How and when to start Insulin: Patient Centered Approach

M. Hamed Farooqi, MD FRCP FACP FACE
Consultant Endocrinologist and Director, Dubai Diabetes Center, DHA
Lecturer, Harvard Medical School, Boston
Healthy individual with normal beta-cell mass

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

Exogenous Insulin Therapy: Why the need?
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
- Patient perceptions of insulin treatment and outcomes
- Beliefs about patient competence
- Impaired quality of life
- Lack of patient adherence to treatment
- Financial restrictions
- hypoglycemia

Patient and physician barriers to insulin initiation

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

Patient and physician barriers to insulin initiation

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

Treatment of type 2 diabetes: IDF guidelines

- **Lifestyle measures**
  - Consider first line
    - Metformin
  - Consider second line
    - Sulphonylurea
  - Consider third line
    - Basal insulin or premix insulin
  - Consider fourth line
    - Basal + mealtime insulin

- **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
  - Consider fourth line
    - Basal + mealtime insulin

- **Usual approach**
  - Sulphonylurea or α-glucosidase
  - or α-gluc or DPP-4i or TZD
  - or GLP-1 agonist

- **Alternative approach**

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>
<thead>
<tr>
<th>Guideline</th>
<th>Initiation</th>
<th>Intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA/EASD 2015 position statement update¹</td>
<td>• Basal</td>
<td>• Add GLP-1RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Basal-plus then basal-bolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Premix BID then basal-bolus</td>
</tr>
<tr>
<td>IDF²</td>
<td>• Basal OD</td>
<td>• Basal-plus or basal-bolus</td>
</tr>
<tr>
<td></td>
<td>• Premix OD/BID</td>
<td></td>
</tr>
<tr>
<td>Diabetes Australia³</td>
<td>• Basal OD</td>
<td>• Basal-plus or basal-bolus</td>
</tr>
<tr>
<td></td>
<td>• Premix OD</td>
<td>• Premix BID or TID</td>
</tr>
<tr>
<td>Canadian Diabetes Association⁴</td>
<td>• Basal OD</td>
<td>• Basal-plus or basal-bolus</td>
</tr>
<tr>
<td></td>
<td>• Premix OD/BID</td>
<td>• Premix BID</td>
</tr>
<tr>
<td>NICE⁵</td>
<td>• Basal insulin OD or BID</td>
<td>• Basal-plus</td>
</tr>
<tr>
<td></td>
<td>• Basal insulin + prandial</td>
<td>• Basal-bolus or premix</td>
</tr>
<tr>
<td></td>
<td>• Premixed insulin</td>
<td>• Add GLP-1RA or SGLT-2i</td>
</tr>
<tr>
<td>AACE⁶</td>
<td>• Basal</td>
<td>• Add GLP-1RA or prandial insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• (premix among other options)</td>
</tr>
</tbody>
</table>

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BID, twice daily; EASD, European Association for the Study of Diabetes; GLP-1RA, glucagon-like peptide 1 receptor agonist; IDF, International Diabetes Federation; NICE, UK National Institute for Health and Care Excellence; OD, once daily; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; TID, three times daily; T2D, type 2 diabetes

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

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>low risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>neutral/loss</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>GI/abdominal pain</td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>moderate risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>gain/neutral/loss</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>hypoglycemia/edema, HF, fxs</td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
</tr>
</tbody>
</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

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
</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 (e.g., adding a fourth antihyperglycemic agent).
Inclusion of premix TID as an intensification option

Switching between intensified regimens when treatment goals are not met

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

Range of HbA$_{1c}$ reduction as a monotherapy

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

Range: 0-4

- Adaptable to include sitagliptin and saxagliptin; adapted to include exenatide and liraglutideAGI, 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>
<thead>
<tr>
<th>Analogue</th>
<th>Modification</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAPID ACTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog®)</td>
<td>Pro^{B28}→Lys</td>
<td>IGF-I-related motif impairs</td>
</tr>
<tr>
<td>Eli Lilly and Co</td>
<td>Lys^{B29}→Pro</td>
<td>dimerization</td>
</tr>
<tr>
<td>Aspart (NovoLog®)</td>
<td>Pro^{B28}→Asp</td>
<td>Charge repulsion at dimer interface</td>
</tr>
<tr>
<td>Novo-Nordisk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glulisine (Apidra®)</td>
<td>Asn^{B3}→Lys</td>
<td>Decreased zinc-free self-association</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>Lys^{B29}→Glu</td>
<td></td>
</tr>
<tr>
<td><strong>BASAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus®)</td>
<td>Arg^{B31}-Arg^{B32} tag</td>
<td>Shift in pI to pH 7 leads to isolectric precipitation on injection</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>Asp^{A21}→Gly</td>
<td></td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
<td>Modification of Lys^{B29} by a tethered fatty acid</td>
<td>Stabilization of hexamer and binding to serum albumin</td>
</tr>
<tr>
<td>Novo-Nordisk</td>
<td></td>
<td></td>
</tr>
</tbody>
</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.\(^6\)
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 Noile (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

Insulin degludec: rationally designed, beyond sequence modification

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

DesB30 insulin

Hexadecandioyl

L-γ-Glu

Glutamic acid ‘spacer’

Fatty diacid ‘side chain’

Sequence: GIVEQCTCSICSLEYQLENVCN

A1

Sequence: FVNHHLCSHLVEALYLVCGERGFYTPKT

B1

DesB30 insulin

Hexadecandioyl

Fatty diacid ‘side chain’

L-γ-Glu

Glutamic acid ‘spacer’

Sequence: GIVEQCTCSICSLEYQLENVCN

A1

Sequence: FVNHHLCSHLVEALYLVCGERGFYTPKT

B1
Insulin degludec: immediately after injection

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

Long multihexamer chains assemble

[● Phenol; ○ Zn$^{2+}$]

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

Insulin type

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Insulin degludec</th>
<th>Insulin glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>0.4 U/kg</td>
<td>0.4 U/kg</td>
</tr>
<tr>
<td></td>
<td>0.6 U/kg</td>
<td>0.6 U/kg</td>
</tr>
<tr>
<td></td>
<td>0.8 U/kg</td>
<td>0.8 U/kg</td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>25.9</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>27.0</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>23.6</td>
<td>11.9</td>
</tr>
<tr>
<td><strong>Mean half-life</strong></td>
<td>25.4</td>
<td>12.1</td>
</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?

