Outpatient Insulin Management:
An Interventional Evolution

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ACOI
AMERICAN COLLEGE OF OSTEOPATHIC INTERNISTS CONVENTION & SCIENTIFIC SESSIONS
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Disclosures

Compensated

Speaker's Bureau:

Novo Nordisk Pharmaceuticals

Janssen Pharmaceuticals

Mist Pharmaceuticals

Medtronic Diabetes

Advisory Board:

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Non-Compensated

International Society of Clinical Densitometry (ISCD) Task Force
Practice Analysis Committee for CCD Certification

Discussion Overview

Learning Objectives

- Highlight guidelines specific to initiating insulin therapy in type 1 and type 2 diabetes
- Underscore the pharmacokinetic attributes of currently-available insulin products
- Recognize and critique strategies related to insulin-specific management in type 1 and type 2 diabetes
- Highlight basic insulin pump operation and the goal of complimenting normal physiologic pancreatic function.
- Differentiate between the advantages and disadvantages of CSII vs. multiple daily injections for people with type 1 and type 2 diabetes.
- Discuss the benefits of CSII for a patient with insulin-requiring type 2 diabetes.

Key Phrases/Terms

- **Physiologic versus Non-physiologic Therapies**
- **Standard Deviation**
- **Legacy Effect**
- **Time-in-Range**

Trending Statistics

≈5,000 Adult and **≈900 Pediatric**

Board Certified Endocrinologists in the U.S.

≈3,900 Clinically Active

84.1 million with "**Pre**-diabetes"

30.3 million "Classic" diabetes

1 Endocrinologist per ≈29,300 (Pre- + Diabetic)

Patients Nationwide

85% of Diabetes Care will require:

↓

Health Care Providers beyond Endocrinologists

- **Primary Care Physicians**
- **Physician Assistants**
- **Nurse Practitioners**

Vigersky RA, Fish L, Hogan P, Stewart A, Kutler S, Ladenson PW, et al. The Clinical Endocrinology Workforce: Current Status and Future Projections of Supply and Demand. J Clin Endocrinol Metab. 2014;99(9):3112–21.

Hua Lu, James B. Holt, Yiling J. Cheng. Population-based Geographic Access to Endocrinologists in the United States. BMC Health Services Research. 2012. (2015) 15:541; 1-13.

“The Whole is Greater Than the Sum of Its Parts”

Aristotle (Greek philosopher/scientist; 384 B.C. → 322 B.C.)

Defines the modern concept of Synergy and the T.E.A.M. acronym:

Together, **E**verything **A**chieves **M**ore.

Applies to physics, engineering, agriculture, business, and ……

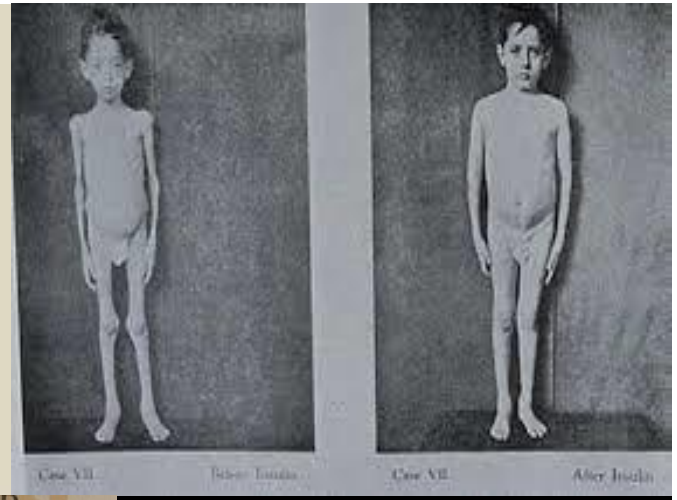
……. **the chemistry and biology of insulin**

Evolution of a Therapeutic Breakthrough

INSULIN: Landmark Discovery

Dr. Frederick Banting & Charles Best

- 1921 – discovered insulin using dogs
- 1922 – 14-yr-old boy with diabetes, near death, first person to receive insulin
- 1923 – Nobel prize



THE TORONTO DAILY STAR

TORONTO DOCTORS ON TRACK OF DIABETES CURE

RAILROAD UNIONS IN U.S. MAY JOIN IN MINERS' STRIKE

DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

"DRY" LAWS HERE CAUSE HARDSHIP IN OLD FRANCE

RESERVES OF COAL ARE HIGH IN CITY, PRICE TO GO DOWN

CIVIL WAR STAGE NOT YET REACHED, BUT DANGER GREAT

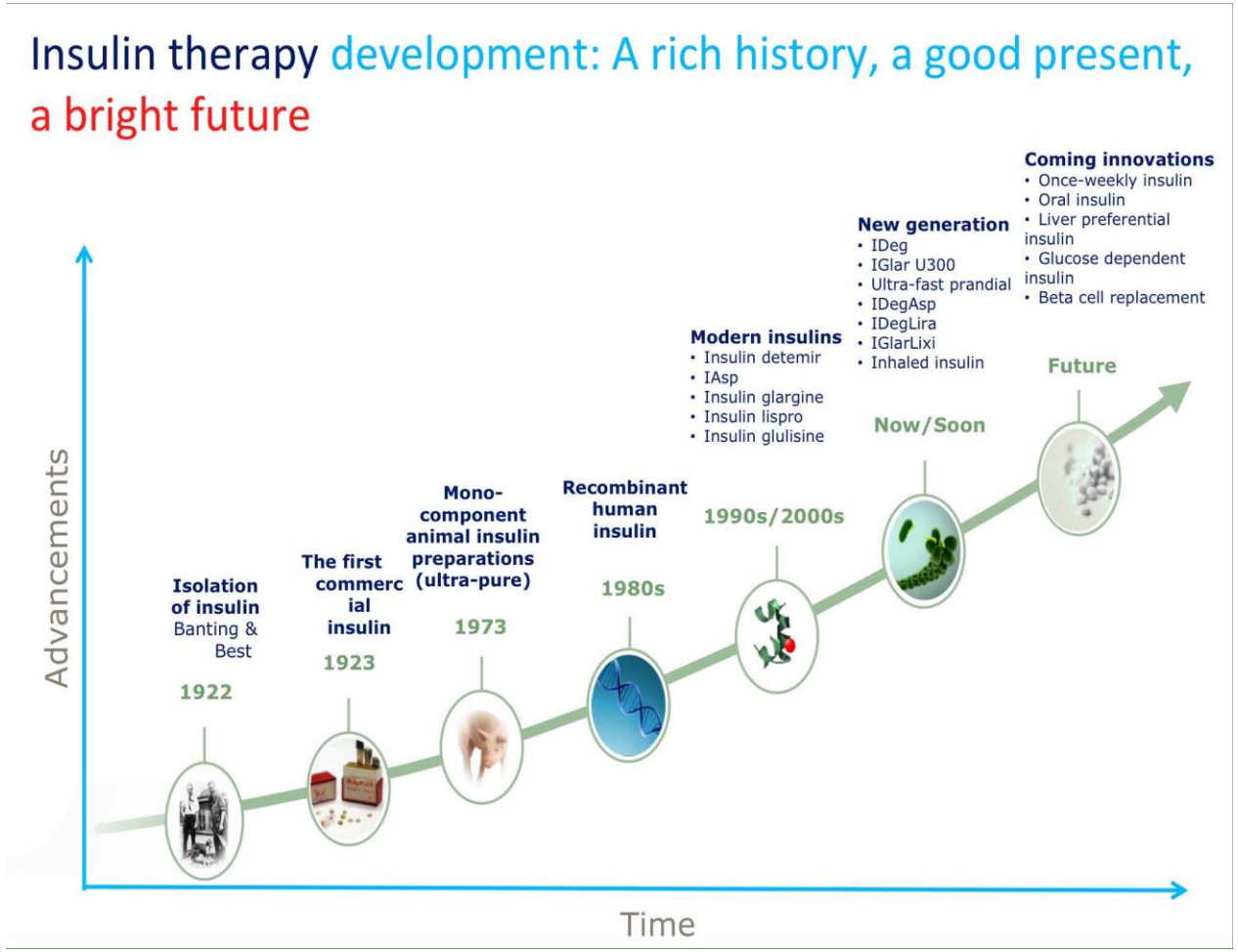
Imperials May Separate Irish

On his discovery of Insulin….

Insulin is **not a cure** for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.

— Sir Frederick Grant Banting

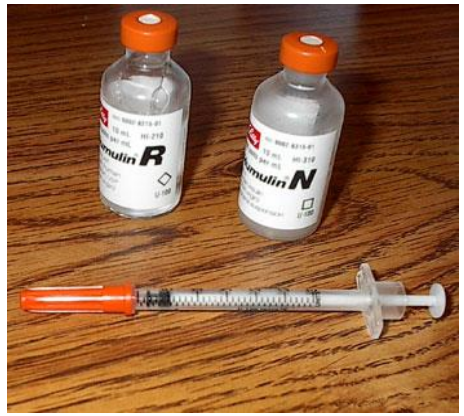
96 Years of Pharmacologic Milestones



Greatest Historical Breakthroughs in Insulin Therapy

- **1973**: Development of **Mono-component "Human" insulin**
  - **Purified pork insulin**; new standard in purity.
  - **Enzymatic conversion: Alanine (B30) →Threonine**
  - **Identical in structure to human insulin**

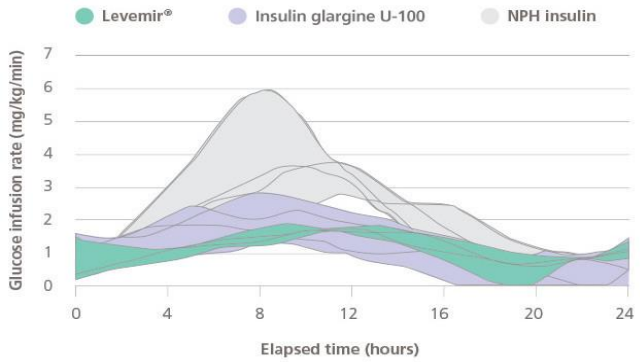
- **1978**: Advancement of **Recombinant DNA "Human" Insulin**
  - Gene manipulation of **E. coli** to produce ***Bio-synthetic human insulin***
  - **Eliminated insulin allergy and immune-mediated lipoatrophy**.
  - **Humulin R** and **Humulin N** (Eli Lilly)



- **1995**: Expansion to **Insulin Analogues**
  - **Laboratory grown** (***E. coli/Baker's Yeast***) but **genetically altered** amino acid sequence)
  - **Pharmaco-kinetic/-dynamic features** striving to simulate "**endogenous**" insulin
  - **Lispro is the first analogue produced** – FDA approved 1996

Primary Goal of Insulin Treatment Strategies

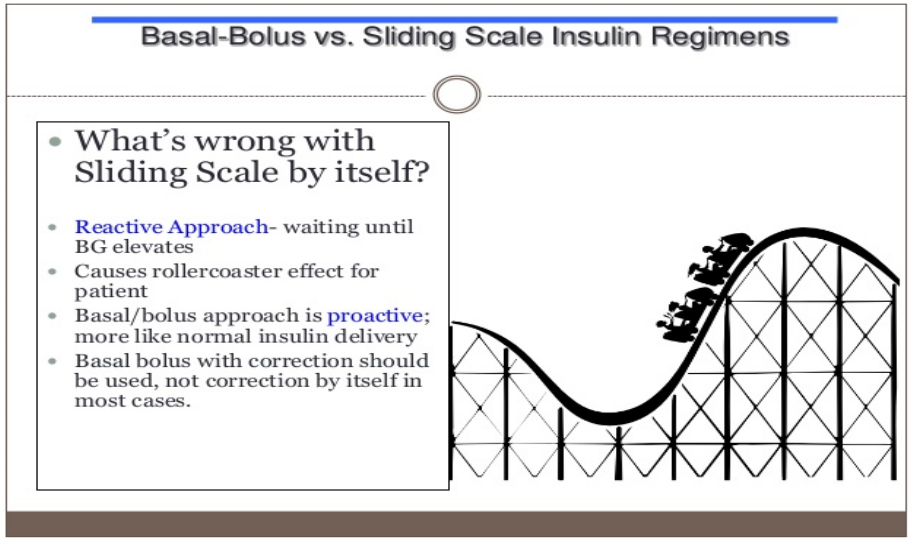
- **Match pharmaco-kinetic/-dynamic profile of "endogenous insulin":**
  - Timing precision; adherence; fewer injections
  - Reduce within-/between-patient variability in plasma glucose



- **Tight glycemic control:**
  - Limit microvascular complications (**DCCT and UKPDS**)
  - **Reduce** glucose variability/**standard deviation** (**oxidative stress → $O_2^{-\cdot}$ free radicals → endothelial damage**)
  - Minimize "**Legacy Effect**"
  - Achieve "**Time-in-Range**" (**HbA1C???**)

- **Minimal risk for exogenous side effects:**
  - hypoglycemia
  - weight gain

- **Achieve "Prospective" treatment models:**
  - Sliding Scale
  - Split-Mixed (both insulins provide potential basal and prandial effects)
  - Basal-Bolus
  - Pump Infusion Therapy



Major Adverse Effects of Insulin

- **Hypoglycemia (unawareness)**
  - **DCCT Study** (**Type 1 Diabetes**)
    - Severe hypoglycemia in **26% of patients**
    - **43% of episodes nocturnal**
  - **UKPDS Study** (**Type 2 Diabetes**)
    - **Insulin cohort**: 2% of patient with at least 1 **severe** episode/year
- **Weight Gain** (***over "insulinization"; hypoglycemia/defensive snacking***)
  - **DCCT Study** (Type 1 Diabetes)
    - **Intensive cohort** with **≈ 10.5 lb. increase**
  - **UKPDS Study** (Type 2 Diabetes)
    - **Insulin Cohort** with **≈ 5.1 lb. increase**
- **Progression of Retinopathy with rapid glycemic control**
  - **Osmotic Hypothesis:** rapid decline in plasma glucose shifts water from a ***higher osmotic pressure interstitium*** to a ***lower intravascular osmotic space***
  - **Synergistic Hypothesis:** ***insulin amplification*** + **expression of** ***vascular endothelial growth factor*** (by ischemic vessels) **promotes retinal vascular proliferation**.
  - **Higher Risk = proliferative retinopathy + HbA1C ≥ 10%**

1982-1993 DCCT Study:
3-fold increase in Hypoglycemia

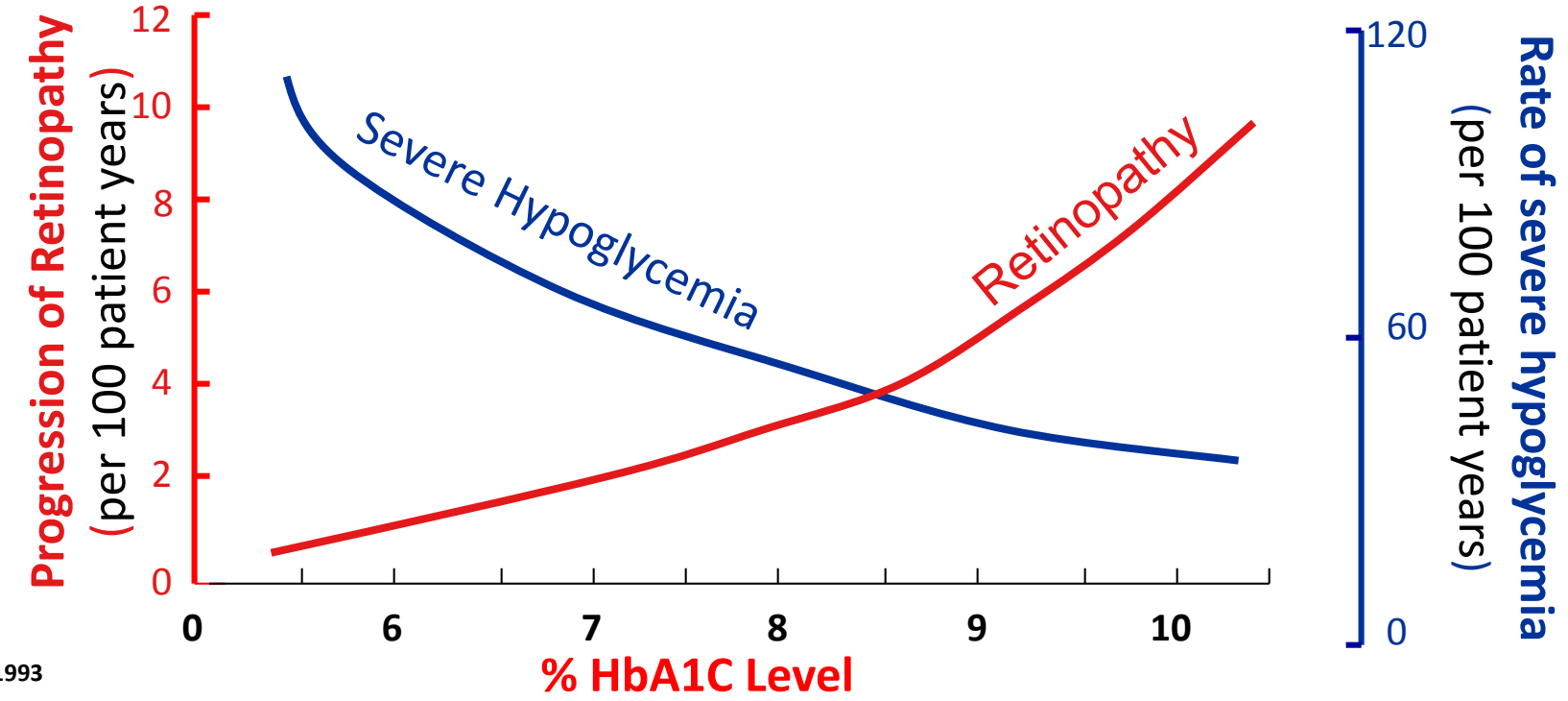
Trade-off between: Reducing Complications & Minimizing Hypoglycemia

