Real-world Evidence from Diabetes Technology in Type 1 Diabetes: Towards Clinically Meaningful, Person-centered and Healthcare-informing Insights

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Introduction

Type 1 diabetes (T1D) is caused by a cellular-mediated autoimmune destruction of the insulin producing β-cells of the islets of Langerhans in the pancreas, leading to an absolute endogenous insulin deficiency. Consequently, people with T1D require lifelong intensive insulin therapy to manage their blood glucose levels and minimize the risk of acute (severe hypoglycaemic event (SHE), diabetic ketoacidosis (DKA)) and chronic diabetes complications (retinopathy, nephropathy, neuropathy and cardiovascular disease). Insulin can be administered via multiple daily injections (MDI) or an insulin pump, both requiring regular self-monitoring of blood glucose levels to adjust insulin doses accurately. This can be done via capillary finger pricks or continuous glucose monitoring (CGM) systems, which use a subcutaneous sensor to provide real-time glucose readings.

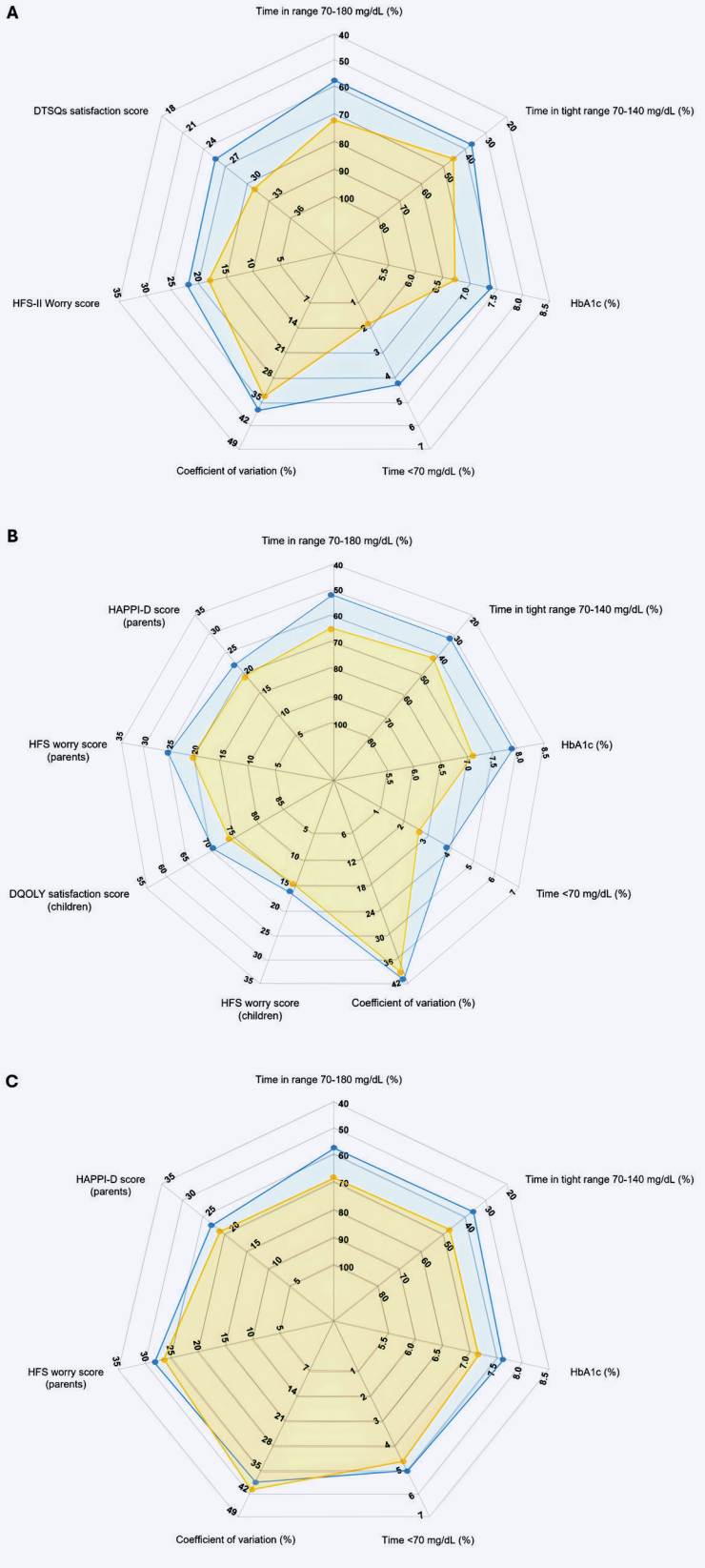
Since the landmark Diabetes Control and Complications Trial established that high haemoglobin A1c (HbA1c; a marker for average blood glucose over the preceding 2-3 months) is strongly associated with an increased risk of developing chronic diabetes complications, monitoring HbA1c has become the gold standard for evaluating glycaemic management and guiding therapeutic decisions in people with T1D, with international guidelines recommending a target value of <7% for HbA1c. The wealth of data generated by CGM has led to the implementation of additional parameters beyond HbA1c, including the time in range parameters (time in range (TIR; glucose 70-180 mg/dL), time in hypoglycaemia (glucose <70 mg/dL and <54 mg/dL) and time in hyperglycaemia (glucose >180 mg/dL and >250 mg/dL)). These measures of short-term glycaemic management complement HbA1c by providing a more comprehensive assessment of an individual's glycaemic profile, addressing the limitations of relying solely on HbA1c. More recently, time in tight range (TITR; glucose 70-140 mg/dL) has been introduced as a marker of normoglycemia.

