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SPEAKER SERIES

Insulin initiation, titration and escalation: a practical guide for busy clinicians in primary care

Making Education Easy 2020

About the speaker

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Dr Carl Peters is a specialist endocrinologist and diabetologist with expertise in the management of diabetes in pregnancy, type 1 and type 2 diabetes, lipid and endocrine disorders. After training as an endocrinologist in New Zealand, Dr Peters moved to the UK to work as a clinician and clinical researcher at the Institute for Cellular Medicine, Newcastle University. His research work focused on remission of type 2 diabetes.

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This publication is a summary of a webinar presented by Dr Carl Peters on Wednesday 23rd October 2019. Dr Peters provided clinicians with a practical guide to the initiation, titration and escalation of insulin in patients with type 2 diabetes mellitus. This webinar was sponsored by Sanofi.

Using the example of a hypothetical patient called Shane, typical of those patients seen in daily practice, Dr Peters provides some practical tips and recommendations for the introduction and titration of insulin.

Shane is a 46-year-old plumber who has had type 2 diabetes mellitus for 6 years. You are his primary carer and, prompted by a reminder letter, he has presented for an annual review of his diabetes. His current medications are as follows:

- Vildagliptin/metformin hydrochloride 50 mg/1000 mg — 1 tab twice daily
- Gliclazide — 80 mg twice daily
- Pioglitazone — 30 mg daily
- Atorvastatin — 40 mg once daily
- Cilazapril — 5 mg once daily

He underwent retinal screening two months ago and no problems were found. He is obese (BMI 32.7 kg/m^2), he has a blood pressure of 135/90 mmHg and has an HbA1c of 99 mmol/mol despite maximal oral funded therapies. His renal function is preserved (eGFR >60 mL/min), but albuminuria is present.

What is an appropriate HbA1c goal for Shane

There is not a perfect number for an HbA1c goal, it is individualised and very patient specific. The frail older adult clearly has a different glycaemic goal to the young otherwise healthy individual. The younger someone is the longer they will live with type 2 diabetes, and the chance of them developing complications over the course of their lifetime is significantly increased, hence the reason to aim for lower HbA1c goals.

Multiple societies around the world debate HbA1c goals, based on sound evidence, and still come up with different numbers, making it hard for clinicians at the coalface.[1-4] My practical suggestion is that in your patient with type 2 diabetes, with preserved life expectancy of 10 years or more, an HbA1c goal of 50-60 mmol/mol is sound, generally aiming for the lower half of that range. Aiming below 50mmol/mol using drug therapy, is not associated with an improved health benefit but does increase the risk of hypoglycaemia. Note, that advice is not relevant in pregnancy or pregnancy planning, and it is not relevant in people with less than 10 years of life expectancy.

What treatment changes would we recommend for Shane?

Currently, Shane has an HbA1c of 99 mmol/mol, and I would be aiming for 50-60 mmol/mol. Shane's HbA1c goal is unlikely to be achieved with further titration of his current oral medication regime. In addition to lifestyle changes, options may include non-funded therapies, acarbose or insulin. Non-funded therapies are available in New Zealand. Whilst an option, for many with type 2 diabetes the cost is unaffordable. Acarbose can reduce HbA1c in some patients, but its use in combination with metformin is often problematic. Those most likely to benefit are also the most likely to have adverse effects. This leaves us with insulin.

You decide to start Shane on insulin, but he wants to know if he can stop any of his other tablets. Sometimes the benefit of a reduction in pill burden can help overcome reluctance to start insulin. Reducing pill burden is a very real benefit to patients. If Shane was my patient, I would stop gliclazide and use that to encourage him to take insulin.

Starting basal insulin

There is very rarely a scenario where you wouldn't start with basal insulin. Other approaches can be more complex, carry a greater risk of hypoglycaemia and may reduce glucose too rapidly. Basal insulin is usually the recommended first insulin. In secondary and tertiary care, we still receive many referrals for insulin initiation, yet such referrals are often not required. However, if more complex regimes are required at initiation, you would usually want to involve diabetes services.

