Efficacy and Safety of Sitagliptin in Various Clinical Settings of T2DM

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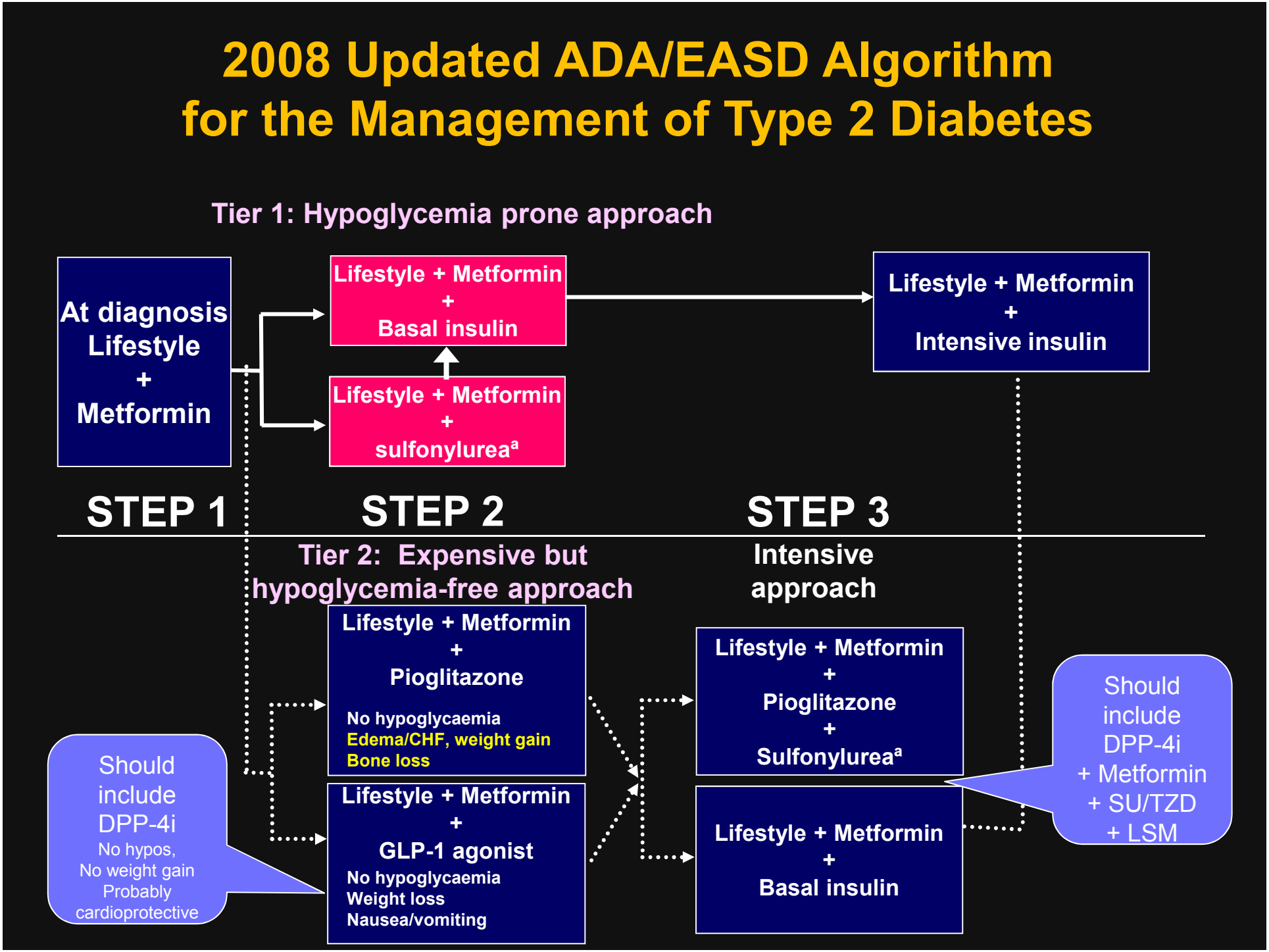
Januvia (sitagliptin) tablets

Janumet (sitagliptin/metformin HCl) tablets

2008 Updated ADA/EASD Algorithm for the Management of Type 2 Diabetes



Glycaemic targets for the management of type 2 diabetes

Glycaemic targets for the management of people with type 2 diabetes as recommended by various organisations[1–5]

Organisation	HbA_{1c} (%)	FPG (mmol/L)	PPG (mmol/L)
ADA-EASD[1]	<7	—	—
IDF-Europe[2]	<6.5	5.5 (<100)*	7.8 (<140)*
AACE[3]	≤6.5	6.1 (<110)*	7.8 (<140)*
NICE[4]	<6.5**	—	<8.5 (<153)*
DDG[5]	<6.5	—	—

*mg/dL

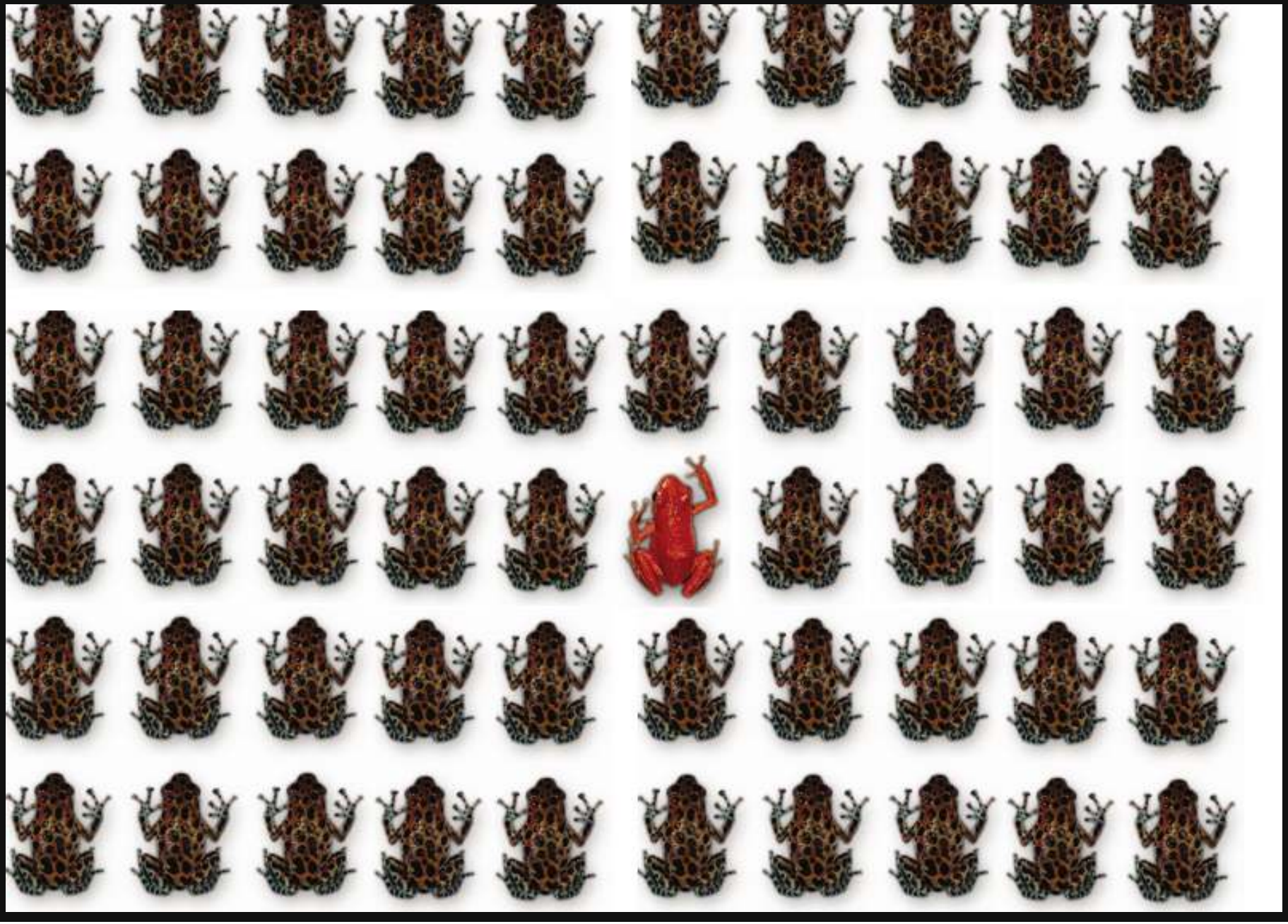
FPG: Fasting plasma glucose; PPG: Postprandial glucose; ADA: American Diabetes Association, IDF: International Diabetes Federation; AACE: American Association of Clinical Endocrinologists; NICE: National Institute of Clinical Excellence; DDG: Deutschen Diabetes-Gesellschaft (German Diabetes Association)

**<7.5% for people receiving two or more oral glucose-lowering drugs or those requiring insulin.

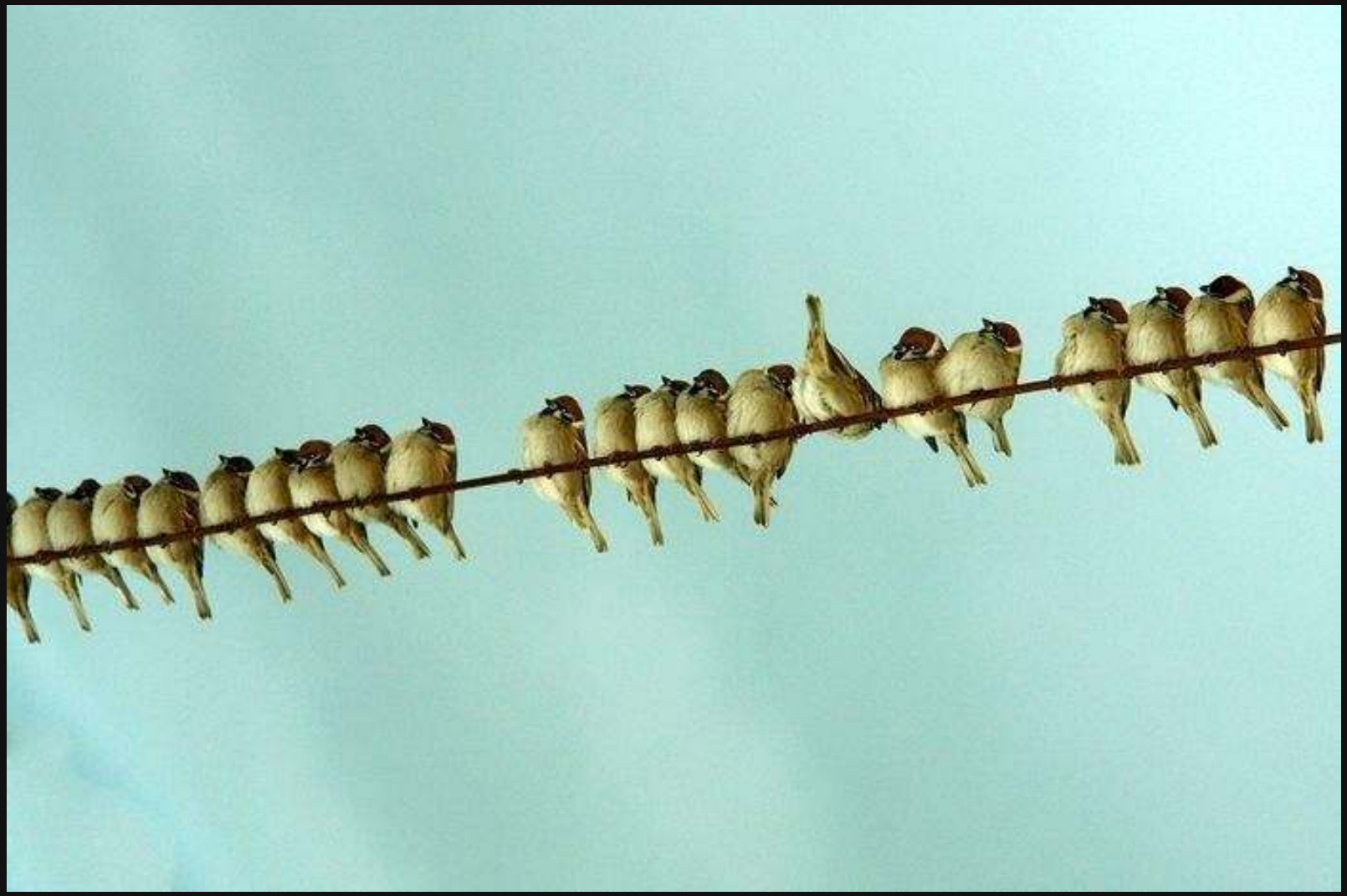
- Lowering blood glucose is critical to type 2 diabetes management in order to decrease the risk of macro- and microvascular complications
- This approach should be tailored according to individual needs

