WHERE TO START:
Oral Medical Treatment
-Vision 2016

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Speaker:

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- Has disclosed that he serves on the Speaker’s bureau and receives consulting fees and honoraria from Lilly, Novo Nordisk, MSD, AstraZeneca, J&J and Servier

- Will not be discussing the off-label or investigational use of products
Objectives

• When Metformin fails
• Dual therapy from the beginning
• Beta cell preservation: Reality or myth?
Natural History of Type 2 Diabetes

Factors That May Drive the Progressive Decline of β-cell Function

- Hyperglycemia (glucose toxicity)
- Insulin Resistance
- Genetics
- “Lipotoxicity” (elevated FFA, TG)
- TG accumulation

FFA=Free fatty acids; TG=Triglycerides.
Adapted from: Kahn SE, J Clin Endocrinol Metab. 2001;86:4047-4058.
Adapted from: Ludwig DS, JAMA. 2002;287:2414-2423.
Pathogenesis of type 2 diabetes - the ominous octet

Multiple defects contribute to the progression of type 2 diabetes mellitus

Hyperglycemia

Decreased Insulin Secretion

Decreased Incretin Effect

Increased Glucagon Secretion

Increased Lipolysis

Increased Glucose Reabsorption

Decreased Glucose Uptake

Neurotransmitter Dysfunction

Increased Hepatic Glucose Production

Islet-α cell

Adapted from De Fronzo RA. Diabetes. 2009;58:773-95.
3A. β-Cell-Centric Construct: Egregious Eleven
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

1. Pancreatic β-cells
   - ↓ β-Cell function
   - ↓ β-Cell mass
   - ↓ Insulin
   FINAL COMMON DENOMINATOR

2. ↓ Incretin effect

3. α-cell defect
   - ↑ Glucagon

4. Adipose
   - Increased lipolysis

5. Muscle
   - Decreased peripheral muscle uptake

6. Liver
   - Increased glucose production

7. Brain
   - Increased appetite
   - Decreased morning dopamine surge
   - Increased sympathetic tone

8. Colon/Biome
   - Abnormal-microbiota; possible decreased GLP-1 secretion

9. Immune Dysregulation/Inflammation
   - ↓ Amylin

10. Stomach/Small intestine
    - Increased rate of glucose absorption

11. Kidney
    - Increased glucose re-absorption

INSULIN RESISTANCE

3B. β-Cell-Centric Construct: Egregious Eleven
Targeted Treatments for Mediating Pathways of Hyperglycemia

8. Colon/Biome
   Probiotics
   Incretins
   Metformin

9. Immune Dysregulation/Inflammation
   Incretins, Anti-Inflammatories
   Immune modulators

10. Stomach/Small intestine
    GLP-1 Agonists
    Pramlintide
    AGI

11. Kidney
    SGLT2 inhibitors

1. Pancreatic β-cells
   ↓ β-Cell function
   ↓ β-Cell mass
   ↓ Insulin
   Incretins, Ranolazine

2. ↓ Incretin effect
   Incretins

3. α-cell defect
   ↑ Glucagon
   Incretins Pramlintide

4. Adipose
   TZDs
   Metformin

5. Muscle
   TZDs
   Metformin

6. Liver
   Metformin
   TZDs

7. Brain
   Incretins
   Dopamine agonist-QR
   Appetite Suppressants

FINAL COMMON DENOMINATOR

INSULIN RESISTANCE

IDF Treatment Algorithm for People with Type 2 Diabetes

**Lifestyle measures**

Then, at each step, if not to target (generally HbA₁c < 7.0%)

**Consider first line**

- Metformin
- Sulfonylurea

**Consider second line**

- Sulfonylurea
- Metformin (if not first line)
- α-Glucosidase inhibitor or DPP-4 inhibitor or Thiazolidinedione

**Consider third line**

- Basal insulin or Pre-mix insulin
- α-Glucosidase inhibitor or DPP-4 inhibitor or Thiazolidinedione
- GLP-1 agonist

