AUSTRALIAN TYPE 2 DIABETES GLYCAEMIC MANAGEMENT ALGORITHM

National Diabetes Services Scheme
An Australian Government Initiative

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

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

Effect of changes in therapy should be reviewed in 3 months.

Weight loss of ≥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 education regarding lifestyle measures, physical activity and review weight management strategies.

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

Metformin | **SU** | **Insulin** | Less commonly used are PBS approved: acarbose or TGA approved (but not PBS approved for monotherapy) DPP-4 inhibitor, SGLT2 inhibitor GLP-1RA, or TZD

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 | **DPP-4 inhibitor** | **GLP-1RA** | **SU** | **Insulin** | Less commonly used are PBS approved: 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 or GLP-1RA with insulin (#). Consider *stopping* any previous medication that has not reduced HbA1c by ≥0.5% after 3 months, **unless indicated for non-glycaemic benefits.**

SGLT2 inhibitor | **DPP-4 inhibitor** | **GLP-1RA** | **SU** | **Insulin** | Less commonly used are PBS approved: 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.
- If on metformin+DPP-4i+SGLT2i consider *adding* SU or *adding* insulin.
- If on GLP-1RA consider *adding* basal or premixed/coformulated insulin (#).
- If on basal insulin, consider *adding* SGLT2i or GLP-1RA# or bolus insulin with meals, or *change* to premixed/coformulated insulin.
- Consider *stopping* medication that has not reduced HbA1c by ≥0.5% after 3 months unless indicated for non-glycaemic benefits.

With increasing clinical complexity consider specialist endocrinology consultation

For patients with high risk/established CVD, studies have shown improved all cause and CV death and non-fatal MI when used with usual care.

For patients with high risk/established heart failure (HF)/HF hospitalisation, studies have shown improved outcomes when used with usual care.

For patients with CKD as defined by albuminuria and/or eGFR >30 ml/min/1.73m^2, studies have shown reductions in important major renal end points, when used with usual care.

Exenatide (Byetta), dulaglutide (Trulicity) and semaglutide (Ozempic) are the GLP-1RA approved on the PBS for use with insulin.

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 =sulfonylurea, TZD = thiazolidinedione, DPP-4i = dipeptidyl peptidase-4 inhibitor, GLP-1RA = glucagon like peptide-1 receptor agonist, SGLT2i = sodium glucose co-transporter inhibitor.

