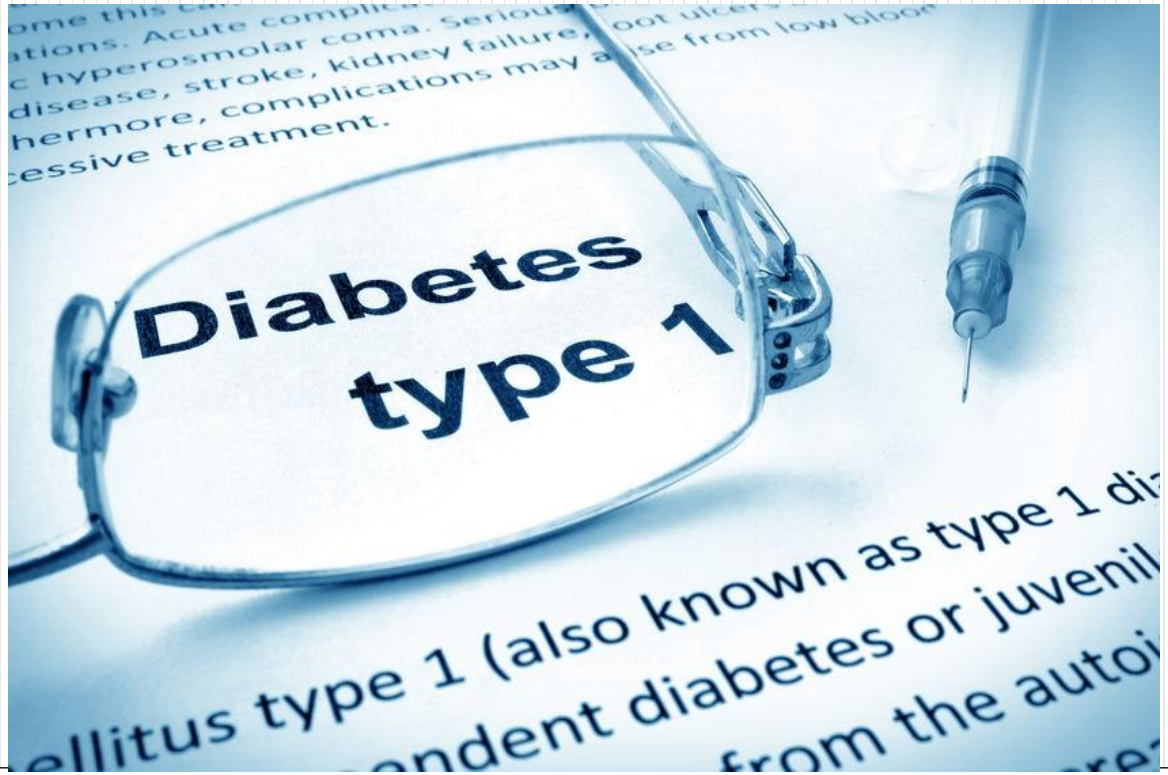
ROLE OF TECHNOLOGY IN TYPE I DIABETES



Incidence and Prevalence of Type 1 Diabetes

- T1D is the major type of diabetes in youth
  - Accounts for ≥85% of all diabetes cases in patients <20 years of age
- Incidence is increasing by 2% to 5% worldwide
- Nearly 75,000 new children are diagnosed every year

Garber AJ et al. Endocr Pract. 2016 Jan;22(1):84-113.

Kumar KH et al. Med J DY Patil Univ 2016;9:195-9

Burden

- T1DM is on a constant rise in Finland, Sweden, Colarado, India, and Germany.
- Increase in incidence - 10/100,000 children to around 60/100,000 children in Finland in the last 50 years.
- Of the existing 490,000 children living with this disorder,
  - 24% are in the European region
  - 23% in the South-East Asian region.

Das AK . Indian J Endocrinol Metab. 2015 Apr; 19(Suppl 1): S31–S33.

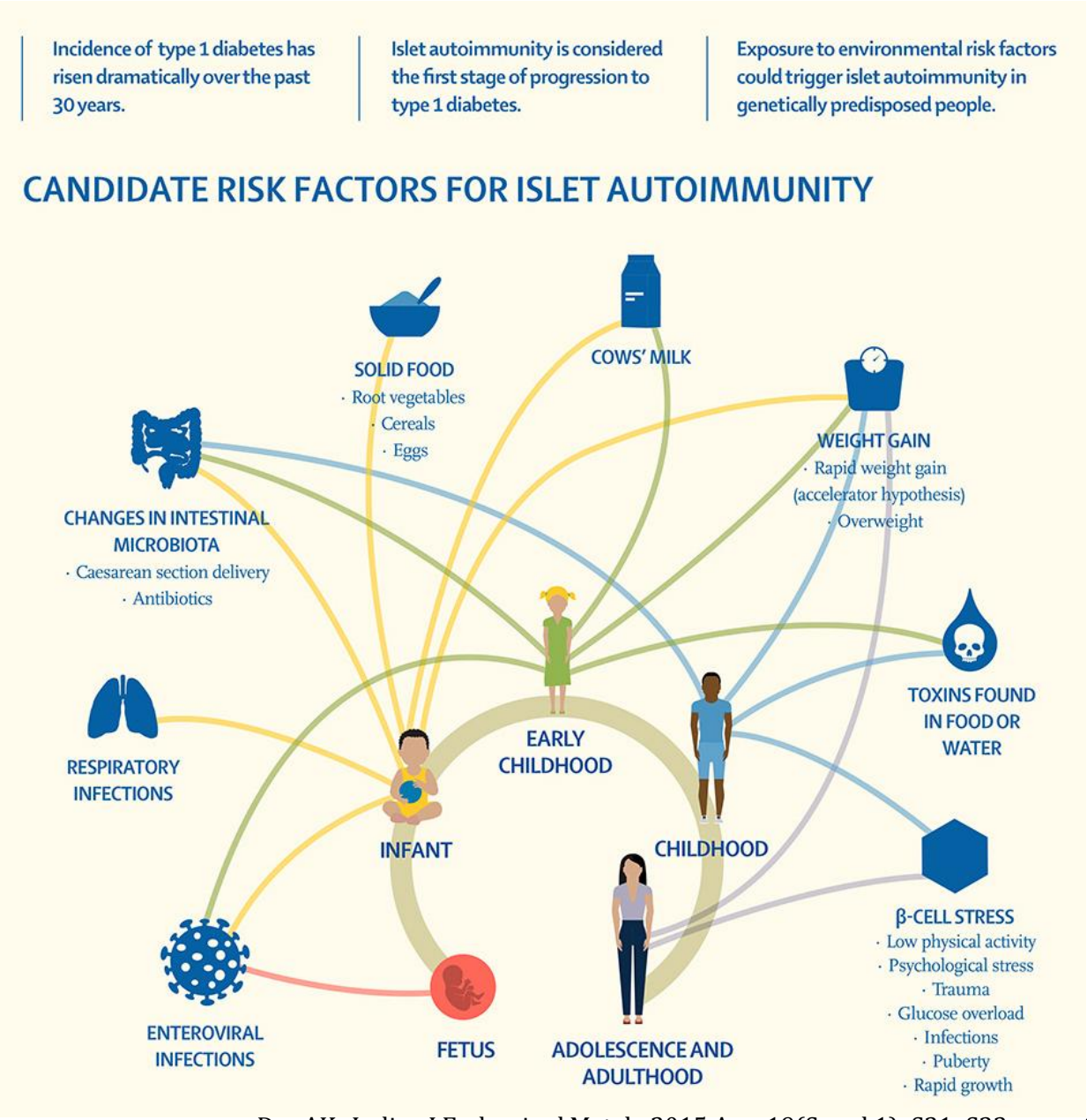
T1DM Indian burden

- India accounts for most of the children with T1DM in South-East Asia.
- 3 new cases/100,000 children of 0–14 years.
- The prevalence of diabetes in India is variable, and three sets of data show
  - 17.93 cases/100,000 children in Karnataka,
  - 3.2 cases/100,000 children in Chennai, and
  - 10.2 cases/100,000 children in Karnal (Haryana).

Das AK . Indian J Endocrinol Metab. 2015 Apr; 19(Suppl 1): S31–S33.

Contributing Factors for T1D Risk

- Infections
- Early childhood diet (dietary proteins)
- Vitamin D exposure
- Environmental pollutants
- Obesity



Das AK . Indian J Endocrinol Metab. 2015 Apr; 19(Suppl 1): S31–S33.

