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REVIEW ARTICLE

Achieving Glycaemic Targets in Type 2 Diabetes: the Role of the Basal Insulin Analogue Insulin Glargine and How to Use it in Clinical Practice: Moving from Evidence to Practice

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This review examines the role of the basal insulin analogue, insulin glargine in the treatment of type 2 diabetes, focusing on how research evidence can inform its use in clinical practice. The importance of achieving optimal glycaemic control has been emphasised by bodies such as the IDF who have set strict targets for HbA1c levels. We know that FPG plays an important role in helping to achieve optimal glycaemic control and basal insulin therapy can play a role in this area.

Insulin glargine is a once-daily, peakless basal insulin which has been shown to achieve the same degree of glycaemic control as NPH insulin but with significantly reduced rates of hypoglycaemia. This allows patients to improve self management of their diabetes by optimising treatment without the risk of hypoglycaemia. Research has shown that patients can safely optimise therapy with a patient-led titration algorithm based on an insulin dose adjustment of 2 units every 3 days. Initiation of insulin glargine has been shown to be effective within a group as well as individually, allowing health care professionals to manage their time more effectively between the growing numbers of people requiring insulin therapy.

Conclusions: This basal insulin analogue is a welcome addition to the plethora of treatments available to treat type 2 diabetes and efficacy data can now be converted into practical methods of optimising insulin therapy for the type of patients healthcare professionals routinely encounter in their practice.

Key Words: Glycaemic control, Insulin analogues, Basal insulin, Insulin glargine

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Introduction

The 2005 Annual Meeting of the European Association for the Study of Diabetes (EASD) reignited the debate regarding what constitutes good glycaemic control. While the American Diabetes Association (ADA) recommend that people with diabetes aim for a HbA1c level <7.0%[1], a global guideline for Type 2 diabetes compiled by the International Diabetes Federation (IDF), recommends a target level of <6.5%.[2] This move mirrors the recommendations of the UK-based National Institute of Clinical Excellence (NICE), which set an HbA1c target for those with Type 2 diabetes of between 6.5%

and 7.5%. The lower target is recommended for people at high risk of macrovascular complications, while the higher target should be set in cases where there is a risk of hypoglycaemia.[3]

Importance of tight glycaemic control

Data from the United Kingdom Prospective Diabetes Study (UKPDS) highlighted the importance of tight glycaemic control in reducing the risk of diabetes complications.[4] This landmark study randomised 3,867 patients with Type 2 diabetes to receive intensive anti-hyperglycaemic therapy using sulphonylureas or insulin, or 'conventional' therapy (diet alone plus pharmacological therapy in the presence of hyperglycaemic symptoms, or fasting plasma glucose [FPG] >15mmol/l). Over 10 years, the mean HbA1c was 7.0% in the intensive group compared with 7.9% in the group receiving 'conventional' therapy. This improvement was associated with a 25% (p=0.0099) decrease in the risk of microvascular endpoints. Furthermore, the risk of myocardial infarction (MI) was reduced by 16%, although this observation was of borderline significance (p=0.052). A further report from the UKPDS demonstrated that each 1% reduction in HbA1c was associated with a 37% (p<0.0001) reduction in the risk of microvascular complications, and a 21% (p<0.0001) reduction in the risk of death related to diabetes.[5] Subsequent reports from the UKPDS have found that the HbA1C was higher in those with fatal versus non-fatal MI (odds ratio 1.17 per 1% HbA1c, p=0.014) and in those with fatal versus non-fatal stroke (odds ratio 1.37 per 1% HbA1c; p=0.007).[6]

Current strategies fail to reach glycaemic goals

Despite this overwhelming evidence of benefit for tight glycaemic control, most patients with Type 2 diabetes fail to reach appropriate levels of HbA1c. The General Medical Services (GMS) contract for England and Wales includes a Quality and Outcome Framework (QOF) target for HbA1c of 7.4% or less.[7] UK data from the National Diabetes Audit for 2004-2005 shows that only 58% of people with diabetes were meeting this standard[8] which was little improvement from data in 2003/2004 which showed just 56% of those with diabetes had a HbA1c lower than 7.5%, while just 23% were achieving a HbA1c lower than 6.5%.[9] Liebel et al reported that just 31% of 7,000 patients from eight European countries who were involved in the Cost of Diabetes in Europe – Type 2 (CODE-2) study had a HbA1c level ≤6.5%, and 42% had a HbA1c level above 7.5%.[10]

These figures for Europe are mirrored in results from the US-based National Health and Nutrition Examination Survey (NHANES). The survey defined glycaemic control rates as the proportion of patients with Type 2 diabetes who achieve a HbA1c level <7.0%. During the period 1988–1994 this proportion was 44.5%, but this dropped to 35.8% for the period 1999–2000.[11]

