META-ANALYSES

# Effects of Continuous Glucose Monitoring on Metrics of Glycemic Control in Diabetes: A Systematic Review With Meta-analysis of Randomized Controlled Trials

Maria Ida Maiorino,[1,2] Simona Signoriello,[3] Antonietta Maio,[2] Paolo Chiodini,[3] Giuseppe Bellastella,[1,2] Lorenzo Scappaticcio,[1,2] Miriam Longo,[2] Dario Giugliano,[1,2] and Katherine Esposito[2,4]

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## BACKGROUND

**Continuous glucose monitoring (CGM) provides important information to aid in achieving glycemic targets in people with diabetes.**

## PURPOSE

**We performed a meta-analysis of randomized controlled trials (RCTs) comparing CGM with usual care for parameters of glycemic control in both type 1 and type 2 diabetes.**

## DATA SOURCES

**Many electronic databases were searched for articles published from inception until 30 June 2019.**

## STUDY SELECTION

**We selected RCTs that assessed both changes in $HbA_{1c}$ and time in target range (TIR), together with time below range (TBR), time above range (TAR), and glucose variability expressed as coefficient of variation (CV).**

## DATA EXTRACTION

**Data were extracted from each trial by two investigators.**

## DATA SYNTHESIS

**All results were analyzed by a random effects model to calculate the weighted mean difference (WMD) with the 95% CI. We identified 15 RCTs, lasting 12–36 weeks and involving 2,461 patients. Compared with the usual care (overall data), CGM was associated with modest reduction in $HbA_{1c}$ (WMD −0.17%, 95% CI −0.29 to −0.06, $I^2 = 96.2\%$), increase in TIR (WMD 70.74 min, 95% CI 46.73–94.76, $I^2 = 66.3\%$), and lower TAR, TBR, and CV, with heterogeneity between studies. The increase in TIR was significant and robust independently of diabetes type, method of insulin delivery, and reason for CGM use. In preplanned subgroup analyses, real-time CGM led to the higher improvement in mean $HbA_{1c}$ (WMD −0.23%, 95% CI −0.36 to −0.10, $P < 0.001$), TIR (WMD 83.49 min, 95% CI 52.68–114.30, $P < 0.001$), and TAR, whereas both intermittently scanned CGM and sensor-augmented pump were associated with the greater decline in TBR.**

## LIMITATIONS

**Heterogeneity was high for most of the study outcomes; all studies were sponsored by industry, had short duration, and used an open-label design.**

## CONCLUSIONS

**CGM improves glycemic control by expanding TIR and decreasing TBR, TAR, and glucose variability in both type 1 and type 2 diabetes.**


[1]*Unit of Endocrinology and Metabolic Diseases, University of Campania "Luigi Vanvitelli," Naples, Italy*
[2]*Department of Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy*
[3]*Medical Statistics Unit, University of Campania "Luigi Vanvitelli," Naples, Italy*
[4]*Unit of Diabetes, University of Campania "Luigi Vanvitelli," Naples, Italy*

*Corresponding author: Maria Ida Maiorino, mariaida.maiorino@unicampania.it*

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The glucose monitoring field represents an essential component of the management of diabetes. Beside self–blood glucose monitoring (SBGM), which primarily supported self-management and medication adjustment of people with diabetes, continuous glucose monitoring (CGM) has emerged as a valuable tool to assess the effectiveness and safety of treatment in many patients with type 1 diabetes and in selected patients with type 2 diabetes treated with intensive insulin regimens (1).

Currently, available CGM systems are made of a sensor, which measures glucose levels in the interstitial fluid at 1- to 5-min intervals, and a transmitter that collects and forwards glucose values to the third component (a receiver), responsible for displaying data. Alternative modalities for continuously monitoring glucose trends are represented by real-time CGM (rtCGM), in which readers, either standalone devices or integrated into insulin pumps or mobile phones, display transmitted interstitial glucose readings in real time, or intermittently scanned glucose monitoring (iCGM), by which glucose values are displayed on demand when the sensor is scanned with a reading device (2). Applying these technologies to diabetes management results in immediate information regarding glucose levels to the user, as well as glucose trend, its current direction, and rate of change, leading to an increased time in the target glucose range by reducing hyperglycemia and minimizing the occurrence of hypoglycemia (2,3). In previous meta-analyses of randomized controlled trials (RCTs) conducted in patients with both type 1 (4–6) and type 2 diabetes (7,8), the use of CGM provided a reduction in $HbA_{1c}$ of ~0.3%, with less hypoglycemia (4,5), compared with usual care.

The large quantity of glucose readings collected by CGM allows users to obtain a more complete profile of the glycemic status over the entire day, including the time spent in the target ranges (TIR) (usually 70–180 mg/dL) and the time spent in hypo- and hyperglycemia, as well as measures of glucose variability, adding some useful information for assessment of the current glycemic profile in addition to what is provided by the $HbA_{1c}$ (9,10). A recent international consensus on the use of CGM highlighted the importance of assessing and reporting the percentages of TIR, time below range (TBR), and time above range (TAR) in conjunction with measures of glucose variability as key metrics for the evaluation of glucose control in clinical studies (9).

Although there have been several systematic reviews with meta-analyses of clinical research assessing the contribution of CGM to glycemic goals over usual care (4–8), none of these studies estimate the effects of the available CGM systems on diabetes control in terms of TIR, TBR, TAR, or glucose variability. The evaluation of the efficacy and safety of different CGM systems (rtCGM, iCGM, or sensor-augmented pump [SAP]) on these emerging metrics may help clinicians to assess the duration, frequency, and degree of fluctuations in blood glucose levels, thus contributing to improve the overall glucose control. We here provide a systematic review with meta-analysis of RCTs including both people with type 1 and with type 2 diabetes, with the aim of determining *1*) whether the use of CGM results in improved glucose control as increased TIR or decreased $HbA_{1c}$ and *2*) whether CGM systems can lower TBR, TAR, and glucose variability, as compared with usual care.

## METHODS

This Systematic Review and Meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). The PRISMA checklist and the protocol of this study are provided in Supplementary Data.

