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Published in:
Diabetes Research and Clinical Practice

DOI:
10.1016/j.diabres.2023.110735

diabetesresearchandclinicalpractice 201 (2023) 110735

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Real-life 24-week changes in glycemic parameters among European users of flash glucose monitoring with type 1 and 2 diabetes and different levels of glycemic control

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ARTICLE INFO

Keywords:
Continuous glucose monitoring
Diabetes
Flash glucose monitoring
Intermittently scanned continuous glucose monitoring
FreeStyle Libre

ABSTRACT

Aim: To evaluate real-life changes of glycemic parameters among flash glucose monitoring (FLASH) users who do not meet glycemic targets.
Methods: De-identified data were obtained between 2014 and 2021 from patients using FLASH uninterrupted for a 24-week period. Glycemic parameters during first and last sensor use were examined in four identifiable groups: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) on basal-bolus insulin, T2DM on basal insulin, and T2DM without insulin treatment. Within each group, subgroup analyses were performed in persons with initial suboptimal glycemic regulation (time in range (TIR; 3.9–10 mmol/L) < 70%, time above range (TAR; >10 mmol/L) > 25%, or time below range (TBR; <3.9 mmol/L) > 4%).
Results: Data were obtained from 1,909 persons with T1DM and 1,813 persons with T2DM (1,499 basal-bolus insulin, 189 basal insulin, and 125 non-insulin users). In most of the performed analyses, both overall and in the various subgroups, significant improvements were observed in virtually all predefined primary (TIR) and secondary endpoints (eHbA1c, TAR, TBR and glucose variability).
Conclusions: 24-weeks FLASH use in real life by persons with T1DM and T2DM with suboptimal glycemic regulation is associated with improvement of glycemic parameters, irrespective of pre-use regulation or treatment modality.

1. Introduction

The possibility to continuously monitor glucose values in the interstitial fluid, either by real time Continuous Glucose Monitoring (rtCGM) or flash glucose monitoring (FLASH) devices has changed diabetes management. Besides information on actual glucose levels and glucose trends rt-CGM and FLASH devices nowadays offer alarm features and allow assessment of other aspects of glucose regulations such as time in range (TIR), time above range (TAR), and time below range (TBR) [1]. Several studies demonstrated improvement of HbA1c among persons with type 1 and type 2 diabetes (T1DM and T2DM) after initiation of FLASH, as compared to conventional fingerstick blood glucose monitoring [2–5], with the most pronounced HbA1c decline in patients with suboptimal glycemic regulation prior to FLASH initiation [2,3,6]. Next to glycemic regulation [7], FLASH initiation has been associated with improved quality of life [2,8,9], less diabetes-distress [3,10], less diabetes-related work absenteeism [9], fewer hospital admissions [9,11,12] and reduced hypoglycemic unawareness [3].

As adjunct to HbA1c, evaluation of glycemic regulation in clinical practice is increasingly based on times spent in different CGM-based

Abbreviations: CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; eHbA1c, estimated HbA1c; FLASH, flash glucose monitoring; IQR, Interquartile Range; MDI, multiple daily injections; rt-CGM, real time Continuous Glucose Monitoring; SMBG, self-monitoring of blood glucose; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range.

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https://doi.org/10.1016/j.diabres.2023.110735
Received 9 February 2023; Received in revised form 5 May 2023; Accepted 30 May 2023
Available online 3 June 2023

glycemic target ranges [13,14]. There is growing evidence relating time in range (TIR, the percentage of time with glucose values between 3.9 and 10 mmol/L) to diabetes-related long-term micro- and macrovascular complications in T1DM and T2DM [15–18]. Improvements in TIR and reduced times spent above and below target ranges have been observed in FLASH and rt-CGM users with T1DM and T2DM [5,19–21].

To date, real-life data about the longer-term effects of FLASH use on glycemic regulation based on times spent in CGM-based glycemic target ranges [13] in persons with T1DM and T2DM with a glycemic regulation outside the internationally defined glycemic target ranges is lacking. The present study aims to evaluate real-life 24-week changes of glycemic metrics among European FLASH users, comparing groups of persons with T1DM and T2DM with different treatment modalities who do not meet the internationally defined glycemic targets [13].

2. Materials and methods

2.1. Study design and aims

This is a retrospective longitudinal analysis of data from European FLASH users (mostly living in Germany, Supplementary Table S3), obtained in the period 2014 to 2021. The aim was to evaluate the baseline glycemic parameters among four groups: persons with (I) T1DM on basal-bolus insulin (combined data of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII)), (II) T2DM on basal-bolus insulin (ibid), (III) T2DM with basal insulin only, and (IV) T2DM with no insulin treatment. Next, in these four different treatment groups, subgroup analyses of 24-week changes were performed in persons with initial suboptimal glycemic regulation (time in range (TIR, 3.9–10 mmol/L) $< 70\%$, time above range (TAR, >10 mmol/L) $> 25\%$, or time below range (TBR, <3.9 mmol/L) $> 4\%$) at FLASH initiation (i.e., during use of the first sensor). Due to the subgroup definition as described above, it should be noted that in the subgroup analyses FLASH users could be included more than once in the analyses (e.g., when showing both a TIR $< 70\%$ and a TAR $> 25\%$).