Patients used: Regular insulin /Intensive therapy via Multiple Injections or Insulin Pump

Intensive Glycemic Control Reduced Microvascular complications overall → **≈60%:**

- **Retinopathy 63%**
- **Neuropathy 60%**
- **Nephropathy 54%**

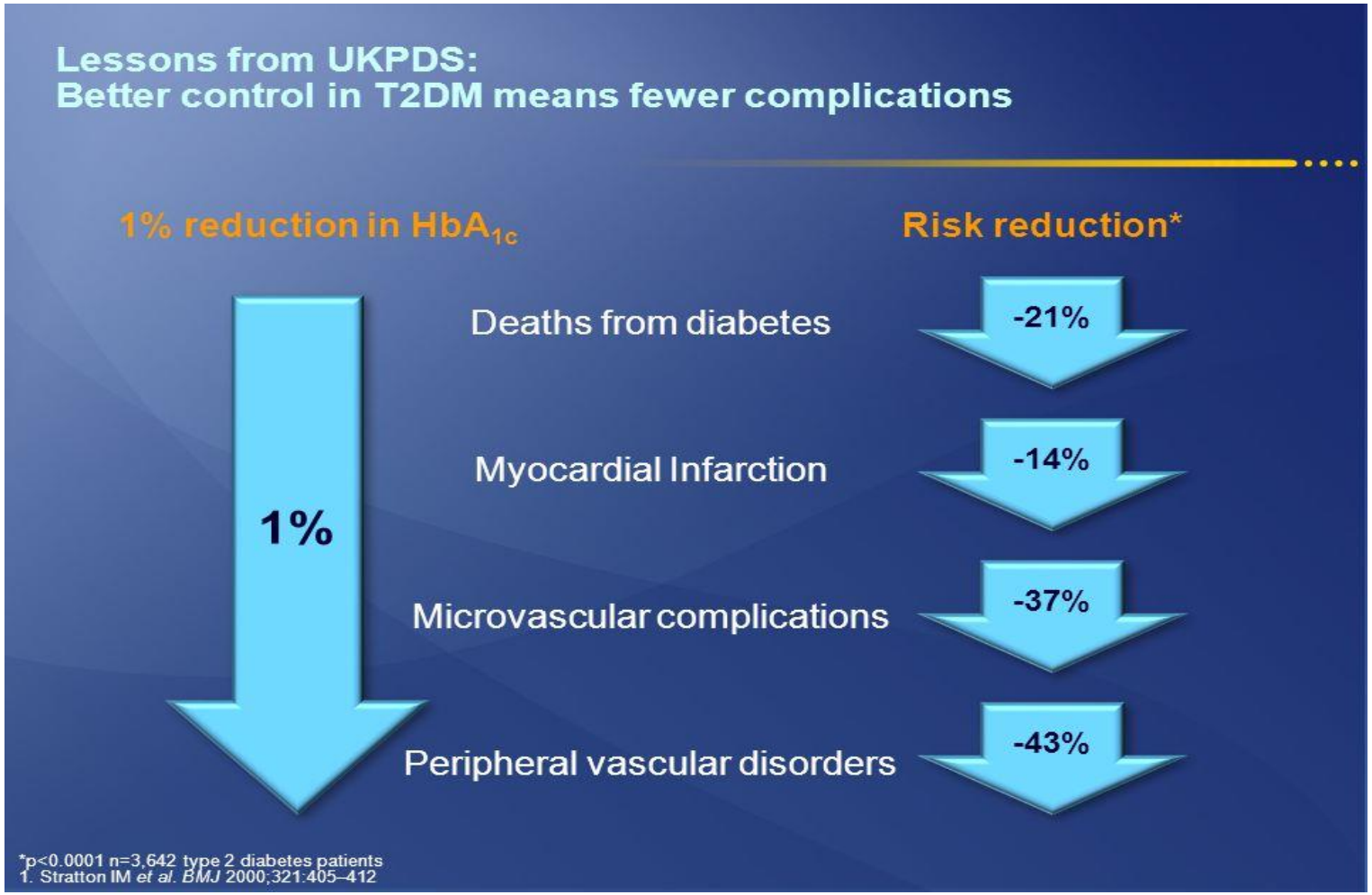
By End of Study 42% of Intensively-Managed Patients on CSII Therapy



DCCT Research Group, 1993

1977-1997:
United Kingdom Prospective Diabetes Study for Type 2 Diabetes
("Newly Diagnosed Patients")
Intensification of Therapy (i.e. sulfonylureas, insulin, MDI therapy)

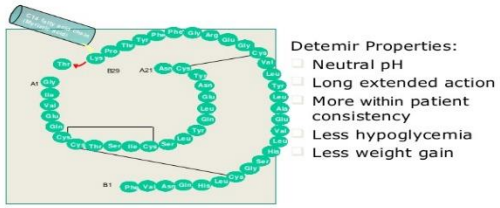
HbA1C Reduction of ≈1.0%



Behavioral, Distribution and Absorption Considerations

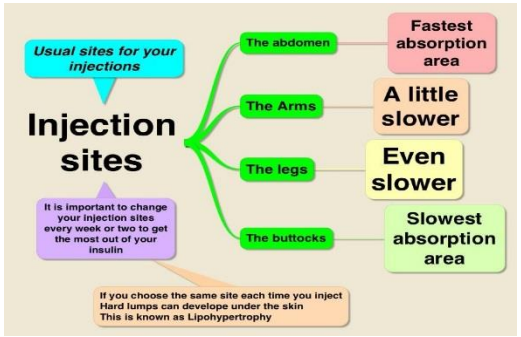
- **Molecular Character:**
  - Human **non-analogue** versus **analogue** insulin → altered kinetic behavior
  - **Fatty-acid side-chain**:
    - dictates self-association/reversible albumin binding features
    - influences portal/peripheral/CNS distribution

Insulin Detemir (2004)



- **Product concentration:**
  - **U-100, U-200, U-300, U-500**
  - absorption rate inverse to concentration

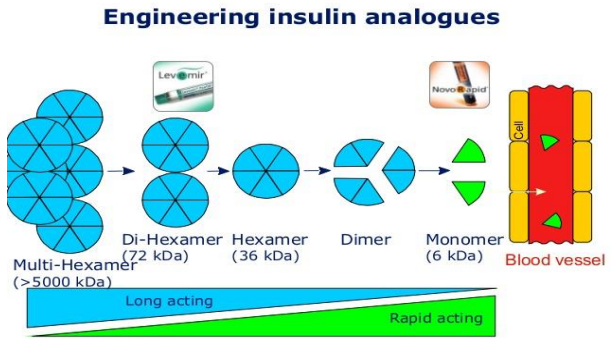
- **Injection sites:**



- **Formulation design**:
  - **Protamination**: "crystalline-based" protracted absorption (limited/variable) **NPH Insulin**
  - **pH-altered precipitation**: protracted absorption (extended/less-variable) **Glargine Insulin** (**Lantus**)
  - **Non-precipitant** (**Fatty-acid side chain**): protracted/reproducible absorption kinetics

    Detemir Insulin (**Levemir**)
  - **Zinc, Phenol, m-cresol components**:
    - Self-association/conformational properties in-solution: multi-hexamers → di-hexamers → hexamers → monomers
    - Dissociation properties SQ → active insulin monomers

    Degludec Insulin (**Tresiba**)



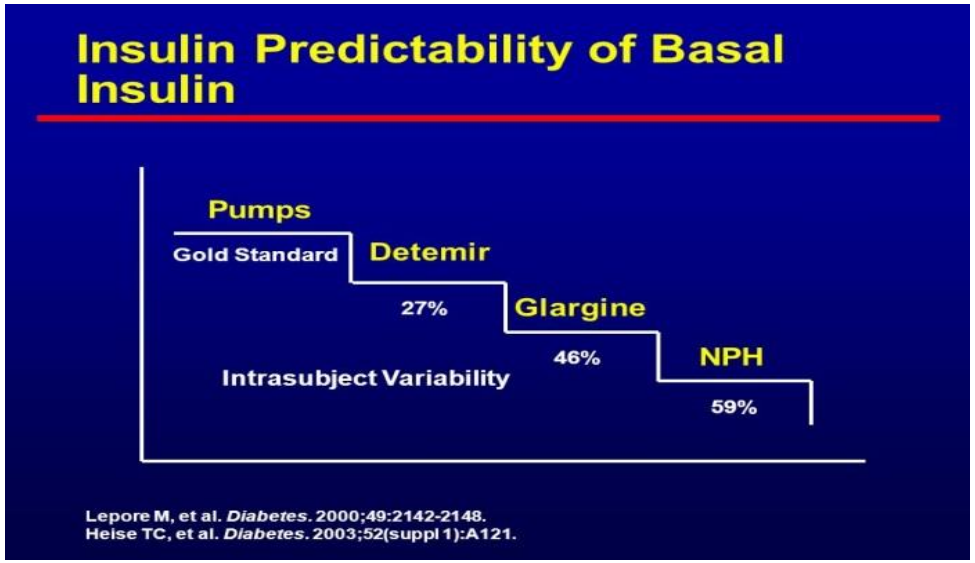
The Ideal Analogue Insulin

Rapid-acting agents:

- **Replicate first- and second-phase endogenous kinetics**
- **High hexameric stability in solution; rapid dissociation into monomers post-SQ injection**
- Match "action time" for meals
- **Predictable end-point** to minimize residual insulin conflicts (hypoglycemia)
- Prevent **ramifications of post-prandial hyperglycemia**:
  - **Insulin "Over Correction" → post-prandial hypoglycemia** (Pump; Basal-Bolus regimens)
  - **Post-prandial-related CV Risk**:
    - **HbA1C 1% ↑ = 50% CV↑ = Type 1 DM**
    - **HbA1C 1% ↑ = 7.5% CV↑ = Type 2 DM**

24-hour Basal agents:

- Achieve **steady-state** pharmacokinetics/dynamics
- **Low peak:trough ratio**
- **Duration of action comfortably exceeds 24-hours**
- Dosing frequency **not to exceed once daily**
- **Low variability of action** from injection to injection
- **Able to mix** with Rapid-acting insulin



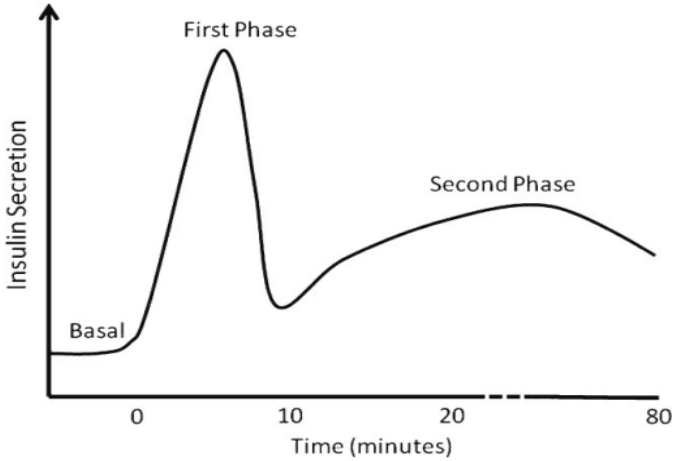
Endogenous Insulin Kinetics

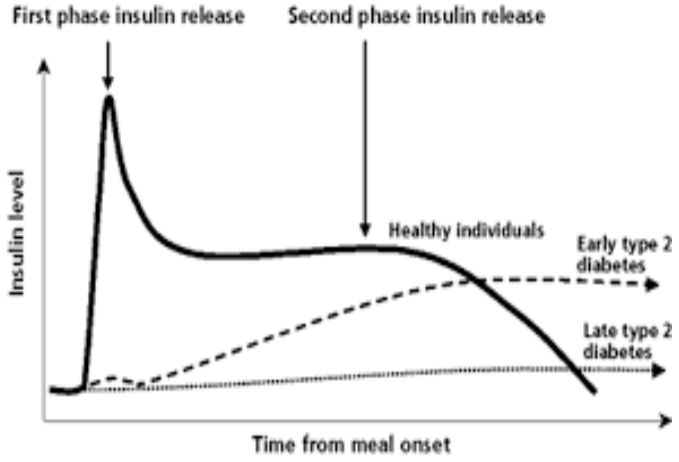
- Secretion is Bi-phasic

- Prandial First-phase Insulin Release:
  - **begins within 2 minutes** of nutrient ingestion
  - **"buffers" postprandial glucose "spike"**
  - **earliest "flaw" in beta-cell function**

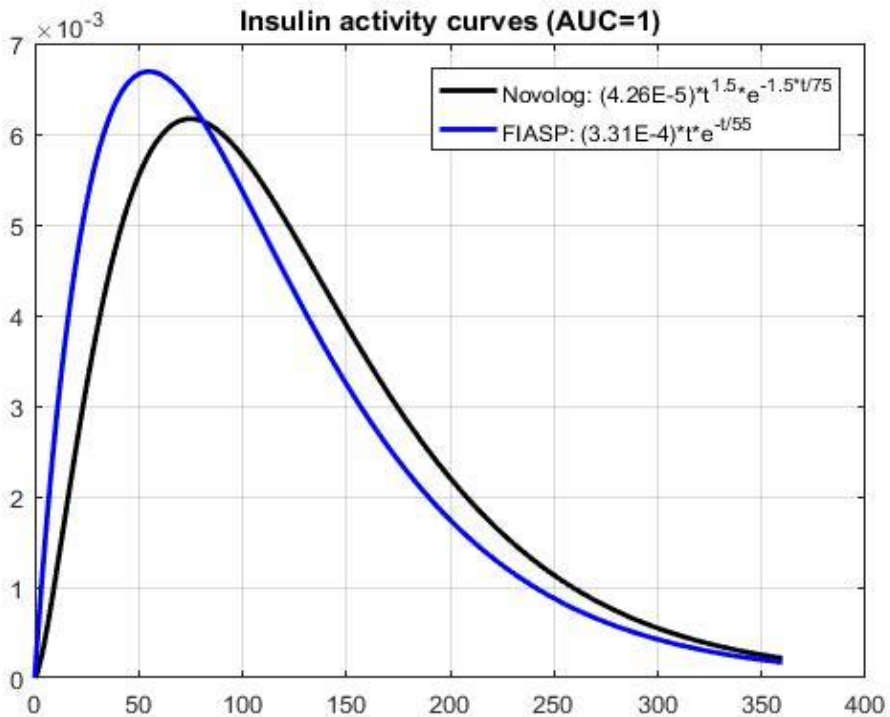
- Prandial Second-phase Insulin Release:
  - sustained until normoglycemia is restored
  - **suppresses hepatic glucose production**