The introduction of automated insulin delivery (AID) systems has fundamentally transformed diabetes management. By integrating CGM data with algorithm-driven insulin delivery, these pumps automatically adapt basal insulin to achieve predefined glucose targets or target ranges. However, current AID systems still require users to manually enter carbohydrate intake and accept a system-generated bolus advice at mealtimes, as well as to announce physical activity in order to appropriately adapt insulin delivery during exercise. Several randomized controlled trials (RCTs) have consistently demonstrated the superiority of AID systems over other intensive insulin regimes in improving glycaemic management, minimizing hypoglycaemia, and enhancing person-reported outcomes (PROs) across all age groups with T1D. While RCTs remain the gold standard for evaluating efficacy and safety of novel interventions, their strict inclusion criteria and controlled settings may limit the generalizability of findings to routine clinical practice. In contrast, real-world studies capture outcomes in broader and more heterogeneous populations in everyday settings, better reflecting variations in demographics, comorbidities, behaviour, and adherence.

Aim

In the context of T1D care, technologies such as CGM, insulin pumps, and AID systems are particularly powerful sources of real-world data, systematically generating detailed, high frequency information on glucose levels, insulin delivery patterns, and user behaviour. The overall aim of this PhD thesis was to leverage real-world data from diabetes technology to generate clinically meaningful, person-centred, and policy-informing evidence for people with T1D. Specifically, the current PhD research was structured around two aims: 1) to validate the clinical relevance of TITR and TIR as key measures of glycaemic management alongside HbA1c, and 2) to evaluate the real-world effectiveness, safety, usability and cost-effectiveness of AID therapy across different age groups with T1D.

FIGURE 1: Radar plots showing the overall performance of AID systems across the three INRANGE cohorts: adults on Tandem Control-IQ (A), children aged ≥6 years on Tandem Control-IQ (B) and children aged 2-6 years on Medtronic 780G. Each axis represents a diabetes metric for which the outcomes are compared at start (blue) with those at 12 months (yellow). AID, automated insulin delivery; HbA1c, haemoglobin A1c; HFS, Hypoglycaemia Fear Survey; DTSQs, Diabetes Treatment and Satisfaction Questionnaire status; HAPPI-D, part of the HAPPI-D Protocol (Hvidøre, Adolescent, Parent, Professional, Instrument, Diabetes); DQOLY, the Diabetes Quality of Life for Youth questionnaire.



Results

To address the first aim, a cross-sectional analysis was conducted with data from 808 adults with T1D who participated in the RESCUE and FUTURE real-world studies at the University Hospitals of Leuven to evaluate the association of CGM-measured TITR and TIR with the presence of various micro- and macrovascular complications. Both TITR and TIR were found to be inversely associated with the presence of microvascular complications (retinopathy, nephropathy and peripheral neuropathy) and a cerebrovascular accident. Specifically, a 10% increase in TITR or TIR was related with 23.8% and 17.2% lower incidences, respectively, of any microvascular complication and 34.9% and 25.1% lower incidences, respectively, of a cerebrovascular accident. Our findings demonstrated that glycaemic management cannot be adequately summarized by a single metric such as HbA1c. Instead, TITR/TIR and HbA1c should be interpreted as complementary measures within a multifactorial framework to estimate complication risk and guide personalized treatment strategies (1).

