Insulin vs GLP-1RA: The first injection?

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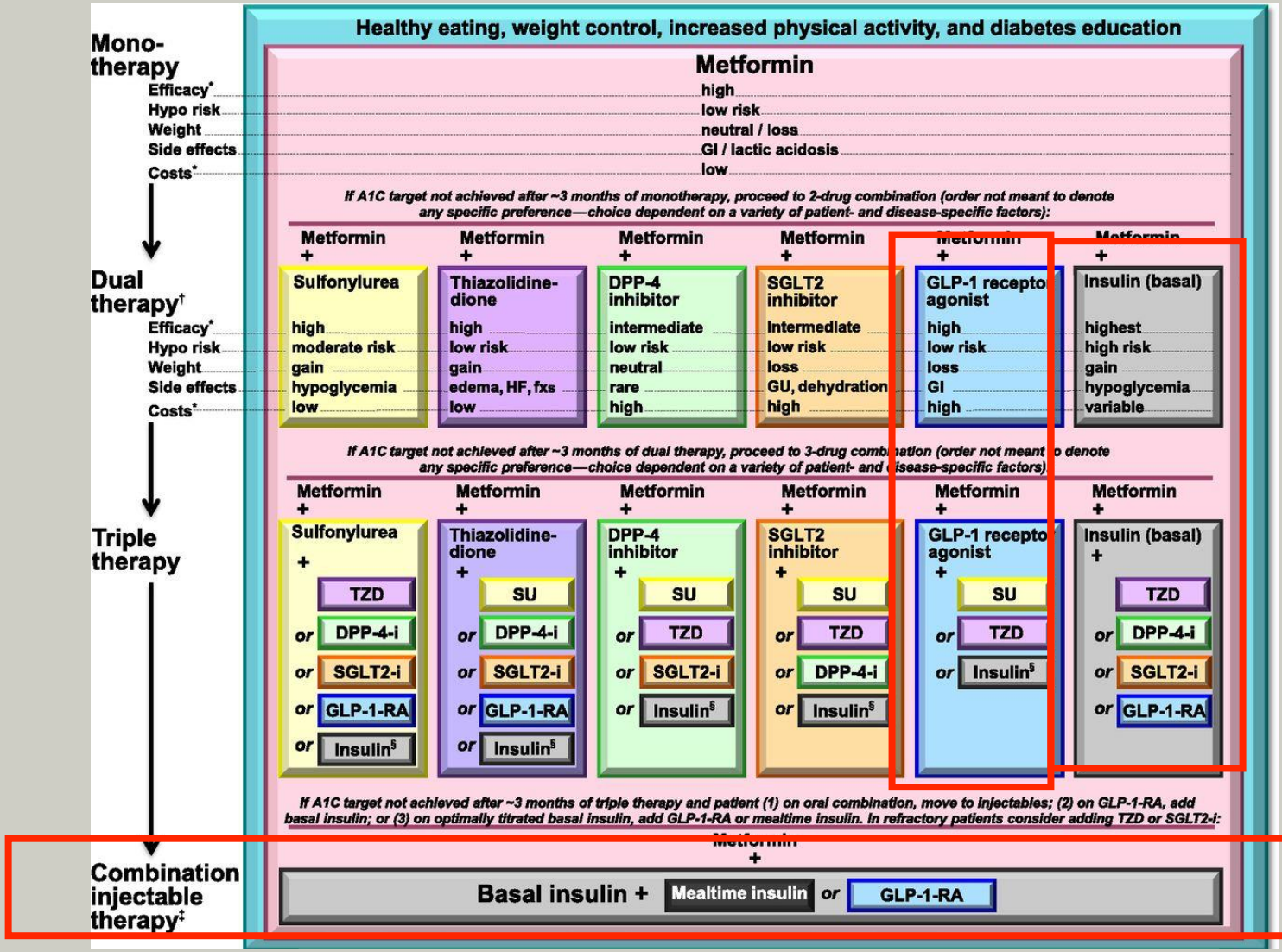
Haryana

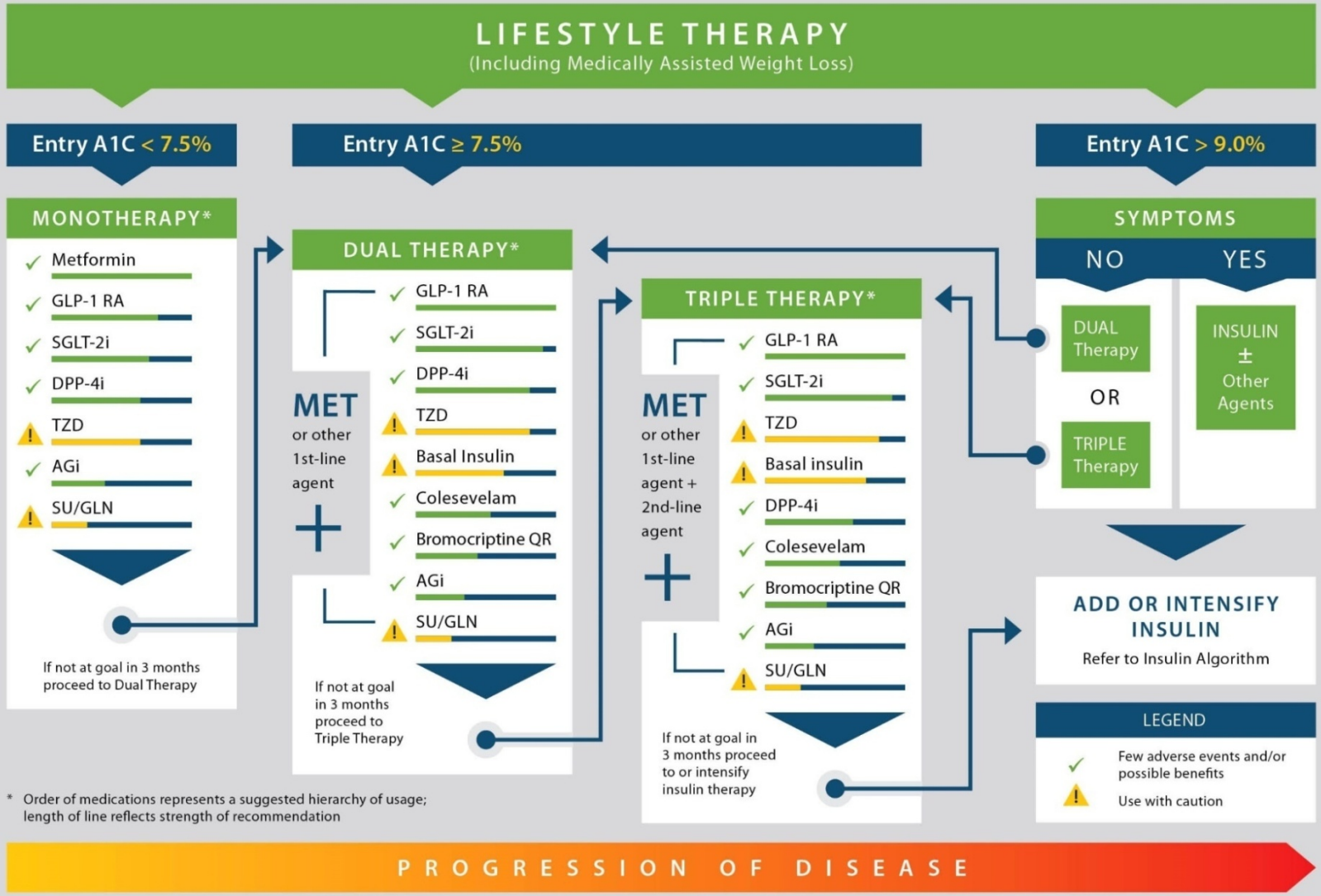
- Who should get GLP1RA?
- Who should get insulin?
- Which insulin should be started?

ADA/EASD recommendations

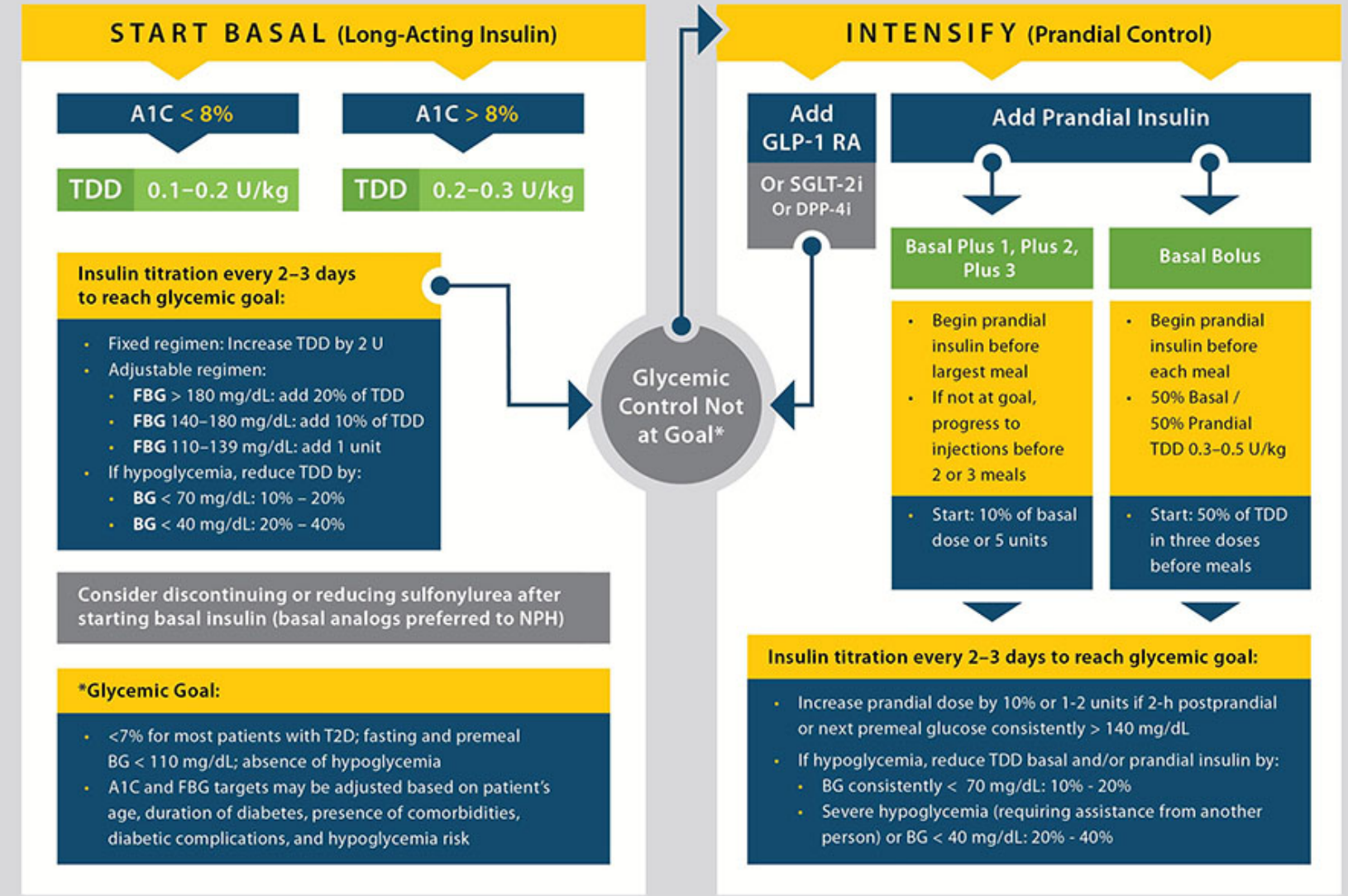


Inzucchi SE, et al.
Diabetes Care, 2015;38:140-149

GLYCEMIC CONTROL ALGORITHM



ALGORITHM FOR ADDING/INTENSIFYING INSULIN



Person centred flexibility

“DO NOT

match lifestyle to the insulin regimens.

