Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (5th Edition) 2015

Topic 6: Oral Anti Diabetic Agents
Oral Anti-Diabetic (OAD) Agents

There are currently 6 classes of OAD agents:

1. Biguanides
2. Insulin Secretagogues
   - Sulphonylureas
   - Meglitinides
3. Alpha-glucosidase inhibitor (AGIs)
4. Thiazolidinediones (TZDs)
5. Dipeptidyl peptidase-4 (DPP-4) inhibitors
6. Na-Glucose Co-Transporter 2 (SGLT2) inhibitors
Biguanides (Metformin)

• Metformin lowers blood glucose especially fasting blood glucose by decreasing hepatic glucose production

• Usage in combination with other OAD agents have synergistic effect to further reduce blood glucose and may reduce insulin requirements.

• Most common adverse effects are nausea, anorexia and diarrhoea.

• Minimised if metformin
  - taken together with/or after meals.
  - best to start with a single daily dose, followed by weekly titration
  - Extended release formulation also reduces side effects
Biguanides (Metformin)

- One of the complications of long term metformin therapy is vitamin B12 deficiency.

- Lactic acidosis is rare and usually associated with renal impairment

- One of the benefits of metformin is weight stability or mild weight loss.

- Dose beyond 2000 mg OD does not confer any further glycaemic benefit and significantly increase gastrointestinal side effects.
Biguanides (Metformin)

- Low dose metformin can be safely prescribed to lactating mothers

- The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes

- Avoid if creatinine $>150$ umol/l or creatinine clearance $<30$ mL/min
# Metformin Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>500 mg</td>
<td>Initial dose 500 mg OD</td>
<td>1000 mg TDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual dose 1500 mg OD</td>
<td></td>
</tr>
<tr>
<td>Metformin SR</td>
<td>850 mg</td>
<td>Usual dose 850 mg BD</td>
<td>850 mg TDS</td>
</tr>
<tr>
<td>Metformin XR</td>
<td>500 mg / 750 mg</td>
<td>Initial dose 500 mg OD</td>
<td>2000 mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual dose 2000 mg OD</td>
<td></td>
</tr>
</tbody>
</table>

*For fixed combination formulations, please refer to specific product inserts.*
Insulin Secretagogues (SUs)

- SUs lower plasma glucose by increasing insulin secretion

- Major adverse side effect is hypoglycaemia. Risk higher in renal impairment, liver cirrhosis and elderly

- Weight gain is common

- Second generation SUs (Glimepiride, Gliclazide MR) cause less risk of hypoglycaemia and less weight gain
Insulin Secretagogues (SUs) (cont.)

- Glibenclamide has been shown to be associated with significant risk of hypoglycaemia and WHO recommends against its use in those above 60 years of age.

- SUs can be combined with other OAD agents or insulin to improve glucose control, if indicated

- SUs should be taken 30 minutes before meals, except Glimepiride and Gliclazide MR which can be taken just before the meal
# SU Formulations and Dosage

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide 5 mg tablet</td>
<td>2.5 mg OM</td>
<td>10 mg BD</td>
</tr>
<tr>
<td>Glibenclamide 10 mg BD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliclazide 80 mg tablet</td>
<td>40 mg OM</td>
<td>160 mg BD</td>
</tr>
<tr>
<td>Gliclazide MR 30/60 mg</td>
<td>30 mg OM</td>
<td>120 mg OM</td>
</tr>
<tr>
<td>Glipizide 5 mg tablet</td>
<td>2.5 mg OM</td>
<td>10 mg BD</td>
</tr>
<tr>
<td>Glimepiride 2 mg / 3 mg</td>
<td>1 mg OM</td>
<td>6 mg OM</td>
</tr>
</tbody>
</table>

*For fixed combination formulations, please refer to specific product inserts*

**Note:**
Glibenclamide is metabolised by the liver but its metabolites are active and excreted by the kidney. The drug should be stopped if renal impairment develops. Other second generation SUs (glimepiride, gliclazide and glipizide) may still be used with caution.
Meglitinides

- Short acting insulin secretagogues which stimulate insulin secretion, although they bind to a different site within the SU receptor

- Shorter circulating half life than SUs, rapidly absorbed from the GI tract with peak level 1-hour post administration and eliminated within 4-6 hours

- It should be taken within 10 minutes before main meals

- Can be added to other OAD(s) except SU
Meglitinides (cont.)

