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ORIGINAL ARTICLE

Effect of an Integrated, Multidisciplinary Nationwide Approach to Type 1 Diabetes Care on Metabolic Outcomes: An Observational Real-World Study

Astrid Lavens, MSc,[1,*] Frank Nobels, MD, PhD,[2] Christophe De Block, MD, PhD,[3] Philippe Oriot, MD,[4] Ann Verhaegen, MD,[3] Suchsia Chao, MSc,[1] Kristina Casteels, MD, PhD,[5,6] Thierry Mouraux, MD,[7] Kris Doggen, MSc, PhD,[1] and Chantal Mathieu, MD, PhD;[8] on Behalf of the Belgian Group of Experts IQED and IQECAD

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 centers with access to technology, diabetes education, and regular follow-up.

Methods: Data were cross-sectionally collected between 2010 and 2018 from more than 100 centers in Belgium. The evolutions over time of hemoglobin A1C (HbA1c), low-density lipoprotein (LDL) cholesterol, and systolic blood pressure (SBP) were investigated, together with the evolutions of use of insulin pump (continuous subcutaneous insulin infusion [CSII]), continuous glucose monitoring (CGM), and lipid-lowering and antihypertensive drugs. Association of HbA1c with gender, age, diabetes duration, and technology use was analyzed on the most recent cohort.

Results: The study population contained data from 89,834 people with T1D (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 SBP remained stable. CGM usage increased, whereas the use of CSII and lipid-lowering and antihypertensive 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 centers with emphasis on linking education to provision of technology, and its quality is monitored.

Keywords: Diabetes care, HbA1c, Type 1 diabetes, Diabetes education, Quality assurance program.

[1]Health Services Research, Sciensano, Brussels, Belgium.
[2]Department of Endocrinology, Onze-Lieve-Vrouw Hospital Aalst, Aalst, Belgium.
[3]Department of Endocrinology, Diabetology and Metabolism, University of Antwerp-Antwerp University Hospital, Antwerp, Belgium.
[4]Department of Endocrinology and Diabetes, Mouscron Hospital Centre, Mouscron, Belgium.
[5]Department of Pediatrics, University Hospitals Leuven-KU Leuven, Leuven, Belgium.
[6]Department of Development and Regeneration, KU Leuven, Leuven, Belgium.
[7]Department of Pediatric Endocronology, University Hospitals de Namur-UC Louvain, Yvoir, Belgium.
[8]Department of Endocrinology, University Hospitals Leuven-KU Leuven, Leuven, Belgium.
*ORCID ID (https://orcid.org/0000-0002-9942-8263).

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 hemoglobin A1C (HbA1c) <58 mmol/mol (<7.5%).[1] Data from the T1D Exchange Registry even show a trend to deterioration of metabolic control in the United States over the years, despite the 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 centers provide free-of-charge specialist multidisciplinary care, with access to diabetes education and 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 continuous glucose monitoring (is-CGM, since 07/2016), and to real-time continuous glucose monitoring (rt-CGM, since 07/2018, restricted use since 09/2014).

All centers 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 centers in 2001 and the Initiative for Quality Improvement and Epidemiology in Children and Adolescents with Diabetes (IQECAD) for pediatric centers in 2008. In these nationwide projects, clinical data are routinely collected and fed back both in national reports and in center individual benchmarking, to monitor characteristics of diabetes patients and their care as part of the DC.[3,4] Distributed all over the country, there are 15 pediatric and 102 adult specialized diabetes centers 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 organized 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 pediatric diabetes centers in Belgium. For IQECAD, IRB approval was requested and obtained.

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 center 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 pseudonymized. 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 ($n=1630$), technology use ($n=3412$), and HbA1c ($n=1977$) were excluded. Patients ≥80 years ($n=2880$) or with a diabetes duration <1 year ($n=2474$) were also excluded.

The final study population contained data from 29,376 patients in cohort 2010–2011 (from 2148 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 2487 children pertaining to audit 01/2015–12/2015 and from 25,161 adults pertaining to audit 10/2015–09/2016), and from 32,809 patients in cohort 2017–2018 (from 3111 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]

Because at the time of analysis use of rt-CGM was restricted to CSII users, 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 nonfasted).

