Insulin and Non- Insulin Injectable Therapies for Diabetes Management

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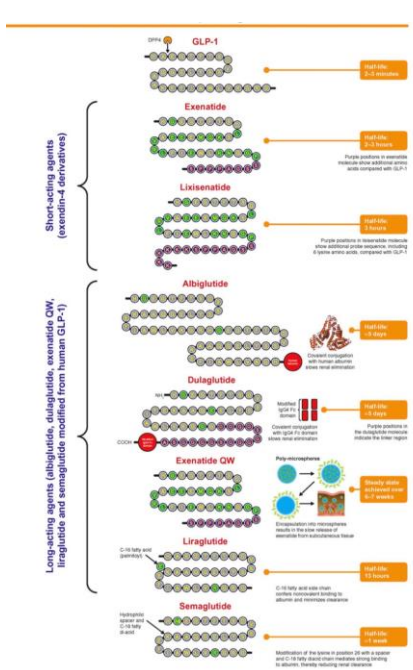
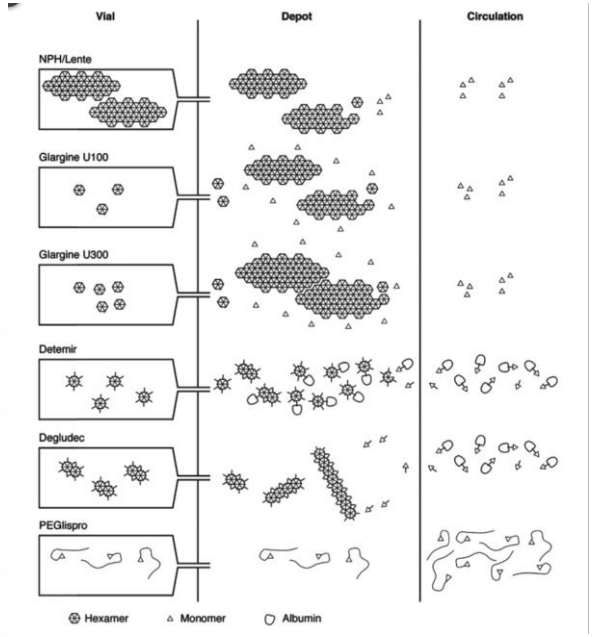
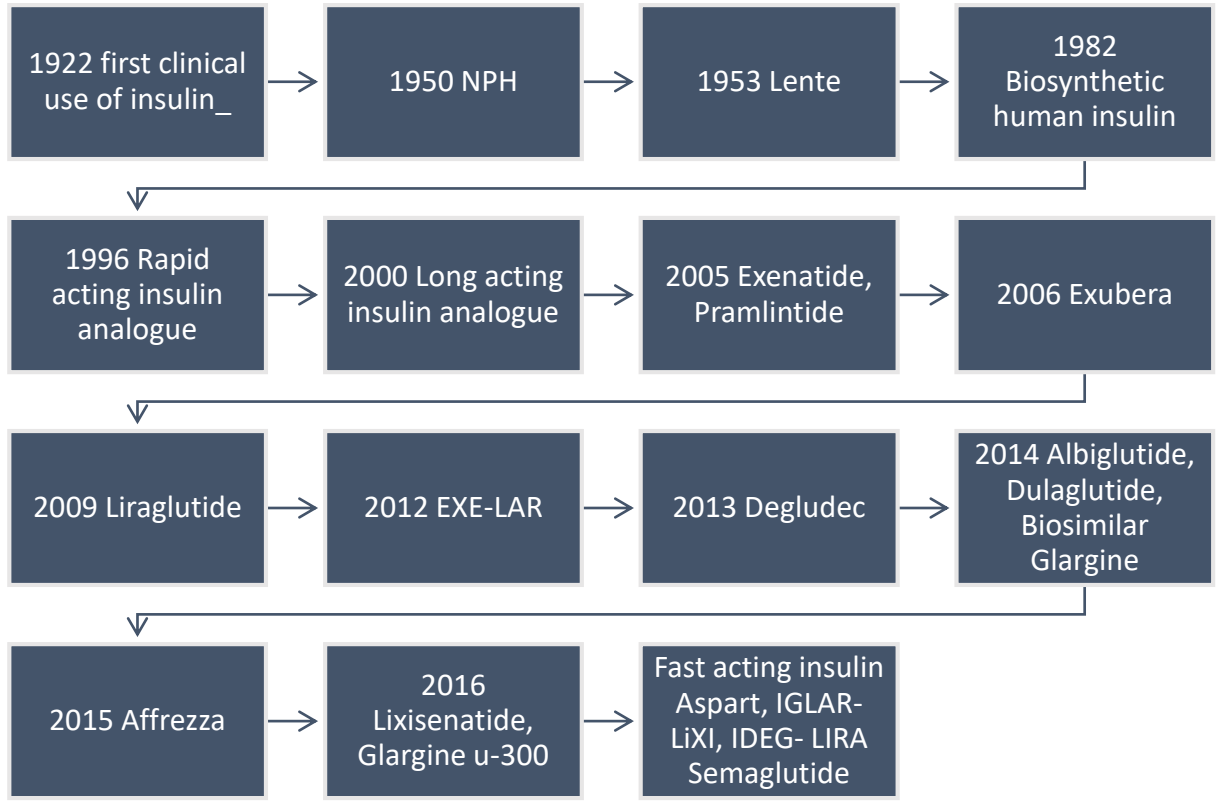
Endocrinology
Diabetes and Dyslipidemia
Sunday , January 26 , 2020
Sheraton PR Hotel , San Juan.





Insulin and non- insulin injectable therapy

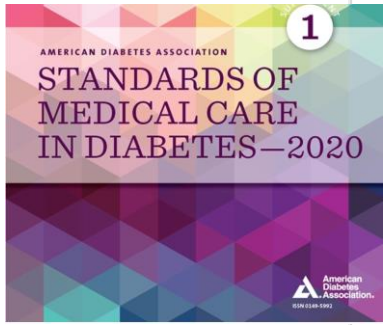


Disclosures

Speaker for the following companies : Janssen, Sanofi, Lilly, Merck

American Diabetes Association

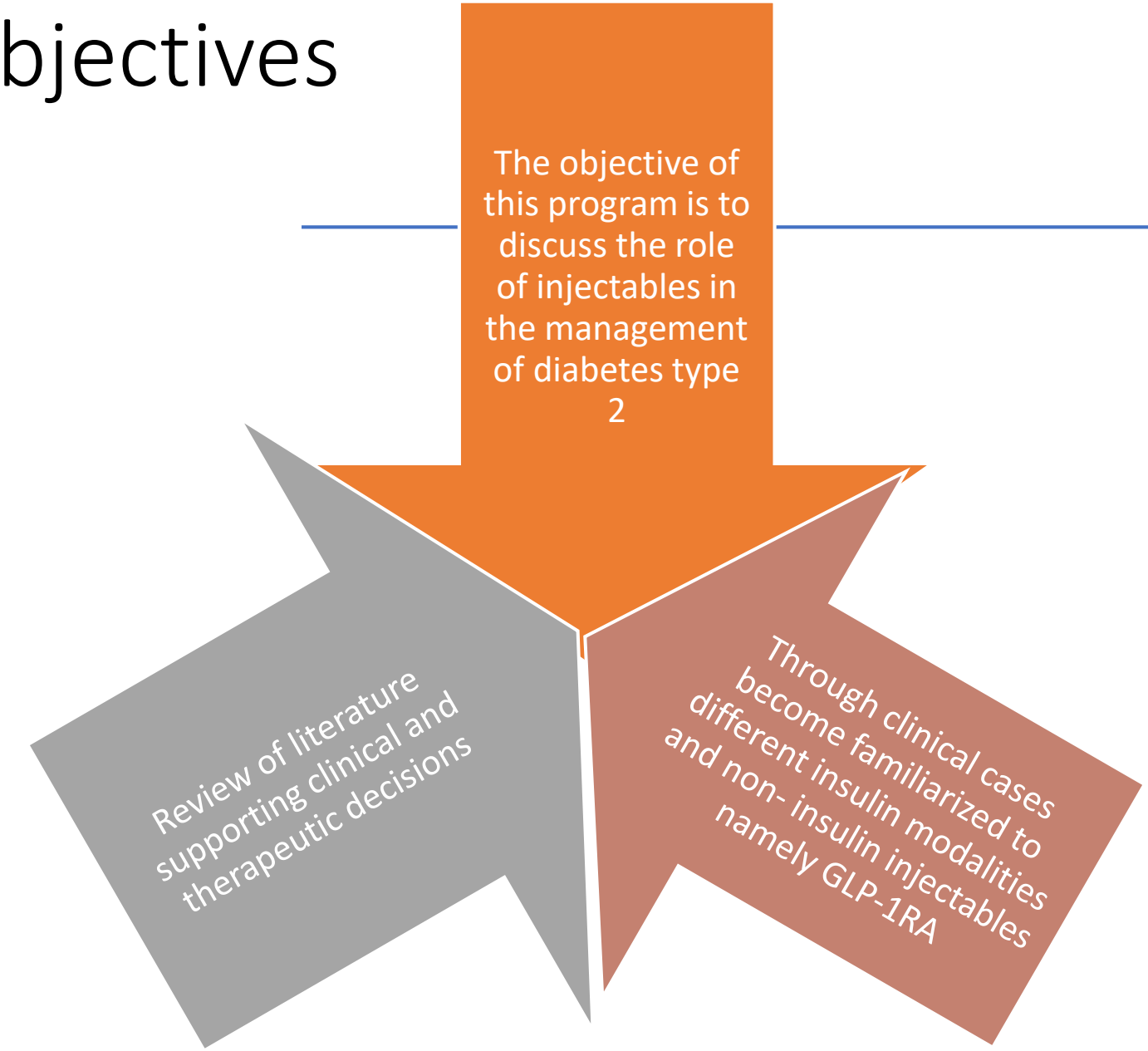
Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including
	• Evidence from a well-conducted multicenter trial
	• Evidence from a meta-analysis that incorporated quality ratings in the analysis
	Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford
	Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including
	• Evidence from a well-conducted trial at one or more institutions
	• Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies
	• Evidence from a well-conducted prospective cohort study or registry
	• Evidence from a well-conducted meta-analysis of cohort studies
	Supportive evidence from a well-conducted case-control study



C Evidence from randomized clinical trials with one major or three or more minor methodological flaws

E Expert consensus

Objectives


The objective of this program is to discuss the role of injectables in the management of diabetes type 2
Review of literature supporting clinical and therapeutic decisions
Through clinical cases become familiarized to different insulin modalities and non- insulin injectables namely GLP-1RA

Pharmacologic therapy for type 1 Diabetes

- Most people with type 1 diabetes should be treated with MDII of prandial and basal insulin or CSII . A.
- Most individuals with type 1 diabetes should use rapid acting insulin analogs to reduce hypoglycemia . A .

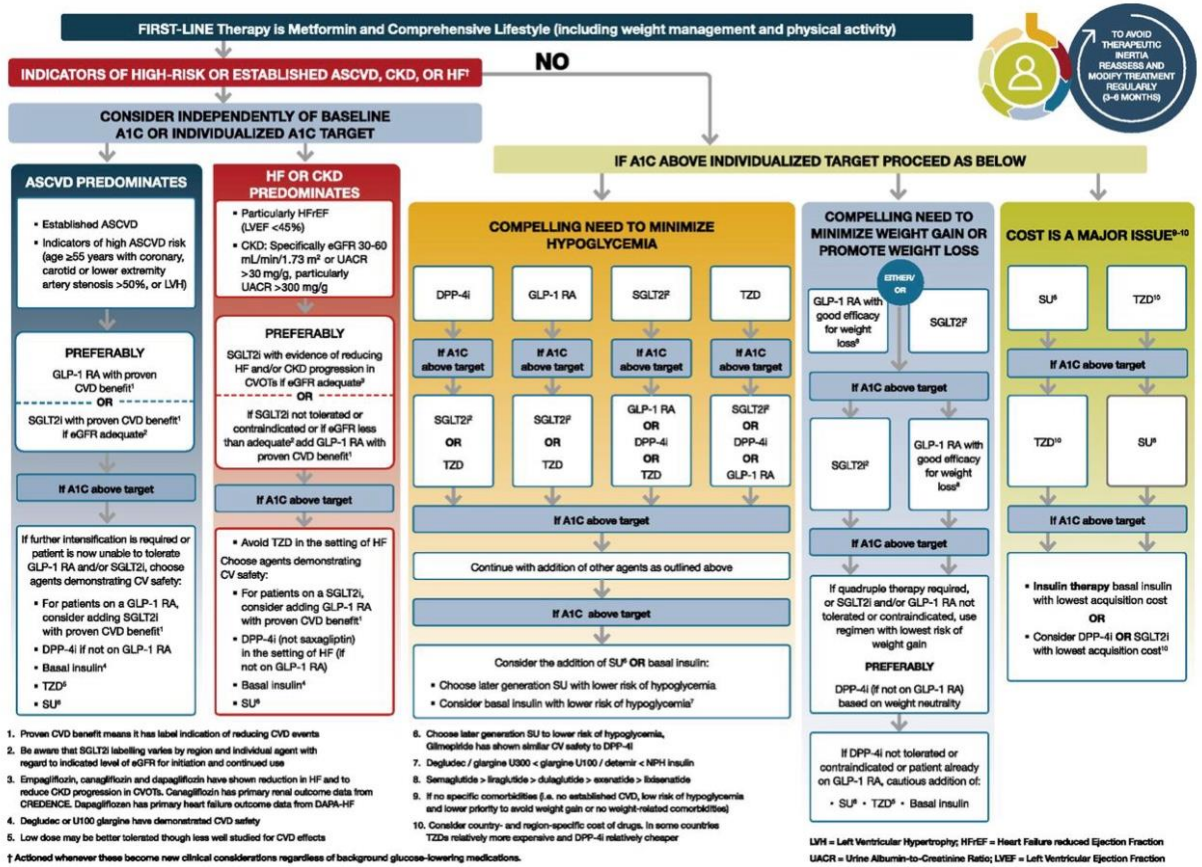
Clinical case : failure to Oral medications

- 52 y/o female DM 29 y evolution, Nephropathy , polyneuropathy
- Complains of diarrhea w metformin, denies hypoglycemia . Chronic smoker , HTN BMI 28 Kg/m2
- Present TX :Janumet 50/1000 bid Canaglifozin 300 mg
- Lab : HBA1c 7.9 % eGFR over 60ml/min EKG : non - specific ST changes

- A) discontinue or decrease metformin and start basal insulin
- B) discontinue DPP4- metformin start premixed insulin bid
- C) decrease metformin , d/c DPP4 , start GLP1
- D) decrease metformin , add SU

Any other thoughts ?

Glucose-lowering medication in type 2 diabetes: overall approach.



American Diabetes Association Dia Care 2020;43:S98-S110

Note : insulin position well below other non-insulin therapies

American Diabetes Association.

SUMMARY OF RECOMMENDATIONS : type 2 diabetes mellitus

- ONCE INITIATED, METORMIN SHOULD BE CONTINUED AS LONG IT IS TOLERATED AND NOT CONTRAINDICATED;OTHER AGENTS, INCLUDING INSULIN SHOULD BE ADDED TO METFORMIN . A .
- THE EARLY INTRODUCTION OF INSULIN SHOULD BE CONSIDERED IF THERE IS EVIDENCE ON ONGOING CATABOLISM, SYMPTOMATIC HYPERGLYCEMIA OR WHEN A1c OVER 10% , OR BG LEVELS OVER 300 MG/dL . E.
- IN MOST PATIENTS WHO NEED THE GREATER GLUCOSE-LOWERING EFFECT OF AN INJECTABLE MEDICATION, GLP1-RA ARE PREFERRED TO INSULIN . B .

- *Diabetes Care 2020;43(Suppl 1) : S98-S110*

What is your therapeutic recommendation at this point?

- A) discontinue or decrease metformin and start basal insulin
- B) discontinue DPP4-metformin start premixed insulin bid
- C) decrease metformin , d/c DPP4 , start GLP1
- D) decrease metformin , add SU

Any other thoughts ?

Overview of GLP-1 Receptor Agonists Available in the United States for the Treatment of Type 2 Diabetes

Generic (Trade) Name; Manufacturer	Dosing Frequency	Recommended Dosage	Administration Before Meals Required?	Available Dosage Form(s); Needle Requirements
Short-acting				
Exenatide BID (Byetta); AstraZeneca	Twice daily	5 µg subcutaneously twice daily within 60 minutes before meals; after 1 month, may increase to 10 µg subcutaneously twice daily based on clinical response	Yes	5-µg pen, 250 µg/mL (1.2 mL); 29-, 30-, or 31-gauge pen needles
Lixisenatide (Adlyxin); Sanofi	Once daily	10 µg subcutaneously once daily within 1 hour before the first meal of the day; on day 15, increase to 20 µg once daily	Yes	50 µg/mL in 3-mL green prefilled pen (14 10-µg doses); 100 µg/mL in 3-mL burgundy pre-filled pen (14 20-µg doses)
Intermediate-acting				
Liraglutide (Victoza); Novo Nordisk	Once daily	0.6 mg subcutaneously once daily for 1 week, then increase to 1.2 mg once daily; if glycemic control not acceptable, can increase dose to 1.8 mg subcutaneously once daily	No	Multi-dose pen delivers 0.6, 1.2, or 1.8 mg, 6 mg/mL (3 mL); 32-gauge pen needles
Long-acting				
Exenatide QW (Bydureon); AstraZeneca	Once weekly	2 mg subcutaneously once weekly (every 7 days) with or without meals	No	Single-dose 2-mg vial and 2-mg pen (require reconstitution); 23-gauge 7-mm needles supplied with pen
Albiglutide (Tanzeum); GlaxoSmithKline	Once weekly	30 mg subcutaneously once weekly; may increase to 50 mg subcutaneously once weekly for inadequate glycemic control	No	Single-dose 30- and 50-mg pens (require reconstitution for 15 [30 mg] to 30 [50 mg] minutes after mixing); 29-gauge, 5-mm, thin-wall needle supplied with pen
Dulaglutide (Trulicity); Eli Lilly	Once weekly	0.75 mg subcutaneously once weekly; may increase to 1.5 mg subcutaneously once weekly for inadequate glycemic control	No	Single-dose pen or prefilled syringes: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL; 29-gauge needle attached to pen

Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectrum. 2017;30(3):202-210.

GLP-1 RA versus insulin treatment

A meta-analysis comparing clinical effects of short or long acting GLP-1 receptor agonists versus insulin treatment from head-to head studies in type 2 diabetic patients

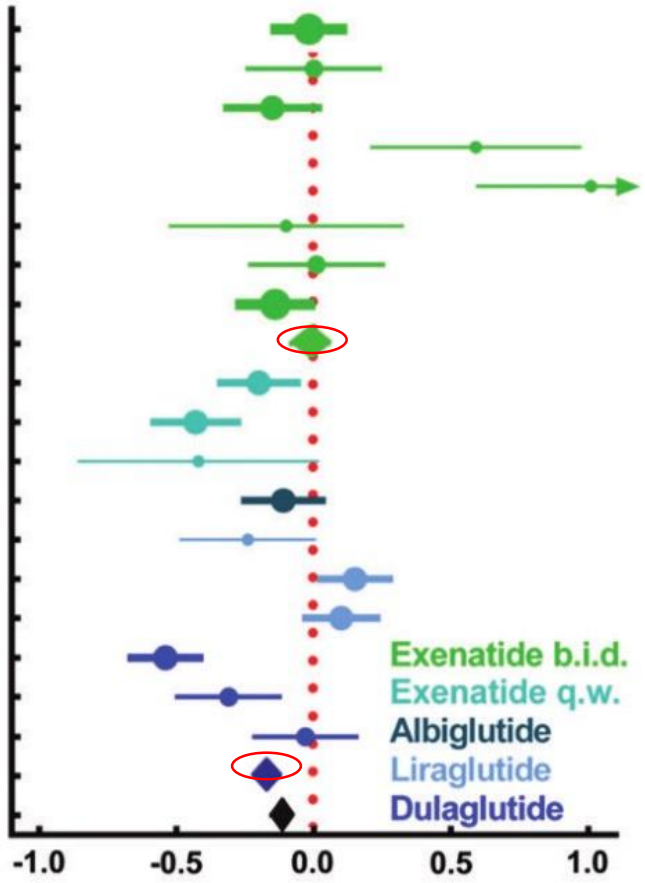
ABD et al, Germany

GLP-1 receptor agonist added to insulin versus basal-plus or basal – bolus insulin therapy in type 2 diabetes : A systematic review and meta-analysis

Castellana et al. , Bari, Italy

GLP-1RA vs Insulin OGLM background
Change in HBA1C

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Heine et al. 2005 [44]	short	-0.02	-0.16	0.12	-0.24	0.81
Barnett et al. 2007 [33]	short	0.00	-0.25	0.25	0.00	1.00
Nauck et al. 2007 [47]	short	-0.15	-0.33	0.03	-1.63	0.10
Bergenstal et al. 2009 a [34]	short	0.59	0.21	0.97	3.02	0.0026
Bergenstal et al. 2009 b [34]	short	1.01	0.59	1.43	4.72	< 0.0001
Bunck et al. 2009 [35]	short	-0.10	-0.53	0.33	-0.46	0.65
Davies et al. 2009 [38]	short	0.01	-0.24	0.26	0.08	0.94
Gallwitz et al. 2011 [41]	short	-0.14	-0.29	0.01	-1.87	0.061
All short-acting GLP-1 RAs		**-0.02**	**-0.09**	**0.06**	**-0.39**	**0.70**
Diamant et al. 2010 [40]	long	-0.20	-0.35	-0.05	-2.57	0.010
Inagaki et al. 2012 [45]	long	-0.43	-0.60	-0.26	-5.08	< 0.0001
Davies et al. 2013 [37]	long	-0.42	-0.86	0.02	-1.87	0.061
Weissman et al. 2014 [50]	long	-0.11	-0.27	0.05	-1.39	0.16
Russell-Jones et al. 2009 [49]	long	-0.24	-0.49	0.01	-1.89	0.059
D'Alessio et al. 2015 [36]	long	0.15	0.01	0.29	2.12	0.034
Gough et al. 2015 [43]	long	0.10	-0.04	0.24	1.37	0.17
Araki et al. 2015 [32]	long	-0.54	-0.68	-0.40	-7.66	< 0.0001
Giorgino et al. 2015 a [42]	long	-0.31	-0.50	-0.12	-3.13	0.0018
Giorgino et al. 2015 b [42]	long	-0.03	-0.22	0.16	-0.30	0.76
All long-acting GLP-1 RAs		**-0.17**	**-0.22**	**-0.12**	**-6.24**	**< 0.0001**
All GLP-1 RAs		**-0.12**	**-0.16**	**-0.07**	**-5.30**	**< 0.0001**



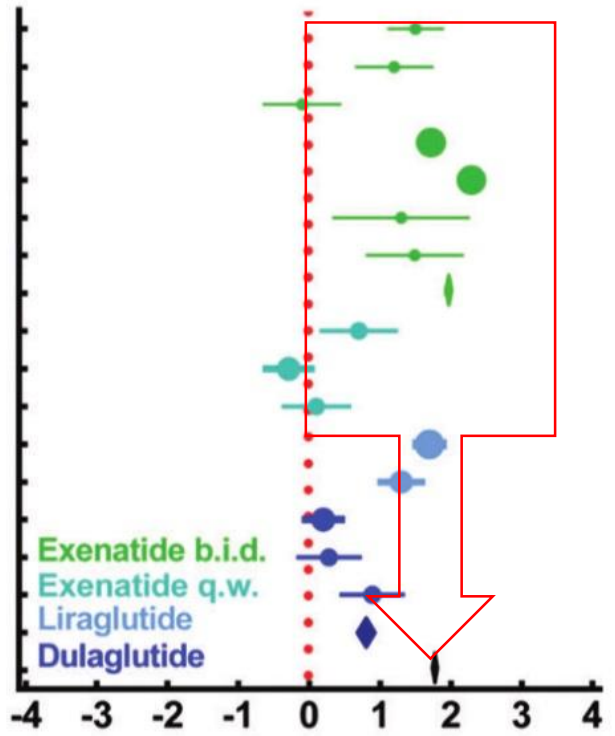
Favours GLP-1RA Favours Insulin

Abd Diabetes Obes Metab 2017;19(2)216-227

GLP-1RA VS INSULIN THERAPY (OGLM BACKGROUND)
Change in FPG

Abd Diabetes Obes Metab 2017;19(2)216-227

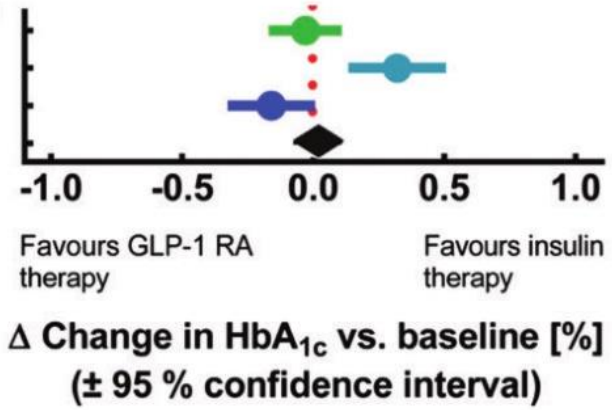
Study	Duration of action	Difference in means	Lower Limit	Upper Limit	t-value	p-value
Heine et al. 2005 [44]	short	1.20	0.65	1.75	7.36	< 0.0001
Barnett et al. 2007 [33]	short	1.72	1.64	1.80	4.25	< 0.0001
Nauck et al. 2007 [47]	short	2.29	2.21	2.37	-0.35	0.72
Bergenstal et al. 2009 a [34]	short	1.30	0.33	2.27	41.67	< 0.0001
Bergenstal et al. 2009 b [34]	short	1.49	0.80	2.18	55.47	< 0.0001
Bunck et al. 2009 [35]	short	1.50	1.10	1.90	2.63	0.0086
Davies et al. 2009 [38]	short	-0.10	-0.65	0.45	4.21	< 0.0001
All short-acting GLP-1 RAs		**1.96**	**1.90**	**2.02**	**68.88**	**< 0.0001**
Diamant et al. 2010 [40]	long	1.70	1.46	1.94	2.47	0.013
Inagaki et al. 2012 [45]	long	1.30	0.96	1.64	-1.54	0.12
Davies et al. 2013 [37]	long	0.10	-0.40	0.60	0.40	0.69
D'Alessio et al. 2015 [36]	long	0.70	0.15	1.26	13.73	< 0.0001
Gough et al. 2015 [43]	long	-0.29	-0.66	0.08	7.48	< 0.0001
Araki et al. 2015 [32]	long	0.28	-0.18	0.74	1.28	0.20
Giorgino et al. 2015 a [42]	long	0.89	0.43	1.35	1.19	0.23
Giorgino et al. 2015 b [42]	long	0.20	-0.11	0.51	3.77	0.0002
All long-acting GLP-1 RAs		**0.80**	**0.67**	**0.93**	**12.17**	**< 0.0001**
All GLP-1 RAs		**1.78**	**1.73**	**1.83**	**68.03**	**< 0.0001**



Favours GLP-1RA Favours Insulin

GLP-1RA vs rapid acting insulin (BI + OGLM) background Change in HBA1c

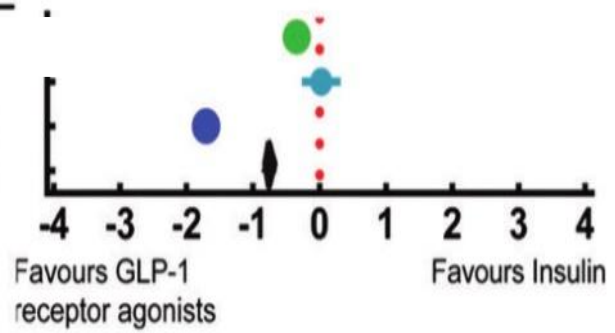
Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Diamant et al. 2014 [39]	short	-0.03	-0.17	0.11	-0.42	0.67
Mathieu et al. 2014 [46]	long	0.32	0.13	0.51	3.37	0.0008
Rosenstock et al. 2014 [48]	long	-0.16	-0.33	0.01	-1.89	0.059
All GLP-1 RAs		**0.02**	**-0.08**	**0.11**	**0.34**	**0.73**



Abd_ Diabetes Obes Metab 2017;19 (2) 216-227

B **GLP-1 RA versus rapid-acting insulin (basal insulin + OGLM background)**

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Mathieu et al. 2014 [46]	long	0.06	-0.65	0.77	0.17	0.87
Rosenstock et al. 2014 [48]	long	-0.28	-0.31	-0.25	-17.39	< 0.0001
All GLP-1 RAs		**-0.28**	**-0.31**	**-0.26**	**-13.15**	**< 0.0001**

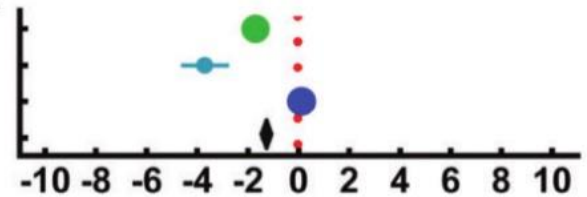


Δ Change in fasting plasma glucose vs. baseline [mmol/l] (± 95 % confidence interval)

ABD_Diabetes Obes Metab 2017;19(2)216-227

B **GLP-1 RA versus rapid-acting insulin (basal insulin + OGLM background)**

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Diamant et al. 2014 [39]	short	-1.70	-1.98	-1.42	-12.02	< 0.0001
Mathieu et al. 2014 [46]	long	3.70	-4.65	-2.75	-7.66	< 0.0001
Rosenstock et al. 2014 [48]	long	0.12	-0.29	0.53	0.57	0.57
All GLP-1 RAs		**-1.28**	**-1.50**	**-1.05**	**-11.19**	**< 0.0001**



Δ Change in body weight vs. baseline [kg]
(± 95 % confidence interval)

Summary
GLP vs Insulin

- If anything , overall glycemic control was slightly better with GLP-1RA than with insulin treatment, more obvious in studies using long-acting GLP-1RA
- FBG was better controlled with insulin especially in comparisons with short acting GLP-1RA
- GLP-1RA had favorable results in BW(-3.7 Kg) and hypoglycemia compared to insulin treatment
- When GLP-1RA were added to basal insulin, there was a significant reduction in BW (-1.3 Kg), hypoglycemia 35%, severe 77 %, lower FBG, but no difference in HBA1c or nocturnal hypos versus short acting insulin analogs along BI
- Limitations : none of the included trials was double blinded

Clinical case : Intensifying from BI + OAD

Patient 45 y/o female DM 2 12 y evolution

Treatment : metformin 1000 mg bid, glimepiride 4 mg bid , Glargine u-300 40 u d canaglifozin 300 mg

BMI: 43 kg/m2 Metabolic surgery recommended, patient denies

Labs HbA1c 10.1% FBG 327mg/dL
Tg 1084 ALT 19 tsh 2.99miliU/L

What is your recommendation ?

