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Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study

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Abstract

OBJECTIVE

Achieving good metabolic control in people with type 1 diabetes (T1D) remains a challenge, despite the evolutions in diabetes technologies over the past decade. Here we investigate the evolution of metabolic control in people with T1D, where care is provided by specialized centres with access to technology, diabetes education and regular follow-up.

METHODS

Data were cross-sectionally collected between 2010 and 2018 from more than 100 centres in Belgium. The evolutions over time of HbA1c, LDL cholesterol and systolic blood pressure (SBP) were investigated, together with the evolutions of use of insulin pump (CSII), continuous glucose monitoring (CGM), lipid-lowering and antihypertensive drugs. Association of HbA1c with gender, age, diabetes duration and technology use was analysed on the most recent cohort.

RESULTS

The study population contained data from 89,834 people with type 1 diabetes (age 1 – 80 years). Mean HbA1c decreased from 65 mmol/mol (8.1%) in 2010-2011 to 61 mmol/mol (7.7%) in 2017-2018 ($P<0.0001$, adjusted for gender, age, diabetes duration and technology use). Respectively, mean LDL cholesterol decreased from 2.45 mmol/L (94.6 mg/dl) to 2.29 mmol/L (88.5 mg/dl) ($P<0.0001$, adjusted for gender, age and diabetes duration), and mean systolic blood pressure remained stable. CGM usage increased, whereas the use of CSII, lipid-lowering and anti-hypertensive drugs remained stable. Gender, age, diabetes duration and technology use were independently associated with HbA1c.

CONCLUSIONS

Our real-world data show that metabolic and lipid control improved over time in a system where T1D care is organized through specialized multidisciplinary centres with emphasis on linking education to provision of technology, and its quality is monitored.

Abbreviations

is-CGM: intermittently scanned continuous glucose monitoring

rt-CGM: real-time continuous glucose monitoring

CI: Confidence interval

CSII: Continuous subcutaneous insulin infusion

CV-history: Cardiovascular history

DC: Diabetes convention

GEE: Generalized estimating equations

HbA1c: Glycosylated hemoglobin

IOTF: International Obesity Task Force

IQECAD : Initiative for Quality Improvement and Epidemiology in Children and Adolescents with Diabetes

IQED: Initiative for Quality improvement and Epidemiology in Diabetes

IQR: interquartile range

LDL: Low density lipoprotein

MDI : Multiple daily injections

NIHDI: National institute for health and disability insurance

SBP: Systolic blood pressure

SD: Standard deviation

T1D: Type 1 diabetes

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Introduction

Treatment of people with type 1 diabetes (T1D) has changed drastically with the introduction of new insulin analogues, insulin pumps and glucose monitoring tools. Still, international data show that it remains a challenge to achieve optimal metabolic control in people with T1D [1,2]. A worldwide assessment showed that less than 30% of people with T1D reached a HbA1c <58 mmol/mol (<7.5%) [1]. Data from the T1D Exchange Registry even show a trend to deterioration of metabolic control in the US over the years, in spite of increasing use of novel technology [2].

In Belgium, a system focusing on multifaceted, multidisciplinary care with emphasis on therapeutic patient education has been installed in 1988 for follow-up of people with diabetes treated with intensive insulin therapy. The vast majority of people living with any form of diabetes requiring intensive insulin therapy (multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII)) have access to specialist care through a system called 'Diabetes convention' (DC), where hospitals sign an agreement with the National Institute for Health and Disability Insurance (NIHDI). Through the DC, hospital-based diabetes centres provide free-of-charge specialist multidisciplinary care, with access to diabetes education, necessary technology (glucose monitoring, CSII) and regular follow-up by a multidisciplinary team including an endocrinologist or pediatrician specialized in endocrino-diabetology, diabetes nurse(s) and educator, dietician and psychologist. Almost all people with T1D adhere to the DC and enjoy full reimbursement of insulin analogues, insulin pumps, glucometers and test strips or sensors. They have a free choice between MDI and CSII (since 2008), and free access to intermittently scanned CGM (is-CGM, since 07/2016) and – for CSII users - to real-time continuous glucose monitoring (rt-CGM, since 07/2018, restricted use since 09/2014).

All centres adhering to this DC are obliged to participate in a quality assurance (QA) program. Two initiatives were launched for this purpose: the Initiative for Quality improvement and Epidemiology in Diabetes (IQED) for adult centres in 2001, and the Initiative for Quality Improvement and Epidemiology in Children and Adolescents with Diabetes (IQECAD) for paediatric centres in 2008. In these nationwide projects, clinical data are routinely collected and fed back both in national reports and in centre individual

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benchmarking, in order to monitor characteristics of diabetes patients and their care as part of the DC [3,4]. Distributed all over the country, there are 15 paediatric and 102 adult specialized diabetes centres treating more than 37 000 people with T1D.

In this study, we examined the evolution from 2010 to 2018 of control of glucose, blood lipids and blood pressure in people with T1D followed in a national organised health care system, where everybody has full access to integrated multidisciplinary specialist care with emphasis on education and novel technologies for glucose monitoring and insulin administration.

Research Design and Methods

Data source

This study is a retrospective analysis of data from patients with T1D collected between 2010 and 2018 in the IQED and IQECAD databases, performed by all adult and paediatric diabetes centres in Belgium.

The study population of IQED is limited to adult (aged ≥18 years, and from 2016 on aged ≥16 years) patients. Patients with a history of pancreas or islet cell transplantation, dementia or pregnant patients were not eligible for inclusion in the IQED study. Data from CSII-treated patients were not eligible for inclusion in the IQED study between 2006 and 2014. More details can be found online [5].

The study population of IQECAD is limited to children and adolescents (aged <19 years). Pregnant patients or patients not having signed the informed consent were not eligible for inclusion in the IQECAD study. More details can be found online [6].

Each centre was asked to review the medical records and complete a standardized electronic questionnaire with the patient's most recent data from the previous year (also called audit period). Data were pseudonimized. Because the data are not anonymous, the data are not publically available.

Study Cohorts

IQED and IQECAD are cross-sectional data collections. Study cohorts were created combining data collections from overlapping audit periods. Patients with missing data on

gender (n= 15), age (n= 9), diabetes duration (n= 1,630), technology use (n= 3,412) and HbA1c (n= 1,977) were excluded. Patients ≥80 years (n= 2,880) or with a diabetes duration <1 year (n = 2,474) were also excluded. The final study population contained data from 29,376 patients in cohort 2010-2011 (from 2,148 children pertaining to audit 01/2010-12/2010 and from 27,228 adults pertaining to audit 10/2010-09/2011), from 27,648 patients in cohort 2015-2016 (from 2,487 children pertaining to audit 01/2015-12/2015 and from 25,161 adults pertaining to audit 10/2015-09/2016), and from 32,810 patients in cohort 2017-2018 (from 3,111 children pertaining to audit 01/2017-12/2017 and from 29,698 adults pertaining to audit 10/2017-09/2018). The final study population did not differ in general patient characteristics from the complete study population (data not shown).

