

Insulin Initiation in Patients not Adequately Controlled on Oral Agents

a report by

Sydney A Westphal¹ and Pasquale J Palumbo²

1. Department of Medicine, Maricopa Medical Center; 2. Department of Medicine, Mayo Clinic

It is well established that tight glycaemic control in type 2 diabetes (T2DM) reduces the risk of microvascular complications. The majority of patients will, at some point, need to start insulin therapy in order to achieve the American Diabetes Association (ADA) goal of a glycated haemoglobin (HbA_{1c}) below 7%. This is largely because of the progressive loss of beta-cell function associated with the course of T2DM. Adding insulin to oral agent therapy can be an effective means of reaching the target level for HbA_{1c}. This approach has proved to be feasible in clinical trials that rely on dose-titration protocols for regular adjustment of the insulin dose. Furthermore, reliable patients should be able to follow such protocols and make dose changes based on their home glucose-monitoring values. The timely addition of insulin to an oral agent regimen along with close attention to its optimal dosing will lead to better glucose control, which will translate into better health for these patients.

T2DM is associated with enormous morbidity and mortality. In the US, it contributes to more cases of adult-onset loss of vision, renal failure and amputation than any other disease.¹ Diabetes is also a major risk factor for cardiovascular disease. Patients with T2DM have a two- to five-fold increased risk for cardiovascular disease compared with patients without diabetes.¹ About 80% will die from cardiovascular disease.²

Clinical trials have shown that maintaining tight glycaemic control can

prevent the onset and slow the progression of microvascular complications in T2DM.^{3,4} Epidemiological data have suggested that cardiovascular disease may be prevented as well.⁵ Data from these studies have helped the ADA establish its 2007 clinical practice recommendations for glycaemic control. For patients in general, the goal is <7%, while the goal for the individual patient is an HbA_{1c} as close to normal (<6%) as possible without significant hypoglycaemia.⁶

The Challenge of Maintaining Glycaemic Control

Maintaining HbA_{1c} <7% is a challenge in clinical practice. Despite publication of an evidence-based HbA_{1c} target, the majority of adults with T2DM in the US probably do not have an HbA_{1c} value <7%. In fact, analysis of data from the National Health and Nutrition Examination Survey (NHANES) III revealed that mean HbA_{1c} values of patients with T2DM actually deteriorated from the study years of 1988–1994 and 1999–2000, and that a smaller percentage had HbA_{1c} values below 7%.⁷ Higher rates of control have been reported in patients with T2DM who are being managed by endocrinologists.⁸ A more common use of insulin in this setting may be a reason for this observation.

Delay in starting insulin is an important reason why patients with T2DM do not reach the HbA_{1c} goal. Insulin is often started after oral agents have failed to control hyperglycaemia for an extended period of time. The lack of timely progression of therapy to maintain good control in patients with T2DM is illustrated in a study that examined the pattern of use of oral agents in the treatment of T2DM.⁹ From the time of diagnosis to the start of insulin therapy, the average patient had spent five years with HbA_{1c} above 8% and 10 years above 7%.

Diminished insulin secretion due to a progressive loss of beta-cell function limits the amount of time during which oral agents by themselves are able to maintain HbA_{1c} below 7%. Most people with T2DM will require insulin therapy in order to maintain this degree of control.¹⁰ Any delay in starting insulin, as the disease progresses, puts patients at risk of developing diabetic complications.

Initiating Insulin in Patients Uncontrolled on Oral Agents

There are two different approaches to initiating insulin therapy in patients with T2DM who are inadequately controlled on oral agents: either using insulin in combination with oral agents or using insulin by itself. Regimens using combination therapy with oral agents plus bedtime neutral protamine hagedorn (NPH) insulin have been proved to be as effective at achieving improved glycaemic control as regimens using insulin as monotherapy, even when two or more daily injections are given.¹¹ Studies have shown potential advantages of continuing metformin in particular when insulin is added. These include improved control with less



Sydney A Westphal is the Chief of the Endocrinology Division at Maricopa Medical Center in Phoenix, Arizona. She is a member of the American Association of Clinical Endocrinologists (AACE) and serves on the Board of Directors for Maricopa Medical Foundation. Dr Westphal's professional interests include diabetes and nutrition. She completed both a residency in internal medicine and a fellowship in endocrinology at the University of Minnesota.



