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TYPE 2 DIABETES MELLITUS: NON-INSULIN GLUCOSE-LOWERING PHARMACOTHERAPY

- **HbA1c targets should be individualised to the patient**
- **Glucose-lowering therapies should be individualised to the patient**
- **Metformin is generally recommended as first-line pharmacological therapy for most people with type 2 diabetes mellitus (T2DM)**
- **The cardiorenal benefits of newer glucose-lowering therapies, regardless of baseline HbA1c, provide important progress in reducing the target-organ complications of T2DM**

INTRODUCTION

This bulletin reviews the non-insulin glucose-lowering pharmacological therapies used in the management of type 2 diabetes mellitus (T2DM). As discussed in the previous bulletin (NMIC 2023;Vol 29:No 5), all patients with T2DM should be offered individualised lifestyle advice including weight management, physical activity, dietary guidance and smoking cessation.[1] Traditionally, the management of T2DM emphasised the importance of using glucose-lowering therapy to reduce the HbA1c (e.g. glucose-centric approach), however recent guidelines recommend a multi-morbidity risk management approach.[2-5] This includes identification of the patient's risk for cardiovascular disease (CVD), and the use of glucose-lowering therapy with proven effects on reducing CVD risk in those with established CVD or at high risk of CVD, in addition to the achievement of a glycaemic target.[2-5] Therefore, a patient-centric approach to the use of glucose-lowering medication based on individual characteristics and co-morbidities is recommended.[2-4]

Similar to other countries the utilisation of glucose-lowering agents in Ireland has increased over the last 10 years, in particular the newer agents such as dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).[6] Ultimately, the choice of glucose-lowering therapy for patients with T2DM should be informed by individualised treatment goals, preferences, and cost-related access.[6] Note that some medicines discussed in this bulletin may not be available and/or reimbursed for all of the referred indications. Table 1 summarises the glucose-lowering medicines that are used in Ireland.

Table 1: Medicines used to lower glucose in type 2 diabetes mellitus[1,7-22]

Class Medicine	Mode of action	Adverse effects, precautions include	Prescribing tips
Biguanide (PO) Metformin	↓ hepatic glucose production and ↑ insulin sensitivity	GI symptoms ↓ vitamin B12 Lactic acidosis	Dose reduction in renal impairment Monitor renal function and vitamin B12 Reduce GI symptoms by dose titration and administration with meals
Sodium-glucose cotransporter-2 inhibitors (SGLT2i) (PO) Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	↓ renal re-absorption of glucose resulting in ↑ urinary excretion of glucose, sodium and water	Volume depletion; urogenital mycotic infections and UTIs; Fournier's gangrene; euglycaemic DKA; lower limb amputations and fractures (with canagliflozin)	Caution with diuretic effect, prior to initiation, especially older people and monitor renal function and fluid status during treatment; dose reduction in renal impairment may be required; monitor for and treat urogenital infections; encourage hygiene in patients to avoid genital mycotic infections; consider DKA especially those at risk (e.g. dehydration, alcohol excess), advise patients of DKA risk Risk of potential drug interactions*
Glucagon-like peptide-1 receptor agonists (GLP-1 RA) (S/C) Liraglutide Semaglutide** Dulaglutide Exenatide	↑ glucose- dependent insulin production and ↓ glucose-dependent glucagon secretion, slow gastric emptying and suppress appetite	GI (e.g. nausea, diarrhoea, vomiting, ↓appetite), pancreatitis, goitre reported	GI symptoms may occur on initiation and dose escalation, which reduce with time; consider gradual dose titration and/or lower dose. Advise patients of risk of pancreatitis. Encourage healthy non-spicy smaller meals, eat slowly and do not eat when full. Vary injection sites
Dipeptidyl peptidase-4 inhibitors (DPP4i) (PO) Linagliptin Sitagliptin Saxagliptin	Inhibits DPP4 enzyme, thereby preventing the degradation of GLP-1 ↑ glucose- dependent insulin production and ↓ glucose-dependent glucagon secretion	Pancreatitis; bullous pemphigoid; arthralgia; hypersensitivity reactions; heart failure (saxagliptin)	Renal dose adjustment and monitoring required for sitagliptin and saxagliptin
Sulfonylureas (PO) Gliclazide Glimepiride	↑ insulin secretion	Hypoglycaemia, weight gain	Use with caution in situations where hypoglycaemia may occur (e.g. poor nutrition, renal impairment) Risk of potential drug interactions*
Thiazolidinediones (PO) Pioglitazone	↑ insulin sensitivity	Weight gain, swelling, risk of bone fracture, bone loss	Not to be used in patients with history of or active bladder cancer or those at risk of HF
Glinides (PO) Repaglinide	↑ insulin secretion	Low risk of hypoglycaemia modest weight gain Risk of ACS	Should be taken before meals Risk of potential drug interactions*

