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# Type 2 diabetes mellitus

## Guidelines for initiating insulin therapy

### BACKGROUND

Insulin is often indicated for patients with suboptimally controlled type 2 diabetes mellitus, despite lifestyle modification and oral antidiabetic agents.

### OBJECTIVE

This article outlines the initiation of insulin therapy for patients with type 2 diabetes in the general practice context.

### DISCUSSION

Insulin initiation options are bed time basal insulin (NPH, glargine) 10 U for patients with fasting hyperglycaemia, or twice daily premixed insulin (eg. aspart 30%/NPH 70%) 6–10 U twice per day targeting day time or postprandial hyperglycaemia. Basal insulin should be titrated regularly on a prophylactic basis (eg. fasting glucose <4.4 mmol/L: -2U, 4.4–7.0: +0 U, 7.1–10.0: +2 U, >10.0: +4 U) or increased by 1 U/day until fasting glucose of 5.5 mmol/L is reached. HbA1c changes of -1.5 to -2.5% are achievable with potential weight gain around 3 kg over 6 months. Approximately 50% of patients can achieve HbA1c ≤7% with insulin doses around 40–70 U/day. Glitazones are an alternative to insulin, but for HbA1c, ≥9.5% insulin results in greater improvement in fasting glucose and HbA1c. Patients require education for blood glucose monitoring, healthy diet, exercise and identifying and responding to hypoglycaemia.

**Type 2 diabetes mellitus (T2DM) is characterised by initial insulin resistance with  $\beta$ -cell dysfunction present at diagnosis with progressive deterioration leading to  $\beta$ -cell exhaustion over time.<sup>1</sup> While endogenous insulin secretion is preserved, weight reduction, exercise and healthy eating are important lifestyle measures to reduce insulin resistance. Metformin is the initial drug of choice for overweight patients with T2DM, to which sulphonylureas, glitazones or acarbose may be added.<sup>2-4</sup>**

If glycaemic control is still inadequate with HbA1c not reaching the preferred target of ≤7% despite lifestyle measures, metformin and sulphonylurea, current options are:

- triple oral therapy with the addition of a glitazone, or
- initiation of insulin therapy.

### Rationale for insulin therapy

Patients with T2DM and predominant insulin resistance but persisting poor glycaemic control despite lifestyle modification, weight loss and metformin therapy, may require insulin to control persistent hyperglycaemia.<sup>5</sup> Patients with approaching  $\beta$ -cell exhaustion and hyperglycaemia would expect less benefit from intensifying oral therapy providing a sound rationale for insulin initiation

and reduction of oral therapy, particularly sulphonylureas which act by stimulating  $\beta$ -cell insulin secretion.<sup>5,6</sup> Intermediate patients need to be encouraged to optimise lifestyle and oral therapy and may sustain reasonable glycaemic control or may progress to require insulin.

### Available insulin regimens

Once the decision to commence insulin therapy has been made, the initiation options depend on the pattern of the patient's blood glucose levels:

- predominantly high fasting (prebreakfast) blood sugars: initiate basal insulin by adding before bed time NPH (Protaphane, Humulin NPH) or glargine (Lantus)<sup>7</sup>
- predominantly high day time or postprandial blood sugars: use twice daily premixed insulin before breakfast and before dinner.<sup>8</sup>

There are several less common scenarios:

- A single prebreakfast injection of premixed insulin can be trialed if only day time blood sugars are high, or a single predinner injection of premixed insulin given if mainly postdinner and prebreakfast blood sugars are high<sup>9</sup>
- Premeal (three times per day) premixed insulin (eg. NovoMix 30, Humalog Mix 50) can be given as a way of providing premeal short acting insulin and

letting repeated injections of NPH build up to a steady state level<sup>9,10</sup>

- A basal-bolus regimen (premeal regular/analogue insulin three times per day and bed time NPH or glargine) is more typically employed in patients with type 1 diabetes mellitus. Most patients with T2DM would not require this type of regimen.<sup>11</sup>

