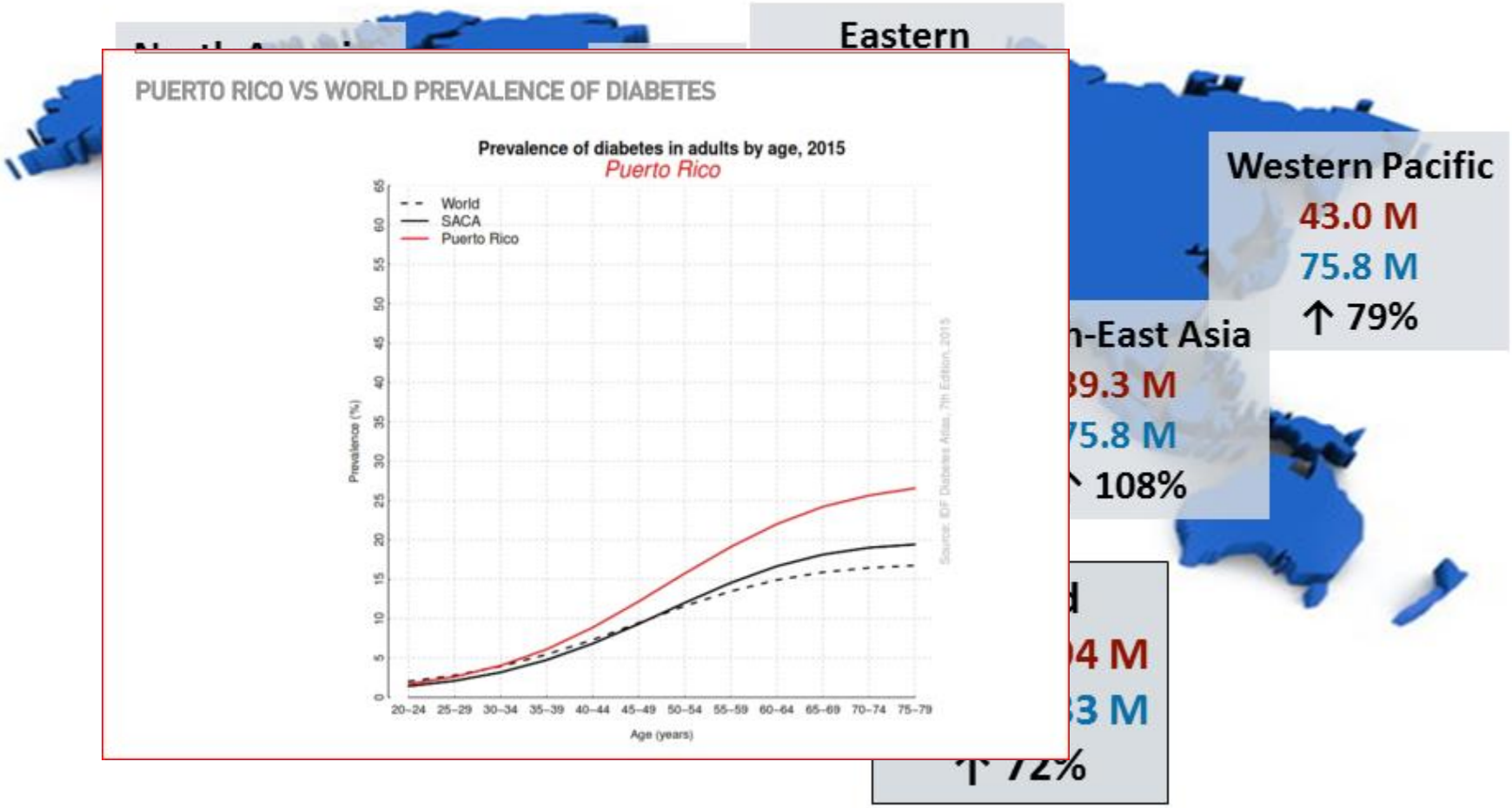
Challenges to optimal therapy: Selecting the Right Anti-Glycemic

Jorge De Jesús MD FACE

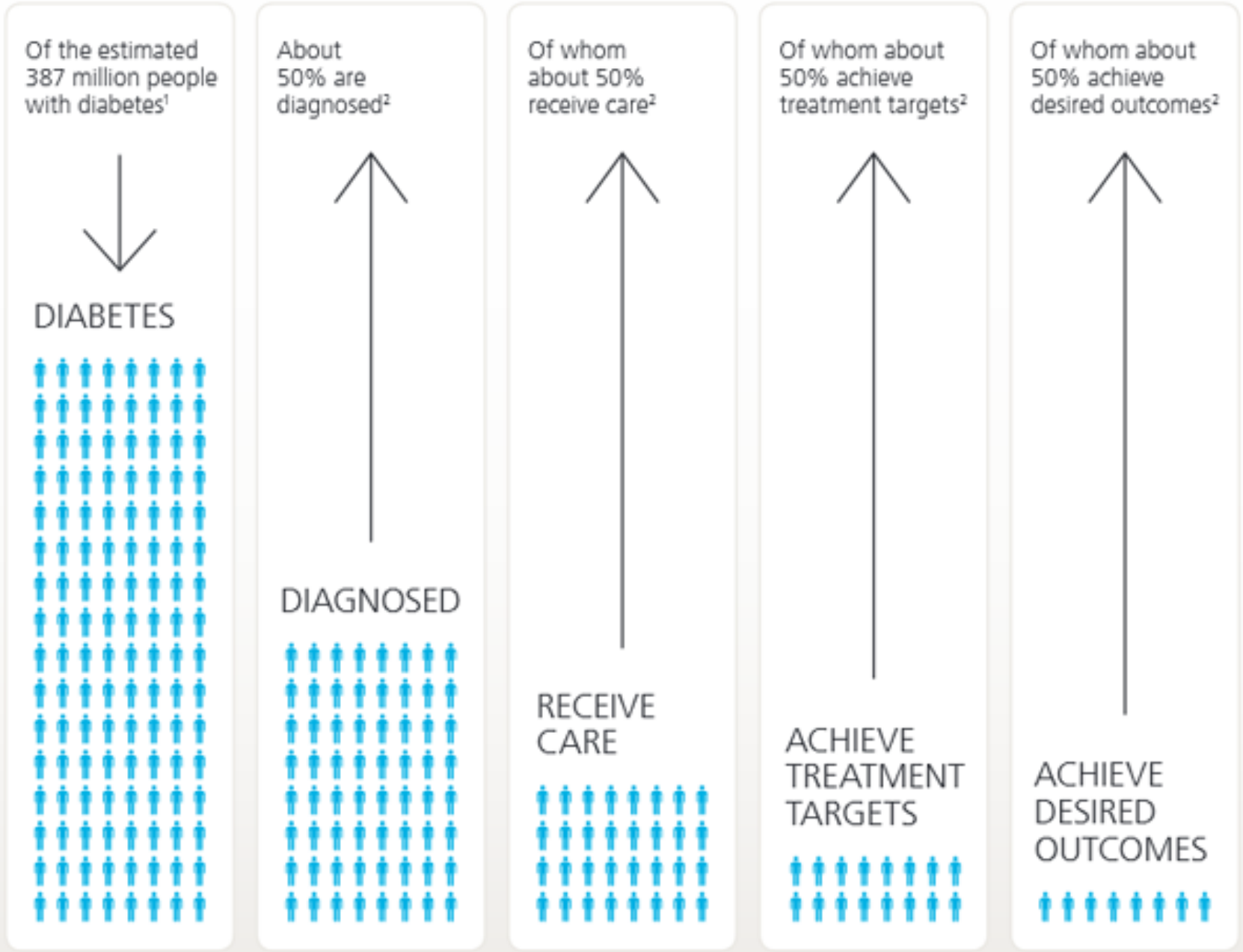
Global Projections for Diabetes: 2003-2025

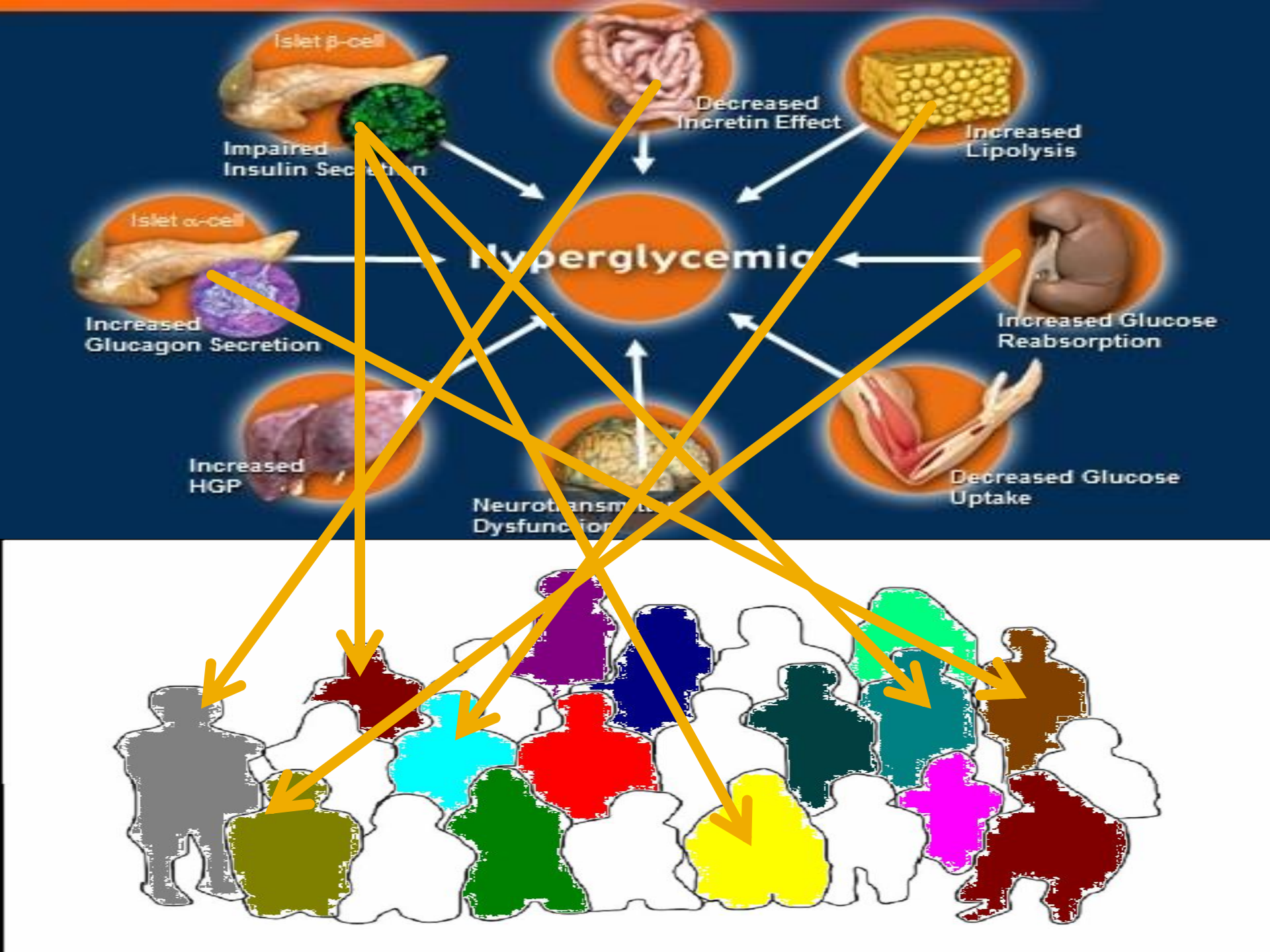
International Diabetes Federation
South and Central America



PUERTO RICO VS WORLD PREVALENCE OF DIABETES

Diabetes Atlas Committee. *Diabetes Atlas,* 2nd Edition. IDF; 2003.


Of the estimated 387 million people with diabetes[1]
DIABETES
About 50% are diagnosed[2]
DIAGNOSED
Of whom about 50% receive care[2]
RECEIVE CARE
Of whom about 50% achieve treatment targets[2]
ACHIEVE TREATMENT TARGETS
Of whom about 50% achieve desired outcomes[2]
ACHIEVE DESIRED OUTCOMES
Actual rates of diagnosis, treatment, targets and outcomes vary in different countries.


Islet β-cell
Decreased
Incretin Effect
Increased
Lipolysis
Impaired
Insulin Sec
Islet α-cell
Hyperglycemic
Increased
Glucagon Secretion
Increased Glucose
Reabsorption
Increased
HGP
Neurot
Dysfunc
Decreased Glucose
Uptake

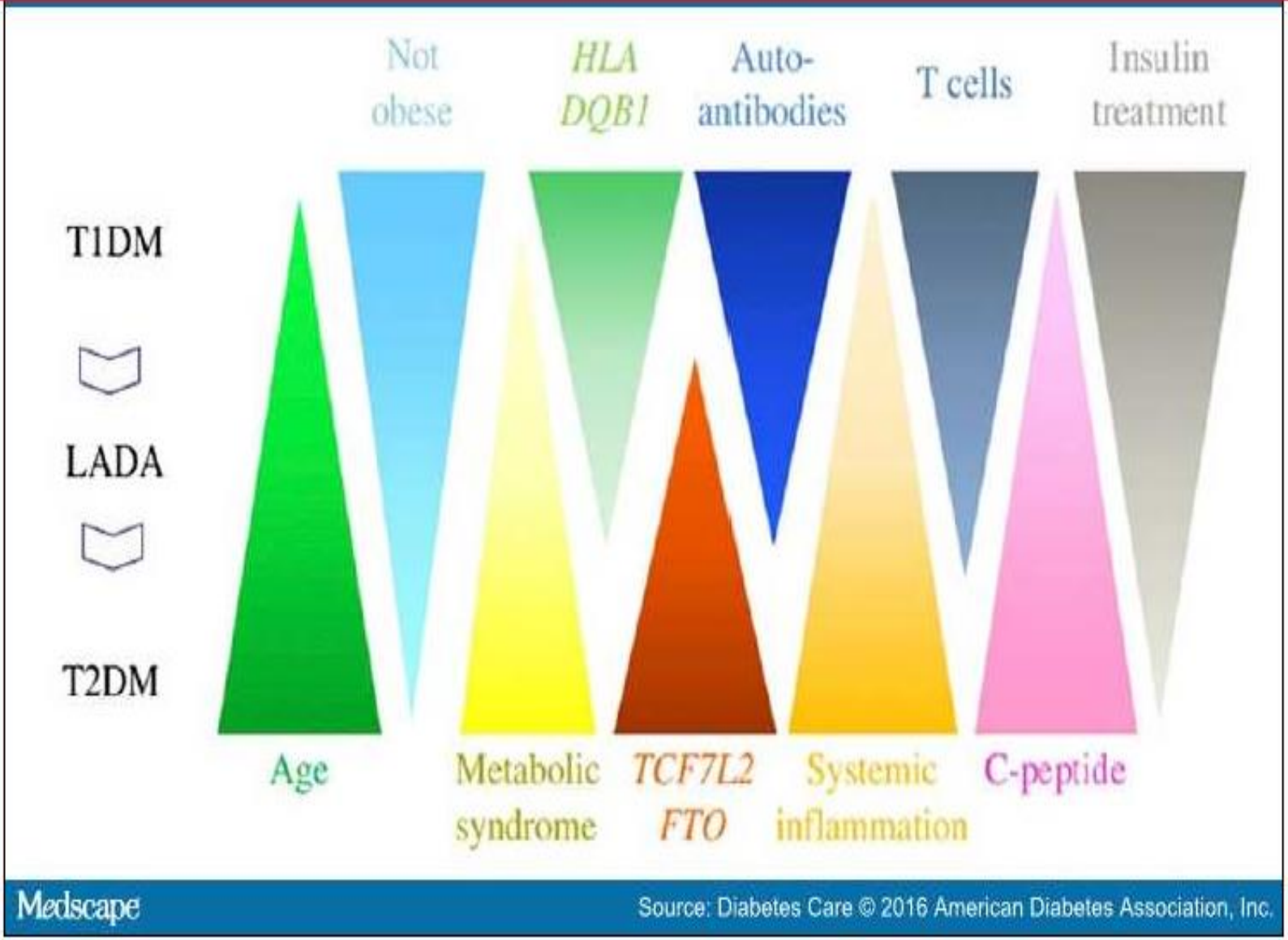


Figure 1.

