IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Continuous interstitial glucose monitoring (CGM) with real-time measurement devices in insulin-dependent diabetes mellitus[1]

Executive Summary

[1] Translation of the executive summary of the final report *Kontinuierliche interstitielle Glukosemessung (CGM) mit Real-Time-Messgeräten bei insulinpflichtigem Diabetes mellitus* (Version 1.0; Status: 25 March 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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This report was prepared in collaboration with external experts.

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Executive summary

On 23 November 2012 the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the assessment of continuous interstitial glucose monitoring (CGM) with real-time measurement devices for therapy management in patients with insulin-dependent diabetes mellitus.

Research question

The aim of the present investigation was to assess the benefit of continuous interstitial glucose monitoring with real-time measurement devices (rtCGM) in comparison with other methods of measurement (e.g. blood glucose self-monitoring [BGSM], retrospective CGM) and with variants of rtCGM in diabetes mellitus patients treated with insulin regarding patient-relevant outcomes.

Methods

Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were included that investigated rtCGM with regard to

- all-cause mortality
- cardiovascular mortality (coronary, cerebrovascular)
- cardiovascular morbidity (coronary, cerebrovascular, peripheral arterial)
- blindness
- end-stage renal impairment (requiring dialysis or kidney transplantation)
- amputation (minor and major amputation)
- ketoacidotic or hyperosmolar coma
- joint consideration of the occurrence of hypoglycaemia, particularly severe hypoglycaemia, and glycosylated haemoglobin A1c (HbA1c) value[3]
- symptoms caused by chronic hyperglycaemia
- other adverse events
- health-related quality of life (including activities of daily living)

[3] The 2 outcomes "hypoglycaemia" and "HbA1c value" cannot be considered independently of each other because they are directly associated. The HbA1c value was used for interpreting the results on hypoglycaemia. The HbA1c value is additionally accepted as surrogate outcome for the occurrence of microvascular complications only in type 1 diabetes mellitus. An interpretation of the HbA1c value in type 1 diabetes mellitus is meaningful when considering the occurrence of hypoglycaemia at the same time.

The following patient-relevant outcomes were additionally used for children and adolescents:

- physical developmental disorders
- psychosocial developmental disorders

The following patient-relevant outcomes were additionally used in pregnant women:

- type of birth (e.g. surgical delivery)
- adverse effects on the woman during pregnancy (e.g. preeclampsia/eclampsia) and during birth (e.g. grade 3/4 perineal tear, postpartum bleeding)
- proportion of miscarriages
- perinatal and neonatal mortality and morbidity of the child (e.g. brachial plexus injury)

For this purpose, a systematic literature search was performed in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The retrieved systematic reviews were scrutinized for further relevant studies. The last search was conducted on 13 August 2014.

Publicly accessible trial registries were also searched. Furthermore, publicly accessible documents for approval, documents sent by the G-BA and publications that had been provided in the hearing procedure for the preliminary report plan and for the preliminary report were also screened. Moreover, manufacturers of real-time measurement devices for CGM (Abbott, Dexcom, Medtronic) were contacted for relevant published or unpublished studies, and authors of relevant study publications were contacted in order to clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of each other for the result from the bibliographic literature search, from the search in publicly accessible trial registries, from documents sent by the G-BA and potentially relevant studies from systematic reviews. The selection of relevant studies from the remaining search sources was performed by one reviewer and checked by a second reviewer.

Data extraction was conducted in standardized tables. To evaluate the certainty of results, the risk of bias at study and outcome level was assessed and rated as low or high respectively. The results of the individual studies were described, organized by outcomes. If the studies were comparable regarding the research question and relevant characteristics, the individual results were pooled quantitatively by means of meta-analyses.

Results

A total of 15 studies were identified as relevant for the research question of the present benefit assessment. The studies were conducted on 3 different comparisons:

- comparison of rtCGM plus BGSM versus BGSM, n = 13
- Comparison of variants of rtCGM plus BGSM, n = 2
  In both studies, the rtCGM that was to be used continuously during the total duration of the study was compared with an rtCGM that was to be used intermittently.
- Comparison of rtCGM plus low-glucose suspend (LGS) plus BGSM versus BGSM, n = 1
  In this study, treatment with a combination device in which the rtCGM is combined with the insulin pump via the LGS function (sensor-augmented insulin pump therapy with LGS function) was compared with insulin pump therapy.

