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REVIEW: **Continuous Glucose Meters in the Management of Diabetes**

Amended following consultation with CCGs on 15.05.14

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INTRODUCTION

The first Continuous Glucose Meter (CGM) was introduced in 1999.¹ Whilst CGMs are still not in common use², their use could potentially revolutionise treatment, making the daily lives easier for patients with diabetes.

Each meter is connected to a sensor or probe which is inserted into the interstitial fluid of the abdomen. The change in potential across the sensor is related to glucose concentration which is ultimately displayed on the meter. This is measured every few minutes and gives the complete pattern of hypo- and hyperglycaemia together with any changes in glucose concentrations or "excursions."³

The meters can be used in "real" time when they are linked to an alarm⁴ or retrospectively, where the data are downloaded and subject to a post hoc analysis which might reveal a post-prandial hypoglycaemia and/or an asymptomatic (overnight) hypoglycaemia.² Although there is a relationship between interstitial and blood glucose, there is usually a lag time between these two measurements of around 10 minutes.⁵

Manufacturers of these devices include Medtronic, Dexcom, and Abbott.⁶ The basic devices can cost several thousand pounds and the running costs to replace the sensors have been estimated to be around \$4,000 per annum in the USA.²

The purpose of this report is to review the evidence on effectiveness (and where possible cost effectiveness) of CGMs to determine their current place in the management of diabetes.

METHOD

A search of Medline and Embase was performed using the keywords "continuous glucose monitoring" and "continuous glucose monitor(s)". The search was limited to those articles published from 2012 onwards. Results were restricted to publications from 2011 onwards based on the assumption that a Cochrane review (2012)⁷ would have picked up all relevant articles up to this time.

In addition, the following websites and databases were also searched:- Cochrane database, National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), NHS Evidence and the UK Medicines Information (UKMI) sites and the Scottish Medicines Consortium website.

FINDINGS

Cochrane Review

A systematic review of continuous glucose monitoring systems for type I diabetes patients was published in 2012.⁷ The literature was reviewed up to June 2011 and 22 randomised controlled trials met the inclusion criteria. Study durations varied between 3 and 18 months.

The meta analysis revealed a 0.7% reduction in HbA_{1c} levels attributed to the CGM system. These data were extracted from two trials (comprising 562 patients) and compared standard therapy with CGM and an insulin pump. The data also revealed that CGM alone produced a much smaller reduction in HbA_{1c} (-0.2%).

Cochrane concluded there is limited evidence for CGM use in children, adults and patients with poorly controlled diabetes. The largest improvements were seen for sensor augmented insulin pump therapy in patients who had not used an insulin pump before. However, as mentioned above, the study population included only 562 patients from two studies for a six month follow-up period.

The following sections describes information published post the Cochrane review.

Meter Accuracy

Despite recent claims of a close correlation between CGM sensor reading and capillary glucose levels⁸, there is a generally recognised discrepancy between these two values. One of the most frequently used measures of accuracy is the Mean* Absolute Relative Difference (MARD) between capillary and meter readings. It is defined as the mean of the sum of the differences between these two readings expressed as a percentage of the blood capillary (reference) value.

In 2013, a German study compared three CGMs in 12 patients with type I diabetes. Two sensors from each type of monitor were applied simultaneously.⁹ The overall MARD varied between 12-16 %. In the hyperglycaemia range, this was higher at 25-35 %. The same authors performed a similar study which compared readings taken in real-life situations.¹⁰ In this context, MARDs of 13.7% and 8.5% were observed in the hypoglycaemic and hyperglycaemic ranges respectively.

In a UK study of two other CGMs in 52 patients, (median) MARDs of 9.9-12.6% were recorded.¹¹ Significant over-reading in both models was observed although one machine was 2-3 times less accurate than the other. This erroneous "hyperglycaemia" has the potential for inappropriate delivery of insulin and thus iatrogenic hypoglycaemia.

Differences have also been observed depending on the setting. A study based in the Netherlands compared readings of a single monitor when used

* sometimes uses the median rather than mean value

at home and in a clinical research centre. ¹² Overall, MARDs of 16.8% and 19.2% respectively were observed.