- Associated with less risk of weight gain compared to SUs and hypoglycaemia may be less frequent.

- Primarily use to control PPG.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>0.5 mg with main meals</td>
<td>4 mg with main meals (not exceeding 16 mg daily)</td>
</tr>
<tr>
<td>0.5 / 1 / 2 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60 mg with main meals</td>
<td>120 mg with main meals (not exceeding 360 mg daily)</td>
</tr>
<tr>
<td>120 mg tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Alpha-glucosidase inhibitor (AGIs)

• AGIs e.g. acarbose reduces the rate of digestion of polysaccharides in the proximal small intestine by inhibiting $\alpha$-glucosidase enzymes. They should be taken with main meals

• Lowers postprandial glucose without causing hypoglycaemia

• Less effective in lowering glycaemia than metformin or SU

• Synergistic effects when used with other OAD agents and may be combined with insulin
Alpha-glucosidase inhibitor (AGIs) (cont.)

- If hypoglycaemia occurs when used in combination with SUs or insulin, advise patients to take monosaccharides, e.g. glucose

- Commonest side effects are bloating, abdominal discomfort, diarrhoea and flatulence

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
</table>
| Acarbose 50 mg / 100 mg tablet | Initial dose 50 mg OD  
Usual dose 50-100 mg during main meals | 100 mg TDS   |
Thiazolidinediones (TZDs)

• Peroxisome proliferator-activated receptor-gamma (PPAR-Ȗ) agonists and act primarily by increasing insulin sensitivity in muscle, adipose tissue and liver

• Improvement in glycaemic control may only be seen after 6 weeks and maximal effect at 6 months

• Side effects include weight gain (due to redistribution of body fat), heart failure, macular edema and osteoporosis
Thiazolidinediones (TZDs) (cont.)

- Contraindicated in patients with CCF and liver failure

- Use of TZDs as first line therapy has been found to have greater durability in glycaemic control compared to metformin and SU

- Use of TZDs with insulin is not recommended.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone 4 / 8 mg tablet</td>
<td>4 mg OD</td>
<td>8 mg OD</td>
</tr>
<tr>
<td>Pioglitazone 15 / 30 mg tablet</td>
<td>15 mg OD</td>
<td>45 mg OD</td>
</tr>
</tbody>
</table>
GLP-1 Modulates Numerous Functions in Humans


GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

Beta cells:
Enhances glucose-dependent insulin secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

Long Term effects in Animals

β Cell mass
Maintains β Cell func
Reduces β cell apoptosis

Incretins Play an Important Role in Glucose Homeostasis

GLP-1 & GIP Secretion and Inactivation

Intestinal GLP-1 & GIP release

Active GLP-1 & GIP

DPP-4

GLP-1 & GIP inactive (>80% of pool)

$t_\frac{1}{2} = 1$ to $2$ min

Inhibition of DPP-IV Increases Active GLP-1

DPP-4 Inhibitor

- Minimal risk of hypoglycaemia and weight neutral
- Efficacy not influenced by the duration of T2DM
- SAVOR-TIMI 53 trial has shown that use of saxagliptin associated with increased risk for hospital admission for heart failure
- TECOS study did not show any increased risk of hospitalisation for heart failure with sitagliptin
- In general, the use of DPP-4 inhibitors not associated with any adverse cardiovascular outcomes
## DPP-4 Inhibitors Formulations and Dosage

