1-20-2022

Flash glucose monitoring in type 2 diabetes managed with basal insulin in the USA: a retrospective real-world chart review study and meta-analysis.

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BMJ Open Diabetes Research & Care

Flash glucose monitoring in type 2 diabetes managed with basal insulin in the USA: a retrospective real-world chart review study and meta-analysis

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To cite: Carlson AL, Daniel TD, DeSantis A, *et al*. Flash glucose monitoring in type 2 diabetes managed with basal insulin in the USA: a retrospective real-world chart review study and meta-analysis. *BMJ Open Diab Res Care* 2022;**10**:e002590. doi:10.1136/bmjdrc-2021-002590

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2021-002590).

Received 9 September 2021
Accepted 10 December 2021

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ABSTRACT

Introduction Evidence supporting use of continuous glucose monitoring in type 2 diabetes treated with basal insulin is unclear. This real-world study aimed to assess the impact on glycated hemoglobin (HbA1c) of flash glucose monitoring use in adults with type 2 diabetes managed with basal insulin.

Research design and methods Medical records were reviewed for adult individuals with type 2 diabetes using basal insulin for ≥1 year with or without additional antihyperglycemic medication, HbA1c 8.0%–12.0% prior to FreeStyle Libre Flash Glucose Monitoring use for ≥90 days and an HbA1c measurement recorded between 90 and 194 days after device use. Exclusion criteria included utilization of bolus insulin. Meta-analysis data are from the current study (USA) and a similar Canadian cohort.

Results Medical record analysis (n=100) from 8 USA study sites showed significant HbA1c decrease of 1.4%±1.3%, from 9.4%±1.0% at baseline to 8.0%±1.2% after device use, p<0.0001 (mean±SD).

Meta-analysis of medical records from USA and Canada sites (n=191) showed HbA1c significantly decreased by 1.1%±0.14% (mean±SE), from baseline 9.2%±1.0% to 8.1%±1.1%, p≤0.0001, with moderate to high heterogeneity between sites (Q=43.9, I^2=74.9, p<0.0001) explained by differences in baseline HbA1c between sites. The HbA1c improvement in both groups was observed by age group, body mass index, duration of insulin use and sex at birth.

Conclusions In a real-world retrospective USA study and a meta-analysis of a larger USA and Canada cohort, HbA1c significantly reduced in basal insulin-treated type 2 diabetes, without bolus insulin initiation and following the commencement of flash glucose monitoring technology.

Significance of this study

What is already known about this subject?

- To date, the reported benefit of continuous glucose monitoring (CGM) use in type 2 diabetes is largely limited to intensive insulin regimens.
- Evidence supporting use of this type of glucose monitoring technology to support management of a basal insulin regimen is limited.

What are the new findings?

In this real-world observational review study in the USA and meta-analysis of a larger USA and Canada cohort:

- Glycated hemoglobin (HbA1c) significantly reduced in both groups 3–6 months after commencing flash glucose monitoring technology use in type 2 diabetes treated with basal insulin and without initiating bolus insulin.
- HbA1c reduction is supported by the sensitivity analysis demonstrating consistent HbA1c values.
- HbA1c improvement was observed in both groups by age group, body mass index, duration of insulin use and sex at birth; over half of the participants had a final HbA1c <8%.

How might these results change the focus of research or clinical practice?

- HbA1c is the gold standard clinical marker used to demonstrate improved glycemic control.
- This finding may suggest that the use of CGM in type 2 diabetes treated with basal insulin has the potential to be a valuable tool to support the improvement of glucose control.

INTRODUCTION

The American Diabetes Association (ADA) recognizes that glycemic management is primarily assessed by glycated hemoglobin (HbA1c) measurements.[1] HbA1c has been the principal clinical marker used in clinical trials to demonstrate the benefits of improved glycemic management.[1] In regard to continuous glucose monitoring (CGM), the ADA acknowledges that this technology has an important role in glucose management for diabetes and notes that the reported benefit of CGM in type 2 diabetes is to date largely limited to its use with intensive insulin regimens.[2] While there is increasing evidence to support CGM use in this population,[3–6] reported evidence of CGM use to support management of a basal insulin regimen is more limited.[7–11] The aim of this real-world study was to evaluate the impact on HbA1c

after the introduction of flash glucose monitoring use in type 2 diabetes managed with basal insulin in diabetes centers in the USA. Analysis of a larger cohort combining data from the USA and Canada is also reported.