Examples of situations in which referral is warranted include:

- Severe symptomatic hyperglycaemia (without easily reversible factors), ketonaemia or ketonuria
- Age < 30 years
- Commercial drivers
- Significant needle phobia
- Pre-pregnancy planning
- Significant glycaemic variability
- Significant comorbidities (e.g. alcoholism)
- Ramadan planning

Fix the fasting first

You decide to start Shane on basal insulin to address his fasting glucose – that is his glucose when he first wakes up in the morning. We always address fasting glucose first **"fix the fasting first".**

If GOAL is not met REST easy with basal insulin

G Goal appropriate?
O Other treatments at maximum?
A Adherent?
L Lifestyle factors optimised?

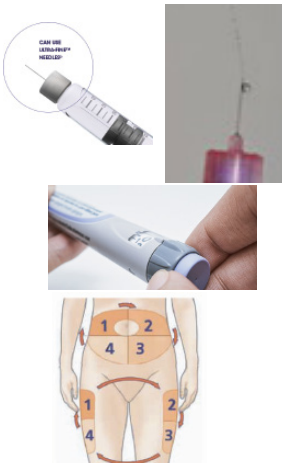
not met?

R Reassure
E Educate
S Start ten
T Titrate

Prepare
Air
Select
Inject

easy with basal insulin

Four is the floor, else a sweet as a treat
Above five to drive



Realistically in someone with Shane's HbA1c of 99 mmol/mol , you are not going to wait for further lifestyle factors to be optimised before initiating insulin. Rather, a more realistic goal would be lifestyle changes assisting Shane to come off insulin after meaningful weight reduction.

Which basal insulin?

Which basal insulin would you recommend for Shane and why?

1. Intermediate-acting, human isophane/NPH insulin
2. Long-acting insulin analogue, insulin glargine (Lantus)
3. Long-acting insulin analogue, insulin detemir - (Levemir – not funded in NZ)

The reality is there is no difference in efficacy between options 1 and 2, both are reasonable. However, there are important differences for patients. Isophane insulins are not available in prefilled pens, meaning patients must be educated on loading cartridges into their own insulin pen, and on appropriate mixing of insulin prior to each injection. Appropriate mixing of insulin (resuspension) is often poorly performed if inadequate education is received. Insulin glargine is available in a prefilled pen, does not require mixing, and has been shown in some studies to carry a slightly lower risk of nocturnal hypoglycaemia. It is also worth noting NPH insulin has greater variability in its duration of insulin action within the same individual than seen with glargine.[5-7]

What starting dose would you select?

My approach is **REST easy with basal insulin: start 10 and titrate.**[8] I believe it is important in primary care to be 'speaking the same language'. If we can move towards a similar and simple titration method, whenever we communicate, we will be familiar with it. When starting with a significantly high glucose, few people are ever grateful for getting to goal quickly. Patients will not like it if you drop their glucose too rapidly, as they will start to feel miserable and hungry, a term we call "pseudo-hypoglycaemia".

Start low, go slow

We start Shane on 10 units of basal insulin. NPH insulin is usually started at night, before bed. For insulin glargine, it doesn't matter if this is given in the morning or the evening: the patient should pick the time they are most likely to remember to keep taking their insulin. As long as it is given at roughly the same time each day (within 2 hours). If you want to shift from one time of day to another, you can do so by progressively moving the dose timing by 2 hours each day.

Titrating basal insulin

Shane started on 10 units of basal insulin at bedtime. The aim of his treatment was to titrate the dose to a fasting blood glucose target of 6-8 mmol/L without hypoglycaemia, to achieve an HbA1c goal of 50-60 mmol/mol.[9] Hypoglycaemia is rarely a problem at initiation in type 2 diabetes, but it does become more of a problem over time with increasing insulin requirements. If you reach a point of battling with variable insulin and glucose profiles, secondary care can be helpful.

