PrescQIPP Community Interest Company

Insulin analogues to human insulin for patients with type 2 diabetes

Human (NPH) insulin is recommended by the National Institute for Health and Care Excellence (NICE) for initiation in all new patients with type 2 diabetes requiring insulin.[1] Usage of long acting insulin analogues has increased markedly over the last nine years despite this recommendation. This has resulted in a significant increase in costs which is much greater than any other medicines used in diabetes management.

QIPP projects in this area are aimed at ensuring NPH insulins are considered first line in all new patients with type 2 diabetes who require insulin, reviewing the use of analogue insulins to ensure these are used in line with recommendations and ensuring cost-effective insulin products are chosen. This includes reviewing the use of rapid acting analogues, including biphasic products, to ensure the most cost-effective products are chosen in line with the evidence base. This bulletin offers guidance and support material for organisations considering reviewing insulin analogue prescribing as a QIPP project.

Recommendations

Please note these recommendations apply to type 2 diabetes only.

- New patients with type 2 diabetes requiring insulin should be prescribed human isophane (NPH) insulin first line.
- Short-acting human insulin should be used in preference to rapid acting insulin analogues. This includes biphasic products.
- Least costly biphasic isophane insulin products are:
  - Insuman® Comb 25 vial
  - Insuman® Comb 15/25/50 cartridges
  - Insuman ®Comb Solostar pre-filled pen
- Least costly soluble insulin products are:
  - Actrapid® vial
  - Insuman® Rapid cartridges
- Least costly short acting insulin analogue products are:
  - Novorapid® vial
  - Apidra® prefilled pen
  - Apidra®, NovoRapid® and Humalog® cartridges are the same cost.
- Patients currently maintained on a rapid acting insulin analogue, i.e. aspart, glulisine, lispro or biphasic preparation containing these, to be audited and considered for a change to human insulin if appropriate.
- Patients with type 2 diabetes currently on a long acting insulin analogue, i.e. insulin detemir, insulin glargine or insulin degludec, to be audited and considered for a change to NPH insulin if it has not previously been tried and HbA1c not within target or two or more injections per day are being used, taking care to tailor any switch to the needs of the individual patient.

- The least costly NPH product, (vial, cartridge or disposable pen) suitable for an individual patient, should be used. Currently, the least costly vial, cartridge and disposable pen per ml of NPH insulin are:
  - Insulatard® vial - least costly vial
  - Insuman® Basal cartridges - least costly cartridge
  - Insuman® Basal Solostar® disposable pen - least costly disposable pen.
- Long acting insulin analogues, insulin detemir or insulin glargine, should only be considered as an alternative to NPH for people in the following categories, those:
  - Who require assistance from a carer or healthcare professional to administer insulin and in whom use of an analogue would reduce injections from twice to once daily.
  - Whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia.
  - Who would otherwise need twice daily NPH insulin injections plus hypoglycaemic drugs.
  - Who cannot use their device to inject NPH insulin.
- CCGs will need to make a local decision around the place in treatment of the ultra-long acting insulin analogue, insulin degludec, in type 2 diabetes considering the evidence alongside that for other basal insulins, taking into account the current NICE guidance which recommends the use of long acting insulin analogues in some limited circumstances. Individual patient factors and their experience of hypoglycaemia together with the higher cost of insulin degludec will need to be taken into account.
- Patients meeting the requirements for an insulin analogue should be prescribed the least costly insulin analogue suitable for the individual patient. Currently, insulin glargine, Lantus® brand (biosmilar glargine will be available in Q3 of 2015 which will be 15% cheaper), is the least costly vial, cartridge and disposable pen device per ml of insulin of the insulin analogue products.

Background

Around 6% of the UK population have diabetes mellitus and of these, around 90% have type 2 diabetes.[2] Many of these people will need insulin therapy for effective control of their diabetes. The different types of insulin, regimens and devices present various advantages and disadvantages that can affect adherence, quality of life and glycaemic control.[3]

Regular human insulin has a slower onset of action and is more prolonged than that of endogenous insulin.[3] NPH insulin is an intermediate acting insulin, and is also known as isophane insulin or isophane protamine insulin. NPH insulin contains protamine which prolongs the action of insulin.[4] The currently available human NPH insulin products in the UK are Insulatard®, Humulin I® and Insuman® Basal insulin and the NPH bovine and porcine isophane insulin injections are available as Hypurin® products.[5]

