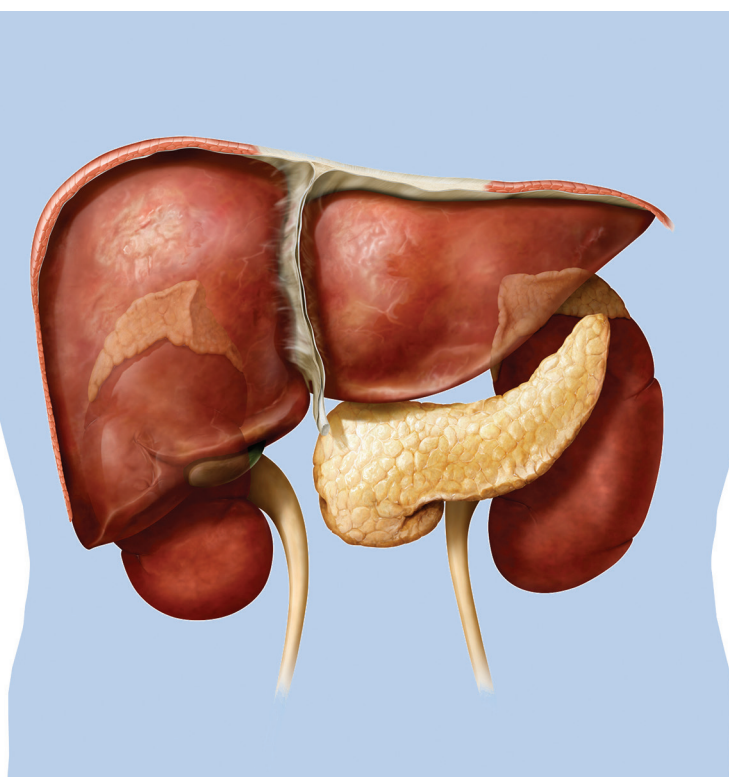


DPP-4/SGLT2 inhibitor combined therapy for type 2 diabetes

STEVE CHAPLIN



DPP-4 inhibitors and SGLT2 inhibitors lower blood glucose by complementary mechanisms of action, and two fixed-dose combinations – Qtern and Glyxambi – have now been approved for the treatment of type 2 diabetes. This article discusses their clinical trial efficacy, adverse effects and place in therapy.

The treatment of type 2 diabetes has undergone radical change since the introduction of drugs that modulate incretin – the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidylpeptidase-4 (DPP-4) inhibitors. These agents expanded the options available before and after prescribing insulin and, compared with the sulfonylureas, they have a low risk of hypoglycaemia.

The DPP-4 inhibitors in particular have achieved remarkable success: in 2016/17, they were, only 10 years after their introduction, the most frequently prescribed “other antidiabetic drug” in primary care in England.¹ (But, with 4.6 million items dispensed in that year, they lagged behind the 8.4 million items for sulfonylureas, a fact that probably reflects conservative treatment guidelines.) Sitagliptin has the lion’s share of DPP-4 inhibitor prescribing (56%), followed by linagliptin (27%) and saxagliptin (7%).

The most significant development since then was the introduction of the sodium-glucose co-transporter 2 (SGLT2) inhibitors in 2012/13, another new class of drug with a low risk of hypoglycaemia. The past year has seen volume growth at a rate comparable with that of the DPP-4 inhibitors, and dapagliflozin, the first SGLT2 inhibitor in class, is now prescribed at about one-quarter of the frequency of sitagliptin in primary care.