Qualitative illustration of the spectrum of factors associated with different forms of DM, including the variable age at onset, lack of obesity, metabolic syndrome, genetic associations, different forms of immune changes, C-peptide secretion, and the need for insulin therapy. T1DM, type 1 DM; T2DM, type 2 diabetes. Adapted with permission from Leslie et al. (1).

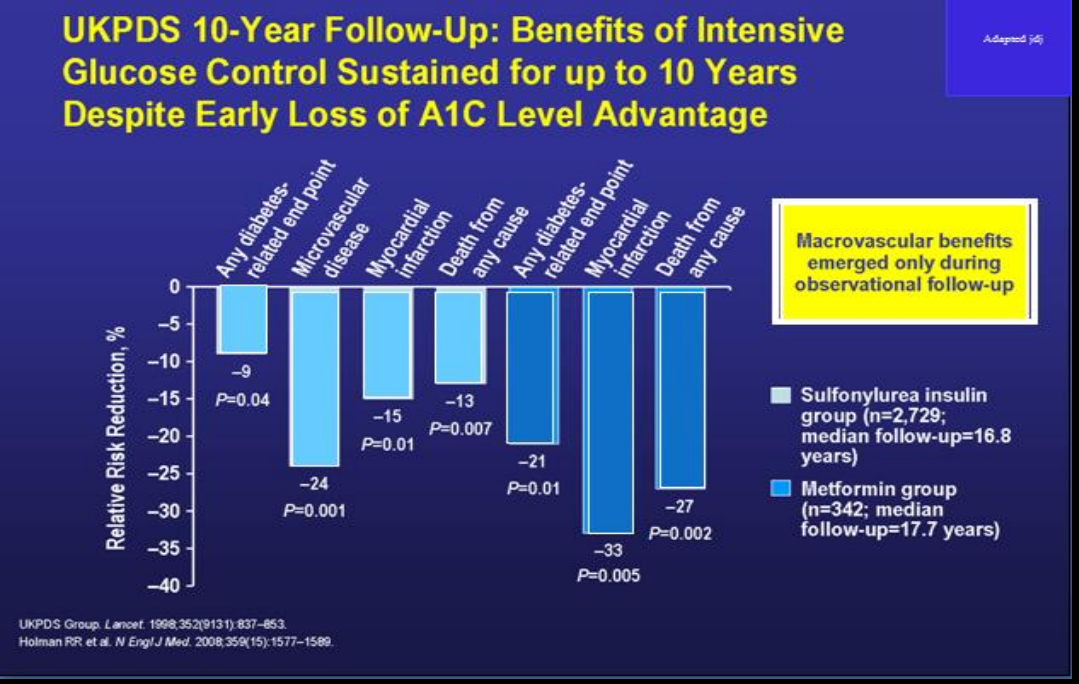
Decision process:

Metformin tolerance
Renal function
Age
Comorbidities; pancreatitis; others

TO MAKE A CHOICE

The Art of Medicine

AFTER THINKING ABOUT IT

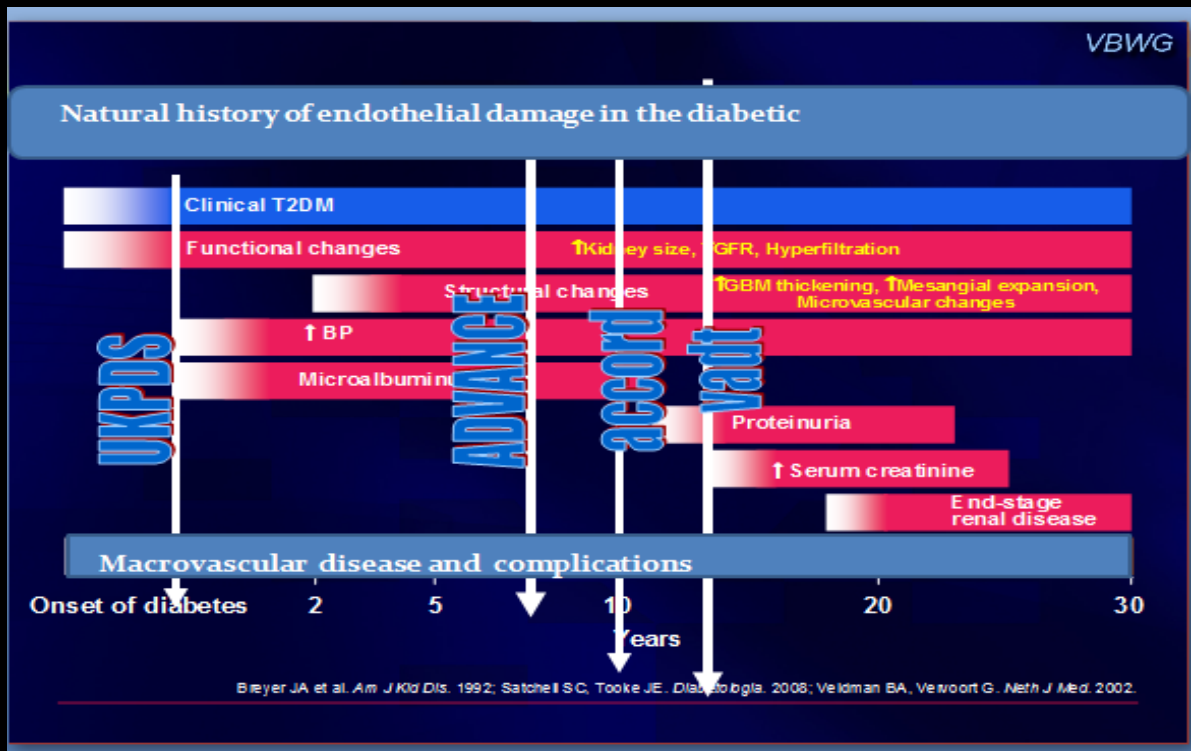


First challenge:

Benefits of early diagnosis and intervention

Then:

Avoid macrovascular and microvascular complications



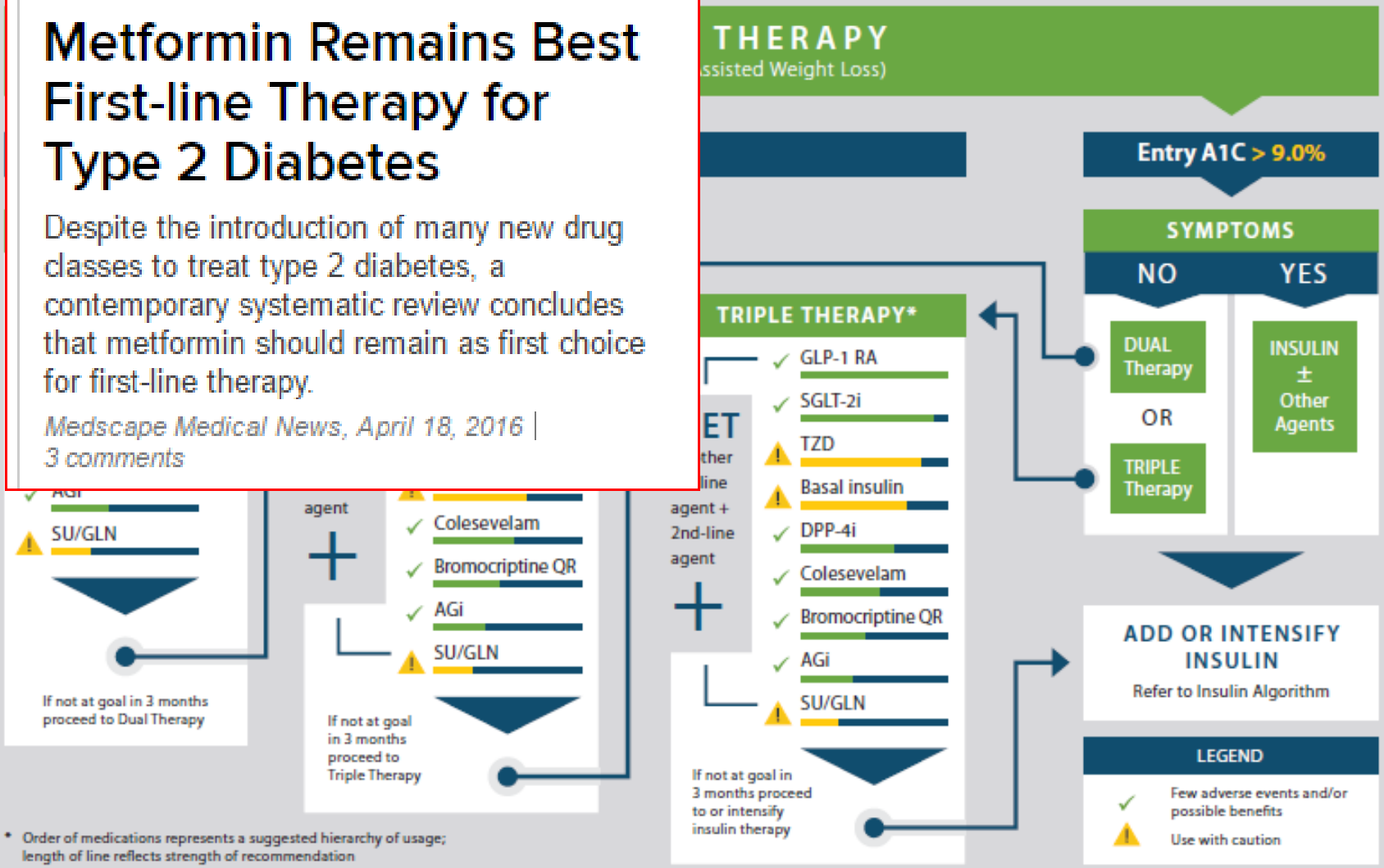
GLYCEMIC CONTROL ALGORITHM

DIABETES & ENDOCRINOLOGY NEWS

Metformin Remains Best First-line Therapy for Type 2 Diabetes

Despite the introduction of many new drug classes to treat type 2 diabetes, a contemporary systematic review concludes that metformin should remain as first choice for first-line therapy.

Medscape Medical News, April 18, 2016 | *3 comments*

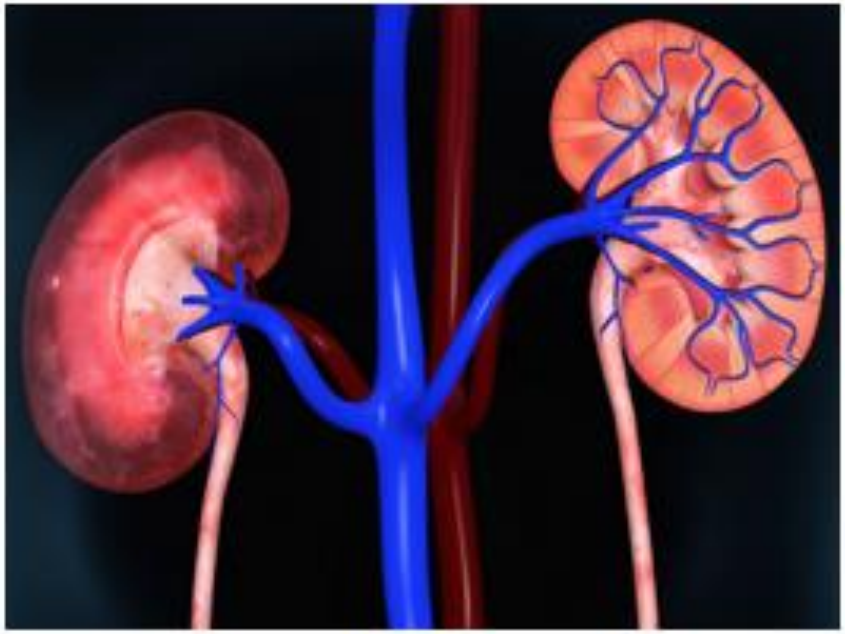


TOP MEDICAL NEWS FROM ACROSS MEDSCAPE

FDA: Metformin Safe for Some Patients With Renal Problems

Changing its course in response to mounting evidence, the agency said the diabetes drug can be used safely in patients with mild and, in some cases, moderate kidney impairment.

News Alerts, April 08, 2016 | 13 comments



Contraindicted in GFR<30ml/min

contraindicated GFR<30

Novel Antihyperglycemic Drugs (After Metformin Then What?)

- GLP-1- RA
- SGLT-2 inhibitors
- DPP4- Inhibitors

Raul: Taxi Driver ; age 54
T2DM x 7 years

Glimepiride 2 mg po once daily
Metformin 1000 mg po bid

Table 2. Raul's Clinical Presentation and Blood Test Results

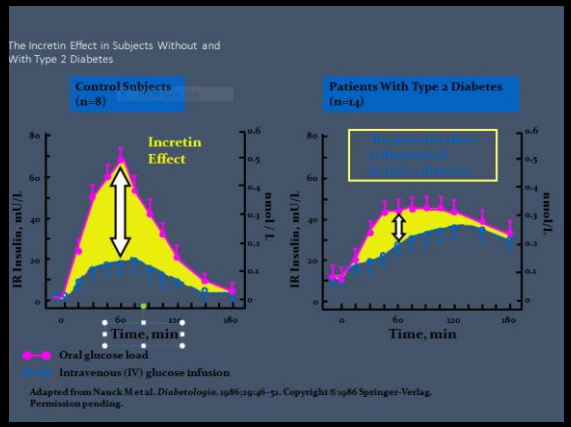
Height	175 cm
Weight	85.7 kg
BMI	28 kg/m^2
Heart rate	80 beats/min
Blood pressure (left arm)	130/80 mm Hg
Skin	Normal
Neurologic	Persistent, mild numbness and tingling in legs
Eye	Dilated fundus exam indicates early retinopathy
HbA1c	7.6%
Mean fasting plasma glucose	126 mg/dL (range: 115-140)
Mean postprandial plasma glucose	160 mg/dL (range: 140-200)
LDL cholesterol	90 mg/dL
HDL cholesterol	44 mg/dL
Triglycerides	240 mg/dL
eGFR	>90 mL/min/1.73 m^2
Serum creatinine	0.7 mg/dL

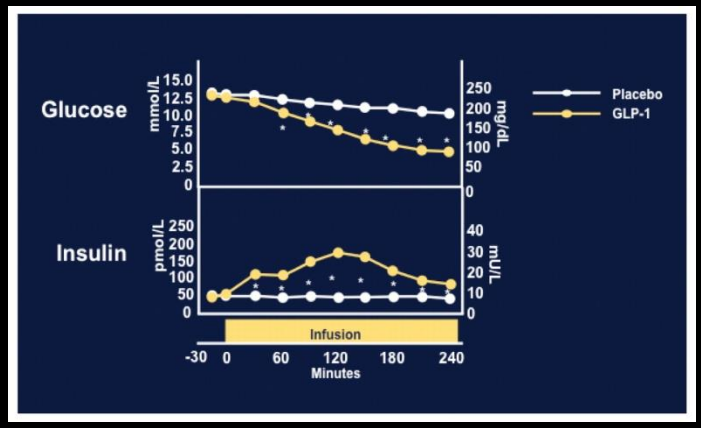
BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate.