The position of the sensor in the body can also affect the reading during sleep. ¹³ Four sensors were placed in each non-diabetic subject and the readings compared throughout the night. Aberrant readings were noted for each sensor dependent on the sleeping position. Readings were generally lower (-1.4 mmol/l) which the authors attributed to reduced blood flow in the area of the sensor. In rare cases the aberrant reading was elevated.

Finally, another study in the Netherlands compared three machines which obtained MARDs of 16.5 – 20.5% in the research centre but 14.5 – 18.9% at home. ¹⁴

In general, other researchers have found marked differences in accuracy and performance between machines. ¹⁵ Whilst acknowledging a 5 to 15 minute delay between blood and interstitial glucose levels, some researchers have warned that real-time CGM could potentially lead to over or under treatment with insulin. ¹⁶ More specifically, the clinical picture should always be taken into account when diagnosing hypoglycaemia and the results of the meter not considered in isolation. ¹⁷ Research is currently being undertaken to introduce an electronic "filter" which takes into account these lag times. ¹⁸

There is recent evidence (2014) that the very latest pumps have narrowed the MARD to less than 15%. ¹⁹

Effect on Glycosylated Haemoglobin (HbA_{1c})

HbA_{1c} is an indicator of the medium-term control of diabetes. In this context, most of the clinical studies published since Cochrane are small, short-term, unblinded and poorly controlled.

In the USA (2013), a real-time CGM, unblinded audit of 35 patients with type I diabetes produced a reduction in HbA_{1c} from 8.1% to 7.6% ²⁰ Follow-up was for one year. It wasn't clear which of the other factors could have influenced the glycosylated haemoglobin.

In an even smaller pilot study (16 patients) in 2013, increasing the use of CGM – by about 20% – didn't significantly change the HbA_{1c}. ²¹ Follow-Up was for six months.

An open crossover study (2012) which compared CGM versus intensive finger prick blood monitoring, found no change in HbA_{1c} after 8 weeks. The population comprised 30 patients. ²² Also, a six months randomised trial (2013) in 95 patients comparing a standard insulin pump with a sensor augmented pump recorded no change in HbA_{1c}. ²³

Perhaps the best data comes from the INTERPRET study which is reported to be the largest and longest multicentre prospective study (2013) ²⁴ This was a 12 months observational study in type I diabetes in 263 patients from 15 countries of all ages and it examined the impact of sensor augmented pump

therapy. Whilst sensor use decreased from 37% in the first three months to 27% in the last, the proportion of people who were very well controlled (HbA_{1c} less than 7%) did reduce.

The proportion of those people with an HbA_{1c} greater than 8% was significantly reduced by 0.43%. This is slightly encouraging and it could lead one to infer that if compliance with the CGM were increased, the reduction in glycosylated haemoglobin might be greater. However this study is potentially prone to bias because it was sponsored heavily by one of the pump manufacturers who also paid one of the authors to write the paper.

Impact on Hypoglycaemia

Similar to above, the number of published studies is small and generally of poor quality.

A retrospective, unblinded audit of 35 patients with type I diabetes who were experiencing problematic hypoglycaemias, showed a reduction in the mean number of hypos per year from 8.1 to 0.6 over one year.²⁰ There was no change in awareness of hypoglycaemia.

Further, in a subgroup analysis of a retrospective review of insulin patients at a university clinic, 14/20 CGM patients with hypoglycaemia difficulties had a drop in the self-reported frequency of hypoglycaemia.²⁵

However, in the crossover study reported above where CGM was compared to intensive finger prick measurement, no difference in the number of severe hypoglycaemic episodes was observed after eight weeks.²²

A randomised trial (six months) of 95 patients on sensor augmented pump therapy experienced fewer hypoglycaemic episodes than those on the pump alone.²³ The incidence per 100 patient-months was 9.5 in the augmented sensor group and 34.2 in the pump only group. This trial has been criticised because the population was younger and had a shorter duration of diabetes than more typical (older) patients with hypoglycaemia.

