

Continuous Glucose Monitoring System in children with type 1 diabetes mellitus: a systematic review and meta-analysis

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Abstract

Aims/hypothesis We investigated the potential effects of the Continuous Glucose Monitoring System (CGMS), as compared with self-monitoring of blood glucose, on glycaemic control in children with type 1 diabetes.

Methods The following electronic databases were searched throughout June 2007: MEDLINE, EMBASE and The Cochrane Library. Additional references were obtained from reviewed articles. Only randomised controlled trials were included.

Results We included five trials involving 131 type 1 diabetic patients in the study. Combined data from all trials showed that the CGMS did not significantly reduce HbA_{1c} levels compared with control groups. The pooled weighted mean difference was -0.02% (95% CI -0.29 to 0.25) with a fixed model and remained insignificant in the random effect model. Sensitivity analysis determined that the findings were stable. There was a trend towards a longer time under the CGMS curve for glucose <3.89 mmol/l in the CGMS group compared with the control group (mean difference 49.00 min, 95% CI -18.00 to 116.00). The CGMS significantly increased the number of insulin dose changes

per patient per month for those managed with CGMS compared with the control groups (mean difference 6.3 changes, 95% CI 2.88–9.72).

Conclusions/interpretation The Continuous Glucose Monitoring System is not better than self-monitoring of blood glucose with regard to improvement of metabolic control among type 1 diabetic children. However, due to the small number of participants and methodological limitations of the studies included, findings of this meta-analysis should be interpreted with caution.

Keywords Adolescent · CGMS · Child · Continuous glucose monitoring · Haemoglobin A_{1c} · HbA_{1c} · Meta-analysis · Randomised controlled trials · Type 1 diabetes mellitus

Abbreviations

CGM	continuous glucose monitoring
CGMS	Continuous Glucose Monitoring System
DCCT	Diabetes Control and Complications Trial
ITT	intention-to-treat
RCT	randomised controlled trial
RR	risk ratio
SMBG	self-monitoring of blood glucose
WMD	weighted mean difference

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Introduction

The Diabetes Control and Complications Trial (DCCT) indicated the importance of improving glucose control when seeking to reduce the risk of microvascular complications of type 1 diabetes [1–3]. For intensively treated participants in the DCCT, frequent glucose monitoring was considered an important factor for attaining better glucose control.

Continuous glucose monitoring (CGM) provides maximal information about changes in blood glucose levels throughout the day and facilitates optimal treatment decisions for the diabetic patient [4]. Moreover, it provides information about the direction, magnitude, duration, frequency and the causes of fluctuations in blood glucose levels. Compared with conventional intensified glucose monitoring, defined as three to four blood glucose measurements per day, continuous monitoring provides much greater insight into glucose levels throughout the day [4].

There are several devices for CGM [5–10]. Generally, two types of CGM are distinguished. One is the Holter-type of glucose monitoring, where results are shown and analysed retrospectively; the second one uses real-time presentation of glycaemia values. The Continuous Glucose Monitoring System (CGMS; Medtronic Minimed, Northridge, CA, USA) was the first device to be approved and is the most utilised one, both in USA and Europe [5]. It provides a retrospective graphical view of the glycaemia profile measured during last three days.

Diabetes in children and adolescents is characterised by high glycaemia variability, tendency towards hypoglycaemia and difficulties in insulin adjustment. Moreover, children are often incapable of handling their self-monitoring and treatment responsibly. The management of this group of diabetic patients creates unique challenges. The need to protect them against long-term consequences of hypoglycaemia, as well as hyperglycaemia, clearly justifies the use of CGM. It is a useful tool in the diagnosis of asymptomatic nocturnal hypoglycaemia and in the clinical care of children with type 1 diabetes, but its effect on metabolic control remains controversial. Several studies, many of them strictly observational, have assessed the effect of CGM on metabolic control of type 1 diabetes [11–13]. We believe that a meta-analysis of all relevant studies available to date is important in order to establish the potential benefits of CGM. As effects of CGM seem to be device-specific, pooling data obtained by different systems might result in misleading conclusions. Hence, we decided to focus on just one continuous subcutaneous glucose monitoring device. Our choice of the CGMS was dictated by the fact that it was the first product on the market and used in most of the studies. In this work, we present results of the systematic review and meta-analysis.

