Microinfusori: diverse soluzioni tecnologiche per una terapia personalizzata

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La dr.ssa Maria Paola Luconi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Abbott

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

INSULIN DELIVERY TECHNOLOGIES (1)

Who would benefit from the use of an insulin pump without CMG?

The use of an **insulin pump without CGM** could be used to manage persons with diabetes who are achieving glycemic targets with **minimal TBR,** or who report **infrequent episodes of symptomatic hypoglycemia**, and who are **using SMBG on a regular basis** (at least 4 times per day for persons with T1D).

Grade B; Intermediate-High Strength of Evidence; BEL 1.

Who would benefit from the use of an insulin pump with CMG?

Insulin pump with CGM or SAP (separate devices or Sensor Augmented Pump) is recommended to manage all persons with diabetes treated with **intensive insulin management who prefer not to use automated insulin suspension/dosing systems** or have no access to them.

Grade A, Intermediate-High Strength of Evidence, BEL 1.

Who would benefit from the use of more advanced insulin pump technologies (LGS, PLGS, HCL or AHCL)?

LGS (Low Glucose Suspend) **is strongly recommended for all persons with T1D to reduce the severity and duration of hypoglycemia**, whereas **PLGS** (Predictive Low Glucose Suspend) **to mitigate hypoglycemia.** Both systems do not lead to a rise in mean glucose, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both persons with diabetes and caregivers. Therefore, anyone with frequent hypoglycemia, impaired hypoglycemia awareness, and those who fear hypoglycemia leading to permissive hyperglycemia, should be considered for this method of insulin delivery.

AID systems (Advanced Insulin Delivery systems) **are strongly recommended for all persons with T1D**, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia**.** For persons with diabetes **with suboptimal glycemia**, **significant glycemic variability**, **impaired hypoglycemia awareness**, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered.

Grade A; High Strength of Evidence; BEL 1.

AACE Guidelines. Grunberger G et al. Endocrine Practice 2021;27:505e537.

INSULIN DELIVERY TECHNOLOGIES (2)

What are safety issues for the use of insulin delivery devices?

All persons with diabetes using an insulin delivery technology should receive **comprehensive training in its proper use and care**.

Grade A; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2.

Clinicians should ensure that persons with diabetes using an insulin delivery technology **are aware of the frequency and relative risk of pump malfunction**, receive instruction for identifying signs of pump malfunction, know who to contact in the event of a pump malfunction, **and have a defined plan for emergency measures** (eg, back-up insulin pen, remediation).

Grade A; Low Strength of Evidence/Expert Opinion of Task Force; BEL 2.

Persons with diabetes using integrated devices should receive requisite training in the use of their device(s) and that the devices are being safely and properly used according to manufacturer instructions.

Grade A; Low-Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 2.

In what settings or special situations is the use of diabetes technologies beneficial?

The continuation of CSII (insulin pump, SAP, LGS/PLGS) **should be considered in hospitalized persons** with diabetes **without cognitive impairment** and **ideally with the presence of a family member** who is knowledgeable and educated in the use of these devices **or** with a **specialized inpatient diabetes team** available for advice and support.

Grade A; Intermediate Strength of Evidence; BEL 1.

What are the criteria for discontinuing the use of insulin pumps in persons with diabetes?

Clinicians should strongly consider the discontinuation of insulin pump therapy **based on an individual's ability to use it effectively and safely or based on the personal preference** of a person with diabetes to discontinue this insulin delivery modality.

Grade A; Intermediate Strength of Evidence; BEL 1.

AACE Guidelines. Grunberger G et al. Endocrine Practice 2021;27:505e537.

Raccomandazione forte a favore dell'intervento, con qualità delle prove moderata

In soggetti con **diabete mellito di tipo 1 scompensato si raccomanda di offrire al paziente l'opzione di una terapia insulinica mediante microinfusore di insulina** rispetto alla terapia insulinica multiniettiva per i **vantaggi sui livelli di HbA1c**, **le ipoglicemie severe, la qualità di vita e la soddisfazione per il trattamento**.

In soggetti con **diabete mellito di tipo 1 non scompensato** si suggerisce di offrire al paziente l'opzione di una terapia insulinica mediante microinfusore di insulina rispetto alla terapia insulinica multiniettiva per i vantaggi su variabilità glicemica, qualità di vita e soddisfazione per il trattamento.

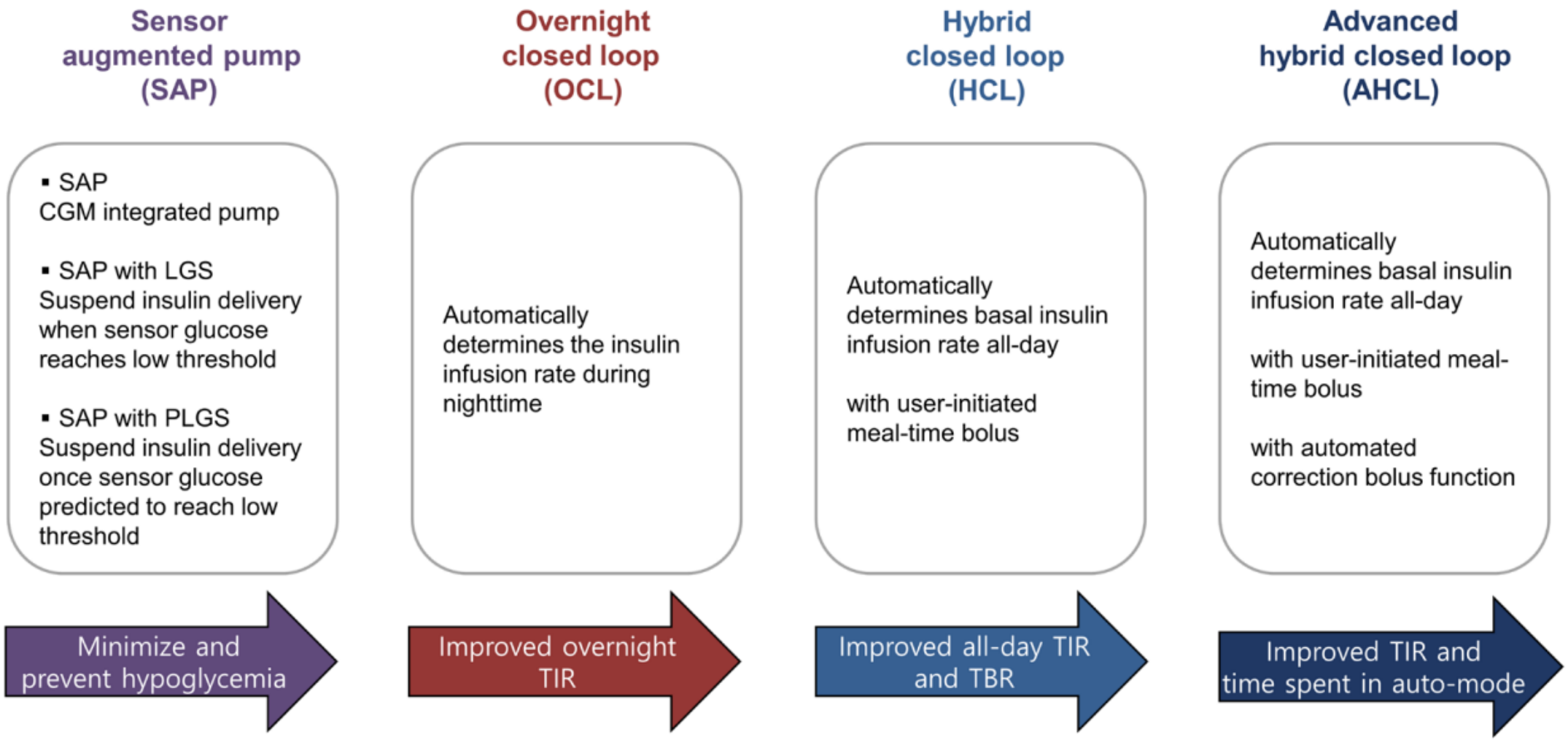
Raccomandazione forte a favore dell'intervento, con qualità delle prove alta

