How and when to start Insulin: Patient Centered Approach

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Lecturer, Harvard Medical School, Boston
Exogenous Insulin Therapy: Why the need?

β-cell mass is reduced in patients with Type 2 Diabetes due to increased apoptosis.

Healthy individual with normal beta-cell mass

Beta-cell mass in Type 2 Diabetic patient
Exogenous Insulin Therapy:

Insulin Replacement Therapy Becomes Necessary Because of Progressive Nature of Disease

Adapted from Bergenstal et al. Endocrinology 2001;821–35
QUESTION 1

• With a patient above target (A1c >8%) on 3 oral antidiabetic agents, how long do physicians wait for to start insulin?
  • A- >2 year
  • B- >4 years
  • C- >6 years
  • D- >10 years
  • E- No idea whatsoever
There is often a delay in the insulin initiation:

Patients with HbA$_{1c}$ ≥8.0%

- Mean HbA$_{1c}$ at Intensification
  - 8.7%: One OAD > 1.6 years
  - 9.1%: Two OADs > 6.9 years
  - 9.7%: Three OADs > 6.0 years

Time to Initiation of Next Level Therapy (years)

Data are in patients taking one oral therapy at baseline with HbA$_{1c}$ above the American Diabetes Association/European Association for the Study of Diabetes goal of 7%. OAD = oral antidiabetes drug.

Clinical inertia: patient and physician barriers

- Lack of appropriate education
- Excess weight gain
- Complex regimens
- Risks in patients with comorbidities
- Resource issues

Barriers

- Patient perceptions of insulin treatment and outcomes
- Beliefs about patient competence
- hypoglycemia
- Impaired quality of life
- Lack of patient adherence to treatment
- Financial restrictions

Patients not treated with insulin

Physicians and patient barriers to insulin initiation

Percentage

<table>
<thead>
<tr>
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<tr>
<td>Insulin makes one fat</td>
<td>20%</td>
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<tr>
<td>Fear of hypoglycemia</td>
<td>80%</td>
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<tr>
<td>Pain from injection</td>
<td>50%</td>
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<td>Pain from blood tests</td>
<td>70%</td>
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</table>

$p<0.001$

$p=0.01$

Patient and physician barriers to insulin initiation

Percentage

Patients not treated with insulin
Physicians

- Insulin makes one fat
- Fear of hypoglycemia
- Pain from injection
- Pain from blood tests

Treatment of type 2 diabetes: IDF guidelines

Lifestyle measures

Then, at each step, if not to target (generally HbA$_1c$ $<$ 7.0%)

Consider first line

Metformin

Consider second line

Sulphonylurea

Consider third line

Basal insulin or premix insulin

or

α-glucosidase or DPP-4i or TZD

Consider fourth line

Basal + mealtime insulin

or

Basal or premix (later basal+mealtime)

Sulphonylurea or α-glucosidase

or

α-gluc or DPP-4i or TZD

or

GLP-1 agonist

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; IDF, International Diabetes Federation; TZD, thiazolidinedione

## Initiation and intensification in T2D: summary of international guidelines

<table>
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<tr>
<th>Guideline</th>
<th>Initiation</th>
<th>Intensification</th>
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<td>• Basal</td>
<td>• Add GLP-1RA</td>
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<td></td>
<td></td>
<td>• Basal-plus then basal-bolus</td>
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<tr>
<td></td>
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<td>• Premix BID then basal-bolus</td>
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<td>IDF²</td>
<td>• Basal OD</td>
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<td>• Premix OD/BID</td>
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<td>Diabetes Australia³</td>
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<td>• Premix BID or TID</td>
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<td>• Basal insulin + prandial</td>
<td>• Basal-bolus or premix</td>
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<td></td>
<td>• Premixed insulin</td>
<td>• Add GLP-1RA or SGLT-2i</td>
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<tr>
<td>AACE⁶</td>
<td>• Basal</td>
<td>• Add GLP-1RA or prandial insulin</td>
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<tr>
<td></td>
<td></td>
<td>• (premix among other options)</td>
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**Notes:**

Start with Monotherapy unless:

- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic. Consider Combination Injectable Therapy (see Figure 8.2).