1. Nathan DM, et al. Diabetologia. 2009;52:17-30. 2. IDF. European Guidelines. 2007. 3. American College of Endocrinology. Endocr Pract. 2007;13 (Suppl. 1):1-68. 4. NICE clinical guideline 87. May 2009. 5. Matthaei S et al. German Diabetes Association guidelines. October 2008.

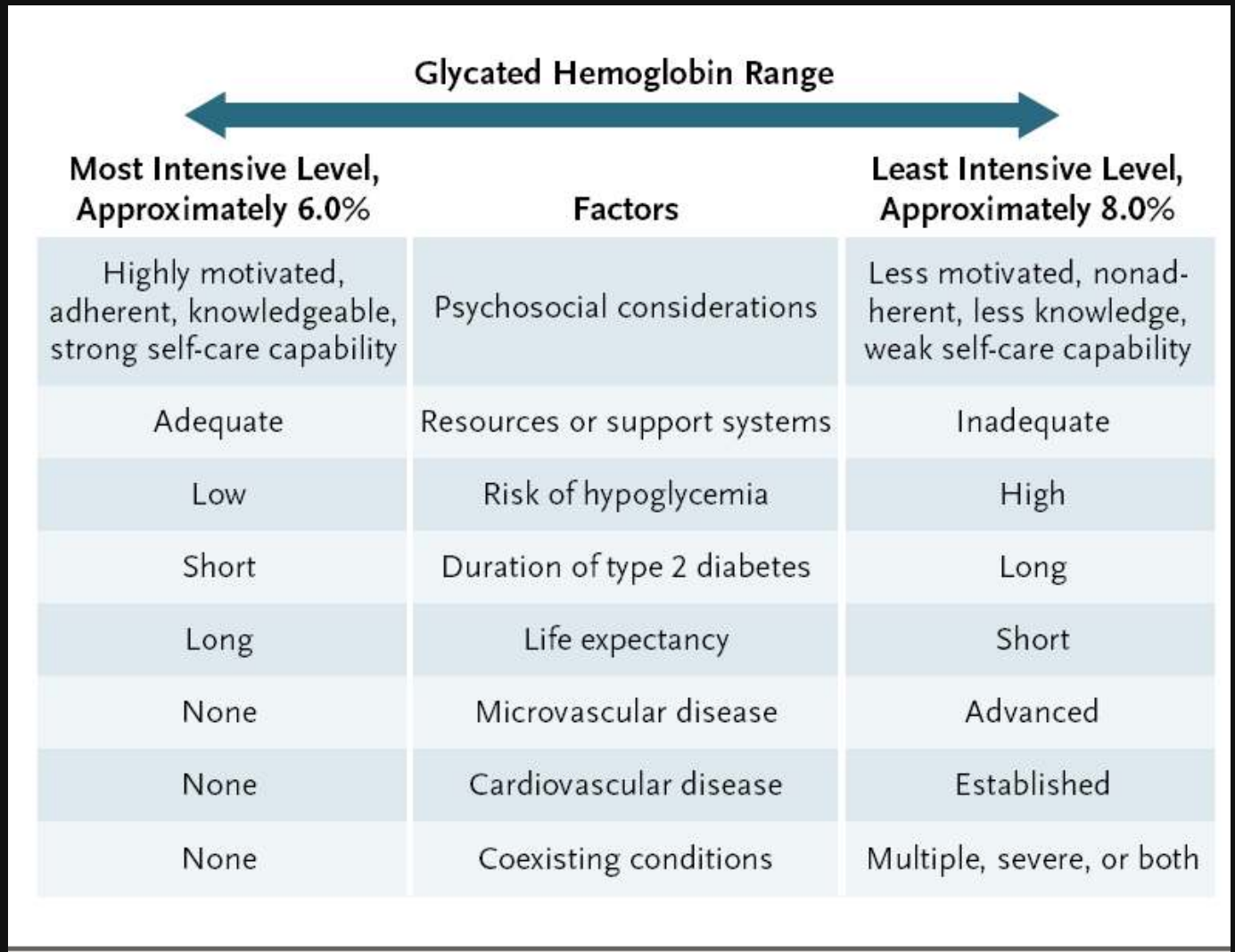
One size does not fit all!



Individualized approach



Individualization



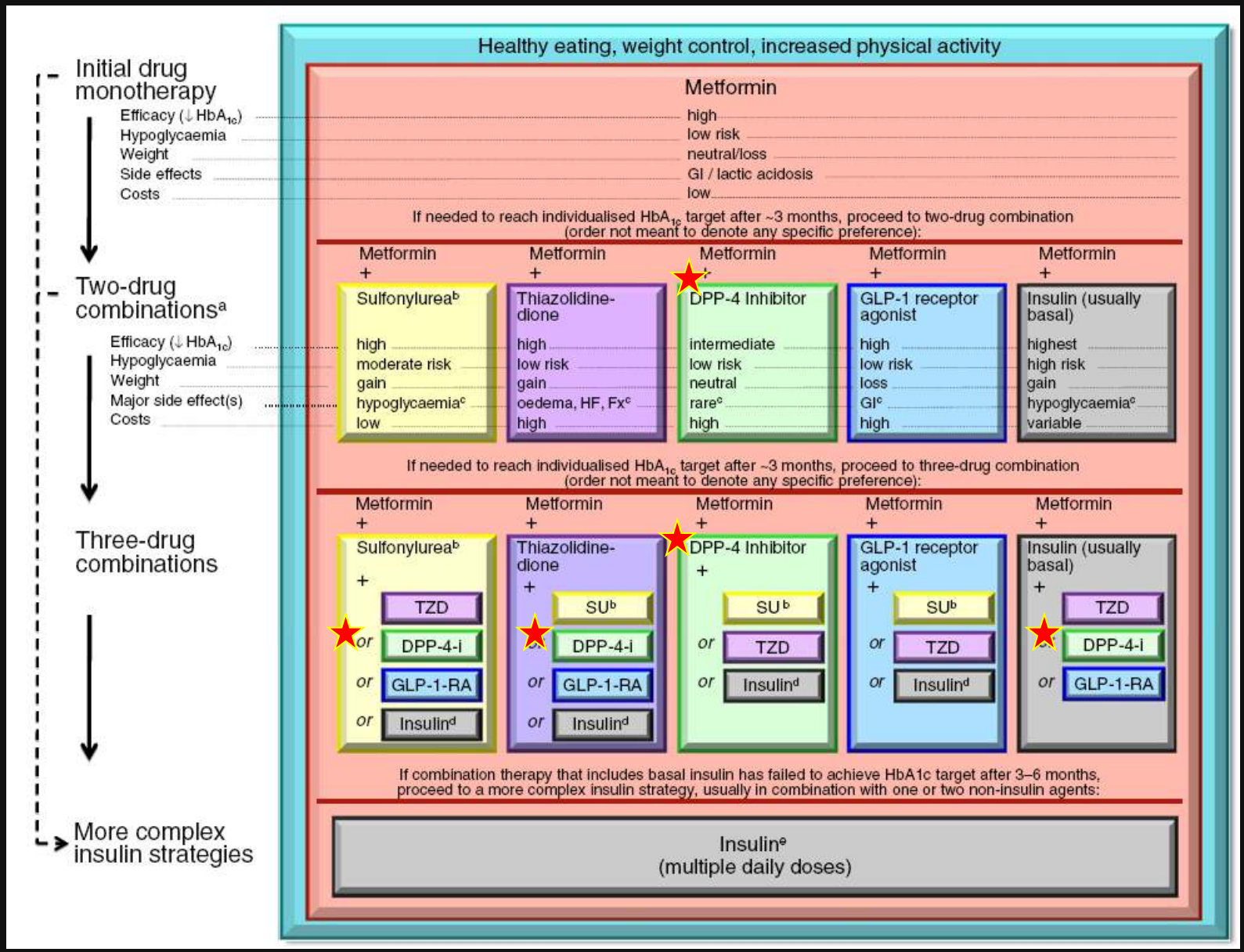
Glycated Hemoglobin Range

Most Intensive Level, Approximately 6.0%	Factors	Least Intensive Level, Approximately 8.0%
Highly motivated, adherent, knowledgeable, strong self-care capability	Psychosocial considerations	Less motivated, nonadherent, less knowledge, weak self-care capability
Adequate	Resources or support systems	Inadequate
Low	Risk of hypoglycemia	High
Short	Duration of type 2 diabetes	Long
Long	Life expectancy	Short
None	Microvascular disease	Advanced
None	Cardiovascular disease	Established
None	Coexisting conditions	Multiple, severe, or both

Figure 2. Suggested Goals for Glycemic Treatment in Patients with Type 2 Diabetes.

Ismail-Beigi F. N Engl J Med 2012;366:1319-27.

Position Statement of ADA and EASD 2012



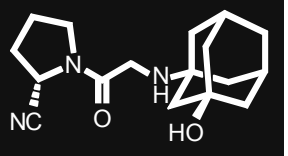
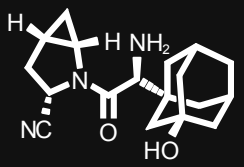
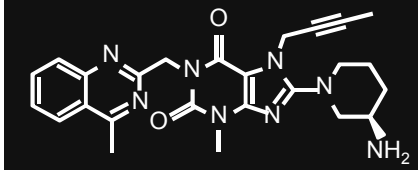
Take Your Pick!

