Individualising Insulin Regimens: Premixed or basal plus/bolus?

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Turkey, April 2015
Optimising insulin therapy
Choose a progressive treatment for a progressive disease

Schematic representation of time action profiles. In clinical practice, the duration of insulin action may be shorter or longer than duration specified. Variations between and within patients may occur depending upon injection site and technique, insulin dosage, diet and exercise. *Insulin profile in a person without diabetes. †Optimised long-acting insulin regimen (one or two injections).
Ilag LL et al. (2007). Clin Ther 29: 1254-70

- Systematic review, once daily injections
- Premixed analogues vs basal analogues

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<thead>
<tr>
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<th>Premixed analogues</th>
<th>Basal analogues</th>
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<tbody>
<tr>
<td>HbA1c</td>
<td>Better vs</td>
<td></td>
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<tr>
<td>PPG</td>
<td>Better vs</td>
<td></td>
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<tr>
<td>“Overall control”</td>
<td>Better vs</td>
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...but none of these were RCTs
OnceMix study

- Double blinded RCT, multi-centre
- **BIAsp30 premix vs glargine**
  - Poorly controlled on Metformin and SU
  - Insulin naïve
  - OHAs continued during trial
    - 26 weeks
    - n = 569
Estimated mean difference in favour of NovoMix® 30 was -0.52 mmol/L (95% CI [-1.02; -0.03]) post-evening meal and -0.78 mmol/L (95% CI [-1.25; -0.31]) at bedtime.
OnceMix HbA1c result

- Similar increases in mean body weight of ~1.7kg
- Mean dose was similar at 0.32 U/kg (aspart 30 mix) and 0.29 U/kg (insulin glargine)

BiAsp 30 mix vs Glargine -0.16%, p=0.029
OnceMix – hypos

Patients reaching HbA$_{1c}$ target at 26 weeks (%)

- Without Hypoglycaemia: 20.0% (BiAsp 30 mix), 19.4% (Insulin glargine)
- Without Daytime Hypoglycaemia: 23.1% (BiAsp 30 mix), 21.6% (Insulin glargine)
- Without Nocturnal Hypoglycaemia: 36.4% (BiAsp 30 mix), 39.7% (Insulin glargine)
DURABLE: study design

- Insulin-naïve patients with type 2 diabetes inadequately controlled with OADs
- HbA$_{1c}$ > 7.0%
- ≥2 OADs > 90 days
- 30–80 years of age

Randomisation (n=2091)

- Lispro Mix 25/75 BID + OADs (n=900 completed)
- Insulin glargine OD + OADs (n=918 completed)

Initiation phase to attain HbA$_{1c}$ < 7.0%

- Week 0

6-month treatment period

- n=473 continued; 239 completed

- n=419 continued; 188 completed

- 24-month treatment period for patients with HbA$_{1c}$ ≤ 7.0%

Maintenance phase to track HbA$_{1c}$ ≤ 7.0% durability

LM, lispro mix; OD, once daily

DURABLE: time to failure to maintain HbA$_{1c}$ goal

$p=0.040$ between-treatment difference

Final daily insulin dose: LM 25/75: 0.45 U/kg; insulin glargine: 0.37 U/kg; $p<0.001$
“Treat-to-target” using basal insulin only

Riddle MC et al, Diab Care, 2003: 3080-86
Mortality risk according to 2-hour glucose (PPG) is independent of FPG.
DECODE study

Mortality risk due to FPG becomes **non-significant** after **adjusting for 2-hour glucose (PPG)**

Lancet 1999;354:617
**Optimising insulin therapy**
Choose a progressive treatment for a progressive disease

**Once-daily Premixed at dinner time**
- One injection
- One insulin
- One device

**Twice-daily Premixed at breakfast and dinner time**
- Two injections
- One insulin
- One device

**Three-daily Premixed at breakfast, lunch and dinner time**
- Three injections
- One insulin
- One device

**Long-acting and rapid-acting insulins**
- One or two injections
- One Insulins
- One devices

**Long-acting and rapid-acting insulins**
- Four or five injections
- Two Insulins
- Two devices

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Galanagos study: Premix vs Basal / Basal-Plus