Parameters

Data included the most recent anthropometric and biological characteristics, treatment, results of care and complications related to diabetes registered in the patients' medical file during the year of audit. Details of the questionnaires are described in the publicly available reports IQED [5] and IQECAD [6].

Technology use was defined as use of MDI alone, CSII alone, MDI in combination with is-CGM, or CSII in combination with is-/rt-CGM.

Treatment with statins as secondary prevention was defined as treatment with statins in patients with a cardiovascular history (CV-history), defined as presence of myocardial infarction, heart attack, percutaneous coronary intervention, coronary artery bypass graft or transient ischemic attack.

Hypertension in adults was defined as having a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure ≥90 mmHg.

The low density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula [7] for the patients with triglycerides <4.52 mmol/L (<400 mg/dl) regardless the condition of the blood sample (fasted and non-fasted).

Children and adolescents (≥2 - <18 years) were classified as overweight or obese using the age and gender-specific BMI (dividing weight by height squared) cut-offs reported by Cole et al. [8] and used by the International Obesity Task Force (IOTF). These cut-offs lie on the centiles passing, at the age of 18, through the cut-offs for overweight (≥25 - <30 kg/m²) and obesity (≥30 kg/m²) for adults.

Statistical Analysis

Given that both IQED and IQECAD use sampling techniques, sampling weights were used to obtain estimates for the entire study population [5,6]. These sampling weights accounted for the 10 or 50% sample, as well as for the potential oversampling produced by requiring a minimum sample of 25 patients in IQED.

Overall patient characteristics from cohort 2010-2011, cohort 2015-2016 and cohort 2017-2018 were tabulated . For each cohort, the proportions of patients with an HbA1c <53 mmol/mol (<7%) and <58 mmol/mol (<7.5%) were calculated. For adults, the proportion of patients with a LDL cholesterol <2.59 mmol/L (<100 mg/dl) and the proportion with hypertension were calculated. Additionally, for adult patients with a CV-history, the proportion with a LDL cholesterol <1.81 mmol/L (<70 mg/dl) was calculated. The between-centre variation for HbA1c, LDL cholesterol, SBP, method of self-monitoring and insulin use was tabulated by cohort.

Average HbA1c, LDL cholesterol and SBP by year of age were plotted for each cohort. Loess regression was used to fit a curve over the plotted averages. The association of these variables across years was tested by generalized estimating equations (GEE), using the identity link function, an exchangeable correlation structure (diabetes centre) and robust standard errors, with cohort as explanatory variable (categorical). The model was adjusted for gender, age (<15 years, 15-<25 years, 25-<50 years and ≥50 years) and diabetes duration (<10 years, 10-<20 years, 20-<30 years and ≥30 years). Only for HbA1c, the model was repeated additionally adjusted for technology use, and when all CSII-treated patients were excluded from all cohorts (sensitivity analysis). To investigate the effect of centre size, the full model was repeated with centre size as additional continuous explanatory variable.

In the 2017-2018 cohort, the association of gender, age, diabetes duration and technology use with HbA1c was tested, by GEE as described above. The model was subsequently used to test pairwise difference of LSMeans of HbA1c by technology use, Tukey adjustment.

Bar charts show the proportions of patients treated by CSII, is-/rt-CGM, lipid-lowering drugs, statins, antihypertensive drugs and ACE inhibitors and/or angiotensin II receptor blockers, by age and cohort.

Results are expressed as proportion (95% CI), as mean (±SD)) for normally distributed variables or median (IQR) for non-normally distributed variables. Unless indicated otherwise, statistical significance was tested using chi² tests, t tests (unpaired) and Kruskal-Wallis tests. Pairwise comparisons after Kruskal-Wallis test were corrected using the Bonferroni method. GEE model estimates are presented with their CI, statistical significance was tested with Tukey pairwise comparison.

All P-values were two sided. P values < 0.05 were considered statistically significant.

Data analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

The characteristics of the 3 cohorts are shown in table 1. The characteristics of the 3 cohorts were similar, but median age tended to increase from 45.2 years in 2010-2011 to 45.2 years in 2015-2016 and 46.2 years in 2017-2018 (not significant), and median diabetes duration increased from 16.2 years in 2010-2011 to 17.2 years in 2015-2016 and 17.3 years in 2017-2018 (P<0.01, significant upon bonferroni correction vs. 2010-2011). CSII and is-/rt-CGM were introduced in 2015-2016.

Metabolic control

Mean HbA1c decreased from 63 mmol/mol (7.9%) in 2010-2011 to 62 mmol/mol (7.8%) in 2015-2016 (P<0.0001) and 61 mmol/mol (7.7%) in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.01 vs. 2015-2016) (Table 1). The proportions of patients with an HbA1c <53 mmol/mol (<7%) increased from 22.2% in 2010-211 to 23.8% in 2015-2016 and 25.9% in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.05 vs. 2015-2016) (Table 1). The proportions of patients with

an HbA1c <58 mmol/mol (<7.5%) increased from 38.4% [36.9-39.8] in 2010-211 to 41.8% [40.5-43.0] in 2015-2016 (P<0.01) and 45.0% [43.8-46.3] in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.001 vs. 2015-2016). Between-centre variation for glycaemic control is shown in Supplementary table 1.

Unadjusted mean HbA1c by year of age for the 3 cohorts are shown in Figure 1a. Analysis show a decrease in the mean HbA1c from 65 mmol/mol [64-66] (8.1% [8.0-8.2]) in 2010-2011, to 63 mmol/mol [62-64] (7.9% [7.8-8.0]) in 2015-2016 (P<0.01) and 62 mmol/mol [61-63] (7.8% [7.7-7.9]) in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.05 vs. 2015-2016), gender, age and diabetes duration adjusted. When additionally adjusted for technology use, the mean HbA1c decreased from 65 mmol/mol [63-66] (8.1% [7.9-8.2]) in 2010-2011, to 62 mmol/mol [61-63] (7.8% [7.7-7.9]) in 2015-2016 (P<0.01) and 61 mmol/mol [60-62] (7.7% [7.6-7.8]) in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.05 vs. 2015-2016). Correcting in addition for centre size did not affect the results (data not shown).