In a Danish evaluation of 72 patients with severe nocturnal hypoglycaemia, the sensitivity of the monitor (i.e. the ability of the machine to identify all cases) was calculated.²⁶ For blood sugars below 4 mmol/l, the sensitivity was 65%. For blood sugars below 3 mmol/l, sensitivity was 40% and only 17% when below 2.2 mmol/l. Thus, sensitivity worsened as blood sugars reduced. It was also observed that the device overestimated by 1.0 mmol/l in the hypoglycaemic range yet underestimated by 1.1 mmol/l in the hyperglycaemic range. Furthermore, in a different study, more than half of the alarms which warned patients of hypoglycaemia were false (false alert rate 53.3%).²⁷ This research also recorded a sensitivity of true hypoglycaemic events of 37.5%.

The observation that interstitial glucose is higher than blood glucose has been confirmed in the laboratory.²⁸ A French literature review has also cast doubts on the reliability of CGM in nocturnal hypoglycaemia.²⁹ It suggested that daily

use had not been associated with a significant reduction in hypoglycaemia frequency and this could be due to patients not being awakened by the alarm.

It is not surprising that FDA approval in America for CGM systems specifies that all treatment decisions are based on additional fingerstick measurements rather than sensor readings alone.² Irrespective of the CGM result, the clinical picture must always be taken into account before changing insulin therapy.¹⁷ It is also apparent that education and training of users/families is essential³⁰ and strategies are required to boost the confidence of users in applying the data.³¹

Other Patient Groups

It has been suggested that CGMs in children could have retrospective and real-time uses.² However, one systematic review concluded that CGM use in paediatrics was no more effective than self-monitoring in reducing HbA_{1c}.³² A randomised trial in 146 children aged 4-9 years found that a reduction of HbA_{1c} greater than 0.5% was only achieved by 19% of the children in the CGM group versus 28% in the control.

In pregnancy[†], a systematic review (2013) could find only two relevant randomised controlled trials.³³ These had conflicting results and further trials are required. Although written in 2008, NICE guidance on diabetes in pregnancy could find no evidence to assess the effectiveness of ambulatory continuous blood glucose monitoring and further research was required.³⁴

Finally, a USA review of CGM in type II diabetes located 12 studies.³⁵ Only five of these showed a decrease in HbA_{1c}.

Adverse Effects

One specific problem is an inflammatory response at the injection site. Work is currently being undertaken to combat this.⁶ Clearly, there is a need for devices which are less painful and easier to use. However, there is also a need for motivated users/carers and appropriate support.³⁰

Apart from lack of motivation (above), other reviews have identified the challenge associated with data interpretation, nuisance alarms, the time required for calibration and individual sensors falling off or causing irritation.² Perhaps less predictably, psychosocial factors are also thought to be important. Some users have stated they didn't trust their machine which obviously affects compliance. In this case, users may require pre-CGM counselling on motivation and alarm coping strategies.³⁶

Cost Effectiveness

Throughout the course of this review, only one paper was identified which was concerned with cost effectiveness. This study³⁷, based in the USA, analysed the cost of CGM versus self-monitoring. The cost per QALY was \$45,033 (this

[†] Additional information on pregnancy is included in ADDENDUM: ([comment on feedback](#)) : Continuous glucose meters in the management of diabetes 9th May 2014, although these data do not change the conclusion above.

is equivalent to around £30,000). This is just on the upper limit of NICE's threshold for cost effectiveness (£20 – £30,000).

Literature Reviews

Published literature reviews during 2012/13 reveal a contrasting and sometimes contradictory interpretation of the evidence base. A USA review concluded that CGM has been shown to promote safer and more effective glycaemic control than self-monitoring. However, imperfections remain such as during hypoglycaemia and in young children.³⁸ A second USA review agreed the evidence was less robust for children and adolescents and noted an improvement in metabolic control. However, in direct contradiction of the first review, it supported the use of CGM in hypoglycaemia ().³⁹

Other researchers have stated the mean change (in adults and children) in HbA_{1c} is - 0.25%. This review concluded that CGM is better than self-management but more work in children and very young children is needed.⁴⁰

In partial agreement with this, a Thailand systematic review noted that CGM was no more effective than self-monitoring in reducing HbA_{1c} in children. However, a subgroup analysis indicated a marginal reduction of HbA_{1c} (- 0.18%) using real-time CGM rather than retrospective.³²

Finally, a UK review of CGM use in children concluded that these devices are effective if used regularly ("real-time" producing HbA_{1c} reductions of between - 0.5% to -1.0%).⁴¹ In practice, most children choose not to use the sensors regularly and thus user-friendly devices need to be developed. More research is required.