Phase 4, randomised, multi-centre, international, comparative open-label trial

$n=934$ patients with T2D >1 year;
Uncontrolled on OADs;
HbA$_{1c}$ $\geq 7.0\%$ and $\leq 10.5\%$;
Age $\geq 35$ years;
BMI $\leq 40$ kg/m$^2$

If HbA$_{1c}$ $\geq 7\%$ (53 mmol/mol) and FPG $<7$mmol/L (126 mg/dL)

Insulin glulisine OD + met ($n=197$)

Insulin glargine OD + met ($n=462$)

BIAsp 30 OD or BD + met + other OADs ($n=461$)

Weeks
-2 0 12 24

Screening

Randomisation 1:1

Met, metformin; SU, sulphonylurea, DPP-4, dipeptidylpeptidase-4

Aschner et al. Diabetes 2013;62(Suppl. 1):948-P
Galapagos study: key results

- Patients achieving HbA$_{1c}$ <7% (53 mmol/mol) with no symptomatic hypoglycaemia at EOT, by overall treatment group and number of injections

There was **no significant difference** between the two groups (overall $p=0.56$)

EOT, end of trial; Gla, insulin glargine; Glu, insulin glulisine

Aschner et al. Diabetes 2013;62(Suppl. 1):948-P
LanScape Premix vs Basal-Plus

Patients with T2D, treated >3 months with titrated basal insulin; HbA1c 7.5–11.0%

Run-in period: insulin glargine titrated to FPG <7.0 mmol/L. All OADs except metformin discontinued

Randomisation 1:1 for patients with FPG <7.0 mmol/L but HbA1c >7.0%

Insulin glargine OD + insulin glulisine OD at main meal (n=170)
BIAsp 30 BD (n=165)

Treatment

Weeks
0 8 or 12 12 24

This was a non-inferiority trial

Vora et al. Diabetes 2013;62(Suppl. 1B):47-LB
LanScape: key results

Primary endpoint: HbA₁c

<table>
<thead>
<tr>
<th>Basal-plus</th>
<th>BIAsp 30</th>
</tr>
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<tbody>
<tr>
<td>-1.22</td>
<td></td>
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</tbody>
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Change from baseline in HbA₁c (%)

<table>
<thead>
<tr>
<th>Basal-plus</th>
<th>BIAsp 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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LS Mean (SE) difference: 0.21 (0.09); $p=NS$

Hypoglycaemia

Incidence: episodes/year

Overall hypoglycaemia

Nocturnal hypoglycaemia

NS difference

Significantly lower with BIAsp 30 $p=0.019$

No dose data reported

Vora et al. Diabetes 2013;62(Suppl. 1B):47-LB
Why not just go for Basal Bolus? After all, it is “the best”, right?

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The 1-2-3 Study
Intensifying with Premixed BiAsp 30 premix

Background

● Failing OADs or basal insulin
● Intensification of BiAsp 30 premix
  - 1x daily → 2x daily → 3x daily
● Will we get $\text{HbA}_{1c} \leq 6.5\%$?

The 1-2-3 Study
Simple start and intensification to achieve glycaemic targets

Study Design

Phase 1: 100 subjects

NovoMix® 30 qd

- Pre-dinner for 16 weeks
- Start 12U at dinner

- (HbA₁c ≤ 6.5%)
- 21 completed Phase 1

- If HbA₁c > 6.5%, go to bd, discontinue secretagogues

Phase 2: 68 subjects

NovoMix® 30 bd

- Pre-breakfast & pre-dinner for 16 weeks
- Add 3U at breakfast if FBG ≤ 6.1mmol/L
- Add 6U at breakfast if FBG > 6.1mmol/L

- (HbA₁c ≤ 6.5%)
- 28 completed Phase 2

- If HbA₁c > 6.5%, go to tds

Phase 3: 25 subjects

NovoMix® 30 tds

- tds x 16 weeks
- Add 3U at lunch

- 25 completed Phase 3

Titrates according to schedule every 3 days. Predetermined dose escalation algorithm designed for patient self-adjustment (qd = once-daily; bd = twice-daily; tds = thrice-daily).