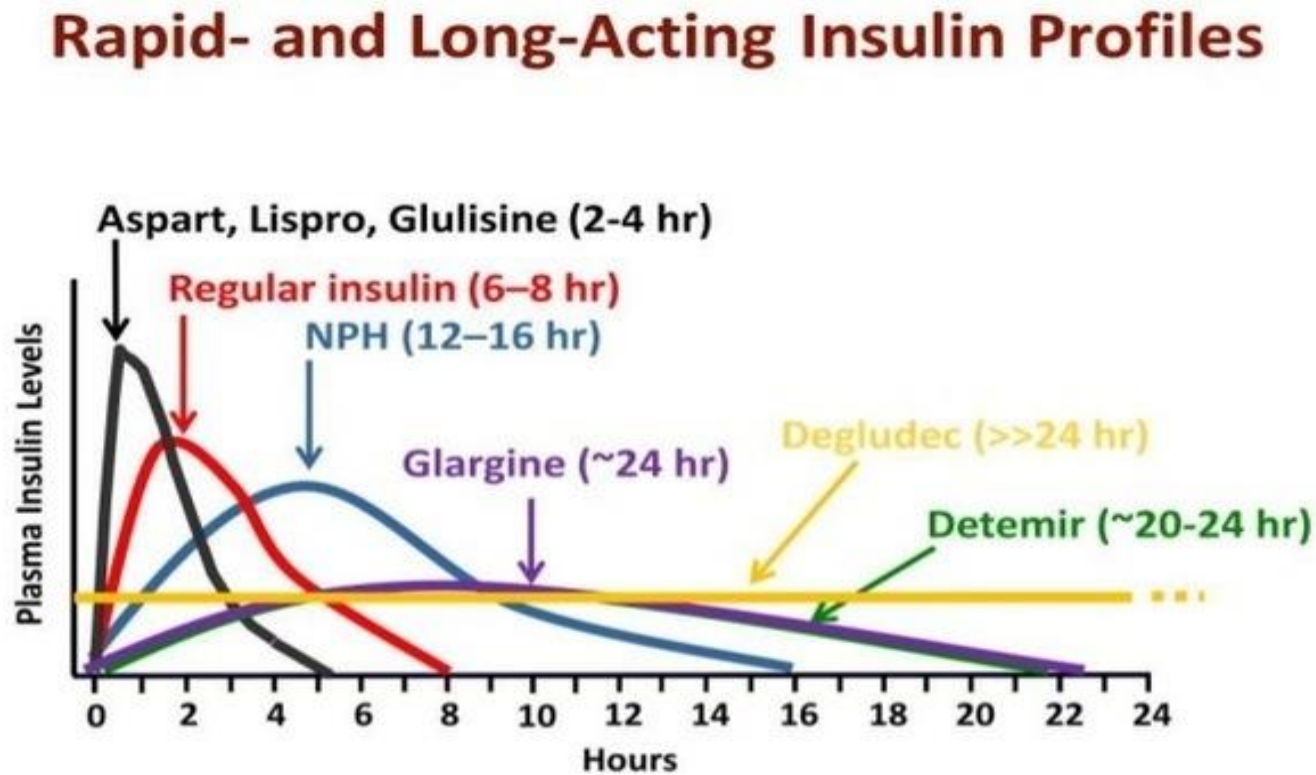
- Basal Insulin Maintenance
  - ≈ 50% of our total daily insulin;
  - **suppresses lipolysis, proteolysis, and glycogenolysis**





Ideal Rapid and Basal Insulins





The Ideal Analogue Insulin

Rapid-acting agents:

	ONSET	PEAK	DURATION	SPECIFICS
Regular insulin:	**30 min.**	3-4 hrs.	6-8 hrs.	Zinc-insulin crystals in sterile, clear solution
Humalog insulin:	15 min.	75-90 min.	3½-4 hrs.	B-chain **inversion** of **Pro^{28}** and **Lys^{29}**
Novolog *RAPID-acting* insulin:	10-15 min.	40-75 min.	3½-4 hrs.	Single B-chain **substitution** **$Proline^{28}$ →Aspartic acid**
Apidra insulin (ZINC-FREE)	< 10 min.	60 min.	2-4 hrs.	B-chain **dual substitution** **$Lysine^{3}$ → Asparagine** and **Glutamic acid^{29} → Lysine**
Novolog *FAST*-acting insulin: (*FIASP*)	**2.5 min.**	1-3 hrs.	3-4 hrs.	**NICOTINAMIDE accelerates absorption + ARGININE stabilizer**

24-hour Basal agents:

	ONSET	PEAK	DURATION	SPECIFICS
Toujeo insulin:	6 hrs.	Minimal Peak	24-36 hrs.	**COMPACT SQ DEPOT reduces re-dissolution rate; U-300 formulation**
Tresiba insulin:	1-4 hrs.	**No Peak**	**up to 42 hrs**.	**"STEADY-STATE" kinetics; ABLE TO MIX; 20% intra-patient variability**
Lantus insulin:	2-4 hrs.	Minimal Peak	22-24 hrs.	**SQ PRECIPITANT; Near-peakless profile; 46% intra-patient variability**
Levemir insulin:	2-3 hrs.	6-8 hrs.	22-24 hrs.	**NON-PRECIPITANT; Reversible Albumin Binding; 27% intra -patient variability**

The Ideal Analogue Insulin

Rapid-acting agents:

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Regular insulin:	30 min.	3-4 hrs.	6-8 hrs.	Zinc-insulin crystals in sterile, clear solution
Humalog insulin:	15 min.	75-90 min.	3½-4 hrs.	B-chain **inversion** of **Pro^{28}** and **Lys^{29}**
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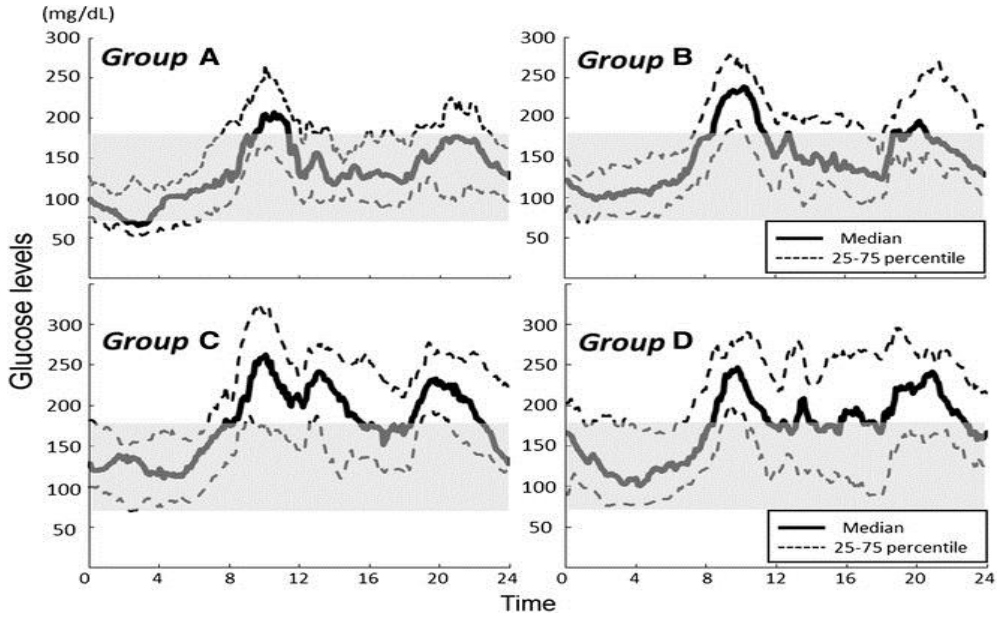
Hypoglycemia:
The Limiting factor to Glycemic Control

- 101 Type 1 diabetic patients receiving basal-bolus insulin therapy enrolled
- CGM data collected to provide insight into glycemic variability.
- Patients **stratified equally by HbA1c values with CGM data** demonstrating
  - All HbA1c subgroups exhibit similar patterns of glycemic variability and SD of ≈50–60 mg/dL
  - The lower the HbA1c value, the longer the duration of hypoglycemia and nocturnal (23:00–6:00) hypoglycemia
  - **Study implication**: **A lower HbA1c is not associated with a lower SD → but may lead to increased hypoglycemic episodes**.

- Group A: HbA1c ≤7.2 %
- Group B: 7.2 % → 8.1 %
- Group C: 8.2 % → 9.1 %
- Group D: HbA1c >9.2 %



Tsujino, T, Nishimura, R. The relationship between HbA1c values and the Occurrence of Hypoglycemia as Assessed by Continuous Glucose Monitoring in Patients with Type 1 Diabetes. Diabetol Metab Syndr. 2016; 8: 53.

Journal of Diabetes Complications. 2005 May-Jun;19(3):178-81.

Should minimal blood glucose variability become the gold standard of glycemic control?

Irl B. Hirsch and Michael Brownlee

Abstract:

The DCCT Trial established HbA1C as the gold standard of glycemic control, with levels ≤7% deemed appropriate for reducing the risk of vascular complications ……..

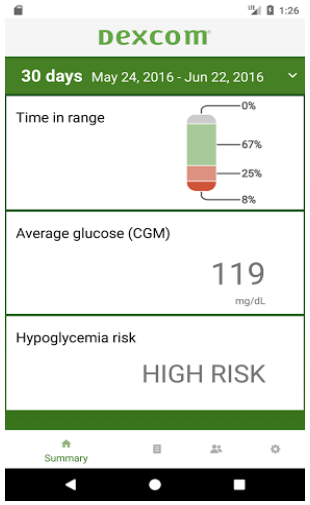
……. Yet, even when A1Cs were comparable between intensively treated subjects and their conventionally treated counterparts, the latter group experienced a markedly higher risk of progression to retinopathy over time.

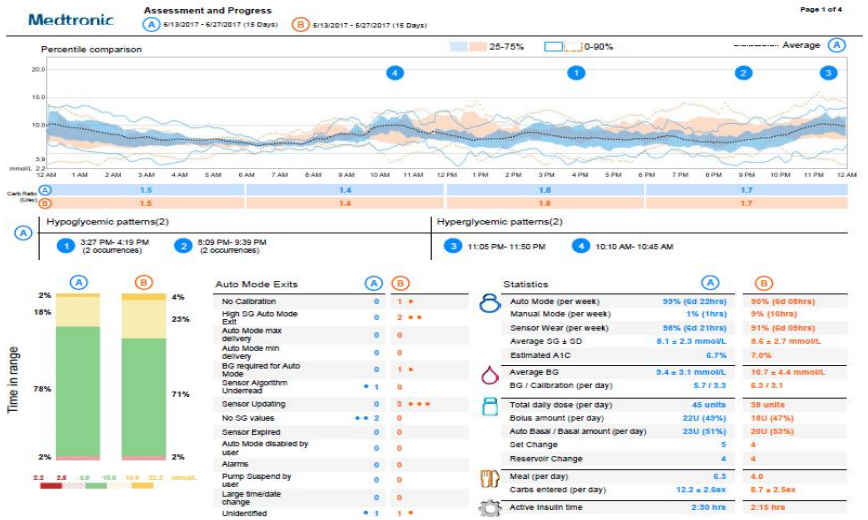
Our speculative explanation, **based on the discovery that hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-mediated vascular damage**, was that **glycemic excursions were of greater frequency and magnitude among conventionally treated patients**, who received fewer insulin injections.

Subsequent **studies correlating the magnitude of oxidative stress with fluctuating levels** of glycemia **support the hypothesis that glucose variability**, considered in combination with A1C, **may be a more reliable indicator of blood glucose control** and the risk for long-term complications than mean A1C alone.

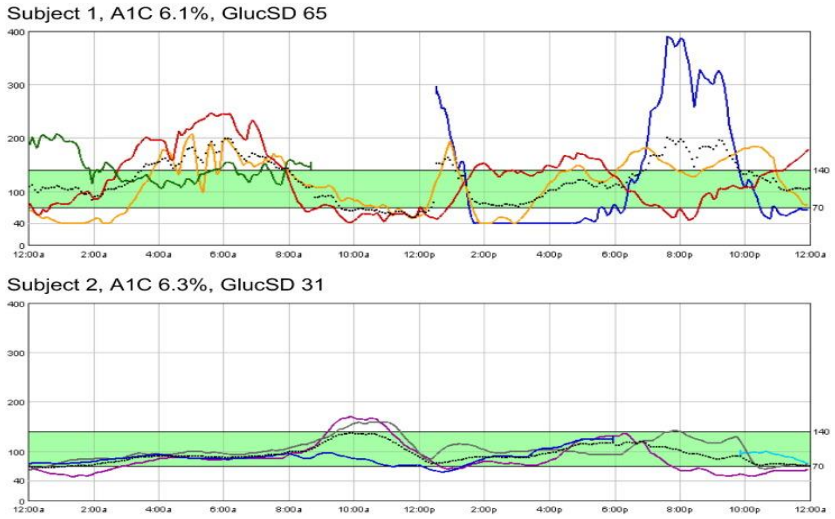
Should Minimal Blood Glucose Variability ("Time in Range") Become the Gold Standard