Children and adolescents (≥2 to <18 years) were classified as overweight or obese using the age- and gender-specific body mass index (dividing weight by height squared) cutoffs reported by Cole et al.[8] and used by the International Obesity Task Force (IOTF). These cutoffs lie on the centiles passing, at the age of 18, through the cutoffs for overweight (≥25 to <30 kg/m^2) and obesity (≥30 kg/m^2) 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 an LDL cholesterol <2.59 mmol/L (<100 mg/dL) and the proportion with hypertension were calculated. In addition, for adult patients with a CV-history, the proportion with an LDL cholesterol <1.81 mmol/L (<70 mg/dL) was calculated. The between-center 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 center), and robust standard errors, with cohort as an explanatory variable (categorical). The model was adjusted for gender, age (<15 years, 15 to <25 years, 25 to <50 years, and ≥50 years), and diabetes duration (<10 years, 10 to <20 years, 20 to <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 center size, the full model was repeated with center size as an 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 angiotensin converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers, by age and cohort.

Results are expressed as proportion (95% confidence interval [CI]), as mean (±standard deviation) for normally distributed variables, or median (interquartile range) for non-normally distributed variables. Unless indicated otherwise, statistical significance was tested using chi-squared 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, and 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).

Results

The characteristics of the three cohorts are shown in Table 1. The characteristics of the three 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-center variation for glycemic control is shown in Supplementary Table S1.

Unadjusted mean HbA1c by year of age for the three cohorts is shown in Figure 1a. Analysis shows 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 center 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 data set 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).

Table 1. Patient Characteristics from Cohort 2010 to 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 = *2148)*	N = *27,648 (IQED:* N = *25,161, IQECAD:* N = *2487)*	N = *32,809 (IQED:* N = *29,698, IQECAD:* N = *3111)*
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 to 5.3])	1510 (5.5 [4.9 to 6.0])	1851 (5.6 [5.1 to 6.2])
15 to <25 years, *n* (% [CI])	3196 (10.9 [9.9 to 11.8])	3333 (12.1 [11.2 to 12.9])	4149 (12.6 [11.8 to 13.5])
25 to <50 years, *n* (% [CI])	13074 (44.5 [43.0 to 46.0])	11295 (40.9 [39.6 to 42.1])	12815 (39.1 [37.8 to 40.3])
≥50 years, *n* (% [CI])	11730 (39.9 [38.5 to 41.4])	11510 (41.6 [40.4 to 42.9])	13994 (42.7 [41.4 to 43.9])
Gender, male, *n* (% [CI])	17134 (58.3 [56.8 to 59.8])	15279 (55.3 [54.0 to 56.5])	18111 (55.2 [54.0 to 56.4])
Diabetes duration, years, median (IQR)	16.2 [8.2 to 29.2]	17.2 [9.0 to 28.7]	17.3 [9.0 to 29.2]
Diabetes duration categories <10 years, *n* (% [CI])	8700 (29.6 [28.2 to 31.0])	7823 (28.3 [27.1 to 29.4])	9382 (28.6 [27.5 to 29.7])
10 to <20 years, *n* (% [CI])	8218 (28.0 [26.6 to 29.3])	7744 (28.0 [26.9 to 29.2])	8916 (27.2 [26.1 to 28.3])
20 to <30 years, *n* (% [CI])	5552 (18.9 [17.7 to 20.1])	5687 (20.6 [19.5 to 21.6])	6709 (20.4 [19.4 to 21.4])
≥30 years, *n* (% [CI])	6905 (23.5 [22.2 to 24.8])	6394 (23.1 [22.1 to 24.2])	7803 (23.8 [22.7 to 24.8])
Age at diagnosis, years, median (IQR)	23.0 [13.0 to 34.0]	22.1 [12.0 to 34.4]	22.5 [12.0 to 34.7]
BMI categories[a]			
Normal weight, *n* (% [CI])	13534 (48.5 [47.0 to 50.1])	12590 (48.3 [47.0 to 49.6])	15085 (48.1 [46.9 to 49.4])
Overweight, *n* (% [CI])	9536 (34.2 [32.7 to 35.7])	9324 (35.8 [34.5 to 37.0])	10896 (34.8 [33.6 to 35.9])
Obesity, *n* (% [CI])	4812 (17.3 [16.1 to 18.4])	4142 (15.9 [14.9 to 16.9])	5373 (17.1 [16.2 to 18.1])
SBP, 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]
HbA1c, %, mean [±SD]	7.9 [±1.3]	7.8 [±1.2]	7.7 [±1.2]
HbA1c categories			
HbA1c <53 mmol/mol (<7%), *n* (% [CI])	6518 (22.2 [20.9 to 23.4])	6582 (23.8 [22.7 to 24.9])	8482 (25.9 [24.8 to 26.9])
HbA1c ≥53 to <69 mmol/mol (≥7 to <8.5%), *n* (% [CI])	14521 (49.4 [47.9 to 50.9])	14418 (52.2 [50.9 to 53.4])	17190 (52.4 [51.2 to 53.6])
HbA1c ≥69 mmol/mol (≥8.5%), *n* (% [CI])	8336 (28.4 [27.0 to 29.7])	6647 (24.0 [22.9 to 25.1])	7138 (21.8 [20.7 to 22.8])
Method of self-monitoring[b]			
Fingerstick tests, *n* (% [CI])	29376 (100 [100 to 100])	21221 (76.8 [75.7 to 77.8])	9591 (29.2 [28.1 to 30.4])
rt-CGM, *n* (% [CI])	—	864 (3.1 [2.7 to 3.6])	1961 (6.0 [5.4 to 6.6])
is-CGM, *n* (% [CI])	—	5563 (20.1 [19.1 to 21.1])	21257 (64.8 [63.6 to 66.0])
Insulin use			
2–3 insulin injections, *n* (% [CI])	2472 (8.4 [7.6 to 9.3])	1137 (4.1 [3.6 to 4.6])	1180 (3.6 [3.1 to 4.1])
≥4 insulin injections, *n* (% [CI])	26654 (90.7 [89.9 to 91.6])	23135 (83.7 [82.7 to 84.6])	27147 (82.7 [81.8 to 83.7])
CSII, *n* (% [CI])	250 (0.8 [0.6 to 1.1])	3376 (12.2 [11.4 to 13.0])	4483 (13.7 [12.8 to 14.5])
Noninsulin medication			
Biguanides, *n* (% [CI])	2267 (8.4 [7.5 to 9.4])	2467 (10.0 [9.0 to 11.0])	2987 (10.1 [9.2 to 11.1])
SGLT-2 inhibitors[c], *n* (% [CI])	—	22 (0.1 [–0.0 to 0.2])	323 (1.1 [0.8 to 1.4])
Lipid-lowering drugs[d], *n* (% [CI])	10966 (41.4 [39.7 to 43.2])	10687 (39.4 [38.2 to 40.7])	12918 (40.1 [38.9 to 41.4])
Statins, *n* (% [CI])	10604 (39.6 [37.9 to 41.3])	10090 (40.5 [38.8 to 42.1])	12199 (41.6 [39.9 to 43.2])

