What next after Metformin?

Sarah Fitzpatrick

Lead Community Diabetes Specialist Nurse

Metformin

Benefits:

- Long-standing use
- Effective
- Safe
- Modest weight loss
- Low hypoglycaemia risk
- Works by reducing hepatic glucose production and improving insulin sensitivity

Limitations:

- Not tolerated in some (GI side effects)
- Contraindicated in renal impairment
- May be insufficient alone as disease progresses

Metformin

Name

Metformin

Contraindications

Acute metabolic acidosis

Effect on weight

None

Hypoglycaemia risk

Low

Renal impairment

Avoid if eGFR less than 30ml/min

Hepatic impairment

Withdraw if tissue hypoxia likely

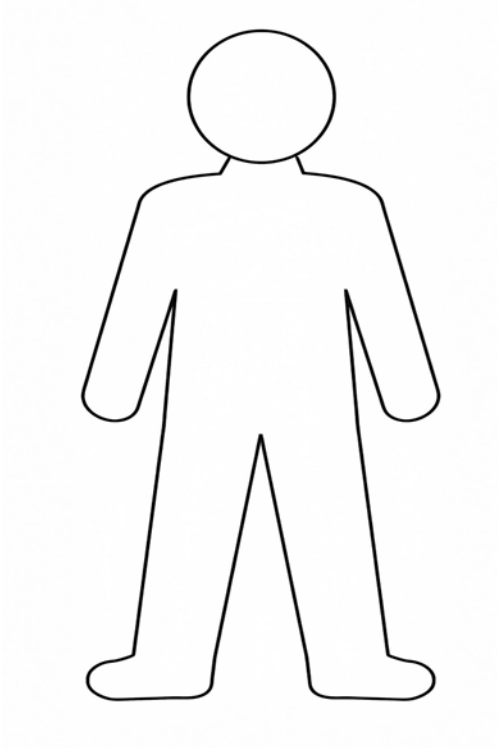
What next after Metformin?

Factors to consider

Comorbidities

Other medications

Side effects



Health status

Priorities

Contraindications

Beneficial effect beyond glucose lowering

When is Metformin not enough?

- HbA1c not at target after 3–6 months of monotherapy.
- Contraindications: renal impairment (eGFR <30), intolerance (GI side effects).
- Disease progression – T2DM is progressive and often needs combination therapy.

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment — Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk

Offer

- Metformin

Or if GI disturbance

- Metformin MR

If metformin contraindicated →

Consider

- DPP-4 inhibitor ('gliptin') or
- Pioglitazone or
- Sulfonylurea

An SGLT2 inhibitor ('flozin') for some people:

- TA 390 Canagliflozin
- TA 390 Dapagliflozin
- TA 390 Empagliflozin
- TA 572 Ertugliflozin

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Chronic heart failure or established atherosclerotic CVD

Offer

- Metformin

or if GI disturbance

- Metformin MR

and as soon as metfomin tolerability is confirmed, offer

- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated →

Offer

- SGLT2 inhibitor alone

High risk of CVD

QRISK2 of 10% or higher or elevated lifetime risk

Offer

- Metformin

or if GI disturbance

- Metformin MR

and as soon as metfomin tolerability is confirmed, consider

- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated →

Consider

- SGLT2 inhibitor alone

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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NICE Guidelines NG28

After Metformin, what determines next choice?

- Presence of **atherosclerotic cardiovascular disease (ASCVD)** or **heart failure (HF)**
- Risk of **hypoglycaemia**.
- **BMI** and potential for weight loss.
- **Renal function**.
- Cost and patient preference.

SGLT2 Inhibitors

- NICE favours them for:
  - Patients with **CVD**, **HF**, or **CKD**.
  - People needing **weight loss**.
- Cardiovascular and renal protective benefits.
- Used as dual therapy with metformin or even monotherapy if metformin is contraindicated.
- Now recommended early in treatment in many cases.
- Work by blocking the SGLT2 protein, preventing it from reabsorbing glucose back into the blood.