The gliptins

Contents

- Sitagliptin : Comparison DPP4-I
- Sitagliptin: Proven Efficacy &Safety
- Sitagliptin : Providing new option for complicated patient

Molecular Structures of DPP-4 inhibitors

Chemical Class	β-Phenethylamines[1]	Cyanopyrrolidines		Xanthine
Generic Name	Sitagliptin[2,3]	Vildagliptin[2,4,5]	Saxagliptin[2,6,7]	Linagliptin[11,12]
Molecular Structure				

1.Kim D et al. *J Med Chem.* 2005;48:141–151. 2. Matsuyama-Yokono A et al. *Biochem Pharmacol*. 2008;76:98–107.
3.JANUVIA European Summary of Product Characteristics. 2010. 4.Villhauer EB et al. *J Med Chem*. 2003;46:2774–2789.
5.Galvus European Summary of Product Characteristics. 2010. 6. Augeri DJ et al. *J Med Chem.* 2005;48(15):5025–5037.
7.Onglyza European Summary of Product Characteristics. 2010. 8.Feng J, et al. *J Med Chem*. 2007;50:2297–2300.
9.Lee B et al. *Eur J Pharmacol*. 2008;589:306–14. 10.Christopher R et al. *Clin Ther*. 2008;30:513–527.
11.Thomas L et al. *J Pharmacol Exp Ther*. 2008;325:175–182. 12.Heise T et al. *Diabetes Obes Metab*. 2009;11:786–794.

Pharmacokinetic Properties of DPP-4 Inhibitors

	Sitagliptin[1]	Vildagliptin[2]	Saxagliptin[3]	Linagliptin
Absorption t_{max}	**1–4 h**	**1.7 h**	**2 h (4 h for active metabolite)**	1.34–1.53 h
Bioavailability	**~87%**	**85%**	**>75 %[4]**	**29.5%**
Half-life ($t_{1/2}$) at clinically relevant dose	**12.4 h**	**~2–3 h**	**2.5 h (parent) 3.1 h (metabolite)**	**113–131 h (1–10 mg)**
Distribution	**38% protein bound**	**9.3% protein bound**	**Low protein binding**	Prominent concentration-dependent protein binding: <1 nM: ~99% >100 nM: 70%–80%
Metabolism	~16% metabolized	69% metabolized mainly renal (inactive metabolite)	Hepatic (active metabolite) CYP3A4/5	~26% metabolized
Elimination	Renal 87% (79% unchanged)	Renal 85% (23% unchanged)	Renal 75% (24% as parent; 36% as active metabolite)	Feces 81.5% (74.1% unchanged); Renal 5.4% (3.9% unchanged)

DPP-4=dipeptidyl peptidase-4.

1. EU-SPC for sitagliptin, 2010. **2.** EU-SPC for vildagliptin, 2010. **3.** EU-SPC for saxagliptin, 2010. **4.** EPAR for saxagliptin. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001039/WC500044319.pdf. Accessed May 4, 2011.

DPP-4 Inhibitors: 제형별 비교

	Sitagliptin[1]	Vildagliptin[2]	Saxagliptin[3]	Linagliptin
Dose adjustment	**100mg QD** **50mg QD**	50mg BID	5mg QD 2.5mg QD	5mg QD
Renal impairment **Mild** **Moderate** **Severe**	**100mg QD** **50mg QD** **25mg QD**	50mg BID 50mg QD 50mg QD	5mg QD 2.5mg QD 2.5mg QD	5mg QD 5mg QD 5mg QD
Drug interaction **- CYP3A4/5 inhibitor**	**None**	None	2.5mg QD	None
FDC **w/ Metformin**	**50/500 BID** **50/850 BID** **50/1000 BID**	50/850 BID 50/1000 BID	N/A (Kombiglyze)	N/A

DPP-4=dipeptidyl peptidase-4.

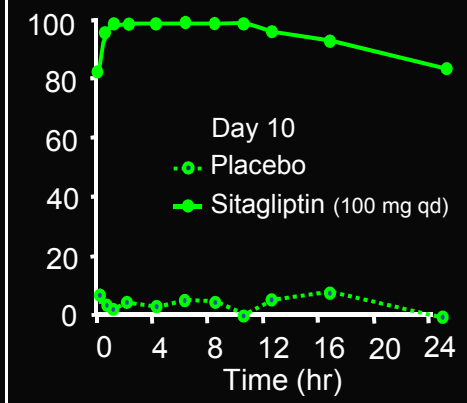
1. EU-SPC for sitagliptin, 2010. **2.** EU-SPC for vildagliptin, 2010. **3.** EU-SPC for saxagliptin, 2010. **4.** EPAR for saxagliptin. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001039/WC500044319.pdf. Accessed May 4, 2011.
5. Heise T et al. Diabetes Obes Metab. 2009;11:786–794. 6. Reitlich S et al. Clin Pharmacokinet. 2010;49:829–840. 7. Fuchs H et al. J Pharm Pharmacol. 2009;61:55–62.
8. http://ezdrug.kfda.go.kr/index.jsp.

Higher DPP-4 inhibition rate & longer duration leads to better efficacy

Sitagliptin

- Max ~97%

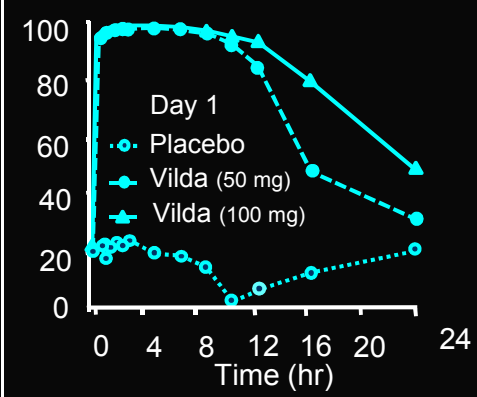
- >80% 24h postdose



Vildagliptin

- **Max ~95%**

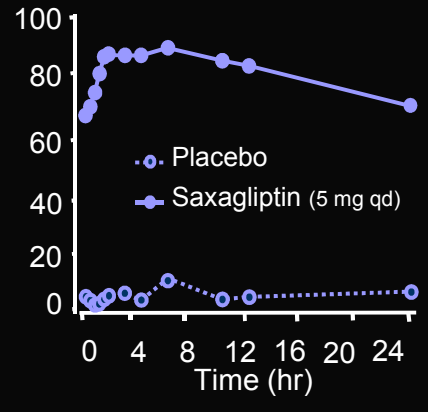
- **>80% 12h postdose**



Saxagliptin

- **Max ~80%**

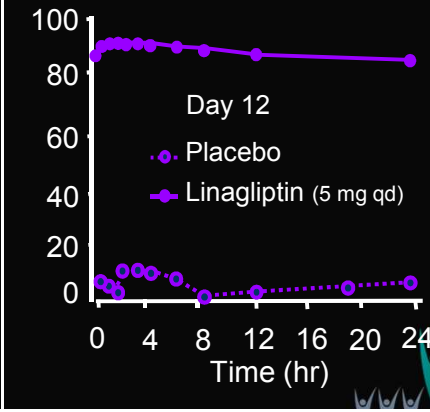
- **~70% 24h postdose**



Linagliptin

- **Max ~80%**

- **~70% 24h postdose**



1. Bergman et al., Clin Ther 2006, 2. He et al., J Clin Pharmacol 2007 3. Boultor et al., Poster 0606-P; ADA 2007, 4. Heise et al., Diab Obes Metab 2009

Nb: No direct comparisons of degree of inhibition attained by different inhibitors

be the Champion

DPP4 enzyme selectivity

IC_{50} fold selectivity for DPP-4 vs. other enzymes

	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin
DPP-8	> 2660	270	390	40000
DPP-9	> 5550	32	77	>10000
FAPα	> 5550	285	> 4000	89
QPP/DPP-2	> 5550	> 100000	> 50000	>100000

Deacon CF, Diabetes, Obesity and Metabolism 2011;13: 7–18
Chen SJ & Jiaang WT, Current Topics in Medicinal Chemistry, 2011; 11: 1447-1463