2.2. Data collection

In 2014 the FreeStyle Libre® Flash Glucose Monitoring System (Abbott Diabetes Care, Witney, UK) was introduced. The sensor is placed on the back of the upper arm and can be worn for 14 days. A dedicated reader or a smartphone app is used to scan the sensor to collect the current glucose level, the trend in glucose levels, and the last 8 h history of glucose levels. Every 15 min glucose readings are automatically stored on the sensor. The mean absolute relative difference (MARD), a measure of accuracy, of the FreeStyle Libre 2 system is 9.2% [22]. This study only included data collected via the sensor-specific reading device, not via the smartphone app. When a reader was connected to personal computer-based software with an internet connection, the 90-day memory of the reader was de-identified and uploaded to a database. The report software, that is available as a free download, includes an agreement that de-identified data will be collected at each internet-connected use of the software [23].

Within this database, anonymized information on the use of scanning devices, connected sensors and the country-level IP address was accumulated. In 2019 additional information about the age category (reported in 10-year batches and only including subjects 18 years and older), gender, type of diabetes, diabetes duration, diabetes treatment and micro- and macrovascular complications was obtained via a voluntary online questionnaire. All users of the desktop reporting software were invited to fill out this questionnaire via a notification. Only persons ≥ 18 years old who completed this questionnaire were included in this study. Further inclusion criteria were: persons with T1DM using basal-bolus insulin therapy (either MDI or CSII), as well as persons with T2DM using basal-bolus insulin therapy (either MDI or CSII), basal insulin or a non-insulin treatment, who consecutively had used 12 sensors paired with one reading device. There were no specific exclusion criteria.

Analyses of glycemia were performed based on all the data that were uploaded. To be included in the longitudinal analyses it was required for each sensor to have had at least 120 operational hours. Data from all sensors belonging to the same reader were combined. The following measures of glycemia were used: mean glucose, eHbA1c, TIR (glucose between 3.9 and 10 mmol/L), TAR (glucose > 10 mmol/L), time in level 2 hyperglycemia (glucose > 13.9 mmol/L), TBR (glucose < 3.9 mmol/L), time in level 2 hypoglycemia (glucose < 3.0 mmol/L), coefficient of variation (CV) and standard deviation (SD) of glucose [13]. eHbA1c is presented in NGSP units (%) and IFCC [mmol/mol]. The scanning frequency for each sensor was calculated by the number of scans divided by the duration of sensor use and expressed as numbers per day. Scanning frequency per reader was assessed by calculating the mean scan rate of all 12 sensors, followed by determining the cumulative frequency distribution and summary metrics (mean, median and interquartile range (IQR)).

2.3. Outcomes

Primary outcome was the difference in TIR between the first sensor (first 2 weeks of FLASH) and the twelfth sensor (week 22 to 24). As secondary outcomes the 24-week change in eHbA1c, TAR, time in level 2 hyperglycemia, TBR, time in level 2 hypoglycemia, glucose CV, glucose SD and the FLASH monitoring frequency was analyzed. The 24-week changes in these glycemic parameters were analyzed in the above-defined subgroups in the four treatment groups of persons with T1DM and T2DM with initial suboptimal glycemic regulation.

2.4. Statistical analysis

The database was analyzed by structured query language routines, the Python programming language (https://www.python.org), and the R statistical package (https://www.r-project.org). Normally distributed data were expressed as means and skewed distributed data as medians. For all data, the paired mean differences with 95% confidence intervals are provided since all paired differences were normally distributed. For analysis of the achievement rates, e.g. the percentage of FLASH users with a TIR $> 70\%$, the 95% confidence interval of the difference was calculated with a t-distribution. A correction for regression to the mean was applied to each subject. The regression to mean corrections were determined by simulating the expected measurement errors and applying them to the first sensor results [24]. The measurement errors were estimated by calculating the standard deviations of residuals from a regression trend during sensors 2 through 12 for each subject.

3. Results

Out of 13,734 FLASH users (7,505 T1DM and 6,229 T2DM) who completed the questionnaires and were eligible for inclusion, a total of 3,722 (1,909 T1DM and 1,813 T2DM) continued to have FLASH data available for at least 24 consecutive weeks. Baseline characteristics are presented in Table 1.

3.1. Type 1 diabetes

The 24-week changes in glycemic parameters during FLASH use by persons with T1DM, comparing the first and last FLASH sensor, are presented in Table 2. A TIR $< 70\%$ at initiation was observed in 63% of persons with T1DM. In this subgroup, improvements in eHbA1c (7.6% (59.2 mmol/mol) to 7.4% (57.3 mmol/mol), $p < 0.0001$), TIR (54% to 57%, $p < 0.0001$), TAR (41% to 37%, $p < 0.0001$), time in level 2 hyperglycemia (14% to 12%, $p < 0.0001$), TBR (4.1% to 3.7%, $p < 0.0001$), time in level 2 hypoglycemia (1.2% to 0.7%, $p < 0.0001$) and CV (38.9% to 37.7%, $p < 0.0001$) were observed over time. The FLASH

Table 1
Characteristics of FLASH users in Europe with type 1 or type 2 diabetes.

