Case 1

- 45 year-old male patient seen at the clinic (Medicine).
- Workplace stress (financial analyst); occasionally goes jogging.
- Two-year duration of T2DM. No previous cardiovascular events. Coexisting mild intermittent asthma.
- BMI: 32.
- On diet + metformin, HbA1C = 7.8%.
- FPG in the morning ≈ 120-130 mg/dl.
- Next step in his medical management?
Physiology of Normoglycemia

If glucose is high → insufficient insulin effect acting at end organs
Tools to Control G Levels

- **Increase the effect of available insulin**
  - Diet +/- weight loss
  - Metformin (liver)
  - Activity
  - TZDs (fat, muscle, liver)

- **Increase the supply of insulin (to increase effect)**
  - Sulfonylureas
  - Glinides
  - Insulin
  - Incretins (GLP-1, DPP4-I)

- **Reduce the need for insulin supply (improve the match between insulin supply & effect)**
  - AGIs (acarbose)
  - SGLT2 inhibitors
  - Incretins (GLP-1, DPP4-I)
  - Pramlintide
Tools to Lower G Levels

- **Insulin:**
  - Long acting: *glargine, detemir, degludec, NPH*
  - Medium: *regular*
  - Rapid: *lispro, aspart, glulisine*

- **Sulfonylurea:** *glyburide*, *gliclazide, glimepiride, glipizide*

- **Glinide:** *repaglinide, nateglinide*

- **Biguanide:** *metformin*

- **TZD:** *pioglitazone, rosiglitazone*

- **SGLT2i:** *canagliflozin, dapagliflozin, empagliflozin*

- **GLP-1 analog:** *exenatide, liraglutide, lixisenatide*

- **DPP4-I:** *sitagliptin, vildagliptin, saxagliptin*

- **Alpha Glucosidase Inhibitor:** *acarbose, miglitol*
Tools to Lower G Levels

Acarbose
Pramlintide
DPP4-I
GLP-1 Analogue
Colesavalam

Sulfonylureas
Glinides
DPP4-I
GLP-1 Analogue

Insulin
GLP-1
Pramlintide
Bromocriptine

Carbohydrate DIGESTIVE ENZYMES
Glucose

Insulin

Glucose (G)

Metformin
TZDs

TZDs
Metformin

SGLT2i

I
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- Next step in his medical management?
Case 2

- 60 year-old male patient, admitted for NSTEMI, treated with angioplasty.
- Roughly, 10-yr duration of T2DM. Hypertension. Hypercholesterolemia. Intermittent claudication.
- eGFR = 70 ml/min/1.73m².
- HbA1C = 8.1%.
- Treatment before current admission: metformin, 850 mg/12 h plus sustained-release gliclazide, 90 mg/day.
- Any changes in treatment before/at discharge?
How to start insulin it: INSIGHT Trial

In people with type 2 diabetes who are treated with lifestyle alone, 1 agent or sub-maximal doses of 2 oral agents by specialists or generalists & can easily be managed without insulin….

… does the addition & titration of basal insulin to a FPG $\leq 5.5$ mmol/L (100 mg/dL) safely achieve an A1c $\leq 6.5\%$ faster & more frequently than increasing or adding oral agents?

Gerstein et al. Diabetic Medicine 2006:736
Trial Design

- Lifestyle alone
- 1 oral agent, (SU, Metformin, Repaglinide)
- 2 oral agents where at least is at ≤ half max. dose

Current Rx + Insulin Glargine Titrated to FPG ≤ 5.5 (100)

RAND

- Oral agent mono-Rx (SU, metformin, repaglinide) OR
- Dose/add a 2nd oral agent OR
- Dose of 2 agents to max OR
- Add a 3rd agent

-2 Wks  Wk 0  Wk 24
(baseline) (end)

