QUESTION

Should professional or personal real time CGM vs. no CGM be used for people with type 2 diabetes in the outpatient setting who take insulin and/or sulfonylureas and are at risk for hypoglycemia?

POPULATION:	people with type 2 diabetes in the outpatient setting who take insulin and/or sulfonylureas and are at risk for hypoglycemia
INTERVENTION:	professional or personal real time CGM
COMPARISON:	no CGM
MAIN OUTCOMES:	Patients with hypoglycemia ≤70 mg/dl; Hypoglycemia (<70mg/dL) – episodes per patient; Patients with hypoglycemia (<54mg/dL) ; Hypoglycemia (<54mg/dL) – episodes per patient; Hypoglycemia (<40mg/dL) – episodes per patient; Time below range (<70 mg/dL) – intervention vs. control; Time below range (<70 mg/dL) – change from baseline in the intervention group; Time below range (<50 mg/dL) – intervention vs. control; Time in range (70-180 mg/dL) – intervention vs. control; Time in range (70-180 mg/dL) – change from baseline in the intervention group; Hemoglobin A1C; Severe hypoglycemia; Hypoglycemia ≤54 mg/dl; Death; Myocardial Infarction; Stroke; Loss of consciousness/Seizure;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective
BACKGROUND:	Hypoglycemia is a significant, potentially life-threatening concern among people with diabetes who take medications including insulin and sulfonylureas. Continuous glucose monitoring provides an effective and patient-friendly method for patients using these medications to detect, prevent and treat impending hypoglycemia in the outpatient setting.
CONFLICT OF INTERESTS:	Endocrine Society conflict of interest management policies were applied and the following panel members were recused as a result of risk of conflicts of interest: Grazia Aleppo

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**This problem is a priority as hypoglycemia is a common concern among people with diabetes, and CGM may reduce both hypoglycemia and fear of hypoglycemia.** From 2017-2018 only 75.4% of adults nationally met an A1c goal of < 8% (1). Self-Monitoring of blood glucose (SMBG) helps patients reach their glycemic targets and alone can improve A1c. However, intensification of T2DM therapy leads to hypoglycemia which is a feared complication and an important barrier for improved glycemic management (2, 3). Hypoglycemia can be both recognized and unrecognized and is common with RCTS noting rates of severe hypoglycemia (that requiring assistance from another to treat) ranging from 0.7 to 12 per 100 person-years(4). Severe hypoglycemia occurs in approximately 25% of people with T2DM treated with insulin for more than 5 years – a percentage that is similar to those with type 1 diabetes(5). Severe hypoglycemia has been suggested as a potential preventable cardiovascular risk factor, with studies linking severe hypoglycemia with life-threatening cardiac arrhythmias and the proinflammatory state associated with cardiovascular events (6). Hypoglycemia may also be more common in those individuals with T2DM coming from lower socioeconomic levels, with less access to diabetes education and employment (7). SMBG aids physicians and patients to achieve a specific level of glycemic control and to prevent hypoglycemia(8). SMBG is now therefore standard of care for monitoring BG levels in patients with T2DM on insulin or oral antidiabetic drugs (OAD). The number of checks a day will vary on the basis of type of therapy. SMBG is inconvenient in that it is painful and disrupts daily activity (9). There is accruing evidence that patients with T2DM who use insulin and are at risk for hypoglycemia can benefit from CGM in the outpatient setting(10) .	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
● Small
○ Moderate
○ Large

○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no CGM	Risk difference with professional or personal real time CGM
Patients with hypoglycemia ≤70 mg/dl follow up: 2 months	96 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**OR 0.71** (0.30 to 1.67)	Study population	
				364 per 1,000	**75 fewer per 1,000** (217 fewer to 125 more)
Hypoglycemia (<70mg/dL) – episodes per patient follow up: 2 months	451 (4 RCTs)	⨁◯◯◯ VERY LOW [c,d,e]	-	The mean hypoglycemia (<70mg/dL) – episodes per patient was **0** episodes per patient	MD **0.06 episodes per patient more** (0.26 fewer to 0.38 more)
Patients with hypoglycemia (<54mg/dL) follow up: 2 months	96 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**OR 1.30** (0.34 to 4.95)	Study population	
				91 per 1,000	**24 more per 1,000** (58 fewer to 240 more)
Hypoglycemia (<54mg/dL) – episodes per patient follow up: 2 months	320 (2 RCTs)	⨁⨁◯◯ LOW [c,e]	-	The mean hypoglycemia (<54mg/dL) – episodes per patient was **0** episodes per patient	MD **0.04 episodes per patient fewer** (0.27 fewer to 0.18 more)
Hypoglycemia (<40mg/dL) – episodes per patient follow up: 6 months	224 (1 RCT)	⨁⨁◯◯ LOW [e,f]	-	The mean hypoglycemia (<40mg/dL) – episodes per patient was **0** episodes per patient	MD **0.04 episodes per patient fewer** (0.09 fewer to 0.01 more)
Time below range (<70 mg/dL) – intervention vs. control follow up: range 6 months to 8 months	574 (4 RCTs)	⨁⨁◯◯ LOW [e,f]	-	The mean time below range (<70 mg/dL) – intervention vs. control was **0** % of time spent	MD **1.42 % of time spent more** (0.47 fewer to 3.32 more)

HBA1c difference of 0.5 considered clinically significant. 5% change in time in range considered clinically significant.

