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**Meta-Analysis**



# Effectiveness of Continuous Glucose Monitoring on Metrics of Glycemic Control in Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials

**Stacey Uhl,[1,*] Anuja Choure,[2,3,*] Benjamin Rouse,[1] Aggee Loblack,[1] and Peter Reaven[3]**

[1]ECRI, Plymouth Meeting, PA 19462, USA
[2]University of Arizona College of Medicine, Tucson, AZ 85724, USA
[3]Phoenix VA Healthcare System, Phoenix, AZ 85012, USA

**Correspondence:** Stacey Uhl, MS, ECRI, 5200 Butler Pike, Plymouth Meeting, PA 19462, USA. Email: suhl@ecri.org.
*First authorship shared by S.U. and A.C.

## Abstract

**Purpose:** To provide a systematic review and meta-analysis synthesizing the findings of randomized controlled trials (RCTs) of continuous glucose monitors (CGMs) in the management of adults with type 2 diabetes mellitus (T2DM) on glucose control and clinical outcomes.

**Methods:** MEDLINE, Embase, and Cochrane were searched for RCTs that assessed the effectiveness of real-time CGM (rt-CGM) or flash CGM (FGM) in adults (≥18 years) with T2DM that reported on at least 1 of the following outcomes: hemoglobin A1c (HbA1c), time in range, time in hyperglycemia, or time in hypoglycemia. The GRADE approach was used to assess certainty of evidence for primary outcomes.

**Results:** Fourteen RCTs assessing CGM were included, with 825 patients in 9 RCTs using rt-CGM and 822 in 5 RCTs using FGM. Moderate certainty of evidence indicated that use of CGM had a modest but statistically significant reduction in HbA1c levels of about 0.32%. Our analyses of each device type separately showed similar reductions in HbA1c (0.34% and 0.33%, respectively, for rt-CGM and FGM), with trends for improvement in other glucose metrics favoring rt-CGM over self-monitored blood glucose.

**Conclusion:** Both rt-CGM and flash CGM led to modest but statistically significant declines in HbA1c among individuals with T2DM, with little heterogeneity in the results. However, the duration of the included RCTs was relatively short and few studies reported on important clinical outcomes, such as adverse events, emergency department use, or hospitalization. Longer term studies are needed to determine if the short-term improvements in glucose control leads to improvements in clinically important outcomes.

**Key Words:** systematic review, meta-analysis, type 2 diabetes mellitus, continuous glucose monitor, glycemic control, flash glucose monitoring

Continuous glucose monitoring (CGM) technology has advanced substantially over the past decade. The 2 main versions of CGM, real-time CGM (rt-CGM) and flash (or intermittent) CGM (FGM), have provided varying frequency of interstitial glucose measurements and capacity for tracking glucose trends and setting low and high glucose alarms. However, both forms of CGM have continued to increase their accuracy, functionality, and ease of use. In parallel with these improvements in technology, clinical studies have begun to highlight potential benefits of CGM use for improved glucose control and shorter term outcomes. These events have led to dramatic increases in the clinical use of CGM. However, the cost of CGM devices and providing technical and educational support to patients and providers to initiate and maintain broad CGM use in health care institutions or systems is substantial. It is therefore of great importance to better understand the real benefits on overall glycemic control and adverse events such as hypoglycemia, emergency room visits, and hospitalizations and eventually longer term complications.

While most studies have examined CGM effects on glucose control, assessing changes in hemoglobin A1c (HbA1c) or time in range, fewer have examined whether use of CGM reduces time in marked hyperglycemia, time below range, or severity of hypoglycemia (1-4). Most of these studies have been conducted in patients with type 1 diabetes mellitus (T1DM). As these patients are typically using multiple injections of insulin per day, there is relative homogeneity of characteristics across these studies, especially in the adult T1DM patients. Moreover, most studies compared only real-time CGMs with standard home blood glucose monitoring as FGM was far less frequently used in T1DM patients. Results from these trials have generally demonstrated improvements in metrics of glucose control and reduced time in hypoglycemia (as determined by CGM values) as well as in patient satisfaction (1, 3, 4).

In contrast, there is far less consensus regarding the value of CGM in the treatment of type 2 diabetes mellitus (T2DM) for several reasons (2, 5-7). First, as noted earlier, fewer studies

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have examined the consequences of CGM use in T2DM. Second, diverse and complex combinations of oral and/or injectable diabetes medications have been used in the completed studies, limiting generalization of study results. Lastly, studies varied in whether they tested rt-CGM or FGM. Thus, it has been difficult to readily aggregate study results and confidently identify the benefits gained through use of CGM in T2DM. Despite these limitations, results from individual studies (7-10) and several smaller reviews (5, 11) have suggested that continuous use or periodic use (2-3 brief intervals over 3-6 months) of CGM may reduce HbA1c levels and possibly episodes of hypoglycemia. However, there are mixed results on the degree of glucose lowering (eg, reductions in HbA1c or time above range) and whether reductions in hypoglycemia may be clinically meaningful. Importantly, several well-conducted trials of CGM in T2DM have recently been completed, and longer longitudinal studies of CGM use examining more intermediate-term outcomes have been reported, thereby providing an opportunity for a more thorough assessment of the clinical value of CGM use in T2DM.

Thus, objectives of the current review are to provide an up-to-date review of CGM use in T2DM with a focus on meta-analyses of randomized clinical trials (RCTs) of CGM on several more commonly used metrics of glucose control. Summary results are presented for use of either rt-CGM or FGM and where possible by each type of CGM separately.

## Research Design and Methods

This review stems from a recently published update of the 2023 U.S. Department of Veterans Affairs (VA) and U.S. Department of Defense Clinical Practice Guideline (CPG) for the Management of Type 2 Diabetes Mellitus (12). The updated CPG covers a wide range of interventions for T2DM, including assessing the clinical value of CGM. This review focuses specifically on the use of CGM in the management of T2DM and extends the work of the CPG by conducting meta-analyses and subgroup analyses on key outcomes relevant to this technology.

## Data Searches and Sources

Electronic databases (MEDLINE ALL, Embase.com, and Cochrane Central Register of Controlled Trials) were searched from January 1, 2016, to August 31, 2022, for English-only publications (Supplementary Table S1) (13). The search dates for this review cover the timeframe from the previous CPG searches (with some overlap) to the time immediately preceding the guideline panel meeting. Reference lists of previously published systematic reviews and relevant studies were hand-searched to identify studies published prior to January 2016. We also searched for unpublished studies in ClinicalTrials.gov. Literature screening was performed in duplicate using DistillerSR (DistillerSR, Ottawa, Canada).

## Study Selection

Using predefined eligibility criteria, we selected RCTs assessing the effectiveness of CGM compared to self-monitoring blood glucose (SMBG). We included studies of patients ages 18 years or older diagnosed with T2DM. In studies that included patients with T1DM or T2DM, we required that at least 80% of the enrolled patients have T2DM or that outcomes for patients with T2DM were reported separately. We included studies of rt-CGM or FGM that reported on at least 1 of the following primary outcomes: HbA1c, time in range (70-180 mg/dL), time in hyperglycemia (> 180 mg/dL), or time in hypoglycemia (<70 mg/dL). We also considered other outcomes, including adverse events, quality of life, emergency department use, hospitalization, and patient satisfaction.

The exclusion criteria were as follows: non-RCT studies, studies limited to individuals with T1DM or gestational diabetes, pregnant individuals, individuals with other health conditions managed exclusively outside of primary care (eg, hospitalized), those with insufficient data for analysis, and duplicate literature. Two reviewers (S.U. and A.C.) independently assessed whether each document satisfied the eligibility criteria, with a third reviewer (P.R.) consulted in cases of disagreement.