RATHER,

match the regimen to the lifestyle”

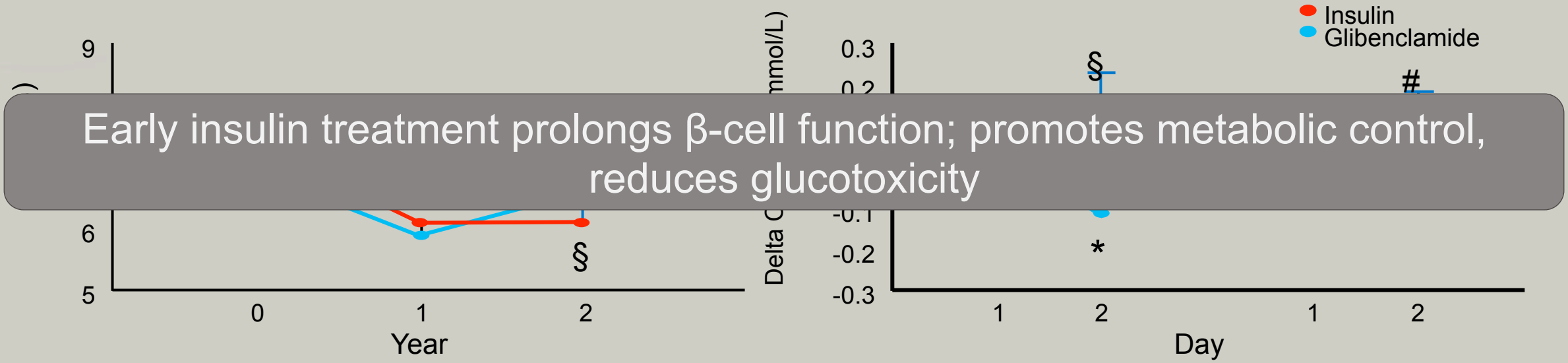
Kalra S, Gupta Y, Unnikrishnan AG. Flexibility in insulin prescription. Indian J Endocr Metab 2016;20:408-11

Insulin

Insulin advantages

- Targeted focus on FPG and/or PPG
- Dose titration addresses glycemic/diet variability
- Does not require preserved beta cell function

Early insulin treatment prolongs β-cell function; promotes metabolic control



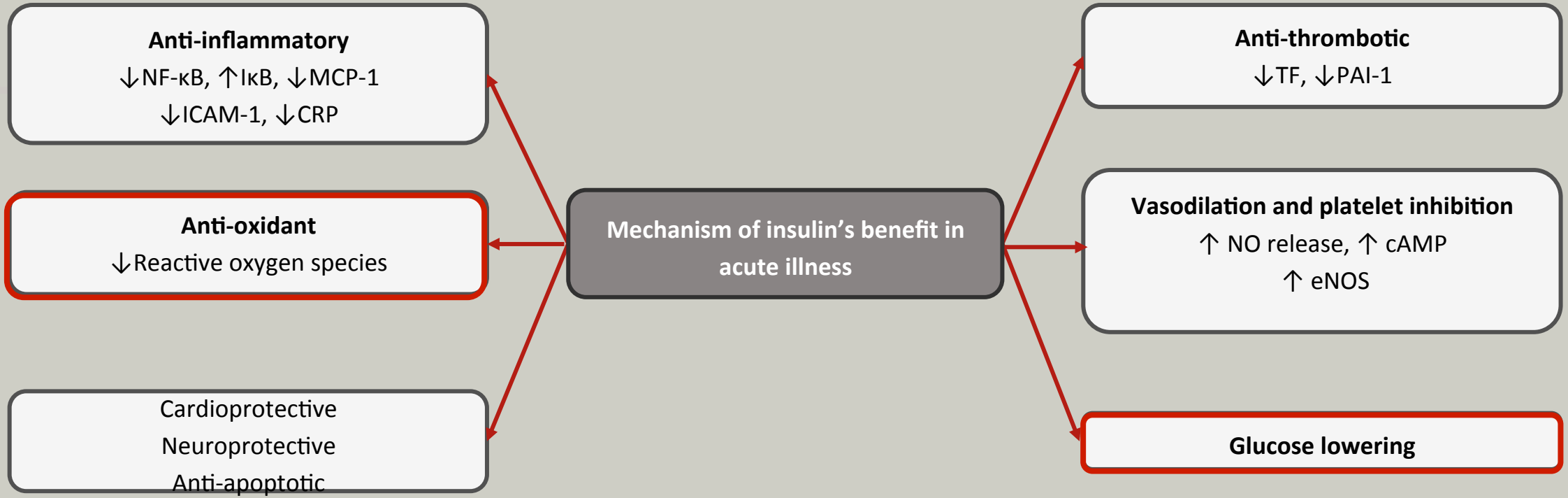
*P< 0.01 year 0 vs. 1,
§ P< 0.005 year 0 vs. 2,
#P< 0.01 year 1 vs. 2

*P= 0.02 glibenclamide vs. insulin
§P< 0.05 year 1 day 1 vs. 2
P< 0.01 year 1 day 1 vs. year 2 day 2

Early insulin treatment prolongs β-cell function; promotes metabolic control, reduces glucotoxicity

Alvarsson M et al. Diabetes Care. 2003 Aug;26(8):2231-7

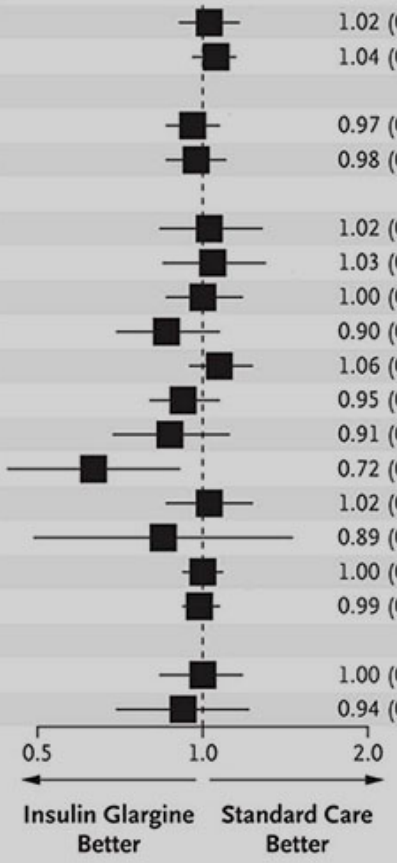
Insulin also has extra-glycaemic benefits



Dandona *et al. Am J Cardiol* 2007;99(4A):15B–26B

Long-term safety of insulin therapy is established

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



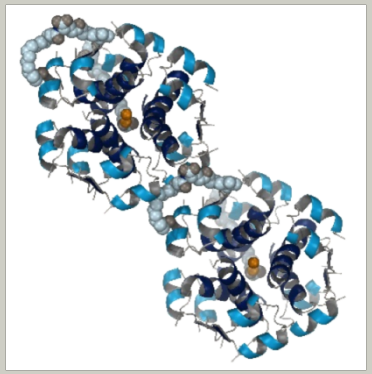
The ORIGIN Trial Investigators. N Engl J Med 2012;367:319-328

Use in special situations

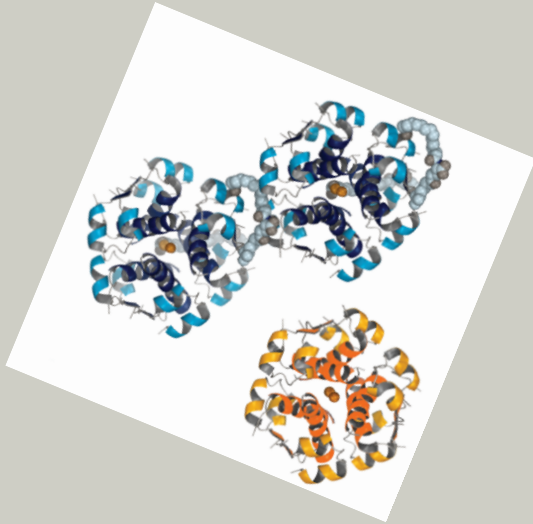
- Insulin preferred in emergency and diabetic ketoacidosis
- Insulin preferred in renal impairment
- Insulin preferred in hepatic impairment
- Insulin Drug of choice for pregnancy

Hypoglycaemia???

- With the introduction of newer basal insulin analogues the risk of hypoglycaemia is minimal.



Insulin degludec



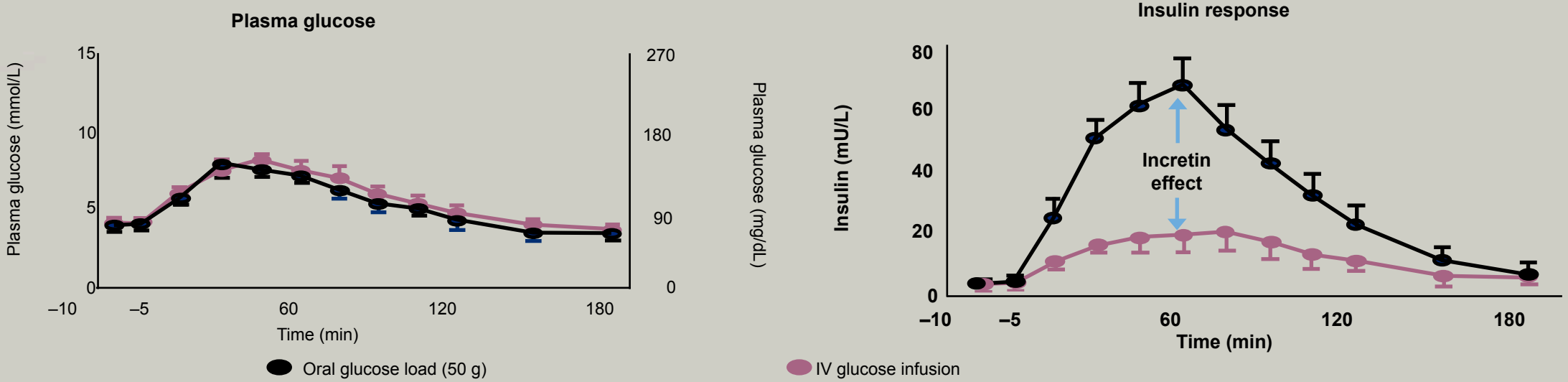
IDegAsp

Evolution of understanding

- From beta cell centric to multiple pathways
- From ominous octet to egregious eleven

GLP1 RA

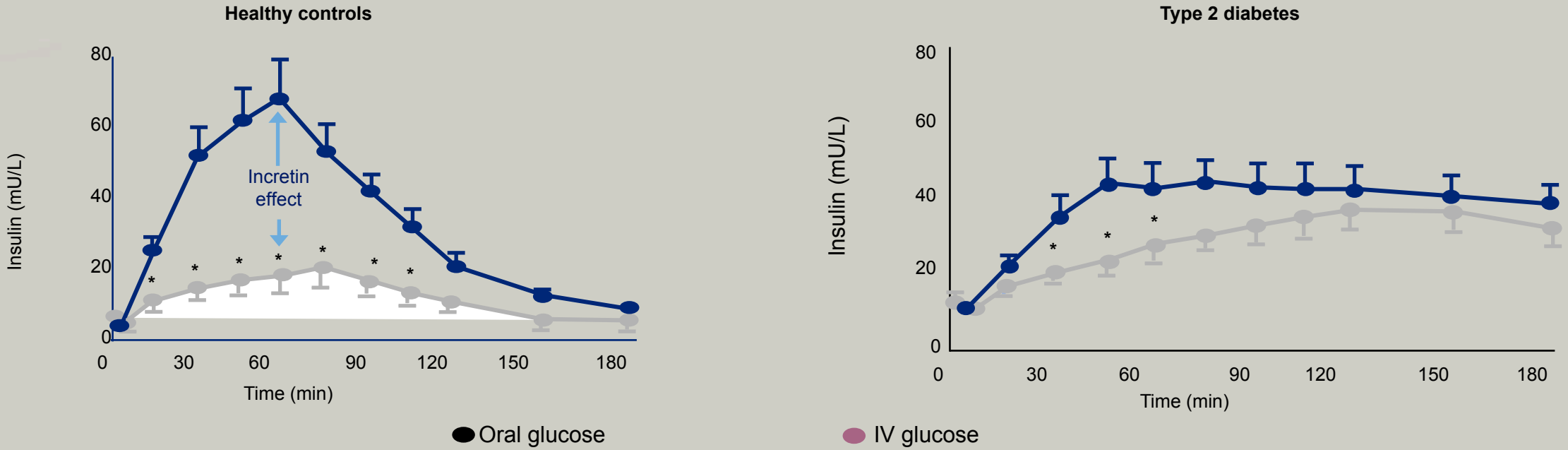
The incretin hormones play a crucial role in a healthy insulin response



- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

Nauck *et al. Diabetologia* 1986;29:46–52, healthy volunteers (n=8)

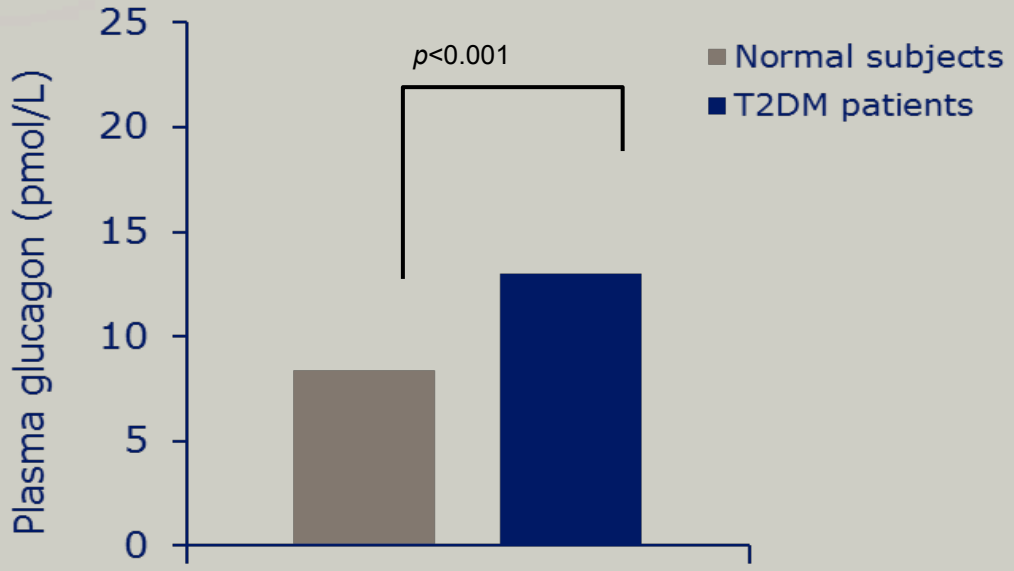
The incretin effect is diminished in patients with type 2 diabetes