Lack of adherence due to hypoglycemic episodes; refuses injections; concerned frequent urination due to his type of work

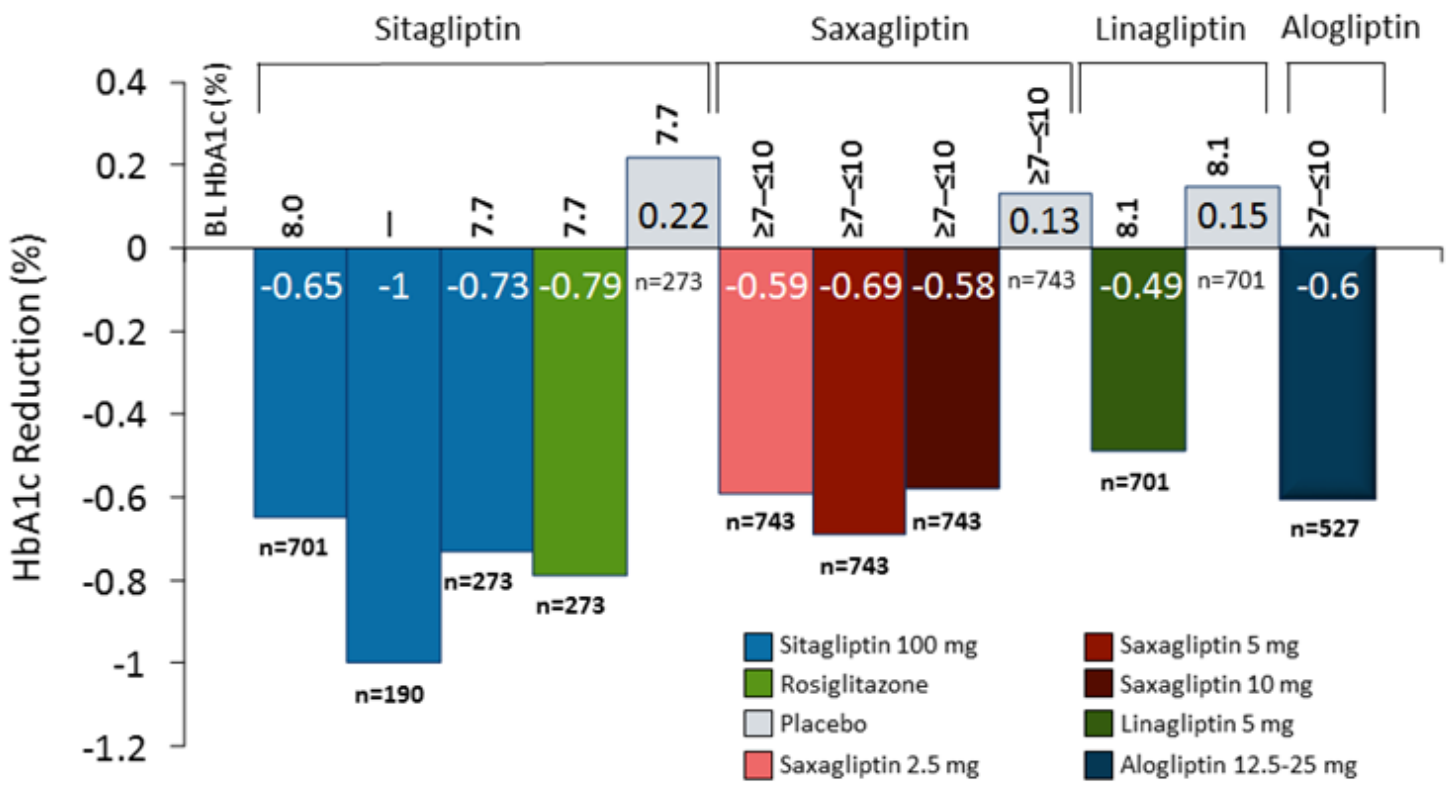
Rationale for using Incretin-Based Therapies in the Treatment of T2 DM

- Incretins play an important role in glucose homeostasis
- Incretin Effects are Diminished in T2DM
- Incretin based therapies (GLP-1RA and DPP4 inh)
- Target multiple defects in DM type 2, not addressed by traditional medications
- Not associated with hypoglycemia
- Either weight neutral or can cause weight loss(GLP-1 RA)





Efficacy of DPP4 inhibition added to Metformin Therapy



Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-43; Raz I, et al. *Curr Med Res Opin*. 2008;24:537-550; Scott R, et al. *Diabetes Obes Metab*. 2008;10:959-969; DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655; Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74; Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55.

DPP-4 Inhibitors Are Weight Neutral

Change in Body Weight From BL as Add-on to Metformin[a,b]

Saxagliptin 5 mg/day	-0.9 kg
Placebo	-0.9 kg
Sitagliptin 100 mg/day	-0.7 kg
Placebo	-0.6 kg
Linagliptin 5 mg/day	-0.4 kg
Placebo	-0.5 kg

a. http://www.ema.europa.eu/ema/
b. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74.

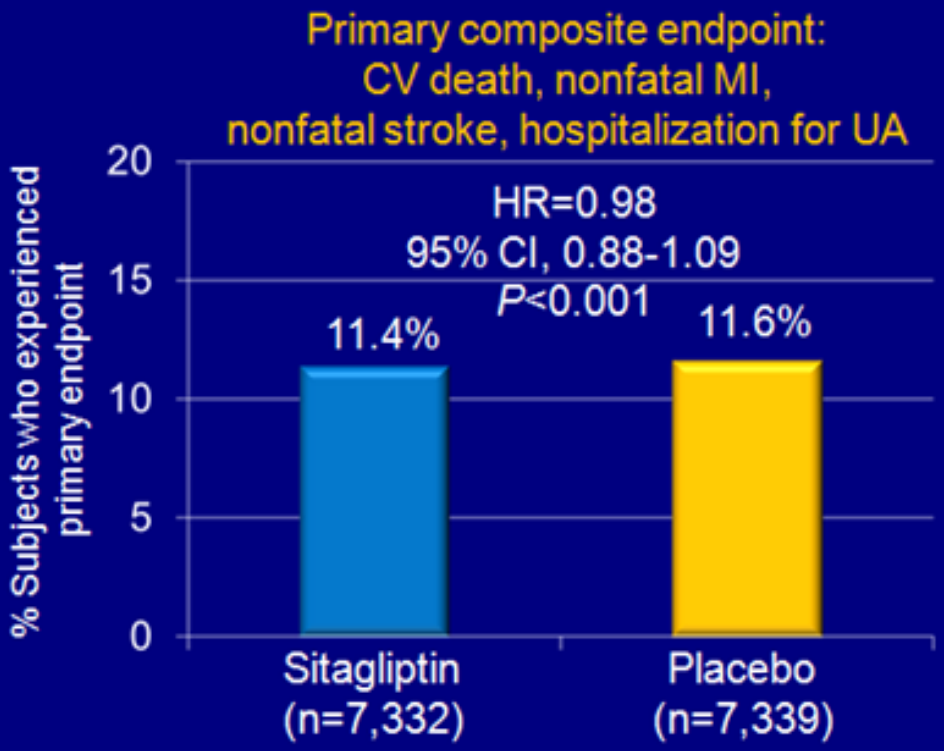
Network Meta-analysis: OADs Added on to Metformin

	Change in HbA1c (%)	Change in Body Weight (kg)	Overall Hypoglycemia
	Mean Diff.	Mean Diff.	RR
Placebo (ref)	0	0	1
SU	-0.79	+2.06	4.57
Meglitinides	-0.65	+1.77	7.50
TZDs	-0.85	+2.08	0.56
AGIs	-0.64	-1.80	0.42
DPP-4 inhibitors	-0.78	-0.14	0.63
GLP-1 RAs	-0.97	-1.74	0.89

Phung OJ, et al. *JAMA*. 2010;303:1410-1418.

ADA 2015 Scientific Sessions

TECOS: No Increased CV Risk With Sitagliptin Vs Placebo in High-Risk Subjects With Type 2 Diabetes



About TECOS

Cardiovascular safety study of the DPP-4 inhibitor, sitagliptin

Randomized, double-blind, placebo-controlled, event-driven trial

N=14,671 subjects with type 2 diabetes and CVD

Randomization + usual care*:

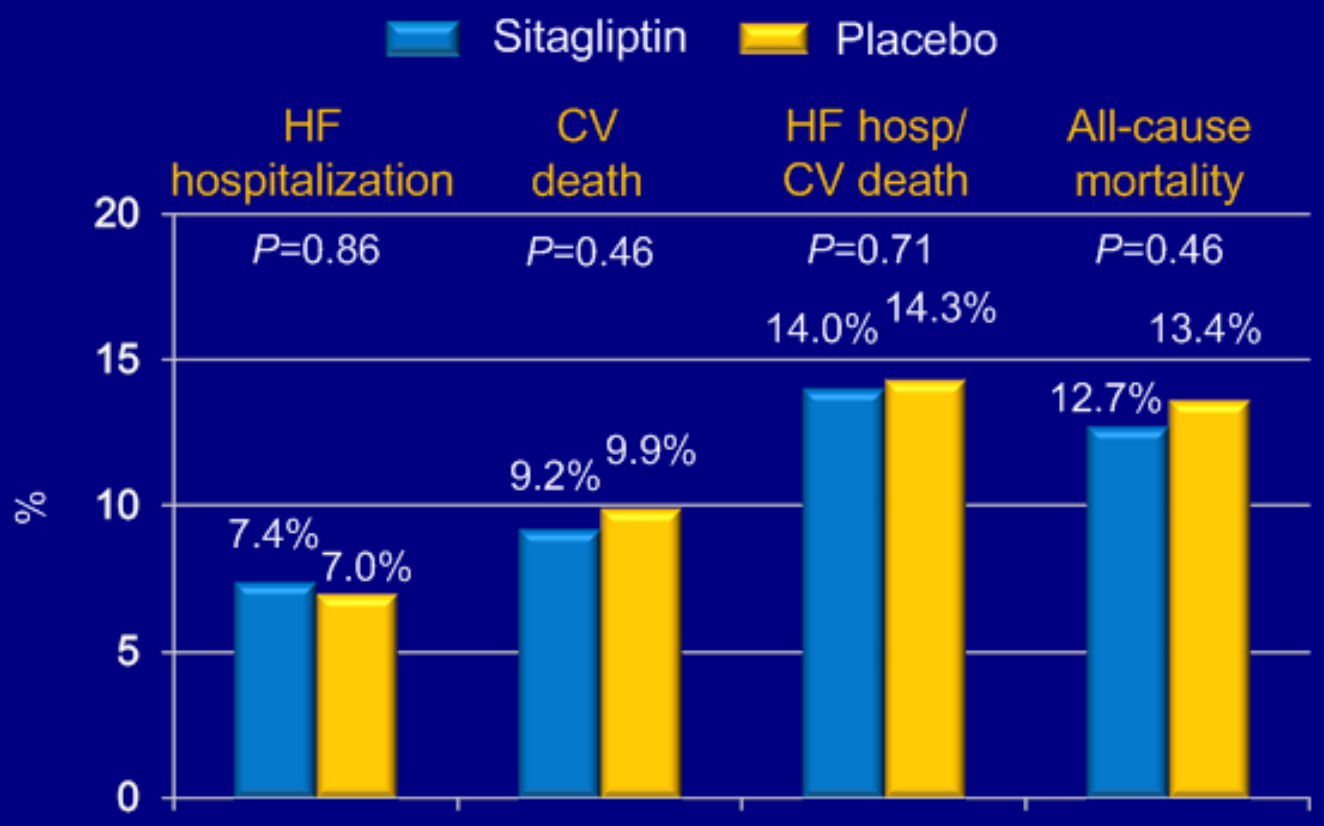
- Sitagliptin 100 mg/d†
- Placebo

TECOS=Trial Evaluating Cardiovascular Outcomes with Sitagliptin
HR=hazard ratio; UA=unstable angina
*Or 50 mg/d if baseline eGFR ≥30 and <50 ml/min/1.73 m^2; †Stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin)

Green JB, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1501352.

TECOS Substudy: Sitagliptin Not Associated With Heart Failure Onset in Subjects With Type 2 Diabetes

ESC Congress 2015



CV=cardiovascular; HF=heart failure

Van der Werf F, et al. Presented at ESC Congress 2015. London, England, UK. Abstract 3147.

SAVOR, EXAMINE, and TECOS Baseline Characteristics

	SAVOR n = 16,492	EXAMINE n = 5380	TECOS n = 14,671
	Saxagliptin vs Placebo	Alogliptin vs Placebo	Sitagliptin vs Placebo
Mean age, y	65	61	66
Median duration of diabetes, y	10.3	7.3	10.0
Mean baseline HbA_{1c}, %	8.0	8.0	7.2
Hypertension, %	82	83	86
Dyslipidemia, %	71	Not reported	77
Current smoker, %	Not reported	14	11
Previous HF, %	13	28	18
Median duration of follow-up, y	2.1	1.5	3.0

a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Bethel MA, et al. *Diabetes Obes Metab*. 2015;17:395-402.

TECOS, EXAMINE, and SAVOR

Hospitalization for HF

Hospitalization for HF	EXAMINE[a]	TECOS[b]	SAVOR[c]
HR (95% CI)	1.07 (0.79-1.46)	1.00 (0.83-1.20)	1.27 (1.07-1.51)
P value	.657	.98	.007

a. Zannad F, et al. *Lancet*. 2015;385:2067-2076; b. Green JB, et al. *N Engl J Med*. 2015;373:232-242; c. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

Ongoing CAROLINA and CARMELINA Trials

Study	CAROLINA®[a]
DPP-4 inhibitor	Linagliptin
Comparator	Sulfonylurea
N	6000
Results	2017

Study	CARMELINA[b]
DPP-4 inhibitor	Linagliptin
Comparator	Placebo
N	8300
Results	2017

a. Marx N, et al. *Diab Vasc Dis Res*. 2015;12:164-174.
b. Clinicaltrials.gov. NCT01897532.


Severe
Joint Pain
from
Diabetes Meds

Lydia : 71 female T2DM x 10 years

Table 5. Leah's Current Medications

Medication	Dosage
Metformin	500 mg PO twice daily
Dapagliflozin	10 mg PO once daily
Atorvastatin	20 mg PO once daily
Enalapril	10 mg PO once daily
Aspirin	81 mg PO once daily

PO = oral administration.

CVD disease
Mild arthritis
Hypertension
Used dpp4 inh and changed to dapaglifozin

Glp-1

Basal Insulin

Table 6. Leah's Clinical Presentation and Blood Test Results

Height	162 cm
Weight	73.4 kg
BMI	31 kg/m^2
Heart rate	75 beats/min
Blood pressure	130/80 mm Hg
Skin	Normal
Neurologic	Mild peripheral neuropathy
Eye	Dilated fundus exam reveals retinopathy
Abdomen	Normal
Mean fasting plasma glucose	150 mg/dL (range: 125-173)
Mean postprandial plasma glucose	190 mg/dL (range: 181-226)
HbA1c	8.5%
LDL	80 mg/dL
HDL	45 mg/dL
Triglycerides	150 mg/dL
eGFR	45 mL/min/1.73 m^2
Albumin	3.5 g/dL
BUN	16 mg/dL
Serum creatinine	1.21 mg/dL

Individualization of Glycemic Targets for Adults With Diabetes

Lowering A1C below or around 7.0% shown to reduce

- Microvascular complications
- Macrovascular disease*

More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events

More stringent (<6.5%)

- Short diabetes duration
- Long life expectancy
- No significant CVD

Less stringent (<8%)

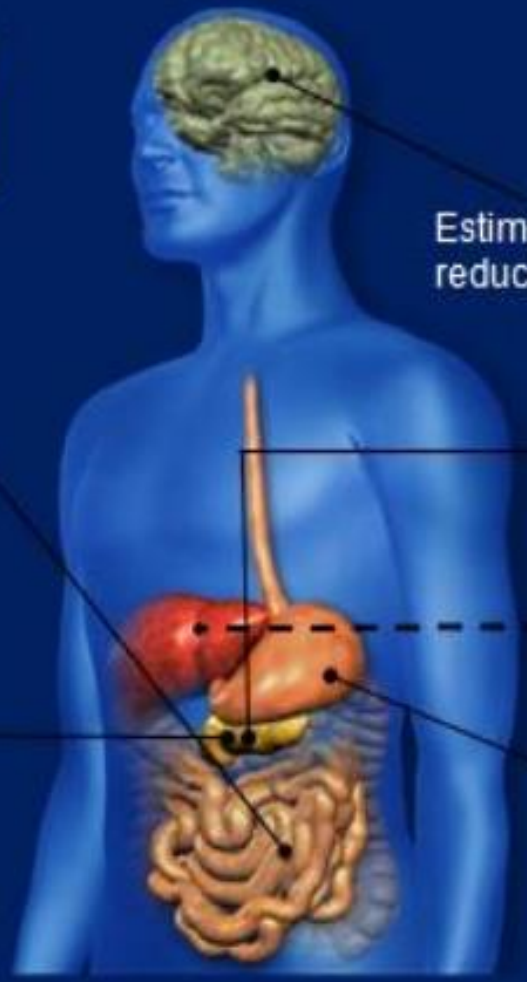
- Severe hypoglycemia history
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbidities
- Long-term diabetes in whom general A1C target difficult to attain†

Targets shown are for nonpregnant adults

*If implemented soon after diagnosis; †Despite diabetes self-management, appropriate glucose monitoring effective doses of antihyperglycemic agents (including insulin)

CVD=cardiovascular disease

Efectos del GLP-1 en humanos: Descripción del Rol Glucorregulador de las Incretinas