### Monotherapy

**Metformin**

- **Efficacy**: High
- **Hypoglycemic Risk**: Low risk
- **Weight**: Neutral/loss
- **Side Effects**: GI/nausea/acidosis
- **Costs**: Low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors).

### Dual Therapy

**Metformin +**

<table>
<thead>
<tr>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>SGLT2 Inhibitor</th>
<th>GLP-1 Receptor Agonist</th>
<th>Insulin (basal)</th>
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<td>Intermediate</td>
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<td>GU, dehydration, fxs</td>
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<tr>
<td>Low</td>
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<td>High</td>
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</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors).

### Triple Therapy

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<th>SGLT2 Inhibitor +</th>
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<th>Insulin (basal) +</th>
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<td>SGLT2-I</td>
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</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
Changes in the current ADA Guidelines:

Switching between intensified regimens when treatment goals are not met

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Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

- **Start:** 10 U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 units once or twice weekly to reach FBG target
- **For hypo:** Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

If A1C not controlled, consider combination injectable therapy

---

**Add 1 rapid-acting insulin injection before largest meal**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by some amount
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to basal-bolus

---

**Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus‘)**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by some amount
- **Adjust:** ↑ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, consider changing to alternative insulin regimen

---

**Add GLP-1 RA**

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, consider changing to alternative insulin regimen

---

**Change to premixed insulin twice daily (before breakfast and supper)**

- **Start:** Divide current basal dose into ½ AM, ½ PM or ⅛ AM, ⅛ PM
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to 3rd injection

---

**Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)**

- **Start:** Add additional injection before lunch
- **Adjust:** ↑ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

---

Inclusion of premix TID as an intensification option

Adapted with permission from Inzucchi et al.
Type 2 diabetes treatment efficacy: insulin is very effective

- DPP-4i
- Glinides
- AGI
- GLP-1 RA
- TZDs
- SUs
- Insulin
- Metformin
- Lifestyle

Range of HbA₁c reduction as a monotherapy

- Adapted to include sitagliptin and saxagliptin; adapted to include exenatide and liraglutide
- AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SU, sulphonylurea; TZD, thiazolidinedione

Campbell et al. J Fam Practice 2010;59:S5–9
What are Insulin Analogs?
Molecular Structures

Normal Human Insulin

Insulin Analog Structures
Types of Insulin Analogs:
Rapid Acting
Long Acting
Pre-mixed
<table>
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<tr>
<th>Analogue</th>
<th>Modification</th>
<th>Mechanism</th>
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<tr>
<td><strong>RAPID ACTING</strong></td>
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<tr>
<td>Lispro (Humalog®)</td>
<td>Pro&lt;sup&gt;B28&lt;/sup&gt;→Lys</td>
<td>IGF-I-related motif impairs dimerization</td>
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<tr>
<td>Eli Lilly and Co</td>
<td>Lys&lt;sup&gt;B29&lt;/sup&gt;→Pro</td>
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<tr>
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<td>Pro&lt;sup&gt;B28&lt;/sup&gt;→Asp</td>
<td>Charge repulsion at dimer interface</td>
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<td>Glulisine (Apidra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Asn&lt;sup&gt;B3&lt;/sup&gt;→Lys</td>
<td>Decreased zinc-free self-association</td>
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<tr>
<td>Sanofi-Aventis</td>
<td>Lys&lt;sup&gt;B29&lt;/sup&gt;→Glu</td>
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<tr>
<td><strong>BASAL</strong></td>
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<tr>
<td>Glargine (Lantus&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Arg&lt;sup&gt;B31&lt;/sup&gt;-Arg&lt;sup&gt;B32&lt;/sup&gt; tag</td>
<td>Shift in pI to pH 7 leads to isoelectric precipitation on injection</td>
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<td>Sanofi-Aventis</td>
<td>Asp&lt;sup&gt;A21&lt;/sup&gt;→Gly</td>
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<tr>
<td>Detemir (Levemir&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Modification of Lys&lt;sup&gt;B29&lt;/sup&gt; by a tethered fatty acid</td>
<td>Stabilization of hexamer and binding to serum albumin</td>
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<tr>
<td>Novo-Nordisk</td>
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</table>