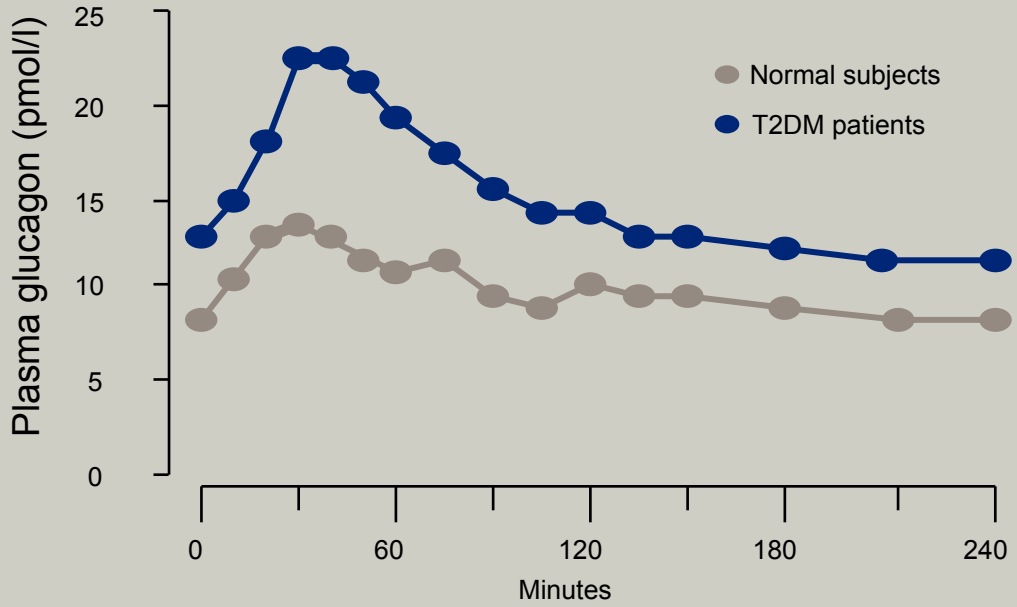
- *p<0.05, healthy volunteers (n=8)
- Nauck M et al. Diabetologia 1986;29:46–52

Glucagon levels are elevated in patients with type 2 diabetes

Fasting glucagon



Postprandial glucagon



n: T2DM patients=54; Normal subjects=33

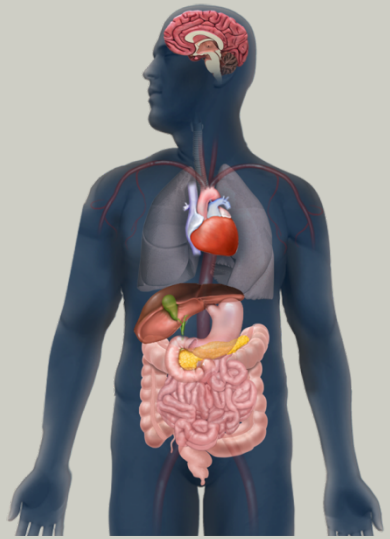
T2DM, type 2 diabetes mellitus

Toft-Nielson MB et al. *J Clin Endocrinol Metab* 2001;86:3717–3723

Effects of GLP-1

Pancreas

- ▲ Insulin secretion[2,3] (glucose-dependent) and beta-cell sensitivity
- ▲ Insulin synthesis[4]
- ▼ Glucagon secretion[3] (glucose-dependent)



Brain

- ▼ Body weight:[5–7]
- ▲ Satiety
- ▼ Energy intake

- ▼ **Cardiovascular system**
  Systolic blood pressure[8]

Liver

- ▼ Hepatic glucose output[4]

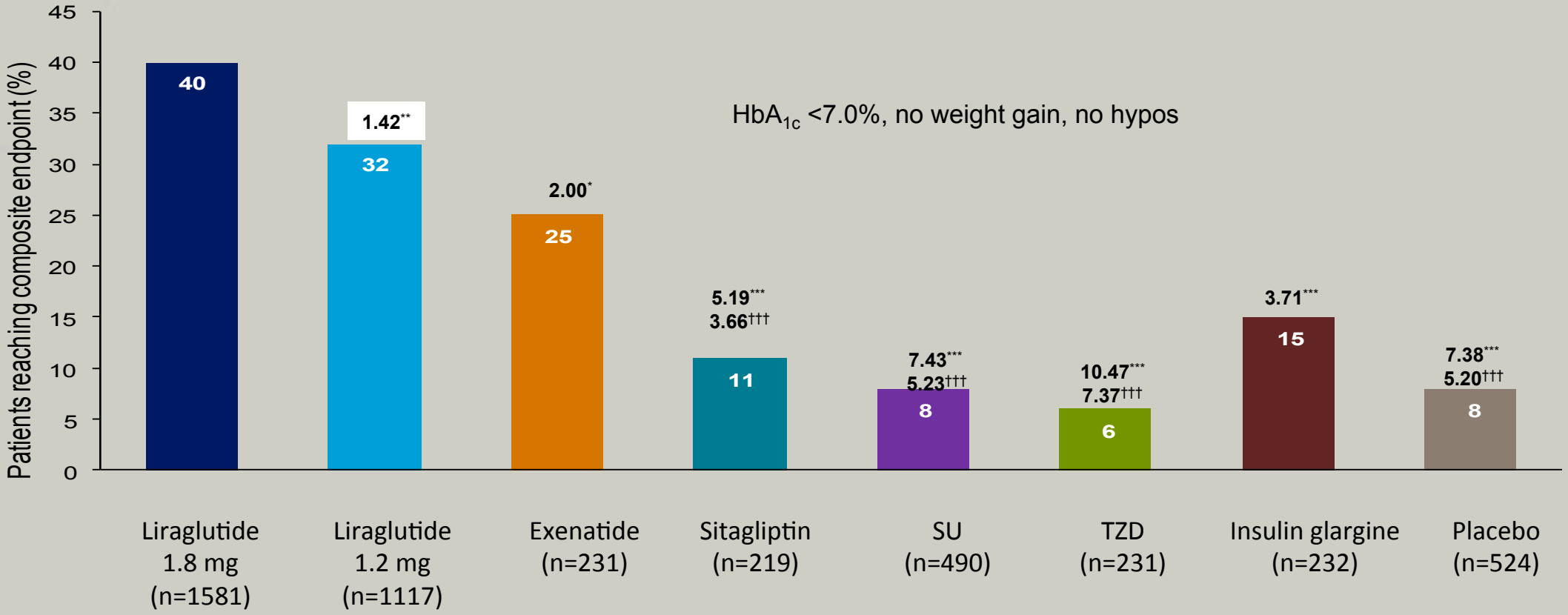
The GLP1RA action spectrum

Appetite, Absorption

Utilization- insulin and incretin vs glucagon fulcrum

Body weight, lipid and blood pressure control

Incretins helps in achieving target without hypo and weight gain

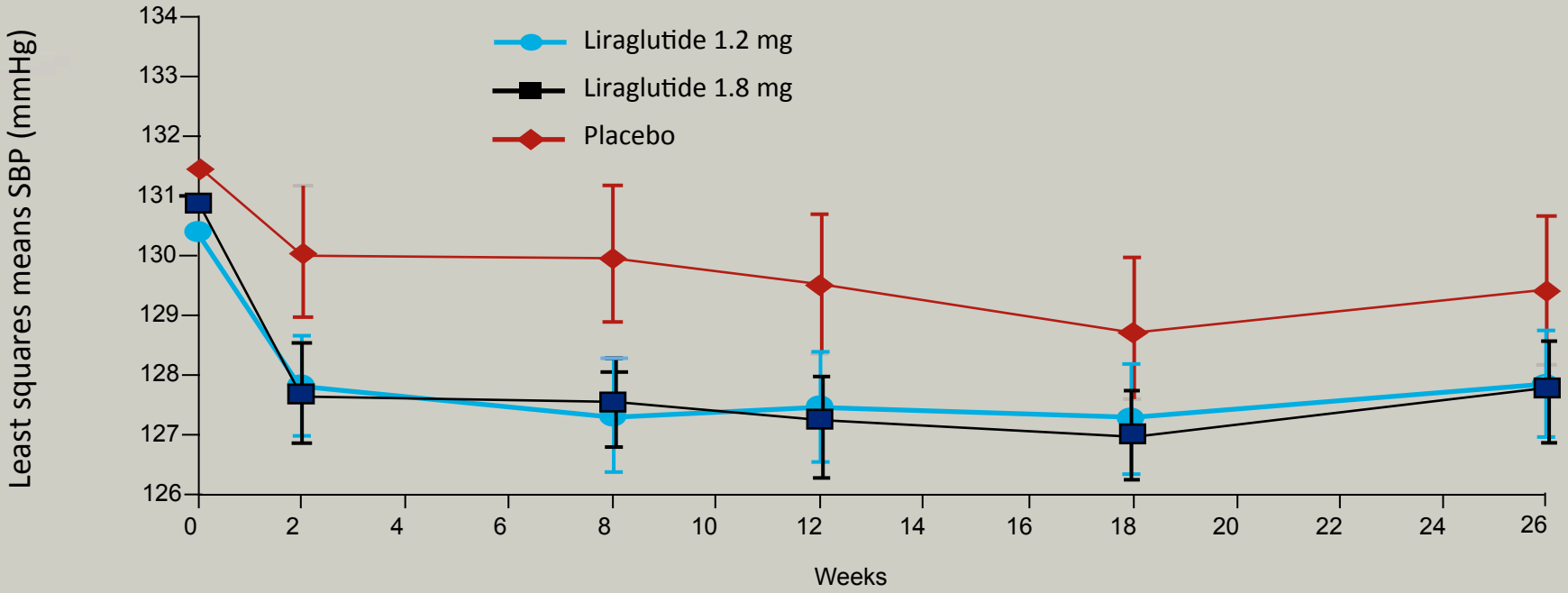


Odds-ratio of achieving composite endpoint with liraglutide 1.8 mg is superior, with *p<0.01; **p<0.001, ***p<0.0001

Odds-ratio of achieving composite endpoint with liraglutide 1.2 mg is superior, with †††p<0.0001

Zinman B et al. Diabetes Obes Metab 2012;14:77–82.

