Summary & General Discussion
In this thesis, the effect of continuous glucose monitoring on glycaemic control and psychological outcomes in patients with type 1 diabetes and impaired awareness of hypoglycaemia is addressed. In addition, the potential modifying effects of psychological distress, the patients’ experiences of continuous glucose monitoring, and the relationship between HbA1c and hypoglycaemia are explored.

In this final chapter, the main findings will be summarised and discussed with special emphasis on the possible implications for clinical practice.

Summary and general discussion

Gap in the evidence

In the mid-20th century, the clinical syndrome of impaired awareness of hypoglycaemia (IAH) in diabetes was well described by Lawrence. Specifically, the absence of forewarning adrenergic symptoms made it difficult to avoid the consequences of neuroglycopena, such as confusion, seizures, coma, and even death. Although there is still debate over whether this is to be considered a maladaptive or adaptive response of the brain to repeated events, the risks from severe hypoglycaemia are a serious burden for roughly 25% of adults with type 1 diabetes (T1D) who suffer from IAH. Historically, patient education and adherence to diabetes management strategies have been the mainstays of hypoglycaemia prevention, but technological developments have provided additional approaches. Continuous subcutaneous insulin infusion (CSII), for example, might be associated with less risk of severe hypoglycaemia compared with multiple daily insulin injections (MDI), but assessing this risk among patients with IAH is difficult without studies designed specifically to look at this group.

Before the IN CONTROL study, described in the present thesis, only a few trials in patients with T1D and IAH have examined the effects of continuous glucose monitoring (CGM). As described in Chapter 2, the Cochrane collaboration found no difference in the incidence rates of severe hypoglycaemia between CGM and self-monitoring of blood glucose (SMBG), when summarising data up to June, 2011, and analysing studies where (unfortunately) patients with IAH had mostly been excluded. Nevertheless, in an observational study one year later, Choudhary et al. demonstrated a reduction of severe hypoglycaemia in patients with IAH supported by CGM, reinforcing the need for targeted randomised studies in patients with IAH. A randomised controlled trial using CGM with low-glucose suspend seemed to confirm a benefit by demonstrating a reduction of severe hypoglycaemia in patients with IAH. However, the population studied was relatively young (mean age 18.6 years) and the reduction of severe hypoglycaemia lost statistical significance when two outliers in the
youngest age groups were excluded from the analyses. Since patients with T1D and IAH are usually older than 40 years and have more than 25 years of diabetes duration, this study left important questions unanswered. It is possible that patients with longer duration of diabetes, who may have associated problems such as lipo hypertrophy, anti-insulin antibodies and more entrenched health beliefs that may predispose to severe hypoglycaemia, may not be able to demonstrate similar reductions in severe hypoglycaemia events. This was addressed in another recent randomised controlled trial specifically focusing on adults with T1D and IAH. This trial reported improved hypoglycaemia awareness and glycaemic control from baseline to endpoint (24 weeks) offering extensive patient guidance that included weekly contact, monthly follow-up visits, and use of a bolus calculator to determine the insulin dose, irrespective of insulin pump use. However, no added benefit of CGM was shown. Importantly, sensors were used a median of 57% of the time in this study; only 17 of the 42 individuals achieved 80% sensor usage threshold, which is often considered the frequency required for meaningful benefit. Therefore, whether CGM adds any benefit in patients with T1D and IAH was still unknown.