Methods

Inclusion and exclusion criteria Systematic review and meta-analysis were conducted according to standards of the Cochrane Collaboration [14]. Studies included in the review had to be randomised controlled trials (RCTs) in which the CGMS and self-monitoring of blood glucose

(SMBG) were compared with SMBG alone in management of type 1 diabetes. Studies on other CGM devices were excluded. The studies had to be performed in children. The primary outcome measure was improvement in diabetes control according to HbA_{1c}. The secondary outcome measures were: improvement in fructosamine, major hypoglycaemic episodes (as defined by the investigators), minor hypoglycaemic episodes, mean daily area under the CGMS curve for glucose <3.89 mmol/l, mean daily area over the CGMS curve for glucose >9.99 mmol/l, adjustments of insulin dose, local adverse effects and adherence. In addition to these outcomes, we also extracted other reported data, if relevant to our review.

Search strategy The following electronic databases were systematically searched for relevant studies: MEDLINE (1966–June 2007), EMBASE (1980–June 2007), The Cochrane Controlled Trials Register (issue 2, 2007) and The Cochrane Database of Systematic Reviews (issue 2, 2007). The text word terms and medical subject headings (MeSH) used were: ‘diabetes type 1’; ‘diabetes mellitus, type 1’; ‘type 1 diabetes mellitus’; ‘T1DM’ and ‘adolescent*’; ‘child*’; ‘infant*’ and ‘CGMS’; ‘CGM*’; ‘continuous glucose monitoring’. Subsequently, reference lists based on original studies and review articles were identified. Despite the lack of limitations with regard to the language of articles, specific types of publications (i.e. letters to the editor, abstracts and proceedings from scientific meetings) were eliminated from the study.

Data extraction Titles and abstracts identified according to the search strategy were screened independently by two reviewers (D. T. Golicki, D. Golicka). All potentially relevant articles were retained and their full text was examined to determine whether they meet the inclusion criteria. Data extraction was carried out independently by two reviewers (D. T. Golicki, D. Golicka) using standard data extraction forms. Extracted data were compared with eliminate errors. Discrepancies between the reviewers were resolved by discussion.

Study quality Reviewers independently, without blinding to authorship or journal, assessed the quality of the studies that met the inclusion criteria. Application of the following strategies associated with good quality studies was examined: (1) allocation concealment; (2) blinding of participants, outcome assessors and data analysts (yes/no/not reported); (3) intention-to-treat (ITT) analysis (yes/no); and (4) comprehensive follow-up. Allocation concealment was considered adequate when the randomisation method used did not allow the investigator or the participant to identify or influence the intervention group before the entry of eligible participants into the study. The quality of allocation

concealment was regarded as unclear when randomisation was used, but no information about the method of randomisation was available. It was regarded as inadequate when inappropriate methods of randomisation (e.g. alternate medical record numbers, unsealed envelopes, tossing the coin) were used. In ITT analysis, a ‘yes’ answer meant that the authors had specifically reported undertaking this type of analysis and/or that our own study confirmed this finding. Conversely, ‘no’ meant that the authors did not report the use of ITT analysis and/or that we could not confirm its use in the study assessment. The completeness of patient follow-up was evaluated by determining the percentage of participants excluded or lost in follow-up. Only studies with >80% follow-up were included. We defined the categories of risk of bias by the number of criteria judged inadequate in each study, i.e. low risk of bias (one or less inadequate criterion), medium risk of bias (three or less inadequate criteria) and high risk of bias (more than three inadequate criteria).