*Panel A describes rapid-acting analogues employed in prandial regimens and in insulin pumps whereas B lists basal insulin analogues with protracted action. Table is reprinted from Berenson et al. with permission of the authors.*

Pharmacological Insulins

Physiologic Blood Insulin Secretion Profile

- **Rapid acting:** Insulin lispro, aspart or glulisine
- **Short acting:** Regular Insulin
- **Intermediate acting:** NPH
- **Long acting:** Insulin detemir, Insulin glargine

Adapted from Noite (2003)

Rapid Acting Insulin Analogs

Current basal analogs: less hypoglycemia but still room for improvement

Most of the time I feel fine, but sometimes my blood glucose values are all over the place without any apparent reason.

Intra-patient daily profiles

Intra-patient variability

- Insulin glargine
- Insulin detemir

Insulin degludec: rationally designed, beyond sequence modification

Des(B30) LysB29(γ-Glu Nε-hexadecandioyl) human insulin

A1

GV EQ CTS IC SL YQ L E N Y C N

B1

F V N Q H L C G S H L V E A L Y L V C G E R G F F Y T P K T

DesB30 insulin

L-γ-Glu

Glutamic acid ‘spacer’

Hexadecandioyl

Fatty diacid ‘side chain’
Insulin degludec: immediately after injection

Insulin degludec injected

[● Phenol; ○ Zn$^{2+}$]

Phenol from the vehicle diffuses quickly, and insulin degludec links up via single side-chain contacts

Long multihexamer chains assemble

Insulin degludec: slow release following injection

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers. Monomers are absorbed from the depot into the circulation.

Half-life of insulin degludec is twice as long as that of insulin glargine

<table>
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<tr>
<th>Insulin type</th>
<th>Insulin degludec</th>
<th>Insulin glargine</th>
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<tbody>
<tr>
<td>Dose</td>
<td>0.4 U/kg</td>
<td>0.4 U/kg</td>
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<tr>
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<td>0.6 U/kg</td>
<td>0.6 U/kg</td>
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<tr>
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<td>0.8 U/kg</td>
<td>0.8 U/kg</td>
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<tr>
<td>Half-life (hours)</td>
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<td>11.5</td>
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<td>27.0</td>
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<td>23.6</td>
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</tr>
<tr>
<td>Mean half-life</td>
<td>25.4</td>
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</tr>
</tbody>
</table>

*Insulin glargine was undetectable after 48 hours

Results from 66 patients with type 1 diabetes (T1D)
IDeg, insulin degludec; IGlar, insulin glargine
Insulin Glargine U300

PK/PD values at steady state in patients with T1D

Gla-300 = glargine U300. Gla-100 = glargine U100.
Basaglar

Biosimilar medications are "highly similar" to an already FDA-approved biological product.

The FDA determined that Basaglar was sufficiently similar to Glargine to justify approval based on the safety and effectiveness of Glargine as well as certain Basaglar-specific data.

