PCDSA-NADC Diabetes Summit
1st June 2019

WHAT'S NEW IN DIABETES?

A/Prof Gary Kilov

If This is Your Response to The Bewildering Array of Changes in The Diabetes Eco-space

What's new in diabetes- An update

- **In search of the Holy grail**
- **What’s changed in 2007?**
- **The era of the CVOT**
- **Insulin**
- **Tech *and* What’s new and around the corner (possibly)**

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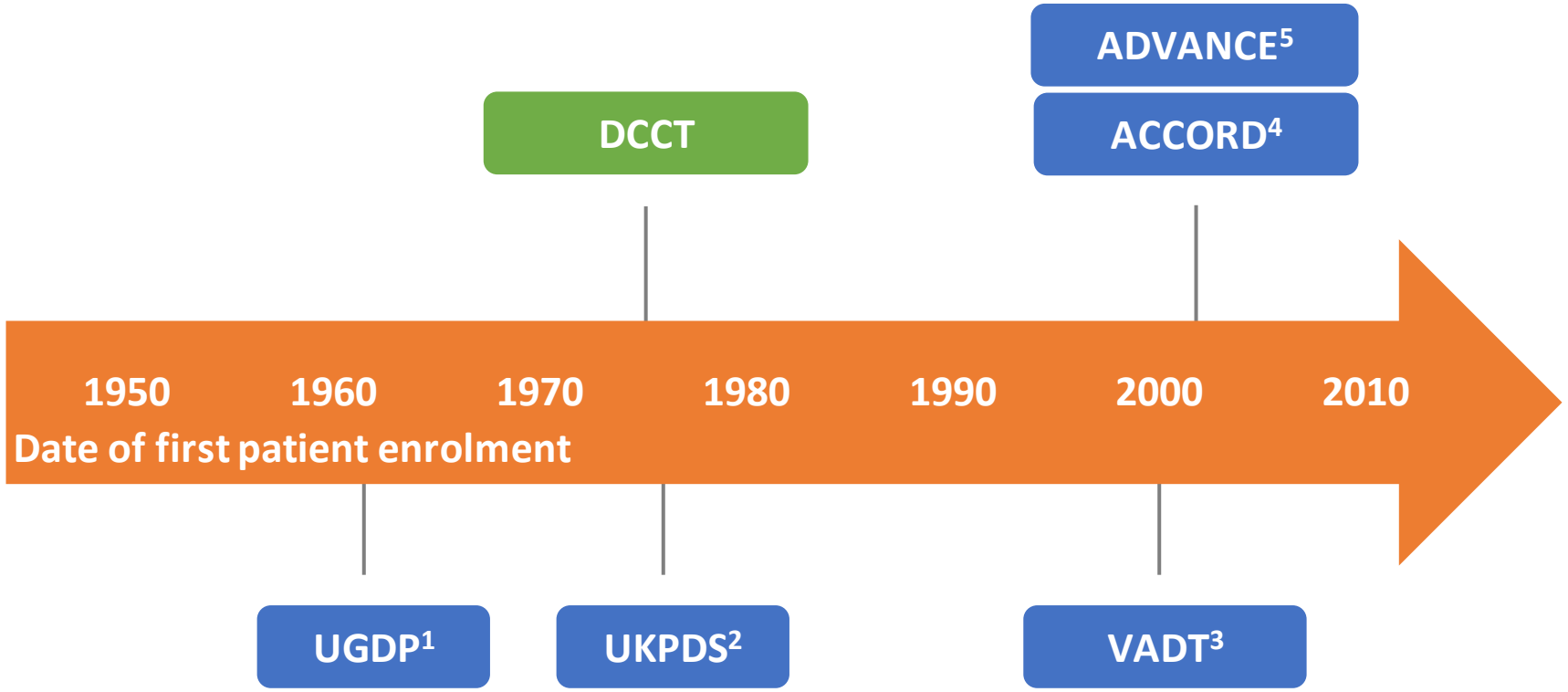
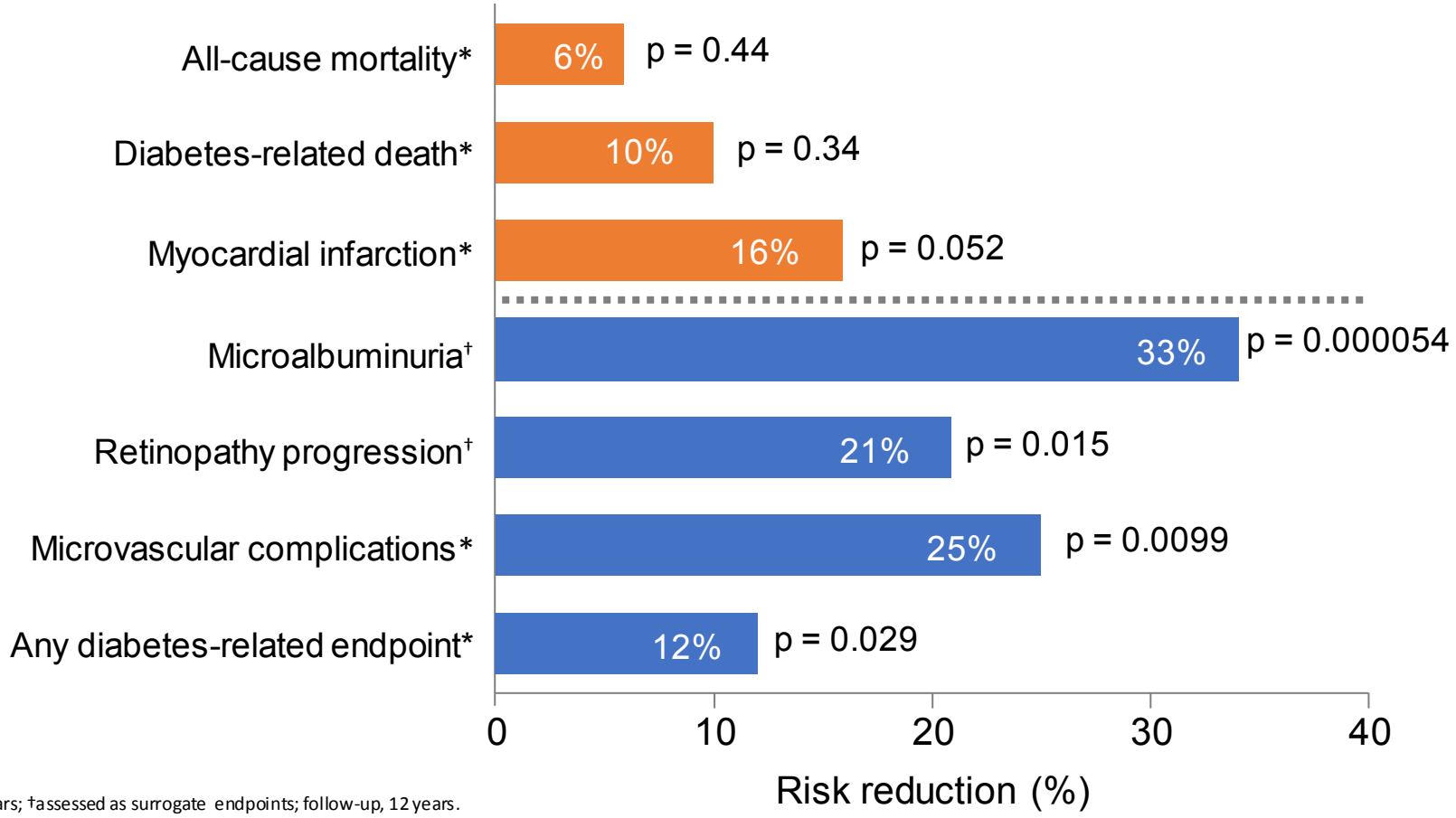
Major historic T2D CV outcomes trials focused on intensive vs conventional glycaemic control



- 1. Meinert et al. Diabetes 1970;19(suppl):789–830. 2. UKPDS 33. Lancet 1998;352:837–53.
  3. Duckworth et al. N Engl J Med 2009;360:129–39. 4. Gerstein et al. N Engl J Med 2008;358:2545–59.
  5. Patel et al. N Engl J Med 2008;358:2560–72.

UKPDS: Intensive glycaemic control reduced microvascular but not (so much) macrovascular outcomes



*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.

UKPDS 33. Lancet 1998;352:837–53.

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	**9%→ 7.9% vs 7%**	**Newly diagnosed**	↓	↓	↔	↓	↔	↓

Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria [2,3]

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.
3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

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The release of the 1st iPhone

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

FDA guidance on CV safety

- In **December 2008**, the FDA recommended that new drugs for type 2 diabetes must generate data demonstrating they are not associated with an unacceptable increase in **CV risk**
- Phase 2 and 3 studies need to be designed to allow reliable **meta-analysis of CV events**
  - Independent blinded adjudication committee for CV events which should include **cardiovascular mortality, myocardial infarction, and stroke**, and can include hospitalization for acute coronary syndrome urgent revascularisation procedures, and possibly other endpoints
  - Include **high-risk patients**

FDA. Guidance for Industry. Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Accessed : 12 Nov, 2010.

MEDPAGE TODAY®

The Most Wonderful Mistake the FDA Ever Made

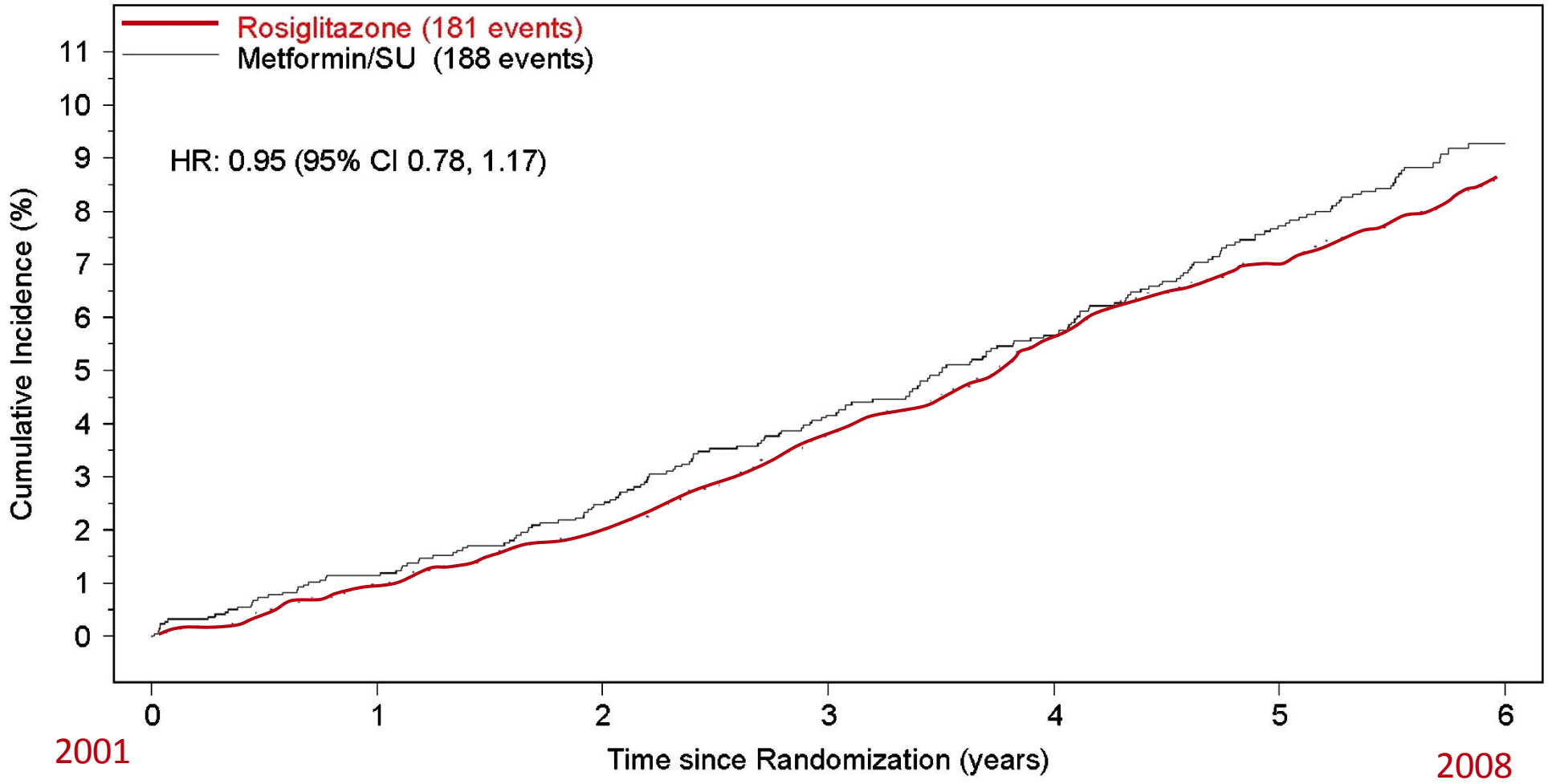
— Milton Packer explains how an FDA error enlightened the practice of medicine

by Milton Packer MD

December 05, 2018

RECORD:

Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes 2001-2008



Rosaglitazone							
Events	0	21	43	79	117	144	170
At Risk	2220	2117	2043	1956	1877	1803	848
Metformin/SU							
Events	0	25	53	88	118	158	183
At Risk	2227	2119	2040	1956	1871	1755	809

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DPP4i Cardiovascular Outcome Trials

- **Preferred DPP4 inhibitors**
  - Sitagliptin (Januvia)
  - Linagliptin (Trajenta)

Generic			Result
Sitagliptin	Januvia		**NEUTRAL**
Saxagliptin	Onglyza	SAVOR	**RAL** **F RISK)**
Alogliptin	Nesina	EXAMINE	**NEUTRAL** (↑ HF SIGNAL)
Linagliptin	Trajenta	CARMELINA	**NEUTRAL**

SGLT2i Cardiovascular Outcome Trials

Generic	Trade Name	Trial	Result
Empagliflozin		EG OUTCOME	POSITIVE
Canagliflozin			ons and
Dapagliflozin	Forxiga	DECLARE-	
Ertugliflozin	Steglatro	VERTIS CV	2019

- Preferred SGLT2 inhibitors for secondary prevention:
- ? Empagliflozin > Dapagliflozin
- Still unclear about secondary prevention but perhaps dapagliflozin if no baseline established CVD
- Ertugliflozin CVOT will be here later this year

GLP1 Agonist Cardiovascular Outcome Trials

Generic	Trade Name	Trial	Result
Liraglutide		LEADER	POSITIVE
Exenatide			
Dulaglutide	Trulicity		)
Lixisenatide	Lyxumia	ELIXA	
Semaglutide	? Ozempic	SUSTAIN-6	POSITIVE
Albiglutide	Tanzeum	HARMONY	POSITIVE
Semaglutide PO		PIONEER 6	

- **Preferred PBS reimbursed GLP1 agonist for secondary prevention:**
- **Dulaglutide>Exenatide**

Choices are based on agent + Patient factors

Second line

AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

Australian Diabetes Society

All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight control

Determine the individual's HbA_{1c} target – this will commonly be ≤ 53 mmol/mol (7.0%).

If not at target, or if an HbA_{1c} reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm.

First line: Metformin is the usual first-line therapy unless contraindicated or not tolerated

Metformin	SU	Insulin	Acarbose	DPP-4 inhibitor	SGLT2 inhibitor	TZD

If HbA_{1c} target not achieved in 3 months:

- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

Second line: If metformin was not used first line, add it now, if not contraindicated.
Choice of second line agent to add to metformin should be guided by clinical factors/considerations, contraindications, side effect profile and cost.