Effects of CGM on glycaemic control and severe hypoglycaemia

Chapter 4 of this thesis demonstrated that, in adults with T1D and IAH, a 16-week intervention with CGM (without low-glucose suspension) significantly improved time spent in normoglycaemia, with less time spent in hypoglycaemia and hyperglycaemia, compared with SMBG. In addition, CGM decreased the frequency of CGM-derived hypoglycaemia and severe hypoglycaemia (i.e. requiring third party assistance). Interestingly, the lower the biochemical cut-off for hypoglycaemia was set, the larger the relative reduction in hypoglycaemia was observed with CGM, which might suggest that patients in the IN CONTROL trial took action only when their glucose level was already ≤3·9 mmol/L, or perhaps defined a lower threshold as relevant for self-treating hypoglycaemia. Importantly, CGM reduced the frequency of hypoglycaemic episodes <2·8 mmol/L by 44.0%, which are prone to cause cognitive dysfunction as a result of neuroglycopaenia. Also, the proportion of patients affected by severe hypoglycaemia during the 16-week intervention periods was lower during CGM than during SMBG. This effect occurred without increasing HbA1c, which is often a price to pay when trying to avoid hypoglycaemia. Also, in Chapter 7, we showed that in this high-risk population of patients with long-standing T1D and IAH, HbA1c is negatively associated with the number of severe hypoglycemic events while using standard SMBG, despite use of rapid- and long-acting insulin analogues, insulin pumps, and a median of five SMBG measurements per day. CGM significantly weakens this association and therefore treating patients with CGM enables them to reach their target HbA1c values more safely. These results support our hypothesis that CGM is a valuable tool in the
Our findings indicate that CGM must be used continuously, not intermittently, by patients in order to be effective. As shown in Chapter 4, the improvements in CGM-derived glycaemic outcomes (i.e. time spent in normoglycaemia, AUC in hypoglycaemia) and reduction in severe hypoglycaemia were found in patients with a median sensor usage of 89.4% (IQR 80.8 to 95.5). Also, the difference in time spent in normoglycaemia between SMBG and CGM shown in Chapter 4 is comparable to the difference between patients using CGM <50% and ≥50% of the time as reported in another intervention trial performed in patients with IAH.10 This is also in line with previous trials that consequently showed that CGM is only effective when used at least 60% of the time.12-14

Effects of CGM on glucose variability

Patients with T1D face an optimisation problem: reducing HbA1c values while simultaneously avoiding hypoglycaemia. It seems common sense that bringing down average glycaemic values is only possible if glucose variability is constrained, otherwise the blood glucose fluctuations would inevitably enter the hypoglycaemic range. Surprisingly, although we demonstrated a strong association between glucose variability and the frequency of CGM-assessed hypoglycaemic events <2.8 mmol/L in Chapter 7, we could not confirm the association between severe hypoglycaemia and glucose variability in adults with T1D and IAH. However, re-analyses of the DCCT data has established that not only HbA1c, but also mean blood glucose level, and glucose variability measurements each have an independent role in determining an individual’s risk of hypoglycaemia in T1D,15 suggesting that all three aspects of glycaemic assessment should thus be considered in patients in whom hypoglycaemia is a real or potential problem. Also, several other trials showed that glucose variability or dispersion, especially when expressed as coefficient of variation, is predictive of severe hypoglycemia.16,17 Future trials should further explore to what extent glucose variability is a determinant of severe, clinically meaningful hypoglycaemia. In Chapter 4, we showed that CGM improved short term (within-day and between-days) glucose variability, without change in HbA1c. Interestingly, the improved CGM-derived measures of glycaemic control (i.e. time spent in target and glucose variability) were indeed paralleled by clinically relevant reduction in severe hypoglycaemia.

Long-term learning effects of CGM

A long-term learning effect of CGM would be extremely beneficial since it would enable clinicians to treat and guide patients with CGM for a short term, and stop CGM as soon as the patient had learned to avoid hypoglycaemia. This would reduce high costs
that go hand in hand with CGM and therefore might result in CGM to be used by more patients (for a short term). Also, a learning effect of CGM could be expected, considering the ability of patients to e.g. recognize patterns in otherwise undetected hypo- or hyperglycaemic events and adjust self-management accordingly. Unfortunately, in Chapter 4, the data seem to confirm that CGM does not have a long-term learning effect, because withdrawal of CGM resulted in time spent in normoglycaemia to fall back to baseline values after 12 weeks. We acknowledge that the IN CONTROL trial was not primarily designed to demonstrate a learning effect, that CGM was not accompanied by a structured educational program, and that we did not formally ask our patients to learn from the real-time and retrospectively assessed CGM-data. But, during the trial patients did attend monthly follow-up visits during which ongoing education (e.g. regarding timing and frequency of mealtime boluses, insulin stacking, alcohol use, exercise, incorporating real-time CGM-data into patients’ self-management etc.) was provided by the research physicians. The research physicians and patients discussed the uploaded CGM-data and previous self-management decisions in detail and made therapy changes together. Even with this frequent guidance and shared decision making, the beneficial effect of CGM completely disappeared after 12 weeks. We should therefore be cautious in expecting relevant long-term effects of CGM. Formal evidence investigating long-term learning effects of CGM, when combined with a structured education program such as HypoAware, is however lacking and trials providing this evidence should be endorsed.