Statistical methods Two trials included in meta-analysis were crossover studies [15, 16]. According to Cochrane Group [14], ‘paired’ analysis is the most appropriate method of analysing crossover trials, where each patient acts as his or her own control. Yet, lack of individual patient data did not allow us to perform this kind of analysis. In effect, we decided to apply a different approach for incorporation of crossover trials, i.e. to include data only from the first period of trial. In the event of parallel groups trials, data from the end of the trial were used. Data were analysed using The Review Manager (Revman Computer program, Version 4.2.9 for Windows; The Nordic Cochrane Centre, Copenhagen, Denmark). The weighted mean difference (WMD) was selected to determine differences in continuous outcomes between the treatment and the control groups. Meta-analysis of continuous data using mean difference demanded extraction of the following: the mean values of the outcomes, the standard deviations of the outcomes and the number of participants in both groups for whom the outcome was assessed. In one study [17], data concerning the effect of treatment on HbA_{1c} were calculated on the basis of individual patient results, presented in the article in form of a table. Yet, these values differed from the summarised results presented by the authors. In another study [18], standard deviations of HbA_{1c} changes were obtained from 95% CIs, using the formula: $SD = \sqrt{N \times (\text{upper limit} - \text{lower limit}) / 3.92}$ [14]. Two trials [15, 16] did not report data on standard deviations of changes in HbA_{1c}. Missing information was sought from the authors without success. As exclusion of both trials from the analysis might have led to bias, we decided to impute standard deviations for the changes from baseline, based on all available data from other trials, using a method described in the Cochrane

reviewers’ handbook [14]. The binary measure for individual studies and pooled statistics was calculated as the risk ratio (RR) between the experimental and control groups with 95% CI. The difference between study groups was considered significant when the *p* value was <0.05 or when the 95% CI for RR did not exceed 1.0 and that for WMD did not exceed 0 (equivalent to *p*<0.05). The weight given to each study was based on variance inversion. Heterogeneity was determined by χ^2 and I^2 , which stand for the percentage of total variations between studies that are attributed to heterogeneity rather than chance. Sensitivity analysis, on the data assessed directly after the use of CGMS, was performed excluding the two trials [15, 16] with imputed standard deviations.

Results

Description of studies Initially, we identified 25 articles that underwent further examination. Table 1 summarises characteristics of the included trials. Five RCTs involving 131 participants met our predefined inclusion criteria [15–19]; the remaining 20 studies were excluded [7, 11–13, 20–35]. Table 2 summarises the characteristics of excluded trials, including reasons for exclusion.

All included trials were small, one-centre studies; two of them were performed in Europe [15, 16], two in the USA [17, 19] and one in Australia [18]. Three of the included trials [17–19] had parallel-group design and two others [15, 16] were crossover. There was considerable clinical heterogeneity among the trials with regard to the children’s age, diabetes duration, frequency of CGMS use and insulin adjustments. Depending on the trial, patients had to wear CGMS: every 5 days [17], every 2 weeks [16], every 3 weeks [18], every 2 months [19] or once during a 3 month period [15]. We also found significant differences in the frequency of insulin changes: >11 times during 1 month (experimental group only) [17], every 3 weeks [18], every 6 weeks [16] and every 2 months [19]. Follow-up periods extended up to 3 months in three trials [15–17] and up to 6 months in the other two trials [18, 19].

The methodological quality of the studies varied [see Electronic supplementary material (ESM) Table 1]. We assessed a risk of low bias in only one trial [19]. Only two trials [18, 19] contained information on the method of generating allocation sequences. In both cases, the method was adequate. Two trials [15, 16] were described as double-blinded, one [19] as single-blinded and two [17, 18] were open. In one trial [16], the authors reported undertaking an ITT analysis, but our own survey did not confirm this finding. Withdrawals and dropouts were described adequately in all studies. All trials contained a sufficient proportion (≥80%) of participants in the final analysis; two

Table 1 Characteristics of included trials

Study	Country	Sample size (Exp./Cont.)	Age (years)	Diabetes duration (years)	Diabetes treatment	Baseline HbA _{1c} (%) (Exp./Cont.)	Frequency of CGMS use in the intervention group (total number)	Frequency of SMBG in the control group
Chase et al. [17]	USA	5/6	10–17	2.1–11.6	CSII (<i>n</i> =6), MDI (<i>n</i> =5)	10.0/9.0	6 times during 1 month	Min. 4 times daily
Deiss et al. [15]	Germany	15/15 ^a	2–16	0.2–7.1	87% IIT, 13% BID	7.8/8.4	Single use	Min. 5 times daily ^b
Lagarde et al. [19]	USA	18/9	7–17	4.5±2.5 ^c (Exp.) 4.2±2.1 ^c (Cont.)	No information	8.4/8.8	Every 2 months (3 times)	Min. 4 times daily ^b
Ludvigsson and Hanas [16]	Sweden	13/14 ^a	5–19	2–15	CSII or MDI	8.0±1.1 ^c	Every 2 weeks (6 times)	Min. 2 times daily ^{b,d}
Yates et al. [18]	Australia	19/17	≤18	Not reported	CSII or MDI including glargine	8.2/7.9	Every 3 weeks (4 times)	4–6 times daily