ads Australian Diabetes Society

diabetes australia

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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
Biguanide • metformin • metformin XR	Reduces hepatic glucose output, lowers fasting glucose levels	**UKPDS**[1]	Renal impairment (eGFR<30 ml/min/m^2) Severe hepatic impairment	**Precautions** Suspend treatment during acute disease/ conditions with the potential to cause tissue hypoxia or alter renal function. **Side Effects** GI side effects, lactic acidosis, weight neutral **Administration** Oral Start at low dose and up-titrate Slow release preparations available	General schedule on PBS **$**
Sulfonylureas • glibenclamide • gliclazide • gliclazide MR • glimepiride • glipizide	Triggers insulin release in a glucose-independent manner	**UKPDS**[2] **ADVANCE**[3] - Gliclazide MR	Severe renal or hepatic impairment	**Precautions** Hypoglycaemia **Side Effects** Weight gain **Administration** Oral Start at low dose and up-titrate Slow release preparation available	General schedule on PBS **$**
Dipeptidylpeptidase-4 (DPP-4) inhibitors • alogliptin • linagliptin • saxagliptin • sitagliptin • vildagliptin	Decreases inactivation of glucagon-like peptide (GLP-1) thereby increasing its availability. GLP-1 stimulates beta cell insulin release.	**EXAMINE**[4,5] - Alogliptin **SAVOR-TIMI 53**[6,7] - Saxagliptin **TECOS**[8] - Sitagliptin **CARMELINA**[9] - Linagliptin **CAROLINA**[10] - Linagliptin vs Glimepiride	Pancreatitis[11] Hospitalisation due to heart failure with saxagliptin[6]	**Precautions** Nasopharyngitis-often subsides in 10-14 days **Side Effects** Rash, pancreatitis, GI disturbances, weight neutral **Administration** Oral Dosage adjustment in renal impairment (except linagliptin)[12]	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin are PBS subsidised for use with either metformin or sulfonylurea (i.e. dual therapy) **$$** Linagliptin, saxagliptin, sitagliptin and vildagliptin are PBS subsidised for use with metformin and sulfonylurea (i.e. triple therapy) If on any DPP4i plus metformin, addition of dapagliflozin, empagliflozin or ertugliflozin (i.e. triple therapy) is PBS subsidised Linagliptin, sitagliptin and vildagliptin are PBS subsidised for use with insulin
Thiazolidinediones (TZD) • pioglitazone • rosiglitazone is no longer available in Australia	Transcription factor peroxisome proliferator-activated receptor gamma agonists. Durably lowers glucose levels through insulin sensitisation.	**PROACTIVE**[13] - Pioglitazone **RECORD**[14] - Rosiglitazone		**Precautions** Symptomatic heart failure **Side Effects** Fluid retention, heart failure, increased risk of non-axial fractures in women, increased risk of bladder cancer, weight gain **Administration** Oral	PBS subsidised for use in combination with metformin or sulfonylurea or both **$$** Patient must have a contraindication or intolerance to metformin- sulfonylurea combination PBS subsidised for use with insulin
Alpha 1 glucosidase inhibitors • acarbose	Slows intestinal carbohydrate absorption and reduces postprandial glucose levels		Severe renal impairment (creatinine clearance < 25 ml/min/m^2)	**Precautions** Gastrointestinal disorders associated with malabsorption **Side effects** Bloating and flatulence, weight neutral **Administration** Oral Take with meals as tolerated	General schedule on PBS **$**
Sodium-glucose co-transporter-2 (SGLT2) inhibitors • dapagliflozin • empagliflozin • ertugliflozin • canagliflozin is no longer available in Australia	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	**EMPA-REG OUTCOME**[15] - Empagliflozin **CANVAS**[16] - Canagliflozin **CREDENCE**[17] - Canagliflozin **DECLARE**[18] - Dapagliflozin **DAPA-HF**[19] - Dapagliflozin **EMPEROR-Reduced**[20] - Empagliflozin **VERTIS-CV**[21] - Ertugliflozin **DAPA-CKD**[22] - Dapagliflozin **EMPEROR-Preserved**[23] - Empagliflozin	Caution and review use with diuretics	**Precautions** very low carbohydrate intake, bowel preparation, perioperatively Reduced or insignificant glycaemic effectiveness at eGFR<45 ml/min/1.73m^2, however heart failure and chronic kidney disease benefits persist down to an eGFR<25 ml/min/1.73m^2. **Side effects** Dehydration, dizziness, genitourinary infections (advise adequate fluid intake and meticulous toileting hygiene), ketoacidosis, weight loss **Administration** Oral	Dapagliflozin and empagliflozin: PBS subsidised for use in combination with metformin, sulfonylurea or both. PBS subsidised for use with insulin **$$** Ertugliflozin: PBS subsidised for use in combination with metformin or sulfonylurea If on any SGLT2 i plus metformin, addition of either saxagliptin, sitagliptin or linagliptin (i.e. triple therapy) is PBS subsidised Not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), or glucagon-like peptide-1
Glucagon-like peptide-1 (GLP-1) receptor agonists • dulaglutide • exenatide • exenatide ER • liraglutide • lixisenatide • semaglutide	Stimulates beta-cell insulin release and slows gastric emptying Benefits include weight loss , BP lowering and very low risk of hypoglycaemia unless used with SU or insulin	**ELIXA**[24,25] -Lixisenatide **LEADER**[26] -Liraglutide **SUSTAIN 6**[27] -Semaglutide **EXSCEL**[28] -Exenatide **REWIND**[29] -Dulaglutide	Avoid with history of pancreatitis or pancreatic malignancy	**Precautions** Dosage adjustment in moderate-severe renal impairment, Increased risk of pancreatitis **Side effects** Nausea, vomiting, weight loss, increased heart rate **Administration** Subcutaneous injection	Exenatide, exenatide-ER, dulaglutide and semaglutide: PBS subsidised for use in combination with metformin, sulfonylurea or both **$$$** Exenatide (but not exenatide ER), 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
Insulin Can be prescribed as basal, prandial or premix/coformulation	Directly activates the insulin receptor	**UKPDS**[2] **ORIGIN**[30] - Insulin glargine **DEVOTE**[31] - Insulin degludec		**Precautions** Consider need for dosage adjustment in moderate-severe renal disease **Side effects** Hypoglycaemia, weight gain **Administration** Subcutaneous injection-consider early if BGL is very high	General schedule on PBS **$-$$$** Levemir Insulin: PBS subsidy restricted to Type 1 diabetes

† Gunton JE et.al. MJA 2014, 201(11), 650-53.

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

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