Blessed with an unparalleled therapeutic choice for the management of diabetes, prescribers only had to decide how best to use these agents and still keep spending under control. NICE favoured a familiar approach, transforming metformin into the most frequently prescribed antidiabetic drug and maintaining the role of sulfonylureas when they might otherwise have trailed in the wake of the intense marketing that supported the newer, more expensive agents. The latest NICE guideline, published in 2015 and updated in 2017, replaced the concept of first- and second-line therapies with that of dose intensification (see Figure 1).² When, as inevitably occurs, glycaemic control cannot be maintained with diet, lifestyle change and metformin,

			DPP-4i (or placebo) add-on to metformin/SGLT2i		SGLT2i (or placebo) add-on to metformin/DPP-4i	
			DPP-4i	placebo	SGLT2i	placebo
Saxagliptin/ dapagliflozin ^{10,11}	change in HbA1c at 24 weeks (%)		-0.51 ^a	-0.16	-0.82 ^a	-0.10
	% patients with HbA1c <53mmol/mol (7%)		35	23	38 ^a	12
Linagliptin/ empagliflozin ^{12,13}	change in HbA1c at 24 weeks (%)	10mg	-0.53 ^b	-0.21	-0.65 ^d	0.14
		25mg	-0.58 ^c	-0.10	-0.56 ^d	
	% patients with HbA1c <53mmol/mol (7%)	10mg	26 ^c	11	37 ^d	17
		25mg	36 ^c	15	33 ^e	
a p<0.0001; b p=0.01; c p<0.01; d p<0.001; e p=0.006						

Table 1. Primary endpoints of phase 3 trials of add-on therapy with DPP-4 inhibitors (DPP-4i) and SGLT2 inhibitors (SGLT2i) vs placebo

this algorithm is a guide on how to introduce combinations of two or three drugs in a rational way.

Perpetuating a practice no doubt welcomed by patients faced with taking handfuls of tablets daily, manufacturers have launched various fixed-dose combinations of their products with metformin (with the exception of the sulfonylureas, probably because it is not financially feasible). The BNF now lists nine such products but, until recently, there have been no combinations of newer drugs with one another. That has now changed: one fixed-dose of combination of a DPP-4 inhibitor and an SGLT2 inhibitor has been introduced and another has been licensed – even though NICE does not specifically recommend such a pairing.

DPP-4/SGLT2 inhibitors

The first of these novel fixed-dose combinations launched in the UK was Qtern (saxagliptin 5mg and dapagliflozin 10mg). Glyxambi (linagliptin 5mg and empagliflozin 10mg or 25mg) has been approved in the EU but is not yet marketed in the UK. Both are licensed for use in adults with type 2 diabetes when metformin and/or a sulfonylurea and one of the component drugs do not provide adequate glycaemic control, or when the patient is already being treated with the two component drugs separately. Both have a one-tablet, once-daily dose but Glyxambi requires titration for patients not previously taking empagliflozin. This is consistent with the dose regimen for empagliflozin, which begins with 10mg daily increasing to 25mg daily if necessary and tolerated.

The prescribing cautions and contraindications for Qtern and Glyxambi are similar, though one notable exception is what to do in the event of deteriorating renal function. Qtern should not be prescribed for patients with moderate to severe renal impairment (estimated glomerular filtration rate (eGFR) <60ml/min/1.73m²). Glyxambi should not be initiated in such cases but if renal function declines during treatment but remains above 45ml/min/1.73m² and tolerability is good, the dose should be reduced to 5mg/10mg. Below that threshold,

Glyxambi should be discontinued. The requirement to titrate the dose of empagliflozin may therefore be an advantage for the subgroup of patients at risk of developing renal impairment.

Complementary mechanisms of action

DPP-4 inhibitors and SGLT2 inhibitors lower blood glucose by separate, complementary mechanisms. Both are glucose-dependent, accounting for the low risk of hypoglycaemia during treatment.

The incretins – GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) – are hormones secreted into the blood within minutes of eating when, among other effects, they regulate insulin and glucagon secretion from the pancreas. They are both rapidly deactivated by the enzyme DPP-4. In people with type 2 diabetes, GLP-1 is the more important of the two incretins for glucose regulation. Inhibition of DPP-4 prevents the breakdown of GLP-1, which increases insulin secretion and lowers glucagon secretion, and also suppresses endogenous glucose production.^{3,4}

Renal tubular reabsorption of glucose is regulated by the enzyme SGLT2. Inhibition of SGLT2 therefore increases urinary glucose excretion, with a prompt effect on blood glucose levels.⁵ However, SGLT2 inhibitors also increase endogenous glucose production⁶ and glucagon secretion⁷ and the full implications of these properties are not fully understood.

