Fighting the Hydra: Optimizing treatment for type 2 diabetes

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Summary and suggestions for future research
This thesis focused on optimizing treatment for type 2 diabetes. We evaluated short-term risk (hypoglycaemia) and long-term risk (cancer) of sulfonylurea derivatives and insulin and reviewed the (dis)advantages of the long-acting insulin analogues, insulin glargine and insulin detemir. Furthermore, we evaluated strategies to optimize insulin dose titration. In particular we investigated the feasibility, safety and effectiveness of an e-health application with computerised decision support to support patients in performing insulin titration.

Part 1. The risks and benefits of current pharmacological treatment for type 2 diabetes

A systematic review and meta-analysis that assessed the proportion of patients with type 2 diabetes mellitus that experiences hypoglycaemia when treated with sulfonylurea is presented in chapter 2. To estimate the risk of hypoglycaemia, we meta-analysed the comparator groups of randomised controlled trials that compared new diabetes drugs with sulfonylureas or insulin. In total, 22 studies including approximately 6,000 patients were meta-analysed. The analysis showed that the vast majority of patients with diabetes type 2 treated with a sulfonylurea derivative remains free of any relevant hypoglycaemia during the study period. Approximately ten percent of the patients experienced a mild hypoglycaemia with a plasma glucose ≤3.1 mmol/L and severe hypoglycaemia was experienced by less than one percent of the patients. Overall, gliclazide seemed to have a more favourable profile than other sulfonylurea derivatives. Too few studies had insulin as comparator and therefore no meta-analysis was performed for insulin therapy.

The association of glucose lowering drugs with the risk of adenocarcinoma, when compared to metformin monotherapy, is described in chapter 3. A primary care research database in the Netherlands (IPCI) was used to conduct a case control study in patients with type 2 diabetes from 1996-2011 (n=29,383). In total, we identified 702 cases with a first-time diagnosis of either colorectal (n=238), breast (n=184), prostate (n=191) or pancreatic (n=84) cancer. This study showed no increased risk of overall adenocarcinoma (a composite endpoint of colorectal, breast, prostate and pancreatic cancer) with sulfonylurea monotherapy or with the addition of insulin and/or sulfonylurea to existing metformin monotherapy, when compared to metformin monotherapy. We also found no evidence for an increased risk when exploring each site-specific cancer separately. The results of this study imply that, with regard to the risk of cancer development, there is no contraindication for patients on metformin monotherapy to intensify their treatment with sulfonylurea or insulin.
In chapter 4 we systematically reviewed the efficacy and safety of insulin detemir and insulin glargine in head-to-head studies in the treatment of type 2 diabetes mellitus. This review examined four trials lasting 24 to 52 weeks involving 2250 people randomised to either insulin detemir or glargine. The analyses suggested that there is no clinically relevant difference in efficacy or safety between insulin detemir and insulin glargine for targeting hyperglycaemia. However, to achieve the same glycaemic control insulin detemir was often injected twice-daily in a higher dose but with less weight gain, while insulin glargine was injected once-daily, with somewhat fewer injection site reactions.

Chapter 5 presented an overview of the candidates for an improved basal insulin in the pharmaceutical pipeline. In particular, insulin degludec, the newest basal insulin is discussed. Its pharmacodynamic profile seems to allow administration three times per week. However, phase 3 trials indicated that the non-inferiority criteria with respect to glycemic control against insulin glargine once a day was not met. On the other hand, a once-daily regimen of degludec showed non-inferiority and was associated with a reduction in hypoglycemic events in type 1 diabetes and in type 2 diabetes, when compared to insulin glargine once a day.

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

To find strategies that could improve quality of diabetes care we wanted to have a better understanding of the decision-making behaviour of diabetes care providers. We hypothesized that some of the decisions of Dutch care providers regarding insulin dose adjustments would diverge from recent evidence and consensus statements. In chapter 6 we explored which patient factors influenced the decisions of these diabetes care providers to adjust the basal insulin dose of their patients with type 2 diabetes. To investigate this, we developed narrative vignettes describing clinical scenarios of patients on basal insulin therapy. For each vignette, respondents were asked to indicate whether they would advise to change the insulin dose, and if so, in what direction and by which amount. Five hundred and twenty paper questionnaires were distributed among physicians and nurses in primary and secondary care in the Netherlands. One hundred and ninety (37%) questionnaires were returned. This study showed that pseudohypoglycaemic events and existing high insulin doses were barriers for intensifying insulin dose, even though this is not supported by evidence. Also, a patient with a history of myocardial infarction did not restrain care providers from increasing the dose while this might reasonably be expected following the
results of the ACCORD study. Based on our results, we recommend that the Dutch clinical practice guidelines directed at care providers performing dose adjustments should mention threshold values for hypoglycaemia and give recommendations on coping with high insulin doses. Furthermore, those guidelines should also increase awareness for the risk of intensive treatment in patients with cardiovascular disease.

