Intensifying Insulin Therapy - Case Based Approach

Dr. Vahid Yousefi M.D
Endocrinologist
2021/Agu/6
### Case Study 1

<table>
<thead>
<tr>
<th>Case</th>
<th>59-year-old Mr Ali (BMI=32.8 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation</td>
<td>Businessman</td>
</tr>
</tbody>
</table>
| **Year 2008** | • Diagnosed with type 2 DM (HbA₁c 8.1%).  
• Multiple OADs for 9 years |
| **Year 2011** | Human Premix Insulin 30/70 initiated. |
| **Year 2015** | • Underwent abdominal vascular operation  
• Discharged on basal–bolus therapy (Analogue insulin) with  
• combination with 2 g of metformin. |
| **Chief complaints** | • **Frequent hypoglycaemias** despite good control initially.  
• Started **defensive eating**  
• **Periodically lowered total daily insulin (by 18 U)** to avoid hypoglycaemia |
| **Current status** | Incidence of hypoglycemia have reduced, but HbA₁c 8.6% |
### Case Study 1

**Interactive question**

<table>
<thead>
<tr>
<th>Options</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accept the Situation</td>
<td></td>
</tr>
<tr>
<td>Renew Diabetes Education</td>
<td></td>
</tr>
<tr>
<td>Change to LM 25 TID</td>
<td></td>
</tr>
<tr>
<td>Change to basal insulin only</td>
<td>with maximum therapy of metformin and a Sulphonylurea</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>
At Diagnosis

Guideline:

Start insulin

At diagnosis

If:
- FPG > 250 mg/dL
- PPG > 300 mg/dL
- HbA₁c > 9% - 10%

Or if patient has:
- Systemic infection
- Sepsis
- Acute myocardial infarction
- Unstable angina
- Diabetic ketoacidosis
- Pregnancy
- Perioperative care

OAD failure

If:
- FPG > 150 mg/dL
- PPG/RBG > 200 mg/dL
- HbA₁c > 8.5%

Despite receiving optimal dose of two or three OADs

Other indications if there is systemic infection, sepsis, acute MI, unstable angina, DKA/HONK, pregnancy, diabetic kidney disease

INCG. National guidelines on initiation and intensification of insulin therapy with premix insulin analogues. 2013.
INCG. J Assoc Physicians India 2009:57(Suppl. 1):42–6
Most patients with T2DM will eventually need insulin therapy as β-cell function declines over time and diet, exercise, and OAMs will not suffice to maintain adequate glucose control. While guidelines recommend basal insulin as the most convenient initial insulin regimen, in reality, several other options are widely used and are based on the concept of personalized care.

- Premix insulins are one of the commonly used options.

This slide set delineates important characteristics of treatment with premix insulins and compare them with alternative insulin therapies.

2. Elizarova S et al. J Diabetes 2014;6:100-10

OAM=oral antihyperglycemic medication
FPG or PPG?

- FPG and PPG have different contribution to HbA1c
- With mild HbA1c elevations (7.3-8.4%), the proportion of HbA1c elevation attributable to postprandial hyperglycaemia increases to as much as 70% of the glycaemic load
- To reach recommended HbA1c targets <6.5% it is important that postprandial hyperglycaemia is specifically addressed.

To normalise blood glucose both FPG and PPG must be reduced

Most insulin is initiated when HbA$_{1c}$ >8.5%

Adapted from Monnier L et al. *Diabetes Care* 2003;26:881–5
The dual-release insulin concept

- Physiological insulin profile:
  - meal-related peak
  - basal component

- Rapid-acting insulin analogue together with a basal insulin analogue provide physiological insulin replacement

- Premix analogues such as NovoMix® 30 mimic physiological insulin secretion

Profiles are schematic
Formulation of premixes

Premixed suspension of:

- Soluble insulin aspart
- Protamine-crystallised insulin aspart
- NovoMix® 30
- Premixed human insulin
- Soluble human insulin
- NPH
Treatments Strategies: Insulins

- **Basal insulin: Targets FPG > PPG**
  - Benefit: Only 1-2 injections per day; physiologic
  - Drawback: Patients may require prandial insulin to reach HbA1c targets

- **Premixed insulin: Targets both FPG and PPG**
  - Benefit: Fewer injections than prandial
  - Drawback: Unable to adjust components separately

- **Prandial (mealtime) insulin: Targets PPG > FPG**
  - Benefit: Most physiologic; best at targeting PPG
  - Drawback: Most injections; requires addition of basal insulin to target FPG