GLP-1 segregado ante la ingesta de alimentos

↓ Beta-cell workload

Estimula la saciedad y reduce el apetito

↑ Beta-cell response

Células alfa:
↓ Secreción posprandial de glucagón

Hígado:
reducción de la producción hepática de glucosa

Células beta:
Mejora la secreción de insulina dependiente de glucosa

Estómago:
Ayuda a regular el vaciado gástrico

Short-Acting vs Long-Acting GLP-1 RAs: Pharmacokinetic Differences

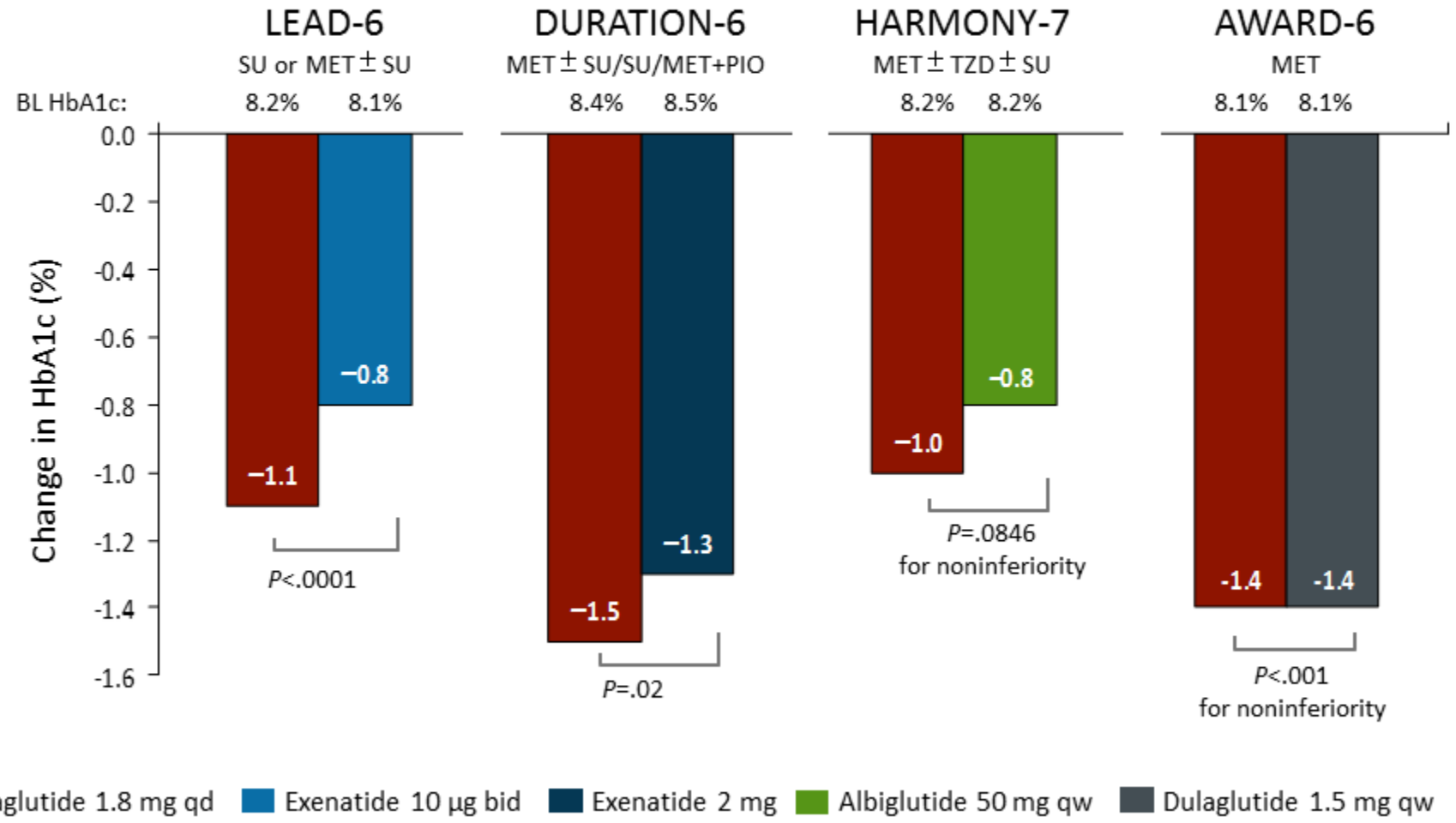
Increasing protraction

Category	Agent	Half-life	T_{max}
Short-acting GLP-1 RAs	**Exenatide bid**[a]	2.4 hours	2 h
	Lixisenatide[a]	2.7-4.3 hours	1.25-2.25 hours
Long-acting GLP-1 RAs	**Liraglutide**[a]	13 hours	8-12 hours
	Dulaglutide[b]	90 hours	24-48 hours
	Albiglutide[a]	5 days	3-5 days
	Semaglutide[a]	~7 days	1-1.5 days
	Exenatide qw[g]	7-14 days	6-7 weeks

Novo-Nordisk's Oral GLP-1 Diabetes Treatment: An Update

a. www.ema.europa.eu/ema/; b. Barrington P, et al. *Diabetes Obes Metab.* 2011;13:434-438; c. Fineman M, et al. *Clin Pharmacokinet.* 2011;50:65-74.

Glycemic Control With GLP-1 RAs: Head-to-Head Studies



Buse JB, et al. *Lancet.* 2009;374:39-47 (LEAD-6); Buse JB, et al. *Lancet.* 2013;381:117-124 (DURATION-6); ClinicalTrials.gov (NCT01029886) (DURATION-6); Pratley RE, et al. *Lancet Diabetes Endocrinol.* 2014;2:289-297 (HARMONY-7); Dungan KM, et al. *Lancet.* 2014;384:1349-1357 (AWARD-6).

Effect of GLP-1 RA on SBP

Trial	No of Patients		Mean Change		Weight (%)	Weighted Mean Difference (95% CI)
	GLP-1 RA Group	Control Group	GLP-1 RA Group	Control Group		
Astrup 2010	82	78	-6.9 (1.3)	-4.0 (1.2)	10.59	-2.90 (-3.29 to -2.51)
Apovian 2010	96	98	-9.4 (1.4)	-2.0 (1.4)	10.59	-7.47 (-7.86 to -7.08)
Bergenstal 2010	160	166	-3.2 (12.7)	0.8 (12.7)	8.72	-4.00 (-6.76 to -1.24)
Bunck 2009	36	33	-3.5 (12.8)	0.9 (18.0)	4.09	-4.40 (-11.83 to -3.03)
Davies 2009	118	117	-2.9 (13.0)	0.7 (13.0)	8.05	-3.60 (-6.93 to -0.27)
Moretto 2008	78	77	-4.3 (13.3)	-0.08 (12.3)	7.23	-4.22 (-8.25 to -0.19)
Garber 2009	217	212	-3.6 (14.1)	0.7 (13.7)	8.86	-4.30 (-6.93 to -1.67)
Zinman 2009	178	177	-5.6 (14.7)	-1.1 (16.0)	8.21	-4.50 (-7.69 to -1.31)
Kendall 2005	241	247	-2.0 (15.0)	1.1 (14.7)	8.85	-3.10 (-5.74 to -0.46)
Buse 2004	129	123	0.8 (15.7)	-1.6 (14.3)	7.61	-2.40 (-1.30 to 6.10)
Diamant 2010	233	223	-3.0 (16.6)	-0.6 (14.9)	8.56	-2.40 (-5.29 to -0.49)
Heine 2005	282	267	-4.1 (17.8)	-0.6 (16.0)	8.63	-3.50 (-6.33 to -0.67)
Overall					100.0	-3.57 (-5.49 to -1.66)

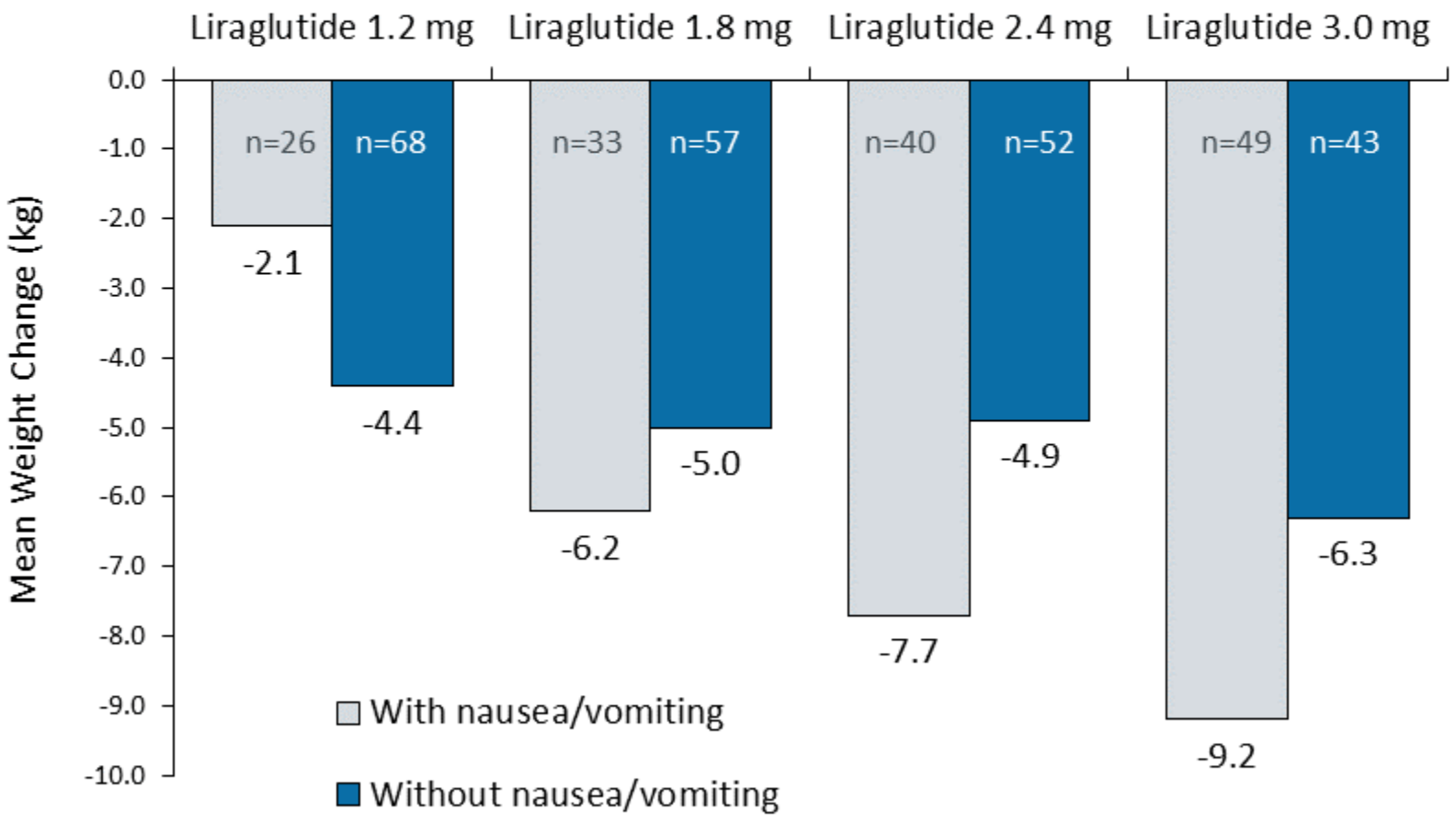
Vilsbøll T, et al. *BMJ*. 2012;344:d7771.

Effect of GLP-1 RA on DBP

Trial	No of Patients		Mean Change		Weight (%)	Weighted Mean Difference (95% CI)
	GLP-1 RA Group	Control Group	GLP-1 RA Group	Control Group		
Astrup 2010	82	78	-2.9 (0.8)	-1.1 (0.8)	19.34	-1.80 (-2.05 to -1.55)
Moretto 2008	78	77	-2.9 (8.4)	0.1 (8.3)	4.60	-3.00 (-5.63 to -0.37)
Apovian 2010	96	98	-2.2 (1.0)	0.5 (1.0)	19.20	-2.69 (-2.97 to -2.41)
Zinman 2009	178	177	-1.9 (9.3)	-0.8 (9.3)	7.08	-1.10 (-3.04 to 0.84)
Bergenstal 2010	160	166	-1.6 (7.5)	-0.2 (8.1)	8.36	-1.40 (-3.09 to 0.29)
Heine 2005	282	267	-1.2 (10.3)	-0.8 (9.8)	8.43	-0.40 (-2.08 to 1.28)
Diamant 2010	233	223	-1.2 (10.1)	-0.7 (8.7)	8.17	-0.50 (-2.23 to 1.23)
Davies 2009	118	117	-0.5 (7.6)	0.9 (7.6)	7.08	-1.40 (-3.34 to 0.54)
Buse 2004	129	123	-0.5 (9.4)	-0.6 (8.6)	5.89	-0.13 (-2.09 to 2.35)
Kendall 2005	241	247	-0.4 (8.9)	-0.9 (9.0)	8.99	-0.50 (-1.09 to 2.09)
Bunck 2009	36	33	-0.3 (6.2)	1.7 (8.4)	2.87	-2.00 (-5.51 to 1.51)
Overall					100.0	-1.38 (-2.02 to -0.73)

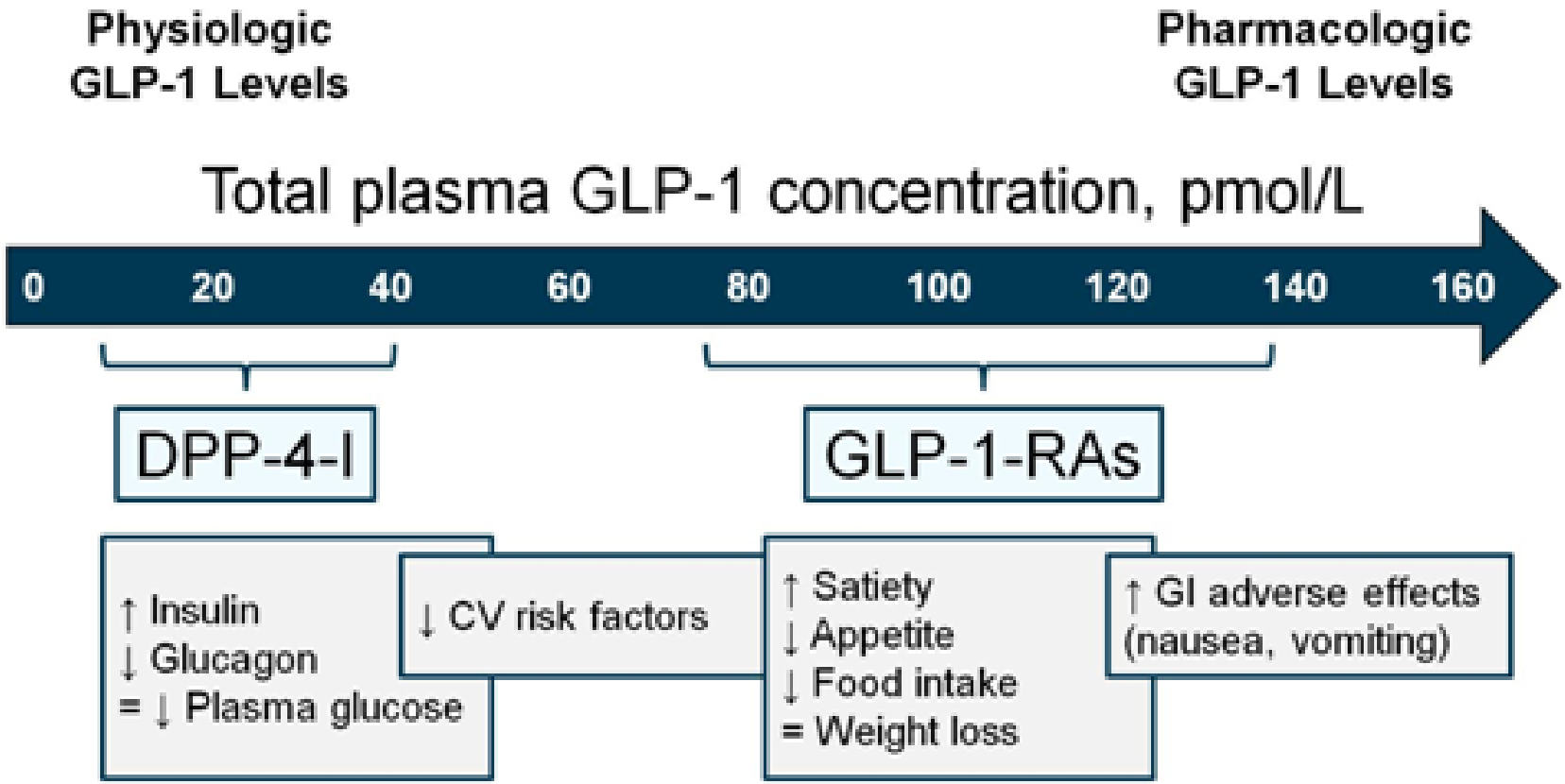
Vilsbøll T, et al. *BMJ.* 2012;344:d7771.