	Type 1 diabetes		Type 2 diabetes					
	Basal-bolus & CSII		Basal-bolus & CSII		Basal		Non-insulin	
	All	FLASH users with 12 sensors	All	FLASH users with 12 sensors	All	FLASH users with 12 sensors	All	FLASH users with 12 sensors
Number	7,505	1,909	4,983	1,499	726	189	520	125
Most prevalent age category (years)	55–64	55–64	65–74	65–74	65–74	65–74	55–64	55–64
18–24 years	359 (4.8%)	46 (2.4%)	3 (0.1%)	0	2 (0.3%)	0	0	0
25–34 years	699 (9.3%)	123 (6.4%)	27 (0.5%)	6 (0.4%)	6 (0.8%)	2 (1.1%)	5 (1.0%)	0
35–44 years	1,018 (13.6%)	183 (9.6%)	121 (2.4%)	21 (1.4%)	16 (2.2%)	2 (1.1%)	24 (4.6%)	6 (4.8%)
45–54 years	1,647 (21.9%)	394 (20.6%)	548 (11.0%)	157 (10.5%)	90 (12.4%)	17 (9.0%)	81 (15.6%)	12 (9.6%)
55–64 years	2,099 (28.0%)	596 (31.2%)	1,627 (32.7%)	426 (28.4%)	236 (32.5%)	61 (32.3%)	189 (36.3%)	46 (36.8%)
65–74 years	1,296 (17.3%)	436 (22.8%)	1,863 (37.4%)	611 (40.8%)	259 (35.7%)	66 (34.9%)	166 (31.9%)	41 (32.8%)
75 + years	387 (5.2%)	131 (6.9%)	794 (15.9%)	278 (18.5%)	117 (16.1%)	41 (21.7%)	55 (10.6%)	20 (16.0%)
Male (%)	65.1	68.5	85.0	87.5	83.3	87.8	89.6	88.8
Diabetes diagnosis past 5 years (%)	13.1	14.6	9.3	7.9	11.4	11.1	31.7	34.4
Diabetes diagnosed < 1 year ago	165 (2.2%)	50 (2.6%)	60 (1.2%)	15 (1.0%)	17 (2.3%)	5 (2.6%)	35 (6.7%)	7 (5.6%)
Diabetes diagnosed 1–5 years ago	821 (10.9%)	228 (11.9%)	403 (8.1%)	103 (6.9%)	66 (9.1%)	16 (8.5%)	130 (25.0%)	36 (28.8%)
Diabetes diagnosed 6–10 years ago	647 (8.6%)	143 (7.5%)	818 (16.4%)	243 (16.2%)	157 (21.6%)	32 (16.9%)	125 (24.0%)	28 (22.4%)
Diabetes diagnosed 11–15 years ago	717 (9.6%)	152 (8.0%)	1,045 (21.0%)	298 (19.9%)	171 (23.6%)	45 (23.8%)	109 (21.0%)	21 (16.8%)
Diabetes diagnosed 16–20 years ago	727 (9.7%)	137 (7.2%)	965 (19.4%)	291 (19.4%)	115 (15.8%)	27 (14.3%)	62 (11.9%)	16 (12.8%)
Diabetes diagnosed > 20 years ago	4,405 (58.7%)	1,196 (62.7%)	1,656 (33.2%)	540 (36.0%)	195 (26.9%)	64 (33.9%)	55 (10.6%)	17 (13.6%)
Unknown	23 (0.3%)	3 (0.2%)	36 (0.7%)	9 (0.6%)	5 (0.7%)	0	4 (0.8%)	0
≥1 micro- or macrovascular complication(s) (%)	36.4	40.4	62.6	64.7	61.2	61.9	45.7	48.2
Less than daily SMBG prior to FLASH (%)	4.0	5.2	4.8	4.8	13.9	15.3	36.2	47.2
Mean sensor use (days)		13.4		13.3		13.5		13.5

Abbreviations: CSII, continuous subcutaneous insulin infusion, SMBG, self-monitoring of blood glucose.

daily scan frequency decreased from 14 to 12 times ($p < 0.0001$).

A TAR > 25% at initiation was observed in 59% of persons. In these patients improvements in eHbA1c (7.7% (61.0 mmol/mol) to 7.5% (58.5 mmol/mol), $p < 0.0001$), TIR (53% to 57%, $p < 0.0001$), TAR (43% to 39%, $p < 0.0001$), time in level 2 hyperglycemia (15% to 12%, $p < 0.0001$), time in level 2 hypoglycemia (0.9% to 0.5%, $p = 0.003$) and CV (37.7% to 36.8%, $p < 0.0001$) were observed over time (Table 2).

>4% time in hypoglycemia was observed in 46% of persons at initiation of FLASH monitoring. In these patients improvements in TIR (65% to 66%, $p = 0.003$), TBR (8.5% to 6.6%, $p < 0.0001$), time in level 2 hypoglycemia (2.6% to 1.8%, $p < 0.0001$), and time in level 2 hyperglycemia (7.5% to 6.8%, $p = 0.0006$) were observed, whereas eHbA1c slightly increased from 6.6% (49.1 mmol/mol) to 6.7% (49.8 mmol/mol) ($p = 0.006$).