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100 / 50 / 25 mg tablet</td>
<td>100 mg OD</td>
<td>100 mg OD</td>
</tr>
<tr>
<td>Vildagliptin 50mg tablet</td>
<td>25 mg BD</td>
<td>50 mg BD</td>
</tr>
<tr>
<td>Saxagliptin 2.5 mg / 5 mg tablet</td>
<td>2.5 mg OD</td>
<td>5 mg OD</td>
</tr>
<tr>
<td>Linagliptin 5 mg tablet</td>
<td>5 mg OD</td>
<td>5 mg OD</td>
</tr>
<tr>
<td>Alogliptin 6.25 mg / 12.5 mg / 25 mg tablet</td>
<td>6.25 mg OD</td>
<td>25 mg OD</td>
</tr>
</tbody>
</table>

*For fixed combination formulations, please refer to specific product inserts*
# DPP-4 Inhibitors: A Pharmacokinetic Comparison

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>mg</th>
<th>t₁/₂ (hr)</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>qd</td>
<td>100</td>
<td>~12</td>
<td>Unchanged</td>
<td>&gt; 80% urine</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>bid</td>
<td>50</td>
<td>~3</td>
<td>Inactive metabolites</td>
<td>~85% urine</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>qd</td>
<td>5</td>
<td>~3</td>
<td>Active metabolite</td>
<td>&gt; 60% urine</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>bid</td>
<td>5</td>
<td>&gt; 10</td>
<td>Mostly unchanged</td>
<td>~80% bile</td>
</tr>
</tbody>
</table>

bid = twice daily; qd = once daily; t₁/₂ = half-life

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c. Bristol-Myers Squibb Company, AstraZeneca Pharmaceuticals LP.
http://packageinserts.bms.com/pi/pi_onglyza.pdf
d. Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company.
SGLT2 inhibitor: A novel insulin-independent approach to remove excess glucose

Proximal tubule
Glucose filtration

SGLT2 inhibitors selectively inhibit SGLT2 in the renal proximal tubule

Increased urinary glucose excretion
Normal glucose homeostasis\textsuperscript{1,2}

**Net balance \(\sim 0\) g/day**

### Glucose input \(\sim 250\) g/day:
- Dietary intake \(\sim 180\) g/day
- Glucose production \(\sim 70\) g/day
  - Gluconeogenesis
  - Glycogenolysis

### Glucose uptake \(\sim 250\) g/day:
- Brain \(\sim 125\) g/day
- Rest of the body \(\sim 125\) g/day

The kidney filters circulating glucose

- Glucose filtered ~180 g/day

The kidney reabsorbs and recirculates glucose

- Glucose reabsorbed ~180 g/day

Glucose handling in Type 2 diabetes\textsuperscript{1,2}

**Glucose input >280 g/day:**
- Dietary intake >180 g/day
- Glucose production ~100 g/day
  - Gluconeogenesis*  
  - Glycogenolysis

**Glucose uptake >250 g/day:**
- Brain ~125 g/day
- Rest of the body >125 g/day

---

Average blood glucose concentration **150 mg/dL**  
Kidney filters all circulating glucose

Glucose filtered ~270 g/day

*Increased* reabsorption and recirculation of glucose

Above the renal threshold for glucose (~200 mg/dL), glucose is excreted in the urine (glucosuria)

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\*Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.  
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

• Inhibits SGLT2, a transporter in the proximal tubule, reducing glucose reabsorption leading to an increase in urinary glucose excretion

• Accompanied by weight loss and modest blood pressure reduction together with lower risk of hypoglycaemia.

• Not recommended for those on concomitant treatment with loop diuretic.

• Efficacy dependent on renal function and not recommended in patients with renal impairment (e-GFR <60 L/min/1.73 m²)
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

- Can be combined with other OAD(s) to improve glucose control.
- Has been shown to increase glucagon level and combining it with DPP-4 inhibitor will compensate this.
- Side effects include significant increased of genitalia and urinary tract infection.
- US FDA has issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture.
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

- Few cases of euglycaemic diabetic ketoacidosis (DKA) had been reported in patients on SGLT2 inhibitors and caution should be exercised when prescribing in those with severe beta-cell insufficiency, latent autoimmune diabetes and in post-surgical patients.

