Insulin vs GLP-1RA: The first injection?

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Bharti Hospital, Karnal
Haryana
• Who should get GLP1RA?
• Who should get insulin?
• Which insulin should be started?
Inzucchi SE, et al. Diabetes Care, 2015;38:140-149

ADA/EASD recommendations
Algorithm for Adding/Intensifying Insulin

**START BASAL** (Long-Acting Insulin)

- **A1C < 8%**
  - TDD 0.1–0.2 U/kg

- **A1C ≥ 8%**
  - TDD 0.2–0.3 U/kg

**Insulin titration every 2–3 days to reach glycemic goal:**
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 U
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

**Consider discontinuing or reducing sulfonylureas after starting basal insulin (basal analog preferred to NPH)**

**Glycemic Goal:**
- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

**INTENSIFY** (Prandial Control)

- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i

- **Add Prandial Insulin**
  - Basal Plus 1, Plus 2, Plus 3
  - Basal Bolus

**Begin prandial insulin before largest meal**
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 3 units

**Begin prandial insulin before each meal**
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

**Insulin titration every 2–3 days to reach glycemic goal:**
- Increase prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% – 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% – 40%

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Person centred flexibility

“DO NOT
match lifestyle to the insulin regimens.
RATHER,
match the regimen to the lifestyle”

Insulin advantages

- Targeted focus on FPG and/or PPG
- Dose titration addresses glycemic/diet variability
- Does not require preserved beta cell function
Early insulin treatment prolongs β-cell function; promotes metabolic control, reduces glucotoxicity.

*P < 0.01 year 0 vs. 1,
§ P < 0.005 year 0 vs. 2,
#P < 0.01 year 1 vs. 2

*P = 0.02 glibenclamide vs. insulin
§P < 0.05 year 1 day 1 vs. 2
P < 0.01 year 1 day 1 vs. year 2 day 2

Insulin also has extra-glycaemic benefits

- **Anti-inflammatory**
  - ↓ NF-κB, ↑ IκB, ↓ MCP-1
  - ↓ ICAM-1, ↓ CRP

- **Anti-oxidant**
  - ↓ Reactive oxygen species

- **Cardioprotective**

- **Neuroprotective**

- **Anti-apoptotic**

- **Mechanism of insulin’s benefit in acute illness**

- **Anti-thrombotic**
  - ↓ TF, ↓ PAI-1

- **Vasodilation and platelet inhibition**
  - ↑ NO release, ↑ cAMP
  - ↑ eNOS

- **Glucose lowering**

*Dandona et al. Am J Cardiol 2007;99(4A):15B–26B*
Long-term safety of insulin therapy is established

