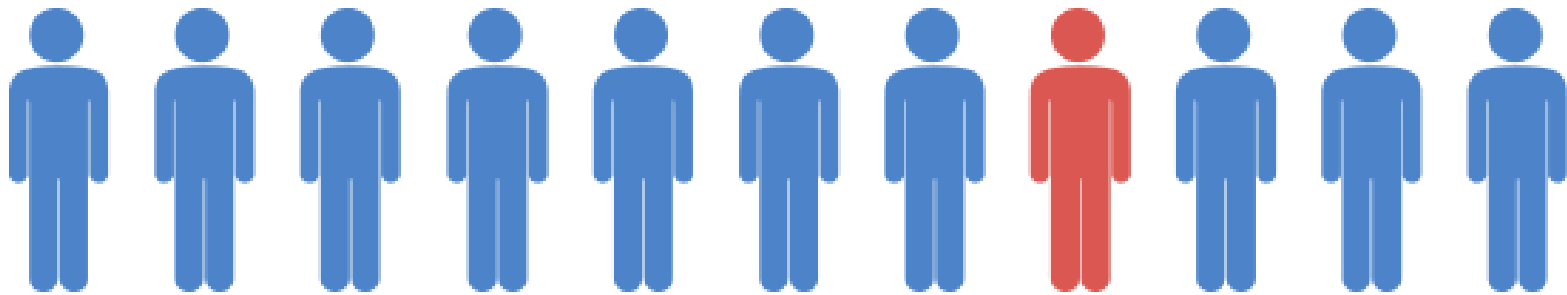


De Artificiële Pancreas

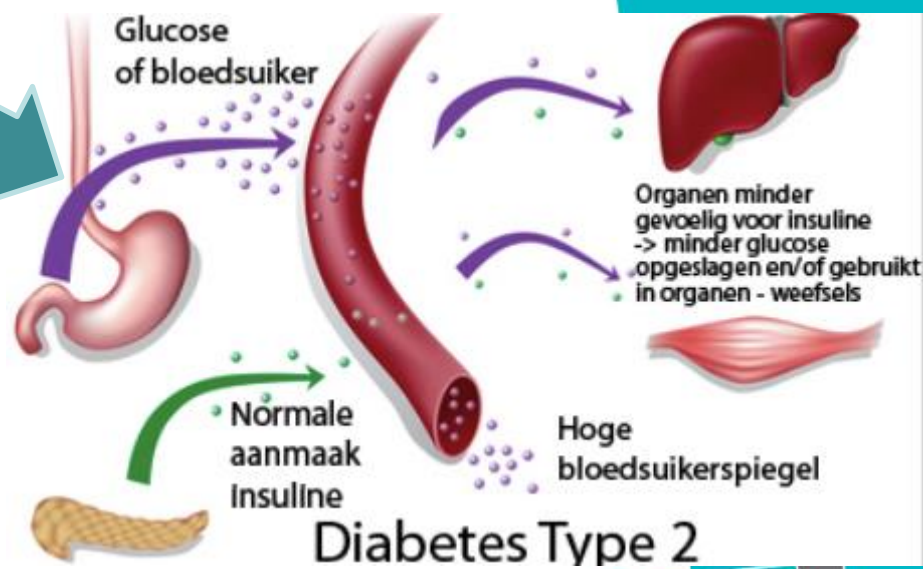
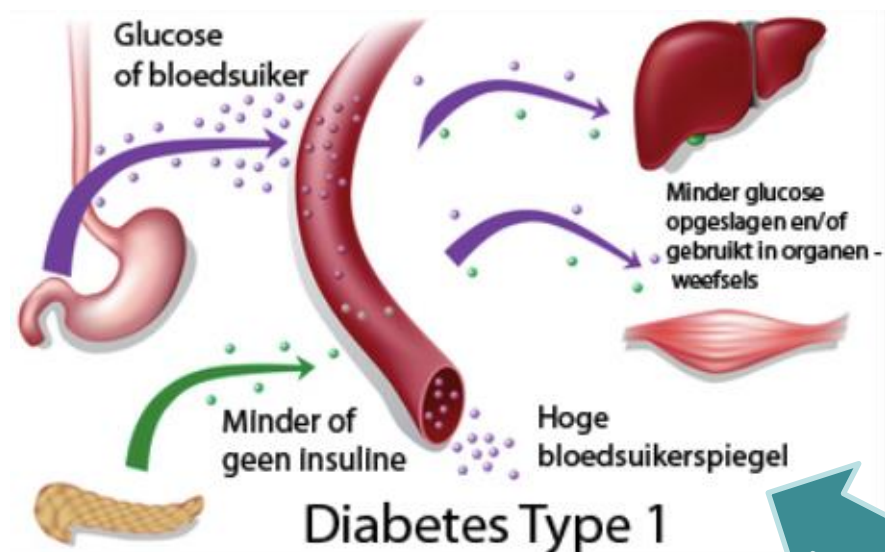
Dr. Stinkens Kirsten

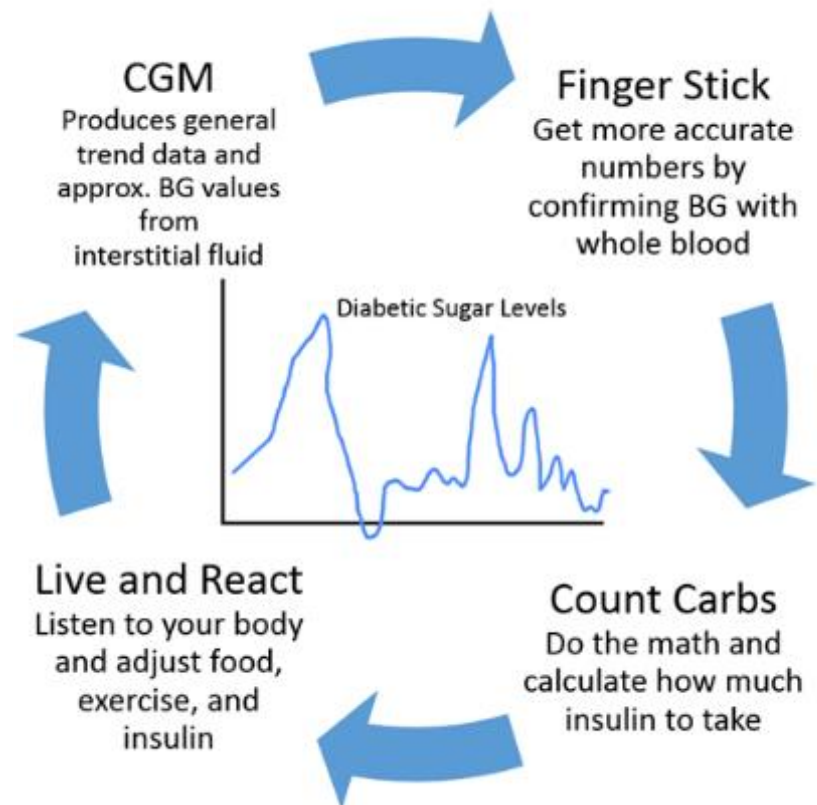
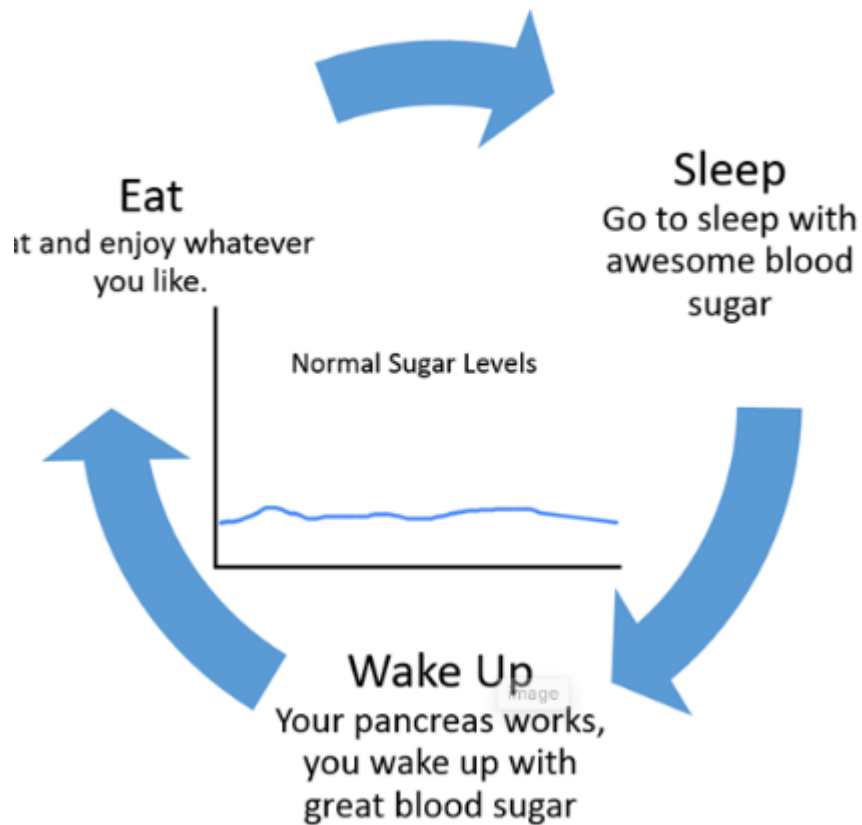
1 in 11 adults has diabetes (425 million)



5-10 % TYPE 1 DIABETES

Type 1 diabetes ≠ Type 2 diabetes





Focus behandeling type 1 diabetes

1. PREVENTIE

- Immuuntherapie

2. BETERE GLUCOSECONTROLE

- Betere insuline
- Bijkomende niet-insuline behandelingen

3. PERFECTE GLUCOSECONTROLE = toename tijd in range

- Continue glucosemonitoring
- Insulinepompen
- Artificiële pancreas

4. GENEZING

- Immuuntherapie + transplantatie

Focus behandeling type 1 diabetes

1. PREVENTIE

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4. GENEZING

- Immuuntherapie + transplantatie

Preventie

- Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes (NEJM, 2019)
- Screening baby's op verhoogd risico op type 1 diabetes – bij verhoogd risico deelname POInT studie
- DIABIL-2 , effect van IL-2 om betaceldestructie tegen te gaan



Focus behandeling type 1 diabetes

1. PREVENTIE

- Immuuntherapie

2. BETERE GLUCOSECONTROLE

- Beter insuline
- Bijkomende niet-insuline behandelingen (Amyline, GLP-1 analogen, SGLT-2 inhibitoren)

3. PERFECTE GLUCOSECONTROLE = toename tijd in range

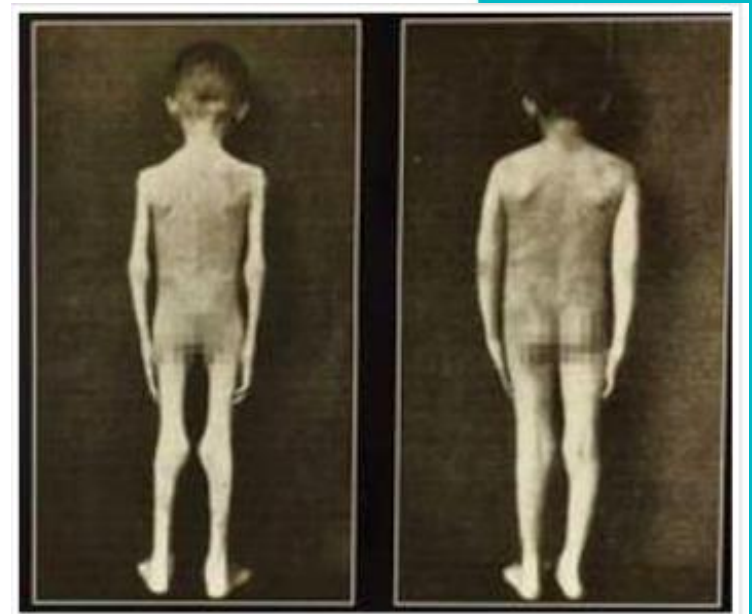
- Continue glucosemonitoring
- Insulinepompen
- Artificiële pancreas

4. GENEZING

- Immuuntherapie + transplantatie

Geschiedenis

- Ontdekking insuline in 1921 door Frederick Grant Banting en zijn assistent Charles Best
- Leonard Thompson, eerste patiënt die behandeld werd met insuline afkomstig van honden en kalveren
- 1932 Nobelprijs voor Geneeskunde

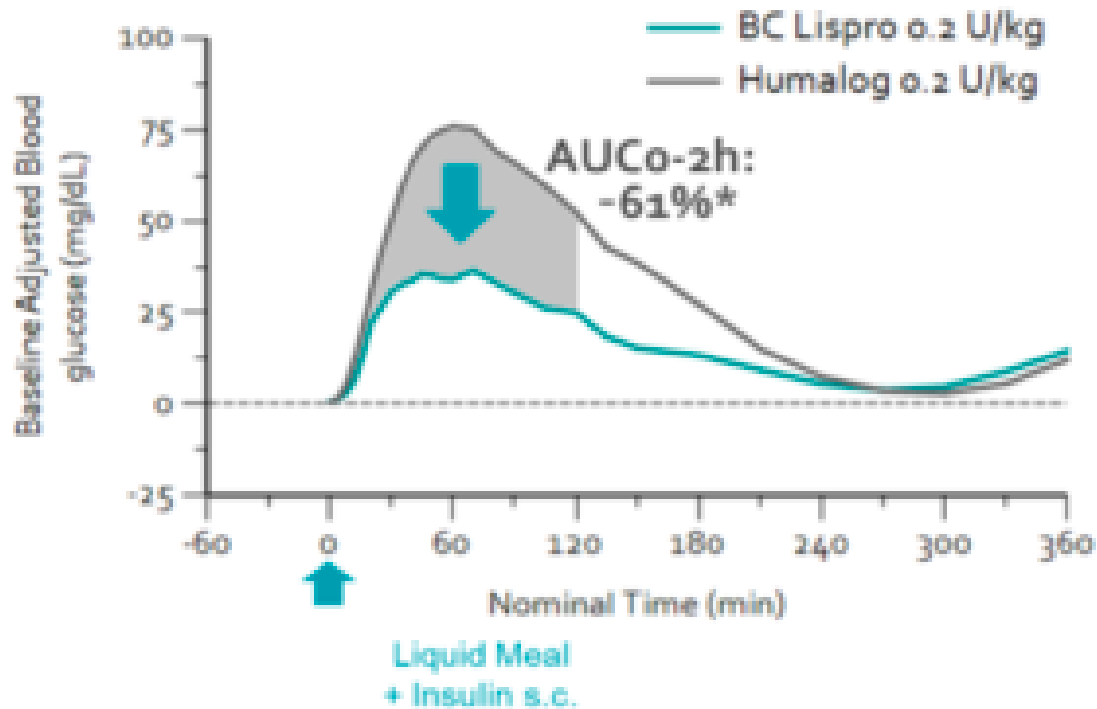




Ontwikkeling nieuwere insulines

Bijv. Biochaperone Lispro

Post-meal glycaemia in T1D



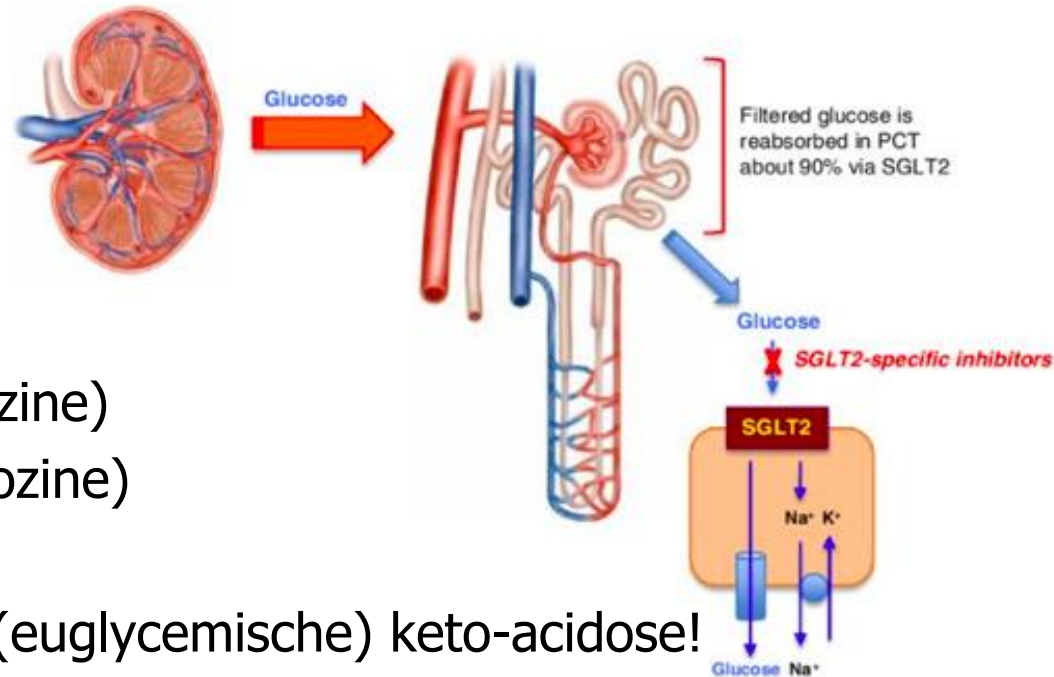
Trial in 38 subjects with type 1 diabetes (NCT#02213146); *CI-95% for LSM ratio.