(*continued*)

Table 1. (Continued)

	Cohort 2010–2011	*Cohort 2015–2016*	*Cohort 2017–2018*
	N = *29,376 (IQED:* N = *27,228, IQECAD:* N = *2148)*	N = *27,648 (IQED:* N = *25,161, IQECAD:* N = *2487)*	N = *32,809 (IQED:* N = *29,698, IQECAD:* N = *3111)*
Antihypertensive drugs[e], *n* (% [CI])	10695 (40.1 [38.4 to 41.8])	9680 (35.5 [34.2 to 36.7])	11373 (35.1 [33.9 to 36.2])
RAAS inhibitors[f], *n* (% [CI])	9149 (34.2 [32.5 to 35.8])	7941 (32.0 [30.4 to 33.5])	9571 (32.7 [31.1 to 34.2])

In pediatric centers, 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 to 2016. In the adult centers, pump-treated patients were not eligible for inclusion between 2006 and 2014.

Cohort 2010–2011: BMI missing for 1494 patients; SBP missing for 987 patients; LDL cholesterol missing for 1047; 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 1592 patients; SBP missing for 702 patients; LDL cholesterol missing for 2721; 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 1455 patients; SBP missing for 1078 patients; LDL cholesterol missing for 3342; 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.

[a]BMI categories for children and adolescents (≥2 to <18 years) are based on the specific BMI cutoffs reported by Cole et al.[8]; for patients ≥18 years defined as normal weight: <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; obesity: ≥30 kg/m^2.

[b]rt-CGM and is-CGM have been asked from audit 2015 to 2016.