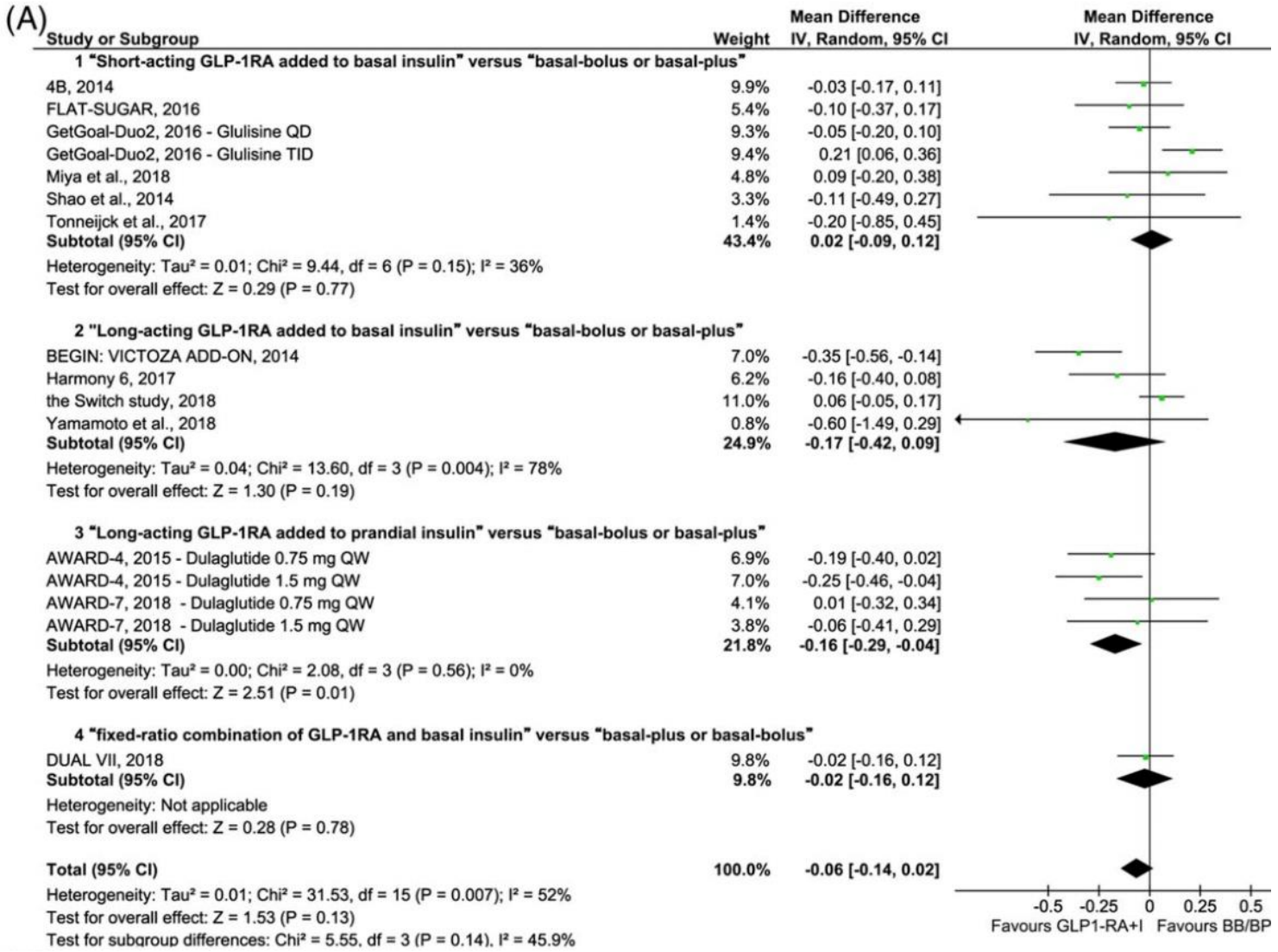
- A) continue intensifying basal dose
- B) start Basal-plus / Basal bolus
- C) add GLP1-RA

GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes :A systematic review and meta-analysis

- 13 trials
- HBA1c 6-11%
- BMI 20-45 Kg/m2
- eGFR 16-60 ml/min
- 96 % on basal insulin
- 27 % prandial
- 82% on metformin
- 2744 randomized to GLP-1RA
- 2564 to Basal plus BP or / Basal Bolus BB

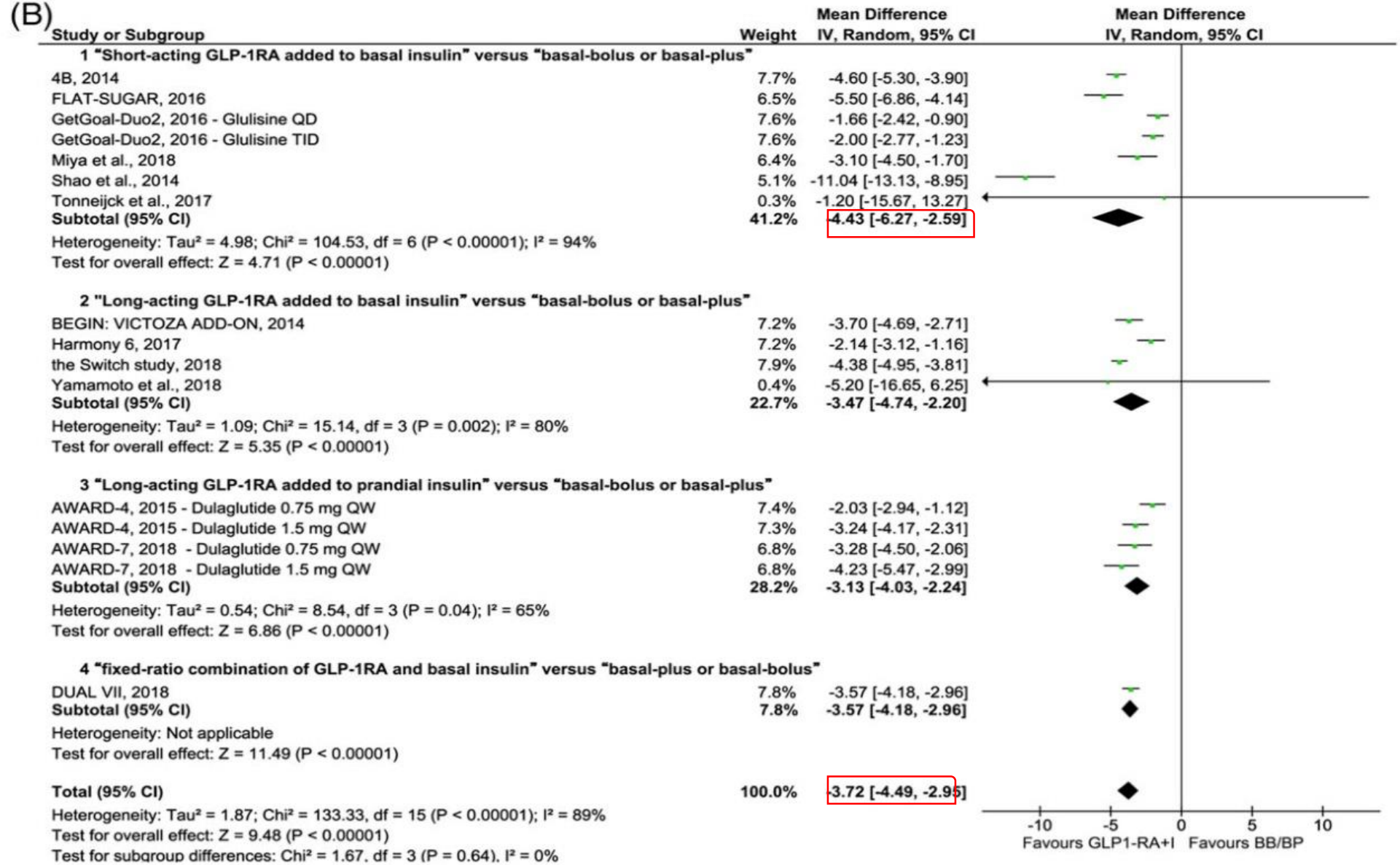
Castellana et al,2018

Meta-analysis for change in HBA1c: GLP1 added to BI vs BB or Bplus



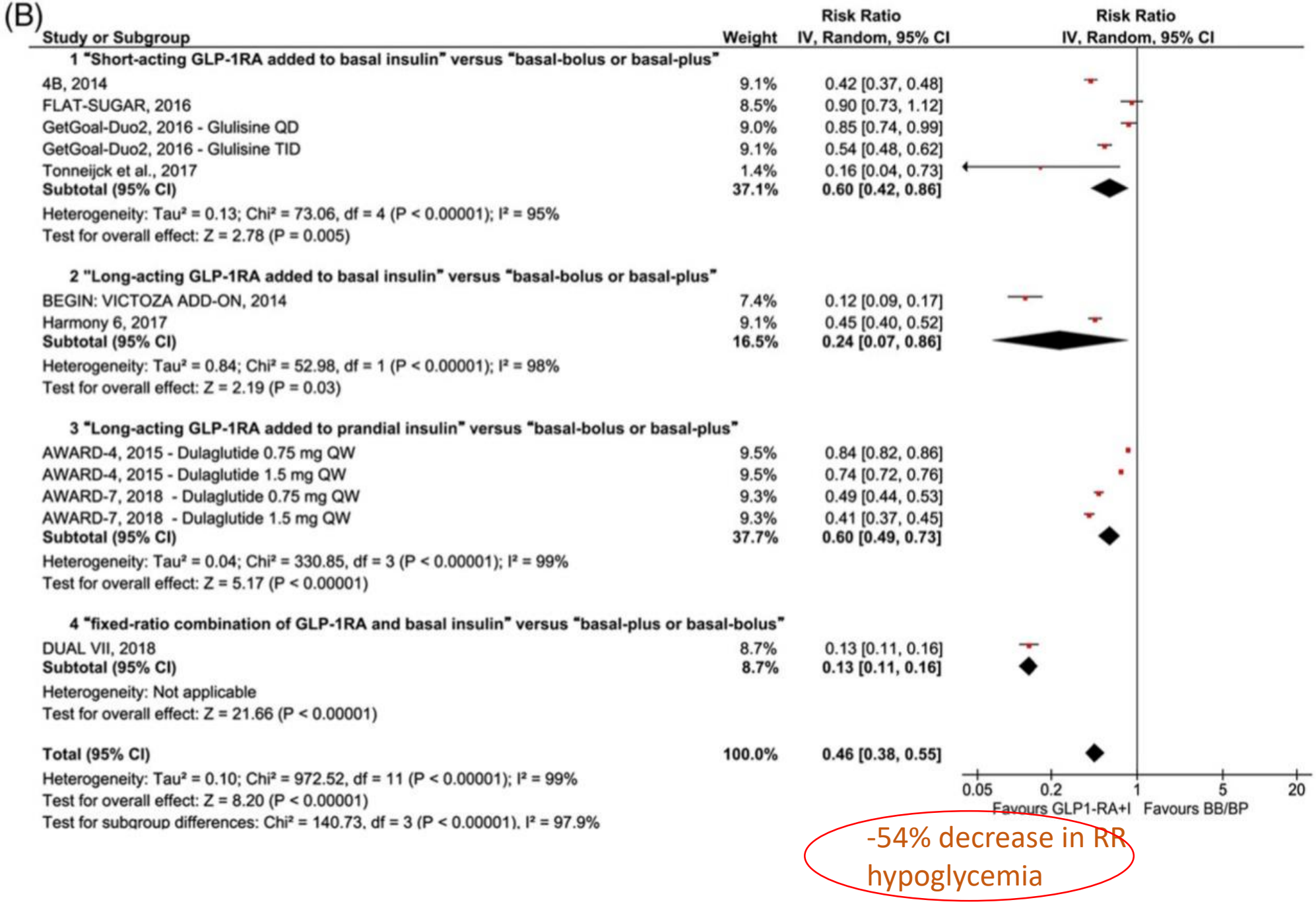
Castellana et al, Diabetes Metab Res Rev 2019; 35;e 3082

Meta-analysis for change in BW : short acting GLP-1RA,long acting added to basal or added to prandial , fixed GLP1 and BI vs B+ or BB



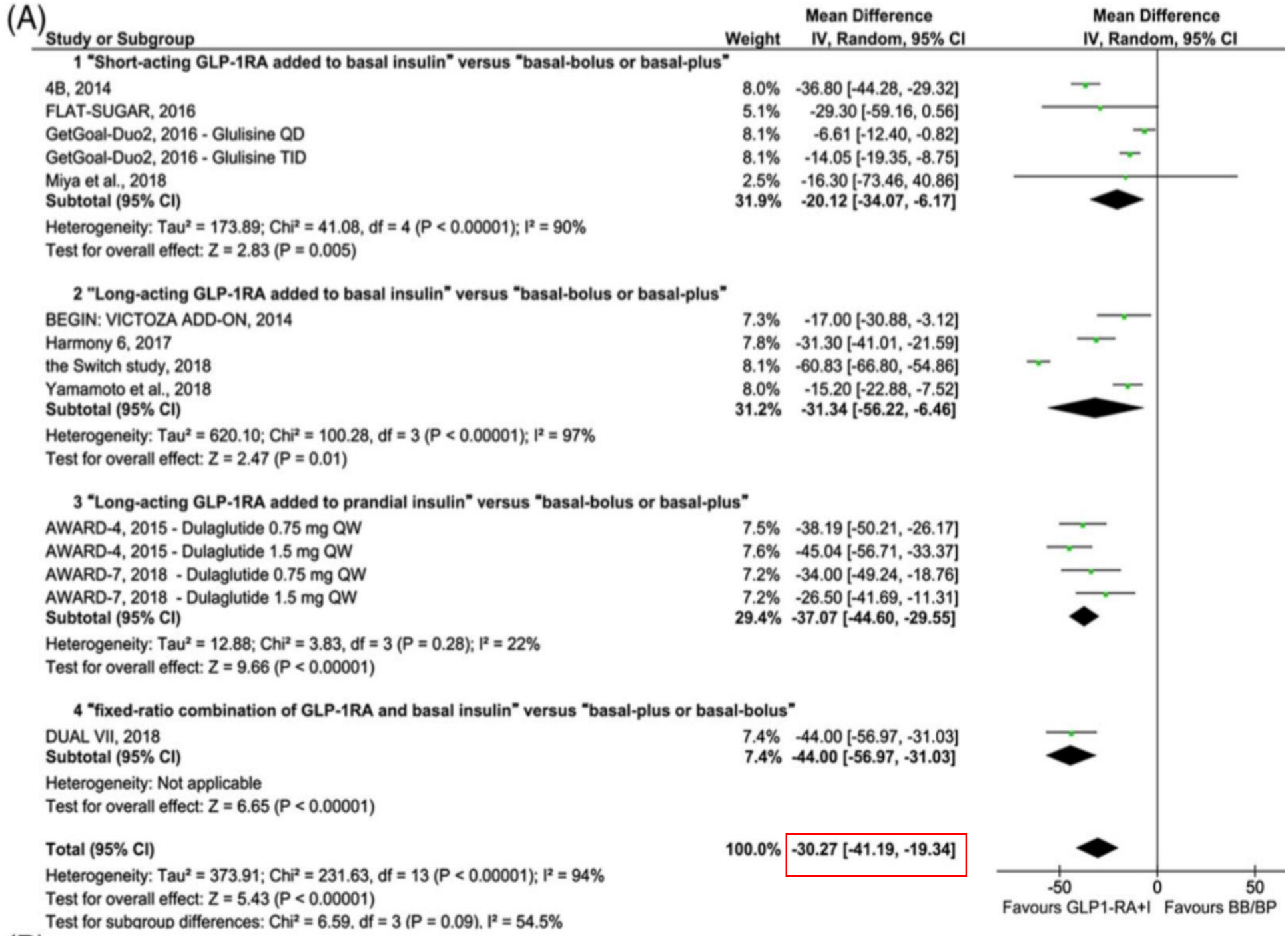
Difference in incidence of hypoglycemia

(B)

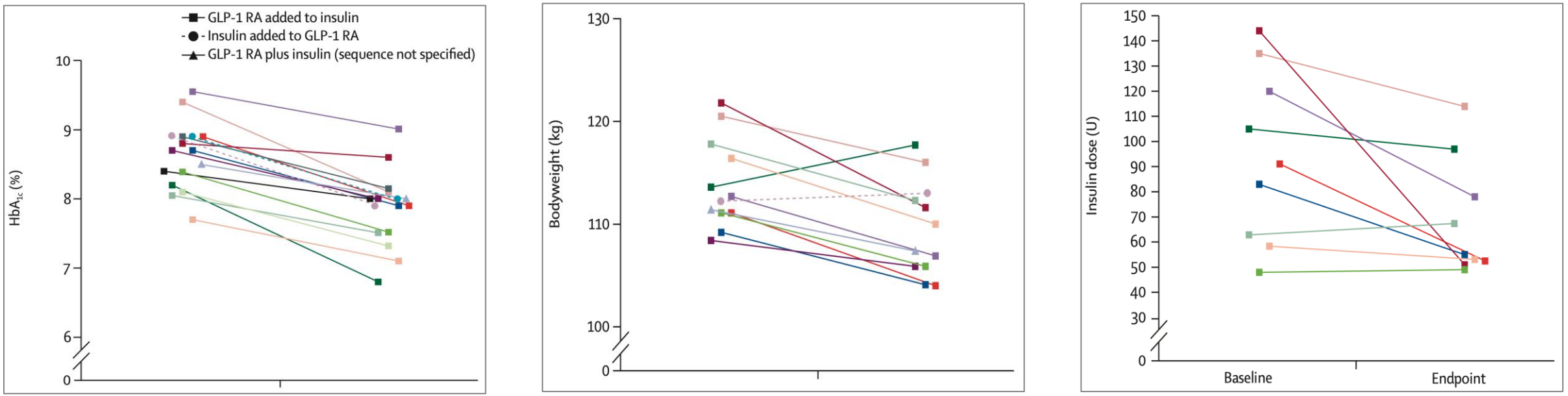


-54% decrease in RR hypoglycemia

Difference in daily insulin dose



Effects of insulin added to existing treatment with glucagon-like peptide-1 receptor agonist or vice versa on glycemic control (HbA_{1c}), bodyweight, and insulin dose



Summary of results from observational studies. All three variables (HbA_{1c}, bodyweight, and insulin dose) decreased from baseline to end of treatment (endpoint). Duration of treatment varied from 26 weeks to 48 months. Every colored line represents one study. Figure is reproduced from Balena and colleagues,77 by permission of Wiley. GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Cahn A, Miccoli R, Dardano A, Del Prato S. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. The Lancet Diabetes & Endocrinology. 2015;3(8):638-652. doi:10.1016/s2213-8587(15)00097-2

Key efficacy and safety results for IDegLira from DUAL trails

FAS/SAS	IDegLira						
	DUAL I *n* = 833/825	DUAL II *n* = 199/199	DUAL III *n* = 292/291	DUAL IV *n* = 289/288	DUAL V *n* = 278/278	DUAL VI 1WT *n* = 210/209	DUAL VI 2WT *n* = 210/210
Population	Met ± pio Insulin naïve	Basal insulin 20–40 U daily + Met ± SU/ glinides	GLP-1RA** + Met ± pio ± SU Insulin naïve	SU ± met Insulin naïve	IGlar U100 20–50 U daily + Met	Met ± pio Insulin naïve	Met ± pio Insulin naïve
Mean baseline HbA1c, % (SD)	8.3 (0.9)	8.7 (0.7)	7.8 (0.6)	7.9 (0.6)	8.4 (0.9)	8.2 (0.9)	8.1 (0.9)
Mean EOT HbA1c, % (SD)	6.4 (1.0)	6.9	6.4 (0.8)	6.4 (0.8)	6.6 (0.9)	6.1	6.0
Mean ΔHbA1c, % (SD)	−1.9 (1.1)	−1.9	−1.3 (0.8)	−1.5 (0.8)	−1.8 (1.1)	−2.0 (1.1)	−2.0 (1.0)
Mean ΔHbA1c, mmol/mol	-21	-21	-14.5	-16	-20	-22	-22
% patients achieving HbA1c < 7.0%	81	60	75	79	72	90	90
% patients achieving HbA1c ≤ 6.5%	70	45	63	64	55	83.6	85.0
Mean EOT FPG, mg/dL (SD)	101 (32.4)	112	108 (28.8)	117	110 (38.4)	N/A	N/A
Mean ΔFPG from baseline, mg/dL (SD)	−65	−62 (53)	−54 (41)	−47 (47)	−50	−78	−82
Mean Δweight from baseline, kg (SD)	−0.5 (3.5)	−2.7	+2.0 (3.9)	0.5	−1.4 (3.5)	−1.0	−2.0
Baseline daily mean insulin dose, U (SD)	N/A	29 (8)	N/A	N/A	31 (10)	11	11
Final daily mean insulin dose, U (SD)	38 (13)	45	43	28	41	41	41
EOT mean 9-point SMPG, mg/dL (SD)	128 (32)	135	N/A	N/A	137 (35)	N/A	N/A
Δ mean 9-point SMPG from baseline, mg/dL (SD)	−58	−58	N/A	−40 (3.8)	−46 (44.9)	N/A	N/A
Confirmed hypoglycemia rates, events per PYE	1.8	1.5	2.8	3.5	2.2	N/A	N/A
Nocturnal hypoglycemia rates, events per PYE	0.2	0.2	0.5	0.5	0.2	N/A	N/A
Nausea, % of participants	9	7	3	5	9	5	5

Valentine V, Goldman J, Shubrook J. Rationale for, Initiation and Titration of the Basal Insulin/GLP-1RA Fixed-Ratio Combination Products, IDegLira and IGlarLixi, for the Management of Type 2 Diabetes. Diabetes Therapy. 2017;8(4):739-752. doi:10.1007/s13300-017-0287-y

Key efficacy and safety results for IGlarLixi from LixiLan-O and LixiLan-L

	IGlarLixi	
	LixiLan-O ***n* = 468**	**LixiLan-L** ***n* = 367**
Population	Met ± 2nd OAD Insulin naïve	Basal insulin 15–40 U daily ± 1–2 OADs
Run-in phase	4 weeks Met	6 weeks Met + IGlar U100
Baseline HbA1c, % (SD)	8.1 (0.7)	8.1 (0.7)
EOT HbA1c, % (SD)	6.5 (0.8)	6.9 (0.9)
Mean ΔHbA1c, % (SD)	−1.6 (0.04)	−1.1 (0.06)
Mean ΔHbA1c, mmol/mol	-17	-7
% patients achieving HbA1c < 7.0%	74	55
% patients achieving HbA1c ≤ 6.5%	56	34
EOT FPG, mg/dL (SD)	113.4 (6.3)	122 (41)
ΔFPG from baseline, mg/dL (SD)	−63.0 (1.8)	−6 (3)
Δweight from baseline, kg (SD)	−0.3 (0.2)	−0.7 (0.2)
Baseline daily mean insulin dose, U (SD)	N/A	27 (8)
Final daily insulin dose, U (SD)	40 (15)	47 (13)
EOT mean 7-point SMPG, mg/dL (SD)	N/A	140 (31)
Δ mean 7-point SMPG from baseline, mg/dL (SD)	−0.69	−27 (2)
Δ 2-h postprandial glucose from baseline, mg/dL	−102.6 (3.6)	−85 (6)
Confirmed hypoglycemia rates, events per PYE	1.4	3.03
Nocturnal hypoglycemia rates, events per PYE	N/A	N/A
Nausea, % of participants	9.6	10.4

Valentine V, Goldman J, Shubrook J. Rationale for, Initiation and Titration of the Basal Insulin/GLP-1RA Fixed-Ratio Combination Products, IDegLira and IGlarLixi, for the Management of Type 2 Diabetes. Diabetes Therapy. 2017;8(4):739-752. doi:10.1007/s13300-017-0287-y

Clinical case : failure to OGLM and BI plus GLP-1RA

Patient 45 y/o female DM 2 12 y evolution

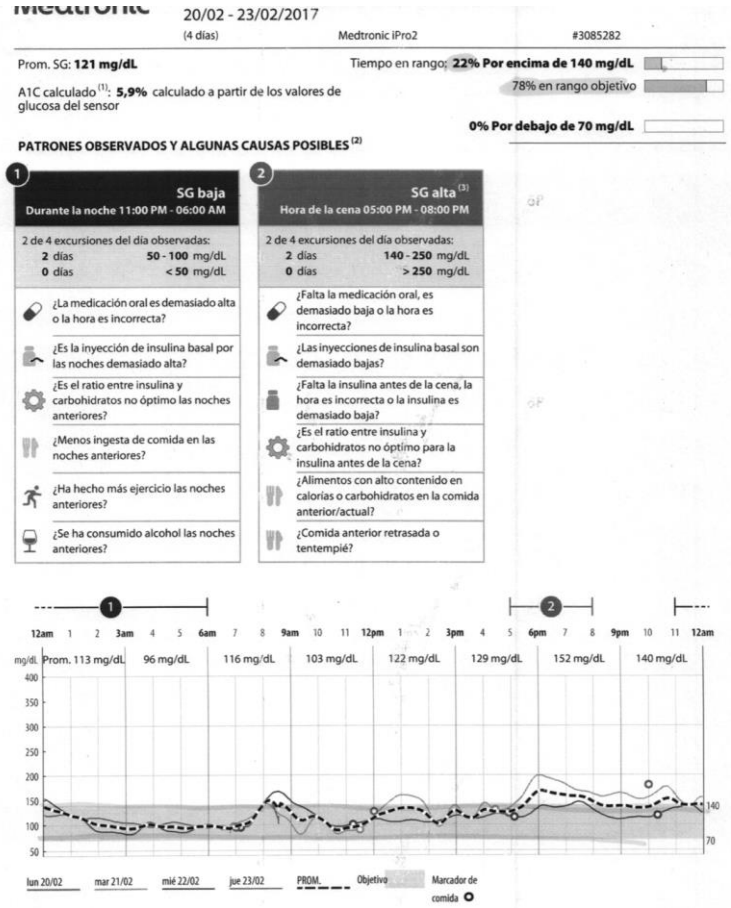
Treatment : metformin 1000 mg bid, glimepiride 4 mg bid , liraglutide 1.8 mg d then dulaglutide 1.5mg Glargine u-300 60 u d canaglifozin 300 mg

BMI: 43 kg/m2 Metabolic surgery recommended, patient denies

Labs HbA1c 10.1% FBG 327mg/dL Tg 1084 ALT 19 tsh 2.99miliU/L

The patient was titrated to 60 u Glar u-300 w added GLP1-RA liraglutide 1.8 mg, no weight gain and HBA1c 7.3% FBG =165 mg/dL TG=232 LDL =77 HDL=31

5 months later



TIR 78%
0% hypoglycemias

Glargine u-300 optimized to 60 u d

COMBINATION INJECTABLE THERAPY

- THE COMBINATION OF BASAL INSULIN AND GLP-1RA HAS POTENT GLUCOSE LOWERING ACTIONS AND LESS WEIGHT GAIN AND HYPOGLYCEMIA COMPARED WITH INTENSIFIED INSULIN REGIMENS

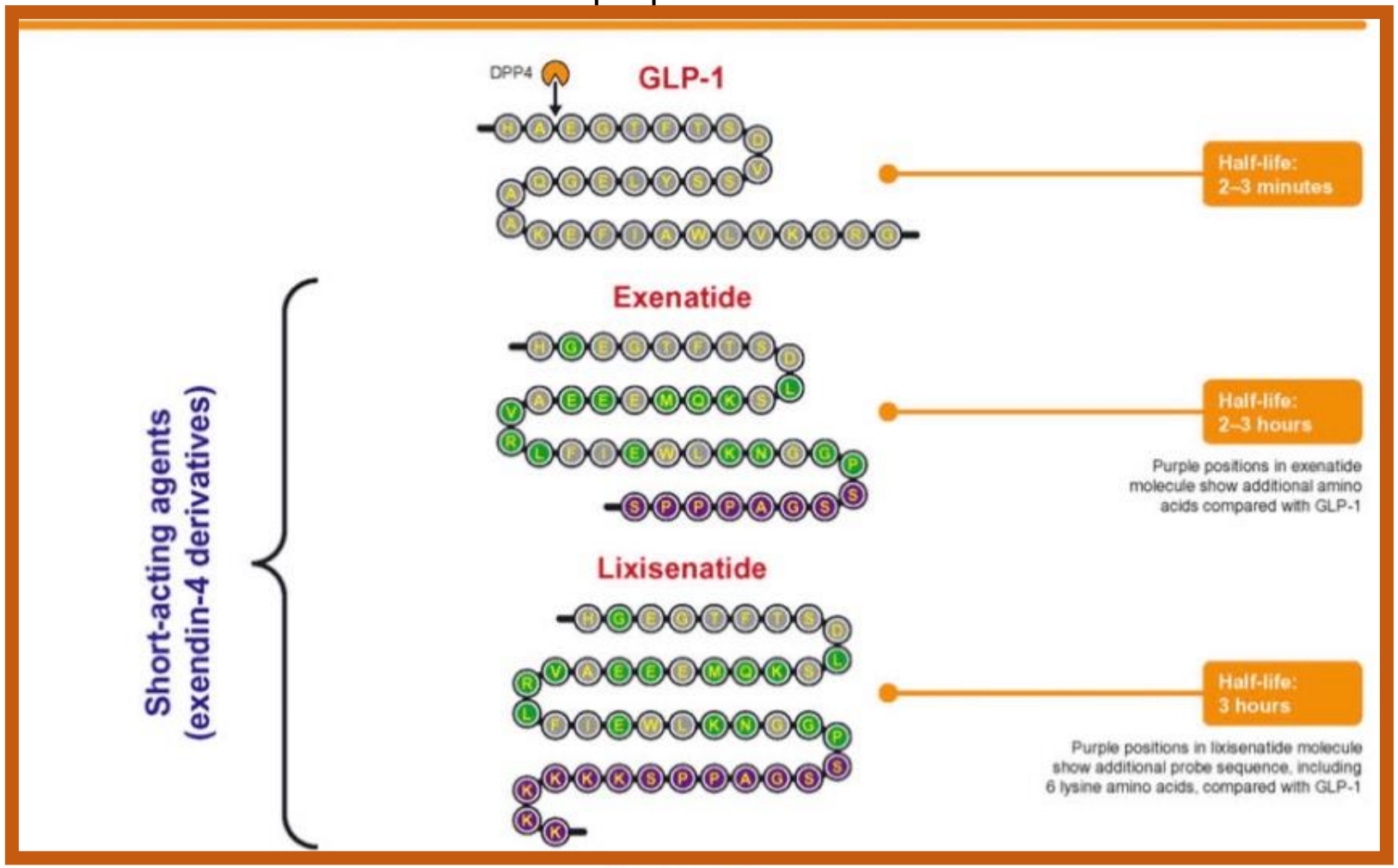
GLP-1RA differentiation within the class

Glucagon –like peptide receptor agonist in type 2 diabetes treatment: are they all the same ?
Raffaella Gentilella et al, Italy

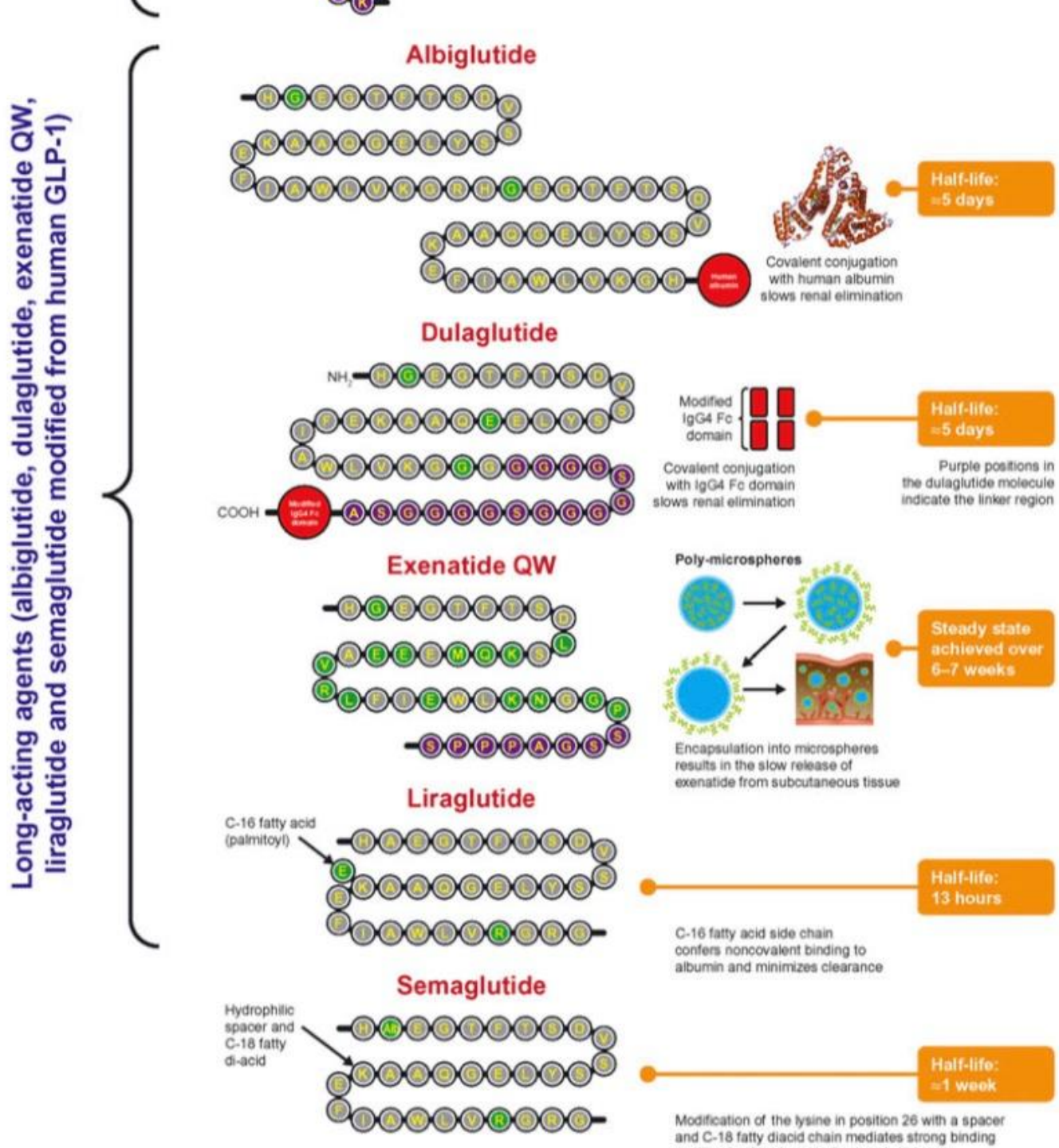
Review of head –to head comparisons of glucagon-like peptide-1 receptor agonists
Madsbad, Denmark

Comparative effectiveness of once-weekly glucagon-like peptide -1 receptor agonists with regard to 6-month glycemic control and weight outcomes in patients with type 2 diabetes
Unni, et al. Utah.