“Ideal” Patient Characteristics for a Premix Insulin$^{1,2}$

♦ Organized lifestyle

♦ Regular intake of meals

♦ Less motivated for frequent blood glucose monitoring and insulin dose adaptation

♦ Prefers fewer injections
  • Older age, poor cognitive ability, limited manual dexterity, need for caretaker

1. Mosenzon O and Raz I. Diabetes Care 2013;36(Suppl 2)S212-8
Who May Benefit From Insulin Mixtures?

Patients:

♦ With inadequate glycemic control (HbA1c above target) on existing therapy

♦ Who are already taking basal insulin and, in the opinion of their physician, may require an insulin formulation change to control glycemia and reduce the risk of hypoglycemia

♦ Who want fewer injections than basal + bolus regimens

Inzucchi SE et al. *Diabetes Care* 2012;35:1364-79
(updated 36:490)
More or less stringent glycaemic goals may be appropriate for individual patients. Goals should be individualised based on duration of diabetes, age/life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, hypoglycaemia unawareness, and individual patient considerations. Patients were on insulin treatment for at least 3 months. Polinski JM, et al. *BMC Endocr Disord.* 2015;15(46):1-9.
Baseline insulin regimens are different around the world,\(^1\) reflecting local needs.

NPH = neutral protamine Hagedorn.

IDF Global Guideline for Type 2 Diabetes. Begin with a basal insulin once daily such as NPH insulin, insulin glargine, or insulin detemir.\(^2\)

Content Overview

♦ Progression of T2DM
♦ Insulin Initiation in T2DM
♦ Introduction to Premix Insulins
♦ Premix vs. Basal Insulin Regimens
♦ Premix vs. Basal-Bolus Regimens
♦ Comparison of Premix, Basal-Bolus, and Basal Insulin Regimens
♦ Guidelines and Treatment Algorithms
♦ Conclusions
What are Premix Insulins?

♦ Premix human insulins¹
  • Composed of human insulin and NPH (intermediate-acting human insulin)
  • Dosing in T2DM: 2-3 injections per day, approximately 30-45 minutes before a meal

♦ Premix insulin analogs¹
  • Composed of a rapid acting analog and the same insulin attached to protamine, which prolongs its absorption
  • Dosing in T2DM: 2-3 injections per day, up to 15 minutes before or right after meals

♦ Target both FPG and PPG²

## Benefits of Premix Insulins

<table>
<thead>
<tr>
<th>Desirable Features</th>
<th>Resulting Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Premix”</strong></td>
<td>• No mixing errors</td>
</tr>
<tr>
<td><strong>Rapid and Basal Components</strong></td>
<td>• Both FPG and PPG control</td>
</tr>
<tr>
<td><strong>“Single Pen”</strong></td>
<td>• Convenient dosing schedule&lt;br&gt;• Less number of injections and glucose testing&lt;sup&gt;a&lt;/sup&gt; than basal-bolus therapy</td>
</tr>
</tbody>
</table>

<sup>a</sup>Less number of glucose testing for premix insulin (QD or BID) vs. basal-bolus insulin with prandial insulin (TID)

Garber AJ. *Drugs* 2006;66:31-49

Copyright © 2016 Eli Lilly and Company
## Premix Insulins Currently Available (US)\(^a\)

### Insulin Analogs
- Insulin lispro mix 75/25\(^1\)
- Insulin lispro mix 50/50\(^2\)
- Insulin aspart 70/30\(^3\)

### Human Insulins
- Human insulin 70/30\(^4,5\)

\(^a\)Insulin components are stated as basal/prandial

1. Humalog\(^®\) Mix75/25\(™\) [Prescribing Information]. 2015
2. Humalog\(^®\) Mix50/50\(™\) [Prescribing Information]. 2015
3. NovoLog Mix 70/30\(™\) [Prescribing Information]. 2015
4. Humulin\(^®\) 70/30 [Prescribing Information]. 2015
5. Novolin\(^®\) 70/30 [Patient information]. 2010

US=available within the United States of America

Copyright © 2016 Eli Lilly and Company
# Premix Insulins Currently Available (OUS)a

<table>
<thead>
<tr>
<th>Insulin Analogs</th>
<th>Human Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Insulin lispro mix 25/75(^1)</td>
<td>♦ Human insulin 15/85(^4)</td>
</tr>
<tr>
<td>♦ Insulin lispro mix 50/50(^2)</td>
<td>♦ Human insulin 25/75(^5)</td>
</tr>
<tr>
<td>♦ Insulin aspart 30/70(^3)</td>
<td>♦ Human insulin 30/70(^6)</td>
</tr>
<tr>
<td></td>
<td>♦ Human insulin 40/60(^7)</td>
</tr>
<tr>
<td></td>
<td>♦ Human insulin 50/50(^8)</td>
</tr>
</tbody>
</table>