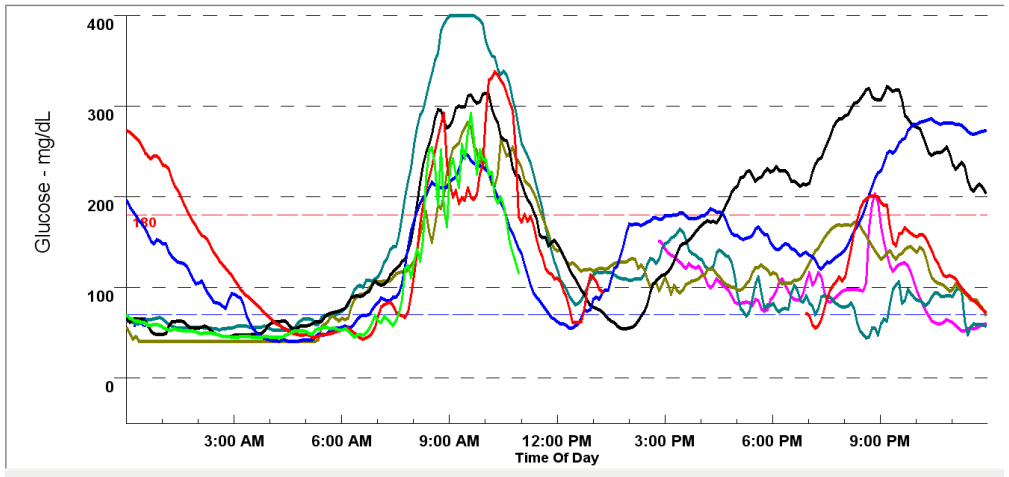
"Time In Range" CGM Bar Graph Summary



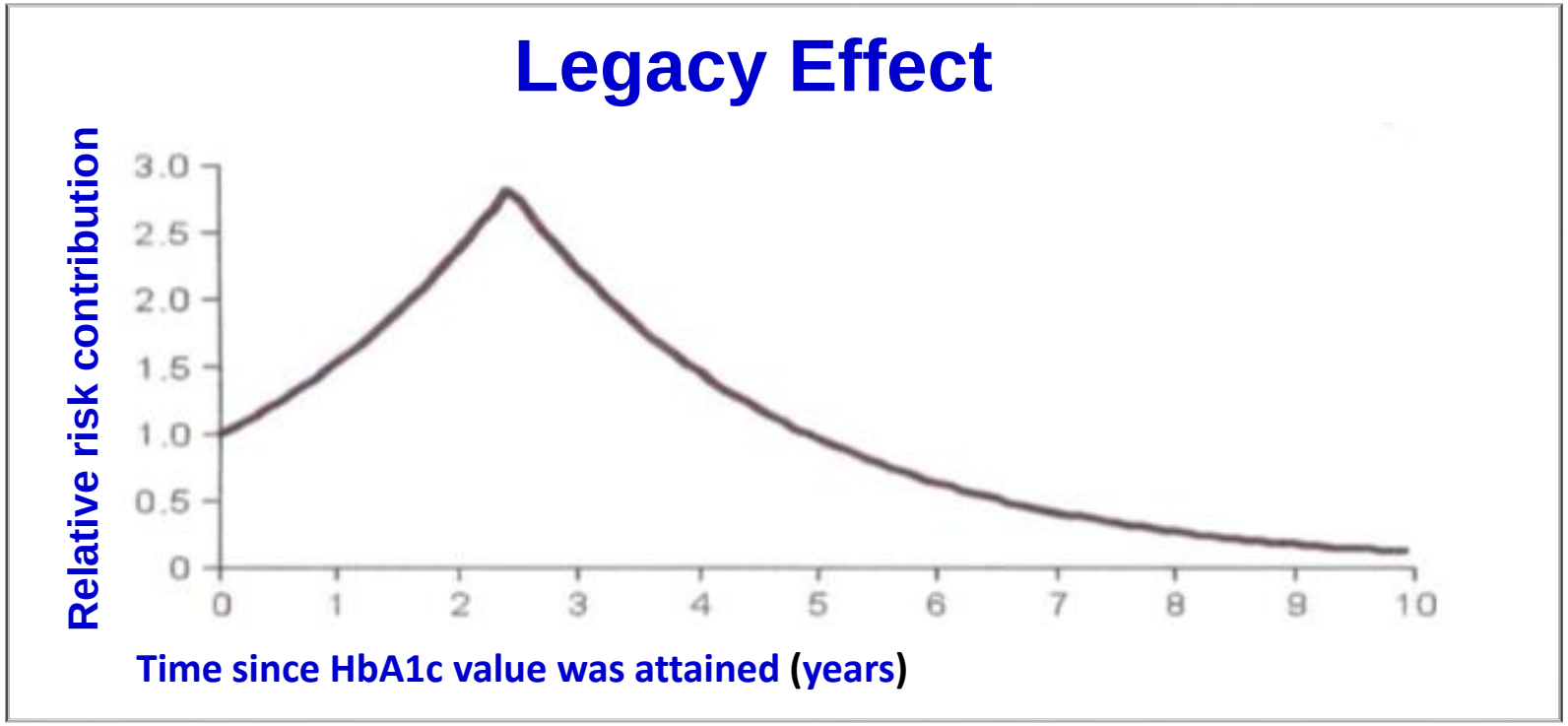


CGMS Analysis: HbA1C 6.1 → 6.3% MDI Therapy





Legacy Effect: Contribution of HbA1C Over Time



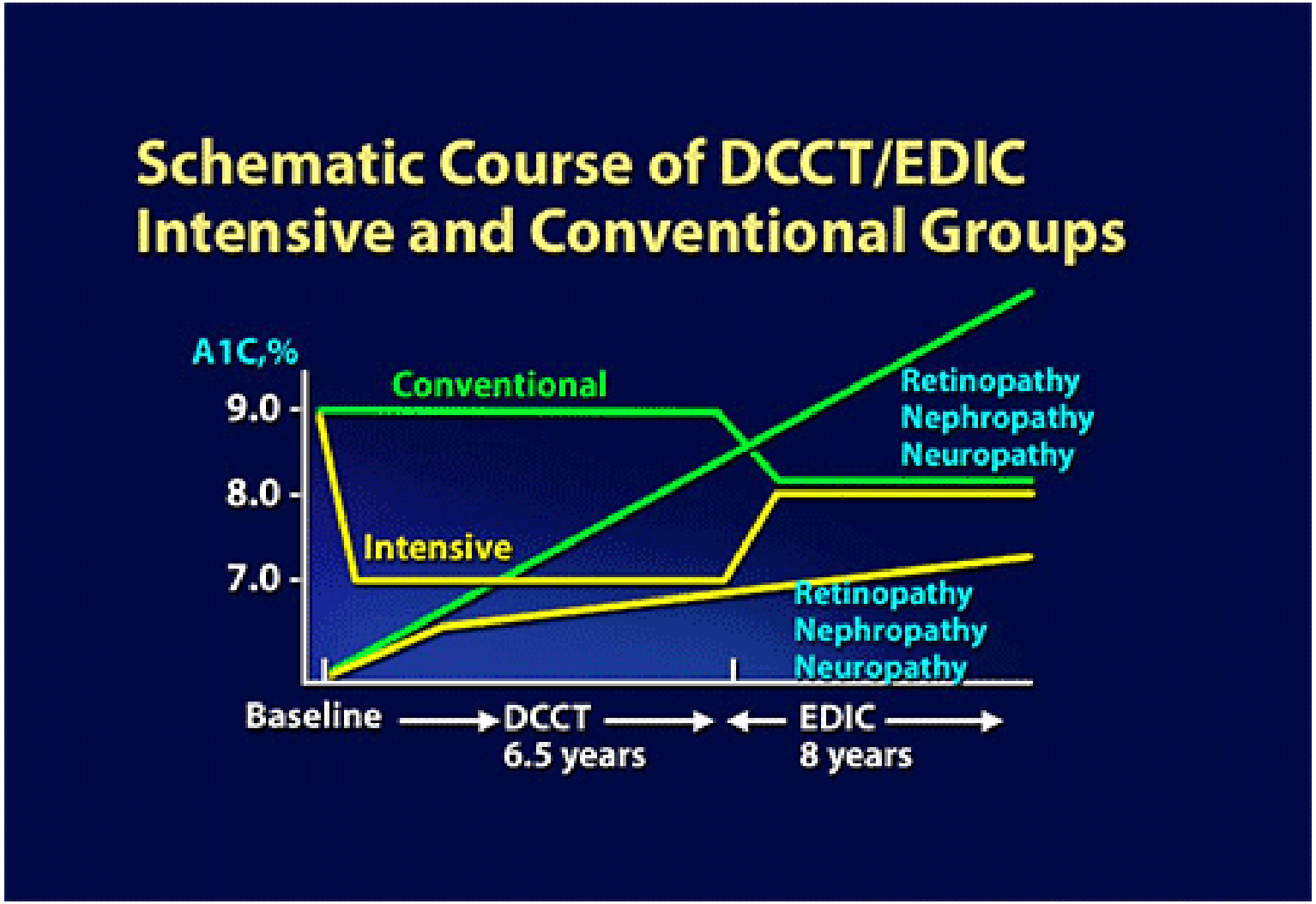
Relative contribution of HbA1c values at different past-points in time to future risk of retinopathy progression

For HbA1C values 2.4 years ago, the relative contribution is ≈ 80%.

For HbA1C values of 6.5 and 8.4 years ago, the contribution is 50% and 25% respectively.

Lind, M., Oden A., Fahlen, M., Eliasson, B (2010). The shape of the metabolic memory of HbA1c: re-analysing the DCCT with respect to time-dependent effects. Diabetalogia, Jun;53(6): 1093-8

DCCT: Legacy Effect of Earlier Glucose Control



UKPDS: Legacy Effect of Earlier Glucose Control

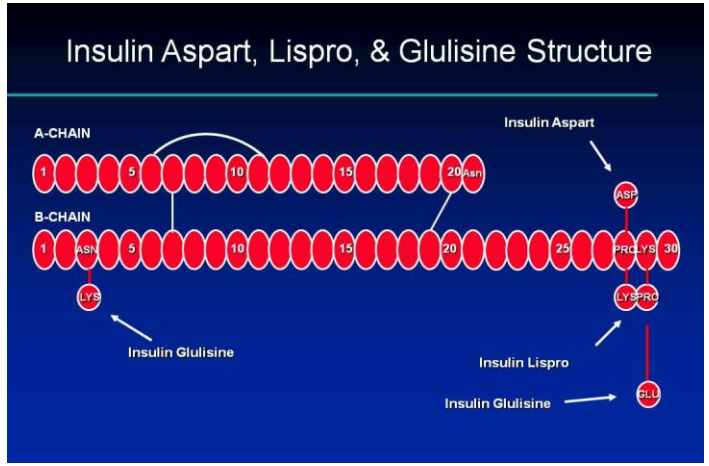
After median 8.5 years post-trial follow-up

Aggregate Endpoint		**1997**	**2007**
Any diabetes related endpoint	*RRR:*	**12%**	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	**25%**	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	**16%**	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	**6%**	**13%**
	P:	0.44	**0.007**

Holman R, et al. *N Engl J Med* 2008;359.

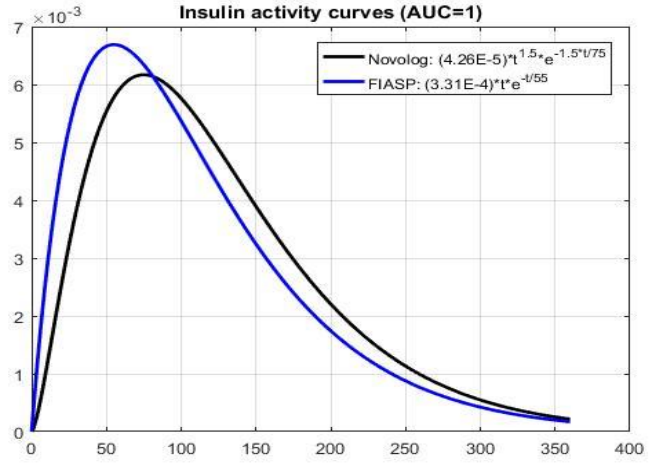
Analogue Insulins: Unique Considerations

- **Insulin Aspart Rapid-acting (Novolog):**
  - Single amino acid substitution at **B28** (Proline →Aspartic Acid)
    - Humalog is a "molecular reversal" of proline (**B28**) and lysine (**B29**)
  - **Zinc-based** product; **pH 7.2-7.6** (Humalog pH 7.0-7.8)
  - Comparatively faster onset compared to Humalog
  - **Administer 5-10 min. before meal** (Humalog 15 min.)



- **Insulin Glulisine (Apidra):**
  - "Dual Substitution": Lysine → Asparagine (**B3**) and Glutamic acid → Lysine (**B29**)
  - **"Zinc-Free"** formulation **accelerates dissociation rate**
  - **Onset of action < 10 minutes**

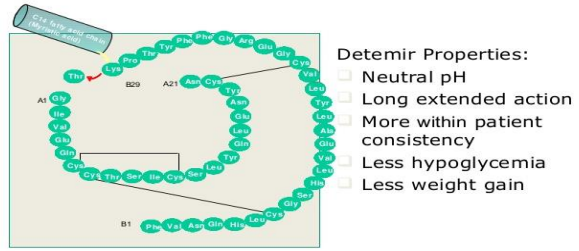
- **Insulin Aspart *Fast-acting* (FIASP):**
  - Novolog insulin product with **2.5 minute onset of action**
  - **Nicotinamide** added to solution to accelerate absorption
  - **Arginine** included as a "stabilizer"



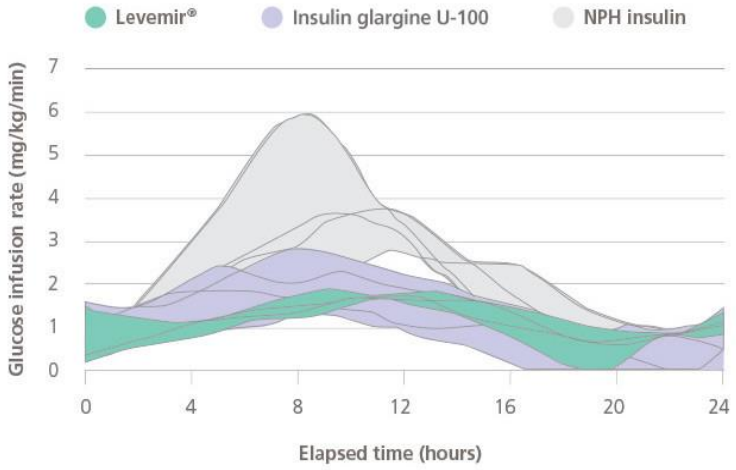
Analogue Insulins: Unique Considerations

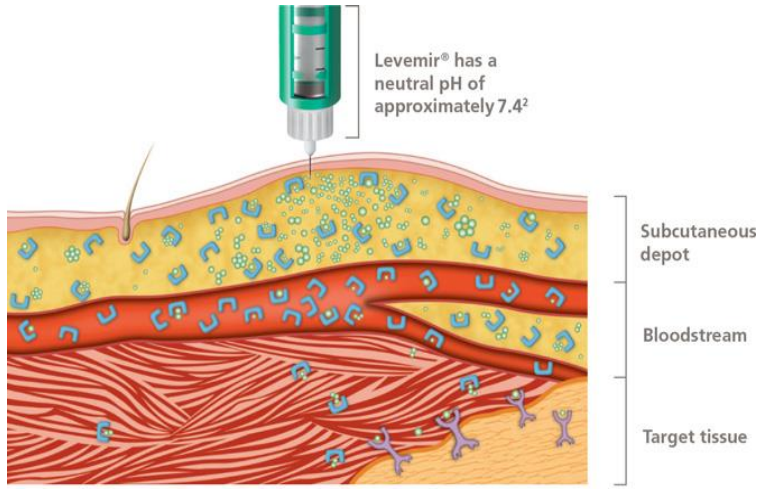
- **Insulin Detemir (Levemir): FDA approved June 16, 2005** (Lantus April 20, 2000)
  - Genetically crafted using Baker's Yeast (***Saccharomyces cerevisiae***)
  - **Molecular Design:**
    - 14-carbon fatty acid (***myristic acid***) moiety covalently bound to Lysine (**B29**)

Insulin Detemir (2004)



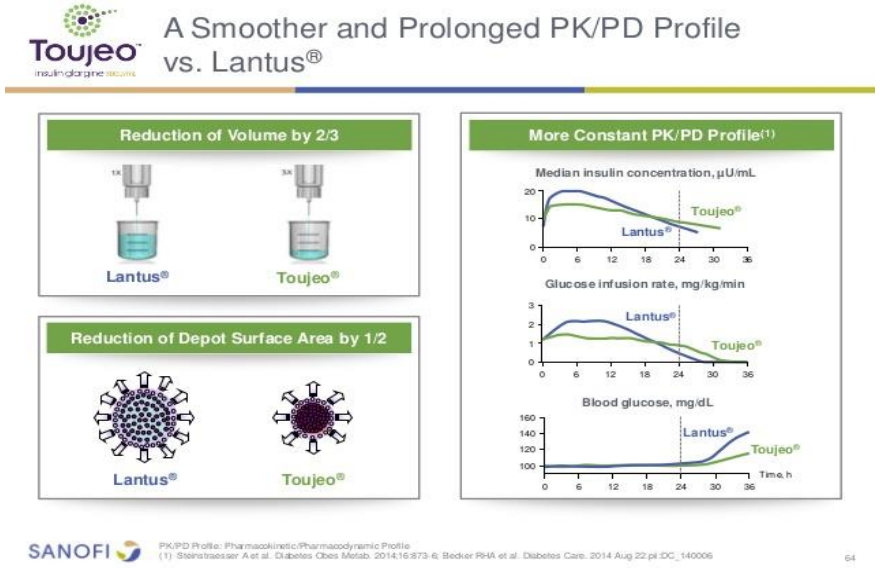
  - **Only insulin to exhibit a weight-sparing effect:**
    - **"Non-precipitant"** formulation offers **less within-subject variability** → less hypoglycemia
    - **C-14 carbon moiety** facilitates **blood-brain-barrier penetration** → hypothalamic satiety centers
    - **C-14 carbon moiety** encourages **reversible-albumin-binding capability** → hepatic insulin extraction → limits peripheral lipogenesis





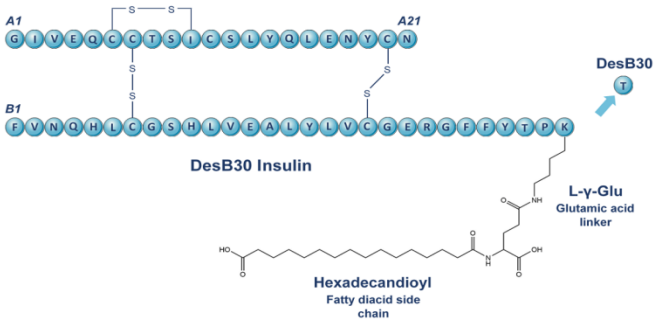
Analogue Insulins: Unique Considerations

- **Insulin Glargine U-300** (**Toujeo**) – "concentrated" form of Glargine U-100
  - **Molecular Design**:
    - 2 arginine amino acids attached to B-chain C-terminus and A21 substitution (asparagine → glycine).
    - **Compact Insulin Formulation**/**smaller surface area**
    - Formulation reduces dissolution rate
    - "Near-Flat" PK/PD profile → more gradual onset → prolonged release.
  - Starting dose is 1:1 match with any current analogue basal agent or 80% of NPH dose.
  - Transitioning from Glargine U-300 → Glargine U-100: Glargine U-100 dose **≈80%** of Glargine U-300 dose.
  - **BRIGHT 24-week Study** (**June 2018**): Toujeo Non-Inferior compared to Tresiba:
    - HbA1C reduction
    - Hypoglycemic event rate (**23%**)
    - Hypoglycemic incidence rate (**26%**)

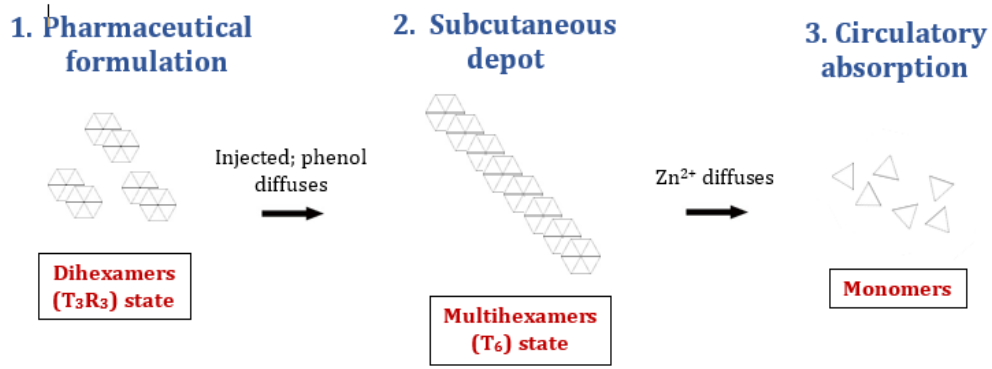


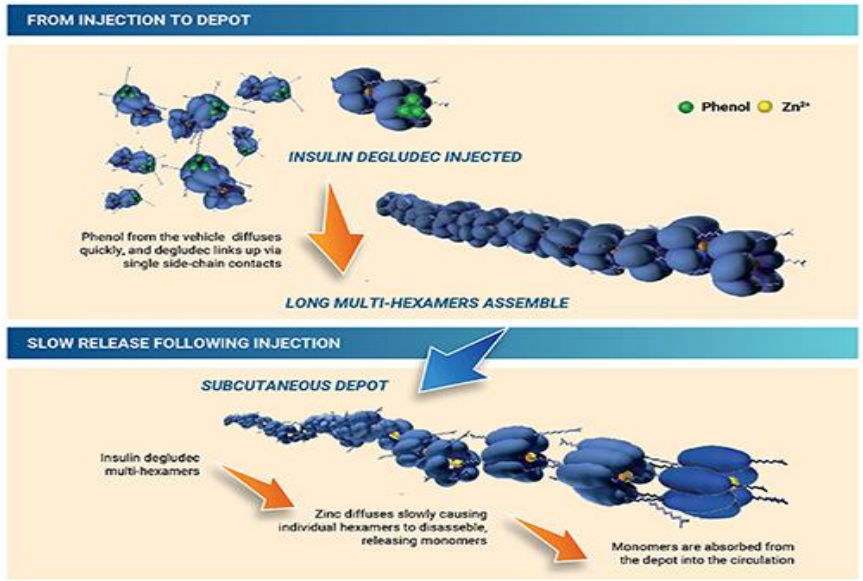
Analogue Insulins: Unique Considerations

- **Insulin Degludec (Tresiba)**
- **Molecular design**:
  - Threonine (B-30) on insulin B-chain **cleaved**
  - **16-carbon fatty diacid side chain** attached to Lysine (B-29) using Glutamate spacer.



