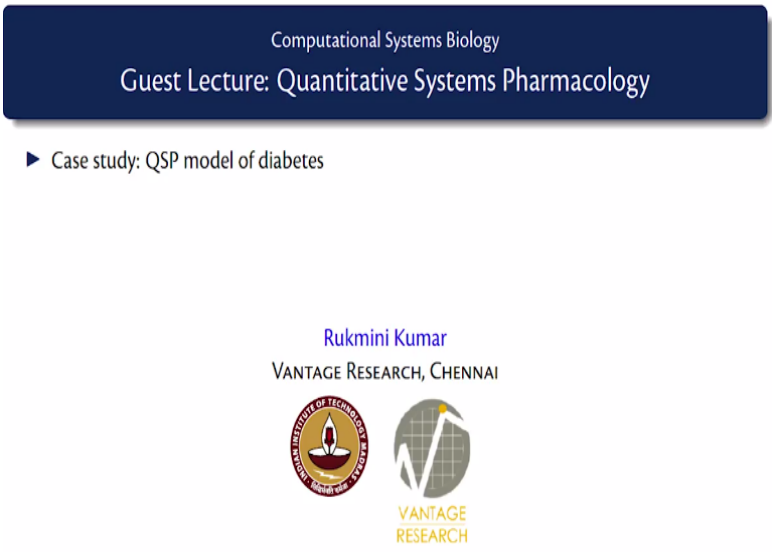

The question they were asking was,

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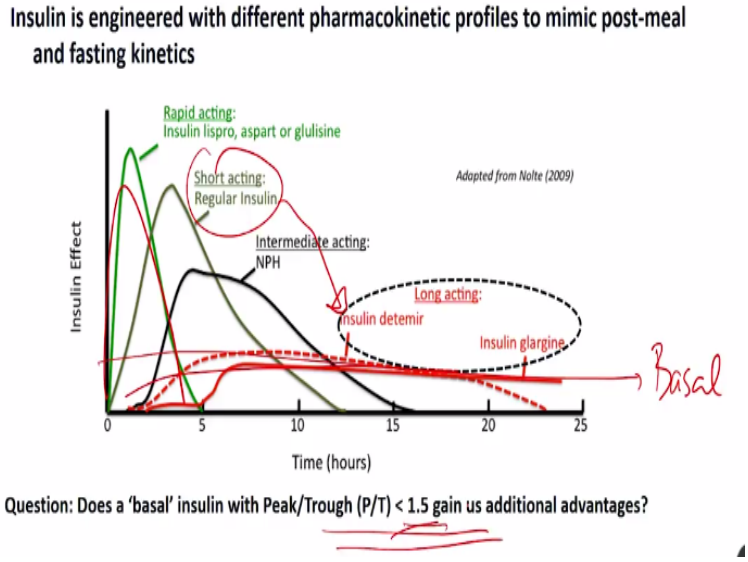

As a Pharma company have done very well in going from regular insulin and flattening it so that the peak over trough is much lower than it was. But how low is good, how low do I want to go. Does it gain any advantage for me to go below a peak over trough of 1.5?

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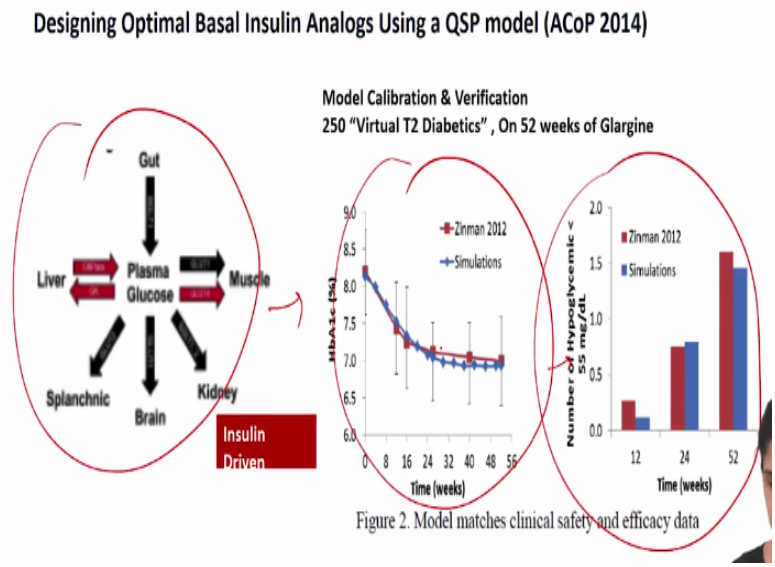