Adapted from Garber AJ et al. 2006. 1-2-3 study is a 48-week, single cohort, treat-to-target study in 100 type 2 patients, mean duration of diabetes 11-12 years.
No patients discontinued because of hypoglycaemia or weight gain at any time during the study.

The 1-2-3 Study
Achieve HbA$_{1c}$ targets with BiAsp 30

<table>
<thead>
<tr>
<th>% patients achieving</th>
<th>NovoMix® 30 OD 1-2-3 Study</th>
<th>NovoMix® 30 BD 1-2-3 Study</th>
<th>NovoMix® 30 TID 1-2-3 Study</th>
</tr>
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<tr>
<td>HbA$_{1c} \leq 7.0%$</td>
<td>41%</td>
<td>70%</td>
<td>77%</td>
</tr>
<tr>
<td>HbA$_{1c} \leq 6.5%$</td>
<td>21%</td>
<td>52%</td>
<td>60%</td>
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1-2-3 Conclusion

- Starting once-daily BiAsp 30 was an effective treatment approach for achieving glycaemic goals.

- Also, can safely achieved HbA1c goals by intensifying treatment
  - from 1 to 2 injections
  - and then 2 to 3 BiAsp 30 doses/day
PREFER
Premixed vs. basal–bolus

Inclusion criteria:
• One or two OADs without insulin
• One or two OADs with OD NPH/insulin glargine
• 7% ≤ HbA1c ≤ 12%

Randomisation 3:1
IAsp TID + IDet OD or BID (n=537)

Screening
BIAsp 30 BID (n=178)

6-week titration phase
20-week treatment phase

OADs were discontinued in both arms

IAsp, insulin aspart; IDet, insulin detemir; NPH, neutral protamine Hagedorn

Liebl et al. Diabetes Obes Metab 2009;11:45–52
## PREFER Study
Liebl A, et al (2008), Diabetes Obes Metab

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<td>HbA1c - insulin naïve</td>
<td>Same vs ➔</td>
<td></td>
</tr>
<tr>
<td>Minor hypos</td>
<td>Same vs ➔</td>
<td></td>
</tr>
<tr>
<td>Major hypos</td>
<td>0%</td>
<td>1%</td>
</tr>
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- No advantage to starting with basal-bolus in insulin naive patients
Ilag LL et al. (2007) Clin Ther 29: 1254-70

- **Meta-analysis**
- **Premixed analogues vs basal bolus**

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<td>Better vs</td>
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</tr>
<tr>
<td>HbA1c - prior insulin Rx</td>
<td></td>
<td>← Better vs</td>
</tr>
<tr>
<td>Minor hypos</td>
<td>Better vs</td>
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Using the right tool for the job

- Basal-bolus is very effective, but very complex
- Benefits only if patient not controlled on a simpler insulin regimen
- No clear benefit to start off on basal-bolus (insulin naïve)
Premix vs Basal / Basal-plus
How much difference is there?

- “No single insulin or regimen was best on all endpoints. Furthermore, while the differences may have reached statistical significance, they were often of limited clinical relevance.”¹

- “The authors of this study found inconclusive evidence...GPs know their patients well and are in a good position to select the appropriate regimen for their patients”²

¹ Wu T, et al. IDF WPR, Singapore Nov 2014
² Mosenzon O, Raz I. Diabetes Care 2013;36 Suppl 2:S212–8
Better Glucose Control

The most important thing is to take the first step: 

Start insulin
IDF Treatment Algorithm for People with Type 2 Diabetes

Lifestyle measures

Then, at each step, if not to target (generally HbA$_{1c}$ < 7.0%)