Pasquale J Palumbo is a Senior Consultant of Endocrinology and Metabolism in the Division of Preventive Medicine at the Mayo Clinic College of Medicine in Arizona. He is also Professor of Medicine at the Mayo Clinic in Rochester. He is a Master of the American College of Physicians (MACP) and a Master of the American College of Endocrinology (MACE). He has authored over 150 scientific publications in the field of endocrinology and metabolism. His publications deal with his work in diabetes mellitus, obesity and hyperlipidaemia. He joined the staff of the Mayo Clinic in Rochester in 1963 as an Associate Consultant and transferred to Mayo Clinic in Arizona in 1993. He served as Chair of the Division of Endocrinology and Metabolism there from 1994 to 1996 and subsequently became Chair of the Department of Internal Medicine in 1996 until 2002. He completed a residency and fellowship in internal medicine with special emphasis on endocrinology and metabolism at the Mayo Clinic Graduate School of Medicine in Rochester and received his MD degree from Albany Medical College of Union University in Albany, New York.

weight gain and hypoglycaemia.¹² The logic of combining basal insulin and oral agents is that the basal insulin suppresses hepatic glucose production and therefore controls the fasting glucose, which allows the oral agents to be more effective in controlling the post-prandial glucose and maintaining glucose control during the day.²

NPH insulin has traditionally been the basal insulin used. Recent trials have evaluated the efficacy of adding long-acting basal insulin analogues to oral agents. In the Treat To Target Trial, Riddle et al. randomised patients inadequately controlled on oral agent therapy (HbA_{1c} 7.5–10%) to bedtime NPH or glargine, and continued the oral agent therapy in both groups.¹³ A dose-titration algorithm was used to try to achieve fasting glucose levels below 100mg/dl. After 24 weeks, both groups achieved similar HbA_{1c} values of about 6.9%, and about 60% from each group reached an HbA_{1c} of <7%. More patients achieved an HbA_{1c} of <7% without documented nocturnal hypoglycaemia with glargine than with NPH ($p<0.05$), and the rates of other categories of hypoglycaemia were also significantly lower with glargine. However, the authors noted that severe hypoglycaemia was uncommon with both treatment groups.

Fritsche et al. randomised patients poorly controlled on oral agents (mean HbA_{1c} was 9.1%) to glimepiride in combination with glargine in the morning or bedtime or bedtime NPH and used an insulin titration algorithm to try to achieve fasting glucoses below 100mg/dl.¹⁴ The greatest HbA_{1c} reduction was seen with morning glargine ($p=0.001$ versus NPH and 0.008 versus bedtime glargine). Regardless of the injection time, glargine was associated with significantly less nocturnal hypoglycaemia than NPH ($p<0.001$), although the number of patients experiencing hypoglycaemia or severe hypoglycaemia was similar in both groups.

In the Lantus®+metformin versus NPH+metformin (LANMET) study, Yki-Jarvinen et al. randomised patients uncontrolled on oral agents (HbA_{1c} >8%) to bedtime glargine plus metformin or bedtime NPH plus metformin and titrated the dose to try to achieve fasting glucose values below 100mg/dl.¹⁵ After nine months, HbA_{1c} values were reduced similarly in both groups to about 7.1%. The frequency of symptomatic hypoglycaemia was significantly lower in the first 12 weeks in the glargine plus metformin group ($p<0.05$), but not significantly different thereafter. There were no differences in biochemical hypoglycaemia and no episodes of severe hypoglycaemia.