Data from a UK community care database suggested that a decline in glycaemic control was manifest even when there was a tangible improvement in other aspects of diabetes care, such as control of hypertension and dyslipidaemia.[12] Approximately 500,000 patients, including 10,000 with Type 2 diabetes, were registered in each year of the study, between 1994 and 2001 and not surprisingly, the prevalence of Type 2 diabetes increased during the study (from 19 to 27/1,000 patients). Surprisingly, while the percentage of patients attaining appropriate cholesterol targets significantly increased (approximately 20% reaching <5.0 mmol/l in 1994, versus 46.2% in 2001; p<0.001), the percentage of those attaining good glycaemic control decreased (28.9% patients with a HbA1c <6.5 in 1997 versus 22.5% in 2001; p<0.001).

Interestingly, the NHANES data found that the use of insulin declined along with deteriorating glycaemic control.[11] Indeed, many experts believe that a reluctance to use insulin, by both physician and patient, may contribute to poor levels of glycaemic control and that insulin should no longer be consid-

ered the anti-hyperglycaemic therapy of last resort, but should be considered in timely manner to ensure tight glycaemic control is maintained in the long term.[13-16] This assertion was emphasised by the results of the UKPDS, which found that Type 2 diabetes was a progressive disease and that glycaemic control deteriorated over time regardless of the intensity of treatment.[17, 18] The UKPDS showed that Type 2 diabetes required progressive therapy with agents that have complementary mechanisms of action and that many patients will require insulin treatment to maintain tight glycaemic control.

Despite a high level of endorsement, patients and practitioners are unwilling to intensify or initiate insulin therapy and often have misconceptions about the therapy. A report from the large, multi-national Diabetes Attitudes, Wishes and Needs (DAWN) survey, which included 2,061 patients with Type 2 diabetes and 3,790 diabetes care providers, found that patients generally rate the clinical efficacy of insulin as low and often attached much self-blame for having to initiate insulin therapy. Furthermore, 50–55% of diabetes care providers indicated that they delayed insulin therapy until absolutely necessary.[19]

In addition to the reluctance to use insulin, it is acknowledged that much remains to be learned about how to maximise the efficacy of insulin regimens. This was emphasised by a recent US Department of Veteran's Affairs registry study of 6,222 adults with Type 2 diabetes. Although those patients prescribed insulin used 77% of their dose (indicating a high willingness to adhere to therapy), the mean HbA1c level was only 7.98±1.66%. The authors concluded that the rate of insulin use, the prescribed regimen, or both, may be inadequate to achieve good glycaemic control in patients with long-term insulin use.[20]

A further issue that may limit the wider use of insulin is the perceived need for hospital based healthcare professionals to guide the initiation of insulin therapy.[21] This is despite the fact that most of the routine management of Type 2 diabetes now occurs in the community setting,[22] a burden which can only increase as the prevalence of Type 2 diabetes continues to rise.

There is clearly a need to refine the way insulin is used in the management of Type 2 diabetes and this review examines the potential of the first available basal insulin analogue, insulin glargine, to address some of these issues and increase the probability of achieving the elusive glycaemic control targets. Insulin glargine has now been available for 5 years. Over this time much evidence has accumulated of its role, particularly in the management of Type 2 diabetes.

Role of insulin versus oral antidiabetes therapy

Perceived patient barriers, such as needle phobia or, as discussed above, the sense of self-blame, have led researchers to look for alternatives to the initiation of insulin. One of these alternatives is use of a combination of three oral agents (metformin plus sulphonylurea plus glitazone). Schwartz et al reported that a combination of insulin 70/30 mix plus metformin was as effective as, and better tolerated than, triple oral therapy.[23] Furthermore, a study by Rosenstock et al compared the addition of rosiglitazone or insulin glargine in patients inadequately controlled on a combination of sulphonylurea and metformin.[24] This randomised trial, which included 217 patients, found that HbA1c levels were lowered by similar amounts in both groups (−1.7±0.1% vs −1.5±0.1 for insulin glargine and rosiglitazone, respectively). However, insulin glargine was associated with a greater reduction in FPG (−3.6±0.2 mmol/l vs 2.5±0.2 mmol/l; p0.001) and a much lower drop-out rate (8% vs 19%; p=0.005) compared with rosiglitazone. Additionally, rosiglitazone was associated with a less favourable lipid profile, more adverse events (including oedema), and significantly more weight gain compared with the insulin glargine group (+1.6±0.4 kg vs 3.0±0.4 kg, p=0.02).[24]

With consideration given to clinical safety[25] early introduction of a glitazone may be a way of avoiding the initiation of insulin if results from the Prospective pioglitAzone Clinical Trial in MacroVascular Events (PROactive) trial can be verified. This trial randomised 5,238 patients with Type 2 diabetes and evidence of macrovascular disease to receive either pioglitazone (titrated from 15–45mg) or placebo, in addition to their existing anti-diabetes regimen. In fact, approximately 33% of patients in the PROactive trial were on a regimen containing insulin plus pioglitazone. The use of glitazones plus insulin in this way reflects the latest thinking on glycaemic control, which is to progressively use dual and triple combinations of complementary antidiabetes therapies to reach appropriate glycaemic targets.