## Data Extraction and Quality Assessment

The following data were extracted from relevant RCTs by 2 reviewers (S.U. and A.C.): author, publication year, follow-up weeks, number of patients, duration of T2DM, diabetes treatment(s), baseline HbA1c, key inclusion criteria, type of CGM, study sponsor, and findings for outcomes of interest. A third reviewer checked all extractions for completeness and accuracy (P.R.).

Risk of bias (ROB) was assessed using the Cochrane Risk of Bias 2.0 tool (14). Two individual reviewers (S.U. and A.L.) conducted initial study ratings, and a third reviewer (B.R.) checked all ratings for accuracy. Discrepancies were resolved through discussion.

## Data Synthesis and Analysis

Meta-analyses were conducted for the primary outcomes for both rt-CGM and FGM studies together and separately by CGM type. As all the primary outcomes were continuous, treatment effects were summarized as mean differences (MDs) and 95% confidence intervals (CIs). All trials in this review reported HbA1c values as a percentage of total hemoglobin standardized to the methods of the Diabetes Control and Complications Trial. We present the findings of our meta-analyses for HbA1c as the difference in percent change of total hemoglobin A1c. Anticipating that related but different effects would be estimated across studies, we used random effects models for the analyses, applying the DerSimonian-Laird method with the Hartung-Knapp-Sidik-Jonkman adjustment (15, 16). Statistical heterogeneity was assessed with the Cochran's Q test, $I^2$, and tau (2). For the analysis, we prioritized change from baseline values. Pooled estimates were based on the data from the longest (or in some cases most consistent) follow-up point. When results were reported only as medians and interquartile ranges, we used these data to estimate the means and standard deviations (17). All analyses were conducted in Stata 13 (StataCorp, College Station, TX, USA).

Sensitivity analyses were conducted to evaluate assumptions made for the analysis. These included using the standard DerSimonian-Laird random effects model; excluding studies at a high risk of bias; using follow-up values instead of change from baseline values; excluding studies that reported median values (and interquartile range) rather than means; and influence analysis, where the meta-analysis is recalculated leaving out 1 study at a time.

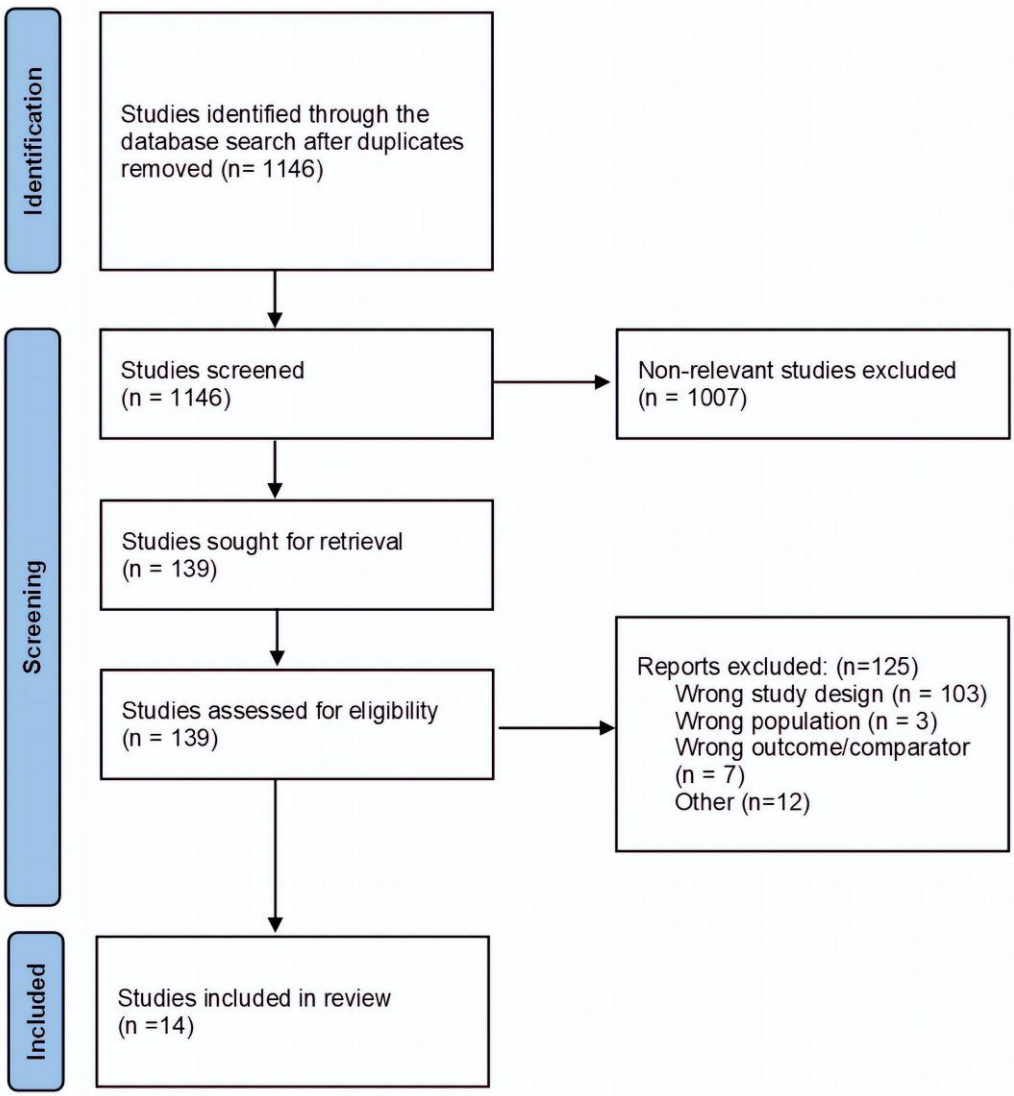


**Figure 1.** Study selection diagram. The figure shows the flow of articles retrieved through our literature searches at the various levels of screening.

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess certainty of evidence for primary outcomes based on risk of bias, inconsistency, indirectness, imprecision, and other considerations, including publication bias (18). Certainty of evidence was rated as high, moderate, low, or very low. One reviewer (S.U.) conducted the initial assessments, and a second reviewer (B.R.) verified the accuracy of the GRADE ratings. Disagreements were resolved through discussion.

### Publication Bias

We assessed small study effects as a potential indication of publication bias using funnel plots and the Egger regression test for meta-analyses including at least 10 studies.

## Results

Of 1146 studies identified for screening, 139 full-text articles were reviewed in depth (Fig. 1). Of these studies, 14 (9 rt-CGM and 5 FGM) were deemed eligible for inclusion in the review. Clinical trial registry searches yielded no additional studies to those found published in the searched databases. The main reasons for study exclusion were wrong study design, wrong comparator, and wrong patient population.

Three of the included studies were rated as high ROB due primarily to limited reporting of randomization procedures and lack of information about allocation concealment in 2 RCTs (19) and additional concerns related to attrition in 1 study (8) (Fig. 2, Supplementary Table S2) (13). Four studies had some ROB concerns (6, 7, 20, 21), mostly related to lack of information about randomization procedures.