GLP-1RA – Beyond Glycaemic Control
Reduced systolic blood pressure

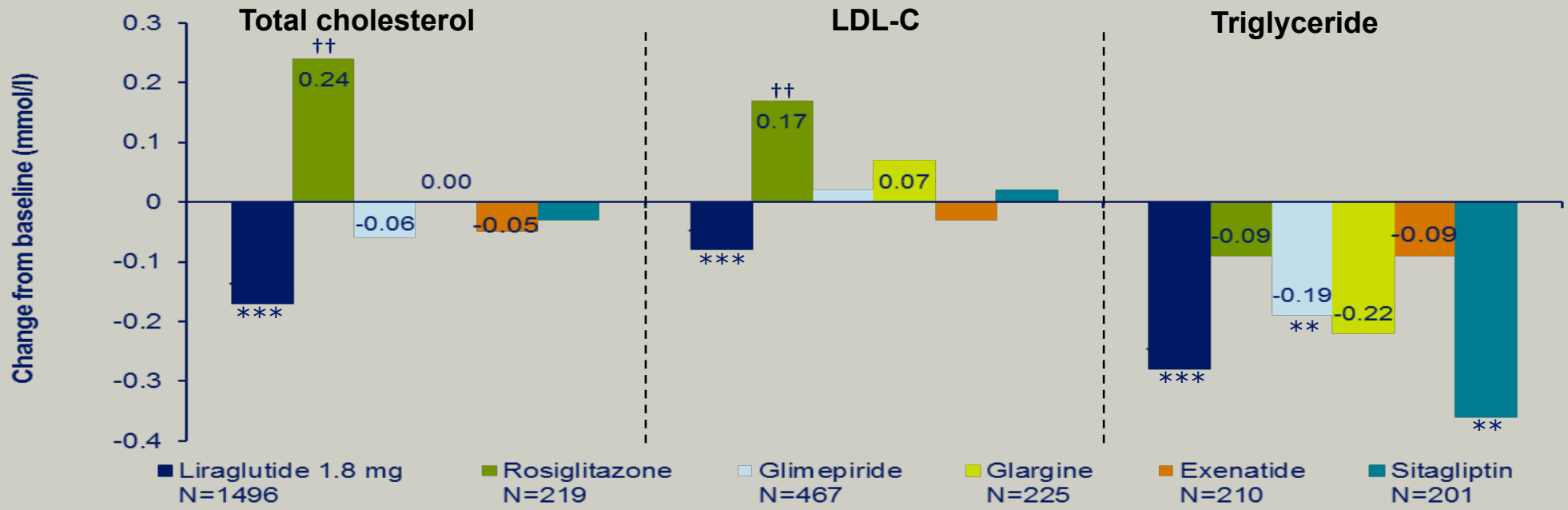


Data are last observation carried forward for the ITT population and expressed as least squares ± confidence intervals

Mean SBP reductions after 26 weeks were 2.7 [0.8] mmHg with liraglutide 1.2 mg, 2.9 [0.7 mmHg] with liraglutide 1.8 mg and 0.5 [0.9] mmHg with placebo

- SBP, systolic blood pressure; ITT, intent-to-treat
- Adapted from Fonseca VA et al. *J Diabetes Complications* 2014;28:399–405

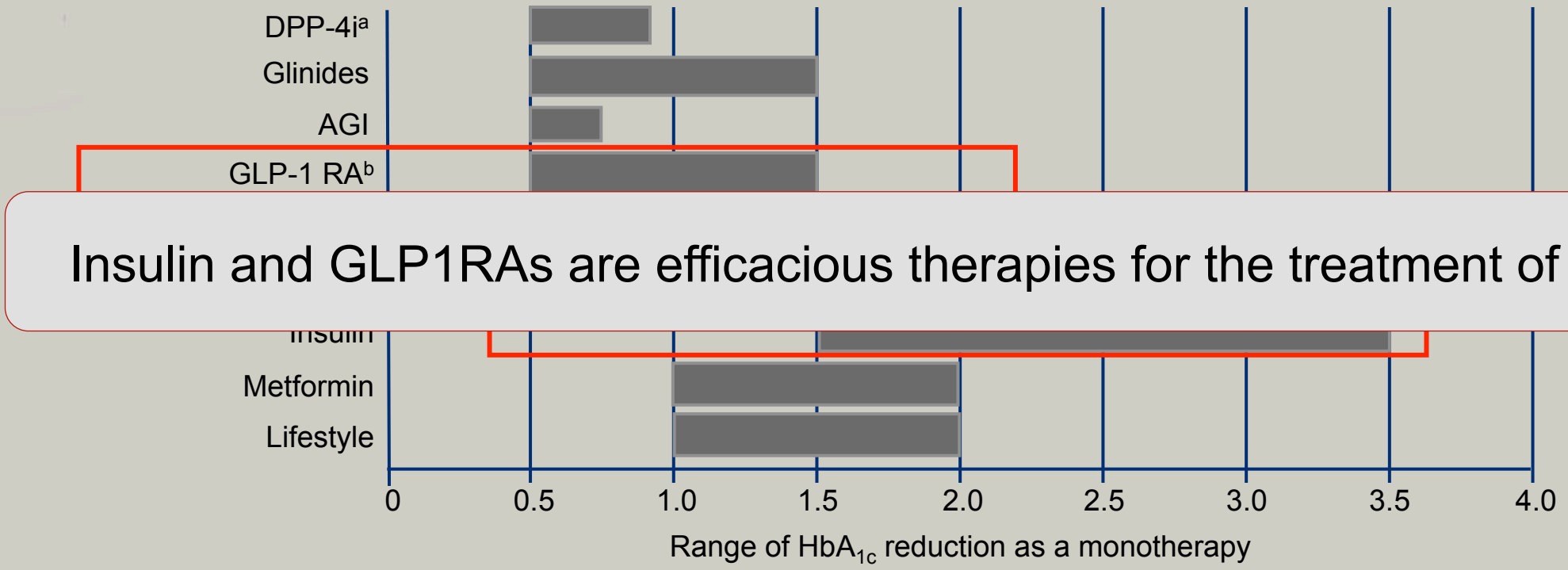
GLP-1RA – Beyond Glycaemic Control
Effect on fasting lipid levels



- LEAD 1–6: meta-analysis
- *p<0.05; **p<0.01; ***p<0.0001; all vs baseline; † is used instead of * to indicate a significant increase from baseline
- LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes
- Fonseca VA et al. International Diabetes Federation 21st World Diabetes Congress, 4–8 December 2011, Dubai, UAE

Head-to-head studies of
Incretin vs Insulin based therapy

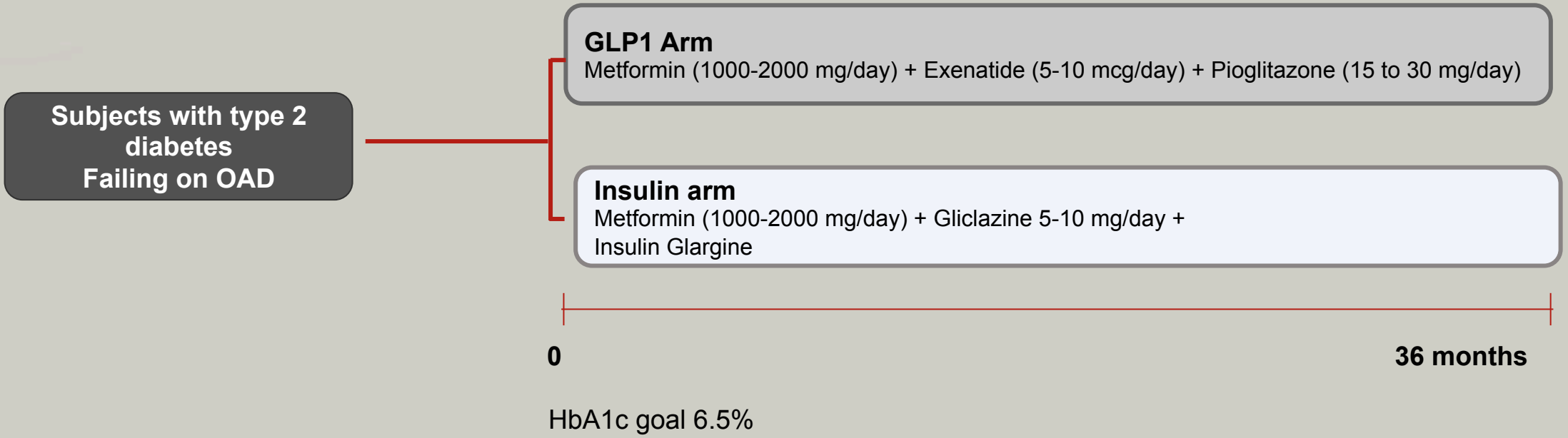
Type 2 diabetes treatment efficacy: both insulin and GLP1 RAs are very effective



Insulin and GLP1RAs are efficacious therapies for the treatment of Type 2 DM

[a] adapted to include sitagliptin and saxagliptin [b]adapted to include exenatide and liraglutide
Campbell *et al. Journal of family practice* September 2010;59:S5-S9

Pathophysiology based algorithm for type 2 Diabetes



EASD 2015 DEFRONZO ET AL

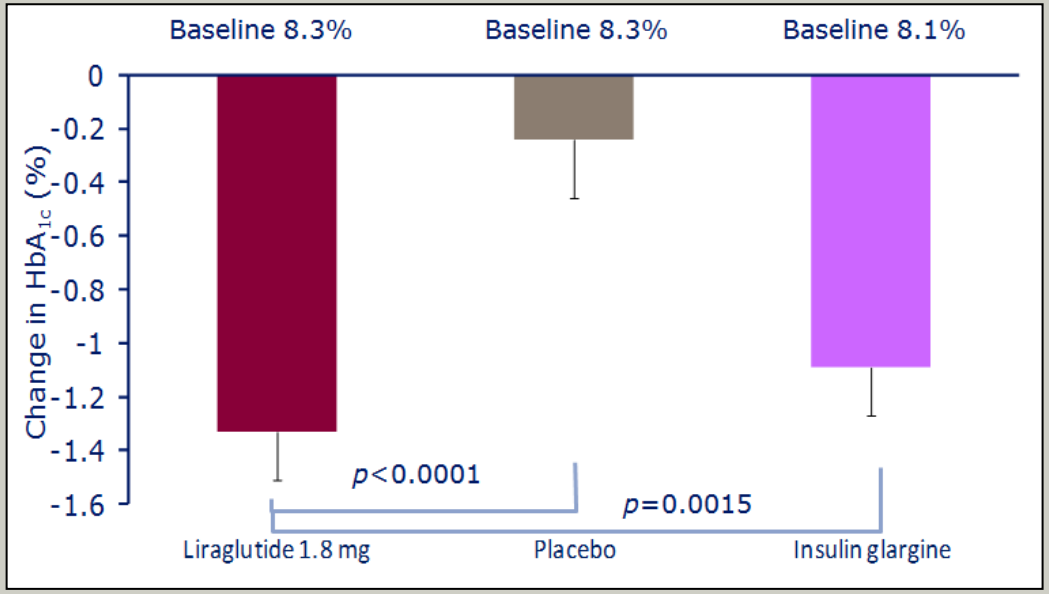
Results Insulin based vs Incretin based therapy

	Insulin based regimen	Incretin based regimen	Insulin based vs incretin based
Primary end point HBA1c at the end of 36 weeks	6.71	5.80	P<0.0001
Weight	+3.7 Kg	-3.1 Kg	P<0.0001
Matsuda index for insulin sensitivity	No change from baseline	Statistically significant improvement in insulin sensitivity	P<0.0001
Hypoglycaemia	46% 2.1 PYE	15% 0.27 PYE	P<0.0001