SGLT2 inhibitors

Name:

BSW 1st line: Dapagliflozin 2nd line: Empagliflozin (Canagliflozin, Ertugliflozin)

Contraindications:

Ketoacidosis / Type 1 diabetes

Effect on weight:

Loss

Hypoglycaemia risk:

Low

Renal impairment:

Avoid initiation if eGFR less than 15ml/min consider additional antidiabetic drug if eGFR less than 45ml/min due to reduced efficacy

Hepatic impairment:

Caution in severe impairment, limited information available.

DPP-4 Inhibitors

- Weight neutral.
- Lower efficacy than GLP-1 or SGLT2.
- Low risk of hypoglycaemia.
- Still used but less favoured due to lack of cardio/renal benefit.
- Work by enhancing the body's own incretin system, leading to improved insulin secretion

DPP-4 Inhibitors

Name:

Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin

Contraindications:

Ketoacidosis

Effect on weight:

None

Hypoglycaemia risk:

Low

Renal impairment:

No adjustment for Linagliptin Dose adjustment needed for Sitagliptin/Saxagliptin/Vildagliptin if creatinine clearance <50ml/min

Hepatic impairment:

Avoid Vildagliptin and avoid Saxagliptin and Alogliptin if severe hepatic failure

Sulfonylureas

- Older, low-cost, effective.
- Blood glucose monitoring required
- Risk of hypoglycaemia and weight gain.

- May still be used in cost-sensitive settings or where rapid control is needed.
- Used as rescue treatment
- Works by stimulating the pancreas to produce more insulin

Sulfonylureas

Name:

Gliclazide, Glimeperide, Glipizide, Tolbutamide

Contraindications:

Ketoacidosis

Effect on weight:

Gain

Hypoglycaemia risk:

Moderate, high in older people

Renal impairment:

Used with care in mild to moderate impairment due to risk of hypoglycaemia. Avoid in severe real impairment.

Hepatic impairment:

Avoid in severe impairment

Thiazolidinediones

- Rarely first choice now due to side effects (fluid retention, weight gain, fracture risk).
- Some benefit in insulin resistance but not widely used unless specific indications.
- Works by improving insulin sensitivity particularly in fat, muscle and liver tissue.

Thiazolidinediones

Name:

Pioglitazone

Contraindications:

Ketoacidosis, history of heart failure, previous or active bladder cancer

Effect on weight:

Gain

Hypoglycaemia risk:

Low

Renal impairment:

No adjustment

Hepatic impairment:

Avoid

GLP-1 Receptor Agonists

- Injectable or oral.
- Particularly useful if **weight loss** is a major goal.
- Cardio and renal protective effects in certain groups.
- NICE recommends only if triple therapy is not effective, not tolerated, or contraindicated, BMI >35 or lower if insulin would have significant occupational implications or if weight loss would benefit other significant obesity related comorbidities.
- Work by mimicking the action of natural GLP1

GLP-1 Receptor Agonists

Name:

BSW 1st line Semeglatide (Ozempic) Tirzepatide (Mounjaro), Exenatide (Byetta), Liraglutide, Dulaglutide (Trulicity)

Contraindications/cautions:

Ketoacidosis, History of pancreatitis, Retinopathy

Effect on weight:

Loss

Hypoglycaemia risk:

Low unless used in combination with insulin

Renal impairment:

Avoid in end stage renal function

Hepatic impairment:

Advise caution (limited information)

Insulin

Can be used as rescue therapy at any time

- At diagnosis when symptomatic
- During intercurrent illness
- Steroid induced hyperglycaemia
- Pregnancy

When HbA1C consistently above 58mmols/mol on 3 non-insulin therapies

Conclusion

- No "one-size-fits-all" after Metformin.
- Discuss diet and lifestyle at each stage of treatment.
- Cardiovascular and renal risk now key drivers of second-line therapy.
- NICE increasingly supports newer agents earlier in the disease.
- Patient-centred care remains the gold standard.