The 24-week changes in glycemic parameters in persons with T1DM on CSII versus MDI are presented in Supplementary Tables S1 and S2. The observed improvements in glycemic metrics were comparable to the overall group of persons with T1DM, except for the smaller group on CSII ($n = 190$) with > 4% TBR where no improvement in TIR, TAR or TBR was observed.

3.2. Type 2 diabetes

Changes over time in persons with T2DM subdivided by treatment modality are presented in Tables 3 and 4. A TIR < 70% at initiation was observed among 39% persons on basal-bolus insulin, 37% on basal insulin, and 17% non-insulin users (Table 3). Within the basal-bolus group improvements of eHbA1c (7.9% (63.4 mmol/mol) to 7.5% (58.6 mmol/mol), $p < 0.0001$), TIR (52% to 61%, $p < 0.0001$), TAR (46% to 37%, $p < 0.0001$), TBR (0.9% to 0.7%, $p = 0.006$) and CV (31% to 30%, $p < 0.0001$) were observed. In the basal insulin group, improvement of eHbA1c (8.2% (65.7 mmol/mol) to 7.6% (59.7 mmol/mol), $p = 0.007$), TIR (49% to 61%, $p < 0.0001$) and TAR (50% to 38%, $p < 0.0001$) was seen. In the small group of non-insulin users ($n = 21$) improvements of eHbA1c (7.9% (62.4 mmol/mol) to 7.1% (54.0 mmol/mol), $p = 0.02$), TIR (53% to 72%, $p = 0.003$) and TAR (45% to 27%, $p = 0.006$) were observed.

A TAR > 25% at initiation was observed among 44% of persons with T2DM on basal-bolus insulin, 43% on basal insulin, and 25% non-insulin users (Table 4). In patients with T2DM on basal-bolus insulin improvements of eHbA1c (7.9% (62.7 mmol/mol) to 7.5% (58.1 mmol/mol), $p < 0.0001$), TIR (54% to 63%, $p < 0.0001$) and TAR (44% to 36%, $p < 0.0001$) were observed. In the basal insulin group improvement of eHbA1c (8.0% (64.2 mmol/mol) to 7.6% (59.1 mmol/mol), $p = 0.001$), TIR (52% to 62%, $p = 0.0002$) and TAR (47% to 36%, $p = 0.0002$) was seen. In the non-insulin group improvements of TIR (59% to 71%, $p = 0.03$) and TAR (40% to 29%, $p = 0.03$) were observed. The mean scan frequency declined from 12 to 10 times daily in the basal-bolus insulin group ($p < 0.0001$), and from 10 to 9 times daily in the basal insulin

Table 2
Changes in glycemic parameters among persons with type 1 diabetes after 24 weeks of FLASH use by starting glycemic levels.

