PrePITstop™ for Diabetes

A summary of oral diabetes medications

24th edition, February 2026

by Anne Goodchild

Content

Metformin	2
Sulfonylureas (SU)	3
SGLT-2 inhibitors (Gliflozins)	4
SGLT-2 inhibitors: cardiovascular outcome trials and other key trials influencing targeted treatment decisions	5
Pioglitazone	6
DPP-4 inhibitors (Gliptins)	7
Repaglinide	8
Combination medications	8
Frailty	8
SGLT-2 inhibitors (when not to use and use with caution). References	9

www.pitstopdiabetes.co.uk

Introduction

This document has been compiled as a resource for delegates during PrePITstop and PITstop courses. Costs taken from NHS Electronic Drug Tariff in Feb 2026 www.drugtariff.nhsbsa.nhs.uk

Metformin (a Biguanide)

Action: reduces hepatic glucose production & improve insulin sensitivity
First line therapy. Can be used in combination with all other options

	Min / Max dose	Recommended therapeutic dose	Time to take
Metformin standard release (sr)	500mg - 2g	2g daily or 1g daily (stable eGFR 30-45)	With or after a meal
Metformin modified release (mr)	500mg - 2g	2g daily or 1g daily (stable eGFR 30-45)	With a meal

Pros	Cons
• High HbA1c efficacy (7-22mmol/mol - dose dependent • Metformin mr first line (NICE NG28) • Reduces insulin resistance • Extensive experience • Rare hypoglycaemia • No weight gain. Evidence of slight weight loss • UKPDS initially showed ↓ microvascular complications. 10-year observational follow-up highlighted the legacy effect: ↓ micro and macrovascular outcomes and mortality (Holman et al 2008). 44-year results: 31% ↓ in MI, 25% ↓ in all-cause mortality, extended life by 2.7 years (Holman et al 2022) • Safe in pregnancy • Combination options available • Low cost: (2g daily) – £2.16 - 4 x 500mg tablets, £12.06 - 2 x 1g tablets – mr preparation £2.90 - 4 x 500mg tablets, £3.66 - 2 x 1g tablets	• Gastrointestinal side effects (1-2 week titration required) • Large tablets, difficult to swallow • Vitamin B12 malabsorption. www.gov.uk/drug-safety-update/metformin-and-reduced-vitamin-b12-levels-new-advice-for-monitoring-patients-at-risk • Lactic acidosis (rare but life threatening) * • **Requires a drug holiday during a dehydrating illness** Contraindications: • **eGFR < 30 (reduce dose to 1g daily eGFR < 45)** • any acute metabolic acidosis • acute conditions that can alter renal function: dehydration, sepsis, MI, cardiac/respiratory failure. All can cause acute kidney injury • hepatic insufficiency: acute alcohol use, alcoholism (liver enzymes 3 x upper limit of normal). Can be used with Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) if diagnosis confirmed. Oral solution – 2g daily 600ml/month (30-day supply 500mg/5ml) £24.92 Higher strengths are more expensive Oral powder sachets – 2g daily 2 x 1g sachets £25.20

NICE NG28 (2015, updated 2026): Introduce medicines one at a time, starting with Metformin mr, check tolerability while titrating to maximum tolerated dose. Then start the SGLT-2 inhibitor. Those already on Metformin sr continue if it remains effective, switch to Metformin mr if not tolerated or person's preference.

*Lactic acidosis. Inadequate clearance of lactic acid from the blood, leading to an excessively low pH (<7.35) and metabolic acidosis. Lactate is a by-product of anaerobic respiration, normally cleared from the blood by the kidneys, liver and skeletal muscle.

To reduce the risk of lactic acidosis

- Assess eGFR before initiating and follow the SPC's advice regarding dose.
- Stop short term if dehydrated (diarrhoea / vomiting), severe infection, acute kidney injury or shock (i.e. post MI)
- Stop before and up to 48-hours after investigations using iodinated contrast agents
- Stop pre-surgery and restart once fully hydrated
- Avoid excessive alcohol intake

Diabetes prevention Cochrane review (Madson et al. 2019).
Metformin compared with placebo or diet and exercise reduced or delayed the risk of T2DM in people at increased risk for the development of T2DM (moderate-quality evidence). However, metformin compared to intensive diet and exercise did not reduce or delay the risk of T2DM (very low-quality evidence)

Sulfonylureas (SU)

Action: stimulates the beta cells to produce insulin
First line for symptomatic relief. Can be used with all other options
When initiating insulin:

- reduce or stop Sulfonylureas when adding basal insulin (SIGN, 2017, updated Jan 2024)
- stop medicines being used solely to manage hyperglycaemia (NICE 2015, updated 2026)

Name	Minimum dose	Maximum	Time to take
Gliclazide 40, 80mg, 160mg tablets	40mg	160mg twice daily	Before a meal
Gliclazide mr 30 and 60mg tablets	30mg 30mg mr = 80mg standard Gliclazide	120mg daily	Similar time each day, before a meal
Glimepiride 1, 2, 3 and 4mg tablets Do not use CKD 4 or 5 (ABCD, 2018)	1mg 1mg = 80mg Gliclazide	6mg	Similar time each day, before a meal