MATERIALS AND METHODS

The methodology and population of the current study are analogous to those described by Elliott *et al*.[10] The current retrospective non-interventional single-arm chart review study was conducted in diabetes centers in the USA. The clinics each performed a database search for potential medical records to be included in the review. Paper or electronic medical records were included for adult individuals (18 years or more) with type 2 diabetes managed with analogue or isophane basal insulin therapy for 1 year or more, with or without additional oral anti-hyperglycemic medication and non-insulin injection therapy, the FreeStyle Libre Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, California, USA) had been used for at least 90 days when the data were collected, an HbA1c measurement between 8.0% and 12.0% was recorded in the medical notes within 90 days before device use commenced and an HbA1c measurement was recorded >90 and <194 days after initiation of device use. The definition of a baseline HbA1c was a result recorded not more than 90 days before device use commenced (the index date). If additional baseline HbA1c measurements were available, the one nearest to the index date was used. The definition of a follow-up HbA1c measurement was a result recorded not less than 90 and no more than 194 days after the index date. If additional follow-up HbA1c measurements were available, the measurement closest to the index date plus 135 days was used. All HbA1c measurements used in the analysis had been recorded in the medical records and were from a laboratory or point-of-care test. In addition to baseline HbA1c concentrations, the study sites also extracted information that had been recorded in the medical records prior to initiation of device use for age, blood pressure, concomitant disease, complications of diabetes, time using insulin, height, glucose-lowering medications, sex and weight.

Medical records were not eligible for inclusion in the study for anyone who was using bolus or biphasic insulin, pregnant, undergoing dialysis therapy or was a participant in another study that might impact their glucose results or management during use of the device.

Analysis of the extracted data from the medical records established final eligibility for inclusion in the analysis.

Additional data for the meta-analysis were from a retrospective non-interventional single-arm chart review study in Canada, as noted above.[10]

Outcomes

The primary end point for the current study and the meta-analysis was evaluation of change in HbA1c from the index date to a follow-up HbA1c measurement taken after device use was commenced (between 90 and 194 days after). Analysis of the primary end point was also performed for the subgroups: age (<65 and ≥65 years), HbA1c at baseline (<9% and ≥9%), body mass index (BMI (<30 and ≥30 kg/m^2)), duration of insulin use (<4 and ≥4 years), rate of daily blood glucose testing and sex at birth. As this was a retrospective chart review study, safety and adverse event information were not collected.

Statistical analysis

A paired t-test was used to assess differences between HbA1c measurements recorded 90 to 194 days after starting device use and at baseline. A total of 78 medical records are needed to detect a change in HbA1c of 0.35% (3.8 mmol/mol) within each country with a power of 80% (at $p<0.05$), based on an SD of change in HbA1c of 1.1%.[12] For the primary end point, if more than one HbA1c test fulfilled the criteria then the test nearest to the device start date +135 days was used. Meta-analysis of change in HbA1c was performed using a random effects model on patient record level data, using center as a random effect. Cochran's heterogeneity statistic (Q) and the I^2 statistic were calculated.[13] A meta-regression analysis was performed on baseline HbA1c with center as a random effect. Subgroups were compared using analysis of covariance on baseline HbA1c. Qualified statisticians at Abbott Diabetes Care (UK) performed the data analysis using V.9.4 of SAS (or higher).

RESULTS

The USA chart review data were extracted from medical records between November 2017 and July 2020. A total of 131 medical records from both primary care (Internal Medicine and Family Practice) and more specialist diabetes centers were identified by 8 study sites. Of these, 11 did not meet the inclusion criteria, 6 had a baseline HbA1c outside the stated range of 8.0%– 12.0%, 3 had not used basal insulin for at least 1 year prior to starting device use (or the duration was unknown) and 2 had bolus insulin therapy use recorded. In addition, 6 medical records did not have a baseline HbA1c within 90 days of starting device use, 12 medical records did not have a HbA1c result logged between 90 and 194 days after starting to use the device and 2 medical records had neither a baseline nor a final HbA1c result. The total number of medical records included in the USA primary end point analysis was 100.