To test whether the lack of data of CSII-treated patients in cohort 2010-2011 biased our results, we repeated the analysis on a dataset where all CSII-treated patients were excluded from all cohorts. The gender, age and diabetes duration adjusted mean HbA1c decreased from 65 mmol/mol [64-66] (8.1% [8.0-8.2]) in 2010-2011 (N=29,126) to 63 mmol/mol [62-64] (7.9% [7.8-8.0]) in 2015-2016 (N= 24,272)(P<0.01) and 62 mmol/mol [61-63] (7.8% [7.7-7.9]) in 2017-2018 (N= 28,326)(P<0.0001 vs. 2010-2011). When additionally adjusted for technology use, mean HbA1c decreased from 65 mmol/mol [64-66] (8.1% [8.0-8.2]) in 2010-2011 to 63 mmol/mol [62-64] (7.9% [7.8-8.0]) in 2015-2016 (P<0.01) and 62 mmol/mol [61-63] (7.8% [7.7-7.9]) in 2017-2018 (P<0.0001 vs. 2010-2011).

Figure 1b shows the evolution in the proportion of patients treated with CSII or is-/rt-CGM by age category. In cohort 2015-2016, patients aged <15 years used more often CSII (23%) compared to those aged ≥15 years (9%-14%), and is-/rt-CGM was more often used by patients aged ≥15 years (20%-29%) compared to those aged <15 years (4%). Compared to cohort 2015-2016, the use of CSII was similar in cohort 2017-2018, whereas the proportion of patients using is- or rt-CGM increased (in all age categories, P<0.0001). Adjunctive therapy was rare (≤10% metformin, ≤1% sodium-glucose cotransporter-2 (SGLT2) inhibitors, Table 1).

The associations of HbA1c with gender, age, diabetes duration and technology use are shown in table 2. Multivariable analyses from the most recent 2017-2018 cohort show that females had a slightly higher HbA1c compared to males. Patients aged 15-<25 years had the highest HbA1c, with all other age groups having a significantly lower HbA1c. Patients with a diabetes duration between 10-<20 years had the highest HbA1c, all other diabetes duration groups had a significantly lower HbA1c. Compared to MDI, CSII in combination with is-/rt-CGM led to a significantly lower HbA1c (Table 2). Multiple pairwise comparison shows that patients combining CSII with is-/rt-CGM had a lower HbA1c compared to MDI users (P=0.05) and MDI with is-CGM users (P<0.0001)(Figure 2).

Serum LDL cholesterol control

Mean LDL cholesterol decreased from 2.46 mmol/L (95.2 mg/dl) in 2010-2011 to 2.37 mmol/L (91.6 mg/dl) in 2015-2016 (P<0.0001) and 2.28 mmol/L (88.0 mg/dl) in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.0001 vs. 2015-2016) (Table 1). The proportions of adults with a LDL cholesterol <2.59 mmol/L (<100 mg/dl) increased from 60.6% [58.8-62.3] in 2010-2011 to 64.7% [63.0-66.3] in 2015-2016 (P<0.01) and 69.5% [67.9-71.1] in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.001 vs. 2015-2016). The proportions of adult patients with a CV-history with a LDL cholesterol <1.81 mmol/L (<70 mg/dl) increased from 38.0% [31.8-44.7] in 2010-2011 to 45.6% [39.6-51.7] in 2015-2016 and 50.2% [44.3-56.1] in 2017-2018 (P<0.05 vs. 2010-2011). Between-centre variation for mean LDL cholesterol is shown in Supplementary table 1.

Figure 3a shows the unadjusted mean LDL cholesterol by year of age for the 3 cohorts. Analysis show that the gender, age and diabetes duration adjusted mean LDL cholesterol decreased from 2.45 mmol/L [2.40-2.49] (94.6 mg/dl [92.8-96.3]) in 2010-2011, to 2.35 mmol/L [2.30-2.40] (91.0 mg/dl [89.0-93.0]) in 2015-2016 (P<0.05 vs. 2010-2011) and 2.29 mmol/L [2.24-2.34] (88.5 mg/dl [86.6-90.4]) in 2017-2018 (P<0.0001 vs. 2010-2011, P<0.05 vs. 2015-2016).

Use of lipid-lowering drugs in children aged <15 years was rare (figure 3b). The proportion of patients treated with lipid-lowering drugs remained stable over the cohorts, but increased by age: about 2% of the patients aged 15-<25 years, 30% of the patients aged

25-<50 years, and 70% of the patients aged ≥50 years. Across cohorts, the proportion of adult patients aged ≥25 years treated with lipid-lowering drugs as secondary prevention ranged between 61.5% and 88.1%. The majority of the adult patients were treated with statins.

Systolic blood pressure control

Mean SBP remained stable over the 3 cohorts (Table 1), whereas the proportion of patients with hypertension tended to increase from 24.8% [23.3-26.3] in 2010-2011, to 29.3% [27.8-30.8] in 2015-2016 (P<0.0001) and to 29.1 [27.7-30.7] in 2017-2018 (P<0.0001 vs. 2010-2011). Between-centre variation for mean SBP is shown in Supplementary table 1.

Figure 4a shows the unadjusted mean SBP by year of age for the 3 cohorts. The gender, age and diabetes duration adjusted mean SBP was 121 mmHg [120-123] in 2010-2011, 123 mmHg [122-124] in 2015-2016 and 122 mmHg [121-124] in 2017-2018. There were no significant differences between cohorts.

Use of antihypertensive drugs in children aged <15 years was rare (figure 4b). The proportion of patients treated with lipid-lowering drugs remained stable over the cohorts, but increased by age: about 5% of the patients aged 15-<25 years, 25% of the patients aged 25-<50 years, and 65% of the patients aged ≥50 years. The majority of adult patients were treated with ACE-inhibitors and/or angiotensin II receptor blockers.

Discussion

This study describes the evolution of HbA1c, lipids and blood pressure in people with T1D in Belgium from 2010 to 2018. In Belgium, all people with T1D have access to full reimbursement of insulin, lipid lowering drugs and diabetes technologies, in a health care system that additionally provides follow-up and therapeutic education by a multidisciplinary team whose quality is monitored by a nationwide program. Our real-world data show that glucose control and lipids improved over time.

Achieving optimal metabolic control in people with T1D is difficult and varies widely among countries. A comparison of > 300 000 children and adults with T1D in 19 different countries or regions across the world showed that the proportion of people with T1D that

reached an HbA1c <58 mmol/mol (<7.5%) varied between 15.7%- 46.4% among people aged <15 years, between 8.9%-49.5% aged ≥15-<25 years and 20.5%-53.6% aged ≥25 years (data collected between 2010-2013) [1]. Possible explanations for this wide variation between countries and regions are differences in data sources (national, regional, clinical studies), differences is population characteristics (like diabetes duration, complications) and differences in the organization of health care systems, such as access to medication and diabetes education [1].