Basaglar was approved in Europe as a biosimilar last year. The FDA is calling the product a "follow-on" biologic rather than a biosimilar.
Pre-mixed insulins
QUESTION 2

• In a pre-mixed insulin such as the BiAsp 30

  • A- 30% is short acting and 70% is long acting
  • B- 30% is long acting and 70% is short acting
  • C- Not sure
The dual-release insulin concept: Pre-mixed insulins

Physiological insulin profile:
Basal component
Meal-related peaks

Insulin analogues together with a basal insulin provide physiological insulin

Analogue mix insulins such as BIAsp 30 replace both meal-related and basal insulin

Garber et al. Diabetes Obes Metab 2007;9:630–9
How is BIAsp 30 different from BHI 30?

**BIAsp 30**
A premixed suspension of:

- Soluble insulin aspart
- Protamine-crystallised insulin aspart

**BHI 30**
A premixed suspension of:

- Regular human insulin
- NPH insulin

BIAsp, biphasic insulin aspart; BHI, biphasic human insulin; NPH, neutral protamine Hagedorn

Twice-daily BIAsp 30 in patients with type 2 diabetes: improved PPG control

* $p<0.05$ in favour of BIAsp 30 for lower PPG levels after dinner and breakfast; $n=13$
PPG, postprandial plasma glucose

Adapted from McSorley et al. Clin Ther 2002;24:53K
Pharmacological profile

Compared with BHI, BIASp 30 has:

- Faster absorption
- Higher peak concentration
- More rapid and pronounced glucose lowering effect
- Similar duration of action of basal component

Initiation and Intensification Strategies in Type 2 Diabetes Management: A Comparison of Basal Plus (basal plus one injection of rapid analog) and Premix Regimens
Insulin optimisation and intensification should follow disease progression

<table>
<thead>
<tr>
<th>Beta-cell function (%)</th>
<th>Lifestyle + OADs</th>
<th>Basal insulin + OADs</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Initiate</td>
<td>Optimise</td>
</tr>
</tbody>
</table>

- **Titrate dose to reach/maintain glycemic targets**
- **Basal and 1–4 bolus or premix**
- **Intensify for mealtime insulin coverage**

Treatment optimisation and intensification

OAD, oral antidiabetic drug

Schematic diagram adapted from Kahn. *Diabetologia* 2003;46:3–19
ADA Guidelines
2017:

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

- Start: 10 U/day or 0.1-0.2 U/kg/day
- Adjust: 10-15% or 2-4 units once or twice weekly to reach FBG target
- For hypo: Determine & address cause; if no clear reason for hypo, dose by 4 units or 10-20%

If A1C not controlled, consider combination injectable therapy

Add 1 rapid-acting insulin injection before largest meal

- Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider basal by same amount
- Adjust: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to basal-bolus

Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus’)

- Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider basal by same amount
- Adjust: ↑ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

Change to premixed insulin twice daily (before breakfast and supper)

- Start: Divide current basal dose into 1/3 AM, ½ PM or ½ AM, ½ PM
- Adjust: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If A1C not controlled, advance to 3rd injection

Add GLP-1 RA

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen
- If goals not met, consider changing to alternative insulin regimen

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

- Start: Add additional injection before lunch
- Adjust: ↑ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

Adapted with permission from Inzucchi et al.
Insulin Initiation and Intensification Strategies

• Starting insulin regimens and their stepwise intensification have been suggested by international guidelines and the regimens outlined in these guidelines are the premixed, basal, basal-plus and basal–bolus regimens.

• **Stepwise insulin intensification** using basal to basal-plus or a QD or BID premixed insulin regimen are simplified potential alternatives to full basal–bolus or TID premixed regimens.