	Sensor 1 TIR < 70%			Sensor 1 TAR (>10 mmol/L) >25%			Sensor 1 TBR (<3.9 mmol/L) >4%		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Number of subjects	1,195	1,195		1,122	1,122		880	880	
Mean glucose (mmol/L)	9.5	9.2	**−0.3; p < 0.0001 (−0.36 to −0.2)**	9.7	9.4	**−0.4; p < 0.0001 (−0.44 to −0.28)**	8.0	8.1	**0.1; p = 0.006 (0.029 to 0.17)**
eHbA1c (%)	7.6	7.4	**−0.2; p < 0.0001 (−0.23 to −0.13)**	7.7	7.5	**−0.2; p < 0.0001 (−0.28 to −0.17)**	6.6	6.7	**0.1; p = 0.006 (0.02 to 0.11)**
eHbA1c (mmol/mol)	59.2	57.3	**−1.9; p < 0.0001 (−2.5 to −1.4)**	61.0	58.5	**−2.5; p < 0.0001 (−3.01 to −1.9)**	49.1	49.8	**0.7; p = 0.006 (0.2 to 1.2)**
TIR 3.9–10.0 mmol/L (%)	53.5	57.3	**3.8; p < 0.0001 (3.09 to 4.52)**	53.3	57.1	**3.9; p < 0.0001 (3.12 to 4.61)**	64.7	65.7	**0.9; p = 0.003 (0.29 to 1.54)**
CV (%)	38.9	37.7	**−1.3; p < 0.0001 (−1.59 to −0.93)**	37.7	36.8	**−1; p < 0.0001 (−1.28 to −0.62)**	41.0	38.8	**−2.2; p < 0.0001 (−2.54 to −1.8)**
Glucose SD (mmol/L)	65.5	61.9	**−3.7; p < 0.0001 (−4.3 to −3.02)**	65.6	61.8	**−3.8; p < 0.0001 (−4.5 to −3.13)**	59.6	56.9	**−2.7; p < 0.0001 (−3.4 to −2)**
Time < 3.0 mmol/L (%)	1.2	0.7	**−0.4; p < 0.0001 (−0.57 to −0.231)**	0.9	0.5	**−0.2; p = 0.003 (−0.34 to −0.07)**	2.6	1.8	**−0.64; p < 0.0001 (−0.88 to −0.41)**
Time < 3.9 mmol/L (%)	4.1	3.7	**−0.5; p < 0.0001 (−0.8 to −0.22)**	3.2	2.9	−0.04; p = 0.73 (−0.28 to 0.2)	8.5	6.6	**−1.4; p < 0.0001 (−1.84 to −1.01)**
Time > 10.0 mmol/L (%)	40.6	37.1	**−3.5; p < 0.0001 (−4.3 to −2.7)**	42.6	38.5	**−4.1; p < 0.0001 (−4.9 to −3.2)**	25.4	25.8	0.4; p = 0.30 (−0.3 to 1.1)
Time > 13.9 mmol/L (%)	13.8	11.6	**−2.2; p < 0.0001 (−2.8 to −1.7)**	14.5	12.0	**−2.4; p < 0.0001 (−3.01 to −1.9)**	7.5	6.8	**−0.7; p = 0.0006 (−1.1 to −0.3)**
Subjects with TIR > 70% (%)	8.5	17.2	**8.6; p < 0.0001 (8.6 to 8.7)**	10.0	17.6	**7.6; p < 0.0001 (7.6 to 7.7)**	36.6	39.1	**2.5; p < 0.0001 (2.5 to 2.5)**
Subjects with time < 3.0 mmol/L < 1% (%)	46.1	57.2	**11.1; p < 0.0001 (11.1 to 11.2)**	53.6	64.4	**10.9; p < 0.0001 (10.9 to 10.9)**	21.5	36.3	**14.7; p < 0.0001 (14.7 to 14.8)**
Subjects with time < 3.9 mmol/L < 4% (%)	48.9	52.6	**3.7; p < 0.0001 (3.7 to 3.7)**	57.6	60.2	**2.6; p < 0.0001 (2.5 to 2.6)**	11.9	26.0	**14.1; p < 0.0001 (14.1 to 14.1)**
Subjects with time > 10 mmol/L < 25% (%)	15.9	23.3	**7.5; p < 0.0001 (7.5 to 7.5)**	9.5	19.5	**10; p < 0.0001 (9.98 to 10.03)**	51.1	51.0	**−0.1; p = 0.0007 (−0.1 to −0.1)**
Subjects with time > 13.9 mmol/L < 5% (%)	20.4	31.0	**10.5; p < 0.0001 (10.5 to 10.55)**	17.3	29.1	**11.8; p < 0.0001 (11.8 to 11.83)**	47.2	54.2	**7; p < 0.0001 (7 to 7.05)**
Daily scans (number/day)	14.0	12.4	**−1.6; p < 0.0001 (−1.9 to −1.3)**	14.2	12.6	**−1.6; p < 0.0001 (−2 to −1.3)**	14.9	13.3	**−1.6; p < 0.0001 (−2 to −1.2)**

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided.
Significant outcome presented in bold (p < 0.05).
Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c;TIR, time in range; SD, standard deviation.

group (p = 0.02).

4. Discussion

Overall, these real-life data indicate that continuous FLASH use is associated with improvement of glycemic parameters in most of the users. Improvements were observed in both type 1 and type 2 diabetes in the subgroups with different types of suboptimal glycemic regulation.

An important observation with regards to the subgroup with T1DM and a TIR < 70% is the concurrent improvement of TIR, time in hyperglycemia, time in hypoglycemia, and CV. This indicates more stable glucose levels after 24 weeks of FLASH. In the T1DM subgroup with > 4% TBR, the initial eHbA1c was much lower (49.1 mmol/L (6.6%)) compared to the other subgroups (<70% TIR and > 25% TAR). After 24 weeks of FLASH, less time in hypoglycemia and level 2 hyperglycemia but a small increase in eHbA1c and decrease in TIR was observed. To the best of our knowledge, these are the first real-life data that confirm that FLASH leads to significant reduction of time spent in hypoglycemia without clinically relevant worsening of (e)HbA1c in T1DM [25,26]. As spending time in hypoglycemia is associated with many risks, a diminished quality of life, and adverse clinical outcomes, the observed decrease of time in hypoglycemia is of relevance for patients with T1DM [27,28]. In the recently published FLASH-UK randomized controlled trial among persons with T1DM and a higher HbA1c at baseline (mean 8.7%±0.9% (72 ± 10 mmol/mol), 24-weeks (second generation) FLASH use was associated with improvement of HbA1c, TIR, TAR, TBR and CV, compared to fingerstick testing [5]. The improvements in TIR (43% to 52%) and TAR (50% to 45%) were more pronounced in their study, presumably because of the higher baseline values, as compared to the subgroup with T1DM and TAR > 25% in our study. Further, due to the real-life nature of our data, the magnitude of changes in glycemic parameters could well be diminished compared to changes observed in clinical trial settings since the present study lacks a pre-utilization comparison to establish baseline measures.

Concerning T2DM, there are several observations noteworthy. First, in persons on basal-bolus insulin with an initial TIR < 70% time in hypoglycemia decreased while improvements in eHbA1c, TIR, and time in hyperglycemia were observed. In a previous RCT setting FLASH initiation in T2DM patients using basal-bolus insulin led to less time in hypoglycemia but no significant change in TIR, time in hyperglycemia and

Table 3
Changes in glycemic parameters after 24 weeks of FLASH use among persons with type 2 diabetes with different treatment modalities who started with a TIR < 70% during sensor 1.

