QUESTION

Should real time CGM and algorithm-driven insulin pumps vs. multiple daily injections with SMBG 3 or more times daily be used for people with Type 1 diabetes?	
POPULATION:	people with Type 1 diabetes
INTERVENTION:	real time CGM and algorithm-driven insulin pumps
COMPARISON:	multiple daily injections with SMBG 3 or more times daily
MAIN OUTCOMES:	Hypoglycemia ≤70 mg/dl; Severe hypoglycemia; Hypoglycemia ≤54 mg/dl; Hemoglobin A1C; Death; Myocardial Infarction; Stroke; Loss of consciousness/Seizure;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	Hybrid closed loop systems contain a sophisticated CGM that feeds information and uses this trend information to automatically adjust insulin administration to aid safe control of glycemia. Studies of hybrid closed loop systems (many available versions with differing algorithms including several commercial systems) have shown improved overall control, lower risk of hypoglycemia with less diabetes distress and a lower burden of glucose management. These systems have the combined benefit of CGM and automatic information processing and insulin adjustment in addition to the CGM aimed to have a dual benefit in better and safer control largely related to the algorithms.
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	**The issue of how to best manage insulin delivery in patients with type 1 diabetes is a priority in clinical practice and the use of technology is recommended by many groups for those unable to achieve optimal glycemic control with multiple daily injections**. However, the selection of which technology should be used is generally based on patient preference(1, 2).	Studies of real-world control still find glycemic control in the Type 1 exchange is seldom reached on a long-term basis with A1c's that are usually above 7.5% and often over 8.5% with considerable instability with lots of highs and lows.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	No research evidence identified in review for Q1. **Indirect Evidence from Q6:**	No research evidence was identified that directly addresses CGM and algorithm driven pumps compared to finger sticks which leaves gaps in decision making. The panel reviewed the indirect evidence that shows moderate benefit. The panel also considered a judgement of large desirable effects, given there is additional value, however we do not have the direct evidence to make that judgement. The panel discussed that closed loop hybrid pumps, even with older CGM devices, provide additional benefit. Closed loop studies reveal benefit beyond that of CGM so that there is a double potential benefit.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SMBG	Risk difference with real time CGM
Patients with hypoglycemia (<54 mg/dL) - nonpregnant population	149 (1 RCT)	⨁⨁◯◯ Low [a,b]	**OR 0.15** (0.05 to 0.41)	Study population	

follow-up: 6 months				932 per 1,000	**258 fewer per 1,000** (524 fewer to 83 fewer)
Episodes of hypoglycemia (<54 mg/dL) - nonpregnant population follow-up: 6 months	0 (1 RCT)	⨁◯◯◯ Very low [c,d]	-	We did not find a significant difference between the intervention and control (n=158; IRR = 1.40; 95% CI: 0.65 to 3.00; I2= N/A).	
Episodes of severe hypoglycemia - nonpregnant population follow-up: 6 months	0 (4 RCTs)	⨁⨁⨁◯ Moderate [e]	-	There was a significant difference in episodes of severe hypoglycemia that favored the intervention (n=794; IRR = 0.39; 95% CI: 0.18 to 0.85; I2 = 25.00%).	
Patients with seizures - nonpregnant population	203 (1 RCT)	⨁◯◯◯ Very low [c,d]	**RR 0.08** (0.01 to 1.58)	Study population	
				50 per 1,000	**46 fewer per 1,000** (50 fewer to 29 more)
Time below range (<70 mg/dL) - nonpregnant population follow-up: 6 months	2771 (5 RCTs)	⨁⨁◯◯ Low [d,e]	-	The mean time below range (<70 mg/dL) - nonpregnant population was **0** percentage of time spent in range	MD **2.05 percentage of time spent in range lower** (4.71 lower to 0.6 higher)
Time below range (<54 mg/dL) - nonpregnant population follow-up: 6 months	2225 (5 RCTs)	⨁⨁◯◯ Low [d,e]	-	The mean time below range (<54 mg/dL) - nonpregnant population was **0** percentage of time spent in range	MD **0.89 percentage of time spent in range lower** (1.94 lower to 0.17 higher)
Time in range (70-180 mg/dL) - nonpregnant population follow-up: 6 months	1156 (6 RCTs)	⨁⨁⨁◯ Moderate [e]	-	The mean time in range (70-180 mg/dL) - nonpregnant population was **0** percentage of time spent in range	MD **5.2 percentage of time spent in range higher** (3.1 higher to 7.29 higher)
Hemoglobin A1c - nonpregnant population follow-up: 6 months	1050 (5 RCTs)	⨁◯◯◯ Very low [d,e,f]	-	The mean hemoglobin A1c - nonpregnant population was **0** %	MD **0.19 % lower** (0.39 lower to 0.02 higher)
Episodes of severe hypoglycemia - pregnant women follow-up: 8 months	0 (1 RCT)	⨁◯◯◯ Very low [d,g]	-	We found no difference between the intervention and control groups (n=207; IRR = 0.87; 95% CI: 0.46 to 1.62; I2 = N/A)	