A 3-arm study was used for 2 different comparisons: the comparison of rtCGM plus BGSM versus BGSM, and the comparison of variants of rtCGM plus BGSM.

Of the 15 relevant studies, 3 were initiated by manufacturers. The manufacturers provided unpublished clinical study reports (CSRs) for these studies and for one further study not initiated by manufacturers. These CSRs were considered in the assessment. The unpublished CSR of one further study, not initiated by manufacturers, which was provided by the study authors, was additionally considered.

13 of the 15 studies included in the benefit assessment were conducted in an unblinded parallel-group design; 2 studies were conducted in an unblinded crossover design. A total of 1952 patients were included in these studies. In all studies, the patients used intensive insulin therapy; no study was identified in which the patients used conventional insulin therapy. The studies lasted between 6 and 12 months.

Almost all the studies exclusively included non-pregnant patients with type 1 diabetes mellitus. Only one study exclusively included patients with type 2 diabetes mellitus. None of the results of this study was considered to be evaluable because the difference between the proportions of patients who were not considered was greater than 15 percentage points between the groups (rtCGM: 7/32 patients [22%]; BGSM: 0/25 [0%]). Only 2 studies exclusively included pregnant diabetic patients. One of these 2 studies also included patients with type 2 diabetes mellitus, but the proportion of patients with type 1 diabetes mellitus was greater (approximately 80%). In this study, separate results for patients with type 1 and type 2 diabetes mellitus were only reported for patient-relevant outcomes that are additionally relevant in pregnant diabetic patients. No studies on patients with gestational diabetes were identified.

Hence the present assessment allows to draw conclusions on the benefit and harm of rtCGM plus BGSM, and on rtCGM plus LGS function plus BGSM, in each case in comparison with

BGSM, regarding patient-relevant outcomes almost exclusively for type 1 diabetes mellitus patients. Conclusions not only for type 1 diabetes mellitus patients but also for type 2 diabetes mellitus patients can only be drawn for patient-relevant outcomes that are additionally relevant for pregnant diabetic patients. However, the latter only applies to the comparison of rtCGM plus BGSM versus BGSM. Due to a lack of data, no conclusions can be drawn for patients with gestational diabetes.

There were statistically significant differences between the treatment options regarding patient-relevant outcomes only for the comparison of rtCGM plus BGSM versus BGSM, but not for the comparison of variants of rtCGM plus BGSM or for the comparison of rtCGM plus LGS function plus BGSM versus BGSM.

In the comparison of rtCGM plus BGSM versus BGSM, there were statistically significant differences only regarding the joint consideration of severe or serious hypoglycaemia and HbA1c value, skin reactions reported as adverse event, and individual instruments or subscales of health-related quality of life.

The joint consideration of hypoglycaemia and HbA1c value was conducted for the outcome "severe hypoglycaemia" and for the outcome "serious hypoglycaemia". In the joint consideration of severe or serious hypoglycaemia and HbA1c value, the subgroup characteristic "age" was shown to be an effect modifier. The joint consideration of severe hypoglycaemia and HbA1c value produced proof of an advantage of rtCGM plus BGSM versus BGSM for the subgroup of adults (> 18 years), whereas there was an indication of an advantage of rtCGM plus BGSM versus BGSM for the subgroup of children. This assessment was based on the finding that a statistically significantly greater proportion of patients in the rtCGM group had good glycaemic control (HbA1c value < 7%) at the end of the study, and that there was a hint of an effect in favour of the rtCGM group regarding the proportion of patients with at least one severe hypoglycaemic event.