## Initiating basal insulin in T2DM

### Pros and cons: NPH vs. glargine

The Treat-to-Target trial<sup>7</sup> randomised 756 patients with T2DM, aged 30–70 years, who were overweight (body mass index [BMI] 26–40) with HbA1c 7.5–10.0% and fasting glucose  $\geq 7.8$  mmol/L, to addition of either bed time glargine or NPH insulin at a starting dose of 10 U. Existing oral medications were continued and insulin doses titrated weekly to target a fasting glucose of 5.5 mmol/L (Table 1). Mean age was 55 vs. 56 years, BMI 32.5 vs. 32.2, fasting glucose 11.0 vs. 10.8 mmol/L and HbA1c 8.61 vs. 8.56% for glargine vs. NPH groups respectively. On completion of the 24 week study, fasting glucose, HbA1c and weight gain were similar in both groups (glargine vs. NPH 6.5 vs. 6.7 mmol/L, 6.96 vs. 6.97%, 3 vs. 2.8 kg). Significant differences were noted in insulin doses (glargine  $47.2 \pm 1.3$  U, 0.48 U/kg vs. NPH  $41.8 \pm 1.3$  U, 0.42 U/kg), hypoglycaemia rates (glargine 13.9 vs. NPH 17.7 symptomatic events per patient year) and nocturnal hypoglycaemia (glargine 4.0 vs. NPH 6.9 events per patient year). HbA1c  $\geq 7.0\%$  was achieved in similar proportions of glargine and NPH recipients (58 and 57.3%), but significantly more in the glargine group achieved this target without nocturnal hypoglycaemia (33.2 vs. 26.7%). The target fasting glucose  $\leq 5.6$  mmol/L was only achieved in a minority (36.2 and 34.4%).

Therefore basal insulin can be given as bed time glargine or NPH, with comparable efficacy when added to existing oral therapy. However, glargine results in less hypoglycaemia compared with NPH.

### Basal insulin and oral therapy vs. premixed insulin alone

In contrast, randomising similar patients with T2DM (n=371) to either glargine in addition

to glimepiride and metformin or twice daily premixed insulin (regular 30%/NPH 70%) without oral agents resulted in inferior results for the premixed insulin only group.<sup>12</sup> Starting doses of insulin were glargine 10 U, 30/70 10 U+10 U with a weekly titration schedule to target fasting glucose of 5.6 mmol/L (both groups) and predinner glucose 5.6 mmol/L (30/70 group) (Table 1). Mean age was 60.9 vs. 60.4 years, BMI 29.5 vs. 29.6, fasting glucose 9.5 vs. 9.6 mmol/L, HbA1c 8.85 vs. 8.83% in glargine vs. 30/70 groups respectively. At completion of the 24 week study significant differences were noted in fasting glucose and HbA1c favouring glargine therapy (glargine vs. regular/NPH 6.4 vs. 7.4 mmol/L, 7.15 vs. 7.49%). Weight gain was 1.4 vs. 2.1 kg. In the glargine group mean doses were glimepiride 3.4 mg, metformin 1.9 g and glargine  $28.2 \pm 15.2$  U compared with 30/70  $33.5 \pm 18.0$  U +  $31.0 \pm 16.1$  U. Glargine treated patients experienced significantly less hypoglycaemia (4.07 vs. 9.87 confirmed events per patient year with glucose  $< 3.3$  mmol/L) and nocturnal hypoglycaemia (0.51 vs. 1.04). Significantly more glargine treated patients reached target HbA1c  $\leq 7.0\%$  without nocturnal hypoglycaemia (45.4 vs. 28.6%).

Therefore combining basal insulin with oral therapy is preferable to using premixed insulin without oral agents.

### Comparing premixed insulin/rapid acting analogues to basal insulin

Two hundred and thirty-three patients with T2DM, aged 18–75 years, BMI  $\leq 40$ , HbA1c  $\geq 8.0\%$ , were randomised to either twice daily premixed insulin incorporating a rapid acting insulin analogue (insulin aspart 30%/NPH 70%, NovoMix 30) or a basal insulin (glargine) with continuation of oral agents including metformin, sulphonylurea or glitazones.<sup>8</sup> Insulin starting doses were aspart/NPH 5–6 U twice per day vs. glargine 10–12 U at bed time with weekly followed by fortnightly dose titration. Increase in total daily dose did not to exceed 10 U or 10% of the dose. At baseline mean age was 52.6 vs. 52.3 years, weight 90.6 vs. 89.9 kg, BMI 31.5 vs. 31.4, glitazone use 38 vs.