Effect of Liraglutide Dose on Mean Weight Change Response



Lean ME, et al. *Int J Obes (Lond).* 2014;38:689-697.

Dose-Related Effects of GLP-1



Courtesty of Vilsbøll T.

CV Effects of GLP-1 Receptor Activation

Improved weight, SBP, lipids
Improved endothelial function
Increased vasorelaxation
Increased peripheral and coronary flow
Increased ventricular function
Decreased microvascular permeability

Effects in isolated vessels/hearts and GLP-1 receptor localization to CV tissues indicate some effects may be direct

Okerson T, et al. *Cardiovasc Ther*. 2012;30:e146-e155.

Ongoing GLP-1 Receptor Agonist CV Outcomes Studies

Study	LEADER[a]
GLP-1 Agonist	Liraglutide
Comparator	Placebo
N	16,500
Results	2016

Study	EXSCEL[b]
GLP-1 Agonist	Exenatide LR
Comparator	Placebo
N	5400
Results	2018

Study	REWIND[d]
GLP-1 Agonist	Dulaglutide
Comparator	Placebo
N	8300
Results	2019

Study	SUSTAIN 6[c]
GLP-1 Agonist	Semaglutide
Comparator	Placebo
N	6000
Results	2016

a. Marso SP, et al. *Am Heart J*. 2013;166:823-830; b. Clinicaltrials.gov. NCT01144338; c. Clinicaltrials.gov. NCT01720446; d. Clinicaltrials.gov. NCT01394952.

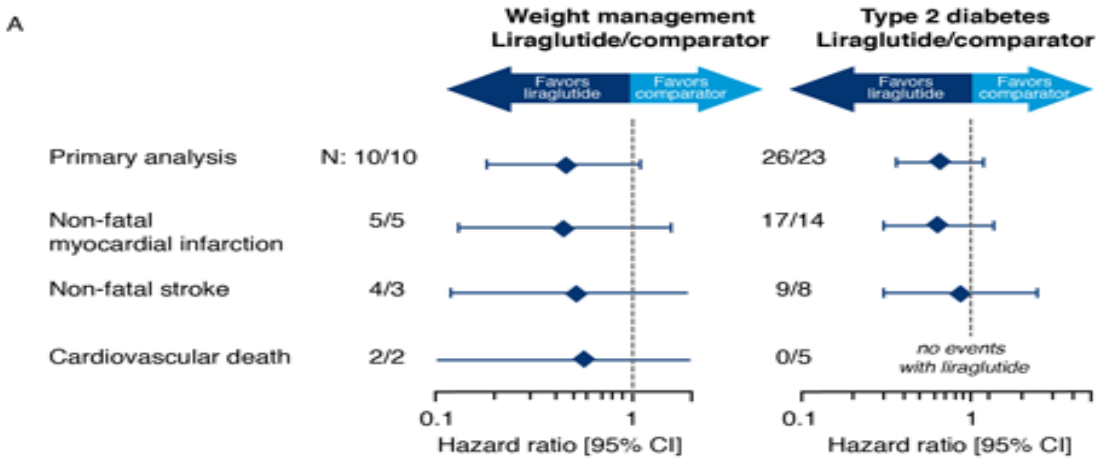
Medscape Medical News

Top-Line Data Show CV Benefit for Liraglutide in Type 2 Diabetes

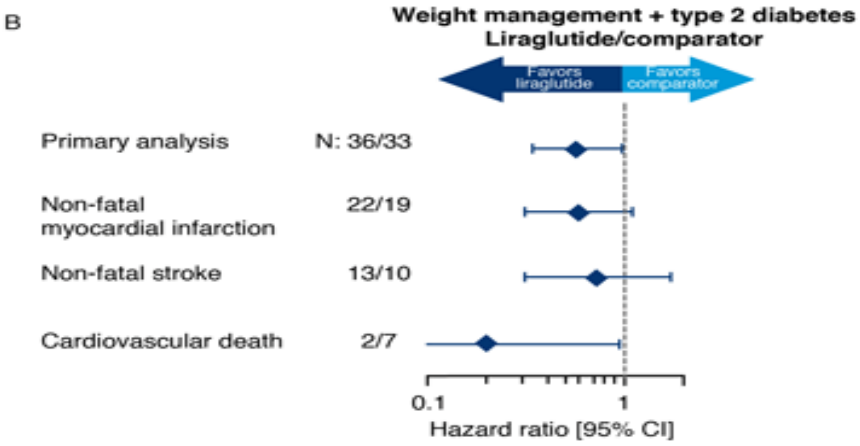
Miriam E Tucker

March 04, 2016

Figure 1: Overall MACE analysis for total liraglutide vs. total comparator in the A) weight management (left) or type 2 diabetes (right) trials and B) pooled weight management and type 2 diabetes trials.



N: number of MACE contributing to the analysis

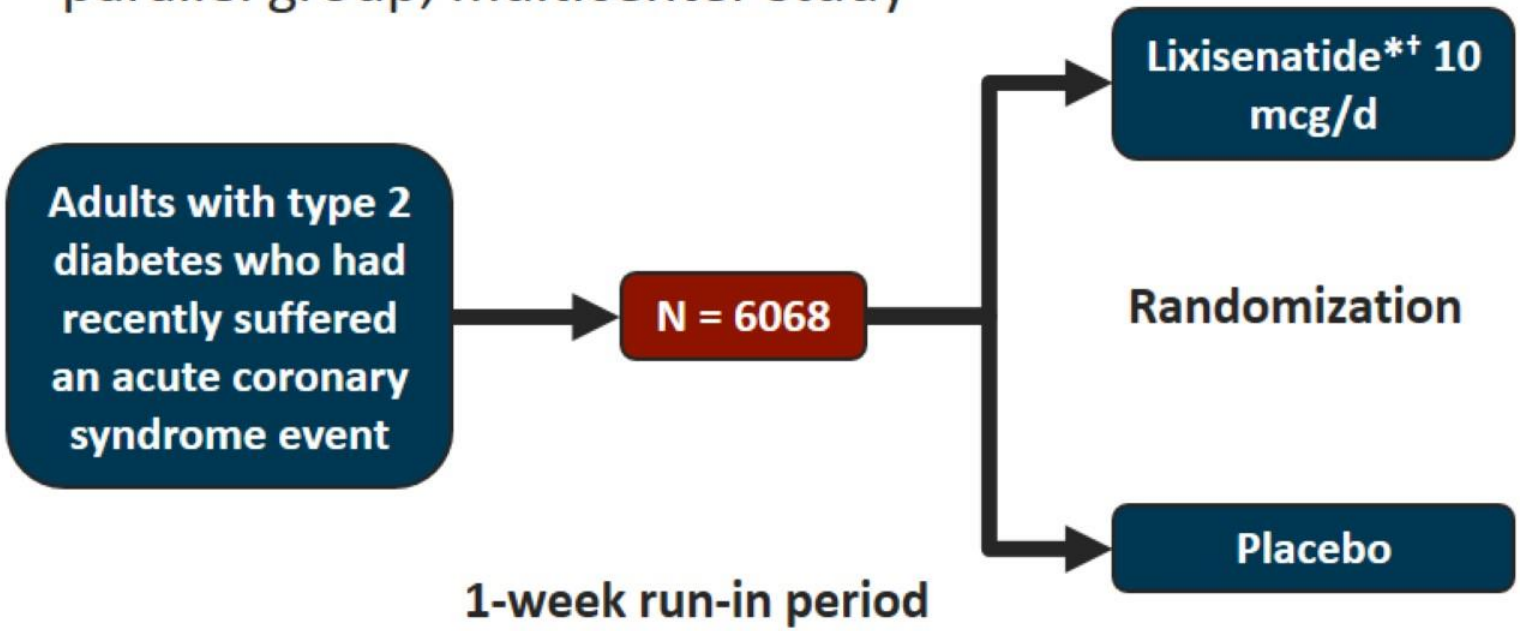


N: number of MACE contributing to the analysis

ELIXA

Study Design

- Phase 3b randomized, double-blind, placebo-controlled, parallel group, multicenter study



*The US FDA has not yet approved this medication for use.
†Up or down-titrated to maximum 20 mcg/d
Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

ELIXA

No CV Risks of Benefits

	Lixisenatide 10 mcg/d* (N = 3034)		Placebo (N = 3034)		HR (95% CI)	*P* Value
	Patients With Event	No. of Events/ 100 Patient-Yr	Patients With Event	No. of Events/ 100 Patient-Yr		
Death from CV causes, nonfatal stroke, nonfatal MI, or unstable angina — no. (%)	399 (13.2)	6.3	406 (13.4)	6.4	1.02 (0.89-1.17)	.81

*The US FDA has not yet approved this medication for use.

Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

Potential for GLP-1 RAs as First-Line Therapy

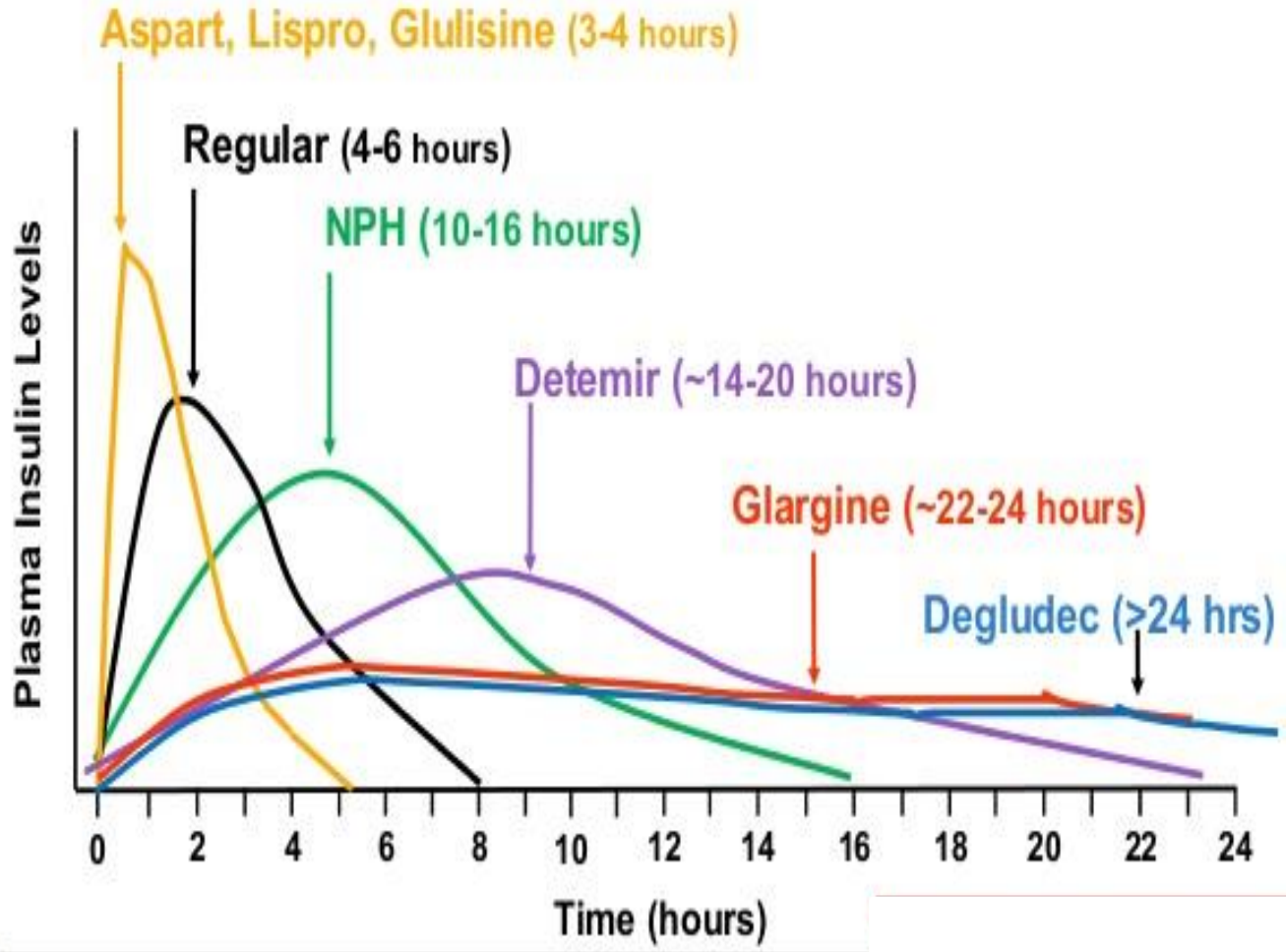
- Metformin will likely remain first-line therapy
- Increasing clinical research into clinical effects of GLP-1 RAs but no current evidence that these agents improve insulin sensitivity
- Can we identify early responders to treatment?
- Cost of GLP-1 RAs currently high; may be a barrier for some

Cernea S, et al. *Diabetes Care*. 2011;34(suppl 2):S264-S271.[8]

69 y/o male pt . DM 2 x 5 years

- Sitagliptin / meformin x 5 years
- Lost from follow up
- Developed balanitis and has phimosis
- A1c=9%
- FBS= 265
- Continued above treatment ;
- added basal insulin;
- stress diet and excercise