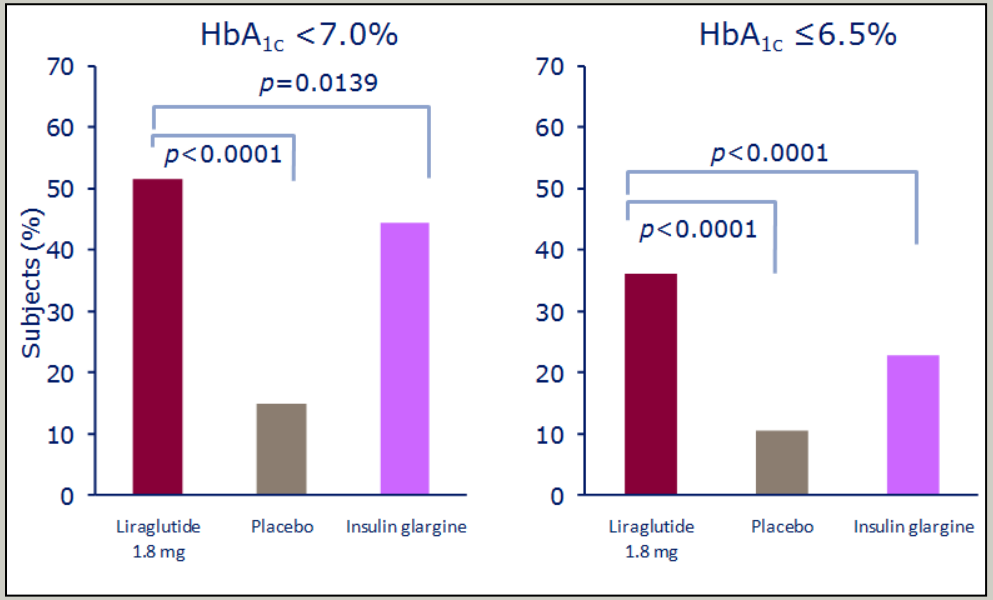
EASD 2015 DEFRONZO ET AL

LEAD 5: Liraglutide vs Glargine

HbA1c change from baseline



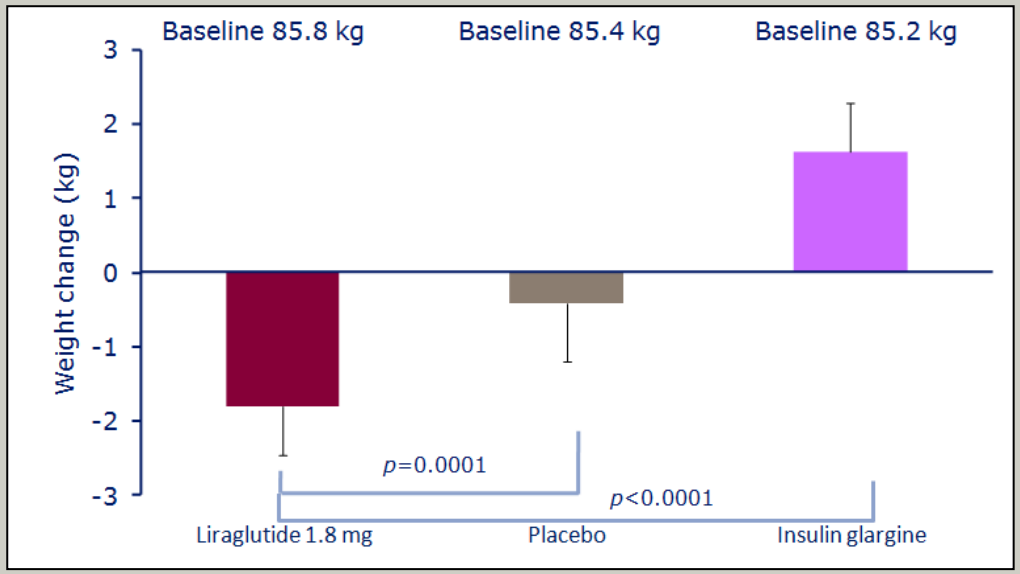
Subjects achieving HbA1c targets



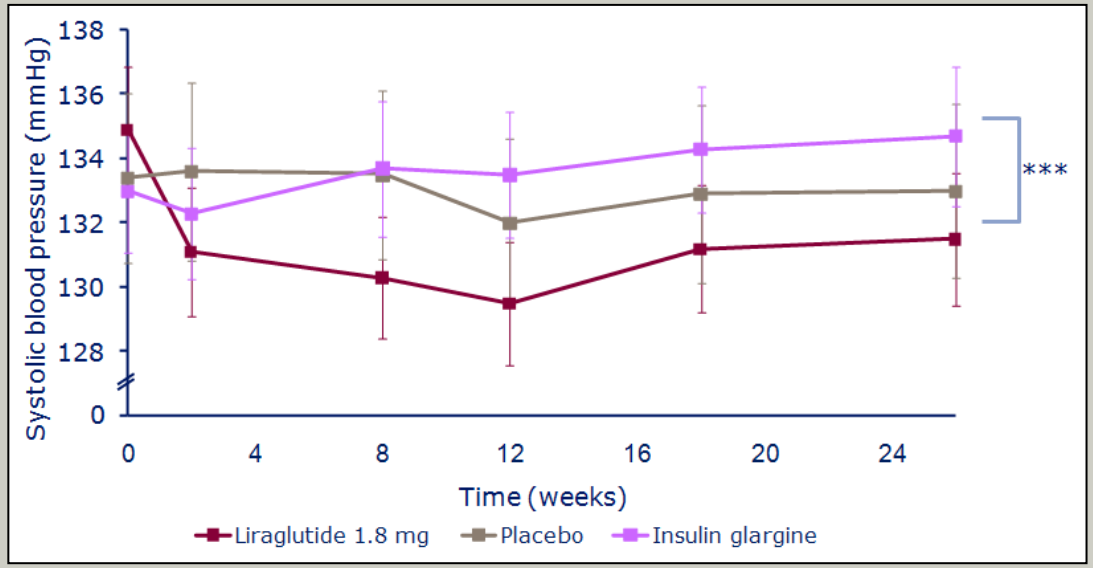
Russell-Jones *et al. Diabetes* 2008;57(Suppl. 1):A159 (LEAD-5)

LEAD 5: Liraglutide vs Glargine

Body weight change from baseline

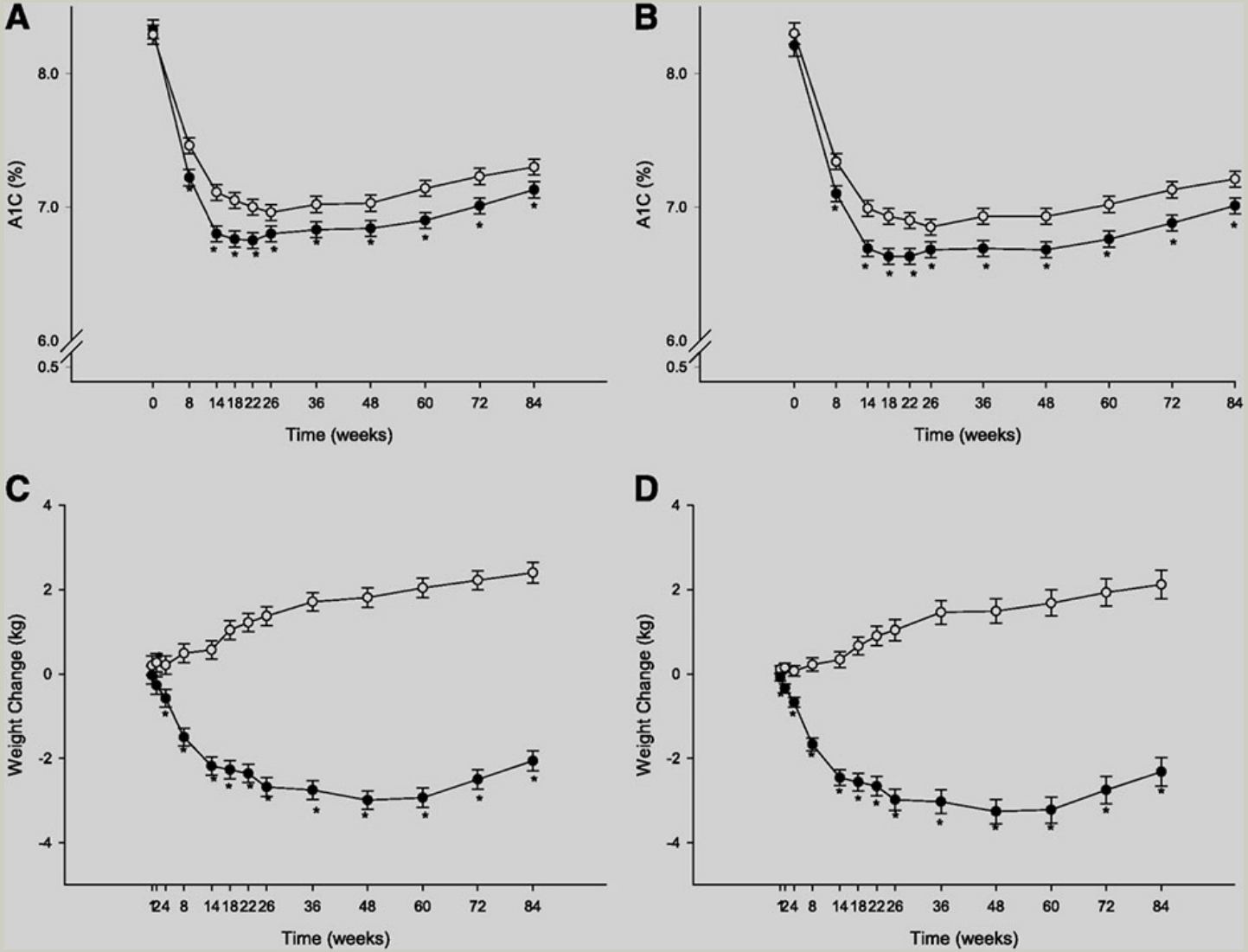


SBP change over 26 weeks

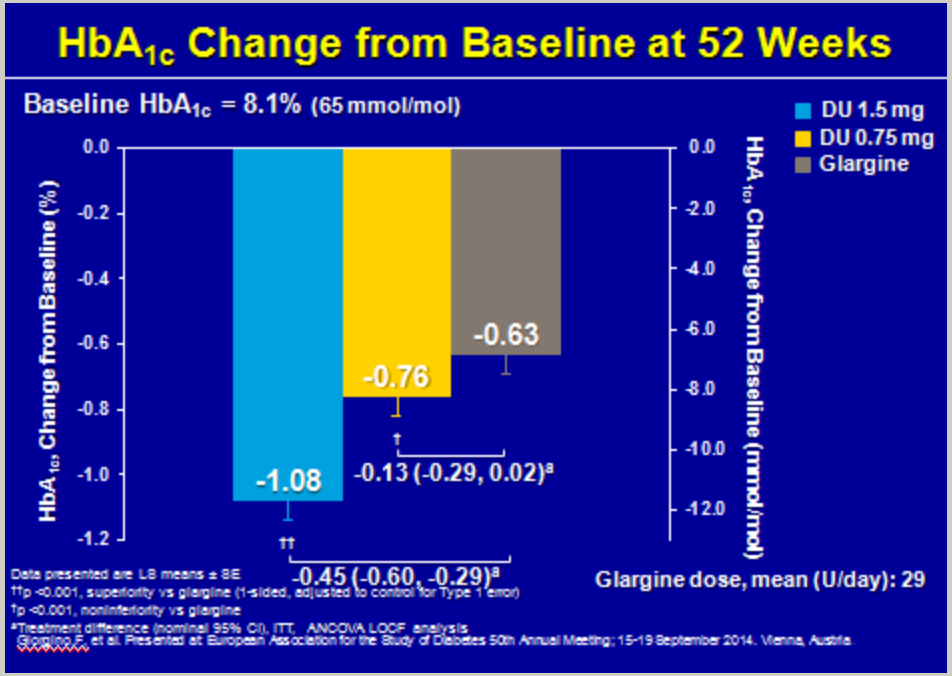


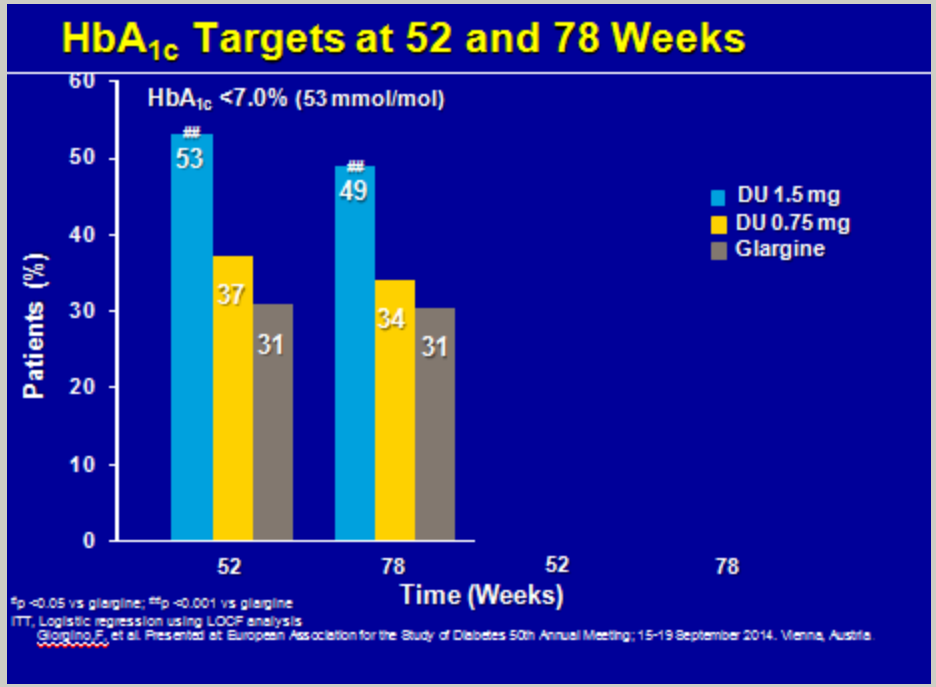
Russell-Jones *et al. Diabetes* 2008;57(Suppl. 1):A159 (LEAD-5)