^aCrossover trials^bCGMS was used in the control group, but was blinded^cMeans±SD^dPlus seven-point profile every week

BID, two daily insulin injections; Cont., control group; CSII, continuous subcutaneous intensive insulin infusion; Exp., experimental group; IIT, intensified insulin therapy, i.e. three or more insulin injections per day; MDI, multiple daily injections; Min, minimum; SMBG, self-monitoring of blood glucose

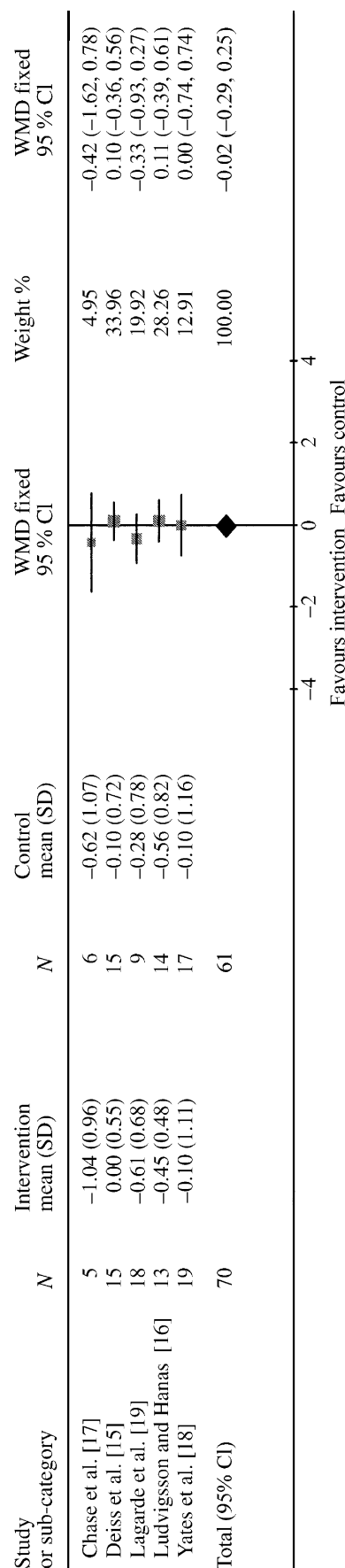


Fig. 1 Weighted mean difference (WMD) and 95% CI of change in HbA_{1c} (%) of children or adolescents whose insulin doses were adjusted on the basis of both CGMS and SMBG data versus SMBG data alone. Values for individual trials and pooled data (fixed-effect model) are shown. Test for heterogeneity: $\chi^2=1.98$; $df=4$ ($p=0.74$); $I^2=0\%$. Test for overall effect: $Z=0.16$ ($p=0.87$)

Table 2 Characteristics of excluded studies

Study	Reason(s) for exclusion
Bode et al. [20]	Non-randomised, uncontrolled trial
Bode et al. [7]	RCT performed in adults. Guardian Continuous Monitoring System used
Boland et al. [21]	Non-randomised, uncontrolled trial
Burdick et al. [22]	Non-randomised, uncontrolled trial. Real-Time glucose sensing system used
Chase et al. [23]	RCT; GlucoWatch G2 Biographer used
Chico et al. [24]	Non-randomised, uncontrolled trial
Deiss et al. [25]	Non-randomised, uncontrolled trial
Deiss et al. [26]	RCT; Guardian RT system used
DirectNet [27]	RCT; GlucoWatch G2 Biographer used
DirectNet [28]	RCT; GlucoWatch G2 Biographer used
Fiallo-Scharer et al. [29]	RCT; GlucoWatch G2 Biographer used
Garg et al. [30]	RCT; DexCom STS system used
Halvorson et al. [31]	Non-randomised, uncontrolled trial. Paradigm Real-Time system used
Kaufman et al. [11]	Non-randomised, uncontrolled trial
Salardi et al. [12]	Non-randomised, uncontrolled trial
Schaepelynck-Belicar et al. [13]	Non-randomised, uncontrolled trial
Tanenberg et al. [32]	Randomised controlled trial performed in adults
Tansey et al. [33]	Non-randomised study; did not report any of our defined outcomes
Weinstein et al. [34]	Non-randomised, uncontrolled trial. FreeStyle Navigator system used
Wilson et al. [35]	Non-randomised, uncontrolled trial. FreeStyle Navigator system used