After a mean duration of follow-up of 34.5 months, pioglitazone reduced the risk of the composite secondary endpoint (all-cause mortality, non-fatal MI and stroke) by 16% (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.72–0.98; p=0.027). Furthermore, pioglitazone was associated with a 53% reduction in the risk of progression to permanent insulin use (HR 0.47, 95% CI 0.39–0.56; p<0.0001).[26] However, the authors point out that this risk reduction may be partly explained by the increased use of insulin in the control arm, as a glitazone would not have been an option for patients with deteriorating glycaemic control.

While these results are encouraging, there is concern that agents of this class can cause oedema and increase the risk of congestive heart failure, especially when used in combination with other oral agents and insulin.[27,28] Indeed, other experts have suggested that the benefits on cardiovascular events achieved by pioglitazone may be offset by the increased incidence of oedema, heart failure and degree of weight gain observed in the study (mean 3.6 kg) associated with this therapy.[29] Therefore, insulin therapy remains a safe and effective means of maintaining tight glycaemic control in the long term in many patients with Type 2 diabetes.

Insulin analogues – a more physiological approach to insulin therapy

To maximise the effectiveness of insulin regimens, a balance between tight glycaemic control and the risk of hypoglycaemia is essential. It is known that episodes of hypoglycaemia can be as frequent in people with Type 2 diabetes treated with insulin as in those with Type 1 diabetes if matched for duration of disease and insulin therapy.[30] Furthermore, it is established that fear of hypoglycaemia is a key barrier to initiating insulin therapy,[13,19] and the DAWN study showed that it was not only those with Type 1 diabetes (48%) who feared hypoglycaemic episodes but also those with Type 2 (39%).[31]

Until recently, insulin formulations have been limited in their ability to mimic physiological insulin release. For example, regular human insulin (RHI), which is used to control prandial glycaemia, must be administered up to 45 minutes before a meal and has an inappropriately long duration of action. In contrast, neutral protamine Hagedorn (NPH) insulin, which is commonly used to supplement basal insulin requirements in those with Type 2 diabetes, has an undesirable peak of activity that can increase the risk of nocturnal hypoglycaemia and an inadequate duration of action that limits its ability to fully supplement basal insulin over a 24-hour period.[32]

These limitations led to the development of insulin analogues with pharmacokinetics and pharmacodynamics tailored to mimic either prandial or basal insulin delivery in a more physiological manner. For example, rapid-acting analogues are absorbed more quickly than RHI and have a much shorter duration of action.[32]

Two long-acting insulin analogues, insulin detemir and insulin glargine, are now available. There is now sufficient data available to assess the ability of insulin glargine to improve insulin regimens and facilitate the safe achievement of glycaemic goals. The re-

mainder of this review assesses evidence for insulin glargine, and the practice implication of the evidence for using insulin glargine in clinical practice in Type 2 diabetes.

Broad approach to insulin therapy and the role of insulin glargine

A number of options exist for insulin containing regimens to treat patients with Type 2 diabetes. As discussed above, both insulin glargine and pre-mixed insulins can improve glycaemic control in those with suboptimal control on oral agents alone. As discussed below, NPH is also effective when used in this manner.[33,34] An 'intensive' regimen of covering fasting and postprandial glycaemia using a basal–bolus regimen is also an option.

Another option is the use of prandial insulin injections, with short or rapid-acting insulin being administered three times daily, before meals. However, Queale et al reported that the use of such a regimen, in the absence of basal supplementation, increases the risk of poor glucose control.[35]

The important question of the efficacy of pre-mixed versus basal versus prandial insulin regimens is being addressed by the current Treat-to-Target Trial (T_4).[36] This ongoing trial recruited 708 patients with Type 2 diabetes who were poorly controlled on oral agents. Patients were randomised to receive one of three treatments: Biphasic insulin aspart twice daily, Prandial insulin aspart three times daily or Basal insulin detemir once daily (twice daily if required).

At one year HbA1c levels were similar in the biphasic (7.3%) and prandial (7.2%) ($p=0.08$) groups but higher in the basal group (7.6%, $p<0.001$ for both comparisons), however lower rates of hypoglycaemia and weight gain were seen in the basal group. The authors concluded that the basal insulin analogue detemir added to metformin and sulphonylurea was insufficient to optimise HbA1c in the majority of patients, suggesting that the majority of patients receiving this regimen will require more than one type of insulin to achieve optimal glycaemic targets. The final two years of this study will examine complex insulin regimens in this group of patients and the 3 year results are planned to report in 2009.