Figure 2. Model matches clinical safety and efficacy data

So we developed a model to try and answer this question. So we first came up with the standard, developed a model, came up with the right parameterization, came up with a bunch of patients who did or who behaved appropriately under other incidents. So this is called a model calibration process. So we are set we know we believe this model because this model behaves appropriately when you give the existing incidence.

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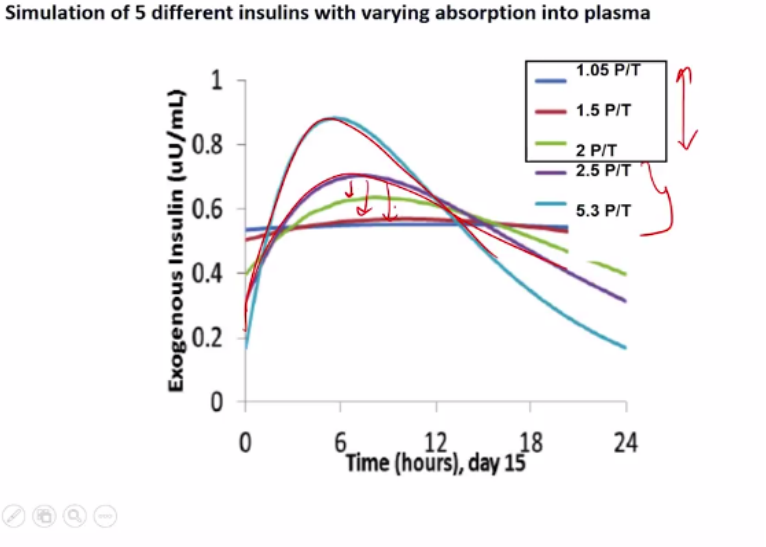

Then we said okay these 2 are the existing incidents, these 3 are the incidents we want to try. So the existing incidents are kind of peaky, but they are still pretty good. Does it matter if I change the PK to something flatter and flatter and flatter? How much advantage will I get that is the question? So now we are all the way from the PK to the PD we know what the HbA1c. See the glucose are within we have covered you know using a model like this.

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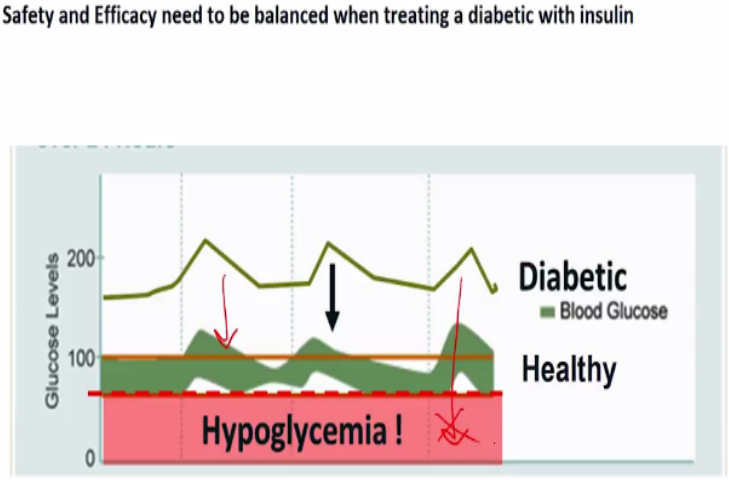

Like we discussed why do we want to make? What are the 2 things we want to make sure when we give a person a drug? What are the 2 things we want to worry about? We want to worry about efficacy which is if you are a diabetic if your sugar is high we want to make it low, but we want to also worry about safety and we want to make sure we do not get it too low. So balancing safety and efficacy using the PK is what we are after.