### Data Sources and Searches

A comprehensive search of MEDLINE (via PubMed), Google Scholar, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov was run from the inception of each database to 30 June 2019. The complete search used for PubMed was: (continuous glucose monitoring[MeSH Terms]) OR CGM[Text Word]) OR real time continuous glucose monitoring[Text Word]) OR FGM[Text Word]) OR flash glucose monitoring[Text Word]) OR intermittently scanned continuous glucose monitoring [Text Word]) OR intermittently viewed continuous glucose monitoring [Text Word]) OR iCGM [Text Word]) OR isCGM [Text Word]) OR SAP[Text Word]) OR sensor augmented pump[Text Word]) OR Low Glucose Suspend [Text Word]) OR LGS [Text Word]) OR suspend before low [Text Word]) OR predictive glucose suspend [Text Word]) OR Predictive Low Glucose Management [Text Word]) OR PLGM [Text Word]) AND type 1 diabetes [Text Word])) OR type 2 diabetes[Text Word]) AND glycemic control[Text Word]) OR diabetes control[Text Word]) OR time in target[Text Word]) OR time in range[Text Word]) AND hypoglycemia[Text Word]) OR time in hypoglycemia[Text Word]) AND hyperglycemia[Text Word]) OR time in hyperglycemia[Text Word]) AND randomized controlled trial[Text Word]). We also did a manual search, using the reference list of prior reviews and meta-analyses, to track relevant RCTs that were not indexed by normal keywords.

### Study Selection

We selected RCTs if they had at least 12 weeks' duration of intervention; included patients of any age with type 1 or type 2 diabetes treated with an intensive insulin regimen (multiple daily injections of insulin [MDI] or continuous subcutaneous insulin infusion [CSII]); compared CGM as rtCGM, iCGM, or SAP with the standard care (usually SBGM); and reported both $HbA_{1c}$ and TIR together with the other outcomes of interest, including time spent in hypoglycemia, time spent in hyperglycemia, and coefficient of variation (CV) at the end of the study period. Studies involving pregnant patients were also included. Moreover, trials were included if CGM was used for >50% of the total follow-up time and a blinded CGM phase at the beginning and at the end of the study was provided to collect data for patients of control groups. Both crossover and parallel-group designs were included. We excluded studies using retrospective CGM without real-time reading of glucose values, trials where the insulin regimen differed between intervention and control groups, extension studies from previous trials, and observational studies or publications without original data or with incomplete data (abstracts, letters, clinical reviews, editorials, and commentaries). Two investigators (M.I.M. and A.M.) independently decided trial eligibility on the basis of the titles and abstracts, and studies that met the inclusion criteria were retrieved for full-text assessment. All disagreements were resolved by consensus.

### Data Extraction and Quality Assessment

Two independent investigators (M.I.M. and A.M.) used a standardized form to

extract data, and disagreements were resolved by consensus after discussion. Any RCTs that met the inclusion/exclusion criteria were included in the analysis. Supplementary material was consulted. The following data were extracted from each retrieved study: *1*) authors and year of publication; *2*) study design; *3*) study duration; *4*) patients' data including type of diabetes, age-group category, and mean age; *5*) CGM modality with type of sensor; *6*) comparator strategy; *7*) baseline $HbA_{1c}$; *8*) insulin regimen in both intervention and control groups; *9*) studies' primary outcome; *10*) study funder; *11*) $HbA_{1c}$ at the end point; *12*) TIR, TBR, and TAR at the end point; and *13*) CV at the end point. TBR was differentiated as level 1 hypoglycemia (<70–54 mg/dL [3.9–3.0 mmol/L]) and level 2 hypoglycemia (<54 mg/dL [3.0 mmol/L]); TAR was differentiated as level 1 hyperglycemia (>180 mg/dL [10 mmol/L]) and level 2 hyperglycemia (>250 mg/dL [13 mmol/L]). When TIR, TBR, or TAR was reported as percentage of time in the 24 h, a conversion in minutes has been made in order to use a single measure unit for all included studies.

The Cochrane Collaboration risk-of-bias tool was used to evaluate the quality of RCTs (12). We assessed risk of bias in random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Studies were rated as having a high, low, and unclear risk of bias. The quality of each RCT was assessed blinded by two reviewers (M.I.M. and A.M.). Disagreements were resolved by consensus after discussion.

### Data Synthesis and Analysis

The coprimary outcomes were the difference in $HbA_{1c}$ and in minutes of time in the target range during the study period (derived from CGM [target range ≥70–180 mg/dL]). Secondary outcomes were minutes of time in hypo- and hyperglycemic ranges and CV as metrics of glucose variability. Changes from baseline in $HbA_{1c}$, TIR, CV, and hypoglycemic and hyperglycemic levels were analyzed as continuous variables using mean difference change between groups and its SD as summary measures. From each study, the mean change from baseline between the two groups and its SD was extracted. If change from baseline was not available, the mean difference and its SD at the end point time were used instead of mean difference change. If not reported, SD of the difference was estimated by standard equations from the reported SE, CI, and *P* value or calculated from SDs of the two groups (13). If variability was reported as interquartile range (IQR), SD was estimated from IQR (14). Heterogeneity between studies was assessed by using Q statistic, and a *P* value <0.10 was considered significant (13). The proportion of variation in observed effects due to heterogeneity rather than sampling error was evaluated by using $I^2$ index (15). For each outcome, for estimation of a weighted mean difference (WMD) a random effects model was used if overall heterogeneity was significant; otherwise, a fixed effects model was used. Publication bias was assessed visually with funnel plots and with Egger test (16) when at least 10 studies were included in the meta-analysis; a *P* value of <0.10 was considered significant. If such bias was evident, the trim-and-fill method was used to generate a pooled estimate that accounted for the unpublished findings (17). For all outcomes, we did preplanned subgroup analyses restricted to glucose monitoring modality (rtCGM, iCGM, and SAP), diabetes type (type 1 and type 2 diabetes) background therapy (CSII, MDI, or both), and different reason for using CGM (improving glycemic control, hypoglycemia awareness, reducing hypoglycemia, pregnancy, or planning pregnancy). Sensitivity analyses were also performed excluding pediatric patients and pregnant women (planned or unplanned pregnancy) and participants with type 2 diabetes. Data were analyzed using Stata, version 14 (StataCorp, College Station, TX). All statistical tests were two sided, and *P* values <0.05 were regarded as significant.