Combining these mechanisms of action should therefore enhance their glucose-lowering effects; a DPP-4 inhibitor could counteract the effects of an SGLT2 inhibitor on endogenous glucose production and glucagon secretion. However, their combined effects on blood glucose are less than additive in patients taking metformin.

In a randomised double-blind trial of adults with type 2 diabetes and poor glycaemic control (HbA_{1c} 64–108mmol/mol [8–12%]) despite stable treatment with metformin ≥1500mg daily, adding both saxagliptin and dapagliflozin reduced fasting plasma glucose and postprandial glucose after 24 weeks significantly more than adding saxagliptin alone but not more than

If the person is symptomatically hyperglycaemic, consider insulin or a sulfonylurea (SU). Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48mmol/mol (6.5%) on lifestyle interventions:

- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

FIRST INTENSIFICATION

If HbA1c rises to 58mmol/mol (7.5%):

- Consider dual therapy with:
 - metformin and a DPP-4i
 - metformin and pioglitazone
 - metformin and an SU
 - metformin and an SGLT-2i
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION

If HbA1c rises to 58mmol/mol (7.5%):

- Consider:
 - triple therapy with:
 - o metformin, a DPP-4i and an SU
 - o metformin, pioglitazone and an SU
 - o metformin, pioglitazone or an SU, and an SGLT-2i
 - insulin-based treatment
- Support the person to aim for an HbA1c level of 53mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic for adults with type 2 diabetes who:

- have a BMI of 35kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) *and* specific psychological or other medical problems associated with obesity *or*
- have a BMI lower than 35kg/m², *and* for whom insulin therapy would have significant occupational implications, *or* weight loss would benefit other significant obesity-related co-morbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48mmol/mol (6.5%) on lifestyle interventions:

- Consider one of the following:
 - a DPP-4i, pioglitazone or an SU
 - an SGLT-2i instead of a DPP-4i if an SU or pioglitazone is not appropriate
- Support the person to aim for an HbA1c level of 48mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone or 53mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION

If HbA1c rises to 58mmol/mol (7.5%):

- Consider dual therapy with:
 - a DPP-4i and pioglitazone
 - a DPP-4i and an SU
 - pioglitazone and an SU
- Support the person to aim for an HbA1c level of 53mmol/mol (7.0%)

SECOND INTENSIFICATION

If HbA1c rises to 58mmol/mol (7.5%):

- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need twice-daily NPH insulin in

combination with oral blood glucose lowering drugs.

- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.
- Monitor people on insulin for the need to change the regimen.
- An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option.

See the guideline for a full version and notes on using the algorithm

Figure 1. Extract of NICE algorithm for dose intensification in the treatment of type 2 diabetes²

adding dapagliflozin alone (see Figure 2).⁸ Furthermore, a second comparison showed that adding saxagliptin/dapagliflozin to metformin improved beta-cell function more than adding saxagliptin alone.⁹

A similar study comparing linagliptin/empagliflozin, empagliflozin, and linagliptin as add-on therapy to metformin found that the linagliptin/empagliflozin combination reduced fasting plasma glucose significantly more than its components; postprandial glucose was not reported.¹⁰

These data should be interpreted cautiously. This use of a DPP-4/SGLT2 inhibitor combination does not match the indication approved for therapeutic use (which would mean that patients were already established on treatment with one of the component drugs and metformin before receiving the combination).