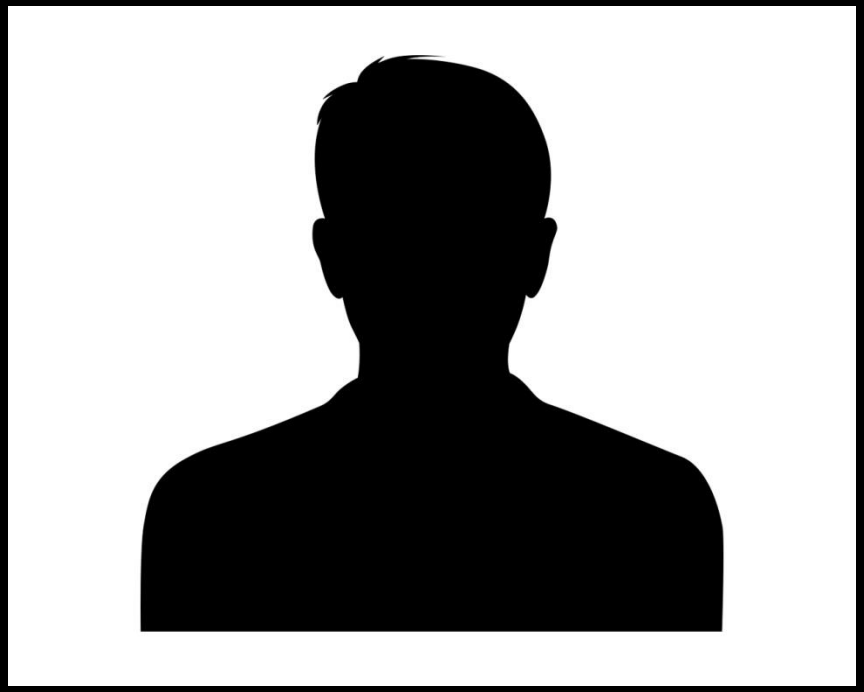
Insulins Available



42 y/o male CKD pending kidney transplant

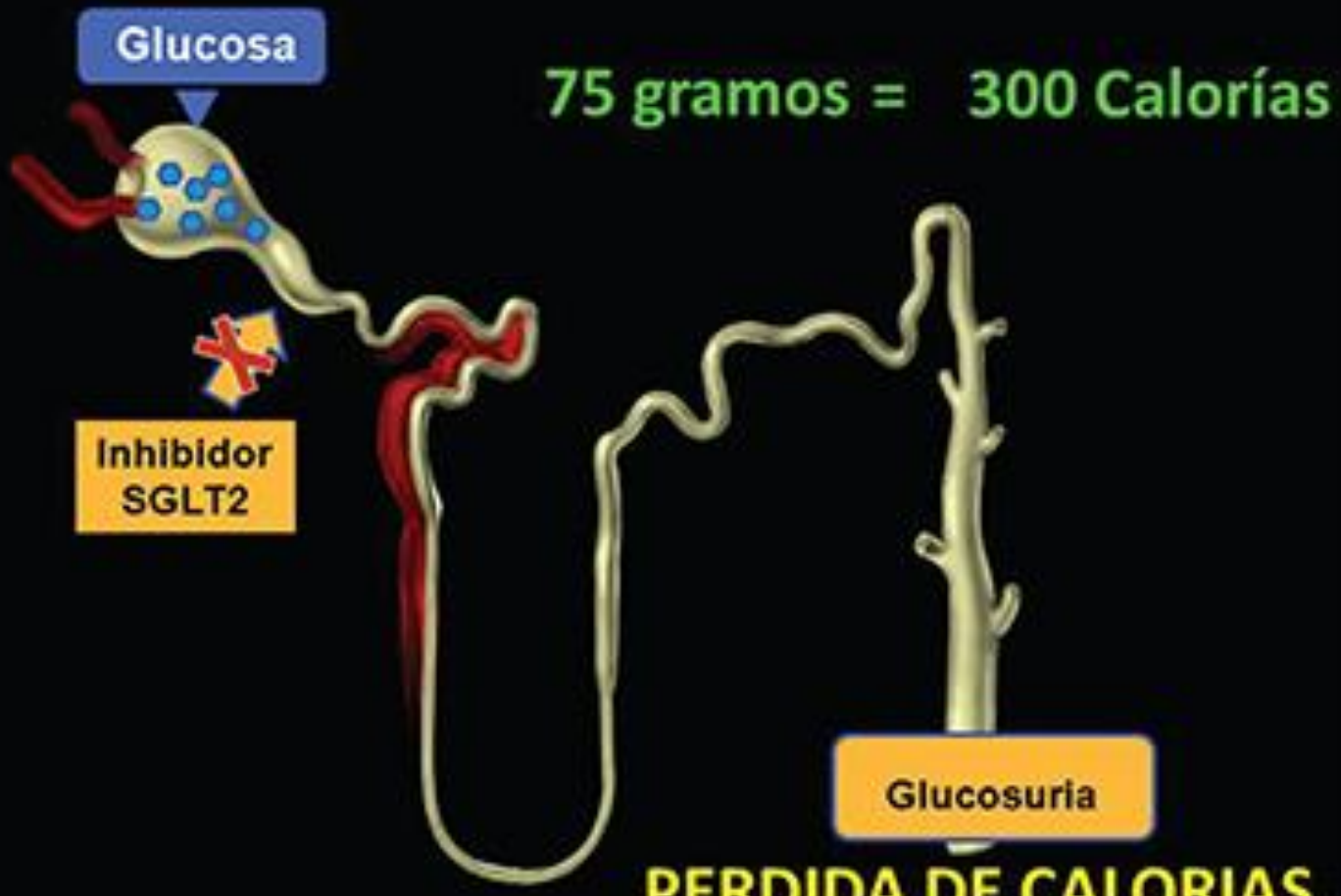
- Pt was on 70/30 mix once in am
- A1c=9.5%
- Frequent hypoglycemic reactions
- Pt was started on basal bolus regimen with Glargine and Humalog

48 male DM2; CAD ; PAD;



- 48 male pt
- s/p coronary bypass x4
- Recent intervention for PAD
- DM 2 uncontrolled
- Metformin 1000 bid
- Sitagliptin 100
- Uncontrolled

Inhibidores de SGLT2
Mecanismo de Acción



Efficacy and Safety: SGLT2 Inhibitor vs Sitagliptin (DPP-4 Inhibitor) Added to Metformin

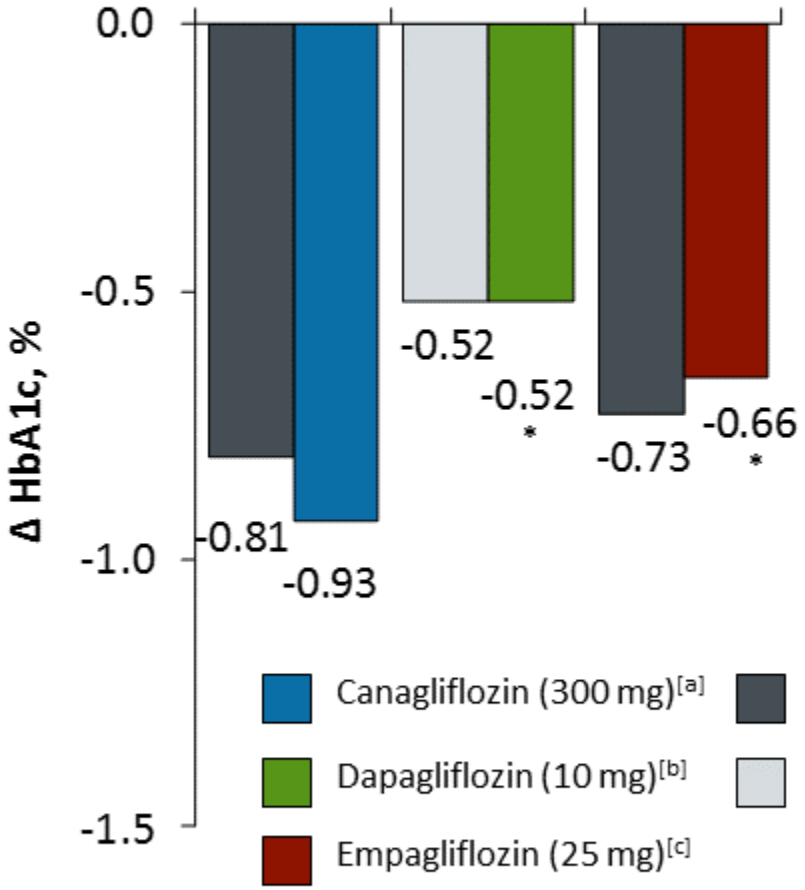
	Δ HbA1c, %		Δ Weight, kg		Hypoglycemia, %	
Agent	**SGLT2**	**Sitagliptin**	**SGLT2**	**Sitagliptin**	**SGLT2**	**Sitagliptin**
Canagliflozin (300 mg)[a] 52 weeks	−0.88*	−0.73	−3.7†	−1.2	6.8	4.1
Empagliflozin (25 mg)[b] 12 weeks	−0.55	−0.45	−2.6	−0.8	0.0	2.8

*Superior vs sitagliptin

†*P*<.001 vs sitagliptin

a. LaValle-Gonzalez FJ, et al. *Diabetologia*. 2013;56:2582-2592.
b. Rosenstock J, et al. *Diabetes Obes Metab*. 2013;15:1154-1160.

SGLT2 Inhibitor vs SU Added to Metformin



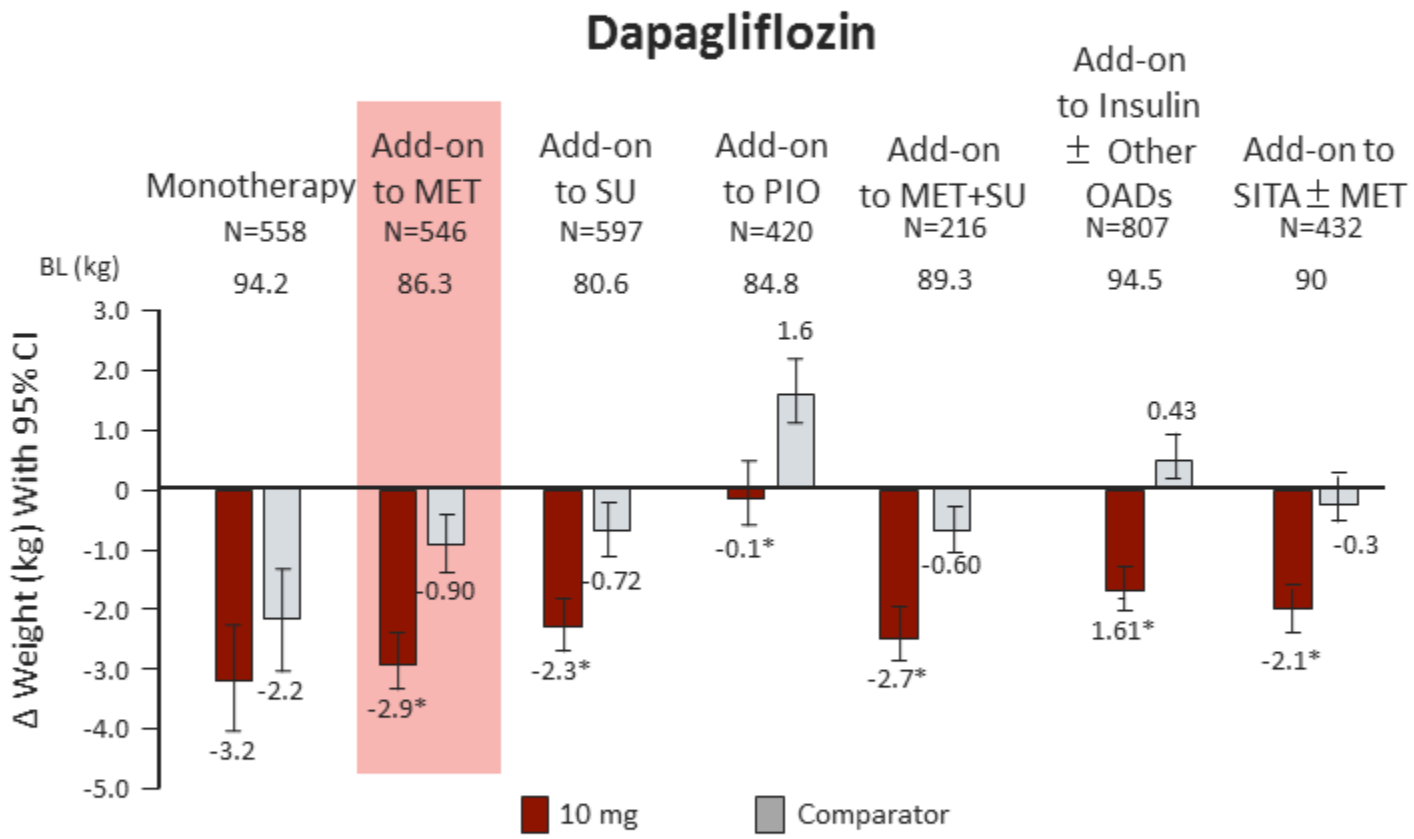
	Δ Weight (kg)		Hypoglycemia (%)	
Agent	**SGLT2**	**SU**	**SGLT2**	**SU**
CANA[a] (300 mg)	-4.0†	0.7	5†	34
DAPA[b] (10 mg)	-3.2†	1.2	4†	41
EMPA[c] (25 mg)	-3.2†	1.6	2†	20

*Noninferior vs SU; superiority demonstrated for canagliflozin vs glimepiride at 52 weeks and for empagliflozin vs glimepiride at 104 weeks

†*P*<.0001 vs placebo

a. Cefalu WT, et al. *Lancet*. 2013;382:941-950.
b. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022.
c. Ridderstråle M, et al. *Lancet Diabetes Endocrinol*. 2014;2:691-700.

SGLT2 Inhibitor Pooled Data: Weight Reduction in Placebo-Controlled Studies

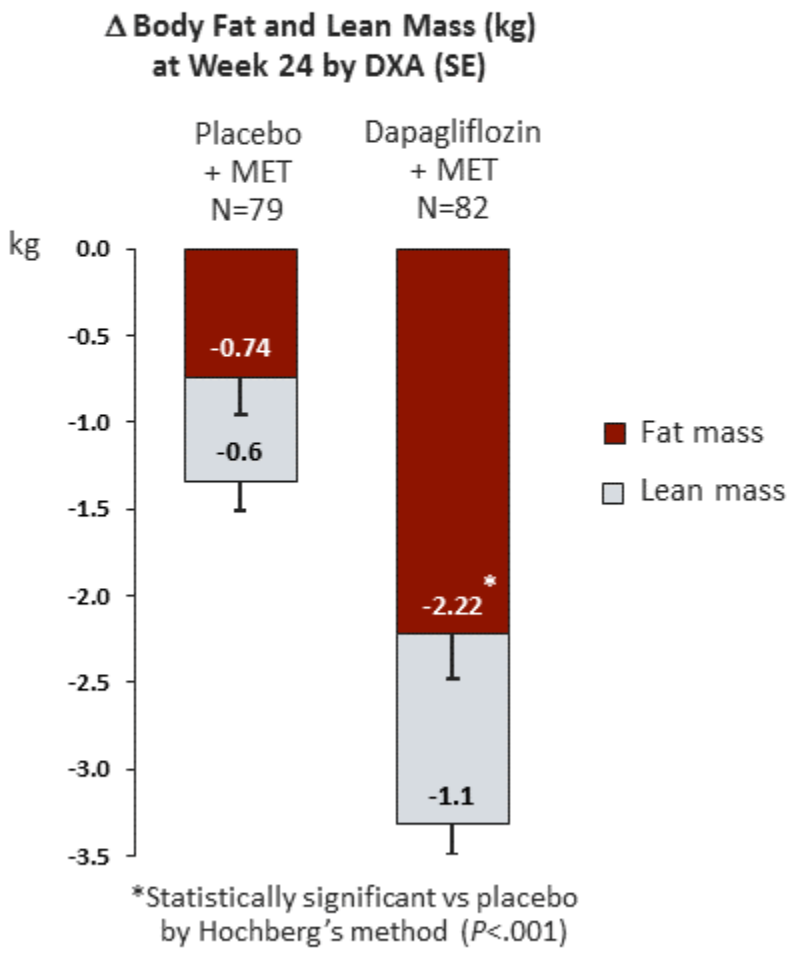


*Statistically significant vs placebo by hierarchical testing rule: *P*<.001
Adjusted mean change from BL using ANCOVA, excluding data after rescue (LOCF)

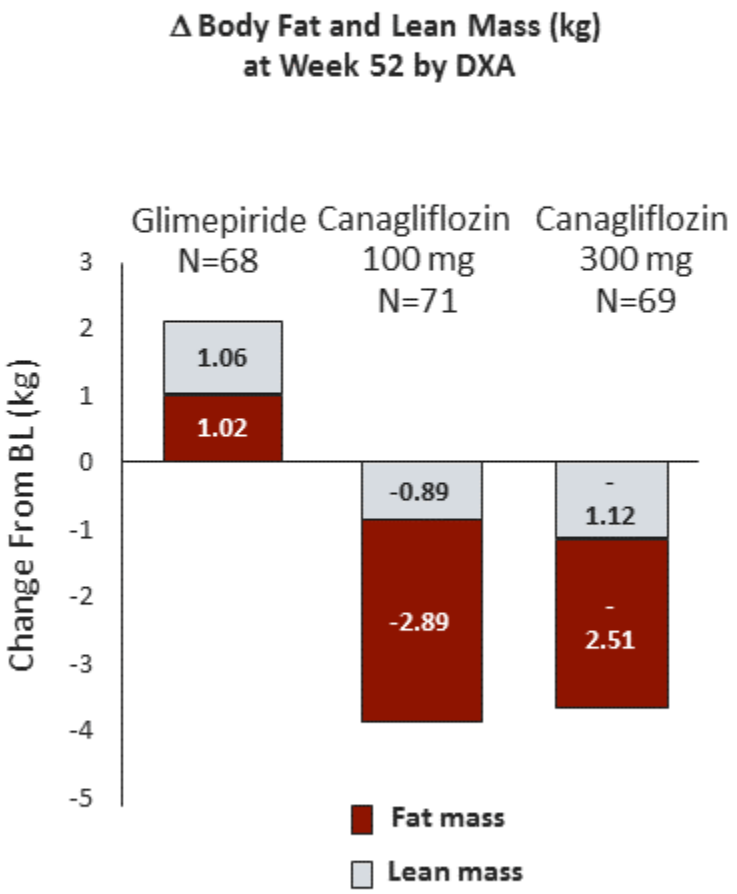
Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224; Bailey CJ, et al. *Lancet*. 2010;375:2223-2233; Strojek K, et al. *Diabetes Obes Metab*. 2011;13:928-938; Rosenstock J, et al. *Diabetes Care*. 2012;35(7):1473-1478; Matthaei S, et al. *Diabetes Care*. 2015;38(3):365-372. Wilding J, et al. *Ann Intern Med*. 2012;156:405-415; Jabbour S, et al. *Diabetes Care*. 2014;37:740-750.