Structures and properties of GLP-1RAs

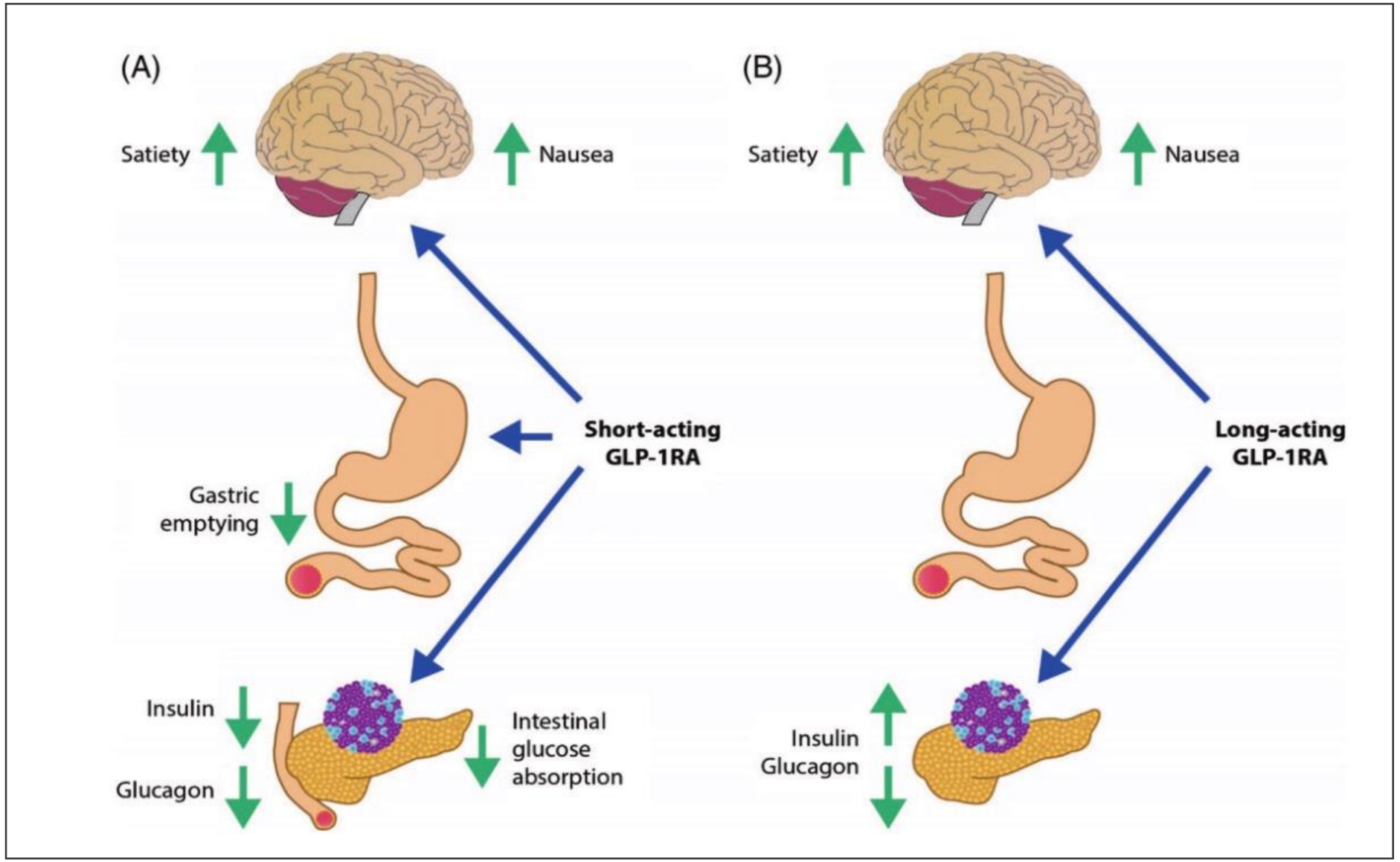


Gentiella ,Diabetes Metabol Res Rev 2018 e 3070



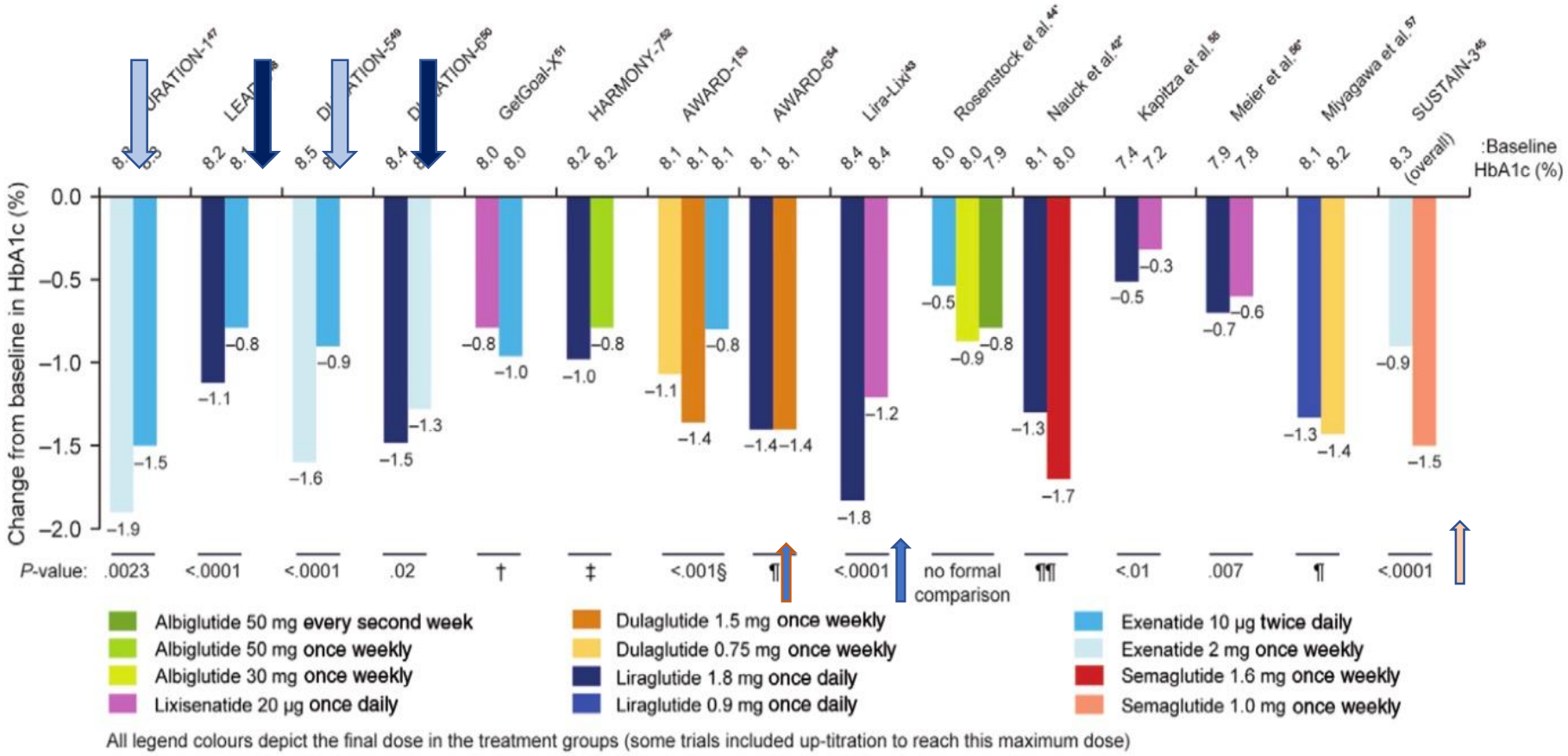
- *Gentilella Diabetes Metab Res Rev*

Gastric emptying effects of short-acting vs long-acting GLP-1RAs



Madsbad_Diabetes Obes Metab 2016 p317-332

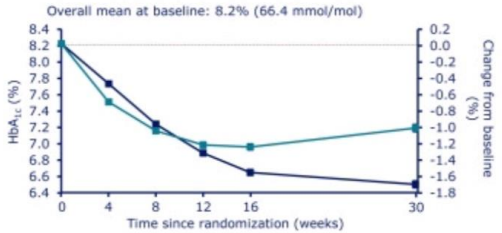
Change in HbA1c in head to head comparison trials of GLP1-RAs

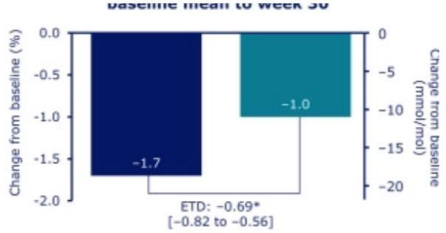


Dalsgaard Diabetes Obes Metab 2018, p508-519

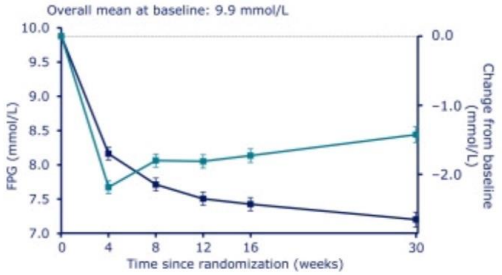
Sustain 10 : Efficacy and safety of once –weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes

Capehorn et al Diabetes and Metabolism sep 2019



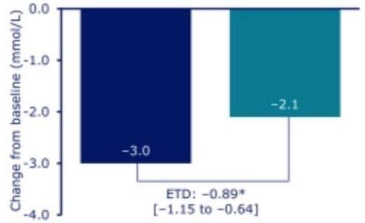


c. Estimated change in FPG over time

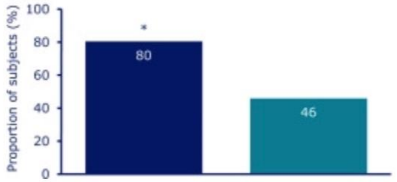


d. Observed mean 7-point SMBG profile at baseline and at week 30

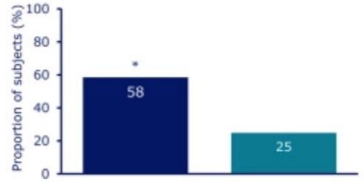
e. Mean 7-point SMBG profile change from baseline to week 30



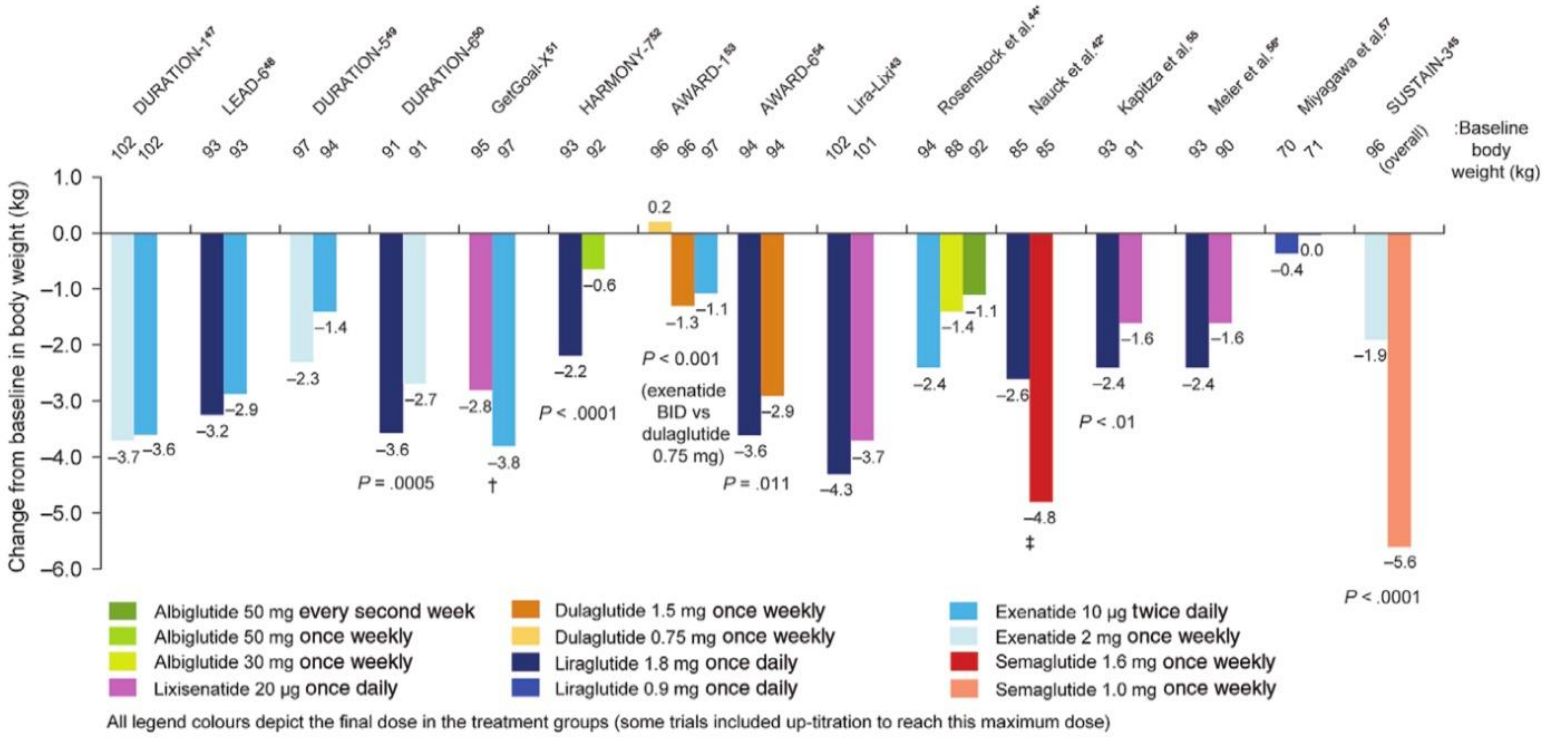
f. Subjects achieving HbA_{1c} <7.0% (<53 mmol/mol; ADA) at week 30



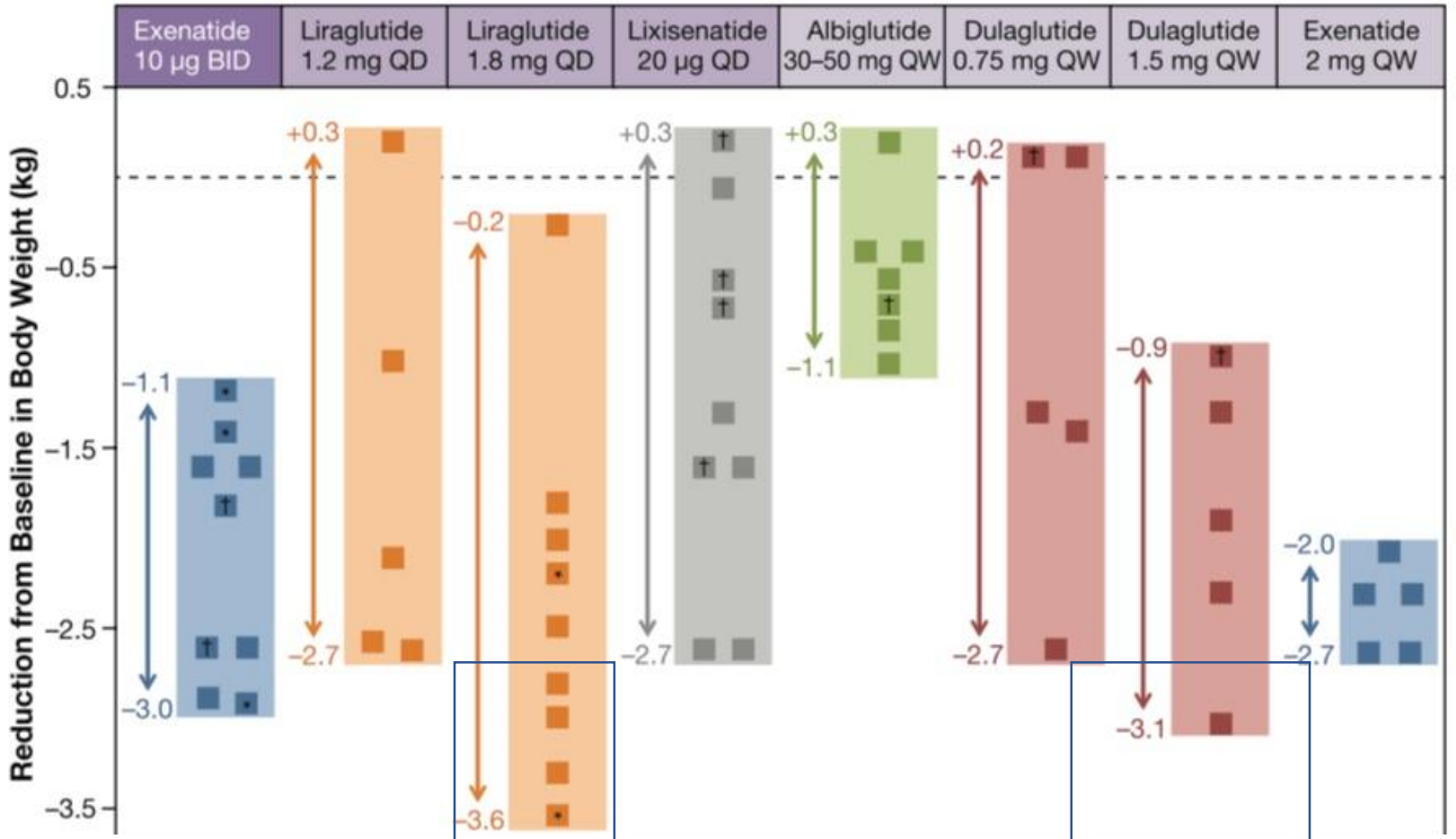
g. Subjects achieving HbA_{1c} ≤6.5% (≤48 mmol/mol; AACE) at week 30



Change in body weight in head to head trials of GLP-1RA



Dalsgaard et al,Diabetes and Metab 2018,5508-519



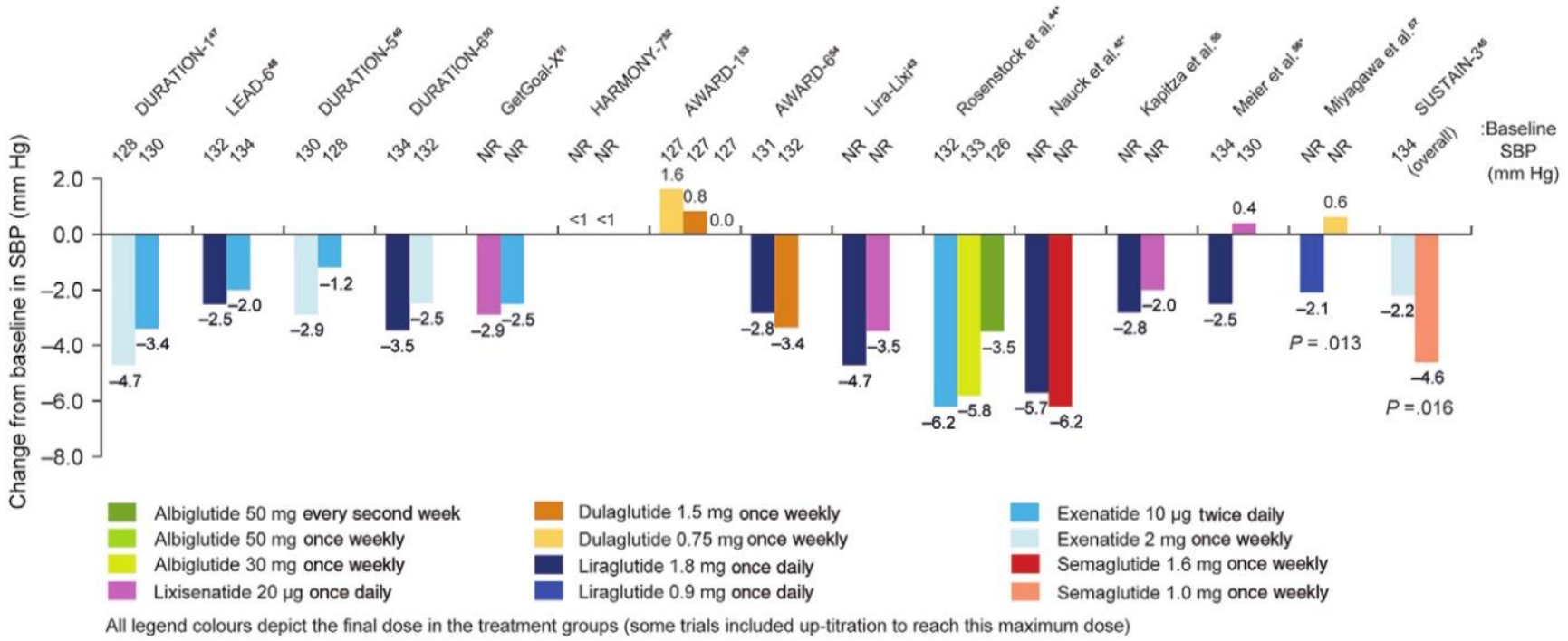
BODY WEIGHT CHANGES BEWTWEEN PI ‘S OF 5 GLP1RA

- - 3.83 Kg

Semaglutide

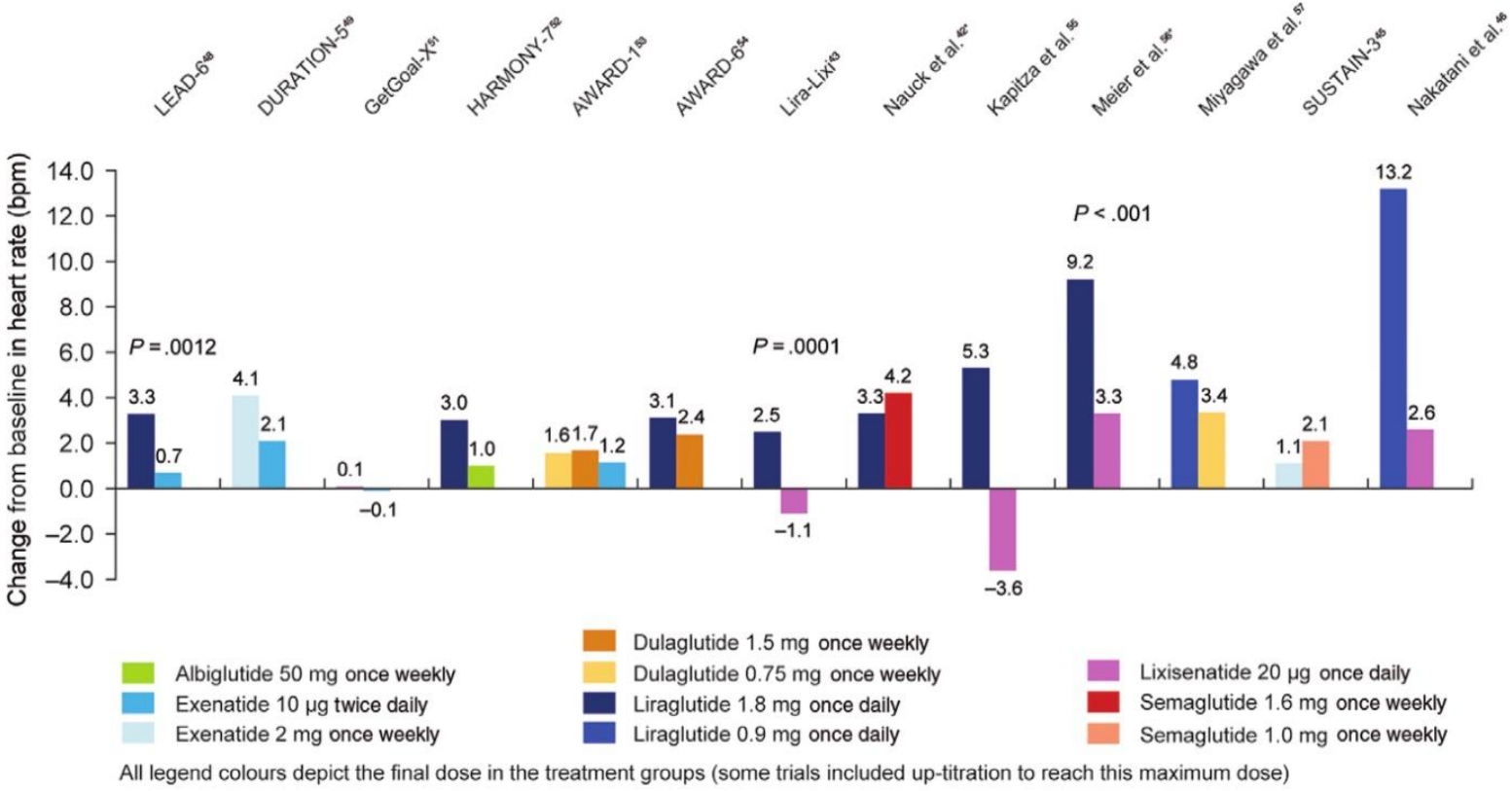
-2.3-3.5 Kg

Change in SBP in head to head trials of GLP1-RAs



Consistent reductions in SBP within the class

Change in HR in head to head trials of GLP-1RAs



Dalsgaard et al,Diabetes and Metab 2018,5508-519

No head to head cardiovascular outcome trials have been done for this drug class

Bethel et al, Cardiovascular outcomes with glucagon-like-1 receptor agonists in patients with type 2 diabetes : a metanalysis, Lancet Diabetes Endocrinol 2018,6: 105-113
,

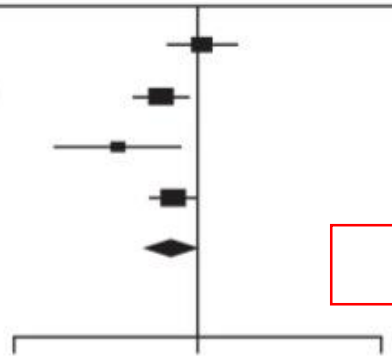
Asharf et al , Cardiovascular outcome trials in type 2 diabetes : A critical analysis
Diabetes and Metabolic Syndrome : Clinical Research and Reviews 13 (2019) 300-305

3 Point MACE

A Three-point MACE

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)	0·776
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)	0·015
SUSTAIN 6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)	0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)	0·061
Overall			**0·90 (0·82–0·99)**	**0·033**

Test for heterogeneity: p=0·11, I^2=50%

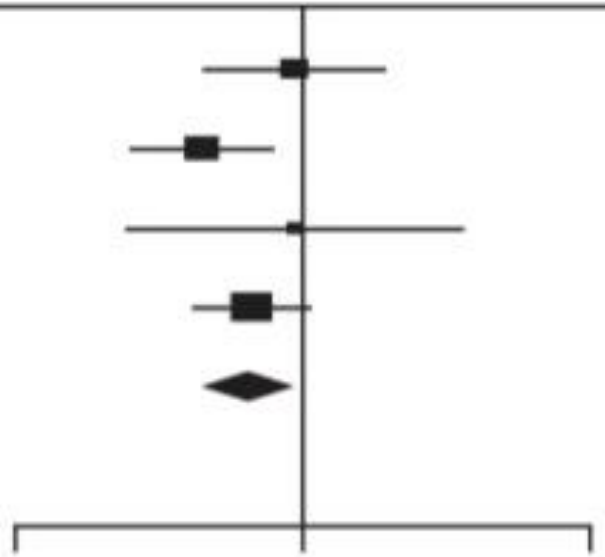


Bethel et al, Cardiovascular outcomes with glucagon-like-1 receptor agonists in patients with type diabetes : a metanalysis, Lancet Diabetes Endocrinol 2018,6: 105-113

Cardiovascular Mortality

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)	0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)	0·007
SUSTAIN 6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)	0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)	0·096
Overall			**0·87 (0·79–0·96)**	**0·007**

Test for heterogeneity: p=0·43, I^2=0%



Cardiovascular outcomes with glucagon-like peptide -1 receptor agonists in patients with type 2 diabetes : a meta-analysis

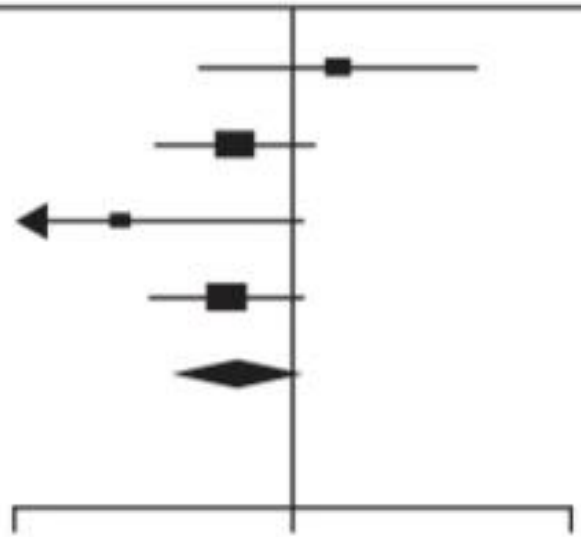
Bethel Lancet Diabetes Endocrinol 2018 6 : 105-13

Fatal and non -fatal stroke

D Fatal and non-fatal stroke

	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)	0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)	0·16
SUSTAIN 6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)	0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)	0·095
Overall			**0·87 (0·75–1·00)**	**0·052**

Test for heterogeneity: p=0·31, I^2=16%



Bethel_Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis
Lancet Diabetes Endocrinol 2018; 6: 105-13

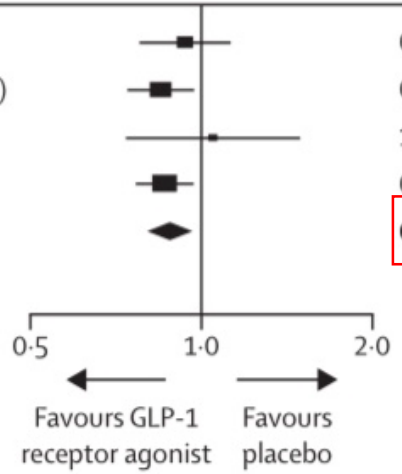
Class effect ?