[15, 19] of them included all (100%) of the initially selected participants.

HbA_{1c} Five papers contained data on HbA_{1c} improvement [15–19]. Meta-analysis of five RCTs (131 participants) showed no reduction in HbA_{1c} (WMD –0.02%, 95% CI –0.29 to 0.25; $p=0.87$) for patients managed with CGMS and SMBG compared with patients monitored with SMBG alone (Fig. 1; ESM Table 2). Adjustment of the meta-analysis model from fixed to random effects did not influence the outcome results. The included studies were homogenous ($\chi^2=1.98$, $p=0.74$, $I^2=0\%$). The main findings were stable in sensitivity analysis based on data obtained directly after CGMS use (WMD –0.05%, 95% CI –0.27 to 0.17; $p=0.65$) and after excluding the two trials [15, 16] with imputed standard deviations (WMD –0.23%, 95% CI –0.66 to 0.21; $p=0.30$).

Fructosamine The reported outcome was based on results from only one RCT [18]. Findings showed no reduction of fructosamine between the CGMS and the control group at 6 weeks (mean difference 0.5 $\mu\text{mol/l}$, 95% CI –40.96 to 41.96; $p=0.98$) and at 12 weeks (mean difference –7.2 $\mu\text{mol/l}$, 95% CI –55.57 to 41.17; $p=0.77$).

Major hypoglycaemic episodes No severe hypoglycaemic events occurred in either the CGMS or the control groups in any study included in the review.

Minor hypoglycaemic episodes For this outcome, based on the results from only one trial [19], no difference was seen

in the number of minor hypoglycaemic episodes during the total CGMS-monitored period between the CGMS and the control group (mean difference 0.53, 95% CI –0.68 to 1.74; $p=0.39$).

Mean daily time and daily area under the CGMS curve for glucose <3.89 mmol/l The only RCT [19] ($n=27$) to report this outcome demonstrated a trend towards a longer time under the CGMS curve for glucose <3.89 mmol/l in the CGMS group than in the control group (mean difference 49.00 min, 95% CI, –18.00 to 116.00; $p=0.15$). The same study reported no significant difference in the daily area under the CGMS curve for glucose <3.89 mmol/l between the CGMS and the control group (mean difference 35.85 $\text{mmol l}^{-1} \text{min}^{-1}$ per day, 95% CI –28.58 to 100.29; $p=0.28$).

Daily area over the CGMS curve for glucose >9.99 mmol/l The only RCT [19] to report on this outcome noted no difference in the daily area over the CGMS curve for glucose >9.99 mmol/l between the CGMS and the control group (mean difference 0.33 $\text{mmol l}^{-1} \text{min}^{-1}$ per day, 95% CI –10.26 to 10.92; $p=0.95$).

Ketoacidosis A single participant in one trial [18] was admitted to hospital with ketoacidosis. The patient was from the CGMS group. Ketoacidosis was thought to be due to insulin omission.

Adjustments of insulin dose Two papers included information on insulin dose adjustments. One trial [17] showed an

increase in the number of insulin dose changes per patient per month for those managed with CGMS compared with the control group (mean difference 6.3 changes, 95% CI 2.88 to 9.72; $p=0.0003$). The second trial [15] demonstrated an increase by 35% in the relative chance of insulin dose changes in the CGMS open group compared with the CGMS-blinded group (95% CI 0.98–1.85; $p=0.07$).