In contrast, the joint consideration of serious hypoglycaemia and HbA1c value produced an indication of an advantage of rtCGM plus BGSM versus BGSM for the subgroup of adults (> 18 years), whereas there was a hint of an advantage of rtCGM plus BGSM versus BGSM for the subgroup of children. This difference in the assessment was based on the fact that no statistically significant effect was found regarding serious hypoglycaemia and that, in addition, the available data were assessed to be insufficient. The available data was assessed to be insufficient because, on the one hand, the confidence interval of the effect estimate for the odds ratio covered an effect both of 0.5 and of 2 and hence was very imprecise, and that, on the other, no evaluable results were available for a relevant proportion of patients.

Evaluable results on skin reactions were reported in one study. There was a statistically significant difference to the disadvantage of the rtCGM group in this study. Hence there was a hint of a disadvantage of rtCGM plus BGSM versus BGSM for skin reactions.

There was no proof of differences between the treatment options for the remaining outcomes because either the results were not statistically significant or no data were available.

Conclusion

The following conclusions apply to a period of 6 to 12 months and exclusively to type 1 diabetes mellitus patients – except for the outcomes marked with an asterisk (*) in the comparison of rtCGM plus BGSM versus BGSM, which additionally apply to type 2 diabetes mellitus patients.

rtCGM plus BGSM versus BGSM

For rtCGM plus BGSM in comparison with BGSM, there was

- proof of benefit in adults (> 18 years) regarding the joint consideration of severe hypoglycaemia and HbA1c value (the joint consideration was based on a hint of superiority regarding severe hypoglycaemia and proof of superiority regarding HbA1c value)
- an indication of benefit in children (< 18 years) regarding the joint consideration of severe hypoglycaemia and HbA1c value (the joint consideration was based on a hint of superiority regarding severe hypoglycaemia and an indication of superiority regarding HbA1c value)
- an indication of benefit in adults (> 18 years) regarding the joint consideration of serious hypoglycaemia and HbA1c value (the joint consideration was based on the fact that, regarding serious hypoglycaemia, there was no hint of superiority and an uncertainty of the available data as well as proof of superiority regarding HbA1c value)
- a hint of benefit in children (< 18 years) regarding the joint consideration of serious hypoglycaemia and HbA1c value (the joint consideration was based on the fact that, regarding serious hypoglycaemia, there was no hint of superiority and an uncertainty of the available data as well as an indication of superiority regarding HbA1c value)
- a hint of harm in adults and children regarding skin reactions
- no hint of benefit or harm for all other outcomes either due to statistically non-significant differences between the treatment options (ketoacidotic and hyperosmolar coma, diabetic ketoacidosis reported as serious adverse event, serious adverse events, health-related quality of life and [in pregnant women] type of birth*, adverse effects on the women during pregnancy*, proportion of miscarriages*, and perinatal and neonatal mortality of the child*) or due to a lack of data.

On a critical note, none of the 13 studies on the comparison of rtCGM plus BGSM versus BGSM completely reported adverse events. In particular, there were no evaluable results on serious adverse events from 8 of the 13 studies, and on adverse events resulting in treatment discontinuation from all studies.

Comparison of variants of rtCGM plus BGSM

In the comparison of variants of rtCGM plus BGSM, there was no hint of benefit or harm from any of the 2 treatment options for all outcomes, either due to statistically non-significant differences (ketoacidotic and hyperosmolar coma, diabetic ketoacidosis reported as serious adverse event, joint consideration of severe hypoglycaemia and HbA1c value and [in pregnant women] type of birth) or due to a lack of data.

It is problematic that both studies on this comparison provided no evaluable results on the number of patients with serious adverse event or with adverse event resulting in treatment discontinuation.

rtCGM plus LGS plus BGSM versus BGSM

For rtCGM plus LGS plus BGSM in comparison with BGSM, there was no hint of benefit or harm for all outcomes, either due to statistically non-significant differences between the treatment options (ketoacidotic and hyperosmolar coma, diabetic ketoacidosis reported as serious adverse event, joint consideration of severe hypoglycaemia and HbA1c value and joint consideration of serious hypoglycaemia and HbA1c value) or due to a lack of data.

Keywords: blood glucose self-monitoring, diabetes mellitus – type 1, diabetes mellitus – type 2, benefit assessment, systematic review

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