In our study population for the same period, 40% of those aged <15 years had an HbA1c <58 mmol/mol (<7.5%), 31% of those aged ≥15-<25 years and 39% aged ≥25 years (data not shown). In addition, 21% of those aged <15 years had an HbA1c <53 mmol/mol (<7%), 18% of those aged ≥15-<25 years and 23% aged ≥25 years (data not shown). These proportions are high given the national span and real-world nature of our study. In Belgium, almost all people with T1D are followed in specialized diabetes centres through the DC, and subsequently included in the IQED and IQECAD studies. In studies where the study populations are not representative for real-world, HbA1c levels are often higher than reported as study populations are biased by geographical variations in socio-economic status and access to healthcare services, or selection of well-motivated highly insured people like is often the case in clinical studies.

Important to note is that we excluded people with a diabetes duration <1 year and older than 80 years. We believe that these two populations are not relevant in the study of quality of diabetes care: the first year after diagnosis patients still (partially) maintain some residual insulin production, making diabetes management less challenging, and older patients often represent a group that through natural selection is showing good diabetes outcomes.

A major finding in our study is the improvement in metabolic control over the past 8 years. Our gender, age and diabetes duration adjusted mean HbA1c significantly decreased by 3 mmol/mol (0.3%): from 65 mmol/mol (8.1%) in 2010-2011 to 62 mmol/mol (7.8%) in 2017-2018. This observation is in contrast to the findings in the T1D Exchange Registry where no improvement and even worsening of metabolic control, in particular HbA1c, was seen over the years [2]. They reported a 6 mmol/mol (0.6%) increase in mean HbA1c (from 62

mmol/mol (7.8%) in 2010-2012 to 68 mmol/mol (8.4%) in 2016-2018, (P<0.001), adjusted for age, diabetes duration, self-monitoring of blood glucose and use of CGM), despite the fact that more than half of the patients were treated with CSII (57% in 2010-2012 to 63% in 2016-2018) and CGM use had more than quadrupled (from 7% to 30% respectively).

In our study control improved, even in the adolescent ages, at least partially mediated by the introduction of technology, in particular combined CSII and is-/rt-CGM. A major evolution over time is the increased use of is-/rt-CGM. The proportion of people with T1D using rt-CGM doubled from 3% in 2015-2016 to 6% in 2017-2018, while the share of is-CGM increased more than 3-fold from 20% to 65% (data not shown). The increase in use of is-CGM should be interpreted with caution as is-CGM was only introduced late in the 2015-2016 cohort study period explaining the initial low proportion of patients using this technology. Nevertheless our data confirm that the increased use of CGM is based primarily on the growing use of is-CGM [9]. Analysis of the 2017-2018 cohort confirms an association between HbA1c and technology use. The adjusted mean HbA1c was significantly lower in patients using sensor-augmented CSII compared to MDI alone. Multiple pairwise comparison showed that the introduction of CSII only or is-CGM only did not impact significantly on HbA1c, whereas those with sensor augmented CSII had a lower HbA1c compared to MDI users (with or without is-CGM). These findings are in line with other studies showing improved outcomes upon CGM such as reduced HbA1c levels, less severe acute diabetes complications, improved quality of life or higher treatment satisfaction [2,10–18]. In contrast to other studies but confirming the results of a recent real-world study [19], the introduction of is-CGM in MDI patients could not statistically impact on HbA1c. Our data indicate however that the availability of CSII and is-/rt-CGM alone does not explain the improved metabolic control over the cohorts. When additionally adjusted for technology use, the mean HbA1c still significantly decreased from 65 mmol/mol (8.1%) in 2010-2011 to 61 mmol/mol (7.7%) in 2017-2018. Our hypothesis is supported by the findings of the Prospective Diabetes Follow-up Registry (DPV) registry showing a significant improvement in metabolic control in children and adolescents with T1D between 1995 and 2009, which could not completely be explained by changes in insulin treatment [20].

Besides an improved metabolic control, our data also show a significant improvement in lipid control over time. The proportions of adults with LDL cholesterol levels in target significantly increased from about 60% in 2010-2011 to about 70% in 2017-2018 (from 40% to 50% respectively for adults with CV-history). This is in line with the proportion of people with T1D with dyslipidaemia observed in other studies [21,22]. The improvement in lipid control over time was not associated with an increase in proportion of people with T1D treated with lipid-lowering drugs. As reported by others [22], the use of lipid-lowering drugs strongly increased by age: about 2% of the patients aged 15-<25 years to 70% of the patients aged ≥50 years. Patients with CV-history were more likely to receive lipid-lowering drugs (from about 60% to about 90% for adults aged ≥25 years). The further decrease in LDL cholesterol over time might be explained by treat-to-target with more potent lipid-lowering drugs. IQED does not collect information about molecules used or dose changes to help to understand the evolution reported.

We did not find a change in blood pressure control. Upon adjustment for gender, age and diabetes duration, the proportion of adults with T1D with hypertension remained stable over time (about 20%, data not shown), which is comparable to the results reported in other studies [21,22]. As for lipid-lowering drugs, treatment with antihypertensive agents increased strongly by age.

We attribute the success of the metabolic control in Belgium to the central organization of diabetes care in the contractual system of the DC, where specialized multidisciplinary centres provide diabetes care combining access to diabetes technology with therapeutic education by dieticians and diabetes nurses, stimulating optimal self-care. Several studies report the importance of structured diabetes education in reducing HbA1c levels [20,23–27]. In addition, these specialist diabetes centres are required to participate in a QA program with feedback reports with anonymized benchmarking and regular meetings where results are discussed. Such quality control programs have been shown to reduce between-centre variation and improve diabetes care [3,20,28–30]. Making global reports public also promotes international comparison.

We believe our study is unique in that it represents unbiased “real-world” data from a large, national population of children and adults with T1D. Given the central organisation

of our health care system, we estimate that almost all people with T1D are followed within specialised diabetes centres and are so captured within the QA-programs.

We do acknowledge some weaknesses of our study. The data are retrospectively collected and self-reported by the centres as part of a mandatory QA program. This could give rise to doubtful validity of the data. The QA programs use the following measures to prevent this: the authorities have no access to the database, publically available reports only show national data (no centre-individual data), centres have to keep a list of the registered people for a possible future quality audit, and the programs are monitored by and performed by endocrinologists who recognize the importance of the program. Hence we assume that the data collected through the QA programs reflect the true diabetes care provided as part of the DC. Another disadvantage of our study is the lack of data on CSII treated people in our study population between 2006 and 2014. As stricter HbA1c targets can be reached using CSII [18,31,32], the inclusion of CSII users in 2015-2016 and 2017-2018 might explain the decrease in HbA1c noticed. However when repeating the analysis in patients without CSII, a similar decline in HbA1c was shown. As third weakness we recognize the lack of granularity of data e.g. on nature of anti-hypertensive agents and – fourth - data to quantify the role of diabetes education.

