AUSTRALIAN TYPE 2 DIABETES **MANAGEMENT ALGORITHM**

Australian Diabetes Society

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 reviewed regularly.

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

Move down the algorithm if not at target HbA1c :

- Check and review current therapies
- Review adherence to medications
- Check for side effects
- Exclude other comorbidities/therapies impacting on glycaemic control
- Check patient understanding of treatment and self-management.

+ Consider intensive weight management. Weight loss of ≥10% may allow a reduction or cessation of glucose lowering medication. Options include:

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

Click here for the Australian Obesity Management Algorithm

If HbA1c not at target: Reinforce education regarding lifestyle measures; physical activity and weight control • Review clinical goals including HbA1c targets.

FIRST LINE: Metformin is usual first line therapy unless contraindicated or not tolerated

Metformin	SU	Insulin	
$	$ *	$$$	Less commonly used are PBS approved acarbose or TGA approved DPP-4 inhibitor, SGLT2 inhibitor or TZD

Check HbA1c target in 3 months: If not achieved move down algorithm

SECOND LINE: Choice of treatment – add on an oral agent or injectable therapy

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

SGLT2 inhibitor	DPP-4 inhibitor	SU	GLP-1RA	Insulin	
$$	$$	$ *	$$$	$$$	Less commonly used are PBS approved acarbose or TZD

THIRD LINE: Choice of treatment : include additional oral agent or GLP-1 RA or insulin

Choice of third-line agent 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 second-line medication that has not reduced HbA1c by ≥0.5% after 3 months unless indicated for non-glycaemic benefits.

SGLT2 inhibitor	DPP-4 inhibitor	SU	GLP-1RA	Insulin	
$$	$$	$ *	$$$	$$$	Less commonly used are PBS approved acarbose or TZD

THEN...

- 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* third-line 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

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

♥ For patients with high risk/established CVD, studies have shown improved major adverse cardiovascular endpoints (MACE) and heart failure (HF)/HF hospitalisation when used with usual care.

For patients with CKD as defined by albuminuria and/or eGFR 45-90 ml/min/1.73m², studies have shown reductions in important major renal end points (MREP) when used with usual care.

* Long-term reduction in end-stage kidney disease associated with intensive glucose control.

\# Exenatide (Byetta) is the only 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.

White boxes indicate less commonly used approaches.

PBS = Pharmaceutical Benefits Scheme, **MACE** = major adverse cardiovascular events, **MREP** = major renal end points, **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.

diabetes australia

NDSS National Diabetes Services Scheme
An Australian Government Initiative

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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	Transcription factor peroxisome proliferator-activated receptor PPARγ agonists. Lowers glucose levels through insulin sensitization	**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	**EMPA-REG OUTCOME**[15] - Empagliflozin **CANVAS**[16] - Canagliflozin **CREDENCE**[17] - Canagliflozin **DECLARE**[18] - Dapagliflozin **DAPA-HF**[19] - Dapagliflozin **EMPEROR-Reduced**[20] - Empagliflozin	Contraindicated at eGFR <45 ml/min/m^2 Avoid use with loop diuretics.	**Precautions** very low carbohydrate intake, bowel preparation, perioperatively **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	**ELIXA**[21,22] - Lixisenatide **LEADER**[23] - Liraglutide **SUSTAIN 6**[24] - Semaglutide **EXSCEL**[25] - Exenatide **REWIND**[26] - 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 **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): 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 a SGLT2 inhibitor
Insulin	Directly activates the insulin receptor	**UKPDS**[2] **ORIGIN**[27] - Insulin glargine **DEVOTE**[28] - Insulindegludec		**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 subsidisation restricted to Type 1 diabetes

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

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.** Zinman B, et al. NEJM 2015;372:2117-28. **16.** Neal B, et al. NEJM 2017;377:644-657. **17.** Perkovic V, et al. NEJM 2019;380:2295-2306. **18.** Wiviott SD, et al. NEJM 2019; 380:347-357. **19**. McMurray JJV, et al. NEJM 2019;381:1995-2008. **20.** Packer M et al. NEJM 2020; In Press. **21.** Pfeff MA, et al. Symposium, 75th Scientific Sessions of the American Diabetes Association; Boston, MA; 2015. **22.** Bentley-Lewis R, et al. Am Heart J 2015;169:631-38. **23.** Marso SP, et al. NEJM 2016;375:311-322. **24.** Marso SP, et al NEJM 2016;375: 1834-1844. **25**. Holman RR, et al. NEJM 2017;377:1228-1239. **26.** Gerstein HC, et al. Lancet 2019; 394:121-130. **27.** ORIGIN Trial Investigators, NEJM 2012, 367:319-328. **28.** Marso SP, et al. NEJM 2017; 377:723-732.