Ontwikkeling nieuwe pennen: “smart pens”

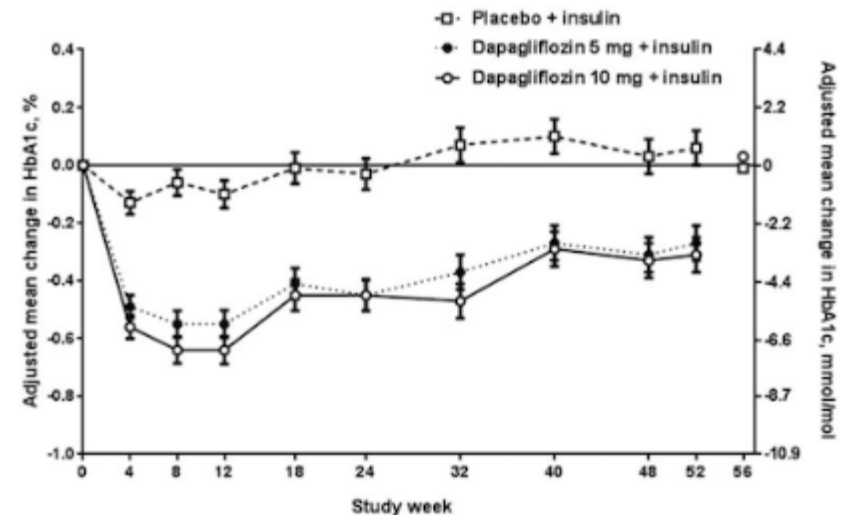
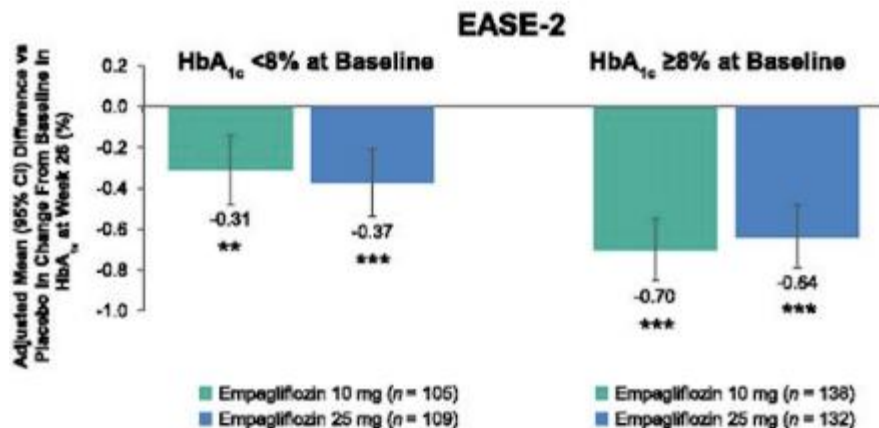
Bijv. Inpen



Add on therapie



- SGLT-2 inhibitoren
 - EASE-trials (empagliflozine)
 - Depict trials (dapagliflozine)
- CAVE verhoogd risico (euglycemische) keto-acidose!
- (nog) NIET terugbetaald



Focus behandeling type 1 diabetes

1. PREVENTIE

- Immuuntherapie

2. BETERE GLUCOSECONTROLE

- Betere insuline
- Bijkomende niet-insuline behandelingen

3. **PERFECTE GLUCOSECONTROLE = toename 'tijd in bereik/Time in Range'**

- Continue glucosemonitoring
- Insulinepompen
- Artificiële pancreas

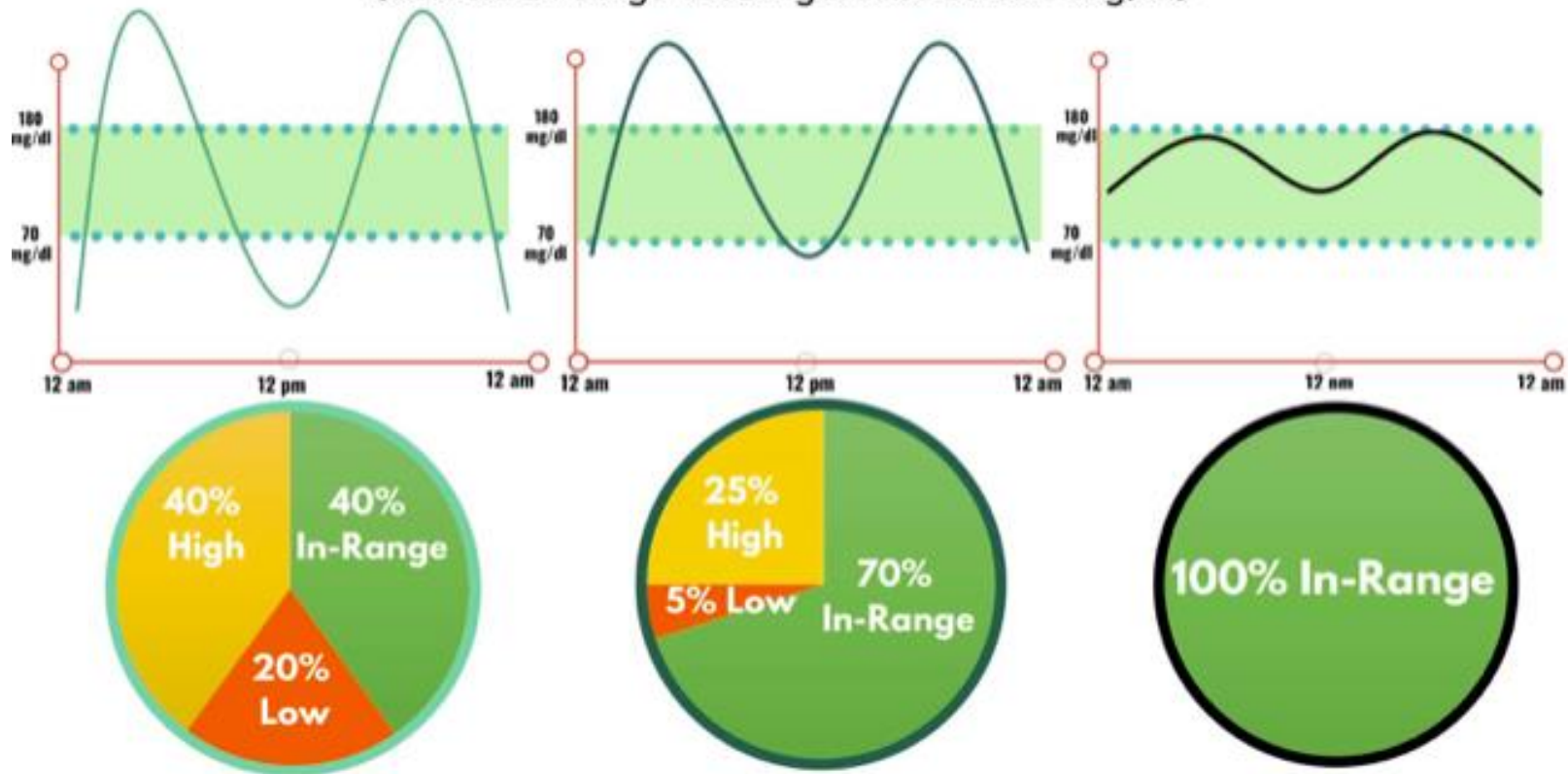
4. GENEZING

- Immuuntherapie + transplantatie

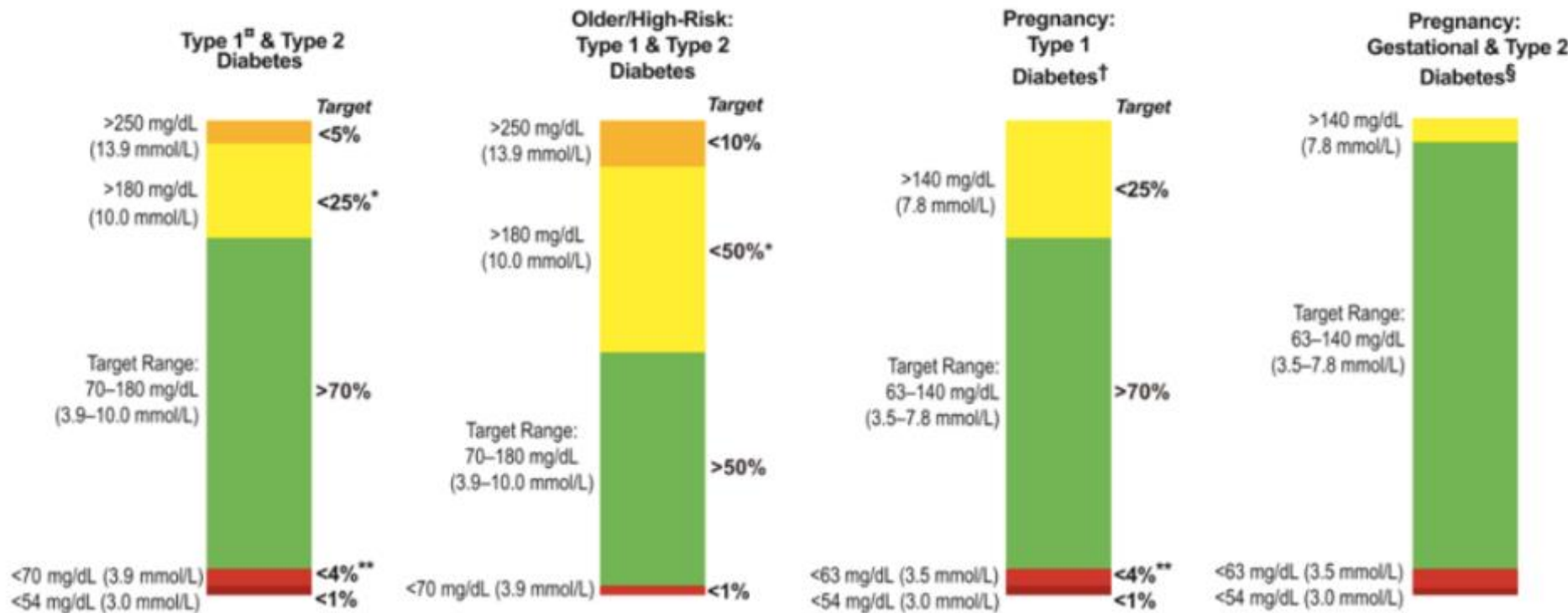
Time in range

THE MANY FACES OF A 7% A1C

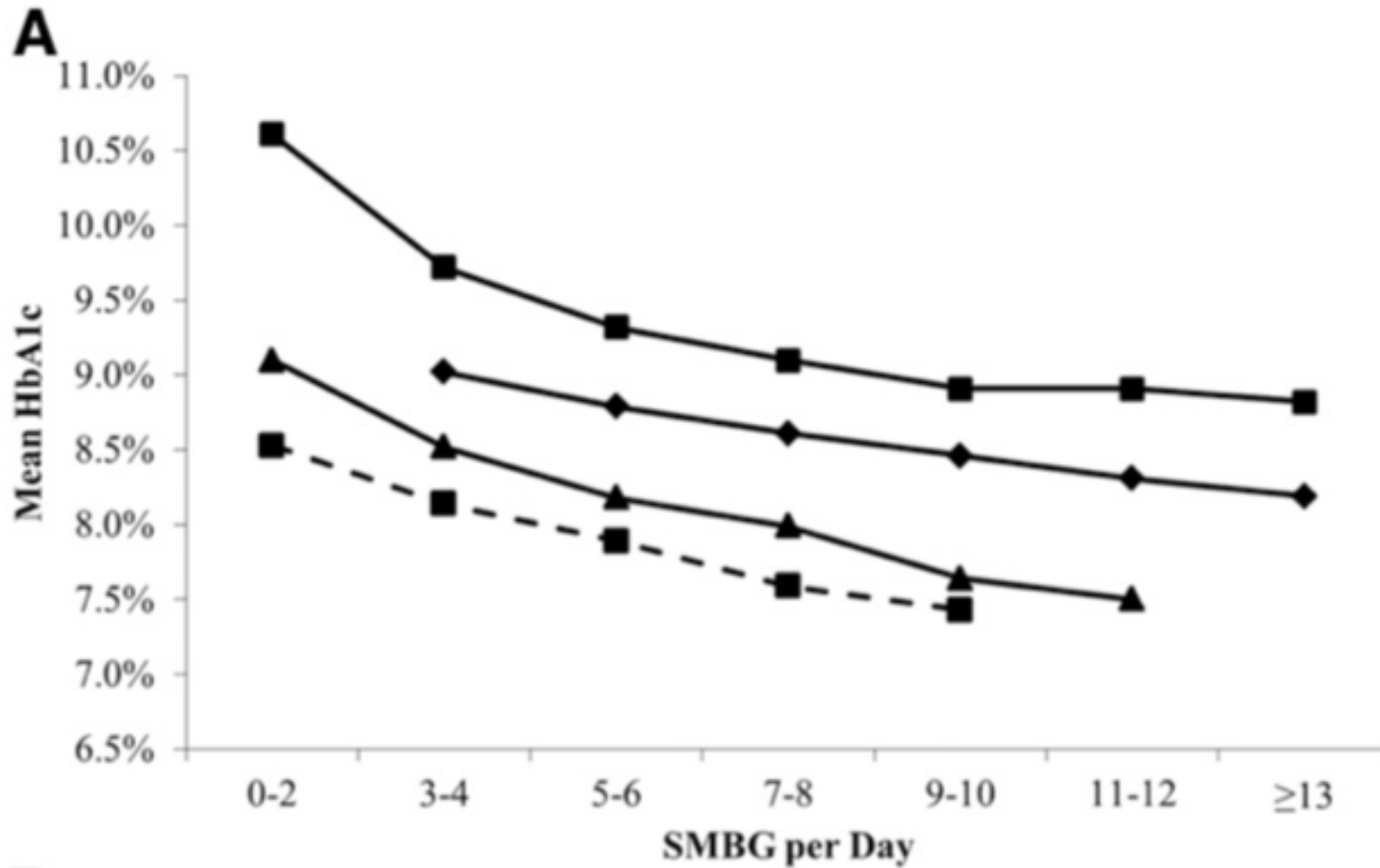
(and an average blood glucose of 154 mg/dl)



Time in range

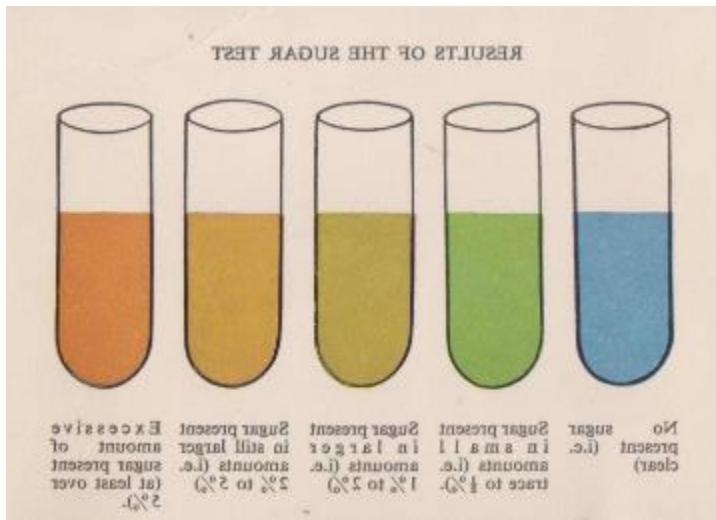


Meten = weten

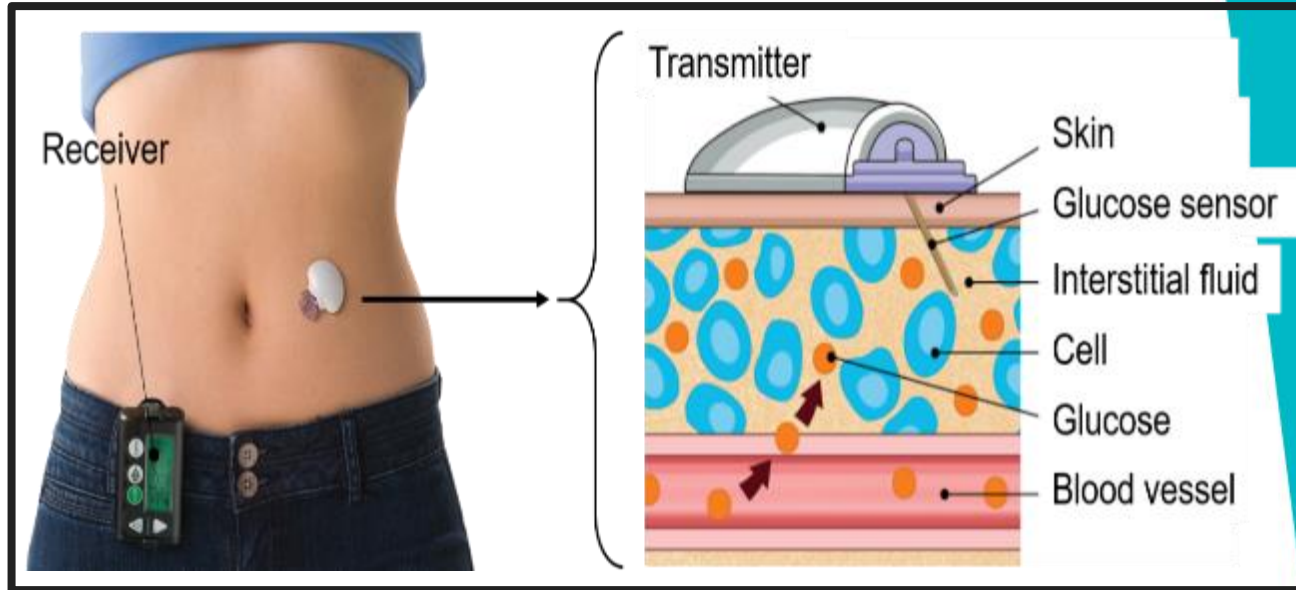


Miller KM et al *Diabetes Care*. 2013;36(7):2009–2014.

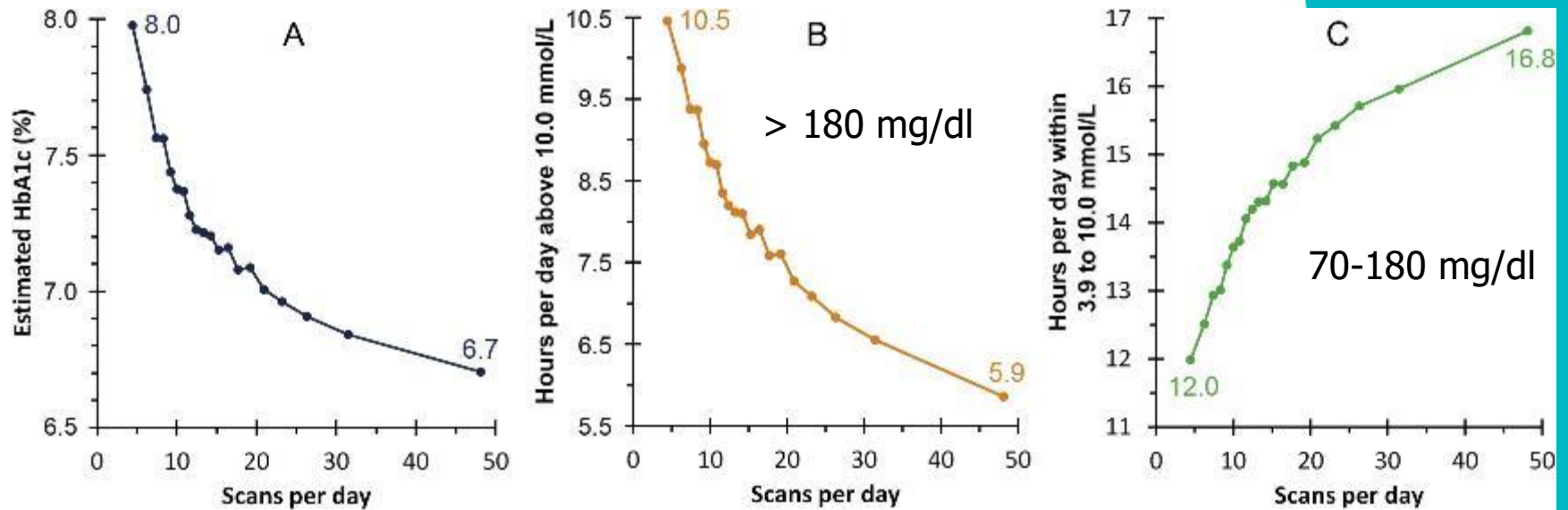
Geschiedenis



Continue glucose monitoring



Waarom continue glucosemonitoring ?