DPP-4 inhibitor	SGLT2 inhibitor	SU	GLP-1RA	Insulin*	Acarbose	TZD

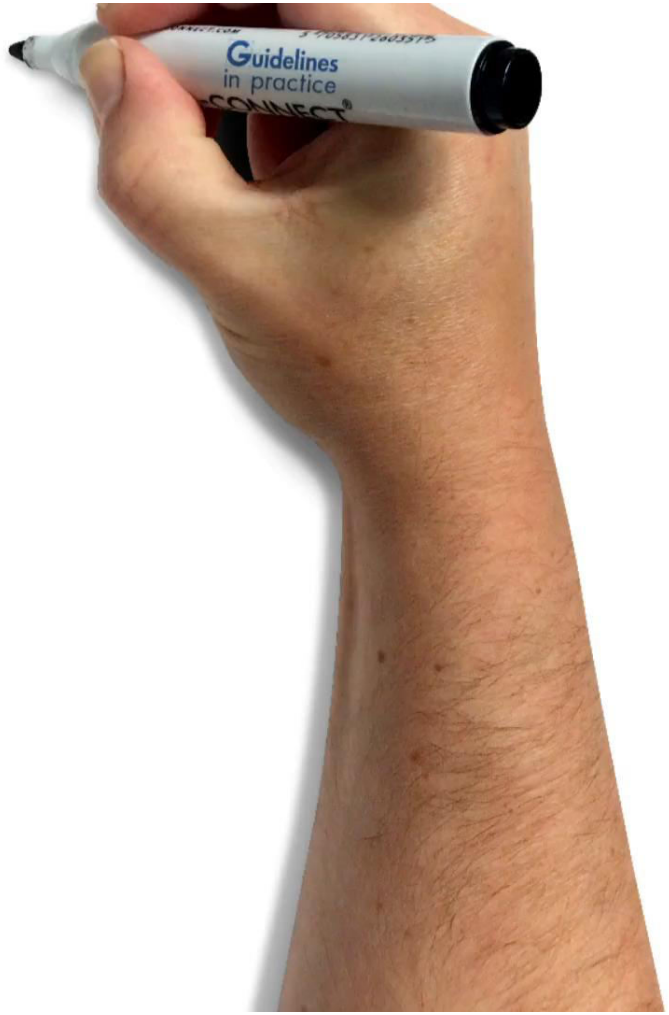
Key Update

ADA/EASD Guidelines

Management of Hyperglycemia in Type 2 Diabetes, 2018.
A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Davies MJ et. al., Diabetes Care 2018 Sep; dci180033. https://doi.org/10.2337/dci18-0033

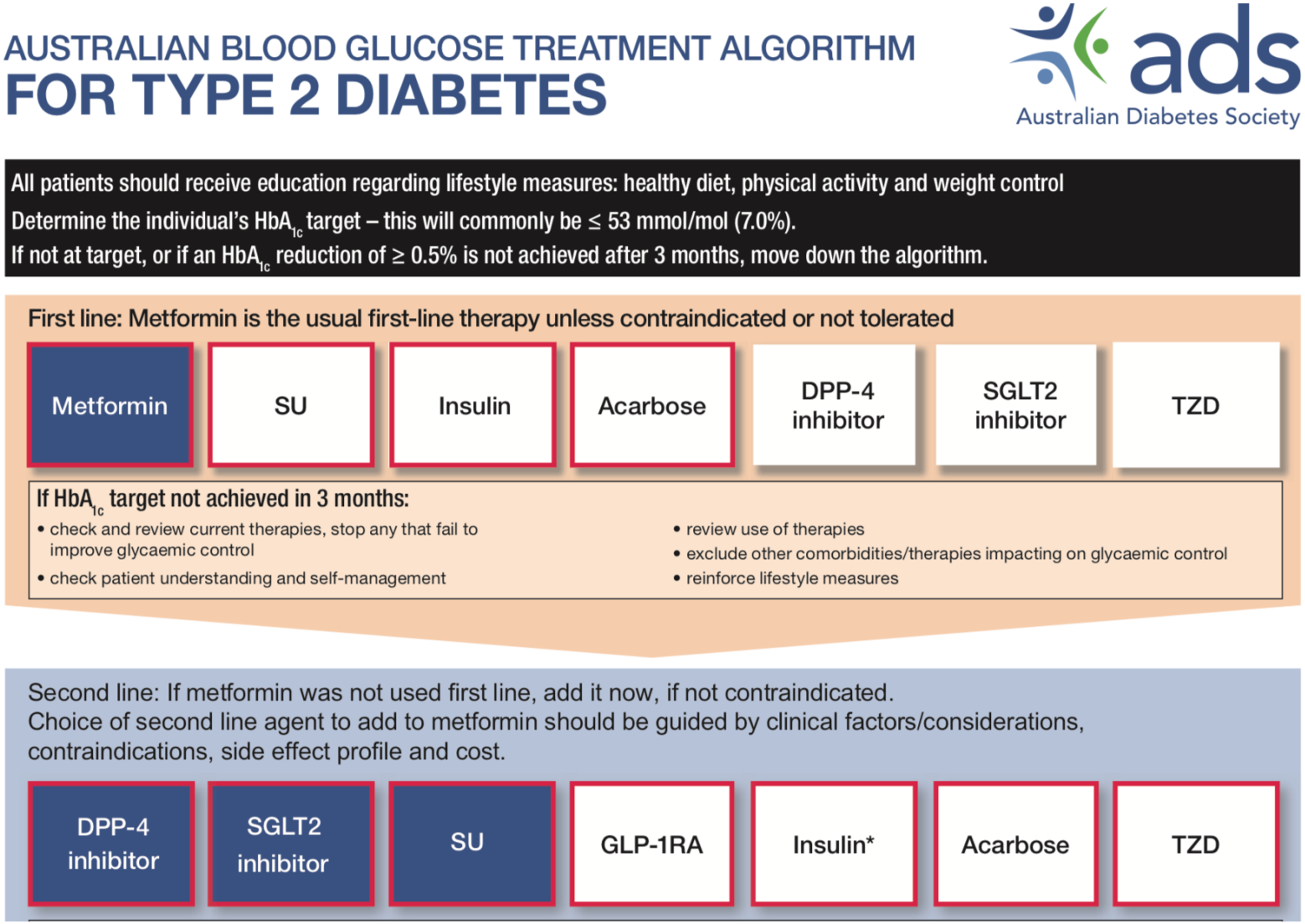
ADA-EASD guidelines- Prof Melanie Davies



Current paradigm:

Choices are based on agent + Patient factors

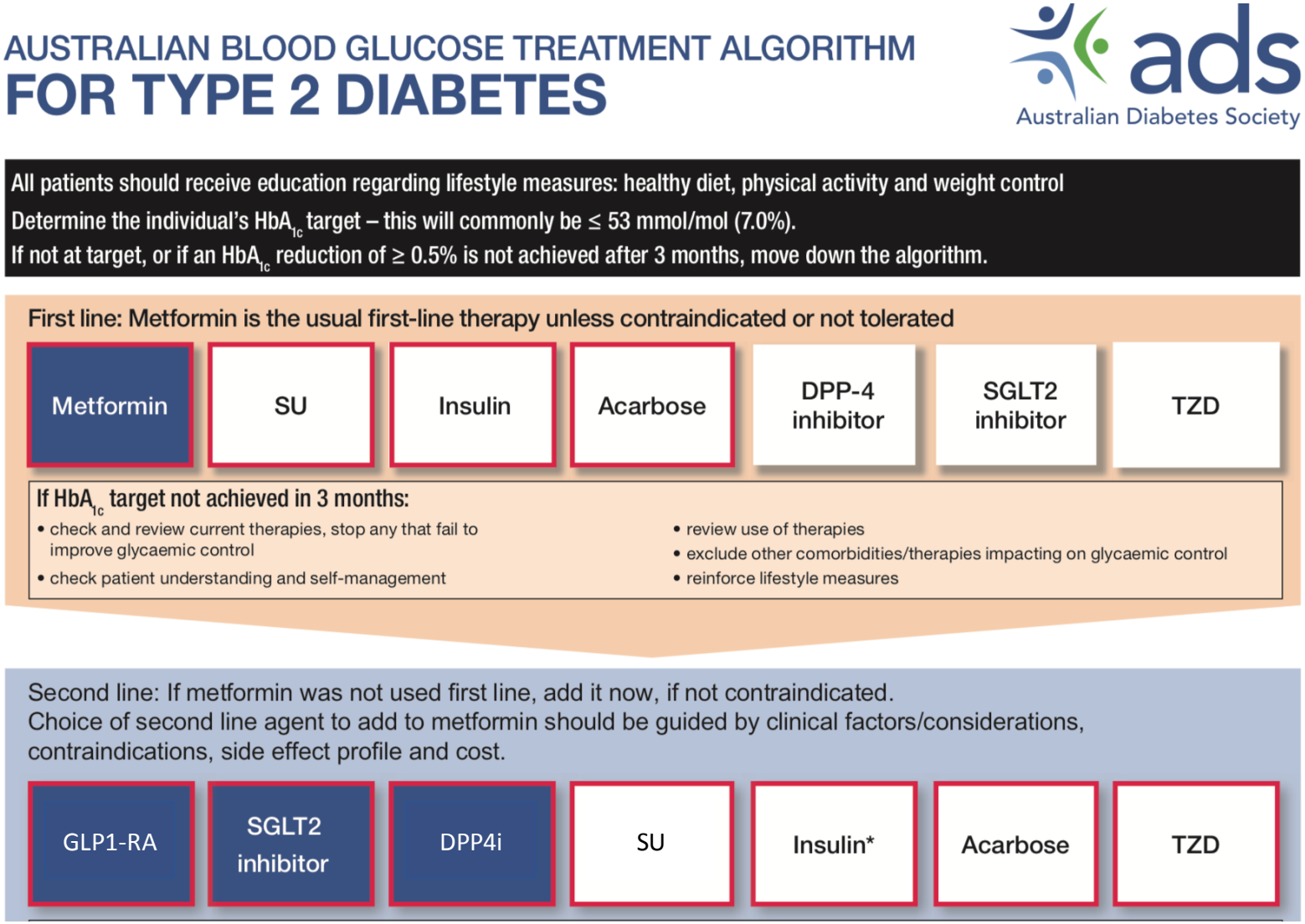
Second line



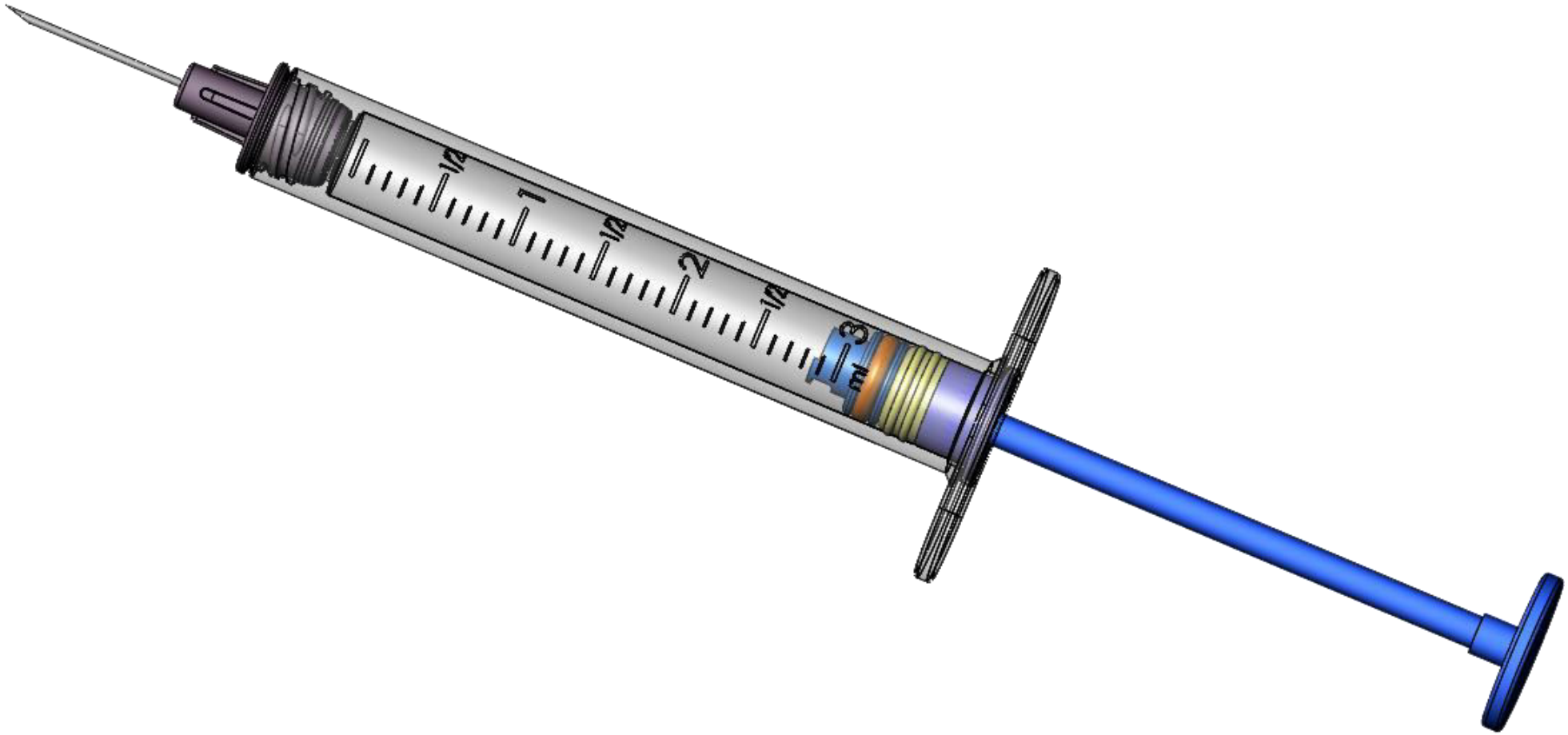
New paradigm:

Choices are based on agent + Patient factors

Second line



Choosing the first injectable



American Diabetes Association (ADA) & European Association for the Study of Diabetes (EASD)
Consensus Guidelines 2018

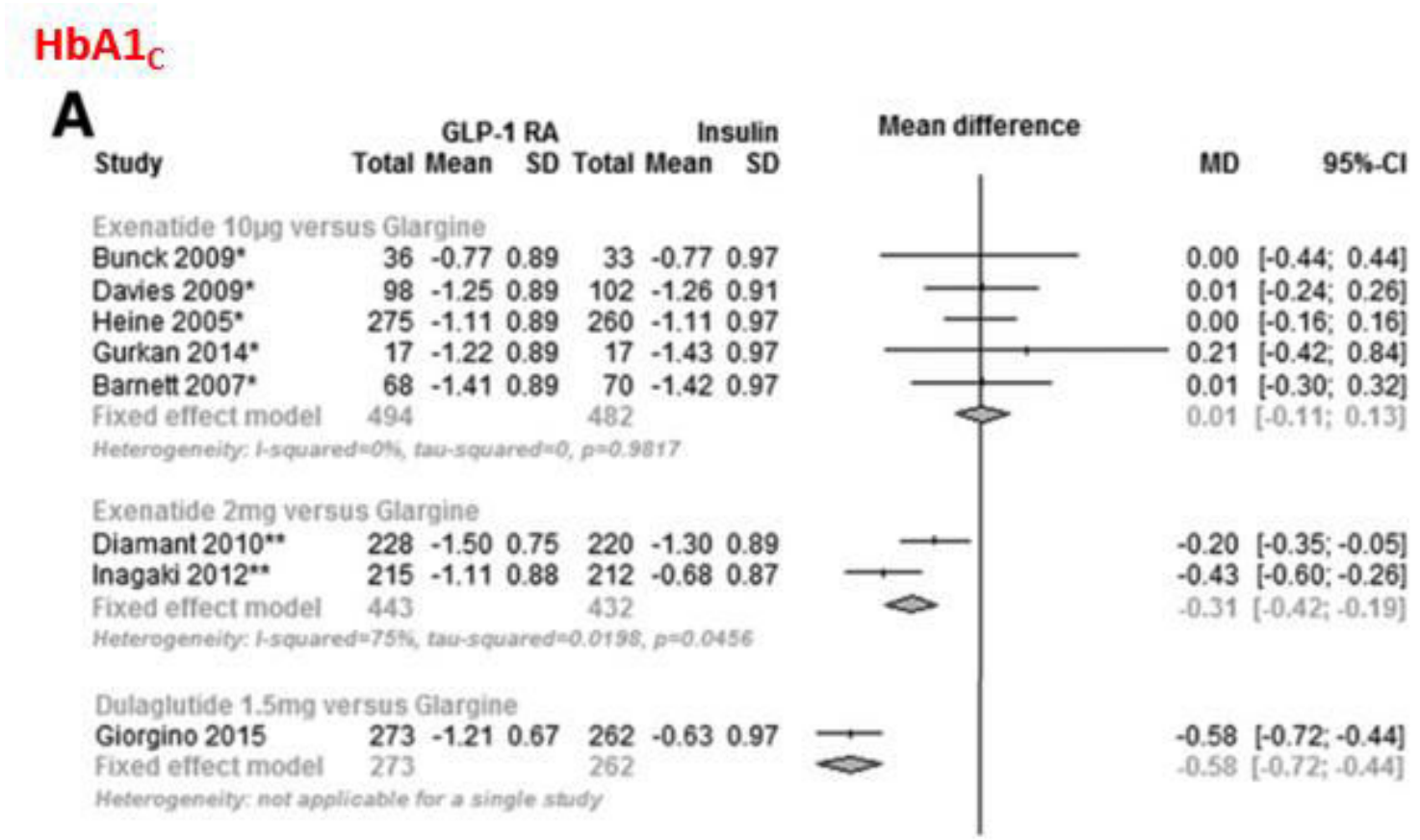
Consensus recommendation

"In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the ***preferred choice to insulin****. For patients with extreme and symptomatic hyperglycaemia, insulin is recommended".*