[c]Treatment with SGLT-2 inhibitors has been asked from audit 2015 to 2016.

[d]Lipid-lowering drugs have been defined as the use of one of these classes: statins, fibrates, ezetimibe.

[e]Antihypertensive drugs have been defined as the use of ACE inhibitors, angiotensin II receptor blockers, or other antihypertensive drugs.

[f]ACE inhibitors and/or angiotensin II receptor blockers.

%, proportion; ACE, angiotensin converting enzyme; BMI, body mass index; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1C; 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; is-CGM, intermittently scanned continuous glucose monitoring; LDL, low-density lipoprotein; RAAS, Renin-Angiotensin-Aldosterone System; rt-CGM, real-time continuous glucose monitoring; *n*, number of patients; SBP, systolic blood pressure; SD, standard deviation; SGLT-2, sodium/glucose cotransporter-2.

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 with those aged ≥15 years (9%–14%) and is-/rt-CGM was more often used by patients aged ≥15 years (20%–29%) compared with those aged <15 years (4%). Compared with 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 with males. Patients aged 15 to <25 years had the highest HbA1c, with all other age groups having a significantly lower HbA1c. Patients with a diabetes duration between 10 and <20 years had the highest HbA1c, all other diabetes duration groups had a significantly lower HbA1c. Compared with 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 with MDI users ($P = 0.05$) and MDI with is-CGM users ($P < 0.0001$) (Fig. 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 an 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 an 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-center variation for mean LDL cholesterol is shown in Supplementary Table S1.

Figure 3a shows the unadjusted mean LDL cholesterol by year of age for the three cohorts. Analysis shows 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).