Pros	Cons
• High HbA1c efficacy (11-22mmol/mol) • Rapid response. Good at tackling osmotic symptoms post diagnosis • Extensive experience • Once daily preparations available (Gliclazide mr and Glimepiride). Avoid elderly and declining eGFR • CAROLINA study (2019): Glimepiride showed no increased CVD when compared to Linagliptin • Short acting SU morning dose recommended to treat steroid-induced glucose excursion (JBDS-IP, 2023) • Low cost – Gliclazide 40mg tablets £0.74 – Gliclazide 80mg tablets £0.70 (x 4 daily £2.80) – Gliclazide 160mg tablets £3.27 (x 2 daily £6.54) – Gliclazide mr 30mg tablets x 4 daily £4.12, **60mg tablets x 2 daily £16.92** – Glimepiride 1mg £1.00, 2mg £0.89, 3mg £0.90, 4mg £1.17 for a 30-day supply	• Hypoglycaemia. Increases with CKD (avoid eGFR < 30) • Blood glucose monitoring recommended by DVLA and in CKD 3b* • DVLA requirement for Group 2 drivers: regular self-monitoring of blood glucose at least twice daily and at times relevant to driving, i.e. no more the 2 hours before the start of the first journey and every two hours while driving • Associated with weight gain (2-5kg) • Lack of durability (maintaining glycaemic control) • Switching from Metformin to a SU causes increased risk MI and all-cause mortality (Douros et al. 2018) **Ensure every person on SUs have a pre-meal glucose target range in line with their agreed HbA1c. This allows dose adjustment (including deescalation when adding new medications)** https://pitstopdiabetes.co.uk/wp-content/uploads/2023/06/HbA1cChart_PITstopA4posters_ed18.pdf

NICE NG28 (2015, updated Feb 2026)

- Consider if symptoms of hyperglycaemia at any stage. Review when blood glucose within target
- Aim for a target HbA1c no lower than 53mmol/mol (7%) for people on a SU
- Sulfonylureas appear in the 'further medication' options in every subgroup

Association of British Clinical Diabetologists (ABCD) (2018)
Patients with type 2 diabetes and CKD on a SU are at greater risk of hypoglycaemia. Regular blood glucose monitoring is required. If eGFR < 45 blood glucose monitoring should be mandatory*. Gliclazide is metabolized in the liver, therefore the preferred SU for people with CKD. If eGFR < 45 use a sub-maximal dose. Avoid alongside insulin when eGFR < 45.

Targeted use of SUs:

- to reduce symptoms related to hyperglycaemia at any time, including at diagnosis (often short term). Blood glucose monitoring required (acute prescription). Agree a pre-meal, alarm blood glucose, allowing structured dose reduction
- insulin requiring (lower BMI, osmotic symptoms, high HbA1c, often younger). Use after Metformin to test the pancreas, helping the patient understand the need for insulin
- to reduce the HbA1c before adding an SGLT-2. A high HbA1c (>86mmol/mol) increases the risk of dehydration. NICE NG28 (2015, updated 2026) state: increased risk of Diabetic Ketoacidosis if at risk of dehydration or volume depletion. Recommend addressing modifiable risks before starting.
- to treat the daytime rise in glucose caused by steroids (JBSD-IP, 2023)
- treatment for specific types of monogenic diabetes

SGLT-2 inhibitors (Gliflozins)

Blocks glucose reabsorption by the kidney leading to glucose excretion in urine & caloric loss.
License includes monotherapy (if intolerant to Metformin) and as an add on to other diabetes medications, including insulin.

Name	Therapeutic dose	Time to take	eGFR ml/min/1.73^2
Canagliflozin	100mg daily. Dose can be increased to 300mg daily.	Before the first meal of the day	Initiate 100mg dose when eGFR > 30* Can continue 100mg if eGFR < 30 Can increase to 300mg if eGFR > 60. If eGFR falls below 60 use 100mg
Dapagliflozin	10mg daily (5mg severe hepatic impairment)	Any time	Initiate when eGFR > 15*. Stop < 15
Empagliflozin (Jardiance)	10mg daily Dose can be increased to 25mg daily	Any time	Initiate 10mg dose when eGFR > 20* For heart failure use 10mg dose eGFR > 20 Can increase to 25mg dose if eGFR> 60. If eGFR falls below 60 use 10mg
Ertugliflozin®▼	5mg daily. Dose can be increased to 15mg daily	In morning, with / without food	Initiate when eGFR > 45. Stop if eGFR persistently < 30 Can increase to 15mg if eGFR > 60. If eGFR falls below 60 use 5mg