Immunological Changes and Incidence of Type 1 Diabetes

- Rising incidence of T1D is associated with altered immunophenotype at diagnosis
- Prevalence of IA-2A and ZnT8A has increased significantly
- IAA and GADA prevalence and levels have not changed
- Suggests T1D is now characterized by a more intense humoral autoimmune response

IAA, autoantibodies to insulin; GADA, GAD; IA-2A, islet antigen-2; T1D, type 1 diabetes; ZnT8A, zinc transporter 8.

Long AE, et al. *Diabetes*. 2012;61:683-686.

Mortality in Childhood-Onset T1D

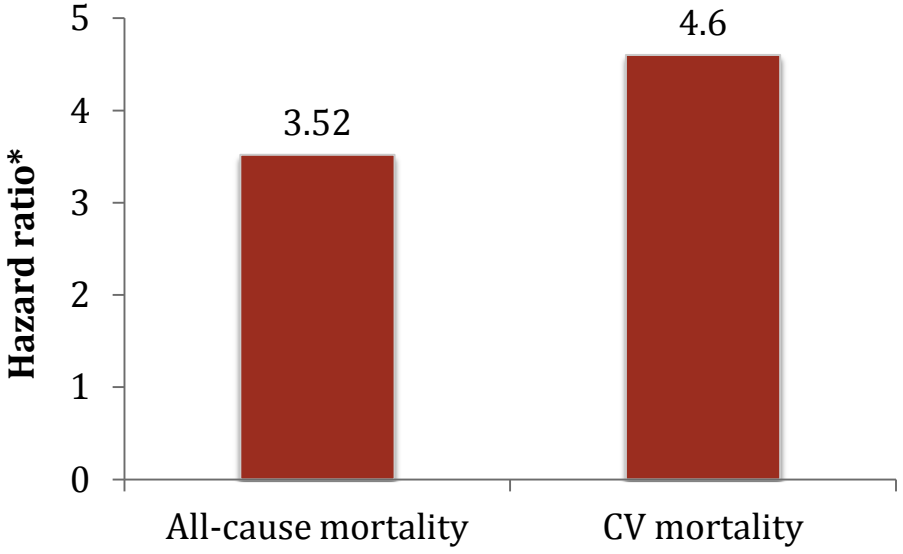
- Mortality rate: 2.2/1000 person-years
- Most common cause of death <30 years of age
  - Acute metabolic complications of diabetes (eg, diabetic ketoacidosis)
- Most common cause of death >30 years of age
  - Cardiovascular disease

Skrivarhaug T, et al. Diabetologia. 2006;49:298-305. Patterson CC, et al. Diabetologia. 2007;50:2439-2442. Libby P, et al. Circulation. 2005;111:3489-3493.

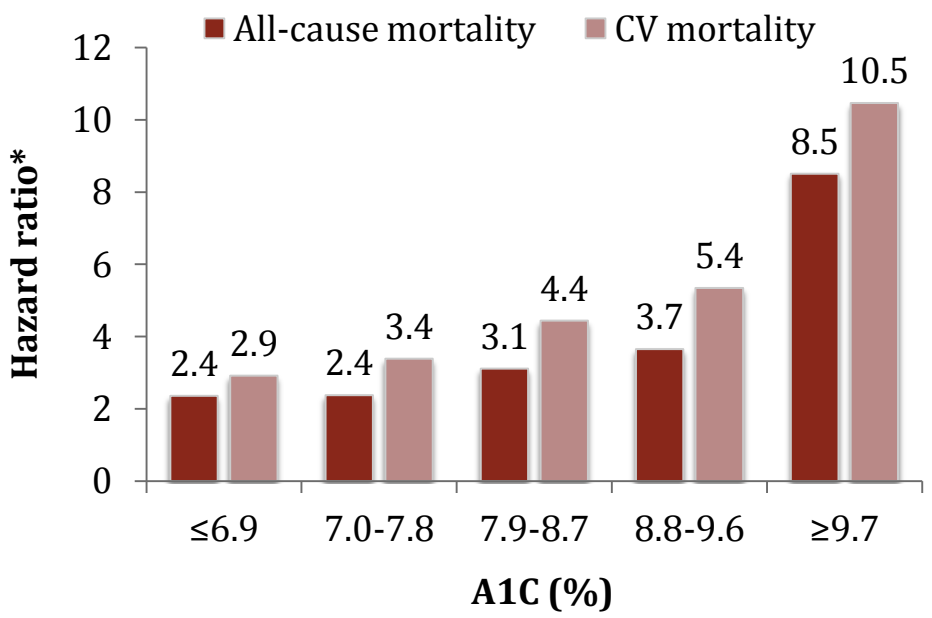
Mortality in Patients With T1D

Swedish National Diabetes Register (n=33,915 with T1D; n=169,249 without diabetes)

Mortality Risk vs Patients Without Diabetes



Mortality Risk by A1C Level



*Adjusted for age, diabetes duration, sex, birthplace, education, CVD status, and cancer status.

CVD, cardiovascular disease; T1D, type 1 diabetes.

Lind M, et al. *N Engl J Med*. 2014;371:1972-1982.

Differential Diagnosis of Type 1 and Type 2 Diabetes

	Type 1 Diabetes	Type 2 Diabetes
Usual clinical course	Insulin-dependent	Initially non-insulin-dependent
Usual age of onset	<20 years (but ~50% over 20 years)	>40 years but increasingly earlier
Body weight	Often lean but ~50% overweight or obese	Usually obese
Onset	Often acute	Subtle, slow
Ketosis prone	Yes	No
Family history	≤15% with 1st-degree relative	Common
Frequency of HLA-DR3, DR4, DQB1*0201, *0302	Increased	Not increased
Islet autoantibodies (GADA, ICA, IA-2A, IAA, ZNT8A)	Present	Absent

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8.

*Needs to be refined for nonwhite population groups.

Rewers M. *Diabetes Metab J*. 2012;36:90-97.

Classifying Diabetes

<table>
<tr><td rowspan="2">High-risk HLA*
DR3/4,
DQ1B1*0302,
DR4/4, DR4/8,
DR3/3
(10% of T1D
population)</td><td rowspan="2">IAA+
GADA+
IA-2A+
or
ZnT8A+</td><td colspan="2">Autoantibody negative at onset</td></tr>
<tr><td colspan="2">C-peptide (ng/mL)</td></tr>
<tr><td>HLA+</td><td rowspan="2">T1aD = 80%</td><td><1.0</td><td>≥1.0</td></tr>
<tr><td>HLA-</td><td>T1bD
5%</td><td>T2D
10%</td></tr>
</table>