Several insulin analogues have been developed. Rapid-acting insulin analogues were developed to mimic more closely the normal mealtime insulin response compared to regular insulin. They have a quicker onset of action which allows injection immediately before, or even just after, a meal, which may offer more flexibility and convenience for those with an irregular eating pattern.[3] However, the rapid-acting insulin analogues do not appear to result in significant reductions in HbA1c compared with short-acting soluble insulin. There is also little evidence that they produce large reductions in episodes of severe, overall or nocturnal hypoglycaemia compared with short-acting soluble insulin in most patients with type 2 diabetes.[6] Currently, the rapid-acting analogues available in the UK are insulin aspart (NovoRapid®), insulin glulisine (Apidra®) and insulin lispro (Humalog®). They are also present in the biphasic insulin products, Novomix 30® and Humalog® Mix products.[5]

The long acting insulin analogues – insulin detemir (Levemir®) and insulin glargine (Lantus®), and the ultra-long acting insulin degludec (Tresiba®) were developed to have more reproducible absorption and prolonged action, to achieve more predictable glycaemic control and fewer hypoglycaemic episodes.[3,7] Insulin glargine and insulin detemir are considered equivalent to NPH (and to each other) in terms of glycaemic control as reflected in HbA1c level, but do have modest advantages in terms of hypoglycaemia, especially at night. Insulin degludec has a lower overall rate of hypoglycaemia, and lower

rate of nocturnal hypoglycaemia compared to insulin glargine, however, there is no evidence that insulin degludec improves long-term survival in type 1 or 2 diabetes compared to other basal insulin regimens[7] or conveys additional clinical benefit compared with insulin glargine.[8] There is no evidence directly comparing all three long acting insulin analogues.

Detemir, when used only once daily, appears to have slightly less weight gain than glargine, but this is probably not clinically significant. Detemir requires a slightly larger daily dose, and has a higher cost with present prices.

NICE,[1] Scottish Intercollegiate Guidelines Network (SIGN)[9] and the Drug & Therapeutics Bulletin[3] all recommend that NPH insulin should be used first in new patients with type 2 diabetes. Yet, nationally, spend on insulin analogues has increased dramatically over the last nine years and represents the largest increase compared to all the other medicines used in diabetes management.

National guidelines

NICE and SIGN have both published guidelines on management of type 2 diabetes.[1,9]

NICE recommended that if insulin therapy is considered appropriate, it should be initiated with NPH insulin, at bedtime or twice daily according to need; and that a long acting analogue should be considered as an alternative for people in the following categories:

- Those who require assistance from a carer or healthcare professional to administer insulin and in whom use of an analogue would reduce injections from twice to once daily;
- Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia;
- Those who would otherwise need twice-daily NPH insulin injections plus hypoglycaemic drugs; or
- Those who cannot use their device to inject NPH insulin.[1]

Similarly, SIGN advises that when starting insulin therapy, NPH insulin should be initiated and the dose titrated against morning fasting blood glucose levels. Long acting insulin analogues can be considered if there are concerns regarding hypoglycaemia risk.[9]

A switch to a long acting insulin analogue from NPH insulin can be considered in people who:

- Do not reach their target HbA1c because of significant hypoglycaemia, or
- Experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, or
- Cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long acting insulin analogue were made, or
- Need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long acting insulin analogue would reduce the number of daily injections.[9]

Evidence base

A Drug and Therapeutics Bulletin review of insulins, regimens and devices in type 2 diabetes was published in December 2010. The report concluded that based on current evidence, most patients should start on NPH insulin, with treatment being intensified by the addition of short acting human insulin if appropriate. For most people, analogue insulins offer no significant clinical advantage and are much more expensive.[3]

Rapid acting insulin analogues

For most patients with type 2 diabetes, the rapid-acting insulin analogues do not appear to result in significant reductions in HbA1c compared with short-acting soluble insulin. There is little evidence that the rapid- acting insulin analogues produce large reductions in episodes of severe, overall or nocturnal hypoglycaemia compared with short-acting soluble insulin in most patients with type 2 diabetes.[6]

A Cochrane systematic review compared short-acting human insulin and rapid-acting analogues. The review included 49 randomised controlled trials (37 studies using lispro, 10 using aspart, one using lispro and aspart, and one using glulisine). The studies included a total of 2028 patients with type 2 diabetes, and found there was no significant difference in HbA1c level, hypoglycaemic episodes, or adverse events between the groups. Severe hypoglycaemia was less frequent in patients on insulin analogues (0.3 vs. 1.4 episodes per 100 person-years), although the definition of severe hypoglycaemia varied between studies. The review concluded that rapid-acting analogues have only a minor advantage over short-acting human insulin in most patients.[3,10]

Long acting analogues – Insulin glargine and insulin detemir

A Cochrane systematic review and meta-analysis of eight clinical trials conducted in 2006 compared the effects of long acting insulin analogues vs. NPH insulin for type 2 diabetes.[11,12]

Six studies investigated insulin glargine and two looked at insulin detemir. No superiority in metabolic control (as measured by HbA1c) was observed for insulin glargine. For insulin detemir, the meta-analysis yielded a statistically significant but probably clinically unimportant superiority in favour of NPH insulin.