Effects of CGM on hypoglycaemia awareness

Our scepticism regarding long-term effects of CGM is supported by our finding that CGM, used as stand-alone intervention, does not seem to improve hypoglycaemia awareness in a clinically relevant manner after 16 weeks. In Chapter 4 we noted no relevant differences in self-reported hypoglycaemia awareness scores, with no relevant between-group differences in 16-week hypoglycaemia awareness scores or significant change in hypoglycaemia awareness scores from baseline to endpoint. In 2011, a clamp study by Ly et al. showed that 4 weeks of CGM improved epinephrine responses in young T1D patients with IAH, suggesting that IAH can be restored in adolescents by using CGM, but this finding was not supported by a larger trial performed by the same study group. An observational trial by Choudhary et al. did not demonstrate a difference in self-reported hypoglycaemia awareness scores before and after CGM. Furthermore, although some randomised controlled trials assessing the effect of CGM on hypoglycaemia awareness did demonstrate a significant improvement in self-reported hypoglycaemia awareness during these trials, these trials failed to demonstrate any between-group differences between SMBG and CGM. Small studies have shown that meticulous avoidance of hypoglycaemia is
required to correct hypoglycaemia-induced counter-regulatory defects which may improve hypoglycaemia awareness.\textsuperscript{21} As shown in Chapter 4, CGM does not prevent all hypoglycaemia, but only decreases the duration and depth of hypoglycaemic episodes. More rigorous avoidance of hypoglycaemic events for a longer period of time might be needed to improve hypoglycaemia awareness.

**Effects of CGM on quality of life and patients’ perspectives**

As shown in Chapter 4 and Chapter 5, CGM enables patients to worry less about hypoglycaemia, as CGM improves glycaemic control and significantly lowers the actual risk of severe hypoglycaemia. CGM increases treatment satisfaction.\textsuperscript{12} but surprisingly, does not seem to have a profound measurable effect on other (diabetes-specific) markers of quality of life,\textsuperscript{22,23} such as diabetes-related distress, emotional well-being and diabetes self-efficacy (Chapter 4). This could be explained by a high level of quality of life at baseline in these studies suggesting a ceiling effect. A recent CGM trial in adults with T1D who use multiple daily insulin injections however did demonstrate that CGM might contribute to improvement in diabetes-specific markers of quality of life, but not to quality of life measures not specific to diabetes.\textsuperscript{24} Data therefore remain inconclusive about the influence of CGM on quality of life measures in patients with T1D.

However, studies using a qualitative research approach consistently demonstrate an overall positive impact of CGM on quality of life.\textsuperscript{25} In Chapter 6, to further our understanding of the individual use and experience of CGM in patients with T1D and IAH, a qualitative study supplementary to the IN CONTROL trial was conducted, using semi-structured interviews. We demonstrated that the positive experiences with CGM clearly outweigh the negative. The benefits experienced with CGM in patients T1D and IAH relate to a better sense of control and reduced stress around hypoglycaemia, positively impacting quality of life. Most patients found CGM and its features helpful to achieve better glucose control, i.e. ‘being more stable’ and having less or no profound hypoglycaemia. For this population at risk for recurrent hypoglycaemia the primary benefits of CGM are feelings of safety and relief rather than convenience. Importantly, participants reported not only the benefits of CGM for themselves but also their partners, who are also affected by worries about (nocturnal) hypoglycaemia and the burden of having to treat the patient in order to restore consciousness.

CGM triggered some patients to engage in understanding trends and more actively manage their glucose levels, while others reported to respond more passively and wait for the alarm to go off, before getting into action. Interestingly, these individual differences in coping with CGM do not predict glycaemic outcomes per se, as all study
participants, but one, responded well to real-time CGM in terms of time spent in normoglycaemia, at least for the study period (Chapter 4). Future studies are needed to examine how attitudes and coping styles influence self-management behaviour during as well as after using CGM and how these may enhance improvement of glycaemic control, both in people with and without IAH.