In soggetti con **diabete mellito di tipo 1 scompensato nonostante l'utilizzo di microinfusore e sensore si raccomanda l'utilizzo di sistemi** costituiti da microinfusore e sensore **con automatismo** rispetto all'uso di sistemi senza automatismo.

INSULIN PUMP THERAPY EFFICACY vs MDI

Type of Study & Authors	Population	Objective	Results
Cross-sectional Study. *Szypowska et al., Pediatr. Diabetes 2016, 17;38-45*	**16,570 youth with T1D** (median age 14 ys)	To examine the **frequency of pump usage** in T1D children treated in SWEET centers and **to compare metabolic control** between patients treated with CSII vs. MDI	**Both HbA1c and daily insulin dose** (U/kg/d) **decreased in children treated with CSII** (44%) compared with MDI (56%), *p < 0.0001*
Cross-sectional Study. *Sherr et al., Diabetologia 2016, 59, 87–91*	**54,410 youth with T1D** (median age 12.1 ys)	To describe **differences in metabolic control and pump use in young individuals with type 1 diabetes** using data collected in 3 multicentre registries (ys 2011–2012)	Intensive treatment with an insulin pump was associated with **lower HbA1c**, *p < 0.0001*
Prospective study. *Zabeen et al., PLoS ONE 2016, 11;e0153033*	**989 patients** (aged 12–20 ys; DM duration > 5 ys) **treated with CSII or MDI for >12 months**	To compare **microvascular complications frequency** in adolescents with type 1 diabetes treated with MDI versus CSII	In adolescents, CSII use is associated with **lower rates of retinopathy and peripheral nerve abnormality**
Population-based cohort study. *Karges et al., JAMA 2017, 318;1358-66*	**30,579 youth with T1D** (mean age 14.1±4.0 ys)	**To determine whether rates of severe hypoglycemia and DKA are lower** with CSII than MDI in children, adolescents, and young adults with type 1 diabetes	Compared with MDI, **CSII was associated with lower risks of severe hypoglycemia and DKA** and better glycemic control during the most recent year of therapy