ACS-acute coronary syndrome; DKA-diabetic ketoacidosis; GI-gastrointestinal; HF-heart failure; PO-oral administration; S/C-subcutaneous; UTI-urinary tract infection;
**-the Summary of Product Characteristics which has full prescribing information should be reviewed; **oral semaglutide is authorised but not currently available for reimbursement in Ireland*

Metformin is generally recommended as first-line pharmacological therapy for most people with T2DM.[1,3,5,23] Metformin is effective at lowering HbA1c and has minimal risk of hypoglycaemia; it may be associated with weight loss and has a good safety profile.[1,3] However, while there is some evidence to suggest that metformin may be associated with CV benefit with respect to myocardial infarction in overweight and obese patients,[24,25] there is no clear evidence as to whether metformin monotherapy reduces the risk of CV disease in patients with T2DM.[26,27]

Practice points: Metformin should not be used in patients with severe renal failure (e.g. glomerular filtration rate <30 mL/min);[7] dose adjustment may be required in those with renal impairment and older patients.[7] Adverse effects include lactic acidosis, gastrointestinal discomfort and vitamin B12 deficiency.[7] Monitoring of renal function (more often in those with renal impairment and those on medicines affecting the kidney) and vitamin B12 levels (e.g. at baseline and annually) is required.[7,28-30] Longer-acting metformin is as effective as immediate-release formulations for glycaemic outcomes, and is associated with reduced gastrointestinal effects.[1] **Metformin should be discontinued in acute conditions with potential to alter renal function (e.g. dehydration) and before surgery and restarted no earlier than 48 hours after surgery or resumption of oral nutrition.[7]**

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have intermediate-to-high glycaemic efficacy (with lower glycaemic efficacy at lower eGFR); they are not associated with hypoglycaemia (as monotherapy) and are associated with intermediate weight loss.[3] In addition, evidence from CV outcome studies have shown that some SGLT2i reduce the risk of CV outcomes (such as CV death, heart failure [HF], all-cause mortality) and the progression of renal disease in patients with T2DM.[31-41] These beneficial effects of SGLT2i, largely independent of their glucose-lowering effect,[3] were seen in those with established CVD and in those with high CV risk,[38,40-42] and in patients who were already on other glucose lowering therapies,[39] with some studies reporting these effects in patients with T2DM independent of metformin use.[36,43] There is also evidence of an improvement in cardiac and renal outcomes in patients without diabetes.[31-34,44] Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin are licensed for the treatment of T2DM;[8-11] dapagliflozin and empagliflozin are also licensed for the treatment of chronic heart failure (CHF) and chronic kidney disease (CKD).[9,10]

Practice points: Recent data have led to increased confidence in the safety of SGLT2i,[3,40,41] however adverse effects include volume depletion (which can result in dehydration and hypotension, especially in older people), increased risk of infections (e.g. fungal genital infections, urinary tract infections and potentially Fournier's gangrene), an increased risk of diabetic ketoacidosis (DKA) (including euglycaemic DKA), an increased risk of lower limb amputations (seen with canagliflozin) and an increased risk of fractures (seen with canagliflozin).[45] The risk of DKA should be considered before prescribing an SGLT2i;[5,8-11] increased risk factors for DKA include excess alcohol, concurrent illness, injury or surgery, very low carbohydrate or ketogenic diet.[46] **Use of SGLT2i should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses.[8-11]** Medicines that potentially interact with SGLT2i include diuretics, insulin, insulin secretagogues, hepatic enzyme inducers, lithium, digoxin and dabigatran.[45] SGLT2i should not be used during pregnancy or in women who are breastfeeding.[45] Treatment options within the drug class vary significantly depending on the degree of renal impairment;[1] the Summary of Product Characteristics (SmPC) provides information on dosing in renal impairment.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) reduce HbA1c in a dose dependent manner; they also reduce appetite and are associated with weight loss.[3] In addition, there is evidence from CV outcome studies that specific GLP-1RA (e.g. liraglutide, semaglutide and dulaglutide) reduce CV outcomes in patients with T2DM,[1,47-51] and some GLP-1 RAs have also been shown to have positive effects on renal function.[52,53] The evidence suggests that the beneficial CV effects are especially evident in those with established CVD,[54] and some evidence suggests that these effects are independent of metformin use.[36,55]