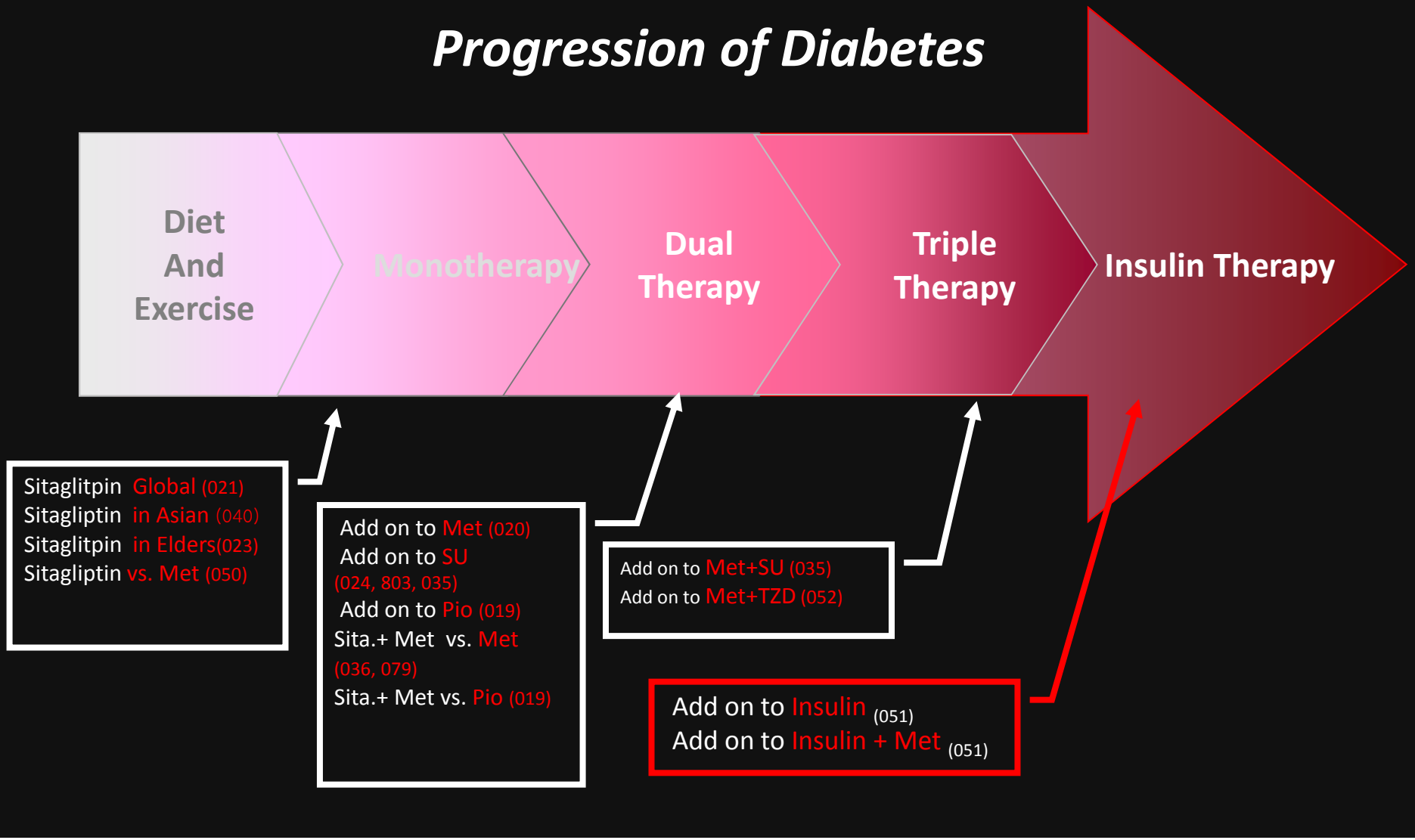
Lead the Change, be the Champion

Sitaglitin: Proven Efficacy and Safety

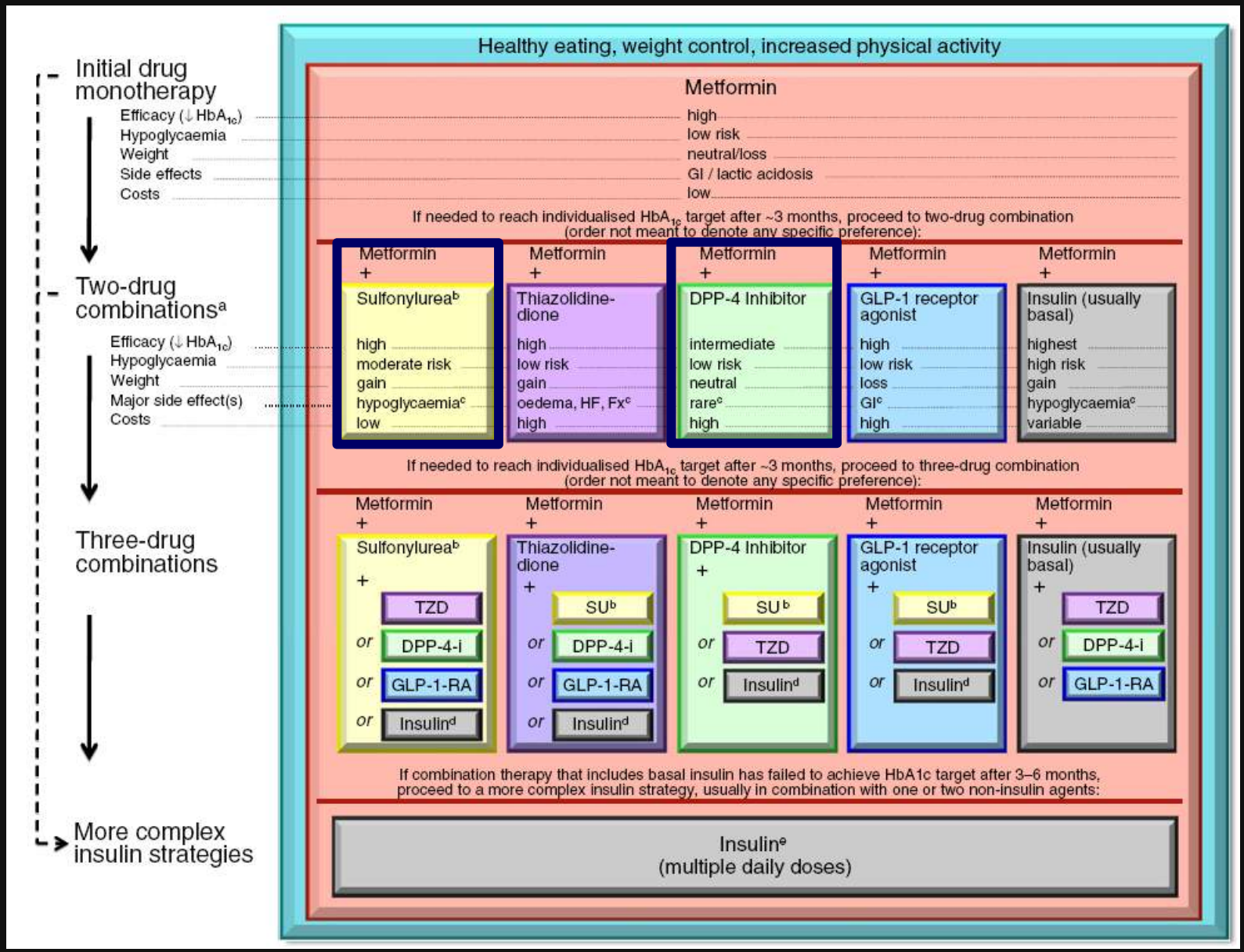
Januvia (sitagliptin) tablets

Janumet (sitagliptin/metformin HCl) tablets

Broad Indications for T2DM patients : Sitagliptin

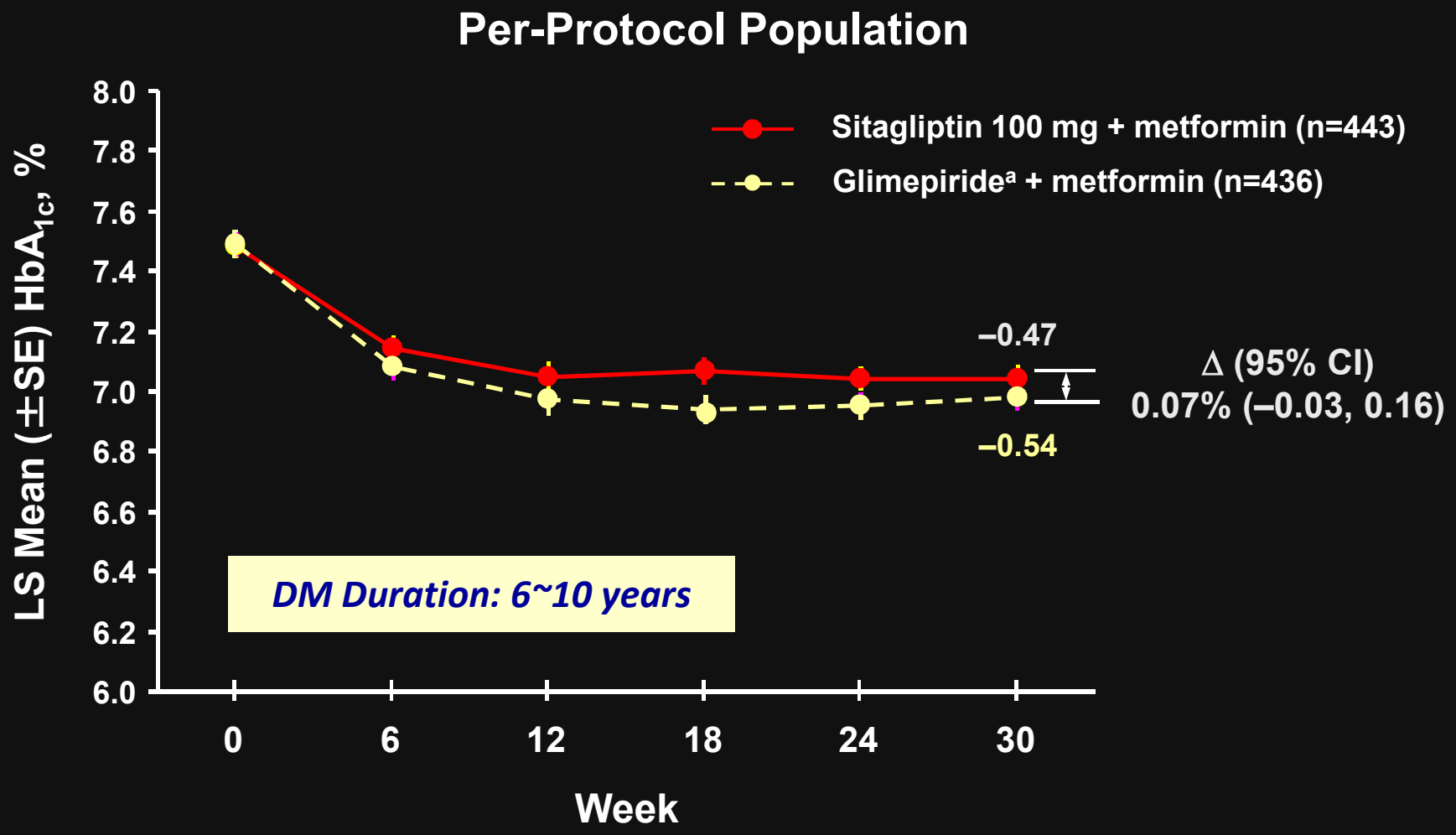


Sitagliptin : proven non-inferiority compared with SU?



Add on to Met

Sitagliptin Provides Comparable A1c Lowering Effect with Glimepiride



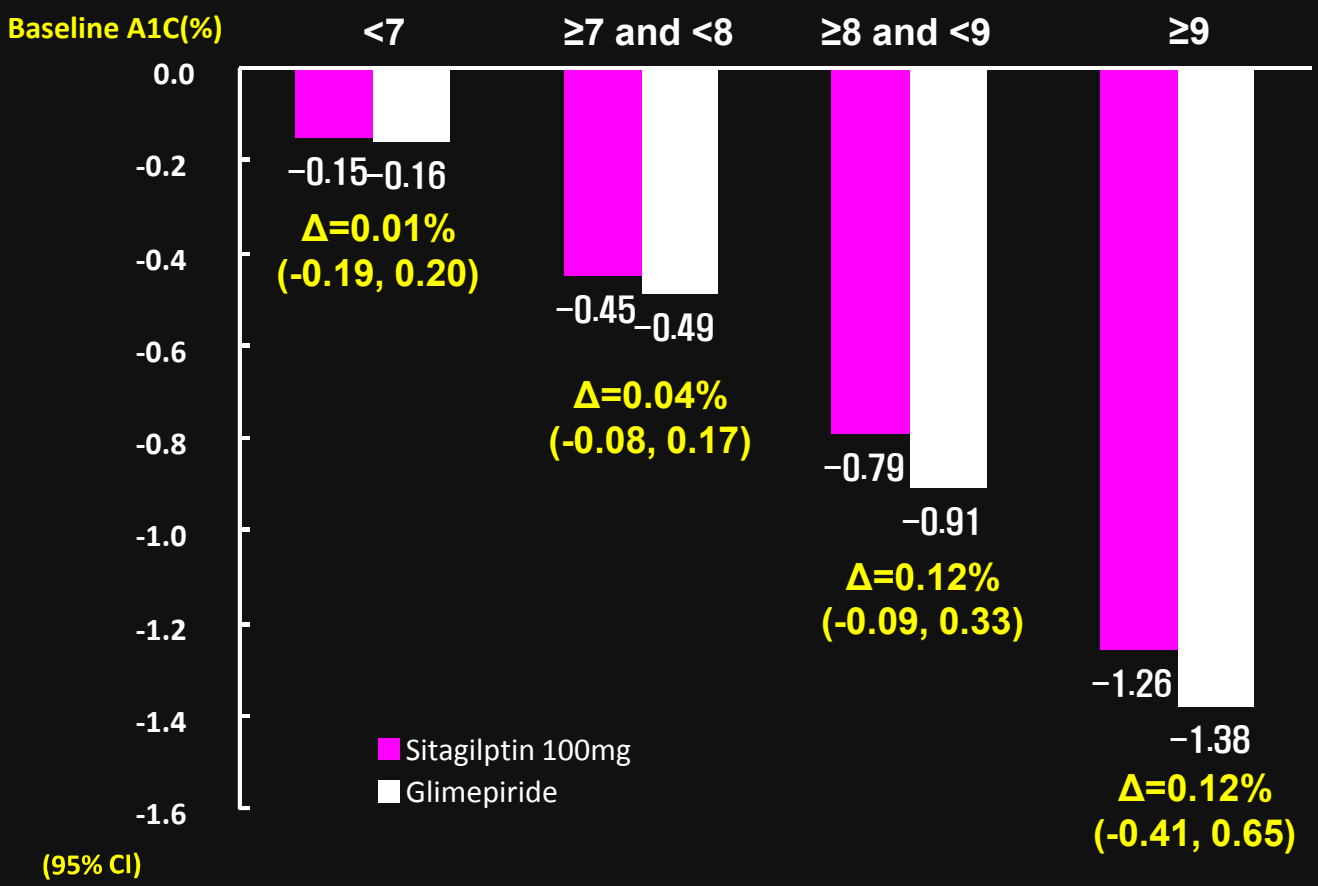
LS=least squares; SE=standard error.