Exenatide QW vs Glargine

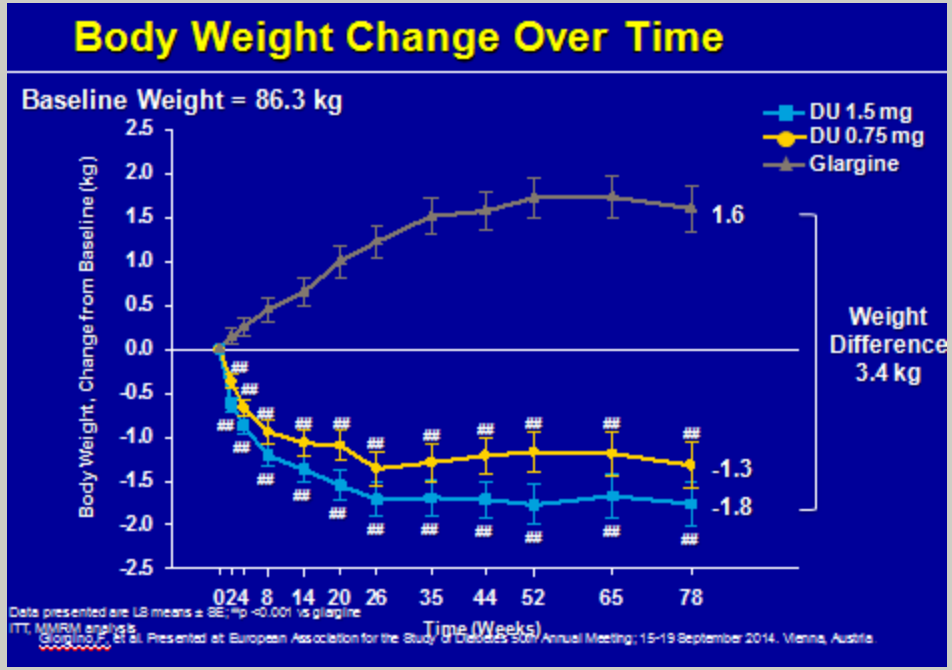


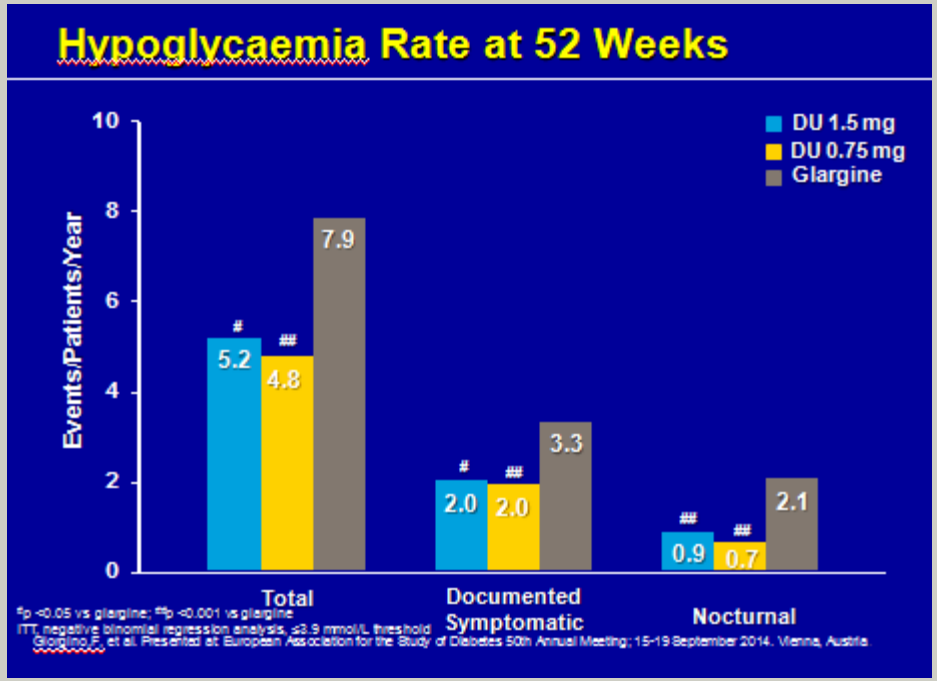
AWARD 2: Dulaglutide vs Glargine





AWARD 2: Dulaglutide vs Glargine





The evidence

- Efficacy – Insulin and GLP1RA equal
- Weight loss with GLP1RA
- Less hypoglycaemia with GLP1RA

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated CKD Stage 3B,4,5	Exenatide Not Indicated CrCl < 30	Not Effective with eGFR < 45 / Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
ASCVD	Benefit		Possible Benefit			Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

McNamara fallacy

Making a decision based solely on quantitative observations and ignoring all others.

1. Measure whatever can be easily measured.
2. Disregard that which can't be easily measured, or give it an arbitrary quantitative value.
3. What can't be measured easily really isn't important.
4. What can't be easily measured really doesn't exist.

The therapeutic pentad

Pragmatic approach

BIOmedical

PSYCHO

SOCIAL model

Biomedical factors: history

Duration of diabetes/poor control

Symptoms and severity

Glycemic variability/brittleness

Biomedical factors: examination

Anthropometry: weight

Vital signs: Resting heart rate

Risk of hypoglycemia

Biomedical factors: comorbidity

Dyslipidemia

Infections/surgical illness

Gallstones/pancreatitis/MTC

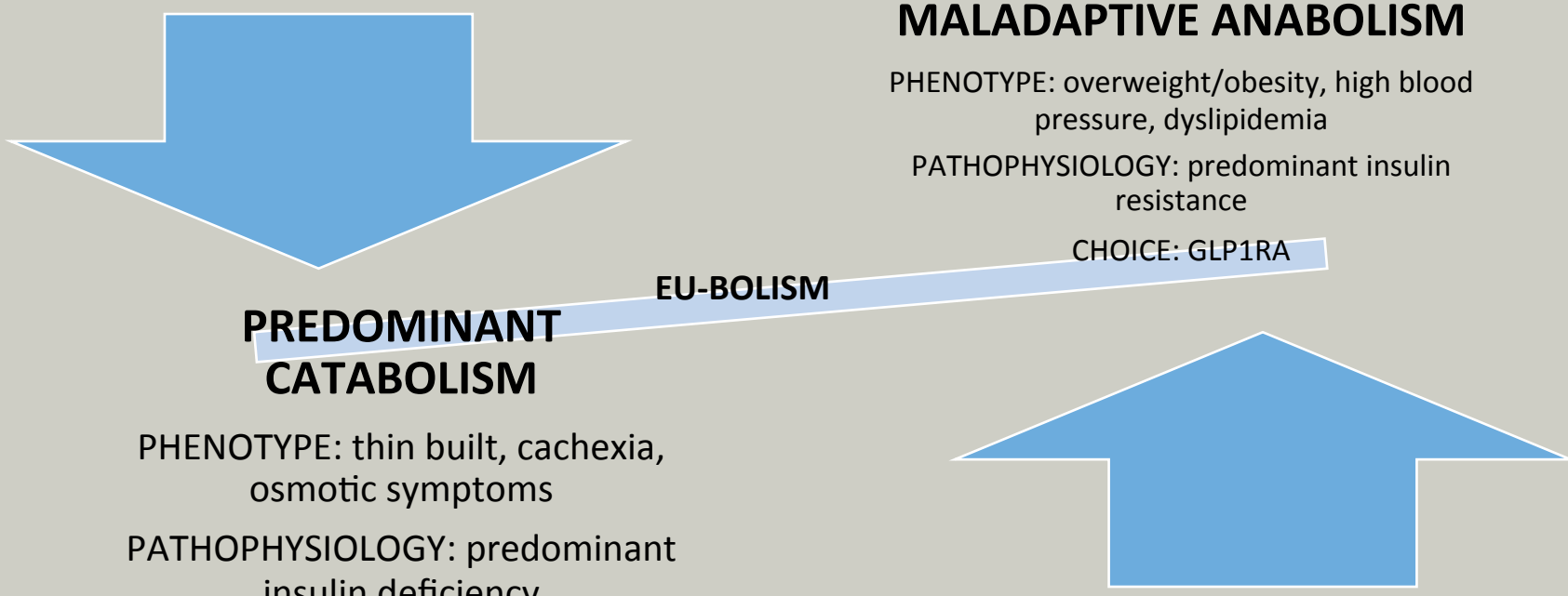
Psychosocial factors

Concern about weight

Ability to SMBG

Diet pattern

Metabolic fulcrum, and metabolic triage



Kalra S, Gupta Y. **Choice of Glucose-lowering Therapy— A Metabolic Fulcrum-based Approach**. **US Endocrinology, 2015**;11(2):79–80

Take home

INSULIN for

- Symptomatic patients
- Catabolic/asthenic state
- Comorbid significant infection/severe renal impairment

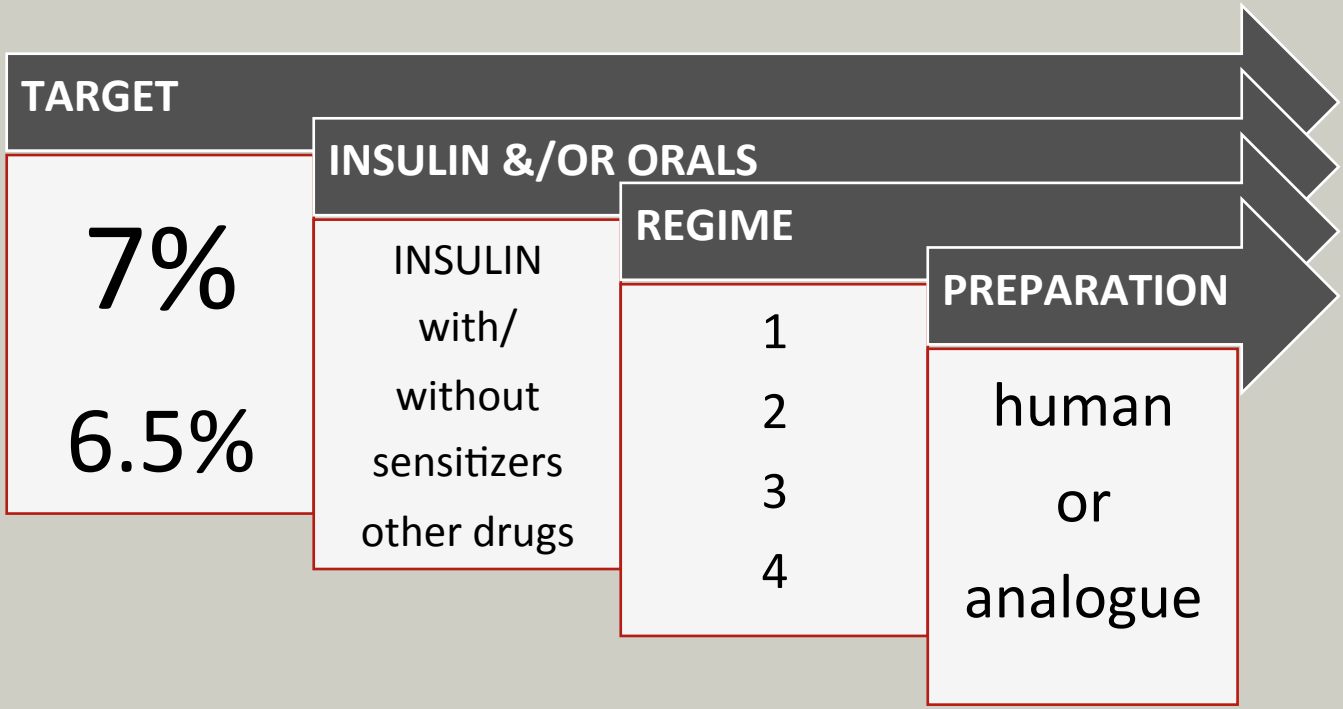
GLP1RA for

- Asymptomatic patients
- Obese/overweight state
- Cardiovascular comorbidity

Targets and strategies

- Define a target
- Plan a strategy
- Pick your tools

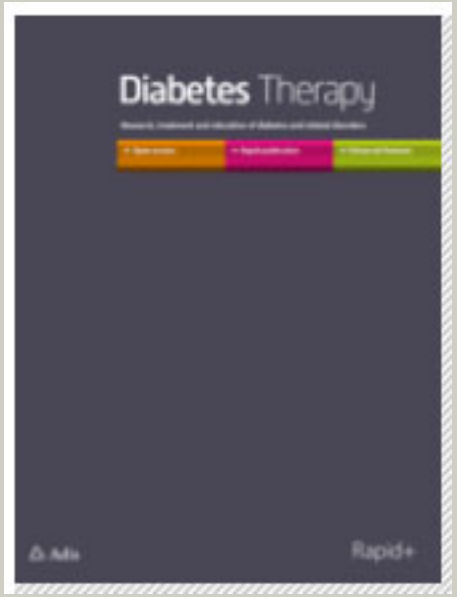
Targets and strategies



Types of regimes

basal	• Usually once daily • May be twice daily
premixed	• Usually twice daily • May be once or thrice daily
intensive	• Thrice daily or more often • Usually four doses [basal bolus]