<table>
<thead>
<tr>
<th></th>
<th>BIASp 30</th>
<th>BHI 30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIAsp 30</strong></td>
<td>A premixed suspension of:</td>
<td>A premixed suspension of:</td>
</tr>
<tr>
<td>Soluble insulin aspart</td>
<td><img src="image" alt="30%" /></td>
<td><img src="image" alt="30%" /></td>
</tr>
<tr>
<td>Protamine-crystallised insulin aspart</td>
<td><img src="image" alt="70%" /></td>
<td><img src="image" alt="70%" /></td>
</tr>
</tbody>
</table>

**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
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

Beta-cell function (%)

Lifestyle + OADs

Basal insulin + OADs

Initiate

Optimise

Intensify

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
Adapted with permission from Inzucchi et al.

**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%

**Add GLP-1 RA**

- **If not tolerated or A1C target not reached, change to 2 Injection 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, ¾ 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 A1C not controlled, 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

<table>
<thead>
<tr>
<th>Studies in insulin-naïve patients</th>
<th>HbA₁c</th>
<th>Overall hypoglycemia</th>
<th>Insulin dose</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aschner et al. 2015 (GALAPAGOS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIAsp 30/LM 25 OD/BID vs. IGlar OD ± IGlu OD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riddle et al. 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIAsp 30 BID vs. IGlar OD ± IGlu OD vs. IGlar OD + IGlu ≤TID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies in patients previously receiving basal insulin</th>
<th>HbA₁c</th>
<th>Overall hypoglycemia</th>
<th>Insulin dose</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinahones et al. 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM 25 BID vs. IGlar OD + insulin lispro OD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jin et al. 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIAsp 30 BID vs. IGlar OD + IGlu OD/BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vora et al. 2015 (LanScape)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIAsp 30 BID vs. IGlar OD + IGlu OD</td>
<td></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.

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%

**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 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, ¾ 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%

---

**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

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>BIAsp 30 N</th>
<th>Mean</th>
<th>SD</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strojeck 2009</td>
<td>225</td>
<td></td>
<td></td>
<td>232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang 2012</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (BIAsp 30 OD)</td>
<td>Q=0.16, df=1 (p=0.687) I²=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kann 2006</td>
<td>128</td>
<td></td>
<td></td>
<td>127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightelm 2011</td>
<td>132</td>
<td>−1.30</td>
<td></td>
<td>127</td>
<td>−1.20</td>
<td></td>
</tr>
<tr>
<td>Raskin 2005</td>
<td>117</td>
<td>−2.79</td>
<td>1.19</td>
<td>116</td>
<td>−2.36</td>
<td>1.18</td>
</tr>
<tr>
<td>Subtotal (BIAsp 30 BID)</td>
<td>Q=5.68, df=2 (p=0.058) I²=65%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>483</td>
<td></td>
<td></td>
<td>482</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>Study or sub-category</th>
<th>BIAsp 30 N</th>
<th>Mean</th>
<th>SD</th>
<th>IGlar N</th>
<th>Mean</th>
<th>SD</th>
<th>WMD [95% CI] random effects model</th>
<th>Weight %</th>
<th>WMD [95% CI] random effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kann 2006</td>
<td>128</td>
<td>-46.80</td>
<td>48.88</td>
<td>127</td>
<td>-39.60</td>
<td>50.71</td>
<td></td>
<td>35.40</td>
<td>-7.20 [-19.43;5.03]</td>
</tr>
<tr>
<td>Lightelm 2011</td>
<td>132</td>
<td>x</td>
<td>x</td>
<td>127</td>
<td>x</td>
<td>x</td>
<td></td>
<td>33.59</td>
<td>28.70 [13.57;45.83]</td>
</tr>
<tr>
<td>Raskin 2005</td>
<td>117</td>
<td>-125.00</td>
<td>72.90</td>
<td>116</td>
<td>-125.00</td>
<td>74.40</td>
<td></td>
<td>31.02</td>
<td>0.00 [-18.92;18.92]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>356</td>
<td>117</td>
<td>116</td>
<td>127</td>
<td>116</td>
<td>116</td>
<td></td>
<td>100.00</td>
<td>7.09 [-15.75;29.94]</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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PPG increment [mg/dL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or sub-category</td>
<td>BIAsp 30</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; $Q = 0.67$, df = 2 (p = 0.0737) $I^2 = 0.00\%$
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>$p=0.043$ I²=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>$p=0.032$ I²=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>$p=0.841$ I²=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

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
WEAKNESS OR TIREDNESS
SWEATINESS
BLURRY VISION
INCREASE HEART RATE
HUNGER
FEELING ANXIOUS

http://www.qualityandsafety.va.gov/ChoosingWiselyHealthSafetyInitiative/Images/HYPOGLYCEMIA_RISK.png
Potential Complications and Effects of Severe Hypoglycemia

Plasma glucose level

Arrhythmia\(^1\)
- Abnormal prolonged cardiac repolarization — ↑ QTc and QT dispersion
- Sudden death

Neuroglycopenia\(^2\)
- 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
Dawn Phenomenon and Somogyi Effect

**CAUSE**

<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