	Basal-bolus			Basal			Non-insulin		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Number of subjects	588	588		70	70		21	21	
Mean glucose (mmol/L)	10.1	9.4	**−0.7; p < 0.0001 (−0.83 to −0.57)**	10.4	9.5	**−0.9; p = 0.0007 (−1.38 to −0.39)**	9.9	8.7	**−1.2; p = 0.02 (−2.21 to −0.24)**
eHbA1c (%)	7.9	7.5	**−0.4; p < 0.0001 (−0.52 to −0.36)**	8.2	7.6	**−0.55; p = 0.0007 (−0.87 to −0.24)**	7.9	7.1	**−0.77; p = 0.02 (−1.39 to −0.15)**
eHbA1c (mmol/mol)	63.4	58.6	**−4.8; p < 0.0001 (−5.66 to −3.9)**	65.7	59.7	**−6.1; p = 0.0007 (−9.46 to −2.66)**	62.4	54.0	**−8.41; p = 0.02 (−15.19 to −1.64)**
TIR 3.9–10.0 mmol/L (%)	51.7	61.0	**9.3; p < 0.0001 (7.84 to 10.77)**	48.6	60.7	**12.1; p < 0.0001 (6.63 to 17.5)**	52.7	72.2	**19.5; p = 0.003 (7.62 to 31.47)**
CV (%)	31.0	30.0	**−1; p < 0.0001 (−1.39 to −0.54)**	30.3	29.2	−1.09; p = 0.11 (−2.44 to 0.25)	29.0	25.5	**−3.5; p = 0.03 (−6.71 to −0.31)**
Glucose SD (mmol/L)	55.6	50.5	**−5.1; p < 0.0001 (−6 to −4.16)**	55.7	50.1	**−5.6; p = 0.001 (−9.02 to −2.27)**	50.6	39.9	**−10.7; p = 0.003 (−17.21 to −4.2)**
Time < 3.0 mmol/L (%)	0.2	0.0	**−0.27; p = 0.0006 (−0.43 to −0.12)**	0.2	0.0	−0.3; p = 0.07 (−0.56 to 0.02)	0.1	0.0	−0.6; p = 0.13 (−1.33 to 0.19)
Time < 3.9 mmol/L (%)	0.9	0.7	**−0.4; p = 0.006 (−0.76 to −0.13)**	0.8	0.4	−0.5; p = 0.10 (−1.04 to 0.09)	0.7	0.0	−1.7; p = 0.13 (−3.99 to 0.55)
Time > 10.0 mmol/L (%)	46.3	37.2	**−9.2; p < 0.0001 (−10.7 to −7.6)**	49.7	37.6	**−12.1; p < 0.0001 (−17.6 to −6.6)**	45.3	27.0	**−18.3; p = 0.006 (−30.7 to −5.9)**
Time > 13.9 mmol/L (%)	13.6	9.4	**−4.2; p < 0.0001 (−5.1 to −3.2)**	16.0	10.1	**−5.9; p = 0.008 (−10.2 to −1.6)**	10.7	4.5	**−6.2; p = 0.04 (−12.1 to −0.3)**
Subjects with TIR > 70% (%)	10.6	33.7	**23.1; p < 0.0001 (23.1 to 23.1)**	10.3	34.3	**24; p < 0.0001 (23.9 to 24.1)**	9.3	66.7	**57.3; p < 0.0001 (57.1 to 57.5)**
Subjects with time < 3.0 mmol/L <1% (%)	82.9	88.6	**5.7; p < 0.0001 (5.7 to 5.8)**	83.3	90.0	**6.7; p < 0.0001 (6.7 to 6.8)**	85.0	100.0	**15; p < 0.0001 (14.8 to 15.2)**
Subjects with time < 3.9 mmol/L <4% (%)	85.4	87.9	**2.5; p < 0.0001 (2.5 to 2.6)**	83.4	88.6	**5.1; p < 0.0001 (5.1 to 5.2)**	84.7	90.5	**5.8; p < 0.0001 (5.6 to 6)**
Subjects with time > 10.0 mmol/L <25% (%)	8.4	28.1	**19.6; p < 0.0001 (19.6 to 19.7)**	7.5	30.0	**22.5; p < 0.0001 (22.4 to 22.6)**	9.4	57.1	**47.7; p < 0.0001 (47.5 to 48)**
Subjects with time > 13.9 mmol/L <5% (%)	24.2	44.9	**20.7; p < 0.0001 (20.7 to 20.7)**	20.6	45.7	**25.16; p < 0.0001 (25 to 25.3)**	29.0	66.7	**37.6; p < 0.0001 (37.3 to 38)**
Daily scans (number/day)	12.0	10.3	**−1.7; p < 0.0001 (−2.2 to −1.2)**	9.5	8.5	−1; p = 0.13 (−2.2 to 0.3)	13.0	10.6	−2.5; p = 0.15 (−5.9 to 1)

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided.
Significant outcome presented in bold (p < 0.05).
Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c; TIR, time in range; SD, standard deviation.