Pros

- Moderate HbA1c efficacy (6 – 14mmol/mol)
- Weight loss (2-3kg). Reduction in visceral fat
- Rare hypoglycaemia
- Blood pressure reduction (systolic 4 mm/Hg)
- Insulin-independent mechanism
- Once daily dosing
- SGLT-2is combined with GLP-1 Agonists reduced MACE outcomes by 30% and serious renal events by 57% (population cohort study) (Simms-Williams et al 2024)
- Favourable renal outcomes:
  - CREDENCE (Perkovic et al 2019) Canagliflozin 100mg
  - DAPA-CKD (Heerspink et al 2020) Dapagliflozin 10mg
  - EMPA-KIDNEY collaborative group (2022) Empagliflozin 10mg
- NICE CKD (2021) Once titrated ACEi/ARB to max. tolerated dose offer SGLT-2i if ACR is > 30mg/mmol. Consider SGLT-2i if ACR 3-30mg/mmol. They must meet the eGFR thresholds
- Favourable CV outcome trials
  - Empagliflozin: EMPA-REG outcome trial (Zinman et al 2015)
  - Canagliflozin: CANVAS programme (Neal et al 2017)
- Class effect: reduction in hospitalisation for Heart Failure (hHF)
- Specific trials showing significant reduction of hHF
  - EMPORER-REDUCED (Packer et al 2020), EMPORER-PRESERVE (Anker et al 2021), DAPA-HF (McMurray et al 2019), DELIVER (Solomon et al 2022)
- Direct benefit MASLD with Dapagliflozin (Jang et al. 2024)
- Meta-analysis comparing Canagliflozin, Dapagliflozin and Empagliflozin (all doses). Greatest HbA1c, triglyceride reduction seen with Canagliflozin 300mg (Zaccardi et al. 2016).
- INTENSIFY study (2023) looked at switching from Canagliflozin 100mg to 300mg. This led to sig.⬇ in HbA1c, weight, BP, liver enzymes and albuminuria. Canagliflozin 300mg achieves urinary glucose excretion up to 119g/day compared to 60-80g/day for all other SGLT-2i doses.

Cons

- Genitourinary infections. Independent risk factors: females, higher BMI, history of genital infections (McGovern et al, 2020)
- Polyuria
- Volume depletion / hypotension / dizziness
- Increased LDL- C
- Increased creatinine (transient for first 1-2 weeks)
- Use with caution > 85 years of age
- **SGLT-2is are less effective in reducing glycaemia when eGFR < 45 and not effective when eGFR < 30.**
- Increased risk of euglycaemic diabetic ketoacidosis
  - Highest risk: people with low beta cell reserve, suspected type 1 diabetes, eating disorders, severe dehydration, increased insulin requirements during acute illness, surgery or excess alcohol consumption
  - Use with caution: BMI < 27, HbA1c > 86mmol/mol, ketogenic diet, cognitive impairment, pancreatic diabetes (Dashora et al. 2023)
  - Check if had previous DKA, unwell with intercurrent illness, at risk of dehydration or volume depletion, on a very low carb. or ketogenic diet. Addressmodifiable risks before starting. Suspend treatment if choosing to follow a very low carb. or ketogenic diet (NICE 20215, updated 2026)
- Temporarily stop during periods of volume depletion, acute serious medical conditions and 48h prior to surgery
- Use with caution with loop diuretics (Canagliflozin: not licensed). NICE committee reassured - amputation risk could not be differentiated between SGLT-2 inhibitors and placebo.
- Canagliflozin** and Ertugliflozin SPCs. Avoid use with lower limb amputation. NICE (2021) committee reassured - amputation risk could not be differentiated between SGLT-2 is and placebo.
- Fournier's Gangrene. Rare necrosing fasciitis of the perineum (*55 cases in 6yrs with SGLT-2is, 19 cases in 35yrs other medications)

Cost (28-day supply)
- Canagliflozin (both doses) £39.20 (30-day supply)
- **Dapagliflozin 10mg £6.59**
- Empagliflozin (both doses) £36.59
- Ertugliflozin (both doses) £29.40

** Warning followed the CANVAS study. Amputation rate, primarily of the toe, higher in pooled intervention groups 6.3/1000 vs. placebo 3.4/1000. Later Canagliflozin studies (CREDENCE, 2019) and OBSERVE-4D real-world meta-analysis (Ryan et al. 2018) reported no increased risk of lower limb amputations.

NICE NG28 (2026). Prescribe alongside Metformin and start after titrating Metformin to max. tolerated dose. Target Hba1c on this 'initial therapy' 48mmol/mol (unless frail). Consider continuing SGLT-2is for cardiovascular and renal benefits, even if they do not help the person reaching their glycaemic or weight targets. Avoid use if level of frailty places the person at risk of adverse events.
Address inequalities regarding access and uptake. Identify and engage with this group

NICE CKS (April 2023). Includes contra-indications and cautions for use.