Symptomatic and nocturnal hypoglycaemic events were lower in patients treated with insulin glargine than in patients with NPH insulin. Also, for insulin detemir the two included studies found a lower number of patients experiencing overall or nocturnal hypoglycaemic episodes in the insulin detemir treatment groups.

The methodological quality of the included studies allowed only a cautious interpretation of the results. No study was designed to investigate possible long-term effects. It remains unclear to what extent the treatment with long acting insulin analogues will affect the development and progression of microvascular and macrovascular events, compared with NPH insulin. The differences in overall effects on metabolic control were small for insulin glargine and NPH and disadvantageous for insulin detemir, so no important improvements in the development of microvascular late complications would be expected from treatment with long acting insulin analogues.

The advantages found in the rate of severe hypoglycaemic events should also be interpreted with caution. No statistically significant advantage was found for therapy with insulin glargine or detemir. Interpretation of the results with regard to the frequency of severe hypoglycaemia is difficult due to bias-prone definitions used in the trials to identify episodes of hypoglycaemia. In all studies, the frequency of severe hypoglycaemia was very low, so seeing an important clinical effect for the different treatments was difficult. The meta-analysis found a consistent reduction in symptomatic or overall hypoglycaemic effects for therapy with long acting insulin analogues, however, no safe inferences can be drawn from these results because defining hypoglycaemia by symptoms (as was done in the trials) only makes the results prone to bias. This is particularly so in open trials with no blinded outcome assessment.

The advantage of insulin glargine and detemir could be a lowering of nocturnal hypoglycaemic events in patients with type 2 diabetes taking basal insulin, but this may only be a minor clinical benefit as again bias cannot be ruled out, thus interpretation of results is difficult.

Owing to the maximum observation period of 12 months, the review cannot provide any further guidance on potential adverse properties, such as progression of microvascular complications under treatment with long acting insulin analogues. One study found a higher rate of progression of diabetic retinopathy in patients treated with insulin glargine, while in another investigation the opposite result was found.

The mean age of patients in the included studies ranged from 55 to 62 years, preventing any conclusions from being drawn on possible differences of the effects of the different insulins in old or young patients.

A Health Technology Assessment published in 2010 conducted a systematic review and economic evaluation of newer agents for blood glucose control in type 2 diabetes. Four classes of drugs were considered including the long acting insulin analogues, glargine and detemir.[13] The assessment report came to the following conclusions:

- HbA1c
  There was no difference in HbA1c level between glargine and NPH insulin, and only a small non-significant difference in trials of detemir versus NPH (HbA1c level was higher with detemir by 0.08%; 95% CI −0.03 to 0.19).
- Hypoglycaemia
  There were no differences in the frequency of severe hypoglycaemia between the analogues and NPH, but, overall, hypoglycaemia was less frequent with both glargine [odds ratio (OR) 0.74, 95% CI 0.63 to 0.89] and detemir (OR 0.51, 95% CI 0.35 to 0.76). Many of the hypoglycaemic episodes were nocturnal, and the ORs for those were 0.47 (95% CI 0.37 to 0.59) for glargine and 0.48 (95% CI 0.37 to 0.63) for detemir.
- Weight
  The meta-analyses showed that those on glargine gained slightly less weight than those on NPH (0.28 kg; 95% CI −0.72 to 0.15) but this was neither clinically nor statistically significant. On detemir, the difference was a little greater (1.2 kg; 95% CI −1.6 to −0.8). In the head-to-head trial of glargine versus detemir, those on glargine gained 3.5 kg on average, compared with a gain of 2.7 kg on detemir, but the difference of 0.8 kg is of doubtful clinical significance. The difference applied only to those on once-daily detemir; those on two injections daily gained 3.7 kg.
- Insulin dose
  In a head-to-head trial, the mean daily dose was higher for detemir (0.52 units/kg with once-daily injections; 1.0 units/kg with twice-daily injections) than for glargine (0.44 units/kg with once-daily injections).