\(^a\)Insulin components are stated as prandial/basal

---

2. Humalog Mix 50, SPC 2016
3. Novo Mix 30, SPC 2014
4. Insuman Comb 15, SPC 2013
5. Insuman Comb 25, SPC 2013
6. Humulin, SPC 2015
7. Novolin®ge Penfill® Premixed insulin preparations, 2011
8. Insuman Comb 50, SPC 2013

OUS=available outside of the United States of America
Time-Action Profile of Premix Insulins

Serum Insulin Concentrations (ng/ml)

- Lispro
- LM50
- LM25
- Lispro NPL

Mean Glucose Infusion Rate (mg/kg/min)

N=30. Nondiabetic subjects. 0.3 U/kg dose.

Data from Heise T et al. Diabetes Care 1998;21:800-3

Copyright © 2016 Eli Lilly and Company
Premix Analogs Have Stronger Early Glucose Lowering Activity and Faster Onset Than Human Premixes

**Humalog® Mix75/25™ (0.3 U/kg)**

- **GIR (mg/min/kg)**
- **Time, hours after dosing**
- **Injection timing:** 0-15 min before meals
- **Peak activity:** 1-2 hours after injection

**Humulin® 70/30 (0.3 U/kg)**

- **GIR (mg/min/kg)**
- **Time, hours after dosing**
- **Injection timing:** 30-60 min before meals
- **Peak activity:** 2-10 hours after injection

Insulin activity after injection of Humalog® Mix75/25™ in nondiabetic subjects; N=30

Insulin activity after injection of Humulin® 70/30 in nondiabetic subjects; N=18

---

1. Data from Humalog® Mix75/25 [Package Insert]; 2015
2. [Package Insert](http://courses.washington.edu/pharm504/Insulin%20Chart.pdf)
Premix Analogs vs. Human Premixes$^{1,2}$

♦ Compared to human premix insulins, premix analogs showed

- An improved PK/PD profile
- Improved postprandial glycemic control
- Similar rates of hypoglycemia
- Similar mean doses of insulin, changes in body weight, and incidence of adverse events

Includes both intermediate- and long-acting insulins


Premix and basal bolus regimens were used at higher baseline HbA1c values

Copyright © 2016 Eli Lilly and Company
Baseline HbA1c was lower for patients on the basal-only regimen
 Endpoint HbA1c was similar between the 3 insulin regimens shown

Choice of insulin regimen needs to be individualized based on needs of the patient. The following parameters may be considered while choosing between basal and premix regimens.

<table>
<thead>
<tr>
<th>Favor Premix</th>
<th>Parameter</th>
<th>Favor Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8.5%</td>
<td>HbA1c</td>
<td>&lt;8.5%</td>
</tr>
<tr>
<td>&gt;200 mg/dl</td>
<td>PPG</td>
<td>&lt;200 mg/dl</td>
</tr>
<tr>
<td>&gt;54 mg/dl</td>
<td>PPG increment</td>
<td>&lt;54 mg/dl</td>
</tr>
<tr>
<td>Predictable</td>
<td>Lifestyle (meal pattern)</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>High Carb load</td>
<td>Diet</td>
<td>Low carb load</td>
</tr>
<tr>
<td>Without comorbidities</td>
<td>Elderly</td>
<td>With comorbidities</td>
</tr>
</tbody>
</table>
In newly diagnosed T2DM patients with symptomatic hyperglycaemia with metabolic decompensation (glucotoxicity), short-term intensive insulin therapy with premix Insulins for 2-3 weeks is recommended for favourable outcomes on recovery and preservation of beta-cell function. (and with view to continue insulin if patients present with diabetes complications)

Premix Insulin analogues are preferred over human insulins due to the benefits of lower risk of Hypoglycemia and flexibility of administration.

It is recommended to initiate twice daily Premix Insulins at 0.2-0.3 U/kg/day in 2 divided doses in severe hyperglycaemia/symptomatic patients.
Once Daily Premix Insulin for Initiation
Recommendations of Iran Guideline

It is recommended to initiate insulin early in the course of disease when two or three oral drugs prove inadequate to achieve the desired glycaemic goal (i.e. when the HbA1c > 7.5%).