Conclusion

Our study shows that access to a nationwide quality-controlled health care system that combines access to medications and diabetes technology embedded in multidisciplinary follow up and therapeutic patient education by a specialized diabetes team is associated with improved metabolic control over time in people with T1D.

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Author's Contributions

AL, FN, and CM developed the concept and design of this study. Data analysis was performed by AL. All authors made substantial contributions to the interpretation of results. AL, FN, CM, KD, CDB, AV and PO drafted the manuscript and all authors contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final manuscript for publication. AL had full access to the data and accepts the responsibility for the integrity of the data and accuracy of the data analysis.

Author Disclosure Statement

All authors declare that no competing financial interests exist.

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Figure legends

Figure 1

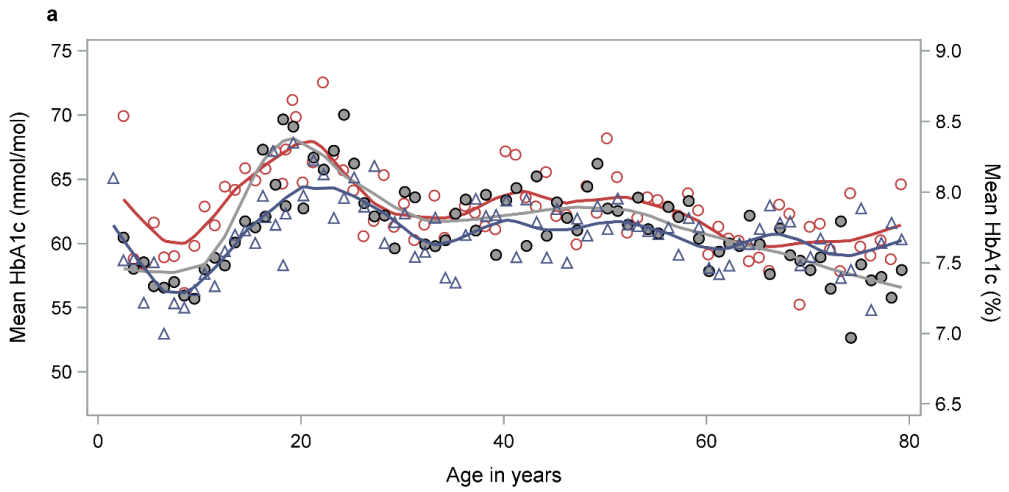

Fig. 1a: Evolution unadjusted mean HbA1c by year of age for cohort 2010-2011 (red), cohort 2015-2016 (grey) and cohort 2017-2018 (blue). The solid line shows the fitted LOESS curve.

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)

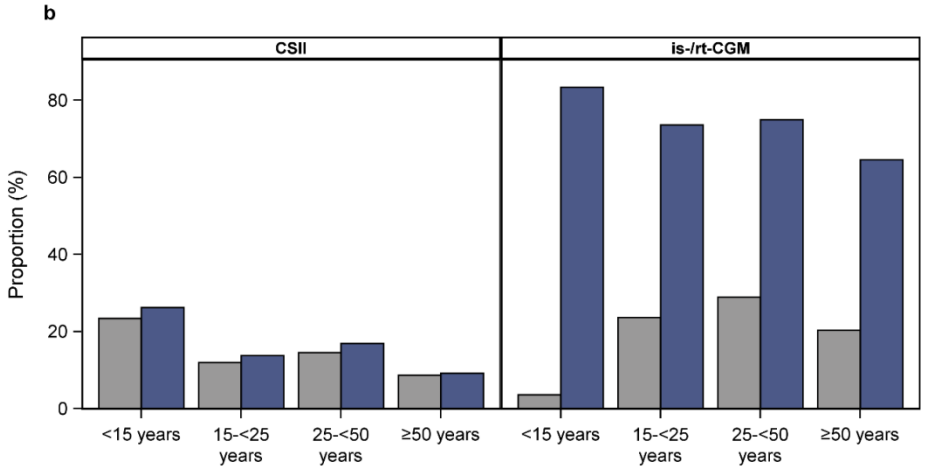

Fig. 1b: Evolution of the proportion of patients (%) with CSII and CGM (real time or intermittently scanned), by age category. Grey bar represents cohort 2015-2016 and blue bar cohort 2017-2018. Cohort 2010-2011 is not shown as adult pump-treated patients were not eligible for inclusion in the IQED study population between 2006 and 2014, and CGM was not available before 2014.

Figure 2

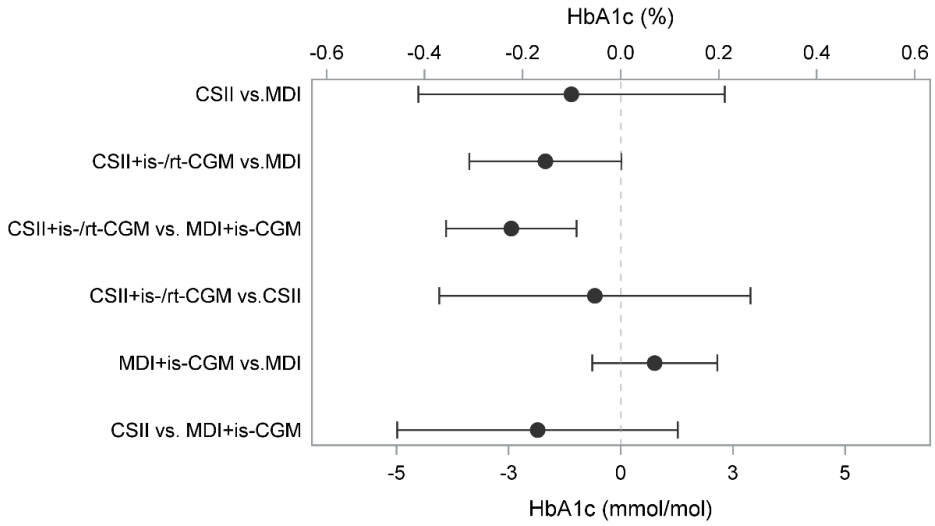

Fig. 2: Pairwise difference of LSMeans (Tukey adjustment) of HbA1c by technology use (MDI: n = 8,914; CSII: n = 678; MDI + is-CGM: n = 19,413; CSII + is-/rt-CGM: n = 3,805) (adjusted for gender, age and diabetes duration), and the 95% confidence intervals of mean difference. Pairs whose intervals contain 0 are not significantly different upon Tukey correction. MDI = multiple daily injections; CSII = continuous subcutaneous insulin infusion; rt-CGM = real time continuous glucose monitoring; is-CGM = intermittently scanned continuous glucose monitoring.