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Insulin Glargine (N=6264)</th>
<th>Standard Care (N=6273)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)  no./100 patient-yr</td>
<td>no. (%)  no./100 patient-yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First coprimary outcome</td>
<td>1041 (16.6)  2.94</td>
<td>1013 (16.1)  2.85</td>
<td>1.02 (0.94–1.11)</td>
<td>0.63</td>
</tr>
<tr>
<td>Second coprimary outcome</td>
<td>1792 (28.6)  5.52</td>
<td>1727 (27.5)  5.28</td>
<td>1.04 (0.97–1.11)</td>
<td>0.27</td>
</tr>
<tr>
<td>Microvascular outcomes</td>
<td>1323 (21.1)  3.87</td>
<td>1363 (21.7)  3.99</td>
<td>0.97 (0.90–1.05)</td>
<td>0.43</td>
</tr>
<tr>
<td>Total mortality</td>
<td>951 (15.2)  2.57</td>
<td>965 (15.4)  2.60</td>
<td>0.98 (0.90–1.08)</td>
<td>0.70</td>
</tr>
<tr>
<td>Total myocardial infarctions</td>
<td>336 (5.4) 0.93</td>
<td>326 (5.2) 0.90</td>
<td>1.02 (0.88–1.19)</td>
<td>0.75</td>
</tr>
<tr>
<td>Total strokes</td>
<td>331 (5.3) 0.91</td>
<td>319 (5.1) 0.88</td>
<td>1.03 (0.89–1.21)</td>
<td>0.69</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>580 (9.3) 1.57</td>
<td>576 (9.2) 1.55</td>
<td>1.00 (0.89–1.13)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>310 (4.9) 0.85</td>
<td>343 (5.5) 0.95</td>
<td>0.90 (0.77–1.05)</td>
<td>0.16</td>
</tr>
<tr>
<td>Revascularization</td>
<td>908 (14.5) 2.69</td>
<td>860 (13.7) 2.52</td>
<td>1.08 (0.96–1.16)</td>
<td>0.24</td>
</tr>
<tr>
<td>Angina</td>
<td>709 (11.3) 2.07</td>
<td>743 (11.8) 2.17</td>
<td>0.95 (0.85–1.05)</td>
<td>0.29</td>
</tr>
<tr>
<td>Unstable</td>
<td>238 (3.8) 0.66</td>
<td>261 (4.2) 0.72</td>
<td>0.91 (0.76–1.08)</td>
<td>0.28</td>
</tr>
<tr>
<td>New</td>
<td>100 (1.6) 0.27</td>
<td>138 (2.2) 0.38</td>
<td>0.72 (0.56–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Worsening</td>
<td>455 (7.3) 1.29</td>
<td>446 (7.1) 1.26</td>
<td>1.02 (0.89–1.16)</td>
<td>0.80</td>
</tr>
<tr>
<td>Limb or digit amputation</td>
<td>47 (0.8) 0.13</td>
<td>53 (0.8) 0.14</td>
<td>0.85 (0.60–1.11)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>2081 (33.2) 6.98</td>
<td>2071 (33.0) 6.91</td>
<td>1.00 (0.94–1.07)</td>
<td>0.90</td>
</tr>
<tr>
<td>Noncardiovascular hospitalization</td>
<td>2339 (37.3) 7.90</td>
<td>2349 (37.4) 7.93</td>
<td>0.99 (0.94–1.05)</td>
<td>0.85</td>
</tr>
<tr>
<td>Any cancer</td>
<td>476 (7.6) 1.32</td>
<td>477 (7.6) 1.32</td>
<td>1.00 (0.88–1.13)</td>
<td>0.97</td>
</tr>
<tr>
<td>Death from cancer</td>
<td>189 (3.0) 0.51</td>
<td>201 (3.2) 0.54</td>
<td>0.94 (0.77–1.15)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Use in special situations

• Insulin preferred in emergency and diabetic ketoacidosis

• Insulin preferred in renal impairment

• Insulin preferred in hepatic impairment

• Insulin Drug of choice for pregnancy
Hypoglycaemia???

- With the introduction of newer basal insulin analogues the risk of hypoglycaemia is minimal.

Insulin degludec

IDegAsp
Evolution of understanding

• From beta cell centric to multiple pathways
• From ominous octet to egregious eleven
GLP1 RA
The incretin hormones play a crucial role in a healthy insulin response

- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

Nauck et al. *Diabetologia* 1986;29:46–52, healthy volunteers (n=8)
The incretin effect is diminished in patients with type 2 diabetes

- *p<0.05, healthy volunteers (n=8)
- Nauck M et al. Diabetologia 1986;29:46–52
Glucagon levels are elevated in patients with type 2 diabetes


n: T2DM patients=54; Normal subjects=33
T2DM, type 2 diabetes mellitus

Effects of GLP-1

**Pancreas**
- Insulin secretion\(^2,3\) (glucose-dependent) and beta-cell sensitivity
- Insulin synthesis\(^4\)
- Glucagon secretion\(^3\) (glucose-dependent)

**Brain**
- Body weight\(^5-7\)
- Satiety
- Energy intake

**Cardiovascular system**
- Systolic blood pressure\(^8\)

**Liver**
- Hepatic glucose output\(^4\)
The GLP1RA action spectrum

- Appetite, Absorption
- Utilization - insulin and incretin vs glucagon fulcrum
- Body weight, lipid and blood pressure control
Incretins helps in achieving target without hypo and weight gain

HbA1c <7.0%, no weight gain, no hypos

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients reaching composite endpoint (%)</th>
<th>Odds-ratio of achieving composite endpoint with liraglutide 1.8 mg is superior, with *p&lt;0.01; **p&lt;0.001, ***p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 1.8 mg</td>
<td>40</td>
<td>*p&lt;0.01; **p&lt;0.001; ***p&lt;0.0001</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg</td>
<td>32</td>
<td>**p&lt;0.001; ***p&lt;0.0001</td>
</tr>
<tr>
<td>Exenatide (n=231)</td>
<td>25</td>
<td>**p&lt;0.001; ***p&lt;0.0001</td>
</tr>
<tr>
<td>Sitagliptin (n=219)</td>
<td>11</td>
<td>***p&lt;0.0001</td>
</tr>
<tr>
<td>SU (n=490)</td>
<td>8</td>
<td>†††p&lt;0.0001</td>
</tr>
<tr>
<td>TZD (n=231)</td>
<td>6</td>
<td>***p&lt;0.0001</td>
</tr>
<tr>
<td>Insulin glargine (n=232)</td>
<td>15</td>
<td>***p&lt;0.0001</td>
</tr>
<tr>
<td>Placebo (n=524)</td>
<td>8</td>
<td>***p&lt;0.0001</td>
</tr>
</tbody>
</table>