Perhaps one of the most informative pieces of work published around the same time as the Cochrane review⁷ is a systematic review and meta-analysis in *Annals of Internal Medicine*.⁴²

This compared effectiveness and safety of insulin delivery and glucose monitoring for diabetes mellitus. A substantial part of this review was the comparison of multiple daily injections of insulin with real time CGM monitoring in type I and II diabetes both in children and adults.

Closer inspection of this paper reveals that two sub-groups were studied. One compared CGM with self monitoring of blood glucose. The other compared multiple daily injections versus "sensor-augmented pump therapy." The latter is a CGM device used in conjunction with a continuous subcutaneous insulin pump.

A summary of the results is abstracted from the paper and shown in appendix 1. The figure shows that a mean reduction in HbA_{1c} of -0.26% was calculated for patients receiving CGM versus those on standard self monitoring of blood glucose. The top part of the diagram displays these data for the 10 trials involved.

It is clear that 5 of these trials achieved reductions in HbA_{1c} which were statistically non-significant. This casts doubt about the general homogeneity of the data (or rather the lack of it). Many more trials (or a single large trial) would need to be conducted to erase the concern about this potential bias.

The middle section of the diagram shows the results for CGM plus continuous insulin pump (“sensor augmented pump”) versus multiple daily injections. These 5 trials give an overall reduction in HbA_{1c} of -0.68%. Of these, 2 trials have wide confidence limits (probably as a result of low patient numbers). The one trial which contributes most to the overall result (n= 485) is that by Bergenstal.⁴³ Published in the *New England Journal of Medicine* (and included in the Cochrane review), this study has been criticised for a number of reasons.

Firstly, the control group received multiple daily injections of insulin rather than a continuous infusion pump as in the intervention CGM (sensor augmented) group. Secondly, the authors acknowledged that patients in the sensor arm received at least 5 weeks of intensive clinical input for sensor and pump training.

Thirdly, Bergenstal’s study was heavily sponsored by the pump manufacturers and Medtronic in particular were closely involved in the final write up.

Finally, the bottom section of appendix 1 shows the data for hypoglycaemia. It is apparent that there was no difference in rates of hypoglycaemia between the intervention and controls. In the context of the paper, this was perceived that sensor augmented therapy did not provide an increased risk of hypoglycaemia. However, it could also be inferred that CGM sensors did not reduce the risk of hypoglycaemia.

In summary, this meta-analysis has suggested that CGM systems are responsible for improved diabetes control as indicated by a reduction in HbA_{1c}. The reduction is greatest for sensor –augmented pumps although the study which is a major contributor to these data has several limitations and should be treated with caution. CGMs appear neither to increase nor decrease the risk of hypoglycaemia.

Consensus Guidelines

The literature search identified various guidelines from the USA and Europe on the current place of CGM in diabetes management. These are shown in appendix 2.

The guidelines were published between 2010 and 2013 and it is noteworthy that most of this work is heavily sponsored by the manufacturers of the CGM devices. The German Diabetes Association used a Medtronic™ employee as one of their main authors.¹

Glancing across the table, it is not unreasonable to conclude that there is little agreement as to how these systems should be used. For hypoglycaemia, 3/5 of the consensus groups recommend use of a CGM. However, the

underpinning “evidence” is described as “weak” or “based on consensus”. Whilst the American association suggests that a CGM “may be” a useful tool, the British association cites this as a “potential” tool. In contrast the German association is quite clear in its recommendation for severe, frequent, nocturnal or unaware hypoglycaemias although the rationale is not evident.

The recommendations for children and young teens are also non-specific. Strangely, the American Diabetes Association describes the evidence as weak yet the USA Endocrine Society recommends use where HbA_{1c} is either less than or greater than 7%.

Despite the conflicting evidence for use in pregnancy³³, half the associations recommend treatment yet the evidence is based on consensus rather than data from controlled trials.

Perhaps the strongest (and most evidence-based) recommendation is for HbA_{1c} control particularly for adults. However, as stated by the Endocrine Society, the benefits have to be weighed up against the cost.