It is recommended to initiate premix insulin Once Daily at a daily dose of 12 U to target the main meal of the day (pre Breakfast or pre Dinner in patients taking one large meal.)

Analogue Premix Insulins should be considered over Human Insulins due to lesser risk of Hypoglycemia and convenience.

Once Daily Premix Insulin for Initiation
Recommendations of Iran Guideline on Titration

<table>
<thead>
<tr>
<th>* mg/dL Pre-breakfast/pre-dinner value</th>
<th>Dose adjustment (Units) Pre-dinner/pre-breakfast dose change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>-2</td>
</tr>
<tr>
<td>80–130</td>
<td>0</td>
</tr>
<tr>
<td>131–160</td>
<td>+2</td>
</tr>
<tr>
<td>161–180</td>
<td>+4</td>
</tr>
<tr>
<td>&gt;180</td>
<td>+6</td>
</tr>
</tbody>
</table>

*For patients initiated on pre-breakfast dose, titrate according to pre-dinner values and vice versa.

It is recommended to titrate the dose once a week based on pre meal value. It is recommended to modify dose based on the lowest/mean value of the 3 most recent values.
Twice Daily Premix Insulin for Initiation
Recommendations of Iran Guideline

It is recommended to initiate Twice daily premix Analouges for achieving recommended glucose targets if baseline HbA1c is > 8.5% ¹

It is recommended to initiate premix insulin Twice Daily at a daily dose of 6U BID to target meals (pre Breakfast and pre Dinner or PreLunch and PreDinner in patients taking two large meals.)²

Twice Daily Premix Insulin for Initiation
Recommendations of Iran Guideline on Titration

<table>
<thead>
<tr>
<th>* mg/dL Pre-breakfast/pre-dinner value</th>
<th>Dose adjustment (Units) Pre-dinner/pre-breakfast dose change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>-2</td>
</tr>
<tr>
<td>80–130</td>
<td>0</td>
</tr>
<tr>
<td>131–160</td>
<td>+2</td>
</tr>
<tr>
<td>161–180</td>
<td>+4</td>
</tr>
<tr>
<td>&gt;180</td>
<td>+6</td>
</tr>
</tbody>
</table>

It is recommended to titrate the dose once/twice a week based on pre meal value. It is recommended to modify dose based on the lowest/mean value of the 3 most recent values if available. Frequency of monitoring may be reduced in the maintenance phase based on pre-breakfast value.
Which patient should be offered a premix versus basal-bolus/basal plus regimen?

<table>
<thead>
<tr>
<th>Premix insulin analogs</th>
<th>Basal plus/basal bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient preference</td>
<td>Type 1 diabetes (any age)</td>
</tr>
<tr>
<td>Older age</td>
<td>Younger age</td>
</tr>
<tr>
<td>Need assistance with injections</td>
<td>Highly motivated and compliant</td>
</tr>
<tr>
<td>Organized lifestyle</td>
<td>Active lifestyle</td>
</tr>
<tr>
<td>Two meals a day or evening main meal</td>
<td>High variability in eating habits</td>
</tr>
</tbody>
</table>

A Practical Approach to Insulin Intensification: Humalog Mix
LM25 QD-TID vs. Glargine + Lispro (PARADIGM): Trial Design

- 48-week, parallel, prospective, multinational, randomized open-label study
- Target FPG of 4.5-6.0 mmol/L (80-109 mg/dL)

Inclusion criteria:
- Age 30-80 years with T2DM
- HbA1c levels \( \geq 7.0\% \) and \(< 11.0\%\)
- On \( \geq 1 \) OAM without insulin for \( \geq 90 \) days before study start

Randomization stratified by country, HbA1c (\( \leq 69 \) mmol/mol [\( \leq 8.5\% \)] and \( > 69 \) mmol/mol [\( > 8.5\% \)]), and continuing use of a sulfonylurea

Bowering K et al. Diabet Med 2012;29:e263-72

Copyright © 2016 Eli Lilly and Company
Similar reductions in HbA1c and similar percentages of patients attaining glycemic targets between the two treatment groups

Bowering K et al. *Diabet Med* 2012;29:e263-72
Similar rates of hypoglycemic events between the two treatment groups

Bowering K et al. *Diabet Med* 2012;29:e263-72
Similar weight gain among patients treated with either treatment regimen

Bowering K et al. *Diabet Med* 2012;29:e263-72
Initiating Therapy With Twice-Daily Premix Insulin Analogs

