

Type 2 diabetes: newer medicines and insulin analogues

First-line management of hyperglycaemia in patients with type 2 diabetes, when diet and exercise alone is inadequate, continues to be metformin and/or an insulin secretagogue, usually a sulfonylurea.¹ With understanding of the hormonal regulation of glucose metabolism expanding, newer therapies have been introduced that offer alternative second- and third-line options, and combination approaches for glycaemic control.

Thiazolidinediones (or "glitazones") were the first of these medicines to offer an alternative for combined therapy in patients unsuited to either metformin or a sulfonylurea.¹ Use of two agents that were licensed in the UK, pioglitazone and rosiglitazone, was substantial; however, these have subsequently been shown to be associated with significant adverse events. The marketing authorisation of rosiglitazone is now suspended and cautions relating to the use of pioglitazone are outlined in Table 1. Two other therapies have become available more recently: the dipeptidyl peptidase-4 (DPP-4) inhibitors (or "gliptins") and the glucagon-like peptide-1 (GLP-1) analogues, exenatide and liraglutide.

This bulletin discusses the newer medicines and the long-acting human insulin analogues. Their place in the management of hyperglycaemia in patients with type 2 diabetes is considered.

Managing type 2 diabetes

It is the chronic, progressive, and multifactorial nature of type 2 diabetes that makes therapy so challenging. The macrovascular and microvascular complications and resulting organ damage represent an enormous burden to society that is growing with increasing prevalence of the disorder.^{1,2}

Controlling blood glucose concentrations is just one aspect of treatment that is undertaken in the context of wider risk management. Lifestyle factors such as smoking cessation, diet, and physical activity can have a significant impact on disease progression and outcomes. With regard to lowering cardiovascular risk, controlling blood pressure and controlling blood lipid concentrations are both more effective than

Summary

- The newer antihyperglycaemic medicines – pioglitazone, the gliptins, and the GLP-1 analogues – are recommended for type 2 diabetes as dual or triple therapy options in combinations that include metformin and/or a sulfonylurea.
- The newer agents all lower HbA_{1c} but have not been shown to reduce vascular complications in diabetes. There are concerns that any benefits of intensive combined therapy may not outweigh the risks and it is not yet clear how drug- and patient-specific variables may influence outcomes. HbA_{1c} targets should be individualised.
- Pioglitazone is associated with weight gain and with serious adverse events that can limit its use. The use of the gliptins and GLP-1 analogues is increasing, but long-term safety data are limited.
- The GLP-1 analogues are associated with weight loss and may have a greater effect on HbA_{1c} levels, but they are costly and require injection. They are reserved for dual therapy when other agents are unsuitable, or for triple therapy in selected patients.
- The long-acting human insulin analogues are not considered cost-effective in type 2 diabetes and are recommended only in specific circumstances.

controlling blood glucose.³ Whereas the significance of some risk factors in patients with type 2 diabetes is established, research continues into genetic and environmental influences, and into molecular mechanisms that contribute to glucose intolerance. These include insulin resistance in muscle and liver cells, β cell failure, fat cell lipolysis, α cell function, incretin deficiency or resistance in the gastrointestinal tract, glucose reabsorption in the kidney, and brain regulation of energy homeostasis.^{2,4}

Because of the complexity associated with managing diabetes, therapy should be tailored for individuals.¹ Improved patient outcomes will not necessarily be achieved by rigidly pursuing targets for surrogate markers of disease (e.g. HbA_{1c} levels).³ Patient education and engagement is key to establishing personalised goals for therapy.

How the newer therapies work

The **glitazones** can be described as insulin sensitisers. They activate the nuclear transcription factor, peroxisome proliferator activated receptor γ (PPAR γ), which is expressed predominantly in adipose tissue, but also in skeletal muscle and the liver. Activation of PPAR γ affects insulin-sensitive genes involved in glucose and lipid metabolism, and improves the response to insulin.

The DPP-4 inhibitors and the GLP-1 analogues both enhance the release of insulin. They utilize the action of intestinal hormones, the incretins, which are produced after eating. These hormones, act on pancreatic β cells to promote glucose-dependent insulin secretion. Of particular interest in type 2 diabetes is the incretin hormone GLP-1, which also suppresses glucagon secretion, delays gastric emptying, and promotes satiety.

