SUMMARY AND DISCUSSION

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Innovations in treatment and patient guidance have significantly improved life expectancy of individuals with type 1 diabetes. Short- and long-term complications such as cardiovascular disease and nerve damage have decreased in incidence and impact through better glucose control, healthier living and better medical care. Still, the disease burden is considerable and treatment targets are often not met. Attaining good glycaemic control requires significant effort by the patient and fear of hypoglycaemia and long-term complications often negatively impact quality of life. The artificial pancreas, a system that automates insulin administration through closed-loop operation, holds promise to improve glycaemic control with less effort required by the patient. Although not a cure, the artificial pancreas can provide a mechanical solution to patients troubled by the disease.

In this thesis we investigated the efficacy of real-life use of artificial pancreas systems starting with use of these systems in a hotel setting and finally 24/7 long-term use at home. We investigated accuracy of continuous glucose monitoring (CGM) systems for use in combination with insulin pump or pen (open-loop use) or to serve as input and control data for artificial pancreas systems (closed-loop use). The left flap of this thesis provides information on the components of a system used for automation of insulin administration also known as an artificial pancreas.

PART 1
TO MEASURE WHAT THEY MEASURE

In **part 1** we assess accuracy of both marketed and novel CGM and propose improvements for assessment of these systems. Since CGM data is used for insulin-dosing both during open-loop and closed-loop use, their accuracy and reliability is essential.

In **chapter 1** we show that different reference methods lead to different CGM accuracy assessment outcomes. CGM accuracy is generally assessed using venous reference glucose measurements. Capillary blood glucose is considered a plausible alternative to venous reference since it allows for assessment of CGM accuracy with glucose obtained from the same compartment as used for calibration of the CGM. Unfortunately frequent capillary sampling is painful and therefore meets practical and ethical constraints. We advise to use capillary reference in addition to venous reference in the hypoglycaemic range and to explicitly describe the used reference method in papers on CGM accuracy.

In **chapter 2** and **chapter 3** we assessed the accuracy of current and novel CGM systems. We show that the Medtronic Enlite and Dexcom G4 CGM systems differ in measurement accuracy to an extent that is clinically relevant. This indicates the importance of head-to-head comparison

of CGM. In chapter 3 we investigate a novel category of implantable CGM and conclude that the system is accurate and safe over a duration of up to 180 days of use, whereas current subcutaneous CGM-systems have a sensor lifetime of up to 7 days. Innovations as these provide opportunities for use of CGM in artificial pancreas systems.

PART 2

AUTOMATION OF INSULIN INFUSION

In **part 2** we assessed out-of-hospital clinical performance of an artificial pancreas system and describe patient acceptance of the system.

In **chapter 4** we describe the evolution that is taking place in technological innovations in diabetes including the introduction of accurate CGM systems, computational strength of portable devices and development of glucose control algorithms leading towards conception and clinical testing of the current artificial pancreas systems.

In **chapter 5** we show that an artificial pancreas system can be used safely and effectively in a hotel environment from dinner to end of the night, a transition from in-clinic studies to studies at home and a vital step towards product commercialisation. Use of the artificial pancreas system significantly reduced time spent in hypoglycaemia and improved time spent in the euglycaemic range compared to combined use of CGM and insulin pump (sensor-augmented pump), the most advanced alternative to artificial pancreas use.

In **chapter 6** we present the outcomes of 2 months evening-and-night use of the artificial pancreas. Results indicate significant improvements in glycaemic control including a reduction of hypoglycaemia, hyperglycaemia and HbA1c compared to sensor-augmented pump use. This study was among the first to support the long-term use of the artificial pancreas as a safe and effective option for patients with type 1 diabetes. Based on these results, we propose artificial pancreas use from evening meal to wake-up time as a first step to introduce these systems on the market.

In **chapter 7** we examine the treatment satisfaction and acceptance of the artificial pancreas system described in chapter 6 using validated questionnaires and semi-structured interviews. Although artificial pancreas acceptance was high, no improvement in treatment satisfaction was found over sensor-augmented pump therapy. Participants appreciate the positive effects on glucose regulation but technical errors and reduced usability limited their appreciation for the system. The results of this study emphasize the need for further development of the technology before commercialisation especially in terms of the usability of the study devices.

In **chapter 8** and **chapter 9** we describe two uncontrolled one month extensions to the 2 month evening-and-night artificial pancreas study. In chapter 8 we present results of day-and-night use of the artificial pancreas and confirm superior glucose control over sensor-augmented pump therapy but conclude that in terms of glycaemic control day use does not add to evening and night use.

In chapter 9 we show that use of an adaptive algorithm improved glycaemic control over time compared to one month use of a non-adaptive artificial pancreas. The adaptive artificial pancreas improved glycaemic control significantly during night-time and numerically during day-time compared to an non-adaptive artificial pancreas. Further improvements can be expected with longer duration use due to conservative tuning of the algorithm used in this study.

FUTURE PERSPECTIVE

Our data show that the artificial pancreas can significantly improve glucose control in patients with type 1 diabetes, in particular during evening and night use. Patient interviews confirm these results but also indicate that usability of the current system is in need of improvement. A transition from proof-of-concept and safety in clinical trials led by academia to commercial development is taking place, speeding up market introduction of these systems. Much gratitude should go to agencies such as the National Institute of Health (NIH, USA), European Commission FP7 programme and the JDRF-programme that permitted the essential first steps in the development of the artificial pancreas.

The first commercial artificial pancreas system is expected to come to patients in 2017. These will be all-in-one devices using a hybrid treatment approach in which treatment proposal confirmation is required before insulin bolus administration. Devices are expected to be marketed at equal cost of an insulin pump and CGM system. Consequently, first candidates to use these systems are patients that currently qualify for reimbursement for sensor-augmented pump therapy, a group of about 40% of patients with type 1 diabetes in the Netherlands. Specific patient groups including those with frequent hypoglycaemia or pregnancy are likely to follow. Introduction in type 2 diabetes is currently not investigated and less likely. Two studies with a duration of up to one year will be performed and are expected to confirm previous study results and show improvement in quality of life which was hampered by device usability issues in previous generations of the artificial pancreas. Post-marketing data on prevalence of severe hypoglycaemia, ketoacidosis, long-term complications and related healthcare cost will be important for future reimbursement status of these devices. Academia can be expected to continue to work on advanced artificial pancreas systems including adaptive algorithms that enable treatment individualization. Also systems that intelligently support the patient with diabetes treatment decisions will be developed for those requiring treatment support but unwilling or not qualifying for artificial pancreas use. Faster acting

insulins and more accurate CGM systems are expected to lead to better glucose control than is achieved with current artificial pancreas systems, including the difficult to control day-time period. Artificial pancreas systems containing glucagon in addition to insulin have been shown to effectively control glycaemia, but until date no long-term studies have been performed, mainly because a stable glucagon analogue or solution is not yet approved. Whether these systems will sufficiently outperform single-hormone approaches to justify additional cost of glucagon and infusion sets is to be determined.

In short, the future of technology based treatment for patients with diabetes is bright. IT innovations will continue to support the patient to achieve tight glycaemic control. The artificial pancreas can be expected to substantially improve the lives of patients with diabetes. Whether, *'the last mile home is the longest'* will become clear in the coming years.