Dunn et al Diabetes Research and Clinical Practice, Volume 137, 37 - 46
2018

Continue glucosemonitoring – nood aan verbetering!



Eversense XL



Dexcom G6



Freestyle libre 2

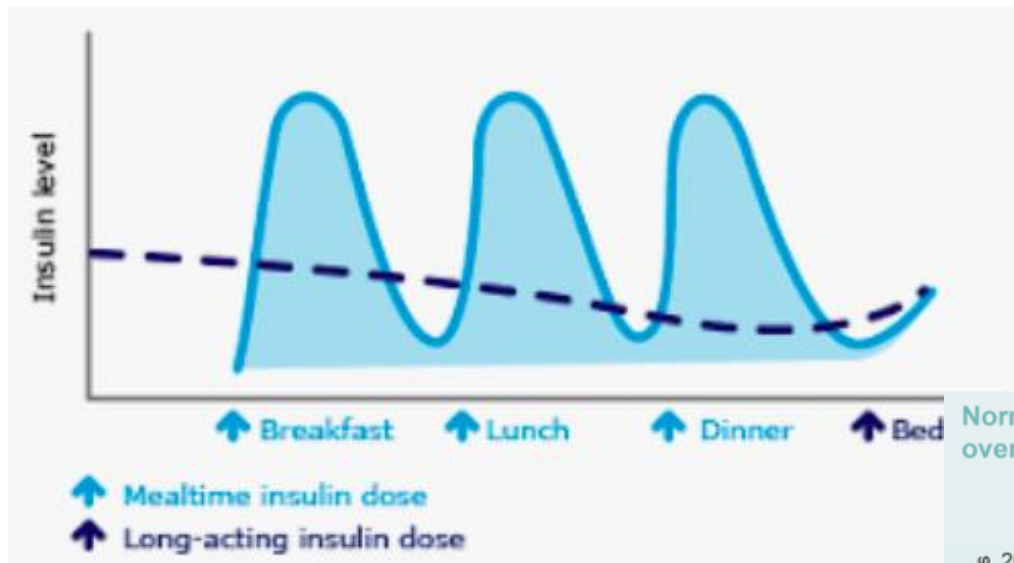


Noviosense

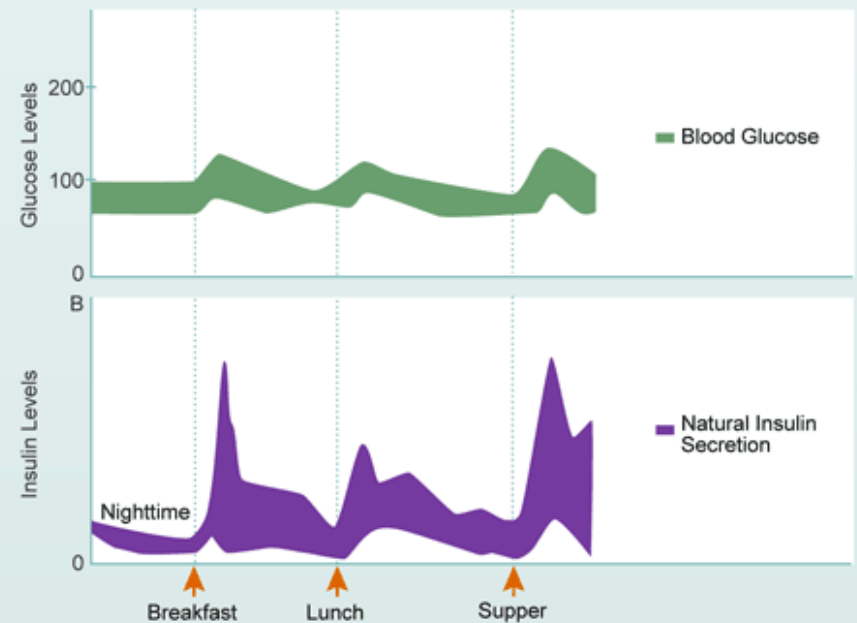


INSULINEPOMP EN DE ARTIFICIËLE PANCREAS

Bolus – Basaal (MDI) vs normale insulinetoediening



Normal (Non-diabetic) Blood Glucose and Insulin Levels over 24 Hours

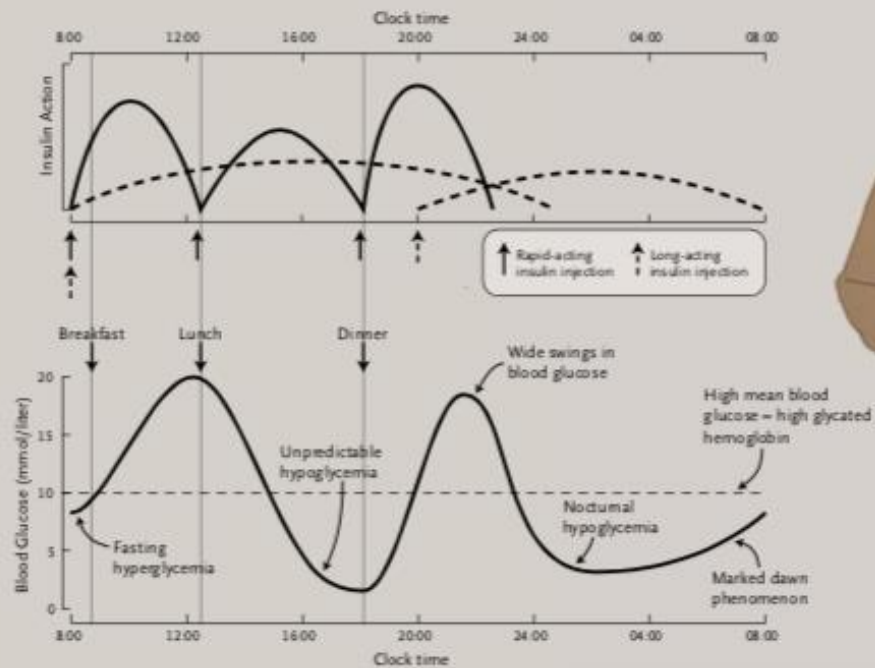


Insulinepomp

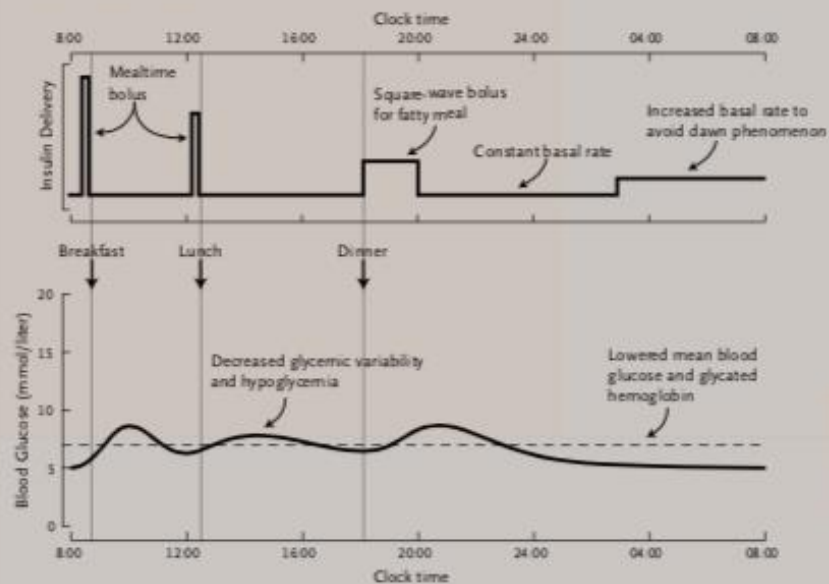


- 1963 eerste pomp
- Dr. Arnold Kadish

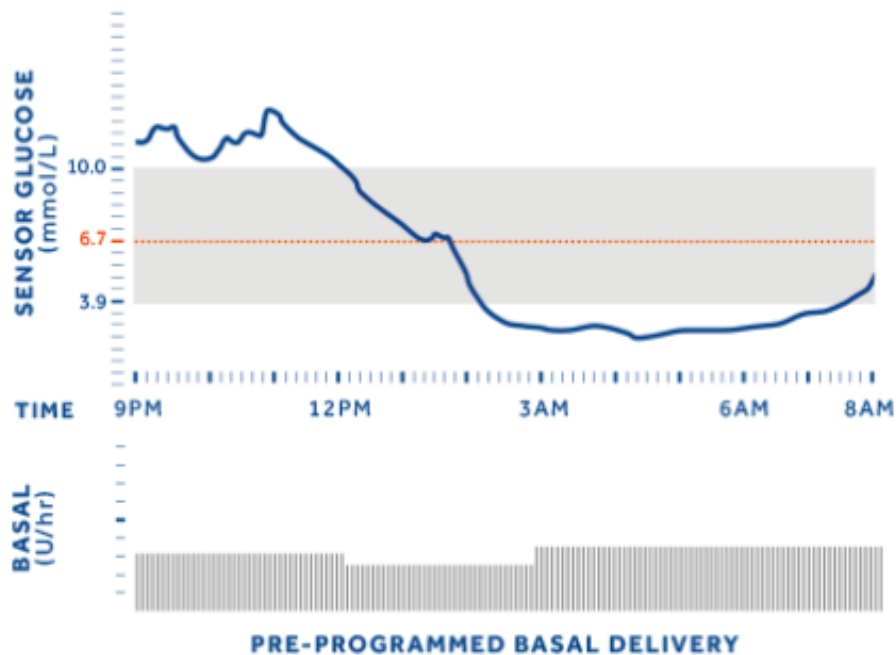
A Multiple Daily Insulin Injections



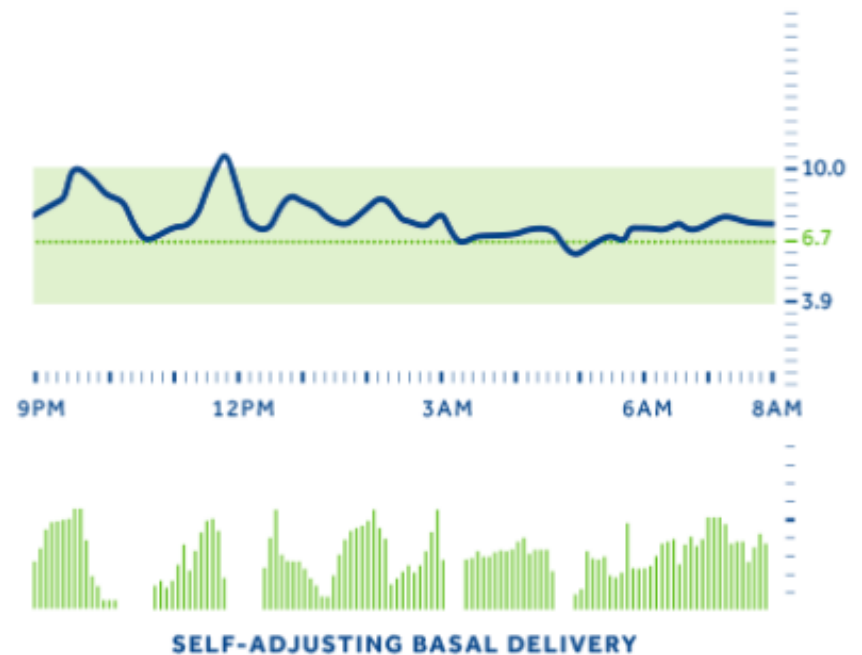
B Insulin-Pump Therapy



TRADITIONAL PUMP THERAPY NO AUTOMATION

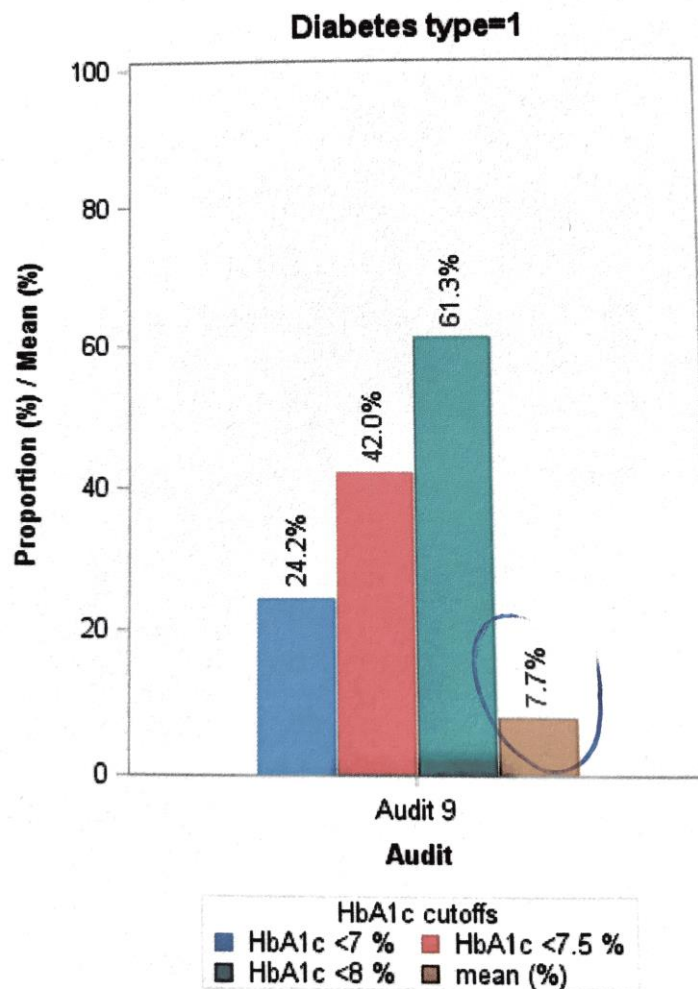


SMARTGUARD™ AUTOMATIC INSULIN ADJUSTMENTS



Waarom artificiële pancreas?

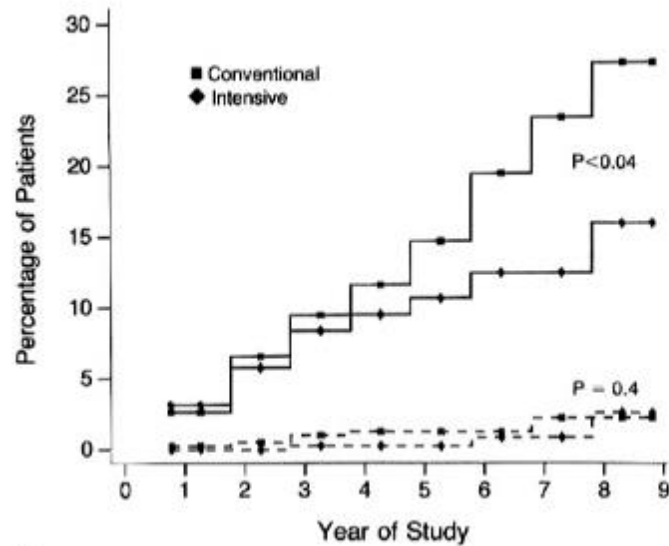
1. Het niet bereiken van $HbA1c < 7\%$



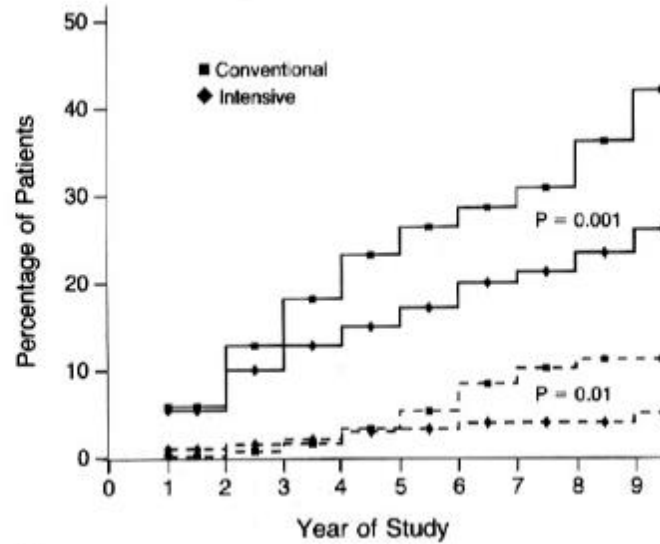
Verbeterde glycemiecontrole leidt tot lager risico op complicaties!