***Dashora et al, 2023 (ABCD) and Seidu et al 2024**. Select the right person and the appropriate clinical setting for SGLT-2 inhibitors

PITstop note - always consider when to use with caution

SGLT-2 inhibitors: cardiovascular outcome trials (CVOT) and other key trials influencing targeted treatment decisions

CVOT	Population. Median follow-up	Established ASCVD	History of Heart failure	MACE-3 outcome (CV death, non-fatal MI or stroke)	Comments	Hosp. for HF (HHF)	Renal outcomes (different renal composites used)	Other related studies
CANVAS[1] **Canagliflozin** 100mg and 300mg	10,142 with Type 2 diabetes 2.4years	65.6% Mainly secondary prevention	14.4%	HR 0.86 14% RRR Superior vs. placebo	Non-significant changes in all-cause mortality. Increased risk of lower extremity atraumatic amputations	HR 0.67 33% RRR	**CANVAS R**[1] 40% renal decline. Regression of albuminuria 293.4 vs. 187.5 placebo	**CREDENCE**[2] Median follow-up 2.6 years. Canagliflozin 100mg vs placebo in high-risk population (no. 4401 all with diabetes). Diabetes duration 15.8 years, eGFR 30-90, albuminuria. Results: 30% RRR in composite endpoint of ESKD, doubling serum creatinine and all-cause mortality (HR 0.70, NNT 22). NNT of 43 to prevent one ESKD over 2.5years. RRR HHF 39%.
DECLARE-TIMI 58[3] **Dapagliflozin** 10mg	17,160 with type 2 diabetes 4.2 years	40.6% Primary and secondary prevention	10%	HR 0.93 7% RRR Non-inferior vs. placebo	Non-significant changes in CV death and in all-cause mortality	HR 0.73 27% RRR	Renal event occurred in 4.3% vs. 5.6% placebo	**DAPA-HF**[4] Population with or without diabetes with HF and an EF < 40%. Results: reduction in primary composite outcome (CV death, HHF and urgent visits) reached P = 0.0001 significance (HR 0.75, NNT 21, RRR HHF 26%). Equally effective in reducing CVD and HHF with or without T2DM **DELIVER**[11] Population 6263 with or without diabetes, HF with mildly reduced or preserved EF. Results: reduction in primary outcome (worsening HF or CV death) reached P= 0.001 significance (HR 0.82). **DAPA-CKD**[5] Median follow-up 2.4years. Dapagliflozin 10mg vs placebo. 4304 population 67.5% with Type 2 diabetes, eGFR 25-75, albuminuria. Results: Primary endpoint - sustained decline eGFR at least 50%, ESKD, death from renal/CV causes 9.2% Dapagliflozin vs 14.5% placebo (HR 0.61, NNT 19)
EMPA-REG[6] **Empagliflozin** pooled analysis 10 and 25mg doses	7,020 with type 2 diabetes 3.1 years	99.4% All secondary prevention	10.1%	HR 0.86 14% RRR Superior vs. placebo	Primary outcome driven by CV related deaths (HR 0.62, 38% RRR). No difference between MI / stroke outcomes. Reduction all-cause mortality (HR 0.68, 32% RRR)	HR 0.65 35% RRR	Slower progression of CKD (RRR 44%). No sig. difference in rate of incident of albuminuria	**EMPORER-reduced**[7] Population 3730 with or without diabetes. Class II-IV HF and < 40% EF. Empagliflozin 10mg vs placebo. Results: reduction in primary composite outcome (CV death or HHF) 0.001 significance, HR 0.75, NNT 19. Equally effective in reducing CV death and hosp. for HF with or without T2D **EMPORER-preserved**[8] Population 5988 Class II-IV HF and EF > 40%. Empagliflozin 10mg vs placebo. Median follow-up 2.2 years. Results: reduction in primary composite outcome (CV death or HHF) reached 0.001 significance, HR 0.79 **EMPA-KIDNEY**[10] Population 6609. CKD eGFR 20-90 and ACR from A1, A2 & A3 categories. Median follow-up 2 years. Empagliflozin 10mg vs placebo. Results consistent across subgroups eGFR and with or without diabetes. Results: lower risk of progression of kidney disease and CV related death (HR 0.72, P,0.001). RRR 28%
VERTIS[9] **Ertugliflozin** 5mg and 15mg	8,246 with type 2 diabetes 3.0 years	100% All secondary prevention	23.1%	HR 0.97 Non-inferior vs. placebo	No superiority for CV death.	HR 0.70 30% RRR	Composite renal outcome was 19% lower (not significant)	

ASCVD- atherosclerotic cardiovascular disease, MI- myocardial infarction, HHF- hospitalisation for heart failure, EF- ejection fraction, HR- hazard ratio, RRR- relative risk reduction, ESKD- end stage kidney disease, NNT- numbers needed to treat, CKD- chronic kidney disease