Basal only insulin regimens have become more popular since the introduction of basal insulin analogues. Evidence suggests that fasting, rather than postprandial glycaemia, plays the major role on overall glycaemia when glucose control is poor.[37] Therefore, while postprandial glycaemia is an important consideration in all patients with diabetes, the use of basal insulin to address fasting glucose levels is likely to be a valuable tool for many of the diabetes patients encountered in primary care. The attributes of insulin glargine that make it an attractive option for basal insulin therapy include a duration of action that allows once-daily injection for most patients, and a peakless time–activity profile[38,39] and a lower risk of hypoglycaemia than NPH insulin.[40]

Janka et al compared the addition of insulin glargine to metformin and sulphonylurea therapy with discontinuation of oral agents and the initiation of twice-daily pre-mix 70/30 insulin, in a 24-week trial of 742 insulin-naïve people with Type 2 diabetes.[41] At study end, HbA1c had reduced more substantially (−1.64 vs −1.31; $p=0.0003$) and more patients reached a HbA1c of ≤7.0% without confirmed nocturnal hypoglycaemia (4.5.5 vs 28.6%; $p=0.0013$) with oral agents and insulin glargine, compared with the pre-mix regimen one. A second 28-week study compared the addition of twice-daily pre-mix 70/30 insulin or once-daily insulin glargine to metformin in 209 insulin-naïve patients. In this study, unlike the previous one, MF was compared in the premix arm and the premix included short-acting insulin analogue. Significant HbA1c reductions were seen in both arms, but were greater in the pre-mix than the insulin glargine arm (–2.79±0.11 vs –2.36±0.11%, $p<0.01$). However, weight gain was significantly greater in the pre-mix versus insulin glargine group (5.4±4.8 vs 3.5±4.5 kg, $p<0.01$) as was

the rate of minor hypoglycaemia (3.4±6.6 vs 0.7±2.0 episodes/year, p<0.05).[42]

These two latter studies demonstrate the fine balancing act and individualistic approach that must be employed when initiating insulin therapy. Both regimens were shown to be effective. Insulin glargine, in addition to oral agents, was very effective in lowering HbA1c, however adding pre-mix insulin was also very effective but was associated with an increased risk of minor hypoglycaemia and additional weight gain.

Insulin glargine in Type 2 diabetes – achieving targets while reducing hypoglycaemia

The concept of triple therapy, discussed earlier, represents a new focus in treating Type 2 diabetes, as it makes treating-to-target possible. The ability of insulin glargine to improve glycaemic control in people with Type 2 diabetes who are failing on oral antidiabetes therapy, was assessed by Riddle et al in the Treat-to-Target trial. This 24-week trial randomised 756 patients (over 80% of whom were failing on dual oral antidiabetes therapy), to receive insulin glargine or NPH insulin in addition to pre-existing regimen.[33] The study involved systematically titrating bedtime insulin to achieve a HbA1c level of <7.0%, a target that was achieved by 60% of patients in each group. However, nearly 25% more patients in the insulin glargine group achieved this level of control without experiencing an episode of documented nocturnal hypoglycaemia (≤4.0 mmol/l) compared with NPH insulin (33.2% vs 26.7%; p<0.05).

This ability to improve glycaemia without increasing the risk of hypoglycaemia was also demonstrated in a year-long trial of similar design.[34] In this case, 426 people with Type 2 diabetes poorly controlled on oral agents were randomised to receive bedtime insulin glargine or bedtime NPH insulin. HbA1c was reduced by a similar amount in both groups (9.1±0.1 to 8.34±0.09 and 8.9±0.1 to 8.24±0.09 for insulin glargine and NPH insulin, respectively; p<0.001 for both observations). However, there was less hypoglycaemia and in particular, nocturnal hypoglycaemia, with insulin glargine than NPH insulin (Fig. 1). Furthermore, postprandial hyperglycaemia was better controlled with insulin glargine than NPH insulin (post-dinner glucose concentrations 9.9±0.2 vs 10.7±0.3 mmol/L; p<0.02).