Least squares means SBP (mmHg)

Data are last observation carried forward for the ITT population and expressed as least squares ± confidence intervals

Mean SBP reductions after 26 weeks were 2.7 [0.8] mmHg with liraglutide 1.2 mg, 2.9 [0.7 mmHg] with liraglutide 1.8 mg and 0.5 [0.9] mmHg with placebo

• SBP, systolic blood pressure; ITT, intent-to-treat
• Adapted from Fonseca VA et al. J Diabetes Complications 2014;28:399–405
GLP-1RA – Beyond Glycaemic Control Effect on fasting lipid levels

- **LEAD 1–6: meta-analysis**
- *p<0.05; **p<0.01; ***p<0.0001; all vs baseline; † is used instead of * to indicate a significant increase from baseline
- **LDL-C**, low-density lipoprotein cholesterol; T2DM, type 2 diabetes
- Fonseca VA et al. International Diabetes Federation 21st World Diabetes Congress, 4–8 December 2011, Dubai, UAE
Head-to-head studies of Incretin vs Insulin based therapy
Type 2 diabetes treatment efficacy: both insulin and GLP1 RAs are very effective

- Insulin and GLP1RAs are efficacious therapies for the treatment of Type 2 DM

- Range of HbA$_1c$ reduction as a monotherapy:
  - DPP-4
  - Glinides
  - AGI
  - GLP-1 RA

- Adapted to include sitagliptin and saxagliptin
- Adapted to include exenatide and liraglutide

Campbell et al. Journal of family practice September 2010;59:S5-S9
Subjects with type 2 diabetes failing on OAD

Pathophysiology based algorithm for type 2 Diabetes

GLP1 Arm
Metformin (1000-2000 mg/day) + Exenatide (5-10 mcg/day) + Pioglitazone (15 to 30 mg/day)

Insulin arm
Metformin (1000-2000 mg/day) + Gliclazine 5-10 mg/day + Insulin Glargine

0 36 months

HbA1c goal 6.5%
# Results Insulin based vs Incretin based therapy

<table>
<thead>
<tr>
<th>Primary end point HBA1c at the end of 36 weeks</th>
<th>Insulin based regimen</th>
<th>Incretin based regimen</th>
<th>Insulin based vs incretin based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.71</td>
<td>5.80</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Weight</td>
<td>+3.7 Kg</td>
<td>-3.1 Kg</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Matsuda index for insulin sensitivity</td>
<td>No change from baseline</td>
<td>Statistically significant improvement in insulin sensitivity</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>46% 2.1 PYE</td>
<td>15% 0.27 PYE</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>
LEAD 5: Liraglutide vs Glargine

HbA1c change from baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Change in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 1.8 mg</td>
<td>8.3%</td>
<td>-1.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.3%</td>
<td>-0.2</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>8.1%</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

Subjects achieving HbA1c targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Baseline</th>
<th>Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt; 7.0%</td>
<td>8.3%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HbA1c ≤ 6.5%</td>
<td>8.1%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Russell-Jones et al. Diabetes 2008;57(Suppl. 1):A159 (LEAD-5)
LEAD 5: Liraglutide vs Glargine

Body weight change from baseline

![Graph showing body weight change from baseline for Liraglutide 1.8 mg, Placebo, and Insulin glargine.]

- Liraglutide 1.8 mg: Baseline 85.8 kg
- Placebo: Baseline 85.4 kg
- Insulin glargine: Baseline 85.2 kg

SBP change over 26 weeks

![Graph showing systolic blood pressure (mmHg) over 26 weeks for Liraglutide 1.8 mg, Placebo, and Insulin glargine.]