SGLT2 Inhibitor: Weight Loss Is Mostly Fat

Dapagliflozin



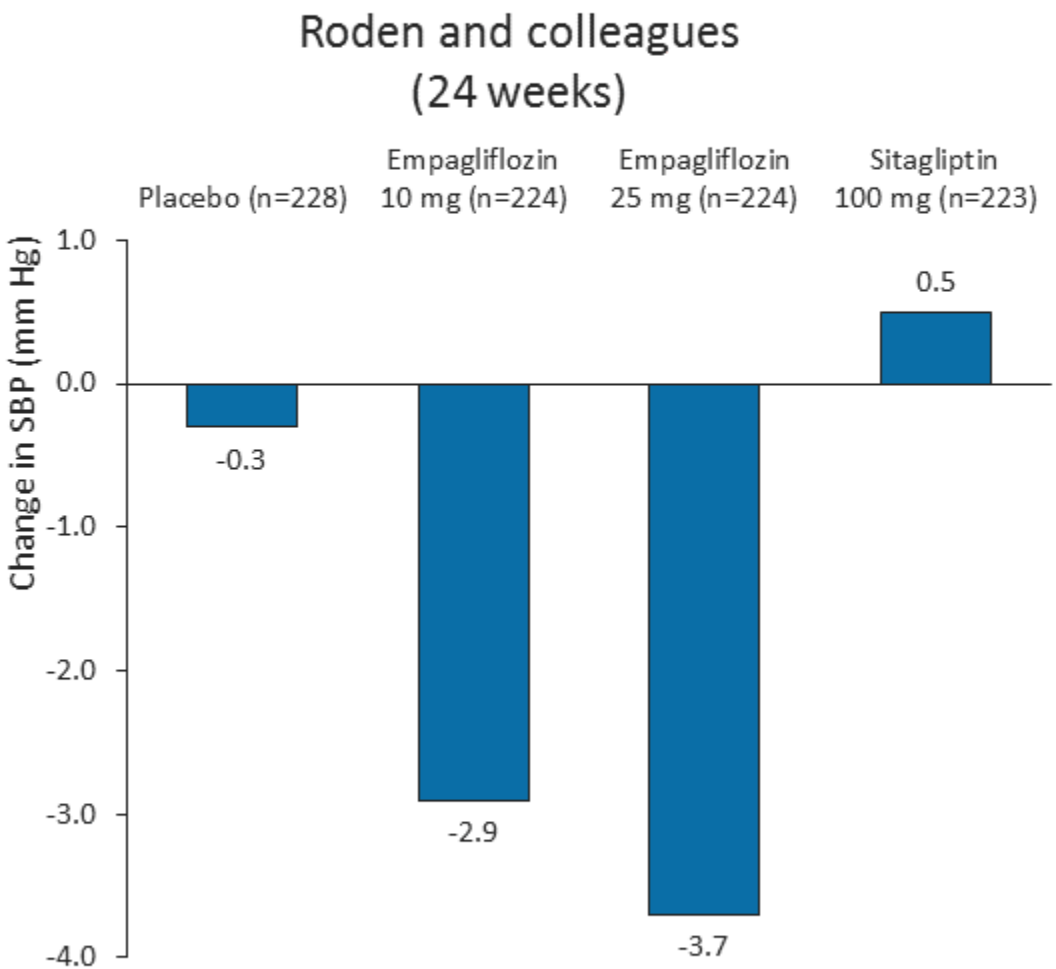
Canagliflozin

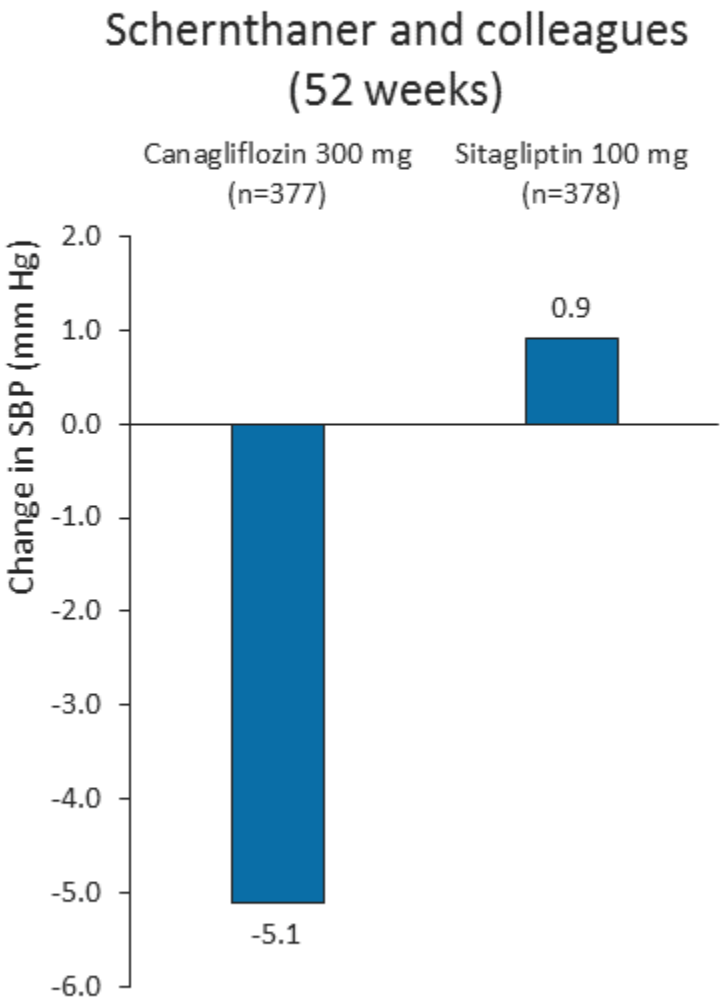


Toubro S, et al. EASD 2012. Abstract 762.

Bolinder J, et al. *J Clin Endocrinol Metab*. 2012;97:1020-1031.

DPP-4 Inhibitor vs SGLT2 Inhibitor: Effect on SBP in T2DM



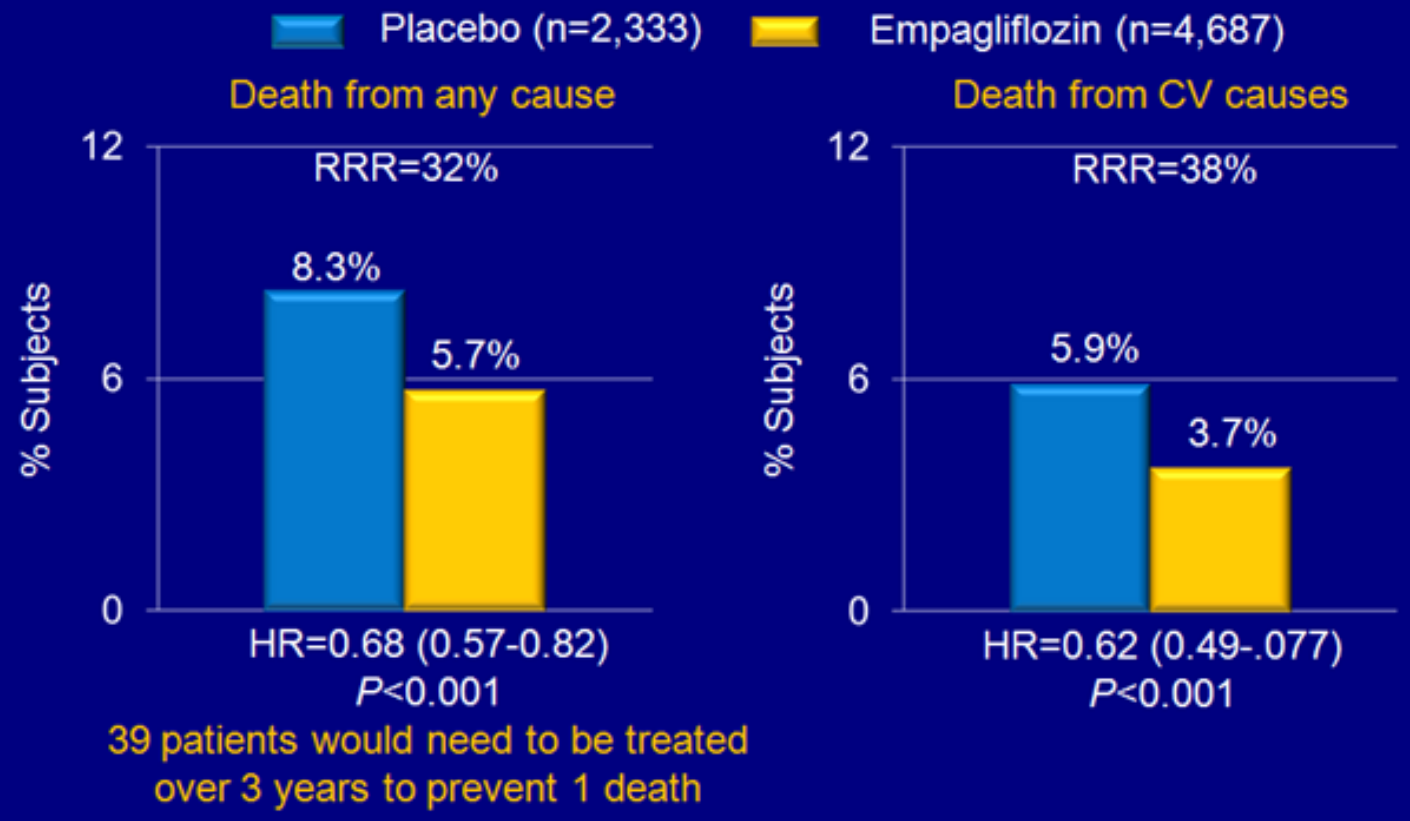


Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219.
Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515.

Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

EASD 2015

EMPA-REG OUTCOME



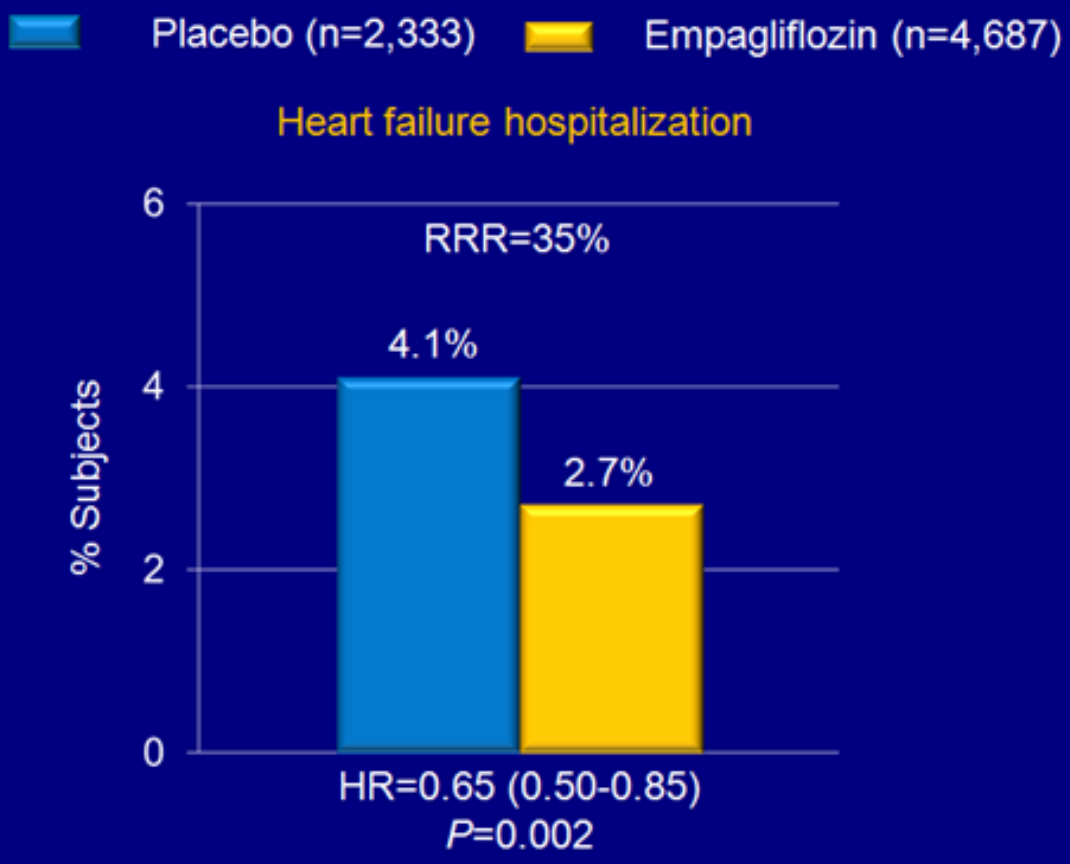
CV=cardiovascular; MI=myocardial infarction; RRR=relative risk reduction

Zinman B, et al; for the EMPA-REG OUTCOME Investigators. *N Engl J Med.* 2015. DOI: 10.1056/NEJMoa1504720.

Lower Heart Failure Hospitalization With Empagliflozin Vs Placebo in High-Risk Patients

EASD 2015

EMPA-REG OUTCOME

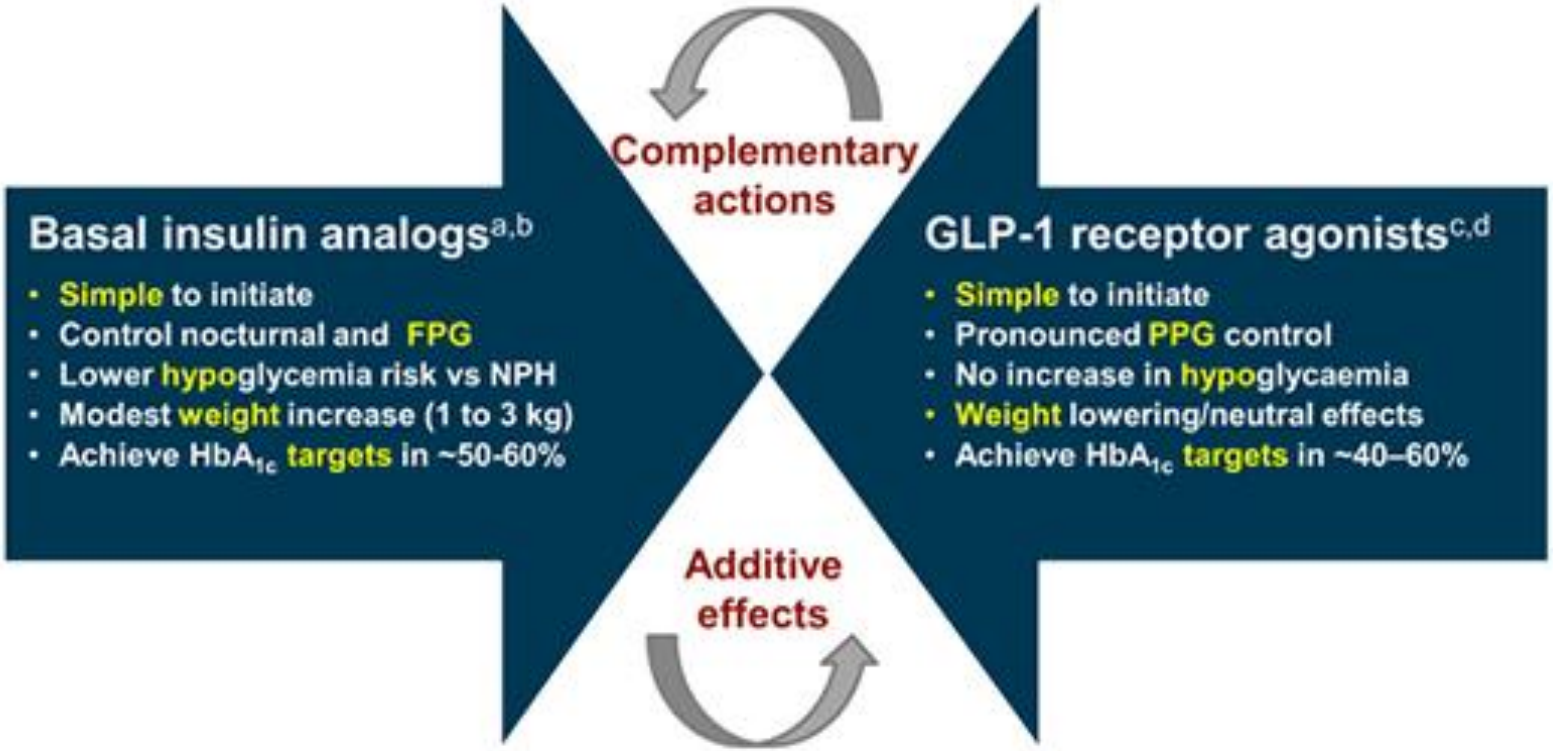


RRR=relative risk reduction

Zinman B, et al; for the EMPA-REG OUTCOME Investigators. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1504720.

Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density

Scientific Rationale for Combining Basal Insulin with a GLP-1 agonist



Courtesy of Julio Rosenstock, MD.

a. Liebl A. *Curr Med Res Opin*. 2007;23:129-132[32]; b. Rosetti P. *Arch Physiol Biochem*. 2008;114:3-10[33];c. Holst JJ, et al. *Mol Cell Endocrinol*. 2009;297:127-136[1]; d. Calabrese D. *Am J Managed Care*. 2011; S52-S58.[2]

Rationale and Proof of Concept

GLP-1 Agonist + Basal Insulin

Basal insulin is the most effective agent to lower fasting glucose but is associated with hypoglycemia and weight gain

GLP-1 agonists lowers both fasting and postprandial glucose without an intrinsic effect to cause hypoglycemia while promoting weight loss

Rationale: combine 2 powerful glucose-lowering agents to get even better efficacy
Clinical trial data: Remarkable efficacy while mitigating the adverse effects of both agents (weight, hypoglycemia, nausea)

Buse JB, et al. *Diabetes Obes Metab*. 2015;17:145-151.

Studies of Once- or Twice-Daily GLP-1 Receptor Agonists Plus Basal Insulin*

Study	Treatment	Reduction in HbA_{1c}	HbA_{1c} Level Achieved (%)
Buse JB, et al. 2011[a]	Insulin glargine + exenatide twice daily	–1.74	6.61
	Insulin glargine + placebo	–1.04	7.49
Diamant M, et al. 2014[b]	Insulin glargine + exenatide twice daily	–1.13	7.20
	Insulin glargine + lispro (3 times daily)	–1.10	7.20
Rosenstock J, et al. 2013[c]	Liraglutide + insulin detemir	–1.04	7.18
Charbonnel B, et al. 2014†[d]	Lixisenatide‡+ basal insulin§	–0.60	6.96
	Lixisenatide‡ + placebo	–0.30	7.30

*With the exception of albiglutide, the FDA has not approved once-weekly GLP-1 receptor agonists for use in combination with basal insulin.
†Meta-analysis of 3 studies/subgroups.
‡The FDA has not approved this medication for this use.
§ Patients were naive to basal insulin treatment; basal insulin was insulin glargine, insulin detemir, or neutral protamine Hagedorn.

a. Buse JB, et al. *Ann Intern Med*. 2011;154:103-112.[37]
b. Diamant M, et al. *Diabetes Care*. 2014;37:2763-2773.[38]
c. Rosenstock J, et al. *J Diabetes Complications*. 2013;27:492-500.[39]
d. Charbonnel B, et al. *J Diabetes Complications*. 2014 July 18. [Epub ahead of print][40]

GLP-1 Receptor Agonist-Insulin Fixed-Dose Combinations

Study	Treatment	HbA_{1c} Reduction	HbA_{1c} Level Achieved
Gough SC, et al. 2014[a]	IDegLira*,†	–1.9	6.4
	Degludec†	–1.4	6.9
	Liraglutide	–1.3	7.0
Rosenstock J, et al. 2014[b]	LixiLan*,†	–1.7	6.3
	Glargine	–1.5	6.5

*IDegLira is a fixed-dose combination of insulin degludec and liraglutide; LixiLan is a fixed-dose combination of insulin glargine and lixisenatide.

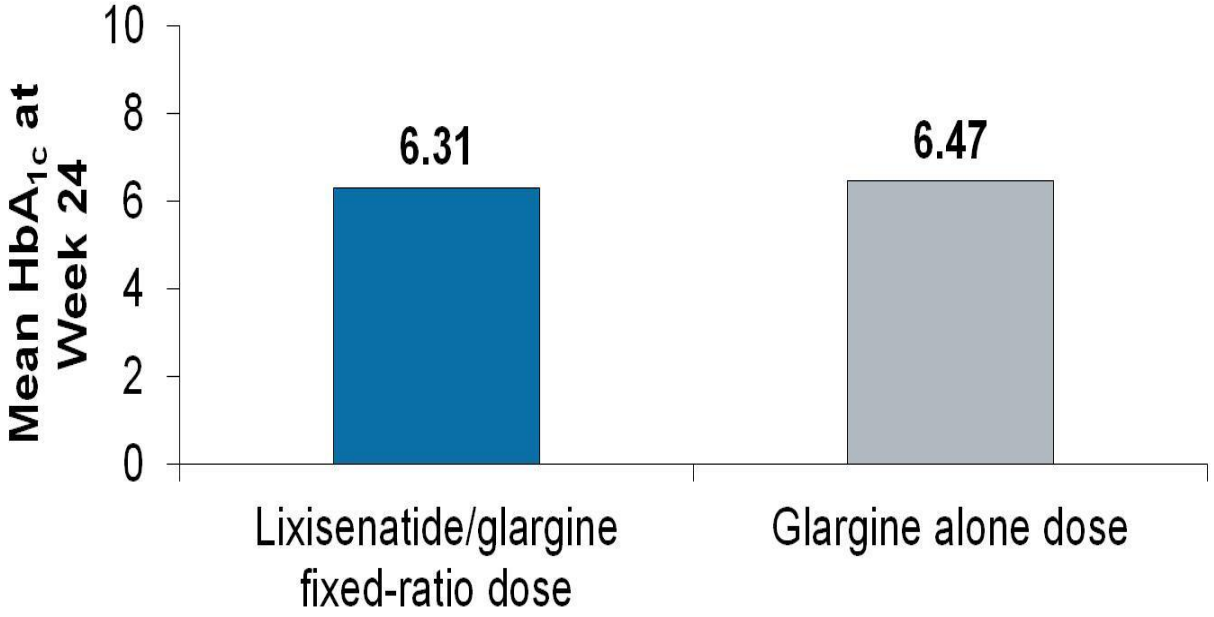
†The FDA has not approved this medication for this use.

a. Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014.[Epub ahead of print].[41]

b. Rosenstock J, et al. *Diabetes.* 2014;63:A87, abstract 332-OR.[42]

Fixed Formulation

LixiLan* – fixed-ratio formulation glargine with lixisenatide in a single-pen device

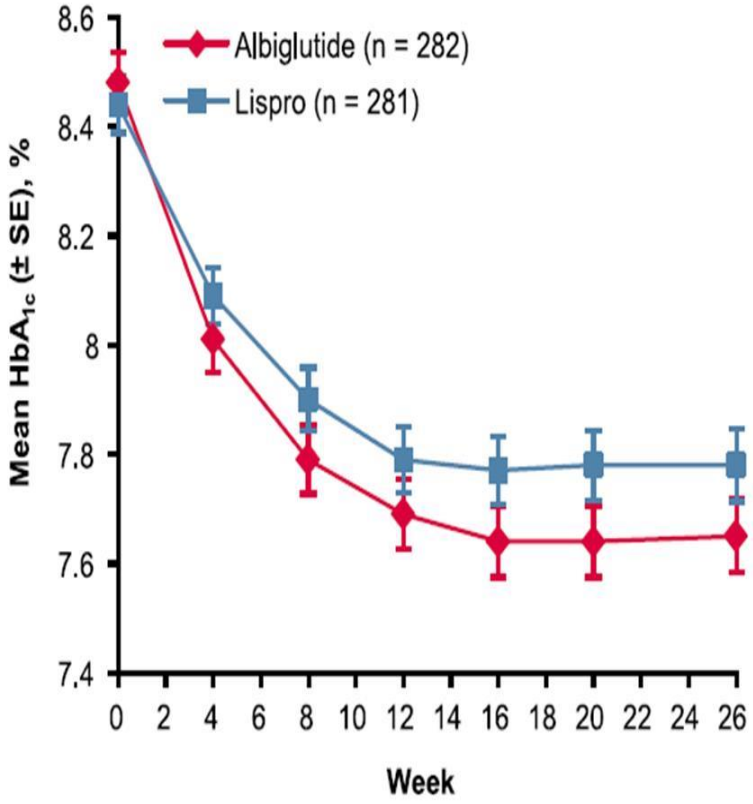


*The FDA has not approved this medication for use in the United States.

Rosenstock J, et al. ADA 2014. Abstract 332-OR.[13]

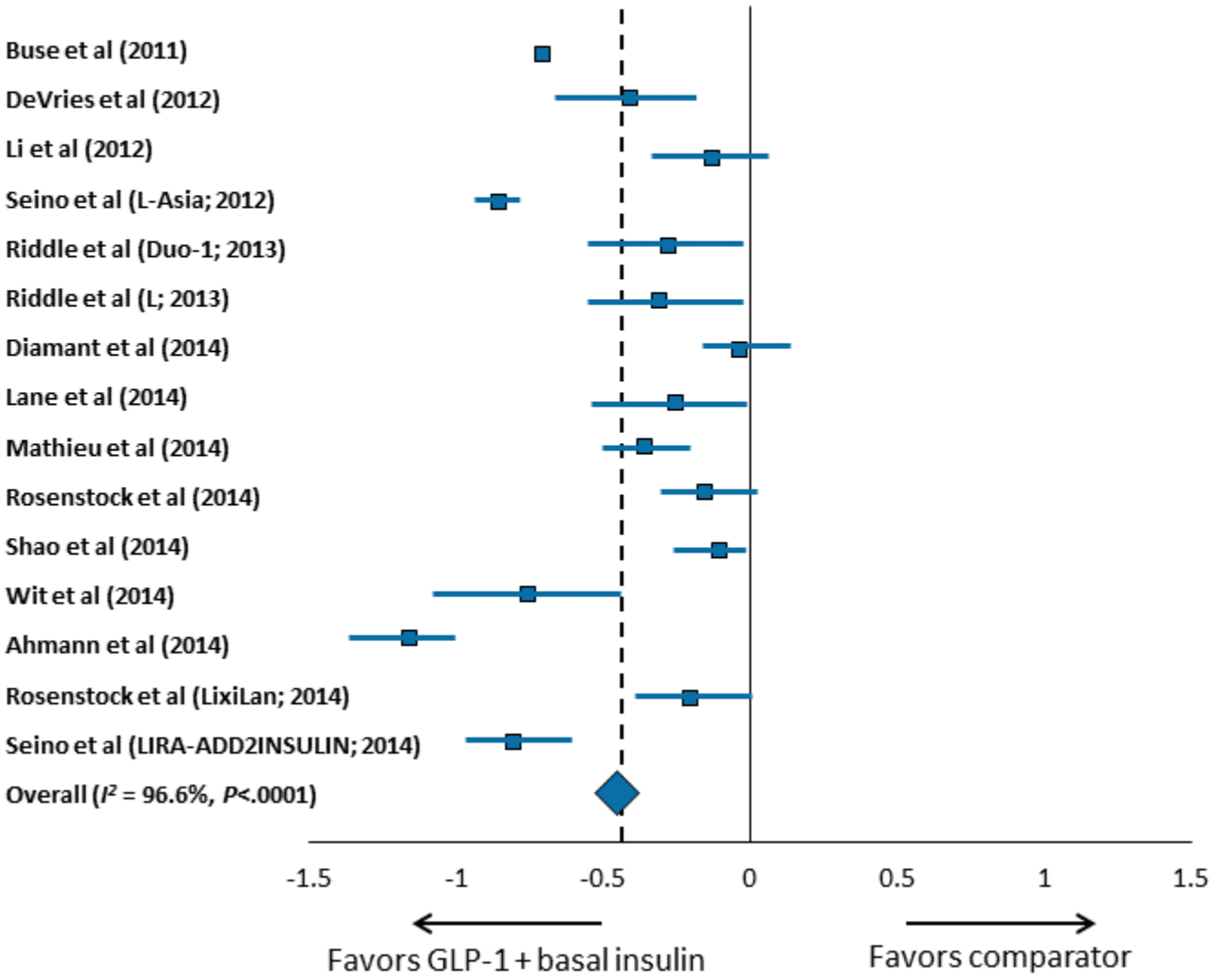
Once-Weekly GLP-1 RA in Combination With Basal Insulin*

Albiglutide plus glargine vs basal bolus



Rosenstock J, et al. *Diabetes Care*. 2014. [Epub ahead of print].[14]

Meta-analysis of GLP-1 RA Plus Basal Insulin: Effect on HbA1c



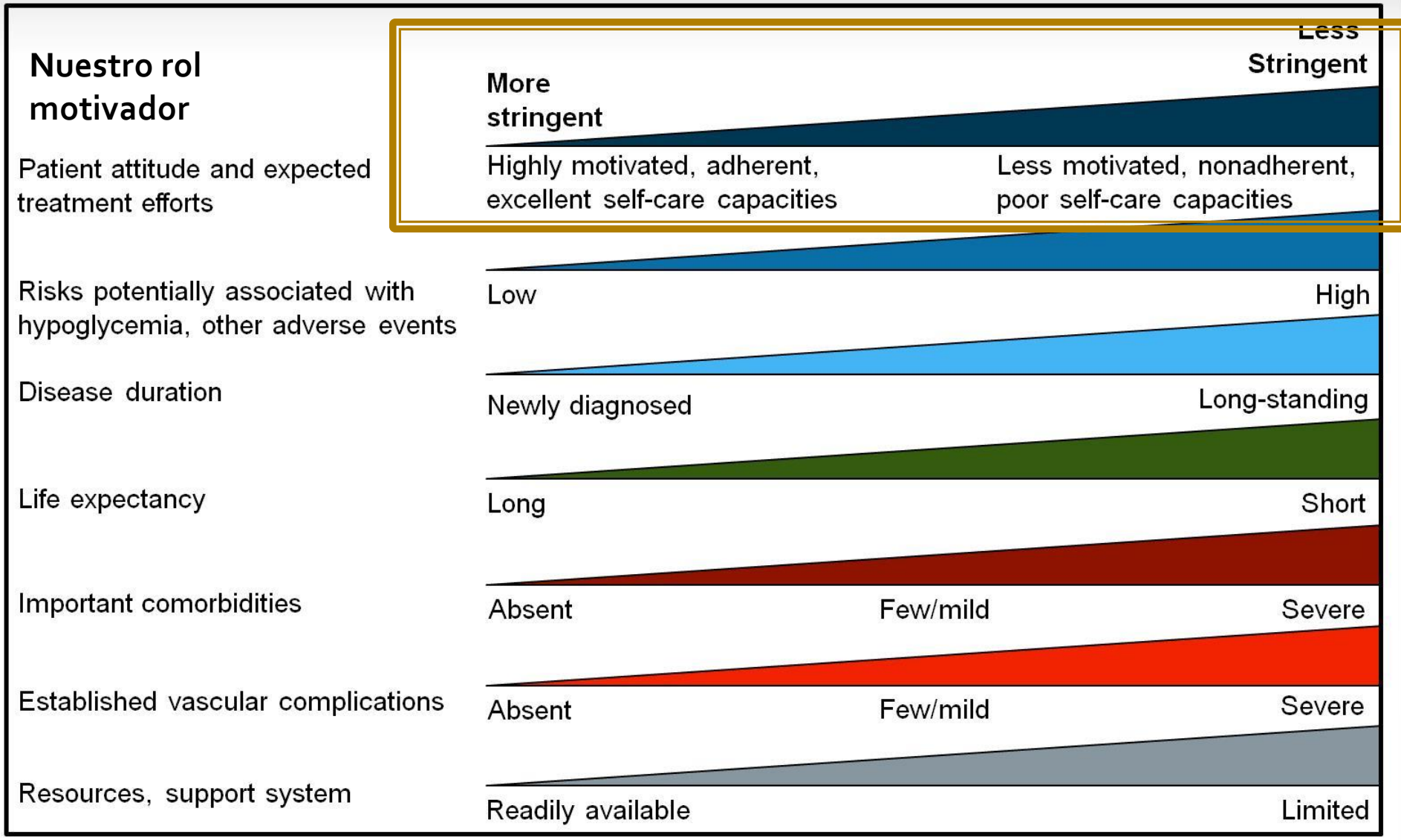
Eng C, et al. *Lancet*. 2014;384:2228-2234.

Safety – Patient Education

- "Both [the FDA and EMA] agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data."[a]
- Educate patients; monitor for signs and symptoms of pancreatitis; ask about medical history of pancreatitis.[a,b]
- Discontinue the GLP-1 receptor agonist if pancreatitis symptoms occur.[a,b]

a. Egan AG, et al. *N Engl J Med*. 2014;370:794-797.[17]
b. EMA website.[18]

Approach to Management of Hyperglycemia



Inzucchi SE, et al. *Diabetologia*. 2012;55:1577-1596.[33]
Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.[34]

Barriers

Medical Inertia

Patient education is time consuming

Sometimes we transmit our concerns to patients even with non-verbal communication

Patients refusal

Costs

Fear of Hypoglycemia

Myths

"A physician is obligated to consider more than a diseased organ, more even than the whole man - he must view the man in his world."

Harvey Cushing