- EMPA-REG clinical trial conducted in T2DM patients with prior cardiovascular events showed a lower rate of cardiovascular events and all-cause mortality. The reasons behind these findings yet to be determined.
# SGLT2 Inhibitors Formulations and Dosage

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>5 mg OD</td>
<td>10 mg OD</td>
</tr>
<tr>
<td>5 mg / 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>100 mg OD</td>
<td>300 mg OD</td>
</tr>
<tr>
<td>100 mg / 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 mg OD</td>
<td>25 mg OD</td>
</tr>
<tr>
<td>10 mg / 25 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General Guidelines for Use of OAD Agents

- OAD can be used as monotherapy or in combination with other OAD(s), and/or injectable agents (e.g. insulin, GLP-1 receptor agonist).

- Agents that are known to improve fasting hyperglycaemia include metformin and TZDs while others reduce mainly postprandial hyperglycaemia.

- As first line therapy, metformin is the preferred choice. Other OAD agents are acceptable alternatives.

- If glycaemic targets are not achieved, intensification of treatment should be made every 3 months.

- If monotherapy fails, combination of other agents is recommended.
### What Comes After Metformin?

Depends on:

- Patient characteristics
- Drug characteristics
- Degree of hyperglycemia
- BG lowering efficacy & durability
- Risk of hypoglycemia
- Risk of inducing hypoglycemia
- Weight
- Effect on weight
- Comorbidities (renal, cardiac, hepatic)
- Contraindications & side effects
- Access to treatment
- Cost and coverage
- Patient preferences
- Other

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Drug characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of hyperglycemia</td>
<td>BG lowering efficacy &amp; durability</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Risk of inducing hypoglycemia</td>
</tr>
<tr>
<td>Weight</td>
<td>Effect on weight</td>
</tr>
<tr>
<td>Comorbidities (renal, cardiac, hepatic)</td>
<td>Contraindications &amp; side effects</td>
</tr>
<tr>
<td>Access to treatment</td>
<td>Cost and coverage</td>
</tr>
<tr>
<td>Patient preferences</td>
<td>Other</td>
</tr>
</tbody>
</table>
General Guidelines for Use of OAD Agents

• Compliance may be improved with daily dosing OAD agents.

• OAD agents are usually not the first line therapy in stress hyperglycaemia. Insulin therapy is recommended.

• Targets for control should be individualised.

• When indicated, start with a minimal dose of OAD agent, while re-emphasising diet and physical activity. This dose should be optimised gradually.

• OAD agents are not recommended for diabetes in pregnancy.
Treat multiple pathophysiological abnormalities that contribute to hyperglycaemia in T2DM

- Increased lipolysis
- Increased glucagon secretion
- Increased hepatic glucose production
- Impaired insulin secretion
- Decreased incretin effect
- Increased glucose reabsorption
- Decreased glucose uptake
- Neurotransmitter dysfunction

...before initiating insulin as long as A1c < 10%

3.7.1 Algorithm 5: Treatment Algorithm for Newly Diagnosed T2DM

**Diagnosis of Type 2 Diabetes**

**Lifestyle Modification**

**LIFESTYLE APPROACH**
- If postprandial is >11.0 mmol/L, consider one of the following:
  - Metformin
  - Meglitinide
  - AGI
  - DPP-4i
  - SGLT2i
- Follow-up with A1c after 3 months
  - If A1c ≤6.5%, continue with Lifestyle Approach.
  - If A1c >6.5%, refer Table 21.