Ultra-long acting insulin analogue – Insulin degludec

A meta-analysis of randomised trials regarding the efficacy and safety of insulin degludec concluded that degludec was associated with a lower incidence of hypoglycaemia than glargine insulin for similar levels of glycaemic control in diabetes.[14] A critical review of this meta-analysis found that the conclusions follow from the evidence presented but caution is advised as several limitations where identified with the review.[15]

A NICE evidence review of insulin degludec concluded that it is non-inferior to insulin glargine in terms of glycaemic control in type 2 diabetes, with statistically significantly lower rates of some, but not all, measures of hypoglycaemia, particularly nocturnal hypoglycaemia. Also, there are no published studies comparing insulin degludec with NPH (isophane) insulin and none that measure patient-oriented efficacy outcomes.[16] The review is based on three randomised controlled trials comparing insulin degludec to insulin glargine in people who had previously used basal insulin and in people who were insulin naïve. Both involved administration of a once-daily subcutaneous (s/c) injection with doses adjusted to achieve plasma glucose target 3.9 to 5 mmol/L, in adults with type 2 diabetes. The other study compared insulin degludec with sitagliptin in people who were insulin naïve. This was included in the NICE evidence review but is thought to be an unlikely target patient group for insulin degludec.[8]

The studies comparing insulin degludec with insulin glargine showed that insulin degludec was non-inferior to insulin glargine in terms of glycaemic control as both insulins reduced HbA1c levels to a similar degree from baseline over 52 weeks and 26 weeks respectively.[7,8,16] With regard to hypoglycaemia, insulin degludec statistically significantly reduced the rate of overall hypoglycaemia, nocturnal hypoglycaemia and daytime hypoglycaemia, compared with insulin glargine in one study; and nocturnal hypoglycaemia and severe hypoglycaemia in another study. Caution should be applied to interpretation of these findings as the absolute differences in the rates of severe hypoglycaemia were small and the overall rates of severe hypoglycaemia were very low.[16] Compared with sitagliptin, insulin degludec was found to be superior in terms of glycaemic control (as measured by estimated treatment difference in HbA1c), but resulted in more episodes of overall confirmed hypoglycaemia (episodes per patient per year). These results are expected as the mean dose of insulin was titrated weekly throughout the study period.[16]

Safety

Rates of severe hypoglycaemia were similar in those treated with insulin glargine and insulin degludec. Compared with insulin glargine, insulin degludec significantly reduced confirmed episodes of hypoglycaemia and nocturnal hypoglycaemia.

Insulin degludec (Tresiba Flexpen touch device) is available in two strengths, 100 units/ml and 200 units/ml. All other approved basal insulins are available in 100 units/ml strength. In April 2013, the Medicines and Healthcare Products Regulatory Agency review (MHRA) issued advice to minimise the risk of medication errors associated with the higher strength, 200 units/ml formulation. Insulin degludec pen products have a dose counter window which displays the number of units of insulin degludec to be injected regardless of strength. Therefore, no dose conversion is needed when changing from one strength product to the other. The MHRA advised care in prescribing insulin degludec to ensure that the correct strength is specified on the prescription and that dose conversion is not required if changing between the two strengths of Tresiba pen products.[17]

Summary

Rapid-acting insulin analogues do not appear to result in significant reductions in HbA1c compared with short-acting soluble insulin. There is little evidence that the rapid- acting insulin analogues produce large reductions in episodes of severe, overall or nocturnal hypoglycaemia compared with short-acting soluble insulin in most patients with type 2 diabetes.

Glargine and detemir are equivalent to NPH (and to each other) in terms of glycaemic control as reflected in HbA1c level, but have modest advantages in terms of hypoglycaemia, especially nocturnal. There is little to choose between the two analogues. Detemir, when used only once daily, appears to have slightly less weight gain than glargine, but the difference in the head-to-head trial was under 1kg and is probably not clinically significant. Detemir requires a slightly larger daily dose, at higher cost with present prices.