38%, fasting glucose 14 vs. 13.5 mmol/L, and HbA1c 9.7 vs. 9.8% in aspart/NPH vs. glargine groups respectively. Aspart/NPH doses were  $78.5 \pm 39.5$  U (0.82 U/kg) broken into 38.7 + 39.9 U vs. glargine  $51.3 \pm 26.7$  U (0.55 U/kg) with comparable weight gain and fasting glucose at the end of the 28 week study (aspart/NPH vs. glargine: 5.4 vs. 4.8 kg and 7.05 vs. 6.5 mmol/L). However, twice daily aspart/NPH resulted in significantly lower final HbA1c (6.91 vs. 7.4%) and a greater proportion achieving HbA1c  $< 7.0\%$  (66 vs. 40%) with increased rates of hypoglycaemia  $< 3.1$  mmol/L (3.4 vs. 0.7 events per patient year) compared with glargine.

Therefore, twice daily premixed insulin incorporating a rapid acting insulin analogue may be preferable for management of day time or postprandial hyperglycaemia.

### Other options using premixed rapid acting analogues

In 100 patients with T2DM receiving oral agents with or without daily insulin, insulin aspart 30%/NPH 70% (NovoMix 30) was initiated or used to replace the previous insulin at a dose of 12 U or 70–100% of the previous insulin dose and given before dinner.<sup>9</sup> Doses were titrated every 3–4 days aiming for fasting glucose of 4.4–6.1 mmol/L. After 16 weeks a prebreakfast dose was added if HbA1c was  $> 6.5\%$ , titrated for predinner glucose 4.4–6.1 mmol/L. After the next 16 weeks, a prelunch dose was added if HbA1c was  $> 6.5\%$ , titrated for 2 hour postlunch glucose 5.6–7.8 mmol/L. With once daily predinner insulin, 42% achieved HbA1c  $\leq 7\%$ . Two injections resulted in 70% reaching these targets, three times per day injections 77%. HbA1c change was  $-1.4\%$ ,  $-1.9\%$  and  $-1.8\%$  in daily, twice daily and thrice daily groups. Mean doses were 0.6 U/kg at dinner,  $0.51 + 0.64$  U/kg for twice daily, and  $0.58 + 0.25 + 0.70$  U/kg for three times daily injections. In 40 patients with T2DM, HbA1c  $\leq 11\%$ , BMI  $\leq 40$ , insulin lispro 50%/NPH 50% (Humalog Mix50) three times per day was compared with regular insulin/NPH 30/70 twice per day using a crossover design.<sup>10</sup> Seven point glucose profiles (before/after meals and before bed) were recorded showing a significantly greater decrease in

**Table 1. Schedules for adjusting insulin doses in patients with T2DM used in published studies**

Treat-to-Target <sup>7</sup> (mean over 2 days)*		Raskin <sup>8</sup> (2 of 3 values)**	
Fasting glucose (mmol/L)	Insulin dose adjustment	Fasting or predinner glucose (mmol/L)	Insulin dose adjustment
<3.1	-2 to -4		
<4.0	0	<4.4	-2
4.0–5.6	0	4.4–6.1	0
5.6–6.7	+2	6.1–7.8	+2
6.7–7.8	+4	7.8–10.0	+4
7.8–10.0	+6	>10.0	+6
>10.0	+8		

\* weekly titration, mean glucose values over 2 days used, no increase in dosage if glucose <4 mmol/L in preceding week, decrease dose if hypoglycaemia requiring assistance or glucose <3.1 mmol/L in preceding week

\*\* weekly titration for 12 weeks, then fortnightly, change dose if 2 of 3 glucose values out of target over the preceding 3 days, adjust according to lower value

mean glucose levels during treatment with lispro/NPH three times per day vs. 30/70 twice per day (-1.1 vs. -0.4 mmol/L). There was a greater change in HbA1c from baseline 8.4% to 7.6% (lispro/NPH three times per day) vs. 8.1% (30/70 twice per day). Insulin doses were lispro/NPH 27.9+13.7+23.5 U (daily average 64.6 U) compared with regular/NPH 36.3+25.6 (daily 61.8 U).

Therefore premixed insulins containing rapid acting analogues can be used with initial predinner dosing or twice daily or three times per day premeal dosing. In the latter case, the largest doses would be given before breakfast and dinner with a smaller dose before lunch.