**Consider fourth line**

- Basal insulin or Pre-mix insulin (later basal + meal-time)

**= usual approach**

**= alternative approach**
Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 58 mmol/mol (7.5%)
- Consider: triple therapy with metformin, a DPP-4i, and a GLP-1 receptor agonist
- Support the person to aim for an HbA1c level of 63 mmol/mol (7.5%)
- If HbA1c rises to 68 mmol/mol (8.0%)
- Consider switching from a trial of modified-release metformin
- If the person is asymptomatic, hypoglycaemia, consider insulin or an SU
- Review treatment when blood glucose control has been achieved

If HbA1c rises to 68 mmol/mol (8.0%)
- Consider: either a DPP-4i, a GLP-1 receptor agonist, a SU, or a sulfonylurea
- Support the person to aim for an HbA1c level of 57 mmol/mol (7.0%)
- If standard dose metformin is not effective or contraindicated, consider combination metformin with a DPP-4i, a GLP-1 receptor agonist, a SU, or a sulfonylurea

METFORMIN CONTRAINDIATED OR NOT EFFECTIVE

If HbA1c rises to 63 mmol/mol (7.5%)
- Consider: either a DPP-4i or a GLP-1 receptor agonist
- Support the person to aim for an HbA1c level of 63 mmol/mol (7.5%)
- If HbA1c rises to 68 mmol/mol (8.0%)
- Consider: either a DPP-4i or a GLP-1 receptor agonist
- Support the person to aim for an HbA1c level of 57 mmol/mol (7.0%)
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- Consider: either a DPP-4i or a GLP-1 receptor agonist
- Support the person to aim for an HbA1c level of 57 mmol/mol (7.0%)

SECOND INTENSIFICATION

Triple therapy is not effective or contraindicated, consider combination metformin with metformin, a DPP-4i, and a GLP-1 receptor agonist
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)
- If HbA1c rises to 68 mmol/mol (8.0%)
- Consider: a DPP-4i or a GLP-1 receptor agonist
- Support the person to aim for an HbA1c level of 57 mmol/mol (7.0%)
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In these groups of drugs, at a high level:
- When prescribing pioglitazone, exercise particular caution if the patient is at high risk of the adverse effects of the drug. Pioglitazone is associated with increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated.
- See the manufacturer's summaries of product characteristics for details.
- Regulatory Agency (MHRA) guidance 2011 advises that breathlessness should be considered for all patients in individuals with 3% or 6 months of treatment to ensure that all patients with cardiac disease continue to be treated.
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Antihyperglycemic Therapy in Type 2 Diabetes

ADA Standards of Medical Care in Diabetes. Approaches to Glycemic Treatment. Diabetes Care 2016; 39 (Supl.1): SX
Before starting Metformin, obtain the patient's eGFR. Obtain an eGFR at least annually in all patients taking Metformin. High risk patients, such as the elderly, renal function should be assessed more frequently.

- **eGFR > 45mL/min/1.73m²**: Metformin can be used
- **eGFR between 30–45mL/min/1.73m²**: Starting Metformin is not recommended.
- **eGFR <30mL/min/1.73m²**: Metformin is contraindicated.

If the eGFR later falls <45mL/min/1.73m², assess the benefits and risks of continuing treatment.
If eGFR further falls <30mL/min/1.73m²: Discontinue Metformin.
If the eGFR is between $30–60\text{mL/min/1.73m}^2$, discontinue Metformin:

• In patients with a history of liver disease, alcoholism, or heart failure

• At the time of or before an iodinated contrast imaging procedure in patients as well as in normal patients, who will be administered intra-arterial iodinated contrast.