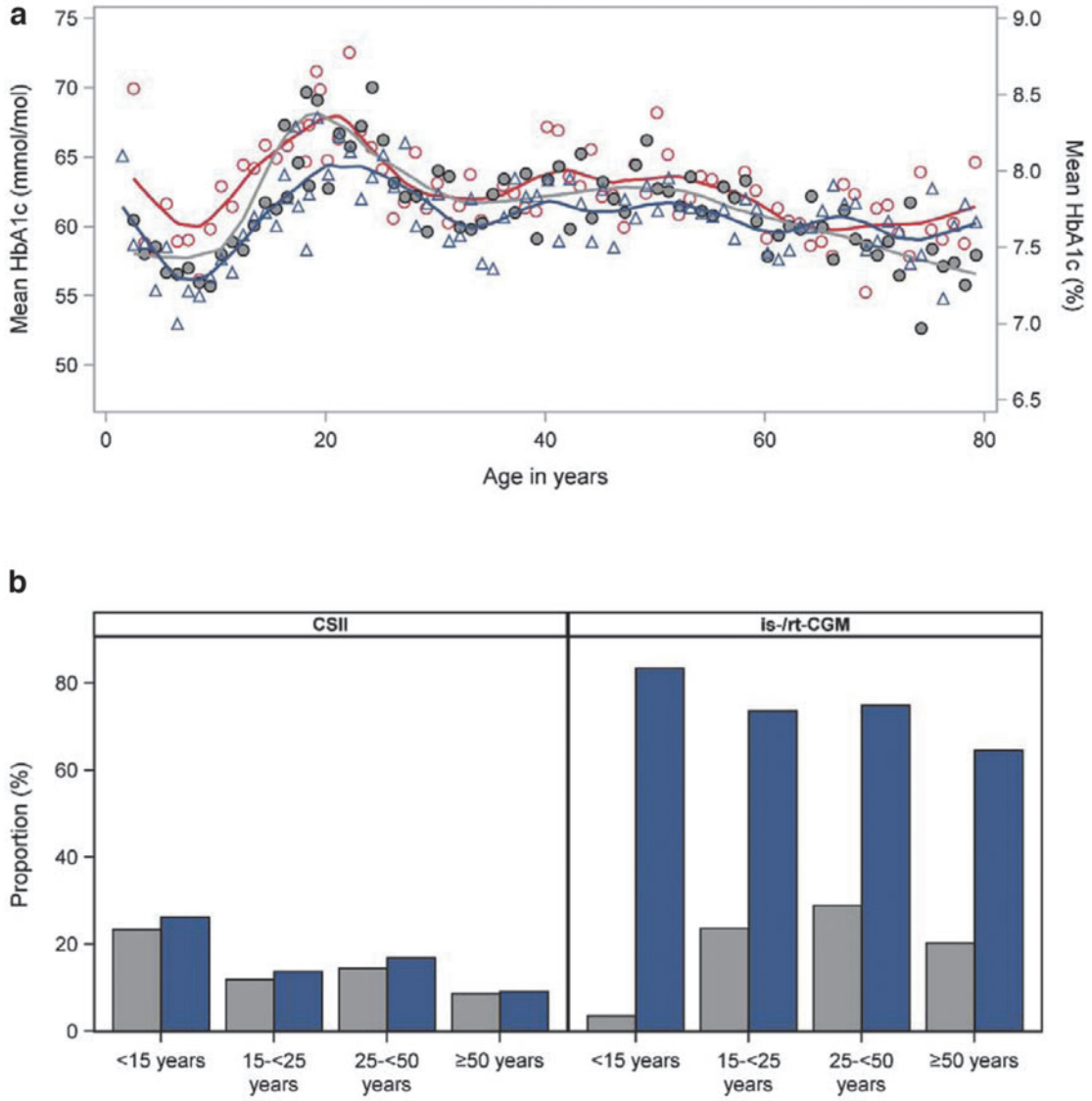

FIG. 1. **(a)** Evolution unadjusted mean HbA1c by year of age for cohort 2010–2011 (red), cohort 2015–2016 (gray), and cohort 2017–2018 (blue). The solid line shows the fitted Loess curve. **(b)** Evolution of the proportion of patients (%) with CSII and CGM (real time or intermittently scanned), by age category. Gray 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. CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA1c, hemoglobin A1C; IQED, Initiative for Quality Improvement and Epidemiology in Diabetes. Color images are available online.

Use of lipid-lowering drugs in children aged <15 years was rare (Fig. 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 to <25 years, 30% of the patients aged 25 to <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.

SBP control

Mean SBP remained stable over the three 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-center variation for mean SBP is shown in Supplementary Table S1.

Figure 4a shows the unadjusted mean SBP by year of age for the three 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 (Fig. 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 to <25 years, 25% of the patients aged 25 to <50 years, and

Table 2. Cohort 2017–2018, Association of Hemoglobin A1C with Gender, Age, Diabetes Duration, and Technology Use

	HbA1c value (mmol/mol)	*95% CI*	*HbA1c value (%)*	*95% CI*	P
Intercept[a]	65	64 to 67	8.1	8.0 to 8.3	
Gender					
Male	(Reference)				
female	+1	0 to 1	+0.1	0.0 to 0.1	0.0124
Age (years)					
<15	−3	−4 to −1	−0.3	−0.4 to −0.1	0.0002
15 to <25	(Reference)				
25 to <50	−2	−4 to −1	−0.2	−0.4 to −0.1	0.0026
≥50	−3	−5 to −2	−0.3	−0.5 to −0.2	<0.0001
Diabetes duration (years)					
<10	−4	−5 to −2	−0.4	−0.5 to −0.2	<0.0001
10 to <20	(Reference)		—		
20 to <30	−1	−2 to 0	−0.1	−0.2 to 0.0	−0.0220
≥30	−3	−4 to −2	−0.3	−0.4 to −0.2	<0.0001
Technology use					
MDI	(Reference)		—		
CSII	−1	−3 to 1	−0.1	−0.3 to 0.1	0.4073
MDI + is-CGM	+1	0 to 2	+0.1	0.0 to 0.2	0.1623
CSII + is-/rt-CGM	−2	−3 to 0	−0.2	−0.3 to 0.0	0.0109

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

Multivariable analysis of association of gender, age, diabetes duration, and technology use with HbA1c. Positive values indicate an increase in HbA1c compared with the intercept, and negative values indicate a decrease in HbA1c compared with the intercept.

CGM, continuous glucose; MDI, multiple daily injections..