Small desirable effects. Studies focused on reaching HBA1c and time in range target, rather than hypoglycemia prevention. Improvement in HBA1c and time in range. The studies show that there was improvement in A1c without increase in hypoglycemia.

Hypoglycemia related to the use of sulfonylureas often leads to lengthy and costly hospitalizations.

The panel noted that with respect to hypoglycemia reduction, any reduction in time below range would be considered significant.

Time bellow range (<70 mg/dL) – change from baseline in the intervention group follow up: range 2 months to 6 months	412 (3 RCTs)	⨁⨁⨁◯ MODERATE [c]	-	The mean time bellow range (<70 mg/dL) – change from baseline in the intervention group was **0** % of time spent	MD **0.57 % of time spent fewer** (0.99 fewer to 0.14 fewer)
Time below range (<50 mg/dL) – intervention vs. control follow up: 6 months	382 (2 RCTs)	⨁◯◯◯ VERY LOW [e,f,g]	-	The mean time below range (<50 mg/dL) – intervention vs. control was **0** % time spent	MD **0.07 % time spent more** (0.24 fewer to 0.1 more)
Time in range (70-180 mg/dL) – intervention vs. control follow up: range 6 months to 8 months	468 (3 RCTs)	⨁◯◯◯ VERY LOW [c,e,h]	-	The mean time in range (70-180 mg/dL) – intervention vs. control was **0** % of time spent	MD **2.54 % of time spent more** (0.92 fewer to 6.01 more)
Time in range (70-180 mg/dL) – change from baseline in the intervention group follow up: 6 months	384 (3 RCTs)	⨁◯◯◯ VERY LOW [b,c]	-	The mean time in range (70-180 mg/dL) – change from baseline in the intervention group was **0** % of time spent	MD **0.93 % of time spent more** (2.83 fewer to 4.69 more)
Hemoglobin A1C follow up: range 2 months to 6 months	656 (6 RCTs)	⨁⨁⨁◯ MODERATE [c]	-	The mean hemoglobin A1C was **0**	MD **0.2 lower** (0.34 lower to 0.05 lower)
Severe hypoglycemia - not reported	-	-	-	**-**	**-**
Hypoglycemia ≤54 mg/dl - not reported	-	-	-	**-**	**-**
Death - not reported	-	-	-	**-**	**-**
Myocardial Infarction - not reported	-	-	-	**-**	**-**
Stroke - not reported	-	-	-	**-**	**-**
Loss of consciousness/Seizure - not reported	-	-	-	**-**	**-**

a. Serious concern about risk of bias due to lack of allocation concealment among other sources of bias.
b. Very serious concerns about imprecision due to very wide CI that has appreciable benefits and harms.
c. All trials were at overall high risk of bias
d. Serious concern about inconsistency due to substantially large I2 estimate (unlikely explained by chance; p=0.03) and poor overalp of CIs.
e. Serious concerns about imprecision due to wide CI that has benefits and harms.
f. Serious concern about risk of bias due to multiple sources of bias.

g. Poor overlap of CIs and substantially high I2.
h. Serious concerns about inconsistency due to considerably large I2 estimate unlikely explained by chance (p<0.01) and lack of overlapping of CIs.

Additional Research Evidence Discussed:
The panel outlined patients at highest risk who may especially benefit from the outpatient use of CGM: e.g. patients with renal disease/renal failure patients and/or hepatic disease; patients with impaired hypoglycemia awareness; anyone who has had recent severe hypoglycemia. High risk subgroup also includes pre-school age children.

CGM has been found to be of benefit in people with T2DM with respect to HbA1c lowering and reductions in ER visits related to hypoglycemia, including those taking basal insulin, and those using both basal and prandial insulin (11, 12, 13) These findings have led many to argue for broadened access to CGM for patients with T2DM (14).

Munshi et al. found that in a population of older adults (those 69 years or older) with T2DM and HbA1c values > 8%, using blinded CGM for three days, a majority of patients experienced an episode of glucose < 70 mg/dL, and close to half experienced a glucose < 50 mg/dL (15). Of note, a striking 93% of the hypoglycemic episodes reported in this study were unrecognized by SMBG done four times daily, or by patient reported symptoms.