- **25-hour ½-life**; 100% steady-state after 8 injections (***90% after 4 injections***)
- Peak level achieved by **8-12 hours**
- **Lasts up to 42-hours** (**detected in blood → 96 hours**).
- **SWITCH Study (July 2017): Tresiba with less Hypoglycemia/Nocturnal Hypoglycemia vs. Lantus**
  - **SWITCH 1 (Type 1 DM): 35% Overall; 36% Nocturnal**
  - **SWITCH 2 (Type 2 DM): 30% Overall; 42% Nocturnal**





Tresiba Mechanism of Action

Benefits of Early Insulin Therapy

- **Preserve Beta-cell function**:
  - restoration of "first-phase" insulin release?
- **Improve Lipid Metabolism**
- **Reduced mortality Post-MI**:
  - Post-prandial glycemic control?
- **Early control → "anti-inflammatory" mechanisms**, reducing macrovascular/microvascular risk:
  - Suppression of intranuclear transcription factor κβ → transcription of proinflammatory cytokines

- **Studies suggest**: **early tight control** achieves and sustains **glycemic stability for extended periods** with less medication.
- **UKPDS (Type 2 DM): B-cell failure progressive**
  - **At time of diagnosis** – 50% normal beta-cell function likely exists
  - By the **time insulin therapy implemented** – 25% function exists
  - **53% of patients treated with SUs** required insulin therapy by **6-years** → **80% by 9-years**
- Reduced morbidity → Net cost reduction
- Diabetes-related costs **≈15%** of the U.S. health-care budget

2018 ADA General Recommendations: Pharmacological Therapy in Type 2 Diabetes

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

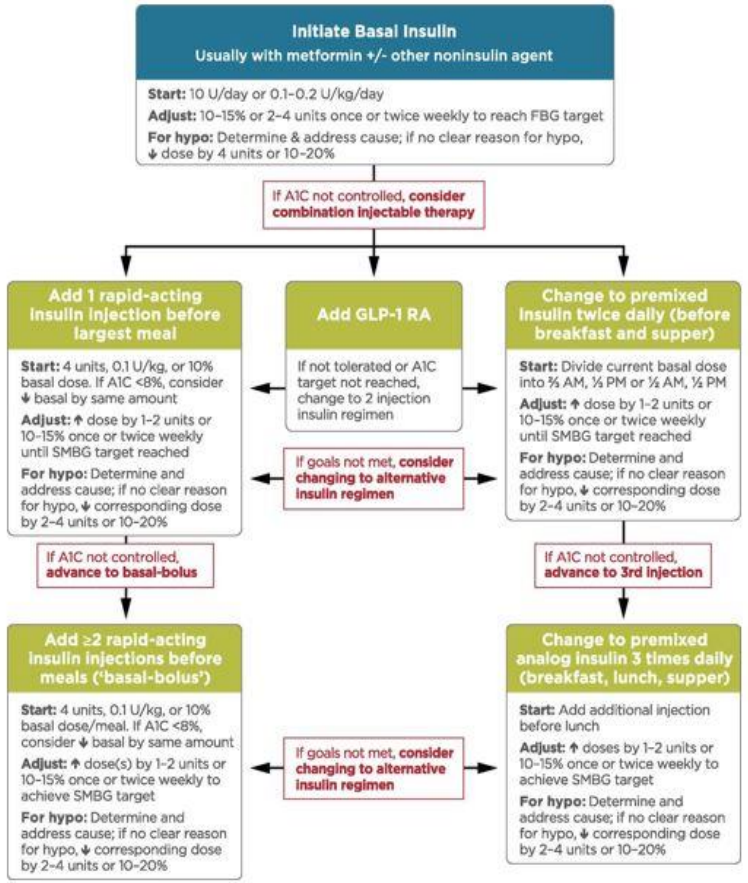
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e.,adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

2018 ADA General Recommendations: Pharmacological Therapy in Type 2 Diabetes

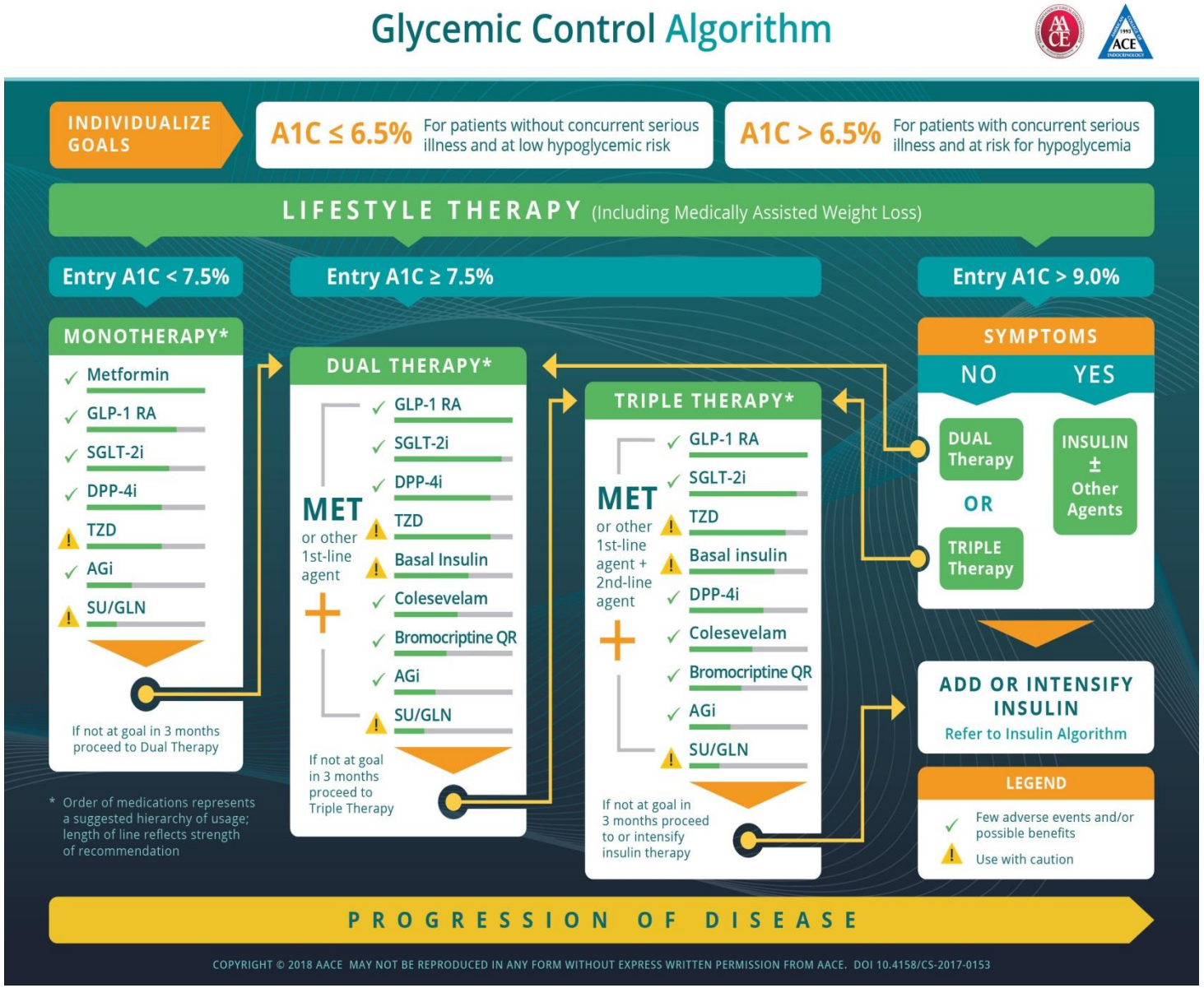
Combination injectable therapy for type 2 diabetes.



American Diabetes Association Dia Care 2017;40:S64-S74

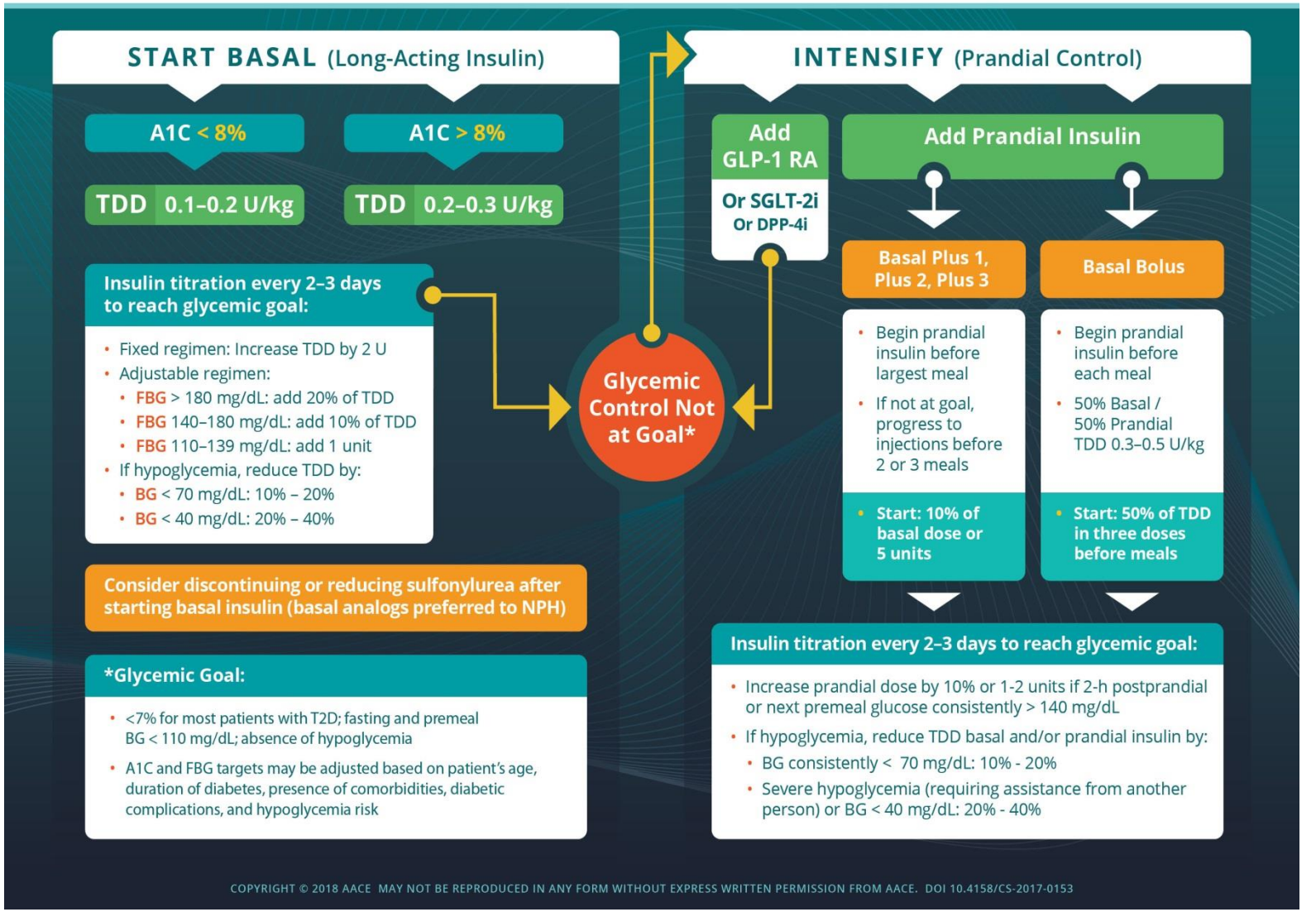
American Diabetes Association.

2018 AACE General Recommendations: Pharmacological Therapy in Type 2 Diabetes



2018 AACE General Recommendations: Pharmacological Therapy in Type 2 Diabetes

Algorithm for Adding/Intensifying Insulin



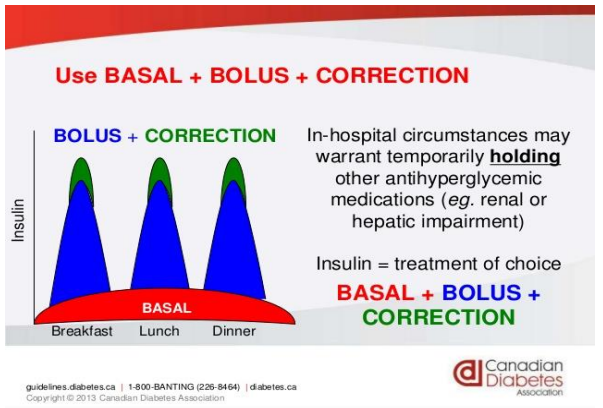
Injectable Insulin Strategies

Non-Physiologic

- **Split-Mixed Regimens**:
  - NPH + "**analogue**"**-R** or "**Human Regular**"**-R**"
  - Each provides a **basal** and **prandial** effect
  - Example → Morning mixed dose:
    - **R** contributes primary prandial-effect for breakfast, secondary prandial for lunch, and basal effect post-breakfast
    - **NPH** contributes basal-effect post-breakfast and Lunch, and primary prandial effect for lunch
  - Requires meticulous attention to life-style organization
  - Risk of "Late-morning overlap" → hypoglycemia
- **Sliding Scale Protocols**:
  - Should be avoided
  - **Retrospective decision-making**

Physiologic

- **Intensified Regimens**
  - True Basal Insulin + OAD agents
  - True Basal Insulin + "selective Prandial" insulin
  - **Basal-Bolus + "correction insulin"**
    - **Dosing flexibility**
    - **Predetermined versus Calculated dosing**
    - **More efficient post-prandial recovery**
    - **Prospective intervention**
    - **Avoid "Insulin Stacking"**



Basal-Bolus Protocol

Developing a "Recipe"

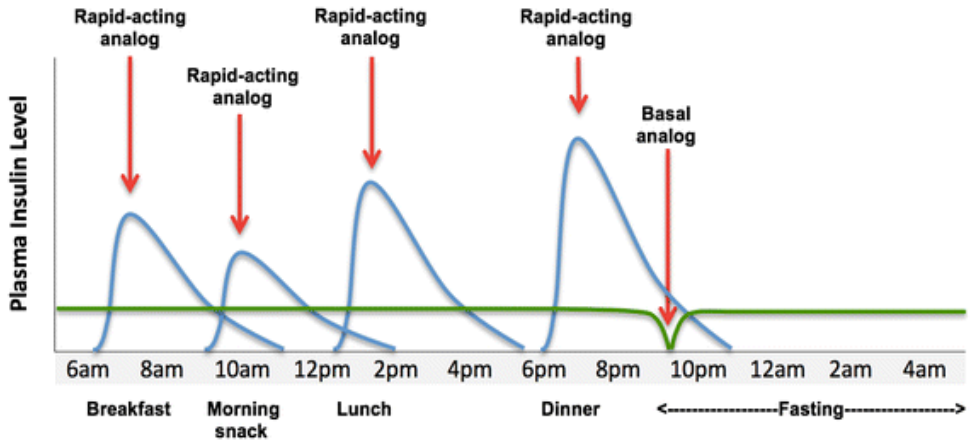
Initiating SC Basal Bolus

- Starting total dose = 0.5 x weight (kg)
  - If weight is 100 kg: 0.5 x 100 = 50 U
- Basal dose (insulin glargine) = 50% of starting dose at HS
  - 0.5 x 50 = 25 U at HS
- Bolus doses (analog preferred) = 50% of starting dose
  - 0.5 x 50 = 25 divided by 3 = ~8 U PC (TID)
- Correction bolus = (BG – 100)/CF, where CF = 1700/total daily insulin dose; CF = 30

- When initiating Basal-Bolus regimen, **reduce calculated basal dose by 20%** to avoid hypoglycemia:
  - **1/3 will receive correct dose**
  - **1/3 will need more**
  - **1/3 will need less**

Clinical considerations:

- If using "correction insulin" between meals:
  - **Remain aware of "insulin-stacking"**
- If **using "correction insulin" ≤ 3-hours** after a prandial dose, **reduce the "correction" by 50%.**
- **If exercising early** in the post-prandial period (1-3 hours), **reduce the prandial insulin dose by 75%**



Typical Basal-Bolus Protocol

Mealtime Insulin: FIASP		Breakfast	Lunch	Dinner	Bedtime
		8	8	8	0
Correction: FIASP		Breakfast	Lunch	Dinner	Bedtime
	<80 mg/dL	0	0	0	0
	81-120 mg/dL	0	0	0	0
	121-160 mg/dL	1	1	1	0
	161-200 mg/dL	2	2	2	0
	201-250 mg/dL	3	3	3	0
	251-300 mg/dL	4	4	4	0
	301-350 mg/dL	5	5	5	0
	351-400 mg/dL	6	6	6	0
	>401 mg/dL	7	7	7	0
Basal Insulin: TRESIBA					25

The Problem with "Sliding Scales"

- **Little evidence for therapeutic efficacy**
- **Fluctuating glucose levels more harmful** → **oxidative stress** → **vascular endothelial damage**
- **Meal time insulin is "comprehensively" based on an isolated value** (activity, caloric variability, "other stressors" NOT CONSIDERED)
- **"Skipping a dose"** when glucose is **below a cutoff point** leaves patient without insulin for hours
- **Failure to individualize insulin protocols** (i.e. age, weight, type of insulin, time of day, caloric variability, type of diabetes??)
- Incorporating basal insulin will not offset peaks and dips in blood glucose

MacMillan DR. The fallacy of insulin adjustment by the sliding scale. J Ky Med Assoc. 1970; 68:577-579.