Evidence shows that a patient-led titration schedule is more effective than a healthcare professional-led schedule. But this does depend upon the patient and how much confidence you have in that patient's ability to self-titrate. I avoid complicated insulin titration advice. This is what I tell people:

"increase your insulin by 1 unit each day until you have a single fasting glucose <5.5 mmol/L, then stop increasing the dose"

It is important to make sure that patients understand to stop increasing the insulin dose at this point, but don't stop the insulin. Also, even in people who are confident and comfortable with insulin titration themselves, I would recommend them making contact with the practice nurse on occasions to ensure communication remains open and potential errors avoided.

A patient-led schedule is usually more effective than having to engage with healthcare providers on a regular basis. However, about one in every five or six patients do not understand titration and need to be walked through it by a healthcare provider. Diabetes nurse specialists are well set up to do this and can help people through this process if a patient-led schedule is not going to work for them.

Shane subsequently returns for a follow-up and his fasting glucose is 5-9 mmol/L and his insulin glargine is up to 35 units. His BP and urinalysis are okay at review, and he has an HbA1c of 56 mmol/mol, now with no evidence of albuminuria. Shane continues on the current dose of insulin, and over the next 2 years his glucose slowly climbs. He then returns to see you with fasting glucose of 8-11 mmol/L.

At this point do we advise Shane to:

1. Repeat the titration schedule
2. Add a prandial insulin
3. Change to a pre-mixed insulin

Fix the fasting first

Shane's fasting glucose is elevated. How did we improve it last time? We titrated basal insulin. This will happen time and time again: at one point fasting glucose is controlled, then it becomes elevated again. Simply advise the same titration schedule:

"increase your insulin by 1 unit each day until you have a single fasting glucose <5.5 mmol/L, then stop increasing the dose"

There may be a one-off glucose that's <5.5 mmol/L and the patient stops the titration, but all the rest are above 8 mmol/L. In this situation, you need to try to work out what was different on that day. There is usually a practical explanation, such as physical activity or a missed meal. If you are able to figure this out, then you can advise the patient that on those days, they will need a lower dose of insulin (the current dose), but the rest of the time they need to keep titrating by 1 unit per day.

Shane sees you over the following 3 years, during which time his fasting plasma glucose ranges from 5 to 8 mmol/L with intermittent changes in his glargine dose. Shane is now confident in his regimen, with a current glargine dose of 45 units daily, and goal fasting glucose levels. But his HbA1c remains above target at 67 mmol/mol. The most likely reason for this is postprandial hyperglycaemia.

Adding meal-time insulin

You explain to Shane that you suspect there are periods of high glucose causing his average glucose to remain high. After talking to Shane, you suspect his evening meal, which is his largest meal of the day, is contributing to his elevated HbA1c.

What measurements do we need before advancing therapy?

a) 2 hours after breakfast
b) 2 hours after lunch
c) 2 hours after evening meal
d) Before bed
e) All the above
f) None of the above

My advice is that the above testing is unnecessary, rarely resulting in changes in subsequent action. If we are looking to introduce prandial insulin and know which meal is likely to be the greatest contributor (the largest meal of the day), let's get started.

The ADA clinical guidance algorithm shows that if HbA1c is above target, despite adequately titrated basal insulin, and we've fixed the fasting first, we add prandial insulin. Usually one dose with the largest meal, or the meal with the greatest prandial excursion (see Figures 1 and 2).[8] Once you start introducing more than two prandial insulin injections to a patient regimen, I would suggest seeking guidance of secondary care, as many patients become challenging at that point. A biphasic (pre-mixed) insulin may be an equally acceptable option at that stage.

Start low, go slow

You and Shane agree that adding a single dose prior to the evening meal would be appropriate, but how do you calculate the dose? In accordance with the ADA guidance, start with 4 units, keep it simple.[8] Follow the **"start low go slow"** mantra.

For patient-led titration, you can ask them to **"increase your meal-time insulin by 1 unit each day until you have a single glucose 2 hours after your evening meal of <8 mmol/L, then stop increasing your dose".** The aim is to achieve a postprandial glucose of 6-10 mmol/L.