**OAD MONOTHERAPY**
- Metformin
- OR
- SU
- Meglitinide
- AGI
- TZD
- DPP-4i
- GLP-1 RA
- SGLT2i
- Optimize dose of OAD agent in the subsequent 3 months.
  - Follow-up with A1c after 3 months
  - If A1c ≤6.5%, continue therapy

**DUAL COMBINATION THERAPY**
- Any two combination of:
  - Metformin
  - SU
  - Meglitinide
  - AGI
  - TZD
  - DPP-4i
  - GLP-1 RA
  - SGLT2i
- Optimize dose of OAD agents in the subsequent 3 months.
  - Follow-up with A1c after 3 months
  - If A1c ≤6.5%, continue therapy

**TRIPLE COMBINATION THERAPY**
- Any three combination of:
  - Metformin
  - SU
  - Meglitinide
  - AGI
  - TZD
  - DPP-4i
  - GLP-1 RA
  - SGLT2i
- Insulin
- Optimize dose of OAD agents in the subsequent 3 months.
  - Follow-up with A1c after 3 months
  - If A1c ≤6.5%, continue therapy

**COMBINATION THERAPY**
- Basal / Premixed Insulin Therapy
  - OR
  - Intensive Insulin Therapy

*The agents above are based on historical order*

**Footnote:**
- Metformin: Efficacious, low risk of hypoglycaemia and weight neutral
- SU, Glinides, Insulin: Efficacious, risk of hypoglycaemia and weight gain
- DPP-4i: Moderate efficacy, low risk of hypoglycaemia and weight neutral
- GLP-1 RA, SGLT-2i: Moderate efficacy, low risk of hypoglycaemia and weight loss
- TZD: Moderate efficacy, low risk of hypoglycaemia and weight gain
- AGI: Modest efficacy, low risk of hypoglycaemia and weight neutral

**Note:** Please note that the diagnosis of diabetes begins at A1c ≥6.3% (based on the MSSM study), while the A1c target for treatment is ≤6.5% (based on the ADVANCE study).
Multiple, Complex Pathophysiological Abnormalities in T2DM

- GLP-1R agonists
- DPP-4 inhibitors
- Amylin mimetics
- Glinides
- SUs
- Insulin
  - pancreatic insulin secretion
- DPP-4 inhibitors
- GLP-1R agonists
- AGLs
- Hyperglycemia
- Metformin
- Bile acid sequestrants
- TZDs
- Peripheral glucose uptake
- Hepatic glucose production
- Renal glucose excretion

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
### Table 21: Treatment Recommendations for Patients on Clinic Follow-up

<table>
<thead>
<tr>
<th>Current Treatment</th>
<th>A1c 6.5–&lt;7.5% or FPG 6–&lt;8 mmol/L</th>
<th>A1c 7.5–&lt;8.5% or FPG 8–&lt;10 mmol/L</th>
<th>A1c 8.5–10.0% or FPG 10–13 mmol/L</th>
<th>A1c &gt;10.0% or FPG &gt;13 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Start metformin (if metformin not tolerated, use an agent from Box 1)</td>
<td>Start metformin and another agent from Box 1 (dual therapy)</td>
<td>Start metformin and 2 other agents from Box 1 (triple therapy)</td>
<td>Start metformin &amp; another agent + insulin (basal or premixed od)</td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td>Add 1 agent from Box 1 (dual therapy)</td>
<td>Add 2 agents from Box 1 (triple therapy)</td>
<td>Add 2 agents from Box 1 + insulin (basal or premixed od)</td>
<td>Initiate &amp; intensify insulin (MDI) and continue metformin</td>
</tr>
<tr>
<td><strong>Dual Therapy</strong></td>
<td>Add 1 agent from Box 1 (triple therapy)</td>
<td>Add 1 agent from Box 1 or insulin (basal or premixed od)</td>
<td>Add 1 agent from Box 1 + insulin (basal or premixed od)</td>
<td>Initiate &amp; intensify insulin (MDI) and continue dual therapy (except SU/glinides)</td>
</tr>
<tr>
<td><strong>Triple Therapy</strong></td>
<td>Add 1 agent from Box 1 (quadruple therapy)</td>
<td>Add 1 agent from Box 1 or insulin (basal or premixed od)</td>
<td>Add insulin (basal or premixed od) and continue triple therapy</td>
<td>Initiate &amp; intensify insulin (MDI) and continue triple therapy (except SU/glinides)</td>
</tr>
</tbody>
</table>