Davies MJ et. al., Diabetes Care 2018 Sep; dci180033. https://doi.org/10.2337/dci18-0033

GLP1a vs basal insulin- Efficacy

- Meta analysis of exenatide and dulaglutide vs basal insulin[1]

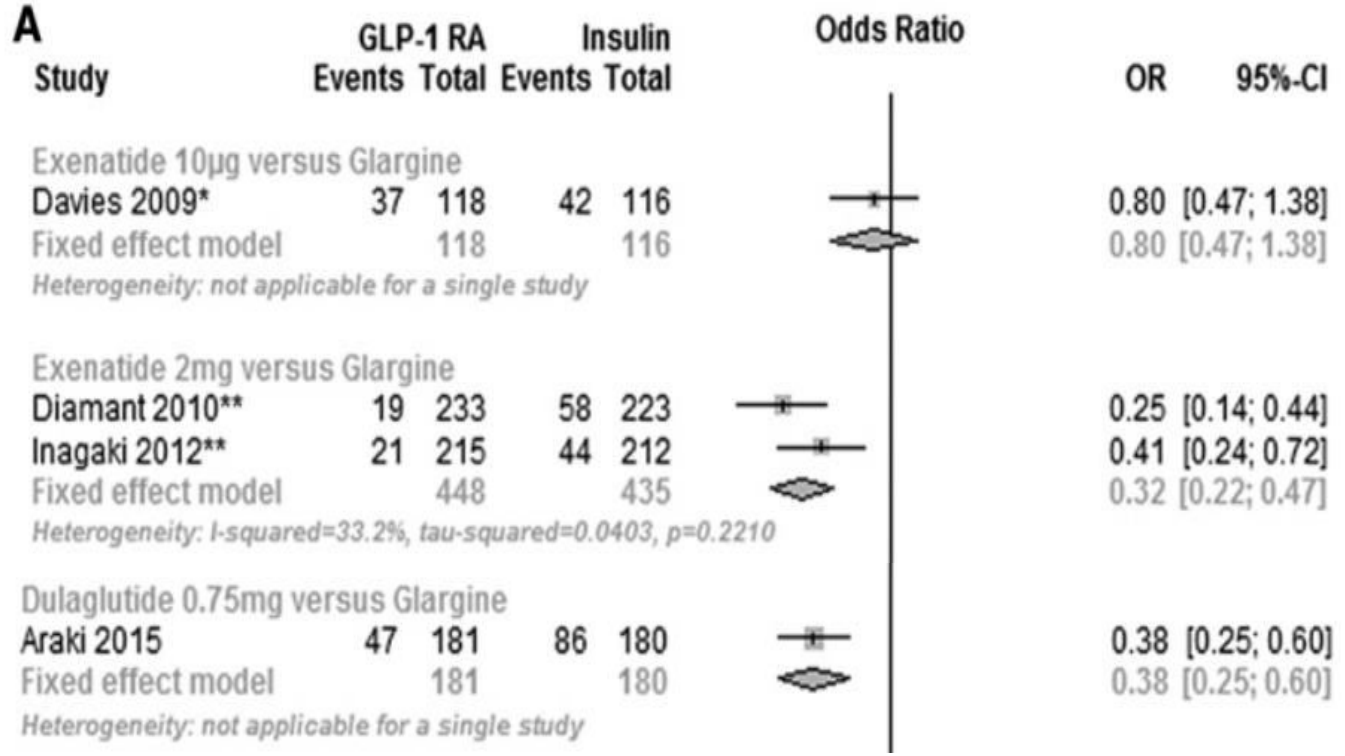


REFERENCE: 1. Singh S Diabetes Obes Metab. 2017 Feb;19(2):228-238. doi: 10.1111/dom.12805. Epub 2016 Dec 5.

GLP1a vs basal insulin- Safety

- Meta analysis of exenatide and dulaglutide vs basal insulin[1]

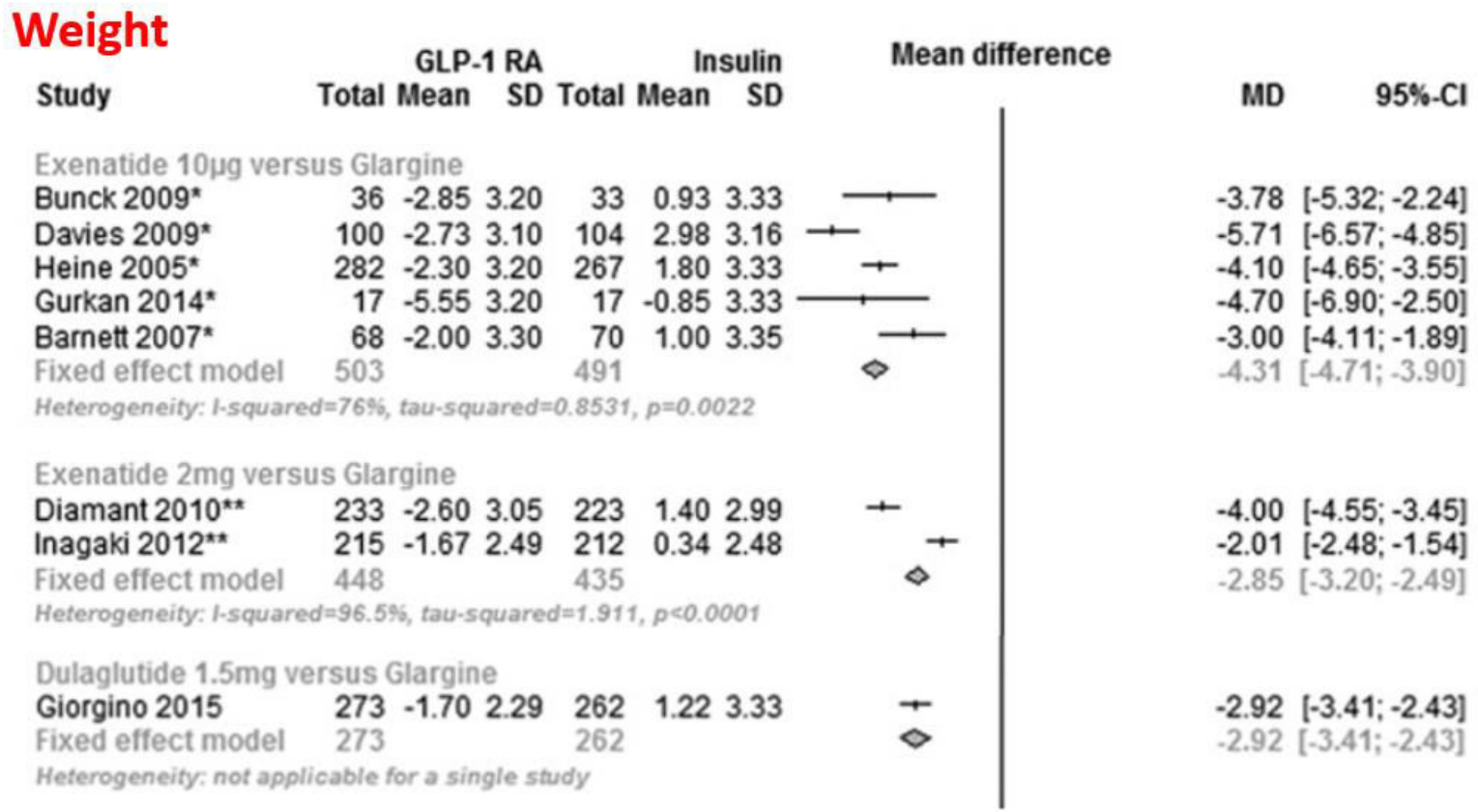
Hypoglycaemia



REFERENCE: 1. Singh S Diabetes Obes Metab. 2017 Feb;19(2):228-238. doi: 10.1111/dom.12805. Epub 2016 Dec 5.

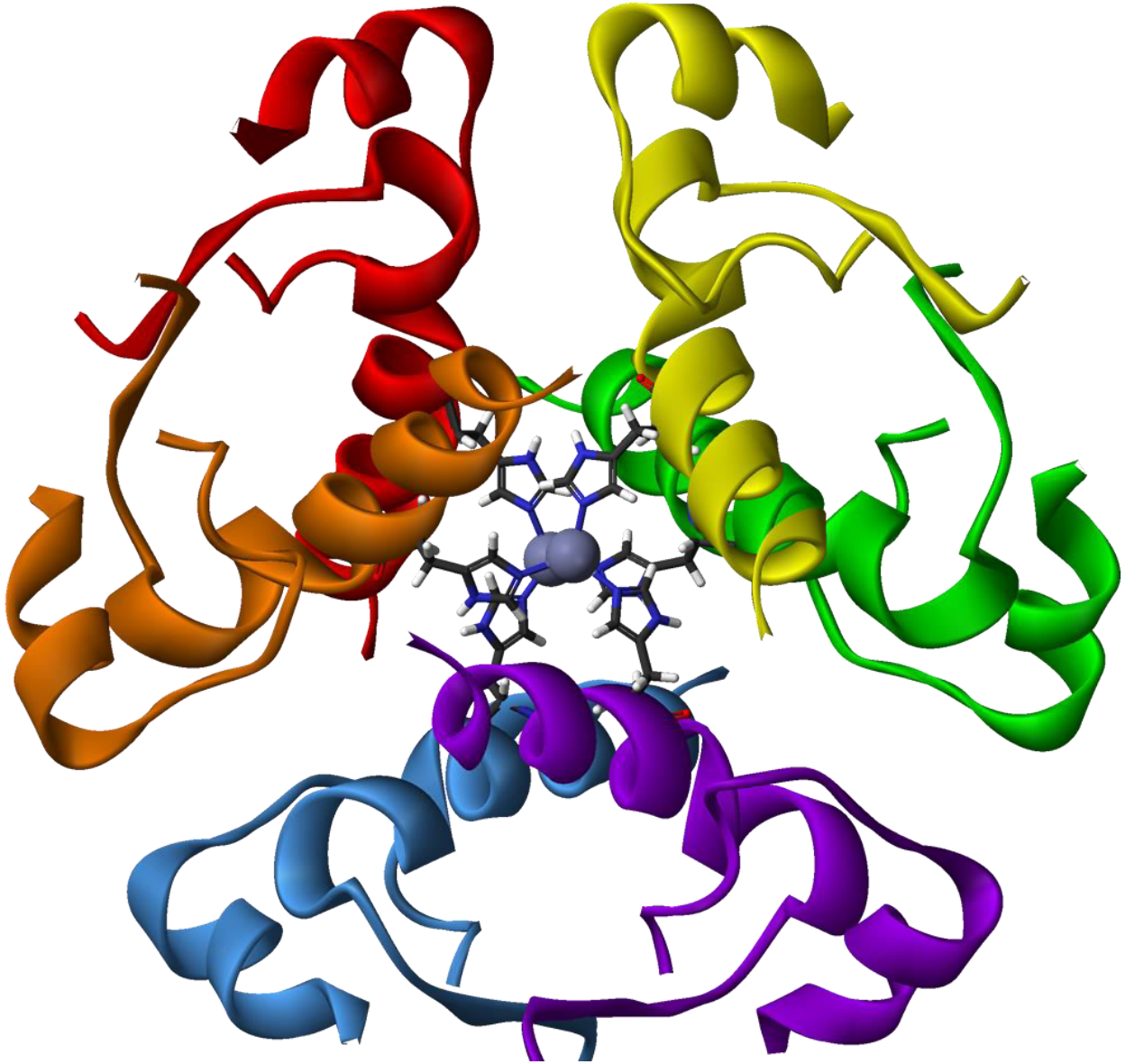
GLP1a vs basal insulin - Tolerability

- Meta analysis of exenatide vs basal insulin[1]

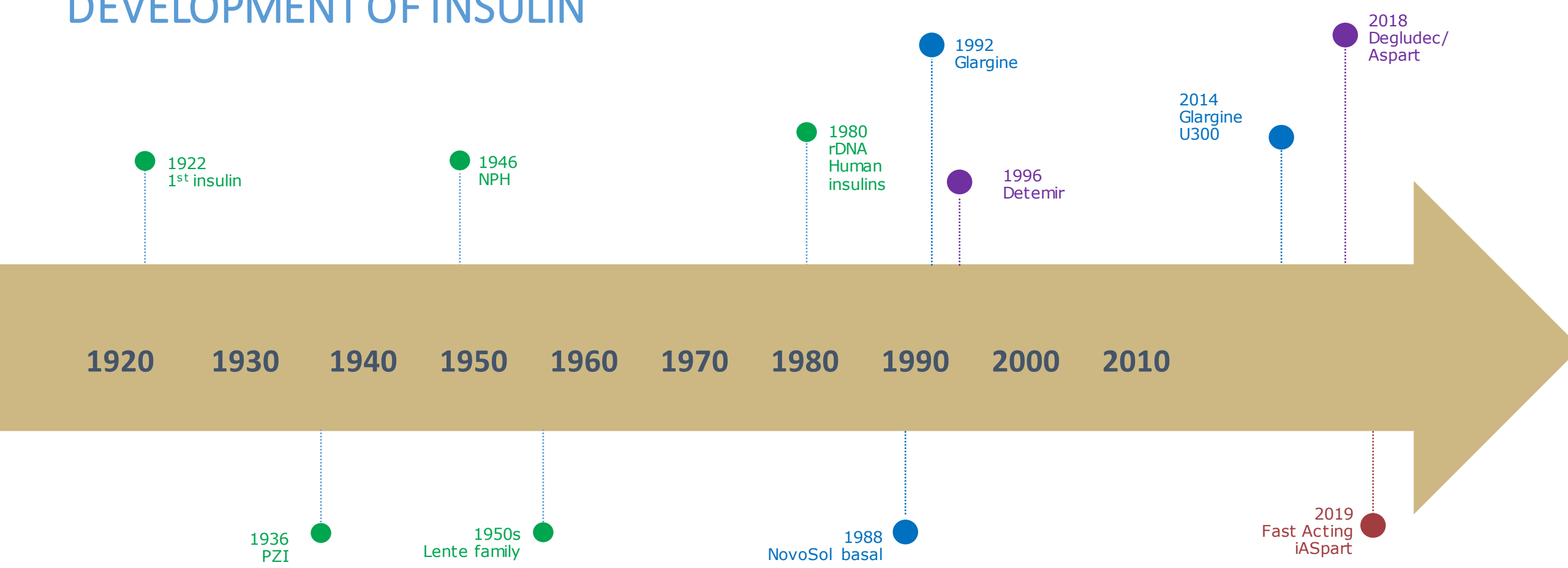


REFERENCE: 1. Singh S Diabetes Obes Metab. 2017 Feb;19(2):228-238. doi: 10.1111/dom.12805. Epub 2016 Dec 5.