The **gliptins** prolong the action of GLP-1 by inhibiting DPP-4, the enzyme responsible for its metabolism. DPP-4 inhibitors also affect the activity of other peptide hormones but potential effects, for example on immune function,⁵ have not been identified with clinical experience of gliptins to date.

The **GLP-1 analogues**, also described as incretin mimetics, bind to and activate GLP-1 receptors and are resistant to DPP-4 degradation. They have been associated with improvements in indicators of β -cell function,⁶ but whether they, or the gliptins, can alter the course of diabetes by preserving β -cell function is not known. The products available in these new therapeutic groups are listed in Table 1.

Measures of efficacy: effects on HbA_{1c}

The addition of pioglitazone or a gliptin to metformin lowers HbA_{1c} by a similar amount to that achieved by adding a sulfonylurea (i.e. by an additional 1% on average).⁷ The effect on HbA_{1c} of once-weekly exenatide is superior to the twice-daily product and comparable to liraglutide 1.2 mg daily.^{8,9} Some study data suggests that both exenatide and liraglutide can have a greater effect on HbA_{1c} than pioglitazone and gliptin therapy, but the National Institute for Health and Clinical Excellence (NICE) recommends that the GLP-1 analogues are reserved for patients in whom the other agents are not suitable, or in selected patients requiring triple therapy (see Figure 1).^{8,9}

Effects on disease outcomes

Despite the potential to improve HbA_{1c} levels, it is unclear whether using the newer medicines in

combination therapies improves vascular outcomes. Only one clinical trial of the newer medicines has demonstrated improvements in cardiovascular risk. It was a study of pioglitazone conducted in patients with macrovascular disease, who were being treated with metformin, a sulfonylurea, or both, often in combination with insulin (>30%).¹⁰ There was no reduction in the primary endpoint after an average of almost three years but analysis did show a reduction in one composite endpoint of all-cause mortality, non-fatal myocardial infarction (MI), and stroke. An increase in oedema, heart failure, pneumonia, and bladder cancer (p=0.069) was also observed.

A further review of 22 randomised pioglitazone trials of at least six months duration found no evidence of benefit on any outcomes.¹¹ Postmarketing experience has confirmed that pioglitazone is associated with significant risks that need to be considered if prescribing (see Table 1).

For the gliptins and GLP-1 analogues, evidence from controlled trials is lacking for any outcomes. A number of warnings and cautions regarding serious events are noted in the prescribing information for these products (see Table 1), but long-term safety data are limited. Common, less serious effects that are reported with these medicines are generally dose-related, self-limiting, and gastrointestinal in nature.

The lack of evidence relating to the newer anti-hyperglycaemic agents on vascular outcomes means that any clinical benefit from their considered use in therapeutic combinations (see Figure 1) lies in providing alternatives to existing therapies. They are associated with less hypoglycaemia than the sulfonylureas and insulins, and have a neutral (the gliptins) or positive (the GLP-1 analogues) effect on weight. Prescribing these medicines with the aim of achieving better glucose control requires care, especially given the lack of clarity about what constitutes optimal antihyperglycaemic therapy (see the discussion below).

Intensive combination therapy

Numerous studies of “intensive” therapy (targeting a “normal” HbA_{1c} of 6.5% or 48 mmol/mol) have been conducted and incorporated in several meta-analyses. Improved glycaemic control has been associated with reduced microvascular complications, specifically retinopathy and nephropathy.^{3,12} However, despite a reduction in non-fatal MI in some settings, a significant effect on cardiovascular events has not been consistently reported,^{3,12} and there is no evidence of benefit on mortality.