- Liraglutide 1.8 mg
- Placebo
- Insulin glargine

Russell-Jones et al. *Diabetes* 2008;57(Suppl. 1):A159 (LEAD-5)
Exenatide QW vs Glargine
AWARD 2: Dulaglutide vs Glargine

**HbA<sub>1c</sub> Change from Baseline at 52 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>DU 1.5 mg</th>
<th>DU 0.75 mg</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HbA&lt;sub&gt;1c&lt;/sub&gt;</td>
<td>-0.1% (6.5 mmol/mol)</td>
<td>-0.2% (6.4 mmol/mol)</td>
<td>-0.3% (6.3 mmol/mol)</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; Change from Baseline (%)</td>
<td>-0.76</td>
<td>-0.63</td>
<td>-0.72</td>
</tr>
</tbody>
</table>

**HbA<sub>1c</sub> Targets at 52 and 78 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>DU 1.5 mg</th>
<th>DU 0.75 mg</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (Weeks)</td>
<td>52</td>
<td>78</td>
<td>52</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; &lt; 7.0% (53 mmol/mol)</td>
<td>53%</td>
<td>33%</td>
<td>44%</td>
</tr>
</tbody>
</table>
AWARD 2: Dulaglutide vs Glargine

**Body Weight Change Over Time**

Baseline Weight = 86.3 kg

- DU 1.5 mg
- DU 0.75 mg
- Glargine

Weight Difference: 3.4 kg

**Hypoglycaemia Rate at 52 Weeks**

- Total: 5.2, 4.8, 7.9
- Documented: 2.0, 2.0, 3.3
- Nocturnal: 0.9, 0.7, 2.1
The evidence

Efficacy – Insulin and GLP1RA equal

Weight loss with GLP1RA

Less hypoglycaemia with GLP1RA
### Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGI</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>COLSvl</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Neutral</td>
<td>Moderate/Severe</td>
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<td>Moderate to Severe</td>
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<td>WEIGHT</td>
<td>Slight Loss</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
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<td>RENAL/GU</td>
<td>Contraindicated</td>
<td>CKD Stage 3B/4</td>
<td>Exenatide Not Indicated</td>
<td>eGFR &lt; 30</td>
<td>Not Effective with eGFR &lt; 45</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
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<tr>
<td>GSx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
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<td>ASCVD</td>
<td>Benefit</td>
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<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
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<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

- **Green**: Few adverse events or possible benefits
- **Yellow**: Use with caution
- **Orange**: Likelihood of adverse effects
- ** вопросите**: Uncertain effect

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McNamara fallacy
Making a decision based solely on quantitative observations and ignoring all others.

1. Measure whatever can be easily measured.
2. Disregard that which can't be easily measured, or give it an arbitrary quantitative value.
3. What can't be measured easily really isn't important.
4. What can't be easily measured really doesn't exist.
The therapeutic pentad

- Efficacy
- Safety
- Tolerability
- Sustainability
- Acceptability
Pragmatic approach

- BIOmedical
- PSYCHO
- SOCIAL model
Biomedical factors: history

- Duration of diabetes/poor control
- Symptoms and severity
- Glycemic variability/brittleness
Biomedical factors: examination

- Anthropometry: weight
- Vital signs: Resting heart rate
- Risk of hypoglycemia
Biomedical factors: comorbidity

- Dyslipidemia
- Infections/surgical illness
- Gallstones/pancreatitis/MTC
Psychosocial factors

- Concern about weight
- Ability to SMBG
- Diet pattern
Metabolic fulcrum, and metabolic triage

MALADAPTIVE ANABOLISM
PHENOTYPE: overweight/obesity, high blood pressure, dyslipidemia
PATHOPHYSIOLOGY: predominant insulin resistance
CHOICE: GLP1RA

PREDOMINANT CATABOLISM
PHENOTYPE: thin built, cachexia, osmotic symptoms
PATHOPHYSIOLOGY: predominant insulin deficiency
CHOICE: insulin

Take home

INSULIN for

• Symptomatic patients
• Catabolic/asthenic state
• Comorbid significant infection/severe renal impairment

GLP1RA for

• Asymptomatic patients
• Obese/overweight state
• Cardiovascular comorbidity
Targets and strategies