The majority of data involving CGM in those using oral hypoglycemic agents comes from studies involving older adults. In a study published by Hay et al. involving older patients (> 65 years) with well-controlled T2DM (HbA1c < 7.5%) taking a sulfonylurea +/- metformin, wearing a CGM, participants experience an average of 0.62 +/- 0.72 episodes of hypoglycemia (defined as an interstitial glucose < 50 mg/dL) per day (four to five episodes in total over two, 72-hour periods), and an average of 0.35 +/- 0.6 episodes per day when glucose was < 40 mg/dL (two to three episodes in total) (16). Of note, none of these hypoglycemic episodes were recorded by patients in their diary. A similar study by van Dijk et al. evaluated older adults (age > 70 years) with T2DM, HbA1c < 7.5% and a high frailty score, who were taking metformin or metformin combined with a sulfonylurea (17). Participants wore a blinded CGM for 5 days and were asked to record any symptoms of hypoglycemia in a diary. 22% of those included experienced a glucose value < 54 mg/dL, and 35% had a glucose < 63 mg/dL. Only those taking a sulfonylurea experienced hypoglycemia, and all episodes were asymptomatic.

An editorial by Arguello and Freeby in 2017 points out that not all insulin using T2D patients need CGM, and that the population that would benefit from CGM is not fully understood (18).

A 2020 RCT conducted at 22 endocrine practices in the US, and involving 203 individuals with type 1 diabetes who were at least 60 years of age, demonstrated that median time with glucose < 70 mg/dL was significantly reduced (by 27 min per day) in the subjects randomized to CGM (95% CI, -40 to -16 min per day, P < 0.001). This suggests, albeit indirectly, that those individuals with type 2 diabetes using insulin (perhaps especially those taking both basal and meal-time insulin) may benefit from CGM with regard to reducing hypoglycemia (19). Of note, the individuals in this study randomized to CGM also noted reductions in their mean HbA1c (adjusted group difference, -0.3%;95% CI, -0.4% to -0.1%; P < 0.001).

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
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ADDITIONAL CONSIDERATIONS