MORTALITY OUTCOMES : GLP1RA

E All-cause mortality

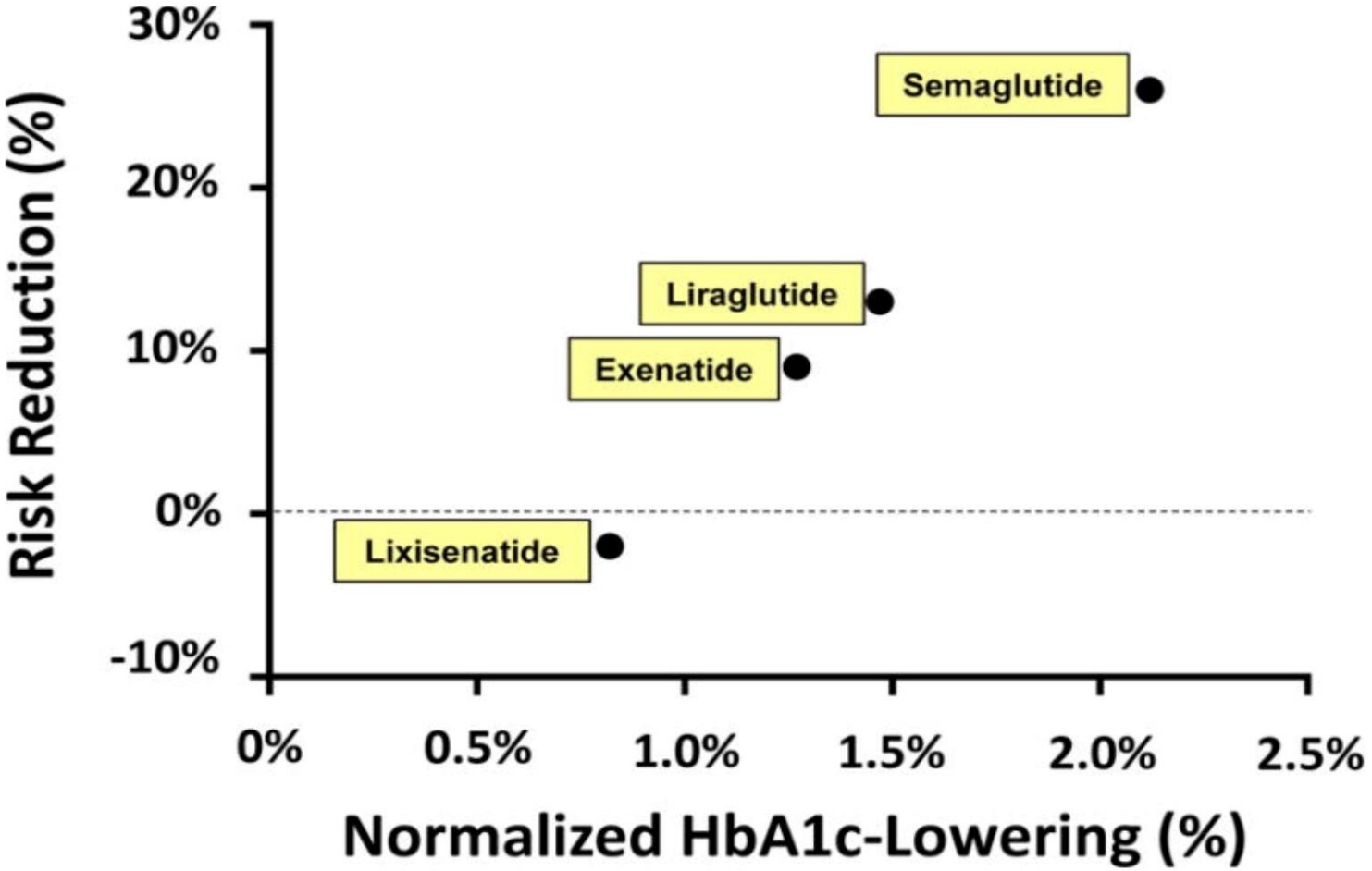
	GLP-1 receptor agonist	Placebo	Hazard ratio (95% CI)	p value
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)	0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)	0·020
SUSTAIN 6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)	0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)	0·016*
Overall			**0·88 (0·81–0·95)**	**0·002**

Test for heterogeneity: p=0·63, I^2=0%



Bethel_Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a metanalysis
Lancet Diabetes Endocrinol 2018; 6: 105-13

MAGNITUDE OF CARDIOPROTECTION IS CORRELATED WITH HBA1C LOWERING

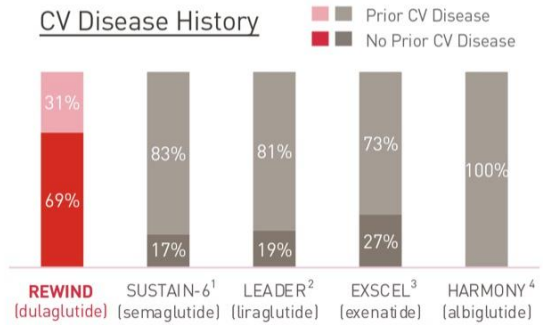


Magnitude of cardioprotection is correlated with HbA1c-lowering

Hazard ratios from SUSTAIN-6, LEADER, EXSCEL, and ELIXA[2–5] are plotted on the vertical axis as a function of 'normalized' HbA1c-lowering

REWIND trial design is different from other GLP-1 RA CVOTs

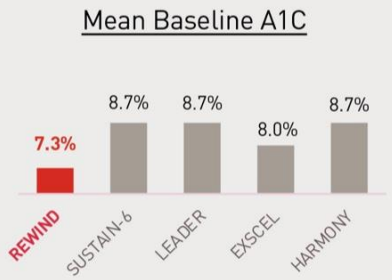
Majority of participants did not have established CV disease*



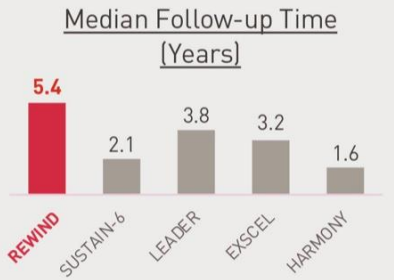
*REWIND defined established CV disease as including at least one of the following conditions: myocardial infarction (MI), ischemic stroke, unstable angina, revascularization, hospitalization for ischemia-related events and/or documented myocardial ischemia.

Definitions of established CV disease vary from trial to trial.

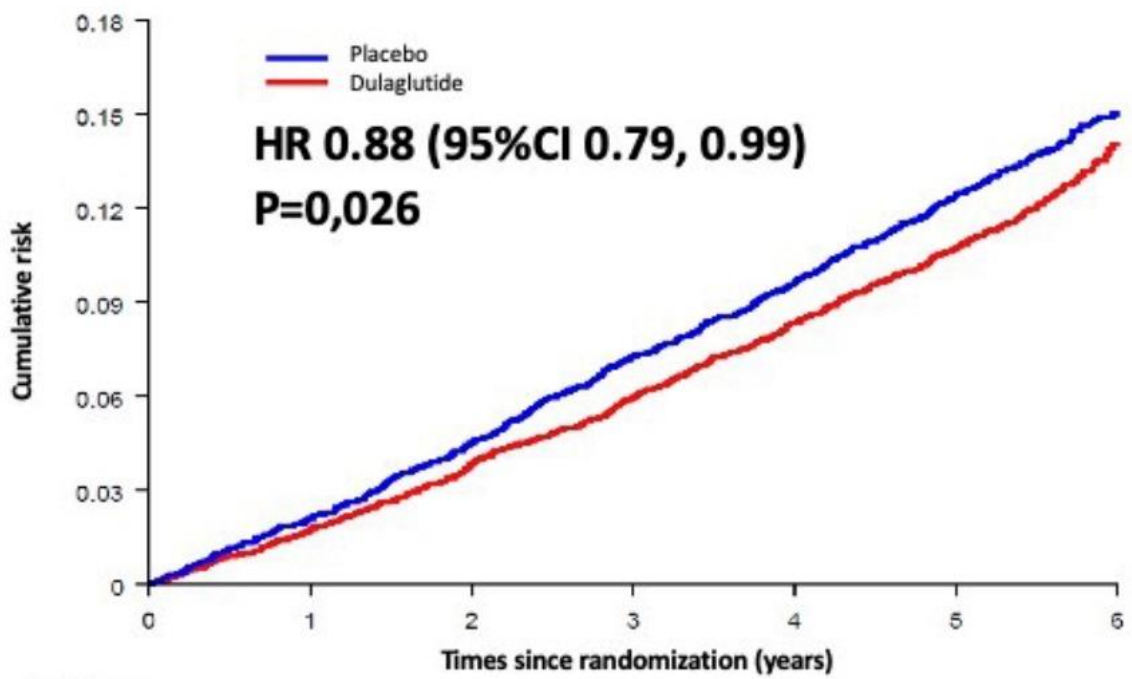
Study population had a lower mean baseline A1C



Longest follow-up period of any CV outcome trial in the GLP-1 RA class



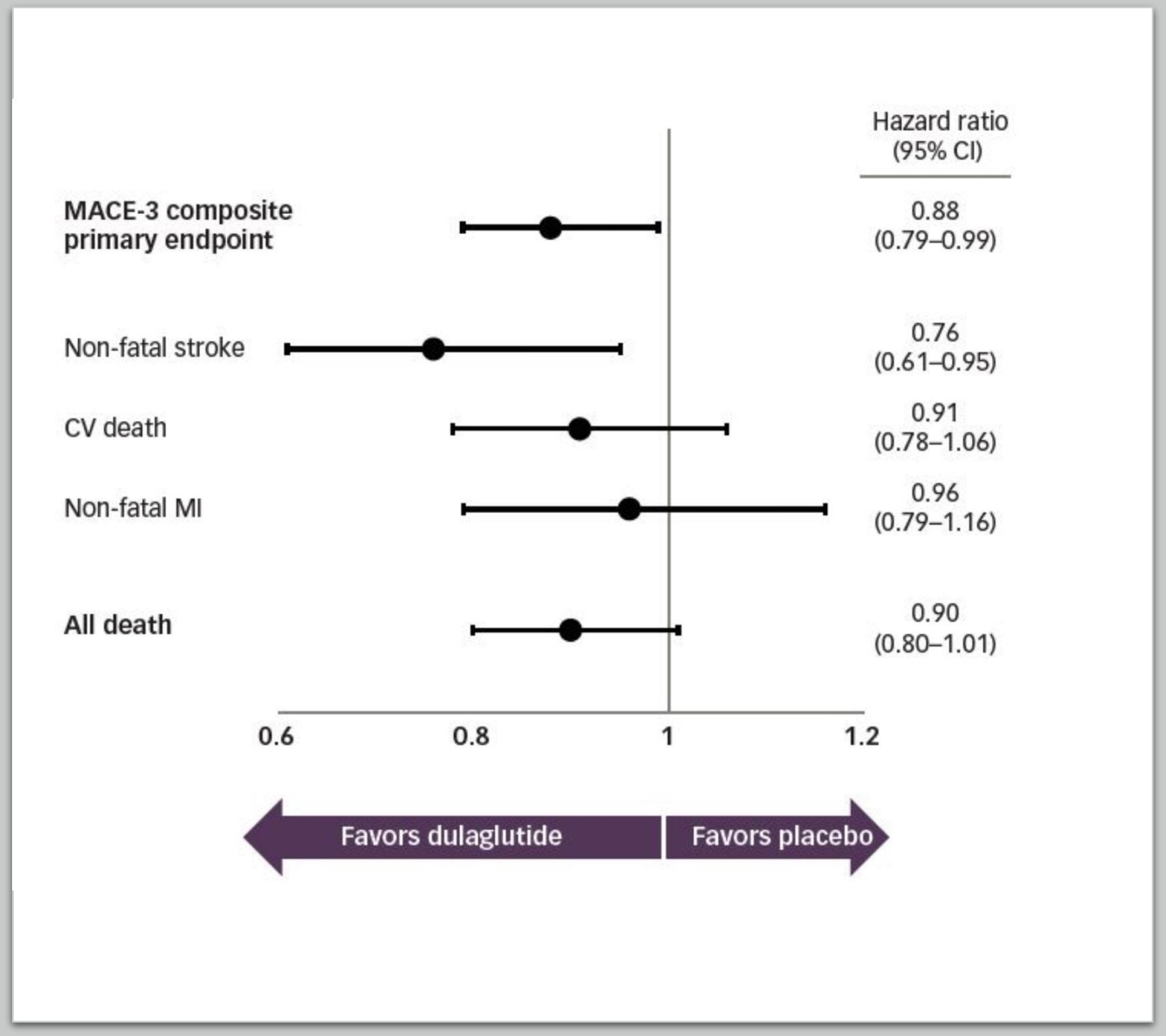
REWIND primary MACE result



CV, cardiovascular; MI, myocardial infarction.

No. at risk							
Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

REWIND Individual cardiovascular outcomes



Updated ADA/EASD Consensus Statement related to REWIND

- “We now also suggest that to reduce risk of MACE, GLP-1RA can also be considered with type 2 diabetes without established CVD with indicators of high risk:
- Aged 55 or older, with
- Coronary, carotid or lower extremity stenosis over 50% ,LVH, eGFR less than 60 ml/min or albuminuria

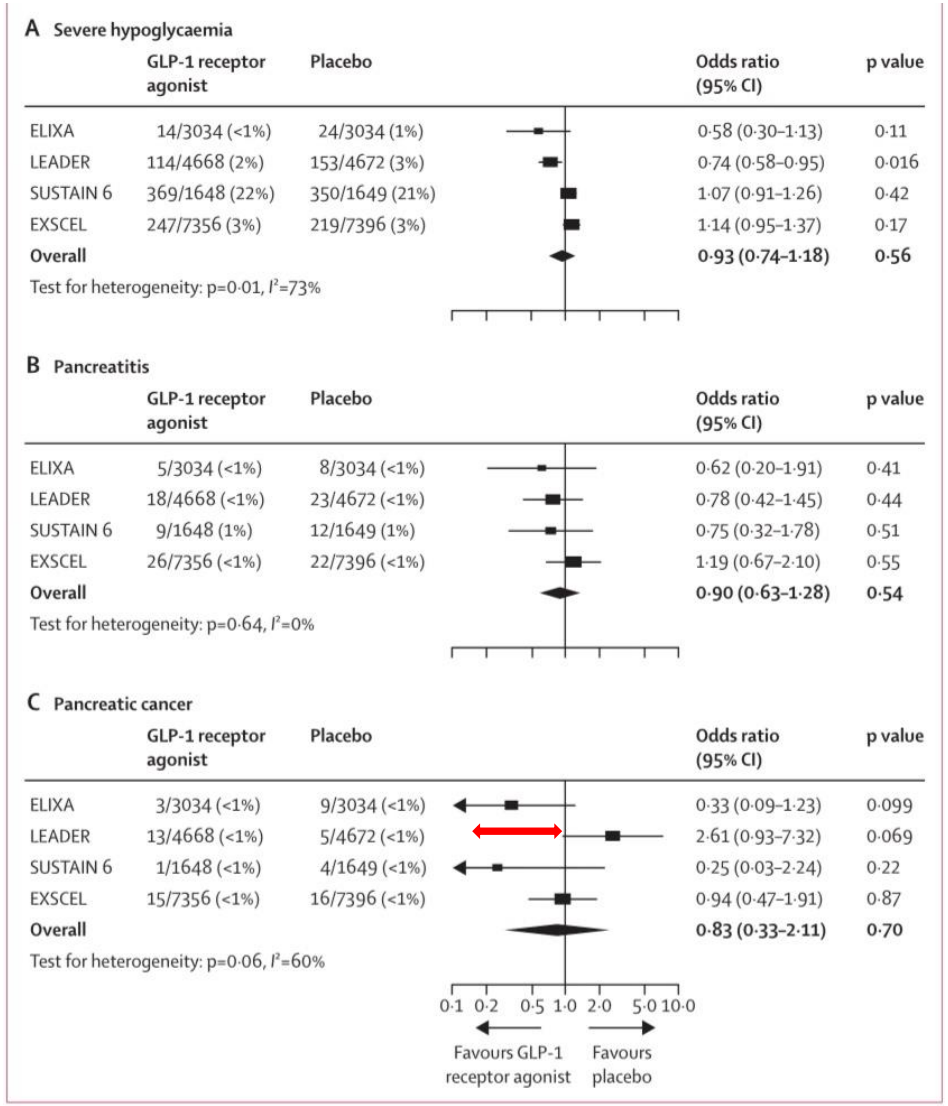
- To date the level of evidence to support the use of GLP-1RA for primary prevention is strongest for Dulaglutide , but lacking for other GLP-1RA “

Renal outcomes

- LEADER : renal composite HR 0.78 driven by reduction in macroalbuminuria
- SUSTAIN-6 : renal composite HR 0.64
- ELIXA :decrease in new-onset macroalbuminuria HR 0.81
- REWIND :renal composite HR 0.85 and new onset macroalbuminuria HR 0.77
- EXSCEL: 40 % reduction eGFR decline , RR , renal death or new macroalbuminuria composite 2 adjusted HR 0.85

Safety outcomes

No overall increase in pancreatitis, pancreatic cancer or severe hypoglycemia



A Severe hypoglycaemia

	GLP-1 receptor agonist	Placebo	Odds ratio (95% CI)	p value
ELIXA	14/3034 (<1%)	24/3034 (1%)	0·58 (0·30–1·13)	0·11
LEADER	114/4668 (2%)	153/4672 (3%)	0·74 (0·58–0·95)	0·016
SUSTAIN 6	369/1648 (22%)	350/1649 (21%)	1·07 (0·91–1·26)	0·42
EXSCEL	247/7356 (3%)	219/7396 (3%)	1·14 (0·95–1·37)	0·17
Overall			**0·93 (0·74–1·18)**	**0·56**

Test for heterogeneity: p=0·01, I^2=73%

B Pancreatitis

	GLP-1 receptor agonist	Placebo	Odds ratio (95% CI)	p value
ELIXA	5/3034 (<1%)	8/3034 (<1%)	0·62 (0·20–1·91)	0·41
LEADER	18/4668 (<1%)	23/4672 (<1%)	0·78 (0·42–1·45)	0·44
SUSTAIN 6	9/1648 (1%)	12/1649 (1%)	0·75 (0·32–1·78)	0·51
EXSCEL	26/7356 (<1%)	22/7396 (<1%)	1·19 (0·67–2·10)	0·55
Overall			**0·90 (0·63–1·28)**	**0·54**

Test for heterogeneity: p=0·64, I^2=0%

C Pancreatic cancer

	GLP-1 receptor agonist	Placebo	Odds ratio (95% CI)	p value
ELIXA	3/3034 (<1%)	9/3034 (<1%)	0·33 (0·09–1·23)	0·099
LEADER	13/4668 (<1%)	5/4672 (<1%)	2·61 (0·93–7·32)	0·069
SUSTAIN 6	1/1648 (<1%)	4/1649 (<1%)	0·25 (0·03–2·24)	0·22
EXSCEL	15/7356 (<1%)	16/7396 (<1%)	0·94 (0·47–1·91)	0·87
Overall			**0·83 (0·33–2·11)**	**0·70**

Test for heterogeneity: p=0·06, I^2=60%

0·1 0·2 0·5 1·0 2·0 5·0 10·0

Favours GLP-1 receptor agonist | Favours placebo

Figure 3: **Safety outcomes**
GLP-1=glucagon-like peptide-1.

GLP-1RA safety

- There were 4 medullary thyroid carcinomas reported in LEADER and EXSCEL
- Papillary thyroid CA were reported in 17 vs 10 in placebo in ELIXA,

LEADER,SUSTAIN 6 , and in EXSCEL.

* In this analysis LEADER was an outlier in adjudicated pancreatic cancer still unexplained

*In SUSTAIN 6 retinopathy events were significantly higher in the Sema group HR 1.76

When the patients without baseline retinopathy were analyzed there was no signal ,and was similar to placebo.

Insulin and cardiovascular effect

- VADT : reduction A1c 1.5 % , neutral cardiovascular despite 24 % vs 17% hypoglycemia between intensive and conventional group
- ADVANCE : reduction of A1c to 6.5% decreased macro and microvascular complications HR hypoglycemia 2.88
- ACCORD : increased mortality in the intensive group,; these patients had higher insulin doses, more weight gain, more hypoglycemia and less use of ACE
- ORIGIN :safety of glargine in type 2 diabetes at high cardiovascular risk
- DEVOTE : 40 % and 53 % less severe and nocturnal hypoglycemia of IDeg compared to glargine and non inferior to glargine in terms of cardiovascular events

Cardiovascular safety of basal insulin established in two long-term, cardiovascular outcome trials

ORIGIN – Glargine U100 Study Design

Open-label design

Glargine vs. standard of care

>12,000 patients at high risk of CV events:

- With IFG, IGT or newly detected T2DM, or established T2DM
- Insulin-naïve
- Mean A1C: 6.5%
- Mean diabetes duration: 5.4 yrs

DEVOTE – Degludec Study Design

Double-blind design

Degludec vs. glargine U100 each in combination with standard of care

>7,000 patients at high risk of CV events:

- With T2DM
- Insulin-naïve or experienced
- Mean A1C: 8.4%
- Mean diabetes duration: 16 yrs

Cardiovascular safety of basal insulin established in two long-term, cardiovascular outcome trials

ORIGIN – Glargine U100 Results

Non-inferiority
- HR: 1.00 vs. SOC

Hypoglycemia
- Severe and non-severe: significantly increased

DEVOTE – Degludec Results

Non-inferiority
- HR: 0.91 vs. IGlar U100

Hypoglycemia
- Severe: significantly decreased

GLP superior to insulin if patient has cardiovascular disease

BUT THEN OF COURSE THERE IS THE COST.

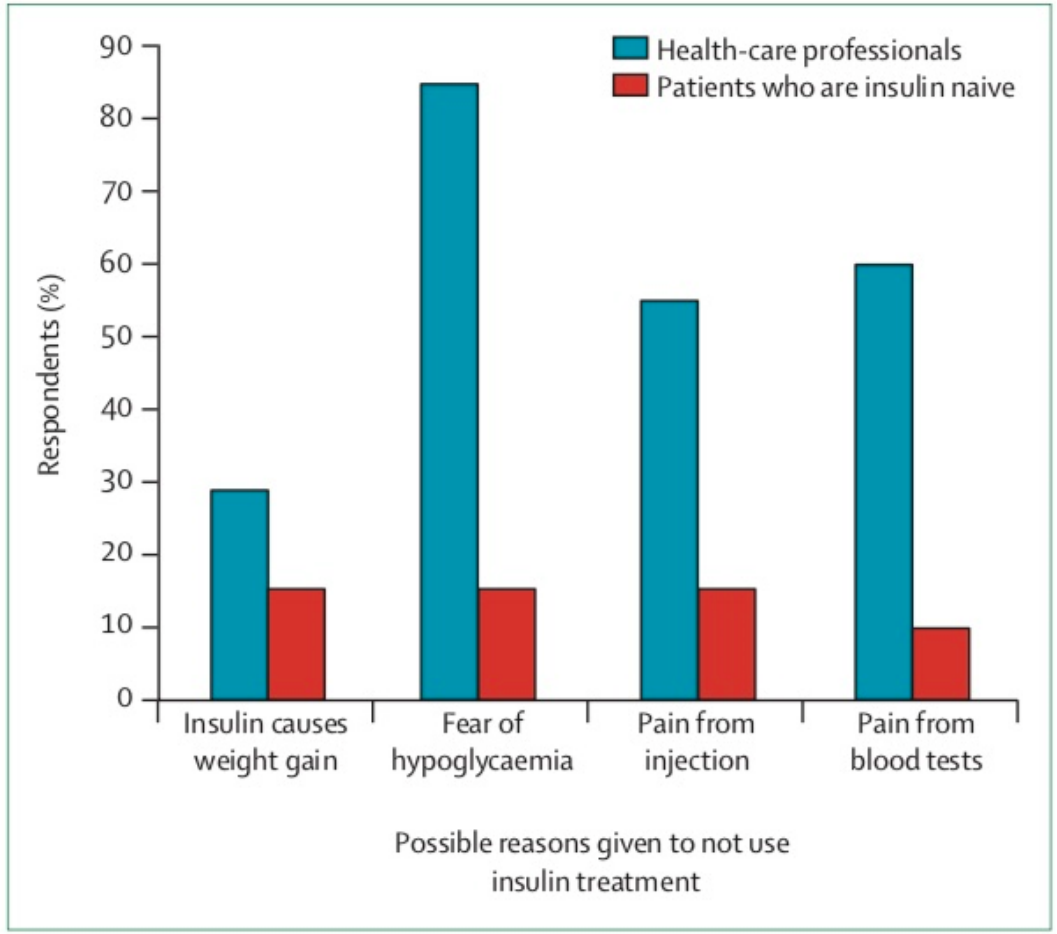
IN USA 30D SUPPLY OF GLP1-RA CAN RUN BETWEEN $600-968, 10-40 X MORE THAN HUMAN INSULIN, AND 2-3 X MORE THAN INSULIN ANALOGS

Umpierrez , IDF Dec 5 2019

ABSOLUTE AND POTENTIAL INDICATIONS TO USE INSULIN OVER GLP1-RA

- TYPE 1 DIABETES
- PEDIATRIC PATIENTS ? LIRAGLUTIDE APPROVED AT AGE 10 Y
- KETOACIDOSIS
- RESCUE TREATMENT
- ACUTE MEDICAL EVENTS : INFECTION , MI, MAJOR SURGERY
- PREGNANCY
- SEVERE HYPERGLYCEMIA
- CIRRHOSIS, PANCREATITIS OR CHRONIC STEROID USE
- DYALISIS
- POST TRANSPLANT DIABETES
- CYSTIC FIBROSIS ASSOCIATED DIABETES
- MEDULLARY CANCER CONTRAINDICATION FOR GLP1
- FAILURE OF NON-INSULIN TREATMENTS AND LADA

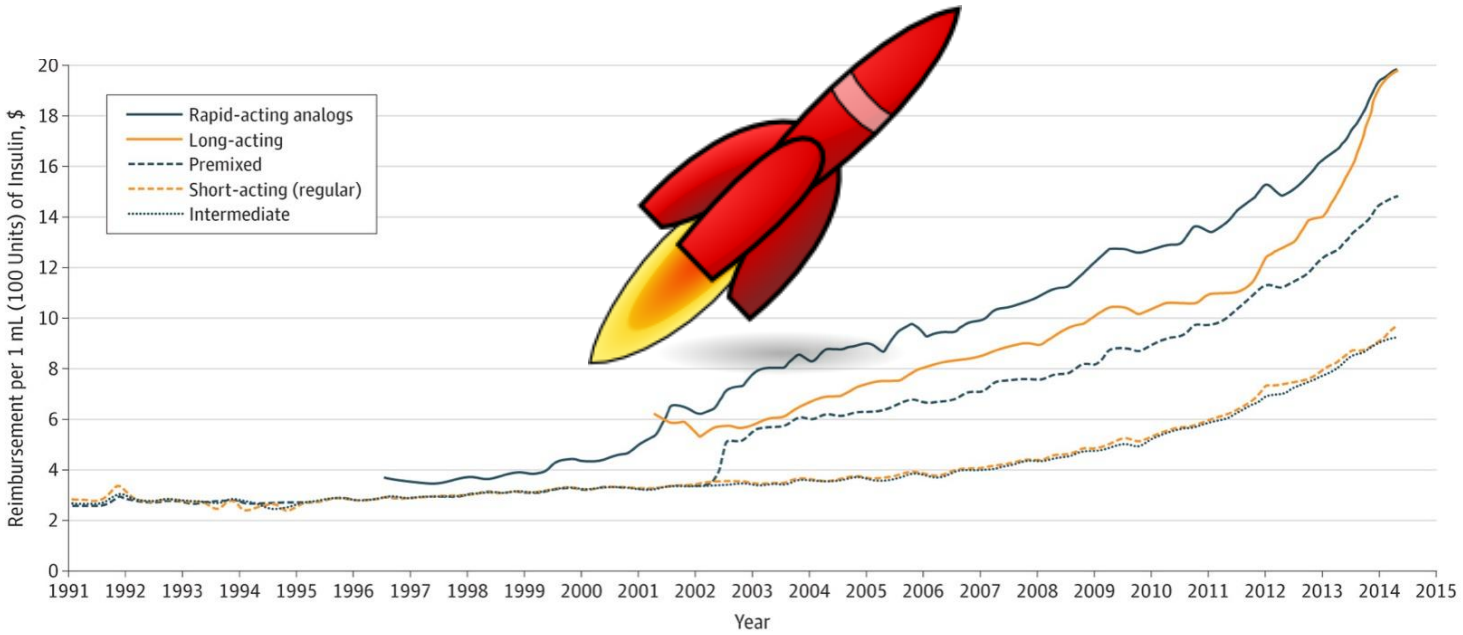
Reasons why health care professionals and patients might refrain from starting insulin treatment



But what about cost ?