Glycaemic control

Clinical trials show that adding a DPP-4 inhibitor or an SGLT2 inhibitor to metformin plus the other component drug improves glycaemic control compared with placebo, as measured by reductions in HbA_{1c} (see Table 1). The 10mg dose of empagliflozin was little different to the higher dose when linagliptin was added to dual therapy and might be more effective when empagliflozin is the third agent added. The studies did not compare the two doses statistically and it is uncertain whether this difference was due to chance.

Overall, after adjustment for placebo, combining a DPP-4/SGLT2 inhibitor with metformin for 24 weeks reduces HbA_{1c} by about 0.3–0.7% compared with metformin plus one of the component drugs in patients with baseline HbA_{1c} of about 8% (64mmol/mol). This is associated with approximately a 1.5–2-fold increase in the proportion of patients with HbA_{1c} ≤53mmol/mol (≤7%), equivalent to about an extra one-quarter to one-third of patients in these trials. Adding dapagliflozin to dual therapy makes a bigger difference than adding saxagliptin; this trend is evident with the lower dose of empagliflozin (added to linagliptin/metformin) but not the higher dose. Further comparisons are needed to clarify whether this was an artefact of the trials, which report different response rates with placebo, or a clinically relevant difference. In these studies, patients were required to be taking metformin at a dosage of at least 1500mg daily but the actual mean dosage was not reported.

Body weight changes little when a DPP-4 inhibitor is added to a metformin/SGLT inhibitor combination but, in patients with baseline BMI 30–32kg/m², adding the SGLT2 inhibitor to a metformin/DPP-4 inhibitor combination is associated with weight loss of approximately 1.5–3.0kg compared with 0.3–0.4kg among placebo recipients.^{11,12}

Adding an SGLT2 inhibitor to metformin/DPP-4 inhibitor is also associated with a small reduction in blood pressure of about 1.0–2.5mmHg above the effect of placebo for systolic and diastolic pressures^{11,12} but there is little impact when a DPP-4 inhibitor is the third drug added.^{10,13}

These trials did not report the effects on glycaemic control according to baseline HbA_{1c} but, according to regulatory reviews, adding empagliflozin to metformin/linagliptin was more