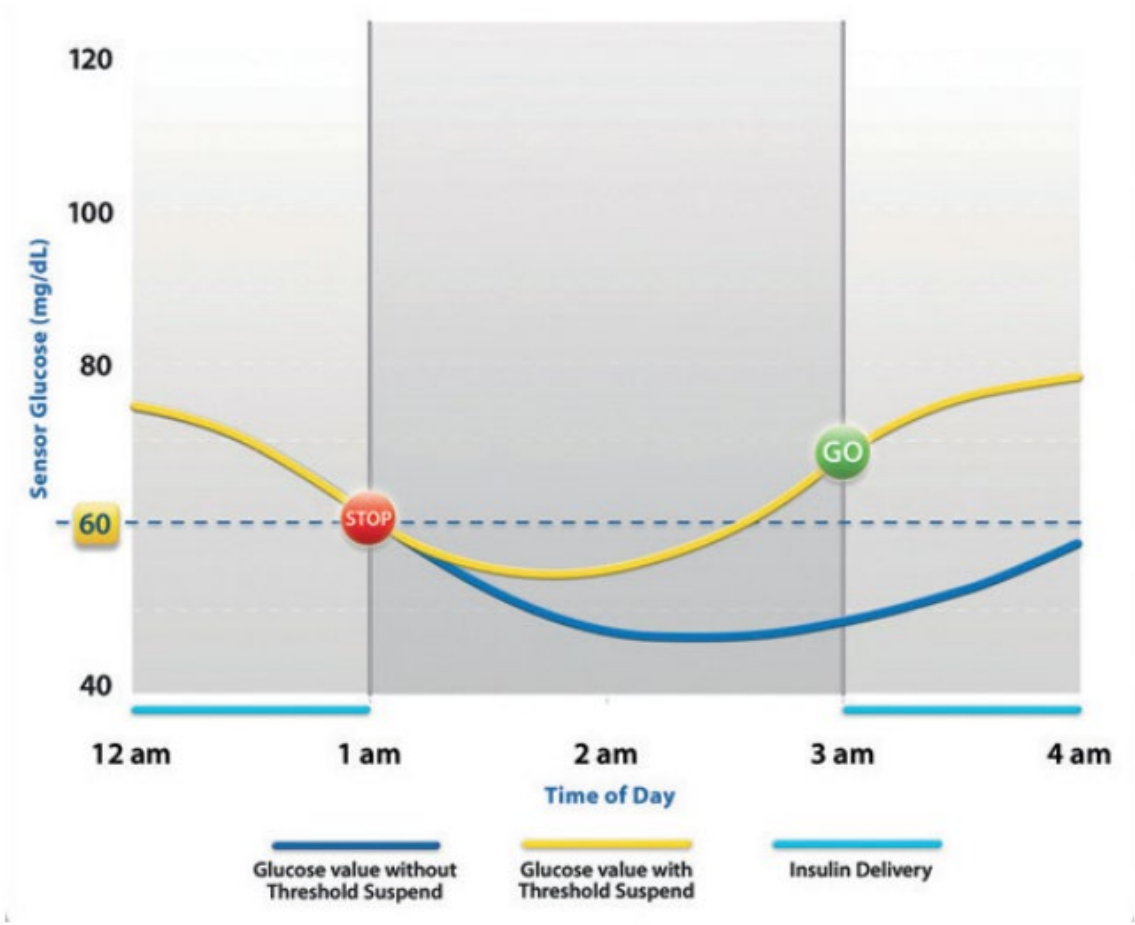
INSULIN DELIVERY SYSTEMS REVOLUTION



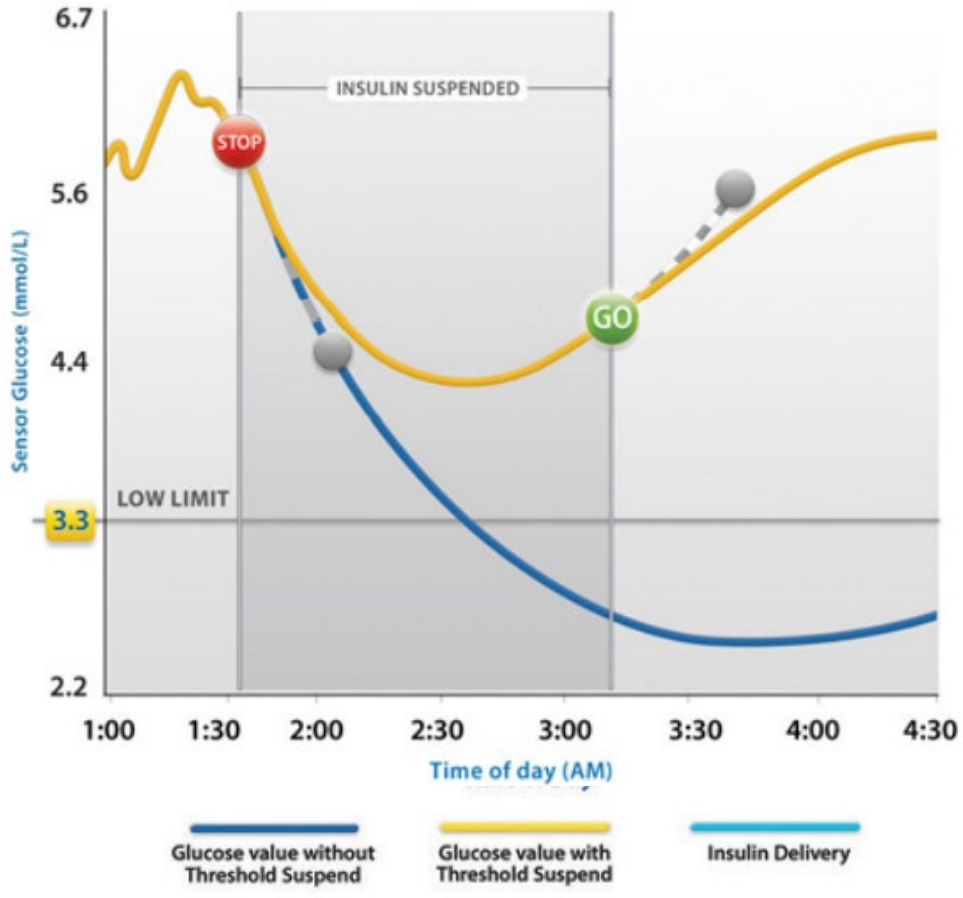
Moon SJ, et al. Diabetes Metab J 2021;45:813-39.

SENSOR AUGMENTED PUMP

LGS (Low Glucose Suspend)



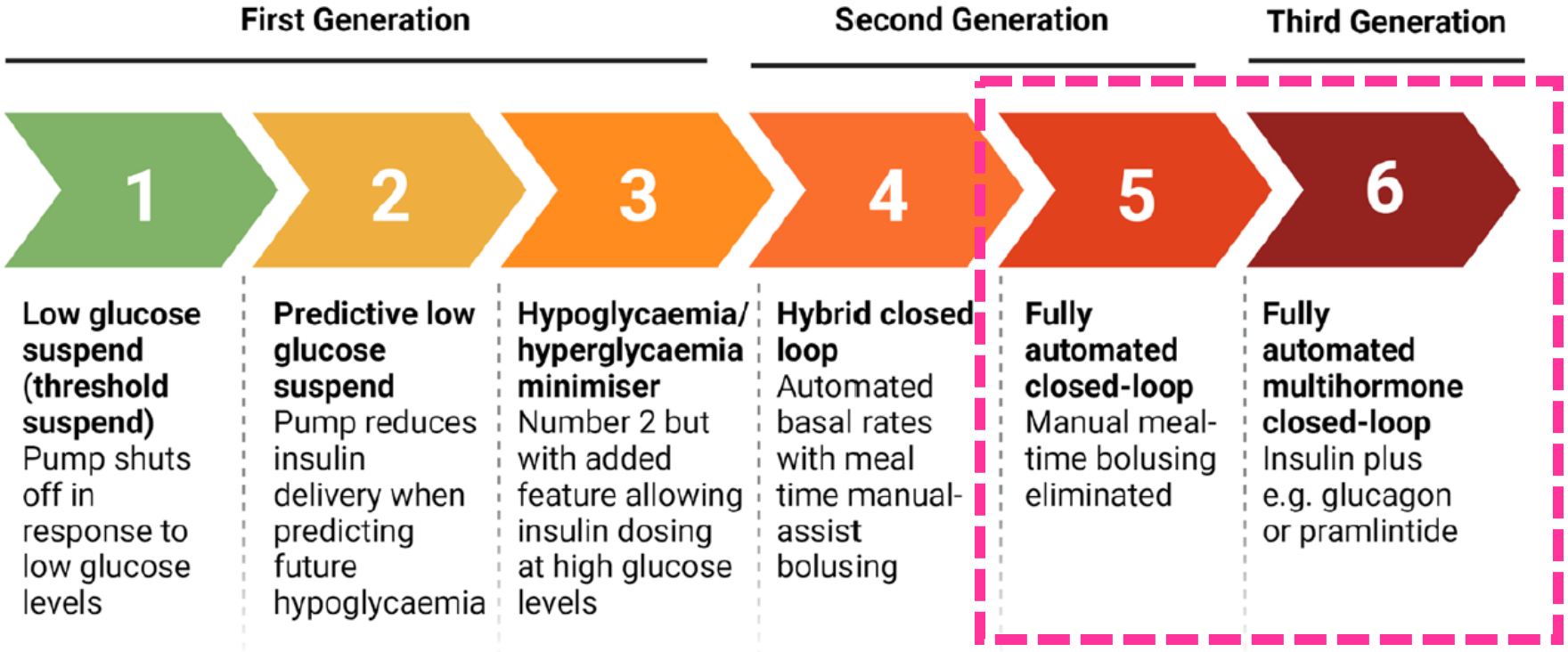
PLGS (Predictive Low Glucose Suspend)