## RESULTS

### Search Results

The process of studies' selection is reported in Fig. 1. The initial search identified 4,015 articles, of which 1,781 were reviewed on the basis of the titles and abstracts after removal of duplicates. Further excluded articles ($n$ = 1,723) were mainly reviews, comments, editorials, meta-analyses, or observational studies. Of the remaining 58 full-text studies retrieved, 43 were excluded because they did not present interest data ($n$ = 24), were extension studies ($n$ = 6), compared two modalities of CGM ($n$ = 4), were study protocols ($n$ = 3), did not use rtCGM ($n$ = 4), or were of short duration ($n$ = 2) (Supplementary Table 1). Finally, 15 RCTs (18–32) with 18 comparisons, including a total of 2,461 participants (1,308 in the intervention groups and 1,153 in the control groups), were included in the quantitative synthesis and meta-analysis.

### Study and Patient Characteristics

Table 1 shows the characteristics of the included RCTs with baseline patients' features. The trials were published between 2008 and 2019, and all of them received industry funding, except two (18,21). All studies used an open-label design; three studies had a crossover design (22,24,29), and the remaining studies had a parallel-group design. The trials had a duration ranging from 12 to 36 weeks. Ten studies used rtCGM (18–27), three studies used iCGM (28–30), and two studies used SAP (31,32). Among the 10 studies using rtCGM, 9 studies compared rtCGM with SMBG (18,19,21–27) and 1 study compared CGM sensor on with CGM sensor off (20). Among the remaining five studies, three studies compared iCGM with SMBG (28–30) and two study studies compared SAP with CSII (31,32). Devices used were Dexcom SEVEN, Dexcom G4 Platinum CGM System, Dexcom G5 mobile, Enilite, Medtronic MiniMed Paradigm, Medtronic MiniMed MiniLink, Guardian REAL-Time, MiniMed 640G with SmartGuard, FreeStyle Libre, and FreeStyle Navigator. Insulin delivery was by CSII alone in three trials (20,31,32), by MDI in five trials (23,24,26,27,30), and by CSII or MDI in seven trials (18,19,21,22,25,28,29). The primary outcome was the change in $HbA_{1c}$ level in seven studies (18,20,23–26,29), the time spent in hypoglycemia in three studies (19,28,30), the difference in the time spent in target range in two studies (22,31), the number of hypoglycemic events in two studies (27,32), and the difference in hypoglycemia awareness in one study (21).

The participants in all trials were adults (>18 years old); five studies (18–20,23,31) included also pediatric patients, and only one study (25) included pregnant women or women planning pregnancy. Twelve studies included patients with type 1 diabetes (18–25,27,30–32), two studies focused on patients with type 2 diabetes (24,29), and one study evaluated both

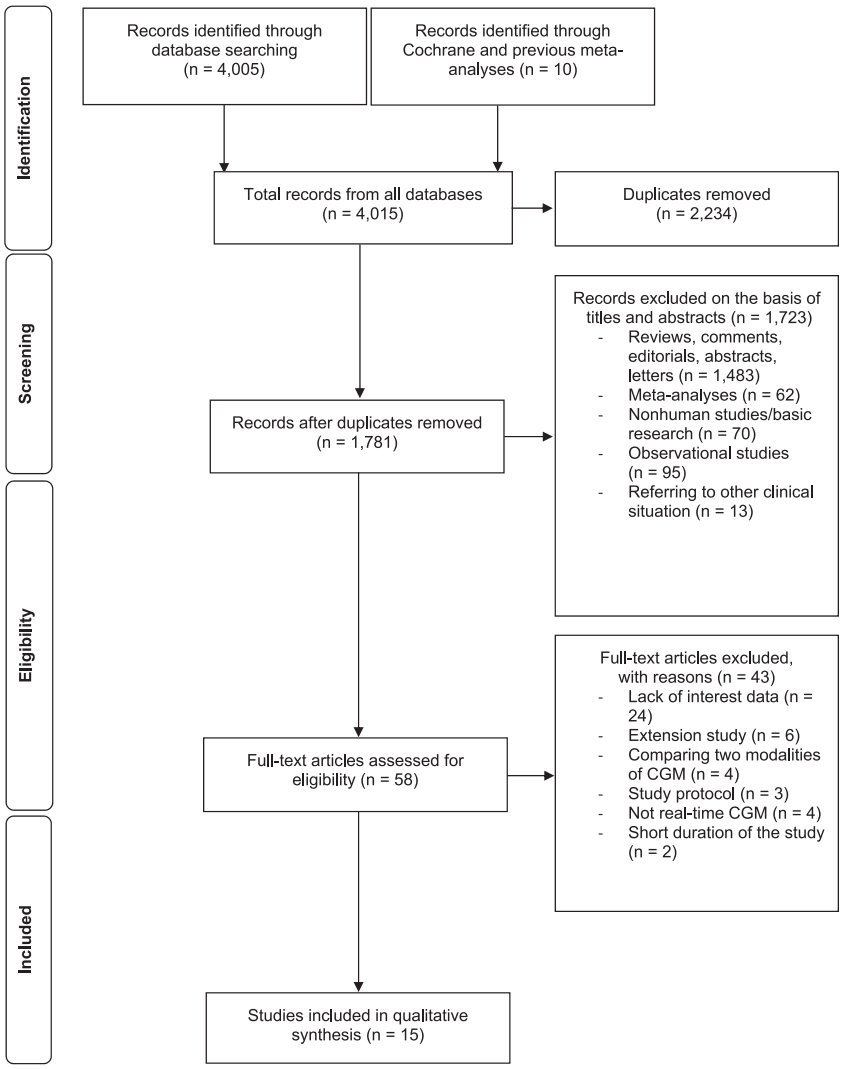


**Figure 1**—Process of study selection.

patients with type 1 and with type 2 diabetes (26). Mean patient age ranged from 11.4 to 67 years, and mean baseline $HbA_{1c}$ levels ranged from 6.7% to 8.9%, with a median of 7.8% (IQR 7.4–8.3) in the intervention groups and 7.7% (IQR 7.4–8.5) in the comparator groups.

### Risk of Bias

According to the Cochrane Collaboration's tool for assessing risk of bias, selection bias was evaluated as low in all trials, except one (18), for allocation concealment; performance bias was evaluated as high in all trials for blinding of participants and personnel, given that none of the trials masked participants to the intervention; and detection bias was evaluated as unclear in 10 trials and high in 4 trials for blinding of outcome assessment. Attrition and reporting biases were generally low risk for all studies, except one (26) (Supplementary Fig. 1 and Supplementary Table 2).