Premix analog twice daily – start with low dose and increase gradually

Insulin naïve patients
♦ Start as 10 U sc prebreakfast and pre-evening meals

Patients already on once-daily insulin
♦ Calculate total daily dose
  • Total daily dose \( \div 2 \)
  • Give \( \frac{1}{2} \) sc prebreakfast and \( \frac{1}{2} \) sc pre-evening meal
♦ OAM recommendation
  • Continue metformin
  • Other OAMs (sulfonylureas or \( \alpha \)-glucosidase inhibitors) can also be maintained
♦ PG measurements
  • Monitor prebreakfast (fasting) and pre-evening meal plasma glucose

2. https://www.idf.org/guidelines

Copyright © 2016 Eli Lilly and Company
Pooled

Study (First Author, Year)

Malone, 2004
Malone, 2005
Raskin, 2005
Kann, 2006
Jacober, 2006
Kazda, 2006
Holman, 2007
Robbin, 2007
Buse, 2009
Strojek, 2009

Data from Giugliano D et al. Diabetes Care 2011;34:510-7
Premix vs. Basal Insulins Meta-Analysis: Incidence of Hypoglycemia

Data from Giugliano D et al. Diabetes Care 2011;34:510-7

Copyright © 2016 Eli Lilly and Company
Premix vs. Basal Insulins Meta-Analysis: Weight Gain

Data from Giugliano D et al. Diabetes Care 2011;34:510-7

Q² Cochrane test for heterogeneity=60.7 (p=.0008); df=9; I²=85.2

Copyright © 2016 Eli Lilly and Company
Premix vs. Basal Insulins: Summary of Key Findings\textsuperscript{1-5}

♦ Compared to basal insulins, most studies showed that premix insulins were associated with:

- Significantly greater reduction in HbA1c
- Significantly higher proportions of patients achieving HbA1c levels ≤7.0%
- Comparable or higher rates of hypoglycemia
- Significantly greater weight gain

5. Giugliano D et al. \textit{Diabetes Care} 2011;34:510-7

Copyright © 2016 Eli Lilly and Company
Identifying Patients who Benefit the Most Using Humalog® Mix25™ Therapy

Clinical Characteristics

Type 2 diabetes patients with A1C >7%

Patient Assessment:  Current Therapy?  Symptoms?  BG Results?

- Insulin naive patients on OAMs
- Usually asymptomatic
- Pre-breakfast BG >110 mg/dL (6.1 mmol/L)

Once daily pre-evening dosing
**Humalog® Mix25™:**
**Initiating Therapy**

**Mix25 Once Daily Dosing**
Start with low dose and increase gradually

**Starting dose and meal:**
- 10 U subcutaneous (sc) injection
- pre-evening meal

**OAM recommendation:**
- Maintain at least metformin 1-1.5 g/day in divided doses
- Other OAM can also be maintained*

**BG measurements:**
- Monitor pre-breakfast fasting BG every 3-4 days†

---

*OAM to be used in accordance with the locally approved package insert. Some OAMs may be contraindicated.
†Physicians and patients should decide if additional BG measurements may be needed. Abbreviations: BG = blood glucose.
Dose adjustment should occur every 3-4 days (twice weekly)

<table>
<thead>
<tr>
<th>Mix25 Once Daily Dosing (pre-dinner)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjust dose based on pre-breakfast fasting blood glucose (BG) using:</td>
</tr>
<tr>
<td>BG &lt;50 mg/dL → decrease by -4 units</td>
</tr>
<tr>
<td>BG 50-79 mg/dL → decrease by -2 units</td>
</tr>
<tr>
<td>BG 110-139 mg/dL → +2 units</td>
</tr>
<tr>
<td>BG 140-199 mg/dL → +4 units</td>
</tr>
<tr>
<td>BG ≥ 200 mg/dL → +6 units</td>
</tr>
</tbody>
</table>
# Case Study 1

<table>
<thead>
<tr>
<th>Case</th>
<th>59-year-old Mr Ali (BMI=32.8 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation</td>
<td>Businessman</td>
</tr>
</tbody>
</table>
| Year 2008                 | • Diagnosed with type 2 DM (HbA₁c 8.1%).  
                             | • Multiple OADs for 9 years          |
| Year 2011                 | Human Premix Insulin 30/70 initiated. |
| Year 2015                 | • Underwent abdominal vascular operation |
|                          | • Discharged on basal–bolus therapy (Analogue insulin) with |
|                          | • combination with 2 g of metformin. |
| Chief complaints          | • Frequent hypoglycaemias despite good control initially. |
|                          | • Started defensive eating          |
|                          | • Periodically lowered total daily insulin (by 18 U) to avoid hypoglycaemia |
| Current status            | Incidence of hypoglycemia have reduced, but HbA₁c 8.6% |
**Case Study 1**