The characteristics of the studies included are presented in Table 1. Overall, 1647 patients were included in the 14 RCTs assessing CGM, with 825 patients in the 9 RCTs on rt-CGM (n = 454 rt-GGM, n = 371 SMBG) and 822 in the 5 RCTs on FGM (n = 446 FGM, n = 376 SMBG). The average age of patients in the rt-CGM RCTs ranged from 55 to 63 years, percent females enrolled was 59%, and duration of diabetes ranged from 10 to 17 years. Follow-up times across the rt-CGM RCTs ranged from 12 to 32 weeks (median 12 weeks). Most patients were taking oral diabetes medications with or without insulin to manage their diabetes, and Dexcom was the most frequently used CGM device across studies (66%).

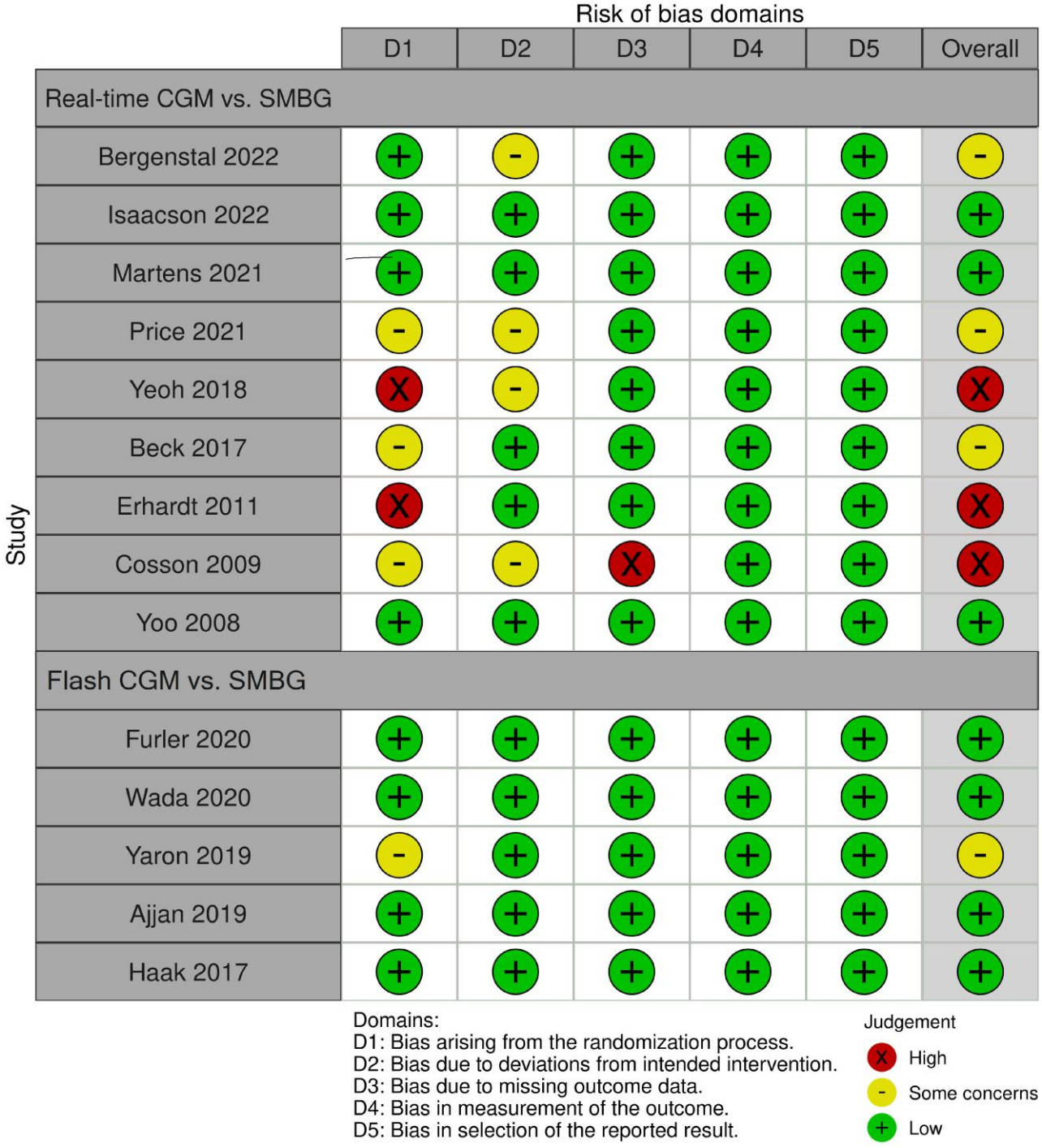


**Figure 2.** Risk of bias rating by domain. This figure shows the risk of bias rating for the individual studies included in the review. The risk of bias ratings is represented as a encircled "+" sign if a study accounts for potential bias, a encircled "– "sign if there are some concerns about the potential for bias, and a encircled "X" if the study fails to account for bias. The biases of concern are biases due to randomization process, deviation from the intended intervention, missing outcome data, measurement of outcome, and selection of reported result.

Age of patients and duration of diabetes in FGM studies were generally similar to those using rt-CGM. The average age of patients in the FGM RCTs ranged from 58 to 68 years, percent females enrolled was 38%, and duration of diabetes ranged from 10 to 20 years. Follow-up times ranged from 10 to 52 weeks (median 24 weeks). In most of the FGM RCTs, patients were taking oral diabetes medications with or without insulin to manage their diabetes; however, patients in 2 studies were on insulin only. FreeStyle Libre (2 RCTs) or FreeStyle Libre Pro (2 RCTs) were the devices used in the FGM studies, with 1 study using both devices (LibrePro during blinded phase and Libre during unblinded phase) (Table 1). Methods used to train and prepare participants to use CGM and other details for each study are described in the supplemental materials (Supplementary Table S3) (13).