The mean age at the start of device use was 56.0±10.3 years (mean±SD), baseline HbA1c was 9.4%±1.0% and 52 (52%) of medical records were for male individuals.

For the meta-analysis, a total of 234 medical records were identified by 14 study sites in the USA (n=8) and Canada (n=6) from November 2017 to July 2020. Fourteen medical records did not meet the eligibility criteria, 9 did not have a baseline HbA1c within 90 days of starting the device, 14 did not have an HbA1c result 90–194 days after starting the device and 3 did not have a baseline

Table 1 Demographics and baseline characteristics for the US and combined cohorts

		US cohort	Combined group cohort
N		n=100	n=191
Male n (%)		52 (52.0)	115 (60.2)
Female n (%)		48 (48.0)	76 (39.8)
Age (years)	Mean±SD	56.0±10.3	60.0±11.3
BMI (kg/m^2)	Mean±SD	36.1±7.8 (n=97)	33.5±8.2 (n=184)
Duration of insulin use (years)	Mean±SD	4.5±3.5	4.3±3.3
Baseline HbA1c (%)	Mean±SD	9.4±1.0	9.2±1.0
Baseline HbA1c (mmol/mol)	Mean±SD	79.2±11.1	76.8±10.7
Additional antihyperglycemic medications at time of starting flash glucose monitoring, n (%)	Any oral antihyperglycemic medication	96 (96.0)	183 (95.8)
	Metformin	82 (82.0)	151 (79.1)
	SGLT inhibitors	28 (28.0)	85 (44.5)
	Sulfonylureas	40 (40.0)	70 (36.6)
	DPP4 inhibitors	11 (11.0)	46 (24.1)
	Thiazolidinediones	4 (4.0)	5 (2.6)
	GLP1 agonists	56 (56.0)	100 (52.4)

BMI, body mass index; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide-1 receptor; HbA1c, glycated hemoglobin; SGLT, sodium-glucose cotransporter.

nor a final HbA1c result. Three records were retrospectively excluded as bolus insulin was used during the study period. The total number of medical records included in the meta-analysis was 191.

For the USA and Canda combined cohort, the mean age at start of device use was 60.0±11.3 years (mean±SD), baseline HbA1c was 9.2%±1.0% and 115 (60.2%) medical records were for male individuals. Baseline characteristics and demographics, and medical history from the medical records for both the USA cohort and the combined USA and Canada cohort are listed in tables 1 and 2, respectively.

Baseline characteristics for the Canada-only cohort are listed in online supplemental table S2.

Primary end point

In the current USA study, baseline HbA1c (mean±SD) significantly reduced between 90 and 194 days after starting device use by 1.4%±1.3% from 9.4%±1.0% to 8.0%±1.2%, p<0.0001 (figure 1 and online supplemental table S1).

In the meta-analysis of combined USA and Canada data, baseline HbA1c significantly reduced 90–194 days after starting device use by 1.1%±0.14% (mean±SE) from 9.2%±1.0% to 8.1%±1.1% (mean±SD), p≤0.0001 (figure 1 and online supplemental table S1). Moderate to high heterogeneity between centers (Q=43.9, I^2=74.9%, p<0.0001) was observed.

The meta-regression of change in HbA1c on baseline HbA1c showed a slope of −0.66%±0.078% per % baseline HbA1c (mean±SE) and low heterogeneity with an I^2 value of 1.6% (Cochran's Q=10.2, p=0.4267).

Sensitivity analysis

For the USA cohort, the mean number of days between initiation of device use (index date) and the final HbA1c value used in the analysis was 131.7 days (median 132.0). A sensitivity analysis was performed on the primary end point of change in HbA1c for different time windows of the final HbA1c value (121–149 days, 107–163 days and 90–180 days) and the change in HbA1c remained similar (p<0.0001 for all time windows, figure 2).