Another long-acting basal analogue, detemir, has also been studied in combination with oral agent therapy.¹⁶ Patients inadequately controlled on oral agents (HbA_{1c} 7.5–10%) were randomised to twice-daily detemir, or NPH with a dose-titration algorithm aimed to reach AM and PM glucose goals of <108mg/dl. After 24 weeks, both groups achieved an HbA_{1c} level of <7%. The proportion achieving this level without hypoglycaemia was significantly higher with detemir than NPH ($p=0.008$), and less hypoglycaemia, including less nocturnal hypoglycaemia, was seen with detemir than with NPH ($p<0.001$).

Pre-mixed insulin preparations that contain short- and intermediate-acting insulins are an alternative way for patients to start insulin. Several recent studies compared initiating insulin with pre-mixed versus basal insulin in patients not achieving adequate control with oral agents. In the INITiation of Insulin to reach A1c TargEt (INITIATE) study, Raskin et al. randomised patients inadequately controlled on

oral agents (HbA_{1c} >8%) to an oral agent regimen of metformin with or without a thiazolidinedione (TZD) combined with either twice-daily biphasic insulin aspart (BIAsp) 70/30 or bedtime glargine.¹⁷ Insulin doses were titrated to target fasting glucoses (and pre-supper glucoses for the group on the pre-mixed insulin) of 70–110mg/dl by an algorithm-directed titration. After 28 weeks, HbA_{1c} was significantly lower in the BIAsp 70/30 group than in the glargine group (6.9 versus 7.4%, $p<0.01$), and more reached an HbA_{1c} of less than 7% (66 versus 40%, $p<0.001$). Of note, a significant difference in HbA_{1c} reduction between the groups was seen only if the baseline HbA_{1c} was >8.5% ($p<0.05$). Hypoglycaemia occurred significantly more often in the BIAsp 70/30 group ($p<0.05$). The authors stated that major hypoglycaemia was rare. The improved glycaemic control with mixed insulin combination is not surprising because there was not adequate post-prandial glycaemic control with the failing oral agent therapy and glargine. A more appropriate comparison group would have been mealtime short-acting insulin and basal glargine in place of the failing oral agent therapy with glargine.

In a similar study, insulin was initiated along with metformin as twice-daily lispro mix 75/25, or once-daily glargine.¹⁸ Reduction in HbA_{1c} was significantly greater with the lispro mix insulin ($p=0.002$), and more reached an HbA_{1c} of <7% ($p<0.001$). Hypoglycaemia rates were lower with glargine ($p=0.041$), although no one experienced severe hypoglycaemia. Again, adding glargine to failing oral therapy with metformin did not provide adequate postprandial glycaemic control. Short-acting insulin with meals is needed along with glargine.

In patients insufficiently controlled on oral agents (HbA_{1c} 7.5–10.5%), Janka et al. compared adding morning glargine to the oral agents with switching patients to twice-daily 70/30 insulin (70% NPH, 30% regular) without oral agents.¹⁹ Insulin dosage was titrated to target fasting glucoses (and pre-supper glucoses in the 70/30 insulin group) of <100mg/dl using a titration algorithm. After 24 weeks, the mean decrease in HbA_{1c} was significantly greater in the glargine group ($p<0.003$). More patients reached an HbA_{1c} of <7% without confirmed nocturnal hypoglycaemia in the glargine group ($p=0.0013$), and this group also had fewer confirmed hypoglycaemic episodes ($p<0.0001$). The authors stated that severe hypoglycaemia was very uncommon in both groups. This study is somewhat at variance with the results of the previous two studies cited above.

Initiating lispro insulin before each meal in combination with a daily sulphonylurea has been shown to be a safe and effective means of introducing insulin therapy to patients inadequately controlled on oral agent therapy.²⁰ However, this method of using prandial insulin is not common in clinical practice, probably because it is a more complex regimen to execute since it involves titration of three insulin injections.