National, Independent Guidelines

Aetna (the American healthcare maintenance organisation) divides its recommendations into short term (72 hours or less) and long term (greater than 72 hours).⁴⁴ Aetna considers short term appropriate for the diagnosis of hypoglycaemia (unawareness or repeated hypos [and hyperglycaemia]).

Long term therapy is funded for adults aged 25 years or older (in combination with fingerstick testing) with type I and as an option for younger people with severe hypoglycaemia despite good compliance and insulin adjustment in both cases. Long term use of CGM is considered experimental and investigational for all other indications.

Similarly, the BlueCross BlueShield organisation specifies short and long term indications as part of its insurance coverage.⁴⁵ For short term, the uses are wider than Aetna recommendations and are diagnostic in patients with poor control, hypoglycaemia, suspected postprandial hyperglycaemia, prior to insulin pump therapy and women pregnant or about to become pregnant with poor control.

Long term use is permitted for type I diabetes when the patient has recurrent, severe and unexplained hypoglycaemia. In addition, CGM is indicated in pregnancy for poorly controlled women with unexplained hypoglycaemia, hyperglycaemia and recurrent ketoacidosis. All other uses including artificial pancreas systems are considered investigational and not funded.

BlueCross acknowledges that the best evidence is for patients aged 25 years or older but suggests that “age” might be a proxy for motivation and thus ability to self-manage. Data on long term impact are lacking and CGM is thus considered investigational in improving glucose control in the general diabetic population.

The National Institute for Health and Care Excellence (NICE) published clinical guideline number 15 on the diagnosis and treatment of diabetes (type I) in adults and children in 2004.⁴⁶ NICE recommends CGM for children with persistent problems with hypo- or hyperglycaemia and also for adults to assess their glucose profiles when experiencing problems with persistent problems with hypo- and hyperglycaemia. Clearly, this guidance is now 10 years old. Both of these recommendations were based on moderate quality evidence.

The more recent Scottish Intercollegiate Guideline Network (SIGN), in 2010, recommended that CGM should not be used routinely in diabetes.⁴⁷

SUMMARY

1. A 2012 review by Cochrane ⁷ found that a reduction of 0.7% in HBA_{1c} can be attributed to the CGM system. However, Cochrane's overall conclusion is there are limited data for adults, children and patients with poorly controlled diabetes.

The summary points below were collected from information published after the Cochrane review.

2. There are concerns about the accuracy of the devices. Despite lag times of 5 -15 minutes between capillary and (sensor measured) interstitial glucose, differences between meters, settings (eg clinic, home or research centre) and position of the probe on the body still persist.
3. The Mean Absolute Relative Difference (MARD), which is indicative of this error, has been reported to be up to 35%. Interestingly, MARDs are higher in the hypoglycaemic range.
4. Such erroneous readings could lead to over or under- administration of insulin with potentially deleterious results. This inference is tempered by the fact that most authors warn that the clinical picture should always be taken into account when administering insulin irrespective of the sensor reading. The FDA approves these devices on the grounds that clinical decisions to alter treatment are based on a parallel fingerprick result.
5. The reported reduction in HBA_{1c} from these recent trials is about - 0.5%. However, the trials are small and very short term.
6. Recent trials on the utility of CGM to detect hypoglycaemia are also small, short term and give conflicting results. A Danish study has shown the sensitivity of the meter (ability to detect all cases of hypoglycaemia) worsens as blood sugar falls. The worst case scenario is at very low blood sugars (< 2.2mmol/l) when only 17% of cases are detected.
7. Worryingly, the meters tend to overestimate blood sugars (by + 1mmol/l) in the hypoglycaemic range, yet underestimate (by – 1.1mmol/l) in the hyperglycaemic range. More than half the alarms for hypoglycaemia in a separate study were false.
8. The data for children (especially very young children) are less convincing than for adults.
9. There are issues about sensor comfort, irritation/inflammation, patient motivation, the need for education and the problem of compliance.
10. Data on use in pregnancy are conflicting.
11. Consideration of recently published reviews and guidelines, suggests there is no clear consensus on the role of CGM in current management.