1. Neal B. et al. for the CANVAS & CANVAS R investigators, Canagliflozin and cardiovascular and renal events in type 2 diabetes, NEJM, 2017;377:644-657, 2. Perkovic V. et al, Canagliflozin and renal outcomes in type 2 diabetes and nephropathy, NEJM, 2019;380:2295-2306, 3. Wiviott et al. for the DECLARE-TIMI 58 study, Dapagliflozin and cardiovascular outcomes in type 2 diabetes, NEJM, 2019;380:347-357, 4. McMurray J. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction, NEJM, 2019;381:1995-2008, 5. Heerspink H. et al. Dapagliflozin in patients with Chronic Kidney Disease, NEJM, 2020;383:1436-1446, 6. Zinman B, et al, EMPA-REG OUTCOME Investigators (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, NEJM, 373:2117–2128. 7. Packer M. et al. Cardiovascular and renal outcomes with Empagliflozin in Heart Failure, NEJM, 2020;383:1413-1424. 8. Anker S. et al. Empagliflozin in heart failure with a preserved ejection fraction, NEJM, 2021;285:1451-1461. 9. Cannon C. et al. Cardiovascular outcomes with Ertugliflozin in Type 2 diabetes, NEJM, 2020;383:1425-1435, 10. EMPA-Kidney collaborative Group, Empagliflozin in patients with Chronic Kidney Disease, NEJM, 2022. 11. Solomon S. et al, (DELIVER) Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction, NEJM, 2022;387:1089-1098.

Pioglitazone (a Thiazolidinedione)

Increases insulin sensitivity. Favourable effect: Lipid profile, metabolic dysfunction-associated steatotic fatty liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH)
Can be first line if Metformin is not tolerated. Normally second/third line

Name	Min/Max dose	Therapeutic dose	Time to take
Pioglitazone	15mg, 30mg, 45mg	30mg (45mg leads to greater weight gain, fracture risk and fluid retention)*	Chosen time, with or without food

Pros	Cons
• Relatively high HbA1c efficacy (11-17mmol/l dose dependent). Takes time to work so a glucose profile after 2-4 weeks may not show any benefit. • Rare hypoglycaemia • Good durability • Hepatic metabolism. No dose reduction as renal function declines. Licensed in end stage renal failure. ABCD and Renal Association (2021) recommend use in all stages of CKD • Favourable effect on lipid profile: increased HDL, reduced Triglycerides, small dense LDL particles converted to large buoyant LDL particles (Lebovitz, 2019) • Reduction in systolic and diastolic BP (7 and 5mmHg respectively) • Reduction in CVD events. ProACTIVE study (Erdman et al. 2007) • Helps restore first phase insulin response and improve other markers of beta cell function (Boughton et al, 2017) • Once daily preparation • Reduced risk of stroke & MIs in patients without diabetes & with insulin resistance & a history of recent stroke or TIA. IRIS trial (Kernan et al., 2016) • Reduction in Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH) (Cusi K. 2016) • Low cost: 15mg £3.67, 30mg £3.42, **45mg £20.00**	• Weight gain. Dose-related*. Increases subcutaneous adipose tissue mass (non-visceral). Change in fat distribution reduces insulin resistance. TOSCA.IT study - Pioglitazone vs. SUs. Mean weight gain < 2kg over 57 months in both groups (Vaccaro et al. 2017) • Fluid retention 3-5% increasing to 15-16% when combined with insulin • Increased Fracture risk men and women, dose dependent. Significant after 4 years of treatment. Distal and proximal fractures. Absolute risk are small but assess fracture risk with FRAX. (Colhoun et al, 2012) https://frax.shef.ac.uk/FRAX/ Note: all the above increase with dose* • Reports of bladder cancer • Last one in its class (bad media) • LFT testing required prior to starting. 3 monthly in year 1, then annually Contra-indicated: • Heart Failure • History of bladder cancer (Lewis et al. 2015 for further insight) • Uninvestigated haematuria • Diabetic Ketoacidosis • Hepatic impairment if ALT > 3 x upper limit of normal (ULN) (do not start if 2.5 x ULN)** Use with caution: Macular Oedema

*Weight gain, fluid retention and risk of fractures increases with higher dose, so advised to start with a low dose and review progress after 3 months. Cusi (2020) reported results from four studies using the lower doses.
15mg: mean HbA1c reduction 11mmol/mol and weight gain 1.5kg.
30mg dose: mean HbA1c reduction 14mmol/mol and weight gain 2.5kg.

ABCD and Renal Association (2021)

- Avoid with heart failure and macular oedema
- Discontinue in patients with CKD who gain > 20% of their body weight in the first 2 weeks
- Specifically highlight hip fractures for both genders. Caution in patients with increased risk of hip fractures
- Do not start in people with known bladder cancer
- Discontinue in people with painless haematuria until bladder cancer is discounted

ABCD (Basu et al, 2021). The accumulated evidence from clinical trials favours the use of Pioglitazone as a drug with CV benefit.

Diabetes prevention Cochrane review (Ipsen et al, 2020). Pioglitazone reduced or delayed onset of type 2 diabetes compare with placebo (low-certainty evidence) and compared with no intervention (moderate certainty evidence)

ADA/EASD (Davies et al. 2022) Prioritise use of organ-protective medications (Pioglitazone: NAFLD and NASH). Benefits must be balanced against possible side effects of fluid retention, congestive HF, weight gain and bone fracture. Minimise side effects by using lower doses and combining with SGLT-2 inhibitors and /or GLP-1 Agonists (GLP-1s) that promote weight loss and sodium excretion.

NICE NG28 (2015, updated 2026). Pioglitazone appears in the 'further medication' options in every subgroup apart from Heart Failure.