GLP-1RA currently available in Ireland include liraglutide (administered subcutaneously [SC] daily), semaglutide (administered SC weekly [oral formulation also developed]), dulaglutide (administered SC weekly) and exenatide (administered SC).[12-15] Exenatide has not shown significant improvements in CV outcomes.[1] Tirzepatide (a glucose-dependent insulinotropic polypeptide receptor agonist [GIP] and GLP-1 RA) administered subcutaneously reduces HbA1c; outcome studies are ongoing.[3] Some GLP-1RA (e.g. liraglutide) are also used for obesity management, as an adjunct to a reduced-calorie diet and increased physical activity for weight management in appropriate patients with pre-diabetes and a high risk of CVD.[3,56,57] The HSE National Clinical Programme issued clinical advice (November 2023) in response to the global shortage of GLP-1 RA; normal supply chains are not expected to resume until late 2024.[58]

Practice points: The main adverse effects associated with GLP-1 RA are gastrointestinal symptoms (see table 1). Studies report an increased number of patients with retinopathy associated with semaglutide therapy;[48,49] this has occurred in patients with previous retinopathy and in patients with the greatest and most rapid reduction in HbA1c.[48,49] Semaglutide is not recommended in patients with uncontrolled diabetic retinopathy.[13] There is inter-individual variation in the magnitude of the effect of GLP-1 RA on HbA1c and weight loss, and the need for continued treatment with these therapies should be re-evaluated after 6 months.[3] No dose reduction in renal impairment is required for the long-acting GLP-1 RA as they are not renally excreted.[1]

Dipeptidyl peptidase-4 inhibitors (DPP4i) are oral glucose-lowering therapies that have a modest effect on lowering glucose; they have a neutral effect on weight and minimal risk of hypoglycaemia.[3] Current evidence from randomised controlled trials does not suggest that DPP4i have beneficial effects on CV outcomes,[59-63] however the evidence does not suggest that they are associated with adverse CV outcomes.[59-63] There is some evidence to suggest that saxagliptin is associated with an increased risk of HF,[59,63] especially in patients with pre-existing HF.[63]

Practice points: DPP4i may be an option in patients with CKD who are not meeting their glycaemic targets.[1] Individual DPP4i are metabolised and excreted in

different ways; reduced doses may be required depending on the specific DPP4i being used and the degree of renal impairment.[1] The SmPC has information on dosing in renal impairment. Note that linagliptin dose adjustment is not required for patients with renal impairment.[16] Caution is recommended in patients with a history of pancreatitis.[16-18] Combinations of incretin-based therapies (e.g. DPP4i with GLP1-RA or dual GIP/GLP-1 RA) are not recommended.[2,4]

Sulfonylureas have high glucose-lowering efficacy, however they are associated with hypoglycaemia and weight gain.[3] Current evidence does not suggest that sulfonylureas are associated with improved CV outcomes in patients with T2DM,[24,64,65] however evidence does not suggest that they are associated with adverse CV and renal outcomes.[64-66]

Practice points: Gliclazide has a reduced risk of hypoglycaemia compared to other sulfonylureas.[1] The use of sulfonylureas is dependent on the level of renal impairment and risk of hypoglycaemia.[1] In view of the risk of hypoglycaemia, patients taking sulfonylureas should do blood glucose monitoring, especially for those who drive.[67]

Thiazolidinediones (TZDs) have high glucose-lowering efficacy; they are associated with weight gain and enhance fluid retention.[1,3] There is some evidence to suggest that pioglitazone may improve CV outcomes (e.g. stroke) in patients with established CVD and those with high risk of CVD.[68-70] Pioglitazone has also shown beneficial effects on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in patients with T2DM.[71,72] Pioglitazone, however can worsen fluid retention, and is associated with an increased risk of heart failure;[68,69] it should not be used in patients with HF.[1]

Practice points: Pioglitazone may be an option for patients with CVD and for those without established CVD who are not reaching their HbA1c targets.[1] Use of pioglitazone has also been associated with an increased risk of bladder cancer and an increased risk of bone fractures in postmenopausal women.[1] Adverse effects associated with TZDs can be reduced by using lower doses and co-administration of other glucose-lowering therapies (e.g. SGLT2i and GLP-1RA) that promote weight loss and sodium excretion.[3]