Number based classification



Review
Diabetes Therapy
pp 1-11

First online: 09 September 2015

Number-Based Approach to Insulin Taxonomy

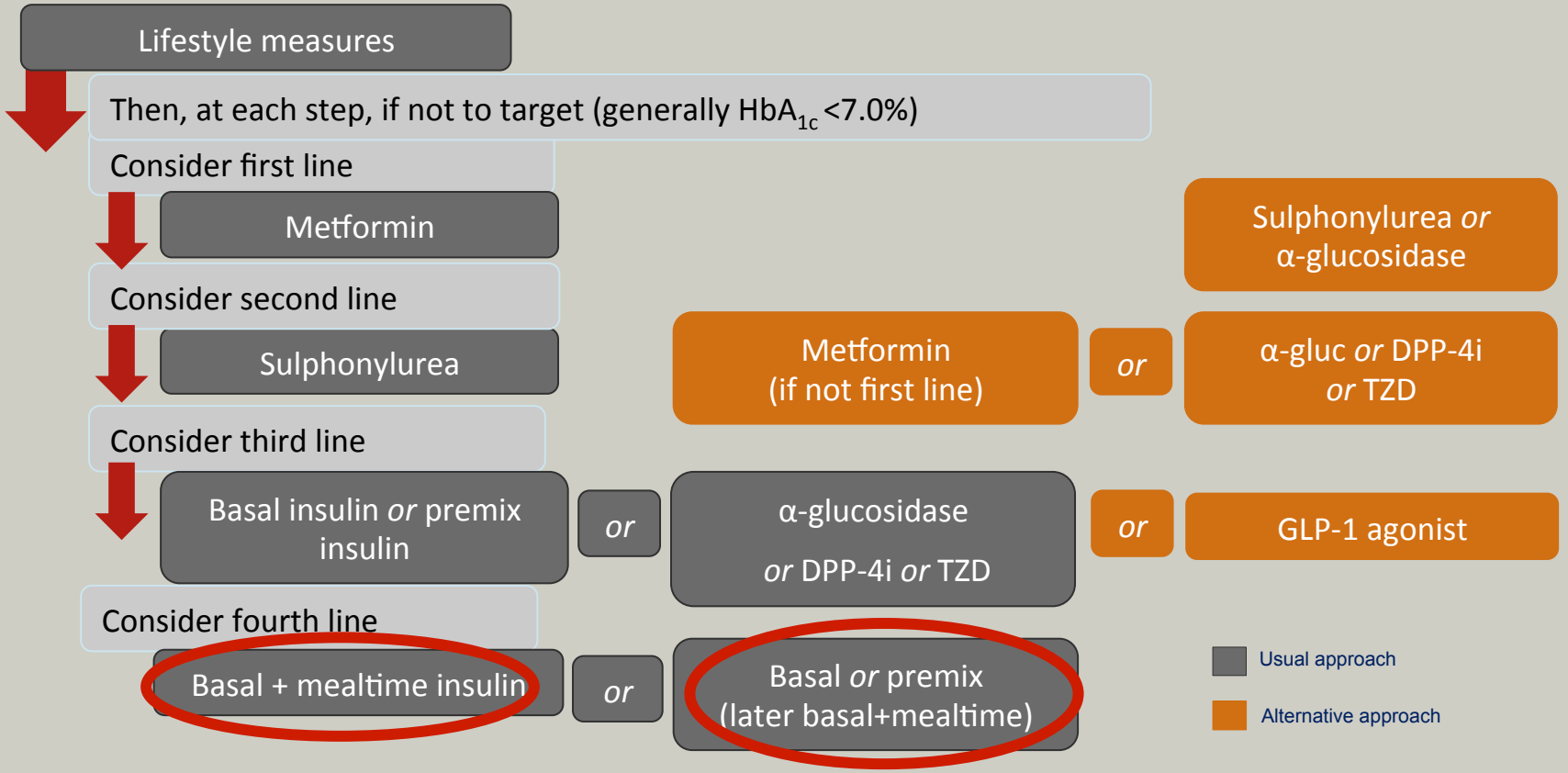
Sanjay Kalra , Yashdeep Gupta

10.1007/s13300-015-0129-8

Types of regimes

1	• Basal • Premixed
2	• Premixed • Basal • Basal plus
3+	• Basal bolus • Basal plus • Rapid –rapid- premixed

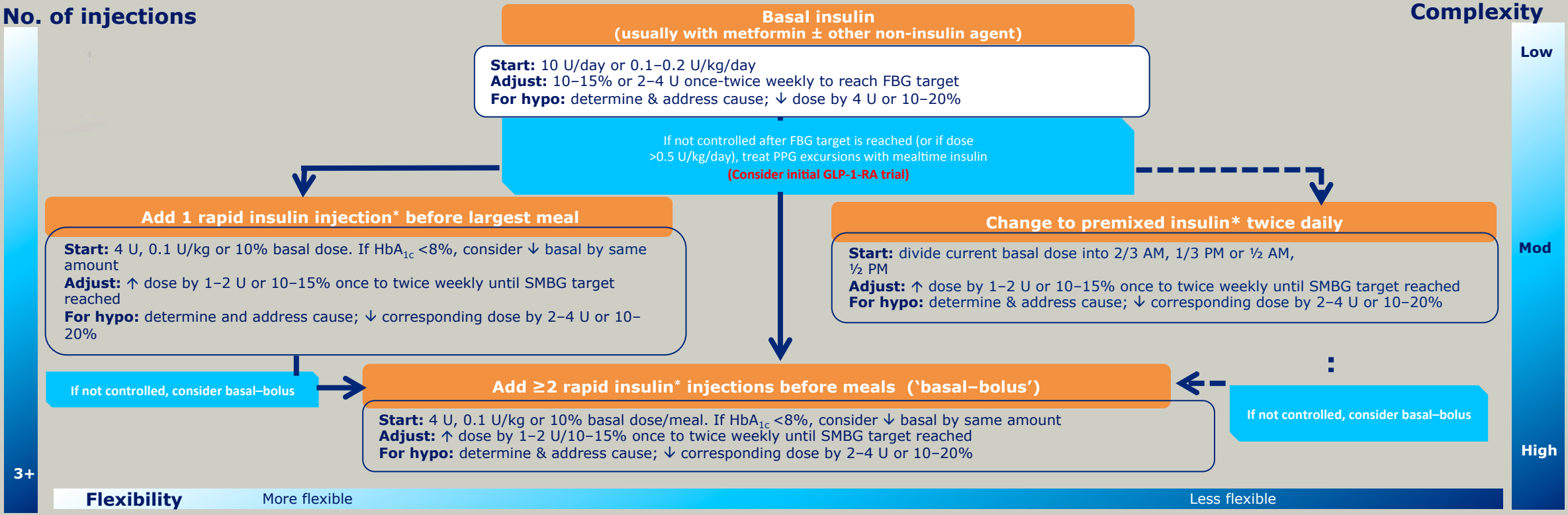
Treatment of type 2 diabetes: IDF guidelines



DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; IDF, International Diabetes Federation; TZD, thiazolidinedione

IDF Global Guideline for Type 2 Diabetes. www.idf.org/global-guideline-type-2-diabetes-2012

Initiation and intensification: ADA/EASD



*Regular human insulin and human NPH-regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogues and premixed insulin analogues, but their pharmacodynamic profiles make them suboptimal for the coverage of postprandial glucose excursions

FBG, fasting blood glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; PPG, postprandial plasma glucose; SMBG, self-monitored blood glucose

Inzucchi *et al. Diabetes Care* 2015;38:140–9

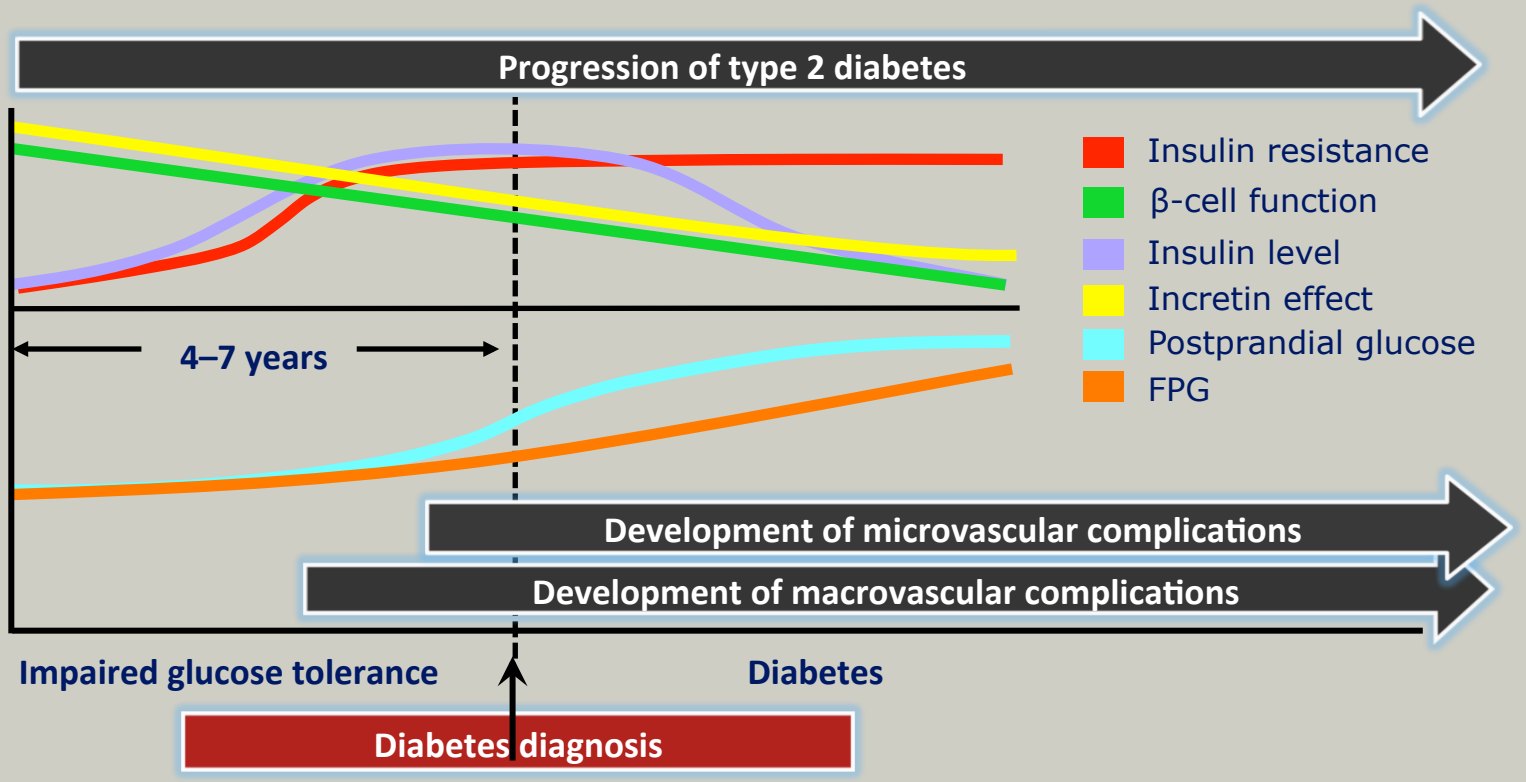
Initiation and intensification in T2D: summary of international guidelines

Guideline	Initiation	Intensification
ADA/EASD 2015 position statement update[1]	• Basal	• Add GLP-1RA • Basal-plus then basal-bolus • Premix BID then basal-bolus
IDF[2]	• Basal OD • Premix OD/BID	• Basal-plus or basal-bolus
Diabetes Australia[3]	• Basal OD • Premix OD	• Basal-plus or basal-bolus • Premix BID or TID
Canadian Diabetes Association[4]	• Basal OD • Premix OD/BID	• Basal-plus or basal-bolus • Premix BID
NICE[5]	• Basal insulin OD or BID • Basal insulin + prandial • Premixed insulin	• Basal-plus • Basal-bolus or premix • Add GLP-1RA or SGLT-2i
AACE[6]	• Basal	• Add GLP-1RA or prandial insulin • (premix among other options)

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BID, twice daily; EASD, European Association for the Study of Diabetes; GLP-1RA, glucagon-like peptide 1 receptor agonist; IDF, International Diabetes Federation; NICE, UK National Institute for Health and Care Excellence; OD, once daily; SGLT-2i, sodium-glucose cotransporter 2 inhibitor;
TID, three times daily; T2D, type 2 diabetes

1. Inzucchi *et al*. *Diabetes Care* 2015;38:140–9; 2. IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes, 2012. www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf; 3. General practice management of type 2 diabetes, 2014–15. Melbourne: The Royal Australian College of General Practitioners and Diabetes Australia. 2014. https://www.diabetesaustralia.com.au/best-practice-guidelines; 4. Harper *et al*. *Can J Diabetes* 2013;37(Suppl. 1):S61–8 (Appendix 3); 5. NICE. Type 2 diabetes in adults: management. NICE Clinical Guideline 28 (2 December 2015) https://www.nice.org.uk/guidance/ng28 [accessed December 2015]; 6. Garber *et al*. *Endocr Pract* 2015;21:438–47