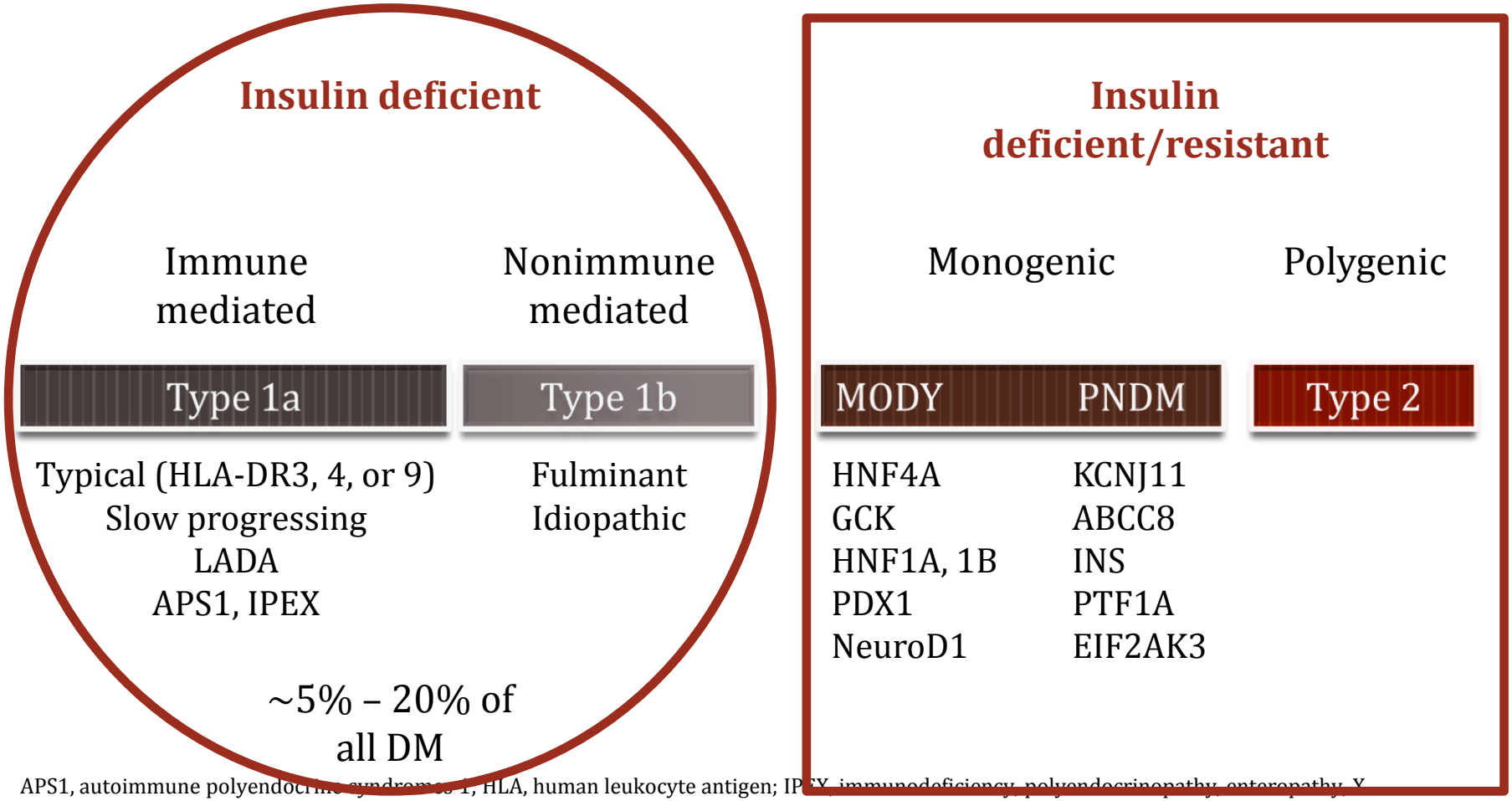
GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, the tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8; T1aD, type 1 (immune-mediated) diabetes; T1bD, type 1 (idiopathic) diabetes; T2D, type 2 diabetes.

*Needs to be refined for nonwhite population groups.

Sharma M, Clin Epidemiol. 2016 Oct 12;8:373-380.

Rewers M. *Diabetes Metab J.* 2012;36:90-97.

Etiologic Classification of Diabetes



APS1, autoimmune polyendocrine syndromes 1; HLA, human leukocyte antigen; IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome; LADA, latent autoimmune diabetes of adults; MODY, maturity-onset diabetes of the young; PNDM, permanent neonatal diabetes mellitus.

Sharma M, Clin Epidemiol. 2016 Oct 12;8:373-380.

Rewers M. *Diabetes Metab J.* 2012;36:90-97.

Genetic Defects of β-Cell Function

- Chromosome 12, HNF-1α (MODY3)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 20, HNF-4α (MODY1)
- Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
- Chromosome 17, HNF-1β (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Mitochondrial DNA

Sharma M, Clin Epidemiol. 2016 Oct 12;8:373-380.

Diabetes Care 2017 Jan; 40 (Supplement 1): S1-S142

Immune-Mediated Diabetes (T1a Diabetes)

β-Cell Destruction

- Variable rate
  - Rapid in infants and children (primarily)
  - Slow in adults (primarily)

Immune Markers

- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b

When fasting hyperglycemia is first detected, 85% – 90% of individuals have ≥1 autoantibody

Diabetes Care 2017 Jan; 40 (Supplement 1): S1-S142

Genetic Markers

- Strong HLA associations, with linkage to the DQA and DQB genes
- Influenced by the DRB genes
- HLA-DR/DQ alleles can be either predisposing or protective

HLA, human leukocyte antigen.

Diabetes Care 2017 Jan; 40 (Supplement 1): S1-S142

Management

of Type 1 Diabetes

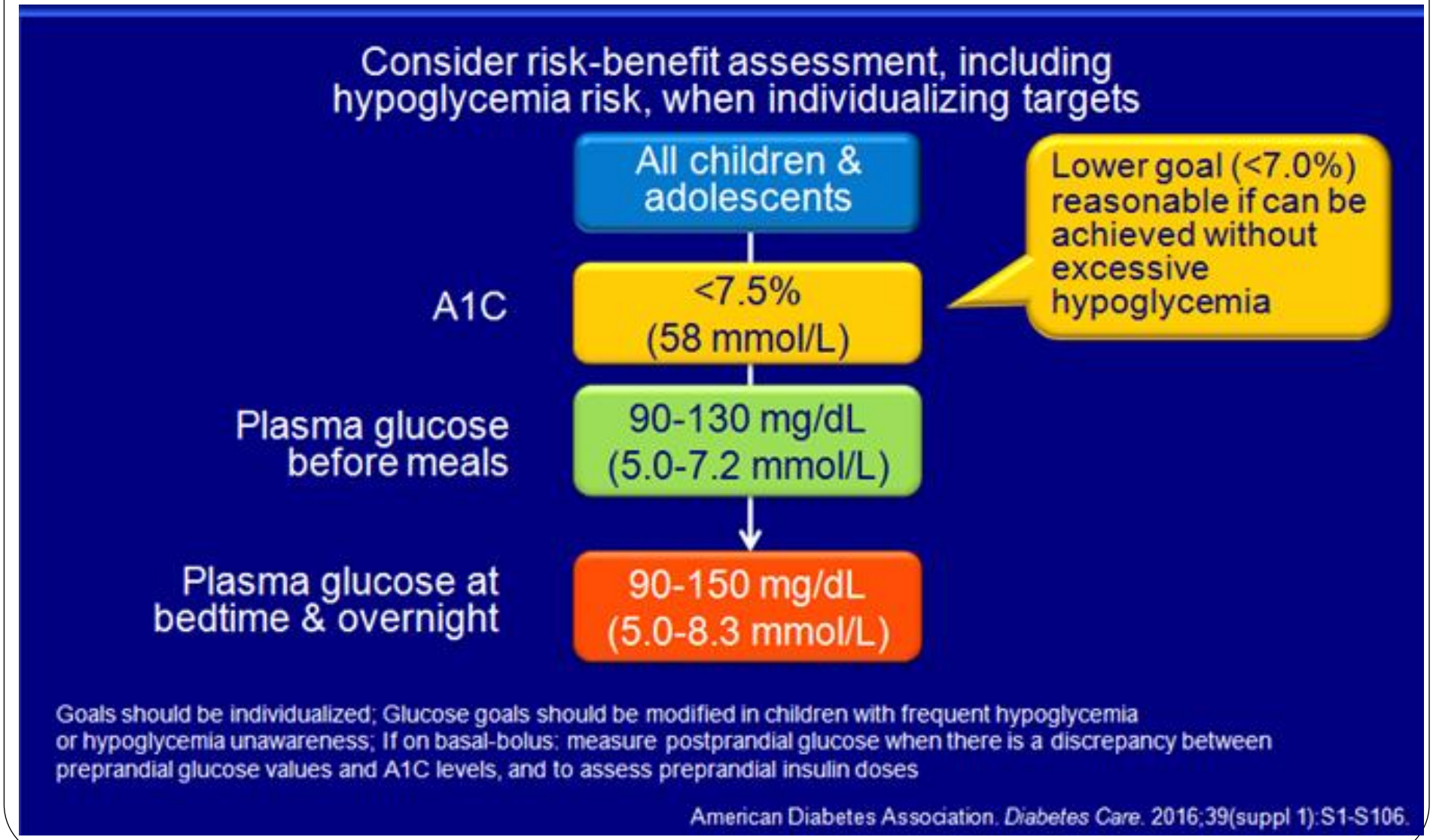
Goals of T1D Management

- Utilize intensive therapy aimed at near-normal BG and A1C levels
- Prevent diabetic ketoacidosis and severe hypoglycemia
- Achieve the highest quality of life compatible with the daily demands of diabetes management
- In children, achieve normal growth and physical development and psychological maturation
- Establish realistic goals adapted to each individual's circumstances

T1D, type 1 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Glycemic Targets in T1DM



Routine Care Recommendations for Patients With T1D

	Children/Adolescents (0-19 years)	Adults (≥20 years)
Height	Every 3 months	N/A
Weight	Every 3 months	
Nutritionist	Diagnosis, then annually	
Retinal examination	Begin 5 years after diagnosis Every 1-2 years thereafter	Begin 5 years after diagnosis or earlier with visual symptoms or if date of T1D onset is unknown Every 1-2 years thereafter
A1C	Every 3 months	
Lipid profile	Annually, once glycemia is stable	Annually or as needed based on treatment
Blood pressure	Every physical examination	
Creatinine clearance, eGFR	At diagnosis, then annually	
ACR	Begin 5 years after diagnosis, then annually	At diagnosis, then annually

ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87

Diabetes Care 2017 Jan; 40 (Supplement 1): S1-S142.