DPP-4 Inhibitors (Gliptins)

Increase insulin secretion & reduce glucagon secretion in response to a meal (both glucose dependent).
Mainly second or third line, although most hold a monotherapy license.
Discontinue when starting a GLP-1 (NICE NG28, 2015, updated 2026, Davies M et al., 2022, SIGN 154 2024).
When initiating insulin:

- stop medicines being used solely to manage hyperglycaemia (NICE NG28, 2026)
- recommend reviewing the need for DPP-4 inhibitors when starting insulin (SIGN 154, 2024)

	Dose	Renal dosing
Alogliptin	25mg daily	12.5mg daily with eGFR ≥ 30 & ≤ 50 6.25mg daily with eGFR < 30 including end-stage renal failure
Linagliptin	5mg daily	5mg daily Biliary tract excretion
Sitagliptin	100mg daily	50mg daily with eGFR ≥ 30 & ≤ 45 25mg daily with eGFR < 30 including end-stage renal failure
Vildagliptin	50mg twice daily 50mg daily with Sulfonylurea	50mg -100mg daily

Time to take: chosen time, with or without food

Pros	Cons
• Modest HbA1c efficacy 7-9mmol/mol • Rare hypoglycaemia • Well tolerated • Mainly once daily dosing • Combination preparations + Metformin • Weight neutral • Suitable for use in CKD 4 (eGFR > 15). • Alogliptin, Linagliptin and Sitagliptin licensed in end-stage renal failure • ABCD (2018) recommend use in all stages of CKD, with appropriate dose reductions • CV outcome trials: non-inferior - cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. – Alogliptin, non-inferiority MACE (EXAMINE, 2013) – Linagliptin: non-inferiority MACE (CARMELINA, 2019) – Linagliptin: non-inferior vs. Glimepiride (CAROLINA, 2019) – Sitagliptin: non-inferiority MACE (TECOS, 2015)	• Pancreatitis has been reported in clinical trials, but causality not established. Discontinue if suspected • Joint pain • Bullous pemphigoid (rare skin condition). Discontinue if suspected Cost – Alogliptin (all doses) £26.60 – Linagliptin £33.26 – **Sitagliptin: 25mg £2.07, 50mg £2.53, 100mg £2.32** – Vildagliptin 50mg x 2 **£7.66**

Targeted use of DPP-4 inhibitors:

- declining eGFR (although if ACR > 3 consider a SGLT-2i with evidence of renal protection, having considered eGFR threshold)
- good side effect profile
- elderly
- to nudge the HbA1c down to an agreed target

Meglitinide

Short-acting insulin secretagogues. Stimulate insulin secretion. May be used in place of Sulfonylureas. Licensed in monotherapy or second line with Metformin.

Name	Minimum dose	Maximum dose	Time to take
Repaglinide 0.5, 1 and 2mg tablets	0.5mg (recommended starting dose)	4mg up to four times daily	15-30 minutes before meals

Pros	Cons
Reduces postprandial glucose excursions. Dosing flexibility. Great for people who eat a low carbohydrate meal one day (omit) but a high carbohydrate meal another day (take). Need an engaged patient	Risk of hypoglycaemia Weight gain Blood glucose monitoring recommended (see SUs) Frequent dosing schedule Not licensed with insulin or other oral hyperglycaemic agents (although works well with basal insulin) Not recommended in the elderly (>75) Variable cost (based on 3 daily): Repaglinide 0.5mg £3.04, 1mg £28.58, 2mg £8.73

Combination medications

Pioglitazone & Metformin
Alogliptin & Metformin
Linagliptin & Metformin
Sitagliptin & Metformin
Vildagliptin & Metformin
Competact
Vipdomet
Jentadueto
Janumet (£33.26)
Eucreas
Dapagliflozin & Metformin
Canagliflozin & Metformin
Empagliflozin & Metformin
Empagliflozin & Linagliptin
Xigduo
Vokanamet
Synjardy
Glyxambi (£55.88)

Frailty

Glycaemic control should be based on individual's function and new therapy (SGLT-2 inhibitors and GLP-1 Agonists) should be based on frailty phenotype. New therapy can be safely used in sarcopenic-obese and cautiously used in anorexic-malnourished individual (Abdelhafiz, Emmerton, Sinclair, 2020).

Anorexic-malnourished frail: This phenotype is unlikely to benefit from the new therapy due to their favourable metabolic profile in addition they may be at risk of serious side effects such as increased risk of further weight loss, dehydration, hypotension, and falls.

Sarcopenic obese frail: This phenotype is likely to benefit from the new therapy due to their less favourable metabolic profile and less risk of side effects.