Glinides (e.g. repaglinide) are secretagogues that have a similar mode of action to sulfonylureas, but they have a shorter duration of action.[1] Glinides are associated with hypoglycaemia and weight gain.[1] In view of the risk of hypoglycaemia, patients using glinides should do blood glucose monitoring, especially for those who drive.[67] The CV effects of glinides have not been extensively assessed.[1]

PRACTICAL ASPECTS OF GLUCOSE-LOWERING TREATMENT

The glucose-lowering therapies that are used in the management of a patient with T2DM need to be individualised to the patient. Choice of therapy not only depends on the patient's HbA1c target, but on other patient characteristics such as a history of established CVD, HF, CKD, obesity and a high risk of CVD.[1] The aim of glucose-lowering therapy is to achieve the desired HbA1c target and to reduce the risk of diabetic complications such as CVD, CKD and mortality. The CV benefits of the newer glucose-lowering therapies (e.g. the SGLT2i and the GLP-1RA) provide important progress in reducing the CV and CKD complications associated with T2DM, which occur largely independently of their glucose-lowering effects.[3]

T2DM is a naturally progressive disease, and patients usually require combination glucose-lowering therapy in order to achieve glycaemic targets and reduce the risk of CVD.[3,73-75] The use of certain combinations of glucose-lowering therapies such as metformin and other glucose-lowering therapies (e.g. SGLT2i, DPP4i, sulfonylurea, GLP-1RA or basal insulin) are not associated with adverse outcomes.[76]

Most guidelines recommend metformin as a first choice glucose-lowering agent (unless contraindicated) for most people with T2DM,[2,4,5,23,77] with sequential addition of other glucose-lowering therapies depending on the patient's characteristics.

Recent guidelines recommend the stratification of patients with T2DM into those with established CVD (including HF, stroke and CKD) and those with a high risk of CVD (see previous bulletin).[2,3] Each medication should be up titrated to the maximally tolerated approved dose and additional glucose-lowering therapies added to achieve glycaemic targets.

No history of established CVD or patients not at high risk of CVD: If a person does not have established or high risk CVD, HF, stroke/TIA or CKD, a glucose-centric approach should be taken. Most guidelines recommend metformin (unless contraindicated),[2,4,5] and/or other glucose-lowering therapies such as DPP4i, pioglitazone or sulfonylurea, depending on the patients' characteristics.[5] Multiple factors should be considered when adding additional glucose-lowering agents such as risk of hypoglycaemia, patient's weight and co-morbidities e.g. renal disease.

Patients with established CVD: For patients with established CVD, emerging evidence supports the initiation of a second therapeutic agent associated with proven CVD benefits (e.g. GLP-1RA or SGLT2i), in addition to metformin depending on the patient characteristics, rather than waiting for treatment failure with metformin before intensification of treatment.[70,78,79] This approach may reduce the therapeutic inertia (a lack of treatment intensification when targets or goals are not achieved) seen in the management of T2DM, and reduce the risk of CV events or renal disease progression.[1,79] There is some evidence to suggest that the benefits of GLP-1RA and SGLT2i for CV and renal outcomes are independent of metformin in patients with established or high risk of CVD.[43,55]

Some recent guidelines on DM (US and European) recommend that, for patients with T2DM and established or high risk of CVD, SGLT2i and/or GLP-1RA should be considered regardless of the use of other glucose-lowering agents (such as metformin) and of the HbA1c goal.[2,4,77] NICE recommends SGLT2i (with proven CVD benefit) in patients with co-existing CVD.[5,80] For patients on dual therapy who are not meeting treatment goals, additional intensification should be considered to improve glycaemic control.[1] The use of other glucose-lowering medications (e.g. pioglitazone, DPP4i, sulfonylureas) may be considered depending on the individual patient's characteristics and co-morbidities.[2,4]

Patients with a high risk of CVD: Some guidelines recommend that for patients with T2DM without ASCVD or severe target organ damage but with a high risk of CVD (e.g. calculated 10-year CVD risk ≥10% in the SCORE2-Diabetes algorithm [see previous bulletin]), treatment with

SGLT2i or GLP-1RA may be considered to reduce CV risk, independent of glucose control considerations.[2,4,77] For those assessed as being at high or very high risk of CVD, metformin may also be considered to reduce CVD risk.[2]