MDI = Multiple daily injections; $^\text{§}$ Intensify involves changing the regimen; SU = sulphonylureas

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**Box 1: Selection of Anti-diabetic Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effectiveness</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU</td>
<td>Efficacious, risk of hypoglycaemia, weight gain</td>
<td>Efficacious, risk of hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Modest efficacy, low risk of hypoglycaemia, weight neutral</td>
<td>Modest efficacy, low risk of hypoglycaemia, weight neutral</td>
</tr>
<tr>
<td>AGI</td>
<td>Efficacious, low risk of hypoglycaemia, weight gain</td>
<td>Efficacious, low risk of hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>TZD</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight neutral</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight neutral</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight loss</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight loss</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight loss</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight loss</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight loss</td>
<td>Moderate efficacy, low risk of hypoglycaemia, weight loss</td>
</tr>
</tbody>
</table>
Suggested Treatment Approach for Specific Patient Profiles

2nd Gen SU: selected 2nd generation sulphonylurea (gliclazide); DPP-4i: dipeptidyl peptidase-4 inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist. DPP-4i should be stopped once GLP-1 RA is introduced.

- Patients who are well-controlled on their existing drugs should continue with the treatment regime.
- Bariatric surgery may be considered in patients with BMI ≥32 kg/m² and their diabetes not controlled by lifestyle changes and pharmacotherapy.
Weight gain in T2DM: a common side effect post treatment

The vicious circle of type 2 diabetes

Treatment → Obesity → Insulin resistance → Type 2 diabetes → Treatment

Weight gain is a common side effect of diabetes treatments

OAD agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin$^{1-3}$</td>
<td>−3.8−0.5</td>
</tr>
<tr>
<td>SU$s^{1-4}$</td>
<td>−0.4−1.7</td>
</tr>
<tr>
<td>TZD$s^{4-6}$</td>
<td>0.9−4.6</td>
</tr>
<tr>
<td>Meglitinides$^{4,7,8}$</td>
<td>0.3−3.0</td>
</tr>
<tr>
<td>Metformin + SU$^{1-3}$</td>
<td>−0.3−1.9</td>
</tr>
<tr>
<td>Metformin + TZD$^{5,6,9}$</td>
<td>0.8−2.1</td>
</tr>
</tbody>
</table>

OAD=oral antidiabetic drug; SU=sulfonylurea; TZD=thiazolidinedione


7Starlix [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2004
9Avandamet [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2005
Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolites</th>
<th>Route of Elimination</th>
<th>eGFR (mL/min)</th>
<th>Acceptable to use</th>
<th>Do not use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin[a,b]</td>
<td>Unchanged</td>
<td>~ 100% urine</td>
<td>&gt; 60</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60-30</td>
<td>✓*</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 30</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 15</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- Metformin is eliminated renally, and (rare) cases of lactic acidosis have been described in CKD patients[a]
- In T2DM patients[b]:
  - Reduce dose if GFR < 45 mL/min
  - Do not use if GFR < 30 mL/min


*Dose adjustment required
## Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment (cont)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolites</th>
<th>Route of Elimination</th>
<th>eGFR (mL/min)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 60</td>
<td>60-30</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Active</td>
<td>~ 60% urine</td>
<td>✓</td>
<td>✓*</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Inactive</td>
<td>~ 70% urine</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Inactive</td>
<td>~ 65% urine</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Dose adjustment required*

Slide courtesy of Clifford J. Bailey, PhD.
## Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment (cont)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolites</th>
<th>Route of Elimination</th>
<th>eGFR (mL/min)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 60</td>
<td>60-30</td>
<td>&lt; 30</td>
<td>&lt; 15</td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Inactive</td>
<td>~ 90% bile</td>
<td>✓</td>
<td>✓</td>
<td>✓*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Active</td>
<td>~ 55% bile</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>Metabolites formed in gut</td>
<td>~ 2% urine</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Dose adjustment required