Figure 3

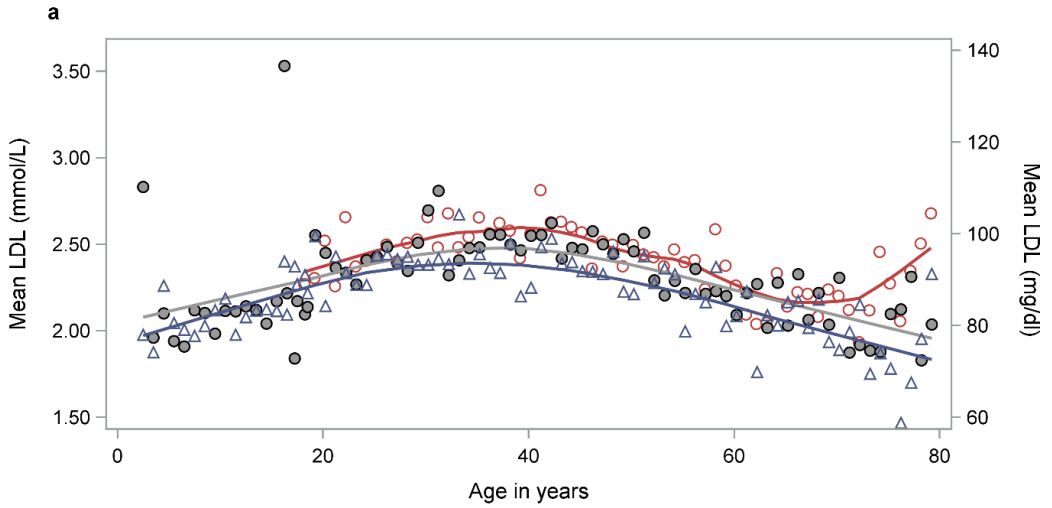

Fig. 3a: Evolution unadjusted mean LDL cholesterol by year of age for cohort 2010-2011 (red), cohort 2015-2016 (grey) and cohort 2017-2018 (blue). The solid line shows the fitted LOESS curve.

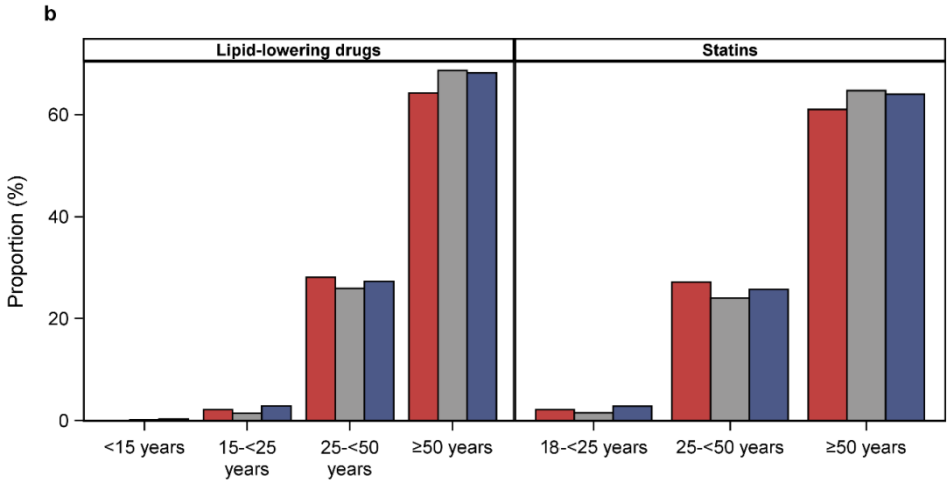

Fig. 3b: Evolution proportion of patients (%) treated with lipid-lowering drugs by age category. Red bar represents cohort 2010-2011, grey bar cohort 2015-2016 and blue bar cohort 2017-2018. In paediatric centres, LDL cholesterol value was not asked in cohort 2010-2011. Lipid-lowering drugs has been defined as the use of either one of these classes: statins, fibrates, ezetimibe. In paediatric centres, treatment with statins was not asked; treatment with lipid-lowering drugs was asked from audit 2015-2016.

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)

Figure 4

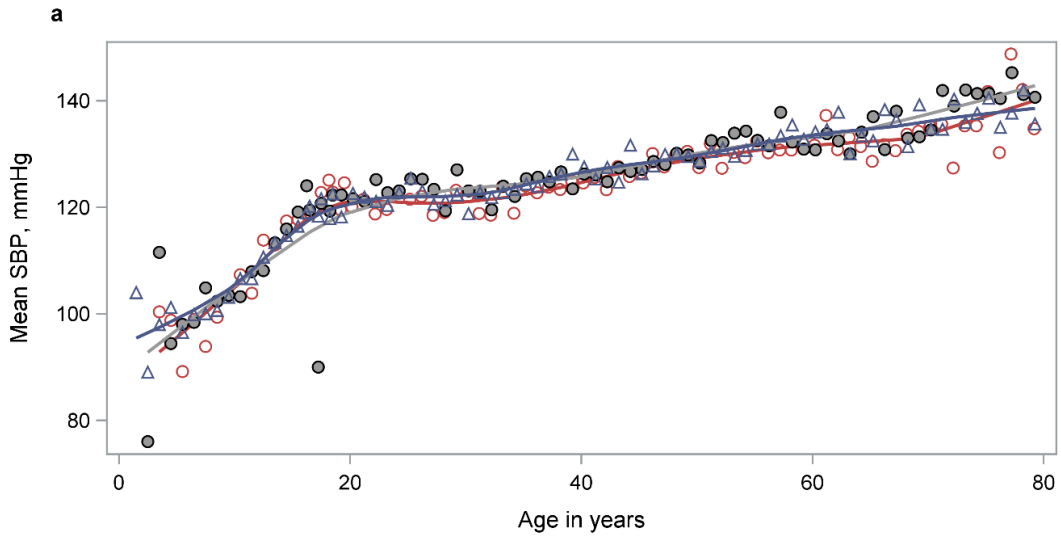

Fig. 4a: Evolution unadjusted mean SBP by year of age for cohort 2010-2011 (red), cohort 2015-2016 (grey) and cohort 2017-2018 (blue). The solid line shows the fitted LOESS curve.