CONCLUSIONS

1. Questions over accuracy raise serious concerns over the “real time” utility and safety of these meters, particularly around detection of hypoglycaemia.
2. The most promising evidence supports the use in adults aged 25 years or older to reduce HbA_{1c}.
3. However, the underpinning evidence is questionable in terms of low patient numbers, the open nature of the trials, the short term outcomes and heavy industry sponsorship.
4. From the published data, it is estimated that fewer than 1,000 patients have been studied worldwide.
5. These devices cost several thousand pounds to purchase and maintain and are unlikely to be cost-effective.
6. Otherwise, there is no clear consensus as to where their role lies.
7. More high quality, long-term research is required.

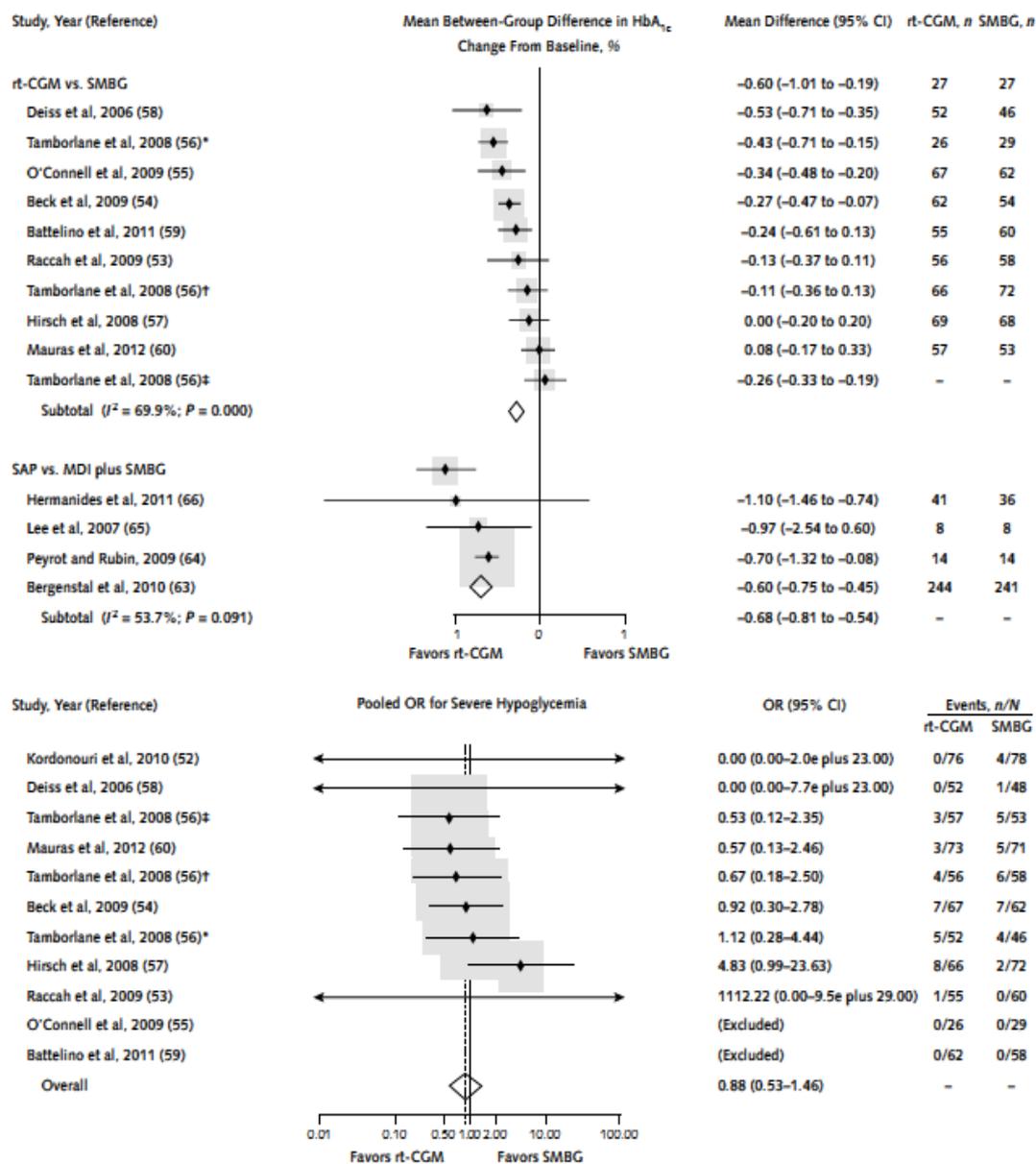
RECOMMENDATIONS

1. There may be an extremely small cohort of patients who would benefit from this intervention, based on the best evidence available. These patients must fulfil the following criteria: –
 - Type I diabetes
 - AND currently on a sensor augmented continuous subcutaneous insulin pump in strict accordance with NICE appraisal TAG 151.
 - AND HbA_{1c} ≥ 8.5%
 - OR experiencing severe hypoglycaemic attacks which require intervention by a carer.
 - AND selected to use an approved sensor augmented pump system of high specification with a low Mean Absolute Relative Difference (MARD) value
 - AND managed by a recognised centre of excellence in diabetes (currently using a minimum of 20 continuous infusion pumps per annum)[‡]
2. The device should be withdrawn from patients who fail to achieve a clinically significant response after 6 months.
3. All other requests will not be funded.

[‡] Within Cheshire & Merseyside, Adult centres are likely to be those at the Royal Liverpool, Whiston and Aintree hospitals. Paediatric centre is Alder Hey Hospital.

Appendix 1: Real time-CGM vs self monitoring and multiple daily injections of insulin

Figure 4. Comparison of rt-CGM with SMBG and SAP use with MDI plus SMBG among patients with T1DM.



