General introduction
The prevalence of type 2 diabetes mellitus is rising rapidly throughout the world as a result of the ageing population, major changes in the type of diet consumed, reductions in physical activity, and consequent increases in overweight and obesity. Worldwide, the number of cases of diabetes is estimated at 382 million. This number is expected to rise to 592 million by 2035 [1]. In the Netherlands, 830,000 patients had diabetes in 2011 [2]. The vast majority of those with diabetes mellitus have type 2 diabetes.

Hyperglycaemia is an important risk factor for the development of micro- and macrovascular disease. Diabetic retinopathy is one of the leading causes of blindness in the world, diabetic nephropathy accounts for 25% of the causes of renal failure in patients with renal replacement therapy and over 70% of patients with diabetes die from cardiovascular disease [2-4]. Type 2 diabetes is therefore considered a threat to global health and a socio-economic burden for the community.

Modern health care uses a vast array of lifestyle and pharmaceutical interventions aiming at preventing and controlling hyperglycaemia to reduce these long-term complications. Despite the large arsenal of available therapies, the clinical management of type 2 diabetes remains a challenge for patients and health care professionals. This challenge in clinical practice is reflected by the low percentage of patients achieving glycaemic targets; in the UK and in the USA only 59% and 44.5% of patients with type 2 diabetes achieve the respective glycated haemoglobin (HbA1c) values of 57 mmol/mol (7.4%) and 53 mmol/mol (7%) [5;6].

This thesis focuses on optimizing treatment for type 2 diabetes. Patients with type 2 diabetes mellitus face unpredictable and unexpected threats in their battle against hyperglycaemia. In the short term, the most important side effect of glucose lowering treatment is hypoglycaemia, which is also a limiting factor in the glycaemic management of diabetes [7;8]. In the long term, a possible link between glucose lowering treatment and cancer is a major safety concern among patients as well as clinicians [9-11]. Both long-term and short-term risks and benefits are weighed by clinicians and patients when making therapy decisions.

Insulin is frequently required among patients with type 2 diabetes due to the progressive beta cell dysfunction [12]. As initial therapy a ‘basal’ insulin alone is typically added [13]. However, either intermediate-acting human insulin (neutral protamine Hagedorn [NPH]) or long-acting insulin analogues (insulin glargine or insulin detemir formulations) may be prescribed [14]. An evaluation of possible (dis)advantages of one over the other is needed to form clear recommendations on when to prescribe which insulin.
The last few years many new pharmaceutical therapies have been developed to improve diabetes care [15;16]. However, newer drugs are often expensive and the potential long-term benefits and risks only become clear over time. New approaches that improve quality of diabetes care are therefore necessary to achieve and maintain target levels of HbA1C. Tricco et al. found that, in general, quality improvement interventions targeting patients showed greater improvements in HbA1c than interventions aimed at clinicians [17]. With the rapid increase in internet access in households, the last decade has witnessed novel opportunities to disseminate such interventions and involve patients in their own care. There is evidence that e-health systems for chronically ill patients improve their knowledge and social support, and can help them to change their behaviour and improve clinical outcomes [18]. Treating patients with T2DM with basal insulin requires frequent evaluation of blood glucose levels and adjustment of the insulin dose, usually referred to as titration. For patients with T2DM specifically, e-health systems with computerized decision support (CDS) functionalities can be used to assist T2DM patients in performing insulin titration at home. Using such applications might help to reach good glycaemic control among patients with diabetes mellitus type 2 using basal insulin.

The main aim of this thesis was to i) evaluate the risks and benefits of current pharmacological treatment for type 2 diabetes and to ii) investigate strategies to optimize insulin dose titration and the role of e-health to support this process.

Part 1. The risks and benefits of current pharmacological treatment for type 2 diabetes
Metformin therapy, sulfonylurea derivatives and basal insulin are the mainstay of pharmacological treatment for hyperglycaemia in type 2 diabetes [19]. Although hypoglycaemia is initially less frequent in type 2 diabetes, it becomes progressively more frequent later in the course of type 2 diabetes [8]. Metformin therapy is not or only rarely associated with hypoglycaemia [20-22]. On the other hand, much is made of the risk for hypoglycaemia with the use of insulin therapy and/or sulfonylurea. Yet little is known about the modern day incidence of hypoglycaemia in patients with type 2 diabetes using sulfonylurea or insulin monotherapy. Chapter 2 presents the result of a systematic review and meta-analysis that assessed the proportion of patients with type 2 diabetes that experience hypoglycaemia when treated with a sulfonylurea or insulin.

Several lines of evidence suggest that glucose lowering treatments may modulate the risk of cancer either positively or negatively. Metformin has either a protective
effect on cancer or does not influence cancer risk in patients with diabetes [23-25]. In contrast, evidence suggests that sulfonylurea and insulin might confer an increased risk for cancer in individuals with diabetes [11]. The best way to establish or refute whether there is a relationship between diabetes treatment and cancer would be through a prospective randomized controlled clinical trial. The concerns regarding the association between insulin glargine and cancer have been much alleviated by the ORIGIN trial; this six-year randomized clinical trial showed no elevated risk of cancer when insulin glargine is used early in the course of T2DM treatment when compared to standard care [26]. However, no such trial has been performed to confirm or refute an increased risk of cancer with the use of other insulins or sulfonylurea and this question still needs to be resolved. In view of the methodological shortcomings of earlier observational studies and a lack of randomized controlled trials, well-conducted and appropriately designed observational studies are needed. In chapter 3 we explored the association between glucose lowering therapy and the risk of adenocarcinoma, when compared to metformin monotherapy. This case control study in patients with type 2 diabetes was performed in the primary care research database in the Netherlands.