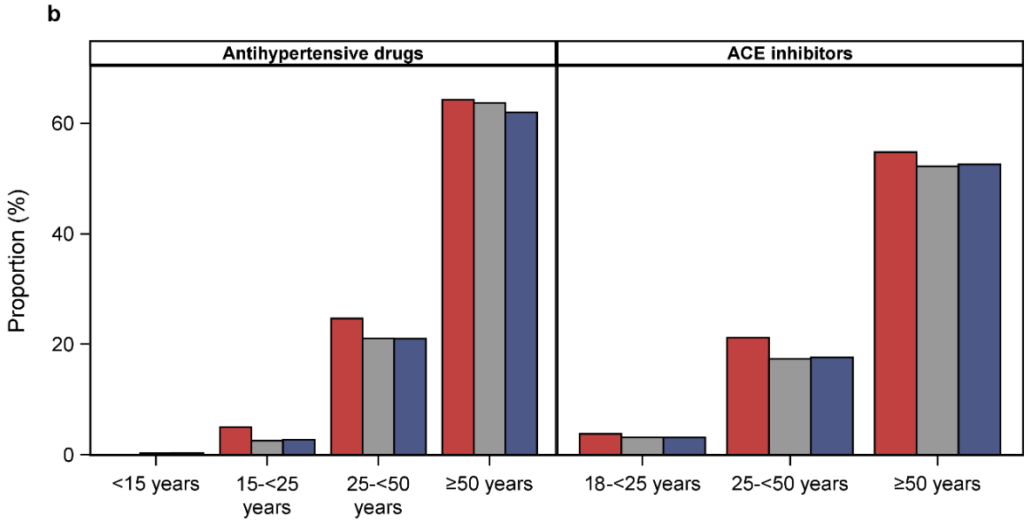

Fig.4b: Evolution proportion of patients (%) treated with antihypertensive drugs by age category. Red bar represents cohort 2010-2011, grey bar cohort 2015-2016 and blue bar cohort 2017-2018. ACE-inhibitors = ACE-inhibitors and/or angiotensin II receptor blockers. Antihypertensive drugs has been defined as the use of either ACE-inhibitors and/or angiotensin II receptor blockers or other antihypertensive drugs. In paediatric centres, treatment with ACE-inhibitors and/or angiotensin II receptor blockers was not asked; treatment with antihypertensive drugs was asked from audit 2015-2016.

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)

Tables

Table 1: Patient characteristics from cohort 2010-2011, cohort 2015-2016 and cohort 2017-2018

	cohort 2010-2011	cohort 2015-2016	cohort 2017-2018
	N=29,376 (IQED: N=27,228, IQECAD: N=2,148)	N=27,648 (IQED: N=25,161, IQECAD: N=2,487)	N=32,810 (IQED: N=29,698, IQECAD: N=3,111)
Clinical characteristics			
Age, years, median (IQR)	45.2 [32.2- 56.2]	45.2 [30.2- 58.2]	46.2 [30.2- 59.2]
Age categories <15 years, n (% [CI])	1376 (4.7% [4.0- 5.3])	1510 (5.5% [4.9- 6.0])	1851 (5.6% [5.1- 6.2])
15-<25 years, n (% [CI])	3196 (10.9% [9.9- 11.8])	3333 (12.1% [11.2- 12.9])	4149 (12.6% [11.8-13.5])
25-<50 years, n (% [CI])	13074 (44.5% [43.0- 46.0])	11295 (40.9% [39.6- 42.1])	12815 (39.1% [37.8-40.3])
≥50 years, n (% [CI])	11730 (39.9% [38.5- 41.4])	11510 (41.6% [40.4- 42.9])	13994 (42.7% [41.4-43.9])
Gender, male, n (% [CI])	17134 (58.3% [56.8- 59.8])	15279 (55.3% [54.0- 56.5])	18111 (55.2% [54.0-56.4])
Diabetes duration, years, median (IQR)	16.2 [8.2- 29.2]	17.2 [9.0- 28.7]	17.3 [9.0- 29.2]
Diabetes duration categories	8700 (29.6% [28.2-	7823 (28.3% [27.1-	9382 (28.6%

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)

<10 years, n (% [CI])	31.0])	29.4])	[27.5-29.7])
10-<20 years, n (% [CI])	8218 (28.0% [26.6-29.3])	7744 (28.0% [26.9-29.2])	8916 (27.2% [26.1-28.3])
20-<30 years, n (% [CI])	5552 (18.9% [17.7-20.1])	5687 (20.6% [19.5-21.6])	6709 (20.4% [19.4-21.4])
≥30 years, n (% [CI])	6905 (23.5% [22.2-24.8])	6394 (23.1% [22.1-24.2])	7803 (23.8% [22.7-24.8])
Age at diagnosis, years, median (IQR)	23.0 [13.0- 34.0]	22.1 [12.0- 34.4]	22.5 [12.0- 34.7]
BMI categories [a] Normal weight, n (% [CI])	13534 (48.5% [47.0-50.1])	12590 (48.3% [47.0-49.6])	15085 (48.1% [46.9-49.4])
Overweight, n (% [CI])	9536 (34.2% [32.7-35.7])	9324 (35.8% [34.5-37.0])	10896 (34.8% [33.6-35.9])
Obesity, n (% [CI])	4812 (17.3% [16.1-18.4])	4142 (15.9% [14.9-16.9])	5373 (17.1% [16.2-18.1])
Systolic blood pressure, mmHg, mean [± SD]	126.6 [± 16.3]	128.0 [± 17.3]	127.8 [± 17.1]
LDL cholesterol, mmol/L, mean [± SD]	2.46 [± 0.74]	2.37 [± 0.78]	2.27 [± 0.73]
LDL cholesterol, mg/dl, mean [± SD]	95.2 [± 28.7]	91.6 [± 30.3]	88.0 [± 28.4]
HbA1c, mmol/mol, mean [± SD]	63 [± 14]	62 [± 13]	61 [± 13]

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)

HbA1c, %, mean [± SD]	7.9 [± 1.3]	7.8 [± 1.2]	7.7 [± 1.2]
HbA1c categories HbA1c <53mmol/mol (<7%), n (% [CI])	6518 (22.2% [20.9-23.4])	6582 (23.8% [22.7-24.9])	8482 (25.9% [24.8-26.9])
HbA1c ≥53-<69mmol/mol (≥7-<8.5%), n (% [CI])	14521 (49.4% [47.9-50.9])	14418 (52.2% [50.9-53.4])	17190 (52.4% [51.2-53.6])
HbA1c ≥69mmol/mol (≥8.5%), n (% [CI])	8336 (28.4% [27.0-29.7])	6647 (24.0% [22.9-25.1])	7138 (21.8% [20.7-22.8])
Method of self-monitoring [b] Fingerstick tests, n (% [CI])	29376 (100% [100-100])	21221 (76.8% [75.7-77.8])	9591 (29.2% [28.1-30.4])
Rt-CGM, n (% [CI])	-	864 (3.1% [2.7-3.6])	1961 (6.0% [5.4-6.6])
Is-CGM, n (% [CI])	-	5563 (20.1% [19.1-21.1])	21257 (64.8% [63.6-66.0])
Insulin use 2-3 insulin injections, n (% [CI])	2472 (8.4% [7.6-9.3])	1137 (4.1% [3.6-4.6])	1180 (3.6% [3.1-4.1])
≥4 insulin injections, n (% [CI])	26654 (90.7% [89.9-91.6])	23135 (83.7% [82.7-84.6])	27147 (82.7% [81.8-83.7])