### Coprimary Outcome

Eighteen comparisons from 15 studies with 2,461 participants (1,308 in the intervention group and 1,153 in the control group) were pooled for the primary outcome (change in $HbA_{1c}$ and change in TIR). Compared with control strategies, $HbA_{1c}$ was 0.17% (95% CI −0.29 to −0.06, $P = 0.003$) lower with the CGM, with high heterogeneity between studies ($I^2 = 96.2\%$, $P < 0.001$) (Fig. 2*A* and Table 2) and no evidence of publication bias (Egger test, $P = 0.166$). In the prespecified subgroup analysis, the mean reduction of $HbA_{1c}$ was 0.23% in the 13 comparisons using rtCGM, with high heterogeneity ($I^2 = 92.2\%$) (Table 2). Neither iCGM nor SAP significantly changed mean $HbA_{1c}$ levels, with no evidence of statistically significant heterogeneity for the three comparisons using iCGM ($I^2 = 0\%$) and high heterogeneity for the two comparisons using SAP ($I^2 = 85.5\%$) (Table 2). CGM produced the greater $HbA_{1c}$ reduction in trials in which its use was aimed at improving glycemic control (−0.31, 95% CI −0.43 to −0.19, $P < 0.001$) (Supplementary Table 3); a significant 0.16% decrease of $HbA_{1c}$ was associated with people with type 1 diabetes but not people with type 2 diabetes. $HbA_{1c}$ levels did not differ based on background therapy with CSII or MDI (Supplementary Table 3).

Compared with control, CGM was associated with a significant increase of TIR (70.74 min, 95% CI 46.73–94.76, $P < 0.001$), with heterogeneity between studies ($I^2 = 66.3\%$, $P < 0.001$) (Fig. 2*B* and Table 2) and no evidence of publication bias (Egger test, $P = 0.243$). In the prespecified subgroup analysis, TIR increased more in trials using rtCGM (83.49, 95% CI 52.68 to 114.30, $P < 0.001$) than iCGM (53.91, 95% CI 28.54–79.27, $P < 0.001$) or SAP (37.10, 95% CI 0.74–73.45, $P = 0.045$) (Table 2). Heterogeneity was found only in the 13 comparisons using rtCGM ($I^2 = 66.5\%$). Results were also consistent with those of the prespecified subgroup analysis based on type of diabetes, background therapy, and CGM reason for use; no evidence of statistical heterogeneity was displayed in the comparisons using CSII therapy and in those in which CGM was used for pregnancy or planning pregnancy or to reduce hypoglycemia (Supplementary Table 4).

The sensitivity analysis performed to exclude the pediatric population and pregnant women/women planning pregnancy showed that CGM did not significantly reduce $HbA_{1c}$ (−0.16%, 95% CI −0.32 to 0.01, $P = 0.066$) (Supplementary Fig. 2*A*), even considering only the adult population with type 1 diabetes (−0.12%, 95% CI −0.27 to 0.02, $P = 0.103$) (Supplementary Fig. 2*B*). Results for TIR change were similar to those obtained in the overall analysis (73.41 min, 95% CI 43.44–103.38, $P < 0.001$) (Supplementary Fig. 3*A*), even excluding studies involving adults with type 2 diabetes (72.18 min, 95% CI 37.93–106.43, $P < 0.001$) (Supplementary Fig. 3*B*), without reducing statistical heterogeneity.

### Secondary Outcomes

The overall analysis of the 18 comparisons that assessed the TBR level 1 hypoglycemia during treatment showed a

**Table 1—Characteristics of trials included in the meta-analysis**

| First author, year (reference no.), characteristics of subjects | Study design | Study duration (weeks) | Diabetes type | *N* intervention/ control | Mean age intervention/ control, years | Baseline $HbA_{1c}$ intervention/ control, % (mmol/mol) | Intervention/sensor/ comparator | Insulin regimen | Primary outcome | Sponsor |
|---|---|---|---|---|---|---|---|---|---|---|
| JDRF, 2008 (18) | P, O | 26 | T1 | | | | rtCGM/Dexcom SEVEN or MiniMed Paradigm REAL-Time or FreeStyle Navigator/SBGM | CSII, MDI | Change in $HbA_{1c}$ level at 26 weeks | JDRF |
| ≥25 years old | | | | 52/46 | 41.2/44.6 | 7.6/7.6 (60/60) | | | | |
| 15–24 years old | | | | 57/53 | 18.8/18.2 | 8.0/7.9 (64/63) | | | | |
| 8–14 years old | | | | 56/58 | 11.4/11.6 | 8.0/7.9 (64/63) | | | | |
| O'Connell, 2009 (31), adult and pediatric | P, O | 12 | T1 | 31/31 | 23.4/23.0 | 7.3/7.5 (56/58) | SAP/MiniMed Paradigm REAL-Time/CSII | CSII | Difference in the proportion of TIR (70–180 mg/dL) | Medtronic |
| Battelino, 2011 (19), adult and pediatric | P, O | 26 | T1 | 62/58 | 25.7/26.0 | 6.9/6.9 (52/52) | rtCGM/FreeStyle Navigator/SBGM | CSII, MDI | Time spent in hypoglycemia (<63 mg/dL) during the 26 weeks | Abbott Diabetes Care |
| Battelino, 2012 (20), adult and pediatric | CO, O | 24 | T1 | 77/76 | 28.0/28.0 | 8.3/8.5 (63/69) | rtCGM/Guardian REAL-Time/CGM sensor off | CSII | Difference in $HbA_{1c}$ levels between the sensor on and sensor off arms after 6 months of follow-up | Medtronic |
| Little, 2014 (21), adult | P, O | 24 | T1 | 42/41 | 50.1/47.1 | 8.2/8.3 (66/67) | rtCGM/CE-marked rtCGM (Medtronic)/ SBGM | CSII, MDI | Difference in hypoglycemia awareness at 24 weeks | Diabetes UK, NIH, Cambridge NIHR |
| Bolinder, 2016 (28), adult | P, O | 24 | T1 | 119/120 | 42.0/45.0 | 6.8/6.8 (51/51) | iCGM/Freestyle Libre/ SBGM | CSII, MDI | Time spent in state of hypoglycemia (<70 mg/dL) | Abbott Diabetes Care |
| van Beers, 2016 (22), adult | CO, O | 16 | T1 | 26/26 | 48.6/48.6 | 7.5/7.5 (58/58) | rtCGM/Enilite/SBGM | CSII, MDI | Mean difference in percentage of time spent in state of normoglycemia | Eli Lilly, Sanofi, Medtronic |
| Beck, 2017 (23), adult and pediatric | P, O | 24 | T1 | 105/53 | 46.0/51.0 | 8.6/8.6 (70/70) | rtCGM/Dexcom G4 Platinum CGM System/ SBGM | MDI | Difference in change in $HbA_{1c}$ levels from baseline to 24 weeks | Dexcom, Inc. |
| Beck, 2017 (24), adult | P, O | 24 | T2 | 79/79 | 60.0/60.0 | 8.5/8.5 (69/69) | rtCGM/Dexcom G4 Platinum CGM System/ SBGM | MDI | $HbA_{1c}$ reduction at 24 weeks | Dexcom, Inc. |
| Feig, 2017 (25) | P, O | | T1 | | | | rtCGM/Guardian REAL-Time or MiniMed MiniLink/SBGM | CSII, MDI | Difference in change in $HbA_{1c}$ from randomization to 34 weeks' gestation in the pregnancy trial and to 24 weeks or conception in the planning pregnancy trial | JDRF, Medtronic |
| Women planning pregnancy | | 24 | | 53/57 | 33.5/32.4 | 7.9/7.8 (63/62) | | | | |
| Pregnant women | | 36 | | 108/107 | 31.4/31.5 | 7.4/7.4 (57/57) | | | | |