SGLT-2 inhibitors: do not use or use with caution. Higher risk of DKA

- Ketogenic, very low calorie, low carbohydrate diet[1, 2, 3]
- Low BMI (<27[1], <25[2]) (specialists may use for cardiac/renal benefits with low BMIs)
- Those at risk of developing high glucose related complications (dehydration, poor compliance to treatment, frequent missed medications)[1]
- Current or previous Diabetes Ketoacidosis (DKA)[1, 2, 3]
- Acute illness (specialists may continue with chronic heart failure even in the elderly)[1, 2]
- Surgery or planned medical procedure that may require starvation[1, 2, 3]
- Excessive alcohol intake[1, 2]
- Intravenous drug use[1]
- Person with HbA1c >86 mmol/mol[1]
- People rapidly progressed to needing insulin within 1-year after diagnosis, suspected type 1 diabetes or LADA[1, 2]
- Pancreatic disease[1, 2]
- Frail and elderly who are at risk of dehydration[1, 2]
- Cognitive impairment[1, 2]
- Frailty (esp. anorexic/malnourished)[3]

1. Dashora U et al. ABCD, 2023, SGLT-2 inhibitors in type 2 diabetes. An education resource for HCPs
2. Seidu S et al. Diabetes Therapy, 2024;15:1009-1124.
3. NICE Clinical Knowledge Summary, SGLT-2 inhibitors (Dec 2024)
4. Abdelhafiz A., Emmerton D., Sinclair A. Diabetes Research and Clinical Practice. 2020:169(108438) `

References

All references accessed Feb 2026 and links checked

Access each medication's SPC for phase III study references and page 5 for the SGLT-2 Cardiovascular Outcome trials (CVOT), renal and heart failure study references.

Abdelhafiz A., Emmerton D., Sinclair A. New hypoglycaemic therapy in frail, older people with diabetes mellitus – phenotypic status likely to be more important than functional status, Diabetes Research and Clinical Practice, 2020;169(108438). https://doi.org/10.1016/j.diabres.2020.108438

Association of British Clinical Diabetologists (ABCD) and The Renal Association), Managing hyperglycaemia in people with diabetes and chronic kidney disease, London: ABCD, 2021. https://abcd.care/resource/abcd-and-renal-association-clinical-practice-guidelines-management-hyperglycaemia-adults

American Diabetes Association (ADA) Standards of Medical Care in Diabetes (chapter 6) Pharmacological Approaches to Glycemic Treatment, Diabetes Care 2025;48(suppl. 1) https://diabetesjournals.org/care/issue/48/Supplement_1

Basu A. et al. Cardiovascular impact of new drugs (GLP-1 and Gliflozins): the ABCD position statement, British Journal of Diabetes, 2021 https://bjd-abcd.com/index.php/bjd/article/view/711

Boughton C., Munro N., Whyte M., 2017, Targeting beta cell preservation in the management of type 2 diabetes, British Journal of Diabetes, 2017; 17:134-144. https://bjd-abcd.com/index.php/bjd/article/view/247

British National Formulary online. https://bnf.nice.org.uk

Colhoun H et al. Scottish Diabetes Research Network Epidemiology Group. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012 Nov;55(11):2929-37. https://doi.org/10.1007/s00125-012-2668-0

Cusi K. Long-term Pioglitazone treatment for patients with nonalcoholic steatohepatitis and pre diabetes and type 2 diabetes, Annals of Internal Medicine, 2016. https://doi.org/10.7326/M15-1774

Cusi L. Tailoring treatment to patients with type 2 diabetes and Nonalcoholic Fatty Liver Disease. ADA conference 2020

Dashora U et al on behalf of the ABCD, SGLT-2 inhibitors in type 2 diabetes. An education resource for Healthcare Professionals, February 2023 https://abcd.care/sites/abcd.care/files/resources/SGLT2-inhibitors-ABCD.pdf

Davies M.J., Aroda V.R., Collins B.S 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, Sept 2022, https://doi.org/10.1007/s00125-022-05787-2

Della Pepa G. et al. Pioglitazone even at low doses improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial, Diabetes Research and Clinical Practice, 2021;178:108984. https://doi.org/10.1016/j.diabres.2021.108984

DVLA, Assessing fitness to drive: a guide for medical professionals, (2025) DVLA. www.gov.uk/guidance/diabetes-mellitus-assessing-fitness-to-drive

Douros A. et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study, BMJ 2018;362:k2693. https://www.bmj.com/content/362/bmj.k2693

Erdman E. et al., PROactive 07: pioglitazone in the treatment of type 2 diabetes: results of the PROactive study, Vascular Health Risk Management, 2007; 3(4):355-370. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2291341/pdf/VHRM_0304_355.pdf

Forbes A. et al. Sodium-glucose cotransporter-2 inhibitors and kidney outcomes in real-world type 2 diabetes populations: A systematic review and meta-analysis of observational studies. Diabetes Obesity Metabolism, 2023;25(8):2310-2330. https://doi.org/10.1111/dom.15111

Green. J. et al., TECOS Study Group (2015) Effect of Sitagliptin on cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine, 2015;373:232–242. www.nejm.org/doi/pdf/10.1056/NEJMoa1501352

Holman (September 2022) 44-year results: UKPDS www.medscape.com/viewarticle/981170

INTENSIFY study group, Effectiveness and Tolerability of the Intensification of Canagliflozin Dose from 100 mg to 300 mg Daily in Patients with Type 2 Diabetes in Real Life: The INTENSIFY Study, Journal of Clinical Medicine, 2023;12(13):4248. https://doi.org/10.3390/jcm12134248