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

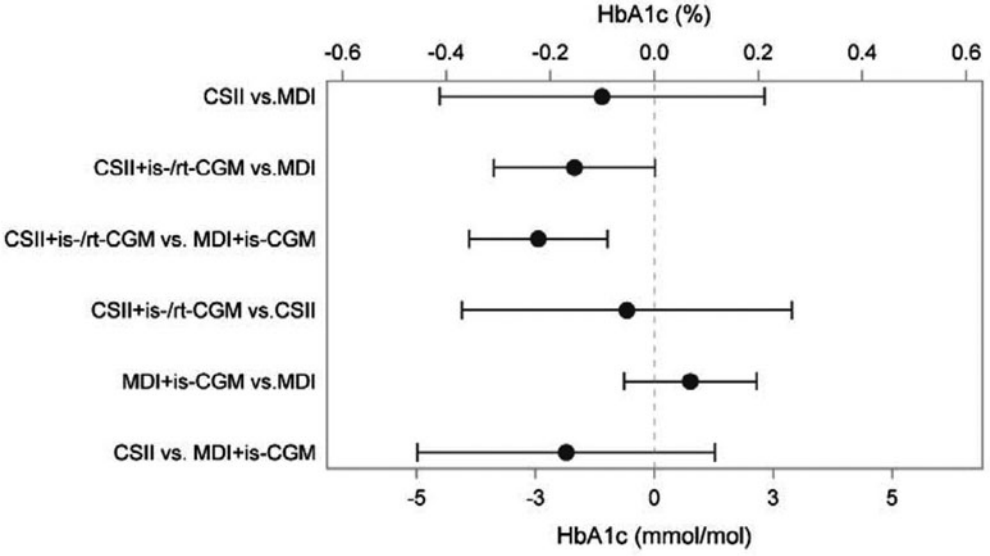

FIG. 2. Pairwise difference of LSMeans (Tukey adjustment) of HbA1c by technology use (MDI: $n = 8914$; CSII: $n = 678$; MDI+is-CGM: $n = 19{,}413$; CSII+is-/rt-CGM: $n = 3805$) (adjusted for gender, age, and diabetes duration), and the 95% confidence intervals of mean difference. Pairs whose intervals contain 0 are not significantly different upon Tukey correction. MDI, multiple daily injections; is-CGM, intermittently scanned continuous glucose monitoring; rt-CGM, real-time continuous glucose monitoring.