## Adjusting insulin doses

Published studies employ preset schedules for adjusting insulin doses according to blood glucose monitoring results to establish improved glycaemic control promptly, generally reaching steady state over 8–12 weeks (Table 1). Outside of clinical trials a more gradual schedule of incremental dose adjustments may be more appropriate to facilitate monitoring and liaison and to minimise hypoglycaemia (Table 2). However, the more aggressive schedules using larger increments of insulin

may be appropriate for patients wanting to achieve control of elevated glucose levels more rapidly. An alternative method of titrating insulin doses was used in the INSIGHT study which randomised 405 patients with T2DM, aged 18–80 years, BMI 21–41, HbA1c 7.5–11.0%, on 0–2 oral agents to either insulin glargine 10 U (no new oral agents) or intensified oral therapy over a 24 week trial.<sup>13</sup> The titration schedule for glargine was to start at 10 U and add 1 U each day until fasting glucose  $\leq$ 5.5 mmol/L was achieved. Glargine resulted in significantly greater reductions in fasting glucose and HbA1c (-3.89 vs. -2.31 mmol/L and -1.55 vs. -1.25%) with mean glargine dose of 38 U (0.41 U/kg) and greater weight gain (+1.89 kg).

Therefore, basal insulin doses can be adjusted either by adding or subtracting increments depending on whether glucose readings are above or below a predetermined optimal range, or by increasing the dose slowly until a set fasting value is obtained.

## What is the evidence for adding a glitazone vs. commencing insulin therapy?

Two recent trials have compared glitazone vs. insulin as third line agents. Sixty-two patients with T2DM, HbA1c >8.0%, aged 30–85 years who were receiving maximal tolerated insulin

secretagogue and metformin (average 2.1 g/day) were randomised to pioglitazone 30 mg (increased to 45 mg after 4 weeks if fasting glucose not <6 mmol/L) vs. bed time NPH 0.3 U/kg with weekly adjustment.<sup>14</sup> Class III/IV heart failure, myocardial infarction (MI) or stroke were exclusion criteria. Mean age was 59 vs. 57 years, BMI 26 vs. 25, HbA1c 9.7 vs. 10.1% for pioglitazone vs. NPH groups. On completion of the 16 week study similar changes in fasting glucose and HbA1c were seen (pioglitazone -2.9 mmol/L and -1.9% vs. NPH -4.3 mmol/L and -2.3% respectively). Pioglitazone resulted in significantly less hypoglycaemia <3.8 mmol/L (37% vs. 68%) and increased HDL (+8 vs. 0%) compared with NPH. Final doses were pioglitazone 45 mg and NPH 31 U (0.35 U/kg/day). Oedema was reported in 9/30, nausea in 3/30, and a 1.4 times increase alanine amino transferase (ALT) in 1/30 of the pioglitazone treated group.

In a separate study, 217 patients with T2DM, HbA1c 7.5–11%, BMI >25, on  $\geq$ 50% maximal sulphonylurea + metformin, were randomised to addition of glargine 10 U/day (titration) or rosiglitazone 4 mg (increased to 8 mg/day after 6 weeks if fasting glucose >5.5 mmol/L).<sup>15</sup> Cardiovascular disease and congestive cardiac failure were exclusions and metformin dose was optimised to 2 g/day. Mean age was 55.9 vs. 55.3 years, BMI 34.6 vs. 33.6, HbA1c 8.8 vs. 8.7% in glargine vs. rosiglitazone groups respectively. On completion of the 24 week study similar decreases in fasting glucose and HbA1c were seen in both groups (glargine -3.6 mmol/L and -1.7% vs. rosiglitazone -2.6 mmol/L and -1.5%). However, there was a significantly greater reduction in HbA1c with glargine if HbA1c was  $\geq$ 9.5% at entry into the study. Final doses were glargine 38 $\pm$ 26 U/day vs. rosi 7.1 $\pm$ 2 mg. Hypoglycaemia (<3.9 mmol/L) was more frequent in the glargine treated group (7.7 vs. 3.4 events per patient year) as was nocturnal hypoglycaemia. In comparing the glargine vs. rosiglitazone groups, significant changes occurred in total cholesterol (-4.4 vs. +10.1%), LDL-C (-1.4 vs. +13.1%), triglycerides (-19.0 vs. +4.6%), HDL-C (0 vs. +4.4%). Weight gain was 1.6 vs. 3.0 kg. Adverse events occurred in 7% of glargine (hypoglycaemia, gastrointestinal upset) vs. 29% of rosiglitazone

(oedema, nausea, hypoglycaemia, elevated LFTs, weight gain) recipients. Peripheral oedema was reported in 0 vs. 12.5%, serious adverse effects in 5/105 vs. 11/112 participants in glargine vs. rosiglitazone groups respectively.

