## Type 2 Diabetes Mellitus Hypoglycaemic Agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Drug Name (eg brand name)</th>
<th>Cost / PBS per 28d mth</th>
<th>Concerns?</th>
<th>&quot;Claimed&quot; Hba1c benefit vs placebo (time maintained)*</th>
<th>Side effects</th>
<th>Keys to remember!</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
<td>Metformin (Diaformin, Diabex)</td>
<td>$10.24 (1.5g dly)</td>
<td>Lactic acidosis - <em>(so not if liver disease, renal impairment, alcohol issues, and careful if &gt;80yo.)</em>&lt;br&gt; B12 defn in long term use and increased homocysteine levels (5)</td>
<td>~1% (10mts-1.5g)</td>
<td>Diarrhoea</td>
<td><strong>First line</strong> Decreased all cause mortality and BETTER CV profile. Reduces LDL <strong>MUST Stop if eGFR &lt;30 or Lactic Acidosis possible!</strong></td>
</tr>
<tr>
<td><strong>Sulfonylurea</strong></td>
<td>Gliclazide (Diamicron), Glipizide, Glipenclamide, (Glimel) Glimepiride (diapride)</td>
<td>$15.77 (1 dly)</td>
<td>?Increased all cause mortality&lt;br&gt; ?Increased CV disease risk&lt;br&gt; ?Stroke Studies ongoing. (4)</td>
<td>~1.25% (2yrs)</td>
<td>Weight gain</td>
<td>Can cause <strong>Hypoglycaemia</strong>&lt;br&gt; Possible all cause mortality issues?&lt;br&gt; <strong>Weight gain</strong> possible!</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td>Pioglitazone (Actos)</td>
<td>$75 (1 dly)</td>
<td>Pioglitazone - Small increase in bladder cancer&lt;br&gt; Rosiglitazone - increased CV events &amp; worse cholesterol profile&lt;br&gt; Fluid retention - Not for NYHF 3/4 Macular oedema&lt;br&gt; ?Osteoporosis&lt;br&gt; Mild increase in weight? (1)</td>
<td>~1 -1.5% (0.5yrs)</td>
<td>Muscle pain Dizziness&lt;br&gt; Headaches&lt;br&gt; Arthralgias&lt;br&gt; Iron deficiency</td>
<td>Be wary in heart failure, elevated cholesterol, and macular family history issues. Expensive.</td>
</tr>
<tr>
<td>DPP4 - Inhibitors</td>
<td>Sitagliptin (Januvia)</td>
<td>Saxagliptin (Onglyza)</td>
<td>$75 (1 dly)</td>
<td>Onglyza - ?increased bone fractures</td>
<td>~0.75% (1 yr)</td>
<td>No weight gain Dizziness Headaches Cold-like symptoms Increased infections Resp/Urinary</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pancreatitis possible in the other types</td>
<td></td>
<td>Expensive. Watch for <strong>abdominal pain for pancreatitis</strong> Possible benefit of CV profile? Ongoing research.</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Dapagliflozin (Forxiga)</td>
<td>Canagliflozin (Invokana)</td>
<td>$75 (1 dly)</td>
<td>Genital infections in 8% (usually thrush - M&amp;F) UTI also more common ?? Bone effects</td>
<td>~1% (0.5yrs) ~ 0.5% (1yr)</td>
<td>Polyuria, frequency, nocturia thirst Weight reduction 2-3kg (at 24wks - uncertain longer) (?). ? Reduction in BP?</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Early days for this medication.</strong> <strong>Genital infections and UTI risks</strong> Maybe not for post menopausal women?</td>
</tr>
<tr>
<td>GLP1-agonists</td>
<td>Exenatide (Byetta)</td>
<td></td>
<td>$36.90 (1 - 60U of 5 or 10mcg doses)</td>
<td>Pancreatitis Not for eGFR &lt;30 (³)</td>
<td>~ -1.5% (²)</td>
<td>Nausea, vomiting, weight loss, heartburn, dizziness, headache</td>
</tr>
<tr>
<td>(Injectable only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Watch for <strong>abdominal pain for pancreatitis.</strong> (Maybe don’t start if risk factors for this.) Not for eGFR &lt;30</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Acarbose (Glucobay)</td>
<td></td>
<td>$36.90 (1dly)</td>
<td>Hepatitis Cannot use in IBD or bowel obstructions (partial) Ileus Anaemia Oedema</td>
<td>~1% v Placebo (2yrs)</td>
<td>Flatulence Diarrhoea Hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Very difficult to tolerate</strong></td>
</tr>
</tbody>
</table>
### Side effects “at a glance” table