Medicaid reimbursements trends for covered insulin products from 1990 to 2014

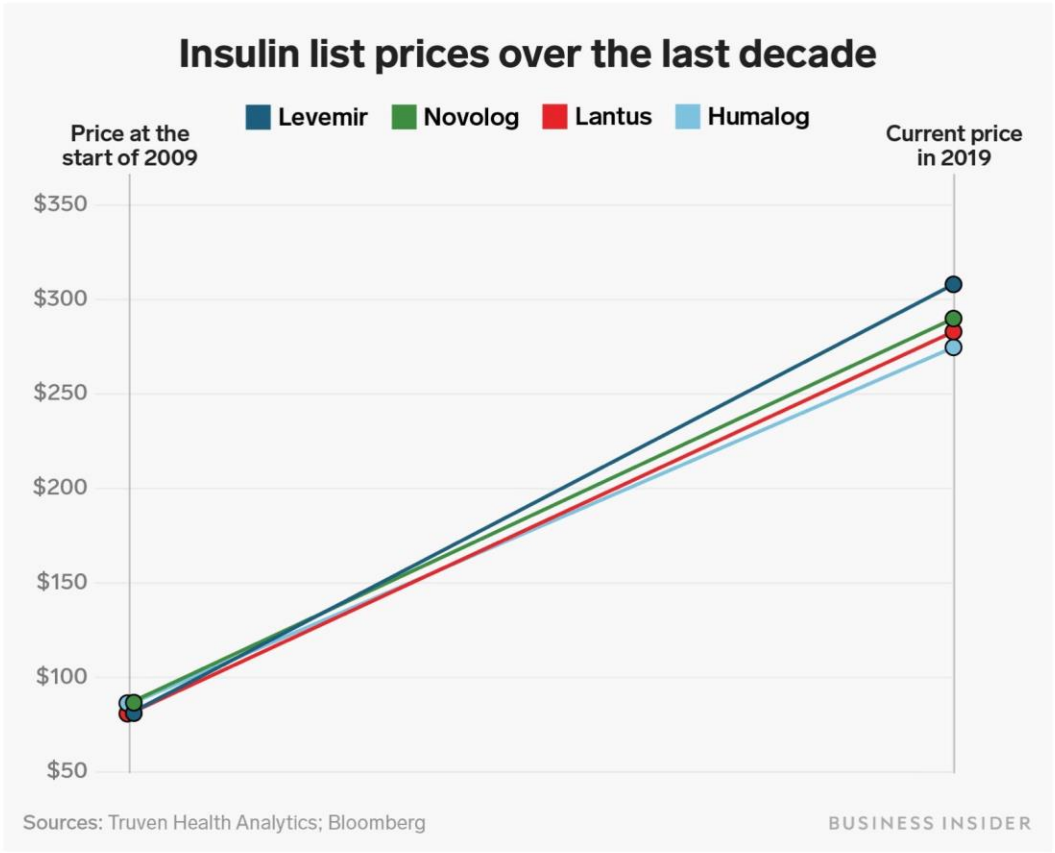
SKY ROCKET



Medicaid reimbursement trends for covered insulin products from 1991 to 2014. | *JAMA Internal Medicine*

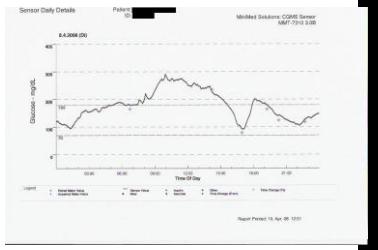
One chart reveals how the cost of insulin has skyrocketed in the US, even though nothing about it has changed

Rachel Gillett and Shayanne Gal Sep 18, 2019, 4:42 PM



The list prices of some insulins have tripled over the past decade, and some people with diabetes are paying the ultimate price.
Shayanne Gal/Business Insider

BG



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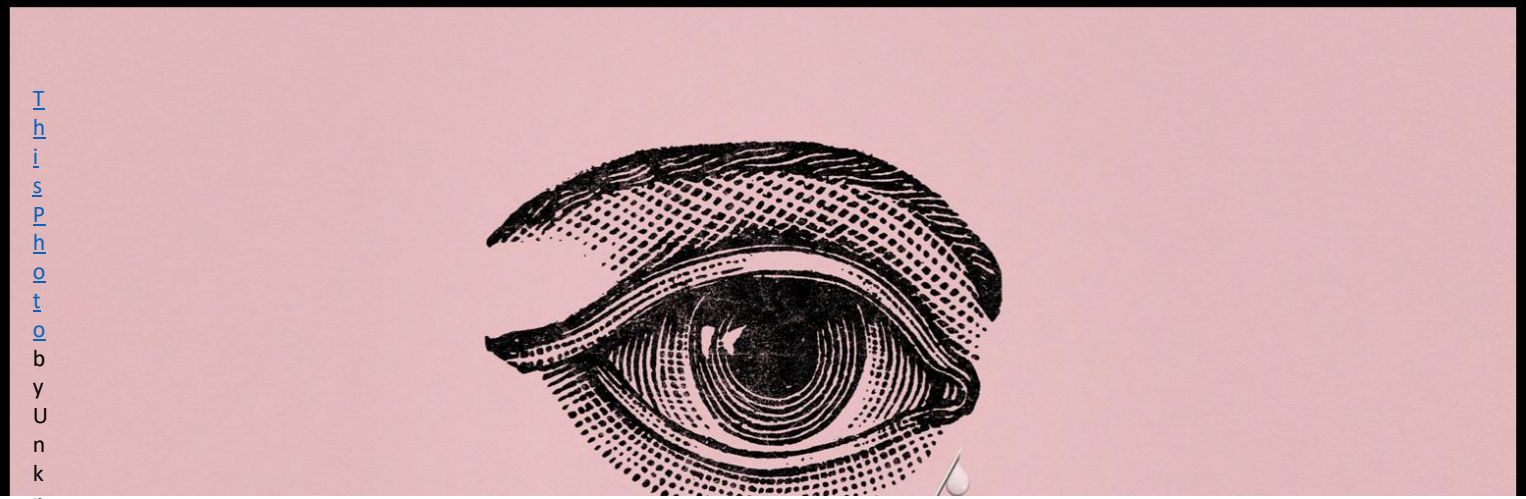
Life, Death and Insulin

As the cost of the lifesaving medication skyrockets, some desperate diabetics are rationing — and risking their lives. Was Alec Raeshawn Smith one of them?



This Photo by Unknown A

promises

Business

Under fire over high prices, Eli Lilly promised cheaper insulin in 2019. The result has some senators steamed.

T1I INTERNATIONAL

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Eli Lilly and Novo Nordisk: More Empty Promises

Novo Nordisk to Launch Cheaper Insulin Options in U.S.

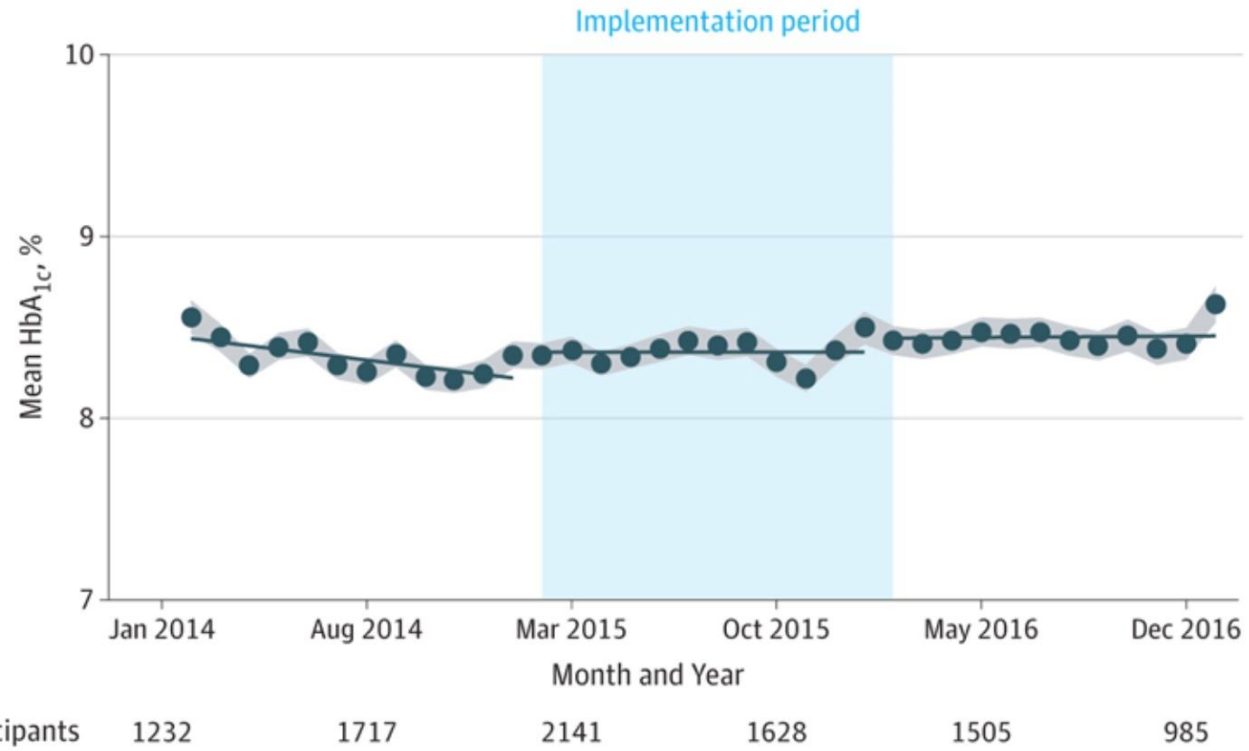
September 6, 2019

CONSIDERATION OF COST IS AN IMPORTANT COMPONENT OF EFFECTIVE MANAGEMENT

FOR MANY PATIENTS WITH TYPE 2 DIABETES INDIVIDUALS WITH RELAXED A1C GOALS, LOW RATE OF HYPOGLYCEMIA AND PROMINENT INSULIN RESISTANCE AS WELL AS THOSE WITH COST CONCERNS), NPH AND REGULAR MAY BE THE APPROPRIATE CHOICE OF THERAPY AND CLINICIANS SHOULD BE FAMILIAR WITH ITS USE .

Diabetes Care ,2019, Pharmacologic approaches glycemic treatment S99

Patient characteristics
No hypoglycemias
Human tdd 80 % analog
Average age 72 y/o



Mean Hemoglobin A_{1c} (HbA_{1c}) of Insulin Users Before, During, and After an Insulin Conversion Intervention

The shaded area represents the intervention period of January 1, 2015, through December 31, 2015. The shading around the data points indicate 95% CIs. Changes in the mean level (circles) and slope (solid lines) of HbA_{1c} were estimated using interrupted time series models (segmented regression analysis) with cut points at the start of 2015 and 2016. Because HbA_{1c} may lag up to 3 months, study participants only contributed HbA_{1c} data if they had an insulin dispensed either in the same month of the laboratory result or within 3 months before.

+0.01 % HBA1c in those who switched vs, -0.01 % in those who didn't
No major hypoglycemias by claims *

Insulin analogs Pharmacokinetic.pharmacodynamic and structural properties of insulin and its analogues.	Alterations	Onset of action	Peak action time	Duration of action
Short acting Regular		30 min	1.5-3.5h	7-8h
Rapid acting insulin Lispro Aspart Glulisine FiASp mixed w L-arg and B3	Reversal of amino acid proline at B28 and lysine at B29 Replacing proline at B28 w aspartic acid Replacing asparagine with lysine at B3 and glutamic acid with lysine at B29	15 min 10-20 min 10-20 min	30-70 min 1-3h 55 min	2-5h 3-5h 6h
Intermediate acting NPH	Neutral protamine insulin	1.5-4 h	2.8-13h	Up to 24h
Long acting Glargine Detemir Degludec	Asp with gly at A21 and 2 arg AA at B31 and 32 Myristic acid acylation to lys B29 and deletion of threo B30 Deletion of threpB30 and addition of 16c fatty acid to lysine at B29	1-3h 1-2 h 0.5-1.5h	No peak 6-8h No peak	Up to 24 h Up to 24h Up to 48 h

Table 3: Comparing Glargine vs. NPH trials (post-FDA approval data)

Study name	Compare arm	Study duration	Mean change in HbA1c (%)	Mean change in FPG (mg/dL)	Hypoglycemia (% of patients reporting at least one episode)	
					Overall	Nocturnal
Type 1						
Hershon *et al.*	IGlar OD NPH BID	28 weeks	NS	Glargine better	Glargine better	NR
Home *et al.*	IGlar OD NPH OD NPH BID	28 weeks	NS	NS	NR	NR
Pieber *et al.*	IGlar 30 OD IGlar 80 OD NPH OD/BD	4 weeks	Glargine better	Glargine better	NS	NS
Raskin *et al.*	IGlar OD NPH OD/BD	16 weeks	NS	Glargine better	NS	NS
Ratner *et al.*	IGlar OD NPH OD/BD	28 weeks	NS	NS	Glargine better	Glargine better
Rosenstock *et al.*	IGlar 30 OD IGlar 80 OD NPH OD/BD	4 weeks	NS	Glargine better	NS	NR
Standl *et al.*	IGlar OD NPH OD/BD	28 weeks	NS	NS	NR	NS
Ashwell *et al.*	IGlar OD NPH OD/BID	32 weeks	NR	NR	NR	Glargine better
Fulcher *et al.*	IGlar OD NPH OD	30 weeks	NR	NR	NR	NR
Porcellati *et al.*	IGlar OD NPH QID	52 weeks	NR	NR	Glargine better	Glargine better
Rossetti *et al.*	IGlar am IGlar OD NPH QID	12 weeks	NS	NR	Glargine better	Glargine better
Type 2						
Fonseca *et al.*	IGlar NPH	28 weeks	NS	NR	Glargine better	NS
Fritsche *et al.*	IGlar am IGlar pm NPH pm	24 weeks	Glargine better	NR	NR	Glargine better
Massi Benedetti *et al.*	IGlar NPH	52 weeks	NS	NS	NR	Glargine better
HOE 901/2004 study investigators group	IGlar 1 IGlar 2 NPH	4 weeks	NS	NR	Glargine better	NR
Raskin *et al.*	IGlar 30 IGlar 80 NPH	4 weeks	NR	NS	NR	NR
Riddle and rosenstock	IGlar NPH	24 weeks	NR	NR	NR	Glargine better
Rosenstock *et al.*	IGlar OD NPH OD/BID	28 weeks	Glargine better	NR	NS	Glargine better
Siegmund *et al.*	IGlar OD NPH BID	78 weeks	Glargine better	NR	NR	NR
Yki-Jarvinen *et al.*	IGlar NPH	52 weeks	Glargine better	NR	Glargine better	Glargine better

NPH: Neutral Protamine Hagedorn insulin; NS: Not significant; NR: Not retrievable; IGlar: Glargine; OD: Once daily; BD: Twice daily

Singh et al,Indian Journal of Endocrinology and Metabolism Nov-Dec2014 Vol 18 Issue 6

Hypoglycemia incidence and rates in head-to-head trials comparing insulin glargine with NPH insulin in patients with Type 2 diabetes

	Hypoglycemia	
Study	**Overall symptomatic hypoglycemia (% of patients)**	**Nocturnal hypoglycemia (% of patients)**
Insulin therapy only		
Rosenstock et al. (2001)	• Similar between groups (glargine, 61.4%; NPH, 66.8%) • Severe: glargine 0.4% (*n*=1); NPH, 2.3% (*n*=6): P=.0581	• ↓ With glargine vs. NPH (26.5% vs. 35.5%, P<.02)
Fonseca et al. (2004)	• ↓ With glargine vs. NPH (46% vs. 60%, P<.05) • Severe: glargine 0 patients, NPH 2.0% (*n*=1)	• Glargine vs NPH: 15% vs. 27%, P<.10
Insulin plus oral agents		
HOE 901/2004 Study Investigators Group (2003)	• Similar between groups (glargine 30, 18.8%; glargine 80, 25.0%; NPH, 32.4%) • No cases of severe hypoglycemia	• ↓ With glargine vs. NPH (7.3% vs. 19.1%, P=.0123)
Yki-Järvinen et al. (2000)	• ↓ With glargine vs. NPH (~33% vs. 43%, P=.04)	• ↓ With glargine vs. NPH (9.9% vs. 24%, P<.001)
Massi Benedetti et al. (2003)	• Similar between groups (glargine, 35%; NPH, 41%)	• ↓ With glargine vs. NPH (12% vs. 24%, P<.002)
Fritsche et al. (2003)	• ↓ With bedtime glargine vs. NPH (43%) vs. bedtime NPH (58%) or morning glargine (56%), P=.002	• ↓ With both morning (17%) and bedtime glargine (23%) vs. NPH (38%), P<.001)
Riddle et al. (2003)	• ↓ With glargine vs. NPH (13.9 vs. 17.7 events per patient-year, P<.02); 21% risk reduction with glargine • Severe hypoglycemia: glargine, 2.5% (*n*=9); NPH 1.8% (*n*=7)	• ↓ With glargine vs. NPH (4.0 vs 6.9 events per patient-year, P<.001); 42% risk reduction with glargine
Ryysy et al. (2004)	• ↓ With glargine vs. NPH (5.5 vs. 8.0 episodes/patient-year, P<.05); 44% less frequent with glargine	Not reported

Duckworth W, Davis S. Comparison of insulin glargine and NPH insulin in the treatment of type 2 diabetes: a review of clinical studies. J Diabetes Complicat. 2007;21(3):196-204. doi:10.1016/j.jdiacomp.2007.01.00

Key efficacy results of head-to-head trials comparing insulin glargine with NPH insulin in patients with Type 2 diabetes

	Glycemic control	
Study	**Mean A1C/FBG**	**Patients reaching target, %**
Rosenstock et al. (2001)	Mean A1C and FBG ↓ from baseline similar between groups (A1C: glargine, -0.41%; NPH, -0.59%; P=.0001 vs. baseline for each)	Similar between groups • FBG <6.7 mmol/ L: glargine, 29.6%; NPH, 27.1%
Fonseca et al. (2004)	Mean A1C and FBG ↓from baseline similar between groups (A1C: glargine, -0.41%; NPH, -0.46%)	Similar between groups • FBG: glargine, 34%; NPH, 24% • A1C <7.0%: 18% each group
HOE 901/2004 Study Investigators Group (2003)	Mean FPG ↓ from baseline similar between groups (-3.10 to -3.49 mmol/L, P=.0001 vs. baseline for each group)	Not reported (4-week study)
Yki-Järvinen et al. (2000)	Mean A1C ↓ from baseline similar between groups • ↓ Postdinner glucose with glargine vs. NPH (9.9 vs. 10.7 mmol/L, P<.02)	FBG ≤6.7 mmol/L: glargine, 40.7%; NPH, 35.1%
Massi Benedetti et al. (2003)	Mean A1C ↓ from baseline similar between groups (glargine, -0.46%; NPH, -0.38%) • Subgroup with BMI >28 kg/m^2: greater A1C ↓ for glargine vs. NPH (-0.42% vs. -0.11%, P=.0237)	FBG ≤6.7 mmol/L: glargine, 42%; NPH, 44%
Fritsche et al. (2003)	A1C ↓ from baseline greater for morning glargine (- 1.24%) vs. bedtime NPH (-0.84%, P<.001) or bedtime glargine (-0.96%, P=.008) (43%) vs. bedtime	• A1C ≤7.5%: more patients with morning glargine (43%) bedtime NPH (32%, P=.017), or bedtime glargine (33%, P=.021)
Riddle et al. (2003)	Mean A1C and FPG ↓ from baseline similar between groups • ↓ Mean A1C at end point: glargine, 6.96%; NPH, 6.97%	Similar between groups • A1C ≤7.0%: glargine, 58.0%; NPH, 57.3%
Ryysy et al. (2004)	Mean A1C and FPG A from baseline similar between groups (mean A1C, 7.1% in both groups) • ↓ Predinner glucose with glargine vs. NPH (155±5 vs. 182±5 mg/dL, P=.002) • ↓ Postdinner glucose with glargine vs. NPH (202±5 vs. 221±5 mg/dL, P<.03)	Not reported

si mi lar

Duckworth W, Davis S. Comparison of insulin glargine and NPH insulin in the treatment of type 2 diabetes: a review of clinical studies. J Diabetes Complicat. 2007;21(3):196-204. doi:10.1016/j.jdiacomp.2007.01.00

Table 6: Comparison of detemir Vs NPH trials (post-FDA approval data)

Study name	Compare arms	Study duration (weeks)	Mean change in HbA1c (%)	Mean change in FPG (mg/dl)	Hypoglycemia (no. of episodes per patient-year of exposure)		
					Overall	Major	Nocturnal
Type 1							
Bartley *et al.*	IDet NPH	104	Detemir better	Detemir better	NS	Detemir better	Detemir better
Hermansen *et al.*	IDet NPH	18	Detemir better	NS	Detemir better	NR	Detemir better
Home *et al.*	IDet m+b IDet Q12h NPH m+b	18	NS	Detemir better	NS	NA	Detemir better
Pieber *et al.*	IDet m+b IDet m+d NPH m+b	16	NS	Detemir better	NS	NR	NS
Russell-Jones *et al.*	IDet NPH	26	NS	Detemir better	NS	NR	Detemir better
Vague *et al.*	IDet NPH	26	NS	NS	Detemir better	NS	Detemir better
De Leeuw *et al.*	IDet NPH	26	NS	NS	NR	NR	Detemir better
Standl *et al.*	IDet NPH	26	NS	NS	NS	NS	Detemir better
Type 2							
Fajardo M et al.	IDet NPH	26	NS	NS	Detemir better	NS	Detemir better
Haak *et al.*	IDet NPH	26	NS	NS	NS	NR	NS
Hermansen *et al.*	IDet NPH	24	NS	NS	Detemir better	NS	Detemir better
Philis-Tsimikas *et al.*	IDet morn IDet eve NPH eve	20	NS	Detemir better	Detemir better	NR	Detemir better
Raslova *et al.*	IDet NPH	22	NS	NS	NS	NA	NS

IDet: Insulin detemir; m+b: Administered in the morning and at bedtime; Q12h: Administered every 12 hours; m+d: Administered in the morning and before dinner; NS: Not significant; NA: Not available; NR: Not retrievable

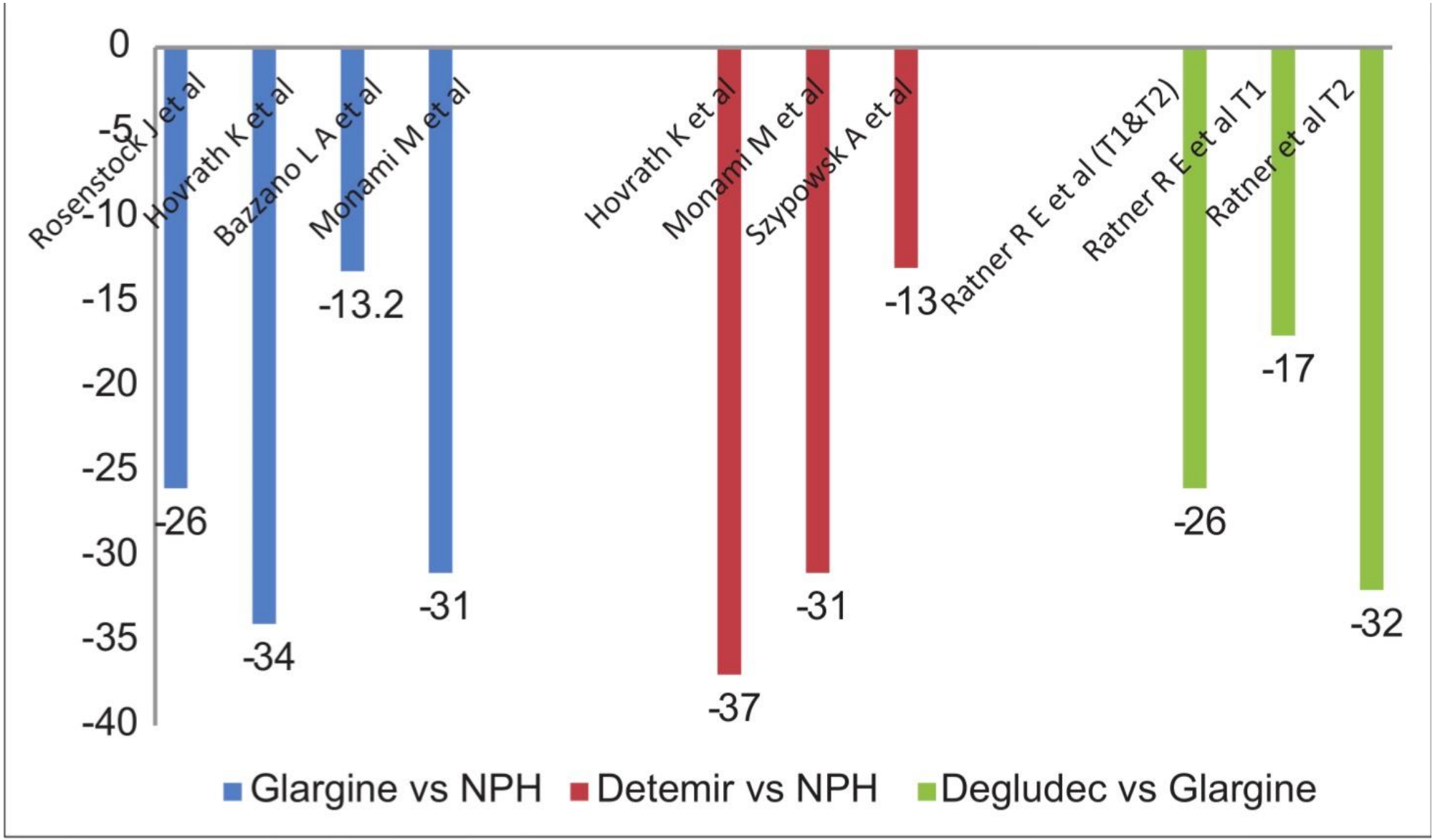
Table 8: Comparison of degludec Vs glargine trial (pre-FDA approval data)

Study name	Compare arm (no.)	Study duration (weeks)	Mean change in HbA1c (%)	Mean change in FPG (mg/dl)	Mean end-of-study dose	Hypoglycemia (no. of episodes per patient-year of exposure)		
						Overall	Severe	Nocturnal
Type 1								
BEGIN basal bolus type 1	IDeg (472) IGlar (157)	52	NS	NS	Degludec better	NS	NS	Degludec better
BEGIN flex T1	IDeg Flex (164) IDeg (165) IGlar (161)	26	NS	Degludec better	Degludec better	NS	NS	Degludec better
Type 2								
BEGIN once long	IDeg (773) IGlar (257)	52	NS	Degludec better	NS		Degludec better	Degludec better
BEGIN basal bolus type 2	IDeg (744) IGlar (248)	52	NS	NS	Degludec better	Degludec better	24-31 % less events per patient/y	Degludec better
BEGIN flex T2	IDeg Flex (230) IDeg (226) IGlar (229)	26	NS	Degludec better	NS	NS	NR	NS
BEGIN once Asia	IDeg (289) IGlar (248)	26	NS	NS	NR	Degludec better	NR	NS
BEGIN low volume	IDeg (228) IGlar (229)	26	NS	Degludec better	Degludec better	NS	NR	NS

IDeg: Degludec fixed; IDeg flex: Degludec flexible; IGlar: Glargine; NS: Not significant; NR: Not reported; @@Hypoglycemia defined as blood glucose <56 mg/dl

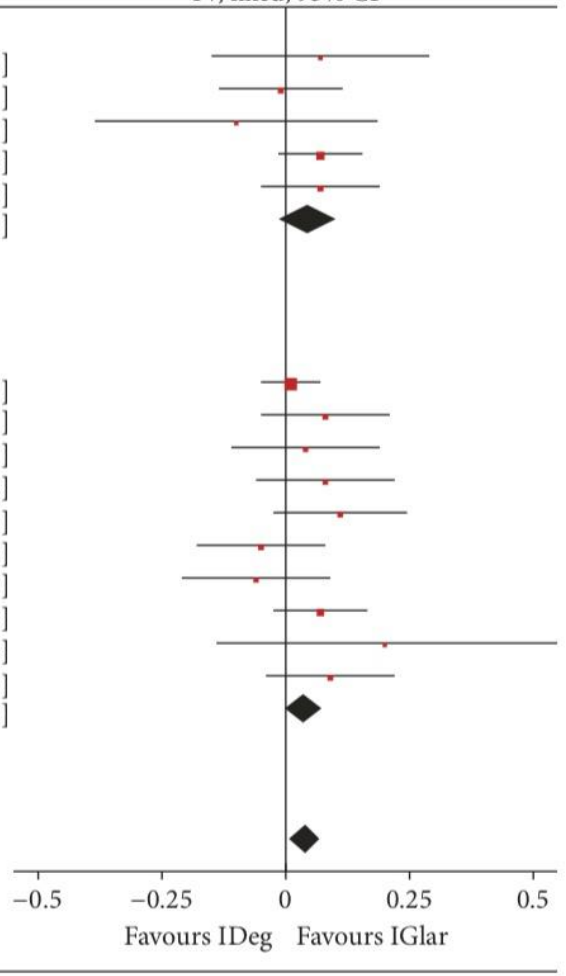
Non -significant difference

Meta-analysis of all the trials : Nocturnal hypoglycemia outcomes



Similar A1c BETWEEN IDEG AND IGLAR

Study or subgroup	Mean difference	SE	IDeg Total	IGlar Total	Weight	Mean difference IV, fixed, 95% CI
1.14.1 T1DM						
Birkeland et al., 2011	0.07	0.1122449	119	59	1.9%	0.07 [−0.15, 0.29]
Heller et al., 2012	−0.01	0.06377551	472	157	6.0%	−0.01 [−0.13, 0.11]
Iga et al., 2017	−0.1	0.14570648	20	20	1.1%	−0.10 [−0.39, 0.19]
Lane, et al., 2017	0.07	0.04336735	501	501	12.9%	0.07 [−0.01, 0.15]
Mathieu et al., 2013	0.07	0.06122449	329	164	6.5%	0.07 [−0.05, 0.19]
Subtotal (95% CI)			1441	901	28.4%	0.05 [−0.01, 0.10]
Heterogeneity: $\chi^2 = 2.28$, df = 4 ($p = 0.68$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.59$ ($p = 0.11$)						
1.14.2 T2DM						
DEVOTE trial, 2017	0.01	0.03061224	3818	3819	25.9%	0.01 [−0.05, 0.07]
Garber et al., 2012	0.08	0.06632653	744	248	5.5%	0.08 [−0.05, 0.21]
Gough et al., 2013	0.04	0.07653061	228	229	4.1%	0.04 [−0.11, 0.19]
Meneghini et al., 2013	0.08	0.07142857	457	230	4.7%	0.08 [−0.06, 0.22]
Onishi et al., 2013	0.11	0.06887755	289	146	5.1%	0.11 [−0.02, 0.24]
Pan et al., 2016	−0.05	0.06632653	555	278	5.5%	−0.05 [−0.18, 0.08]
Warren et al., 2017	−0.06	0.07653061	145	145	4.1%	−0.06 [−0.21, 0.09]
Wysham et al., 2017	0.07	0.04846939	721	721	10.3%	0.07 [−0.02, 0.16]
Zinman et al., 2011	0.2	0.17346939	121	62	0.8%	0.20 [−0.14, 0.54]
Zinman et al., 2012	0.09	0.06632653	773	257	5.5%	0.09 [−0.04, 0.22]
Subtotal (95% CI)			7851	6135	71.6%	0.04 [−0.00, 0.07]
Heterogeneity: $\chi^2 = 8.00$, df = 9 ($p = 0.53$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.02$ ($p = 0.04$)						
Total (95% CI)			9292	7036	100.0%	0.04 [0.01, 0.07]
Heterogeneity: $\chi^2 = 10.35$, df = 14 ($p = 0.74$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.55$ ($p = 0.01$)						
Test for subgroup differences: $\chi^2 = 0.07$, df = 1 ($p = 0.79$); $I^2 = 0\%$						

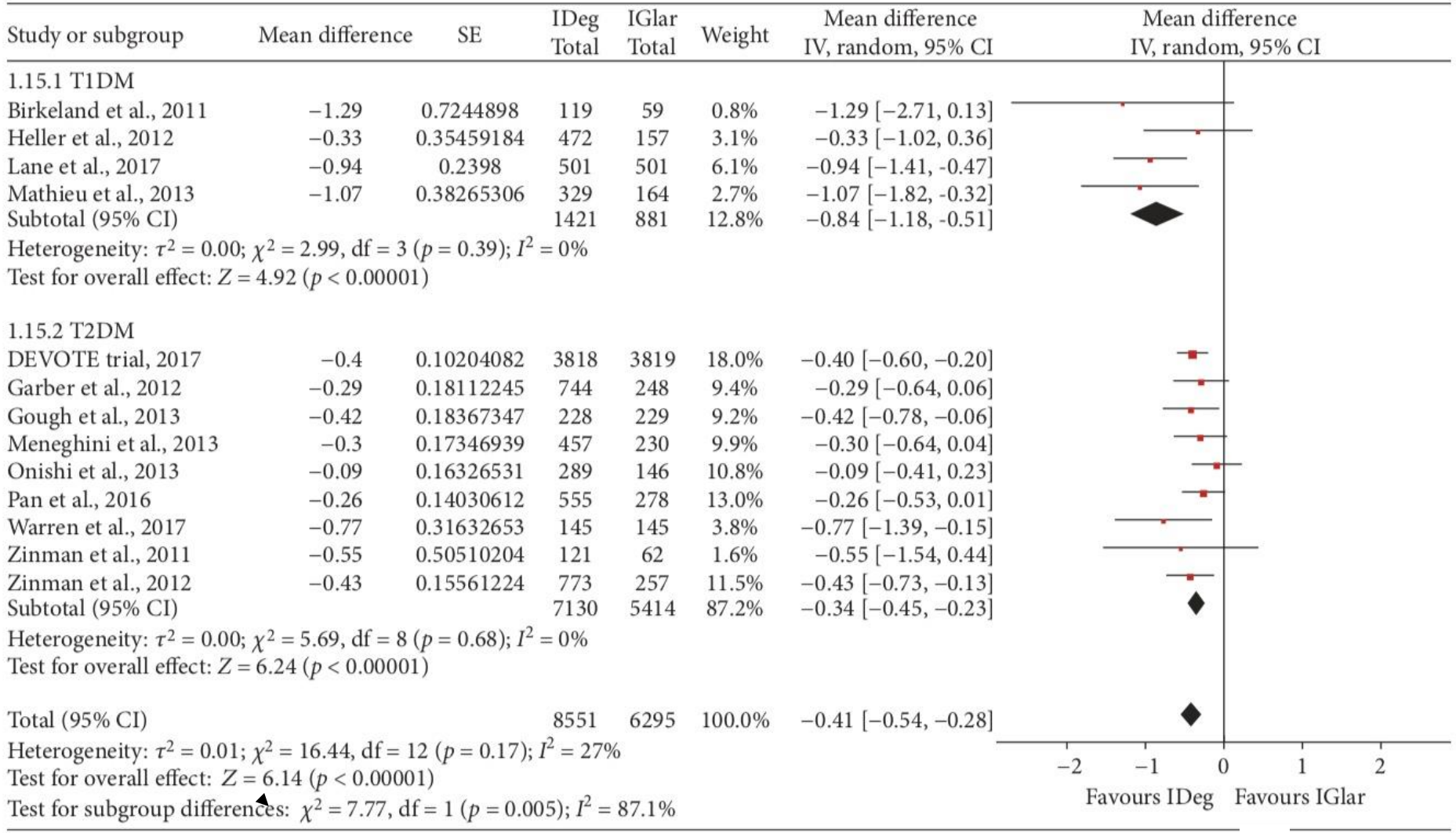


P value=0.04

FIGURE 1: Mean difference in the changes in the glycosylated hemoglobin (HbA1c) level between the IDeg and IGlar groups: IDeg: insulin degludec; IGlar: insulin glargine; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; CI: confidence interval; IV: inverse variance.