The panel panel noted being able to have more granular control of blood glucose with CGM and hybrid closed loop pumps.

Time below range (<70 mg/dL) - pregnant women follow-up: 6 months	154 (1 RCT)	⨁⨁◯◯ Low [d,g]	-	The mean time below range (<70 mg/dL) - pregnant women was **0** percentage of time spent in range	MD **1 percentage of time spent in range lower** (2.28 lower to 0.28 higher)
Time below range (<54 mg/dL) - pregnant women follow-up: 6 months	154 (1 RCT)	⨁⨁◯◯ Low [b,g]	-	The mean time below range (<54 mg/dL) - pregnant women was **0** percentage of time spent in range	MD **1 percentage of time spent in range lower** (1.6 lower to 0.41 lower)
Time in range (70-180 mg/dL) - pregnant women follow-up: 6 months	154 (1 RCT)	⨁⨁◯◯ Low [b,g]	-	The mean time in range (70-180 mg/dL) - pregnant women was **0** percentage of time spent in range	MD **7 percentage of time spent in range higher** (2.57 higher to 11.43 higher)
Episodes of severe hypoglycemia - women planning pregnancy follow-up: 6 months	0 (1 RCT)	⨁◯◯◯ Very low [d,g]	-	We found no difference between the intervention and control groups (n=109; IRR = 2.19; 95% CI: 0.82 to 5.84; I2 = N/A).	
Time below range (<54 mg/dL) - women planning pregnancy follow-up: 6 months	91 (1 RCT)	⨁⨁◯◯ Low [b,g]	-	The mean time below range (<54 mg/dL) - women planning pregnancy was **0** percentage of time spent in range	MD **1 percentage of time spent in range higher** (0.2 higher to 1.8 higher)
Time below range (<70 mg/dL) - women planning pregnancy follow-up: 6 months	91 (1 RCT)	⨁◯◯◯ Very low [d,g]	-	The mean time below range (<70 mg/dL) - women planning pregnancy was **0** percentage of time spent in range	MD **1 percentage of time spent in range higher** (0.92 lower to 2.92 higher)
Time in range (70-180 mg/dL) - women planning pregnancy follow-up: 6 months	91 (1 RCT)	⨁◯◯◯ Very low [d,g]	-	The mean time in range (70-180 mg/dL) - women planning pregnancy was **0** percentage of time spent in range	MD **5 percentage of time spent in range higher** (0.96 lower to 10.96 higher)
Death - not reported	-	-	-	**-**	**-**
Myocardial Infarction - not reported	-	-	-	**-**	**-**
Hypoglycemia ≤70 mg/dl - not reported	-	-	-	**-**	**-**
Stroke - not reported	-	-	-	**-**	**-**