Papa G et al. JAMD 2021 | VOL. 24 | N° 2

AID SYSTEMS:
a changing landscape in the management of T1DM

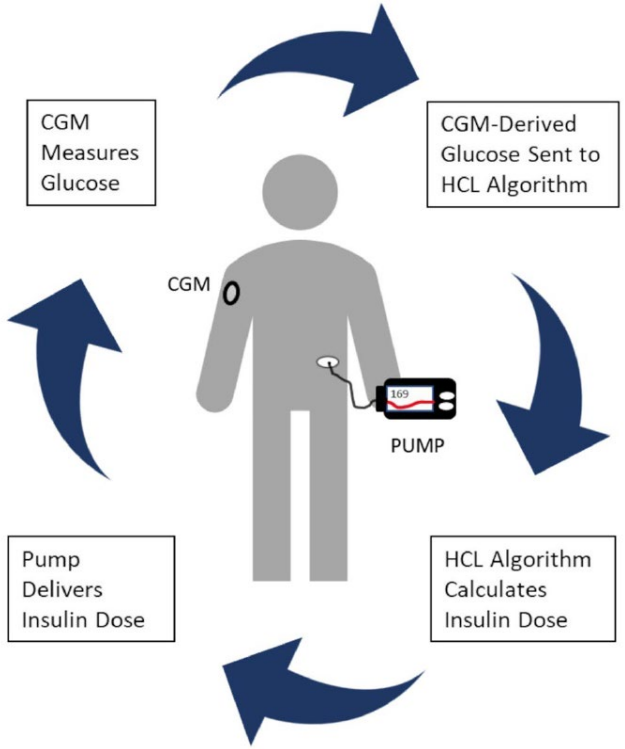
Automated Insulin Delivery Systems, also known as **closed-loop or artificial pancreas systems**, are transforming the management of T1DM. These systems consist of an **algorithm which responds to real-time glucose sensor levels by automatically modulating insulin delivery through an insulin pump.**



Lakshman R. Endocr Connect. 2023 Jul 31;12(8):e230132.

AVALABLE AID SYSTEMS:
CHARACTERISTICS and DIFFERENCES

- **Algorithm Type and Location:**
  - **PID** (Proportional, Integral, Derivative) with insulin feedback or additional model-based auto-correction
  - **MPC** (Model Predictive Control): pump-integrated, app-based, with dedicated handset
- **Possible Mobile Control** (partial or fully)
- **Licenced indications:**
  - **minimum ≥1 year and ≥10kg**
  - **pregnancy** included or excluded
- **Licenced insulins:**
  - for all available systems: **rapid insulin**
  - for one available system: **ultra-rapid insulin**
- **Personalized target**, minimum 80 mg/dl
- **Pre-set basal insulin rates influence AID:** Yes/No
- **Other modes**: "**activity mode**", "**boost mode**", "**sleep activity**", "**exercise activity**", "**ease-off mode**", "**zen mode**"
- **Bolus correction delivery**: automated correction boluses, automated corrections via intensive basal rate adjustments, automated basal rate adjustment plus automated correction boluses, optional user-initiated correction boluses
- **Active insulin time**: fixed, adjustable, automatically adjusted based on adaptive learning ("learns the patient").



Seget S et al. Pediatr Endocrinol Diabetes Metab. 2023;29(1):30-36. Lakshman R et al. Endocr Connect. 2023 Jul 31;12(8):e230132.

AID SYSTEMS: common characteristics

- ✓ An Algorithm to provide automatic insulin delivery based on rtCGM data
- ✓ Provides continuous insight into blood glucose
- ✓ Improves TIR and reduces risk of hypoglycaemia
- ✓ Alarms to inform of risks

If high technology systems are satisfactory tools for improving glycaemic control in the real word, they still create a challenge for the patient: they can add stress and burden.

Hypoglycaemia-specific: fear and confidence in managing hypoglycaemia

Diabetes-specific: QoL, well-being and distress, satisfaction with treatment

Generic: health or functional status, emotional well-being, depressive symptoms, subjective sleep quality

PROMs = Patient Related Outcomes Measures

assessing several psychological constructs

Seget S et al. Pediatr Endocrinol Diabetes Metab. 2023;29(1):30-36. Lakshman R et al. Endocr Connect. 2023 Jul 31;12(8):e230132.