COMPLICATIONS	PRIMARY PREVENTION			SECONDARY INTERVENTION			BOTH COHORTS [†]
	CONVENTIONAL THERAPY	INTENSIVE THERAPY	RISK REDUCTION	CONVENTIONAL THERAPY	INTENSIVE THERAPY	RISK REDUCTION	RISK REDUCTION
	<i>rate/100 patient-yr</i>		<i>% (95% CI)</i>	<i>rate/100 patient-yr</i>		<i>% (95% CI)</i>	<i>% (95% CI)</i>
≥3-Step sustained retinopathy	4.7	1.2	76 (62–85) [‡]	7.8	3.7	54 (39–66) [‡]	63 (52–71) [‡]
Macular edema [§]	—	—	—	3.0	2.0	23 (–13–48)	26 (–8–50)
Severe nonproliferative or proliferative retinopathy [§]	—	—	—	2.4	1.1	47 (14–67) [¶]	47 (15–67) [¶]
Laser treatment [§]	—	—	—	2.3	0.9	56 (26–74) [‡]	51 (21–70) [¶]
Urinary albumin excretion (mg/24 hr)							
≥40	3.4	2.2	34 (2–56) [¶]	5.7	3.6	43 (21–58) [‡]	39 (21–52) [‡]
≥300	0.3	0.2	44 (–124–86)	1.4	0.6	56 (18–76) [¶]	54 (19–74) [¶]
Clinical neuropathy at 5 yr ^{**}	9.8	3.1	69 (24–87) [¶]	16.1	7.0	57 (29–73) [‡]	60 (38–74) [‡]

Nefropathie

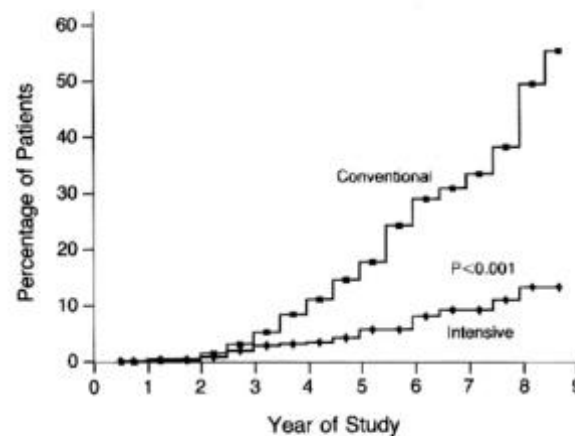


A

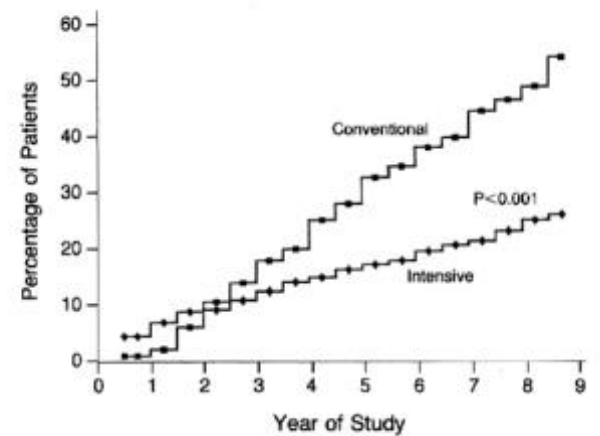


B

Retinopathie



A



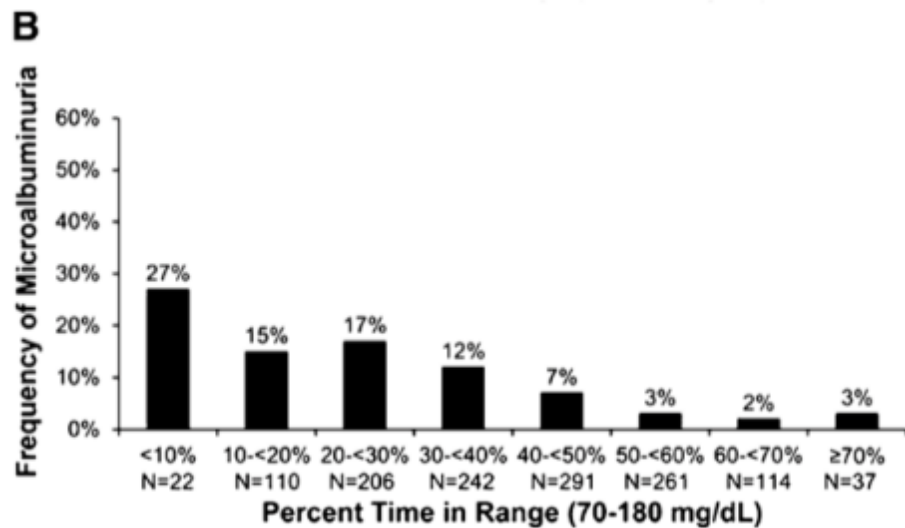
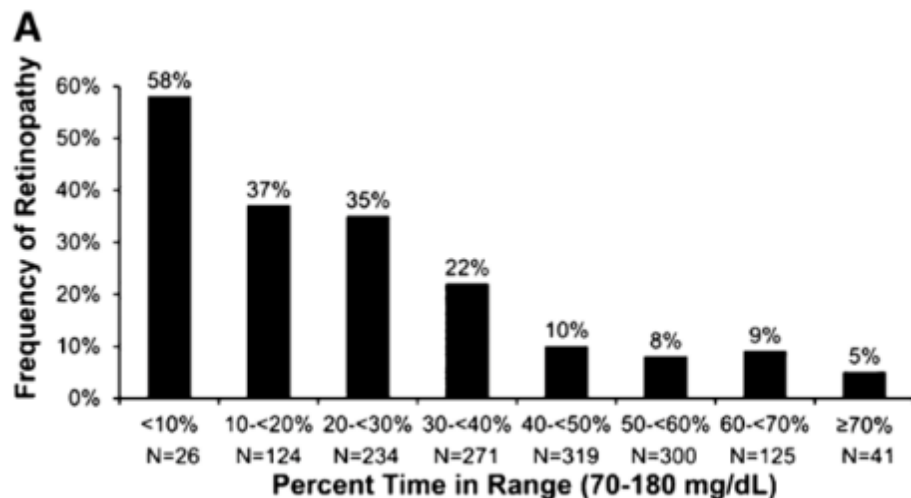
B

DCCT trial

Conventional	375	220	79	52
Intensive	342	202	76	49

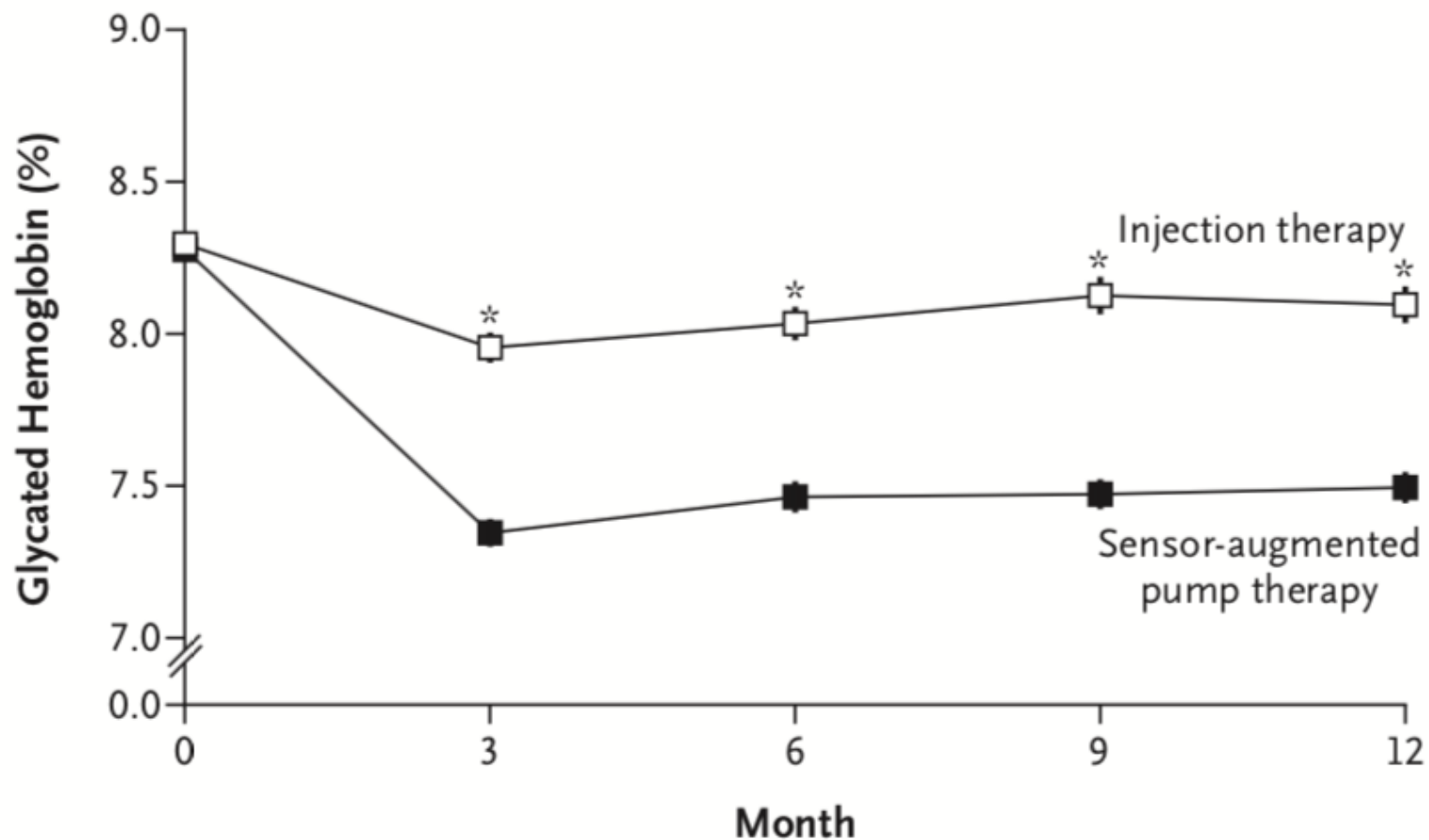
Conventional	348	324	128	79
Intensive	354	335	136	93

Time in range > 70% als nieuw streefdoel



Insulinepomp + glucosesensor leidt tot HbA1c daling!

A All Patients



Bergenstal et al – STAR 3 study – NEJM 2010

Pomptherapie geassocieerd met daling cardiovasculaire mortaliteit

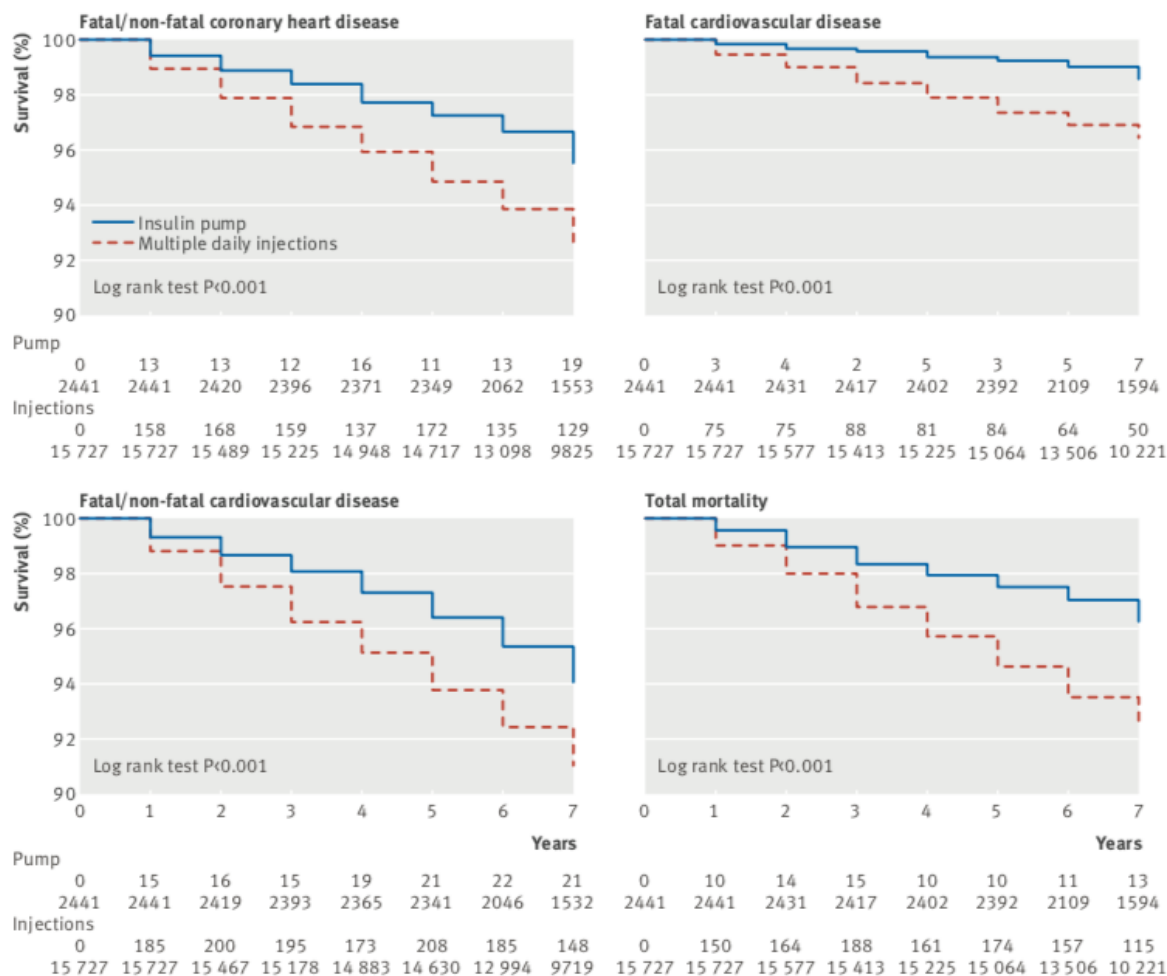
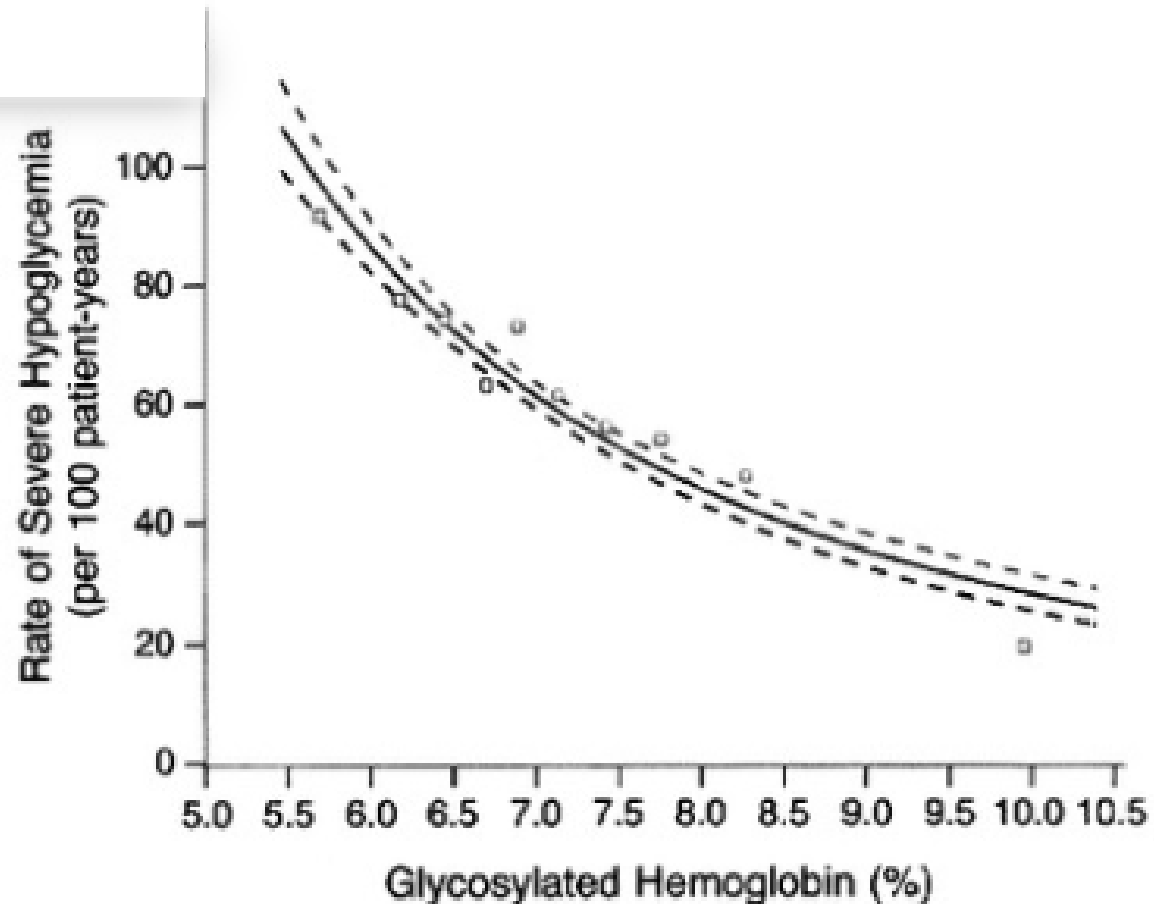


Fig 1 | Kaplan-Meier crude survival curves in 18 168 individuals with type 1 diabetes according to treatment with insulin pump therapy or multiple daily injections. No of cases and individuals at risk are given in each group

Hoe beter de glycemiecontrole, hoe hoger het risico op hypoglycemie!



DCCT trial

Waarom artificiële pancreas?

2. Het vermijden van hypoglycemies

Angst

Mentale
weerslag

Slaap

Belemmering
fysieke
activiteit

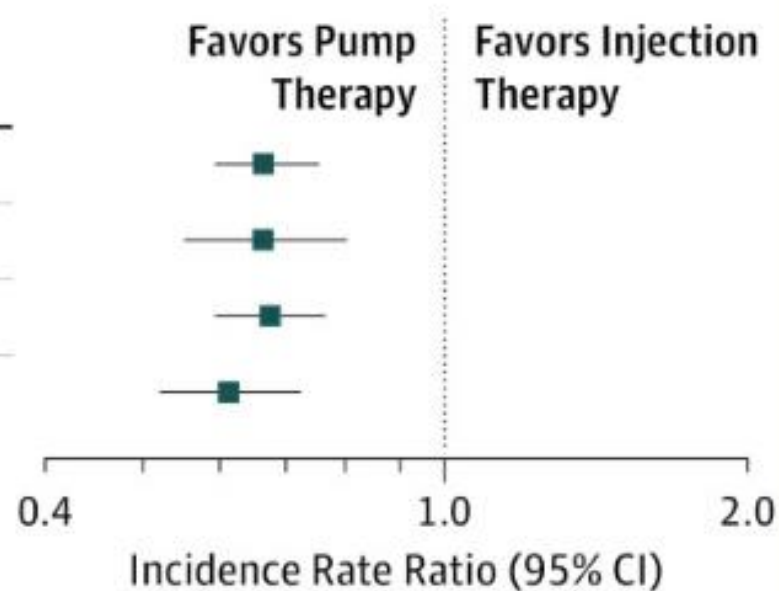
Gewicht

Dood

Pompbehandeling leidt tot minder hypoglycemies

B Entire cohort

	Incidence Rate Ratio (95% CI)
Severe hypoglycemia	0.66 (0.59-0.75)
Hypoglycemic coma	0.66 (0.55-0.80)
Diabetic ketoacidosis	0.67 (0.59-0.76)
Severe ketoacidosis	0.61 (0.52-0.72)



Voordelen insulinepomp

- Verbetering van HbA1c
- Minder hypoglycemies
- Minder variabiliteit door lager subcutaan depot en variatie
- Boluscalculator en mogelijkheid verlengde bolus (square-wave/dual-wave bolus)
- Basaal patroon in verschillende blokken
- Tijdelijk basaal



Nadelen insulinepomp

- Steeds gebonden aan toestel
- Allergie pleisters
- Technische problemen pomp of kathterproblemen
- Infectie insertieplaats

De Weg naar de Artificiële Pancreas

First Generation

Second Generation

Third Generation

1

Very Low Glucose Insulin Off Pump
Pump shuts off when user not responding to low-glucose alarm

2

Hypoglycemia Minimizer
Predictive hypoglycemia causes alarms followed by reduction or cessation of insulin delivery below low threshold

3

Hypoglycemia/Hyperglycemia Minimizer
Same as Product #2 but added feature allowing insulin dosing above high threshold (e.g., 200mg/dl)

4

Automated Basal/Hybrid Closed Loop
Closed loop at all times with meal-time manual assist bolusing