Pharmacological Therapy

Insulin treatment is the mainstay for individuals with type 1 diabetes

- Treat with multiple-dose insulin injections* or continuous subcutaneous insulin infusion (CSII)
- Match prandial insulin to carbohydrate intake, premeal glucose, and anticipated physical activity
- Use insulin analogs to reduce risk of hypoglycemia
- Consider using sensor-augmented low glucose suspend threshold pump in patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness

Non-insulin agents	Investigational agents†
Pramlinitide (amylin analog) • Delays gastric emptying • Blunts pancreatic secretion of glucagon • Enhances satiety • Induces weight loss • Lowers insulin dose • Use only in adults	Metformin + insulin • May reduce insulin requirements & improve metabolic control in obese/ overweight with poor glycemic control Incretins • GLP-1 receptor agonists • DPP-4 inhibitors • SGLT2 inhibitors

*3-4 injections/day of basal and prandial insulin)
†Not FDA approved for the treatment of type 1 diabetes in the United States

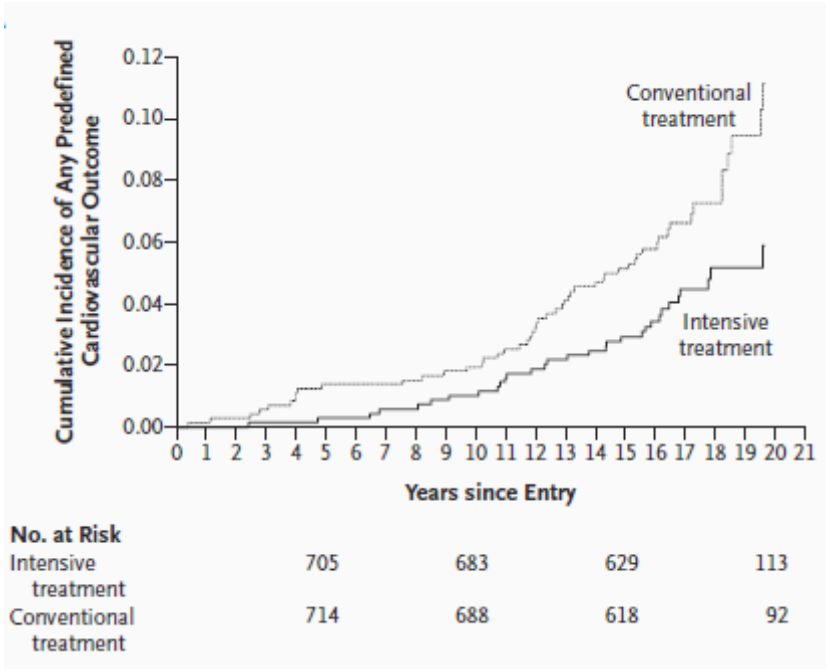
American Diabetes Association. *Diabetes Care*. 2016;39(suppl 1):S1-S106.

Predictors of Poor Glycemic Control

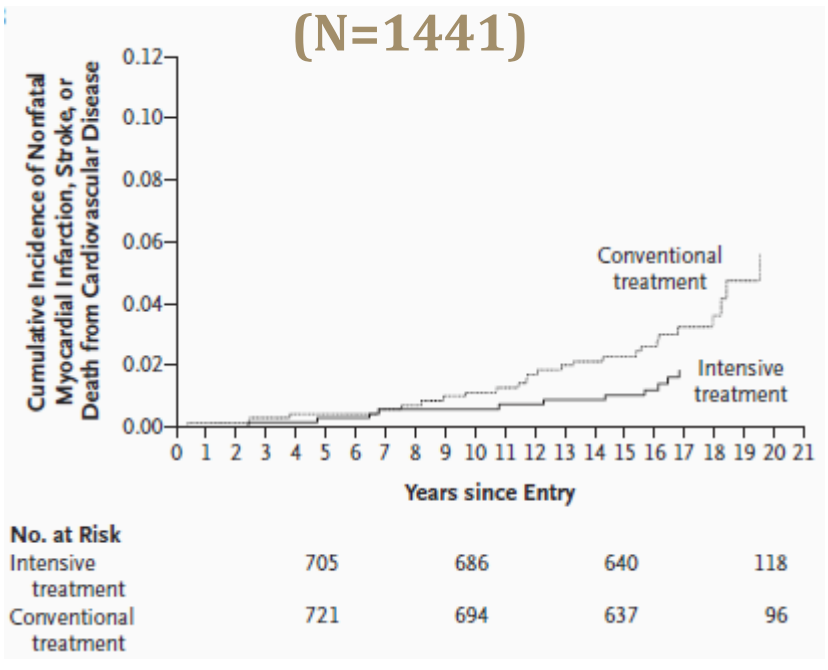
- Younger age
- Longer diabetes duration
- Weight <85th percentile
- Not living in a 2-parent household
- Type of diabetes care provider
- Nonwhite race/ethnicity
- Female gender
- Lower parental education
- Poor early glycemic control (2nd year after diagnosis predictive of poor glycemic control later)

Diabetes Care 2017 Jan; 40 (Supplement 1): S1-S142.

Long-Term Benefits of Early Intensive Glycemic Control



(N=1441)



Intensive glycemic control over a mean of 6.5 years reduced CVD complications by 57% after a mean of 17 years of follow-up

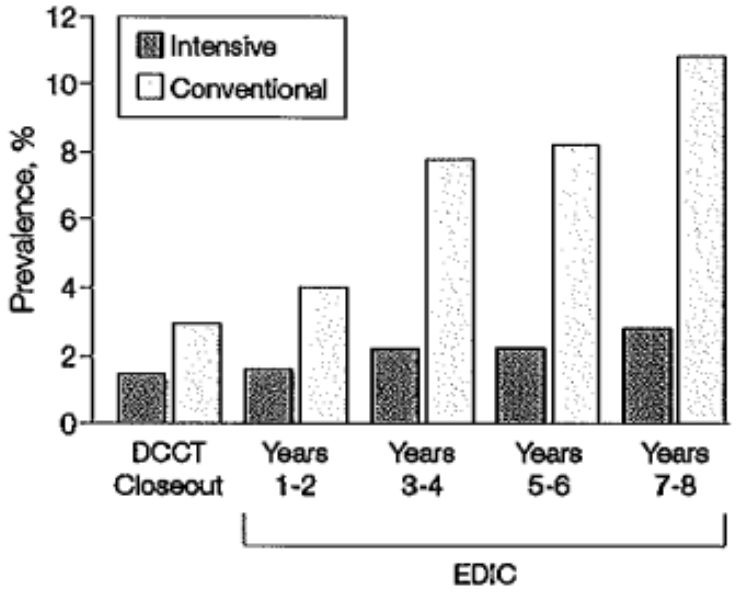
DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications .

Milligan S et al. J Diabetes Complications. 2016 Aug;30(6):1177-85

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653.