• A review of the available evidence comparing basal plus and premix regimens would facilitate a better understanding of the similarities and differences between both regimens which may aid in clinical decision making.
## Key findings from RCTs

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<th>Overall hypoglycemia</th>
<th>Insulin dose</th>
<th>Weight</th>
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<tr>
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<td>BIAsp 30/LM 25 OD/BID vs. IGlar OD ± IGlu OD</td>
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<td>⬆️</td>
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<table>
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<td>LM 25 BID vs. IGlar OD + insulin lispro OD</td>
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<td>Jin et al. 2015</td>
<td>BIAsp 30 BID vs. IGlar OD + IGlu OD/BID</td>
<td>⬆️</td>
<td>⬇️</td>
<td>⬆️</td>
</tr>
<tr>
<td>Vora et al. 2015 (LanScape)</td>
<td>BIAsp 30 BID vs. IGlar OD + IGlu OD</td>
<td>⬆️</td>
<td>⬆️</td>
<td>⬆️</td>
</tr>
</tbody>
</table>

BIAsp, biphasic insulin aspart; BID, twice daily; IGlar, insulin glargine U 100; IGlu, insulin glulisine; LM, lispro mix; OD, once daily; RCT, randomised controlled trial; TID, three-times daily.

Key findings from RCTs

RCT findings

No clinically relevant differences in terms of:

- Glycemic control
- Risk of overall hypoglycemia
- Insulin dose
- Weight gain

Practical aspects during intensification

<table>
<thead>
<tr>
<th></th>
<th>Premix</th>
<th>Basal-plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of injections</td>
<td>2</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Number of devices</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SMBG</td>
<td>2</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Regimen complexity</td>
<td>Simple</td>
<td>Slightly more complex</td>
</tr>
</tbody>
</table>

RCT, randomised controlled trial; SMBG, self-monitored blood glucose
Key findings from RCTs

• Both basal plus and premix regimens have comparable efficacy and safety in both insulin initiation and intensification contexts with similarities between both regimens being greater than their differences

• A patient-centered approach considering various practical and clinical factors becomes of heightened importance in clinical decision-making

Individualize the treatment algorithm for your patients

Initiation with premix and basal insulin: A meta analysis
ADA Guidelines 2017:

**Initiate Basal Insulin**
Usually with metformin +/− other noninsulin agent

- **Start:** 10 U/day or 0.1–0.2 U/kg/day
- **Adjust:** 10–15% or 2–4 units once or twice weekly to reach FBG target
- **For hypo:** Determine & address cause; if no clear reason for hypo, ♣ dose by 4 units or 10–20%

**Add 1 rapid-acting Insulin injection before largest meal**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ♣ basal by same amount
- **Adjust:** ♣ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ♣ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, advance to basal-bolus

**Add GLP-1 RA**

- **If not tolerated or A1C target not reached, change to 2 injection insulin regimen**
- **If goals not met, consider changing to alternative insulin regimen**

**Change to premixed insulin twice daily (before breakfast and supper)**

- **Start:** Divide current basal dose into ½ AM, ½ PM or ¼ AM, ⅛ PM
- **Adjust:** ♣ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ♣ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, advance to 3rd injection

**Add ≥2 rapid-acting Insulin injections before meals (‘basal-bolus’)**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ♣ basal by same amount
- **Adjust:** ♣ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ♣ corresponding dose by 2–4 units or 10–20%

If goals not met, consider changing to alternative insulin regimen

**Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)**

- **Start:** Add additional injection before lunch
- **Adjust:** ♣ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ♣ corresponding dose by 2–4 units or 10–20%

Adapted with permission from Inzucchi et al.
BIAsp 30 reduced HbA1c significantly compared with insulin glargine in type 2 diabetes

- Three studies demonstrated that patients treated with BIAsp 30 had a greater decrease in the HbA1c level when compared with glargine