Of note, the ADA guidance is slightly more cautious, recommending dose increases of 1-2 units twice a week.[8] I have not experienced any problems with 1 unit each day – but you could tell your patients every second or third day if you were concerned about hypoglycaemia risk in a particular patient.

You see Shane four weeks after adding prandial insulin, and he's now taking insulin glulisine 15 units at his evening meal.

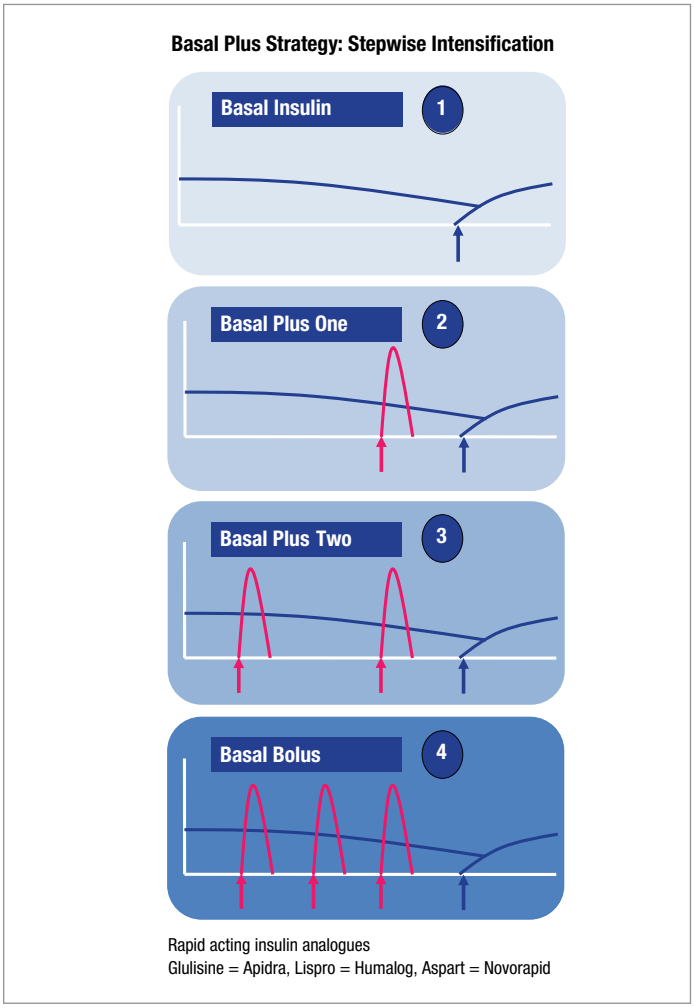


Figure 1. Basal plus strategy: stepwise intensification

Shane's summary

- Shane self-titrated basal insulin with practice nurse support from 10 to 35 units, achieving the goal of 6-8 mmol/L
- Over time, further titration of basal insulin to 45 units was needed to remain at goal
- Over time, despite fasting glucose at goal, HbA1c rose above goal
- Evening meal hyperglycaemia was suspected
- Mealtime insulin was introduced, starting at 4 units
- Shane self-titrated his evening mealtime insulin with practice nurse support to 15 units at dinner, achieving the goal of 6-10 mmol/L

Practice points summary

- Don't delay insulin initiation
- Fix the fasting first!
- Keep it simple for you and the patient – start at 10 units of basal insulin
- Ensure the patient understands that the dose will increase
- Consider meal-time insulin when fasting glucose at goal, but HbA1c remains above goal