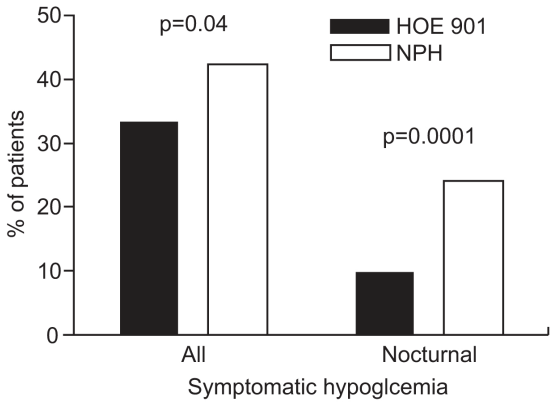

Fig. 1. Percentage of patients treated with insulin glargine or NPH insulin with symptomatic hyperglycaemia[34]

A meta-analysis encompassing these and two other trials, further supports the assertion that insulin glargine reduces the risk of hypoglycaemia.[40] The study included 1,142 patients treated with insulin glargine and 1,162 patients treated with NPH insulin. Compared with NPH insulin, insulin glargine reduced the risk of overall symptomatic hypoglycaemia by 11% (p=0.0006) and nocturnal hypoglycaemia by 26% (p<0.0001). Importantly, the risk of severe hypoglycaemia and severe nocturnal hypoglycaemia were reduced by 46% (p=0.0442) and 59% (p=0.0231), respectively (Table 1).

Table 1. Percentage of patients reporting one or more hypoglycaemic episodes and degree of risk reduction achieved with insulin glargine versus NPH insulin[40]

Type of documented symptomatic hypoglycaemia	Insulin glargine (% of patients)	NPH insulin (% of patients)	% risk reduction (where significant)	P value
Overall	54.2	61.2	11	0.0006
Nocturnal	28.4	38.2	26	<0.0001
Non-nocturnal	49.6	51.7	–	–
Severe	1.4	2.6	46	0.0442
Severe nocturnal	0.7	1.7	59	0.0231
Severe non-nocturnal	0.8	0.9	–	–

Advantages of insulin glargine in perspective

NICE recommends insulin glargine for Type 1 diabetes patients and for certain patients with Type 2 diabetes, including those who require assistance from a carer or healthcare professional to administer insulin and those whose life is restricted by recurrent episodes of symptomatic hypoglycaemia.[43,44]

A major advantage of insulin glargine is the fact that most patients will only require a once-daily injection to provide basal insulin requirements. In fact, the Treat-to-Target trial showed that both insulin glargine and NPH insulin can improve glycaemic control with a once-daily regimen.[33] In these situations, titration becomes easier as the dose can be adjusted according to a single blood measurement taken in the morning. The simplicity of this regimen facilitates its management in the community setting and is an easy concept to discuss in groups of patients initiating insulin. These are important considerations as the burden of routine care for diabetes patients moves from being hospitals based. Furthermore, insulin glargine based therapy can be safely and effectively initialised in suboptimally controlled subjects with Type 2 diabetes in both hospitals and in the community setting.[45]

A study involving 120 individuals with poor glucose control despite treatment with maximal doses of oral agents has provided evidence that a group education strategy is effective for the initiation of insulin. In this study, patients were randomised to receive education on an individual basis, or in groups of 4–8 patients.[46] The education programme comprised visits before initiation of insulin glargine and at 0, 6, 12 and 24 weeks after initiation. Regular phone calls, preceded by electronic transfer of fasting glucose values, were also carried out to encourage self-adjustment of the insulin dose. The algorithm involved adjusting the dose of insulin glargine by 2 insulin units (IU) every 3 days to reach a fasting glucose of 5.5 mmol/L.

While patients had an average HbA1C level of approximately 8.8% at baseline, both groups were below 7.0% at 24 weeks (6.9±0.1% and 6.8±0.1% for individual and group education, respectively) and levels of symptomatic hypoglycaemia were similar in both groups (3.1 episodes per patient for both groups). Treatment satisfaction was also equal in both groups. Importantly, the total time spent by healthcare professionals addressing diabetes cares was reduced by 49% with group education.[46]

As well as being a simple regimen, the initiation of insulin therapy with insulin glargine may have other benefits. The initiation of insulin glargine or NPH insulin in combination with metformin was compared in the LANMET study.[47] This 36-week study involved 110 insulin-naive type 2 diabetes patients with poor glycaemic control on oral agents. Patients were taught to self-adjust their insulin dose to achieve FPG levels of 4.0–5.5 mmol/l. During the last 12 weeks, FPG levels were 5.75±0.02 versus 5.96±0.03

mmol/l ($p<0.001$) in the insulin glargine and NPH insulin groups, respectively. The corresponding insulin doses and HbA1C levels were 68±5 versus 70±6 IU/day (p=NS) and 7.14±0.12 versus 7.16±0.14% (p=NS), respectively. While good glycaemic control was achieved with both types of insulin, the incidence of symptomatic hypoglycaemia was significantly lower during the first 12 weeks in the insulin glargine group than in the NPH insulin group (4.1±0.8 versus 9.0±2.3 episodes/patient-year, $p<0.05$). Furthermore, better control of postprandial glucose was achieved with insulin glargine (8.6±0.3 versus 10.1±0.3 mmol/l, p=0.002).