Local adverse events and adherence A narrative synthesis of the data on local adverse events and adherence was undertaken. Among the five trials included in the review, local adverse effects were reported only in two [15, 18]. Deiss et al. [15] observed mild local side-effects like redness at the application site in 21 (23%) cases, redness and itching in 14 cases (16%), and painful redness in one case. None of these complaints led to a preterm removal of CGMS. Yates et al. [18] reported that one participant on continuous subcutaneous intensive insulin infusion withdrew after 12 h of CGMS due to skin irritation at the sensor site.

Discussion

The main findings of our meta-analysis show that the CGMS is just as suitable as self-monitoring of blood glucose levels when it comes to improving HbA_{1c} in children with type 1 diabetes. Findings were stable with both fixed and random effect models, and in sensitivity analysis. We found a trend towards a longer time under the CGMS curve for glucose <3.89 mmol/l in the CGMS group than in the control group. CGMS also significantly increased the number of insulin dose changes per patient per month.

Every meta-analysis is only as good as the constituent studies. All but one of the trials included in our analysis had methodological limitations, including unclear or inadequate allocation concealments, lack of ITT analysis and no blinding. In the only trial with an estimated low risk of bias [19], participants in the intervention group were significantly younger than those in the control group. In all trials, small study sample sizes were also limiting. The overall quality of studies was low, especially compared with typical trials in drug development.

Meta-analysis trials included two crossover studies [15, 16]. The Cochrane Group reported [14] that the most suitable method for analysing crossover trials is 'paired' analysis, where each patient acts as his/her own control. Due to the lack of individual patient data, we were unable to perform this kind of analysis. As a result, the second most common approach was applied, with inclusion of data from the first trial period. Another difficulty with the crossover trials [15, 16] was due to the lack of data on standard deviations of HbA_{1c} changes. Moreover, requests

made directly to the authors failed to provide the missing information. As elimination of both trials from the analysis might have led to bias, we decided to assign standard deviations to changes from baseline from all other trials with available data, using the method proposed in the Cochrane Handbook [14]. Estimated standard deviations were small, confidence intervals narrow and trials were over-weighted in pooled analysis. Despite this, the main findings were stable in sensitivity analysis, excluding those trials with imputed standard deviations.

No formal attempt to search for publication bias was made, as only a few studies on any given endpoint were reported and any formal method would have had little power. To reduce the risk of publication bias, language restrictions were abolished. An extensive search strategy for the identification of published trials was made; yet, we did not attempt to identify unpublished trials.

Although studies included in the meta-analysis were not statistically heterogeneous, they varied in the clinical context of CGMS use and timing of insulin adjustments. Depending on the trial, patients had to carry out CGMS: every 5 days [17], every 2 weeks [16], every 3 weeks [18], every 2 months [19] or even once in 3 months [15]. Variations in the frequency of insulin changes were noted: over 11 times during 1 month [17], every 3 weeks [18], every 6 weeks [16] and every 2 months [19]. There seems to be no standard way of using CGMS in order to improve the metabolic control of diabetes.

The analysis conducted by us was limited to only one device, namely the Continuous Glucose Monitoring System (Medtronic MiniMed). There are several CGM devices, which differ in terms of sensor type, mechanism and location, frequency of testing and blood glucose data presentation (retrospective or real time). The fact that access to the CGMS data is retrospective can be regarded as a major technical limitation and explains, at least in part, the negative outcome of the trials included. It cannot be ruled out that other devices, especially real-time systems with alarm options or integrated insulin pumps, could improve the metabolic control of type 1 diabetes. In time, the Holter-type CGM will probably be replaced by the real-time CGM in diabetic practice, but can still remain a useful tool for conducting research, in which new parameters, such as mean amplitude of glycaemic excursions, variability of glucose and duration of hypoglycaemia can be considered as risk factors for late complications.

The limitations discussed suggest steps towards improving the quality of research in this area. Further well-conducted clinical studies should have more participants, probably parallel group rather than crossover design and longer than 6 month observation periods. Future studies should also address the question of establishing a standard protocol on the basis of optimum efficiency for the use of CGMS.

Conclusion The CGMS did not prove more advantageous than self-monitoring of blood glucose levels in improving metabolic control of type 1 diabetic children. Nonetheless, results of meta-analysis should be regarded with caution, due to the small study group sizes and methodological limitations of the included studies.

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