Insulin and hypoglycaemia



DEVELOPMENT OF INSULIN



Change is isoelectric point towards neutral pH

Acylation of insulin with fatty acids C14-C16

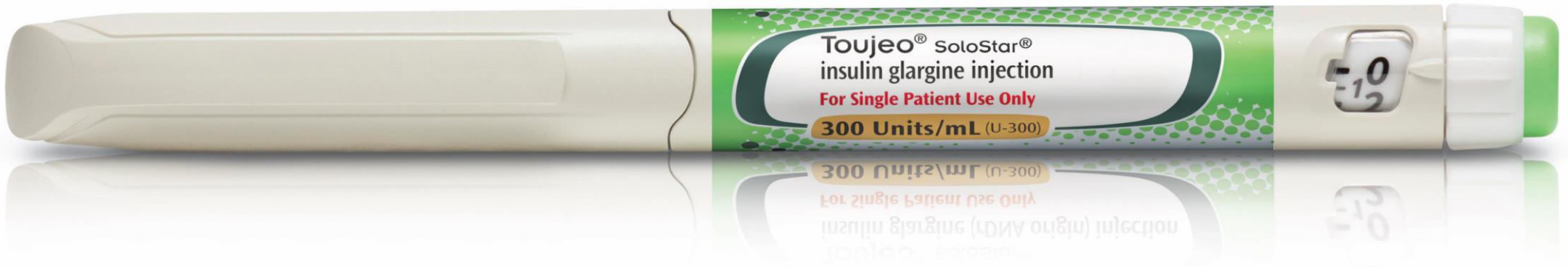
2nd generation analog Insulin

- Glargine u300
- IdegAsp Degludeg
- Insulin Aspart
  withVitamin B3 (niacinamide) to accelerate absorption and an amino acid (L-Arginine), to stabilise the formulation.
- Glargine u300 upsised

- Toujeo
- Ryzodeg
- FiAsp

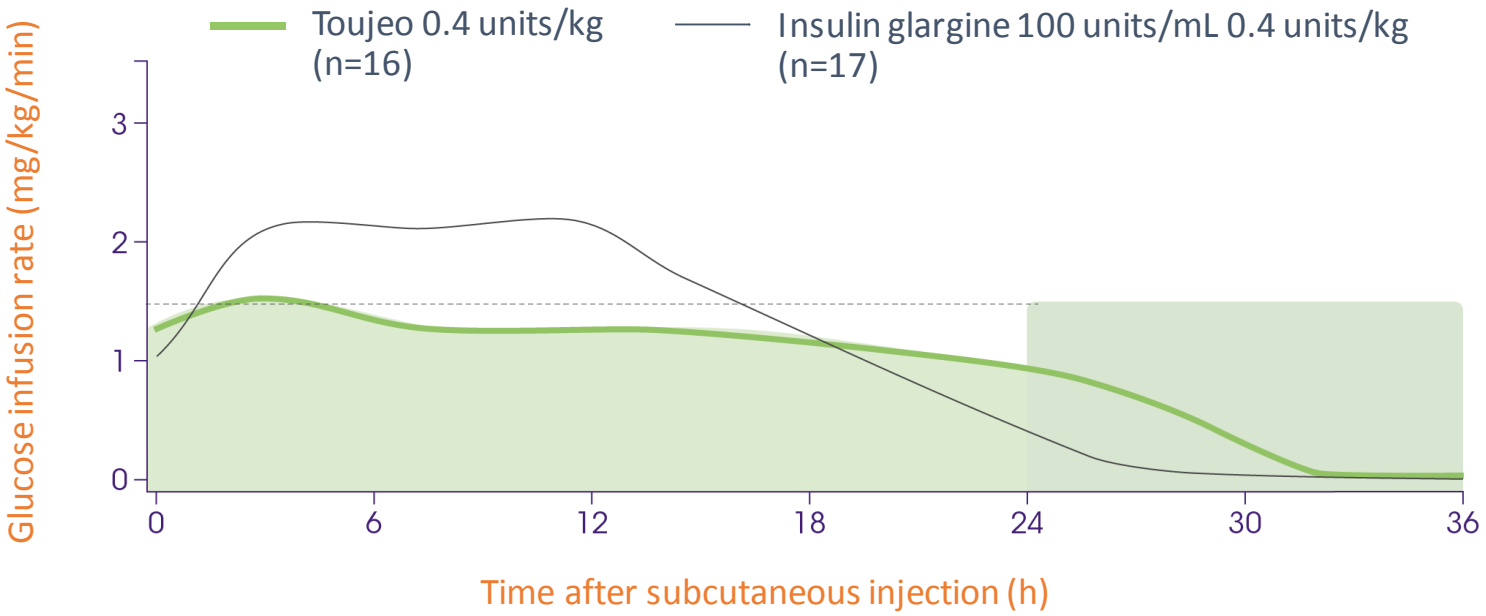
- Toujeo Max

Toujeo (2JO)


Toujeo® SoloStar®
insulin glargine injection
For Single Patient Use Only
300 Units/mL (U-300)

Toujeo: more stable and prolonged activity vs insulin glargine 100 units/mL[1,2]

- SMOOTH PROFILE AND STABLE ACTIVITY FOR AT LEAST 24 HOURS[1,2]



Adapted from Becker *RHA et al. Diabetes Care* 2015[1]

Pharmacodynamics

Even steady-state profile

Prolonged duration of action

Pharmacokinetics

Reduced fluctuation in insulin exposure

Constant activity over 24 h

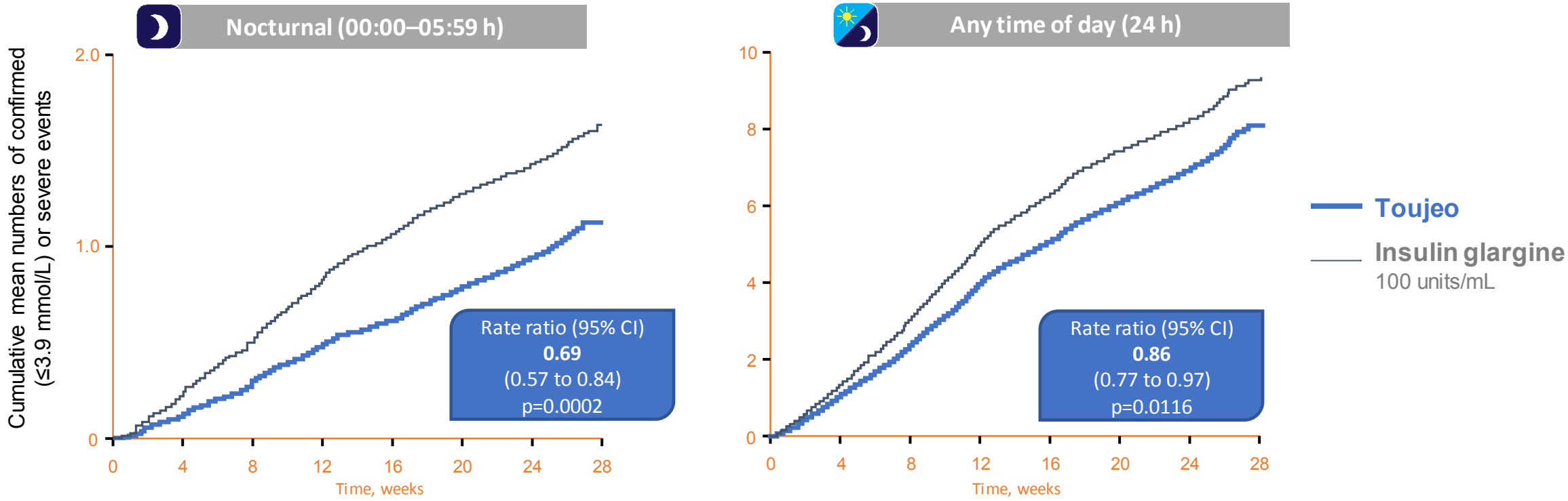
Study Design: Randomised, double-blind, two-treatment, two-period, two-sequence, cross-over study evaluating the pharmacokinetic and pharmacodynamic profiles of Toujeo compared with Lantus at steady state in people with T1DM (n=30). Cohort 1: 18 participants received Toujeo 0.4 U/kg/day for 8 days followed by Lantus 0.4 U/kg/day for 8 days. Cohort 2: 12 participants received Toujeo 0.6 U/kg/day for 8 days followed by Lantus 0.4 U/kg/day for 8 days. The euglycaemic clamp technique was applied over 36 hours.

- 1. Becker RHA *et al. Diabetes Care* 2015; 38(4):637–43. 2. Toujeo Approved Product Information.

EDITION 1–3 meta-analysis: Hypoglycaemia at 6 months in people with T2D[1]

META-ANALYSES

- RATE OF CONFIRMED (≤3.9 mmol/L) OR SEVERE HYPOGLYCAEMIA



Adapted from Ritzel R *et al. Diabetes Obes Metab* 2015.

Safety population; rate ratio and 95% CI are based on annualised rates per patient-year for confirmed (≤3.9 mmol/L]) or severe hypoglycaemia

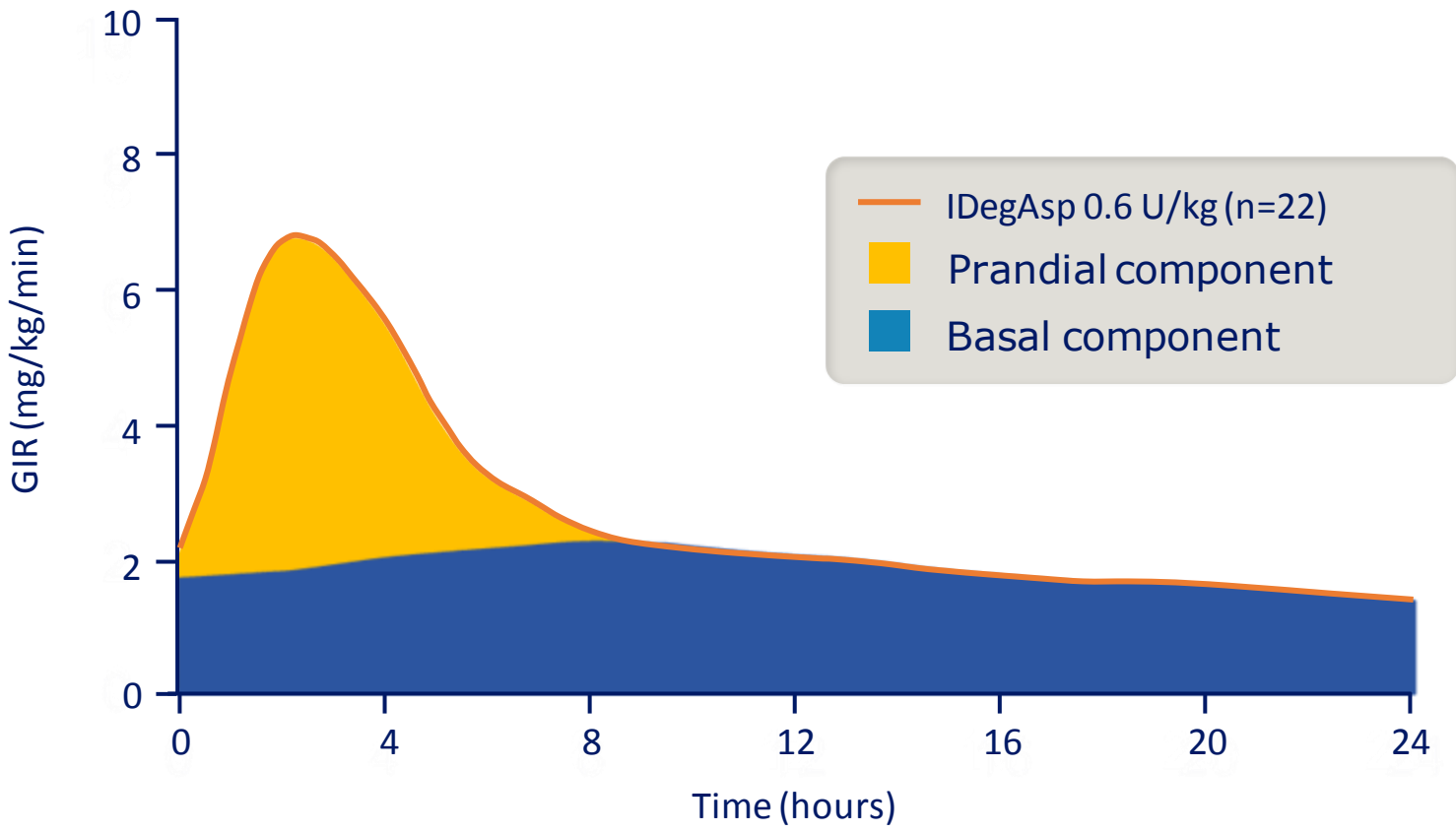
CI = confidence interval; RR = relative risk; T2D = type 2 diabetes

- 1. Ritzel R *et al. Diabetes Obes Metab* 2015; 17:859–67.

Ryzodeg


3 mL
Ryzodeg®
100
FlexTouch®
units/mL
Solution for injection
20

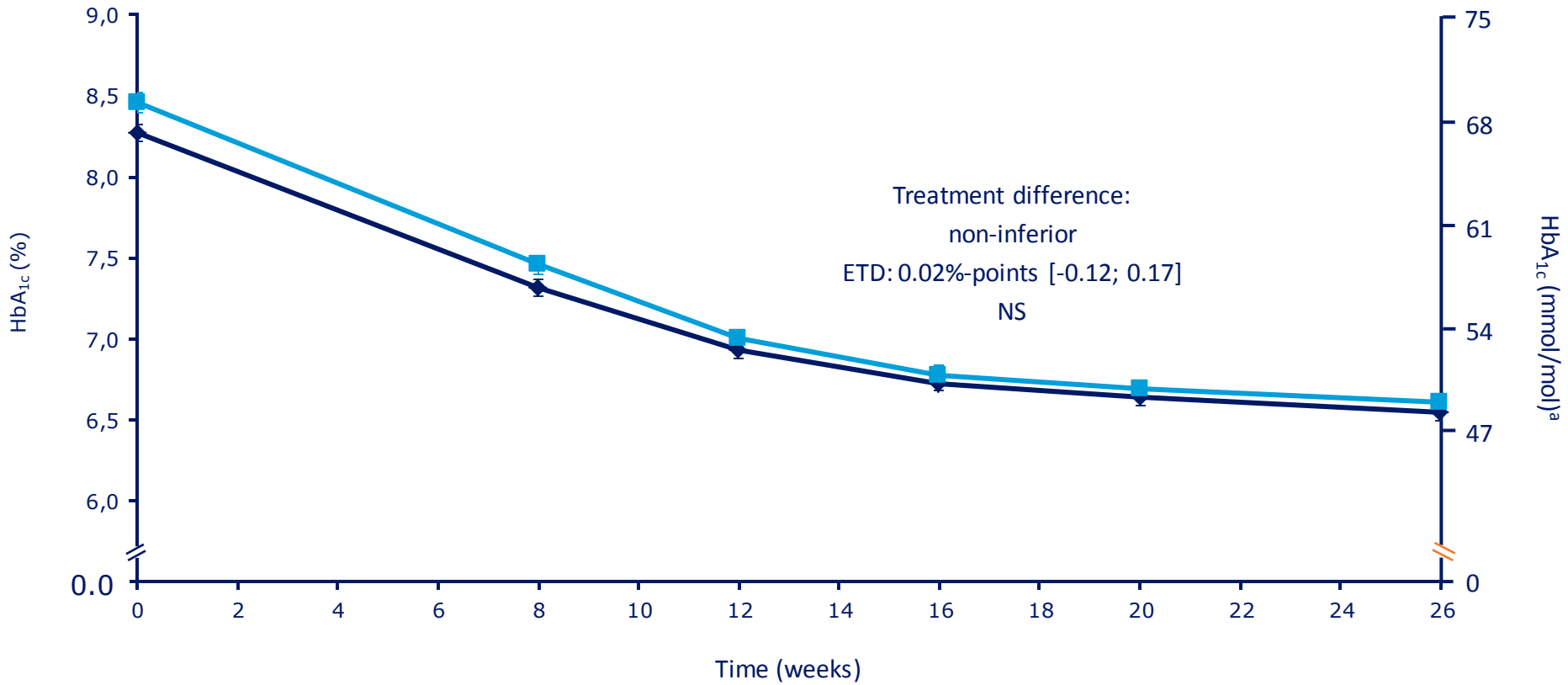
Distinct prandial and basal glucose-lowering effects of IDegAsp at steady state



GIR, glucose infusion rate; IDegAsp, insulin degludec/insulin aspart; T1D, type 1 diabetes
Heise *et al. Diabetes Ther* 2014;5:255–65