Optimising insulin glargine regimens

One area of diabetes management that has received little attention is insulin dose titration. Indeed, optimizing the titration algorithm is likely to facilitate the long-term acceptance of insulin therapy for many patients. Two approaches to titration of basal insulin analogues have been reported in the literature that have both been effective, but differ in terms of initiation dose, titration algorithm and extent of patients self-management in the titration process.[48-50] The AT.LANTUS study is one of the largest prospective studies in Type 2 diabetes and its primary aim was to compare the effects of these different titration strategies in more general clinical practice.[51]

This multicentre, multinational, open-label, 24-week trial included 4,961 patients with Type 2 diabetes who were poorly controlled with any oral and/or insulin therapy. These patients were switched to insulin glargine plus oral therapy or to insulin glargine plus prandial insulin and randomised to one of two initiation/maintenance algorithms (Table 2).

Table 2. Design of the AT.LANTUS study[51]

Algorithm 1 (n=2493)	Algorithm 2 (n=2468)
Physicians-led insulin dose titration	Patients self-adjusted insulin dose
Insulin doses adjusted on a weekly basis during practice visits or through telephone contact	Insulin dosage self-adjusted every three days Dose adjustments reviewed at clinical visits or over the telephone

Target FPG ≤5.5 mmol/l. Insulin glargine was administered once daily at bedtime. The starting dose for insulin-naïve subjects was 10 IU/day for algorithm 1. For algorithm 2, the dose was numerically equivalent to the highest FPG value in millimols per litre over the previous 7 days. In those switching from once-daily intermediate- or long-acting insulin to insulin glargine, an equivalent dose was recommended. For those switching from twice-daily NPH, a reduction by 20–30% from the total NPH dose was recommended.

HbA1c levels were reduced by >1% in both arms, despite 72% of participants already being on insulin at baseline. However, the patient-led algorithm (Algorithm 2) was associated with a significantly greater improvement in glycaemic control at study end, with HbA1c being lowered to a significantly greater degree in algorithm 2 versus algorithm 1 (–1.22% vs. –1.08%; $p<0.001$). Furthermore, fasting blood glucose (FBG) levels were lowered to a significantly greater degree in algorithm 2 versus algorithm 1 (–3.4 vs. 3.1, $p<0.001$ and Figure 1). Importantly, although glycaemic control was improved to a greater degree with algorithm 2, the incidence of severe hypoglycaemia was similar between arms (0.9% and 1.1% for algorithm 1 and algorithm 2, respectively). Both algorithms were associated with a low incidence of hypoglycaemia, although rates of overall (29.8% vs. 33.3%; $p<0.01$), symptomatic (26.3% vs. 29.7%, $p<0.05$) and nocturnal (3.2% vs. 4.1%, $p<0.05$) hypoglycaemia were lower in algorithm 1 versus algorithm.[2] In addition, improvements in glycaemic control were achieved with only marginal mean

increases in body weight (+1.0 kg and +1.3 kg in algorithm 1 and algorithm 2, respectively). Figure 2 shows how individuals using algorithm 2 intensified their treatment to a greater degree than those in algorithm 1, resulting in significantly greater reductions in fasting blood glucose (FBG) (Fig. 2).

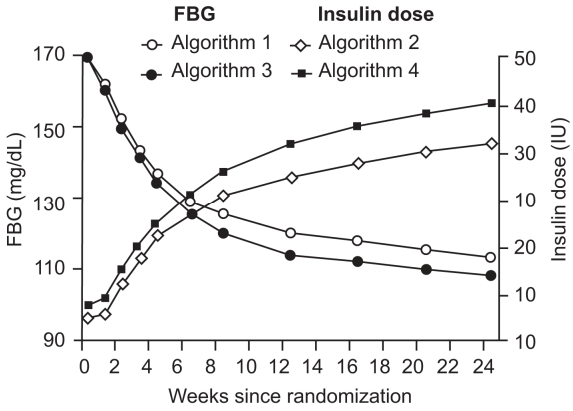

Fig. 2. Mean decrease in FBG throughout the study compared with mean insulin glargine dose (IU) in the AT.LANTUS study[51]

Although this study was limited by the absence of a control group, the results indicate that patients with Type 2 diabetes can safely and effectively be involved in the management of their disease. Not only does this increase patient empowerment, but also has the potential to reduce the burden on healthcare professionals.