Insulin is still the considered the most potent glucose lowering drug and the question remains which insulin is the best. Many studies have already compared basal insulin analogues to human insulin; these studies showed that insulin analogues attain similar glycaemic control, but with lower risk of nocturnal hypoglycaemia compared to human insulin [27]. But also the two long-acting insulin analogues, insulin detemir or insulin glargine differ in their mechanism of attaining protracted action, leading to possible differences in glycaemic control and safety outcomes [28]. Research directly comparing both long-acting insulin analogues is limited. In chapter 4 we systematically reviewed the efficacy and safety of the two currently available long-acting insulin analogues, insulin detemir and insulin glargine, in head-to-head studies in the treatment of type 2 diabetes mellitus. An overview of the candidates for an improved basal insulin in the pharmaceutical pipeline are presented in chapter 5.

Part 2. Strategies to optimize insulin dose titration and the role of e-health to support this process

Multiple ‘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 [29-31]. However, when turning evidence into daily practice, many patients fail to reach treatment targets [5;6].
A few explanations might contribute to this gap between achievements in a research setting and current practice when implementing basal insulin therapy. In a research setting health professionals are more or less forced to follow strict treat-to-target guidelines [29-31]. In clinical practice, the options for the practical implementation of insulin treatment are manifold and it might be the case that some of the decisions of health care professionals would diverge from recent evidence and consensus statements. Little is known about the actual strategies that are followed by care providers in clinical practice. In chapter 6 we explored which patient factors influenced the decisions of diabetes care providers to adjust the basal insulin dose of their patients with type 2 DM, using a discrete choice experiment among 190 care professionals. A better understanding of the decision-making behaviour of diabetes care providers can inform strategies to improve quality of diabetes care.

Another typical aspect of a research setting is the intensive guidance of patients by study personnel [32]. In daily practice, the far less intensive clinical visits of patients to the general practice or outpatient clinic probably fail to utilize basal insulin’s full potential [33]. Current guidelines recommend to start with 10 units of insulin [19;33]. Yet, stepwise insulin dose titration to reach glycaemic treatment targets can take a long time, particularly in those with high insulin needs. Tailoring the starting dose would allow for easier and more rapid titration in patients who need higher insulin doses. To this end we wanted to explore the possibility to predict the final insulin dose based on clinical characteristics that can be assessed ‘at the bedside’. Previous studies have already examined the correlation between numerous clinical parameters and final insulin dose [34]. To increase the practical relevancy we investigated the possibility to subsequently tailor the starting insulin dose based on these patient’s characteristics in chapter 7. We used data from the L2T3 study, a ‘treat-to-target’ basal insulin initiation study that compared insulin detemir twice daily to insulin glargine once daily in patients with type 2 diabetes [35].

A more patient-oriented solution to facilitate optimal use of insulin is to let insulin titration successfully be undertaken by patients themselves [38]. E-health can support and activate patients to perform insulin titration at home, and might thus be effective in improving glycaemic control in patients with diabetes mellitus type 2 using basal insulin. To this end, our research group developed a web-based system to guide patients in self-titration, called PANDIT (Patient Assisting Net-based Diabetes Insulin Titration). The last three chapters of this thesis focus on the development, implementation, and clinical evaluation of PANDIT.
The use of e-health can improve the quality of care, but sometimes leads to unexpected adverse consequences for patients [36]. For instance, a web-based insulin self-titration system such as PANDIT might produce erroneous insulin advice. But even when the advice is safe, patients may enter incorrect data, misinterpret advice by the system, or experience other usability problems that lead to safety issues. Moreover, typical target users of computer-based insulin titration systems are older people that often have minimal experience with computers. Incorrect insulin dosing might induce hypoglycaemic events with potential risks of coma or convulsions [37]. These safety concerns could undermine confidence of patients and stakeholders in e-health systems and hinder their widespread utilization. In a pilot study with PANDIT, described in chapter 8, we assessed whether patients experienced usability problems when they interacted with the system, whether these problems could compromise patient safety, and whether PANDIT advice are considered clinically safe according to a panel of experienced diabetes physicians.

Computer-assisted insulin self-titration systems such as PANDIT would only be useful with a proper implementation of the system in clinical practice. Systems like these focus on helping patients overcome barriers related to the cognitive components of insulin titration. Yet other barriers, e.g. psychological or physical barriers accompanied with the use of insulin, could still impede effective use of such systems. For example, patients might refuse to perform frequent measurements of blood glucose. Furthermore, the use of computer-assisted systems by patients could induce new barriers during their self-management. In a qualitative study, described in chapter 9, we examined diabetes patients’ experiences with the implementation of insulin therapy and their perceptions of computer-assisted insulin self-titration using in-depth, semi-structured interviews. This informs us about feasibility of these decision support systems to be implemented in the near future.

Finally, to evaluate whether computer-based insulin titration is effective in improving glycaemic control in patients with diabetes mellitus type 2 when compared to usual care, we performed a randomized controlled trial. Patients were randomized to either the intervention group (web-based insulin titration with usual care) or the control group (usual care only). We set the minimum follow-up duration to 12 weeks with optional extensions of 12 weeks until the end of the study period. The primary outcome was change in HbA1c. Secondary outcomes included laboratory FPG and treatment satisfaction as measured with the Diabetes Treatment Satisfaction Questionnaire status questionnaire (DTSQs). Results of this study are described in chapter 10.
Reference List