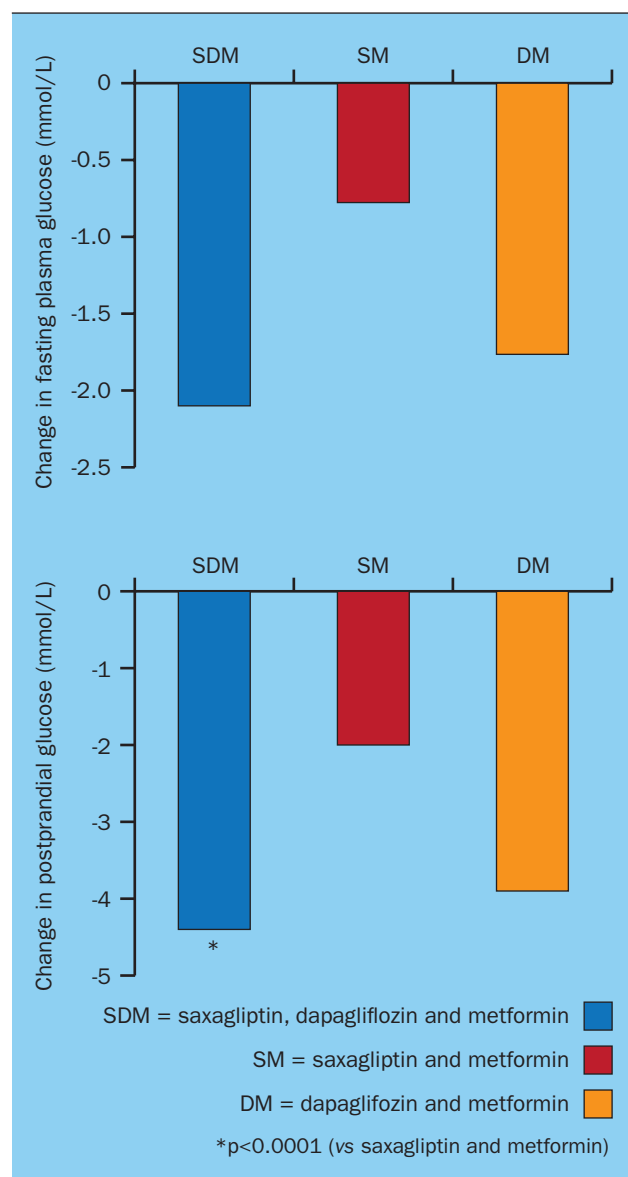


Figure 2. Comparative effects of saxagliptin/dapagliflozin, saxagliptin and dapagliflozin when added to metformin on fasting plasma glucose and postprandial glucose after 24 weeks' treatment⁸

effective in patients with higher pretreatment HbA_{1c}¹⁴ whereas adding saxagliptin to metformin/dapagliflozin had limited effect in patients with high HbA_{1c} (defined as ≥75mmol/mol, ≥9%).¹⁵ However, patients in the linagliptin/empagliflozin study had better baseline glycaemic control than those in the saxagliptin/dapagliflozin study, suggesting that comparison between the trials is inappropriate.

Extension studies have reported one year's treatment with metformin/saxagliptin/dapagliflozin.^{16,17} Improvements in glycaemic control were maintained and the proportion of patients who needed rescue treatment for HbA_{1c} >64mmol/mol (>8%) or who discontinued treatment was lower than with placebo

(19% with saxagliptin added on to metformin/dapagliflozin vs 28% with placebo add-on; and 21% with dapagliflozin added on to metformin/saxagliptin vs 48% with placebo add-on). The reduction in body weight associated with add-on dapagliflozin was also maintained (-2.1kg vs -0.4kg with placebo add-on).

Adverse effects

The nature of adverse events reported with triple therapy with metformin plus DPP-4/SGLT2 inhibitors was typical of the component drugs. Adding a DPP-4 inhibitor to metformin/SGLT2 inhibitor was not associated with an increase in the frequency of adverse events in phase 3 trials.^{10,13} Urinary tract infection was slightly but consistently more frequently reported with add-on linagliptin (8–10% vs 5–6% with placebo) or add-on saxagliptin (5% vs 4%); hypoglycaemia was rare.

The overall frequency of adverse events was also similar to that with placebo after adding an SGLT2 inhibitor to metformin/DPP-4 inhibitor.^{11,12} In this instance, the frequency of urinary tract infection ranged from 3% to 7%, no greater than with placebo (6%) but genital infections were more common with add-on SGLT2 inhibitor in men and women (5% vs 1–2% with placebo) (except with empagliflozin 10mg – about 2%). The difference between adding a DPP-4 inhibitor and adding an SGLT2 inhibitor on frequency of genital infections is probably explained by the selection of patients less likely to develop genital infection during early SGLT2 inhibitor use. Adverse events resulted in treatment discontinuation in more patients taking dapagliflozin (5% vs 1% with placebo) but not empagliflozin (2% vs 2% with placebo; none with the 25mg dose).

These trends were maintained during one year's treatment with saxagliptin/dapagliflozin/metformin, with small increases in the proportions of patients reporting urinary tract infection (8–10%). Saxagliptin added on to dapagliflozin/metformin was associated with fewer genital infections than placebo (3% vs 6%)¹⁶ whereas dapagliflozin added on to saxagliptin/metformin was associated with more than placebo (6% vs 1%).¹⁷

Costs

According to the November 2017 *Drug Tariff*, a month's treatment with saxagliptin 5mg daily and dapagliflozin 10mg daily separately costs £68.19 compared with £49.56 for Qtern. The cost of Glyxambi is not yet known.