Insulin-naïve T2D BID: HbA_{1c} over time

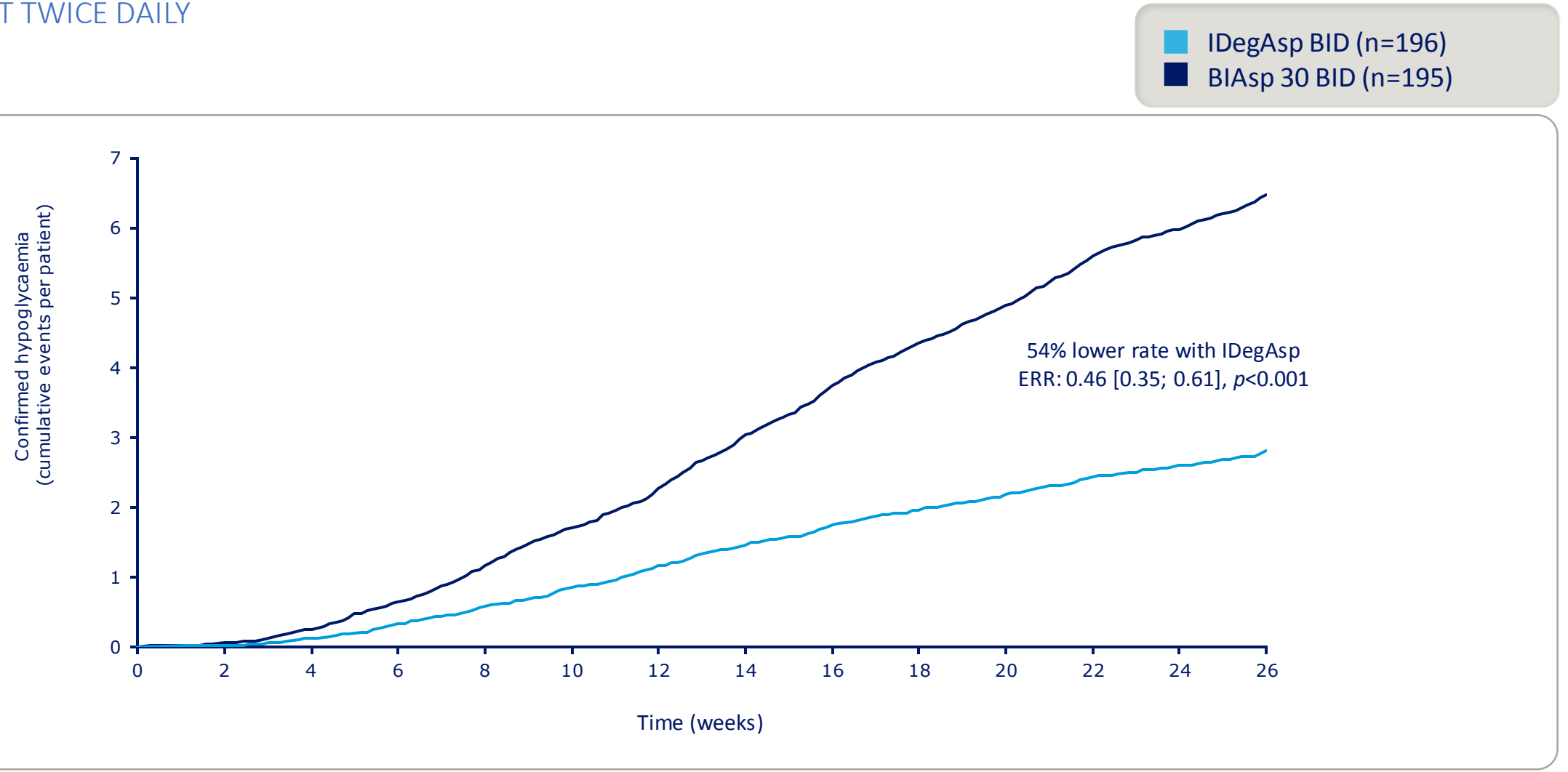
BOOST START TWICE DAILY



Mean±SEM; FAS, full analysis set; LOCF, last observation carried forward. [a]Calculated, not measured
Comparisons: estimates adjusted for multiple covariates
BIAsp 30, biphasic insulin aspart 30; BID, twice daily; ETD, estimated treatment difference; IDegAsp, insulin degludec/insulin aspart; NS, not significant; T2D, type 2 diabetes
Franek *et al. Diabetic Med* 2016;33:497-505

Insulin-naïve T2D BID: confirmed hypoglycaemia

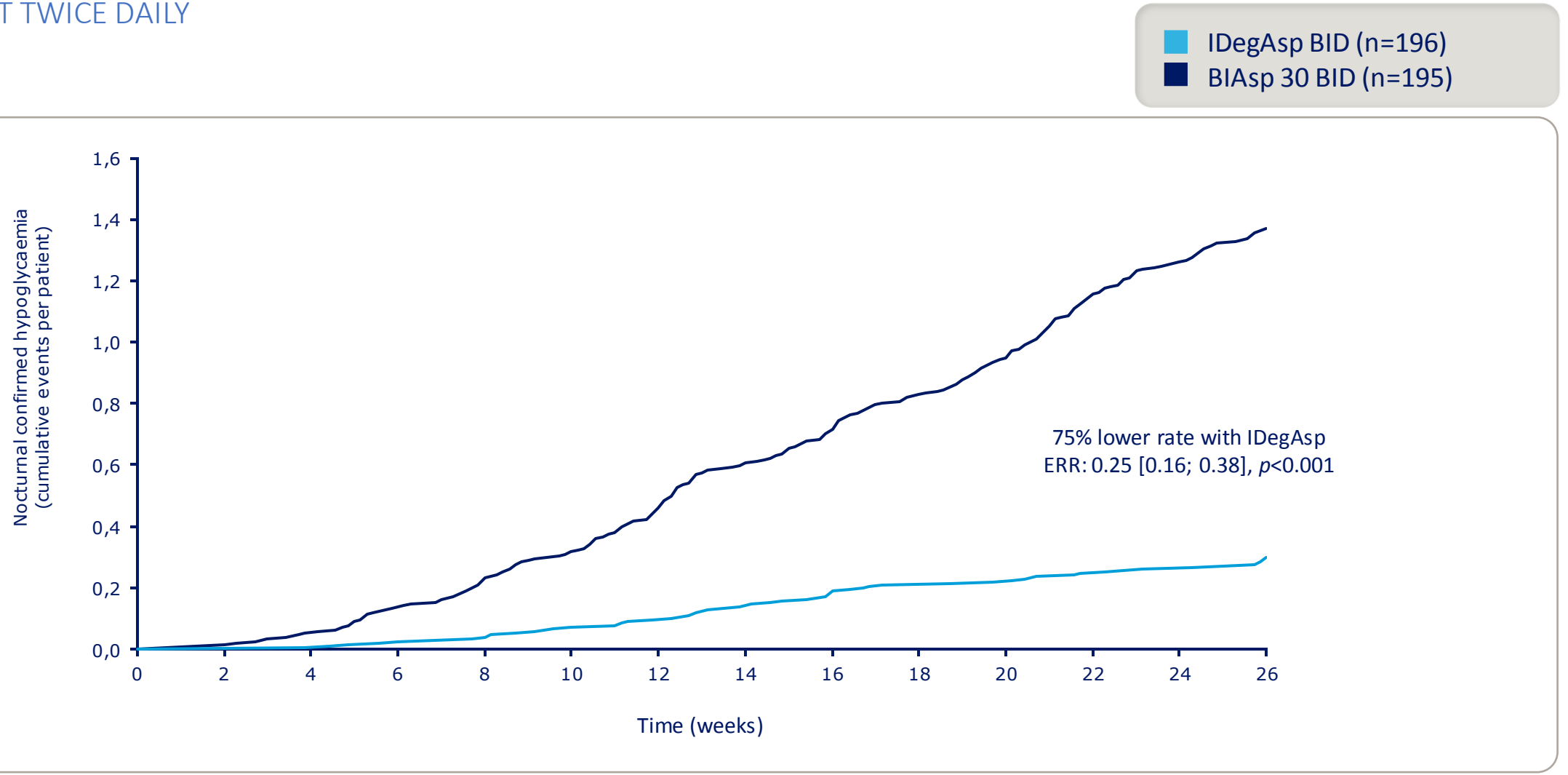
BOOST START TWICE DAILY



SAS, safety analysis set
Comparisons: Estimates adjusted for multiple covariates
BIAsp 30, biphasic insulin aspart 30; BID, twice daily; ERR, estimated rate ratio; IDegAsp, insulin degludec/insulin aspart; T2D, type 2 diabetes
Franek *et al. Diabetic Med* 2016;33:497-505

Insulin-naïve T2D BID: nocturnal confirmed hypoglycaemia

BOOST START TWICE DAILY



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Franek *et al. Diabetic Med* 2016;33:497-505

FiAsp:


NDC 0169-3204-15 List 320415
Fiasp®
FlexTouch®
(insulin aspart injection)
For Single Patient Use Only
100 units/mL (U-100)

Dissociation of insulin hexamers – Schematic representation

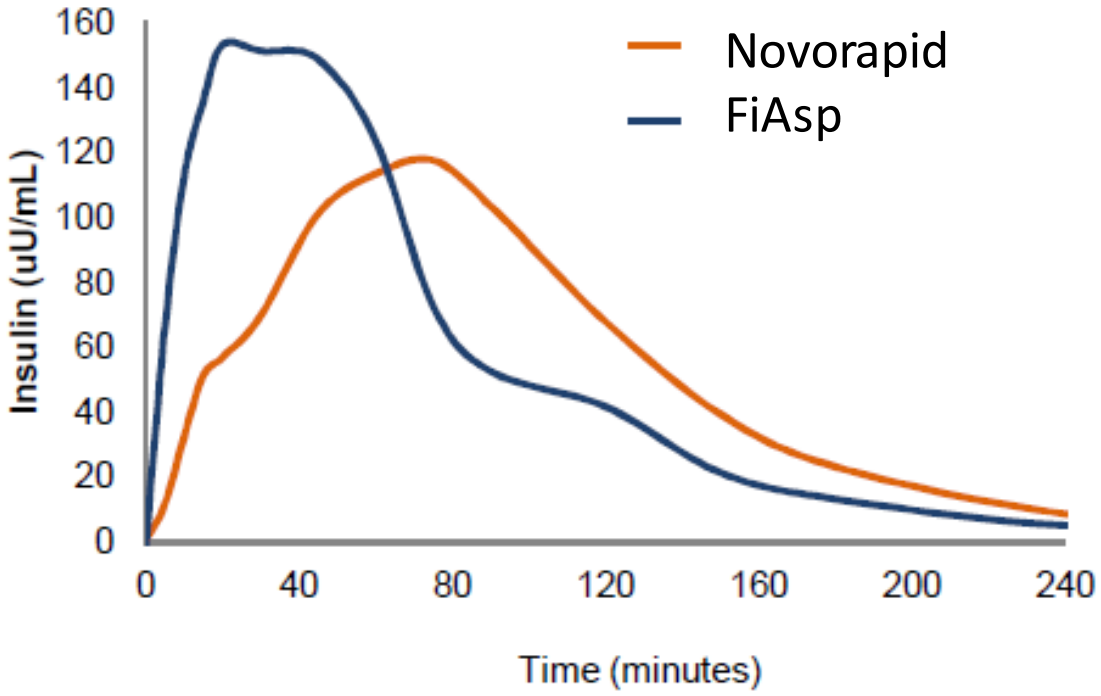
Increasing early monomer fraction after injection

Human insulin

Insulin aspart

Faster aspart

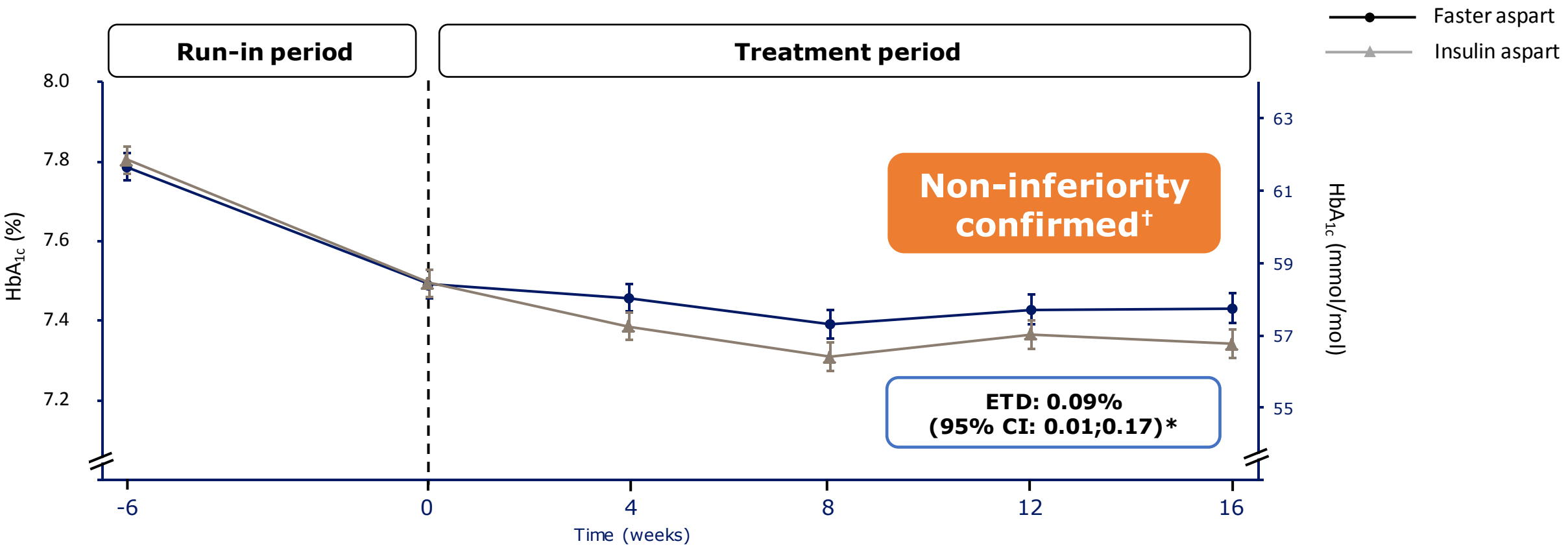
FiAsp:



Addition of EDTA and citrate to RAI

Addition of EDTA and citrate shifts equilibrium towards monomerised insulin

CSII study-onset 5: mean HbA_{1c} over time

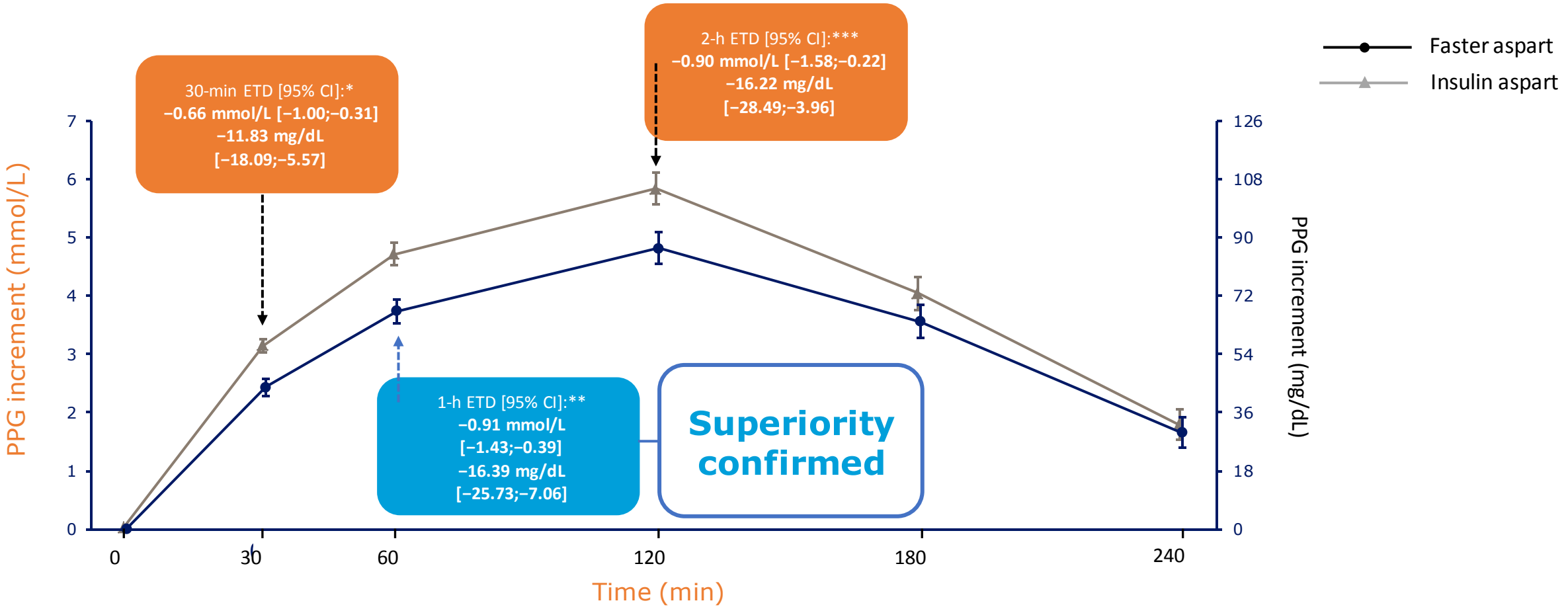


Error bars: ± standard error (mean)
All available information regardless of treatment discontinuation was used.
Change from baseline in HbA_{1c} was analysed using a multiple imputation model.
† Non-inferiority confirmed at 0.4% level, p-value for non-inferiority: $p<0.001$. *p=0.022. ETD represents faster aspart minus insulin aspart values.
Faster aspart, fast-acting insulin aspart; CI, confidence interval; ETD, estimated treatment difference