---

Slide courtesy of Clifford J. Bailey, PhD.
## Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment (cont)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolites</th>
<th>Route of Elimination</th>
<th>eGFR (mL/min)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 60</td>
<td>60-30</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Mostly eliminated through glomerular filtration</td>
<td>Mostly urine</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Degraded in the circulation, liver, and kidney</td>
<td>Partly urine</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Insulin</td>
<td>Degraded in the circulation, liver, and kidney</td>
<td>Partly urine</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Dose adjustment required

---

Slide courtesy of Clifford J. Bailey, PhD.
## Efficacy of Various Anti-diabetic Agents

<table>
<thead>
<tr>
<th>MET</th>
<th>SU</th>
<th>GLN</th>
<th>AGI</th>
<th>TZD</th>
<th>DPP4-i</th>
<th>SGLT2-i</th>
<th>GLP-1 RA</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c reduction, %</td>
<td>1.0-1.5</td>
<td>0.4-1.6</td>
<td>1.0-1.2</td>
<td>0.5-0.8</td>
<td>0.5-1.4</td>
<td>0.5-0.8</td>
<td>0.2-0.8</td>
<td>0.5-1.4</td>
</tr>
<tr>
<td>FPG vs PPG</td>
<td>FPG</td>
<td>FPG</td>
<td>Both</td>
<td>PPG</td>
<td>FPG</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>←→</td>
<td>↑↑</td>
<td>↑</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Weight change</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
<td>←→</td>
<td>↑↑</td>
<td>←→</td>
<td>←→</td>
<td>↓↓</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>↑↑</td>
<td>←→</td>
<td>←→</td>
<td>↑↑</td>
<td>←→</td>
<td>←→</td>
<td>↑</td>
<td>←→</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>↑</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>↓</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>↓?</td>
<td>←→</td>
</tr>
<tr>
<td>Bone loss</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>CKD</td>
<td>Avoid if GFR&lt;30</td>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>←→</td>
<td>Fluid retention</td>
<td>Dose adjustment</td>
<td>Avoid if GFR&lt;60</td>
<td>Avoid if GFR&lt;30</td>
</tr>
</tbody>
</table>

**References**

77 (Level I) 168,169 (Level I) 85 (Level I) 170 (Level I) 88-92 (Level I) 151-153 (Level I) 113-116 (Level I) 121 (Level I) 160,161,171, 172 (Level I)

MET = metformin; SU = sulphonylureas; GLN = glinides; GLP-1 RA = glucagon-like peptide-1 receptor agonists; DPP4-i = dipeptidyl peptidase-4 inhibitors; SGLT2-i = sodium-glucose co-transporter 2 inhibitors; AGI = α-glucosidase inhibitor; TZD = thiazolidinediones

The efficacy data for the above anti-diabetic agents were established with baseline A1c level below 10%. Efficacy of all OADs is dependent on the baseline A1c levels. The higher the A1c level, the more efficacious is the agent.
Proactive management of glycaemia: Early combination approach

- Diet
- OAD monotherapy
- OAD combinations
- OADs up-titration
- OAD + basal insulin
- OAD + multiple daily insulin injections

HbA1c (%)

Duration of diabetes
Treatment strategy

• Choice of monotherapy – cost, availability, durability of drug, fit the phenotype

• More aggressive strategy – combination therapy for those with more severe hyperglycemia at diagnosis

• Earlier intensification of treatment

• Rational use of drugs with complementary mechanisms of action

• Ongoing patient education – adherence to lifestyle interventions and pharmacotherapy
“The ability of clinicians to judge the merits of new medications is already limited — most receive their information about them from drug companies' representatives and promotional materials.”

Summary

• Need to treat early & more aggressively.

• Treat to goal, treat to phenotype, individualised.

• Early combination therapy but keep regimens simple.

• Achieve effective and sustained glycaemic control.

• Continuous strong multidisciplinary patient support and education.