

This Type 2 Diabetes Glycaemic Management Algorithm should be read in conjunction with the Living Evidence Guidelines in Diabetes (please click here).

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and **weight management**.

Determine the individual's HbA1c target – commonly  $\leq 53$  mmol/mol (7.0%) but should be appropriately individualised (refer to ADS position statement).

**+** Weight loss of  $\geq 10\%$  will likely allow a reduction or cessation of glucose lowering medication. Consider intensive weight management options including:

- Low energy or very low energy diets with meal replacements
- Pharmacotherapy
- Bariatric surgery.

 **Click here for the Australian Obesity Management Algorithm**

**Review treatment:** if **not** at target HbA1c or if presence of cardiovascular/chronic kidney disease –

- Check patient understanding of self-management including drug treatment
- Ensure current therapies are clinically appropriate including comorbidities/therapies impacting glycaemic control
- Review medication adherence
- Assess tolerability, adverse effects and risk of interactions

Review treatment in 3 months. If HbA1c not at target: Reinforce lifestyle measures and review weight management strategies.

### MONOTHERAPY: Metformin is the usual monotherapy unless contraindicated or not tolerated

Metformin	SU	Insulin	Less commonly used: acarbose, DPP-4 inhibitor, SGLT2 inhibitor GLP-1RA, or TZD. Only acarbose is PBS reimbursed for monotherapy.
-----------	----	---------	--

### DUAL THERAPY: Choice of treatment – add on an oral agent or injectable therapy

Choice of dual therapy should be guided by clinical considerations (presence of, or high risk of, cardiovascular disease, heart failure, chronic kidney disease, hypoglycaemia risk, obesity), side effect profile, contraindications and cost.

SGLT2 inhibitor	GLP-1RA	DPP-4 inhibitor	SU	Insulin	Less commonly used are: acarbose or TZD.
-----------------	---------	-----------------	----	---------	--

### MULTIPLE THERAPIES: Choice of treatment : include additional oral agent or GLP-1 RA or insulin

Choice of agents should be guided by clinical considerations as above. Note: combinations not approved by PBS include GLP-1RA with SGLT2i. Consider reviewing any previous medication that has not reduced HbA1c by  $\geq 0.5\%$  after 3 months and take into consideration **glycaemic AND non-glycaemic benefits**.

SGLT2 inhibitor	GLP-1RA	DPP-4 inhibitor	SU	Insulin	Less commonly used are: acarbose or TZD.
-----------------	---------	-----------------	----	---------	--

THEN...

#### To intensify treatment to meet glycaemic targets

- If on metformin+SU+DPP-4i, consider *adding* SGLT2i, or *switching* DPP-4i to a GLP-1RA, or an SGLT2i.
- When adding incretin therapy, use either a DPP4i or GLP-1RA (not both together).

- If on basal insulin, consider *adding* SGLT2i or GLP-1RA or bolus insulin with meals, or *change* to premixed/coformulated insulin.
- If on metformin+DPP4i+SGLT2i consider adding SU or insulin.

With increasing clinical complexity consider specialist endocrinology consultation

**Note: combinations not approved by PBS include GLP-1RA with SGLT2i. Consider reviewing any previous medication that has not reduced HbA1c by  $\geq 0.5\%$  after 3 months, and take into consideration glycaemic AND non-glycaemic benefits.**

- **Recommendation** for addition of an SGLT2i (or GLP-1RA where SGLT2i is not tolerated or contraindicated) to other glucose lowering medication(s) in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.
- **Conditional recommendation** for metformin as first-line monotherapy in adults with type 2 diabetes.
- **Conditional recommendation** for DPP-4i addition to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT2i or a GLP-1RA due to either intolerance or contraindication.
- **Conditional recommendation against** sulphonylurea being the first choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of severe hypoglycaemia.

■ Dark blue boxes indicate usual therapeutic strategy (order is not meant to denote any specific preference); usual refers to commonly available, evidence based, cost effective therapy.

■ Light blue boxes denote alternate approaches (order is not meant to denote any specific preference).

□ White boxes indicate less commonly used approaches.

PBS = Pharmaceutical Benefits Scheme, HF = heart failure, CKD = chronic kidney disease, SU = sulphonylurea, TZD = thiazolidinedione, DPP-4i = dipeptidyl peptidase-4 inhibitor, GLP-1RA = glucagon like peptide-1 receptor agonist, SGLT2i = sodium glucose co-transporter inhibitor.

For more details click here to access the Living Evidence Guidelines in Diabetes.