PERSON REPORTED OUTCOME MEASURES (PROMs) FINDING BY TECHOLOGY COMPARISON (1)

Technology	Study	Study duration & design (N)	PROMs	Results
CSII vs MDI	**HypoCOMPaSS** *(2018, 2019)*	6-month multi-centre RCT + 18 month observation (N=96 at 6-m; N=76 at 24-m)	DTSQ, HFS-II, ITSQ, Gold, Clarke, HypoA-Q	**At 6-m: in CSII group DTSQ and ITSQ where higher than in the MDI group** *(both $p < 0.001$)*. No between-group differences for HFS-II, IAH, DTSQ items 2/3 **At 24-m** (continuing preferred technology): improvements maintained; no significant differences between groups for any of the PROMs
	REPOSE *(2017)*	24-month cluster RCT with data analysed at 6, 12 and 24-m (N tot=317; N=245 at 6-m; N=237 at 12-m and 24-m)	SF-12, DSQOL, WHOQOL-BREF, HFS, HADS, EQ-5D, DTSQ	**At 6-m**: no statistically significant difference between groups. **At 12-m and 24-m: CSII group reported greater DTSQ** *(both periods $p < 0.001$)* and **greater improvements in DSQOLS** *(respectively $p = 0.010$ and $p = 0.006$)* No between-group differences at any timepoints in SF-12, EQ-5D, WHOQOL-BREF, HADS
SAP+PLGS vs CSII/SMBG	**SMILE** *(2019)*	6-month open-label, multi-centre and multi-country RCT (N=153)	DTSQ (s+c), HFS, Gold, Clarke	At 6-m: **SAP group compared to CSII/SMBG group showed increased DTSQ** *($p < 0.0001$)*, **reduced HFS** *($p = 0.0010$)*. No between-group differences in IAH (Gold and Clarke)

***CES-D**: Centre for Epidemiological Studies Depression Scale; **DDS**: Diabetes Distress Scale; **DIDS**: Diabetes Impact and Devices Satisfaction; **DIDP**: Dawn2 Impact of Diabetes Profile; **DQOL**: Diabetes Quality Of Life; **DSQOL**: Diabetes-Specific Quality of Life; **DTSQ (s+c)**: Diabetes Treatment Satisfaction Questionnaire (status and change versions); **EQ-5D**: EuroQoL five dimensions; **HFS**: Hypoglycaemia Fear Survey; **HypoA-Q**: Hypoglycaemia Awareness Questionnaire; **IDDS**: Insulin Device Satisfaction Survey; **ITSQ**: Insulin Treatment Satisfaction Questionnaire; **PAID**: Problem Areas in Diabetes; **PRMQ**: Prospective and Retrospective Memory Questionnaire; **PSQI**: Perceived Sleep Quality Index; **SF-12**: 12-item short-form health survey (MCS: Mental health Component Summary; PCS: Physical health Component Summary); **W-BQ28**: 28-item Well-Being Questionnaire; **WHO-5**: Well-Being Index Scale; **WHOQOL-BREF**: World Health Organization Quality Of Life-BREF.*

Speight J et al. Diabet Med 2023;40(1):e14944.

PERSON REPORTED OUTCOME MEASURES (PROMs) FINDING BY TECHOLOGY COMPARISON (2)

Technology	Study	Study duration & design (N)	PROMs	Results
HCL vs Current Therapy (CSII or MDI)	**Australian HCL trial** *(2020)*	6-month RCT (N=120)	DTSQ, PAID, DIDP, PSQI, PRMQ, W-BQ28 subscale	**At 6-m**: **HCL group** compared to CSII/MDI group had **greater W-BQ28 subscale** *(p = 0.0048)* **and DIDP** *(p = 0.023).* No between-group differences for DTSQ, PAID, PSQI or PRMQ
HCL vs SAP	**Diabeloop** *(2019)*	12-week multi centre, open-label crossover RCT with 8-week washout (N=63)	DTSQ	**At 12-ws**: No between-group difference in DTSQ
	Kropff et al *(2017)*	2-month, multi-centre, crossover RCT evening/night HCL with	HFS-II, DTSQ(s+c)	**At 2-m:** no between-group differences for DTSQ Total or DTSQ (s+c), or HFS-II Total and subscales
	Bisio et al *(2021)*	4-week washout (N=32) Single-arm SAP and HCL (N=15)	HFS-II, DDS, CES-D, PSQI	**At 4-ws**: **HCL was associated with reduced DDS** *(p = 0.046)*. No between-group differences for HFS-II, CES-D, PSQI

***CES-D**: Centre for Epidemiological Studies Depression Scale; **DDS**: Diabetes Distress Scale; **DIDS**: Diabetes Impact and Devices Satisfaction; **DIDP**: Dawn2 Impact of Diabetes Profile; **DQOL**: Diabetes Quality Of Life; **DSQOL**: Diabetes-Specific Quality of Life; **DTSQ (s+c)**: Diabetes Treatment Satisfaction Questionnaire (status and change versions); **EQ-5D**: EuroQoL five dimensions; **HFS**: Hypoglycaemia Fear Survey; **HypoA-Q**: Hypoglycaemia Awareness Questionnaire; **IDDS**: Insulin Device Satisfaction Survey; **ITSQ**: Insulin Treatment Satisfaction Questionnaire; **PAID**: Problem Areas in Diabetes; **PRMQ**: Prospective and Retrospective Memory Questionnaire; **PSQI**: Perceived Sleep Quality Index; **SF-12**: 12-item short-form health survey (MCS: Mental health Component Summary; PCS: Physical health Component Summary); **W-BQ28**: 28-item Well-Being Questionnaire; **WHO-5**: Well-Being Index Scale; **WHOQOL-BREF**: World Health Organization Quality Of Life-BREF.*