Place in therapy

The role of dual DPP-4/SGLT2 inhibition at second-dose intensification is not established. The options recommended by NICE are triple therapy with metformin plus two of a sulfonylurea, pioglitazone, a DPP-4 inhibitor and an SGLT2 inhibitor (or insulin-based therapy), but NICE does not specifically recommend a DPP-4 inhibitor and an SGLT2 inhibitor in the same triple therapy combination (see Figure 1).²

According to the summaries of product characteristics, the indication for the use of DPP-4/SGLT2 inhibitor combinations is inadequate glycaemic control with metformin and/or a sulfonylurea plus one of the component drugs, implying that quadruple therapy might be an option (ie metformin/sulfonylurea/DPP-4

inhibitor/SGLT2 inhibitor). However, the phase 3 trials specifically excluded treatment with drugs other than metformin.

What other indication might there be for metformin plus DPP-4/SGLT2 inhibition? According to NICE, options at the first-dose intensification include combining metformin with a DPP-4 inhibitor or an SGLT2 inhibitor; individuals who are not controlled on these therapies and who do not want or cannot take a sulfonylurea or pioglitazone might find the new combination more appealing. The trials suggest that glycaemic control improves more when an SGLT2 inhibitor is added to dual therapy with metformin/DPP-4 inhibitor; this difference was more marked with dapagliflozin than empagliflozin but it's unclear whether this is a true difference between the drugs or a chance finding.

Summary

The combination of a DPP-4 inhibitor and an SGLT2 inhibitor, together with metformin, improves glycaemic control compared with metformin plus one of the component drugs and may have a role when the usual options are unsatisfactory. The impact on glycaemic control appears to be greater when an SGLT2 inhibitor is the new addition but so too is the risk of genital infections.

Clinical trials of the two available combinations report broadly similar outcomes for efficacy and tolerability and it is unclear whether the small differences between them reflect the true effects of the component drugs or are due to chance. Qtern is less expensive than its component drugs taken separately.

References

1. NHS Digital. *Prescription Cost Analysis. England 2016*. March 2017. Available from: <https://digital.nhs.uk/catalogue/PUB23631>
2. National Institute for Health and Care Excellence. *Type 2 diabetes in adults: management*. NG28. December 2015 (updated May 2017). Available from: <https://www.nice.org.uk/guidance/ng28>. NICE guidance is prepared for the National Health Service in England, and is subject to regular review and may be updated or withdrawn. NICE has not checked the use of its content in this article to confirm that it accurately reflects the NICE publication from which it is taken.
3. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev* 2008;60:470–512.
4. Balas B, et al. The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. *J Clin Endocrinol Metab* 2007;92:1249–55.
5. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 2017;60:215–25.
6. Merovci A, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014;124:509–14.
7. Kibbey RG. SGLT-2 inhibition and glucagon: Cause for alarm? *Trends Endocrinol Metab* 2015;26:337–8.
8. Rosenstock J, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care* 2015;38:376–83.
9. Ekholm E, et al. Combined treatment with saxagliptin plus dapagliflozin reduces insulin levels by increased insulin clearance and

improves β -cell function. *Endocr Pract* 2017;23:258–65.

10. Matthaie S, et al. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes. *Diabetes Care* 2015;38:2018–24.

11. Mathieu C, et al. Randomized, Double-blind, Phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care* 2015;38:2009–17.

12. Søfteland E, et al. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: a 24-week randomized, double-blind, parallel-group trial. *Diabetes Care* 2017;40:201–9.

13. Tinahones FJ, et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-group trials. *Diabetes Obes Metab* 2017;19:266–74.

14. European Medicines Agency. Glyxambi (empagliflozin/linagliptin) European Public Assessment Report. September 2016.

15. European Medicines Agency. Qtern (dapagliflozin/saxagliptin) European Public Assessment Report. May 2016.

16. Matthaie S, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. *Diabetes Obes Metab* 2016;18:1128–33.

17. Mathieu C, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. *Diabetes Obes Metab* 2016;18:1134–7.

Declaration of interests

None to declare.

Steve Chaplin is a medical writer specialising in therapeutics