# AUSTRALIAN TYPE 2 DIABETES MANAGEMENT ALGORITHM

Table of Evidence and Properties of Glucose-Lowering Agents†

Glucose-lowering Class and Drugs	Mechanism of Action	Outcome data	Contraindications	Precautions, Side Effects and Administration	Cost* and Accessibility
<b>Biguanide</b> • metformin • metformin XR	Reduces hepatic glucose output, lowers fasting glucose levels	<b>UKPDS</b> <sup>1</sup>	Renal impairment (eGFR<30 ml/min/1.73m <sup>2</sup> )  Severe hepatic impairment	<b>Precautions</b> Suspend treatment during acute disease/ conditions with the potential to cause tissue hypoxia or alter renal function.  <b>Side Effects</b> GI side effects, lactic acidosis, weight neutral  <b>Administration</b> Oral Start at low dose and up-titrate Slow release preparations available	General schedule on PBS  \$
<b>Sulfonylureas</b> • glibenclamide • gliclazide • gliclazide MR • glimepiride • gliclazide	Triggers insulin release in a glucose-independent manner	<b>UKPDS</b> <sup>2</sup>  <b>ADVANCE</b> <sup>3</sup> - GliclazideMR	Severe renal or hepatic impairment	<b>Precautions</b> Hypoglycaemia  <b>Side Effects</b> Weight gain  <b>Administration</b> Oral Start at low dose and up-titrate Slow release preparation available	General schedule on PBS  \$
<b>Dipeptidylpeptidase-4 (DPP-4) inhibitors</b> • alogliptin • linagliptin • saxagliptin • sitagliptin • vildagliptin	Decreases inactivation of glucagon-like peptide (GLP-1) thereby increasing its availability. GLP-1 stimulates beta cell insulin release.	<b>EXAMINE</b> <sup>4,5</sup> - Alogliptin  <b>SAVOR-TIMI 53</b> <sup>6,7</sup> - Saxagliptin  <b>TECOS</b> <sup>8</sup> - Sitagliptin  <b>CARMELINA</b> <sup>9</sup> - Linagliptin  <b>CAROLINA</b> <sup>10</sup> - Linagliptin vs Glimepiride	Pancreatitis <sup>11</sup>  Hospitalisation due to heart failure with saxagliptin <sup>6</sup>	<b>Precautions</b> Nasopharyngitis-often subsides in 10-14 days  <b>Side Effects</b> Rash, pancreatitis, GI disturbances, weight neutral  <b>Administration</b> Oral Dosage adjustment in renal impairment (except linagliptin) <sup>12</sup>	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin are PBS subsidised for use with either metformin or sulfonylurea (i.e. dual therapy)  Linagliptin, saxagliptin, sitagliptin and vildagliptin are PBS subsidised for use with metformin and sulfonylurea (i.e. triple therapy)  If on any DPP4i plus metformin, addition of dapagliflozin, empagliflozin or ertugliflozin (i.e. triple therapy) is PBS subsidised  Linagliptin, sitagliptin and vildagliptin are PBS subsidised for use with insulin
<b>Thiazolidinediones (TZD)</b> • pioglitazone  • rosiglitazone is not available in Australia	Transcription factor peroxisome proliferator-activated receptor gamma agonists. Durably lowers glucose levels through insulin sensitisation.	<b>PROACTIVE</b> <sup>13</sup> - Pioglitazone  <b>RECORD</b> <sup>14</sup> - Rosiglitazone		<b>Precautions</b> Symptomatic heart failure  <b>Side Effects</b> Fluid retention, heart failure, increased risk of non-axial fractures in women, increased risk of bladder cancer, weight gain  <b>Administration</b> Oral	PBS subsidised for use in combination with metformin or sulfonylurea or both  Patient must have a contraindication or intolerance to metformin- sulfonylurea combination PBS subsidised for use with insulin
<b>Alpha 1 glucosidase inhibitors</b> • acarbose	Slows intestinal carbohydrate absorption and reduces postprandial glucose levels		Severe renal impairment (creatinine clearance < 25 ml/min/1.73m <sup>2</sup> )	<b>Precautions</b> Gastrointestinal disorders associated with malabsorption  <b>Side effects</b> Bloating and flatulence, weight neutral  <b>Administration</b> Oral Take with meals as tolerated	General schedule on PBS  \$
<b>Sodium-glucose co-transporter-2 (SGLT2) inhibitors</b> • dapagliflozin • empagliflozin • ertugliflozin	Inhibits a Sodium-glucose cotransporter to induce urinary glucose loss and decrease blood glucose levels  Non-glycaemic benefits shown in heart failure and CKD still to be defined	<b>DECLARE</b> <sup>15</sup> - Dapagliflozin <b>DAPA-HF</b> <sup>16</sup> - Dapagliflozin <b>DAPA-CKD</b> <sup>17</sup> - Dapagliflozin  <b>EMPA-REG OUTCOME</b> <sup>18</sup> - Empagliflozin <b>EMPEROR-Reduced</b> <sup>19</sup> - Empagliflozin <b>EMPEROR-Preserved</b> <sup>20</sup> - Empagliflozin  <b>VERTIS-CV</b> <sup>21</sup> - Ertugliflozin	Caution and review use with diuretics	<b>Precautions</b> very low carbohydrate intake, bowel preparation, perioperatively  Reduced or insignificant glycaemic effectiveness at eGFR<45 ml/min/1.73m <sup>2</sup> , however heart failure and chronic kidney disease benefits persist down to an eGFR<25 ml/min/1.73m <sup>2</sup> .  <b>Side effects</b> Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss  <b>Administration</b> Oral	Dapagliflozin and empagliflozin: PBS subsidised for use in combination with metformin, sulfonylurea or both. PBS subsidised for use with insulin  Ertugliflozin: PBS subsidised for use in combination with metformin or sulfonylurea  If on any SGLT2 i plus metformin, addition of either saxagliptin, sitagliptin or linagliptin (i.e. triple therapy) is PBS subsidised  Not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), or glucagon-like peptide-1
<b>Glucagon-like peptide-1 (GLP-1) receptor agonists</b> • dulaglutide • liraglutide • semaglutide	Stimulates beta-cell insulin release and slows gastric emptying  Benefits include weight loss, BP lowering and very low risk of hypoglycaemia unless used with SU or insulin	<b>REWIND</b> <sup>22</sup> -Dulaglutide <b>LEADER</b> <sup>23</sup> -Liraglutide <b>SUSTAIN 6</b> <sup>24</sup> -Semaglutide	Avoid with history of pancreatitis or pancreatic malignancy	<b>Precautions</b> Dosage adjustment in moderate-severe renal impairment, Increased risk of pancreatitis  <b>Side effects</b> Nausea, vomiting, weight loss, increased heart rate  <b>Administration</b> Subcutaneous injection	Dulaglutide and semaglutide: PBS subsidised for use in combination with metformin, sulfonylurea or both  Dulaglutide and semaglutide: PBS subsidised for use with insulin  Not PBS subsidised for use as monotherapy or in combination with DPP-4 inhibitor (gliptin), a thiazolidinedione (glitazone) or an SGLT2 inhibitor
<b>Insulin</b> Can be prescribed as basal (eg glargine), prandial (eg aspart, glulisine) or premix/ coformulation (eg degludec/aspart)	Directly activates the insulin receptor	<b>UKPDS</b> <sup>2</sup> <b>ORIGIN</b> <sup>25</sup> - Insulin glargine  <b>DEVOTE</b> <sup>26</sup> - Insulin degludec		<b>Precautions</b> Consider need for dosage adjustment in moderate-severe renal disease  <b>Side effects</b> Hypoglycaemia, weight gain  <b>Administration</b> Subcutaneous injection-consider early if BGL is very high	General schedule on PBS  \$-\$\$\$