The improved sense of control many participants (and partners) experienced concurs with the demonstrated objective glycaemic improvement such as more time spent in the target range, reduced glycaemic variability, and less frequent nocturnal and severe hypoglycaemia as shown in Chapter 4. Interestingly, according to the majority of participants, the improved sense of control washed away after discontinuation of CGM, implicating there was no psychological legacy effect. Again, this implies that CGM does not have an effect beyond the actual intervention and that CGM should be used continuously instead of for a short term.

The combination of the benefit of CGM in terms of improving glycaemic outcomes (Chapter 4) and the overall positive experience of living with CGM (Chapter 6) strongly supports the use of CGM in adult patients with T1D and IAH.

**Potential barriers for CGM use**

To date, relatively few patients with T1D use CGM regularly.\(^{26}\) One major barrier for continuous use of CGM is the costs associated (i.e., in most countries no reimbursement is provided by the health insurance companies). In case reimbursement is in place, like in The Netherlands, only certain patient groups get reimbursement that fulfills strict indications. Fortunately, “Zorgverzekeraars Nederland” (ZN), the umbrella organization of nine health insurers in The Netherlands, has very recently approved reimbursement of CGM for T1D patients with IAH and/or recurring severe hypoglycaemia.

When treating T1D patients with IAH and severe hypoglycaemia in clinical practice, healthcare professionals frequently first try to improve glycaemia by optimising self-management (e.g., by giving structured education regarding flexible insulin therapy) and changing insulin delivery method from MDI to CSII, before considering CGM,\(^4\) since structured education programs such as HypoAware, DAFNE and BGAT, and CSII might also prevent severe hypoglycaemia, at least for a proportion of the patients with severe hypoglycaemia, and cost less than CGM.\(^{19,27,28}\) In Chapter 4 of this thesis, we showed that in our study population, 18 out of 52 patients (34.6%) used carbohydrate counting and 23 out of 52 patients (44.2%) were on CSII. Interestingly, we showed equal benefit of CGM in patients on CSII compared with MDI, and in patients who practised carbohydrate counting compared with those who did not. This indicates that CGM can
be used in a wide variety of patients, including those not willing or able to change to CSII or to practise carbohydrate counting.

It is important to note that CGM can aid patients to self-manage their diabetes more precisely, provided they are capable of handling the device and data feedback adequately, with support of a diabetes health care team. In this context, the question comes up whether CGM is suitable and beneficial for patients with an unfavourable psychological profile, e.g. with high psychological distress. Psychological distress is common in diabetes, including low emotional well-being, high diabetes-related distress, and fear of hypoglycaemia, negatively affecting patients’ daily self-care and glycaemic control. With CGM, patients are faced with real-time feedback on blood glucose variation and alarms that may be experienced as stressful and difficult to handle for those with pre-existing high levels of distress. Therefore, in Chapter 5, we investigated whether psychological distress, operationalized as either low emotional well-being, high diabetes-related distress, and/or elevated fear of hypoglycaemia modify the effect of CGM on glycaemic outcomes in patients with T1D and IAH. We observed lower effect sizes in the low emotional well-being group compared with the ‘normal’ emotional well-being group, which could suggest that CGM is less effective in patients with low emotional well-being. However, the effect of CGM on the primary outcome (time in target) remained significant also in patients with low emotional wellbeing. Furthermore, the lower effect sizes were mainly due to better glycaemic control during the SMBG phase, rather than to poorer glycaemic control during the CGM phase. No relevant or consistent interaction effects were observed between diabetes-related distress or fear of hypoglycaemia and the glycaemic outcomes.