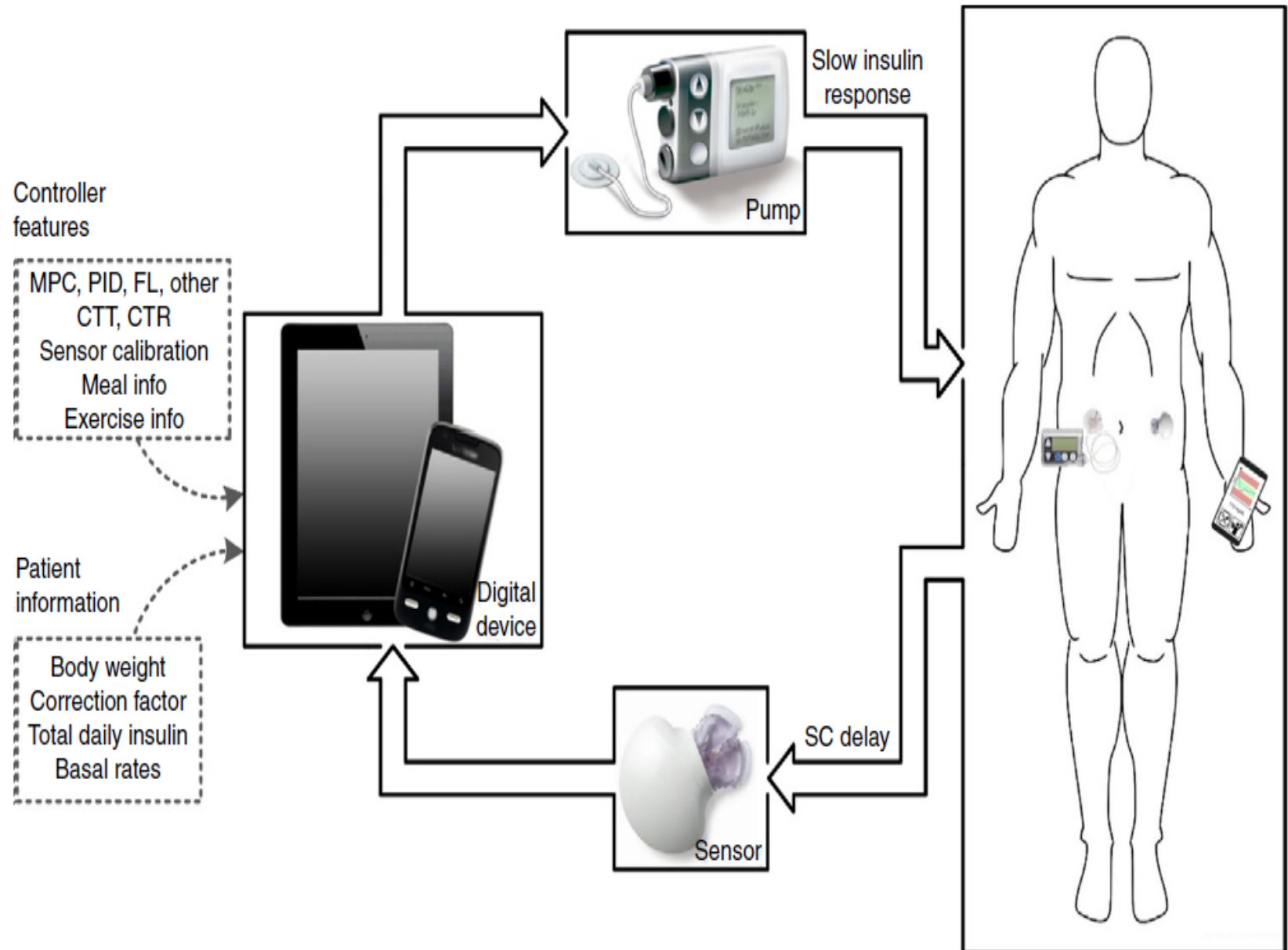
5

Fully Automated Insulin Closed Loop
Manual meal-time bolus eliminated

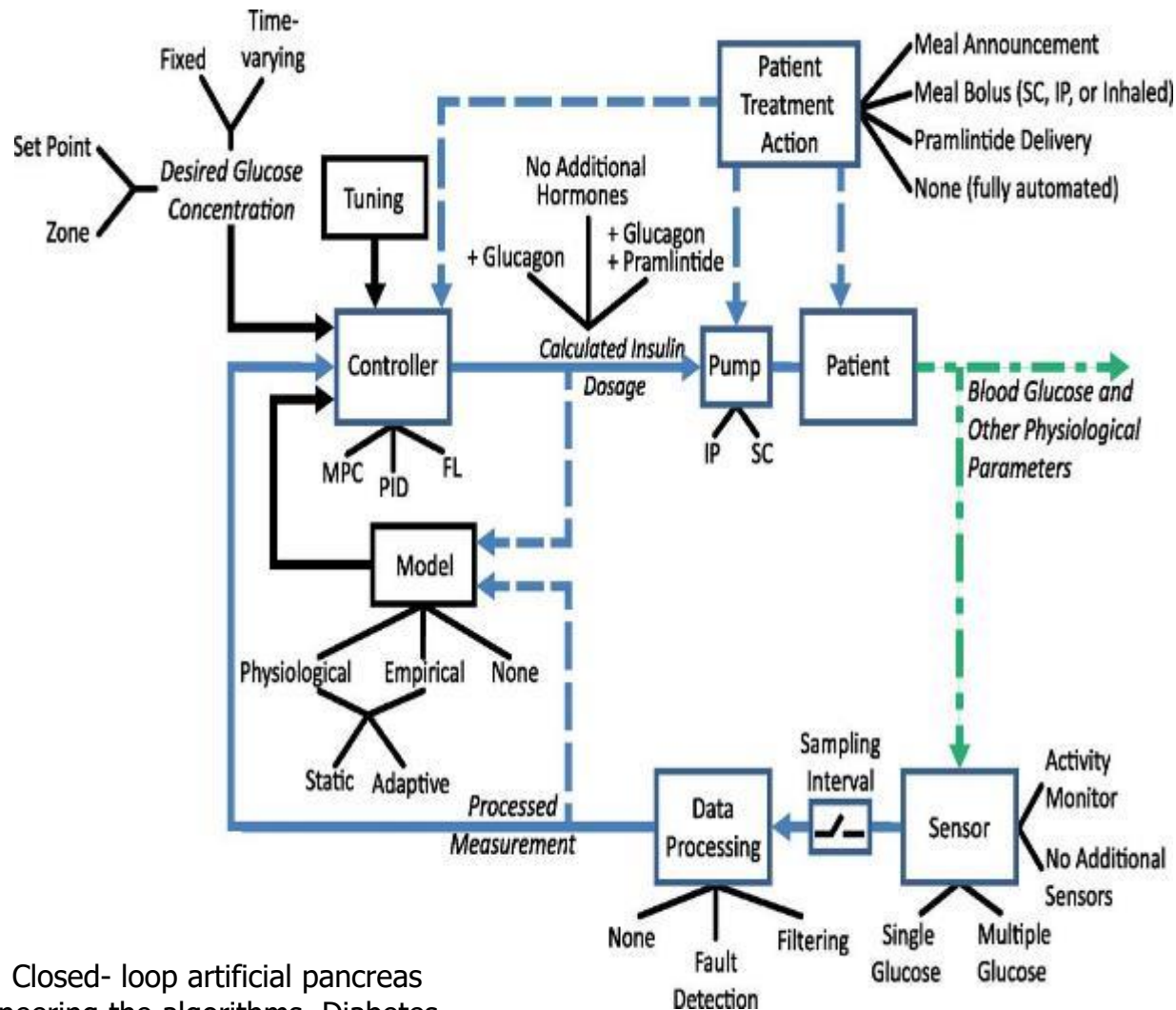
6

Fully Automated Multi-Hormone Closed Loop

Artificiële Pancreas: onderdelen



Algoritme artificiële pancreas



Doyle FJ et al. Closed- loop artificial pancreas systems: engineering the algorithms. Diabetes Care 2014; 37: 1191–1197.

De Weg naar de Artificiële Pancreas

Medtronic Paradigm Veo

Second Generation

Third Generation

1

Very Low Glucose Insulin Off Pump
Pump shuts off when user not responding to low-glucose alarm

2

Hypoglycemia Minimizer
Predictive hypoglycemia causes alarms followed by reduction or cessation of insulin delivery below low threshold

3

Hypoglycemia Minimizer
Same as #2 but allows dosing below threshold

4

5

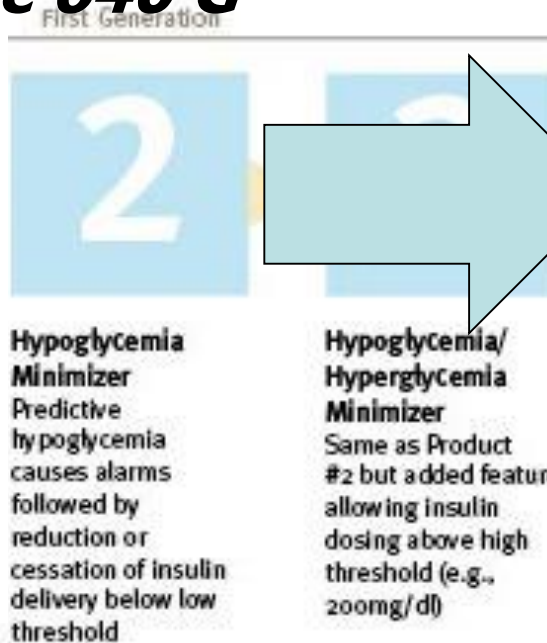
6

Fully Automated Multi-Hormone Closed Loop

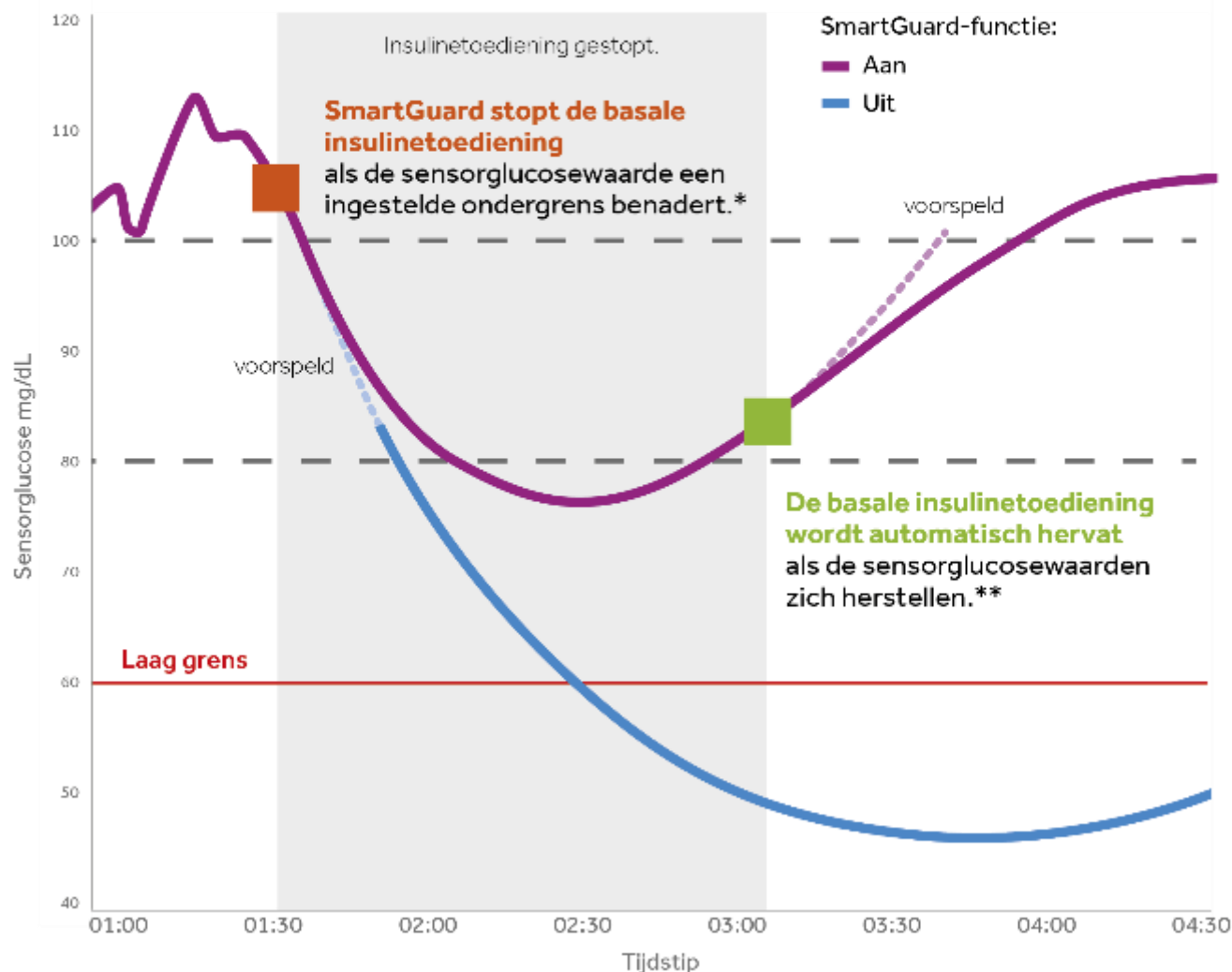
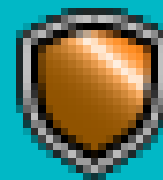


De Weg naar de Artificiële Pancreas

Medtronic 640 G



SmartGuard™: de optimale bescherming tegen hypoglycemie



* De dynamische pompstopfunctie is gebaseerd op de volgende criteria: de sensorglucosewaarde ligt minder dan 70 mg/dL boven de ondergrens en verwacht wordt dat de waarde binnen 30 minuten 20 mg/dL boven de ondergrens ligt EN de pomp bevindt zich niet in de wachtijd periode.

** De dynamische hervatfunctie is gebaseerd op de volgende criteria: de sensorglucosewaarde ligt minimaal 20 mg/dL boven de ondergrens en de verwachting is dat de waarde binnen 30 minuten 40 mg/dL boven de ondergrens zal liggen EN de toediening van insuline is gedurende minimaal 30 minuten gestopt.

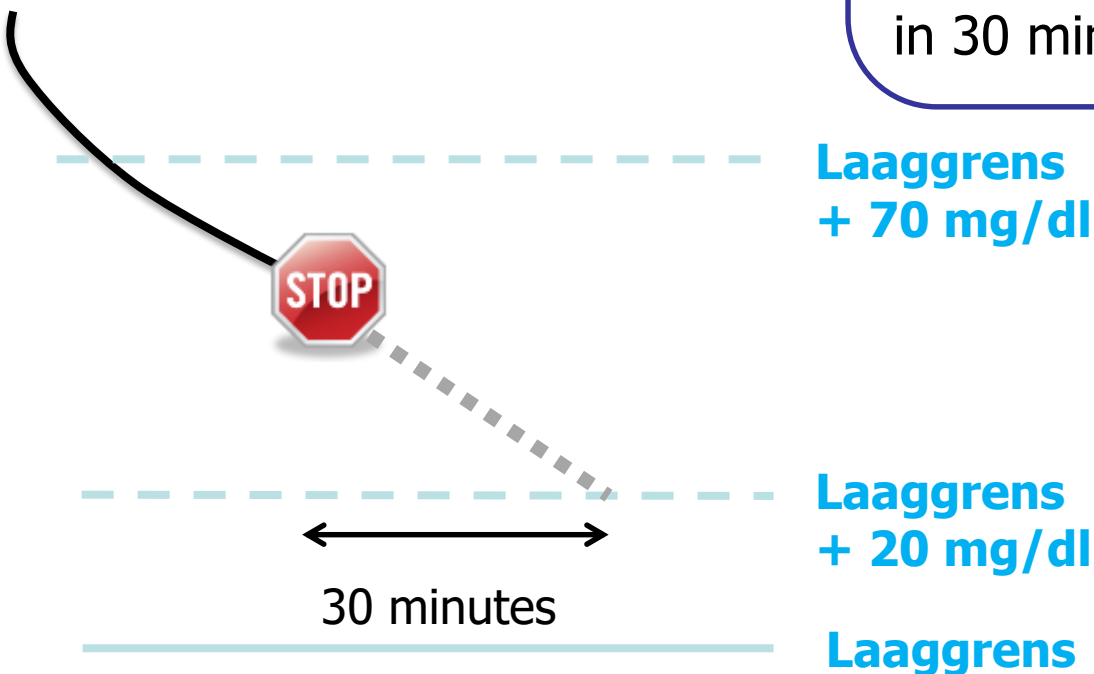
Stop voor laag

Basaal wordt gestopt

De glucose bevindt zich in het interval van de laaggrens + 70 mg/dl

EN

Zal de laaggrens + 20 mg/dl in 30 minuten bereiken



Hervatten van basaal

Automatisch na een stop van maximal 2 uren

Handmatig

Automatisch en gebaseerd op de
sensorglucosewaarde

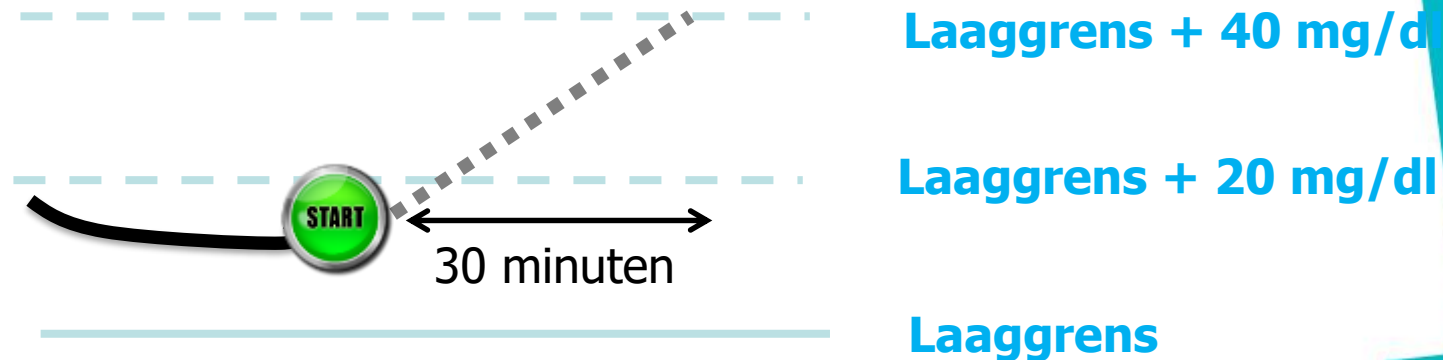
De glucose bevindt zich in het interval laaggrens + 20 mg/dl