**Table 1. Patient characteristics of included studies**

| Reference | Follow-up (weeks) | Number of patients | Age (mean years [SD]) | Duration T2DM (mean years [SD]) | BL diabetes treatment (n)[a] | BL HbA1c (% mean [SD]) | Key inclusion criteria | Type of CGM/use | Study sponsor |
|---|---|---|---|---|---|---|---|---|---|
| RT CGM vs SMBG | | | | | | | | | |
| Bergenstal et al 2022 (6) | 16 | RT: 59<br>SMBG: 55 | RT: 59.3 (8.9)<br>SMBG: 58.8 (10) | NR | SU ± MET (34); DPP4 or GLP ± MET (29); or insulin ± MET (51) | RT: 8.19 (1.2)<br>SMBG: 7.85 (0.79) | Uncontrolled T2DM (HbA1c ≥ 7.0%); age 18-75 years, and treated with common diabetes therapies | Dexcom 7 Plus/ continuous | Roche Diagnostics |
| Beck et al 2017 (7) | 24 | RT: 79<br>SMBG: 79 | RT: 60 (11)<br>SMBG: 60 (9) | Median 17 years | Insulin only (50); noninsulin glucose lowering medication + insulin (108) | RT: 8.5 (0.6)<br>SMBG: 8.5 (0.7) | Age ≥25 years; T2DM treated with multiple daily injections of insulin ≥ 1 year; HbA1c 7.5%-10.0%, stable diabetes medication regimen | Dexcom G4/ continuous | Dexcom Inc |
| Cossen et al 2009 (8) | 12 | RT: 11<br>SMBG: 14 | RT: 57.2 (4.4)<br>SMBG: 57.3 (5.9) | RT: 10.5 (8.0)<br>SMBG: 12.6 (9.9) | Oral diabetes medication w/ out insulin RT (8); SMBG (8); insulin RT (6); SMBG (12) | RT: 9.22 (0.3)<br>SMBG: 9.7 (0.16) | Age 40-70 years; T2DM treated with oral diabetes medications with/without 1 insulin injection/day; HbA1c 8.0%-10.5% | GlucoDay/ intermittent, 3 days for 12 weeks | Menarini Diagnostics |
| Isaacson et al 2022 (9) | 24 | RT: 50<br>SMBG: 49 | 64% between 55-74 years | NR | NR | NR | Uncontrolled T2DM (HbA1c ≥ 6.5%); age 18-80 years. Patients selected without consideration of dietary, oral, or injectable diabetes therapies | Dexcom G6/ continuous | Intermountain health care |
| Martens et al 2021 (10) | 32 | RT: 116<br>SMBG: 59 | RT: 56 (9)<br>SMBG: 59 (9) | RT: 14 (9)<br>SMBG: 15 (10) | Insulin only (16); MET + insulin (44); SU + insulin (7); DPP-4 (3); GLP1 (5); SGLT2 (3); ≥ 2 medications + insulin (97) | RT: 9.1 (1.0)<br>SMBG: 9.0 (0.9) | Age ≥30 years, T2DM treated with 1-2 daily injections of basal insulin for at least 6 months, HbA1c 7.8%-11.0% | Dexcom G6/ continuous | Dexcom Inc. |
| Yeoh et al 2016 (19) | 12 | RT: 14<br>SMBG: 16 | 63 (10) | 86.7% ≥ 10 years | Basal insulin (27); SU (11); MET (23) | RT: 9.8 (1.2)<br>SMBG: 9.9 (1.3) | Age ≥21 years; T2DM with DKD stage 3 (eGFR 30-60 mL/min per 1.73 $m^2$) and above > 3 months; HbA1c > 8.0% | iPro: Medtronic/ retrospective CGM | NR |
| Price et al 2021 (20) | 12 | RT: 46<br>SMBG: 24 | RT: 58.9 (11.8)<br>SMBG: 60.9 (9.5) | RT: 13.9 (11.0)<br>SMBG: 12.3 (6.7) | SU (47); DPP-4 (23); SGLT-2 (35); MET (56); other (33) | RT: 8.4 (0.7)<br>SMGB: 8.5 (0.8) | Age ≥30 years; T2DM treated with 2 or more noninsulin diabetes drugs; HbA1c ≥ 7.8% | Dexcom G6/ episodic use, 1 10-day wear per month for 3 months | Dexcom Inc |
| Ehrhardt et al 2011 (22) | 12 | RT: 50<br>SMBG: 50 | RT: 55.5 (9.6)<br>SMBG: 60.0 (11.9) | NR | Diet/exercise only (7); oral medications only (60); basal insulin alone or w/ medication (33) | RT: 8.4 (1.3);<br>SMBG: 8.2 (1.1) | Age ≥18 years, T2DM for ≥3 months, HbA1c ≥ 7.0 but ≤ 12.0%, treated with diet/exercise or other diabetes medications except prandial insulin | Dexcom 7/ episodic use, consisting of 4 cycles of 3 weeks with 2 weeks of CGM use and 1 week off | Dexcom Inc |

(*continued*)

**Table 1. Continued**

| Reference | Follow-up (weeks) | Number of patients | Age (mean years [SD]) | Duration T2DM (mean years [SD]) | BL diabetes treatment (n)[a] | BL HbA1c (% mean [SD]) | Key inclusion criteria | Type of CGM/use | Study sponsor |
|---|---|---|---|---|---|---|---|---|---|
| Yoo et al 2008 (23) | 12 | RT: 29<br>SMBG: 28 | RT: 54.6 (6.8)<br>SMBG: 57.5 (9.0) | RT: 11.7 (5.8)<br>SMBG: 13.3 (4.9) | Insulin: RT (4), SMBG: (5); oral diabetes medication RT (13), SMBG (10); insulin + oral diabetes drug: RT (11), SMBG (12) | RT: 9.1 (1.0)<br>SMBG: 8.7 (0.7) | Age 20-80 years; T2DM with oral antidiabetic drug or insulin ≥1 year; HbA1c 8.0%-10% | Guardian/ intermittent use, 3 days per month for 12 weeks | Korean Ministry of Health and Welfare with support from Medtronic |
| Flash CGM vs SMBG | | | | | | | | | |
| Yaron et al 2019 (21) | 10 | FGM: 53<br>SMBG: 48 | FGM: 67.5 (6.7)<br>SMBG: 65.9 (8.4) | FGM: 22.1 (7.0)<br>SMBG: 21.5 (8.3) | Insulin + MET: FGM (71.7%), SMBG (72.9); DPP4: FGM (7.5%), SMBG: (14.6%); SGLT2: FGM: (24.5%), SMBG: (27.7%)<br>GLP-1-RA: FGM (35.8%), SMBG (31.3%); SU: FGM 0.0%), SMBG (4.2%) | FGM: 8.68 (0.87)<br>8.34 (0.74) | Age 30-80 years, T2DM for ≥1 year, treatment by 2 or more insulin injections daily for ≥6 months; HbA1c of 7.5-10.0% | FreeStyle Libre | Abbott |
| Wada et al 2020 (24) | 24 | FGM: 49<br>SMBG: 51 | FGM: 58.1 (9.8)<br>SMBG: 58.7 (10.0) | NR | Antidiabetic drugs (no insulin): FGM: (48); SMBG: (49) | FGM: 7.83 (0.25)<br>SMBG: 7.84 (0.27) | Age ≥20 to <70 years; T2DM; HbA1c ≥ 7.5% to <8.5%; did not use insulin | FreeStyle Libre Pro (during blinded baseline)/ unblinded FreeStyle during study period | Nagoya University Hospital |
| Haak et al 2017 (25) | 24 | FGM: 149<br>SMBG: 75 | FGM: 59.0 (9.9)<br>SMBG: 59.0 (11.0) | FGM: 17 (8.0)<br>SMBG: 18 (8.) | Insulin: Basal (n = 208); bolus (n = 211) | FGM: 8.65 (1.01)<br>SMBG: 8.7 (0.98) | Age ≥18 years; T2DM treated with insulin for ≥6 months; HbA1c level between 7.5% and 12.0% | FreeStyle Libre | Abbott |
| Furler et al 2020 (26) | 52 | FGM: 149<br>SMBG: 150 | FGM: 60.4<br>SMBG: 59.8 (10.3) | FGM: 13.6, 9 -20 years<br>SMBG: 11.0, 8-20 years | Insulin (156); MET (265); SU (126): DPP-4 (82); GLP-1 (49): SGLT2 (104); acarbose (13); thiazolidinediones (4) | FGM: 8.9 (1.3)<br>SMBG: 8.9 (1.2) | Age 18-80 years; T2DM with HbA1c above target range of 7.0% on at least 2 noninsulin glucose-lowering drugs or insulin or both | FreeStyle Libre Pro | National Health and Medical Research Council of Australia |
| Ajjan et al 2019 (27) | 30.4 | FGM-B: 46<br>FGM-C: 50<br>SMBG: 52 | FGM-B: 63.9 (10.7)<br>FGM-C: 61.7 (11.1)<br>SMBG: 65.0 (11.2) | NR | Insulin | FGM-B: 8.7 (1.1)<br>FGM-C: 8.6 (0.9)<br>SMBG: 8.6 (1.1) | Age ≥18 years; T2DM treated with insulin therapy for ≥ 6 months; HbA1c level between 7.5% and 12.0% | FreeSyle Libre Pro | None received |

Abbreviations: BL, baseline; DPP-4, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; FGM, flash glucose monitor; GLP, glucagon-like peptide; HbA1c, hemoglobin A1c; MET, metformin; NR, not reported; RT, real-time; RT-CGM, real-time continuous glucose monitor; SGLT2, sodium-glucose transport protein 2 inhibitor; SMBG, self-monitored blood glucose; SU, sulfonylureas; T2DM, type 2 diabetes mellitus.