	a. Serious concerns about risk of bias due to risk of deviations from intented interventions, inadequate measurement of the outcome, and selective reporting. b. Small sample size. c. Very serious concerns about the process of random sequence generation. d. Very serious concerns about imprecision due to very wide CI that has appreciable benefits and harms. e. Serious concerns about risk of bias due to overall high risk of bias in all trials. f. Serious concerns about inconsistency due to high heterogeneity in the results (confidence intervals do not overlap and I2 estimate is substantially large). g. Serious concerns about risk of bias due to risk of deviations from intented interventions, inadequate measurement of the outcome, and selective reporting.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No research evidence identified in review for Q1. Used indirect evidence from Q6.	While not a prioritized outcome, the panel discussed contact dermatitis from the adhesive which affects a minority of patients using CGM. There are a variety of useful strategies for managing contact dermatitis that may ameliorate the problem. There are some individuals (especially adolescents) who do not want a medical device attached to their bodies. The panel noted that malfunctioning of a pump is incredibly rare.

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	No research evidence identified.	The panel considered the indirect evidence from studies on CGM vs. SMBG for patients with Type 1 diabetes receiving multiple daily injections, however the evidence was viewed as sufficiently direct and we did not downgrade the certainty further for indirectness.

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 are several advantages to the use of algorithm-driven pump therapy – however, variability exists regarding which aspects of that technology patients value (including ease of use of technology and effect that technology has on quality of life, such as sleep quality).** Advantages of using a real-time CGM and algorithm-driven pump therapy instead of multiple daily injections include having real-time blood glucose information available at all times without pricking a finger for blood to place on a test strip, having insulin delivery altered automatically to achieve desired targets thereby reducing hyper- and hypoglycemia, and receiving alarms when a drop in blood sugar cannot be stopped by the device. Advantages of MDI include having a greater sense of personal control over diabetes management, being free from sensors and infusion sets on your body, not having alarms, and lower cost. How a given patient rates these advantages is dependent on their own values, including how much they value reduction in hypoglycemia, time needed to use technology, and sleep quality (reduced with frequent pump alarms). In one study up to 30% of young people who started one such pump had discontinued its use by 6 months due to the above factors (3). However, adults randomized to a hybrid closed-loop pump (vs conventional therapy – pump or MDI) without CGM noted higher diabetes-specific positive well-being over 6 months (4).	

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	No research evidence identified.	Balance of effects probably favors the intervention, based on lack of direct evidence.

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	**There are significant costs associated with the use of insulin pump therapy when compared with multiple daily injections.** The original cost of an insulin pump is greater than MDI. Grip et al. determined costs of care for 14,238 individuals with type 1 diabetes in Sweden and determined annual costs for standard pump users was $12,928 compared with costs for mdi $9,005 (5).	The panel noted that better control with fewer highs and lows should mean both fewer complications and a lower 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	**The use of sensor-augmented insulin pump therapy may be cost-effective in certain circumstances – though more data is needed as this is still new technology.** A recent study in Australia compared the cost-effectiveness of a hybrid closed-loop pump with standard of care that included injections and capillary glucose testing. They found that there was an incremental cost effectiveness ratio of $37,767 (Australian) per quality-adjusted life-year, but this was below the traditionally cited threshold of $50,000 per QALY used in Australia (6).	

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**	The panel noted that lack of access is the main issue. The cost of CGM, not the intervention itself, would limit access to the technology and probably lead to reduced equity. If consistent outcomes in studies show safer control and fewer complications with closed loop hybrid systems, more people with Type 1 diabetes will likely be supported by insurance.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**No research evidence identified**	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Studies identified suggest that it is feasible to implement the use of sensor-augmented insulin pump therapy in real-world use, though costs may be a limiting factor.	Personal costs of augmented pump therapy are patient-dependent factors, including insurance coverage, where someone lives, etc. Because of the difference in cost, many patients may be unable to use the hybrid closed-loop pumps. Information regarding acceptability is noted in the current ADA Standards of Care 2021. The panel also shared concern about patients receiving diabetes care not at major centers falling behind, not getting same access and keeping up with latest interventions.

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 using real-time CGM and algorithm-driven (using real-time glucose sensor data including hybrid closed-loop[DL1]) pumps rather than multiple daily injections with SMBG 3 or more times daily for adults and children with Type 1 diabetes. (2⊕⊕◯◯) (Conditional recommendation, low certainty of evidence)

Remarks:
· Fingerstick blood glucose monitoring may still be necessary to validate or confirm CGM values, therefore with respect to use and insurance coverage there will be times where SMBG will still need to be used.