Taken together, these studies provide some important general messages with respect to initiating insulin in patients suboptimally controlled on oral agent therapy:

- It is possible to achieve good glycaemic control within 24 weeks in many of these patients. This can be safely achieved using detemir, glargine, NPH, pre-mixed insulin or even pre-meal lispro insulin, and adjusting the dose regularly with a dose-titration protocol.
- Most of the studies found that less hypoglycaemia, especially at night-

time, occurs with the long-acting basal analogues than with NPH or pre-mixed insulins. Therefore, basal analogues may present an advantage in this regard. However, it is important to note that severe hypoglycaemia was distinctly uncommon in any of the groups studied.

- Regimens using just one injection of basal insulin a day were successful in safely bringing patients to HbA_{1c} levels below 7%. These regimens used glargine or NPH and focused on a daily self-monitored fasting glucose level for making regular dose adjustments. Thus, initiating insulin can be a relatively simple step to take.
- The results of the study of Raskin et al. might suggest that pre-mixed insulin offers an advantage over glargine in the more poorly controlled patients with HbA_{1c} levels >8.5% because it provides basal as well as prandial insulin. These patients probably have a greater deficiency of endogenous insulin secretion and therefore are more likely to require prandial insulin in addition to basal insulin.
- The results of the study of Janka et al. could be interpreted as supporting the notion that adding insulin to oral agent therapy is a more effective way to initiate insulin than discontinuing oral agent therapy and using insulin by itself. See above regarding concerns related to the comparison of mixed insulin preparations with failing oral agents to which glargine is added.

Insulin Initiation in Clinical Practice

The Treat To Target Trial could serve as an example of a practical strategy for initiating basal insulin therapy in overweight patients without renal insufficiency who are uncontrolled on oral agent therapy.¹³ Patients continued with their oral agent therapy and started with 10 units of glargine or NPH at bedtime. Glargine can be taken in the morning instead, as it has been shown to be effective whether taken consistently in the morning or evening.^{14,21} The dose was then titrated weekly based on self-monitored fasting glucose levels. The mean value of the two preceding fasting levels determined the adjustment. The dose increase was two units for a value of 100–120mg/dl; four for 120–140; six for 140–180; and eight for >180. The occurrence of hypoglycaemia had an influence on the titration. No increase was made if a glucose was <72mg/dl during the week and decreases were allowed if a glucose was below 56mg/dl or hypoglycaemia requiring assistance occurred during the week.

The insulin dose could be adjusted using a simple protocol that is followed by the patient. The multinational ATLANTUS Study showed that this is a feasible approach.²² In this study, Davies et al. compared two treatment algorithms for initiating and titrating glargine in patients with T2DM who were suboptimally controlled on oral agents and/or insulin. One titration algorithm was investigator-led. The other involved dose adjustments made by the patient. After 24 weeks, there was a significantly greater HbA_{1c} reduction with the patient-driven algorithm ($p<0.01$). The rate of hypoglycaemia was lower with the investigator-driven algorithm ($p<0.01$), but there was no significant difference in the incidence of severe hypoglycaemia between the two groups. Thus, having the patient adjust his or her basal insulin dose with a specific protocol appears to be an effective option for improving glucose control. Many patients should be capable of making adjustments to their basal-insulin dose using home glucose-monitoring values and a simple dose-titration method. Such an approach might allow the optimal insulin dose to be reached more quickly than if the patient were relying on periodic physician office visits for dose adjustments.

Summary

The number of people in the world with diabetes is projected to more than double between 2000 and 2030.²³ The vast majority of these people will have T2DM, since this type of diabetes accounts for about 85–90% of the diabetic population.² The incidence of T2DM is also increasing in young people, including children and adolescents, and represents a growing paediatric problem.²⁴ The increasing number of people with T2DM and the development of T2DM at a younger age means that there will potentially be an epidemic of people with diabetic complications.