Re-evaluate eGFR 48 hours after the imaging procedure; restart Metformin if renal function is stable.
Conservative management of glycemia: Traditional Stepwise Approach

OAD = oral antihyperglycaemia drug

Adapted from Campbell IW. Br J Cardiol. 2000;7:625–631.
Delay between stepping up from monotherapy to combination therapy

Length of time between first monotherapy HbA$_{1c}$ > 8.0% and switch/addition to therapy (months)

- Metformin only: 14.5 months (n = 513)
- Sulphonylurea only: 20.5 months (n = 3394)

The Legacy Effect

10-year post-trial monitoring from 1997 to 2007 of UKPDS Study

- Randomized intervention to achieve either intensive or conventional targets - stopped at the trial end (1997)
- Differences in mean HbA1c between the 2 groups were lost by Year 1 of post-trial follow-up
- Relative reductions in risk in patients who had been treated to intensive goals, compared with conventional targets, persisted after 10 years

The legacy effect – a reduction in complications persists 10 years after intensive therapy

Durability of glycemic control with sulfonylureas
Early Dual Therapy

After diet and lifestyle modification, monotherapy may assist patients in achieving a target of HbA1c less than 7%. However, with disease progression, usually the monotherapy loses efficacy over time as evidenced by a continued increase in A1c. For example, in patients with high mean baseline A1c of 8.2–8.4%, glycemic control was reached by only 25% of patients with metformin monotherapy.

The primary objective of combining oral antidiabetic treatments is to address the dual problems of insulin deficiency and insulin resistance. This has been shown to be helpful in establishing glycemic control and lowering A1c levels by an additional 0.5–1.0%.

The chosen regimen, should ideally exert a physiologically rapid prandial insulin response to maintain tight glycemic control with minimal side effects such as hypoglycemia and weight gain. It is also important for the combination to be at least additive and possibly synergistic in their mechanisms of action.

What about early Triple Therapy?

The combination of metformin, TZD and GLP-1 analog (or DPP-IV inhibitor) addresses the 3 core defects of type 2 diabetes in a complementary manner (up to HbA1c Δ -2%)

GLP-1 analog (or DPP-IV inhibitor) for islet β-, α-cell dysfunction and extra-islet actions

β-, α-cell dysfunction

Insulin resistance

TZD for insulin resistance in adipose tissue (lipolysis)

TZD, metformin for insulin resistance in skeletal muscle (impaired glucose uptake)

Metformin, TZD for hepatic insulin resistance (HGP)

http://dx.doi.org/10.4093/kdj.2010.34.6.331
Beta cell Preservation

- Intensive Lifestyle Modification
- Sulfonylureas
- Metformin
- Acarbose
- Thiazolidinediones (TZDs)
- GLP-1 Receptor Agonists
- Bariatric Surgery
### Intensive Lifestyle Modification

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants at high-risk for diabetes</th>
<th>Intervention</th>
<th>Relative reduction in risk of diabetes&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>DPP</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>58 %</td>
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<tr>
<td>Finnish DPS</td>
<td>IGT</td>
<td>Lifestyle</td>
<td>58 %</td>
</tr>
<tr>
<td>XENDOS</td>
<td>IGT</td>
<td>Orlistat + lifestyle</td>
<td>45%&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>TRIPOD</td>
<td>Prior GDM</td>
<td>Troglitazone</td>
<td>55 %</td>
</tr>
<tr>
<td>DPP</td>
<td>IGT</td>
<td>Troglitazone</td>
<td>75 %</td>
</tr>
<tr>
<td>DREAM</td>
<td>IGT</td>
<td>Rosiglitazone</td>
<td>60 %</td>
</tr>
<tr>
<td>ACT NOW</td>
<td>IGT</td>
<td>Pioglitazone</td>
<td>72 %</td>
</tr>
<tr>
<td>DPP</td>
<td>IGT</td>
<td>Metformin</td>
<td>31 %</td>
</tr>
<tr>
<td>Stop-NIDDM</td>
<td>IGT</td>
<td>Acarbose</td>
<td>25 %</td>
</tr>
</tbody>
</table>