The possibility to predict the final insulin dose based on certain physical characteristics would allow for easier and more rapid titration of patients with higher dose needs. In chapter 7 we investigated the possibility to predict the final insulin dose and to tailor the starting insulin dose accordingly based on certain physical characteristics. 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. Our data showed a major clinical effect of BMI on final insulin dose. Although final dose varied among groups stratified by both BMI and age, all strata showed similarly low minimal final insulin dose (5-17 IU). We therefore conclude that it does not seem possible to tailor the starting dose of insulin based on the variables BMI and age. Consequently, we suggest to use a maximum of 20 IU when applying the commonly recommended starting dose of 0.1-0.2 IU/kg.

E-health applications can activate diabetes patients and support them in performing insulin self-titration at their homes. Using such applications might help to reach good glycaemic control, which is currently often not achieved in practice. For this reason, our research group developed a web-based system with computerised decision support (CDS) functionalities, called PANDIT. The system assists patients with diabetes mellitus type 2 using basal insulin in self-titrating their insulin dose.

In a pilot study, described in chapter 8, we showed that patients without prior experience with PANDIT were capable of consulting the system without encountering significant usability problems. Furthermore, the large majority of system advice provided was considered clinically safe by experienced physicians specializing in diabetes care. One advice was considered unsafe. This could however easily be remedied by implementing a small modification to the system’s knowledge base. The results of the study imply that patients with T2DM can safely interact with computer-based self-care systems, and CDS systems can safely support patients in self-adjusting their drug therapy.

To investigate the feasibility of implementing such CDS systems, we first examined diabetes patients’ experiences with insulin therapy and their perceptions of computer-assisted insulin self-titration in chapter 9. We performed in-depth, semi-structured interviews which were qualitatively analyzed. This study showed that patients face
physical, emotional and cognitive barriers in the implementation of insulin therapy. Some patients are ignorant of treatment targets and find it difficult to cope with unpredictable blood glucose levels. In particular, patients have difficulties to increase their insulin dose because they fear hypoglycaemia and associate it with disease progression. The use of a computer to assist patients in performing insulin titration could introduce new barriers: there might be a lack of trust in a computerised insulin dosing advice that, based on guidelines, is primarily based on blood glucose values and does not take into account other patient factors such as lifestyle and diet. Also, for some patients the absence of personal contact with their caregiver when advice is provided can be a drawback. To increase acceptance of dosing advice by computer systems, we recommend that patients have the possibility to involve their caregiver, e.g. through telemedicine functionalities.

In chapter 10 we performed a randomized controlled trial to assess whether computer-based insulin titration with PANDIT is effective in improving glycaemic control in patients with diabetes mellitus type 2 when compared to usual care. This study suffered from a low number of included patients and did not establish better glycaemic control through web-based insulin titration in the overall patient group. Subgroup analyses showed that web-based insulin titration was effective in improving glycaemic control in patients from primary care and suggested a similar effect in patients that have been using insulin for a longer period as opposed to insulin starters. In this selected group of trial participants that were willing and able to participate in the PANDIT trial, treatment satisfaction was higher among PANDIT users than among non-users. We recommend that e-health to support patients in self-adjusting insulin dose should be implemented in primary care and should primarily be targeting those that have been using insulin for some time.

Based on our findings, we suggest the following agenda for future research in this field. The majority of patients on sulfonylurea remain free of hypoglycaemia during the study period, supporting its position as a second treatment added to metformin therapy. However, we could not meta-analyse the incidence of hypoglycaemia among patients on insulin monotherapy. Once more data are available, this still needs to be investigated as it would enable both clinicians and patients to make an informed decision when considering insulin therapy.

With regard to the risk of adenocarcinoma, we found no contraindication for intensifying metformin monotherapy with sulfonylurea or insulin. Still, the best way to refute a relationship between diabetes treatment and cancer would be through a prospective randomized controlled clinical trial, similar to the ORIGIN trial.
This thesis showed no significant differences between insulin glargine and insulin detemir with regard to efficacy and safety. The last search for the systematic review has been performed in 2010. Since that time, multiple studies investigating the new insulin analogue insulin degludec have been published. In the future, we will update our meta-analysis and include the results of this new insulin analogue.

We established that some of the decisions of care providers regarding insulin dose adjustments diverge from available evidence and consensus statements. However, in this study we limited ourselves to nine factors that we initially suspected to influence the decision-making behaviour of caregiver. Further research is needed for the identification of other prevailing misconceptions when adjusting the insulin dose.

Our e-health application to support patients on basal insulin in performing insulin self-titration is safe, usable and effective in improving glycaemic control in primary care. In the randomized controlled trial that tested the effectiveness of PANDIT, we were unable to enrol sufficient patients for adequate statistical power to detect improvements in patient outcomes. In this study, eligible patients were recruited by care providers from participating general practices and hospitals. Due to this two-stepped recruitment process we were faced with technology resistance by both health care professionals and patients that are often sceptical and show little support for e-health. So far, much research has focused on the effectiveness of e-health systems. However, to really benefit from those new e-health applications in the pipeline, research should also focus on the question how to increase the uptake of e-health technologies. Furthermore, due to our relatively small sample size, the finding of our study that patients in primary care and patients that have been using insulin for a longer period benefited from web-based insulin titration, still need to be confirmed in a large-scaled trial. Future studies investigating e-health applications in general should either avoid the inclusion of large and heterogeneous populations which makes finding an effect unlikely or perform subgroup analysis to detect subgroup of patients that would benefit from this type of care.