*Continued on p. 1151*

**Table 1—Continued**

| First author, year (reference no.), characteristics of subjects | Study design | Study duration (weeks) | Diabetes type | *N* intervention/ control | Mean age intervention/ control, years | Baseline $HbA_{1c}$ intervention/ control, % (mmol/mol) | Intervention/sensor/ comparator | Insulin regimen | Primary outcome | Sponsor |
|---|---|---|---|---|---|---|---|---|---|---|
| Haak, 2017 (29), adult | P, O | 24 | T2 | 149/75 | 59.0/59.5 | 8.7/8.9 (72/74) | iCGM/FreeStyle Libre/ SBGM | CSII, MDI | Difference in $HbA_{1c}$ at 6 months | Abbott Diabetes Care |
| Ruedy, 2017 (26), adult | CO, O | 24 | T1, T2 | 63/53 | 67.0/67.0 | 8.4/8.6 (68/70) | rtCGM/Dexcom G4 Platinum/SBGM | MDI | Change of $HbA_{1c}$ from baseline to 24 weeks | Dexcom, Inc. |
| Heinemann, 2018 (27), adult | P, O | 24 | T1 | 75/74 | 45.8/47.3 | 7.6/7.3 (60/56) | rtCGM/Dexcom G5 Mobile/SBGM | MDI | No. of hypoglycemic events measured by rtCGM during the follow-up phase compared with baseline | Dexcom, Inc. |
| Oskarsson, 2018 (30), adult | P, O | 24 | T1 | 82/81 | 42.0/44.0 | 6.8/6.7 (51/50) | iCGM/FreeStyle Libre/ SBGM | MDI | Change in time spent in a state of hypoglycemia ($<$70 mg/dL) from baseline | Abbott Diabetes Care |
| Bosi, 2019 (32), adult | P, O | 24 | T1 | 76/77 | 49.0/47.4 | 7.7/7.6 (60/59) | SAP/MiniMed 640G with SmartGuard/CSII plus SBMG | CSII | Mean no. of sensor hypoglycemic events: sensor glucose values $\leq$55 mg/dL (3.1 mmol/L) for $>$20 min | Medtronic |

CO, crossover; NIH, National Institutes of Health; NIHR, National Institute for Health Research; O, open-label; P, parallel; T1, type 1 diabetes; T2, type 2 diabetes.