**Interactive question**

<table>
<thead>
<tr>
<th>Options:</th>
<th>Accept the Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renew Diabetes Education</td>
</tr>
<tr>
<td></td>
<td>Change to BIAsp 30 TID</td>
</tr>
<tr>
<td></td>
<td>Change to basal insulin only with maximum therapy of metformin and a Sulphonyliurea</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>


Case Study 1

- What is the evidence that he would benefit with a premixed insulin analogue?
Case Study 1
Evidence from Clinical Trials

Studies in patients naïve to insulin

- **Malek et al. 2015**
  - BIAsp 30 or
  - IDet + IAsp

- **Riddle et al. 2014**
  - BIAsp 30 BID or
  - IGlar OD + ≤IGlu TID or
  - Basal-plus regimen: IGlar OD ± IGlu OD*

**Premix vs Basal Bolus therapy:**

**Similar in terms of:**
- Glycaemic control
- Risk of overall hypoglycaemia
- Insulin dose
- Weight gain

Studies in patients previously receiving basal insulin

- **Liebl et al. 2009 (PREFER)**
  - BIAsp 30 BID
  - IDet OD (/BID) + IAsp TID

*Basal-plus regimen included here only for context. (B)IAsp, (biphasic) insulin aspart; BID, twice daily; IDet, insulin detemir; IGlar, insulin glargine; IGlu, insulin glulisine; LM, lispro mix; OAD, oral antidiabetic drug; OD, once daily; TID, three times daily
**Case Study 1**

**Evidence from Clinical Trials: Malek et al, 2015**

**Patients (N=403)**
- Insulin-naïve patients with T2D on OADs for >6 months
- HbA$_1$c 7.0–11.0% (metformin monotherapy) or 7.0–<10.0% (OAD combination therapy)
- BMI ≤40 kg/m$^2$

**Study design**
- Multicentre (Egypt, Algeria, Tunisia, South Africa)
- Open-label
- Randomised

**Trial objective**
To evaluate the non-inferiority of initiation and stepwise intensification of a basal-bolus insulin analogue regimen (IDet and IAsp) vs. a premixed analogue (BIAsp 30)

**Key endpoints**
- **Primary efficacy endpoint:** change in HbA$_1$c after 50 weeks
- **Secondary efficacy endpoints:** proportion of patients achieving HbA$_1$c <7.0% with or without hypoglycaemia; mean prandial PG increments; eight-point blood glucose profile; total insulin dose
- **Safety:** hypoglycaemia, adverse events, change in body weight, number of daily injections

**Duration (weeks)**
- Randomisation (1:1)
- End of treatment

**Malek et al. Diabetes Metab 2015;41:223–30**
### Case Study 2
Evidence from Clinical Trials: Malek et al, 2015

#### Titration steps

<table>
<thead>
<tr>
<th>Week</th>
<th>BIAsp 30 arm</th>
<th>Basal bolus arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 (Initiation)</td>
<td>OD before dinner (0.1U /kg)+met</td>
<td>IDet OD at bedtime (0.1 U/kg)+met</td>
</tr>
<tr>
<td>14-26 (Intensification1)</td>
<td>Additional dose before breakfast (if HbA1c&gt;7)</td>
<td>Additional IAsp at the largest meal (if HbA1c&gt;7)</td>
</tr>
<tr>
<td>26-38 (Intensification2)</td>
<td>Additional dose before lunch (if HbA1c&gt;7)</td>
<td>One more I Asp added with second meal (if HbA1c&gt;7)</td>
</tr>
<tr>
<td>38-50</td>
<td>Dose optimization</td>
<td>Additional IAsp at the third meal</td>
</tr>
</tbody>
</table>
Case Study 2
Evidence from Clinical Trials: Malek et al, 2015: HbA1c

Change in HbA1c after 50 weeks*

Baseline
8.6 0

Change in HbA1c (%)

-0.1% [95% CI: −0.1; 0.3]; FAS

-1.4
-1.2

*Full analysis set (FAS). (B)IAsp, (biphasic) insulin aspart; CI, confidence interval; EOS, end of study; EOT, end of trial; IDet, insulin detemir
Malek et al. Diabetes Metab 2015;41:223–30
Case Study 1
Evidence from Clinical Trials: Malek et al, 2015
HbA1c < 7%