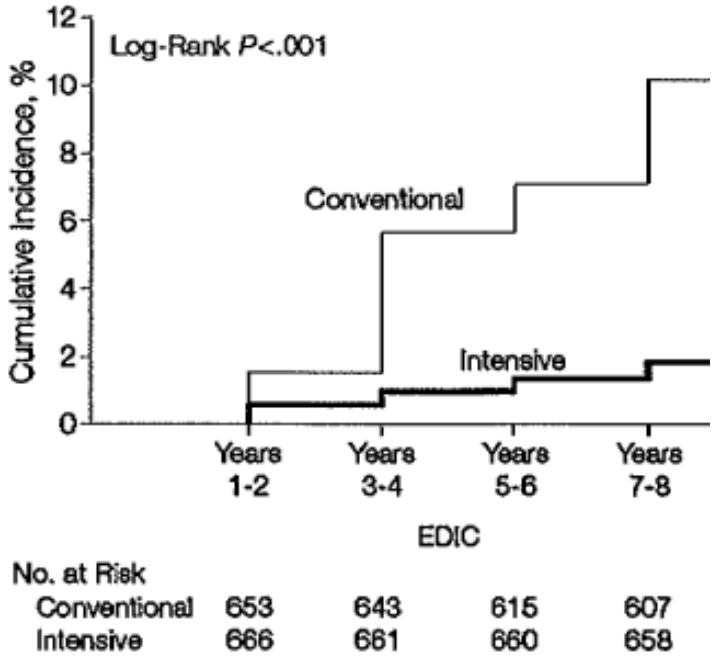
Sustained Effect of Intensive Treatment on Nephropathy in T1D

Annual Prevalence



(N=1349)

Cumulative Incidence



DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes. DCCT/EDIC. *J* Milligan S et al. J Diabetes Complications. 2016 Aug;30(6):1177-85

JAMA. 2003;290:2159-2167.

Therapeutic Options for Type 1 Diabetes

- Multiple daily injections of rapid acting insulin with meals combined with a daily basal insulin
- Continuous subcutaneous insulin infusion via an insulin pump
- Adjunctive therapy with pramlintide

Handelsman YH, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

Advances in the Care of Persons With Type 1 Diabetes

- Development of insulin analogues
- Insulin pump therapy
- Home glucose monitoring
- Advent of continuous glucose monitoring (CGM)

Handelsman YH, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

Type 1 Diabetes and Insulin

Physiologic Multiple Injection Regimens: The Basal-Bolus Insulin Concept

Basal insulin
~50% TDD

- Controls glucose production between meals and overnight
- Near-constant levels

Bolus insulin
~50% TDD

- Limits hyperglycemia after meals
- Immediate rise and sharp peak at 1 hour post-meal
- 10% to 20% of total daily insulin requirement at each meal

For ideal insulin replacement therapy, each component should come from a different insulin with a specific profile or via an insulin pump (with 1 insulin)

TDD, total daily dose.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Pharmacokinetics of Insulin

	Agent	Onset (h)	Peak (h)	Duration (h)	Considerations
Basal	NPH	2-4	4-10	10-16	Greater risk of nocturnal hypoglycemia compared to insulin analogs
	Glargine Detemir	~1-4	No pronounced peak*	Up to 24†	Less nocturnal hypoglycemia compared to NPH
Basal-Prandial	Regular U-500	≤0.5	~2-3	12-24	• Inject 30 min before a meal • Indicated for highly insulin resistant individuals • Use caution when measuring dosage to avoid inadvertent overdose
Prandial	Regular	~0.5-1	~2-3	Up to 8	• Must be injected 30-45 min before a meal • Injection with or after a meal could increase risk for hypoglycemia
	Aspart Glulisine Lispro Inhaled insulin	<0.5	~0.5-2.5	~3-5	• Can be administered 0-15 min before a meal • Less risk of postprandial hypoglycemia compared to regular insulin

* Exhibits a peak at higher dosages. † Dose-dependent. NPH, Neutral Protamine Hagedorn.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Moghissi E et al. *Endocr Pract*. 2013;19:526-535. Humulin R U-500 (concentrated) insulin prescribing information. Indianapolis: Lilly USA, LLC.

Principles of Insulin Therapy in Type 1 Diabetes

- Starting dose based on weight
  - Range: 0.4-0.5 units/kg per day
- Daily dosing
  - Basal
    - 40% to 50% TDI
    - Given as single injection of basal analog or 2 injections of NPH per day
  - Prandial
    - 50% to 60% of TDI in divided doses given 15 min before each meal
    - Each dose determined by estimating carbohydrate content of meal
- Higher TDI needed for obese patients, those with sedentary lifestyles, and during puberty

TDD, total daily dose.

Handelsman YH, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

Use of Technologies

in the Management Diabetes Mellitus

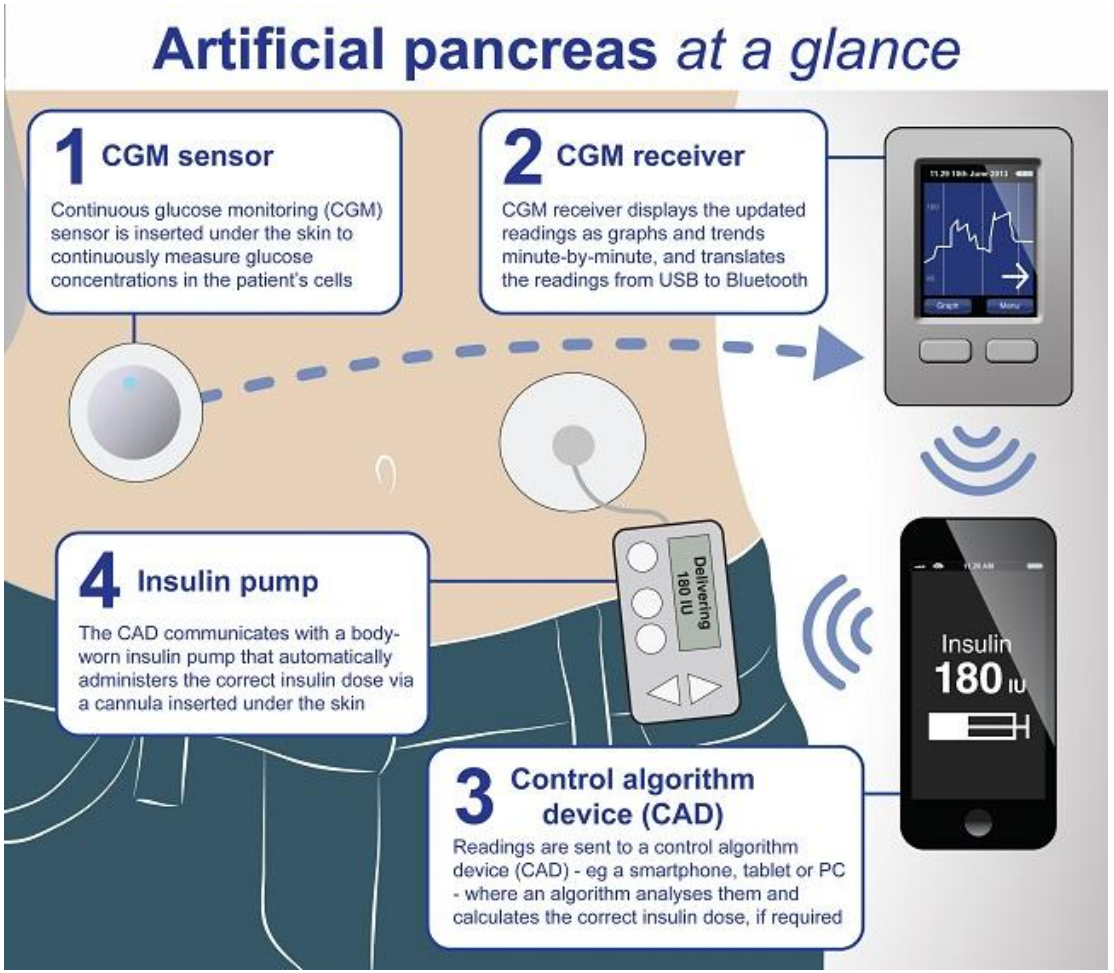
Technology and Diabetes

- In the past decade, significant interest in the use of technology.
- Numerous advanced technologies viz., Closed Loop Systems offer benefits to patients w.r.t optimizing glycemic control and avoiding severe hypoglycemia
- The selection of treatment tools available to the patients is large and diverse including
  - insulin delivery and glucose sensing devices,
  - various applications for phones and computers,
  - insulin dose calculators and web-based tools

Boulos et al. JMIR Serious Games 2015;3(1):e3

Closed Loop Systems: Artificial pancreas

- Several groups around the world are currently studying the benefits and risks of artificial pancreas (AP) systems.
- Studies have progressed from hospital settings to the outpatient world over the last 2 years.



Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Effectiveness and Safety of an Artificial Pancreas

- Study comparing 2 systems in patients with T1D
  - Age 5-18 years (N=17)
  - Closed loop "artificial pancreas" linking CSII insulin delivery with CGM (33 nights)
  - Standard CSII (21 nights)
- No significant difference in glycemic outcomes in primary analysis

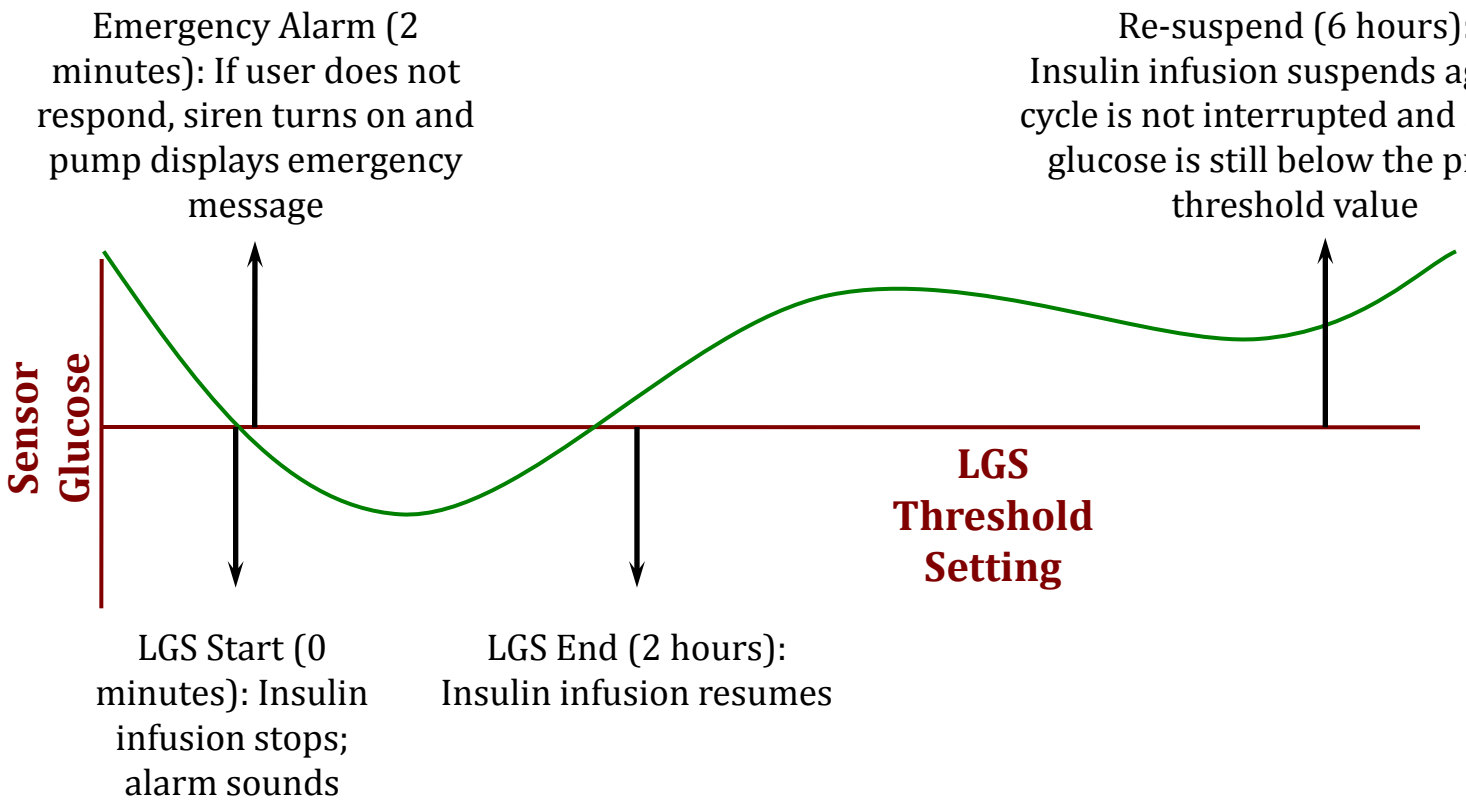
Secondary analysis of pooled data

	Closed loop	CSII	P value
Time in target BG range (%)	60 (51-88)	40 (18-61)	0.0022
Time BG ≤70 mg/dL (%)	2.1 (0.0-10.0)	4.1 (0.0-42.0)	0.0304
BG <54 mg/dL (no. events)	0	9	

BG, blood glucose; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; T1D, type 1 diabetes.

Hovorka R, et al. *Lancet*. 2010;375):743-751.

Emerging Options: CSII with "Low Glucose Suspend" Feature



BG, blood glucose; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; T1D, type 1 diabetes.

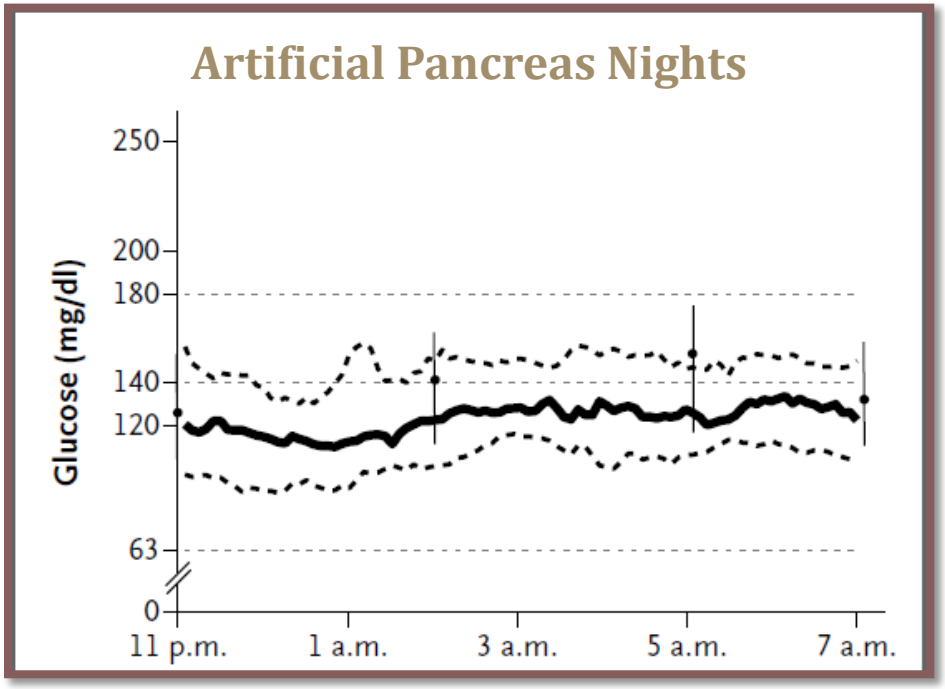
Hovorka R, et al. *Lancet*. 2010;375):743-751.

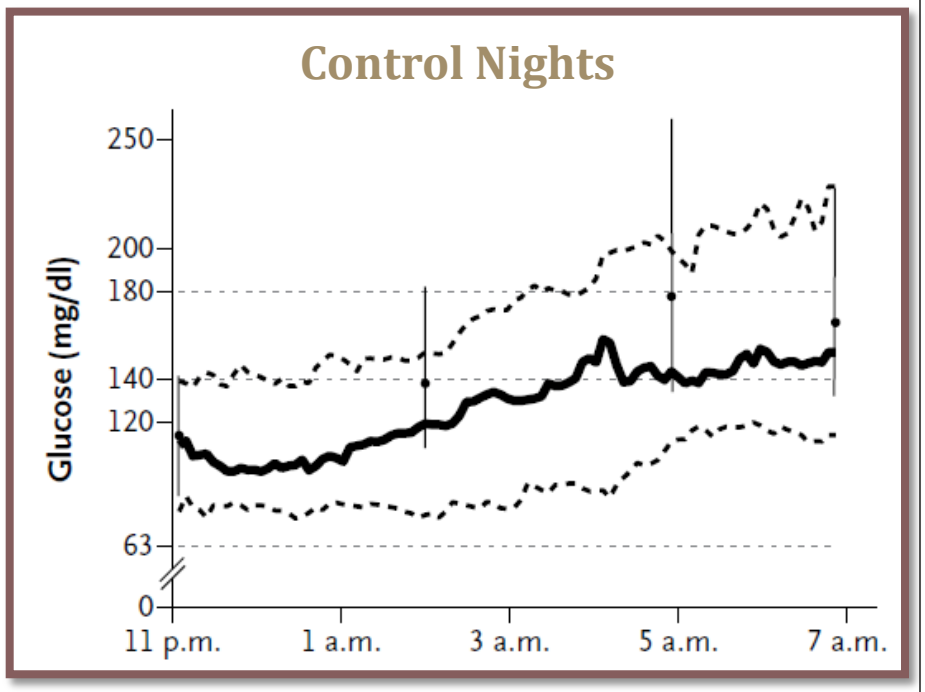
Initial Closed-Loop Studies Result in Less Nocturnal Hypoglycemia

- MD-Logic: a fully automated closed-loop system
- Study participants
  - Children, mean age 14 years (N=54)
  - Randomized to 1 night on closed-loop, then 1 night on sensor augmented pump (or vice versa)
- Results
  - Nocturnal hypoglycemia (glucose <63 mg/dL)
    - Closed-loop system: 7 episodes
    - Control: 22 episodes
  - Less glucose variability with closed-loop system

Philip M, et al. *N Engl J Med.* 2013;368:824-833.