Klonoff *et al. Diabetes Technology & Therapeutics* 2018;20(Suppl 1):A32; Evans *et al.* ABCD meeting 2018 (poster)

onset 5: PPG increment at week 16

Significantly greater reduction at 30 min, 1 h and 2 h with faster aspart vs. insulin aspart



Error bars: ± standard error (mean). *$p<0.001$, **$p=0.001$, ***$p=0.01$

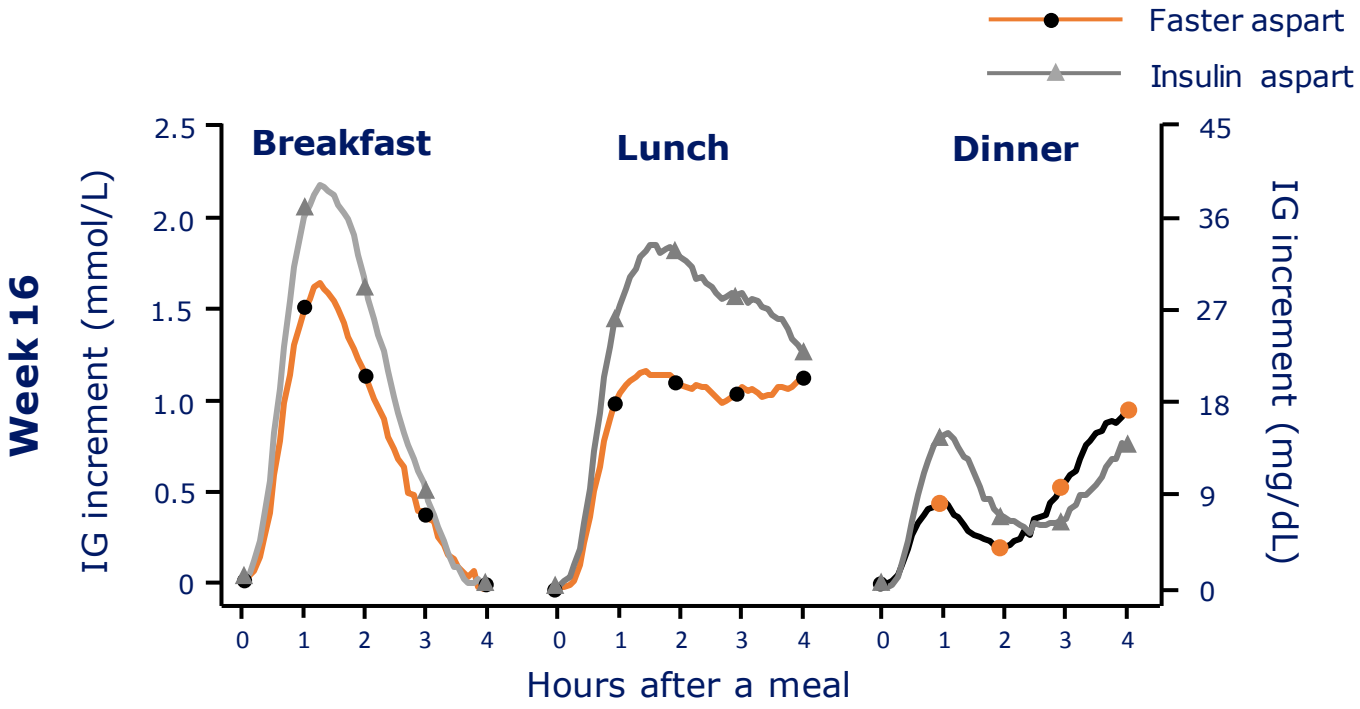
All available information regardless of treatment discontinuation was used. The conversion factor between mmol/L and mg/dL is 0.0555. Change from baseline in PPG increment was analysed using a multiple imputation model. Faster aspart, fast-acting insulin aspart; PG, plasma glucose; PPG, postprandial plasma glucose; CI, confidence interval; ETD, estimated treatment difference (faster aspart − insulin aspart) for PG changes from baseline

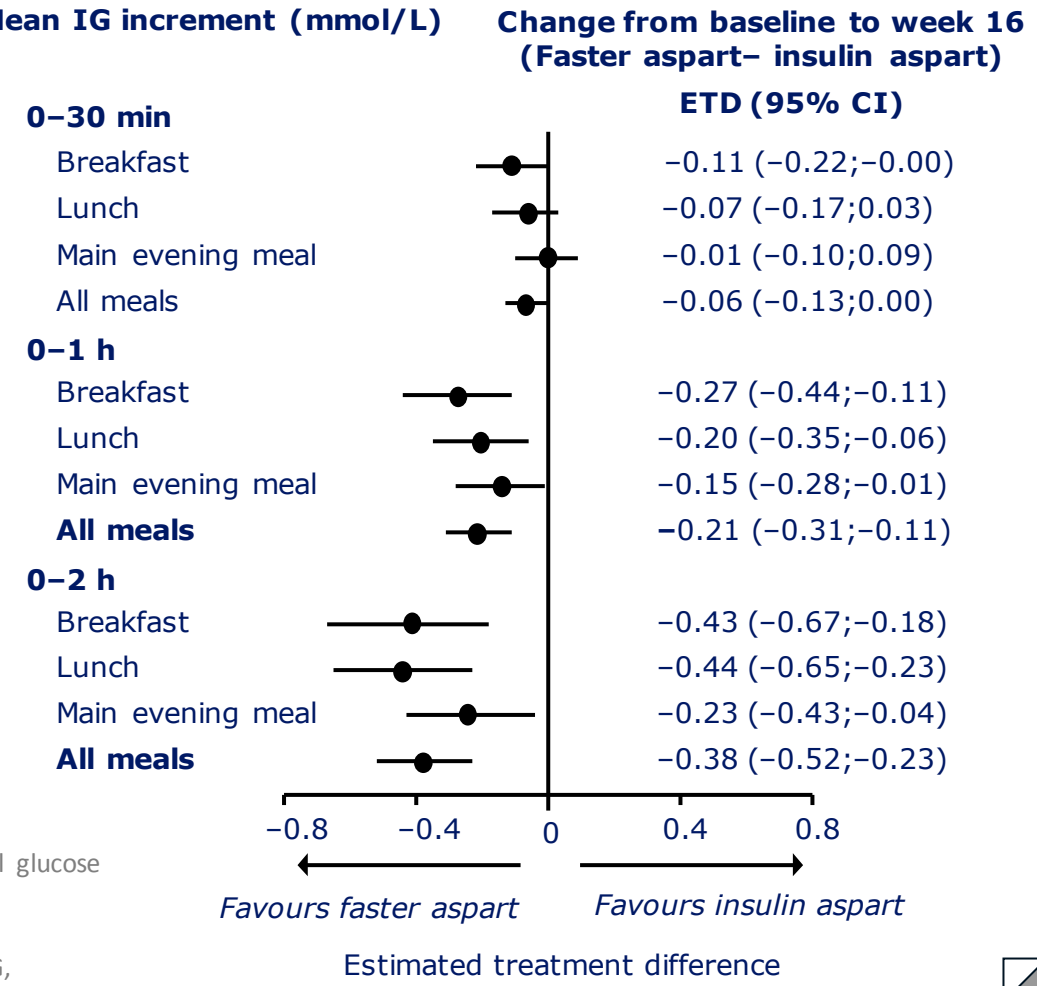
Klonoff *et al. Diabetes Technology & Therapeutics* 2018;20(Suppl 1):A32; Evans *et al.* ABCD meeting 2018 (poster)

ACROSS T2D | The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

onset 5: prandial IG increments at week 16

2-week CGM - Reductions in 1-h and 2-h PPG increments with faster aspart vs insulin aspart





All available information regardless of treatment discontinuation was used.
Prandial interstitial glucose increment is derived as the interstitial glucose values subtracted by the mean of interstitial glucose values within 15 minutes before the start of the meal.
Change from baseline in mean IG increment was analysed using a multiple imputation model.
CGM, continuous glucose monitoring; ETD, estimated treatment difference; faster aspart, fast-acting insulin aspart; IG, interstitial glucose
Klonoff *et al. Diabetes Technology & Therapeutics* 2018;20(Suppl 1):A32; Evans *et al.* ABCD meeting 2018 (poster)

onset 5: treatment-emergent hypoglycaemia

No statistically significant difference in rates of severe or BG-confirmed hypoglycaemia

	Faster aspart				Insulin aspart			
	N	%	E	R	N	%	E	R
Severe or BG-confirmed	231	97.9	3279	45.07	228	96.6	3247	45.29
BG-confirmed	231	97.9	3258	44.78	227	96.2	3240	45.20
Severe	11	4.7	21	0.29	5	2.1	7	0.10
Excluding subjects with severe hypoglycaemic episodes during the run-in period								
Severe	8	3.4	11	0.15	5	2.1	7	0.10

Treatment-emergent is defined as an event that has onset up to 1 day after last day of randomised treatment and excluding the events occurring in the run-in period BG-confirmed: PG value <3.1 mmol/L (56 mg/dL). Statistical analysis is based on a negative binomial regression model

%, percentage of subjects; BG, blood glucose; E, number of events; faster aspart, fast-acting insulin aspart; N, number of subjects with at least one event; R, number of events per patient-year of exposure

Klonoff *et al. Diabetes Technology & Therapeutics* 2018;20(Suppl 1):A32; Evans *et al.* ABCD meeting 2018 (poster)

Toujeo Max Solostar

The Max Solostar pen is to be introduced in Australia.

Insulin	Comparator	Efficacy	Tolerability	Safety
Toujeo	Lantus	↔	↔	Fewer hypos, in particular, nocturnal
Ryzodeg	Novomix/ Lantus Plus RAI	↔	↔	Fewer hypos, in particular, nocturnal
Fiasp	Novorapid	Reduced postprandial excursions but no Δ in A1c	↔	Increased severe hypos 2-4X

What's new in diabetes- An update

- In search of the Holy grail
- What’s changed in 2007?
- The era of the CVOT

- Insulin and **hypoglycaemia**

- Tech *and* What’s new and around the corner (possibly)

The evolving face of hypoglycaemia

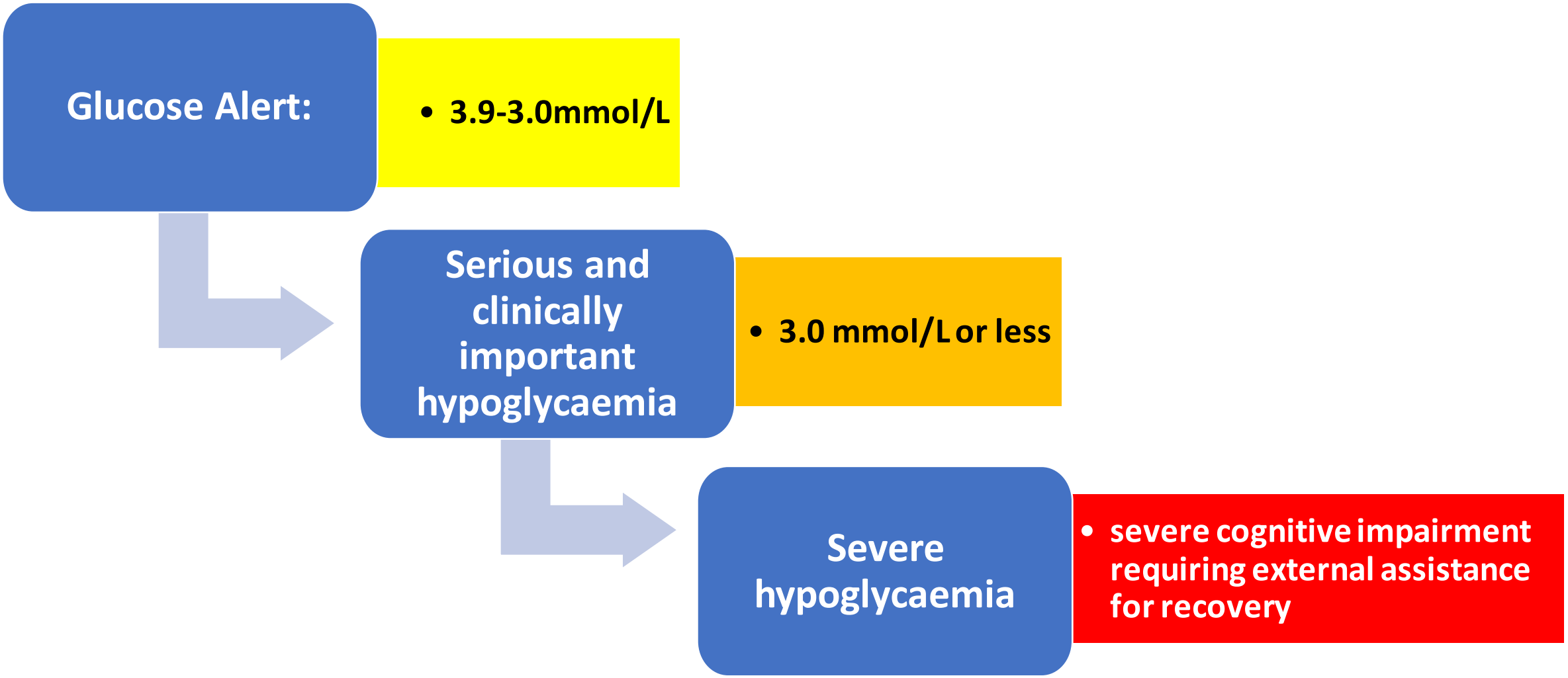
HYPOGLYCAEMIA WAS ORIGINALLY DEFINED BY 'WHIPPLE'S TRIAD' OF LOW BLOOD GLUCOSE, THE PRESENCE OF SYMPTOMS, AND THE REVERSAL OF SYMPTOMS WHEN BLOOD GLUCOSE IS RESTORED, IN PATIENTS WITH INSULINOMA.

THE ONSET OF SYMPTOMS IS NOT A RELIABLE GUIDE TO BLOOD GLUCOSE LEVELS, AND THERE HAS NOT BEEN A CLEAR CONSENSUS ON THE DEFINITION OF HYPOGLYCAEMIA IN CLINICAL STUDIES.

THE ISSUE WAS ADDRESSED BY A JOINT STATEMENT OF THE ADA AND EASD IN 2017, REFLECTING RECOMMENDATIONS OF THE INTERNATIONAL HYPOGLYCEMIA STUDY GROUP.