Using insulin earlier – as soon as it is evident that oral agent therapy by itself will be inadequate – should help maintain glycaemic control throughout the course of the disease and minimise the amount of time for which the patient is exposed to hyperglycaemia. The addition of basal insulin to oral agent therapy is a safe and effective means of achieving this. Taking this relatively simple step should, in turn, help prevent the devastating morbidity and mortality that characterises T2DM. ■

- Nathan DM, Initial management of glycaemia in type 2 diabetes mellitus, *NEJM*, 2002;347:1342–9.
- Davis T, Edelman SV, Insulin therapy in type 2 diabetes, *Med Clin N Am*, 2004;88:865–95.
- UK Prospective Diabetes Study (UKPDS) Group, Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet*, 1998;352:837–53.
- Ohkubo Y, Kishikawa H, Araki E, et al, Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: A randomized prospective 6-year study, *Diabetes Res Clin Pract*, 1995;28:103–17.
- Stratton IM, Adler AI, Neil AW, et al., Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Propective observational study, *BMJ*, 2000;321:405–12.
- American Diabetes Association, Standards of medical care in diabetes-2007, *Diabetes Care*, 2007;30(Suppl 1):S4–S41.
- Koro CE, Bowen 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.
- Miller CD, Phillips LS, Tate MK, et al., Meeting American Diabetes Association guidelines in endocrinologist practice, *Diabetes Care*, 2000;23:444–8.
- Brown JB, Nichols GA, Perry A, The burden of treatment failure in type 2 diabetes, *Diabetes Care*, 2004;27:1535–40.
- Turner RC, Cull CA, Frighi V, et al., Glycemic control with diet, sulphonylurea, metformin, or insulin in patients with type 2 diabetes, *JAMA*, 1999;281:2005–12.
- Goudswaard AN, Furlong NJ, Valik GD, et al., Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus, *The Cochrane Library*, 2006;Vol 6.
- Yki-Jarvinen H, Ryssy L, Nikkila K, et al., Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus, a randomized, controlled trial, *Ann Intern Med*, 1999;130:389–96.
- Riddle MC, Rosenstock J, Gerich J, et al., The Treat-to-Target Trial, *Diabetes Care*, 2003;26:3080–86.
- Fritsche A, Schweitzer MA, Haring HU, et al., Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes, *Ann Intern Med*, 2003;138:952–9.
- Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, et al., Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study, *Diabetologia*, 2006;49:442–51.
- Hermansen K, Davies M, Derezinski T, et al., A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes, *Diabetes Care*, 2006;29:1269–74.
- Raskin P, Allen E, Hollander P, et al., Initiating insulin therapy in type 2 diabetes, *Diabetes Care*, 2005;28:260–65.
- Malone JK, Kerr LF, Campaigne BN, et al., Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy, *Clinical Therapeutics*, 2004;26:2034–44.
- Janka HU, Plewe G, Riddle MC, et al., Comparison of basal insulin added to oral agents versus twice-daily pre-mixed insulin as initial insulin therapy for type 2 diabetes, *Diabetes Care*, 2005;28:254–9.
- Bastyr EJ, Stuart CA, Brodows RG, et al., Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}, *Diabetes Care*, 2000;23:1236–41.
- Standl E, Maxeiner S, Raptis S, et al., Good glycemic control with flexibility in timing of basal insulin supply, *Diabetes Care*, 2005;28:419–20.
- Davies M, Storms F, Shuter S, et al., Improvement of glycemic control in subjects with poorly controlled type 2 diabetes, *Diabetes Care*, 2005;28:1282–8.
- Wild S, Roglic G, Green A, et al., Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030, *Diabetes Care*, 2004;27:1047–53.
- Rosenbloom AL, Joe JR, Young RS, Winter WE, Emerging epidemic of type 2 diabetes in youth, *Diabetes Care*, 1999;22:345–54.