[a]Mean dose of glimepiride (following the 18-week titration period) was 2.1 mg per day.

1. Arechavaleta R et al. *Diabetes Obes Metab*. 2011;13(2):160–168.

Add on to Met

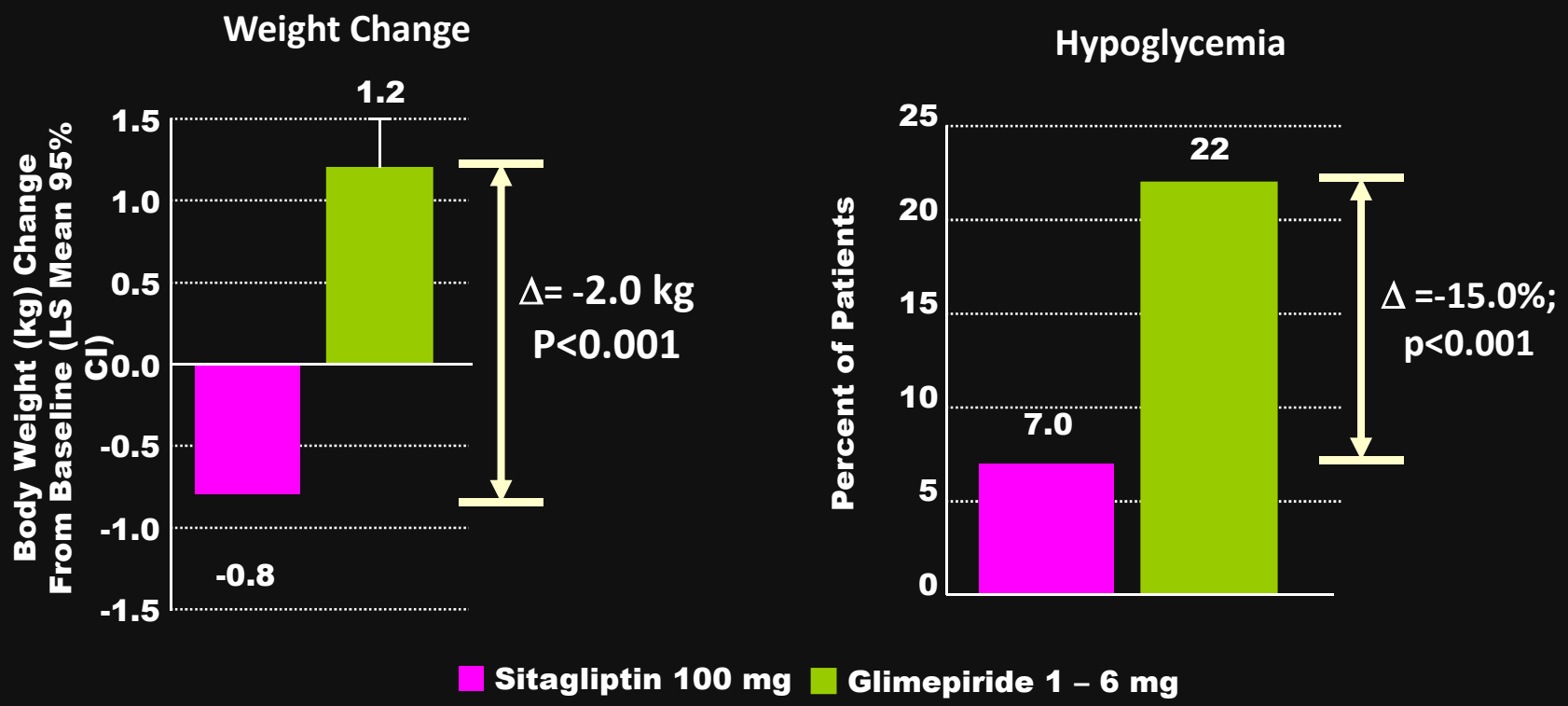
Sitagliptin provides comparable A1c Reductions Associated With Higher Baseline A1c with Glimepiride



CSR PN803 (4/21/10)

Adapted from Arechavaleta R et al. *Diabetes Obes Metab*. 2011;13(2):160–168.

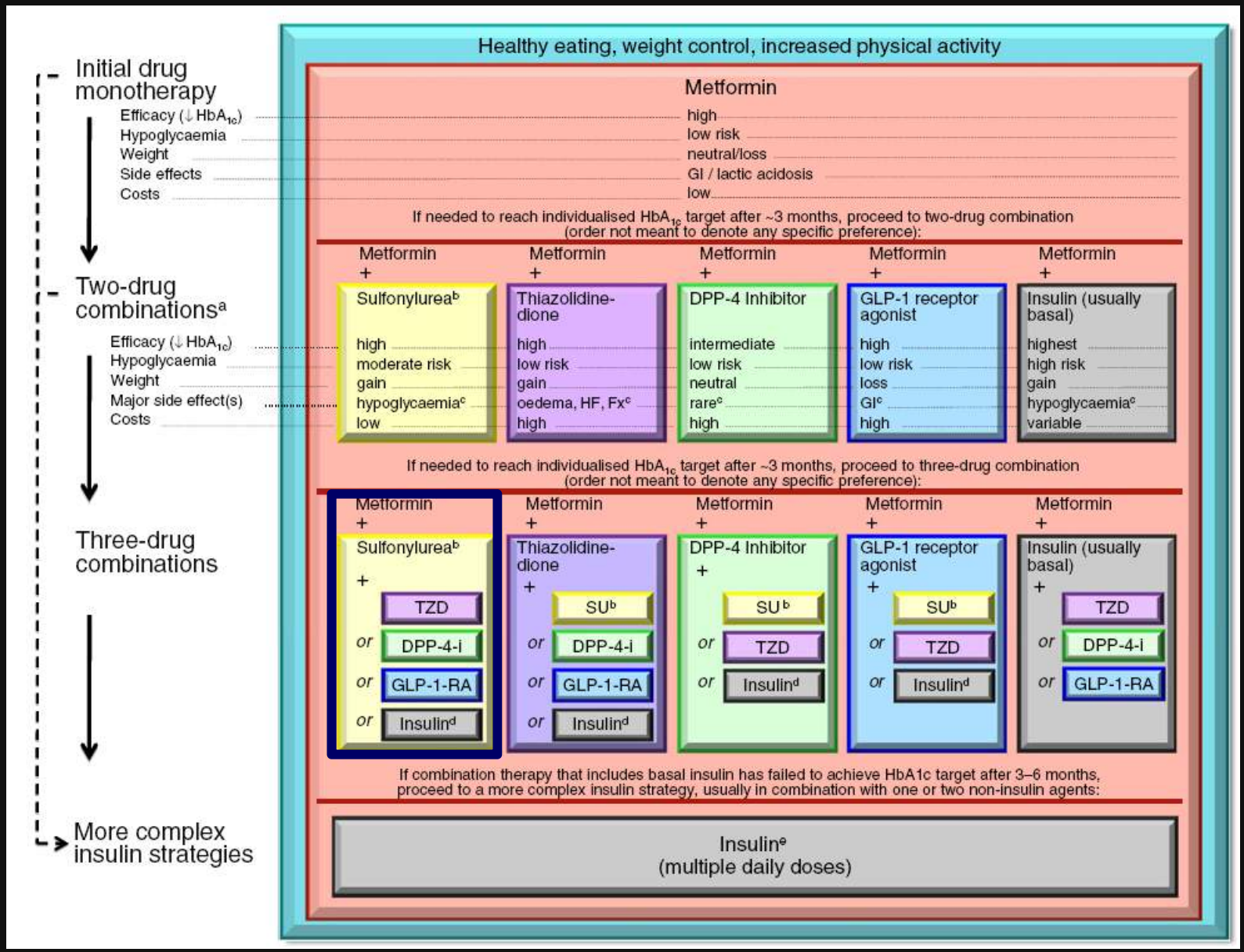
Sitagliptin vs. Glimepiride Added to Metformin in Patients With Type 2 Diabetes Mellitus: Body weight gain and Hypoglycemia



- Patients on Sitagliptin lost weight while those on glimepiride gained weight
- Incidence of hypoglycemia was higher with glimepiride therapy

Adapted from Diabetes, Obesity and Metabolism 13: 160–168, 2011.

