A tale of two insulins: Understanding basal insulin therapy in type 2 diabetes
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Chapter 1

Introduction
‘Intravenous injections of extract from dog’s pancreas, removed from seven to ten weeks after ligation of the ducts, invariably exercises a reducing influence upon the percentage sugar of the blood and the amount of sugar excreted in the urine. The extent and duration of the reduction varies directly with the amount of extract injected.’

Frederick G. Banting and Charles H. Best
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‘An honest tale speeds best, being plainly told.’

William Shakespeare
King Richard III, act 4, scene 4
We have certainly come a long way since Frederick Banting and Charles Best first successfully lowered ‘the percentage sugar of the blood’ of diabetic dogs by means of a pancreatic extract in the summer of 1921. Initial problems, such as the sometimes severe allergic reactions and the disfiguring lipodystrophies (1), were solved by purification and crystallisation of the extract, now named ‘insulin’. The limited duration of the glucose-lowering effect was ameliorated by the addition of zinc or protamine (the latter resulting in a preparation known as neutral protamine Hagedorn or NPH insulin), abolishing the need for nocturnal injections. The next milestone in the history of insulin therapy occurred in 1969, when the full structure of the hormone was deciphered, for the first time allowing treatment with (biosynthetic) human insulin.

Nevertheless, insulin therapy with highly purified animal insulin or with biosynthetic human insulin still has many shortcomings (summarised in chapter 2). Regarding the basal NPH insulin, treatment is limited by its distinct peak glucose-lowering effect, its considerably shorter than 24-h duration of action and its variable absorption rate, which predispose to both hypoglycaemia and hyperglycaemia (1,2). Trying to overcome the imperfections of the available insulin preparations, scientists started to modify the amino acid sequence of the human insulin molecule, thereby producing analogues of insulin.

After the introduction of the prandial, short-acting insulin analogues, the first long-acting insulin analogue, insulin glargine, reached the market in 2000. The second of the two basal insulin analogues treated in this ‘tale’, insulin detemir, followed in 2004. Initially, the new long-acting analogues were proclaimed to be the ideal basal insulin replacement as pharmacodynamic or glucose clamp studies had found ‘peakless’, nearly 24-h durations of action (3). However, these first pharmacodynamic data raised quite some criticism (4,5), and also, as discussed in chapter 3, glucose clamp results are often difficult to interpret and the study outcomes lack reproducibility. Therefore, clamp data should be regarded as no more than an indication of insulin action. Clinical trials are needed to determine the clinical action of insulin preparations.

A number of such clinical trials have established that intensive insulin therapy reduces the microvascular complications of diabetes, both in type 1 and type 2 disease (6-8). More recent data suggest that early intensive glucose control
also lowers the risk of macrovascular events (9-11). Based on these studies, the current glycaemic goal for glucose-lowering therapy is an HbA1c level <7% (12), and in type 2 diabetes it is recommended that insulin therapy is initiated when lifestyle interventions and oral agents fail to achieve this target (13). However, as extensively discussed in chapter 2, the options for the practical implementation of insulin treatment are many. Thus, it is the difficult task of clinicians to design individualised management plans for their type 2 diabetic patients based on the merits and drawbacks of the various insulin preparations and treatment regimens available.

Clinical trials are essential to elucidate the advantages and disadvantages of different strategies. Regarding insulin initiation in type 2 diabetes, a major topic of this thesis, we have been served promptly in this respect. A recent meta-analysis of randomised trials and the 3-year results of the 4-T study demonstrated that, although insulin initiation with biphasic or prandial insulin may result in greater HbA1c reductions than initiation of basal insulin, these regimens are associated with more hypoglycaemia and weight gain and higher insulin doses (14,15). In addition, the ‘treat-to-target’ trials established that the addition of systematically titrated basal insulin to existing oral glucose-lowering therapy achieves adequate glycaemic control in the majority of patients with type 2 diabetes (16-18). These studies also showed that the two basal insulin analogues attain this with a lower risk of hypoglycaemia than the conventional basal NPH insulin (16,17). Additionally, insulin detemir appeared to result in less weight gain than NPH insulin (16). So the benefits of the basal insulin analogues had been demonstrated, but (up until last year) there was no research directly comparing insulin detemir and insulin glargine in patients with type 2 diabetes. A clinical trial was urgently needed to evaluate possible (dis)advantages of one over the other, such as the higher daily dose requirements found for insulin detemir in the case series outlined in chapter 4.

As already indicated by chapter 3, a study’s design may greatly affect its results. This issue is further addressed in chapters 5 and 6. Chapter 5 investigates the relationship between various plasma glucose definitions for hypoglycaemia and the reported frequency of hypoglycaemia. Chapter 6 explores whether factors related to the design of clinical trials examining basal insulin initiation in type
2 diabetes, such as the predetermined frequency of contact with the study team, affect the outcomes of these studies.

Keeping the findings of the previous two chapters in mind, chapter 7 describes the rationale and methods for the large, direct, randomised comparison of the two basal insulin analogues that we carried out in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs who needed to start insulin therapy. The results of this clinical trial, the largest head-to-head study of insulin detemir and insulin glargine so far, are given in chapter 8. Chapter 9 addresses the important clinical question whether, in addition to metformin (13), insulin secretagogues should be continued when basal insulin therapy is initiated.

Chapter 10 summarises the most important findings of this thesis and advises on future directions. Chapter 11 is the Dutch-language summary.
References