Liu, et al, International Journal of Endocrinology vol 2018

DIFFERENCES IN FBG BETWEEN IDEG AND IGLAR

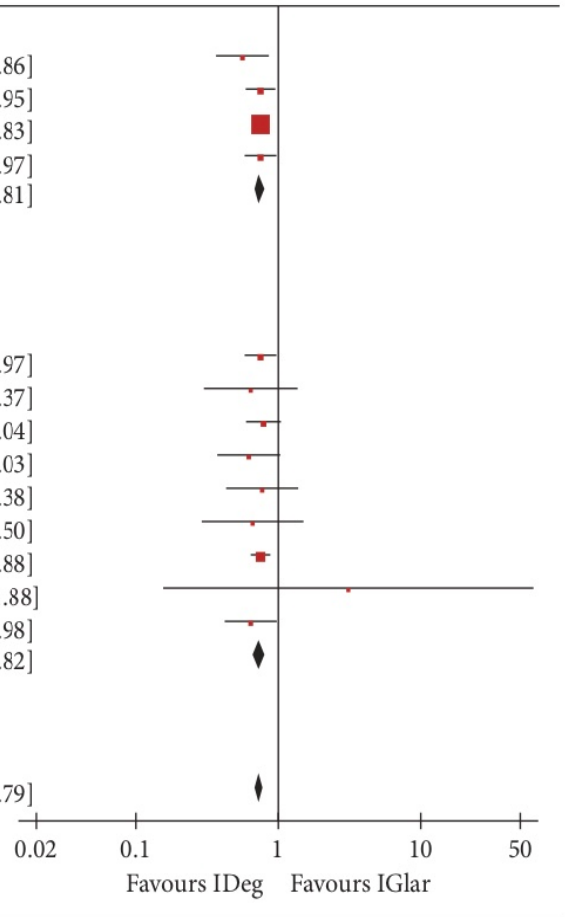


Study or subgroup	Mean difference	SE	IDeg Total	IGlar Total	Weight	Mean difference IV, random, 95% CI
1.15.1 T1DM						
Birkeland et al., 2011	−1.29	0.7244898	119	59	0.8%	−1.29 [−2.71, 0.13]
Heller et al., 2012	−0.33	0.35459184	472	157	3.1%	−0.33 [−1.02, 0.36]
Lane et al., 2017	−0.94	0.2398	501	501	6.1%	−0.94 [−1.41, -0.47]
Mathieu et al., 2013	−1.07	0.38265306	329	164	2.7%	−1.07 [−1.82, -0.32]
Subtotal (95% CI)			1421	881	12.8%	−0.84 [−1.18, -0.51]
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.99$, df = 3 ($p = 0.39$); $I^2 = 0\%$						
Test for overall effect: $Z = 4.92$ ($p < 0.00001$)						
1.15.2 T2DM						
DEVOTE trial, 2017	−0.4	0.10204082	3818	3819	18.0%	−0.40 [−0.60, −0.20]
Garber et al., 2012	−0.29	0.18112245	744	248	9.4%	−0.29 [−0.64, 0.06]
Gough et al., 2013	−0.42	0.18367347	228	229	9.2%	−0.42 [−0.78, −0.06]
Meneghini et al., 2013	−0.3	0.17346939	457	230	9.9%	−0.30 [−0.64, 0.04]
Onishi et al., 2013	−0.09	0.16326531	289	146	10.8%	−0.09 [−0.41, 0.23]
Pan et al., 2016	−0.26	0.14030612	555	278	13.0%	−0.26 [−0.53, 0.01]
Warren et al., 2017	−0.77	0.31632653	145	145	3.8%	−0.77 [−1.39, −0.15]
Zinman et al., 2011	−0.55	0.50510204	121	62	1.6%	−0.55 [−1.54, 0.44]
Zinman et al., 2012	−0.43	0.15561224	773	257	11.5%	−0.43 [−0.73, −0.13]
Subtotal (95% CI)			7130	5414	87.2%	−0.34 [−0.45, −0.23]
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.69$, df = 8 ($p = 0.68$); $I^2 = 0\%$						
Test for overall effect: $Z = 6.24$ ($p < 0.00001$)						
Total (95% CI)			8551	6295	100.0%	−0.41 [−0.54, −0.28]
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 16.44$, df = 12 ($p = 0.17$); $I^2 = 27\%$						
Test for overall effect: $Z = 6.14$ ($p < 0.00001$)						
Test for subgroup differences: $\chi^2 = 7.77$, df = 1 ($p = 0.005$); $I^2 = 87.1\%$						

Liu, et al, International Journal of Endocrinology vol 2018

NOCTURNAL HYPOGLYCEMIA BETWEEN IDEG AND IGLAR

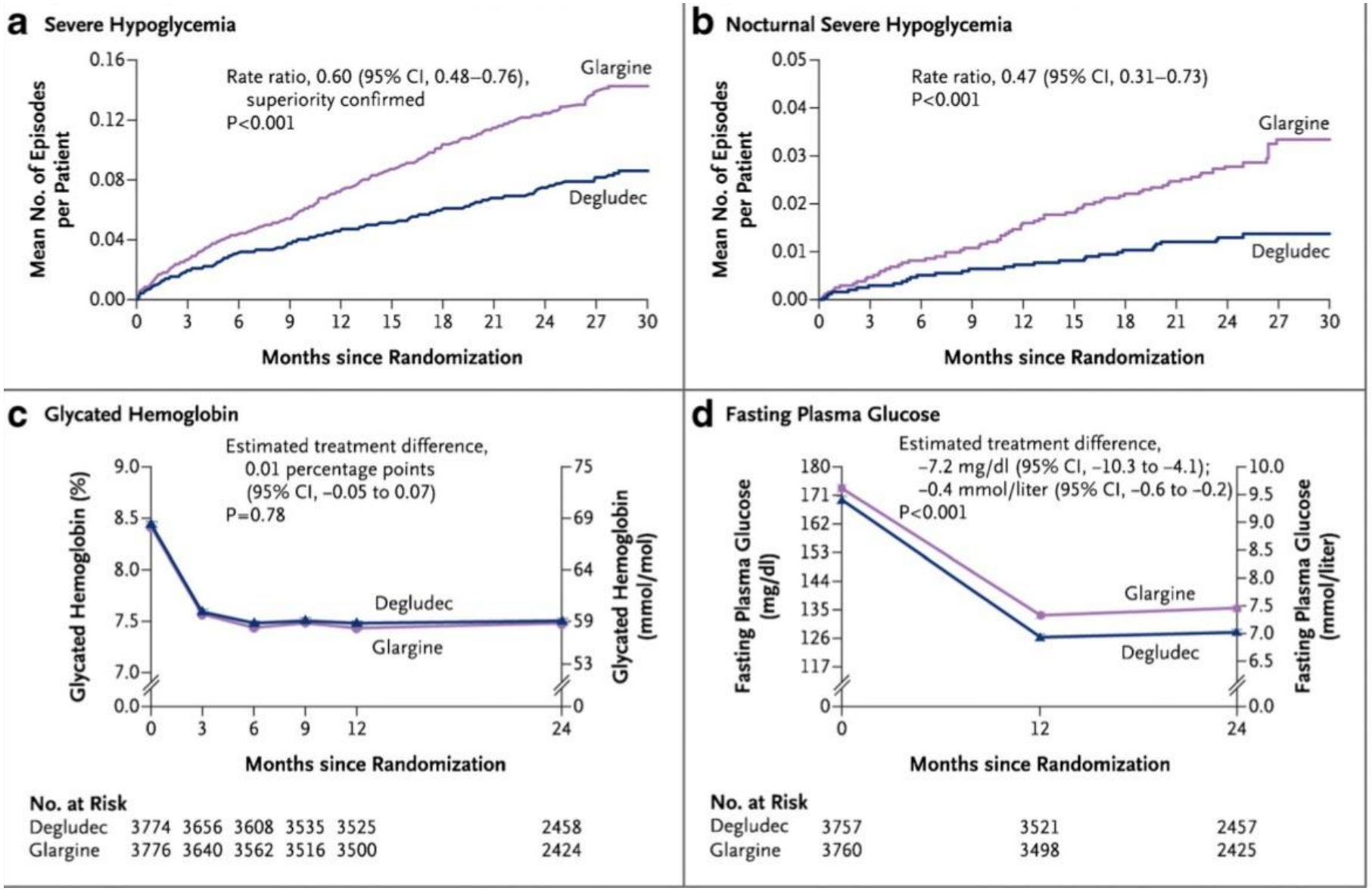
Study or subgroup	log[risk ratio]	SE	IDeg Total	IGlar Total	Weight	Risk ratio IV, fixed, 95% CI
1.19.1 T1DM						
Birkeland et al., 2011	−0.5798	0.218	119	59	2.4%	0.56 [0.37, 0.86]
Heller et al., 2012	−0.2877	0.1224	472	157	7.7%	0.75 [0.59, 0.95]
Lane et al., 2017	−0.2877	0.05	501	501	46.2%	0.75 [0.68, 0.83]
Mathieu et al., 2013	−0.2877	0.1311	329	164	6.7%	0.75 [0.58, 0.97]
Subtotal (95% CI)			1421	881	63.0%	0.74 [0.68, 0.81]
Heterogeneity: $\chi^2 = 1.73$, df = 3 ($p = 0.63$); $I^2 = 0\%$						
Test for overall effect: $Z = 6.99$ ($p < 0.00001$)						
1.19.2 T2DM						
Garber et al., 2012	−0.2877	0.1311	744	248	6.7%	0.75 [0.58, 0.97]
Gough et al., 2013	−0.4463	0.3866	228	229	0.8%	0.64 [0.30, 1.37]
Meneghini et al., 2013	−0.2399	0.1437	457	230	5.6%	0.79 [0.59, 1.04]
Onishi et al., 2013	−0.478	0.2598	289	146	1.7%	0.62 [0.37, 1.03]
Pan et al., 2016	−0.2614	0.2973	555	278	1.3%	0.77 [0.43, 1.38]
Warren et al., 2017	−0.4155	0.4196	145	145	0.7%	0.66 [0.29, 1.50]
Wysham et al., 2017	−0.2877	0.0809	721	721	17.6%	0.75 [0.64, 0.88]
Zinman et al., 2011	1.1314	1.5275	121	62	0.0%	3.10 [0.16, 61.88]
Zinman et al., 2012	−0.4463	0.2149	773	257	2.5%	0.64 [0.42, 0.98]
Subtotal (95% CI)			4033	2316	37.0%	0.74 [0.66, 0.82]
Heterogeneity: $\chi^2 = 2.25$, df = 8 ($p = 0.97$); $I^2 = 0\%$						
Test for overall effect: $Z = 5.42$ ($p < 0.00001$)						
Total (95% CI)			5454	3197	100.0%	0.74 [0.69, 0.79]
Heterogeneity: $\chi^2 = 3.98$, df = 12 ($p = 0.98$); $I^2 = 0\%$						
Test for overall effect: $Z = 8.84$ ($p < 0.00001$)						
Test for subgroup differences: $\chi^2 = 0.00$, df = 1 ($p = 0.96$), $I^2 = 0\%$						



Pvalue= 0.001

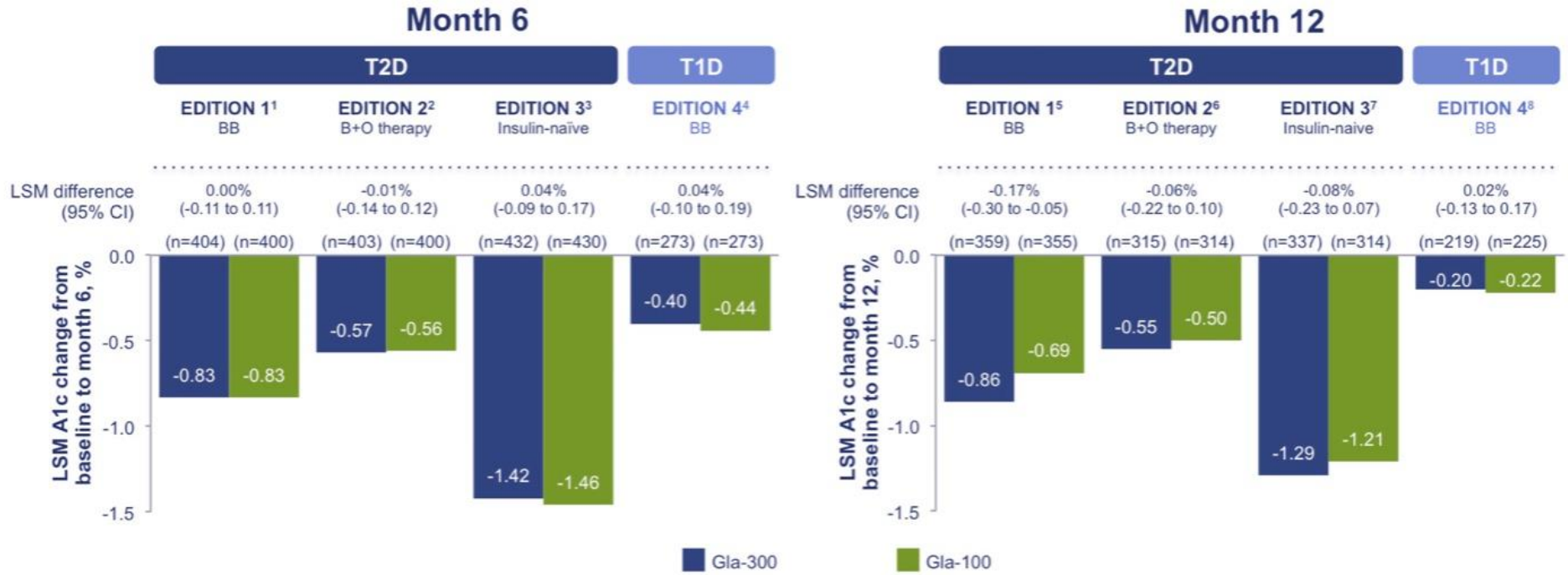
FIGURE 4: Comparison of the risk of nocturnal hypoglycemia (events per patient-year of episode) between IDeg and IGlar across subgroups: the abbreviations are the same as Figure 1.

Liu, et al, International Journal of Endocrinology vol 2018


a Severe Hypoglycemia
Mean No. of Episodes per Patient
0.16
0.12
0.08
0.04
0.00
Rate ratio, 0.60 (95% CI, 0.48–0.76), superiority confirmed
P<0.001
Glargine
Degludec
0 3 6 9 12 15 18 21 24 27 30
Months since Randomization
b Nocturnal Severe Hypoglycemia
Mean No. of Episodes per Patient
0.05
0.04
0.03
0.02
0.01
0.00
Rate ratio, 0.47 (95% CI, 0.31–0.73)
P<0.001
Glargine
Degludec
0 3 6 9 12 15 18 21 24 27 30
Months since Randomization
c Glycated Hemoglobin
Glycated Hemoglobin (%)
9.0
8.5
8.0
7.5
7.0
0.0
Estimated treatment difference,
0.01 percentage points
(95% CI, −0.05 to 0.07)
P=0.78
Degludec
Glargine
75
69
64
59
53
0
Glycated Hemoglobin (mmol/mol)
0 3 6 9 12 24
Months since Randomization
No. at Risk
Degludec 3774 3656 3608 3535 3525 2458
Glargine 3776 3640 3562 3516 3500 2424
d Fasting Plasma Glucose
Fasting Plasma Glucose (mg/dl)
180
171
162
153
144
135
126
117
0
Estimated treatment difference,
−7.2 mg/dl (95% CI, −10.3 to −4.1);
−0.4 mmol/liter (95% CI, −0.6 to −0.2)
P<0.001
Glargine
Degludec
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
0.0
Fasting Plasma Glucose (mmol/liter)
0 12 24
Months since Randomization
No. at Risk
Degludec 3757 3521 2457
Glargine 3760 3498 2425

Change in A1c

A1c Change form Baseline: Insulin Glargine 300 Units/mL vs Insulin Glargine 100 Units/mL*



Long-term consistency in glycemic control across EDITION studies

*In the modified intent-to-treat population. BB: basal-bolus therapy; B+O: basal plus oral; CI: confidence interval; Gla-100: insulin glargine 100 units/mL (Lantus); Gla-300: insulin glargine 300 units/mL; LSM: least squares mean; T1D: type 1 diabetes; T2D: type 2 diabetes.

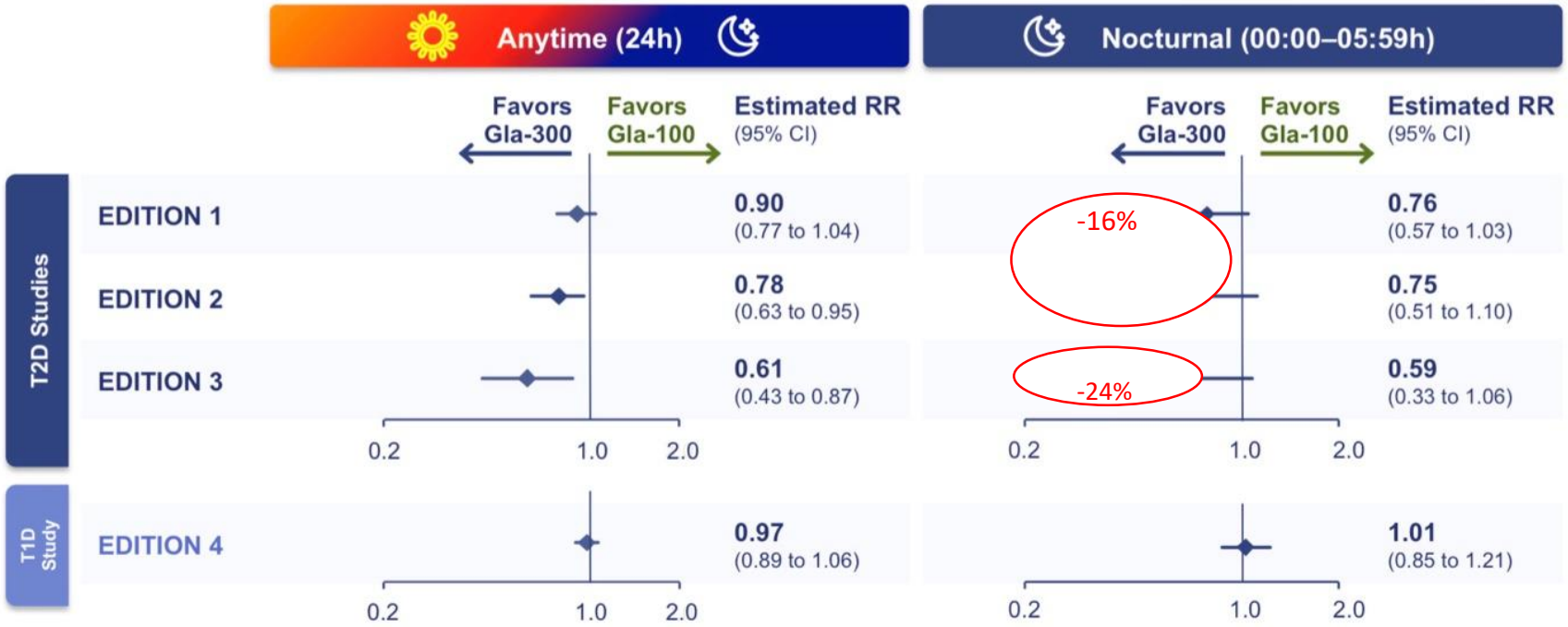
1. Riddle MC, et al. *Diabetes Care*. 2014;37(10):2755-2762. **2.** Yki-Järvinen H, et al. *Diabetes Care*. 2014;37(12):3235-3243. **3.** Bolli GB, et al. *Diabetes Obes Metab*. 2015;17(4):386-394. **4.** Data on file, EDITION 4 CSR (6 months) pg 88. **5.** Riddle MC, et al. *Diabetes Obes Metab*. 2015;17(9):835-842. **6.** Yki-Järvinen H, et al. *Diabetes Obes Metab*. 2015;17(12):1142-1149. **7.** Bolli GB, et al. *Diabetes Metab*. 2017;43(4):351-358 (Main Article and Supplementary Table 2). **8.** Home PD, et al. *Diabetes Obes Metab*.

EDITION

Relative Risk of ≥1 Hypoglycemic Event in EDITION Trials

Gla-300 vs Gla-100 (EDITION trials)

Participants with one or more confirmed (<54 mg/dL) or severe hypoglycemia event at month 6[1,2]



CI: confidence interval; Gla-100: insulin glargine 100 Units/mL (Lantus); Gla-300: insulin glargine 300 Units/mL; h: hour; RR: relative risk; T1D: type 1 diabetes; T2D: type 2 diabetes.

1. Adapted from Rosenstock J, et al. Poster presentation at ADA 76th Scientific Sessions 2016; Abstract 962-P. 2. Home PD, et al. *Diabetes Care*. 2015;38(12):2217-2225 (Supplementary Table 2).

Summary

- No significant differences in efficacy has been shown with any second-generation basal analog over other
- Rates of hypoglycemia have differed ; in the BEGIN BB and BEGIN Flex, nocturnal hypoglycemia was significantly lowered with Ideg .
- EDITION 1 and 2 symptomatic hypoglycemia was lowered for Iglar u-300 vs Iglar u-100
- In BRIGHT (insulin naïve) there was a difference in the incidence of hypoglycemia and confirmed nocturnal hypoglycemia ,between Ideg vs IGlar300, being lower for Glar u-300 in the 0-12 w titration period
- It is interesting to note that elder T2DM treated with Glar-300 have been found with more glycemic control, lesser hypoglycemia and lesser weight gain as compared to Gla-100
- CONCLUDE : Glar u-300 vs IDeg u-200 no difference in overall hypoglycemia

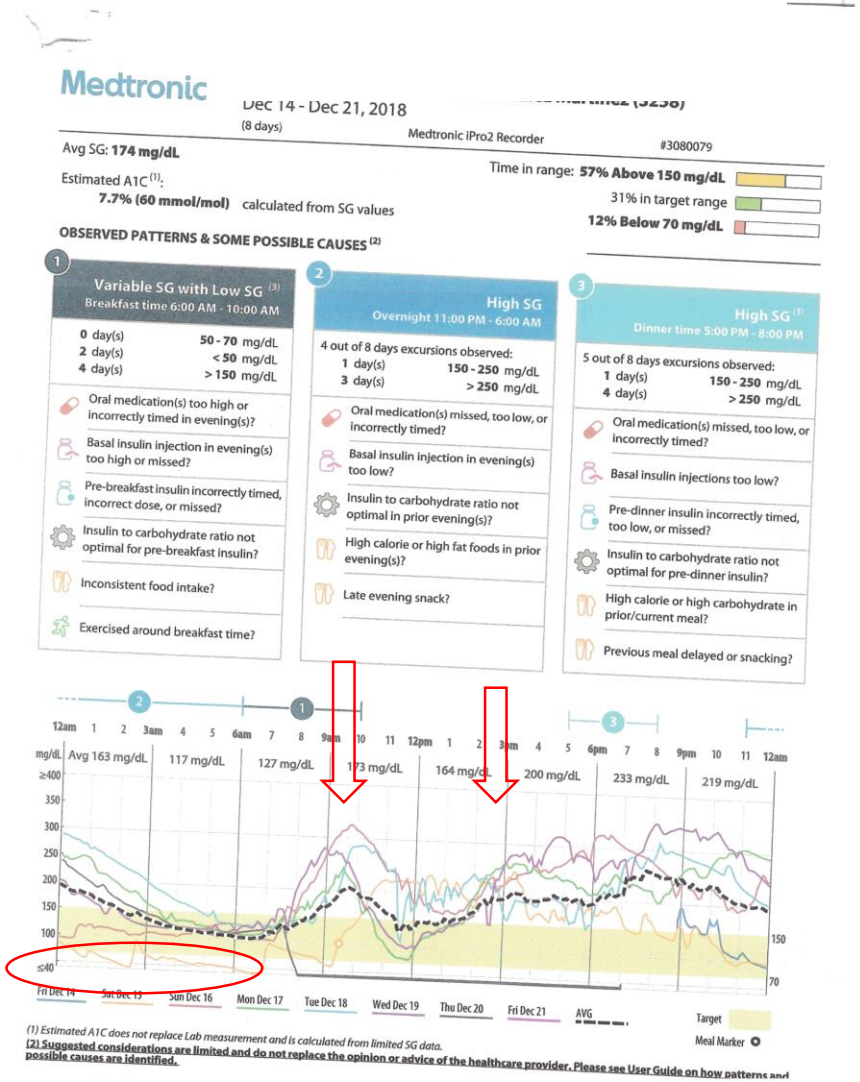
WHO MAY BENEFIT FROM A LONGER-ACTING BASAL INSULIN ?

- PATIENT IN WHOM THEIR CURRENT BI DOSE ， DOES NOT LAST FULL 24 H
- PATIENT WITH HECTIC/ERRATIC SCHEDULES
- PATIENT WHO REQUIRE LARGE DAILY DOSES OF BI
- PATIENT EXPERIENCING NOCTURNAL HYPOGLYCEMIA WITH THEIR CURRENT BI

Clinical case : human premixed vs analog vs BB

- 87 y/o female DM 2 26 y evolution complains of hypoglycemia post meals
- DM neuropathy, sleep apnea , HTN , dyslipidemia , 1 Hypothyroidism , AVR
- Present tx : Humulin 70/30 12 u sub am and pm
- BMI 30 Kg/m2 B/P 133/74
- Labs : HBA1c 8.16 % FBG 203 mg/dL ALT 14 eGFR 37 ml/min LDL 62 HDL 53 mg/dL TG 152 mg/dL

Human premixed insulin



- What are your recommendations at this point ?