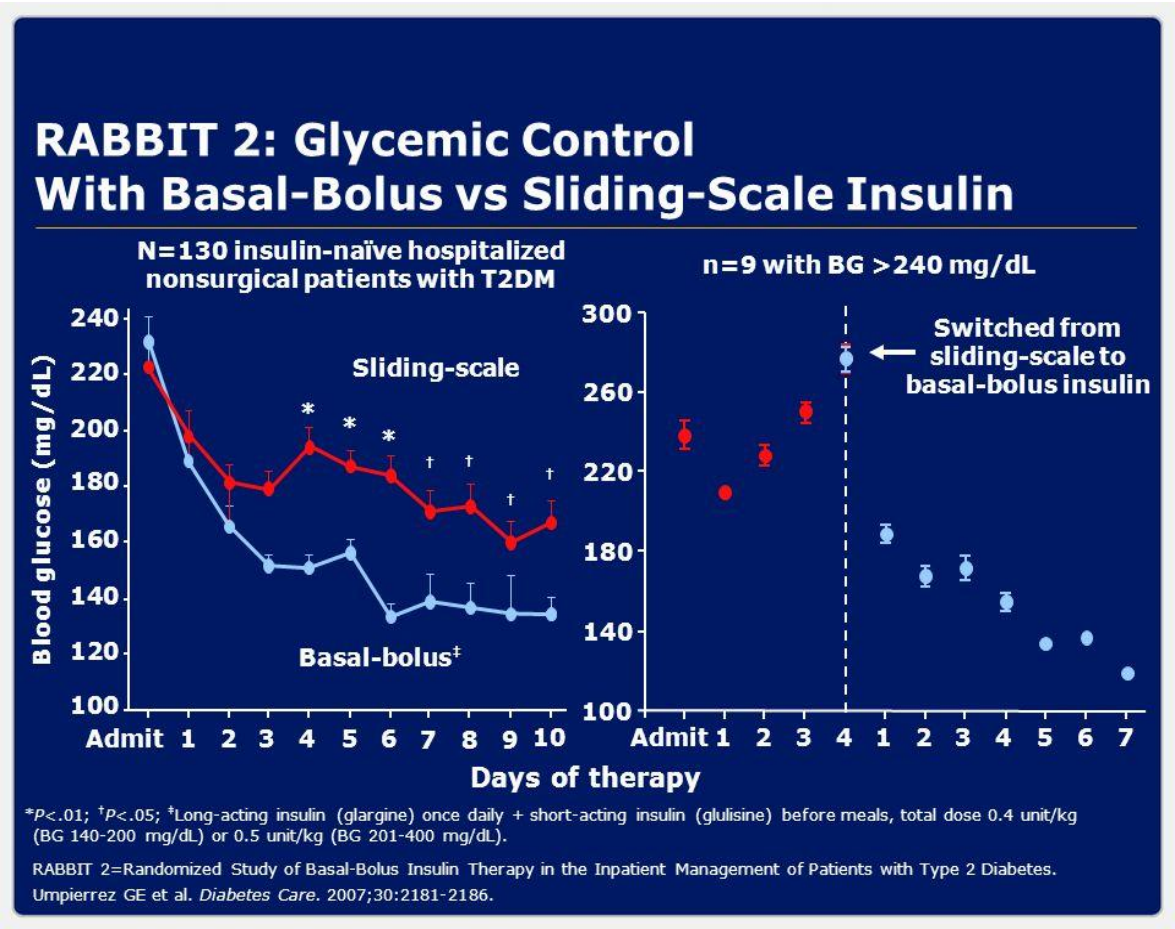
Robbins L. Let's get the sliding scale out of medicine. Med Rec Ann. 1963; 56:201.

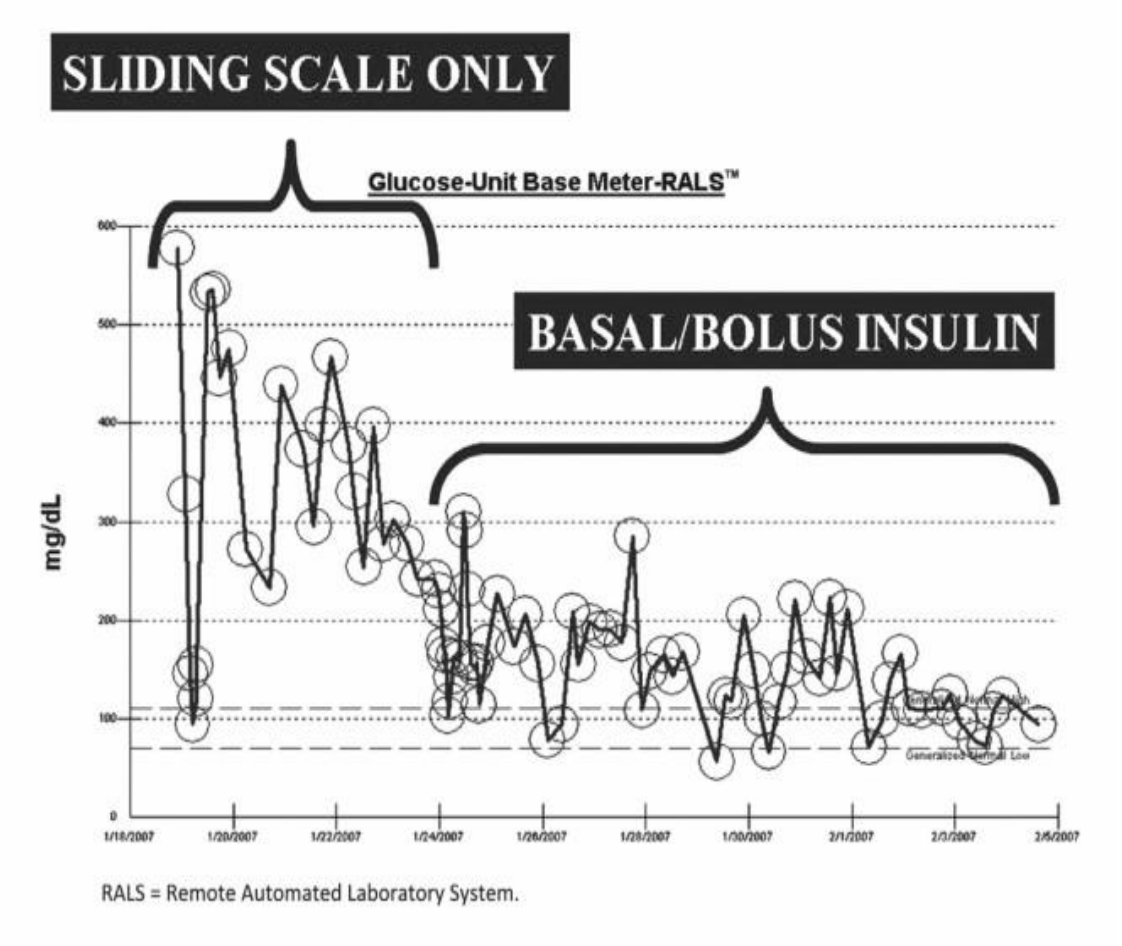
Umpierrez GE, Palacio A, Smiley D. Sliding scale insulin use: myth or insanity? Am J Med. 2007; 120:563-567.

Rains JL, Jain SK. Oxidative stress, insulin signaling, and diabetes. Free Rad Biol Med. 2011; 50:567-575.

Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295:1681-1687.

The Problem with "Sliding Scales"

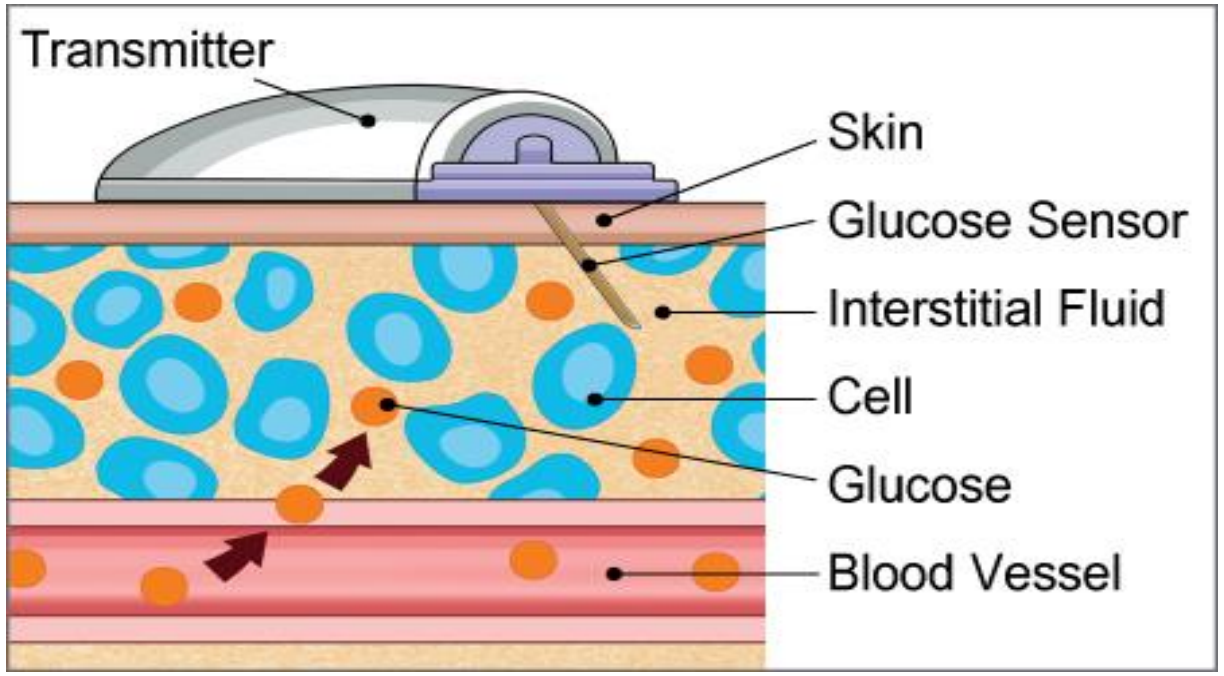


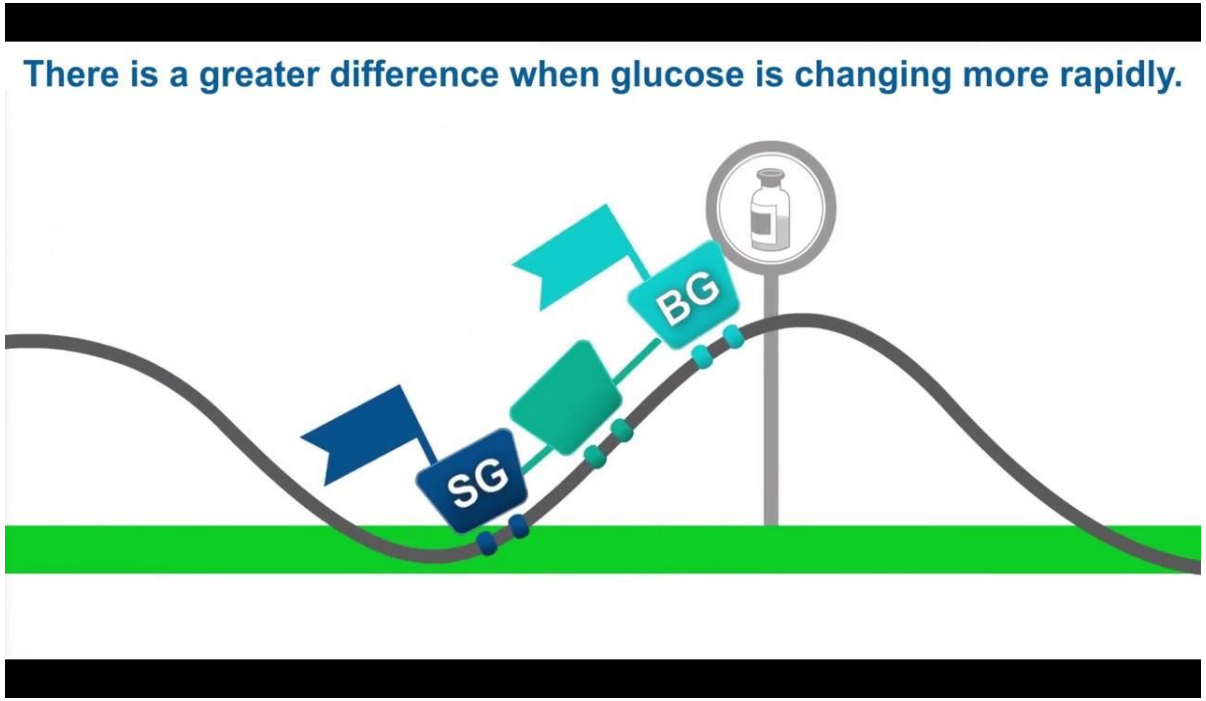


Umpierrze, GE., Smiley, D. Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial). Diabetes Care 30:2181–2186, 2007

Umpierrez, GE, Smiley, D. Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery). Diabetes Care. 2011 Feb; 34(2): 256–261.