Ensuring optimal control – adding prandial to basal insulin

While a single dose of insulin glargine will effectively control glycaemia in some patients, evidence suggests that in others basal insulin alone will not be sufficient to improve or maintain glycaemia to acceptable levels. Monnier pooled evidence from six studies to show that for people below a baseline HbA1c of 9%, good glycaemic control (HbA1c <7%) can be achieved by titrating basal insulin up to 0.5U/kg body weight/day.[52] However, for those above the HbA1c 9% threshold, further increments in basal insulin cause less improvement in glycaemic control. (Fig. 3)

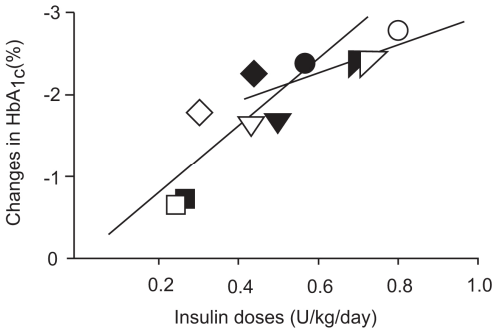

Fig. 3. Relationship between insulin doses (unit/kg bodyweight/day) and decrements in HbA1c[52]

It is essential that patients are up-titrated to an adequate level of basal insulin. Although the upper limit of this titration is open to debate, and needs further explorations, doses of 0.5–0.7 U/kg body weight/day may be required. If, at this point, HbA1C and FPG levels rise or cannot be brought into line with targets, then prandial insulin may be added, although the exact timings and optimal methods of introducing prandial insulin therapy remain to be defined.

Conclusions

The quest for effective pharmacotherapy to achieve tight glycaemic control continues and the stricter glycaemic goals recommended by the IDF emphasie the need to achieve these. Evidence suggests that fasting glucose levels play a primary role in overall glycaemia when glucose control is poor. The ability of basal insulin therapy to effectively address fasting glucose levels means that this therapy is likely to occupy an increasingly important role as a tool to improve and maintain tight glycaemic control in people with Type 2 diabetes. Insulin glargine fulfils much of the requirements for a once-daily, peakless basal insulin and clinical trials have demonstrated that insulin glargine achieves the same degree of glycaemic control as NPH in-

sulin with significantly reduced rates of hypoglycaemia.

Studies such as AT.LANTUS have demonstrated that low rates of hypoglycaemia allow patients to improve their self-management; glycaemic control can, therefore, be safely improved using a simple patient-led titration algorithm based on an insulin dose adjustment of 2 units every 3 days. However, it is important that titration to adequate insulin dose (often 0.5-0.7 units per kg) is achieved. Furthermore, evidence that group initiation of insulin therapy is as effective as individual patient education and may help manage the ever-increasing burden of diabetes. These studies allow the conversion of the evidence of the clinical efficacy of insulin glargine into practical methods of optimising insulin therapy for the type of patients healthcare professionals routinely encounter.

References

1. American Diabetes Association.Standards of medical care in diabetes--2008. Diabetes Care 2008; 31 Suppl 1: S12-54.
2. International Diabetes Federation, 2005. Global guideline for type 2 diabetes. [cited 2007 Nov 22: 82 pages]. Available from:http://www.idf.org/webdata/ docs/ IDF%20GGT2D.pdf
3. National Institute of Clinical Excellence, 2002. Management of Type 2 diabetes: Management of blood glucose. [cited 2007 Nov 22: 27 pages]. Available from:http://www.nice.org. uk/nice media/ pdf/NICE_INHERITEG_ guide lines.pdf.
4. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabe-tes (UKPDS 33). Lancet 1998; 352: 837-53.
5. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12.
6. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care 2004; 27: 201-7.
7. British Medical Association. Focus on the quality and outcomes framework 2006. What has changed. [cited 2007 Nov 22, 1 page]. Available from: http://www.bma.org.uk/ap.nsf/Content/focusqoffeb06.
8. NHS Information Centre. National Diabetes Audit. Key findings about the quality of care for people with diabetes in England, incorporating registrations from Wales. Report for the audit period 2004/05. [cited 2007 Nov 22: 69 pages]. Available from http://www.ic.nhs.uk/webfiles/Services/NCASP/Diabetes/ National Diabetes_Audit_Full_Version_13090601.pdf.
9. The Health and Social Care Information Centre. National Diabetes Audit. Key findings about the quality of care for people with Diabetes in England. Report for the audit period 2003/04. [cited 2007 Nov 22: 76 pages]. Available at http://www.icservices.nhs.uk/webfiles/Services/NCASP/Diabetes/CSD05085NDAReport.pdf.
10. Liebl A, Mata M, Eschwège E; ODE-2 Advisory Board. Evaluation of risk factors for development of complications in Type II diabetes in Europe. Diabetologia 2002; 45: S23-8.
11. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004; 27: 17-20.
12. Lusignan S, Sismanidis C, Carey IM, DeWilde S, Richards N, Cook DG. Trends in the prevalence and management of diagnosed type 2 diabetes 1994-2001 in England and Wales. BMC Fam Pract 2005; 6: 13.
13. Davies M. The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges. Int J Obes Relat Metab Disord 2004; 28 Suppl 2: S14-22.
14. Farooqi A. A question of timing. Insulin treatment and type 2 diabetes. Diabetes Update 2003:24-26
15. Home PD, Boulton AJM, Jimenez J, Landgraf R, Osterbrink B, Christiansen JS, et al. Issues relating to the early or earlier use of insulin in type 2 diabetes. Pract Diab Int 2003; 20: 63-71.
16. Campbell RK, White JR Jr. Insulin therapy in type 2 diabetes. J Am Pharm Assoc (Wash) 2002; 42: 602-11.
17. UK Prospective Diabetes Study Group. (UKPDS 16). Overview of 6 years' therapy of type II diabe-