Consider first line
- Metformin

Consider second line
- Sulfonylurea
- Metformin (if not first line)
- α-Glucosidase inhibitor or DPP-4 inhibitor or Thiazolidinedione

Consider third line
- Basal insulin or Pre-mix insulin
- α-Glucosidase inhibitor or DPP-4 inhibitor or Thiazolidinedione

Consider fourth line
- Basal insulin or Pre-mix insulin
- Basal insulin, or Pre-mix insulin (later basal + meal-time)

Lifestyle Modification
- diet modification
- weight control
- physical activity

Metformin

Sulphonylurea

Acarbose

DPP-4 inhibitor #

Glitazone®

Insulin

Basal

Premixed

Basal Bolus insulin

Australian NHMRC, National Evidence Based Guideline for Blood Glc Control in T2DM, 2012
NHMRC guideline, 2012

- **Premixed insulin and basal insulin** are **equal first line option** for starting insulin in T2DM (level 1 evidence)
  - Premixed insulin is an intensification option if not controlled on basal insulin + OHA

- If equal first line, which one to choose?
  - Individualise
  - High FPG only → Add daily glargine
  - High PPG → Add daily premixed
Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**:
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**:
  - low
  - high

- **Disease duration**:
  - newly diagnosed
  - long-standing

- **Life expectancy**:
  - long
  - short

- **Important comorbidities**:
  - absent
  - few / mild
  - severe

- **Established vascular complications**:
  - absent
  - few / mild
  - severe

- **Resources, support system**:
  - readily available
  - limited
“Practical guidance on the use of premix insulin analogues in initiating, intensifying or switching insulin regimens in T2DM”

- **Ted Wu**, Bryan Betty, Michelle Downie, Manish Khanolkar, Gary Kilov, Brandon Orr-Walker, Gordon Senator, Gregory Fulcher

- Expert panel convened in February 2014

- First published, IDF Western Pacific Forum
  - Singapore, November 2014

- Gives guidance on individualising insulin regimens
<table>
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<tr>
<th>&lt;1 mmol</th>
<th>What is the post-prandial increment?</th>
<th>&gt;3 mmol</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>Will the patient likely manage basal-bolus therapy when intensification is needed?</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>I there a large carbohydrate intake at one or 2 meals?</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Is the patient’s lifestyle predictable (eating pattern, working hours etc)?</td>
<td>Yes</td>
</tr>
<tr>
<td>OK with more injections</td>
<td>Patient preference regarding number of injections</td>
<td>Prefers fewer injections</td>
</tr>
<tr>
<td>OK with more frequent</td>
<td>Patient preference regarding SMBG</td>
<td>Prefers less frequent</td>
</tr>
<tr>
<td>Good</td>
<td>Patient ability to inject (cognitive ability, manual dexterity, need for carer etc)</td>
<td>Poor</td>
</tr>
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Wu T, et al. IDF WPR, Singapore Nov 2014
“Begin as you mean to go on”
Think about which regimen is most suitable for your patient, and start on that regimen
Hospital patients are mostly on Basal-Bolus

- RPA Hospital at forefront of intensive Basal-Bolus insulin for all inpatients needing insulin
- “Triple-B” (basal-bolus-booster) subcutaneous insulin regimen: a pragmatic approach to managing hospital inpatient hyperglycaemia
- But what happens when the patient is discharged?

Switching from basal-bolus back to premix insulin analogue

- Reduce total daily dose of all insulin by 20–30%
- Then split this to give you the starting dose of premix insulin analogue at breakfast and evening meal
  - 50% AM, 50% PM
  - Unusual meal patterns may lead you to reconsider the initial dose ratio
- Titrate the dose. Adjust the evening meal dose first, followed by the breakfast dose.
Summary

- Modern insulin analogs → excellent results from both Premixed and Basal / Basal-Plus regimens

- The key in **individualisation**
  - We **individualise regimens** just as we do HbA$_{1c}$ targets
  - **New guidance** is available to help with individualising
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