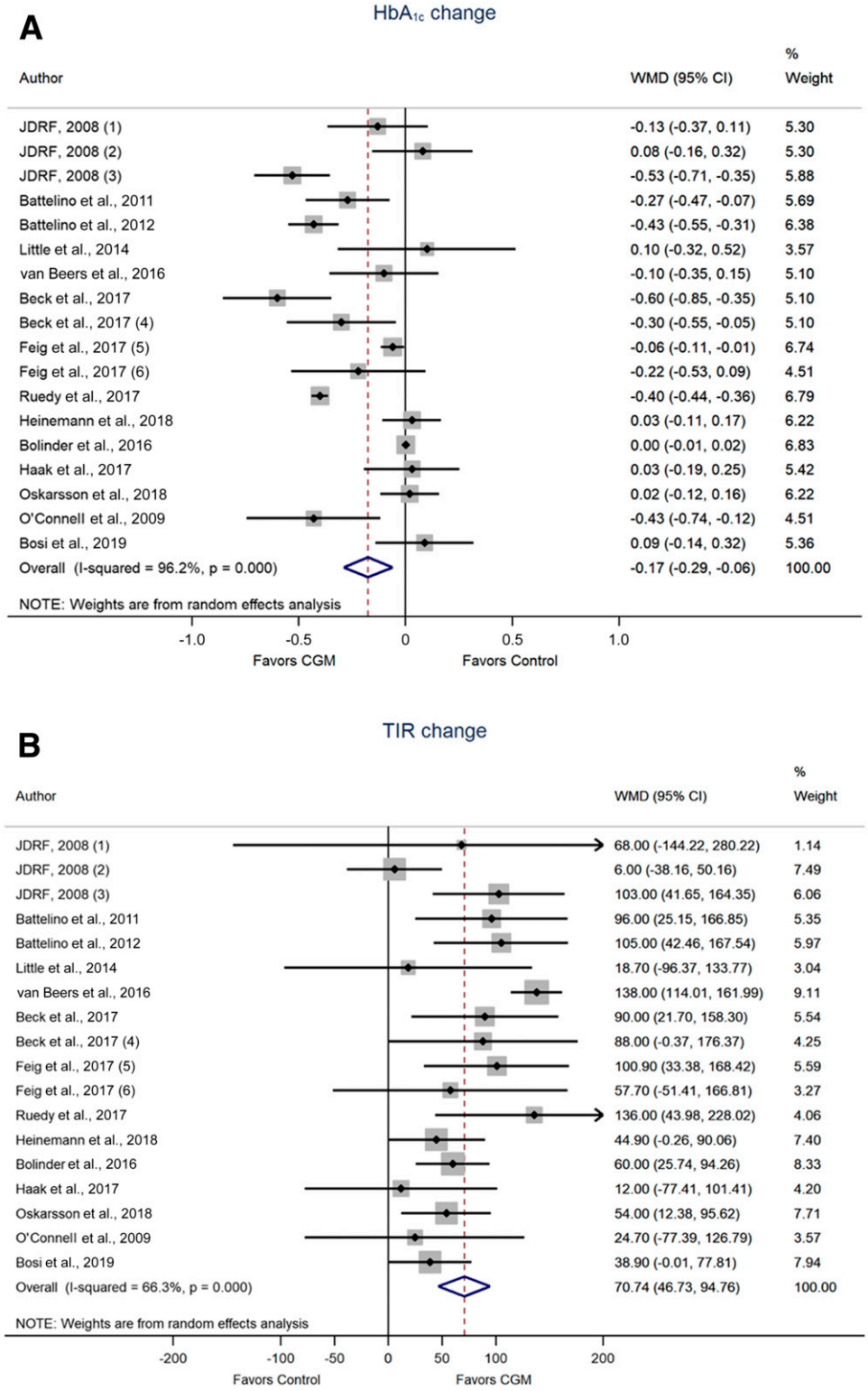


**Figure 2**—Forest plots of meta-analysis for $HbA_{1c}$ (*A*) and TIR (*B*) change from baseline in all 16 comparisons. The results are expressed as WMD. TIR, 70–180 mg/dL. (1), (2), and (3) refer to different arms of the same study (ref. 18) and specifically age-group 8–14 years (1), age-group 15–24 years (2), and age-group >25 years (3); (4) refers to ref. 24; and (5) and (6) refer to different arms of the same study (ref. 25) and specifically to pregnant women (5) and women planning pregnancy (6).

significant reduction in the proportion of time spent <70 mg/dL when CGM was compared with control strategies (−27.16 min, 95% CI −42.08 to −12.25, $P < 0.001$) (Table 2), with high heterogeneity ($I^2 = 98.9\%$, $P < 0.001$) and no evidence of publication bias (Egger test, $P = 0.669$). In the prespecified subgroup analysis, TBR (level 1 hypoglycemia) significantly decreased in trials using rtCGM (−15.82, 95% CI −25.70 to −5.95, $P = 0.002$) and iCGM (−56.26, 95% CI −88.91 to −23.60,

**Table 2—Preplanned subgroup analysis**

| | Comparisons | Patients | Control subjects | Estimated WMD (95% CI) | *P* | $I^2$ | *P* value of Q test |
|---|---|---|---|---|---|---|---|
| $HbA_{1c}$ | | | | | | | |
| rtCGM | 13 | 851 | 769 | −0.23 (−0.36 to −0.10) | <0.001 | 92.2% | <0.001 |
| iCGM | 3 | 350 | 276 | 0.00 (−0.01 to 0.02) | 0.861 | 0.0% | 0.934 |
| SAP | 2 | 107 | 108 | −0.16 (−0.67 to 0.35) | 0.542 | 85.5% | 0.009 |
| Overall | 18 | 1,308 | 1,153 | −0.17 (−0.29 to −0.06) | 0.003 | 96.2% | <0.001 |
| TIR | | | | | | | |
| rtCGM | 13 | 851 | 769 | 83.49 (52.68–114.30) | <0.001 | 66.5% | <0.001 |
| iCGM | 3 | 350 | 276 | 53.91 (28.54–79.27) | <0.001 | 0.0% | 0.617 |
| SAP | 2 | 107 | 108 | 37.10 (0.74–73.45) | 0.045 | 0.0% | 0.799 |
| Overall | 18 | 1,308 | 1,153 | 70.74 (46.73–94.76) | <0.001 | 66.3% | <0.001 |
| TBR level 1 | | | | | | | |
| rtCGM | 13 | 851 | 769 | −15.82 (−25.70 to −5.95) | 0.002 | 96.6% | <0.001 |
| iCGM | 3 | 350 | 276 | −56.26 (−88.91 to −23.60) | 0.001 | 93.7% | <0.001 |
| SAP | 2 | 107 | 108 | −41.04 (−127.10 to 45.02) | 0.350 | 88.1% | 0.004 |
| Overall | 18 | 1,308 | 1,153 | −27.16 (−42.08 to −12.25) | <0.001 | 98.9% | <0.001 |
| TBR level 2 | | | | | | | |
| rtCGM | 8 | 524 | 450 | −5.65 (−10.83 to −0.46) | 0.033 | 74.3% | <0.001 |
| iCGM | 3 | 350 | 276 | −26.23 (−49.07 to −3.40) | 0.024 | 86.8% | 0.001 |
| SAP | 1 | 76 | 77 | −37.40 (−46.05 to −28.75) | <0.001 | — | — |
| Overall | 12 | 950 | 803 | −13.58 (−20.63 to −6.53) | <0.001 | 91.7% | <0.001 |
| TAR level 1 | | | | | | | |
| rtCGM | 12 | 788 | 716 | −54.34 (−75.03 to −33.64) | <0.001 | 21.7% | 0.230 |
| iCGM | 2 | 231 | 156 | 35.52 (−3.00 to 74.03) | 0.071 | 0.0% | 0.588 |
| SAP | 2 | 107 | 108 | 23.98 (−34.95 to 82.90) | 0.425 | 26.3% | 0.244 |
| Overall | 16 | 1,126 | 980 | −30.26 (−58.15 to −2.38) | 0.033 | 67.9% | <0.001 |
| TAR level 2 | | | | | | | |
| rtCGM | 8 | 545 | 462 | −44.79 (−74.97 to −14.61) | 0.004 | 69.6% | 0.002 |
| iCGM | 3 | 350 | 276 | −16.16 (−30.57 to −1.74) | 0.028 | 0.0% | 0.562 |
| SAP | 1 | 76 | 77 | −1.44 (−28.09 to 25.21) | 0.916 | — | — |
| Overall | 12 | 971 | 815 | −27.68 (−45.31 to −9.97) | 0.004 | 63.9% | 0.002 |
| CV | | | | | | | |
| rtCGM | 7 | 509 | 449 | −2.56 (−5.28 to 0.17) | 0.066 | 93.1% | <0.001 |
| iCGM | 3 | 350 | 276 | −3.86 (−5.15 to −2.57) | <0.001 | 78.1% | 0.010 |
| SAP | — | — | — | — | — | — | — |
| Overall | 10 | 859 | 725 | −3.09 (−4.43 to −1.74) | <0.001 | 90.7% | <0.001 |