Screening phase  Treatment phase

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## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total 405</th>
<th>Insulin 206</th>
<th>OADs 199</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert (%)</td>
<td>145 (35.8)</td>
<td>75 (36.4)</td>
<td>70 (35.2)</td>
</tr>
<tr>
<td>Family MD (%)</td>
<td>260 (64.2)</td>
<td>131 (63.6)</td>
<td>129 (64.8)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56.5 (9.8)</td>
<td>56.3 (9.4)</td>
<td>56.8 (10.1)</td>
</tr>
<tr>
<td>DM Duration (yrs)</td>
<td>7.9 (6.0)</td>
<td>7.6 (5.4)</td>
<td>8.2 (6.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.3 (4.5)</td>
<td>31.1 (4.4)</td>
<td>31.5 (4.6)</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>8.6 (1.0)</td>
<td>8.6 (1.0)</td>
<td>8.5 (1.0)</td>
</tr>
<tr>
<td>Drug Naïve (%)</td>
<td>68 (16.8)</td>
<td>38 (18.4)</td>
<td>30 (15.1)</td>
</tr>
<tr>
<td>Metformin or SU (%)</td>
<td>165 (40.7)</td>
<td>81 (39.3)</td>
<td>84 (42.2)</td>
</tr>
<tr>
<td>Metformin &amp; SU (%)</td>
<td>172 (42.5)</td>
<td>87 (42.2)</td>
<td>85 (42.7)</td>
</tr>
</tbody>
</table>
Achieved A1c (95% CI)

Unadjusted Diff. in A1c: 7.04% vs. 7.28%; P = 0.0047
*Adjusted Diff. in A1c: 6.96% vs. 7.24%; P = 0.0007

* Adjusted for baseline values, stratum or site
A1c ≤ 6.5%
Adj. HR 1.71 (1.02-2.88); P=0.04
Wilcoxon P (Curves) = 0.0409

A1c ≤ 7.0%
Adj. HR 1.75 (1.27 - 2.41); P=0.001
Wilcoxon P (Curves) = 0.0035
Hypoglycemia & Weight

- P > 0.2 for group differences at each visit

(Adj. baseline, site stratum)

<table>
<thead>
<tr>
<th></th>
<th>Glargine</th>
<th>OAD</th>
<th>Diff. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final – Initial Waist</td>
<td>1.23</td>
<td>-0.74</td>
<td>1.97 (0.96, 2.98)</td>
</tr>
<tr>
<td>Final – Initial BMI</td>
<td>0.72</td>
<td>0.06</td>
<td>0.65 (0.39, 0.92)</td>
</tr>
<tr>
<td>Final – Initial Weight</td>
<td>2.11</td>
<td>0.16</td>
<td>1.94 (1.16, 2.73)</td>
</tr>
</tbody>
</table>
### Other Endpoints

<table>
<thead>
<tr>
<th>Glargine</th>
<th>Oral</th>
<th>Outcome</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.55</td>
<td>-1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3.89</td>
<td>-2.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.38</td>
<td>-0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.01</td>
<td>-0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.37</td>
<td>-0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.08</td>
<td>-0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.03</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-95% C.I. -2.5 -2.0 -1.5 -1 -0.5 0 0.5

Not adjusted for baseline values, stratum or site
Case 2

- 60 year-old male patient, admitted for NSTEMI, treated with angioplasty.
- Roughly, 10-yr duration of T2DM. Hypertension. Hypercholesterolemia. Intermittent claudication.
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- **Any changes in treatment before/at discharge?**
Case 3

- 38 year-old man; formerly unknown diabetes; admits having recently experienced polyuria and polydipsia.
- Admitted to the ICU for pneumonia and shock, needing steroids and mechanical ventilation.
- BMI at admission: 40 (weight: 130 kg). At discharge: 36.
- HbA1c = 9%.
- At the Medicine ward he is treated with metformin 850 mg/12h plus basal-boluses insulin.
- After spending 19 days in the hospital, he is close to be discharged in good condition. Gone off steroids now.
- Basal glargine dose has been gradually reduced to 14 IU at night, needing additional glulisine 5 IU for lunch.
- Would you keep this treatment at discharge?
Potential Approaches

• Consider the big picture!!!
• What type of diabetes does he have???
• Intensive medical therapy
  – *Lifestyle*
  – *Drugs*
• Metabolic surgery
Features of Basal Insulin Therapy

The G level tells you when the dose is right

There is no maximum or minimum dose

Easily titrated & virtually painless

No contraindication & no true drug interactions

Easy-to-use insulin preparations & delivery devices

Often only need 1 dose/day

Medicine has more experience with insulin therapy than almost any other agent (i.e. 91 years)
Case 4

- 75 year-old female patient seen at the clinic.
- 25 year-duration T2DM. Long-standing stable angina due to small vessels obstruction, not amenable to PCI. LVEF: 55%.
- CKD with confirmed microalbuminuria (180 mg/g) and eGFR = 58 ml/min/1.73m$^2$.
- Recent weight gain; BMI: 30.5.
- HbA1C = 8%.
- Current treatment: metformin 850 mg/12h plus linagliptin 5 mg/day.
- Next step?