IT PROPOSED THREE LEVELS OF HYPOGLYCAEMIA:

Graphic of stages of hypoglycaemia



What's new in diabetes- An update

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- **Tech *and* What’s new and around the corner (possibly)**

Technology

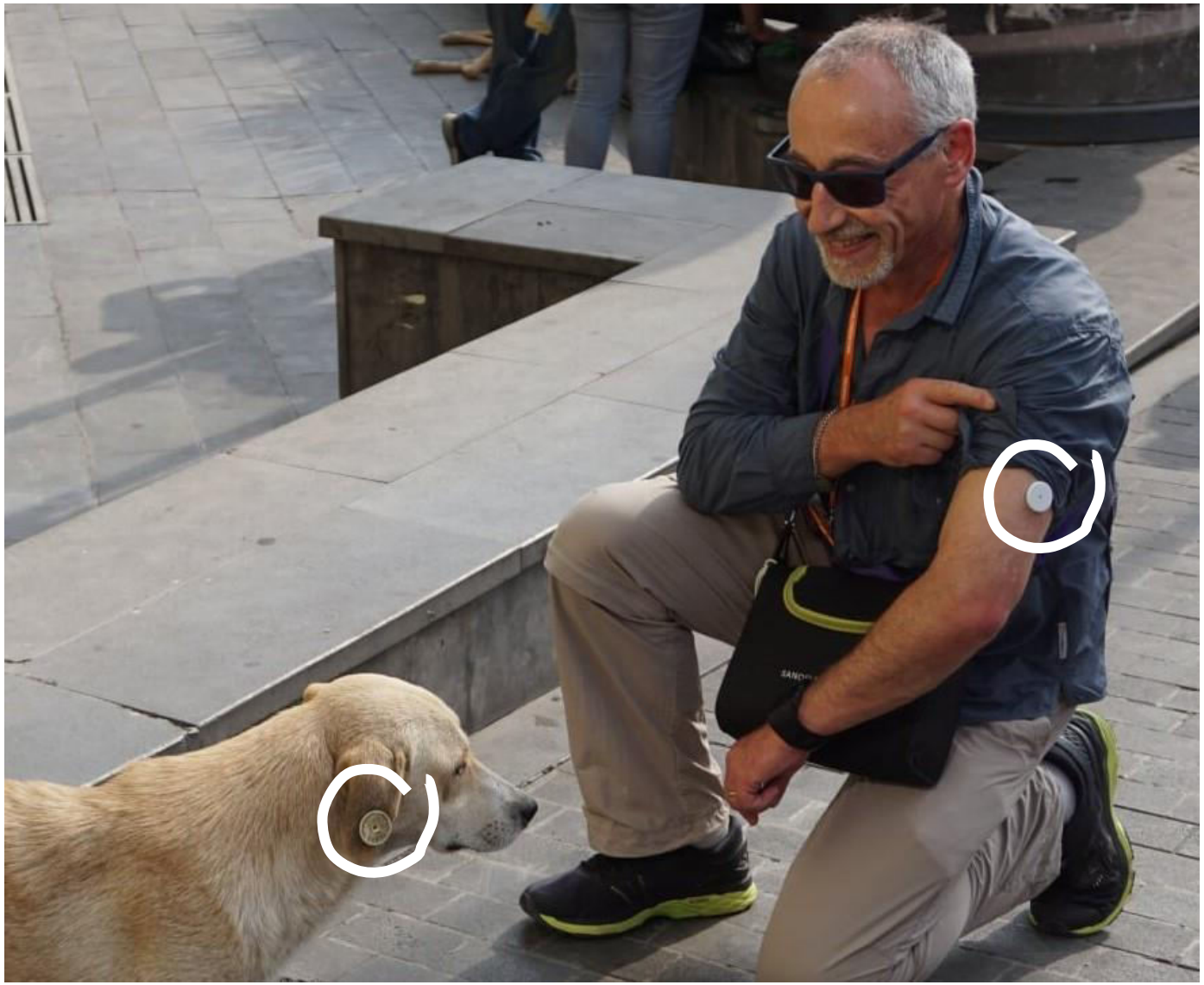
FGM

CSII

CGM

FGM

The new way to make friends



FGM: How it Works

- Glucose sensor is inserted in subcutaneous tissue and connected to a transmitter

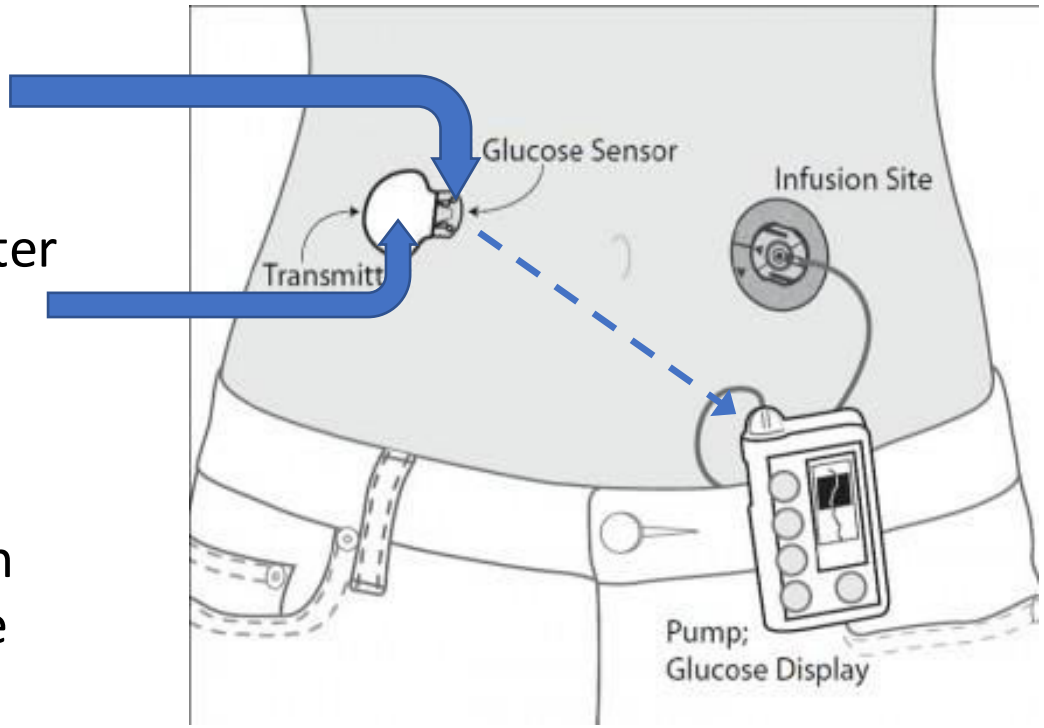
- Handheld monitor or compatible smart phone receives data from the sensor by waving or flashing the reader over the sensor. This can be done as often as desired but must be performed at least once every 8hrs, where data can be viewed and acted upon in real-time

MIAOMIAO

Diabetes
Life
Hacks

CGM

- Glucose sensor is inserted in subcutaneous tissue and connected to a transmitter
- Glucose sensor sends values to the transmitter
- Transmitter then sends data wirelessly to a pump or handheld monitor every 5 minutes, where data can be viewed and acted upon in real-time OR stores the information until the end of the monitoring period.
- Real time vs ‘blinded’

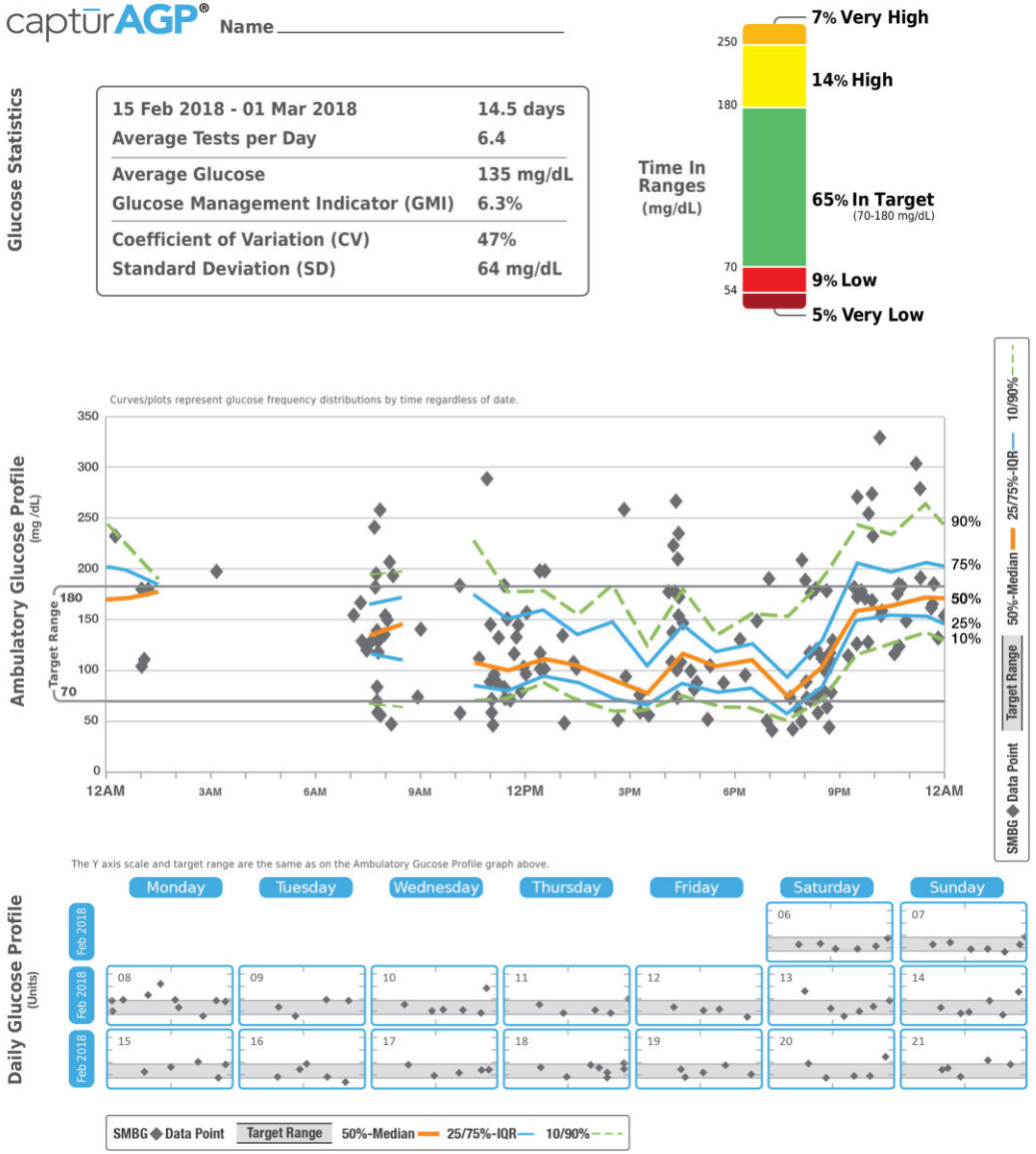


Implantable CGM

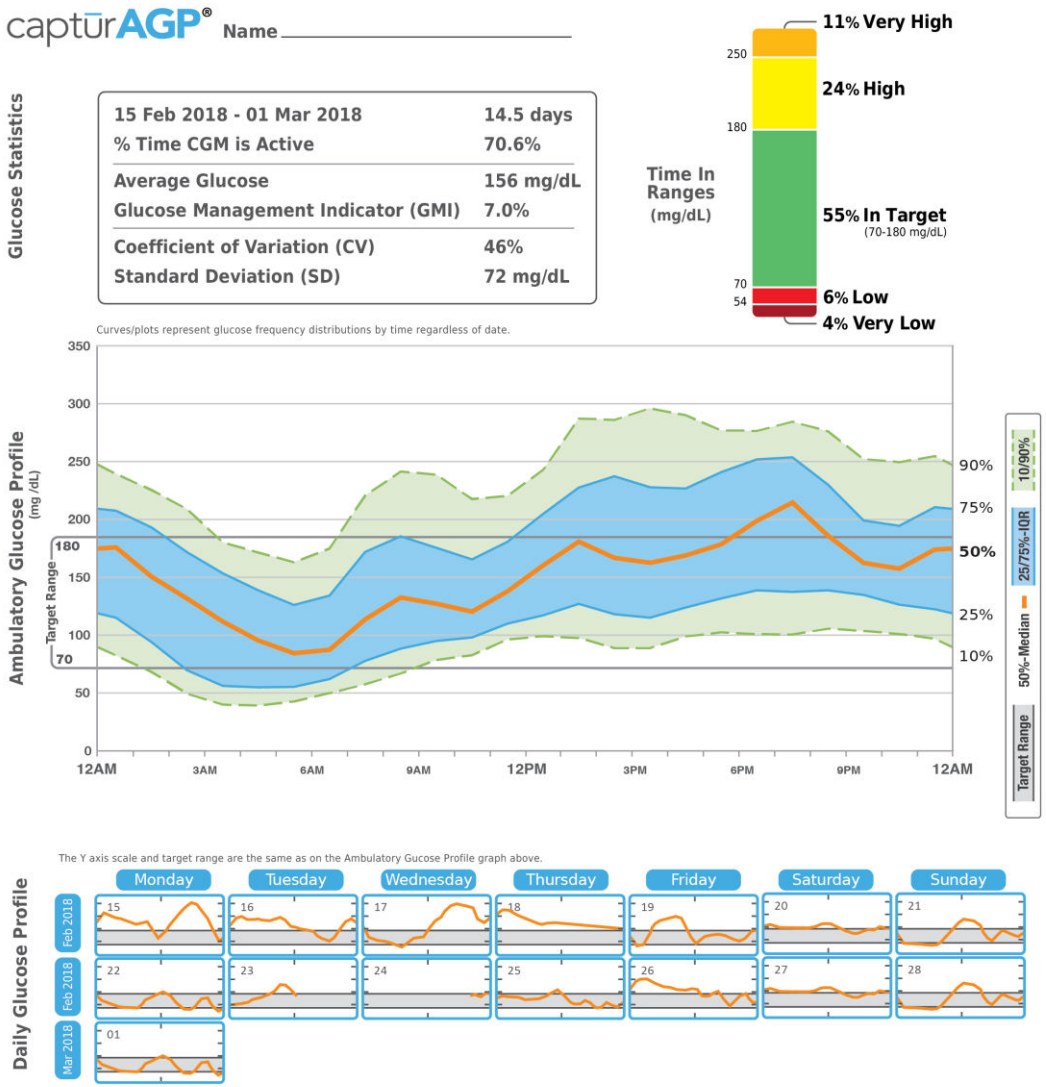
AGP

- **The Ambulatory Glucose Report (AGP) is a standardized, single page glucose and insulin report.**
- It includes summary statistics, a glucose profile graph and an insulin profile graph.
- Like an ECG, the AGP offers a report that is consistent regardless of device.