Hypoglycemia (<70mg/dL) – episodes per patient follow up: 2 months	451 (4 RCTs)	⨁◯◯◯ VERY LOW [c,d,e]	-	The mean hypoglycemia (<70mg/dL) – episodes per patient was **0** episodes per patient	MD **0.06 episodes per patient more** (0.26 fewer to 0.38 more)
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g. Poor overlap of CIs and substantially high I2.
h. Serious concerns about inconsistency due to considerably large I2 estimate unlikely explained by chance (p<0.01) and lack of overlapping of CIs.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty, due to selection of patients in the studies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**There is likely not uncertainty about these outcomes, as hypoglycemia is feared, increases diabetes distress and is associated with poor quality of life.** Fear of hypoglycemia prevents escalation of diabetes regimens and prevents patients from reaching their glycemic targets. Hypoglycemia reduces QOL, increase hospitalization, ER visits, 911 call outs and health care utilization (2).	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low certainty, due to selection of patients in the studies.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	**No research evidence identified**	This question focuses on those at high-risk for hypoglycemia, whereas research studies on cost would include mixture of low-risk and high-risk patients. Unit cost for the intervention is one component. CGMs with and without alarms would differ in costs. This is less of an issue with the Libre 2 now having alarms. Some patients do not like alarms. The panel noted that other costs were not known. These would include costs of emergency and ER treatments of severe hypoglycemia. There may be a group of patients for whom there may be moderate savings, including those with hypoglycemia unawareness, as well as patients with complexity of co-morbidities at high risk of hypoglycemia.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	**No research evidence identified**	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified	Without insurance, out-of pocket costs are substantial, and those without coverage would typically not be able to afford CGM, within the U.S. healthcare system. T2D is more common in low SES minorities many of whom are uninsured or underinsured. The current health insurance landscape likely makes obtaining CGM difficult, if not impossible, for these individuals. Higher SES individuals with private insurance will probably have easier access to CGM. With regard to health equity, not all patients will have the resources to afford CGM. Arguello et al. discuss in an editorial that it was not fully clear which patients with type 2 diabetes have clear evidence of the need for and ability to use CGM. With these issues in mind, equity is probably reduced; with the healthcare system and insurance coverage being the driver for inequity, rather than the CGM intervention itself.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Data suggests that the intervention is likely acceptable to key stakeholders.** Treatment satisfaction scores are higher in those using CGM than in those measuring finger stick blood glucose, and studies suggest little if any serious adverse events related to CGM devices (2, 3). CGM is associated with reductions in time with hypoglycemia, and with fewer episodes of nocturnal hypoglycemia, both sought after hypoglycemia-related outcomes by patients and their health care providers. Yaron et al. found that those using CGM found their treatment to be more flexible than SMBG, and that they would recommend CGM use to others (9).	The research studies summarized included older devices. Newer devices include warnings and there are devices available with alerts (e.g. connected to the phone). For example, the older FreeStyle Libre 14 day system does not include the real-time alarms altering the user to hypoglycemia that are seen with the newer FreeStyle Libre 2. The panel noted recent changes to Medicare rules (Beginning 7/2021) removing the requirement for four-time-daily fingerstick blood glucoses in order for individuals to qualify for coverage of continuous glucose monitors.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**An increasing number of patients are finding CGMs to be helpful, and as the devices become more easy to acquire and use, we believe there will be much more data to support their use. Additional features like trend arrow, alarms for glucose levels trending to hypo or hyperglycemia are very valuable features.** CGM is expensive and requires training of the patient and also on the part of the physician in interpreting the reports. CGM management needs to be with simplified devices that are acceptable to PCPs. This is especially important since majority of type 2 diabetes patients are cared for by her primary care physicians. Additionally, the device acquisition, implementation, patient education and data reports need to straightforward, simplified and standardized (3). The sensor is worn on the back of the arm for up to 14 days and automatically stores glucose data every 15 min. A real-time glucose level may be obtained as often as every minute by scanning the sensor with the reader. A glucose trend arrow (indicating rate and direction of change in glucose levels) and a graphical trace of glucose values for the previous 8-h period are also displayed on the screen. Data are transferred by radio frequency identification (RFID) from the sensor to the reader memory which stores historical sensor data for 90 days. This data can be uploaded using the device software to generate summary glucose reports (including an ambulatory glucose profile) for review by the patient at home or in clinic with their healthcare professional (HCP). Flash monitoring with Libre 2 is less costly and more accurate at low BG levels (improved MARD) (2). Training is relatively simple with YouTube free videos on installation and wearing of the device. Physician training is also available through experience and Endocrinology training and free education online.	Minimal data about costs of CGM for T2DM is available. Newer flash CGM is less expensive in comparison to standard new model for Dexcom. Older devices are more costly, require repeated calibration, and are constantly attached to the patient, all key factors preventing widespread use. However it can inferred that overall cost reduction for the healthcare system may be seen due to decrease hospitalizations, ER visits and ambulance calls (given reductions in serious hypoglycemia). Patients with T2D who receive care at major centers will have access to physicians, NPs and diabetes educators who are knowledgeable and oriented to use of diabetes technologies. Obtaining CGM technology requires overcoming barriers (e.g. certificate of medical necessity to obtain insurance approval) and training in proper use of the device and how to interpret the data it provides. Both health care providers and patients must be highly motivated. The panel noted the increased use/more widespread availability of telehealth and telemedicine services, and noted that with easy-to-use, secure CGM software, endocrine care providers and their patients can more easily review glucose trends, including hypoglycemic episodes, remotely.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know

UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest real time CGM be used versus no CGM for outpatients with T2D who take insulin and/or sulfonylureas and are at risk for hypoglycemia. (conditional recommendation, very low certainty of evidence) (2⊕◯◯◯)

Remarks:

- Professional CGM is a diagnostic tool used for the short-term investigation of an individual's glycemic profile to determine glycemic patterns, to assist with therapeutic management.
- Personal CGM is a tool for patients to use in real-time at home to assist in the patient and their HCPs making both short- and long-term adjustments in their therapeutic management.

Justification

The panel's decision for a conditional recommendation was due to limited data and very low certainty of evidence available in the population of interest. Some of the panel's decisions were based upon indirect evidence involving data from studies that included people with type 1 diabetes.

However, the panel agreed that severe hypoglycemia is a life-threatening comorbid condition for those at risk with type 2 diabetes and felt that that the available direct and indirect evidence supported their recommendation.

Subgroup considerations

The panel outlined patients at high risk who may benefit more from CGM: e.g. patient profile with co-morbidities, renal disease/renal failure patients, patients with hepatic disease (i.e. not able to mount glucogenic response), as those at high risk of hypoglycemia, patients with hypoglycemia unawareness, anyone who has had recent severe hypoglycemia.

Implementation considerations

The panel noted that there are different CGM devices available, including those that have alarms that will notify users of impending hypoglycemia, and those that do not. The panel also noted that there were CGM devices that required regular calibration with fingerstick blood glucoses values.

Monitoring and evaluation

This recommendation should be monitored with respect to new data regarding CGM use in reducing hypoglycemia specifically in individuals having type 2 diabetes. Further, the recommendation should be monitored with respect to new CGM technologies that will become available in the future.

Research priorities

The panel highlighted the following research priorities:

- Studies specifically in patients who may be at higher risk of hypoglycemia (as defined above)
- Studies in those coming from lower socioeconomic status and populations, with a goal of reducing health disparities
- Studies evaluating the resources need and cost-effectiveness of CGM

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