Ipsen et al., Does pioglitazone prevent or delay type 2 diabetes and its complications in people at risk of developing type 2 diabetes mellitus? Cochrane Database of Systematic reviews, 2020;11. https://doi.org/10.1002/14651858.CD013516.pub2

Jang H, Kim Y, Lee DH, et al. Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease. JAMA Intern Med. 2024;184(4):375–383. https://doi.org/10.1001/jamainternmed.2023.8029

Joint British Diabetes Society for In-Patient Care. JBDS-IP (2023) Management of hyperglycaemia and steroid (glucocorticoid) therapy. 3rd edition. https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group

Kernan et al., Pioglitazone after Ischemic Stroke or Transient Ischemic Attack, New England Journal of Medicine, 2016; 374: 1321-31. www.nejm.org/doi/full/10.1056/NEJMoa1506930#t=article

Kushay M. et al. E-LIFT trial (Empagliflozin) Diabetes Care 2018; 41(8): 1801-1808. https://doi.org/10.2337/dc18-0165

Leboviz H. Thiazolidinediones: the forgotten diabetes medication, Europe PMC, 2019; 19(12):151. https://europepmc.org/article/med/31776781

Madsen K et al. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complication in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2019;12. DOI: 10.1002/146518558.pub2

McGovern et al. Risk factors for genital infections in people initiating SGLT-2 inhibitors and their impact on discontinuation, BMJ Open Diabetes Research and Care, 2020;8:e001238. https://drc.bmj.com/content/8/1/e001238

NICE, Type 2 diabetes in adults: management, NG28, 2015, updated 2026, NICE publication. www.nice.org.uk/guidance/ng28

NICE (2021) Evidence review A for SGLT-2 inhibitors and people with chronic kidney disease and type 2 diabetes. For NICE NG28. www.nice.org.uk/guidance/ng28/evidence/a-sglt2-inhibitors-for-people-with-chronic-kidney-disease-and-type-2-diabetes-pdf-10958150413

NICE CKS (April 2023), SGLT-2 inhibitors, NICE online. https://cks.nice.org.uk/topics/diabetes-type-2/prescribing-information/sglt-2-inhibitors/

Rosenstock J. et al, Effect of Linagliptin versus placebo on major cardiovascular events in adults with type 2 diabetes with high cardiovascular and renal risk: the CARMELINA randomized clinical trial, JAMA, 2019, 1;321(1):62-79. doi:10.1001/jama.2018.18269

Rosenstock J. 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(12):1155-1166. doi:10.1001/jama.2019.13772

Ryan P., Buse J., Schuemie M. et al. (2018) Comparison effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D), Diabetes Obes Metab, 20(11):1-13. https://doi.org/10.1111/dom.13424

Seidu S et al. SGLT-2 inhibitors: the new standard of care for cardiovascular, renal and metabolic protection in type 2 diabetes: a narrative review, Diabetes Therapy, 2024;15:1009-1124. https://link.springer.com/article/10.1007/s13300-024-01550-5

SIGN 154, Pharmaceutical management of glycaemic control in people with type 2 diabetes: a national clinical guideline, 2017, updated 2024, Healthcare Improvement Scotland. www.sign.ac.uk/our-guidelines/pharmacological-management-of-glycaemic-control-in-people-with-type-2-diabetes/

Simms-Williams N. et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study, British Medical Journal, 2024;385,e078242 www.bmj.com/content/385/bmj-2023-078242

Solomon S. et al, (DELIVER) Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction, NEJM, 2022;387:1089-1098.

Summary of Product Characteristics (SPCs) https://www.medicines.org.uk/emc/

Vaccaro O. et al Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial, The Lancet, 5(11):887-897. https://doi.org/10.1016/S2213-8587(17)30317-0

White W et al. Examination of cardiovascular outcomes with Alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE), Am Heart J 2011 Oct;162(4):620-626. doi: 10.1016/j.ahj.2011.08.004

Yadagiri et al. ABCD audit Dapagliflozin Abstract Diabetes UK Conference 2016. Diabetic Medicine 33(Sup 1)30-31

Yadagiri et al. ABCD audit Canagliflozin. Abstract EASD 2017. https://abcd.care/canagliflozin-audit

Zaccardi F. et al. 2017 Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis, Diabetes Obesity and Metabolism, 2016 ;18(8):783-94. https://doi.org/10.1111/dom.12670

Zannand F. et al., EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking Alogliptin versus placebo in EXAMINE: a multicenter, randomised, double-blind trial, The Lancet, 2015;358 (9982): 2067-76. doi: 10.1016/S0140-6736(14)62225-X

Zelniker et al, SGLT-2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes; a systematic review and meta-analysis of cardiovascular trials, The Lancet, 2019; 393:31-39. https://doi.org/10.1016/S0140-6736(18)32590-X

PrePITstop™ for Diabetes PITstop™ for Diabetes

Published by Dime Square Limited, 24th edition, February 2026