EN

Zal de laaggrens + 40 mg/dl in 30 minuten

EN

De toediening is minimal 30 minuten gestopt

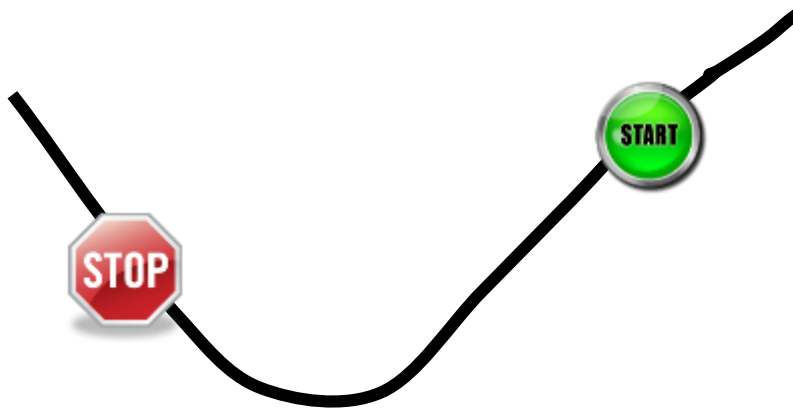


Refractie of herstelperiode

Na een stop bij laag en een stop voor laag

- **30 min na elke stop**
- **4 u na een stop van maximal 2 uren**

Smartguardicoontje
met een staafje



SmartGuard in actie

L. Bally et al.

International Journal of Pharmaceutics xxx (xxxx) xxx-xxx

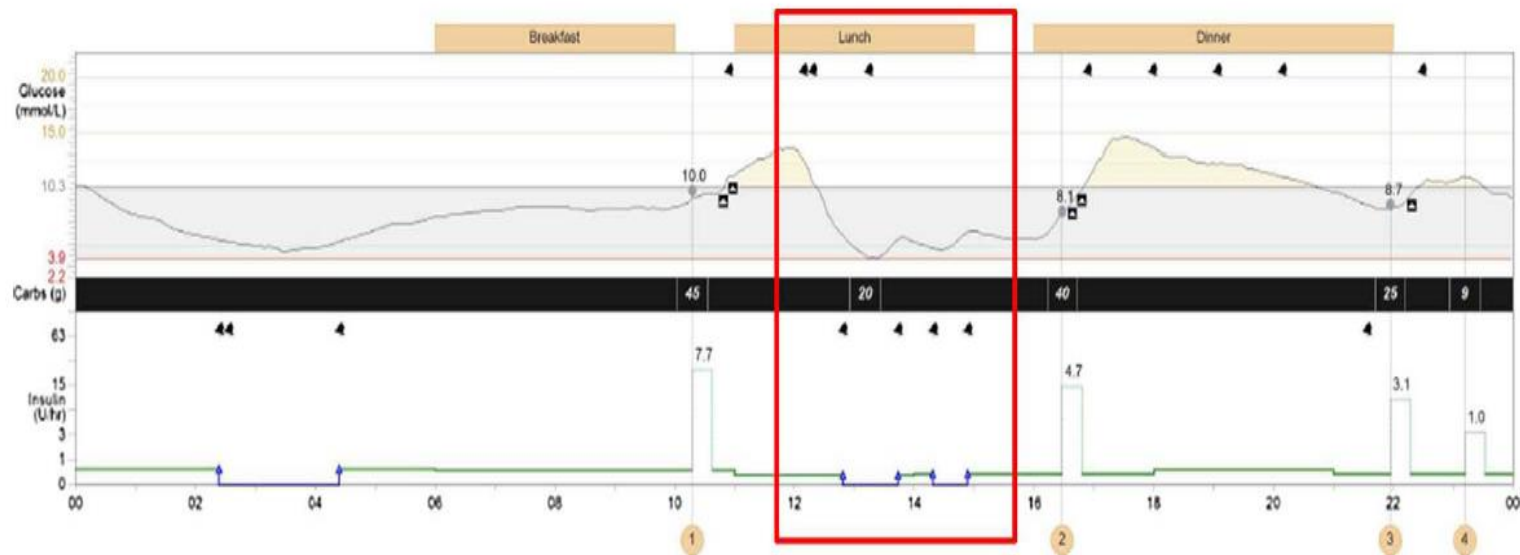
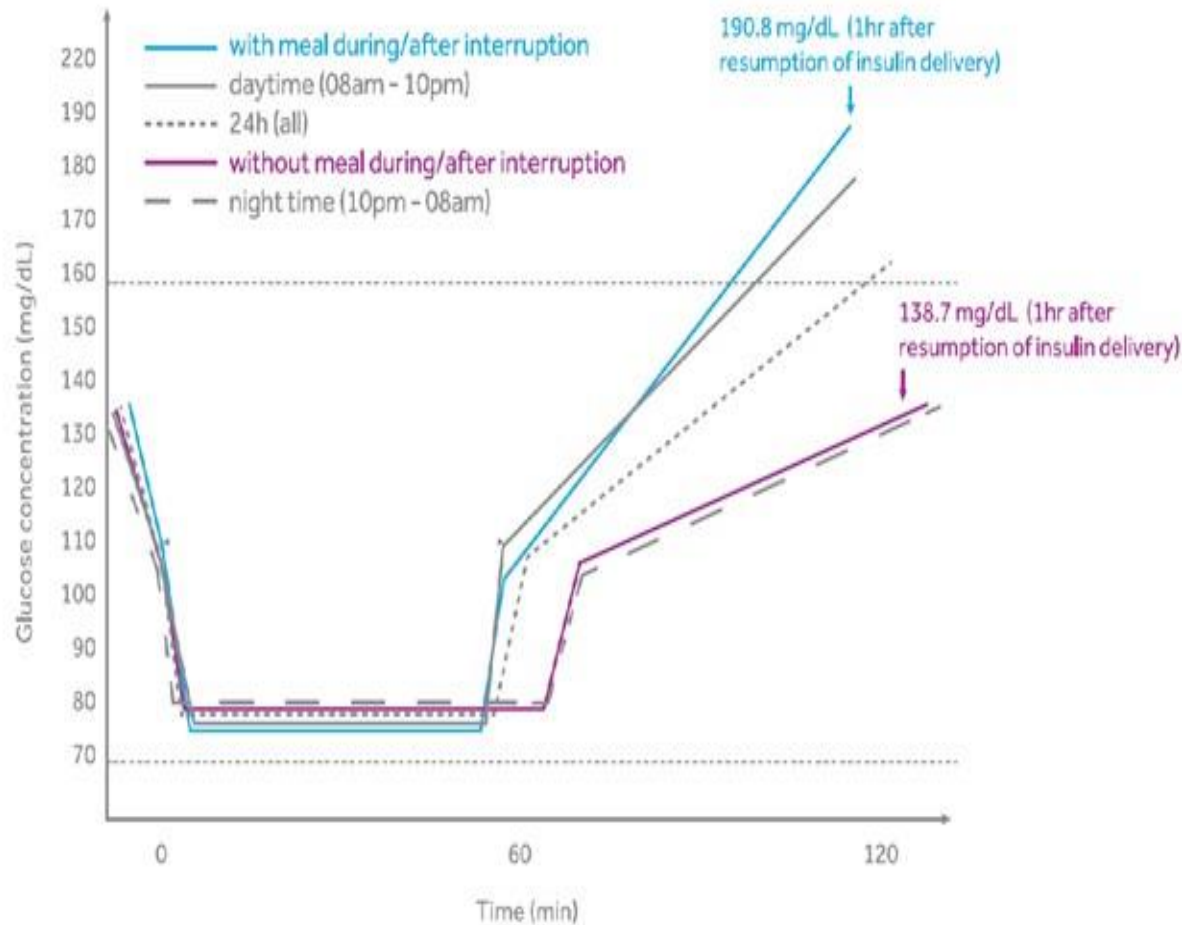


Fig. 2. Two predictive low glucose suspend events (including alarms) are shown within the red square. The upper panel shows the sensor glucose profile. Insulin delivery profile is shown in the lower panel.

SmartGuard: vertrouw het systeem



Mean glucose level 1 hour after insulin resumption

Intervention

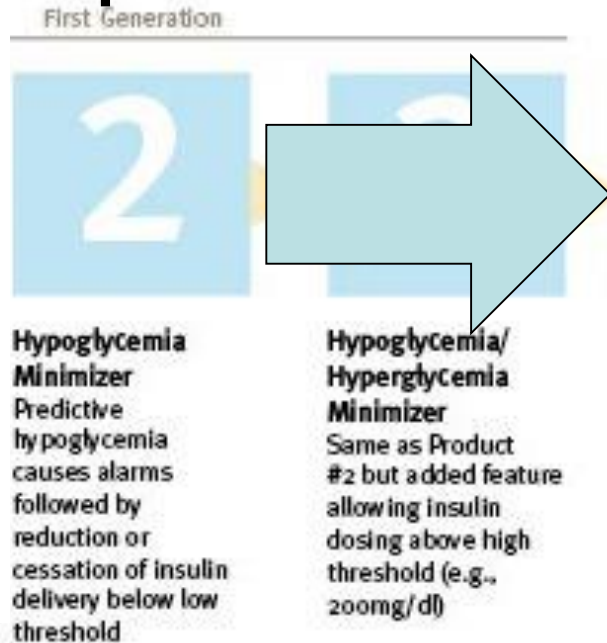
190.8 mg/dL (10.6 mmol/L)

No Intervention

138.7 mg/dL (7.7 mmol/L)

De Weg naar de Artificiële Pancreas

T: Slim X2 pomp van Tandem Care



De Weg naar de Artificiële Pancreas

First Generation

HET MINIMEDTM 670G-SYSTEEM HET EERSTE SYSTEEM MET AUTOMATISCHE BASALE INSULINE TOEDIENING

when user not
responding to
low-glucose alarm

hypoglycemia
causes alarms
followed by
reduction or
cessation of insulin
delivery below low
threshold

Same as Product
#2 but added feature
allowing insulin
dosing above high
threshold (e.g.,
200mg/dl)

Second Generation



**Automated
Basal/Hybrid
Closed Loop**
Closed loop at
all times with
meal-time manual
assist bolusing

**Fully Automated
Insulin Closed
Loop**
Manual meal-time
bolus eliminated



HET MINIMED™ 670G-SYSTEEM

Guardian™ -sensor 3

Onze meest accurate⁵ sensor stuurt onze exclusieve SmartGuard™ -technologie met een slim en betrouwbaar ontwerp⁶.

BESCHIKBAAR DIT NA JAA

Ages 14 and up	Abdomen	Arm
Conditions	MARD*	
3-4 calibrations/day	9.6%*	8.7%*
2 calibrations/day	10.5%*	9.1%*

MiniMed™ Mio™ Infusieset

Medtronic biedt een breed scala aan infusiesets zodat u de MiniMed™ Mio™ Infusieset kunt kiezen voor uw comfort en veiligheid.

MEER WETEN



Levensduur 7 dagen



CONTOUR® NEXT LINK 2.4 Bloedglucosemeter

De enige meter die draadloos verbinding maakt met de MiniMed™ 670G-insulinepomp voor uiterst nauwkeurige sensorkalibratie⁷.



CareLink™ -software

Upload naar CareLink™ - software om uw glucoseregeling gemakkelijk te volgen en deze informatie op afstand te delen met uw zorgverlener.

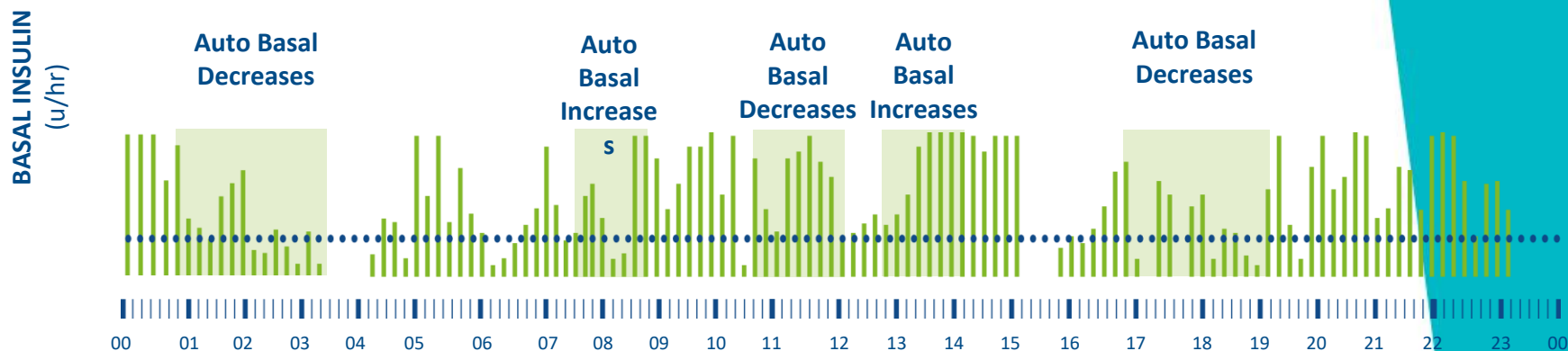
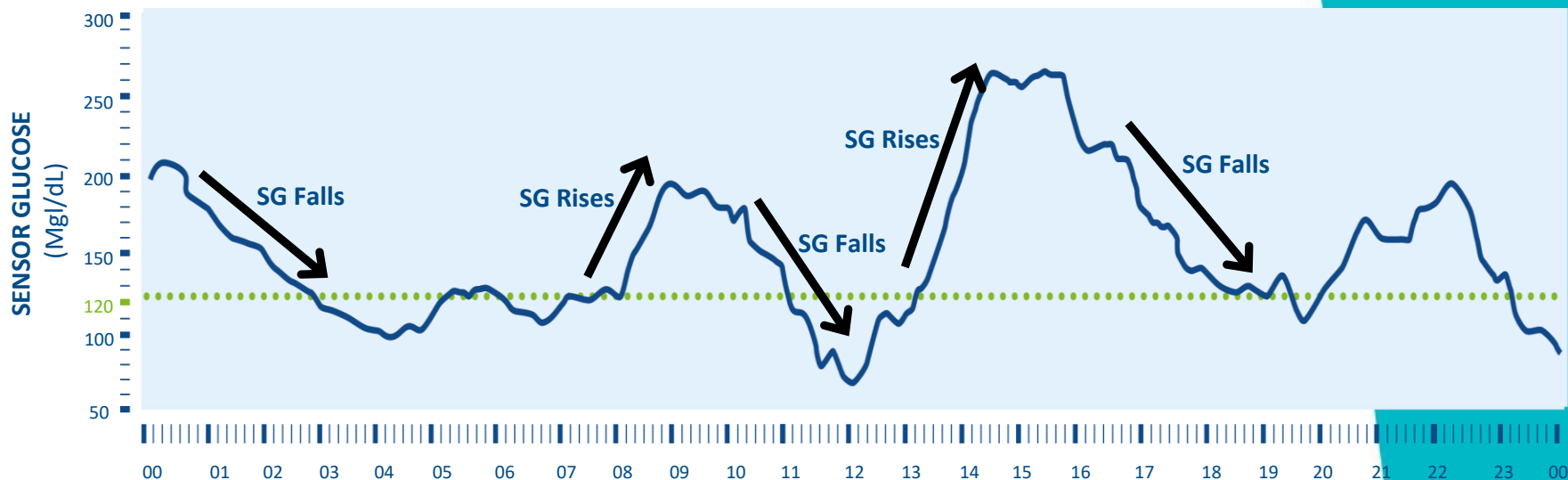
MEER WETEN



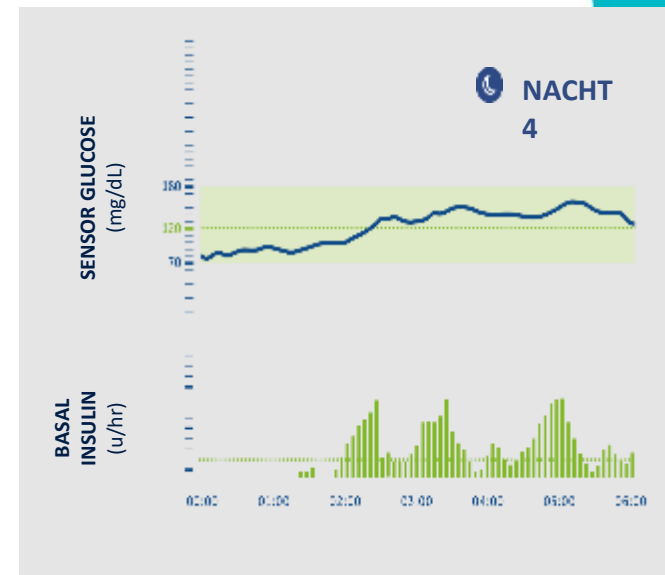
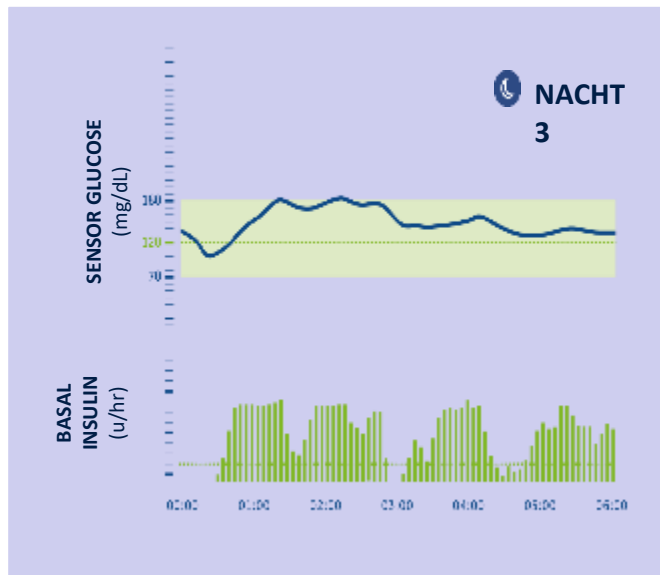
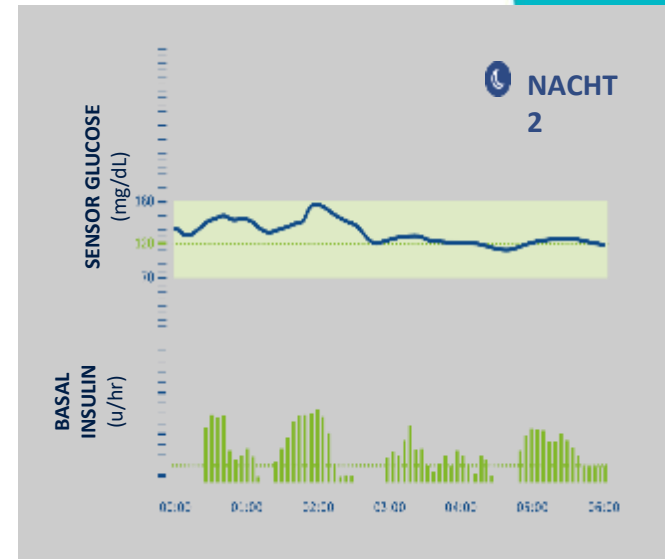
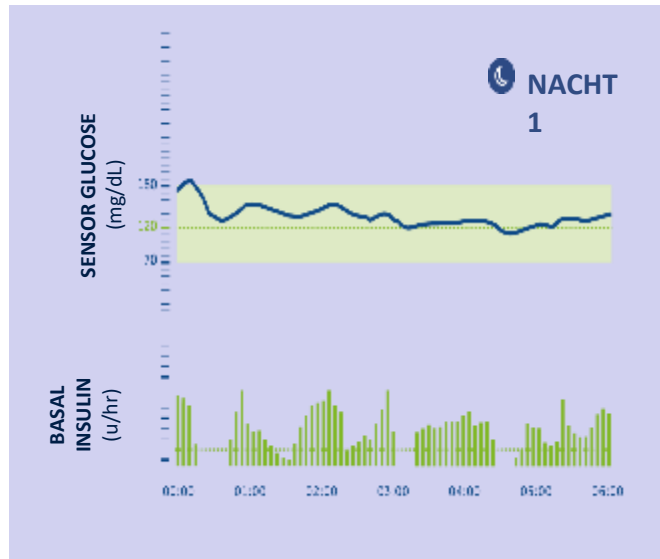
Hoe werkt het?