CGMS Technology reflects Interstitial Glucose





CGM sensors should be worn continuously

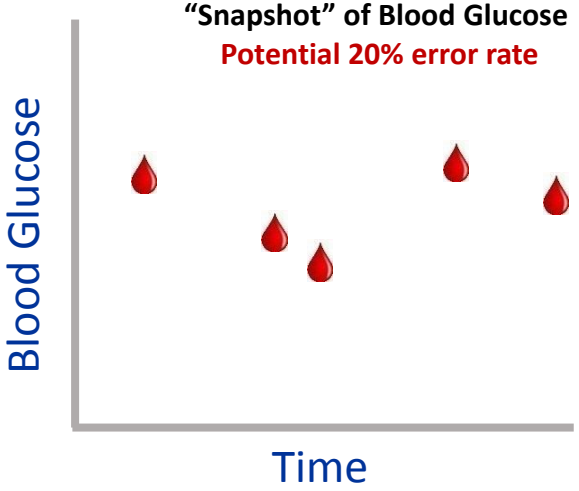
CGM indicated as an adjunct to SMBG and does not replace SMBG

SMBG

(Self Monitoring Blood Glucose)

"Snapshot" of Blood Glucose

Potential 20% error rate



Measures Capillary Whole Blood glucose

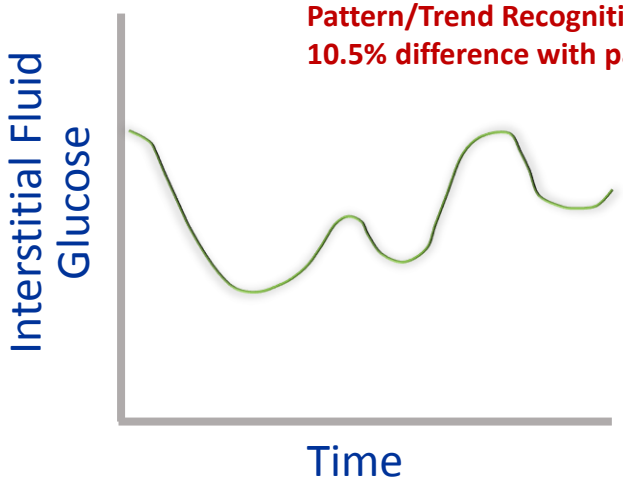
1-12+ Readings per day

CGM

Rate change

Pattern/Trend Recognition → 24-hour surveillance

10.5% difference with paired laboratory reading



Measures Interstitial fluid glucose

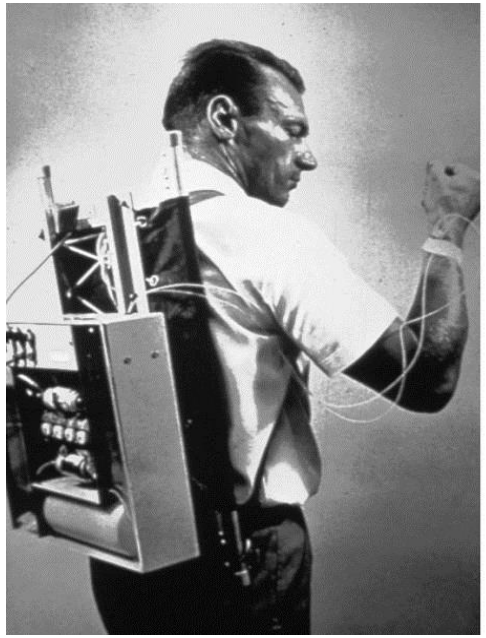
Up to 288 readings per day

- **CGM and SMBG measure glucose in different compartments**

Insulin Pump Technology: A Brief History

Dr. Arnold Kadish, 1963

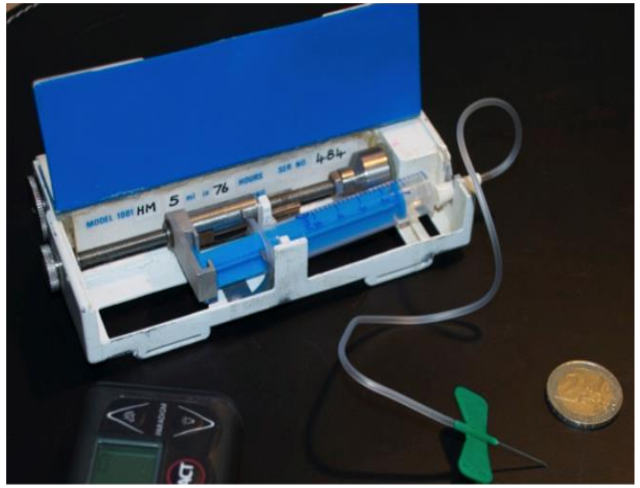
First Prototype Insulin Pump



Delivers Insulin and Glucagon

1976

Mill Hill Infusor

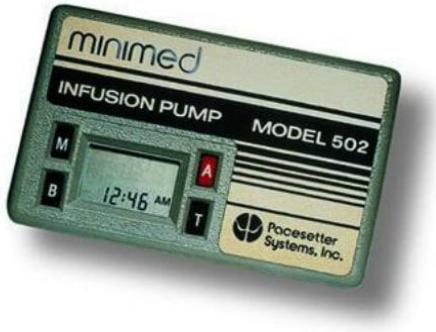


Battery-operated syringe

allows continuous release of insulin

1983

MiniMed® 502 Pump

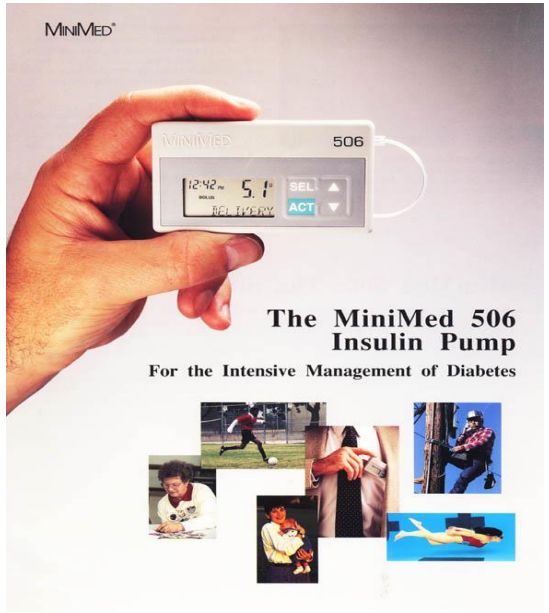


Medtronic's First pump

(502A improves size/programming)

1992

MiniMed® 506 Pump



Offered meal bolus memory

and daily insulin totals

Insulin Pump Technology

November 2011

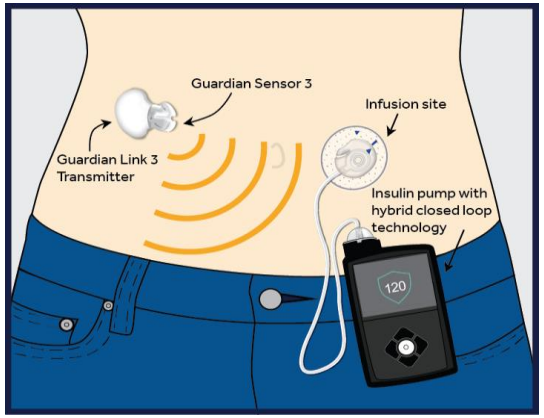
Tandem t:slim X2™ + G6® CGM

November 2012

Omnipod Tubeless Insulin Pump

September 2016

MiniMed® 670G Pump



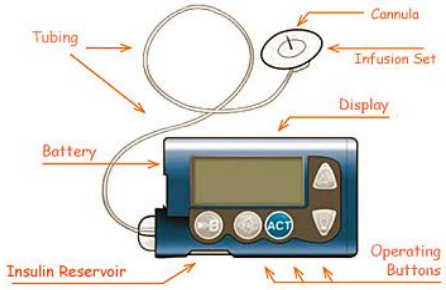
Pump Basics

- Size of a pager

PUMP → 

PAGER → 

- Insulin is stored in a disposable cartridge (reservoir) and delivered by a small catheter inserted into the SQ fat layer



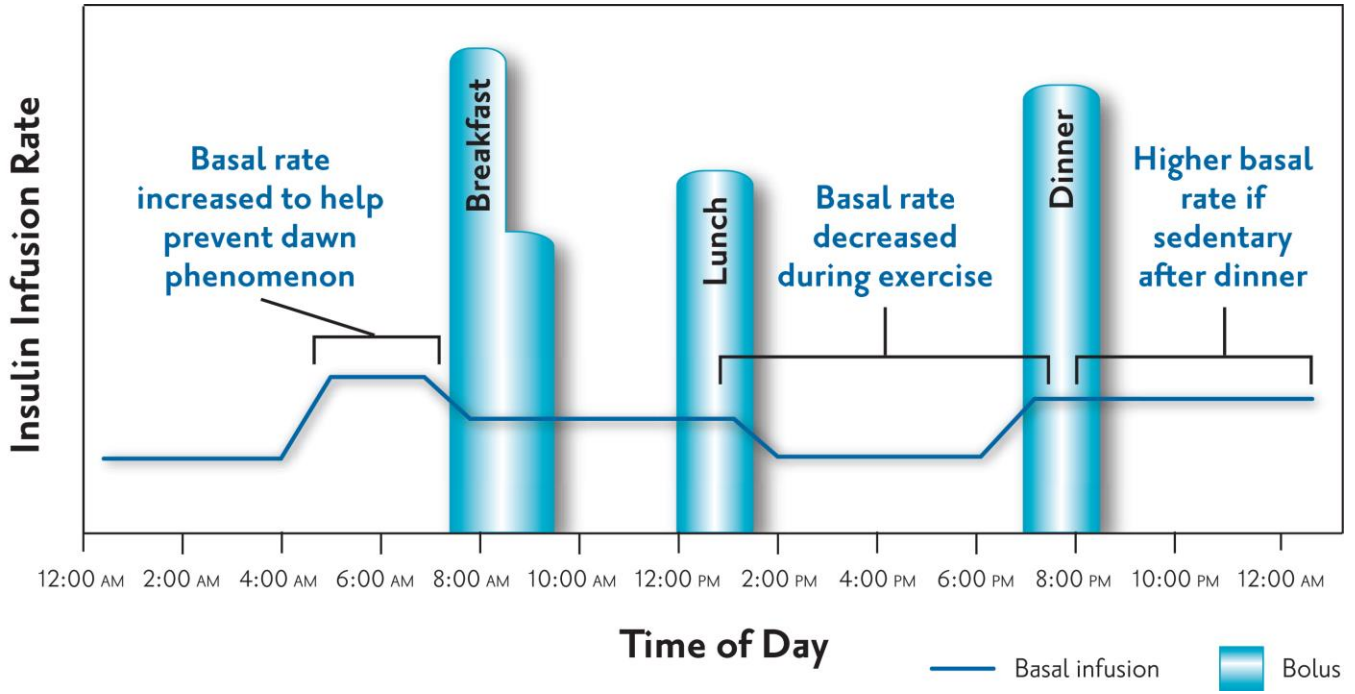
- The **catheter** (part of an infusion set) and **insulin reservoir** are removed and **changed every 2-3 days**

- Only **ONE type** of Insulin is used **(Humalog, Novolog, Apidra ……. Fiasp??)**

- Infusion-set attachment sites (SQ fatty skin layer) are the same used for MDI therapy:
  - **abdomen, back of the arms, upper buttocks, and thighs**

Radermecker R.P., Scheen A.J. Continuous subcutaneous insulin infusion with short-acting insulin analogues or human regular insulin: Efficacy, safety, quality of life, and cost-effectiveness. Diabetes Metab. Res. Rev. 2004;20:178–188.

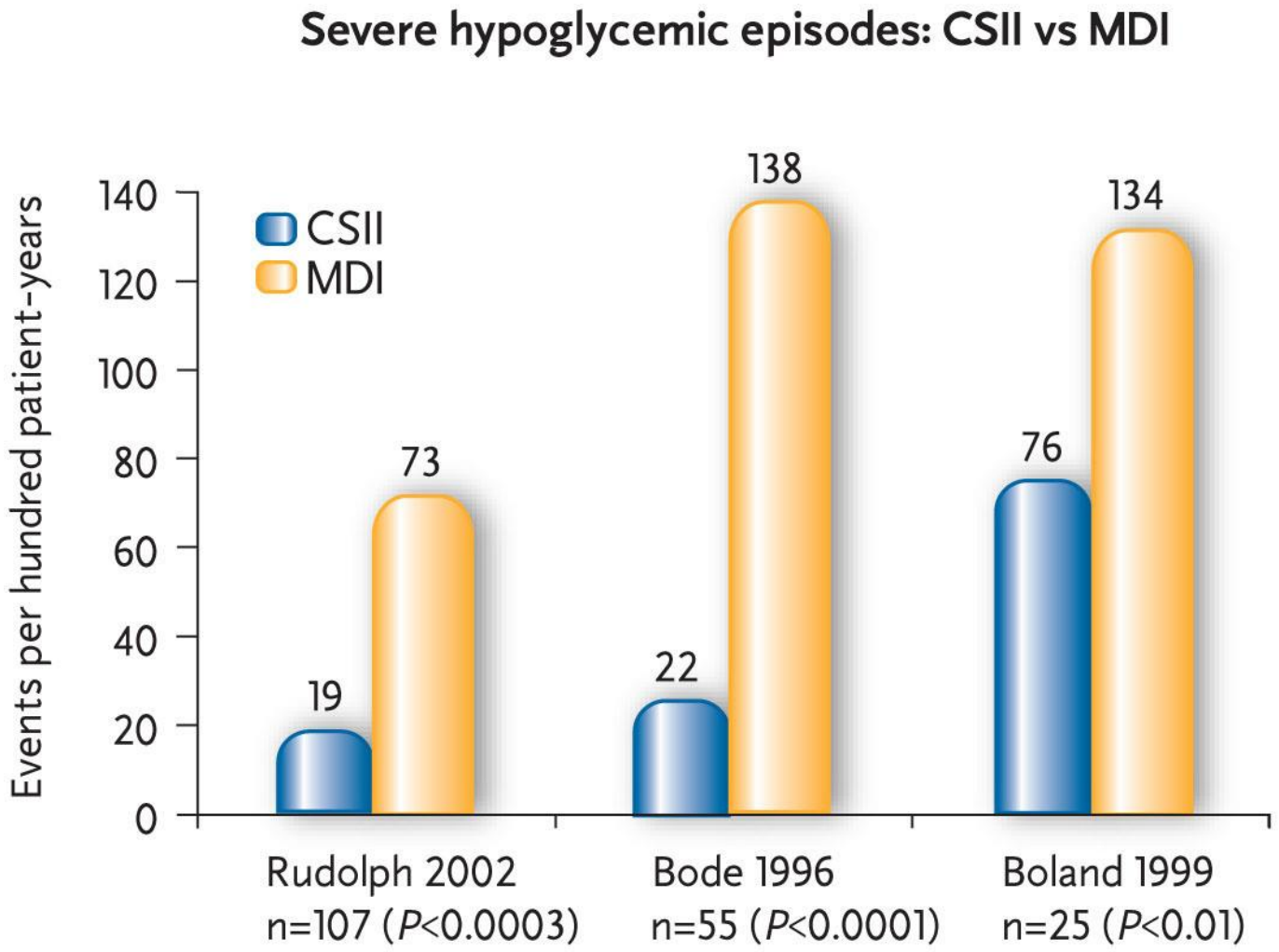
Insulin Pumps Can Deliver **Customized Basal Infusion Rates** at Increments **as low as 0.01 units/hour** over 24-hours to Modulate Hepatic Gluconeogenesis, avoid Nocturnal Hypoglycemia, etc.



Upon entering food **carbohydrate content** and **blood sugar level**, pumps accurately calculate **"pre-meal"** and glycemic target **"correction"** insulin requisites

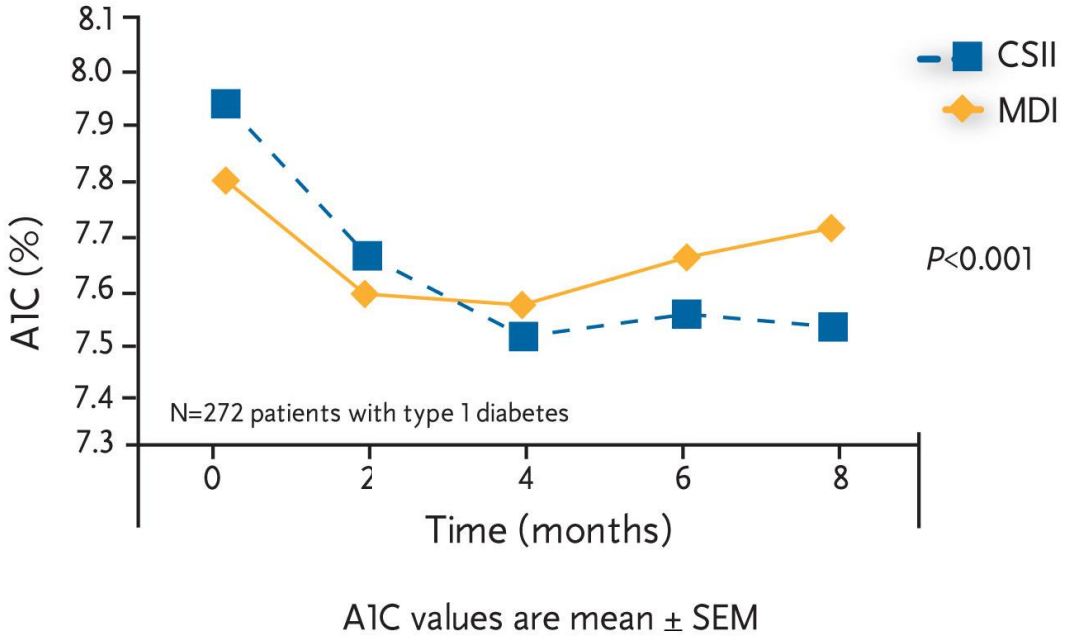
Lenhard MJ, Reeves GD. *Arch Intern Med.* 2001;161:2293-2300.