Justification

Because evidence is lacking to demonstrate the relative benefits and harms of using real-time CGM and algorithm-driven pumps vs MDI with SMBG, the panelists relied on the evidence used to support the recommendation of using CGM vs SMBG in Recommendation 1 to justify their recommendation. In addition, panelists were influenced by the opinions their patients had expressed about the benefits of using real-time CGM and algorithm-driven pumps in managing their diabetes.

Subgroup considerations

Implementation considerations

Many CGMs require that finger sticks are still used to validate CGM, therefore with respect to use and coverage (e.g. private insurers) there will be times when SMBG will still need to be used. (e.g. during the warm up period, for calibration, as a back-up when there is loss of sensor signal). The panel highlighted that artificial intelligence still needs to have a clinician checking in on it.
Education on how to use the devices and interpret the data is required for individuals to gain familiarity with the tools. Monitoring and communication with diabetes specialists are still quite important with use of CGM and algorithm driven pumps, and there is a need for diabetes educators to be up to speed on available technologies.

Monitoring and evaluation

None

Research priorities

Research priorities include studies that measure quality of life, diabetes distress, family/caregiver acceptability, reduction of burden of diabetes care; patient-important outcomes going beyond measuring hypoglycemia outcomes.
There is a need for more studies on cost effectiveness. Several studies found less hypoglycemia, especially overnight. Cost-effectiveness may be substantial if there is lower risk of serious hypoglycemia – this assessment needs more data for evaluation.
The panel noted that additional studies comparing CGM and algorithm driven pumps versus multiple daily injections with SMBG are unlikely as future studies will focus on comparing newer versions of CGM and algorithm driven pumps.

REFERENCES SUMMARY

1. . 7. Diabetes Technology: Standards of Medical Care in Diabetes-2021. Diabetes Care; Jan 2021.
2. Choudhary, P., Campbell, F., Joule, N., Kar, P.. A Type 1 diabetes technology pathway: consensus statement for the use of technology in Type 1 diabetes. Diabet Med; May 2019.
3. Messer, L. H., Berget, C., Vigers, T., Pyle, L., Geno, C., Wadwa, R. P., Driscoll, K. A., Forlenza, G. P.. Real world hybrid closed-loop discontinuation: Predictors and perceptions of youth discontinuing the 670G system in the first 6 months. Pediatr Diabetes; Mar 2020.
4. McAuley, S. A., Lee, M. H., Paldus, B., Vogrin, S., de Bock, M. I., Abraham, M. B., Bach, L. A., Burt, M. G., Cohen, N. D., Colman, P. G., Davis, E. A., Hendrieckx, C., Holmes-Walker, D. J., Kaye, J., Keech, A. C., Kumareswaran, K., MacIsaac, R. J., McCallum, R. W., Sims, C. M., Speight, J., Stranks, S. N., Sundararajan, V., Trawley, S., Ward, G. M., Jenkins, A. J., Jones, T. W., O'Neal, D. N.. Six Months of Hybrid Closed-Loop Versus Manual Insulin Delivery With Fingerprick Blood Glucose Monitoring in Adults With Type 1 Diabetes: A Randomized, Controlled Trial. Diabetes Care; Dec 2020.
5. Toresson Grip, E., Svensson, A. M., Miftaraj, M., Eliasson, B., Franzén, S., Gudbjörnsdottir, S., Steen Carlsson, K.. Real-World Costs of Continuous Insulin Pump Therapy and Multiple Daily Injections for Type 1 Diabetes: A Population-Based and Propensity-Matched Cohort From the Swedish National Diabetes Register. Diabetes Care; Apr 2019.
6. Pease, A., Zomer, E., Liew, D., Earnest, A., Soldatos, G., Ademi, Z., Zoungas, S.. Cost-Effectiveness Analysis of a Hybrid Closed-Loop System Versus Multiple Daily Injections and Capillary Glucose Testing for Adults with Type 1 Diabetes. Diabetes Technol Ther; Nov 2020.