[a]In some studies the number of patients indicated for the treatment regimens does not equal the number of patients randomized to the study due to some patients on multiple regimens.

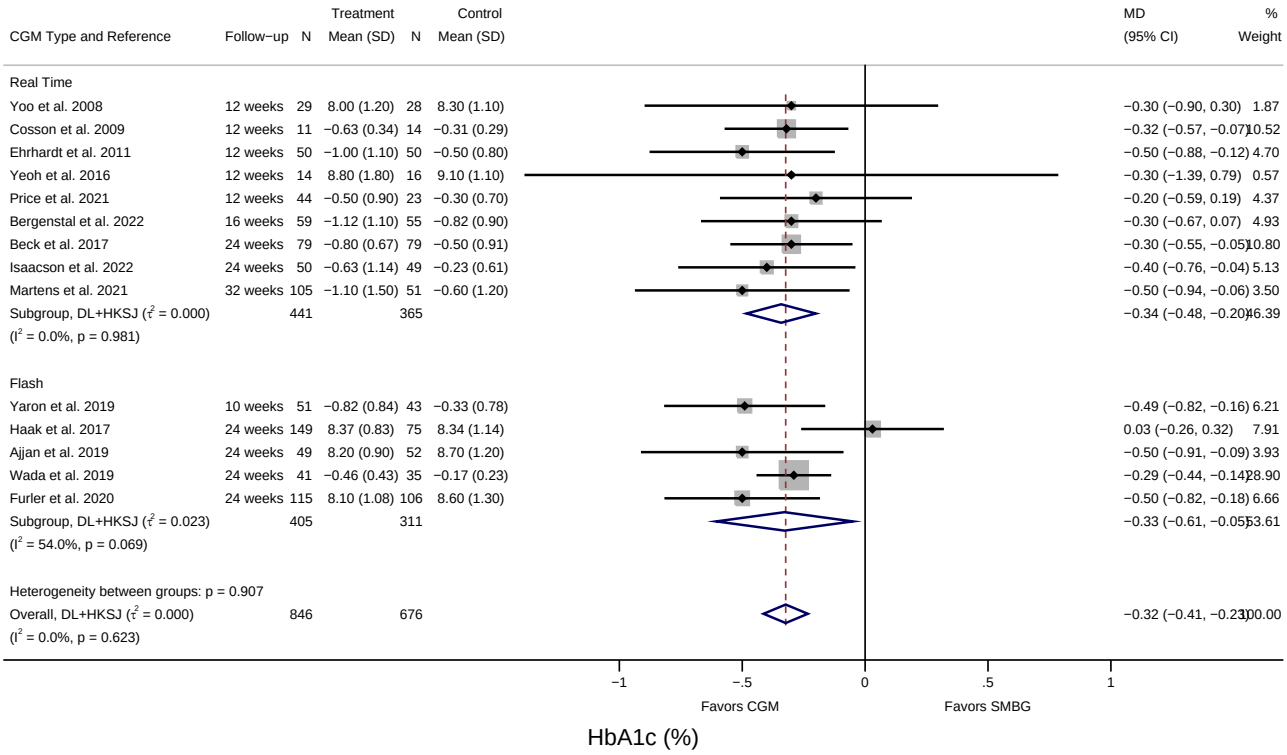


**Figure 3.** Forest plot of the meta-analysis on the effect of CGM on HbA1c. The plot summarizes relative effect of CGM compared to SMBG on the HbA1c level as the MD (and 95% CI) in real-time and flash CGM subgroups and overall. The dashed line represents the overall meta-analytic MD. Abbreviations: CGM, continuous glucose monitor; CI, confidence interval; DL + HKSJ, DerSimonian-Laird method with the Hartung-Knapp-Sidik-Jonkman adjustment; HbA1c, hemoglobin A1c; MD, mean difference; SMBG, self-monitoring blood glucose.

## Change in HbA1c

Data from all 14 RCTs were included in a meta-analysis assessing the overall effectiveness of CGM on HbA1c levels. The pooled MD for all studies showed a statistically significant decrease in percent HbA1c in patients using CGM compared with SMBG (MD: −0.32%, 95% CI: −.41 to −.23, Fig. 3). No evidence of heterogeneity was observed ($I^2 = 0.0\%$, $P = .62$). The certainty of evidence for HbA1c was rated moderate due primarily to ROB concerns (Table 2). Sensitivity analyses (described in the Methods section) revealed no impact on the overall findings for this outcome (Supplementary Fig. S1; Supplementary Table S4) (13). Funnel plot analysis suggests no evidence of publication bias (Supplementary Fig. S2) (13). We considered conducting subgroup analyses to determine if insulin use, duration of diabetes, or baseline HbA1c impacted our findings for change in HbA1c. However, without patient-level data, these subgroup analyses required comparisons between studies; yet only 2 RCTs included patients on insulin only (patients in most studies were on a mix of insulin and oral diabetes medications), and diabetes duration and baseline HbA1c values were similar across studies.

Three studies provided data in a manner that allowed us to conduct a pooled analysis of studies in which all patients were on medication regimens without insulin or the findings for these patients were reported separate from patients on insulin or on a mix of insulin and oral medications. Two studies compared rt-CGM to SMBG (6, 20), and 1 study compared FGM to SMBG (24). The pooled analysis showed an improvement in HbA1c levels for patients only on oral medications (and/or glucagon-like peptide-1 receptor agonists) using CGM that was similar to that of all CGM users compared with SMBG (MD: −0.26, 95% CI: −.53 to .01, n = 206) (Supplementary Table S4) (13). The wider CIs observed for the pooled effect of patients not on insulin is likely due to the smaller number of patients contributing to the pooled analysis.

Separate analysis of rt-CGM and FGM revealed similar findings to the overall effect of CGM on HbA1c levels. The pooled MD from 9 RCTs comparing rt-CGM with SMBG was −0.34% (95% CI: −.48 to −.20, n = 806), and −0.33% (95% CI: −.61 to −.05, n = 716) from 5 RCTs comparing FGM with SMGB (Fig. 3). Removing the 2 RCTs in which patients were blinded while using FGM yielded similar results for change in HbA1c: −0.30, 95% CI −.40 to −.21. While there was little evidence of heterogeneity in the analysis of rt-CGM studies ($I^2 = 0.0\%$, $P = .98$), with all studies demonstrating significant improvements or trends for improvement in HbA1c, moderate heterogeneity was observed in the analysis of the FGM studies ($I^2 = 0.54\%$, $P = .07$). Most of the heterogeneity was explained by removing the RCT by Haak et al (2017) (25), which demonstrated a nonstatistically significant reduction in HbA1c for FGM vs SMBG. Unlike other studies of FGM, patients in the Haak et al study were on intensive insulin regimens. The authors did note that in a prespecified subgroup analysis based on age, a significant improvement in HbA1c favoring FGM over SMBG was detected in those younger than 65 years compared to no difference observed in those >65 years. The authors hypothesized that the difference may be due to the convenience associated with CGM readings compared to SMBG that may prompt younger patients, who have reported being "too busy" for finger-stick testing, to test more frequently.