<table>
<thead>
<tr>
<th>Name</th>
<th>Increased CVR</th>
<th>Weight Change</th>
<th>Hypo Risk</th>
<th>LDL Change [6]</th>
<th>GI side effects</th>
<th>Genital infection and ?maybe UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>‼️</td>
<td>-</td>
<td>-</td>
<td>‼️</td>
<td>✔️ - significant</td>
<td>✗</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>‼️?</td>
<td>↑</td>
<td>✔</td>
<td>✗</td>
<td>✗ - mild</td>
<td>✗</td>
</tr>
<tr>
<td>Glitazones</td>
<td>‼️?</td>
<td>↑</td>
<td>✗</td>
<td>✗</td>
<td>Min</td>
<td>✗</td>
</tr>
<tr>
<td>DPP4-Inhib</td>
<td>‼️? (10)</td>
<td>-</td>
<td>✗</td>
<td>✗</td>
<td>Min</td>
<td>✗</td>
</tr>
<tr>
<td>SGLT2 inhib</td>
<td>?</td>
<td>↓</td>
<td>✗</td>
<td>✗</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>‼️?</td>
<td>‼️ (76%) (9)</td>
<td>✗</td>
<td>✗</td>
<td>✔️ - Mild</td>
<td>✗</td>
</tr>
<tr>
<td>Acarbose</td>
<td>‼️ (13)</td>
<td>‼️ (12)</td>
<td>✔</td>
<td>Reduced (11)</td>
<td>✔️! - SIGNIF</td>
<td>✗</td>
</tr>
</tbody>
</table>
References:

Primary Reference: Systematic review and Meta-analysis on type 2 DM medications.

Metformin reference:
http://bjcardio.co.uk/2010/09/drugs-for-diabetes-part-1-metformin/

Sulfonylurea Reference:
http://www.medscape.com/viewarticle/811641#2 (Though careful as researcher sponsored by AstraZeneca, Novo-Nordisk, and Bristol-Myers Squibb)

Glitazones reference:

SGLT2 reference:

DPP4 - Glitins Reference:

(1) - http://www.who.int/selection_medicines/committees/expert/19/applications/Oralhypoglycemics_18_5_A_R.pdf
(3) - http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088117
(4) - http://www.medscape.com/viewarticle/811641 & http://dvr.sagepub.com/content/early/2013/01/03/1479164112465442.full
(7) - http://bjcardio.co.uk/2012/03/drugs-for-diabetes-part-8-slt2-inhibitors/
(8) - https://secure.sherbornegibbs.com/bjdvd/pdf/1008.pdf
(9) - http://www.diabetesincontrol.com/articles/54/12066-successful-weight-loss-with-glp-1-agonists
(13) - http://bjcardio.co.uk/2011/04/drugs-for-diabetes-part-4-acarbose/
Mode of Action – Physiology Refresher

Metformin:
Decreases gluconeogenesis of the liver
Increases glucose uptake at muscle.
Increases insulin sensitivity in the liver

Sulfonylurea:
Causes an increased release of insulin from the pancreas

Glitazones:
Increases insulin sensitivity

SGLT-2 inhibitors:
These BLOCK reuptake of glucose by the nephron and therefore you urinate out the extra glucose

Acarbose:
Inhibits enzymes required to digest carbohydrates

DPP4 Inhibitors: *(Remember this is ONE STEP BEFORE GLP1 agonists - Byetta - so remember them together!)*
Glucagon increases blood glucose --> DPP4 inhibitors increase incretin. Incretin BLOCKS glucagon release and increases insulin release. This DECREASES blood glucose.

Combinations

**Avandamet** = Rosiglitazone + Metformin
**Galvumet** = Vildagliptin + Metformin
**Glucovanse** = Glibenclamide + Metformin
**Janumet XR** = Sitagliptin + Metformin
**Kombiglyze XR** = Saxagliptin + Metformin
**Nesina Met** = Alogliptin + Metformin
**Trajentamet** = Linagliptin + Metformin
**PBS Restrictions brief summary**

**SUMMARY** of PBS restrictions for second line medications (other than sulfonylureas) (see full details on PBS website - Link).

You *need all 3 of these...*

1. Must be used either with metformin OR Sulfonylurea
2. Must have a contraindication to combination of Metformin and Sulfonylurea or have not tolerated them
3. Must have HbA1c measurement >7%, within the last 4mths, PRIOR to initiation despite treatment with metformin or sulfonylurea and you must write this in the notes