When baseline HbA1c measurements were compared with follow-up HbA1c measurements for each month of the 3–6 months period after device use was initiated (months 3–4, 4–5, 5–6 and 5.5–6.5), HbA1c change remained significant (figure 2).

Subgroup analysis

For the current USA study and the larger cohort of both countries combined, prespecified subgroup analysis showed HbA1c improvement by age group (<65 and ≥65 years), baseline HbA1c (<9% and ≥9%), BMI (<30 and ≥30 kg/m^2), duration of insulin use (<4 and ≥4 years) and sex at birth.

In the 2 countries combined cohort, there was a similar change in HbA1c between the subgroups for age (p=0.0900), BMI (p=0.2811), duration of insulin use (p=0.4057), blood glucose testing frequency (p=0.1495) or sex at birth (p=0.6966). All subgroup analysis results are shown in figure 3.

In the current USA study, recorded data for frequency of self-monitoring of blood glucose (prior to flash glucose monitoring use) were available from 55% (n=55/100) of the US medical records and 56% (n=107/191) of the USA and Canada group medical records (online supplemental table S1).

Table 2 Medical history at baseline for the US and combined cohorts

N (%)	US cohort n=100	Combined group cohort n=191
CVD complications	19 (19.0)	54 (28.3)
Myocardial infarction	4 (4.0)	16 (8.4)
Angina	6 (6.0)	25 (13.1)
Peripheral vascular disease	6 (6.0)	11 (5.8)
Stroke	4 (4.0)	9 (4.7)
Heart failure	3 (3.0)	6 (3.1)
Atrial fibrillation	0 (0.0)	5 (2.6)
Left ventricular hypertrophy	1 (1.0)	10 (5.2)
Renal complications	13 (13.0)	60 (31.4)
Microalbuminuria	12 (12.0)	57 (29.8)
Gross proteinuria	2 (2.0)	7 (3.7)
End-stage renal disease	1 (1.0)	1 (0.5)
Retinopathy complications	15 (15.0)	27 (14.1)
Background diabetic retinopathy	13 (13.0)	22 (11.5)
Proliferative diabetic retinopathy	3 (3.0)	5 (2.6)
Severe vision loss	0 (0.0)	1 (0.5)
Foot ulcer Complications	2 (2.0)	5 (2.6)
Uninfected ulcer	0 (0.0)	1 (0.5)
Infected ulcer	0 (0.0)	1 (0.5)
Healed ulcer	2 (2.0)	4 (2.1)
Amputation	0 (0.0)	1 (0.5)
Cataract	10 (10.0)	30 (15.7)
Macular oedema	5 (5.0)	5 (2.6)
Neuropathy	17 (17.0)	35 (18.3)
Depression	23 (23.0)	35 (18.3)

CVD, cardiovascular disease.

The majority of this subgroup reported testing twice per day or less (n=42/55 and n=89/107, respectively). Baseline HbA1c reduced by 1.4%±1.0% and 1.2%±1.1% (mean±SD), respectively, p<0.0001 for both groups. For more than 2 tests per day (n=13 and n=18), baseline HbA1c fell by 0.9%±1.5% (p=0.0579) in the USA group and by 1.0%±1.5% (p=0.0104) in the larger USA and Canada group.

Post hoc analysis demonstrated 56% (n=56/100) of USA participants had a final HbA1c <8%.

DISCUSSION

This USA retrospective chart review clinical study observed significant improvement in HbA1c 3–6 months after use of flash glucose sensor monitoring technology was commenced in individuals with type 2 diabetes managed with basal insulin. Bolus insulin initiation and use were not permitted either before or during the study. The unequivocal achievement of the primary end point