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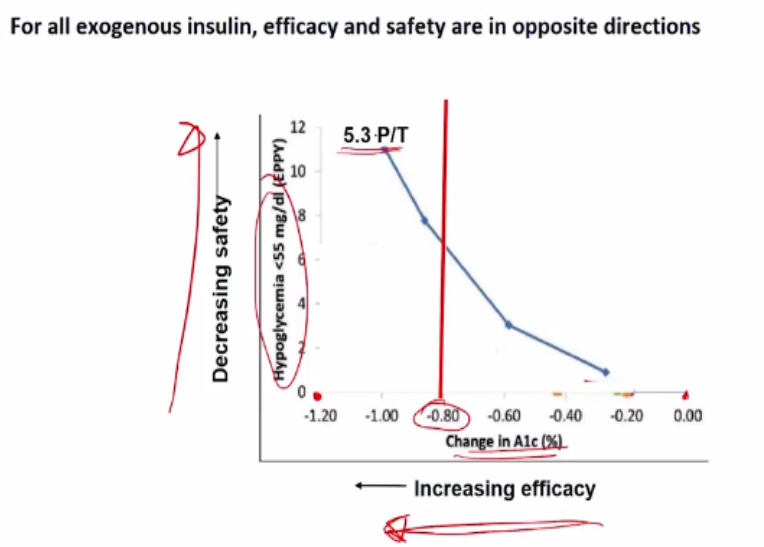

So then we said, generally for a lot of drugs and even in our case as you increase the efficacy so this is how much glucose you are lowering. This would be a completely useless drug it does not lower glucose at all. This would be an extremely effective drug because it lowers the glucose a lot. This is the threshold. You at least want to lower the glucose that much for it to be an effective diabetes drug.

So as you increase the efficacy what usually happens is the safety decreases. So as you decrease glucose you increase the number of hypoglycemic events which you do not want the patient to have. You do not want the patient to feel faint. You do not want the patient to lose control, but what you see is in general the harder you push on efficacy the more safety events you see. This is for you know a normal insulin which already exists.

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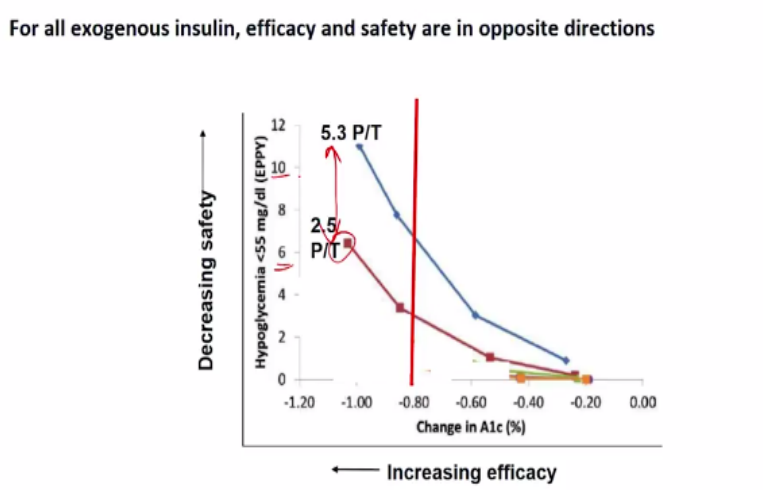

Now you make the PK a little flatter. Your curve characteristic start to look better. You are able to get the same efficacy for a lot less safety events. So this guy is seeing 4 fewer events. So that is great. We are on to something.