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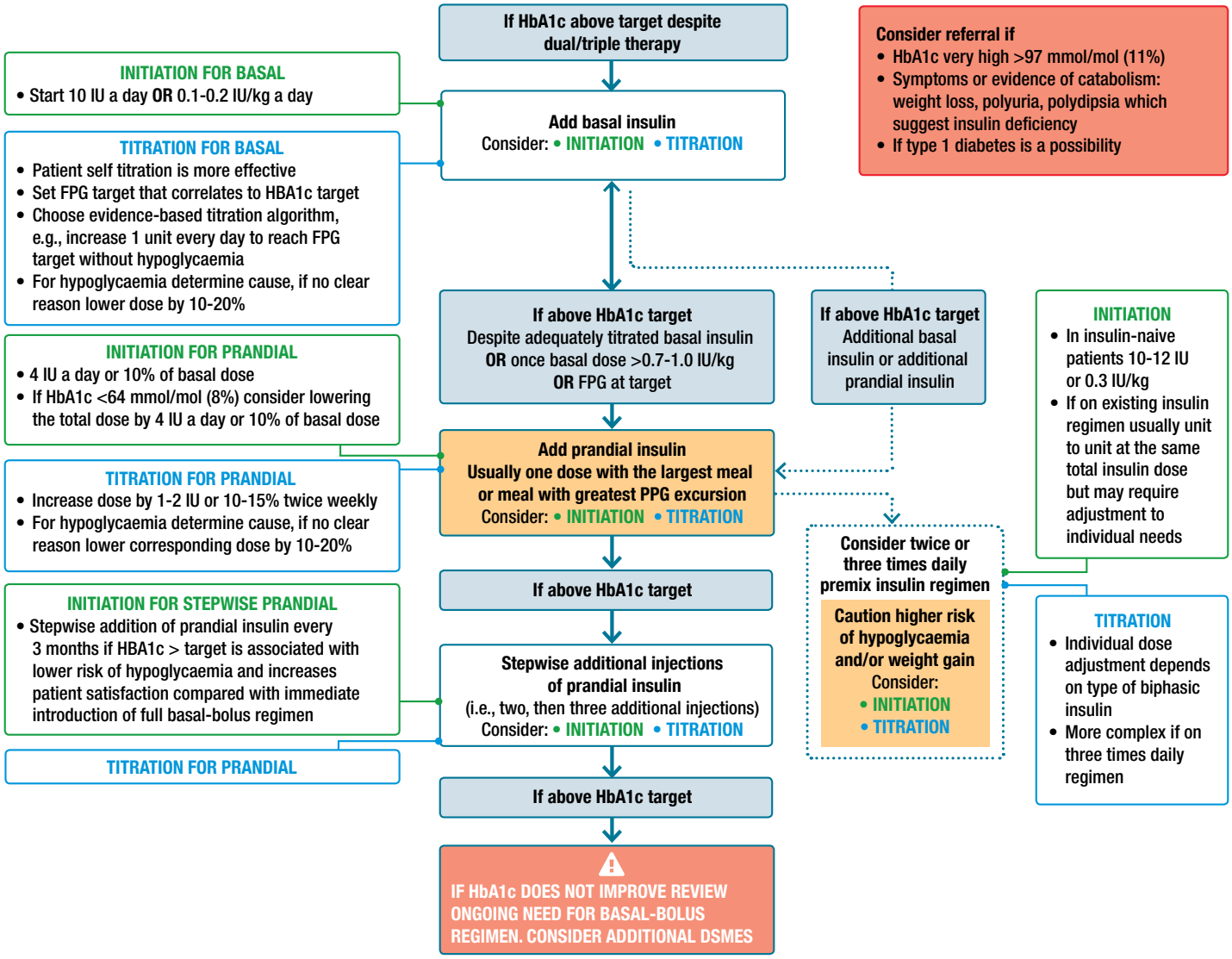

Goal for most non-pregnant adults with type 2 diabetes	Age < 65	Older adults with intact cognitive and functional status	Frail, multiple comorbidities, limited life expectancy
HbA1c (mmol/mol)	50 – 60	55 – 65	65 – 75
Fasting glucose (mmol/mol)	6 – 8	7 – 9	8 – 12
Post meal glucose (mmol/mol)	6 – 10	7 – 11	10 – 14

Figure 2: Intensifying to injectable therapies. Adapted from Standards of Medical Care in Diabetes 2019.[8]

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