tes: a progressive disease. Diabetes 1995; 44: 1249-58.
18. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabe-tes (UKPDS 33). Lancet 1998; 352: 837-53.
19. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, et al; The International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005; 28: 2673-9.
20. Cramer JA, Pugh MJ. The influence of insulin use on glycemic control: How well do adults follow prescriptions for insulin? Diabetes Care 2005; 28: 78-83.
21. Richmond J. Insulin initiation: who should do it and who could do it? Diabetes and Primary Care. Summer 2004. [cited 2007 Nov 22: 4 pages]. Available from http://findarticles.com/p/ articles/mi_m0MDP/is_1_6/ai_n6046289
22. Khunti K, Ganquli S. Who looks after people with diabetes: primary or secondary care? J R Soc Med 2000; 93: 183-6.
23. Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P; INS-2061 Study Team.Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. Diabetes Care 2003; 26: 2238-43.
24. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006; 29: 554-9.
25. El-Hage J. Preclinical and clinical safety assessments for PPAR agonists. FDA Presentation, 2004. [cited 2007 Nov 22] Available from http:// www.fda.gov/cder/present/DIA2004/Elhage.ppt#1.
26. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366: 1279-89.
27. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al; American Heart Association; American Diabetes Association. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation 2003; 108: 2941-8.
28. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368: 1096-105.
29. Yki-Järvinen H. The PROactive study: some answers, many questions. Lancet 2005; 366: 1241-2.
30. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005; 28: 1245-9.
31. Snoek F. Understanding the human side of diabetes. Diab Voice 2002; 47: 37-40.
32. Owens DR, Zinman B, Bolli GB. Insulins today and beyond. Lancet 2001; 358: 739-46.
33. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-6.
34. Yki-Järvinen H, Dressler A, Ziemen M; HOE 901/300s Study Group.Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. Diabetes Care 2000; 23: 1130-6.
35. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. Arch Intern Med 1997; 157: 545-52.
36. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al; 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007; 357: 1716-30.
37. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003; 26: 881-5.
38. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000; 49: 2142-8.
39. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care 2000; 23(5): 644-9.

40. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005; 28: 950-5.
41. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005; 28: 254-9.
42. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al; INITIATE Study Group.Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; 28: 260-5.
43. National Institute of Clinical Excellence. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. Technology Appraisal 53. 2002. N0179 1P 50k [cited 2007 Nov 22: 26 pages]. Available from http://www.nice.org.uk/nicemedia/pdf/53_Insulin_analogues_full_guidance.pdf.
44. Chatterjee S, Tringham JR, Davies MJ. Insulin glargine and its place in the treatment of Types 1 and 2 diabetes mellitus. Expert Opin Pharmacother 2006;7: 1357-71.
45. Davies M, Evans R, Storms F, Gomis R, Khunti K. Initiation of insulin glargine in suboptimally controlled patients with type 2 diabetes: subanalysis of the AT.LANTUS trial comparing treatment outcomes in subjects from primary and secondary care in the UK. Diabetes Obes Metab 2007; 9: 706-13.
46. Yki-Järvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I, Davies M, et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care 2007; 30: 1364-9.
47. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006; 49: 442-51.
48. Yki-Jarvinen H, Haring H, Zeger S, Arbet-Engels C, Nguyen H, Riddle M. The relationship between HbA1c, fasting blood glucose (FBG), and hypoglycaemia using insulin glargine versus NPH insulin: a meta-regression analysis in type 2 diabetes. Diabetes 2003; 52 Suppl 1: A149. (Abstract)
49. Rosenstock J, Massi Benedetti M, Haring HU, Lin Z, Salzman A. Confirmed lower risk of hypoglycemia with insulin glargine versus NPH insulin: a meta-analysis of 2304 patients with type 2 diabetes. Diabetologia 2003; 46: A304. (Abstract)
50. Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999; 130: 389-96.
51. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R; ATLANTUS Study Group. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. Diabetes Care 2005; 28: 1282-8.
52. Monnier L, Colette C. Addition of rapid-acting insulin to basal insulin therapy in type 2 diabetes: indications and modalities. Diabetes Metab 2006; 32: 7-13.