Insulin degludec has a lower overall rate of hypoglycaemia, and lower rate of nocturnal hypoglycaemia compared to insulin glargine, however, there is no evidence that insulin degludec improves long-term survival in type 2 diabetes compared to other basal insulin regimens[7] or conveys additional clinical benefit compared with insulin glargine.[8]

A NICE Quality and Productivity bulletin published in December 2011 advises that in the absence of evidence to suggest the superiority of insulin analogues over NPH insulin in terms of improved safety, glycaemic control or reduction of long term diabetic complications, a cautious approach to prescribing of these insulin analogues is advised. There are clear productivity savings to be generated by reducing prescribing of these insulin analogues. Practitioners should consider the individual features of the patient and the NICE recommendations before prescribing these insulin analogues.[12]

It has been suggested by the chair of the NICE guidance committee that 90% of patients with type 2 diabetes could receive human insulin instead of long acting insulin analogues, with around two-thirds of these patients remaining on human insulin.[18]

Cost effectiveness

The Health Technology Assessment economic evaluation stated that for the comparison of glargine with NPH, there is an additional anticipated cost of around £1,800 which is associated with an insignificant QALY gain (0.006 to 0.007); yielding cost-effectiveness estimates of between £280,000 and £320,000 per QALY. Within the comparison of detemir and NPH, the overall treatment costs from detemir are slightly higher, being between £2,700 and £2,600. QALY gains are again slight – about 0.015–0.006. Cost per QALY ranges from £188,000 to £412,000.[13] These costs are substantially greater than the £20,000 to £30,000 per QALY threshold usually considered in NICE's cost-effectiveness evaluation.[18]

On cost-effectiveness grounds, NPH should be the first-choice insulin in type 2 diabetes, rather than a long acting analogue. However, some patients will have more trouble with hypoglycaemia than others

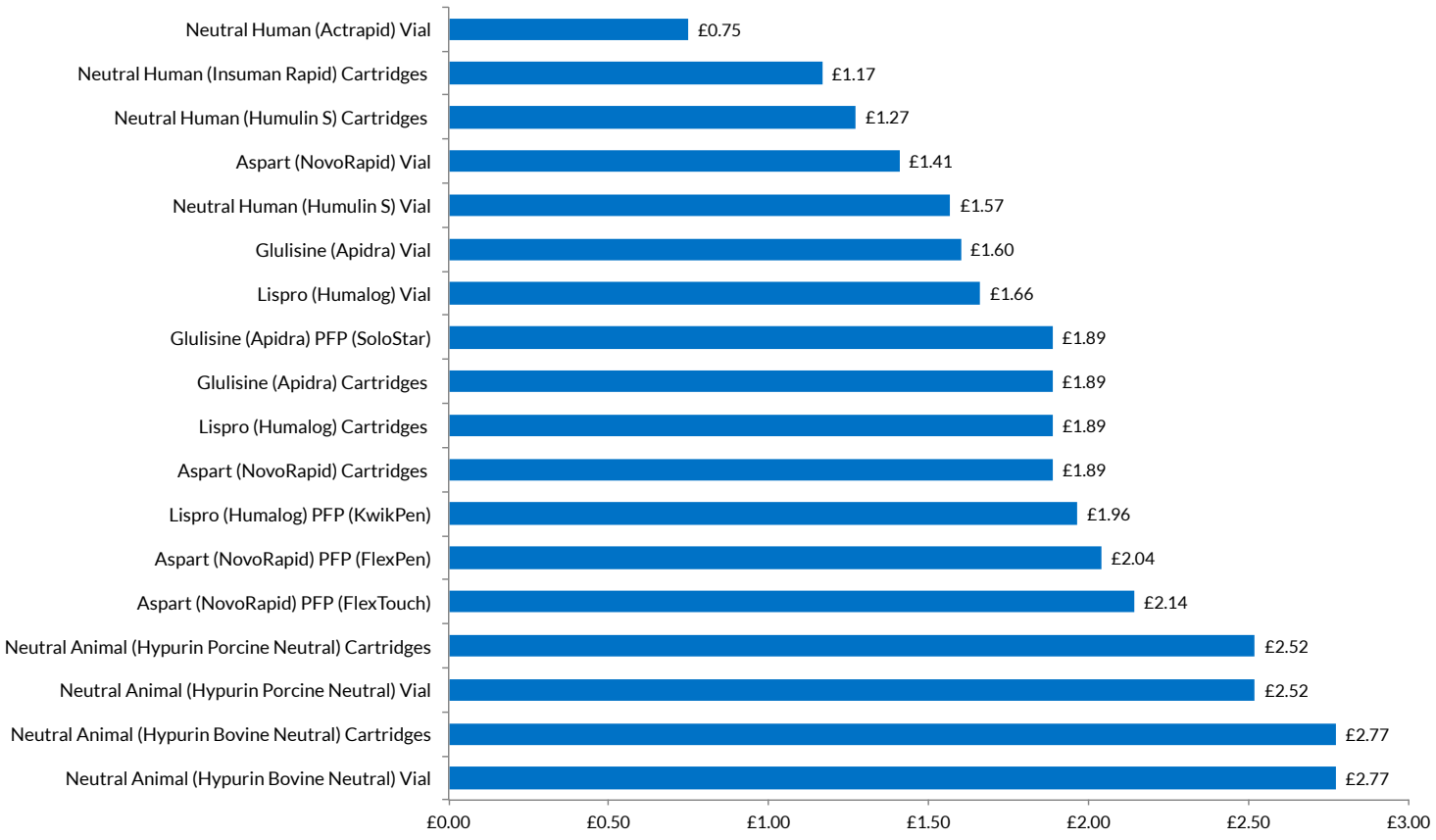
and will potentially have more to gain. The analogues have modest advantages but, at present, much higher cost. In some patients, the benefits of the analogues relative to NPH may be greater and cost-effectiveness correspondingly better.[13]