CSII, n (% [CI])	250 (0.8% [0.6-1.1])	3376 (12.2% [11.4-13.0])	4483 (13.7% [12.8-14.5])
Non insulin medication Biguanides, n (% [CI])	2267 (8.4% [7.5-9.4])	2467 (10.0% [9.0-11.0])	2987 (10.1% [9.2-11.1])
SGLT-2 inhibitors [c], n (% [CI])	-	22 (0.1% [-0.0-0.2])	323 (1.1% [0.8-1.4])
Lipid-lowering drugs [d], n (% [CI])	10966 (41.4% [39.7-43.2])	10687 (39.4% [38.2-40.7])	12918 (40.1% [38.9-41.4])
Statins, n (% [CI])	10604 (39.6% [37.9-41.3])	10090 (40.5% [38.8-42.1])	12199 (41.6% [39.9-43.2])
Antihypertensive drugs [e], n (% [CI])	10695 (40.1% [38.4-41.8])	9680 (35.5% [34.2-36.7])	11373 (35.1% [33.9-36.2])
RAAS inhibitors [f], n (% [CI])	9149 (34.2% [32.5-35.8])	7941 (32.0% [30.4-33.5])	9571 (32.7% [31.1-34.2])

a. BMI categories for children and adolescents (≥2 - <18 years) are based on the specific BMI cut-offs reported by Cole et al. [8]; for patients ≥18 years defined as normal weight: <25 kg/m²; overweight: ≥25 - <30 kg/m²; obesity: ≥30 kg/m².
b. rt-CGM and is-CGM has been asked from audit 2015-2016.
c. Treatment with SGLT-2 inhibitors has been asked from audit 2015-2016.
d. Lipid-lowering drugs has been defined as the use of either one of these classes: statins, fibrates, ezetimibe.
e. Antihypertensive drugs has been defined as the use of either ACE inhibitors, angiotensin II receptor blockers or other antihypertensive drugs.
f. ACE inhibitors and/or angiotensin II receptor blockers.

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Table 1. Patient characteristics from cohort 2010-2011, cohort 2015-2016 and cohort 2017-2018. BMI = body mass index; rt-CGM = real time continuous glucose monitoring; is-CGM = intermittently scanned continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; n = number of patients; % = proportion; CI = 95% confidence interval; IQR = interquartile range; SD = standard deviation

In pediatric centres treatment with biguanides, SGLT-2 inhibitors, statins, or ACE inhibitors and/or angiotensin II receptor blockers was not asked; treatment with antihypertensive drugs, treatment with lipid-lowering drugs and blood lipids asked from audit 2015-2016. In the adult centres, pump-treated patients were not eligible for inclusion between 2006 and 2014.

Cohort 2010-2011: BMI missing for 1,494 patients; systolic blood pressure missing for 987 patients; LDL cholesterol missing for 1,047; treatment with biguanides missing for 378 patients, treatment with lipid-lowering drugs missing for 758 patients; treatment with statins missing for 436 patients; treatment with antihypertensive drugs missing for 573 patients; treatment with ACE inhibitors and/or angiotensin II receptor blockers missing for 449 patients.

Cohort 2015-2016: BMI missing for 1,592 patients; systolic blood pressure missing for 702 patients; LDL cholesterol missing for 2,721; treatment with biguanides missing for 443 patients, treatment with SGLT-2 inhibitors missing for 422 patients; treatment with lipid-lowering drugs missing for 530 patients; treatment with statins missing for 245 patients; treatment with antihypertensive drugs missing for 354 patients; treatment with ACE inhibitors and/or angiotensin II receptor blockers missing for 314 patients.

Cohort 2017-2018: BMI missing for 1,455 patients; systolic blood pressure missing for 1078 patients; LDL cholesterol missing for 3,342; treatment with biguanides missing for 263 patients; treatment with SGLT-2 inhibitors missing for 424 patients; treatment with lipid-lowering drugs missing for 635 patients; treatment with statins missing for 356 patients; treatment with antihypertensive drugs missing for 367 patients; treatment with ACE inhibitors and/or angiotensin II receptor blockers missing for 387 patients.

Diabetes Technology and Therapeutics
Effect of an integrated, multidisciplinary nationwide approach to T1D care on metabolic outcomes: An observational real-world study (DOI: 10.1089/dia.2021.0003)

Table 2: Cohort 2017-2018, association of HbA1c with gender, age, diabetes duration and technology use.

	HbA1c value (mmol/mol)	95% CI	HbA1c value (%)	95% CI	P
Intercept[a]	65	[64 – 67]	8.1	[8.0 - 8.3]	
Gender					
Male	(reference)				
female	+1	[0 - 1]	+0.1	[0.0 - 0.1]	0.0124
Age (years)					
<15	-3	[-4 - -1]	-0.3	[-0.4 - -0.1]	0.0002
15-<25	(reference)				
25-<50	-2	[-4 - -1]	-0.2	[-0.4 - -0.1]	0.0026
≥50	-3	[-5 - -2]	-0.3	[-0.5 - -0.2]	<.0001
Diabetes duration (years)					
<10	-4	[-5 - -2]	-0.4	[-0.5 - -0.2]	<.0001
10-<20	(reference)		-		
20-<30	-1	[-2 - 0]	-0.1	[-0.2 - 0.0]	0.0220
≥30	-3	[-4 - -2]	-0.3	[-0.4 - -0.2]	<.0001
Technology use					
MDI	(reference)		-		

CSII	-1	[-3 - 1]	-0.1	[-0.3 - 0.1]	0.4073
MDI + is- CGM	+1	[0 - 2]	+0.1	[0.0 - 0.2]	0.1623
CSII + is-/rt-CGM	-2	[-3 - 0]	-0.2	[-0.3 - 0.0]	0.0109

a. Intercept HbA1c value = the mean HbA1c value when all explanatory variables are set to their reference category.

Table 2: Multivariable analysis of association of gender, age, diabetes duration and technology use with HbA1c. Positive values indicate an increase in HbA1c compared to the intercept, negative values indicate a decrease in HbA1c compared to the intercept. MDI = multiple daily injections; CSII = continuous subcutaneous insulin infusion; rt-CGM = real time continuous glucose monitoring; is-CGM = intermittently scanned continuous glucose monitoring; CI = 95% confidence interval.