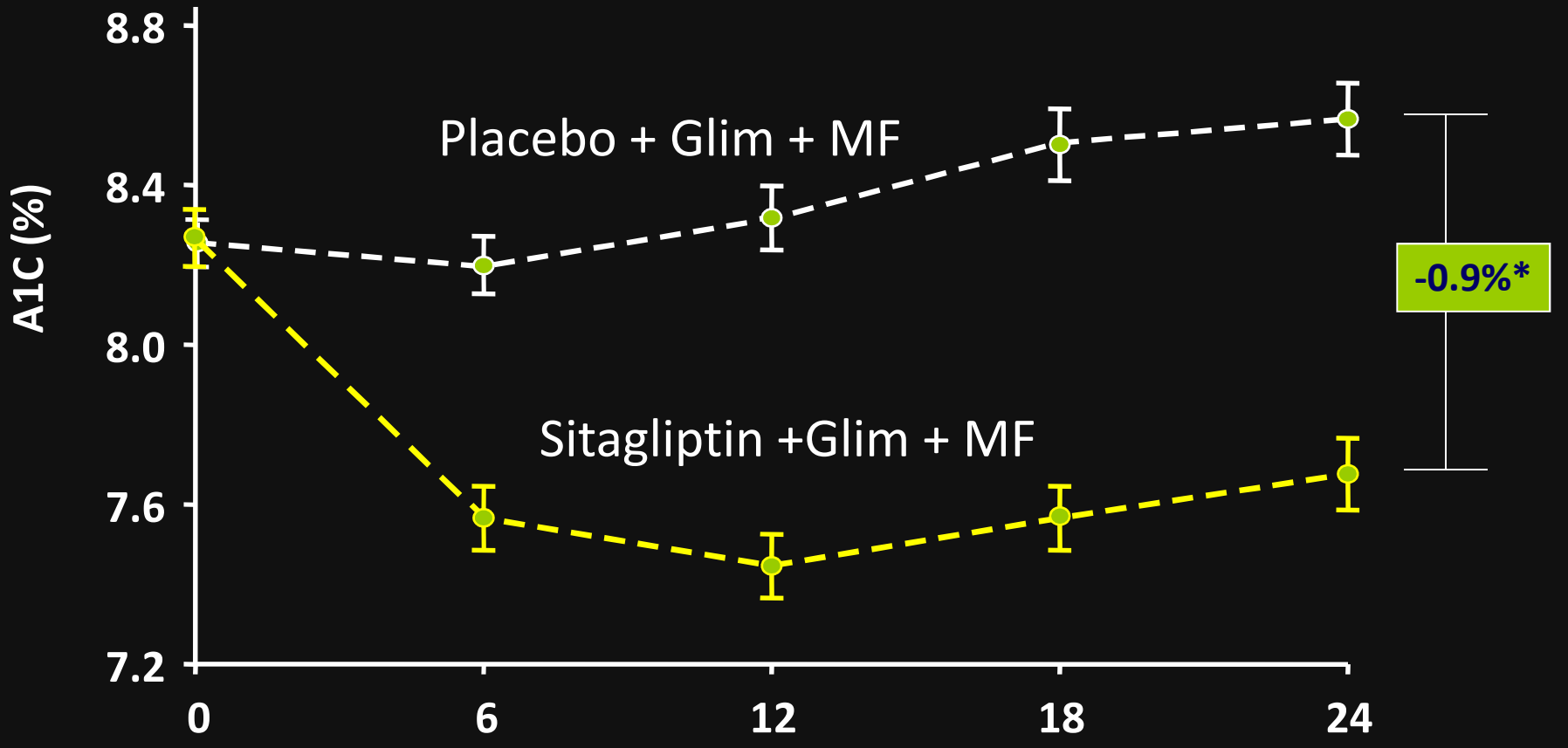
Sitagliptin : Proven triple therapy



Add on to Met+SU

Patients with Met+SU Therapy

Placebo-controlled Add-on to Glimepiride + metformin Study

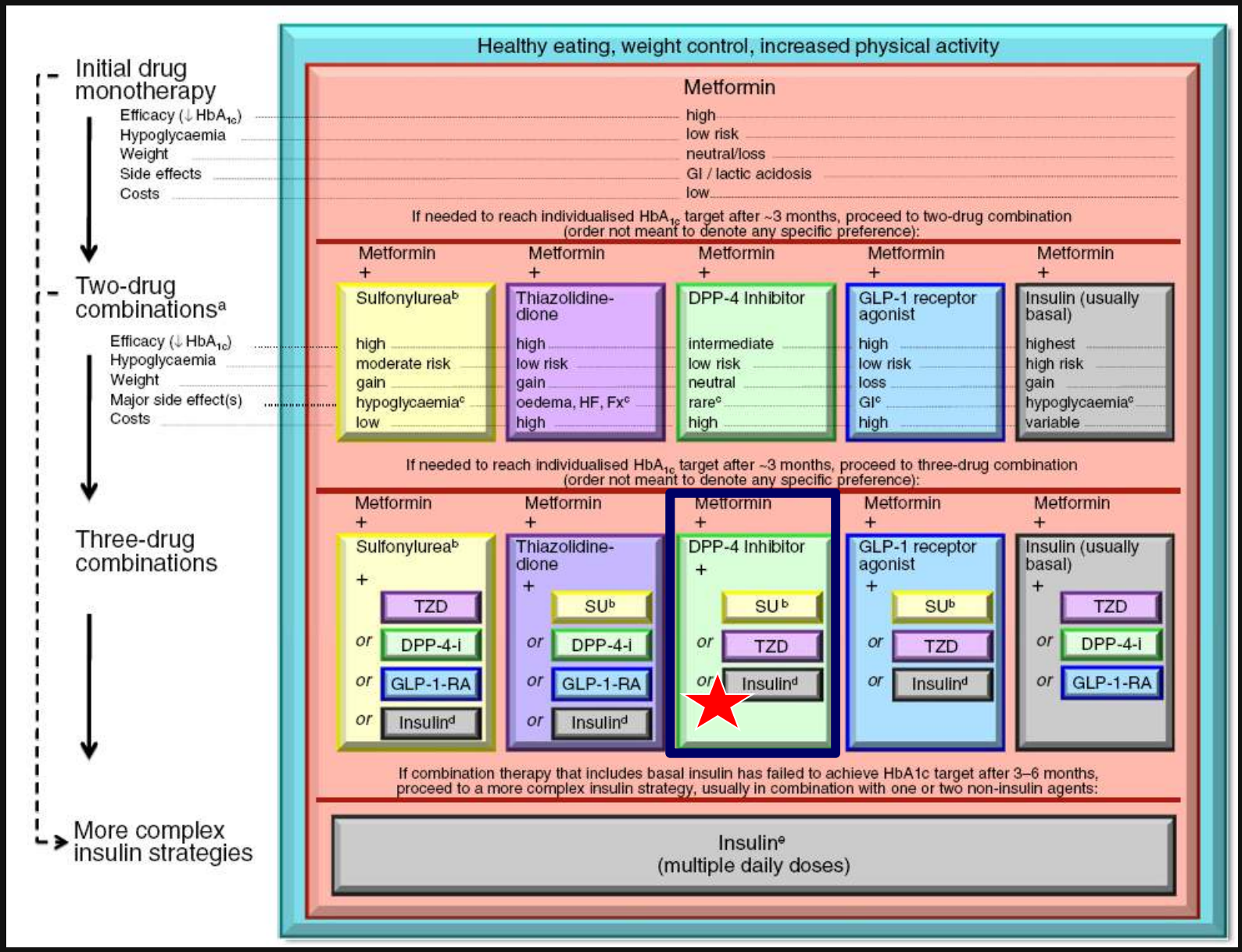


Mean duration of T2DM: 8.8 years

*Difference in LS Mean change from baseline

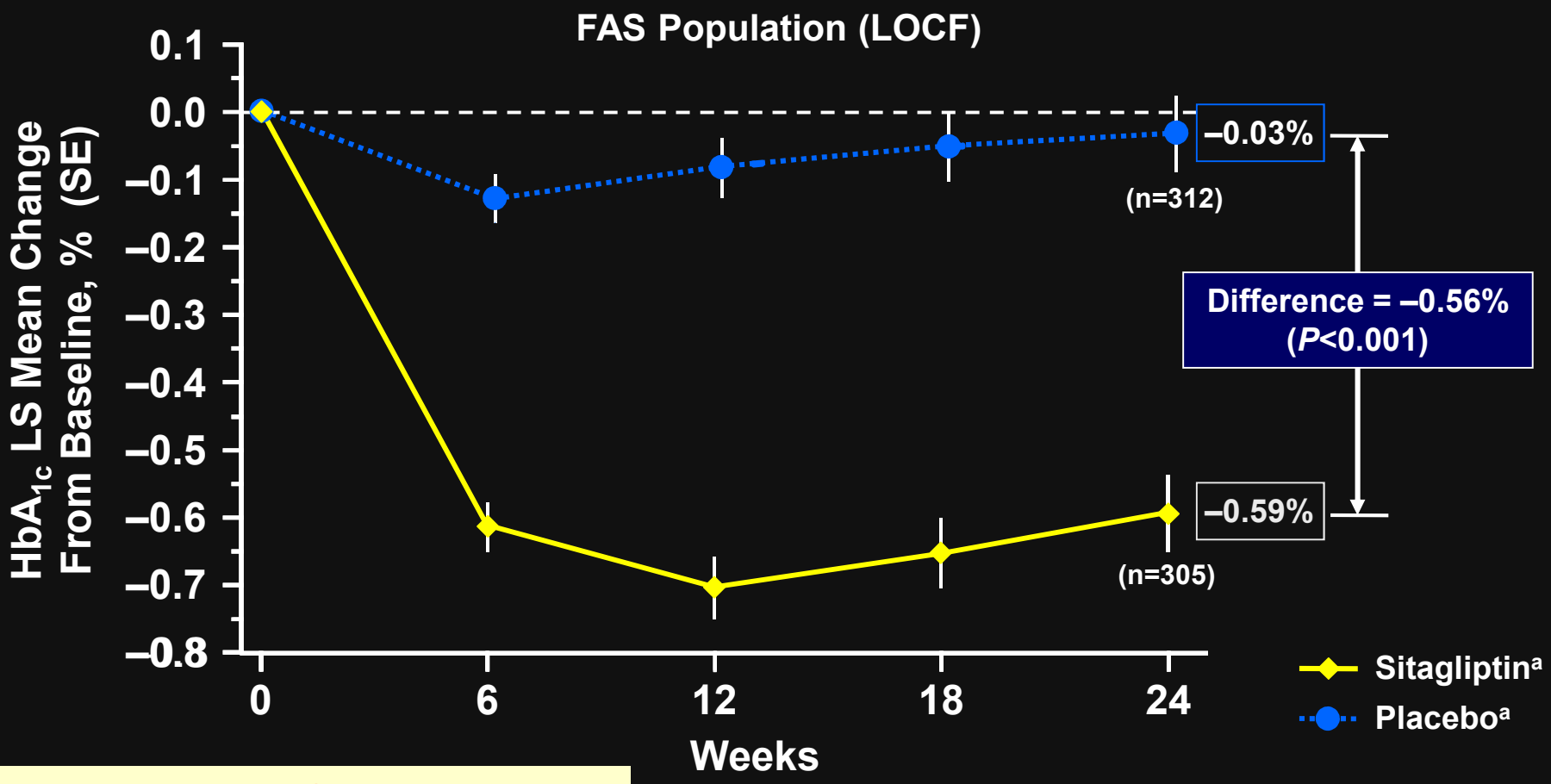
Adapted from Hermansen et al. *Diabetes Obes Metab* 2007;9:733-745

Sitagliptin : Proven triple therapy



Add on to Insulin (+/- Met)

Addition of Sitagliptin to Insulin Therapy: HbA_{1c} Change From Baseline Over Time



Mean duration of T2DM: 13 years

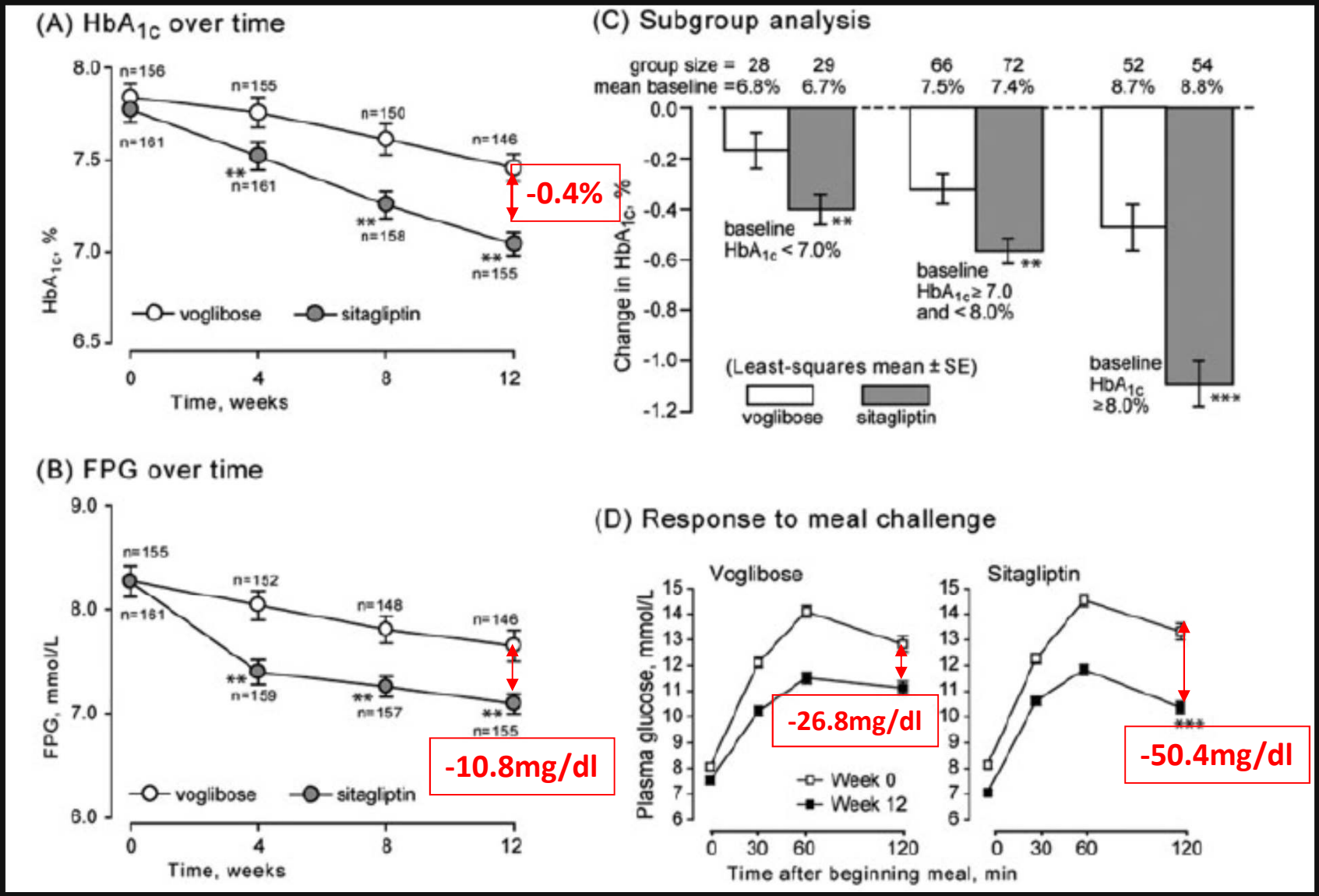
[a]Baseline mean HbA_{1c}: 8.72% for sitagliptin, 8.64% for placebo
FAS=full analysis set; LOCF=last observation carried forward; LS=least squares; SE=standard error.
Data on file, MSD.