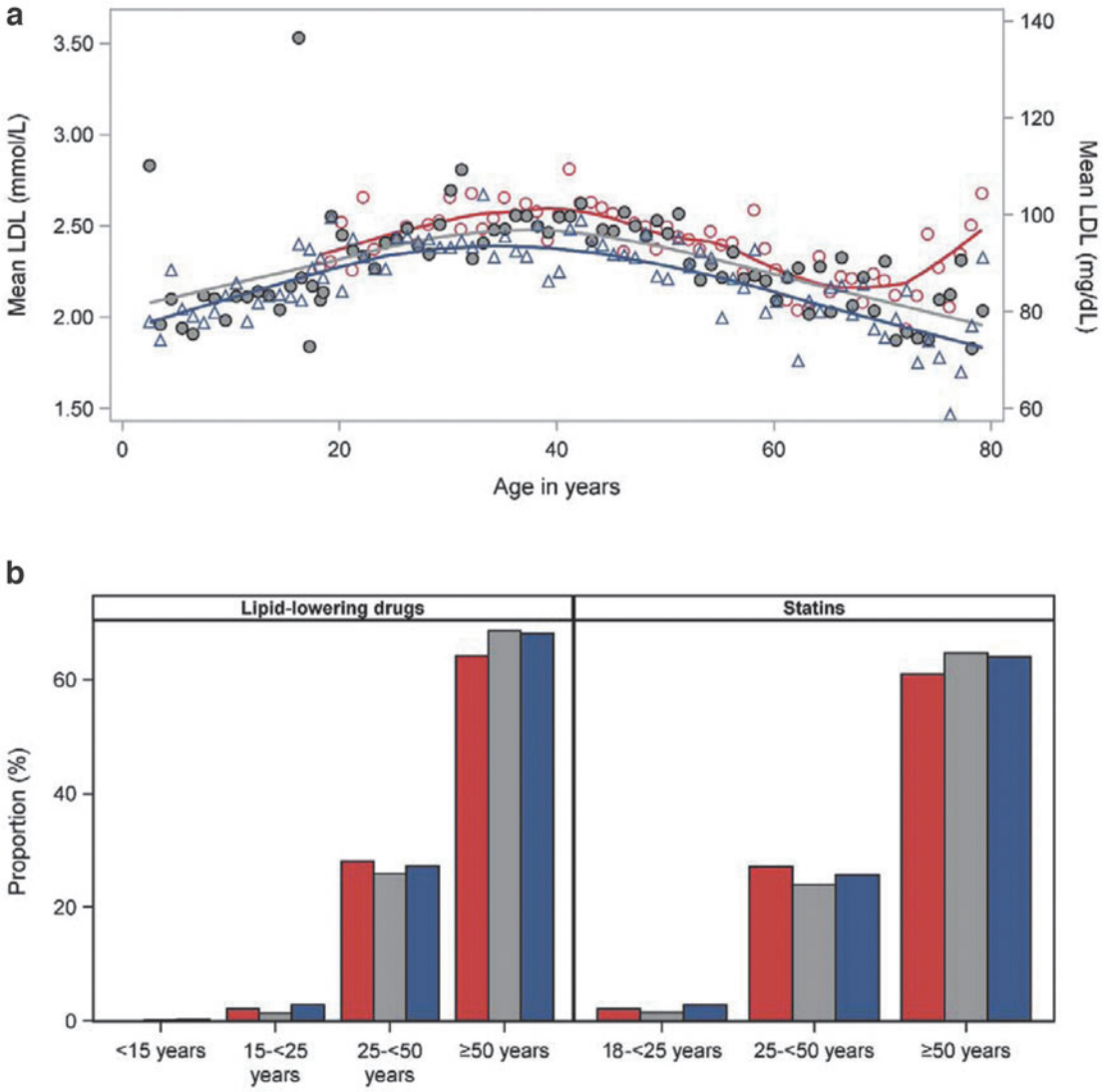

FIG. 3. **(a)** Evolution unadjusted mean LDL cholesterol by year of age for cohort 2010–2011 (red), cohort 2015–2016 (gray), and cohort 2017–2018 (blue). The solid line shows the fitted Loess curve. **(b)** Evolution proportion of patients (%) treated with lipid-lowering drugs by age category. Red bar represents cohort 2010–2011, gray bar cohort 2015–2016, and blue bar cohort 2017–2018. In pediatric centers, LDL cholesterol value was not asked in cohort 2010–2011. Lipid-lowering drugs have been defined as the use of one of these classes: statins, fibrates, ezetimibe. In pediatric centers, treatment with statins was not asked; treatment with lipid-lowering drugs was asked from audit 2015 to 2016. LDL, low-density lipoprotein. Color images are available online.

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% and 46.4% among people aged <15 years, between 8.9% and 49.5% aged ≥15 to <25 years, and between 20.5% and 53.6% aged ≥25 years (data collected between 2010 and 2013).[1] Possible explanations for this wide variation between countries and regions are differences in data sources (national, regional, and clinical studies), differences is population characteristics (such as diabetes duration and 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 to <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 to <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 centers 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 socioeconomic status and access to health care 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