Patients with heart failure: Most guidelines recommend those SGLT2i with proven outcome benefits to reduce HF hospitalisations and CV death in patients with T2DM and HF.[2,4,5,77,80] GLP-1RA have a neutral effect on the risk of HF hospitalisation and can be considered for glucose-lowering on a patient-specific basis for those with T2DM and HF.[1,2] DPP4i (sitagliptin and linagliptin) also have a neutral effect on HF hospitalisation and can be considered as a glucose-lowering therapy in patients with T2DM at risk or with HF.[2] **Pioglitazone and the DPP4i saxagliptin should be avoided in patients with T2DM at risk or with HF.[1,2]**

Patients with chronic kidney disease: CKD puts limitations on the glucose-lowering therapies that can be used, making good glycaemic control increasingly difficult.[1] Guidelines recommend that SGLT2i with proven outcome benefits are considered in patients with T2DM and CKD (if eGFR >25 ml/min/1.73m^2 [dapagliflozin] and eGFR >20 ml/min/1.73m^2 [empagliflozin]) to reduce future CVD, reduce progression of diabetic kidney disease and total mortality.[2,4,5,77] Some guidelines recommend GLP-1RA to improve glycaemic control in patients with co-existing CKD.[2] An alternative to GLP-1RA in patients with CKD are DPP4i;[2] the **DPP4i should be dosed according to the licensed prescribing instructions.[1] Sulfonylureas or metformin should be discontinued in patients with severe renal impairment.[1]**

OTHER CONSIDERATIONS

Hypoglycaemia is associated with an increased risk of adverse outcomes, including mortality.[2,4] The optimal treatment of a patient with T2DM should consider the risk of hypoglycaemia, especially in frail patients; glucose-lowering therapies and HbA1c goals should be chosen to avoid hypoglycaemia.[4] Insulin, sulfonylureas and glinides are associated with an increased risk of hypoglycaemia.[4] Patients at risk of hypoglycaemia should do regular blood glucose monitoring,[5] especially for those drive.[67] In addition, patients should be aware of the specific regulations around driving (see the NDLS Medical Fitness to Drive Guidelines [2022]).

Weight: Sulfonylureas, pioglitazone and insulin are associated with weight gain.[1,2] Metformin and DPP4i are weight neutral or may result in small amounts of weight loss; SGLT2i and GLP-1RA are associated with clinically meaningful weight loss.[1,2] In patients who are overweight, avoid using insulin, sulfonylureas and other medication that may cause weight gain.[1]

Older people (>65 years): Frailty is associated with poorer prognosis and there may be less benefit from use of intensive glucose-lowering therapies.[3] In older patients it is recommended to avoid strict glycaemic targets (see previous bulletin) and medications that impose hypoglycaemic risk.[3] Deprescribing of some medications may be considered to avoid unnecessary medication or medication associated harm such as hypoglycaemia.[3] DPP4i are safe, with minimal side-effects for patients whose quality of life is a priority.[1] In older patients, SGLT2i seem to be well tolerated, although older patients are under-represented in most randomised controlled trials.[81]

Medication non-adherence affects up to 50% of patients with T2DM.[1,3] Multiple factors contribute to poor adherence in patients with T2DM including perceived lack of medication efficacy, fear of hypoglycaemia, lack of access to medication and adverse effects.[3] Facilitators of adherence include social/family support, patient choice, motivation, education and access to medication.[1,3] In addition, using combination glucose-lowering agents potentially improves adherence.[3,82] Improved adherence is associated with better glycaemic outcomes, reduced mortality and lower hospital admissions;[3] a meta-analysis found that patients with T2DM and good medication adherence had a 10% lower rate of hospitalisation and 28% lower rate of all-cause mortality compared to those with poor adherence.[83]

Sick day medication guidance: Patients should be informed that glucose-lowering medication may need to withheld or adjusted in patients with acute illnesses, especially in patients with dehydration.[84,85] It is recommended that medicines may need to be withheld in patients who are unwell and become dehydrated and/or have an acute decline in renal function, particularly for medicines that increase the risk of a further reduction in renal function (e.g. angiotensin converting enzymes inhibitors [ACEi], angiotensin receptor blockers [ARB], non-steroidal anti-inflammatory drugs [NSAIDs], diuretics, SGLT2iA) or have reduced clearance and increased risk for adverse effects (e.g. metformin, sulfonylureas).[85] The mnemonic **SADMANS** may be useful as an aide memoir: **S**ulfonylureas, **A**CEi, **D**iuretic, **M**etformin, **A**RB, **N**SAID, **S**GLT2i.[85]