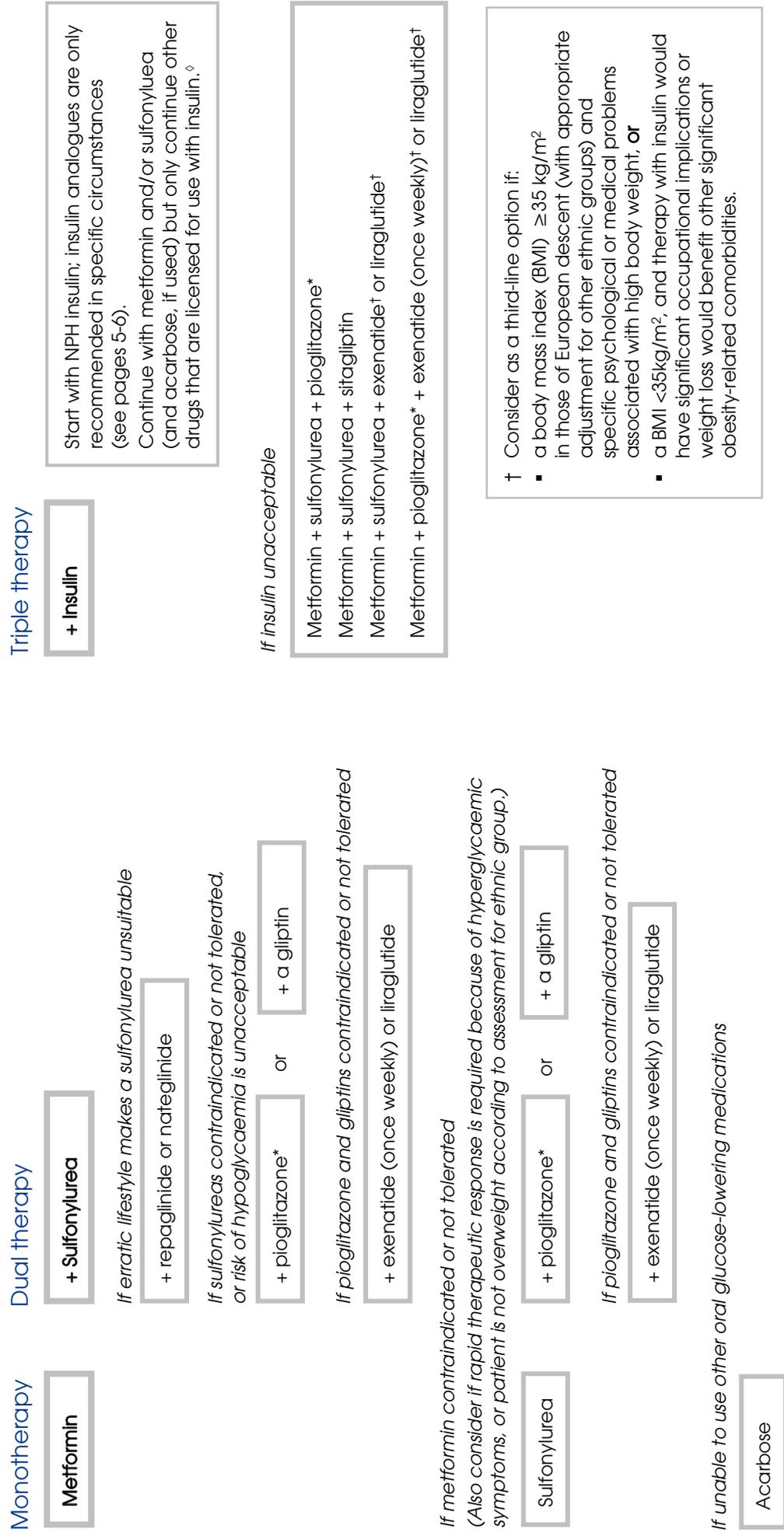
Table 1. Newer antihyperglycaemic agents (excluding insulins) used when diet and exercise fails to control diabetes