<table>
<thead>
<tr>
<th>Week</th>
<th>BIAsp 1-2-3</th>
<th>IDet/IAsp</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>13.5</td>
<td>7.8</td>
</tr>
<tr>
<td>38</td>
<td>54.8</td>
<td>45.6</td>
</tr>
<tr>
<td>50</td>
<td>44.9</td>
<td>40.3</td>
</tr>
</tbody>
</table>

BIAsp, biphasic insulin aspart; IAsp, insulin aspart; IDet, insulin detemir

Malek et al. Diabetes Metab 2015;41:223–30
### Case Study 1
Evidence from Clinical Trials: Malek et al, 2015

**Hypoglycaemia**

<table>
<thead>
<tr>
<th></th>
<th>BIAsp 30 1-2-3 (n=203)</th>
<th>IDet + IAsp (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
<td><strong>Events</strong></td>
</tr>
<tr>
<td>All events</td>
<td>120</td>
<td>651</td>
</tr>
<tr>
<td>Major events</td>
<td>10</td>
<td>4.9</td>
</tr>
<tr>
<td>Nocturnal events</td>
<td>43</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Percentage of patients who experienced at least one treatment-related hypoglycaemic episode during the trial period was comparable between the two groups:

IDet + IAsp, 76.0%; BIAsp 30 1-2-3, 83.7%; p=0.327

BIAsp, biphasic insulin aspart; IAsp, insulin aspart; IDet, insulin detemir

Malek et al. *Diabetes Metab* 2015;41:223–30
Case Study 1
Evidence from Clinical Trials: Meta Analysis: HbA1c

Premix regimen provides similar HbA1c reduction compared to Basal Bolus therapy

Favours premix

Favours basal-bolus

CI, confidence interval; ES, estimate


Basal-bolus and Premix groups: small and non-significant difference
Case Study 1
Evidence from Clinical Trials: Meta Analysis: Hypoglycaemia

Similar event rates for overall Hypoglycaemia between Premix and Basal Bolus regimens.

No statistically significant difference in the event rate for overall hypos, which averaged 12.1 PYE in the basal-bolus group and 12.2 PYE in the premix group.
Case Study 1
Evidence from Clinical Trials: Meta Analysis:
Change in weight

Weight gain with premix numerically lower as compared to that with basal bolus therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowering, 2012</td>
<td>-0.14 (-0.85, 0.57)</td>
</tr>
<tr>
<td>Fritsche, 2010</td>
<td>-1.40 (-2.35, -0.45)</td>
</tr>
<tr>
<td>Miser, 2010</td>
<td>-0.30 (-1.08, 0.48)</td>
</tr>
<tr>
<td>Jain, 2010</td>
<td>-0.10 (-3.66, 3.46)</td>
</tr>
<tr>
<td>Liebel, 2009</td>
<td>-0.30 (-0.98, 0.38)</td>
</tr>
<tr>
<td>Rosenstock, 2008</td>
<td>-0.50 (-1.37, 0.37)</td>
</tr>
<tr>
<td>Overall (I²=48.6%, p=0.049)</td>
<td>-0.21 (-0.61, 0.19)</td>
</tr>
</tbody>
</table>

No statistically significant difference in weight change at the endpoint, which averaged 2.4 kg in the basal-bolus group and 2.2 kg in the premix group.

CI, confidence interval; PYE, patient-years of exposure; ES, estimate
Case Study 1
Evidence from Clinical Trials: Meta Analysis:
Insulin dose

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malek, 2015</td>
<td>3.00 (-6.67, 12.67)</td>
</tr>
<tr>
<td>Jia, 2015</td>
<td>-1.00 (-4.80, 2.80)</td>
</tr>
<tr>
<td>Gugliano, 2014</td>
<td>-1.00 (-7.16, 5.16)</td>
</tr>
<tr>
<td>Tinahones, 2014</td>
<td>2.20 (-1.99, 6.39)</td>
</tr>
<tr>
<td>Fritsche, 2010</td>
<td>-7.00 (-17.26, 3.26)</td>
</tr>
<tr>
<td>Miser, 2010</td>
<td>0.00 (-7.92, 7.92)</td>
</tr>
<tr>
<td>Rosenstock, 2008</td>
<td>-23.00 (-38.69, -7.31)</td>
</tr>
<tr>
<td>Overall (I²=31.6%, p=0.165)</td>
<td>-0.54 (-2.67, 1.59)</td>
</tr>
</tbody>
</table>

CI, confidence interval; ES, estimate; WMD, weighted mean difference

Case Study 1
Evidence from Clinical Trials: Meta Analysis: Summary

No significant differences between premix and basal-bolus regimens for:

- Glycaemic control, as measured by change in HbA\(_{1c}\)
- Overall risk of hypoglycaemia
- Weight gain
- Total insulin dose

Key conclusion
“... our analyses suggest that there is no clinically relevant difference in the efficacy of basal-bolus versus premixed insulin regimens for HbA\(_{1c}\) decrease in type 2 diabetic patients who intensified insulin therapy”

Case Study 1
How did Mr Ali fare?