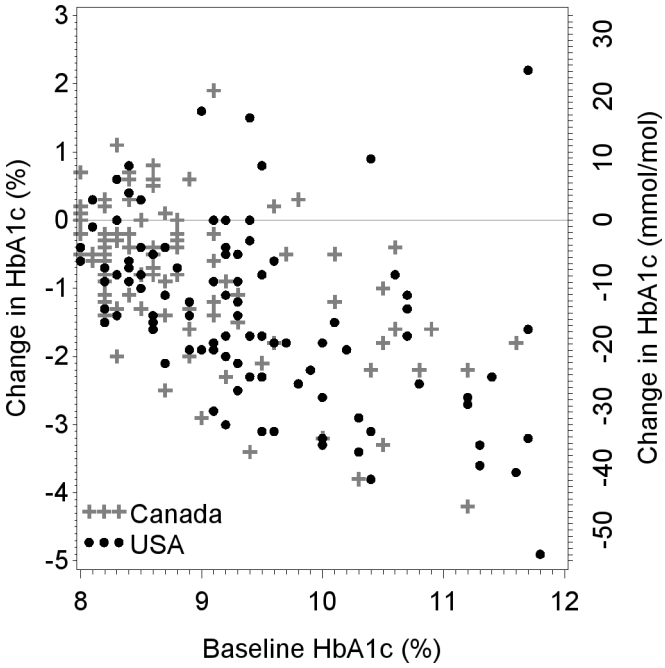

Figure 1 Change in glycated hemoglobin (HbA1c) (%) between baseline and at 3–6 months (90–194 days) after commencing flash glucose monitoring.

is supported by the observed HbA1c reduction in the larger meta-analysis cohort and the sensitivity analysis demonstrating consistent HbA1c values, which was also reported separately for the Canada cohort.[10]

The observed significant decrease in HbA1c in the USA cohort is supported by an earlier prospective randomized controlled trial in intermittent use of real-time CGM in

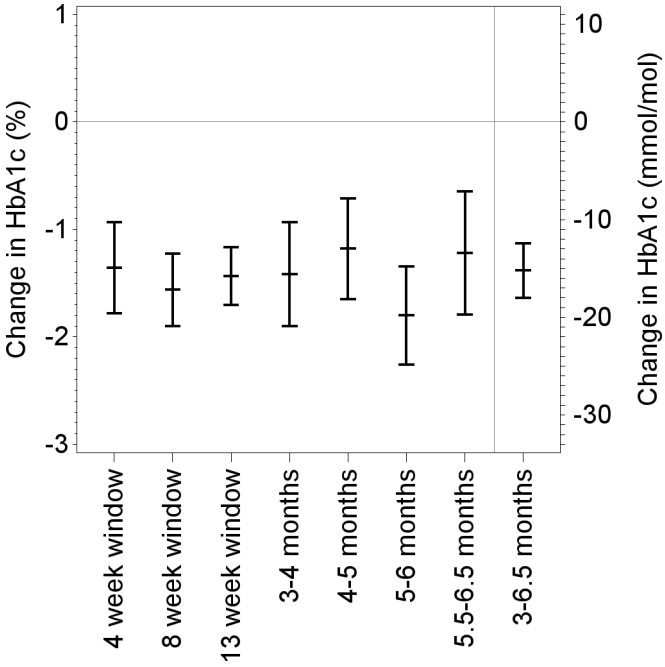

Figure 2 CI plot of change in glycated hemoglobin (HbA1c) (%) with narrower time windows around day 135 and change in HbA1c (%) for each month of the 3–6 months after commencing flash glucose monitoring for the US cohort.