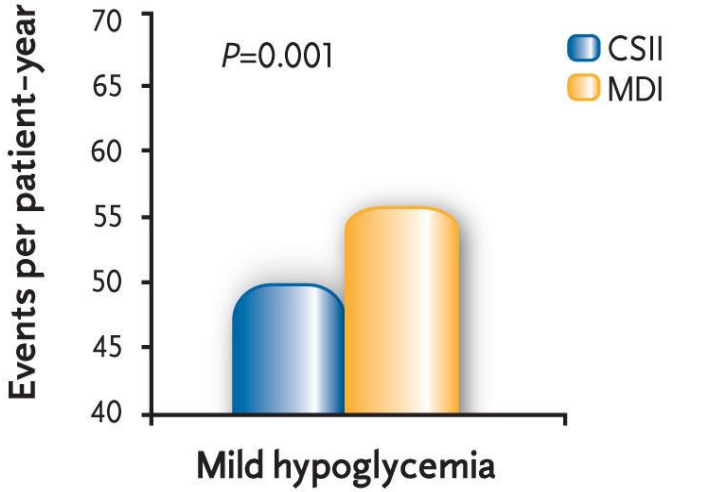
CSII Reduces Incidents of Severe Hypoglycemia

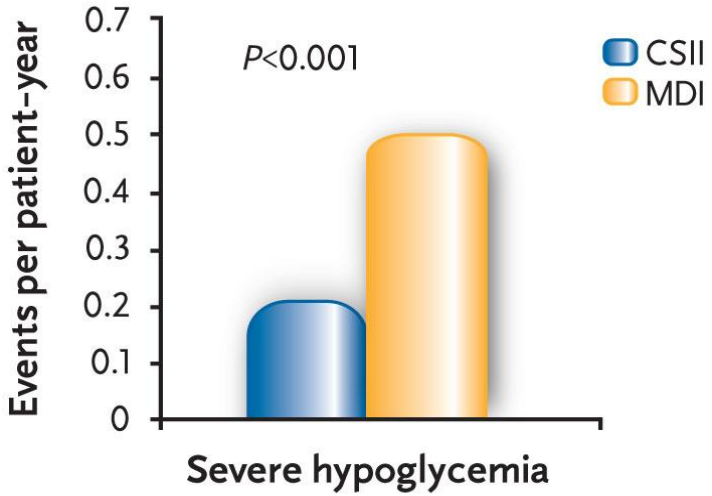


Rudolph JW, Hirsch IB. *Endocrine Practice.* 2002; 8:401 – 405.
Bode,BW, Steed RD, Davidson PC. *Diabetes Care.* 1996;19:324-7.
Boland EA, Grey M, Oesterle A, et al. *Diabetes Care.* 1999; 22:1779 – 84.

In the 5-Nations Study
CSII Improved HbA1C
without Increased Risk of Hypoglycemia







Hoogma RP et al. *Diabet Med*. 2006;23:141-147.
GINSS ; Type 1 DM; CSII vs. MDI with NPH

CSII Helps Reduce Daily Insulin Requirements in Type 2 Patients

	Insulin		A1C	
	Before CSII	Post 1-Yr CSII Use	Before CSII	Post 1-Yr CSII Use
Patient 1	630 u/day	111 u/day	10.3%	5.7%
Patient 2	402 u/day	315 u/day	10.4%	7.6%
Patient 3	218 u/day	81 u/day	7.5%	6.2%
Patient 4	Patient 4 is not included in this analysis because he was not on CSII for 1 year.			

Neilsen et al., *Diabetes Educator* 2005 Vol. 31

Pump Pros and Cons

PROS

- "**Micro-Management**" **of Insulin Delivery** → Less glucose variability (**standard deviation**)
- Reduction in number and severity of hypoglycemic episodes → **improved quality of life**
- **No injections**; discreetness of insulin administration
- **Reduced hospitalizations due to hypoglycemia/DKA**
- Patient generally becomes **better educated** & **more independent**
- **Bolus calculator**, prevents insulin stacking; provides **precision of dosing** → **up to 25-30% less insulin**

CONS

- **Mechanical device attached to body**
- **Perception of weight gain** (not necessarily so)
- **Extra cost** of pump and supplies
- Time and **personnel needed** to initiate, supervise, and fine-tune therapy (**patient participation crucial**)
- **More rapid** (not more frequent) **onset of DKA** if insulin delivery interrupted for extended periods.
- **Infusion site infections** (**rare**) or irritation, leading to inadequate insulin absorption (minimized by **maintaining scheduled visits for remedial care and education**).

Choosing the Right Candidate

- **Patient is motivated** to accelerate their management and invest time to learn.
- **MDI/Basal-Bolus regimen no longer meets treatment goals**.

- **Patient experiencing** …….
  - **Frequent hypoglycemia**; Hypoglycemic unawareness
  - **Unpredictable fluctuations** in blood glucose levels
  - **Gastroparesis**

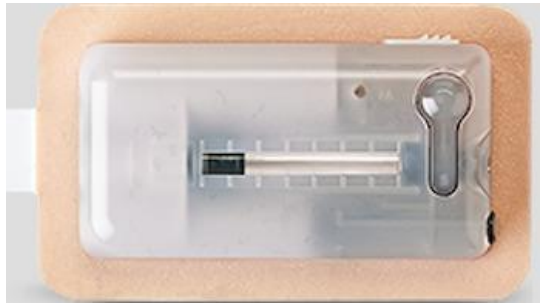
- Children/young adults who desire more **life-style flexibility**
- Challenging glycemic control with **adolescent "growth spurt"**

- **Preconception planning and pregnancy**

Pump Technology Options

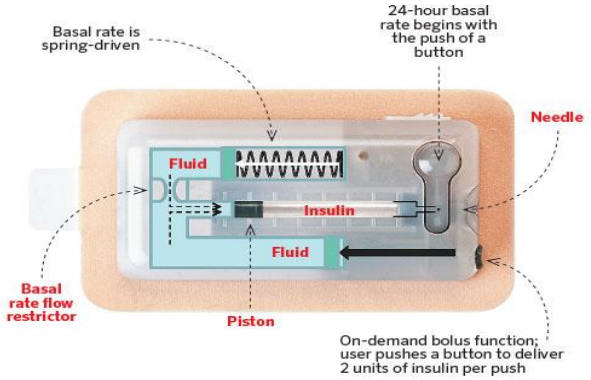
V-Go Insulin Delivery System

- **Wearable insulin delivery device** for adults managing **Type 2 diabetes**.
- **Does not require batteries, electronics, or software to function**.
- **Does not have tubes, cannulas, monitors, or alarms**.
- **Insulin advances via spring-activated hydraulic system**



Insulin Delivery for Type 2 Diabetes worn like a patch

- **It's worn like a patch; Discreet**
- Simply place on skin (such as arm or stomach area), click a button, and wear it 24-hours
- **Use ONE type of insulin (Humalog, Novolog, Apidra)**
- Can translate into **30% less insulin** per day
- "Just Stick It and Click It"



V-Go Option	Preset Basal Insulin Rate Over 24 Hours	+	Available Prandial Insulin†	=	Total Available Insulin
VGO 20	20 Units	+	36 U†‡	=	56 Units
VGO 30	30 Units	+	36 U†‡	=	66 Units
VGO 40	40 Units	+	36 U†‡	=	76 Units

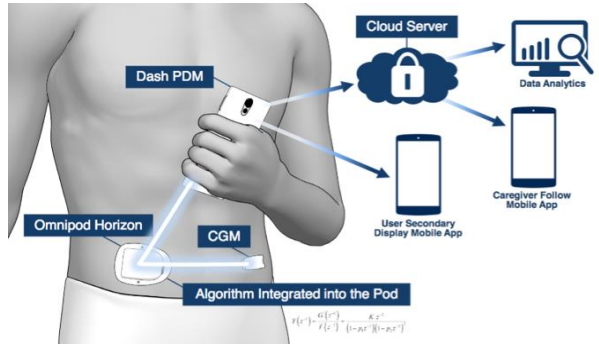
Pump Technology Options

Tandem: t:slim X2™ Pump + Dexcom G6® CGM

- **Touchscreen technology;** smallest pump available
- **Capable of remote software updates**
- **Integrated Dexcom G6® CGM with Basal-IQ™ Technology:**
  - **Acquire Glycemic Data without finger sticks**.
  - **High and Low alert settings** indicate when glucose is above or below a preset target range.
  - **NEW Predictive Low Glucose Suspend Algorithm:** Reduces frequency and duration of hypoglycemic events by predicting glucose levels 30 minutes ahead and suspending insulin if expected to drop below 80 mg/dL.
  - **Compatible with iPhone, iPad, iPod touch, any Android Device using OS version 6.0 or later, Android wear watches, Apple watch, etc.**

Omnipod Tubless Insulin Pump

- **Built-in 200-unit insulin reservoir, angled infusion set**
- **Weighs <30 grams**
- **A Tubeless, Waterproof*, Bluetooth®-Enabled Pod**
- **Bluetooth®-Enabled Blood Contour Next One Glucose Meter**
- Color Touch-Screen Personal Diabetes Manager
- **NEW Omnipod Dash™ System**
  - Mobile applications for quick/easy access to SmartPhone Personal Diabetes Manager
  - Ability to share status information by SmartPhone with up to 12 people.
  - ***Today View Widget*** allows **single-screen viewing of CGM and insulin delivery** information on iOS mobile device.
  - Available early 2109



Pump Technology Options

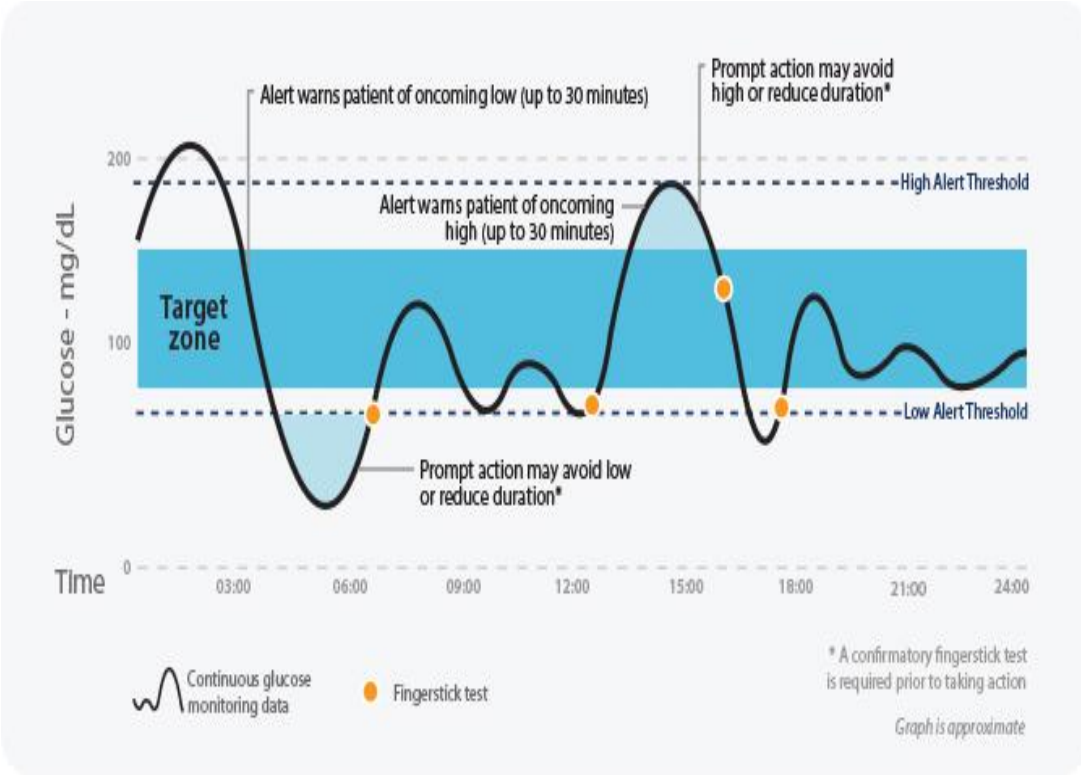
MiniMed 630G + Guardian™ Sensor 3

SmartGuard® Technology

- **High Limit**
  - The high limit can be set from 100 to 400 mg/dL.
- **Low Limit**
  - This can be set from 60 to 90 mg/dL.
- **Alert before High**
  - Receive an alert any time the sensor glucose is predicted to reach preset high limit.
- **Time before High**
  - Determines number of minutes (5-30) before reaching high limit that patient receives an Alert.
- **Alert on high**
  - Receive an alert any time sensor glucose reaches or exceeds high limit.
- **Alert before Low**
  - Receive an alert when sensor glucose is predicted to reach low limit in 30 minutes.
- **Alert on Low**
  - Receive an alert when sensor glucose reaches/falls below preset low limit.
- **Suspend on Low**
  - Pump temporarily stops delivering insulin when sensor glucose reaches/falls below pre-set low limit.

MinMed 630G + Guardian™ Link 3 Transmitter

Alert Before Low & High Features



Threshold Suspend/Suspend-On-Low

Threshold Suspend

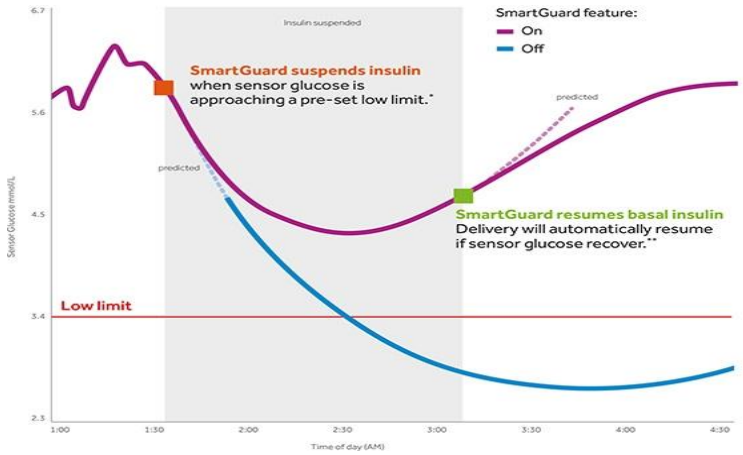
Threshold Suspend

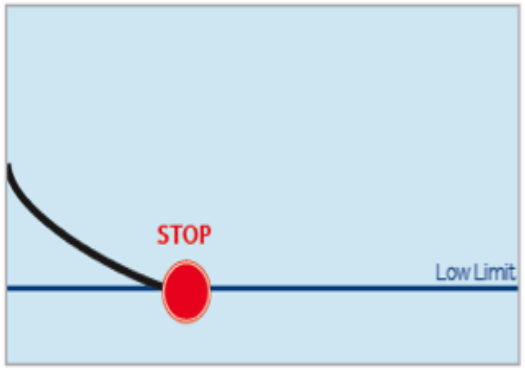
- Automatically suspends all insulin delivery when sensor values reach or fall below Suspend Threshold
- Suspend Threshold is set based on your needs

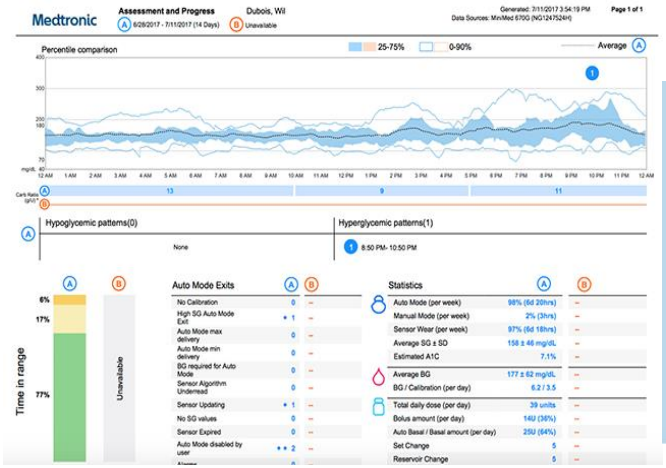
Pump Technology Options

MiniMed 670G System: WORLD'S FIRST HYBRID CLOSED LOOP SYSTEM

- **SmartGuard®** HCL technology (**Guardian® Sensor 3**) offers 3 levels of personalization:
  - ***Predictive Alerts*** → **Alert Before High, Alert Before Low** and **Alert On Low** options
  - ***Suspend Features*** → ***BEFORE Low → ON Low*****:**
    - Suspend **BEFORE LOW**: Proactively avoids lows/rebound highs by **stopping insulin 30 minutes before** a pre-selected low limit is reached, then automatically resumes insulin once glucose levels recover ……. all without bothersome alerts.
    - Suspend **ON LOW**: Pump temporarily **stops delivering insulin** when sensor glucose reaches/falls below pre-set low limit.
  - ***Auto Mode:*** automatically adjusts basal insulin delivery every 5 minutes based upon glucose level to maintain target range of 120 mg/dL, for 24-hours.







Smart Guard™ Technology: Suspend-Before-Low

Pump or MDI: Which Is Better?

CSII offers advantages over MDI therapy, but …..

- Properly selecting pump candidates and adequately training them is key to optimal outcomes.

- As technology continues to advance new challenges and opportunities for patients and practitioners will predictably arise.

- **No better time than the present** to become familiar with pump technology and related operational skill set, as the number of patients with **both Type 1 and Type 2 Diabetes** desiring and using pumps will continue to grow.