Nocturnal Glycemia With Closed-Loop vs Sensor-Augmented Pump





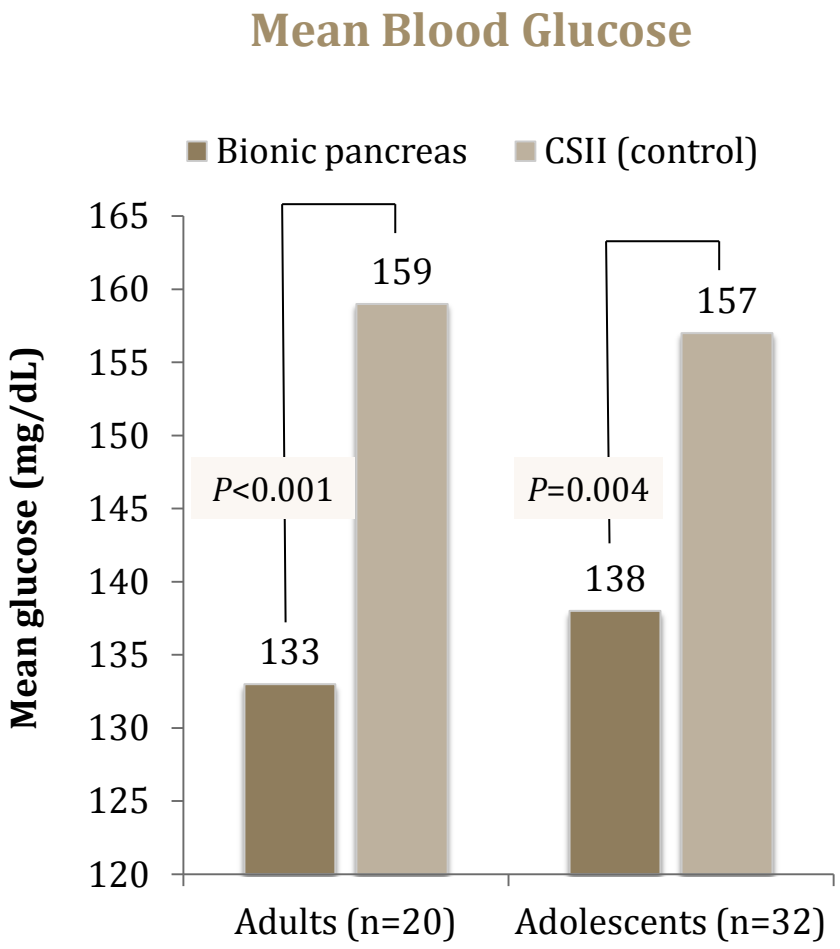
Philip M, et al. *N Engl J Med.* 2013;368:824-833.

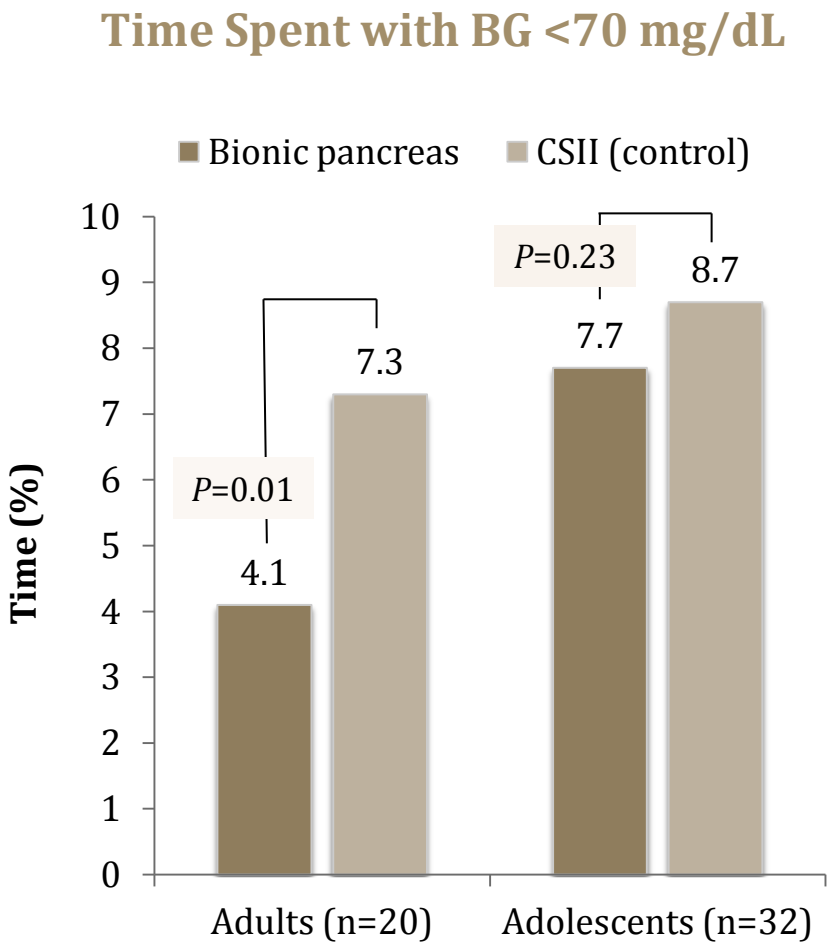
Bionic Pancreas

- Bihormonal secretion
  - Insulin
  - Glucagon
- Integrated continuous glucose monitor
- Fully automated
  - Control algorithm run on smart phone
  - Insulin and glucagon secreted in response to CGM data every 5 minutes
- Insulin bolus priming based on qualitative assessment of meal type and size
- Type
  - Breakfast
  - Lunch
  - Dinner
- Size
  - Typical
  - More than usual
  - Less than usual
  - Small bite

Russell SJ, et al. *N Engl J Med.* 2014;371:313-325.

Effect of Bionic Pancreas on Glycemic Control





Russell SJ, et al. *N Engl J Med.* 2014;371:313-325.

Digital Games for Type 1 Diabetes

- Digital games are an important class of eHealth interventions in diabetes, made possible by the Internet
- Gamifying disease management help children, adolescents, and adults with diabetes to better cope with T1DM
- Gamification and social in-game components are used to:
  - motivate players/patients and
  - positively change their behavior and lifestyle.

Boulos et al. JMIR Serious Games 2015;3(1):e3

The Ayogo Model

- The Ayogo Model used in designing the game apps is an evidence-based approach to designing games and gamified apps to:
  - build self-efficacy—the belief in one's own ability to manage and
  - demonstrate self-control—among people managing chronic illness and diabetes in particular.
- This approach blends Design Thinking, evidence from cognitive and behavioral psychology, and video game design.

Screenshots of Monster Manor. *Children can input their blood glucose measurements using an on-screen numeric pad and earn virtual coins to buy various in-game items that are essential for progression through the game*

Boulos et al. JMIR Serious Games 2015;3(1):e3

Bolus Calculators (BC)

- Bolus calculators are widely available in a variety of formats—
  - applications for smart phones,
  - incorporation into blood glucose meters, and
  - incorporation into insulin pumps.