Mean between-group difference in the change from baseline HbA_{1c} among patients with T1DM comparing rt-CGM with SMBG and SAP with MDI plus SMBG (top). Pooled OR of severe hypoglycemia comparing rt-CGM with SMBG among patients with T1DM (bottom). Error bars represent 95% CIs. Shaded boxes represent individual study point estimates. Box size corresponds to weight of study. HbA_{1c} = hemoglobin A_{1c}; MDI = multiple daily injections; OR = odds ratio; rt-CGM = real-time continuous glucose monitoring; SAP = sensor-augmented pump for insulin delivery; SMBG = self-monitoring of blood glucose; T1DM = type 1 diabetes mellitus.

* Patients aged 15-24 y.

† Patients aged 8-14 y.

‡ Patients aged >25 y.

Appendix 2: Table of selected consensus guidelines on CGM systems

		German Diabetes Association 2013 ¹	American Diabetes Association 2012 ⁴⁸	Endocrine society (USA) 2011 ⁴⁹	Association of British Clinical Diabetologists (ABCD) 2010 ⁵	European Society for Pediatric Endocrinology 2012 ³⁰
AUTHORS' COMMENTS		Contra-indications: Lack of user motivation, technology phobia, drug/alcohol misuse, mental health problems		Acknowledges that routine use will be dependent on cost relative to benefits.	One recommendation is evidence-based. Others based on consensus.	Not enough direct evidence available to identify children most likely to benefit.
INDICATIONS	Hypoglycaemia	Severe, frequent, nocturnal or unawareness	May be a useful tool, especially if unawareness and/or frequent (<i>weak evidence</i>)		Potential indication for diagnosis (<i>consensus</i>)	
	HbA_{1c} control	1) Poor control despite intensive therapy & good compliance. 2) Need to perform >10 BMs to achieve target	Age ≥ 25 in conjunction with intensive insulin - may be a useful tool (<i>strong evidence</i>)	Adults - HbA _{1c} ≥7% and <7% able to use on a near daily basis	HbA _{1c} is above target despite intensive insulin (<i>evidence based</i>)	
	Pregnancy	Before/during with inadequate control using conventional methods			Potential indication if HbA _{1c} ≥6.1% or problems with hypoglycaemia (<i>consensus</i>)	
	Children & young teens		Evidence less strong but may be useful (<i>weak evidence</i>)	1) HbA _{1c} <7% to maintain control. 2) HbA _{1c} ≥7% able to use on a near daily basis 3) Age <8yrs: No recommendation		
GENERAL COMMENTS		Authors sponsored by pump manufacturers. One author is a Medtronic employee		4/7 authors sponsored by pump manufacturer. Employed a medical writer.	"Evidence" is old data 2006 – 2008. Paper drafted at a meeting sponsored by Medtronic.	Authors sponsored by pump manufacturers

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