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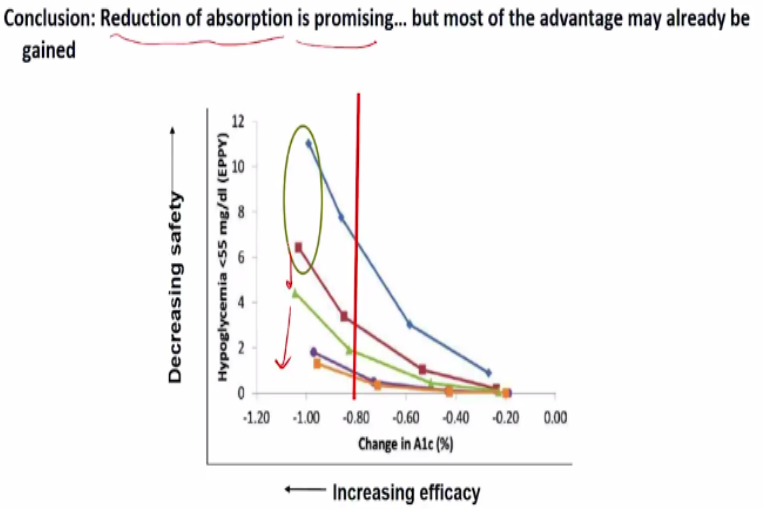

So what happens if you lower it more and more and more that is the question we asked with the model? So after this it is all just modelling and simulation this is not data. Then we see that yes there is some effect to be gained. There is some more effect to be gained, but effect is saturating. If you are going to spend a billion dollars to make a drug it is not going to keep on increasing in its efficiency there are going to be there are limits that you are going to get, and that is what the

model says. Most of the advantage that you get in changing the PK by reducing absorption its promising and it was important to push on it the past few decades.

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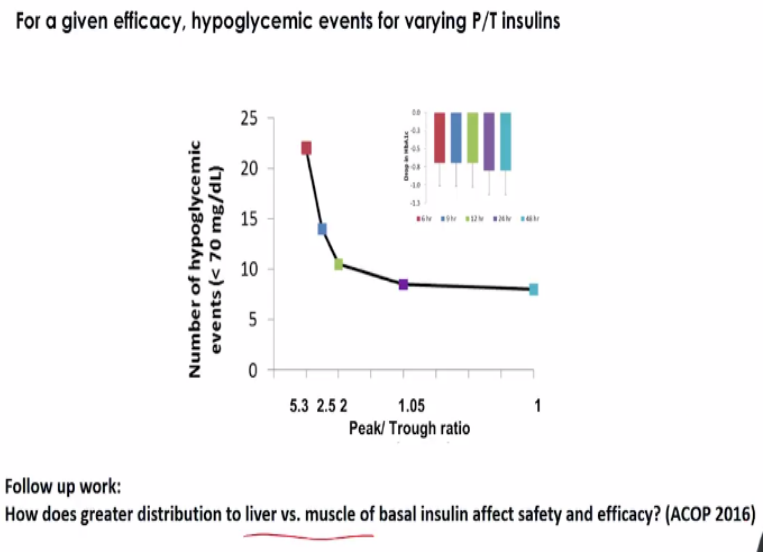

But now the more you pusher it you are reaching the spot by really not going to see a lot of advantage. So that is what we are able to kind of say as a first order response with modelling and simulation. It is more to it you know more subtle question you can ask how much insulin does the liver see. How much insulin does the muscle see? How does that affect the patient? Does it help the patient be more consistent with the dosing?

There are lot of things you can ask and we did more work on that as well, but this is a quick result. **"Professor - student conversation starts"** Can we take combination of drugs such that for some drugs we take care of the safety and the insulin supplement will only take care of the efficacy such that you can push that boundary a little forward. That is a very good question. Lot of people try combination therapies for exactly that reason to push efficacy while managing safety.

"Professor - student conversation ends" Diabetes is an interesting case because safety and efficacy are almost exact same thing you know you want glucose not to be low. So for instance in autoimmune diseases for example it is possible it is potentially possible that you can reduce the

overall inflammation, but still be responsive to infection. So that is a side effect. So when somebody has arthritis their immune system is too inflamed.

So you wanted to calm down, but the immune system has a role when you get bacterial infection you still want the immune system to respond. So for things like that you can kind of titrate it better. For diabetes it is a lot harder because it is the exact same thing. There is only 1 axis that you have.

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