**Outcome** | ∆HbA1c level [%] | BIAsp 30  | IGlar | WMD [95% CI] random effects model | Weight % | WMD [95% CI] random effects model
--- | --- | --- | --- | --- | --- | ---
Study or sub-category | N | Mean | SD | N | Mean | SD | random effects model | random effects model
Strojeck 2009 | 225 | x | x | 232 | x | x | 28.13 | −0.16 [−0.30;−0.02]
Yang 2012 | x | x | x | x | x | 28.74 | −0.12 [−0.25;0.02]
Subtotal (BIAsp 30 OD) | Q=0.16, df=1 (p=0.687) I²=0%
Kann 2006 | 128 | x | x | 127 | x | x | 13.58 | −0.50 [−0.80;−0.02]
Lightelm 2011 | 132 | −1.30 | x | 127 | −1.20 | x | 16.26 | −0.06 [−0.32;0.20]
Raskin 2005 | 117 | −2.79 | 1.19 | 116 | −2.36 | 1.18 | 13.29 | −0.43 [−0.73;−0.13]
Subtotal (BIAsp 30 BID) | Q=5.68, df=2 (p=0.058) I²=65%
Total | | | | | | | 100.00 | −0.21 [−0.35;−0.08]

Test for heterogeneity; Q=8.61, df=4 (p=0.0717) I²=53.53%
Test overall effect; Z=−3.09 (p=0.0020)

BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; IGlar, insulin glargine; OD, once daily; SD, standard deviation; WMD, weighted mean difference

No observed difference in FPG with BIASp 30 compared with insulin glargine

• Two out of three studies demonstrated no difference between treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FPG [mg/dL]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIASp 30</td>
</tr>
<tr>
<td>Study or sub-category</td>
<td>N</td>
</tr>
<tr>
<td>Kann 2006</td>
<td>128</td>
</tr>
<tr>
<td>Lightelm 2011</td>
<td>132</td>
</tr>
<tr>
<td>Raskin 2005</td>
<td>117</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity; Q=13.50, df=2 (p=0.0012) I²=85.19%
Test overall effect; Z=0.61 (p=0.5429)
BIAsp 30 significantly reduced PPG increments compared with insulin glargine

- In two out of three studies, superiority of BIAsp 30 over glargine was demonstrated and, in the remaining one, no significant difference between the groups was observed.

**Outcome**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>PPG increment [mg/dL]</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>WMD [95% CI]</th>
<th>Weight %</th>
<th>WMD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td>random effects model</td>
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<td>random effects model</td>
</tr>
<tr>
<td>BIAsp 30</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>128</td>
<td>127</td>
<td>25.20</td>
<td>25.20</td>
<td>39.60</td>
<td>32.40</td>
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<td>57.17</td>
<td>-14.40 [-21.53; -7.27]</td>
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<tr>
<td>Lightelm 2011</td>
<td>132</td>
<td>127</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>26.58</td>
<td>-17.76 [-28.20; -7.29]</td>
</tr>
<tr>
<td>Raskin 2005</td>
<td>117</td>
<td>116</td>
<td>32.47</td>
<td>51.04</td>
<td>43.20</td>
<td>32.40</td>
<td></td>
<td>16.25</td>
<td>-10.73 [-24.10; 2.64]</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>-14.70 [-20.09; -9.31]</td>
</tr>
</tbody>
</table>

Test for heterogeneity; Q=0.67, df=2 (p=0.0737) I²=0.00%
Test overall effect; Z=−5.34 (p<0.00010)
Comparison of BIAsp 30 with insulin glargine

<table>
<thead>
<tr>
<th></th>
<th>Number of trials</th>
<th>Sample size</th>
<th>Estimate</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (kg)</td>
<td>3</td>
<td>747</td>
<td>WMD: -1.16 (-0.41; 2.74)</td>
<td>(p=0.043) (I^2=68)%</td>
</tr>
<tr>
<td>hypoglycemia*</td>
<td>2</td>
<td>748</td>
<td>63% vs. 51% OR: 1.77 (0.91; 3.44)</td>
<td>(p=0.032) (I^2=78)%</td>
</tr>
<tr>
<td>Severe hypoglycemia*</td>
<td>4</td>
<td>1236</td>
<td>0.98% vs. 1.12% OR: 0.88 (0.31; 2.53)</td>
<td>(p=0.841) (I^2=0)%</td>
</tr>
</tbody>
</table>