HbA1c after a 12 month period [29]. Differences in study results may be explained by a higher number of participants in the present study and by differences in study design. Also, subgroup analyses in the RCT might have identified subgroups with different patterns of improvement in glycemic parameters.

Second, in previous studies among persons using basal insulin [30,31] HbA1c improvement after FLASH initiation was observed. The present study adds to these studies by demonstrating improvements in different sensor-derived glycemic target ranges. Third, in the subgroup of persons with T2DM without insulin treatment and suboptimal glycemic regulation (TIR < 70%, n = 21; or TAR > 25%, n = 31, with overlap) significant improvement of eHbA1c, TIR and TAR was observed. Although these findings should be interpreted with caution given the small number of patients, we suggest that FLASH use may be of benefit for persons with T2DM without insulin treatment for those with suboptimal glucose regulation. Apparently, FLASH contributes to a greater understanding of how food, physical activity and stress affect blood glucose levels which in turn may lead to improved self-care behavior, quality of life and adequate lifestyle measures to improve glycemic metrics [32 33].

The highest scanning frequency in our study was observed among the subgroup of persons with T1DM and > 4% TBR, who had the highest TIR and an eHbA1c < 7% (<53 mmol/mol). Previous research also showed an association between higher glucose monitoring frequency with FLASH and improvement of eHbA1c, TIR, time in hyperglycemia and a lower glycemic variability in patients with diabetes [34,35]. At this stage we cannot add much to these observations, except that the occurrence of hypoglycemia is associated with a higher monitoring frequency. Whether this higher frequency is associated with a proactive stance (i.e., frequent checks to prevent or diminish hypoglycemic

Table 4
Changes in glycemic parameters after 24 weeks of FLASH use among persons with type 2 diabetes with different treatment modalities who started with a TAR (>10 mmol/L) > 25%.

	Basal-bolus			Basal			Non-insulin		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Number of subjects	667	667		82	82		31	31	
Mean glucose (mmol/L)	10.0	9.3	**−0.7; p < 0.0001 (−0.78 to −0.55)**	10.2	9.4	**−0.7; p = 0.001 (−1.2 to −0.29)**	9.7	8.9	−0.7; p = 0.08 (−1.55 to 0.08)
eHbA1c (%)	7.9	7.5	**−0.4; p < 0.0001 (−0.49 to −0.35)**	8.0	7.6	**−0.5; p = 0.001 (−0.76 to −0.18)**	7.7	7.2	−0.46; p = 0.08 (−0.98 to 0.05)
eHbA1c (mmol/mol)	62.7	58.1	**−4.6; p < 0.0001 (−5.38 to −3.79)**	64.2	59.1	**−5.1; p = 0.001 (−8.25 to −2.02)**	60.7	55.6	−5.05; p = 0.08 (−10.66 to 0.55)
TIR 3.9–10.0 mmol/L (%)	54.4	62.6	**8.2; p < 0.0001 (6.82 to 9.53)**	52.2	62.2	**10; p = 0.0002 (4.84 to 15.1)**	59.1	70.6	**11.4; p = 0.03 (1.4 to 21.5)**
CV (%)	30.2	29.4	**−0.8; p < 0.0001 (−1.15 to −0.4)**	29.5	28.6	−0.93; p = 0.13 (−2.15 to 0.29)	26.7	25.3	−1.4; p = 0.20 (−3.64 to 0.84)
Glucose SD (mmol/L)	54.0	49.2	**−4.7; p < 0.0001 (−5.55 to −3.88)**	53.5	48.6	**−4.9; p = 0.001 (−7.82 to −1.93)**	46.2	41.1	−5; p = 0.10 (−11.12 to 1.03)
Time < 3.0 mmol/L (%)	0.1	0.0	**−0.09; p = 0.03 (−0.18 to −0.01)**	0.1	0.0	−0.2; p = 0.06 (−0.49 to 0.003)	0.1	0.0	**−0.2; p = 0.02 (−0.34 to −0.04)**
Time < 3.9 mmol/L (%)	0.8	0.5	0; p = 0.68 (−0.23 to 0.15)	0.7	0.2	−0.4; p = 0.08 (−0.89 to 0.05)	0.5	0.0	−0.8; p = 0.13 (−1.82 to 0.25)
Time > 10.0 mmol/L (%)	44.4	35.9	**−8.5; p < 0.0001 (−9.9 to −7)**	46.5	36.4	**−10; p = 0.0002 (−15.2 to −4.9)**	40.0	28.8	**−11.3; p = 0.03 (−21.5 to −1.1)**
Time > 13.9 mmol/L (%)	12.4	8.8	**−3.7; p < 0.0001 (−4.5 to −2.8)**	14.1	9.5	**−4.6; p = 0.02 (−8.4 to −0.7)**	8.0	5.9	−2.1; p = 0.41 (−7.3 to 3.04)
Subjects with TIR > 70% (%)	17.9	38.2	**20.3; p < 0.0001 (20.3 to 20.4)**	18.4	36.6	**18.2; p < 0.0001 (18.1 to 18.4)**	27.1	64.5	**37.4; p < 0.0001 (37.2 to 37.7)**
Subjects with time < 3.0 mmol/L <1% (%)	87.8	91.2	**3.4; p < 0.0001 (3.4 to 3.4)**	86.5	92.7	**6.2; p < 0.0001 (6.1 to 6.3)**	92.5	100.0	**7.5; p < 0.0001 (7.5 to 7.6)**
Subjects with time < 3.9 mmol/L <4% (%)	90.4	90.1	**−0.3; p < 0.0001 (−0.3 to −0.3)**	86.9	91.5	**4.6; p < 0.0001 (4.5 to 4.6)**	91.8	93.5	**1.7; p < 0.0001 (1.6 to 1.8)**
Subjects with time > 10.0 mmol/L <25% (%)	10.6	31.5	**20.9; p < 0.0001 (20.8 to 20.9)**	11.8	32.9	**21.2; p < 0.0001 (21.1 to 21.3)**	16.1	54.8	**38.8; p < 0.0001 (38.6 to 39)**
Subjects with time > 13.9 mmol/L <5% (%)	29.5	48.3	**18.7; p < 0.0001 (18.7 to 18.79)**	28.3	48.8	**20.45; p < 0.0001 (20.3 to 20.6)**	45.7	67.7	**22; p < 0.0001 (21.8 to 22.3)**
Daily scans (number/day)	12.0	10.3	**−1.7; p < 0.0001 (−2.2 to −1.3)**	10.0	8.6	**−1.3; p = 0.02 (−2.4 to −0.2)**	12.1	9.8	−2.3; p = 0.07 (−4.7 to 0.2)