Therapeutic group Medicine (Brand)	Administration	Prescribing considerations/cautions and adverse drug events 13. #	Cost/ Month*
Thiazolidinediones "glitazones"	oral	Not suitable in heart failure; can cause peripheral oedema (particularly with insulin). Increased risk of bone fractures, particularly in women. Small increased risk of bladder cancer.	£25-40
Pioglitazone (Actos®) Generic product available but not licensed for use with metformin. {Rosiglitazone withdrawn 2010}	daily	Increased risk of pneumonia and lower respiratory tract infection. Monitor liver function before and during treatment. New-onset or worsening diabetic macular oedema with decreased visual acuity has been reported. {Rosiglitazone withdrawn due to risk of ischaemic heart disease}	
Combination product: Pioglitazone with metformin (Compefact®)	twice daily	Weight gain. Only continue if HbA _{1c} ↓0.5% in 6 months. ¹	
Dipeptidyl peptidase-4 (DPP-4) inhibitors "gliptins"	oral	Acute pancreatitis and serious hypersensitivity reactions have been reported. If impaired renal function: adjust dose in moderate to severe impairment; caution with saxagliptin in severe disease (not suitable for end stage renal disease). If impaired liver function: avoid vildagliptin; saxagliptin and sitagliptin not suitable in severe impairment; use caution with saxagliptin in moderate impairment. Liver function should be monitored with vildagliptin If moderate to severe heart failure: no experience with vildagliptin.	£30-35
Saxagliptin ▼ (Onglyza®) Sitagliptin ▼ (Januvia®) Vildagliptin ▼ (Galvus®) {Linagliptin ▼ (Trajenta®) is not recommended for use in Wales (see Figure 1)}	oral daily daily twice daily		
Combination products: Sitagliptin with metformin (Janumet®) ▼ Vildagliptin with metformin (Eucreas®) ▼	twice daily twice daily	Weight "neutral". ⁵ Only continue if HbA _{1c} ↓0.5% in 6 months. ¹	
Glucagon-like peptide-1 (GLP-1) analogues "incretin mimetics"	subcutaneous injection	Pancreatitis has been reported. If impaired renal function: avoid in severe disease; exenatide (once weekly) and liraglutide not recommended in moderate impairment and care required when titrating dose of exenatide twice daily. If impaired hepatic function: avoid liraglutide. (Weight loss associated with use is a benefit of treatment). ⁶	£75 £70 £80
Exenatide ▼ (Bydureon®) Exenatide ▼ (Byetta®) Liraglutide ▼ (Victoza®)	weekly twice daily daily † (‡ 1.8 mg not recommended for type 2 diabetes)	Third-line use: continue only if HbA _{1c} ↓1% and weight ↓3% in 6 months. ^{8,9} Second-line use of exenatide (once weekly) and liraglutide 1.2mg: continue only if HbA _{1c} ↓1% in 6 months. ^{8,9}	

See also the Summaries of Product Characteristics (SPCs)

* value/range approximations given to nearest £5

Figure 1. Recommendations for using antihyperglycaemic medicines[§]



[§] Based on NICE recommendations when HbA_{1c} targets are not met. Note that NICE clinical guideline 87 (2009)^{1,14} was published before marketing of saxagliptin or linagliptin; however, linagliptin has since been assessed for use in NHS Wales and is not recommended (2012).¹⁵ Exenatide (once weekly) and liraglutide are covered separately in NICE technology appraisal guidance 248⁸ and 203.⁹ **See Table 1 for conditions for continuing newer medicines beyond 6 months.**

[◇] Licensed uses of these medicines are outlined in the Summaries of Product Characteristics (SPCs).

* A generic product is available but with a restricted marketing authorisation compared with branded pioglitazone; it is not licensed for use with metformin.

One clinical study has, in fact, demonstrated an increase in mortality with intensive glycaemic control.¹⁶ This association has also been observed in two cohort studies.^{17,18} To what extent factors such as the duration of disease, weight, the presence of co-morbidities, or the way in which glucose is lowered have an impact, is not known.^{3,18,19} The speed with which therapy is intensified and the use of specific medicines or combinations of medicines, including insulin, may be significant.