No evidence for higher risk of overall and severe hypoglycemic episodes with BIAsp 30 compared with IGlar

Twice-daily administration of BIAsp 30 resulted in larger weight gain

*Patients with at least one episode
BIAsp 30, biphasic insulin aspart 30; OR, odds ratio; WMD, weighted mean difference
Overall conclusions:

• Early glycemic control reduces complications: conversely, poor glycemic control is an important driver for diabetes complications
• Insulin is most effective glucose lowering agent having multiple positive effect beyond glycemic control
• Premix insulin can:
  • Help improve glycemic control while maintaining tolerability and safety
  • Address postmeal glucose excursions, which might have a beneficial effect on CV risk
• Premix insulin leads to better glycemic control than basal insulin when used as initial insulin therapy
• Switching from Biphasic Human Insulin to Premix analog insulin results in the better glycemic control and improved quality of life
Hypoglycemia
Hypoglycemia is a problem with diabetes therapy

95% of all endocrine emergency hospitalizations in people >65 years are caused by Hypoglycemia

Data given are number and percentage of annual national estimates of hospitalisations. Data from the NEISS-CADES project.
ER visits n=265,802/Total cases n=12,666. ER, emergency room
HEADACHE
RINGING IN THE EARS
TREMBLING
IRRITABILITY
SWEATINESS
BLURRY VISION
INCREASE HEART RATE
HUNGER
FEELING ANXIOUS
WEAKNESS OR TIREDNESS
Potential Complications and Effects of Severe Hypoglycemia

Plasma glucose level

Arrhythmia
- Abnormal prolonged cardiac repolarization — ↑ QTc and QT dispersion
- Sudden death

Neuroglycopenia
- Cognitive impairment
- Unusual behavior
- Seizure
- Coma
- Brain death

Management of Hypoglycemia

- Patients with asymptomatic or symptomatic hypoglycemia should ingest carbohydrates. 15 to 20 grams of oral glucose is typically sufficient. Glucose may be ingested in the form of tablets, juice, milk, other snacks, or a meal.
- For the treatment of hypoglycemia in a person with impaired consciousness and no established intravenous (IV) access, administer glucagon, The usual dose is 0.5 to 1.0 mg given SC or IM. Education and training for clinicians, friends, and family on the recognition and treatment of severe hypoglycemia, including the use of glucagon kits, is necessary.
- IV dextrose (25 g of 50% glucose [dextrose]) can be administered to treat hypoglycemia in patients with impaired consciousness and established IV access (typically in a hospital).
- A subsequent glucose infusion (or food, if patient is able to eat) is often needed, depending upon the cause of the hypoglycemia, to prevent recurrence of symptoms.
Severe events often require hospitalisation and inpatient care

Percentage of severe events requiring hospital services

- Ambulance: 91%
- Accident and Emergency: 63%
- Inpatient admission: 21%

Based on 8,655 patients with diabetes experiencing 244 events

QUESTION 3

• In a patient with a bedtime blood glucose of 120mg/dl and a fasting reading the next day of 200mg/dl, the possible cause can be:

  • A- Inadequate insulin
  • B- Dawn phenomenon
  • C- Somogyi effect
  • D- Any of the above
  • E- I have no clue
Dawn Phenomenon and Somogyi Effect

- Lack of available insulin
- Dawn phenomenon
- Somogyi’s or rebound effect

Blood Glucose (mg/dl)

Counterregulation activated
Dawn Phenomenon and Somogyi Effect

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>BLOOD GLUCOSE LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime</td>
<td>3-4AM</td>
</tr>
<tr>
<td>Inadequate Insulin</td>
<td>120</td>
</tr>
<tr>
<td>Dawn Phenomenon</td>
<td>120</td>
</tr>
<tr>
<td>Somogyi Effect</td>
<td>120</td>
</tr>
</tbody>
</table>
Thank you for your kind attention