For the second aim, the multicentre, prospective, observational INRANGE study was set up to assess real-world changes in glycaemic outcomes and PROs over one year following initiation of AID therapy. The study included three cohorts: adults using the Tandem Control-IQ, children aged ≥6 years using the Tandem Control-IQ and young children aged 2-6 years using the Medtronic 780G. Data were collected from system initiation through 12 months of routine clinical follow-up as part of standard care. For the first cohort, a total of 473 adults on Tandem Control-IQ were included, of whom 453 (95.8%) completed the 12-month follow-up and 20 (4.2%) discontinued system use. The primary endpoint, TIR, increased from 58.8% at start to 72.1% at 4 months ($p<0.001$) and remained stable at 12 months (70.9%, $p<0.001$ vs start). HbA1c decreased from 7.4% to 6.7% and time <70 mg/dL from 4.2% to 1.9% (all $p<0.001$ vs start). Participants reported more diabetes-related quality of life, higher treatment satisfaction, and reduced fear of hypoglycaemia. The number of self-reported SHEs decreased significantly in the year following AID initiation (15.7 per 100 person-years [PY]) compared to the year before (37.5 per 100 PY, $p=0.002$). Work absenteeism declined significantly from 116 to 69 days per 100 PY ($p=0.034$) (2). The paediatric cohort on Tandem Control-IQ included 114 children, of whom 108 (94.7%) completed the 12-month follow-up, 5 (4.4%) discontinued system use and 1 (0.9%) was lost to follow-up. Despite lower TIR (51.6%) and higher HbA1c (7.8%) at start compared with adults, similar relative improvements were observed after one year (TIR 64.4%, HbA1c 7.1%; all $p<0.001$ vs start). Children were more satisfied with their current treatment and experienced less impact of diabetes on their

daily life, while they reported no effect of system use on diabetes-related or hypoglycaemia-related concerns. Parents experienced less burden of diabetes on the quality of life of their child and family and they reported fewer worries about hypoglycaemia. Significant reductions in school absenteeism among children (287 vs 30 days per 100 PY, p=0.001) and work absenteeism among parents (247 vs 47 days per 100 PY, p<0.001) were observed (3). The final cohort included 114 children aged 2-6 years using the Medtronic 780G off-label at the time of the study. Over 12 months, 5 children (3.4%) discontinued system use and 2 (1.3%) were lost to follow-up. TIR increased from 56.8% to 66.6% and HbA1c decreased from 7.6% to 7.2% (all p<0.001 vs start). Time <70 mg/dL remained stable (5.0% at start vs 4.6% at 12 months, p=0.172). Use of the system was associated with a reduction in diabetes-related parental burden, whereas no significant change in hypoglycaemia-related parental fear was observed. No hospitalizations for SHEs occurred during follow-up, and one hospitalization for DKA due to infusion set occlusion was reported, supporting the safety of the system in this age group. A positive effect on school or daycare absenteeism in children (591 vs 278 days per 100 PY, p=0.006), as well as work absenteeism in parents (687 vs 430 days per 100 PY, p=0.043) was observed (4). The overall performance of AID systems across the three INRANGE cohorts is summarized in Figure 1 using radar plots.

Finally, the cost-utility of Tandem Control-IQ relative to MDI and standard insulin pump therapy (both in combination with CGM) was evaluated in adults with T1D in Belgium using data from the adult INRANGE cohort as input into the validated IQVIA Core Diabetes Model. Tandem Control-IQ yielded 19.50 quality-adjusted life years (QALYs) vs 17.92 for MDI and standard insulin pump therapy plus CGM, with total costs of €193,588 and €160,129, respectively, resulting in an incremental cost-utility ratio (ICUR) of €21,111/QALY. Scenario analyses confirmed the robustness of these findings across alternative assumptions: MDI + CGM as sole comparator (ICUR: €41,701/QALY), reduced HbA1c efficacy (ICUR: €25,967/QALY), and a 20-year time horizon (ICUR: €30,183/QALY). Overall, the QALY gains achieved with Tandem Control-IQ were sufficiently large to offset the additional costs of AID therapy, keeping the ICURs below commonly accepted thresholds (5).

Conclusion

This PhD thesis highlighted the power of real-world data generated by diabetes technologies to provide clinically relevant, person-centred, and policy-informing insights into T1D care. By validating novel glycaemic metrics, confirming the real-world benefits of AID systems across different age groups, and establishing their economic value, this research bridged the gap between evidence from RCTs and routine practice. Collectively, our findings underscored the importance of integrating real-world evidence into clinical and policy decision-making, with the ultimate goal of optimizing individualized diabetes management and improving long-term outcomes for people living with T1D.

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