1)D/c premixed human insulin, start BB analog therapy
2)Decrease premixed HUMAN INSULIN doses , add metformin
3)Change human insulin for premixed analog
4)D/c premixed, start basal plus

Type of premixed insulin	Low-mix formulations	Mid-mix formulations	High-mix formulations
Premixed regular insulin-NPH	30% insulin regular/70% insulin NPH	50% insulin regular/50% insulin NPH	Biphasic huma insulin 75 75% insulin regular/25% insulin NPH
Premixed insulin analogs	30% insulin aspart/70% insulin aspart protamine 25% insulin lispro/75% insulin lispro protamine	50% insulin lispro/50% insulin lispro protamine 50% insulin aspart/50% insulin aspart protamine	Biphasic huma lispro 75 Biphasic huma lispro 70 Biphasic huma aspart 70
Coformulation	70% insulin degludec/30% insulin aspart		

NPH neutral protamine Hagedorn

Metanalysis of randomized and observational studies comparing premixed insulin vs basal-bolus in T2 DM

Studies	⌐ HGbA1c with premixed	Hypoglycemia Total	nocturnal	severe	weight
BI/ASP/Glar on OA 5studies 4-28 week n=1758 A1chieve study 60000 observational	Premixed better PM BIASP 30 better than BHI 30	- -	- -	- -	+ - +0.1Kg
Premixed intensification vs basal-bolus 13 studies 16-24 week n =5401 GiugLiano 13 RCT premixed lispro vs Glar Sun et al 28 RCT IGLAr+OAD or bolus vs NPH, premixed or Det Rys ,P	= premixed better IGlar +OAD = Idet +OAD = Mix + OAD IGlar BB = NPH + bolus Iglar BB better than PM	= + -	= + = for PM	= + =PM =	= + =

Rys P et al. Int Clin Pract 2014;68:304-313
Giugliano D et al. Endocrine 2016 Mar;51(3) 417-428
Sun D et at. Diabetes Technol Ther 2018; 20:622
Rosenstock et al. Diabetes Care vol 31 no 1 2008

Premixed vs basal-bolus insulin regimen in type 2 diabetes: comparison of clinical outcomes from randomized controlled trials and real-world data

- Data : 8 RCT BB(n=1893) vs PM(n=1517)
- Similar reduction in HBA1c and weight between therapies at 6 month
- Better glycemic control in BB at 6 month of insulin initiation -0.085 p=0.0001
- No significant difference in weight gain between the two
- More weight gain in RTC than in real-world
- Choice of insulin regimen should therefore be individualized according to personal ,social, and clinical characteristics

Anyanwagu et al, Diabet Med 2017 Dec;34 (12):11728-1736

COMPARISON BETWEEN ONCE A DAY BASAL VS TWICE-THRICE PREMIXED INSULIN

Premixed analogues achieved greater change in A1c
FBG lower in basal insulin
Improved 24h BG with premixed compared to Basal
*No episodes of severe hypoglycemia in past users of insulin
Insulin doses higher in pre-mixed and gained more weight

Those on mix 75/25 had lower nocturnal hypoglycemia and higher non-nocturnal

Ilag et al, Clinical Therapeutics / Vol 29 , theme issue 2007

Clinical Therapeutics

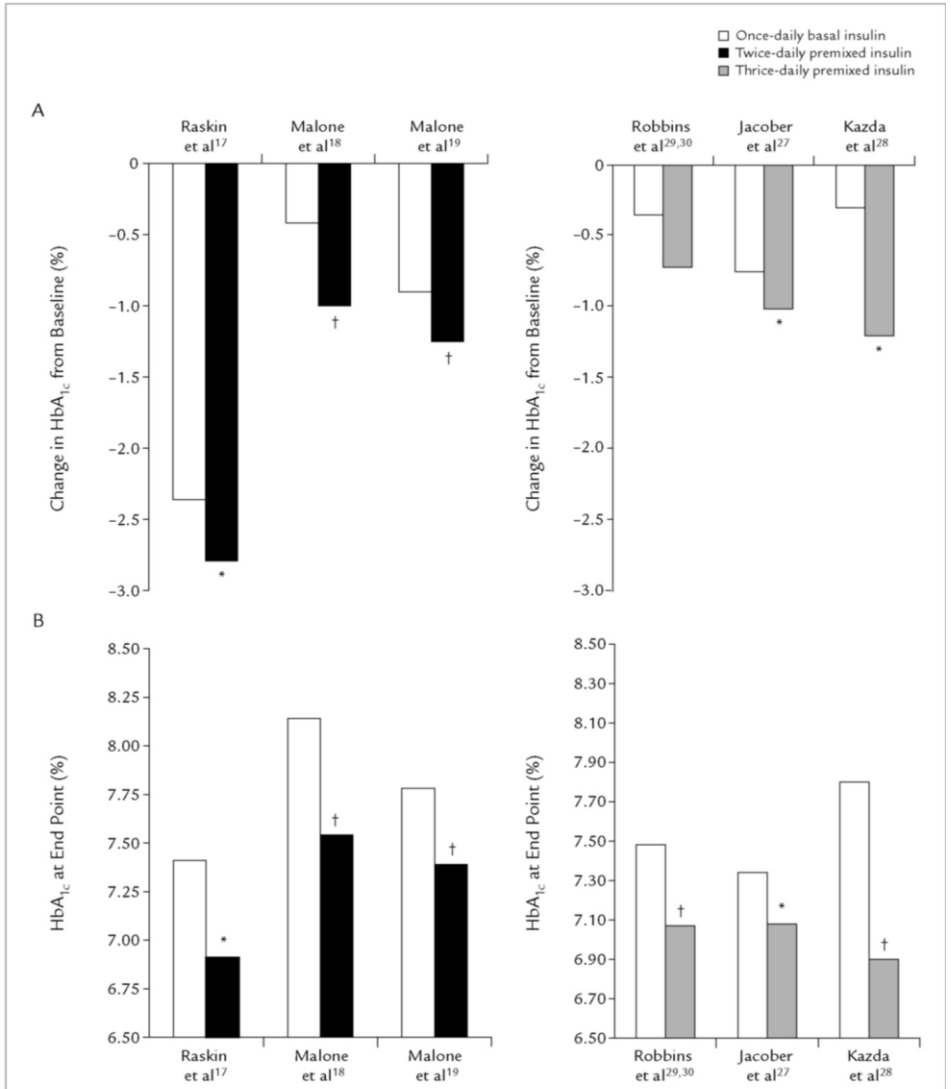


Figure 1. (A) Change in mean glycosylated hemoglobin (HbA_{1c}) from baseline, and (B) mean HbA_{1c} at end point in studies comparing twice- or thrice-daily premixed insulin analogue regimens with a once-daily basal insulin analogue. *$P < 0.01$; †$P < 0.001$.

Indices	Prefer premix[a]	Prefer basal[a]
PPGE = PPG – FPG	40–74 mg/dl	< 40 mg/dl
	2.2–4.1 mmol/l	< 2.2 mmol/l
$PFI = \frac{PPG - FPG}{FPG}$	0.4–0.6	< 0.4
FPG/HbA1c[b]	≤ 20	≥ 20

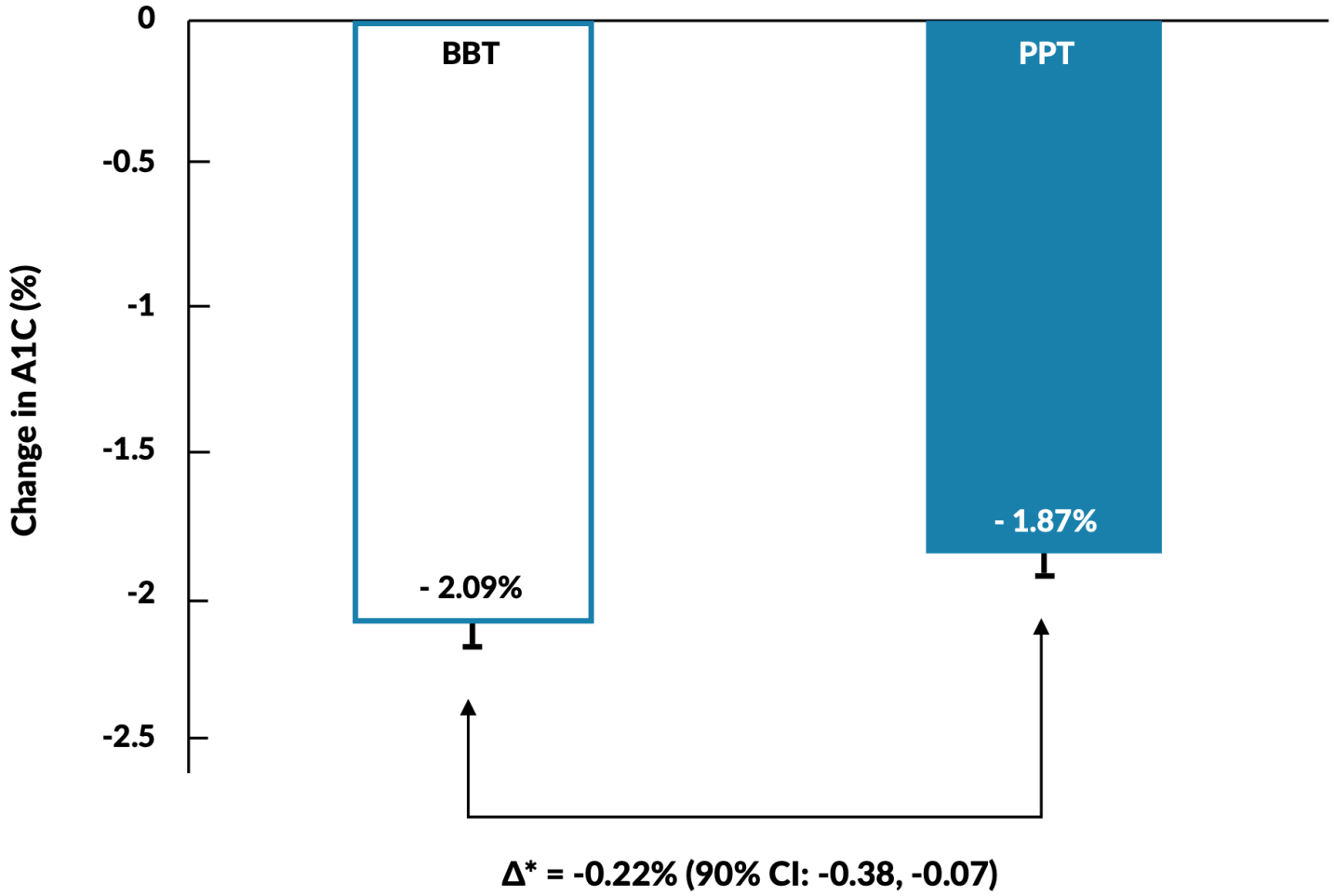
FPG fasting plasma glucose, *PPG* postprandial plasma glucose, *PPGE* postprandial glucose excursion, *PFI* prandial fasting index

[a]The cutoff values are arbitrary and are based upon diagnostic values for prediabetes and diabetes. For derivation, refer to Kalra [32]

[b]Using FPG (126 mg/dl) and currently accepted HbA1c (6.3%) levels

Kalra et al, Diabetes Ther (2018)9,2185-2199

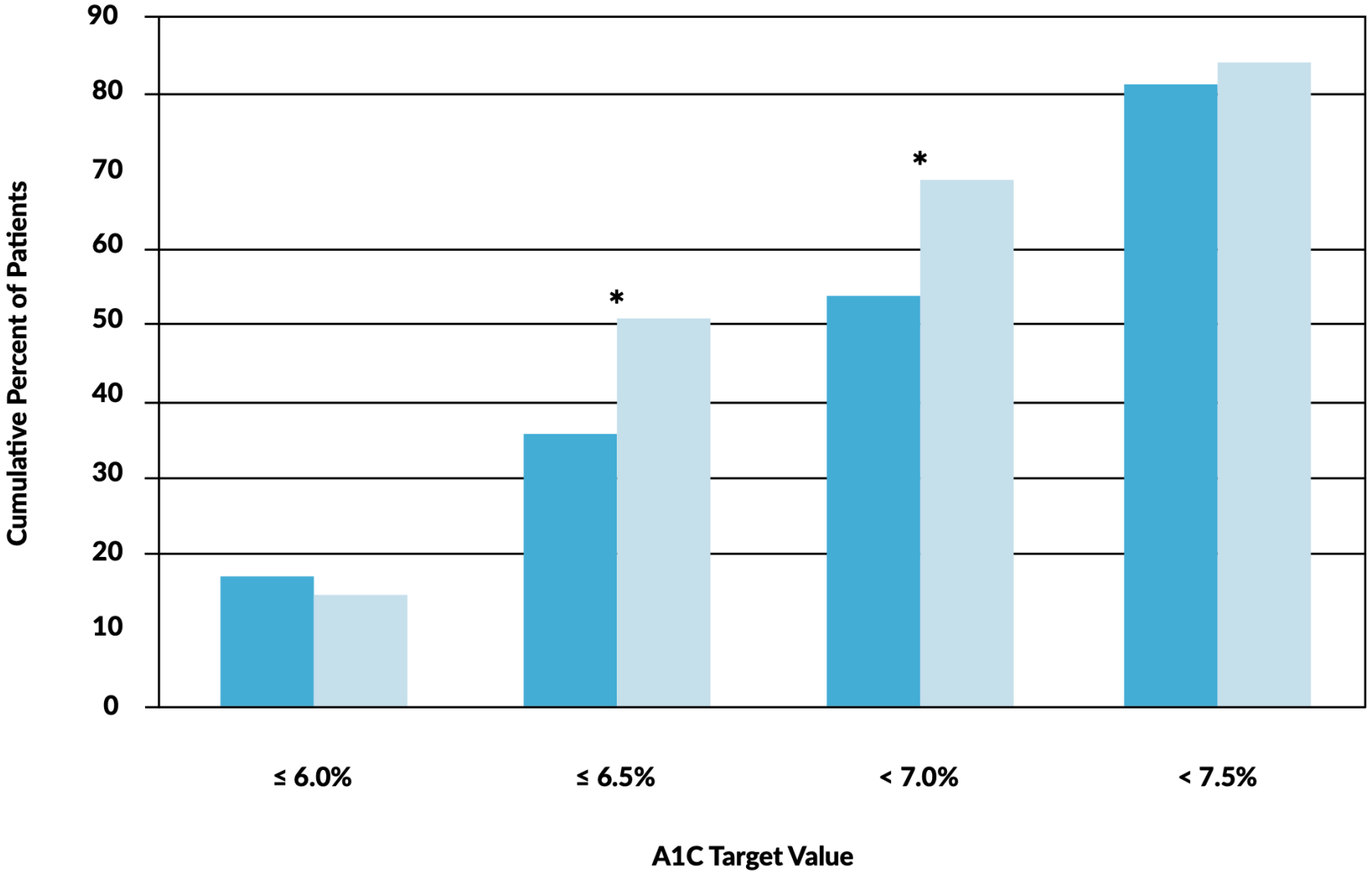
PRANDIAL PREMIXED LISPRO VERSUS BASAL-BOLUS



Change in mean A1C SEM from baseline to end point for the BBT (□) and PPT (■) groups and the difference (BBT - PPT) in A1C change, with the 90% CI.

Rosenstock J, Ahmann A, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing Insulin Therapy in Type 2 Diabetes Previously Treated With Glargine Plus Oral Agents: Prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care. 2007;31(1):20-25. doi:10.2337/dc07-1122

Prandial premixed lispro versus BB



Cumulative percentage of patients achieving specific target A1C values after 24 weeks of treatment with PPT (■) or BBT (■). *P < 0.05.

Rosenstock J, Ahmann A, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing Insulin Therapy in Type 2 Diabetes Previously Treated With Glargine Plus Oral Agents: Prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care. 2007;31(1):20-25. doi:10.2337/dc07-1122

Pre-mixed insulin analogues versus IBB insulin therapy

1. Greater HBA1c reduction with IBB vs premixed in patients already on basal therapy, similar reduction in insulin naïve patients
2. Mean insulin doses greater in the IBB
3. Similar weight changes
4. During the study there was no difference in the rate of incidence of overall, nocturnal or severe hypoglycemia

Rosenstock et al, Diabetes Care vol31 n01 Jan2008

Type 2 Diabetes: Exemplars for initiation/intensification with premixed insulin analogs

Current therapy	Current medical status	Current glycemic status	Dietary pattern	Intervention
Monotherapy OAD	Symptoms of hyperglycemia/catabolism/asthenia Acute medical or surgical comorbidity requiring timely resolution of hyperglycemia	Inadequate fasting + postprandial control	Regular meals	Initiation with premixed insulin, preferably twice daily
OAD, dual or triple combination	Symptoms of hyperglycemia/catabolism/asthenia Acute medical or surgical comorbidity requiring timely resolution of hyperglycemia Asymptomatic persons	Inadequate fasting + postprandial control	One heavy meal Two heavy meals	Initiation with premixed insulin once daily Initiation with premixed insulin twice daily
Basal insulin + OADs	Symptoms of hyperglycemia/catabolism/asthenia Acute medical or surgical comorbidity requiring timely resolution of hyperglycemia Asymptomatic persons	High HbAlc inspite of adequate FPG control High PPG, unacceptable nocturnal hypoglycemia	One heavy meal Two heavy meals	Intensification to premixed insulin once daily Intensification to premixed insulin twice daily
Premixed insulin once daily + OADs	Symptoms of hyperglycemia/catabolism/asthenia Acute medical or surgical comorbidity requiring timely resolution of hyperglycemia Asymptomatic persons	High HbAlc inspite of adequate FPG control High PPG, unacceptable nocturnal hypoglycemia	Heavy meals	Intensification to premixed insulin twice daily
Premixed insulin twice daily + OADS	Symptoms of hyperglycemia/catabolism/asthenia Acute medical or surgical comorbidity requiring timely resolution of hyperglycemia Asymptomatic persons	High HbAlc inspite of adequate FPG control High PPG, unacceptable nocturnal hypoglycemia Post-lunch hyperglycemia	Heavy meals Three heavy meals	Intensification to high mix insulin Heteromix insulin Intensification to premixed insulin thrice daily meals

Kalra S, Czupryniak L, Kilov G et al. Expert Opinion: Patient Selection for Premixed Insulin Formulations in Diabetes Care. Diabetes Therapy. 2018;9(6):2185-2199. doi:10.1007/s13300-018-0521-2

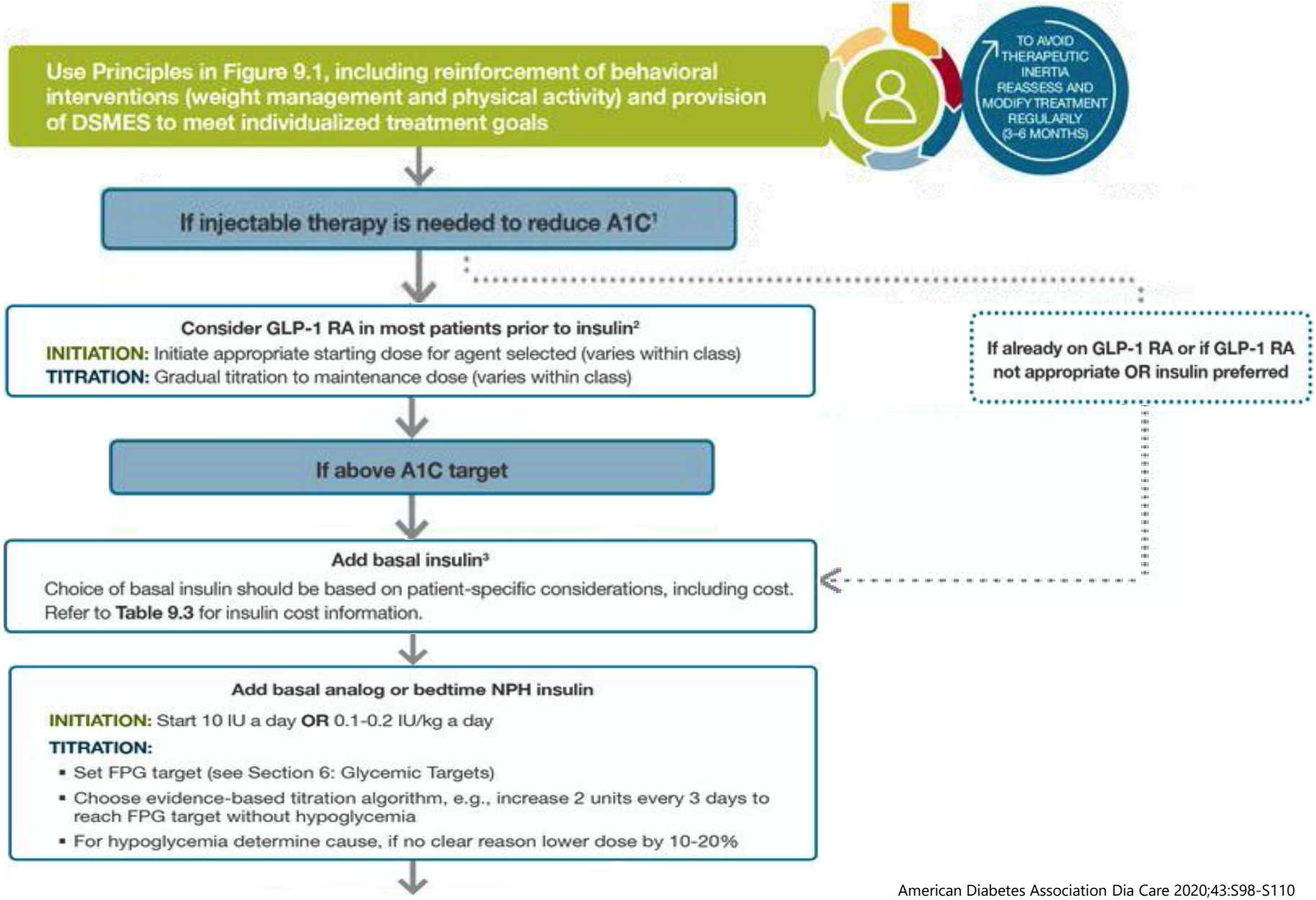
When to use premixed in a patient with T2 DM

ADA/EASD : premixed insulins can be an alternative therapy to those on basal insulin who need post prandial coverage with 2 or 3 doses. Can be a simple way to control glycemia all day. Consider at initiation and titration

AACE/ACE : premixed insulin provide less flexibility and are associated to an increase hypoglycemia compared to basal/bolus. Some patients benefit for it is simple, in which case the premixed analogs are preferred over human premixed due lo lower risk of hypoglycemia

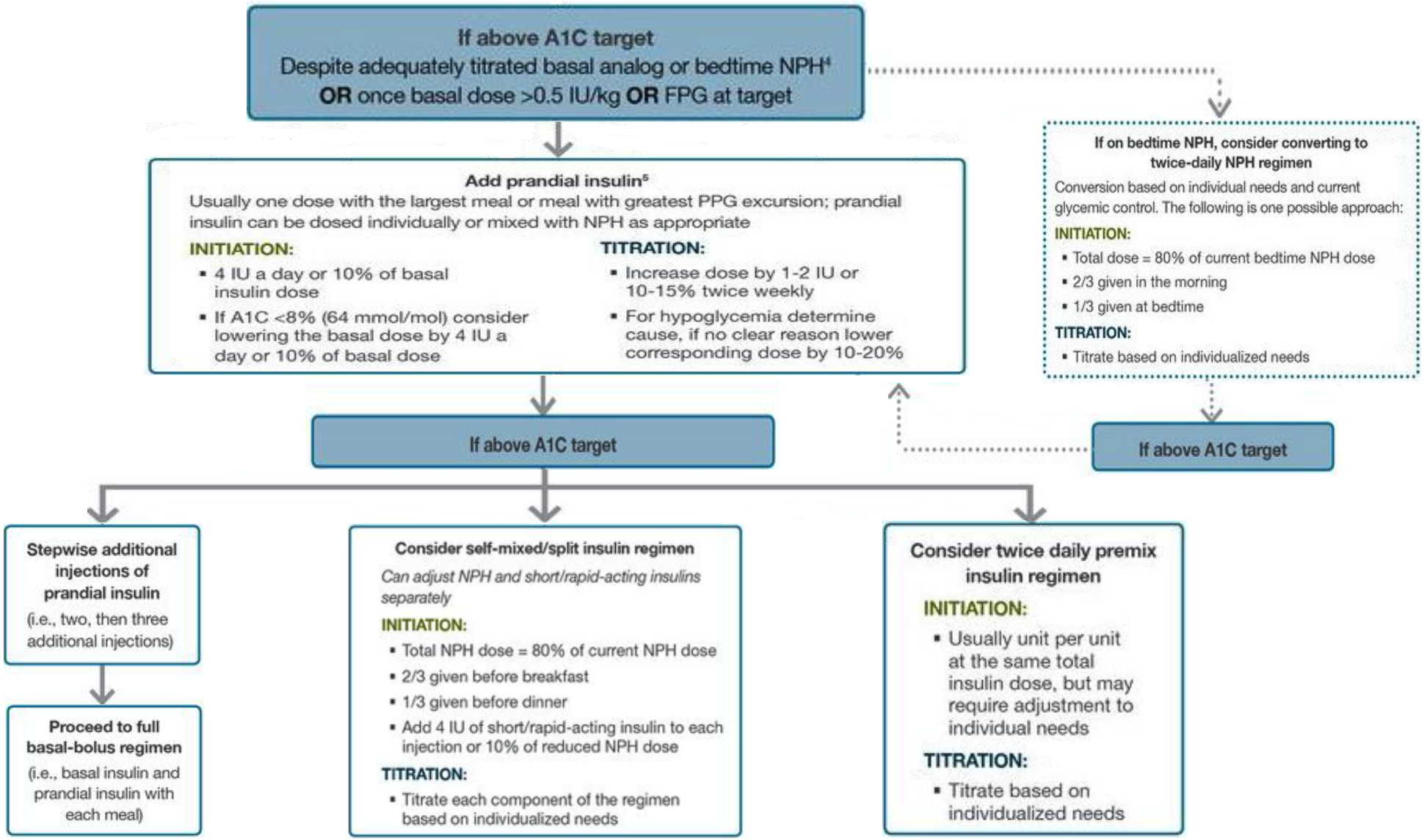
Davies MJ at al. Diabetes Care January 2019;42 S90-S102
Garber et al. Endocr Pract January 2019 25;69-100

Intensifying to Injectable Therapies



American Diabetes Association Dia Care 2020;43:S98-S110

Intensifying to Injectable Therapies



American Diabetes Association Dia Care 2020;43:S98-S110

Clinical case

- 54 y/o female referred due to MNG
- DM 2 nephropathy, RA , HTN, dyslipidemia, 1 hypothyroidism , depression
- Present tx : glargine 100 u d lispro 20 u q meal Liraglutide 1.8 mg
- BMI : 48 Kg/m2 B/P 103/60 Goiter 25 gr
- Labs HbA1c 7,9 % ma-131 mg/gr creat
- FBG 138 eGFR 65 ml/min

- What would you recommend at this point ?

Health plan will not over liraglutide, substitute or d/c

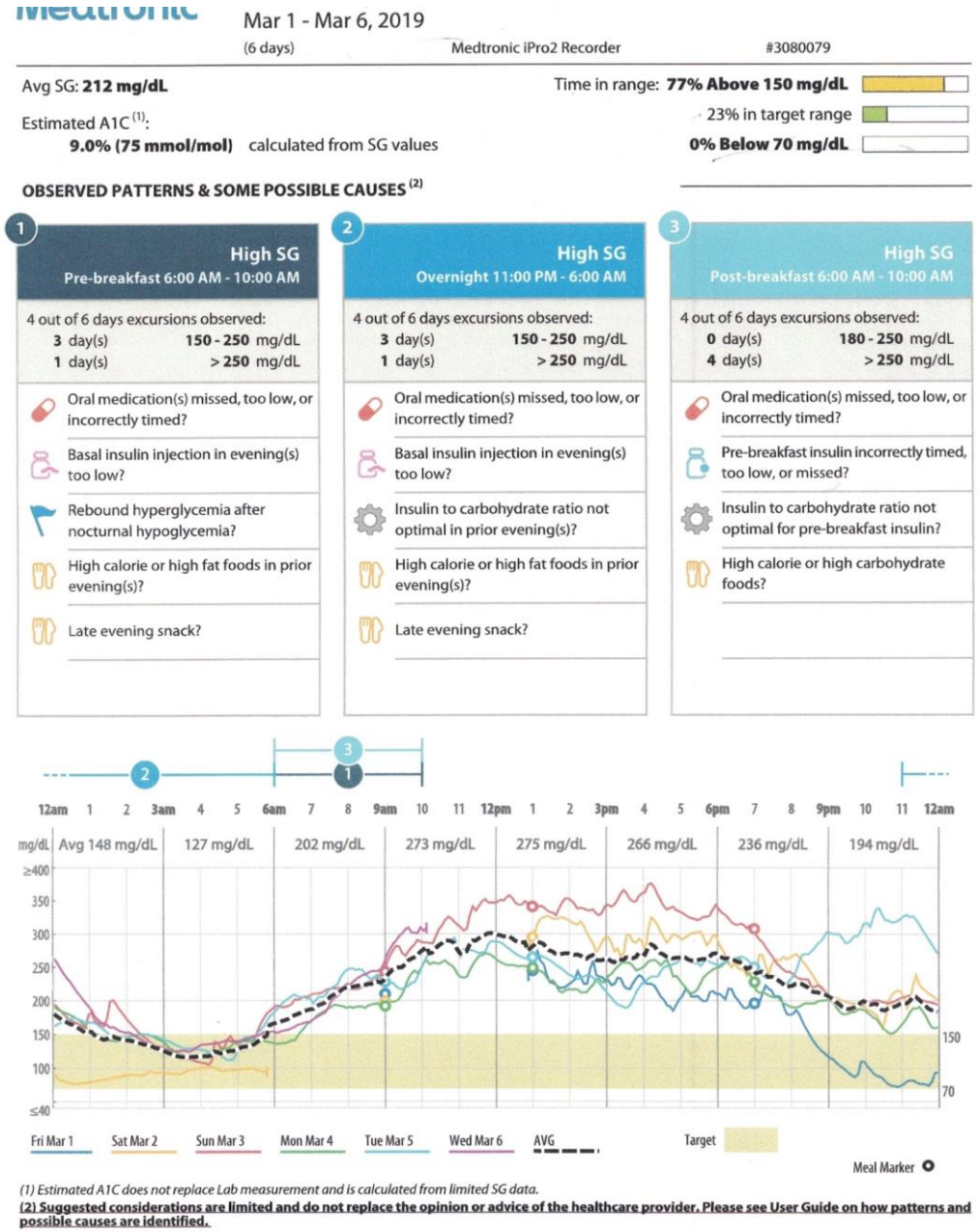
Add SGLT2, metformin

Add DPP4, metformin

Continue intensifying insulin doses

Any other thoughts ?

Pre- treatment CGMS: Baseline A1c 7.9 %



Mar 1 - Mar 6, 2019
(6 days) Medtronic iPro2 Recorder #3080079

Avg SG: **212 mg/dL**
Time in range: **77% Above 150 mg/dL**
23% in target range
0% Below 70 mg/dL

Estimated A1C (1):
9.0% (75 mmol/mol) calculated from SG values

OBSERVED PATTERNS & SOME POSSIBLE CAUSES (2)

1 High SG Pre-breakfast 6:00 AM - 10:00 AM	2 High SG Overnight 11:00 PM - 6:00 AM	3 High SG Post-breakfast 6:00 AM - 10:00 AM
4 out of 6 days excursions observed:	4 out of 6 days excursions observed:	4 out of 6 days excursions observed:
3 day(s) 150 - 250 mg/dL	3 day(s) 150 - 250 mg/dL	0 day(s) 180 - 250 mg/dL
1 day(s) > 250 mg/dL	1 day(s) > 250 mg/dL	4 day(s) > 250 mg/dL
Oral medication(s) missed, too low, or incorrectly timed?	Oral medication(s) missed, too low, or incorrectly timed?	Oral medication(s) missed, too low, or incorrectly timed?
Basal insulin injection in evening(s) too low?	Basal insulin injection in evening(s) too low?	Pre-breakfast insulin incorrectly timed, too low, or missed?
Rebound hyperglycemia after nocturnal hypoglycemia?	Insulin to carbohydrate ratio not optimal in prior evening(s)?	Insulin to carbohydrate ratio not optimal for pre-breakfast insulin?
High calorie or high fat foods in prior evening(s)?	High calorie or high fat foods in prior evening(s)?	High calorie or high carbohydrate foods?
Late evening snack?	Late evening snack?	