An evaluation of the incremental cost to the NHS of prescribing analogue insulin published in the BMJ in 2011 found that if all analogue insulin dispensed in the UK between 2000 and 2009 had been for human insulin alternatives, the NHS would have saved an estimated £625 million. The adjusted annual cost of analogue insulin increased from £18 million in 2000 (12% of total insulin cost) to £305 million in 2009 (85% of total insulin cost). The study authors acknowledge that insulin analogues are associated with reduced weight gain, less hypoglycaemia (particularly nocturnal), improved lowering of post prandial glucose and improved dosing schedules, however, most commentators agree that these benefits are modest in comparison to human insulin. Despite the substantial financial impact of using insulin analogues, there has been no observable clinical benefit to justify the investment and more worryingly, the clinical role and safety of insulin for use in people with type 2 diabetes is being questioned.[18]

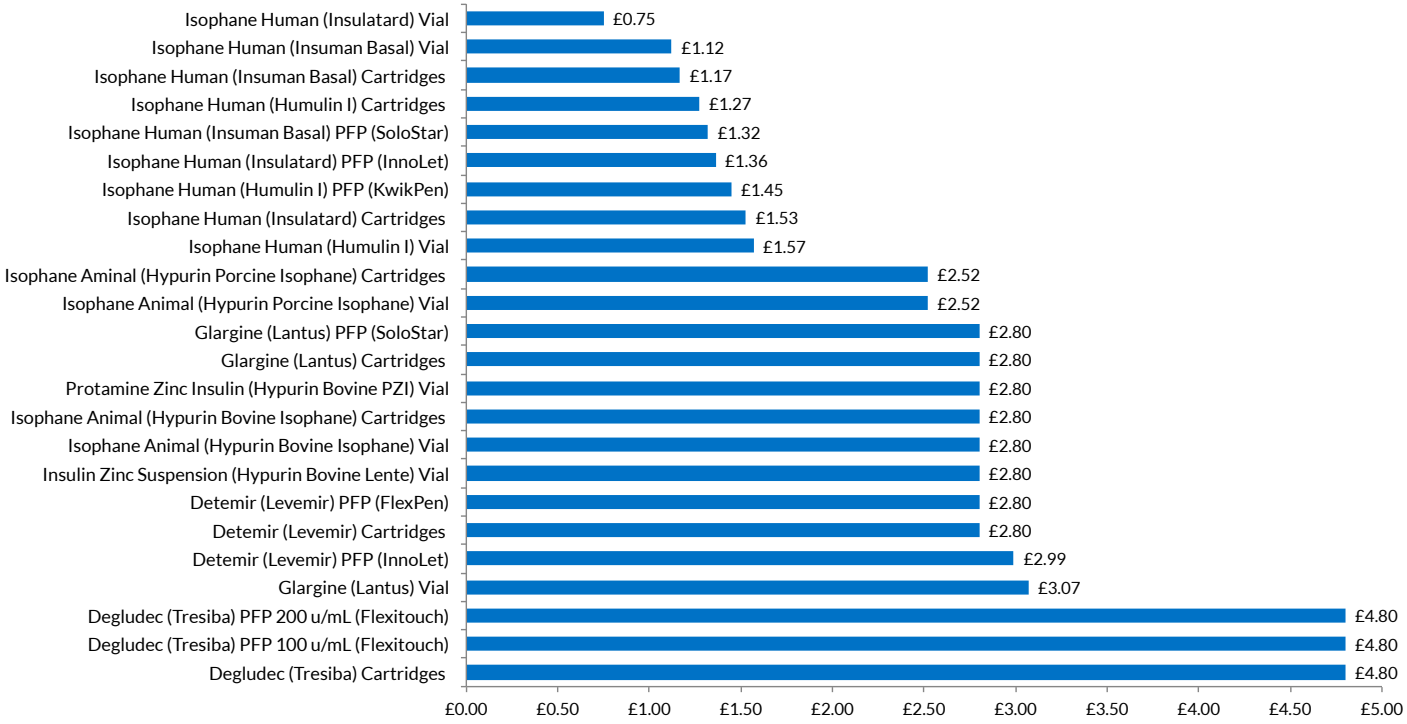
Costs

There is a significant difference in costs between insulin analogues and NPH insulin and between different devices, such as vials, cartridges and disposable pens.

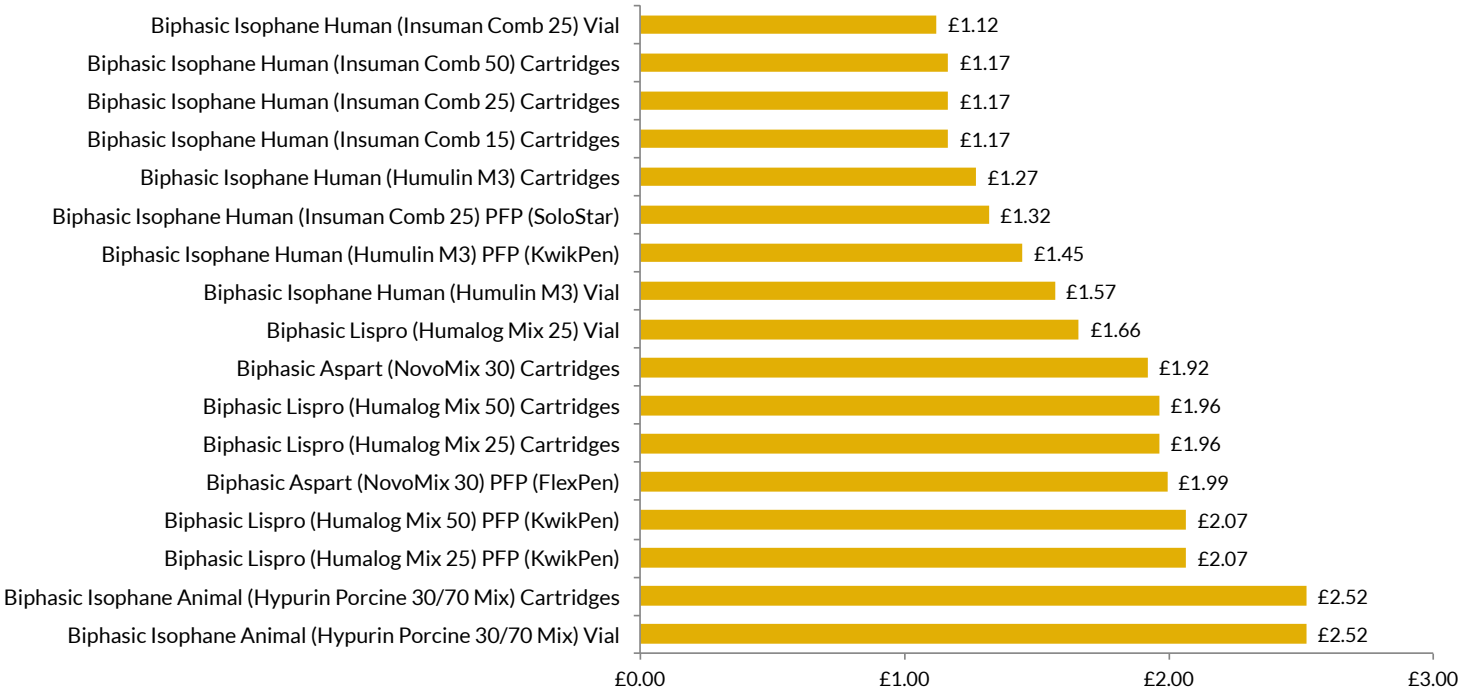
Graph 1: Cost differences between the short acting insulins - Cost per 100 units of insulin



Graph 2: Cost differences between long and intermediate acting insulins - Cost per 100 units of insulin



Graph 3: Cost differences between the biphasic insulin products - Cost per 100 units of insulin



Currently, the least costly vial, cartridge and disposable pen per ml of NPH insulin are:

- Insulatard® vial - least costly vial
- Insuman® Basal cartridges - least costly cartridge
- Insuman® Basal Solostar® disposable pen - least costly disposable pen
- Insulin glargine, Lantus® brand, has the least costly vial, cartridge and pen devices per ml of insulin of the insulin analogue products.