Therefore glitazones are suitable third line agents in addition to sulphonylurea + metformin, with comparable effect to insulin for patients with HbA1c <9.5%. However, insulin was more efficacious in patients with HbA1c ≥9.5%.

### Glitazones and vascular disease in T2DM

In the PROactive study, 5238 patients with T2DM and known vascular disease were

randomised to pioglitazone 15 mg increasing to 30 mg then 45 mg monthly vs. placebo.<sup>16</sup> NYHA Class II heart failure or above and ALT >2.5 x ULN were exclusions. Mean age was 61.9 vs. 61.6 years, BMI 30.7 vs. 31.0, HbA1c 7.8 vs. 7.9% in pioglitazone vs. placebo groups; 25% of both groups were receiving metformin + sulphonylurea at randomisation. After an average of 34.5 months follow up, the primary endpoint of time to death, nonfatal MI, stroke, acute coronary syndrome, intervention to coronary or leg arteries or amputation above ankle was reached in 21.0 of pioglitazone and 23.5% of placebo treated participants ( $p=0.095$ ). The predetermined secondary endpoint of time to death, nonfatal MI or stroke was reached in 12.3% of pioglitazone vs. 14.4%

of placebo treated participants ( $p=0.027$ ). Progression to permanent insulin use occurred in 11.1% of pioglitazone vs. 21.0% of placebo treated participants ( $p<0.001$ ). On completion of the study, comparing pioglitazone vs. placebo there were significant differences in HbA1c (-0.8% vs. -0.3%), triglycerides (-11.4 vs. +1.8%), LDL-C (+7.2 vs. +4.9%), HDL-C (+19.0 vs. +10.1%), systolic blood pressure (-3 vs. 0 mmHg), occurrence of angina (3 vs. 5%) and hospitalisation for diabetes control (2 vs. 3%), but also significant differences in pneumonia (2 vs. 1%), any report of heart failure (11 vs. 8%) and heart failure needing hospitalisation (6 vs. 4%). There was no significant difference in fatal heart failure (1% in both groups). In pioglitazone vs. placebo groups, oedema without heart failure occurred in 21.6 vs. 13.0% and weight gain was +3.6 vs. -0.4 kg. Ninety-three percent of the pioglitazone treated group received the 45 mg dose.

This is a major randomised controlled clinical trial indicating pioglitazone in patients with T2DM and known vascular disease reduced the incidence of death, nonfatal MI and stroke and also reduced the likelihood of progressing onto insulin use.

### Summary guidelines for insulin initiation

#### Starting basal insulin for fasting hyperglycaemia

- Selection criteria: patients with T2DM aged 30–70 years, BMI 26–40, HbA1c 7.5–10% and fasting glucose ≥7.8 mmol/L on 1 or 2 oral medications
- Insulin type and starting dose: either NPH or glargine 10 U at bed time
- Expected efficacy: achievable HbA1c reduction of 8.6 to 7.0%, HbA1c ≤7% in 57% with weight gain of 3 kg over 24 weeks, fewer hypos with glargine.

#### Starting twice daily premixed insulin for day time or postprandial hyperglycaemia

- Selection criteria: patients with T2DM aged 18–75 years, BMI ≤40, HbA1c ≥8% on metformin and sulphonylurea or glitazone
- Insulin type and starting dose: insulin aspart 30%/NPH 70% (NovoMix 30) 6–10 U before

**Table 2. Guidelines for insulin initiation and dose adjustment in patients with T2DM**

#### Insulin initiation

Options are either bed time basal insulin 10 U for patients with fasting hyperglycaemia, or twice daily premixed insulin 6–10 U twice per day targeting day time or postprandial hyperglycaemia