$P = 0.001$) but not in the studies using SAP (Table 2). Heterogeneity remained high in all subgroup comparisons (Table 2). The greater decrease in TBR level 1 hypoglycemia was associated with studies using CGM for hypoglycemia awareness, improvement of glycemic control, or reducing hypoglycemia; moreover, CGM led to greater reduction of TBR level 1 hypoglycemia in type 1 diabetes and in people using MDI (Supplementary Table 5). Twelve comparisons with 1,753 patients were pooled for TBR level 2 hypoglycemia. The time <54 mg/dL was 13.58 min (95% CI −20.63 to −6.53, $P < 0.001$) less with CGM compared with control strategies (Table 2), with high heterogeneity ($I^2 = 91.7\%$, $P < 0.001$) and evidence of publication bias (Egger test, $P = 0.010$). The trim-and-fill test reduced this estimate without changing its statistical significance (−1.66, 95% CI −1.99 to −0.34, $P = 0.006$). In the prespecified subgroup analysis, the greater decline in TBR level 2 hypoglycemia was associated with SAP (−37.40 min, 95% CI −46.05 to −28.75, $P < 0.001$) (Table 2). Moreover, CGM led to significant reduction in TBR level 2 hypoglycemia in studies involving a population with type 1 diabetes or using CGM to reduce hypoglycemia; heterogeneity remained high in all subgroup comparisons (Supplementary Table 6). The sensitivity analysis performed to exclude the pediatric population and pregnant women or women planning pregnancy showed that CGM led to TBR reduction (both level 1 and level 2 hypoglycemia) slightly greater than for those obtained in the overall analysis (Supplementary Figs. 4*A* and 5*A*), even in the studies restricted to type 1 diabetes (Supplementary Figs. 4*B* and 5*B*), without reducing statistical heterogeneity.

In the overall analysis of the pooled 16 comparisons, CGM led to a significant reduction of TAR level 1 hyperglycemia (180 mg/dL) compared with control regimens (−30.26 min, 95% CI −58.15 to −2.38, $P = 0.033$), with heterogeneity ($I^2 = 67.9\%$, $P < 0.001$) and no evidence of publication bias (Egger's test, $P = 0.689$). In the prespecified subgroup analysis, the mean change was significant only in the 12 comparisons using rtCGM (−54.34 min, 95% CI −75.03 to −33.64, $P < 0.001$) and not in those using iCGM or SAP (Table 2). Heterogeneity was low in all of the subgroups based on CGM modality (Table 2). Moreover, TAR level 1 hyperglycemia was lower in the 14 comparisons involving type 1 diabetes and in those in which the reasons for CGM use were the improvement of glycemic control and pregnancy or planning pregnancy (Supplementary Table 7). Twelve comparisons were pooled for TAR level 2 hyperglycemia (>250 mg/dL). Compared with control regimens, CGM significantly decreased time >250 mg/dL (−27.68 min, 95% CI −45.31 to −9.97,

$P = 0.004$), with heterogeneity ($I^2 = 63.9\%$, $P = 0.002$) and no evidence of publication bias (Egger test, $P = 0.358$). The prespecified subgroup analysis showed that the highest decrease in TAR level 2 hyperglycemia was associated with rtCGM (−44.79 min, 95% CI −74.97 to −14.61, $P = 0.004$); heterogeneity was found between the trials using rtCGM ($I^2 = 69.6\%$, $P = 0.002$) but not in those using iCGM or SAP (Table 2). Moreover, TAR level 2 hyperglycemia significantly decreased in studies involving type 1 diabetes, using MDI as background therapy or aiming at improving glycemic control or reducing hypoglycemia with CGM (Supplementary Table 8). After exclusion of the pediatric population and pregnant women or women planning pregnancy, and people with type 2 diabetes, the mean change in TAR level 1 hyperglycemia was not significant (Supplementary Fig. 6*A* and *B*); on the contrary, the decrease in TAR level 2 hyperglycemia was similar to that obtained in the overall analysis (Supplementary Fig. 7*A*), even in the studies restricted to type 1 diabetes (Supplementary Fig. 7*B*), without reducing statistical heterogeneity.

The overall analysis of the 10 comparisons that assessed the CV during intervention showed a significant decrease of CV with CGM compared with usual care (−3.09%, 95% CI −4.43 to −1.74, $P < 0.001$), with high heterogeneity ($I^2 = 90.7\%$, $P < 0.001$) and no evidence of publication bias (Egger test, $P = 0.263$) (Table 2). In the prespecified subgroup analysis, the highest mean reduction of CV was associated with iCGM (−3.86%, 95% CI −5.15 to −2.57%, $P < 0.001$); on the other hand, a not significant reduction of CV was found in the seven comparisons using rtCGM (Table 2). Heterogeneity was high in both subgroups (Table 2). In the sensitivity analysis, the exclusion of the pediatric population and pregnant women or women planning pregnancy led to results similar to those obtained in the overall analysis, without reducing the statistical heterogeneity (Supplementary Fig. 8).

## DISCUSSION

In this systematic review and meta-analysis of RCTs comparing CGM with conventional therapy in both type 1 and type 2 diabetes, use of CGM led to a modest 0.17% reduction in $HbA_{1c}$, with a 70.74 min increase of time spent in the target range. Moreover, CGM provided additional benefits in glycemic control, including the significant reduction of TBR (both level 1 and 2 hypoglycemia), TAR (both level 1 and level 2 hyperglycemia), and CV, thus suggesting an improvement of glucose variability compared with usual care. rtCGM led to better improvement in $HbA_{1c}$, TIR, and TAR, whereas both iCGM and SAP were associated with higher decline in TBR. CGM efficacy was evident primarily in adults with type 1 diabetes. These results are novel, as no previous meta-analyses have been conducted to evaluate the efficacy of CGM on emerging metrics of glycemic control, including TIR, TBR, and TAR as well as CV, which is a measure of glucose variability.