† Gunton JE et al. MJA 2011, 201(11), 650-53.

\*COST: \$ = \$0-\$499 \$\$ = \$500-\$999; \$\$\$ = > \$1,000 per annum cost to the PBS

References:

1. UKPDS Group. Lancet 1998;352:854-65. 2. UKPDS Group. Lancet 1998;352:837-53. 3. ADVANCE Collaborative Group. NEJM 2008;358:2560-72. 4. White WB, et al. NEJM 2013;369:1327-35. 5. Zannad F et al. Lancet 2015;385:2067-76. 6. Scirica BM, et al. NEJM 2013;369:1317-26. 7. Scirica BM, et al. Circulation 2014;130:1579-88. 8. Green JB, Bethel MA, et al. NEJM 2015;373:232-42. 9. Rosenstock J, et al. JAMA 2018; 321:69-79. 10. Rosenstock J, et al. JAMA 2019; In Press. 11. Meier JJ, et al. Diabetologia 2014;57:1320-1324. 12. McGill JB, et al. Diabetes Care 2013;36:237-44. 13. Dormandy JA, et al. Lancet 2005;366:1279-89. 14. Home PD, et al. Lancet 2009; 373:2125-35. 15. Wiviott SD, et al. NEJM 2019; 380:347-357. 16. McMurray JVV, et al. NEJM 2019;381:1995-2008. 17. Heerspink HJL, et al. NEJM 2020;383:1436-1446. 18. Zinman B, et al. NEJM 2015;372:2117-28. 19. Packer M et al. NEJM 2020; 383:1413-24. 20. Anker SD, et al. NEJM 2021; 385:1451-61. 21. Cannon CP, et al. NEJM 2020; 383:1425-1435. 22. Gerstein HC, et al. Lancet 2019; 394:121-130. 23. Marso SP, et al. NEJM 2016;375:311-322. 24. Marso SP, et al. NEJM 2016;375: 1834-1844. 25. ORIGIN Trial Investigators, NEJM 2012; 367:319-328. 26. Marso SP, et al. NEJM 2017; 377:723-732.  
 © Australian Diabetes Society 2023.