- Bolus calculators estimate the "correction" insulin dose using
  - patient's current glucose level,
  - insulin sensitivity,
  - target glucose level and insulin-on-board and
  - the prandial insulin dose

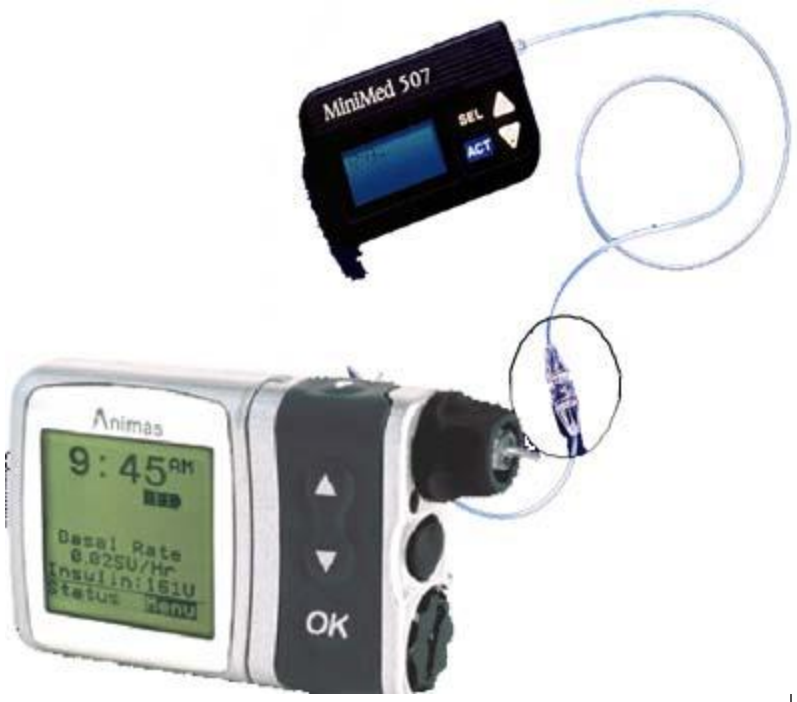
  based on the carbohydrate content of the meal and the pre-established insulin:carbohydrate ratio.

- BCs have been shown to reduce the fear of hypoglycemia and improve glycemic control.
- Provides more flexibility and improves QOL

Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Continuous Subcutaneous Insulin Infusion (CSII) Pumps

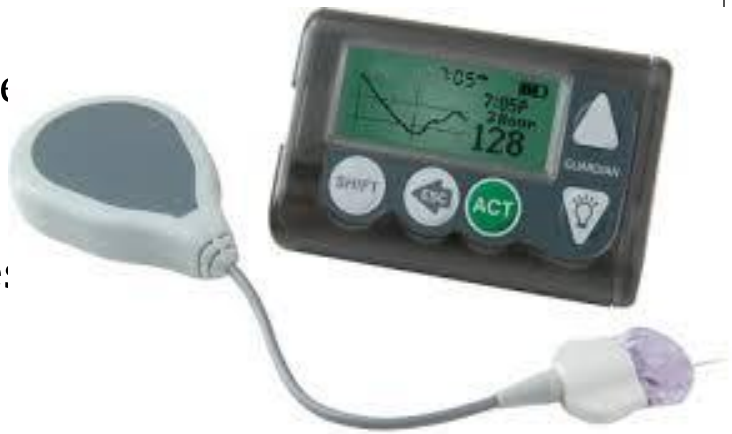
- Insulin pumps have been used by patients with type 1 diabetes for over 30 years.
- *CSII* effectiveness in improving A1c has been demonstrated in a number of studies
- Sutton *et al.* found that CSII can reduce A1c by about 0.6% when compared to multiple daily injection (M DI) therapy in both adults and children



Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Real-Time Continuous Glucose Monitors (RTCGM)

- The accuracy and usability of continuous glucose monitors (CGM) have gradually improved over the past decade.
- As opposed to retrospective CGM, RT-CGM devices offer opportunities to improve both hyper- and severe hypoglycemia as they provide actionable information to patients in "real-time."

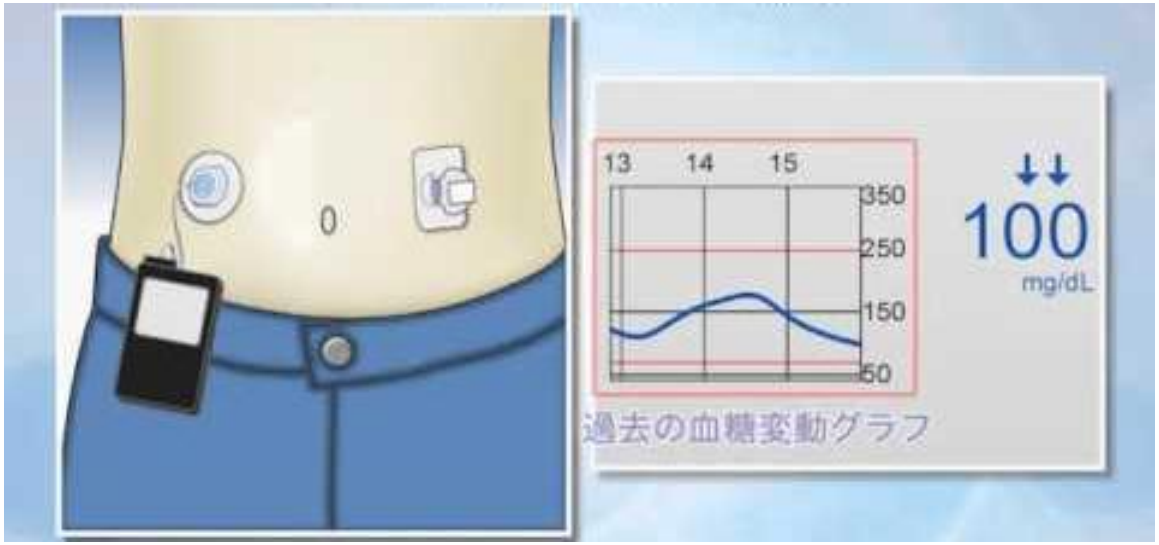


- Two recent meta-analyses of randomized controlled trials showed that RT-CGM was superior to self-monitoring of blood glucose (SMBG) in reducing A1c by almost 0.4% in both children and adults

Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Sensor-Augmented Pumps (SAP)

- The combination of RT-CGM and CSII—sensor augmented pumping or SAP—would be predicted to be the best combination of advanced technologies for improving A1c and the rates and severity of hypoglycemia.
- Bergenstal *et al.* demonstrated that SAP produced an overall sustained reduction in A1c of 0.6% over 12 months compared to SMBG plus MDI in both adults and children.
- Golden *et al* found an A1c reduction of 0.68% in 4 studies using SAP



Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Low-Glucose Threshold Suspend (LGTS) Systems

- LGTS systems are an extension of SAP and represents the first step toward an artificial pancreas.

- Bergenstal and colleagues reported a significant reduction in rate and severity of hypoglycemia during a 3 months trial in adults using an LGTS system compared to those using SAP without an increase in A1c in either group.

- The severe hypoglycemia rate decreased from 2.2 per 100 patient-months to 0 per 100 patient-months

Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Low-Glucose Predictive Suspend (LGPS) Systems

- LGPS systems represent the next step in the advance toward the artificial pancreas.

- The LGPS system differs from the LGTS system in using a predictive algorithm to suspend insulin prior to reaching a predetermined threshold.

- Maahs et al. conducted a study of an LGPS system in 45 individuals with type 1 diabetes over 42 days.
  - 50% reduction in the rate of hypoglycemia
  - duration of time with glucose levels under 60 mg/dl and 50 mg/dl were reduced from 23 to 7 minutes and 10 to 2 minutes, respectively.

Vigersky RA J Diabetes Sci Technol. 2015 Mar;9(2):320-30.

Effects of Currently Approved Technologies on Key Aspects of Management in Patients With Diabetes

The evidence for the benefits and limitations of several currently available technologies in managing patients with diabetes

	A1c	Hypoglycemia	Limitations
CSII	↓	↓	1. Cost 2. Socioeconomic barriers
BC	↓	→	1. Most are not FDA-approved 2. Meal content not included in calculation
RT-CGM	↓	↓	1. Cost 2. Low adherence rates
SAP	↓	→	1. Cost 2. 2 insertion sites
LGTS	→	↓	1. Cost 2. 2 insertion sites 3. Limited number of studies
LGPS	↓	↓	1. Cost 2. 2 insertion sites 3. Limited number of studies

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Conclusion

- The prevalence of diabetes is rising globally.
- Technology for diabetes management is rapidly developing and changing.
- With each new development, there are numerous factors to consider, including medical benefits, impact on quality of life, ease of use, and barriers to use.
- Focusing on the effectiveness of new technologies and the limitations of the use of such technologies in the real world may help find a way to achieve the A1c goals for many patients.
- In addition, it could give us greater insight into barriers to sustain the use of these therapeutic advances and how to overcome them

Thank You