$HbA_{1c}$ has been recognized as the most important surrogate index of glycemic control, given its correlation with chronic complications in people with type 1 and type 2 diabetes (33–35). Our results of a 0.17% reduction in $HbA_{1c}$ levels obtained with CGM indicate only a slight effect of CGM on the average mean glucose over the last 3 months. Such a result may appear insufficient for the great majority of people with diabetes; on the other hand, it may also reflect a more intense effect in reducing hypoglycemia, thus expressing the effort in ameliorating glucose control while reducing glucose variability. According to our analysis, the greater decrease in $HbA_{1c}$ level was obtained in trials with rtCGM (−0.23%) and in those with the aim of improving glycemic control (−0.31%). These findings are consistent with those emerging from previous meta-analyses of studies including both people with type 1 (4–7) and people with type 2 (7–8) diabetes, showing an $HbA_{1c}$ reduction of 0.2%–0.3% with CGM compared with usual care (mainly SBGM). Moreover, neither iCGM nor SAP was associated with a significant $HbA_{1c}$ reduction; this may be due to lack of real-time data and alerts and lower baseline $HbA_{1c}$ in trials with iCGM or to the reduction in hypoglycemia that can minimally affect $HbA_{1c}$ levels.

CGM offers the opportunity to acquire a great abundance of glycemic data that allow observation of daily glycemic excursions and identification of patterns of hypo- and hyperglycemia. A number of metrics have recently been proposed for use in clinical practice to help physicians better define the glycemic status of persons with diabetes (36). The three key metrics include the percentage of readings and per day TIR, TBR, and TAR; the increase in the TIR while reducing the TBR is considered the primary glycemic goal to achieve effective and safe glucose control. Our finding of a nearly 5% significant increase of TIR with CGM associated with the reduction in TBR and TAR supports the effectiveness of CGM in improving blood glucose levels in people with diabetes, although results are limited by moderate to high heterogeneity. This is relevant, as recent studies showed correlations between TIR and microvascular complications of diabetes (37,38) as well as $HbA_{1c}$ levels (39,40). Moreover, greater time in target was robust and significant across all of the variables explored in the prespecified subgroup analysis, including diabetes type, background therapy, CGM modality, and reason for use it, with moderate to low or null heterogeneity in most cases.

Our meta-analysis is also the first evaluating the effect of CGM on hypoglycemia and hyperglycemia measured as TBR and TAR, respectively. CGM reduced time <70 mg/dL (TBR level 1 hypoglycemia) of 27 min, which is equivalent to 1.9% time per day spent in hypoglycemia. The highest effect was found in the three trials using iCGM, two of which were specifically designed to study time spent in hypoglycemia (28,30). Of note, the CGM-based target for time in hypoglycemia (<70 mg/dL) is <4% or <1 h in both adults with type 1 and adults with type 2 diabetes (36). On the other hand, the greater reduction of time spent <54 mg/dL (TBR level 2 hypoglycemia) was associated with the only study using SAP (32). This finding is consistent with results from other short-term RCTs comparing devices provided with predictive low glucose management (PLGM) with SAP (41–43), which showed the significant reduction of time spent in hypoglycemia favoring the PLGM modality in children and adolescents with type 1 diabetes (Supplementary Table 9). The ability of these systems to prevent hypoglycemia by suspending insulin delivery when the sensor glucose value is predicted to reach 20 mg/dL above a preset low-glucose limit within 30 min may be the principal explanation for these results. Certainly, the clinical relevance of using SAP provided with low glucose suspend (LGS) or PLGM is high for selected categories of people with diabetes, including children/adolescents and people with high glucose variability or hypoglycemia awareness. Moreover, the highest decrease in TAR for both

level 1 (>180 mg/dL) and level 2 (>250 mg/dL) was found in studies using rtCGM, compared with those using iCGM or SAP. The higher median baseline $HbA_{1c}$ values of patients included in the studies using CGM (7.9% [63 mmol/mol]) compared with those presented by patients of trials using iCGM (6.8% [51 mmol/mol]) and SAP (7.5% [57 mmol/mol]) may partly explain this finding. Targeting the reduction of the high glucose values while minimizing hypoglycemia could be another useful strategy that clinicians should address to expand the time in the target range of patients with diabetes.

The benefits exerted by CGM on parameters of glucose control were mainly evident in individuals with type 1 diabetes who showed better improvement in TIR and in both hypoglycemia and hyperglycemia. Data are less clear in people with type 2 diabetes, who represent the great majority of patients with diabetes. Potential benefits of CGM in this population include the possibility of providing additional information about glycemic control beyond $HbA_{1c}$ (44). Moreover, a significant improvement of both TAR and TBR was observed in patients using MDI therapy, supporting the validity of CGM regardless of the insulin delivery methods used (45). Furthermore, the greater improvement in mean $HbA_{1c}$, TIR, and TAR was associated with studies in which the reason for using CGM was the improvement of glycemic control, suggesting that CGM represents a valid tool to manage diabetes in people with poor control of the disease. On the other hand, TBR was lower when the reason for CGM use was hypoglycemia awareness or reducing hypoglycemia, providing a further benefit for glycemic status even in patients with fair diabetes control.

The strengths of this analysis are the comprehensive systematic literature search, the inclusion of studies with different technical and clinical factors, the use of valuable emerging metrics of glycemic control as primary or secondary outcomes, and the conduction of preplanned subgroup analyses. Some limitations also have to be acknowledged. As none of the trials masked participants to the intervention, performance biases are high for all studies. Adequate assessment of detection bias was limited due to insufficient information relative to the blinding of outcome assessors or data analysts to the data assessment. Heterogeneity was high for most of the study outcomes; this result was partly explained in the subgroups analysis. Other reasons may include the heterogeneity of patients included in the trials, the background therapy, and the studies' design. There was evidence of publication bias for one of the secondary outcomes (TBR level 2 hypoglycemia), which may limit the generalizability across clinical settings of the benefits of CGM on risk of hypoglycemia, giving more credit to the characteristics of each single trial. Moreover, all studies were sponsored by industry, had short duration, and used an open-label design.

In conclusion, this systematic review and meta-analysis is the first to show that CGM improves glycemic control of both patients with type 1 and patients with type 2 diabetes by expanding the TIR and reducing the time spent in hypoglycemia or hyperglycemia. Further studies with longer follow-up are needed to assess the effectiveness of CGM systems in the long-term and its relationship with diabetes complications.

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