DPP Diabetes Prevention Program, DPS Diabetes Prevention Study, TRIPOD troglitazone in prevention of diabetes, DREAM diabetes reduction assessment with ramipril and rosiglitazone medication, ACT NOW Actos now, IGT impaired glucose tolerance, GDM gestational diabetes mellitus avs placebo and/or usual care
Sulfonylureas

ADVANCE trial indicates that Gliclazide, may protect β cells from apoptosis potentially through antioxidant effects of the aminoazabicyclo-octyl ring grafted onto the sulfonylurea group. This causes inhibition of LDL oxidation. It has been shown to scavenge superoxide radicals, hydroxyl radicals, and NO in a dose-dependent manner. No clinical studies have demonstrated a beneficial effect of sulfonylureas in the prevention of T2DM.
Metformin is effective at reducing hyperglycemia primarily by inhibiting hepatic glucose production and by increasing insulin sensitivity. DPP showed that metformin reduced the conversion from IGT to T2DM by 31% suggesting that it has modest effects on slowing the progression of T2DM.

UKPDS showed similar rates of deterioration of β-cell function (assessed with HOMA-B index) and loss of glycemic control with metformin treatment compared with sulfonylureas or insulin treatment in patients with recently diagnosed T2DM.
Acarbose

Acarbose is an α-glucosidase inhibitor that improves post-prandial hyperglycemia by inhibiting the activity of enzymes in the small intestine resulting in reduced glucose absorption. The Study to Prevent NIDDM (STOP-NIDDM) found a 25 % relative risk reduction in the development of T2DM over 3.3 years in patients with impaired glucose levels treated with acarbose compared with placebo. However, in the 3-month observation period after acarbose was discontinued, the incidence of diabetes in patients who had not converted was higher in the group initially assigned to acarbose (15 %) compared with group first randomized to placebo (10 %) suggesting that the benefit of acarbose is lost after discontinuation of active treatment.
Thiazolidinediones (TZDs)

TZDs reduce lipotoxicity, prevent β-cell apoptosis, increase serum adiponectin levels and improve β-cell function. Prevention trials show that TZDs prevent the onset of T2DM in high-risk patients by ~50 %–75 % including DPP, TRIPOD, PIPOD, DREAM, ACT-NOW.

TRIPOD showed that protection from diabetes in women with previous gestational diabetes persisted 8 months after T2DM treatment stopped, and patients who were protected from diabetes during TZD treatment had stable β-cell function and insulin resistance for almost 5 years. This was supported by DREAM and DPP, in which the protection from diabetes that was achieved during treatment persisted after treatment was stopped.

The clinical use of TZDs for the prevention of T2DM is limited due to adverse side effects, including fluid retention and weight gain, increased risk for bone fractures and bladder cancer.
GLP-1 Receptor Agonists

GLP-1 potentiates glucose stimulated insulin secretion, suppresses glucagon secretion, delays gastric emptying and suppresses appetite. Studies indicate that at least 3 years of Exenatide treatment may be necessary to delineate a significant, prolonged benefit on β-cell function.

A 20-week treatment with Liraglutide (in doses ranging from 1.8 to 3 mg per day) resulted in greater weight loss and an 84 %–96 % reduction in the prevalence of prediabetes compared with placebo.

Longer term prevention trials in high-risk patients are needed to determine whether GLP-1 agonists can modify the progressive course of T2DM.
DPP-4 inhibitors

The incretin receptor signaling is associated with activation of protein kinase A, induction of gene transcription, enhanced levels of insulin biosynthesis, and stimulation of β-cell proliferation. Both GLP-1R and GIP receptor activation also promote resistance to apoptosis and enhanced β-cell survival, in human islets cells. In preclinical studies, DPP-4 inhibitors mimic many of the actions ascribed to GLP-1R agonists, including stimulation of insulin and inhibition of glucagon secretion, and preservation of β-cell mass through stimulation of cell proliferation and inhibition of apoptosis.