Previous studies have shown that psychological distress is common in diabetes. There is little evidence to date on the impact of CGM on distress. Giani and colleagues did not find a deterioration of psychosocial functioning in youth with T1D on CGM for six months. In the DIAMOND study, a positive effect of CGM was observed on diabetes-specific distress but not on other markers of quality of life. To the best of our knowledge we are the first to study the interaction effect of CGM in high distressed T1D patients with IAH. As noted by Kubiak et al., CGM systems can be experienced as intrusive causing patients to feel overwhelmed. In this context, research has identified several themes, such as ‘coping with frustrations’ (confrontation with unexpected glucose values; false alarms), ‘use of CGM information’ (when to act and how), and ‘technical hassles’ (failures of CGM). Our study showed no differences in glycaemic outcomes between patients with and without psychological distress. Our findings are reassuring in the sense that the effectiveness of CGM in terms of improved glycaemic control and less risk of hypoglycaemia is robust, and not attenuated by higher distress
at baseline. This would suggest that CGM is ‘safe’ to use in a broad category of type 1 diabetes patients at risk for hypoglycaemia, including those with a less favourable psychological profile. Whether this is true for more severe psychological or psychiatric disorders, including major depression and anxiety disorders, is yet unknown. Further research should help clarify if and to what extent more severe psychological problems are contra indications for CGM or at least require additional counselling and support.

Implications for clinical practice

How does this contribute to current clinical practice in The Netherlands? The findings shown in this thesis add further evidence in support of CGM use in patients with T1D and IAH. It has taken roughly 15 years to provide the final verdict that proper CGM use truly affects hypoglycaemia, which has been anticipated by the diabetes community for a long time. Our findings strengthen the evidence in favour of reimbursement of CGM use in patients with evident impaired awareness of hypoglycaemia. As stated previously, based on i.a. results of our IN CONTROL trial, regulatory agencies in The Netherlands have recently approved reimbursement of CGM for T1D patients with IAH and/or recurring severe hypoglycaemia.

But, does this implicate that clinicians should thus treat all patients with T1D and IAH with CGM? There are approximately 100,000 patients with T1D in The Netherlands and roughly 25% of them have IAH. If we were to treat of all 25,000 of them with CGM continuously (not intermittently or for a short term), this would be a far to great burden on healthcare cost. One could argue to treat only those patients with T1D and IAH with CGM who recently have experienced a severe hypoglycaemic event. During the 16-week SMBG phase in the IN CONTROL trial, 35% of the study population experienced at least one severe hypoglycaemic event. Extrapolating these results to real-life, roughly 8750 patients in The Netherlands would qualify for CGM, which is still a lot from a healthcare cost point of view. We are therefore obligated to search for other effective, but cheaper options.

Parallel with the IN CONTROL trial, another randomised controlled trial was performed in the VU University Medical Center (Amsterdam, The Netherlands), investigating the effectiveness of a brief, partly web-based group intervention (HypoAware) in a largely comparable population compared to the IN CONTROL trial (Table 1). Interestingly, HypoAware also resulted in fewer severe hypoglycaemic episodes. In addition, it significantly improved hypoglycaemia awareness, and reduced hypo-distress in comparison with usual care. We thus now know that, in Dutch patients with IAH and/or problematic hypoglycaemia, both CGM and HypoAware are effective interventions. Of course, there are many questions that remain unanswered. Is there
a difference in effectiveness of CGM versus HypoAware in terms of reducing risk of severe hypoglycaemia? What intervention is (more) cost-effective? Could we predict, based on individual patient characteristics, if CGM or HypoAware is more effective in an individual? And, what is the effectiveness of a combined intervention (structured education in combination with diabetes technology) in this specific population? Trials
providing answers to these question should be prioritised.

We propose a stepped-care approach for clinicians when treating adult patients with T1D and IAH. First, we would like to emphasise the importance of frequent and close patient-provider contact. Although CGM use was suboptimal in the HypoCOMPaSS study, Little and colleagues were able to show a tremendous drop in the rate of severe hypoglycaemia using strategies available in clinical practice, underscoring the importance of close and frequent contact.\textsuperscript{10} Close patient-provider contact should therefore always be the main component of diabetes care. Since it seems common sense that a brief group intervention as HypoAware costs less than CGM, certainly on the long-term, we propose that when faced with a patient with IAH and/or problematic hypoglycaemia despite close contact, clinicians should consider starting with a structured education program such as HypoAware. The problem of hypoglycaemia (awareness) will probably be solved in a proportion of those patients, but certainly not in all. Therefore, continuous glucose monitoring should be available for all patients with T1D in whom hypoglycaemia (awareness) remains a major and devastating problem.