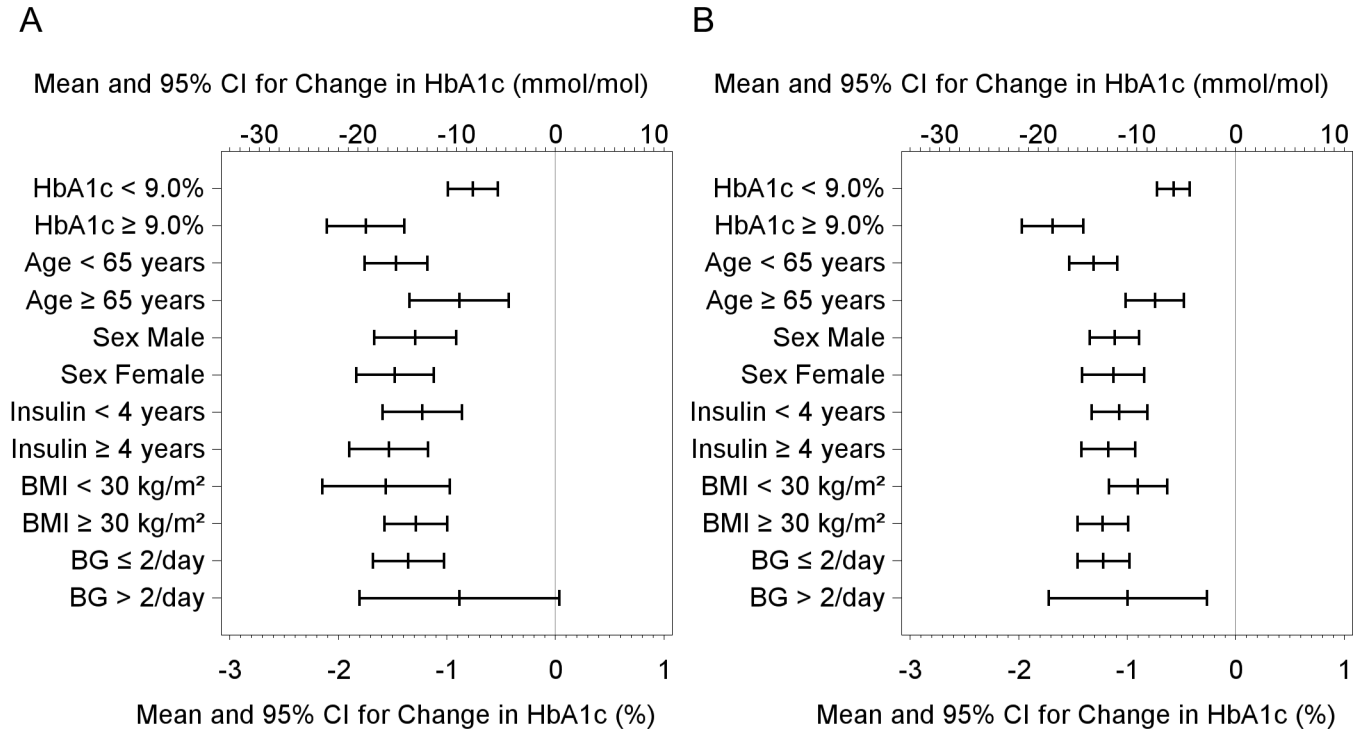

Figure 3 Change in glycated hemoglobin (HbA1c) by baseline HbA1c, age, sex at birth, duration of insulin use, body mass index (BMI) and blood glucose (BG) testing frequency for the US cohort (A) and the combined group cohort (B).

a type 2 diabetes cohort using either basal insulin and/or antihyperglycemic medications, which demonstrated a 1.2% (within group) HbA1c reduction after 6 months.[7] In this mixed cohort, the majority of these participants were non-insulin users who may show a more pronounced change in HbA1c with CGM.[9] However, a recent randomized controlled trial in a similar cohort to the current study reported a comparable within-group HbA1c reduction at 8 months in the CGM group.[11]

The current chart review study supports reported findings by studies in flash glucose monitoring with a similar population and methodology from Canada (0.8%)[10] and the USA (0.6%).[9] In 2021, Wright *et al* reported a 1.1% reduction in type 2 diabetes managed with basal insulin therapy and flash glucose monitoring use.[8] The observed reduction in HbA1c in the current study is consistent with other studies in flash glucose monitoring and CGM in type 2 diabetes with multiple insulin injection therapy (MDI), which have demonstrated HbA1c reductions of 0.8%–0.9%.[4–6]

The current meta-analysis of the larger USA and Canada combined cohort adds to other recent meta-analyses. These included randomized controlled trials and showed an overall improvement in HbA1c of 0.26%–0.56% in adults with diabetes using flash glucose monitoring and 0.42% in type 2 diabetes only.[14 15] The meta-analysis from Castellana *et al*[15] found that a 0.4% decrease in HbA1c was associated with each 1% increase in baseline levels over 7.2%, which correlates with the observed improvement in HbA1c.[14] The observed moderate to high heterogeneity was likely due to differences in the baseline HbA1c measurements between centers.