- Define a target
- Plan a strategy
- Pick your tools
Targets and strategies

<table>
<thead>
<tr>
<th>TARGET</th>
<th>INSULIN &amp;/OR ORALS</th>
<th>REGIME</th>
<th>PREPARATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>INSULIN with/without sensitizers other drugs</td>
<td>1 2 3 4</td>
<td>human or analogue</td>
</tr>
<tr>
<td>6.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of regimes</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| basal            | - Usually once daily  
                  | - May be twice daily |
| premixed         | - Usually twice daily  
                  | - May be once or thrice daily |
| intensive        | - Thrice daily or more often  
                  | - Usually four doses [basal bolus] |
Number based classification

Review
Diabetes Therapy
pp 1-11

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Number-Based Approach to Insulin Taxonomy

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## Types of regimes

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| 1 | • Basal  
   • Premixed                       |
| 2 | • Premixed  
   • Basal  
   • Basal plus                       |
| 3+| • Basal bolus  
   • Basal plus  
   • Rapid –rapid- premixed           |
Treatment of type 2 diabetes: IDF guidelines

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

**Initiation and intensification: ADA/EASD**

**Basal insulin** (usually with metformin ± other non-insulin agent)

- **Start:** 10 U/day or 0.1–0.2 U/kg/day
- **Adjust:** 10–15% or 2–4 U once-twice weekly to reach FBG target
- **For hypo:** determine & address cause; ↓ dose by 4 U or 10–20%

If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin
(Consider initial GLP-1-RA trial)

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

- **Start:** 4 U, 0.1 U/kg or 10% basal dose. If HbA1c <8%, consider ↓ basal by same amount
- **Adjust:** ↑ dose by 1–2 U or 10–15% once to twice weekly until SMBG target reached
- **For hypo:** determine and address cause; corresponding dose by 2–4 U or 10–20%

If not controlled, consider basal–bolus

**Add ≥2 rapid insulin* injections before meals (‘basal–bolus’)**

- **Start:** 4 U, 0.1 U/kg or 10% basal dose/meal. If HbA1c <8%, consider ↓ basal by same amount
- **Adjust:** ↑ dose by 1–2 U/10–15% once to twice weekly until SMBG target reached
- **For hypo:** determine & address cause; corresponding dose by 2–4 U or 10–20%

If not controlled, consider basal–bolus

**Change to premixed insulin* twice daily**

- **Start:** divide current basal dose into 2/3 AM, 1/3 PM or ½ AM, ½ PM
- **Adjust:** ↑ dose by 1–2 U or 10–15% once to twice weekly until SMBG target reached
- **For hypo:** determine & address cause; corresponding dose by 2–4 U or 10–20%

Start:

4 U, 0.1 U/kg or 10% basal dose.
If HbA1c <8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 U or 10–15% once to twice weekly until SMBG target reached
For hypo: determine & address cause; corresponding dose by 2–4 U or 10–20%

If not controlled, consider basal–bolus

**Complexity**

- **Low**
- **Mod**
- **High**

**Flexibility**

- More flexible
- Less flexible

**No. of injections**

- 3+

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*Regular human insulin and human NPH-regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogues and premixed insulin analogues, but their pharmacodynamic profiles make them suboptimal for the coverage of postprandial glucose excursions.

FBG, fasting blood glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; PPG, postprandial plasma glucose; SMBG, self-monitored blood glucose.

Inzucchi et al. Diabetes Care 2015;38:140–9
### Initiation and intensification in T2D: summary of international guidelines

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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

Progression of type 2 diabetes

- Insulin resistance
- β-cell function
- Insulin level
- Incretin effect
- Postprandial glucose
- FPG

FPG, fasting plasma glucose

The addition of mealtime coverage is needed when basal insulin is no longer enough. This may lead to hypoglycaemia if food changes or meals are missed.

Mealtime insulin response is missing; high postprandial readings at every meal.

Garber. Diabetes Obes Metab 2009;11(Suppl. 5):14–18
Glycemic Pentad- Association with CV risk

- Elevated FPG is strongly associated with CV mortality
- Mean Amplitude of Glycemic Excursions (MAGE) predicts coronary artery disease
- Each variable of the glycemic pentad is associated with CV morbidity and mortality
- Meta analysis finds 18% increased CV risk per 1% higher HbA1c
- PPG independently predicts CVD risk
- Hypoglycaemia is linked with a 79% increased risk of acute CV events

Ukrainian proverb

No matter how hard you try, the bull will never give you milk.

- Think before prescribing, don’t prescribe before thinking.
- THINK BEFORE INK
Participant distribution to BIAsp ± OGLD by pre-study therapy

Use of the different insulin types during the study (BIAsp ± OGLD)