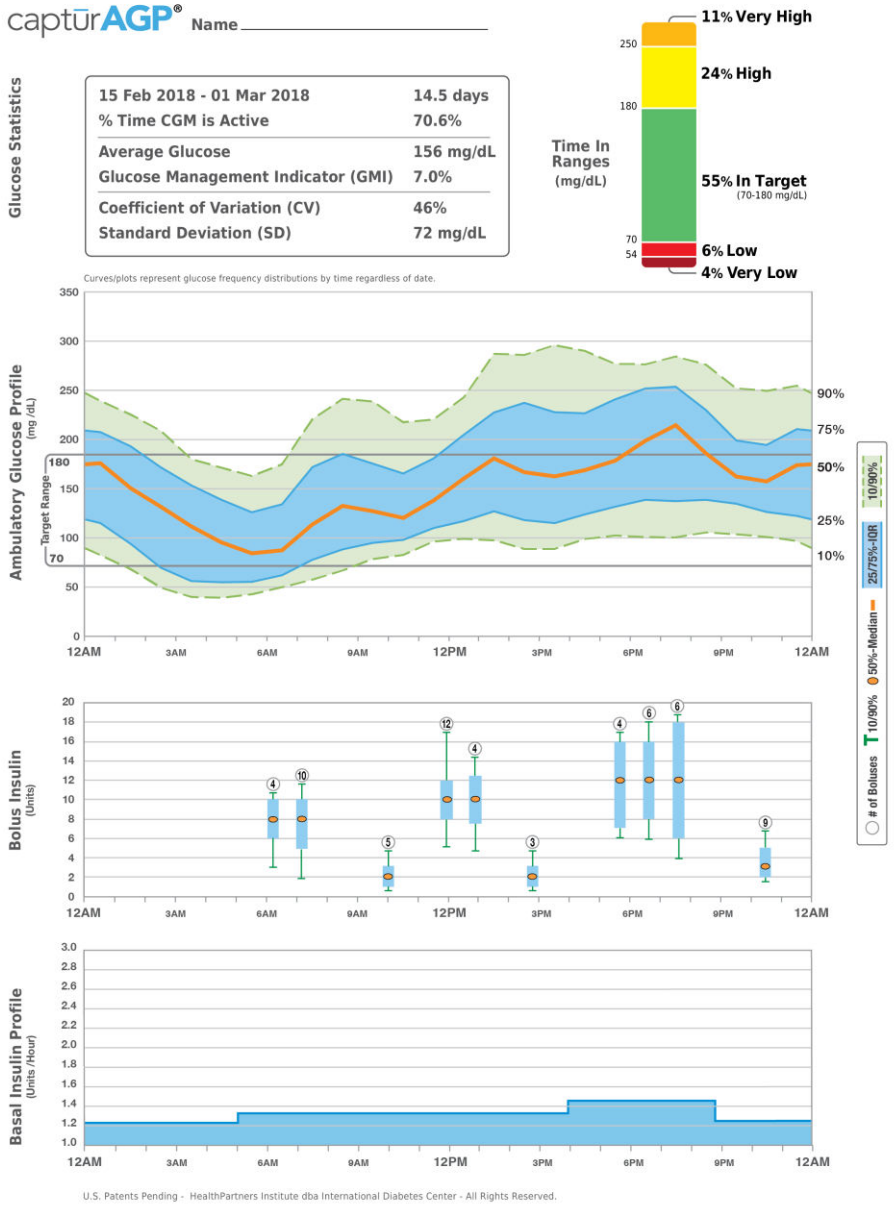
SMBG



CGM/FGM



CGM and PUMP


captürAGP®
Name
Glucose Statistics
15 Feb 2018 - 01 Mar 2018 14.5 days
% Time CGM is Active 70.6%
Average Glucose 156 mg/dL
Glucose Management Indicator (GMI) 7.0%
Coefficient of Variation (CV) 46%
Standard Deviation (SD) 72 mg/dL
Time In Ranges (mg/dL)
11% Very High
24% High
55% In Target (70-180 mg/dL)
6% Low
4% Very Low
Curves/plots represent glucose frequency distributions by time regardless of date.
Ambulatory Glucose Profile (mg/dL)
Target Range
90%
75%
50%
25%
10%
Bolus Insulin (Units)
Basal Insulin Profile (Units/Hour)
10/90%
25/75%-IQR
50%-Median
# of Boluses
12AM
3AM
6AM
9AM
12PM
3PM
6PM
9PM
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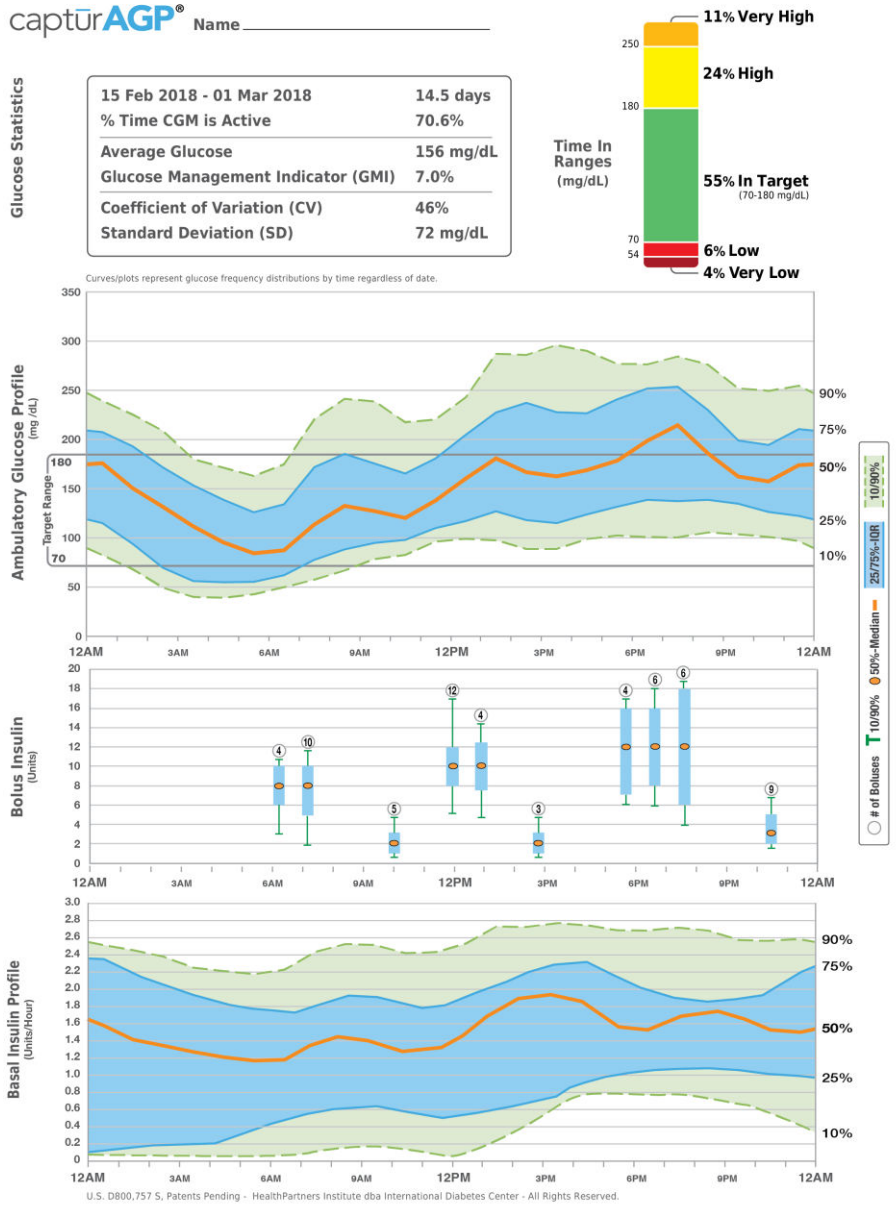
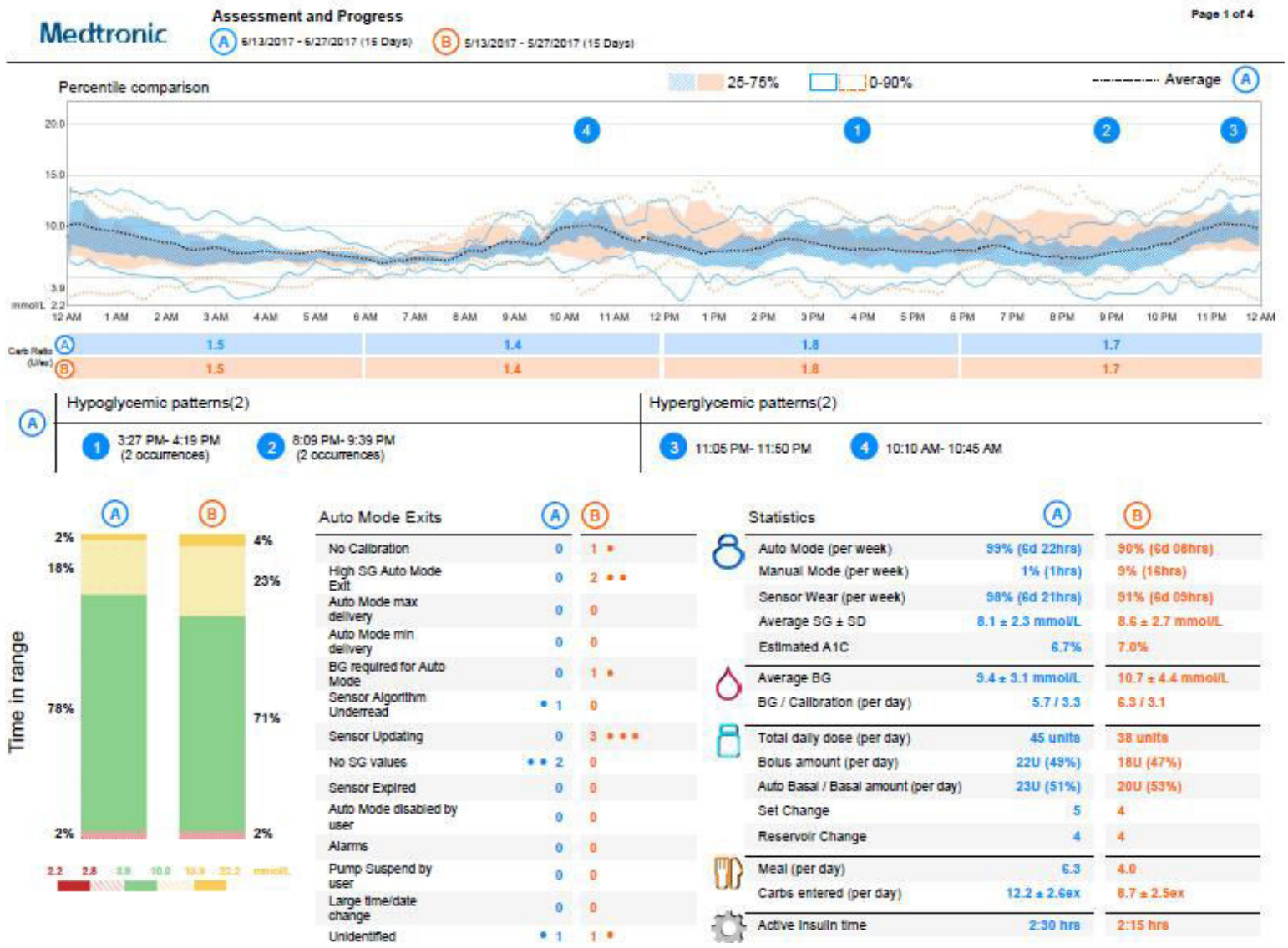
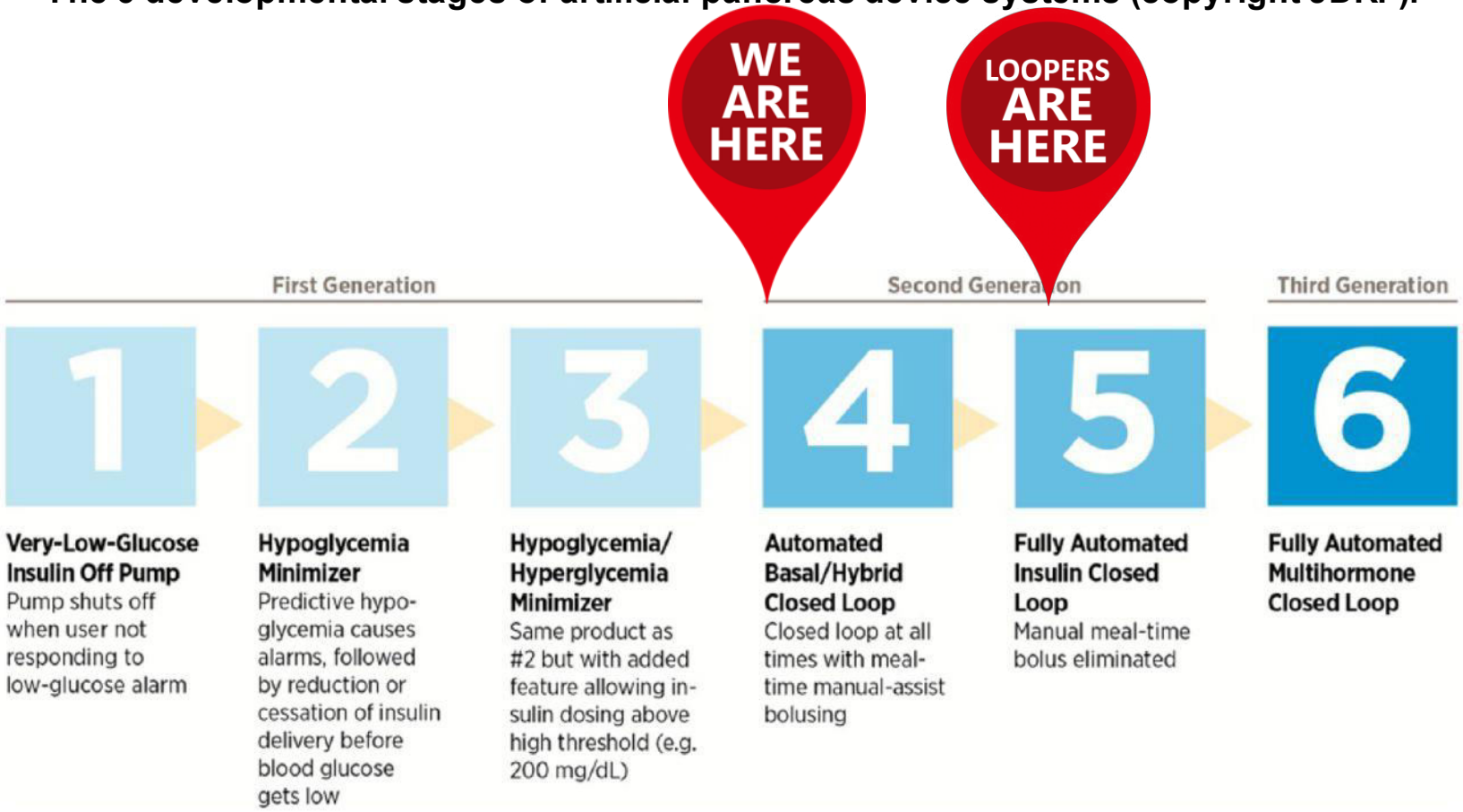
CGM and PUMP Adaptive basal (Semi closed loop)



Medtronic CSII and CGM Report



The 6 developmental stages of artificial pancreas device systems (copyright JDRF).



Sara Trevitt et al. J Diabetes Sci Technol 2015;1932296815617968

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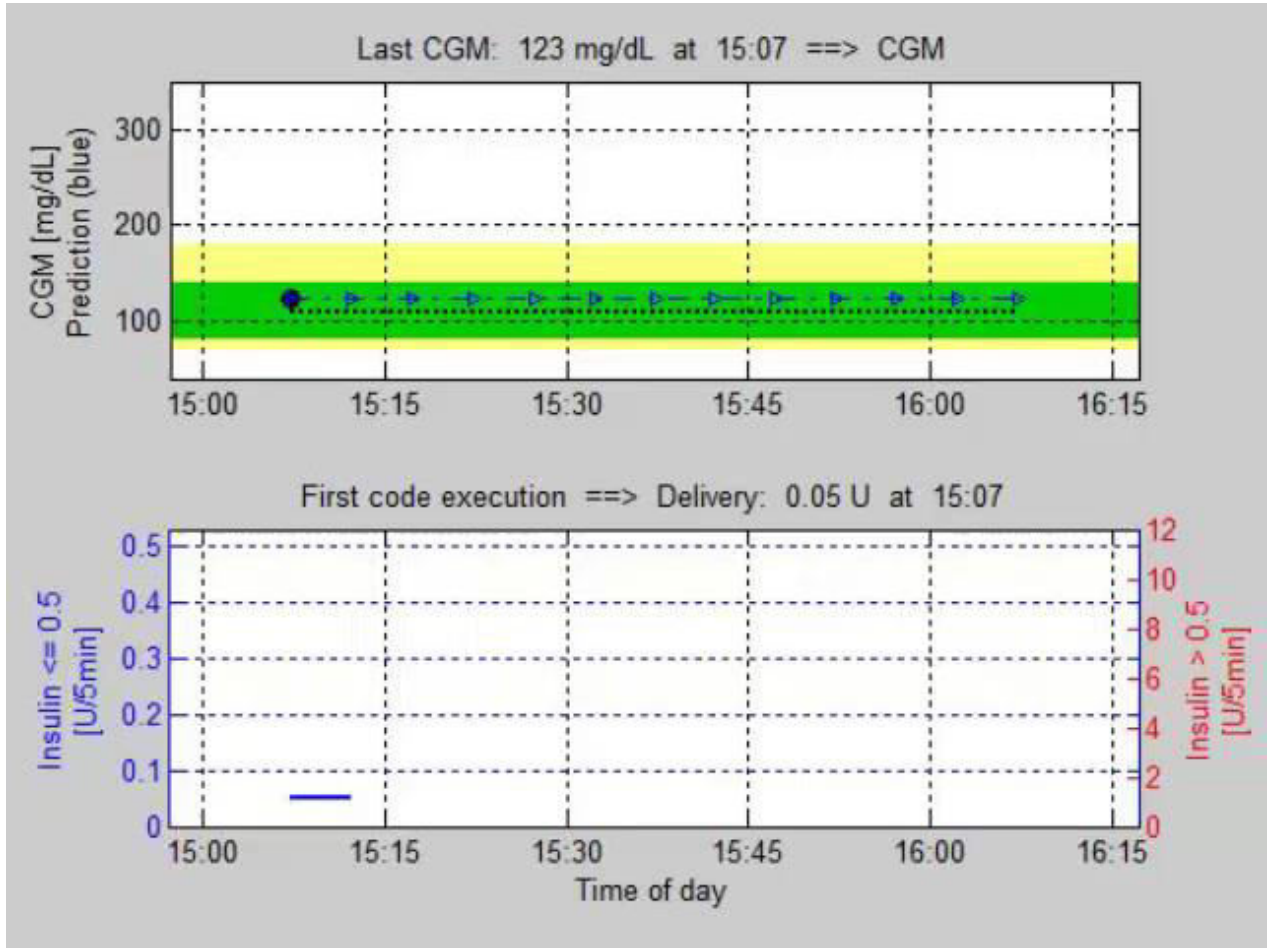
Closed Loop CGM (bionic pancreas)



Francis J Doyle III PHD
Harvard John A. Paulson School of Engineering and Applied Sciences
Randomized Crossover Clinical Trial Comparing MPC and PID Control Algorithms for Artificial Pancreas

Smart Pens

- **Roche:** Novo Nordisk insulin pen data will sync to the mySugr app and Accu-Chek SmartPix software.
- **Dexcom** continuous glucose monitoring (CGM) data will be combined with Novo Nordisk connected insulin pen data and "guidance information" to "give advice" that makes diabetes easier.
- **Glooko:** In January 2017, Novo Nordisk and Glooko announced a partnership to develop digital diabetes tools together. Since that time, they have launched the Cornerstones4Care app.


So much more to talk about but not enough time…

Thank you

QUESTIONS?
COMMENTS?