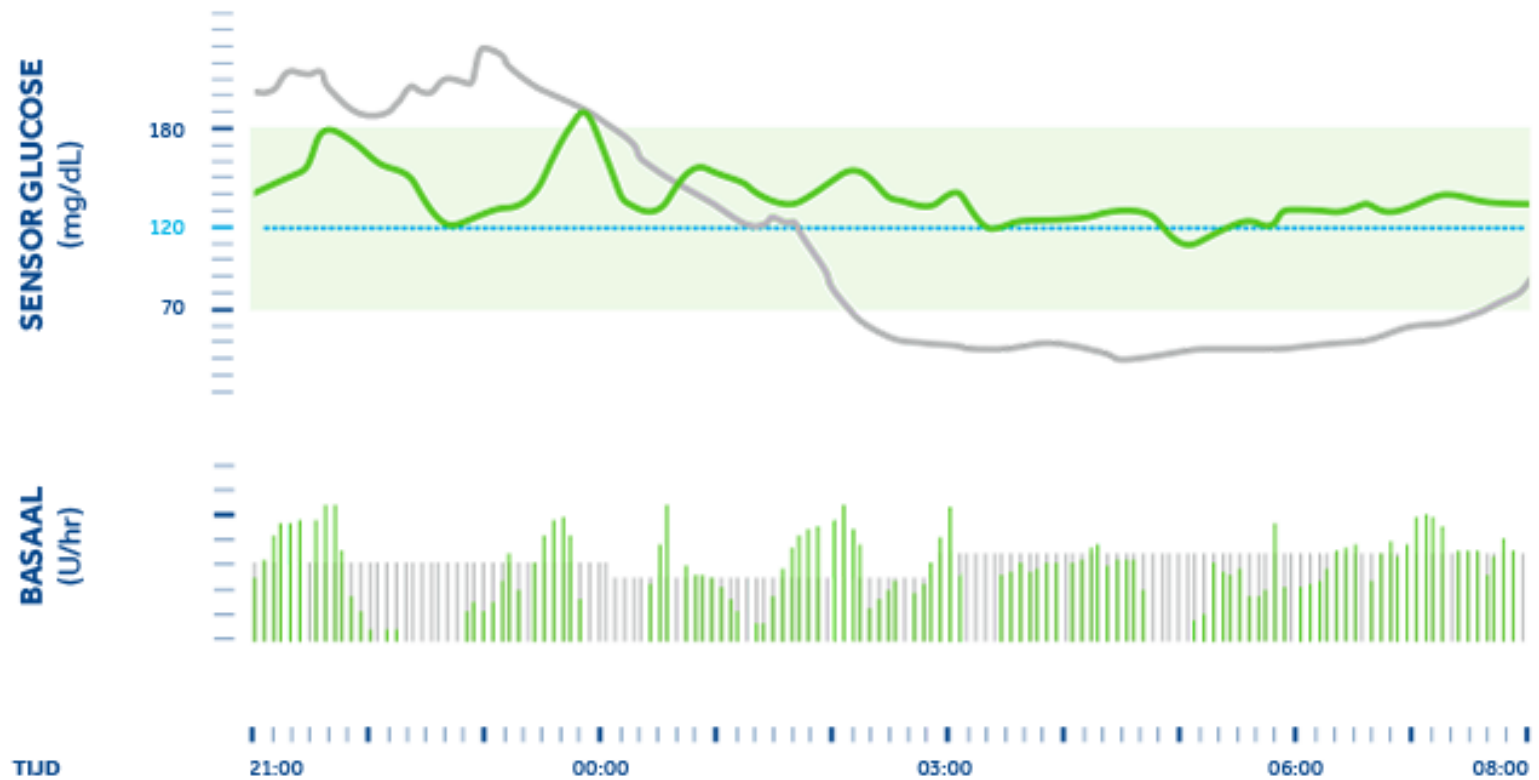
- 'Modified proportional-integral-derivative (PID) insulin feedback algorithm'
- Automatische insulinetoediening elke 5 minuten op basis van sensorwaarde
- Streefwaarden 120 mg/dl
- Stop insuline bij 80 mg/dl
- Elke nacht herberekening van minimaal basaal, maximaal basaal, insulinegevoeligheid
- "Automodus"

MINIMED™ 670G



ZICHZELF AANPASSENDE BASALE INSULINE
TOEDIENING (ELKE 5 min)





 SmartGuard™
automatische
insulinebijsturing

 Traditionele pomptherapie
met handmatige
geprogrammeerde basaal

Hoe werkt het?

- Automodus → Veilig basaal → Manuele modus
- Veilig basaal
 - = vaste basaalratio bepaald obv insulinetoediening laatste vier uur
 - Wanneer?
 - Geen sensorwaarden meer (kalibratie? Warming-up?)
 - 'Sensor-underreading'
 - Als > 1 uur > 300mg/dl of > 3 uur boven >250 mg/dl
 - 4 uur op maximaal basaal
 - 2,5 uur op minimaal basaal
 - ...
 - Vaak extra kalibratie of bloedglucosewaarde nodig
- Manuele modus
 - Als langer dan 90 minuten in veilig basaal naar manuele modus gaan

Hoe werkt het?

- Bolus bij maaltijd ZELF toe te dienen VOOR de maaltijd!
 - Geen correctie mogelijk!
 - Bolus kan wel vervroegd gestopt worden!
 - Bolus-wizard zelf instellen
 - Geen dual wave of squarewave bolus meer mogelijk
- Correctiebolus
 - Bij waarden boven 150 mg/dl
 - Suggestie door smartguard, zelf toe te dienen
 - Geen mogelijkheid tot aanpassing
- Duur en snelheid van insulinetoediening zelf te bepalen
- Gevoeligheid voor insuline wordt door pomp zelf bepaald
- Tijdelijk basaal NIET meer mogelijk, wel tijdelijk target van 150 mg/dl (max 12 uur)

MINIMED™ 670G

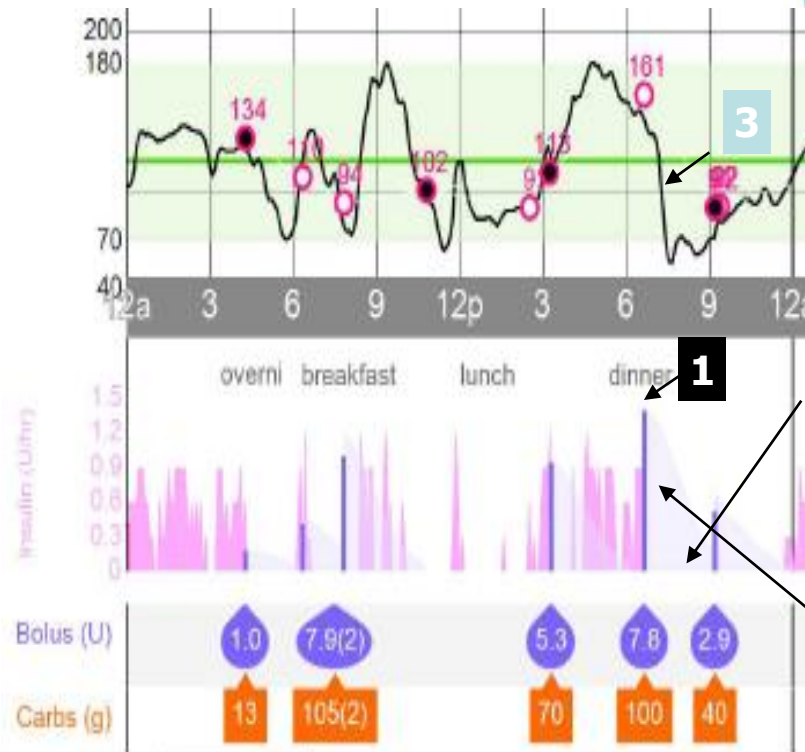


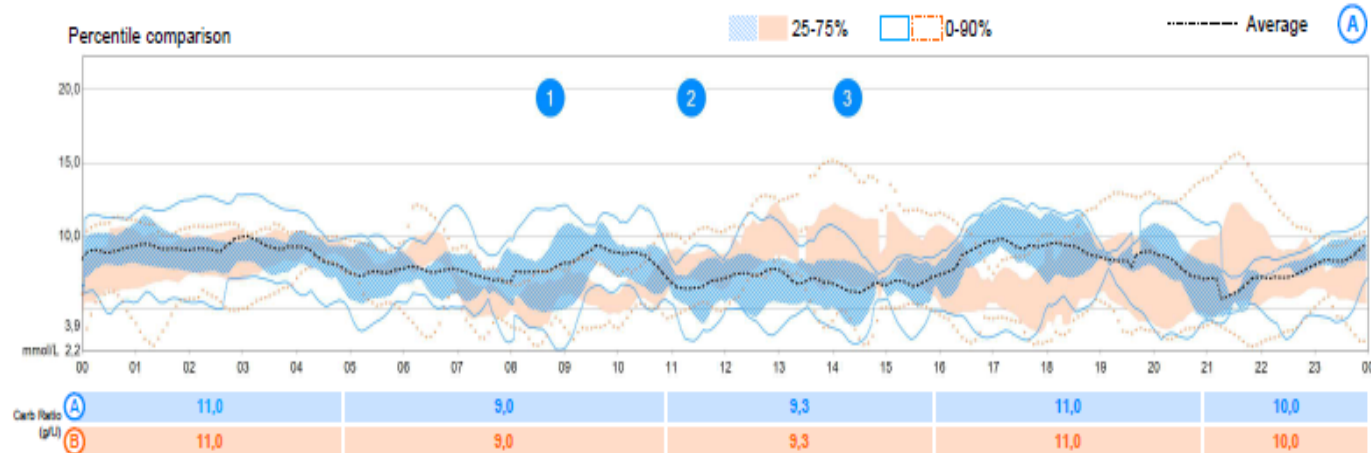
1 Maaltijdbolus 7.8U (100gr)

2 Actieve Insuline

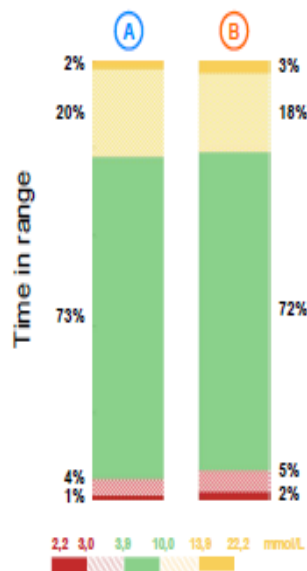
3 Dalende trend +
Actieve insulinen

4 >> Geen basaal





A	Hypoglycemic patterns (5)**			Hyperglycemic patterns (0)	
	1 08:19- 09:09 (1 occurrences)	2 11:09- 11:34 (1 occurrences)	3 13:57- 14:37 (1 occurrences)	None	

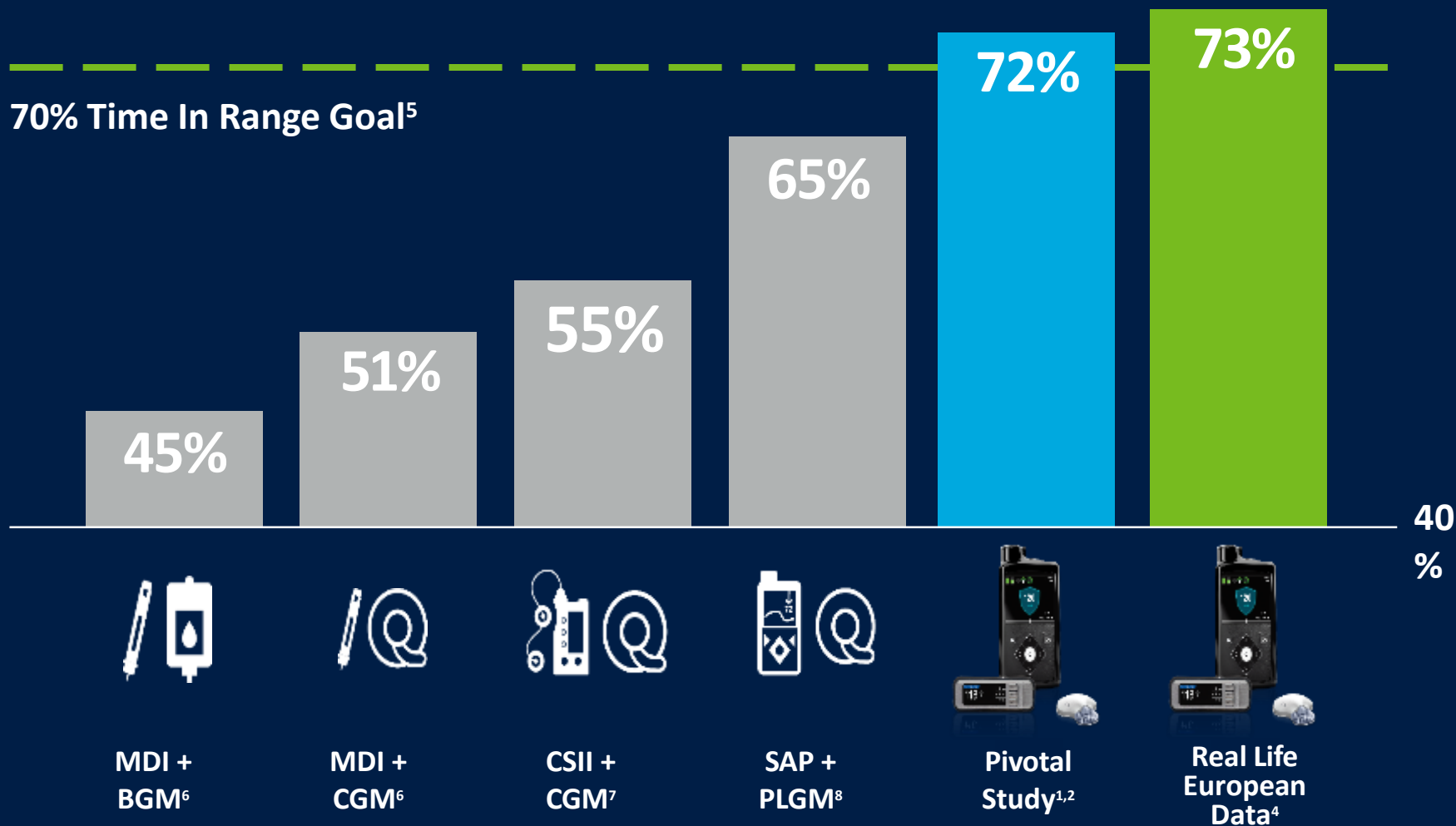


Auto Mode Exits	A	B
No Calibration	0	0
High SG Auto Mode Exit	0	1
Auto Mode max delivery	0	0
Auto Mode min delivery	2	0
BG required for Auto Mode	0	1
Sensor Algorithm Underread	0	0
Sensor Updating	0	1
No SG values	1	0
Sensor Expired	0	0
Auto Mode disabled by user	0	0
Alarms	0	0
Pump Suspend by user	0	0
Auto Mode Warm Up	0	0
Unidentified	0	0

Statistics	A	B
Auto Mode (per week)	96% (6d 18h)	97% (6d 19h)
Manual Mode (per week)	4% (06h)	3% (05h)
Sensor Wear (per week)	98% (6d 21h)	97% (6d 18h)
Average SG $\pm$ SD	8,1 $\pm$ 2,6 mmol/L	7,8 $\pm$ 2,9 mmol/L
Estimated A1C	6,7%	6,5%
Average BG	10,0 $\pm$ 2,9 mmol/L	9,8 $\pm$ 4,0 mmol/L
BG / Calibration (per day)	6,5 / 2,8	6,2 / 3,0
Total daily dose (per day)	35 units	28 units
Bolus amount (per day)	23U (66%)	17U (61%)
Auto Basal / Basal amount (per day)	12U (34%)	11U (39%)
Set Change	Every 3,0 days	Every 3,0 days
Reservoir Change	Every 3,0 days	Every 3,0 days
Meal (per day)	7,8	6,0
Carbs entered (per day)	207 $\pm$ 43 g	151 $\pm$ 37 g
Active Insulin time	2:45 hrs	2:45 hrs