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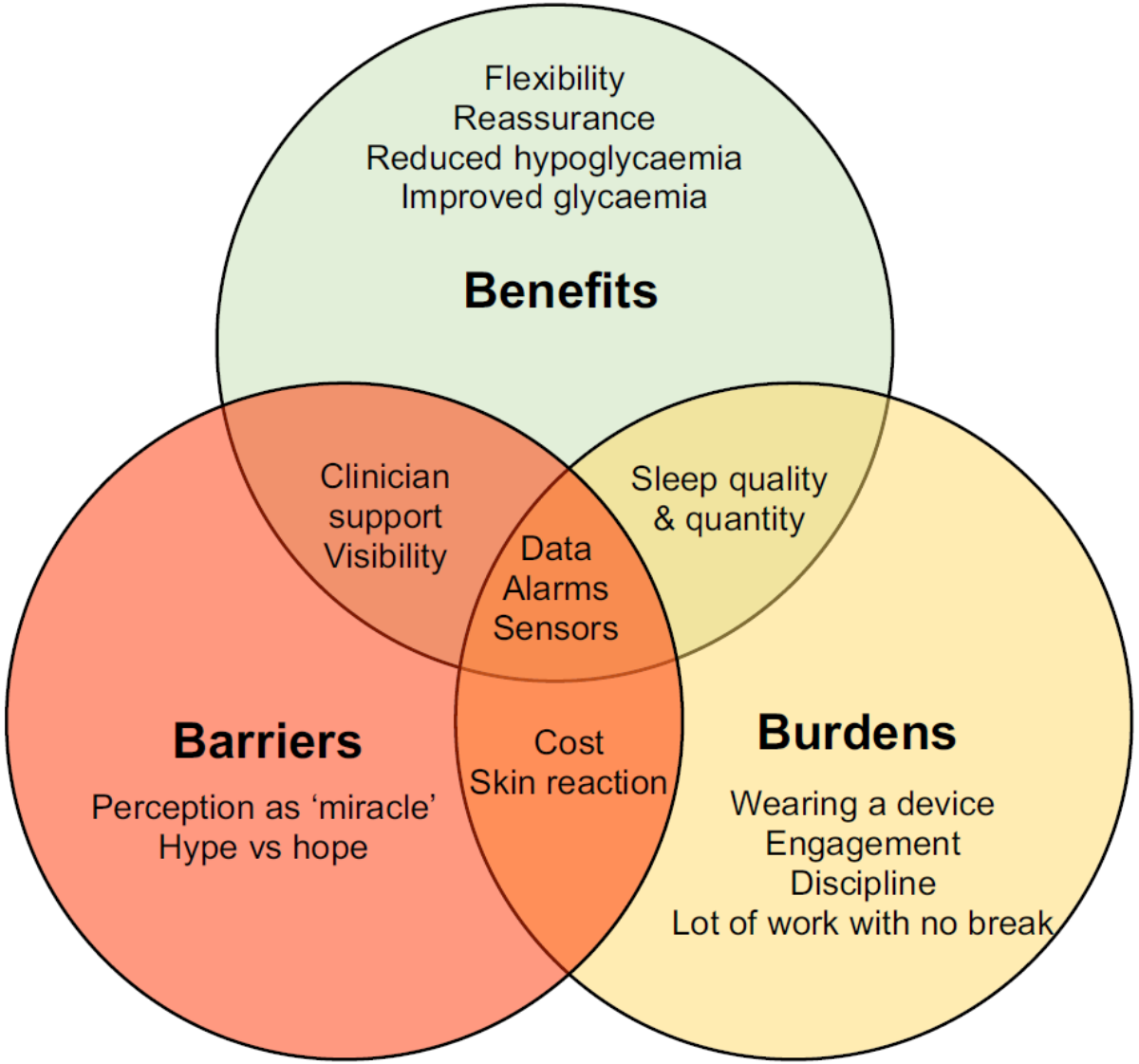


Potential benefits, burdens and barriers associated with using diabetes technologies from the perspective of the person with type 1 diabetes

Speight J et al. Diabet Med 2023;40(1):e14944.

INSULIN PUMP DISCONTINUATION

Monitor and discuss the **working relationship** **Peer-to-peer contact** may aid finding practical solutions for some issues.

Manage **expectations** (heavily influenced by social media) and the **added burden.**

Set up the treatment plan to meet both physician and patient goals and preferences, to balance the benefits of insulin pump use with its daily burden. **Update periodically** this plan.

STRATEGIES for MINIMIZING the RISK of INSULIN PUMP DISCONTINUATION

The **team approach** should be **multidisciplinary,** because the insulin pump use need **not only medical but also practical and mental support**.

Give the opportunity to experience a insulin pump system during a **short term trial** to **facilitate the decision** to switch to such a system and **improve trust** in technology.

Once insulin pump (system) treatment has started, especially **during the initial months, monitor the patient closely and provide ongoing support and education**. Keep skills and knowledge up-to-date.

Dekker P et al. Diabetes Technol Ther 2023;25(8):559-70.

PATCH PUMPS: WHAT ADVANTAGES FOR PEOPLE WITH DM

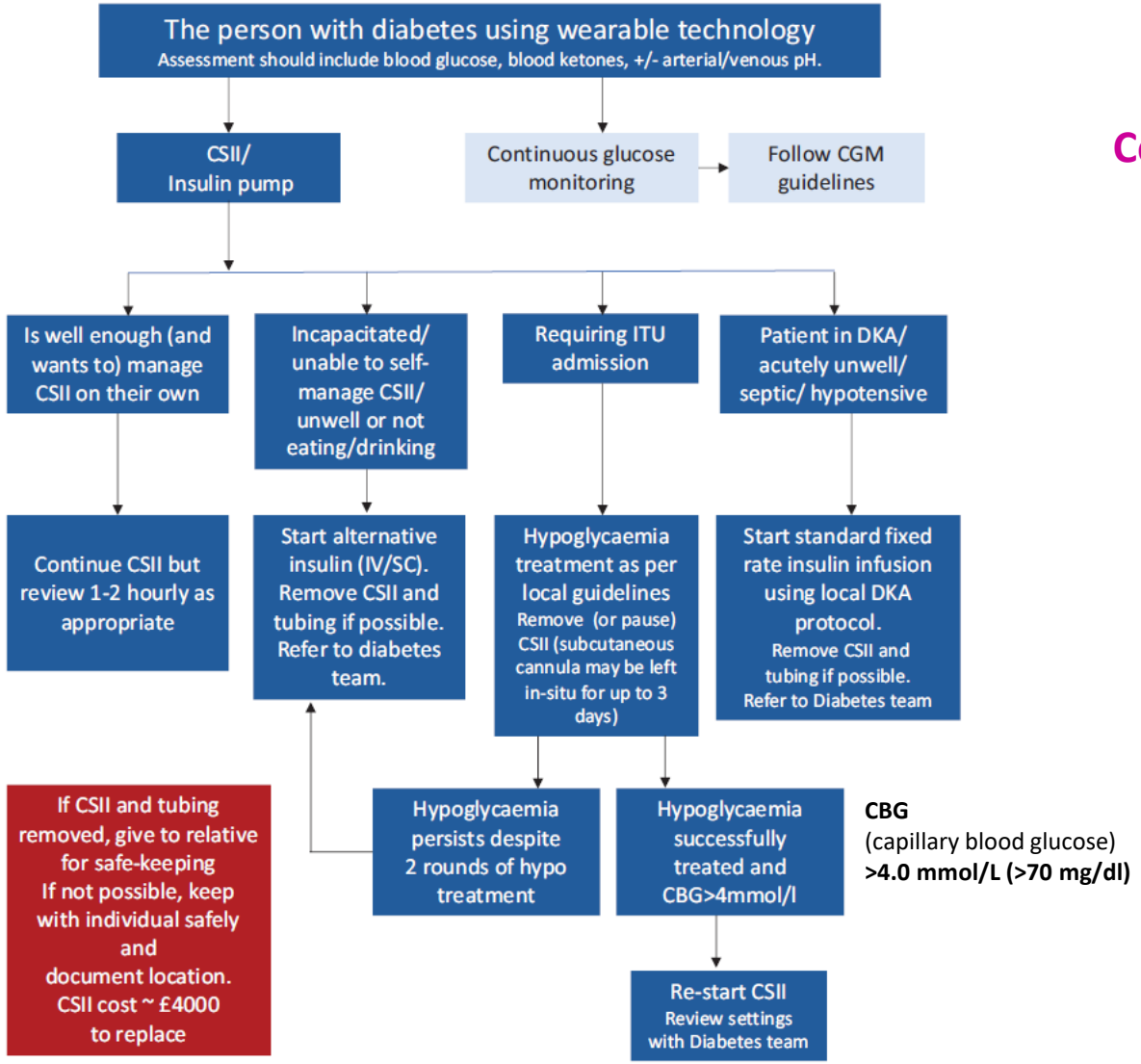
Review: 12 Studies included and analyzed.
Aim: To assess potential **patient-relevant advantages and disadvantages of patch pumps** and patient-reported outcomes (**PROs**).
Results: This analysis provide evidence that **patch pumps improve quality of life**, **reduce diabetes-related distress**, **increase patient satisfaction**, and **are preferred** by patients compared to conventional insulin pumps and MDI.