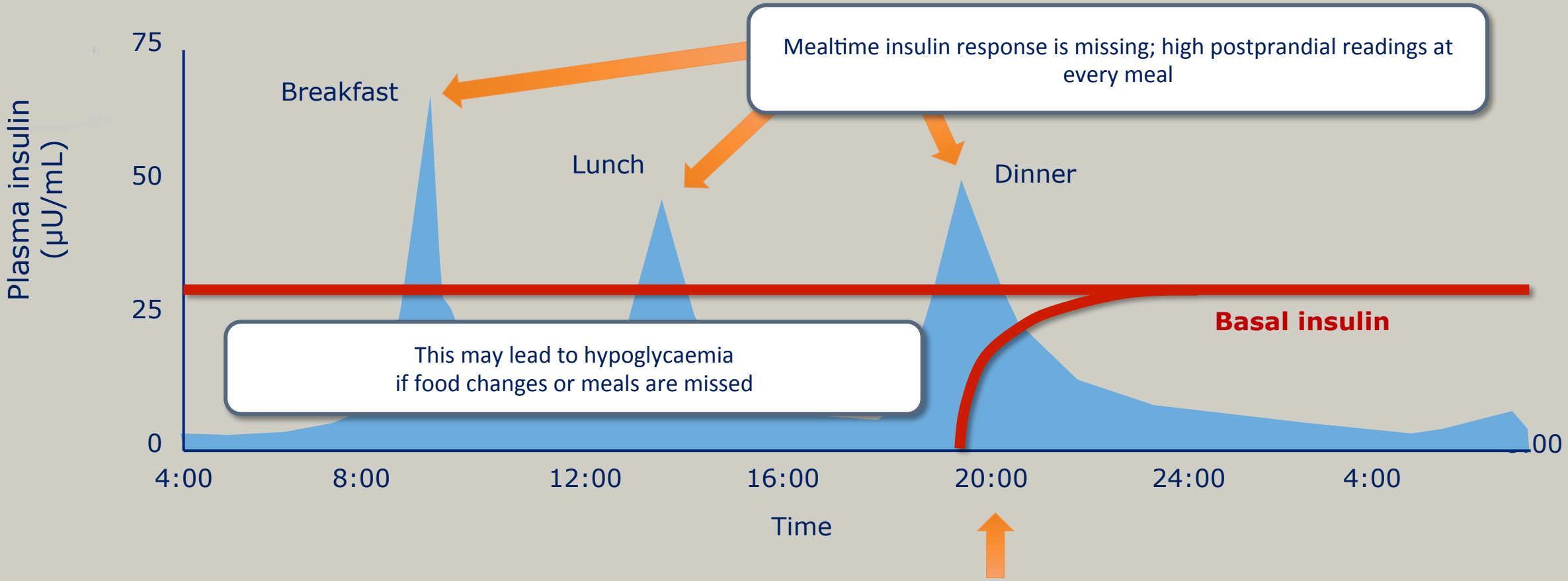
Progression of type 2 diabetes



FPG, fasting plasma glucose

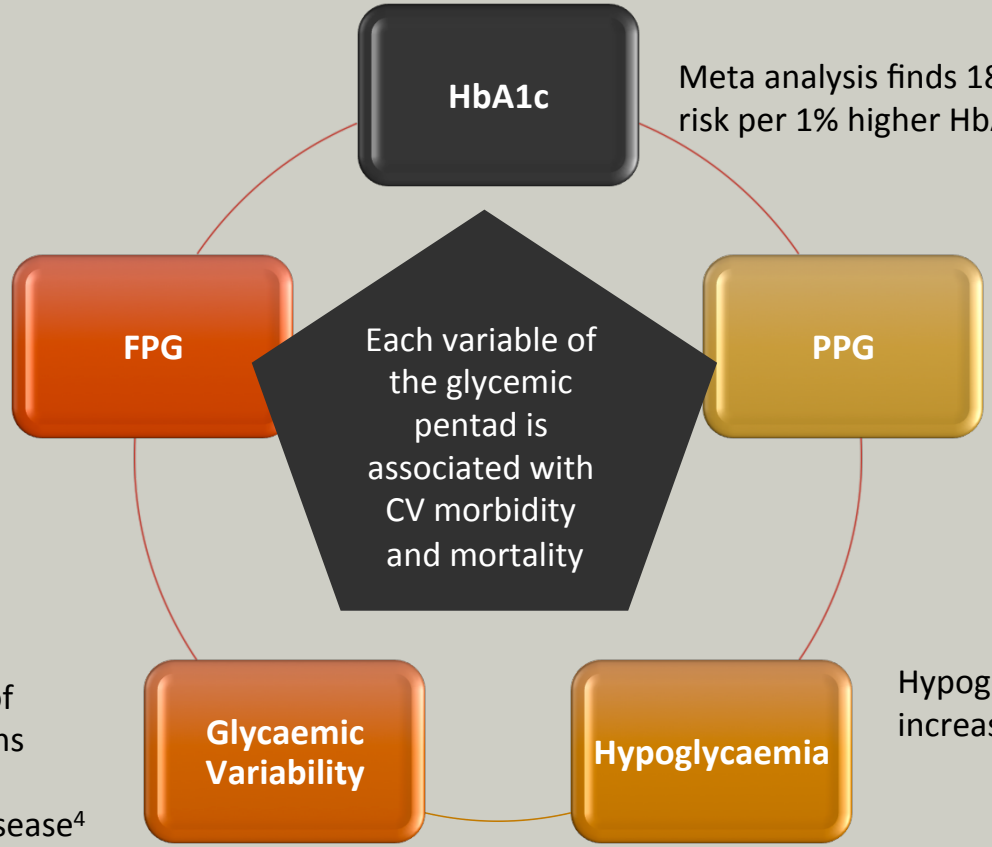
Adapted from Kendall *et al*. *Am J Med* 2009:122(Suppl. 6):S37–50

The addition of mealtime coverage is needed when basal insulin is no longer enough



Garber. *Diabetes Obes Metab* 2009;11(Suppl. 5):14–18

Glycemic Pentad- Association with CV risk



Meta analysis finds 18% increased CV risk per 1% higher HbA1c[1]

Elevated FPG is strongly associated with CV mortality[2]

PPG independently predicts CVD risk[2,3]

Mean Amplitude of Glycemic Excursions (MAGE) predicts coronary artery disease[4]

Hypoglycaemia is linked with a 79% increased risk of acute CV events[5]

1.Selvin E, et al. *Ann Intern Med*. 2004 ;141(6):421-31. 2. Einarson et al. *Curr Med Res Opin* 2011;27:1–9.
3.Cavalot *et al. J Clin Endocrinol Metab* 2006;91:813–9 4. Su et al. Cardiovascular Diabetology 2011, 10:19
5.Johnston et al. Diabetes Care 2011;34:1164–70

Ukrainian proverb

No matter how hard you try, the bull will never give you milk.

- Think before prescribing, don’t prescribe before thinking.
- THINK BEFORE INK

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A1CHIEVE STUDY REPORTS

Video tutorial

Select a country or region to view the study results

Country or region: Pakistan

Select treatment

Treatment: BIAsp ± OGLD

Compare pre-study treatments

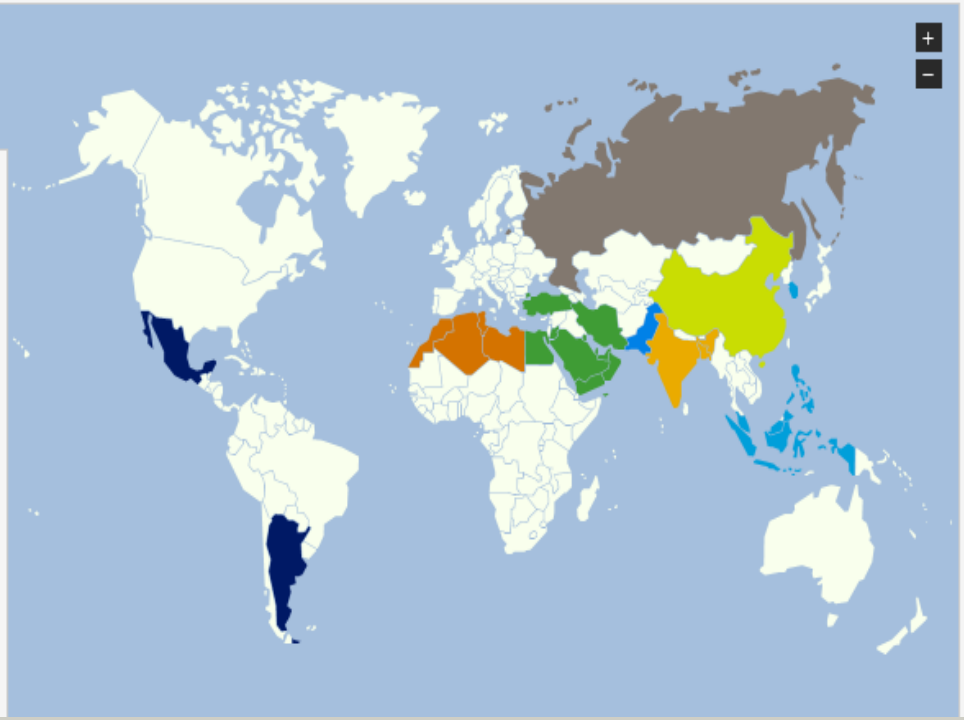
Pre-treatment 1: Insulin naïve

Pre-treatment 2: Insulin users

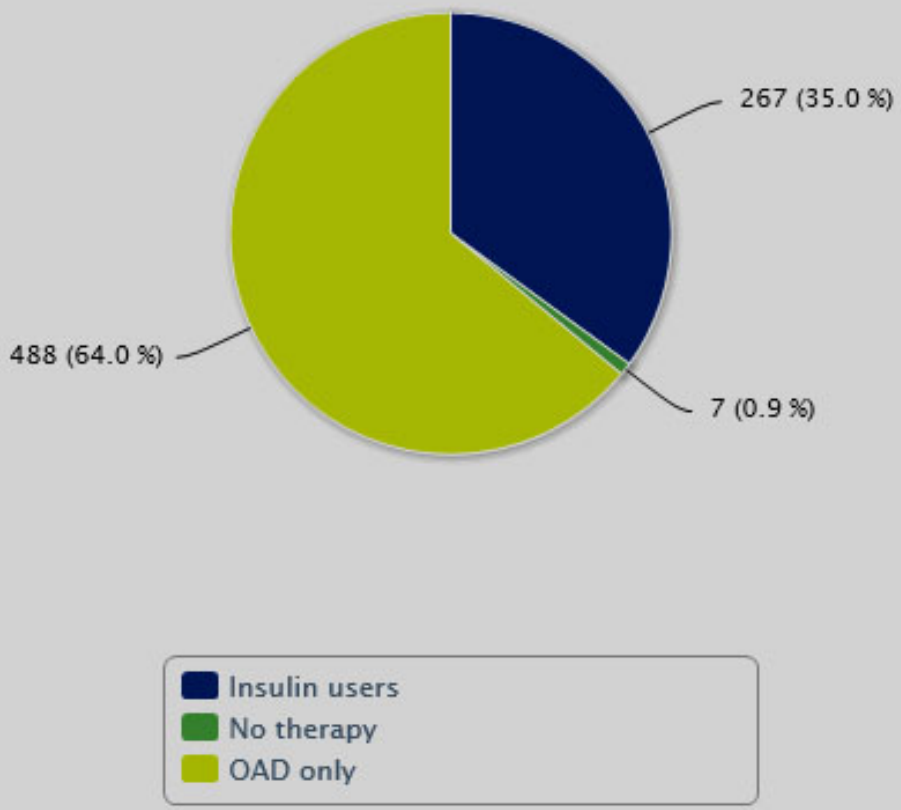
Choose measurement units

Blood glucose	(•) mmol/l	( ) mg/dl
Lipid profile	(•) mmol/l	( ) mg/dl
HbA1c output	(•) %	( ) mmol/mol

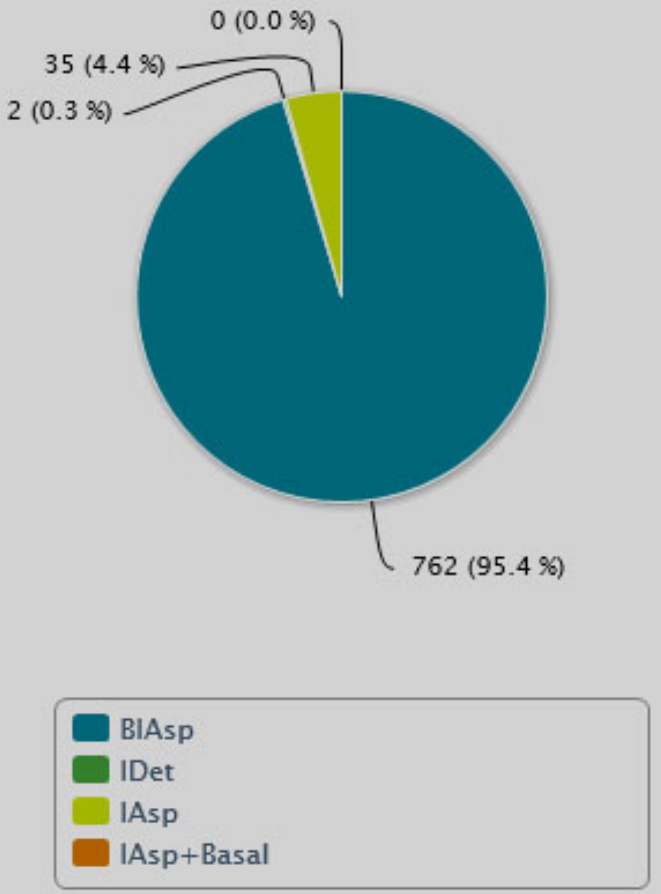
GENERATE REPORT



Participant distribution to BIAsp ± OGLD by pre-study therapy



Use of the different insulin types during the study (BIAsp ± OGLD)



THANK YOU