**Table 2. Certainty of evidence ratings for primary outcomes**

| Certainty assessment | | | | | | | Effect | Certainty |
|---|---|---|---|---|---|---|---|---|
| Outcome | Number of studies (n) | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Mean difference (95% CI) | |
| CGM vs SMBG | | | | | | | | |
| HbA1c | 14 RCTs (1647) | Serious[e] | Not serious | Not serious | Not serious | No publication bias | −.32 (−.41 to −.23) | Moderate ⨁⨁⨁◯ |
| Real-Time vs SMBG | | | | | | | | |
| HbA1c | 9 RCTs (806) | Serious[e] | Not serious | Not serious | Not serious | None | −.34 (−.41 to −.27) | Moderate ⨁⨁⨁◯ |
| Change in % time in range (70 to 180 mg/dL) | 4 RCTs (477) | Serious[e] | Not serious | Not serious | Not serious | None | 11.06 (1.80 to 20.3) | Moderate ⨁⨁⨁◯ |
| Change in % time in hyperglycemia (> 180 mg/dL) | 4 RCTs (467) | Serious[e] | Not serious | Not serious | Serious[f] | None | −10.37 (−21.5 to .80) | Low ⨁⨁◯◯ |
| Change in % time hypoglycemia (<70 mg/dL) | 5 RCTs (492) | Serious[e] | Not serious | Not serious | Serious[f] | None | −.44 (−1.19 to .31) | Low ⨁⨁◯◯ |
| Flash vs SMBG | | | | | | | | |
| HbA1c | 5 RCTs (716) | Serious[e] | Not serious | Not serious | Not serious | No publication bias | −.33 (−.61 to −.05) | Moderate ⨁⨁⨁◯ |
| Hours, time in range (70 to 180 mg/dL) | 3 RCTs (401) | Not serious | Not serious | Not serious | Serious[f] | None | 1.11 (−1.03 to 3.25) | Moderate ⨁⨁⨁◯ |
| Hours, time in hyperglycemia (>180 mg/dL) | 3 RCTs (401) | Not serious | Not serious | Not serious | Serious[f] | None | −1.10 (−3.92 to 1.73) | Moderate ⨁⨁⨁◯ |
| Hours, time hypoglycemia (<70 mg/dL) | 3 RCTs (401) | Not serious | Not serious | Not serious | Serious[f] | None | −.10 (−1.07 to .86) | Moderate ⨁⨁⨁◯ |

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; RCT, randomized controlled trial; SMBG, self-monitored blood glucose.
[a]Risk of bias considers the overall methodological quality of all the studies included in the evidence base.
[b]Inconsistency of results considers if the studies demonstrated similar findings or estimates of effect (an inconsistent rating would indicate that the findings across studies was heterogeneous).
[c]Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population.
[d]Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.
[e]Downgraded for risk of bias due to limited reporting of randomization procedure, no information about allocation concealment, and attrition.
[f]Downgraded due to lack of precision as evidenced by wide 95% confidence intervals.

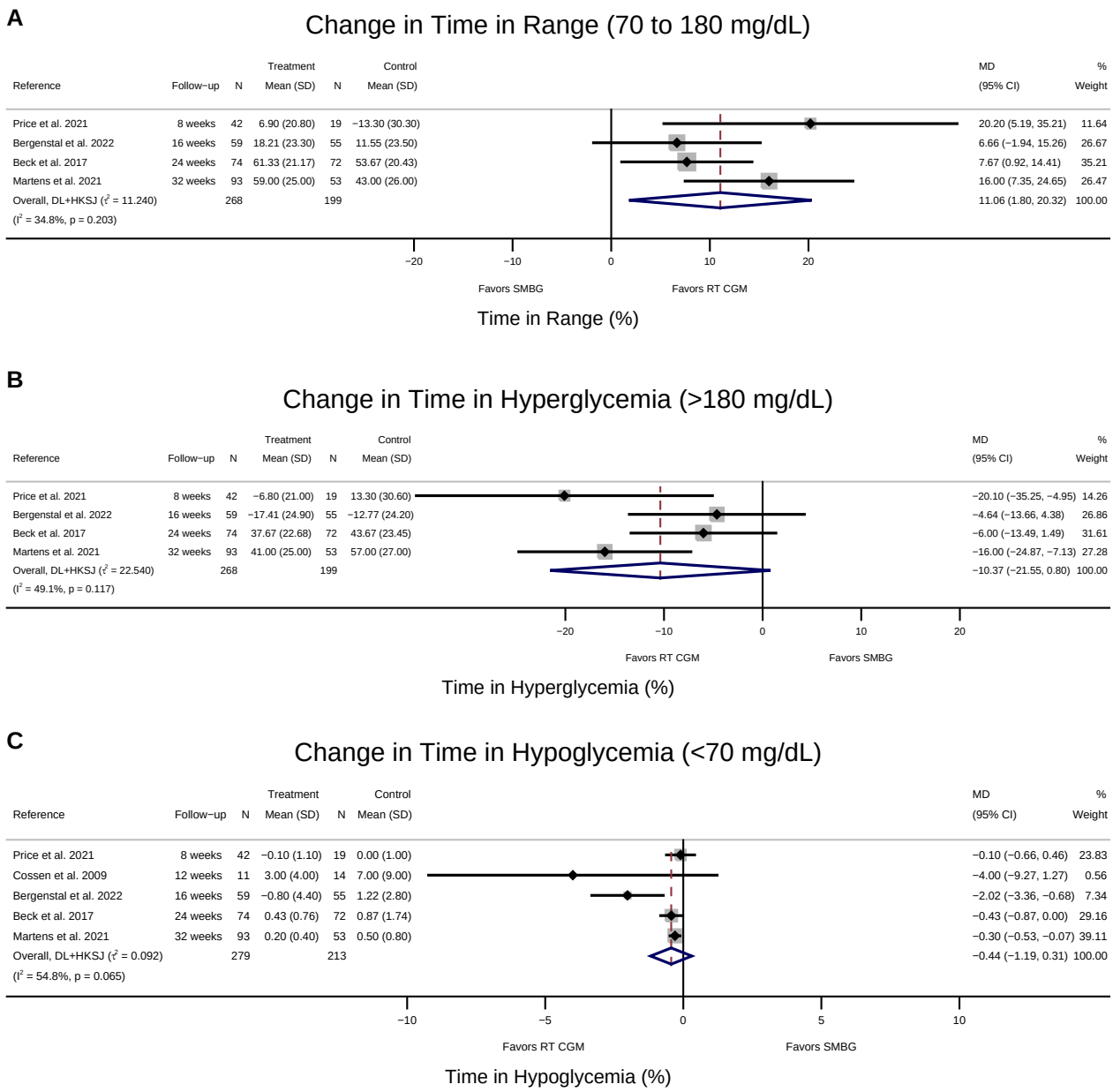


**Figure 4.** Forest plots of the meta-analyses on the effect of real-time CGM on other glycemic parameters: (A) time in range (70-180 mg/dL), (B) time in hyperglycemia (>180 mg/dL), and (C) time in hypoglycemia (<70 mg/dL). The plots summarize the relative effects of real-time CGM compared to SMBG on the percentage of time in range, hyperglycemia, and hypoglycemia as the MD (and 95% CI). The dashed line represents the overall meta-analytic MD.
Abbreviations: CGM, continuous glucose monitor; CI, confidence interval; DL + HKSJ, DerSimonian-Laird method with the Hartung-Knapp-Sidik-Jonkman adjustment; MD, mean difference; RT, real-time; SMBG, self-monitoring blood glucose.

## Other Glucose Control Outcomes

Differences in presentation of additional major outcomes in studies using rt-CGM or FGM required that we present the findings of our pooled analyses for these outcomes separately for each CGM device.