- **Tubeless**
- **Reduction of problems with the IIS (occlusions, tubing kinks, risk of getting tangled with the tube)**
- **Many parts of the body usable for the attachment**
- **Smaller and lighter than conventional pumps**
- **Freedom of movement and discreet carrying options**
- **Simple handling, simple education and training**
- **Lower costs for certain PPs compared to conventional pumps**

- **Accuracy of insulin delivery is often lower than that of conventional pumps, in particular at low basal rates**
- **Infusion site is not visible and cannot be regularly inspected (an infection might not be recognized immediately)**
- **Sometimes poor ecological balance**
- **Higher costs compared to MDI**

Kulzer B et al. Diabetes Res Clin Pract 2022;187:109858.

Insulin Pump Therapy Within Hospital



Contraindications to Insulin Pump Therapy in Hospital:

- Impaired level of consciousness or confusion
- Critical illness requiring intensive care/high-dependency care
- DKA or HHS
- Psychiatric illness or suicidal ideation
- Person unable to use hands and/or physically manipulate pump due to medical condition
- Person unwilling to participate in diabetes self-management, or share pump management decisions with hospital clinical staff
- Lack of pump supplies or mechanical pump malfunction
- Lack of trained health care providers or available diabetes specialists to supervise pump therapy
- Medical team decision for health and safety of the person.

Diabetes Technology Network guidelines. The Joint British Diabetes Societies for Inpatient Care; Avari P et al. J Diabetes Sci Technol 2023;17(3):625-34.