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided.
Significant outcome presented in bold (p < 0.05).
Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c; TIR, time in range; SD, standard deviation.

episodes) or a reactive stance (i.e. frequent checks as soon as hypoglycemia is present) is unknown.

In addition to the existing literature, the present study provides information about the impact of FLASH use in groups with different treatment modalities and different types of suboptimal glycemic regulation. Whether the observed improvements in glycemic metrics eventually translate into relevant differences in outcomes merits further study. In the present work there is – in line with other reports on CGM metrics – focus on TIR as measure of glycemic control. Recent work by Rodbard et al. [36] suggests that TAR (instead of TIR) is more valuable as a substitute for glucose control. In the present study TAR also improved in all subgroups.

Limitations include the real-life observational nature of the study with the lack of a comparator group, but strengths include having a greater number of patients. In total 3,722 out of 13,734 persons (27%) continuously used FLASH for 24 weeks, as was recorded by sequential use of 12 sensors paired with the same reader. Information about the reasons for lack of continued data uploading, discontinuation of FLASH use or the lack of consistent use of FLASH could not be obtained, because of the anonymous nature of the data. Hypothetically, persons who continued FLASH for 24 weeks might be more motivated to make thorough use of the system because of the experienced benefits and this potentially resulted in selection bias. Also, differences in reimbursement for FLASH between healthcare systems in Europe should be taken into account: as FLASH use is not reimbursed for non-insulin users in Europe, this group of FLASH users must have paid the costs of FLASH themselves, which likely have led to selection of persons with type 2 diabetes and a high motivation to make optimal use the device including more frequent glucose checks. Another notable observation is the high percentage of male FLASH users with T2DM. Although T2DM is more common among middle aged men than women, this percentage was higher than might be expected [37,38], possibly because men had more resources to start FLASH (on their own costs) [39]. Due to the anonymous nature of the database used for this study, detailed information concerning characteristics of FLASH users, including socioeconomic factors, available income, lifestyle data (e.g., carbohydrate intake and exercise patterns) and BMI was unavailable. Information about use of oral glucose lowering medication is lacking, as it was not included in the questionnaire. Furthermore, we do not have information on aspects of the health status of persons with diabetes that are relevant to their quality of life, in terms of patient-reported outcome measures (PROMs) or patient-reported experience measures (PREMs) [40]. Lastly, it should be noted that sensor derived estimates of the eHbA1c does not always closely approximate a laboratory measured HbA1c [41]. eHbA1c was calculated using the linear regression formula presented by the ADAG Study group [42].

5. Conclusions

The findings of this study extends existing literature about the effects of FLASH use on various measures of glycemic regulation, by providing data regarding the effects of FLASH use among groups with different treatment modalities and subgroups with different types of glycemic dysregulation. The findings suggest that use of FLASH for 24 weeks by persons with T1DM and T2DM is associated with an improvement of glycemic parameters in the majority of analyses. More data is needed on persons with T2DM without insulin use to allow firmer conclusions for that specific group.

Data availability statement

Data are available upon reasonable request and with permission by the authors.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Initial study design was by TCD, HJGB, PRD, and AL. Data collection and statistical analysis was performed by employees of Abbott Diabetes Care (TCD, KK, YX). Further detailing after the original study design was possible in cooperation of the above named and ROBG, and JB. All authors contributed to the interpretation of the results and in writing the manuscript. This work was partly funded by the University Medical Center Groningen (Department of Internal Medicine) and partly by Abbott Diabetes Care (the last part being in the form of an unconditional research grant).

Data availability statement

Data are available upon reasonable request and with permission by the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110735.

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