### rt-GCM

The pooled analysis of the 4 RCTs that reported these outcomes indicated a statistically significant increase in percent time in range (70-180 mg/dL) associated with use of rt-CGM compared to SMBG (MD: 11.06%, 95% CI: 1.80-20.32, n = 467, Fig. 4A), with minimal presence of heterogeneity ($I^2 = 34.8\%$, $P = .20$). Due to ROB concerns, the certainty of the evidence was rated as moderate (Table 2).

The pooled analysis of 4 RCTs showed a moderate but non-statistically significant decrease in hyperglycemia (>180 mg/dL) (−10.37%, 95% CI: −21.55 to .80, Fig. 4B) with evidence of moderate heterogeneity ($I^2 = 49\%$, $P = .12$). There was also a small and nonsignificant decrease in percent time in hypoglycemia (<70 mg/dL) associated with rt-CGM (MD: −0.44%, 95% CI: −1.99 to .31, n = 492, $I^2 = 54.8\%$, $P = .06$, Fig. 4C) with evidence of moderate heterogeneity. In general, patients across studies experienced little time with glucose levels <70 mg/dL, which likely explains the small decrease in hypoglycemia.

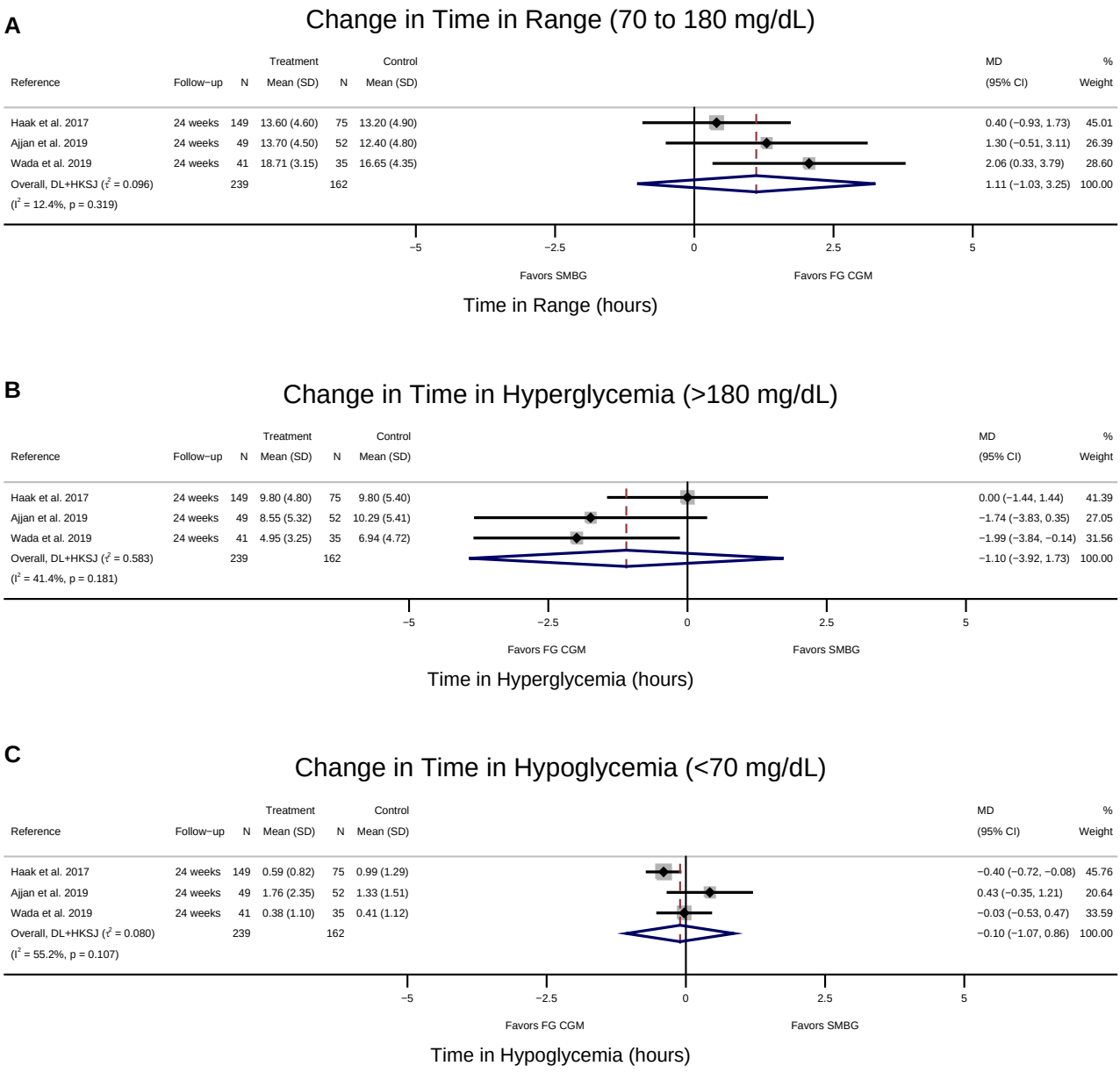


**Figure 5.** Forest plots of the meta-analyses on the effect of flash CGM on other glycemic parameters: (A) time in range (70 to 180 mg/dL), (B) time in hyperglycemia (>180 mg/dL), and (C) time in hypoglycemia (<70 mg/dL). The plots summarize the relative effects of real-time CGM compared to SMBG on the hours of time in range, hyperglycemia, and hypoglycemia as the MD (and 95% CI). The dashed line represents the overall meta-analytic MD.

Abbreviations: CGM, continuous glucose monitor; CI, confidence interval; DL + HKSJ, DerSimonian-Laird method with the Hartung-Knapp-Sidik-Jonkman adjustment; FG, flash glucose; MD, mean difference; SMBG, self-monitoring blood glucose.

Few RCTs reported on quality of life, patient satisfaction, emergency room visits, hospitalization, or adverse events, which precluded meta-analyses of these outcomes. Based on the findings of the individual RCTs that did report on these outcomes, no statistically significant differences were observed. In 1 RCT, patients in the rt-CGM group reported more overall adverse events compared to patients in the SMBG group (30 vs 12, respectively) (10). However, the difference in events was not statistically significant, and none of the events were believed related to the CGM device (relative risk 1.27, 95% CI .70-2.30). The most frequently reported adverse events across studies reporting events was a nonserious hypoglycemic event (n = 5).

### FGM

Due to differences in how outcomes were reported across studies, only 3 RCTs were included in the meta-analyses assessing the effectiveness of FGM on time in range, time in hypoglycemia, and time in hyperglycemia. These RCTs reported these outcomes as change in hours, whereas the other 2 RCTs either did not report on these outcomes at all (21) or reported them as change in percentage time—which could not be converted to hours (26). Findings of our pooled analysis indicated no statistically significant difference between FGM and SMBG for these outcomes, with low to moderate evidence of heterogeneity (Fig. 5). Certainty of the evidence across these outcomes was rated moderate due to imprecision of the estimated effects as evidenced by wide 95% CIs (Table 2).

Four RCTs using FGM reported on patient satisfaction using the Diabetes Treatment Satisfaction Questionnaire. The pooled mean difference indicated increased overall satisfaction among patients using FGM compared with SMBG (MD: 4.08, 95% CI: 3.90-4.26). As with RCTs of rt-CGM, few studies of FGM reported on adverse events, quality of life, emergency room, or hospital admissions. In general, the adverse event profiles were similar between FGM and SMBG. However, in 2 RCTs, patients in the FGM group reported more frequent overall events compared with SMBG (155/199 vs 76/127, relative risk: 1.30, 95% CI: 1.11-1.52) (25, 27). The most reported adverse event across studies reporting events was a nonserious hypoglycemic event (n = 27). Overall, 12 patients in the FGM group reported a device-related adverse event, with most related to skin irritation.