Key Studies Assessing Hybrid Closed-Loop Use in Hospital

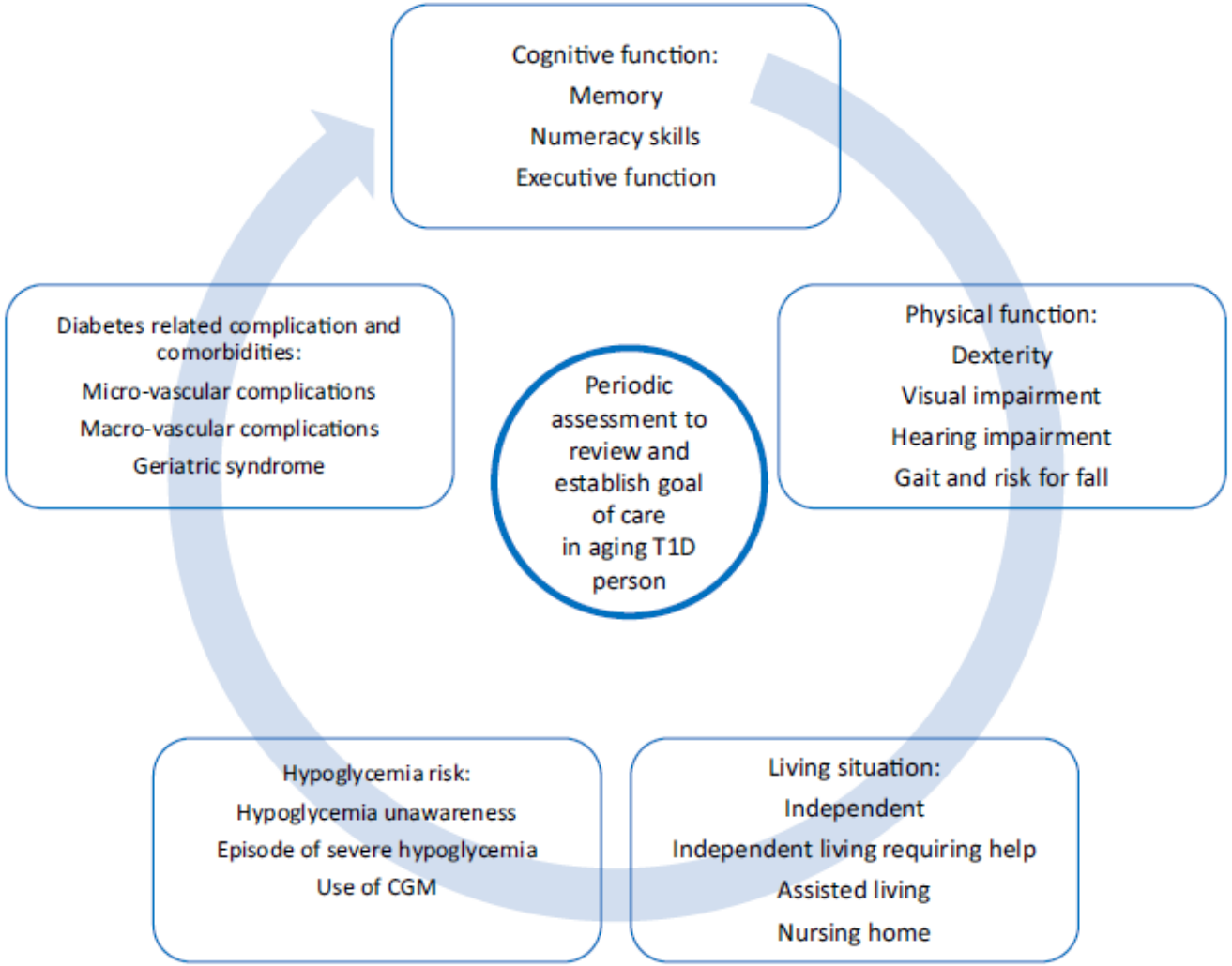
Study	Population	Design	Outcome
Bally et al; *N Engl J Med 2018*	**N=136, T2D** **General wards**	RCT	**HCL vs control: improved TIR** (100-180 mg/dL) 65.8±16.8% vs 41.5±16.9% *(P < 0.001)* No difference in TBR (<70 mg/dL) **No episodes of severe hypoglycemia/DKA**
Stewart et al; *Diabetes Technol Ther 2018*	**N=32, T1D** **Labor, delivery** (vaginal, emergency and elective C-section) **and post-partum**	RCT (data from 2 RCTs analyzed)	**HCL performed well during labor and delivery**, TIR (63-140 mg/dL) 82.0% (N=27/32, 49.3-93.0), **and post-partum**, TIR (70-180 mg/dL) 83.3% (75.2-94.6)
Bally et al; *Kidney Int 2019*	**N=17, T2D** **Hemodialysis**	RCT, post hoc analysis	**HCL vs control: greater TIR** (100-180 mg/dL) 69.0±12.0% vs 31.5±13.5 respectively *(P <0.001)*; **lower TAR** (>180 mg/dL) difference 37.2% *(P = 0.001)*; no difference in TBR
Thabit et al; *Lancet Diabetes Endocrinol 2017*	**N=40, T2D** **General wards**	RCT	**HCL vs control: greater TIR** (100-180 mg/dL) 59.8±18.7% vs 38.1±16.7% *(P = 0.0004)* No severe hypoglycemia or hyperglycemia with ketonemia
Boughton et al; *Lancet Diabetes Endocrinol 2019*	**N=136, T2D** **General wards, on EN o PN**	RCT	**HCL vs control: greater TIR** (100-180 mg/dL) 68.4±15.5% vs 36.4±26.6% One cardiac arrest in the control group; one acute respiratory failure in the HCL group (both deemed unrelated to study) No severe hypoglycemia or hyperglycemia with ketonemia

The Joint British Diabetes Societies for Inpatient Care; Avari P et al. J Diabetes Sci Technol 2023;17(3):625-34.

Type 1 DIABETES and AGING

Older adults with T1DM are heterogenous due to dynamic process of aging

- ✓ High incidence of hypoglycemia unawareness
- ✓ High risk of severe hypoglycemia
- ✓ Need for periodic assesment to adjust glycemic targets and mitigate hypoglycemia



Toschi E. Endocrinol Metab Clin North Am 2023;52(2):389-403.

OLDER ADULTS WITH T1DM: MDI vs INSULIN PUMPS

HEALTH STATUS	Healthy	Complex/Intermediate	Very Complex/Poor
INSULIN VIA PEN (MDI)			
Benefit **Consideration**	No data Low cost, dexterity, visual impairment No need of downloadable data	No data **Consider use of fixed dose for meals and correction dose** Consider support from **caregiver**	No data Need support from caregiver
SMART PEN			
Benefit **Consideration**	No data Built-in bolus calculator, **information on time and dose of insulin administered,** downloadable records Dexterity, visual impairment	No data	No data
CSII			
Benefit **Consideration**	**Reduce hypoglycemia, improve A1c** Availability of **bolus calculators**, **smaller accurate doses**, keep track of **active insulin** Downloadable reports High cost	No data Consider support from **caregiver** **Simplify regimen** with fixed dose pre-meals and correction dose **Assess ability** to use getting and changing various parts, dexterity, visual impairment High cost	No data Consider support from caregiver and/or switch to MDI High cost
HYBRID CLOSED-LOOP			
Benefit **Consideration**	**Improve TIR** Potential negative effect on sleep	No data Challenges to start a new technology	Potential reducing burden while mitigating hypo- and hyperglycemia Need to be operated by caregiver

Toschi E. Endocrinol Metab Clin North Am 2023;52(2):389-403.

INSULIN PUMP THERAPY IN T2DM PATIENTS

Potential Benefits

Significant ↓HbA1c
(especially if not controlled on MDI)
↓ glycaemic variability
↑ TIR
↓ TDD
↑ patient satisfaction
No increase in hypoglycaemia rates
Weight-neutral or slight ↓ weight

Barriers

Complexity of the CSII systems
Extensive clinic resources required to train/educate
High costs
Reservoir/cartridge size insulin capacity
Few RCTs

Modified from *Ekanayake P & Edelman S. Diabetes Obes Metab 2023;25 Suppl 2:3-20.*

Considerations:

Thanks

- Diabetes-related technology constantly change the treatment modalities in diabetes (especially in type 1 diabetes).
- Conventional insulin pumps, patch pumps and hybrid closed-loop systems, are promising tools to improve glycemic control and mitigate hypoglycemia.
- Their use in special contexts (e.g. hospitalized patients, older adults with type 1 diabetes, and pregnancy with type 1 diabetes) requires further studies and evaluations.
- Patients recognize in insulin pump use not only benefits, but also burdens and barriers. Life-long Day-to-Day management is burdensome and can result in burn-out. PROMs are important measures to assess psychological constructs and aid diabetes management.
- A tailored treatment plan, periodically updated, is useful to minimize the risk of technology use discontinuation.