#### Titrating basal insulin

Basal insulin (eg. NPH or glargine) initially should be adjusted regularly on a prophylactic basis according to fasting glucose results

Small increments: <4.4 mmol/L: -2 U, 4.4–7.0: +0 U, 7.1–10.0: +2 U, >10.0: +4 U

Change insulin dose if 2 of 3 glucose values out of target over the preceding 3 days, adjust according to lower value

Alternatively, increase by 1 U/day until target fasting glucose of 5.5 mmol/L is reached

No increase in insulin dose if glucose <4 mmol/L in preceding week, decrease dose if hypoglycaemia requiring assistance or glucose <3 mmol/L in preceding week

#### Titrating twice daily premixed insulin

Twice daily premixed insulin (eg. aspart 30%/NPH 70%) can be given prebreakfast and dinner. Predinner dose should be adjusted according to fasting glucose results as for basal insulin, and prebreakfast dose should be adjusted according to predinner glucose

Small increments <4.4 mmol/L: -2 U, 4.4–8.0: +0 U, 8.1–10.0: +2 U, >10.0: +4 U

#### Achievable results

HbA1c changes of -1.5 to -2.5% are feasible with potential weight gain around 3 kg over 6 months. Approximately half of patients can achieve HbA1c ≤7%, with insulin doses in the order of 40–70 U/day

#### Glitazones vs. insulin

For HbA1c <9.5% glitazones are an alternative to initiating insulin but for HbA1c ≥9.5% insulin results in greater improvement in fasting glucose and HbA1c

#### Patient education

Patients require education for home blood glucose monitoring, appropriate diet and exercise and ability to identify and respond to hypoglycaemia

breakfast and before dinner

- C. Expected efficacy: achievable HbA1c reduction of 9.7 to 6.9%, HbA1c <7% in 66% with weight gain of 5.4 kg over 28 weeks.

### Adjusting insulin doses

- A. Adjust basal insulin every 3–4 days or weekly according to glucose results as follows: fasting glucose <4.4 mmol/L: –2U, 4.4–7.0+0 U, 7.1–10.0+2 U, >10.0+4 U
- B. Dose adjustments if 2 of 3 fasting glucose values are out of the target range, based on the lower of the two elevated glucose readings
- C. If twice daily premixed insulin is being used, adjust morning dose according to predinner glucose and predinner dose according to fasting glucose readings
- D. Alternative regimen: start basal insulin 10 U at bed time and add 1 U/day until target fasting glucose of 5.5 mmol/L is reached
- E. Insulin dose(s) could be decreased in event of glucose <4.4 mmol/L or hypoglycaemia requiring assistance.

### Glitazones vs. initiating insulin

- A. Selection criteria: patients with T2DM, HbA1c 7.5–11%, BMI >25 on sulphonylurea and metformin, without cardiovascular disease or heart failure
- B. Glitazone vs. insulin: either rosiglitazone (4–8 mg) or glargine
- C. Expected efficacy: with rosiglitazone, potential HbA1c reduction from 8.7 to 7.2%, 3 kg weight gain over 24 weeks and adverse effects (oedema in 12.5%). Glargine is as effective with fewer side effects and has greater efficacy in patients with HbA1c  $\geq$ 9.5%.

### Other considerations

It is necessary to individualise and allow for specific patient circumstances when applying guidelines. There is no 'one size fits all' insulin regimen as patients with T2DM are a heterogeneous group spanning the range of overweight to nonoverweight, from predominant insulin resistance to  $\beta$ -cell failure, and every insulin regimen must take diet, exercise, alcohol and other lifestyle factors into account. Older patients or patients

who are not overweight with predominantly  $\beta$ -cell exhaustion may require lower doses of insulin, ie. <40 U/day. Special care is needed for patients with significant renal impairment. Before commencing insulin both lifestyle (diet, exercise) and oral therapy (compliance) should be optimised. Postprandial glucose concentrations have not been incorporated into these guidelines, but a rigorous target would be <10 mmol/L 2 hours after a meal.<sup>17</sup> Once insulin has been initiated and glycaemic control improved, oral agents can be rationalised, however this should be individualised according to circumstances. As a general rule, once  $\beta$ -cell exhaustion is present sulphonylureas can be withdrawn.

Conflict of interest: none declared.

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