Reviewing drug treatment: A person's needs and circumstances should be assessed at each review and consideration given to stopping any medicines that are not effective.[5] In addition, at each review it is important to consider nutrition and lifestyle advice, adverse effects of medicines, adherence to treatment and whether doses and formulations remain or are as appropriate.[5]

SUMMARY

Many classes/formulation of non-insulin glucose-lowering agents are available for patients with T2DM. The choice of therapy depends on the individual patient characteristics as outlined above.

Useful resources

- The HSE National Clinical Programme on Diabetes includes:
  - The HSE Diabetic RetinaScreen programme freely available for people with DM
  - The HSE Diabetic Foot Model of Care (2021)
  - The HSE DISCOVER (Diabetes Insights and Self Care Options via Education and Reflection) course freely available for people with T2DM
- Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 2022;65:1925-1966
- 2023 European Society of Cardiology (ESC) Guidelines on diabetes mellitus available at www.escardio.org
- 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice available at www.escardio.org
- ESC SCORE2-Diabetes algorithm is available on the ESC CVD Risk Calculation App.
- ICGP: Diagnosis and management of uncomplicated Type 2 Diabetes in Adults (T2DM) – a succinct practical guide for Irish General Practice (December 2019) available at www.icgp.ie (ICGP members only)

List of references available on ePublication on www.nmic.ie.
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1. Seidu S, Cos X, Brunton S et al, 2022 update to the position statement by Primary Care Diabetes Europe: a disease state approach to the pharmacological management of type 2 diabetes in primary care, Primary Care Diabetes 2022;16:223-244
2. Marx N, Federici M, Schutt K et al, 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes, European Heart Journal 2023;doi.org/10.1093/eurheartj/ehad192
3. Davies M, Arora V, Collins B, et al, Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 2022;65:1925-1966
4. Samson S, Vellanki P, Blonde L et al, American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update, Endocrine Practice 2023;29:305-340
5. NICE: Type 2 diabetes in adults: management – guideline (Published 2nd December 2015, updated 29th June 2022) accessed at www.nice.org.uk/guidance/ng28 on the 17th October 2023
6. Smith A, Kennedy C, Clarke S et al, Utilisation and expenditure on glucose-lowering drugs used for the treatment of type 2 diabetes mellitus in Ireland, a repeated cross-sectional study, Diabetes Epidemiology and Management 2022;doi.org/10.1016/j.deman.2021.100038
7. SmPC Glucophage® (metformin) accessed from www.medicines.ie on the 24th August 2023
8. SmPC Invokana® (canagliflozin) accessed from www.medicines.ie on the 24th August 2023
9. SmPC Forxiga® (dapagliflozin) accessed from www.medicines.ie on the 24th August 2023
10. SmPC Jardiance® (empagliflozin) accessed from www.medicines.ie on the 24th August 2023
11. SmPC Steglatro® (ertugliflozin) accessed from www.medicines.ie on the 24th August 2023
12. SmPC Victoza® (liraglutide) accessed from www.medicines.ie on the 28th August 2023
13. SmPC Ozempic® (semaglutide) accessed from www.medicines.ie on the 28th August 2023
14. SmPC Trulicity® (Dulaglutide) accessed from www.medicines.ie on the 4th October 2023
15. SmPC Byetta® (exenatide) accessed from www.hpra.ie on the 23rd November 2023
16. SmPC Trajenta® (linagliptin) accessed from www.medicines.ie on the 24th August 2023
17. SmPC Januvia® (sitagliptin) accessed from www.medicines.ie on the 24th August 2023
18. SmPC Onglyza® (saxagliptin) accessed from www.medicines.ie on the 24th August 2023
19. SmPC Diamicron ® (gliclazide) accessed from www.medicines.ie on the 28th August 2023
20. SmPC glimepiride accessed from www.hpra.ie on the 24th November 2023
21. SmPC Actos® (pioglitazone) accessed from www.hpra.ie on the 24th November 2023
22. SmPC Novo-Norm® (repaglinide) accessed from www.medicines.ie on the 28th August 2023
23. ICGP Diagnosis and management of type 2 diabetes (T2DM) in adults: a succinct practical guide for Irish General Practice (10th December 2019) accessed from www.icgp.ie on the 23rd November 2023
24. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-853

25. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589

26. Griffin S, Leaver J, Irving G, Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes, Diabetologia (2017) 60:1620–1629

27. Gnesin F, Thuesen A, Kahler L et al, Metformin monotherapy for adults with type 2 diabetes mellitus, Cochrane Database Systematic Review 2020;6(6): CD012906

28. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101:1754–1761

29. Diabetes Care 2024;47(Suppl. 1):S52–S76 | https://doi.org/10.2337/dc24-S004

30. MHRA, Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk, accessed from https://www.gov.uk/drug-safety-update/metformin-and-reduced-vitamin-b12-levels-new-advice-for-monitoring-patients-at-risk on the 15th December 2023

31. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with Empagliflozin in heart failure. N Engl J Med 2020;383:1413–24

32. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–61

33. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008

34. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089–98

35. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–306

36. Masson W, Lavalle-Cobo A, Lobo M, Masson G, Molinero G. Novel antidiabetic drugs and risk of cardiovascular events in patients without baseline metformin use: a meta-analysis. Eur J Prev Cardiol 2021;28:69–75

37. McGuire D, Shih W, Cosentino F et al, Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis, JAMA Cardiology 2021:6:148-158

38. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-39

39. Beernink J, Persson F, Jongs N et al, Efficacy of dapagliflozin by baseline diabetes medications: a prespecified analysis from the DAPA-CKD trial, Diabetes Care 2023;46(3):1-6

40. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

41. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657

42. Rodriguez-Valadez J, Tahsin M, Fleischmann K et al, Cardiovascular and renal benefits of novel diabetes drugs by baseline cardiovascular risk: a systematic review, meta-analysis, and meta-regression, Diabetes Care 2023;46:1300-1310

43. Neuen BL, Arnott C, Perkovic V, et al. Sodium-glucose co-transporter-2 inhibitors with and without metformin: a meta-analysis of cardiovascular, kidney and mortality outcomes. Diabetes Obes Metab 2021;23:382–390

44. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–46

45. Karagkounis D, Cardiac and renal effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors, Drug and Therapeutics Bulletin 2023;61(7):103-107
46. Moran G, Bakhi C, Song S et al, Guidelines – Type 2 diabetes: summary of updated NICE guidance, BMJ 2023;377:0775
47. Marso S, Daniels G, Brown-Frandsen K et al, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, New England Journal of Medicine 2016;374(4):311-322
48. Marso S, Bain S, Consoli A, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes, New England Journal of Medicine 2016;375:1834-1844
49. Husain M, Birkenfeld A, Donsmark M et al, Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes, New England Journal of Medicine 2018;381;841-851
50. Gerstein H, Colhoun H, Dagenais G et al, Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial, Lancet 2019;394:121-130
51. Banerjee M, Pal R, Mukhopadhyay S et al, GLP-1 receptor agonists and risk of adverse cerebrovascular outcomes in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials, Journal of Clinical Endocrinology & Metabolism 2023;108(7):1806-1812
52. Sloan L, Review of glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus in patients with chronic kidney disease and their renal effects, Journal of Diabetes. 2019;11:938–948
53. Sattar N, Lee MM, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653–662
54. Guo X, Sang C, Tang R et al, Effects of glucagon-like peptide-1 receptor agonists on major coronary events in patients with type 2 diabetes, Diabetes Obes Metab 2023;doi:10.1111/dom.15043
55. Crowley MJ, McGuire DK, Alexopoulos AS, et al. Effects of liraglutide on cardiovascular outcomes in type 2 diabetes patients with and without baseline metformin use: post hoc analyses of the LEADER trial. Diabetes Care 2020;43: e108–e110
56. SmPC Saxenda ® (liraglutide) accessed at www.medicines.ie on the 20th November 2023
57. HSE Medicines Management Programme, Managed Access Protocol: Liraglutide (Saxenda®), accessed from https://www.hse.ie/eng/about/who/cspd/medicines-management/ the 20th November 2023
58. HSE National Clinical Programme, Glucagon-like peptide 1 receptor agonist (GLP-1RA) supply shortage, clinical advice from the HSE National Clinical Program for Diabetes Mellitus (HSE Ireland 1st November 2023), accessed from www.hpra.ie on the 22nd November 2023 (https://www.hpra.ie/docs/default-source/Shortages-Docs/glp1-ra-shortage-clinical-advice-ncpd-01112023.pdf?sfvrsn=2)
59. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326. https://doi.org/10.1056/NEJMoa1307684
60. White WB, Cannon CP, Heller SR, et al, Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335. https://doi.org/10.1056/NEJMoa1305889
61. Green JB, Bethel MA, Armstrong PW, et al, Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242. https://doi.org/10.1056/NEJMoa1501352
62. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal

risk: the CARMELINA randomized clinical trial. JAMA 2019;321:69–79. https://doi.org/10.1001/jama.2018.18269

63. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579–1588. https://doi.org/10.1161/CIRCULATIONAHA.114.010389

64. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al, Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-2572

65. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322:1155–1166. https://doi.org/10.1001/jama.2019.13772

66. Rados D, Pinto L, Remonti L et al, The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials, PLoS 2016;Med 13 (4): e1001992. doi:10.1371/journal.pmed.1001992

67. NDLS, Medical Fitness to Drive Guidelines (April 2022) accessed at https://www.ndls.ie/images/PDF_Documents/NDLS_Sla%CC%81inte_&_Tioma%CC%81int_2022_v8.pdf on the 15th December 2023

68. Dormandy J, Charbonnel B, Eckland D et al, Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial, Lancet 2005;366(9493):1279-1289

69. De Jong M, van der Worp H, van der Graaf Y et al, Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials, Cardiovasc Diabetol (2017) 16:134 DOI 10.1186/s12933-017-0617-4

70. Ghani-Abdul A, Pluckett C, Triplitt C et al, Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes(EDICT): a randomized trial, Diabetes, Obesity and Metabolism, 2015;17: 268–275

71. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016; 165:305–315

72. Della Pepa G, Russo M, Vitale M, et al. Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial. Diabetes Res Clin Pract 2021; 178:108984

73. Richardson T, Halvorson A, Hackstadt A et al, Primary occurrence of cardiovascular events after adding sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists compared with dipeptidyl peptidase-4 inhibitors: a cohort study in veterans with diabetes, Annals of Internal Medicine 2023;176:751-760

74. Xie Y, Bowe B, Xian H et al, Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic records, Lancet: Diabetes & Endocrinology 2023;doi:10.1016/S2213-8587(23)00171-7

75. Palmer S, Tendal B, Mustafa R et al, Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials, BMJ 2021;372:m4573

76. Wexler D, de Boer I, Ghosh A et al, Comparative effects of glucose-lowering

medications on kidney outcomes in type 2 diabetes, JAMA Internal Medicine 2023;doi: 10.1001/jamainternmed.2023.1487

77. Visseren FLJ, Mach F, Smulders YM et al, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice (**Version 2021**). Developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies, European Heart Journal 2021;42:3227-3337

78. Matthews D, Paldanius P, Proot P et al, Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial, Lancet 2019; 394: 1519–29

79. Matthews D, Del Prato S, Mohan V, et al. Insights from VERIFY: early combination therapy provides better glycaemic durability than a stepwise approach in newly diagnosed type 2 diabetes. Diabetes Ther 2020;11:2465–2476

80. NICE: Type 2 diabetes in adults – quality standard (QS209) published 2nd March 2023 accessed from www.nice.org.uk/guidance/qs209 on the 17th October 2023

81. Rigato M, Fadini G, Avogaro A, Safety of sodium-glucose cotransporter 2 inhibitors in elderly patienst with type 2 diabetes: a meta-analysis of randomised controlled trials

82. Lavernia F, Adkins S, Shubrook J, Use of oral combination therapy for type 2 diabetes in primary care: Meeting individualized patient goals, Postgraduate Medicine 2015;127(8):808-17

83. Khunti K, Seidu S, Kunutsor S, et al, Association Between Adherence to Pharmacotherapy and Outcomes in Type 2 Diabetes: A Meta-analysis, Diabetes Care 2017; 40(11):1588–1596

84. Watson K, Dhaliwal K, Robertshaw S et al, Consensus Recommendations for Sick Day Medication Guidance for People With Diabetes, Kidney, or Cardiovascular Disease: A Modified Delphi Process, American Journal of Kidney Disease 2022; 81(5):564-574

85. Diabetic Canada Clinical Guidelines Expert Committee, Pharmacologic Glycemic Management of Type 2 Diabetes in Adults - Sick Day Medication List (Appendix 8), Canadian Journal of Diabetes 2018;42 (Supplement 1): S316