** Only highest priority shown.

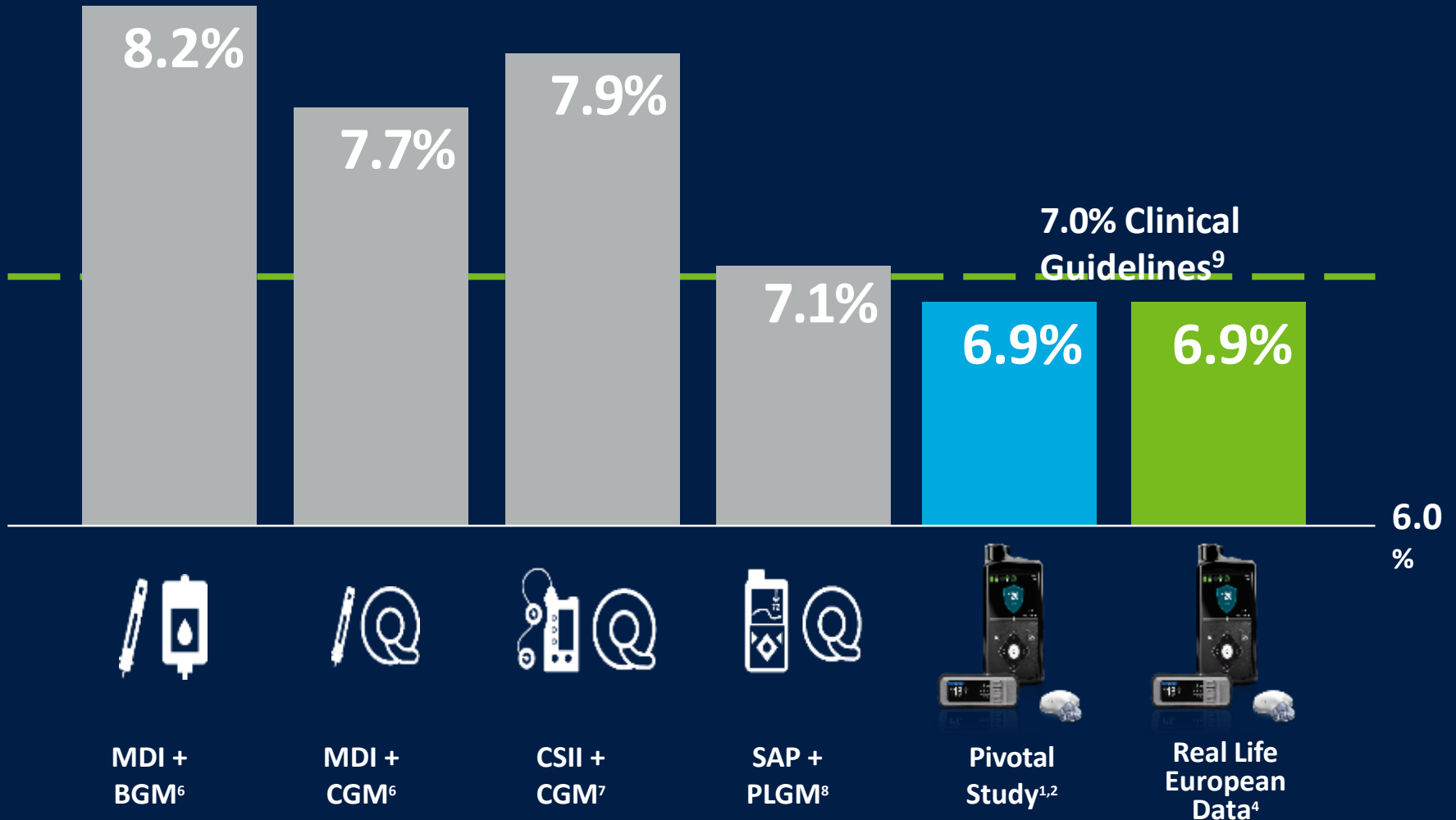
THE ONLY COMMERCIALY AVAILABLE SYSTEM
ACHIEVING THE TIME IN RANGE GOAL OF 70%
IN CLINICAL TRIALS AND IN REAL LIFE



Bergental, R. M. et al. Jama. 2016; 316 (13): 1407 – 1408 - Garg SK et al. Diabetes Technol Ther. 2017 Mar;19(3):155-163 -

Medtronic data on file. MiniMed™ 670G data uploaded voluntarily by 4,369 users in Europe to CareLink™ Personal, from 01 October 2018 to 14 August 2019.

**GLYCAEMIC CONTROL DATA HAS SHOWN THAT THE
MINIMED™ 670G SYSTEM IS THE ONLY COMMERCIALY
AVAILABLE SYSTEM ACHIEVING AN HBA1C <7.0%**



*Glucose Management Indicator

(GMI)

Garg SK et al. Diabetes Technol Ther. 2017 Mar;19(3):155-163.

Traditionele pomp vs smartguard

Voordelen

- Automatische bepaling van basaal
- Automatisch bepalen van insulinegevoeligheid
- Daling HbA1c en toename 'time in target'
- Minder hypoglycemies
- "Minder met diabetesregeling bezig zijn"

Nadelen

- Meer kalibraties nodig en extra bloedglucosewaarden
- Doelglycemie 120 mg/dl
- Geen square wave/geen dual wave
- Geen tijdelijk basaal
- Meer meldingen, meer handelingen
- Kostprijs



NIGHTSCOUT

#WeAreNotWaiting



OpenAPS

Automated Insulin Delivery:
How artificial pancreas “closed
loop” systems can aid you in
living with diabetes (introducing
“the APS book” by
@DanaMLewis)

Voorbeelden

Loop



OpenAPS



AndroidAPS



De Weg naar de Artificiële Pancreas

First Generation

Second Generation

Third Generation

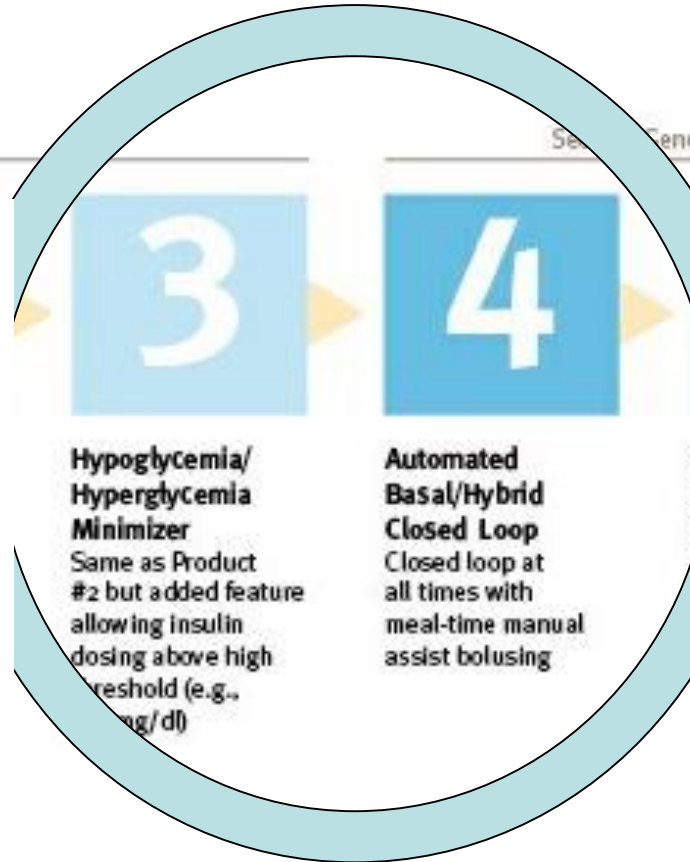
780 G Medtronic pomp

Automatische correctie bolus !

Lagere targets!

Bleutooth

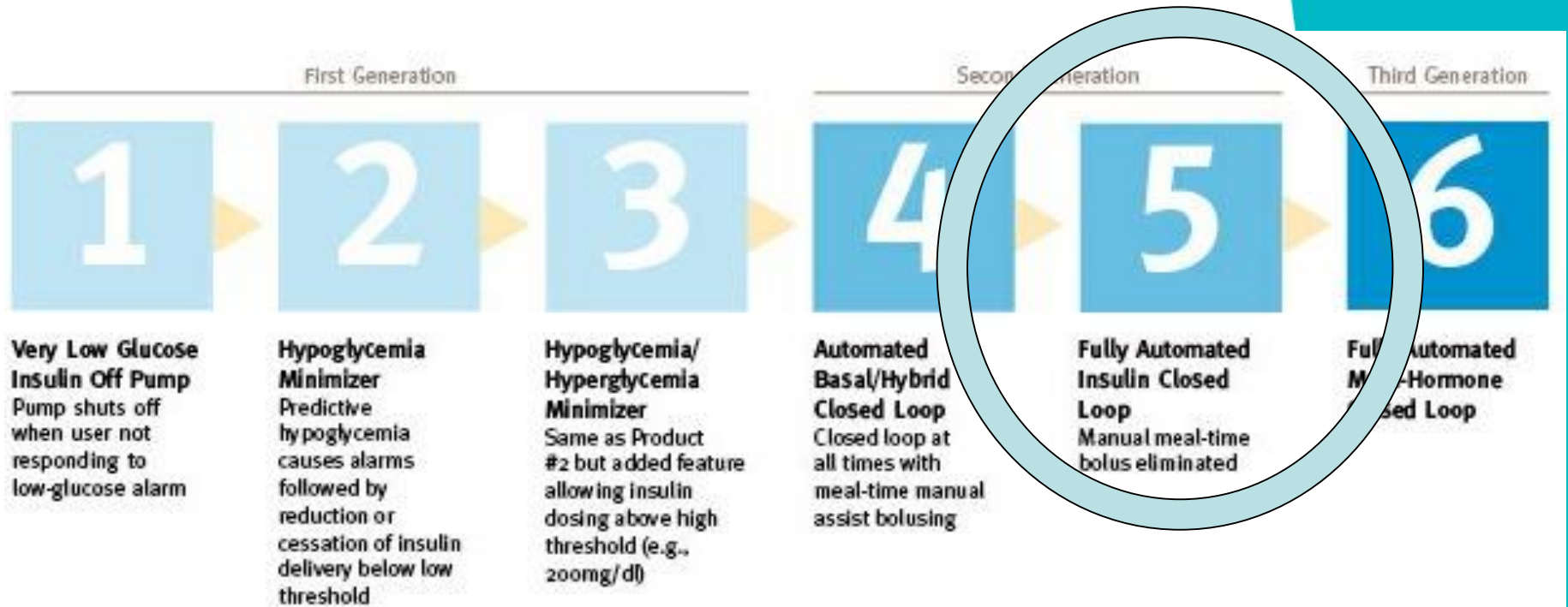
cessation of insulin delivery below low threshold



In studie lopende!

Lancering verwacht 2020!

De Weg naar de Artificiële Pancreas



De Weg naar de Artificiële Pancreas

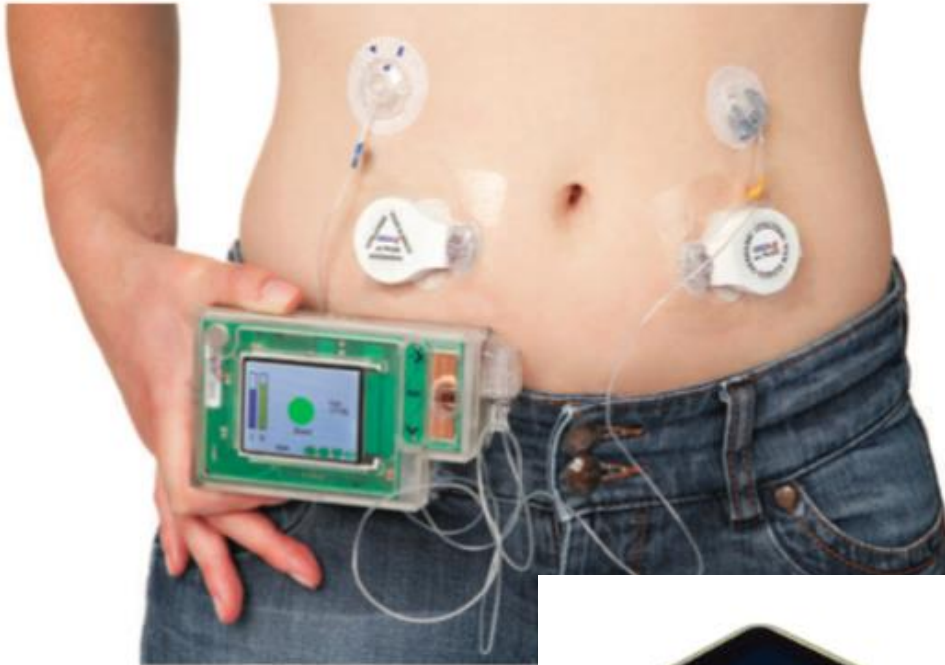
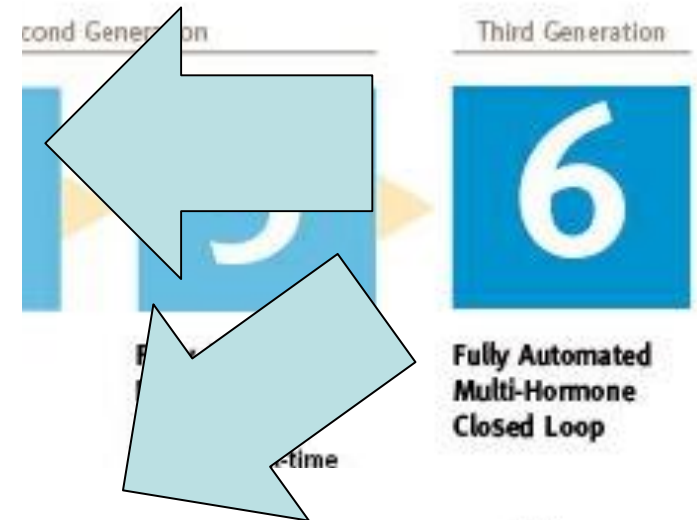


Figure 1. The Inreda integrated bionic pancreas is worn on a belt. One infusion set is connected to the insulin pump and the other to the glucagon pump. The device measures glucose levels and provides real-time feedback to the pumps.



Beta Bionics
A Massachusetts Public Benefit Corporation



iLet™

The one and only fully integrated, fully automated, bi-hormonal bionic pancreas



Focus behandeling type 1 diabetes

1. PREVENTIE

- Immuuntherapie

2. BETERE GLUCOSECONTROLE

- Betere insuline
- Bijkomende niet-insuline behandelingen

3. PERFECTE GLUCOSECONTROLE = toename tijd in range

- Continue glucosemonitoring
- Insulinepompen
- Artificiële pancreas

4. GENEZING

- Pancreas- en betaceltransplantatie
- Bioartificiële pancreas

Betacel – en pancreastransplantatie

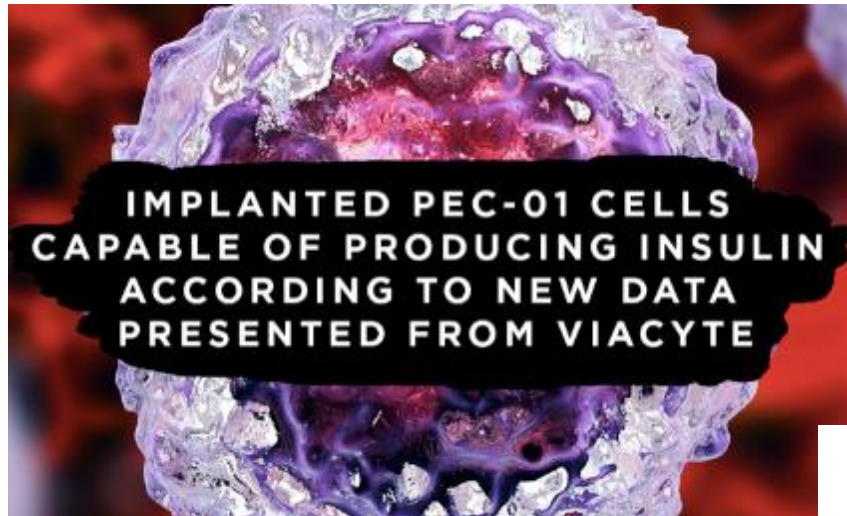
Pancreastransplantatie

- Strikte criteria
- Zware abdominale ingreep
- Immunosuppressiva
- Vaak combinatie met niertransplantatie
- Goede resultaten op lange termijn

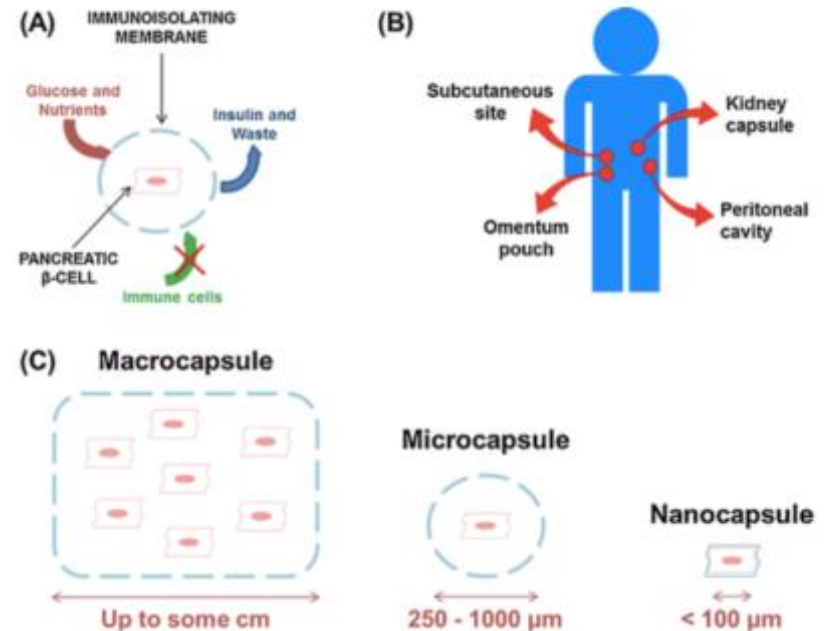
Betaceltransplantatie

- Strikte criteria
- Relatief eenvoudige ingreep
- Immunosuppressiva
- Meerdere donoren noodzakelijk
- Langetermijn overleving van betacellen beperkt

Bioartificiële pancreas

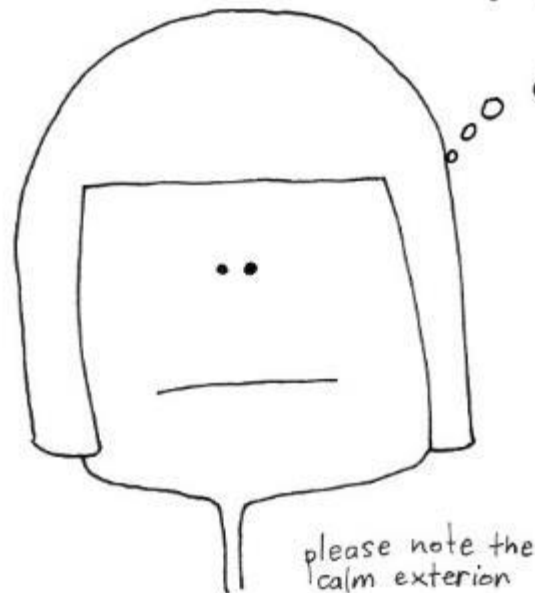


VIACYTE
Regenerating Health®



Vragen?

what goes on in a diabetic's head:



When did I last eat? Where's my meter? What's my blood sugar? How many carbs in that cookie? That pie? That salad? Do I need to pee? Are my feet dry? How long until lunch? Who will attend my funeral? How will people know I died? Any doctor's appointments today? tomorrow? Am I shaky? Am I nervous or is my blood sugar low? Is my blood sugar low or am I just a bitch? Is there sugar nearby? Am I doing my best? What does the clock say? What does the meter say? What does the pump say? What does the A1C say? What will my friends say? Am I acting normally? Am I pale? Can I make it to lunch? Am I ok to drive? do I have enough test strips? Does he know I'm diabetic? Am I hungry or am I full? How many Oreos can I make a serving? Do I have bad genes? Can I afford health care? why does my head hurt? Who's...