Sitagliptin vs AGI?

Januvia (sitagliptin) tablets

Janumet (sitagliptin/metformin HCl) tablets

Sitagliptin monotherapy offers SUPERIOR Efficacy compare to Voglibose



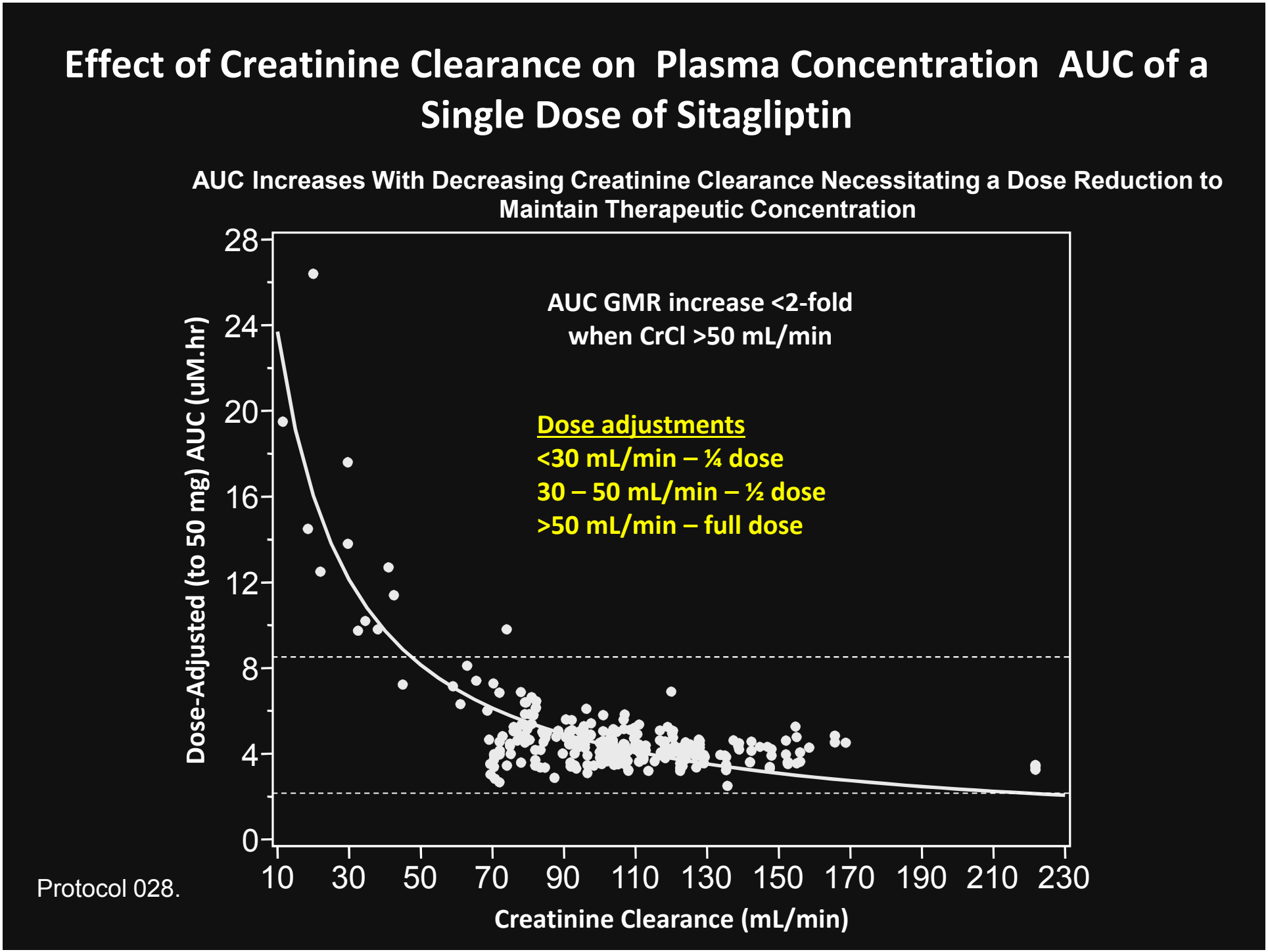
Iwamoto et al. Diabetes, Obesity and Metabolism 12: 0–0, 2010.

Launch Sitaliptin 50mg

Januvia (sitagliptin) tablets

Janumet (sitagliptin/metformin HCl) tablets

Effect of Creatinine Clearance on Plasma Concentration AUC of a Single Dose of Sitagliptin



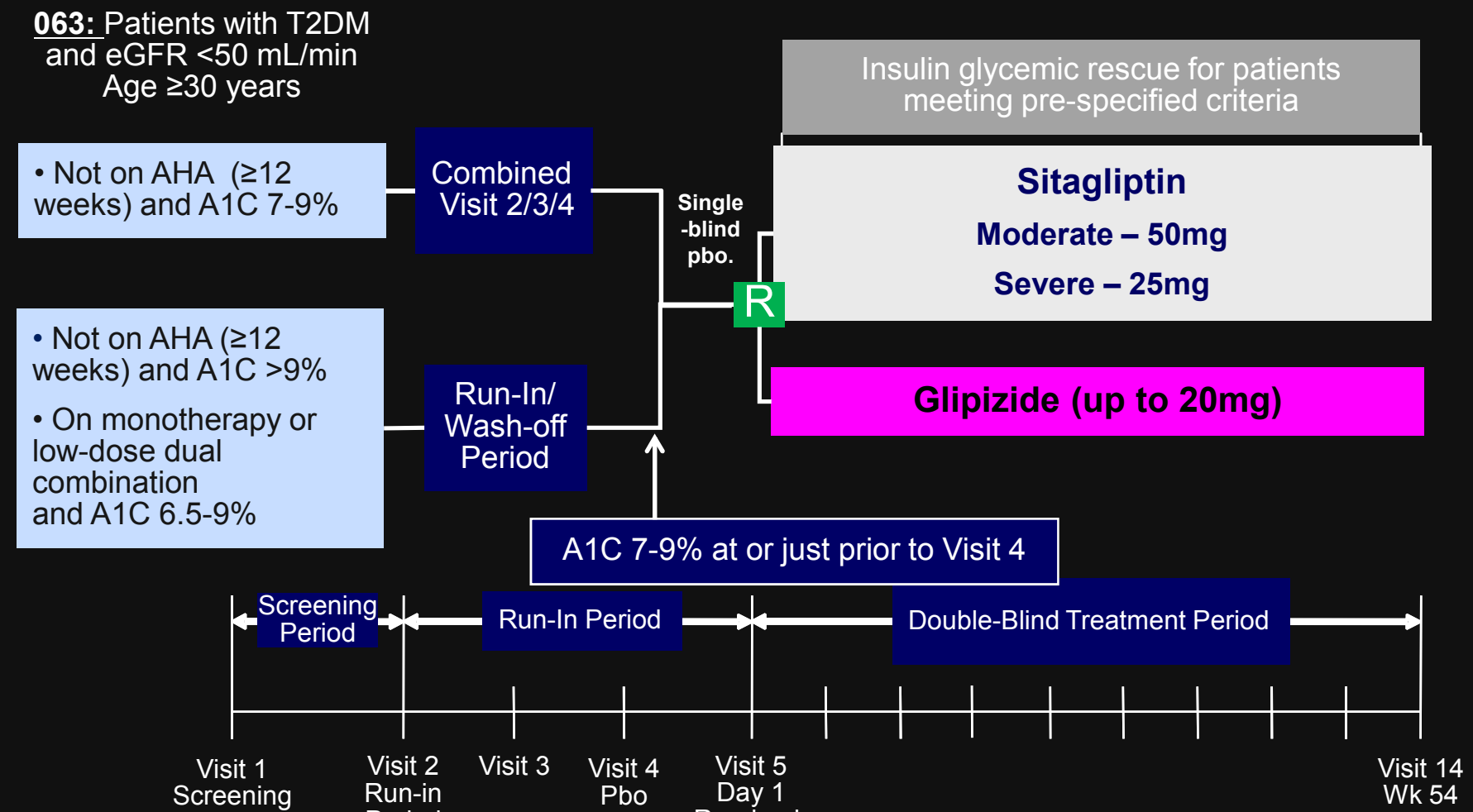
Protocol 028.

EASD & ASN

Poster

Study 063: **Efficacy and Safety of Sitagliptin Versus Glipizide in Patients With Type 2 Diabetes Mellitus and Chronic Renal Insufficiency Who Have Inadequate Glycemic Control**

Sitagliptin vs. Glipizide in Patients with T2DM and Moderate to Severe Renal Insufficiency: Study Design[1]