Significant change in HbA1c was demonstrated in the current study and the meta-analysis data sets regardless of age group (figure 3 and online supplemental table S1). The REPLACE (Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes) study, a randomized controlled study in use of this monitoring technology and type 2 diabetes managed with MDI, demonstrated a decrease in HbA1c only in individuals <65 years of age.[3] Haak *et al*[3] speculated that a more cautious approach to therapy adjustments in the older participants due to the risk of hypoglycemia may have been a factor. The finding in the current studies for the age subgroups contrasts with this and supports recent studies showing benefit from use of this technology irrespective of age in individuals with type 2 diabetes managed with MDI.[5 6]

The observed change in HbA1c was more marked for HbA1c levels >9%. A greater reduction in HbA1c from a higher baseline measurement has been observed in other studies in flash glucose monitoring and type 2 diabetes managed with either insulin or non-insulin therapies.[5 6 8]

At baseline, the most common oral antihyperglycemic medication used with basal insulin was metformin followed by a sulfonylurea for the USA cohort and a sodium-glucose cotransporter (SGLT) inhibitor in the Canada cohort. The use of SGLTs inhibitors in the USA cohort (28%) was similar to a report of national prescribing trends[16] and lower than in the Canada cohort (62%). Dipeptidyl peptidase-4 (DPP4) inhibitor prescribing was also lower in the USA group (11%) than the Canada group (39%) and compared with national prescribing trends.[17] Use of glucagon-like peptide-1

receptor agonists (GLP1 agonists) was similar in both countries as was the low use of thiazolidinedione therapy reflecting the overall decreasing trend for prescribing this medication.[18] Details of antihyperglycemic medications for the Canada-only cohort are listed in online supplemental table S2.

The baseline medical history and the prevalence of cardiovascular disease, angina and stroke, depression and renal disease in the current study (table 2) are broadly similar to other studies in this population.[6 17 19] Baseline demographics and characteristic data for age and use of basal insulin were also typical of patients with type 2 diabetes.[7 20–22] Mean baseline HbA1c at 9.4% confirms a trend for therapeutic inertia and general tolerance of suboptimal glycemic control in type 2 diabetes.[23 24] Mean BMI was >30 kg/m^2 in the current study reflecting the high prevalence of obesity in the USA and its association with type 2 diabetes.[21 25 26]

Achieving glycemic targets in type 2 diabetes remains one of the key goals of diabetes management. Review of glucose control and titration of basal-only insulin therapy is generally supported by an HbA1c measurement and blood glucose testing results.[1] The optimum frequency of self-monitoring in this population is imprecise. In the present study and the meta-analysis, the majority of medical records showed a daily testing frequency of 2 tests or less per day. This minimal utilization of fingerstick glucose monitoring by an individual does not appear to automatically influence HbA1c reduction with flash glucose monitoring use.[6 10]

Study strengths and limitations

A limitation of this study is the single-arm retrospective chart review methodology which, by definition, precludes a control group. Recent randomized controlled trials in CGM and type 2 diabetes managed with either MDI or basal insulin therapy reported change in HbA1c in the control arm of up to 0.6%.[4 5 11] Speculatively, if this indicates potential study effect, the observed change in HbA1c would remain clinically relevant in the present study and meta-analysis.

The methodology prevented more individualized data collection and although bolus insulin use was excluded before and during the data collection period, the potential impact of any additional oral medications is unknown. Therefore, the observed HbA1c reduction following initiation of flash monitoring may be due to a combination of different factors. Basal insulin dose titration, oral medication adjustments, clinical contact and behavior or lifestyle modifications, supported by device use, likely all contributed to achieving the primary end point. The use of glucose reports, such as the ambulatory glucose profile, as an educational resource for clinicians and patients to use together at review visits has been reported by prospective studies in flash glucose monitoring use in type 2 diabetes.[3 27] Correspondingly, a strength of the study's retrospective, pragmatic methodology is the lack of mandated glucose management or study administration during clinical interactions resulting in negligible impact on selection for study inclusion and clinical care during the study. These factors, together with the participant demographics and characteristics, which are typical of the individuals with type 2 diabetes, suggest the observed finding may be generalized and applied in other clinical settings. The length of the current study is potentially a limitation as the observed change in HbA1c may not be sustained after 6 months. However, the breakdown for change in HbA1c for each month after a minimum of 3–6 months use of this technology suggests that the change is durable. Vigersky *et al* reported that HbA1c reduction following intermittent CGM use in a mixed cohort of type 2 diabetes managed with basal insulin or non-insulin therapies was significant at 12 months.[7] More recently, Miller *et al* reported HbA1c improvement was sustained at 12 months in type 2 diabetes managed with basal insulin and using flash glucose monitoring.[9]