Undisputed, however, is that intensive therapy has been associated with a substantially increased risk of hypoglycaemia.^{3,10} It is recommended that HbA_{1c} targets be individualised, usually to between 6.5% and 7.5% (48-59mmol/mol), and that lower targets are avoided in type 2 diabetes.^{1,20}

Insulin analogues

In type 2 diabetes, insulin is indicated when blood glucose requires stabilising for short periods, such as in the peri-operative setting,²¹ or when adequate glucose control cannot be achieved with other therapies. Insulin is generally introduced third line; however, the associated risk of hypoglycaemia, the need for injections, and the weight gain experienced by most patients on long-term therapy, may make it acceptable only when maximum oral therapy or a GLP-1 analogue (if appropriate) has proven ineffective (see Table 1 and Figure 1). The introduction of insulin earlier in the course of disease is being investigated in clinical trials.

Recommendations for type 2 diabetes support the introduction of basal insulin administered at bedtime. There are several suitable insulin products available, but the use of human NPH insulin is recommended (Table 2).¹ The long-acting human insulin analogues are associated with lower rates of hypoglycaemia but offer no benefit in terms of lowering HbA_{1c}; they are much more expensive than the intermediate-acting products and are not calculated to be cost-effective using standard thresholds. They may be recommended for specific patients, such as those with problematic hypoglycaemia, or those who require assistance with administration and/or in whom therapy can be significantly simplified.^{1,22}

Despite insulin analogues offering no significant clinical advantage for many patients, NHS expenditure on these products has increased dramatically, rising in patients with type 2 diabetes from approximately £7 m in 2000 to £190 m in 2009 (i.e. from 8% to 83% of total analogue and human insulin costs).²³

In Wales in 2011, insulin analogues constituted 93% of long- and intermediate-acting insulins prescribed (excluding biphasic products).²⁴ This measure has been introduced for 2012-13 as a national prescribing indicator, for both hospital and primary care prescribing in Wales.²²

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Table 2. Human insulins*

Type of Insulin (Trade Name)	Manufacturer	Onset#	Peak#	Duration#
Rapid-acting recombinant human insulin analogues				
insulin aspart <i>NovoRapid</i> [®]	Novo Nordisk			
insulin glulisine <i>Apidra</i> [®]	Sanofi-Aventis	15 mins	1-3 hrs	4 hrs
insulin lispro <i>Humalog</i> [®]	Lilly			
Short-acting soluble insulin (regular/neutral)				
<i>Actrapid</i> [®]	Novo Nordisk			
<i>Humulin S</i> [®]	Lilly	30 mins	2-4 hrs	4-8 hrs
<i>Insuman</i> [®] <i>Rapid</i>	Sanofi-Aventis			
Intermediate-acting isophane insulins (protamine/neutral protamine hagedorn (NPH))				
<i>Insulatard</i> [®]	Novo Nordisk			
<i>Humulin I</i> [®]	Lilly	1-2 hrs	4-12 hrs	14-24 hrs
<i>Insuman</i> [®] <i>Basal</i>	Sanofi Aventis			
Biphasic insulins				
soluble/isophane insulin premixes				
<i>Humulin M3</i> [®]	Lilly			
<i>Insuman</i> [®] <i>Comb 15</i>				
<i>Insuman</i> [®] <i>Comb 25</i>	Sanofi-Aventis			
<i>Insuman</i> [®] <i>Comb 50</i>				
human insulin analogue premixes				
Activity varies depending on the combination.				
insulin lispro/lispro protamine <i>Humalog Mix</i> [®] <i>25</i>	Lilly			
<i>Humalog Mix</i> [®] <i>50</i>				
insulin aspart/aspart protamine <i>NovoMix</i> [®] <i>30</i>	Novo Nordisk			
Long-acting recombinant human insulin analogues				
insulin detemir <i>Levemir</i> [®]	Novo Nordisk			
		1-3 hrs	minimal peak	24 hrs
insulin glargine <i>Lantus</i> [®]	Sanofi-Aventis			

* Information compiled from various sources including www.mims.co.uk, www.patient.co.uk, www.diabetes.co.uk, and BNF.^f

Times given are approximate and may vary between patients, and between injection sites; these are a guide only.

Note: Most insulin products are available in a range of delivery devices, i.e. pre-filled pens, cartridges, and vials. Animal insulins are available (from Wockhardt UK) for the foreseeable future.

The Summaries of Product Characteristics should be consulted for full prescribing information.

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