The least costly biphasic ispohane insulin are:

- Insuman® Comb 25 vial
- Insuman® Comb 15/25/50 cartridges
- Insuman® Comb Solostar pre-filled pen.

The least costly soluble insulin products are:

- Actrapid® vial
- Insuman® Rapid cartridges.

The least costly rapid-acting insulin analogue products are:

- Novorapid® vial
- Apidra® prefilled pen
- Apidra®, NovoRapid and Humalog cartridges are the same cost.

Savings available

Any changes in prescribing should be tailored to the individual needs of the patient. Guidance on undertaking an audit to compare current insulin prescribing against the recommendations outlined in this bulletin is given in the next section.

For biphasic insulin, switching to the least costly alternative insulin products Insuman® Comb 25 vial, Insuman® Comb 15/25/50 Cartridges or Insuman® Comb Solostar pre-filled pen **could save approximately £21.9 million annually across England. This equates to approximately £38,569 per 100,000 patients** (ePACT Jan to March 2015)**.**

For long-acting insulin analogues, switching to NPH human insulin products **could save £55.4 million annually across England. This equates to £97,234 per 100,000 patients** (ePACT Jan to March 2015)**.**

Audit guidance

Reviewing insulin therapy in patients with type 2 diabetes provides an ideal vehicle for assessing practice against the recommendations set out in this bulletin. These audits are suitable for being carried out in primary care by GPs with a special interest (GPWSi) in diabetes or diabetes specialist nurses or in conjunction with secondary care consultant in diabetes or diabetes specialist nurses.

Tools to support audit are given in attachments 1 to 4.

Summary

- NICE recommends that if insulin therapy is considered appropriate, it should be initiated with human isophane (NPH) insulin, at bedtime or twice daily according to need; and that a long acting analogue should only be considered in specific circumstances.
- On cost-effectiveness grounds, NPH should be the first-choice insulin in type 2 diabetes, rather than a long acting analogue.
- Based on current evidence, most patients should start on NPH insulin, with treatment being intensified by the addition of short acting human insulin if appropriate. For most people, analogue insulins offer no significant clinical advantage and are much more expensive.
- In terms of HbA1c lowering, there is no difference between long acting insulin analogues (glargine or detemir) and NPH insulin.
- There are no differences in the frequency of severe hypoglycaemia between the analogues and NPH, but, overall, hypoglycaemia (particularly nocturnal) is less frequent with the analogues.
- 90% of patients with type 2 diabetes could receive human insulin instead of long acting insulin analogues, with around two-thirds of these patients remaining on human insulin.
- There is no evidence that insulin degludec improves long-term survival in type 2 diabetes compared to other basal insulin regimens or conveys additional clinical benefit compared with insulin glargine. CCGs will need to make a local decision around the place in treatment of the ultra-long acting insulin analogue, insulin degludec, in type 2 diabetes considering the evidence alongside that for other basal insulins, taking into account the current NICE guidance which recommends the use of long acting insulin analogues in some limited circumstances. Individual patient factors and their experience of hypoglycaemia together with the higher cost of insulin degludec will need to be taken into account.
- Long acting insulin analogues, insulin detemir or insulin glargine, should only be considered as an alternative to NPH for people in the following categories, those:
  - Who require assistance from a carer or healthcare professional to administer insulin and in whom use of an analogue would reduce injections from twice to once daily,
  - Whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia,
  - Who would otherwise need twice daily NPH insulin injections plus hypoglycaemic drugs,
  - Who cannot use their device to inject NPH insulin.

There is little to choose between the two long acting analogues, detemir and glargine. Detemir, when used only once daily, appears to have slightly less weight gain than glargine, but this is probably not clinically significant. Detemir requires a slightly larger daily dose, at higher cost with present prices.

Despite the substantial financial impact of using insulin analogues, there has been no observable clinical benefit to justify the investment and more worryingly, the clinical role and safety of insulin for use in people with type 2 diabetes is being questioned.

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Additional PrescQIPP resources

 Briefing  Data pack  Audits, patient letter, guides

Available here: http://www.prescqipp.info/resources/viewcategory/219-insulin-analogues

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