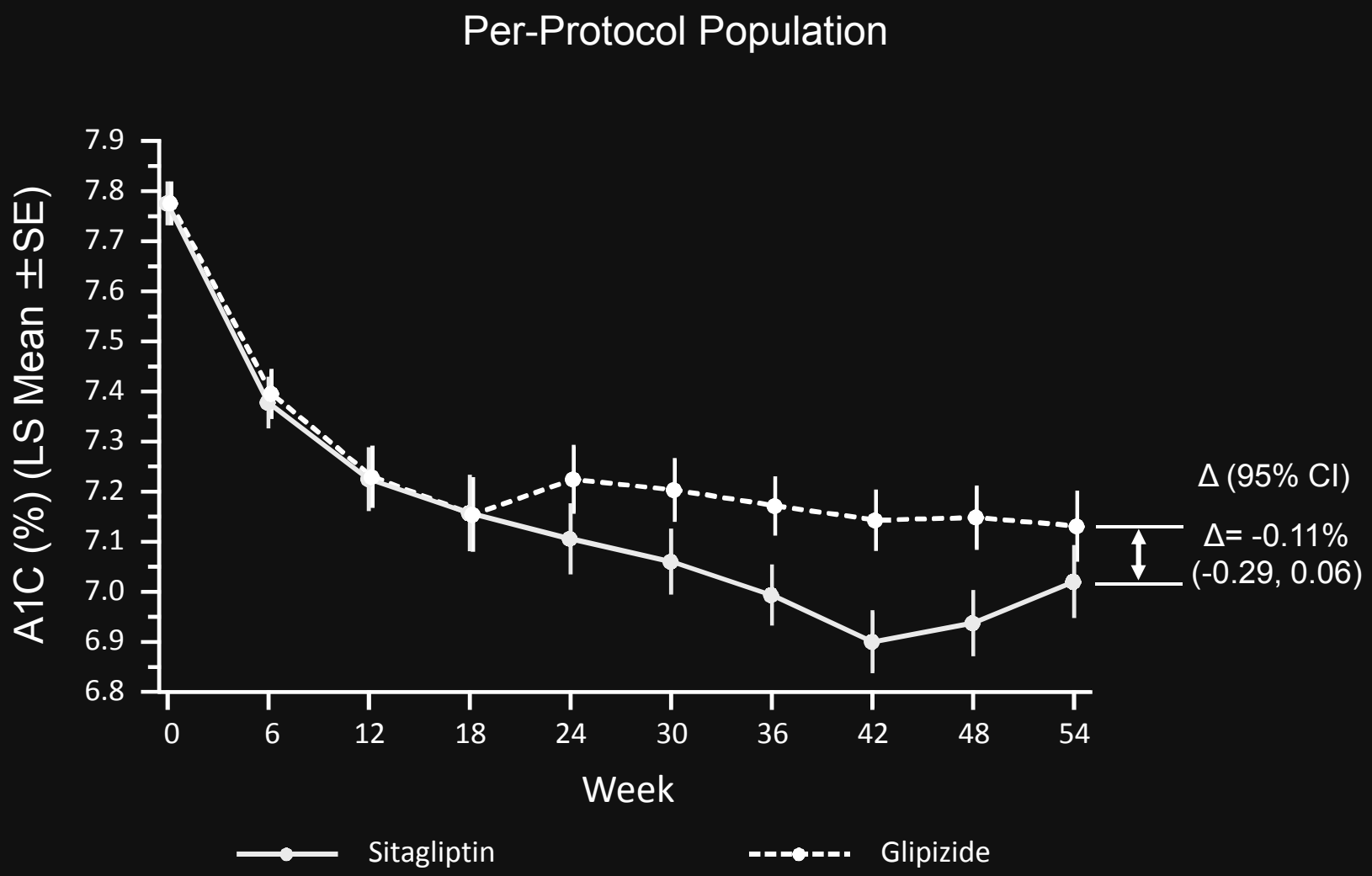


Visit 2 to Visit 4 Run-In/Washoff period of variable duration depending on Visit 1 status, including diet and exercise, antihyperglycemic therapy and baseline A1C

AHA=antihyperglycemic

1. Data on file, MSD.

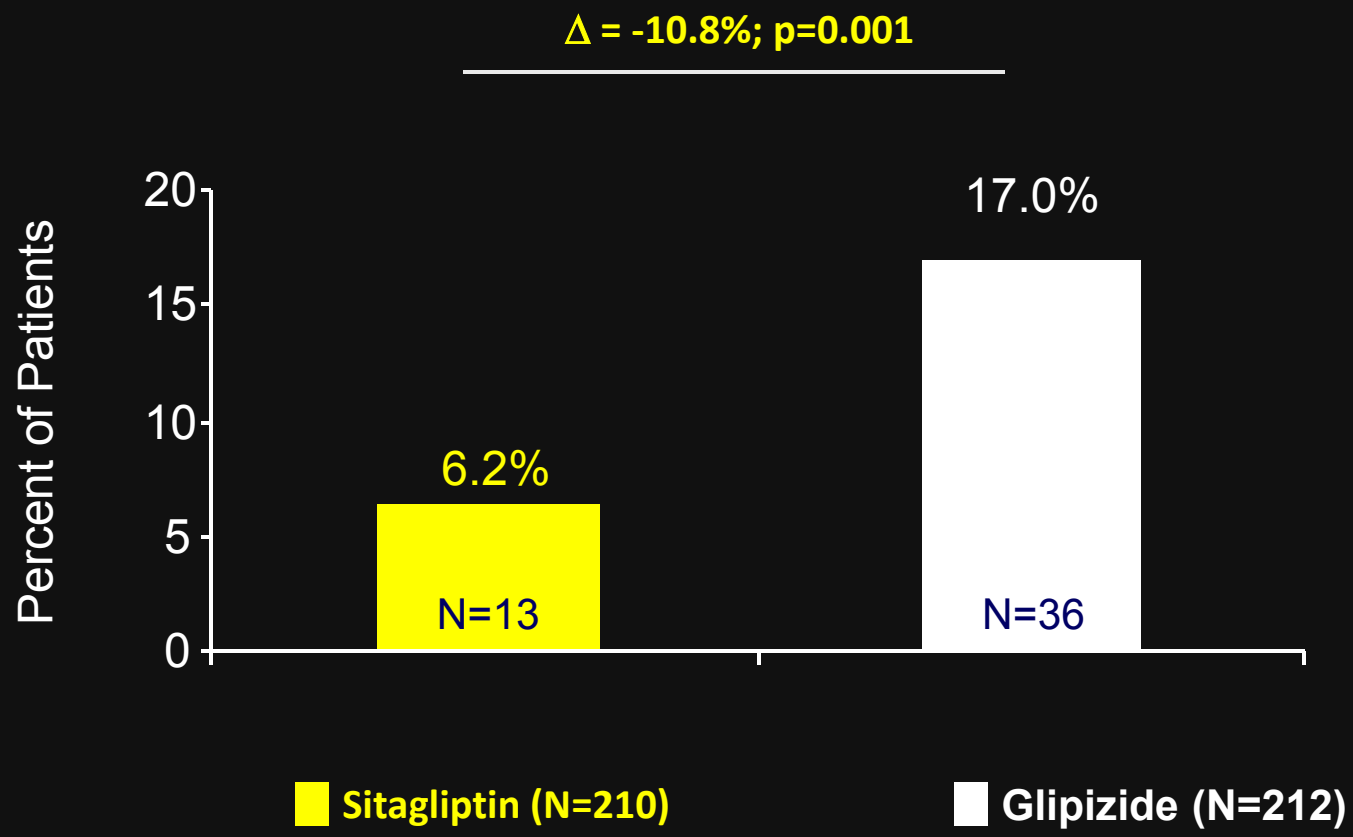
A1c over time: Moderate to Severe renal insufficiency in T2DM



CSR PN063 9/1/11

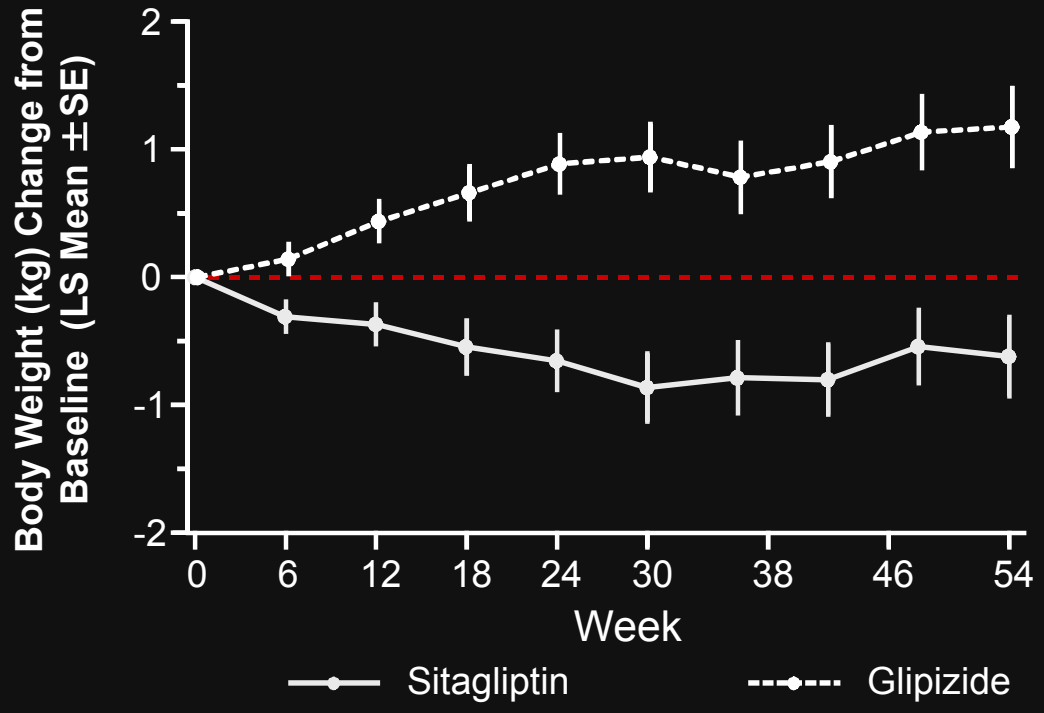
Lower hypoglycemia in Sitagliptin than Glipizide

(APaT, Excluding Data After Initiation of Glycemic Rescue Therapy)



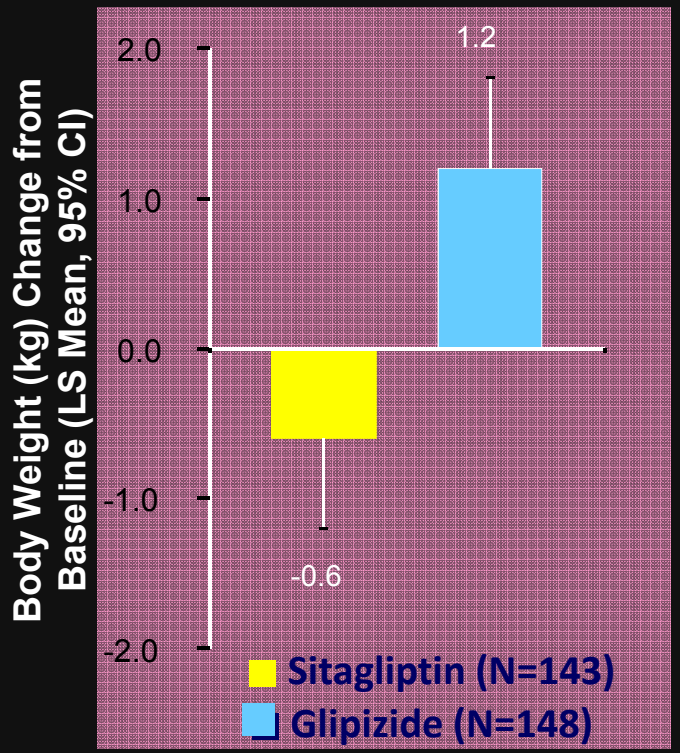
Body Weight

(APaT, Excluding Data After Initiation of Glycemic Rescue Therapy)



Week 54

Δ = -1.8 kg; p<0.001



CSR PN063 9/1/11

DPP-4 Inhibitors: Indication Comparison

		Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin
Mono	DPP4-I	V		V	V
Dual	MET	V	V	V	V
	SU	V	V	V	V
	TZD	V	V	V	
Triple	Met + SU	V			V
	Met + TZD	V			
Insulin	Insulin +	V			
	Insulin + met	V			
Approval	FDA	V		V	V
	EU	V	V	V	V

1. 2011 Januvia 제품 설명서, 2. 2011 가브스 제품 설명서, 3. 2011 온글리자 제품 설명서, 트라젠타 제품설명서

Versatile roles of the DPP-4i in the management of T2DM