The current study and meta-analysis add to the growing evidence for use of this technology in type 2 diabetes. Bolus insulin was not initiated during the study and the observed improvement in HbA1c is comparable to the expected impact on glucose control from basal insulin initiation in insulin-naïve type 2 diabetes.[21] However, it should also be acknowledged that despite the pronounced change in the HbA1c level, it remained above the ADA recommended target for this cohort.[1] As an HbA1c level of >8% is an indication of basal and postprandial hyperglycemia,[28] further studies in management of type 2 diabetes with all therapies and CGM technology are warranted.[11]

CONCLUSION

In conclusion, significantly reduced HbA1c was retrospectively observed following commencement of flash glucose monitoring technology in type 2 diabetes treated with basal insulin and without prandial insulin use.

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Acknowledgements The authors thank all those who contributed to the collection of data at the study sites: International Diabetes Center IDC, HealthPartners Institute, Minneapolis, Minnesota; Diabetes Wellness Clinic, Pearland, Texas; The Charlotte-Mecklenburg Hospital Authority d/b/a Atrium Health, Charlotte, North Carolina; Thomas Jefferson University, Diabetes Research Center, Philadelphia,

Pennsylvania; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Henry Ford Health System, Division of Endocrinology, Diabetes, Detroit, Michigan; Diabetes and Obesity Care, Bend, Oregon; Texas Diabetes & Endocrinology, Round Rock, Texas and BC Diabetes, Vancouver, British Columbia, Canada. In addition, the authors thank Marcus Green and Zoe Welsh for statistical support (Statistics, Abbott Diabetes Care, UK) and Amanda Cartmale (Scientific Affairs Manager, Abbott Diabetes Care, UK) for editorial support during manuscript preparation.

Contributors All named authors have contributed towards writing, reviewing and revising the manuscript, meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, assume responsibility and accountability for the results, and have given their approval for this version to be published. ALC, as the guarantor, accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding In collaboration with the chief investigator, Abbott, Diabetes Care designed the study protocol. Abbott, Diabetes Care provided all study materials and was involved in data analysis and reporting. Abbott, Diabetes Care did not participate in the authors' interpretation of the study results. All authors had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of its analysis.

Competing interests ALC received research support, acted as a consultant or served on a scientific advisory board for Abbott Diabetes, Dexcom, Eli Lilly, Insulet, Medtronic, Novo Nordisk, Sanofi, Senseonics and United Healthcare, but did not receive any personal income. ALC is on the Board of Directors, JDRF Minnesota and Dakota chapter. TDD has served on a scientific advisory board for Abbott Diabetes. The healthcare system that ADeS works for receives research funding, but that money is not part of her current compensation arrangement, nor does she receive additional personal income. SJ, EKF and EM declare no relevant or material financial interests relating to the research described in this paper. DK has received research support and acted as a consultant for Abbott Diabetes. KO received research support from Abbott Diabetes but did not receive any personal income. KO received grants or served on a scientific advisory board for Eli Lilly, Novo Nordisk and Sanofi. KO is President of the Texas AACE chapter. TE has participated in advisory boards and received honoraria from Abbott Laboratories.

Patient consent for publication Not applicable.

Ethics approval An institutional review board approved the current study protocol and concluded that informed consent was not required (reference number Pro00039954). This method of anonymized data collection and analysis without consent is considered ethical. Human participants were not enrolled in the current study, which used retrospective, anonymized data collected from medical records.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets generated during and/or analyzed in the current study are available from the corresponding author on reasonable request.

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