## Discussion

This systematic review assessed the effectiveness of CGM in patients with T2DM and poor glucose control. We conducted meta-analyses of major glucose monitoring metrics for both real-time and flash (or intermittent) CGM together and separately by CGM type. The findings of our pooled analysis of 14 RCTs, reflecting both real-time and FGM compared with SMBG, indicated a modest reduction of HbA1c levels of 0.32% with CGM. Improvement in HbA1c levels with CGM in this analysis included studies with patients on various treatment regimens, including those using or not using insulin. Importantly, a subgroup analysis of studies that provided data on patients who were not taking insulin indicated a similar but nonstatistically significant improvement among those using CGM compared to those using SMBG. Our analyses of each device type separately showed similar reductions in HbA1c levels (0.34% and 0.33%, respectively, for rt-CGM and FGM).

The overall quality of the evidence supporting these main findings was rated moderate using the GRADE system. The moderate rating was due to methodological limitations, with some studies not adequately reporting randomization procedures or allocation concealment. While no heterogeneity was observed in our overall analysis combining CGM devices, modest heterogeneity was present in our separate analysis of FGM. The heterogeneity, however, was explained by removing 1 study in which patients were on more intensive insulin regimens compared to other studies in the analysis. Other sensitivity analyses, which included varying the specifications of our meta-analysis models (eg, using follow-up values instead of baseline values), had no impact on the findings. Limitations in how the data were reported in studies precluded subgroup analyses on factors such as baseline HbA1c levels or duration of diabetes.

Our additional analyses based on CGM type showed benefits of rt-CGM for other metrics of glucose monitoring. The pooled analysis of 4 RCTs indicated a statistically significant increase in percent time in range (70-180 mg/dL) associated with use of rt-CGM compared with SMBG. And, while not statistically significant, improvements in percent time in hypoglycemia and hyperglycemia range were also observed with the use of rt-CGM. No such patterns of improvement for time in range, time in hypoglycemia, or time in hyperglycemia were seen for studies of FGM. Although the explanation for this difference is unknown, it is consistent with prior studies (28-30). One may speculate that the continuous nature of blood glucose collection, the greater availability of alarm notifications, and glucose trend arrows with rt-CGM may help individuals avoid or reduce their duration of time in less favorable ranges of blood glucose.

Few studies reported on other clinical or patient-oriented outcomes, such as quality of life, patient satisfaction, emergency room visits, hospitalization, or adverse events, which precluded meta-analyses of these outcomes. Four studies assessing the use of FGM did report on patient satisfaction in a manner suitable for meta-analysis. The findings of the pooled analysis indicated increased satisfaction among patients using FGM compared to those using SMBG. Adverse event profiles were similar between CGM users and SMBG, with the most frequently reported event across study groups nonserious hypoglycemic events. Few CGM device related events were reported.

### Strengths and Limitations

This review provides a more comprehensive and updated assessment of CGM use in the management of individuals with T2DM compared to previously published systematic reviews on this topic (1, 2, 5, 31). We considered the evidence of 2 widely used CGM devices (RT and flash) together to assess the overall impact of CGM and separately to determine the differential effects of these devices. We also considered the impact of CGM compared with SMBG across multiple glucose monitoring metrics, including HbA1c levels, time in range, and time in hypoglycemic and hyperglycemic range. It has been suggested that these different estimates of glucose control may be complimentary to HbA1c in assessing overall glycemic control and predicting more severe or longer term diabetes outcomes (32-38). For example, while time above range may be indicative of future severe hyperglycemia events and related hospitalization, glucose levels below 50 and 70 mg/dL have been closely linked with hypoglycemia events (38). Thus, demonstrating the potential of CGM to influence these metrics may have additional clinical implications.

Due to limitations in how data were reported in the included studies, we were not able to conduct subgroup analysis to determine if insulin use, duration of diabetes, or baseline HbA1c impacted our findings for change in HbA1c levels. Additional sensitivity analysis to determine the impact of patient blinding suggests little difference in overall reduction of HbA1c levels when removing studies in which patients were blinded while using FGM. We could not perform meta-analyses for several important patient-oriented outcomes, such as emergency room use, hospitalization due to severe hypoglycemia, or other adverse events due to shorter follow-up duration of the available studies and limited reporting of these outcomes across studies in our review. Additionally, the CGM technology assessed in this review reflects what was available during the conduct of the included RCTs, which spans the past 2 to 15 years. As the technology in this field is rapidly changing, particularly with respect to the additional features becoming available on FGM, future studies will need to reconsider some of the comparisons reported in the current review.

Finally, the generalizability of our findings may be limited as populations within RCTs could differ from real-world patients in key areas such as diabetes disease status, baseline medication regimens, and general health compliance.

However, 2 recent large real-world observational studies, 1 conducted within the VA Healthcare System and 1 within Kaiser Permanente Northern California (39, 40), have taken advantage of relatively closed health care systems to provide comprehensive and longer term follow-up of CGM users compared with non-CGM users. Both studies followed diabetes patients receiving insulin and in poor control. The VA Healthcare System study included more than 15 000 T2DM participants initiating CGM (both rt-CGM and FGM) and a similar number of participants using home glucose monitoring but not CGM. Although the Kaiser cohort was largely comprised of T1DM patients, it did include more than 300 patients with T2DM who were assigned rt-CGM and more than 35 000 T2 DM controls. Characteristics of T2DM patients within these studies were similar to those participating in the RCTs assessed in this review. Both these real-world observational studies confirmed the degree of lowering of HbA1c illustrated in the meta-analyses for both rt-CGM and FGM, suggesting that, in T2DM patients receiving insulin and in poor control, one can expect a reduction in HbA1c % of 0.3 to 0.4 with the addition of CGM. As the follow-up for the observational studies was generally longer than that of the RCTs included in our meta-analyses (12 months vs 6 months), these improvements in HbA1c may be relatively long lasting. Like rt-CGM users within the analyzed RCTs, rt-CGM users in the Kaiser study also appeared to gain reasonable increases in time in range and demonstrated trends for reduction in hypoglycemia. Thus, real-world data on CGM users with T2DM appear very consistent with the currently reported meta-analyses results.

## Conclusion

Our analyses demonstrated that initiation of CGM led to a modest but significant decline in HbA1c of 0.32% among individuals with T2DM. Despite analyzing studies that included patients on a broad variety of baseline treatment regimens, there was minimal heterogeneity of results, which strengthens our confidence in these results. Of note, while declines in HbA1c were similar for both rt-CGM and FGM, there was a trend for improvements in other metrics of glucose control that favored rt-CGM over SMBG. However, the duration of the RCTs included in our review was relatively short, and only a few studies reported on important patient-oriented outcomes, such as emergency room use, hospitalization due to severe hypoglycemia, and other adverse events. Thus, longer term studies are needed to determine if the short-term improvements in glucose control observed with the use of CGM lead to improvements in clinically important outcomes. Finally, given that not all patients will achieve the same benefits of CGM demonstrated in this review, future studies should assess what patient features (eg, activity level, duration of insulin use) and other factors (eg, cost associated with hospitalizations and other severe adverse events) influence use and benefits of CGM.

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## Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References (13).

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