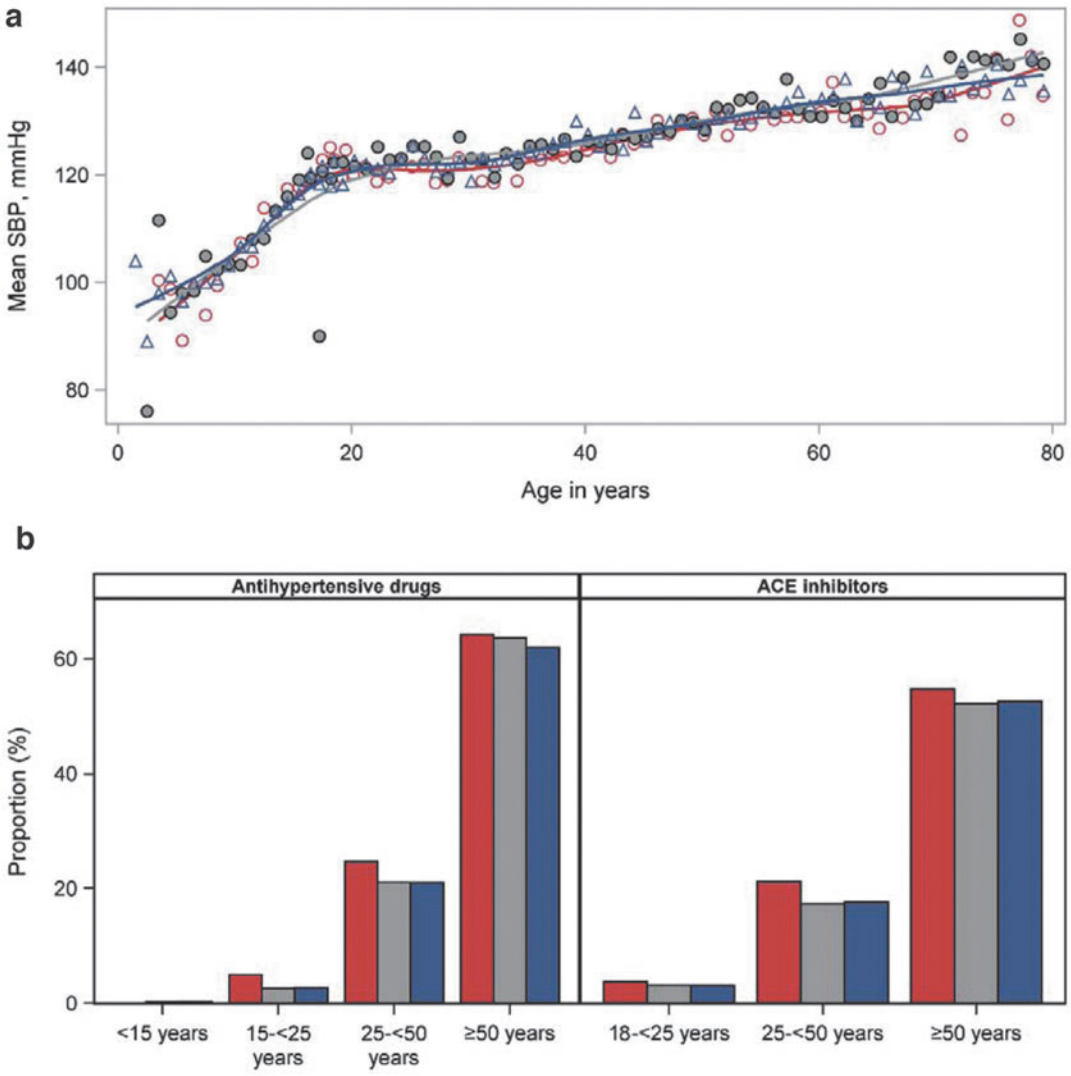

FIG. 4. **(a)** Evolution unadjusted mean SBP by year of age for cohort 2010–2011 (red), cohort 2015–2016 (gray), and cohort 2017–2018 (blue). The solid line shows the fitted LOESS curve. **(b)** Evolution proportion of patients (%) treated with antihypertensive drugs by age category. Red bar represents cohort 2010–2011, gray bar cohort 2015–2016, and blue bar cohort 2017–2018. ACE-inhibitors = ACE-inhibitors and/or angiotensin II receptor blockers. Antihypertensive drugs have been defined as the use of ACE-inhibitors and/or angiotensin II receptor blockers or other antihypertensive drugs. In pediatric centers, treatment with ACE-inhibitors and/or angiotensin II receptor blockers was not asked; treatment with antihypertensive drugs was asked from audit 2015 to 2016. SBP, systolic blood pressure. Color images are available online.

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 threefold 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 with 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 with 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 dyslipidemia 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 to <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 with 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 centers 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 centers 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-center 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 organization of our health care system, we estimate that almost all people with T1D are followed within specialized diabetes centers and are thus captured within the QA-programs.

We do acknowledge some weaknesses of our study. The data are retrospectively collected and self-reported by the centers 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 center-individual data), centers must 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 a third weakness, we recognize the lack of granularity of data, for example, on the nature of antihypertensive 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.

Author's Contributions

A.L., F.N., and C.M. developed the concept and design of this study. Data analysis was performed by A.L. All authors made substantial contributions to the interpretation of results. A.L., F.N., C.M., K.D., C.D.B., A.V., and P.O. drafted the article and all authors contributed to the critical revision of the article for important intellectual content. All authors approved the final article for publication. A.L. had full access to the data and accepts responsibility for the integrity of the data and accuracy of the data analysis.

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Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1

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Address correspondence to:
Astrid Lavens, MSc
Health Services Research
Sciensano
Brussels 1050
Belgium

E-mail: astrid.lavens@sciensano.be