Long-term clinical data assessing the durability and efficacy of these agents in the treatment of type 2 diabetes are not yet available.
Bariatric Surgery

The effect of bariatric surgery (LAGB, VBG, RYGB) on the prevention of T2DM in obese adults was examined in the SOS study which followed surgically treated and matched controls for 15 years. Bariatric surgery compared with standard care reduced the long-term relative risk of T2DM by 78% in obese adults, and in IFG it reduced the relative risk of by 82%. The postoperative mortality was 0.2%, and 2.8% of patients had complications that required a reoperation. These findings indicate that bariatric surgery has effective and durable effects on the prevention of T2DM in obese adults, particularly among those with IFG. RCTs are needed to confirm whether bariatric surgery is an effective and safe approach for preventing T2DM in high-risk individuals.
Effect of Weight Loss on β-cell Function in Obese Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mode of action in β-cell</th>
<th>Animal data</th>
<th>Human data</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARγ agonists</td>
<td>Upregulate Pdx-1 expression [25]</td>
<td>Reduced oxidative stress [28]</td>
<td>Slow the rate of loss of β-cell function and improve insulin sensitivity in</td>
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<tr>
<td></td>
<td>Increase insulin gene transcription, GLUT2, and glucokinase [26]</td>
<td>Inhibited β-cell apoptosis [29]</td>
<td>ADOPT trial [23], ACT NOW study [30], PIPOD, and TRIPOD study [31]</td>
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<td></td>
<td>Reverse lipotoxicity [27]</td>
<td>Increased β-cell mass and function [28,29]</td>
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<tr>
<td>GLP-1 analogues</td>
<td>Enhance glucose-stimulated insulin secretion [33]</td>
<td>Increased β-cell mass [36]</td>
<td>Improved insulin secretory capacity and insulin sensitivity [39]</td>
</tr>
<tr>
<td></td>
<td>Act as a growth factor by promoting β-cell proliferation and inhibiting β-cell apoptosis</td>
<td>Modulated the expression of β-cell specific genes [37]</td>
<td>Reduced proinsulin to insulin ratio [40]</td>
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<tr>
<td></td>
<td>Stimulate insulin gene expression and biosynthesis [34]</td>
<td>Inhibited β-cell apoptosis [38]</td>
<td>Restore 1st and 2nd phase insulin secretion [41]</td>
</tr>
<tr>
<td></td>
<td>Attenuate ER stress [35]</td>
<td></td>
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<tr>
<td>DPP-4 inhibitors</td>
<td>Inhibit the incretin degrading enzyme DPP-4 [32]</td>
<td>Increased β-cell mass and pancreatic insulin content [42,43]</td>
<td>Improved β-cell function [44.45]</td>
</tr>
<tr>
<td></td>
<td>Increase the bioavailability of active GLP-1 [42]</td>
<td>Enhanced insulin secretion [42]</td>
<td></td>
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<tr>
<td>GSK3β inhibitors</td>
<td>Regulate glycogen metabolism by inhibiting glycogen synthase [48]</td>
<td>Enhanced insulin signaling [53]</td>
<td></td>
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<tr>
<td></td>
<td>Inhibit ER stress induced β-cell apoptosis [51]</td>
<td>Improved insulin resistance [53]</td>
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<tr>
<td></td>
<td>Improve β-cell function by preserving β-cell transcriptional factor Pdx1 [52]</td>
<td>Increased β-cell mass [54]</td>
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<tr>
<td>GPR40 agonists</td>
<td>Induce insulin secretion by modulating G protein-coupled receptor involved in free fatty</td>
<td>Enhanced glucose-dependent insulin secretion with elevation of Ca^{2+} [57]</td>
<td>Increased insulin secretion [59]</td>
</tr>
<tr>
<td></td>
<td>acid [55]</td>
<td>Decreased glucose and insulin level [58]</td>
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Thank You