Switched to BIAsp 30 TID

• Intense re-education by the nurse-educator and the dietician
• Importance of Physical Activity emphasised
• HbA$_{1c}$ 7.4 %
• One hypoglycaemic episode when he injected his morning insulin but did not eat breakfast
• No other documented hypos have occurred
• He cycles in the evening has lost 0.6 kg
• He no longer feels he needs to eat to avoid hypos
Conclusion

- Insulin intensification is essential in order to prevent complications associated with elevated blood glucose.
- Changing from basal insulin analogues to premix insulin analogues improves HbA$_{1c}$ may be associated with hypoglycaemia benefits.
- Premix insulin twice or three times daily is comparable to the gold standard basal-bolus.
Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals.

If injectable therapy is needed to reduce A1C¹

Consider GLP-1 RA in most patients prior to insulin²

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titration to maintenance dose (varies within class)

If above A1C target

Add basal insulin³

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

To avoid therapeutic inertia, reassess and modify treatment regularly (3-6 months).
Add basal analog or bedtime NPH insulin

**INITIATION:** Start 10 IU a day OR 0.1-0.2 IU/kg a day

**TITRATION:**
- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

Assess adequacy of basal insulin dose

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-prandial differential, hypoglycemia [aware or unaware], high variability)

If above A1C target

Consider GLP-1 RA if not already in regimen

For addition of GLP-1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors

Add prandial insulin

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

**INITIATION:**
- 4 IU a day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

**TITRATION:**
- Increase dose by 1-2 IU or 10-15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH regimen

Conversion based on individual needs and current glycemic control. The following is one possible approach:

**INITIATION:**
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

**TITRATION:**
- Titrate based on individualized needs
If above A1C target

Stepwise additional injections of prandial insulin (i.e., two, then three additional injections)

Consider self-mixed/split insulin regimen
   Can adjust NPH and short/rapid-acting insulins separately
   **INITIATION:**
   - Total NPH dose = 80% of current NPH dose
   - 2/3 given before breakfast
   - 1/3 given before dinner
   - Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
   **TITRATION:**
   - Titrate each component of the regimen based on individualized needs

Consider twice daily premix insulin regimen
   **INITIATION:**
   - Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
   **TITRATION:**
   - Titrate based on individualized needs
Insulin Dose Titration Algorithms

**Insulin Glargine and Once-, Twice-, and Thrice-daily Insulin Lispro**

- **Once-daily Glargine**
  - Up to Thrice-daily Insulin Lispro

**Fasting Blood Glucose (mmol/L) (mg/dL)**

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>Dose Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.5 (&lt;80)</td>
<td>2 units</td>
</tr>
<tr>
<td>&lt;2.8 (&lt;50)</td>
<td>4 units</td>
</tr>
<tr>
<td>4.5 - 6.0 (80 - 109)</td>
<td>No change</td>
</tr>
<tr>
<td>2.8 - 4.4 (50 - 79)</td>
<td>-2 units</td>
</tr>
<tr>
<td>6.1 - 6.6 (110 - 120)</td>
<td>+2 units</td>
</tr>
<tr>
<td>6.7 - 7.7 (121 - 140)</td>
<td>+4 units</td>
</tr>
<tr>
<td>7.8 - 8.8 (141 - 160)</td>
<td>+6 units</td>
</tr>
<tr>
<td>≥7.8 (≥140)</td>
<td>+4 units</td>
</tr>
<tr>
<td>≥8.9 (≥161)</td>
<td>+8 units</td>
</tr>
</tbody>
</table>


- Therapy was initiated with one 10-U injection of insulin glargine administered at bedtime.
- Insulin lispro injections were added one at a time in order to target the higher blood glucose values first.
- Additional prandial injections of insulin lispro were added to the patient's regimen as needed, of approximately 10% of the total daily units of insulin glargine administered.
- Patients taking a sulphonylurea discontinued prior to adding an insulin lispro injection.