12am 1 2 3am 4 5 6am 7 8 9am 10 11 12pm 1 2 3pm 4 5 6pm 7 8 9pm 10 11 12am

mg/dL Avg 148 mg/dL | 127 mg/dL | 202 mg/dL | 273 mg/dL | 275 mg/dL | 266 mg/dL | 236 mg/dL | 194 mg/dL

≥400 350 300 250 200 150 100 ≤40

150 70

Fri Mar 1 Sat Mar 2 Sun Mar 3 Mon Mar 4 Tue Mar 5 Wed Mar 6 AVG Target

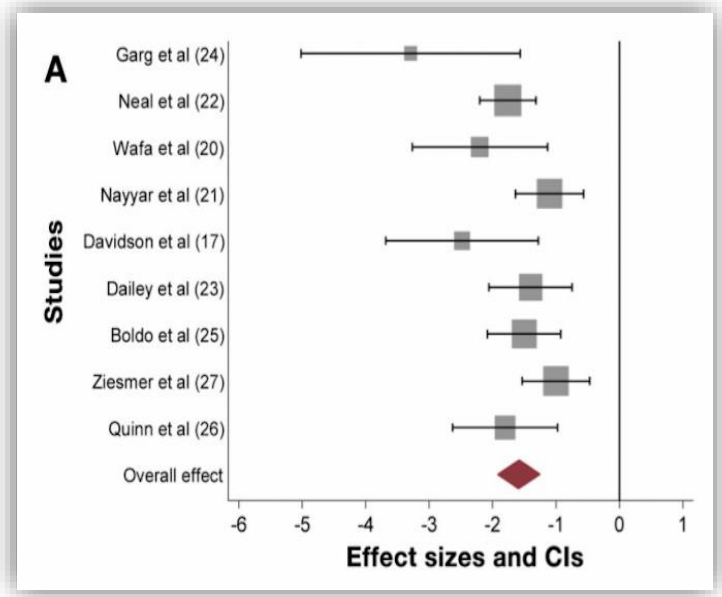
Meal Marker

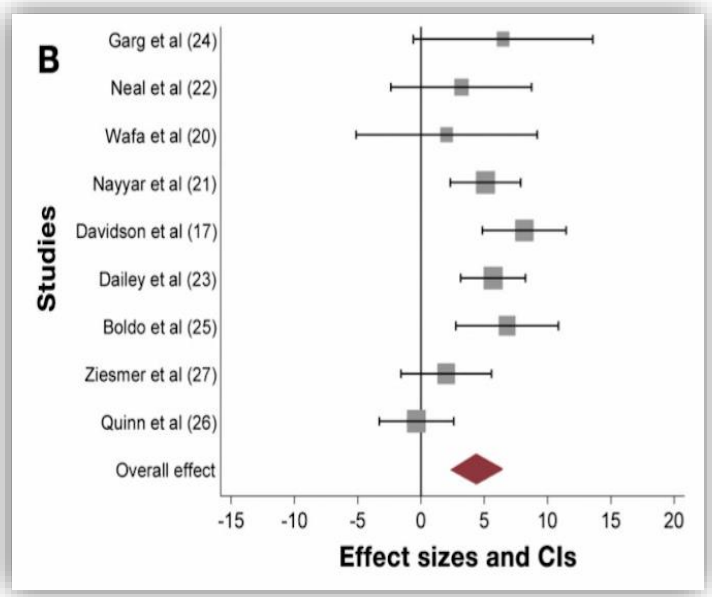
(1) Estimated A1C does not replace Lab measurement and is calculated from limited SG data.
(2) Suggested considerations are limited and do not replace the opinion or advice of the healthcare provider. Please see User Guide on how patterns and possible causes are identified.

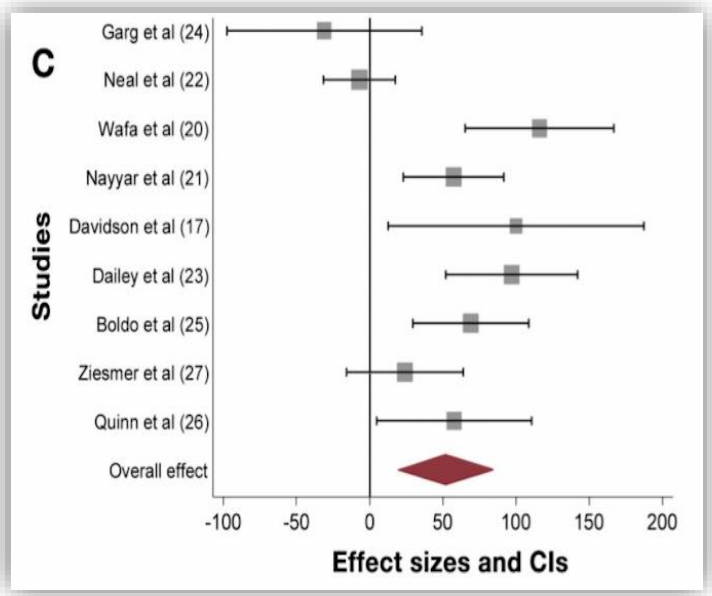
What I did :
Liraglutide was substituted by dulaglutide for health plan issues
SGLT2/met was added
Genital hygiene discussed
Lantus 100 u and Humalog 60 were d/c
Humulin ru-500 was added 105 u am, 75 u lunch and 75 u dinner

6 months later at doses 125-95-75
HBA1c 6.3 %
FBG 119 mg/dL eGFR 80 ml/min
Actually wearing a freestyle pro for reevaluation of continuous monitoring

Studies using U-500R MDI



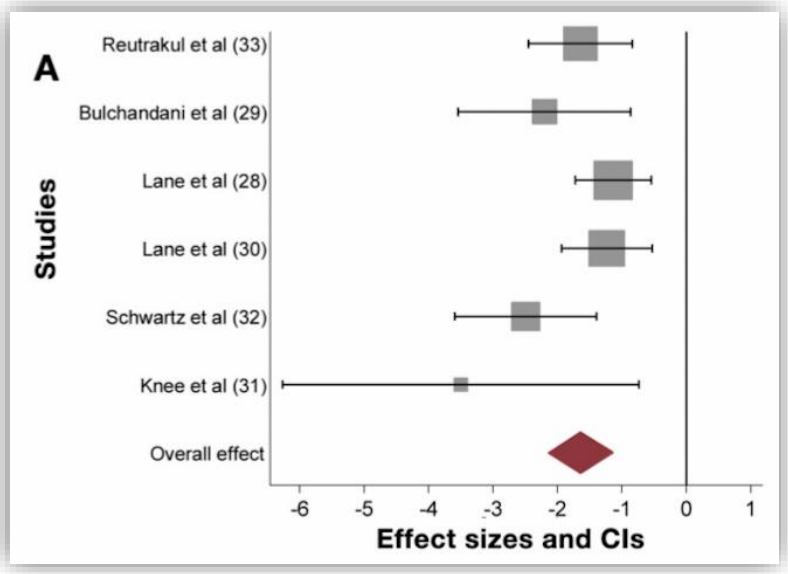


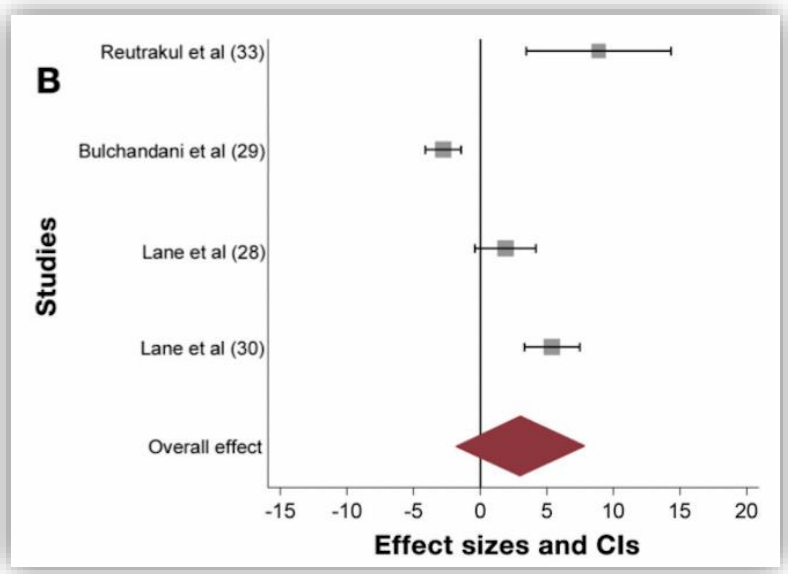


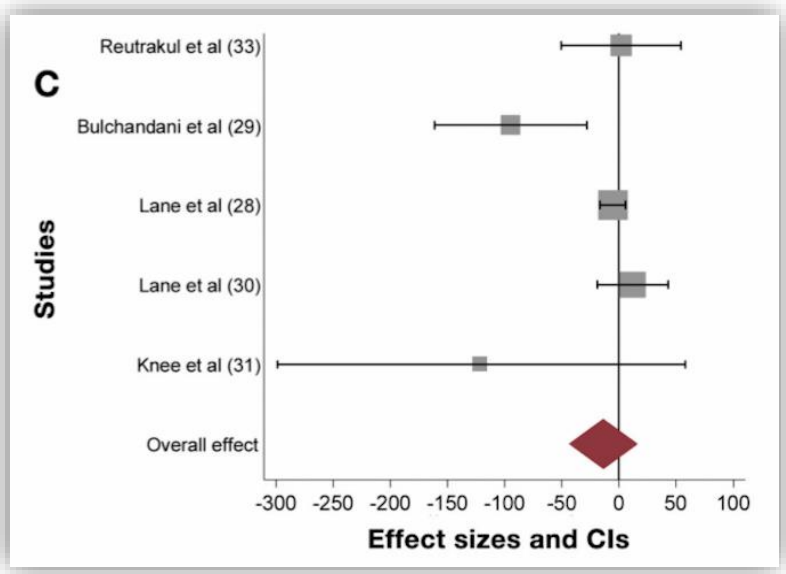
(A) Changes in HbA1c with an overall significant reduction of 1.59% (95% CI, 1.26–1.92); (B) Changes in weight with an overall significant increase of 4.38 kg (95% CI, 2.35–6.41); (C) Changes in TDD with an overall significant increase of 51.9 units (95% CI, 19.6–84.1)

Reutrakul S, Wroblewski K, Brown R. Clinical Use of U-500 Regular Insulin: Review and Meta-Analysis. J Diabetes Sci Technol. 2012;6(2):412-420. doi:10.1177/193229681200600229

Studies using U-500R via CSII

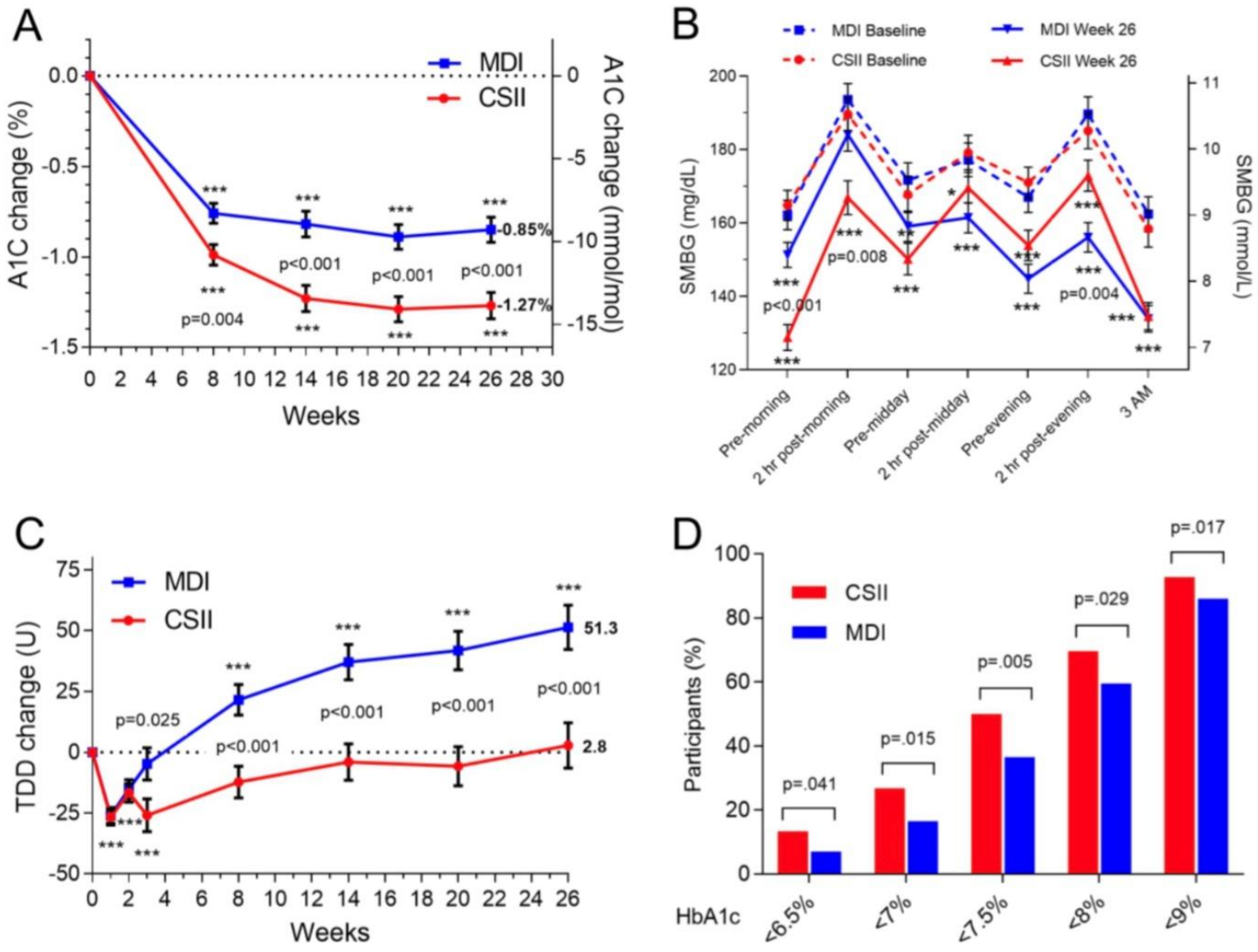






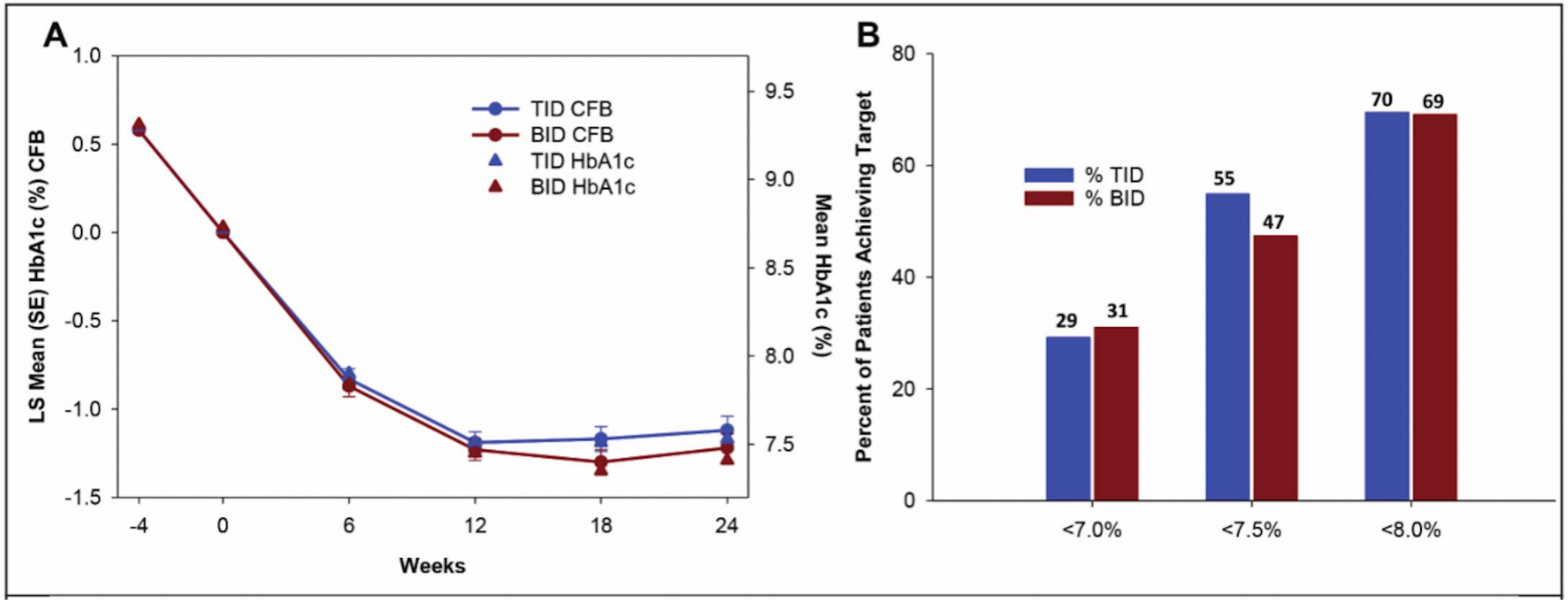
(A) Changes in HbA1c with an overall significant reduction of 1.64% (95% CI, 1.14–2.14); (B) Changes in weight with an overall nonsignificant increase of 2.99 kg (95% CI, -1.83–7.81); (C) Changes in TDD with an overall nonsignificant decrease of 13.6 units (95% CI, -42.4–15.2)

Reutrakul S, Wroblewski K, Brown R. Clinical Use of U-500 Regular Insulin: Review and Meta-Analysis. J Diabetes Sci Technol. 2012;6(2):412-420. doi:10.1177/193229681200600229



Grunberger et al the VIVID STUDY

Comparison of thrice-daily (TID) and twice-daily (BID) U-500R regimens (full analysis set)



(A) Actual and change from baseline (CFB) glycated hemoglobin (HbA_{1c}) (%) values versus time profile (0-24 weeks), mixed model for repeated measures (MMRM). (B) Percentage of patients achieving HbA_{1c} target values (<7, <7.5, and <8%) at 24 weeks for those not at target at randomization, longitudinal logistic regression (baseline percentages: 1.9, 9.9, and 24.8%, respectively). Percentage of patients achieving ≤6.5% HbA_{1c} was 15% (TID) and 17% (BID); baseline percentage, 0.9%.

Hood R, Arakaki R, Wysham C, Li Y, Settles J, Jackson J. Two treatment approaches for human regular u-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose u-100 insulin therapy with or without oral agents: a randomized, titration-to-target clinical trial. Endocrine Practice. 2015;21(7):782-793. Doi:10.4158/ep15612.Or

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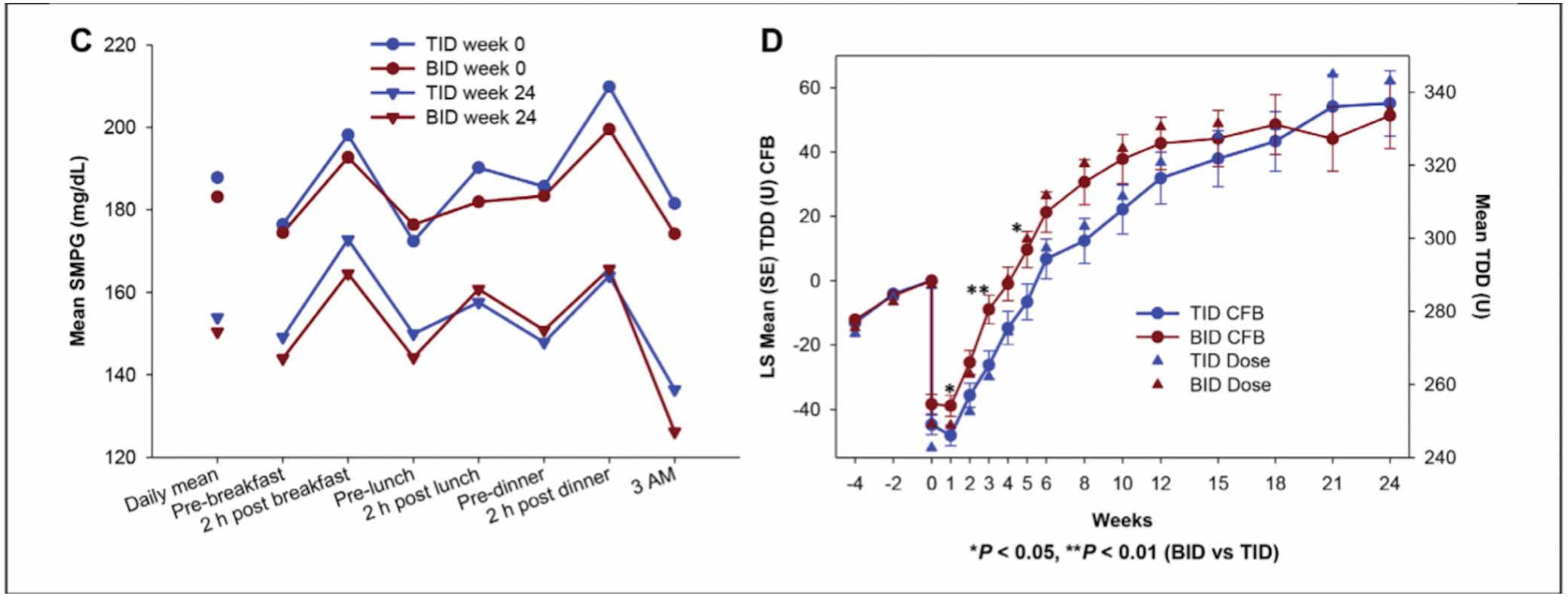
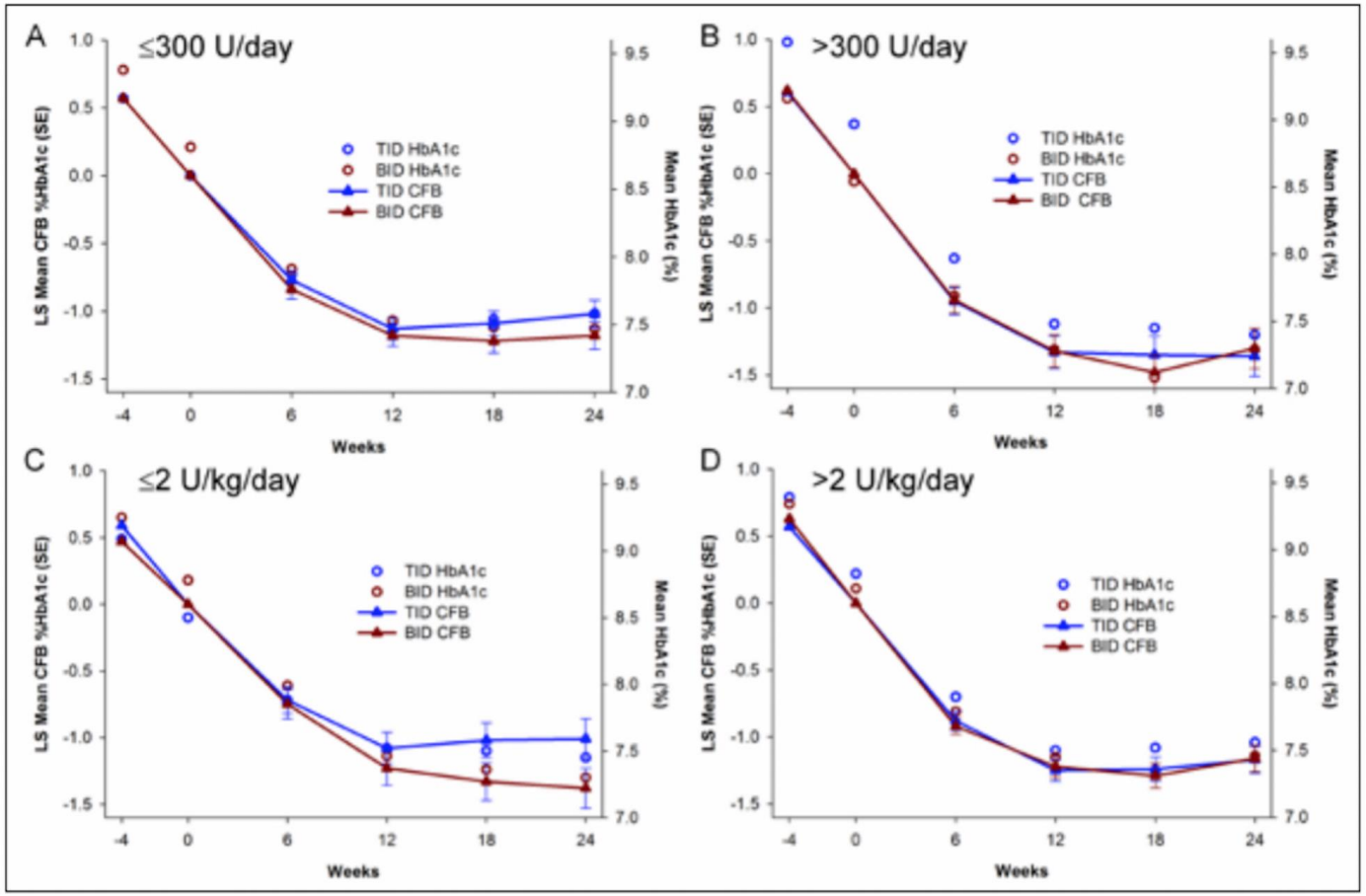


(C) Seven-point self-monitored plasma glucose (SMPG) profiles (week 0 and week 24), MMRM. (D) Actual and CFB total daily dose (TDD) values (units [U]) versus time profile (0-24 weeks), MMRM.

Hood R, Arakaki R, Wysham C, Li Y, Settles J, Jackson J. Two treatment approaches for human regular u-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose u-100 insulin therapy with or without oral agents: a randomized, titration-to-target clinical trial. Endocrine Practice. 2015;21(7):782-793. Doi:10.4158/ep15612.Or

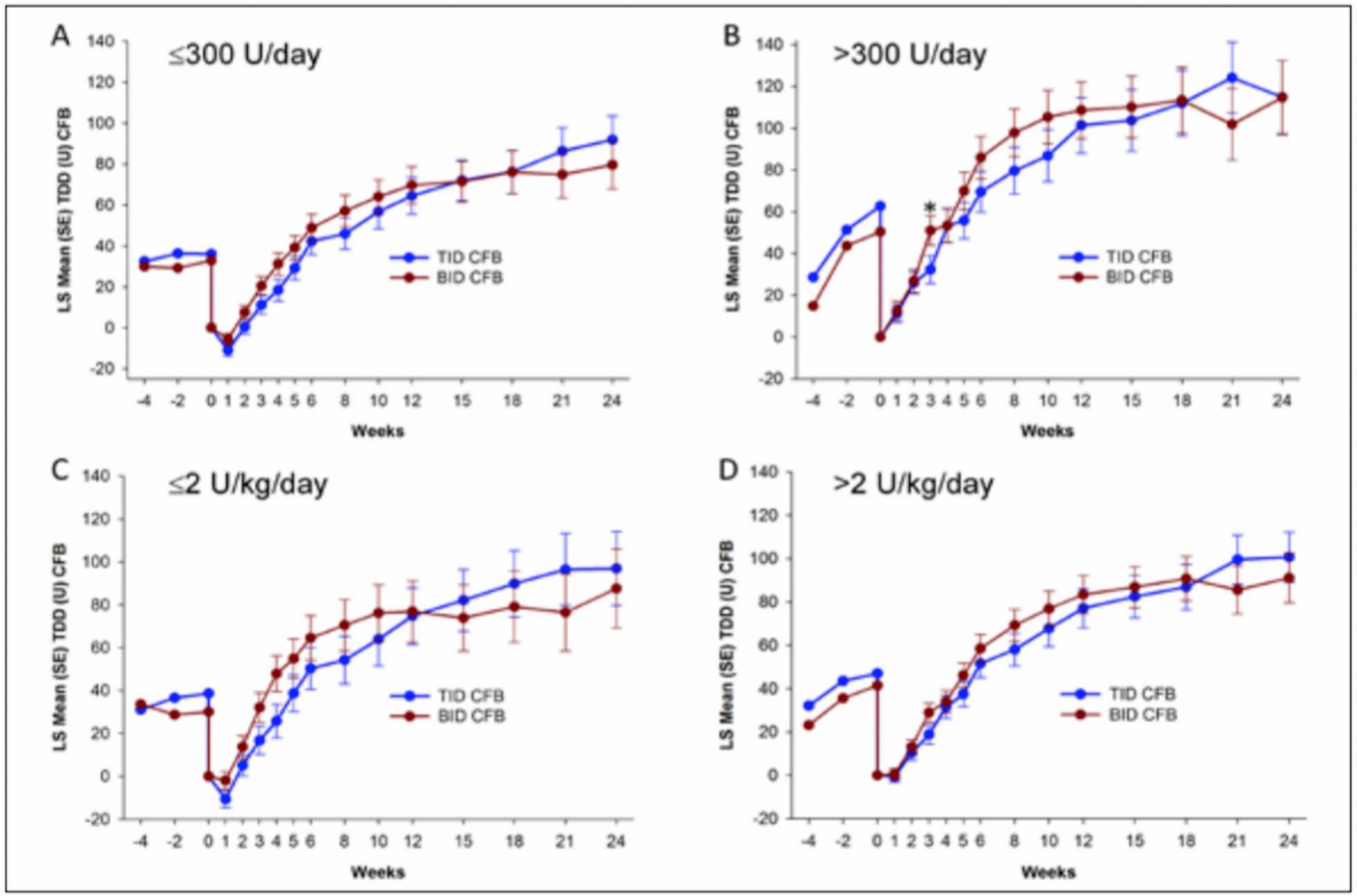
HbA_{1c} CFB for TID versus BID U-500R by TDD subgroup (baseline, final U-100 insulin TDD)



(A) ≤300 units (U), (B) >300 U, (C) ≤2 U/kg, (D) >2 U/kg. BID = twice daily; CFB = change from baseline; HbA_{1c} = glycated hemoglobin; TDD = total daily dose; TID = thrice daily.

Wysham C, Hood R, Warren M, Wang T, Morwick T, Jackson J. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular u-500 insulin in severely insulin-resistant patients with type 2 diabetes. Endocrine practice. 2016;22(6):653-665. Doi:10.4158/ep15959.Or

TDD CFB for TID versus BID U-500R by TDD subgroup (baseline, initial U-500R TDD)



(A) ≤300 units (U), (B) >300 U, (C) ≤2 U/kg, (D) >2 U/kg. *P<.05 (within-subgroup treatment effect). BID = twice daily; CFB = change from baseline; TDD = total daily dose; TID = thrice daily.

Wysham C, Hood R, Warren M, Wang T, Morwick T, Jackson J. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular u-500 insulin in severely insulin-resistant patients with type 2 diabetes. Endocrine practice. 2016;22(6):653-665. Doi:10.4158/ep15959.Or

U-500R Initiation

HbA_{1c} > 10% ➜ Increase TDD by 10%
HbA_{1c} 8-10% ➜ Maintain same TDD
HbA_{1c} < 8% ➜ Decrease TDD by 10-20%

TDD 150-300 units	Twice daily injections (60/40) Three daily injections (40/30/30, 45,35,20, 40/40/20, or 33/33/33)
TDD 300-600 units	Three daily injections (as above) Four daily injections (30, 30, 30, 10) CSII (50% as basal infusion and 50% as bolus)
TDD > 600 units	Four daily injections (25, 25,25,25 or 30, 30, 30, 10) CSII

Conclusions

- The importance of the GLP-1RA seems poised to increase in the treatment of T2D . They are emerging as a strong therapeutic class with studies showing similar efficacy to more complex insulin regimens and definite benefit in terms of weight reduction and hypoglycemia
- Cardiovascular safety has been demonstrated with both secondary and primary prevention with some agents of the class
- Differences in head to head trials need to be considered when selecting a GLP-1RA for an individual patient if feasible. However in some instance's patient access, tolerability and preference should be an important element of treatment decision
- It is not yet known if cardiovascular risk reduction is indeed a class effect as no head to head cardiovascular studies have been done
- Semaglutide now joins liraglutide for secondary prevention of cardiovascular outcomes
- Now that oral formulation of Semaglutide is available , it would be interesting to see what the future hold for these injectables

Conclusion

- The search continues for new insulin analogs with more physiologic actions and better safety profiles
- Whether these new pharma-tech developments of insulin will have a truly tangible effect on long-term maintenance of metabolic control and related outcomes will need careful assessment especially with respect to cost-effectiveness and long--term safety to efficacy ratio
- Unless a solution is soon found to reduce the already huge insulin cost , it would probably be likely that human insulin will reborn now that cgms is available allowing to identify those patients not at high risk of hypoglycemia(from my perspective)
- Insulin intensification is a challenge for many physicians

6 + 3 = 9
But so does 5 + 4.
The way you do things isn’t always the only way to do them.
Respect other people’s way of thinking .

Unknown

- “ Insulin is a remedy primarily for the wise and not for the foolish, be they patient or doctors “

- Elliot P. Joslin