Learning Objectives

- Discuss individualization of therapy in Type Diabetes mellitus
- Identify relevant aspects each new class of drugs
- Assess cardiovascular effects of the new class of drugs

Conflict of Interest Declaration: Nothing to Disclose

Presenter: DR. A. ABU-BAKARE

Title of Presentation: CHOOSING THE RIGHT DRUG FOR TYPE 2 DIABETES

I have no financial or personal relationships to disclose

Faculty/Presenter Disclosure

- **Faculty:** Dr Asiru Abu-Bakare

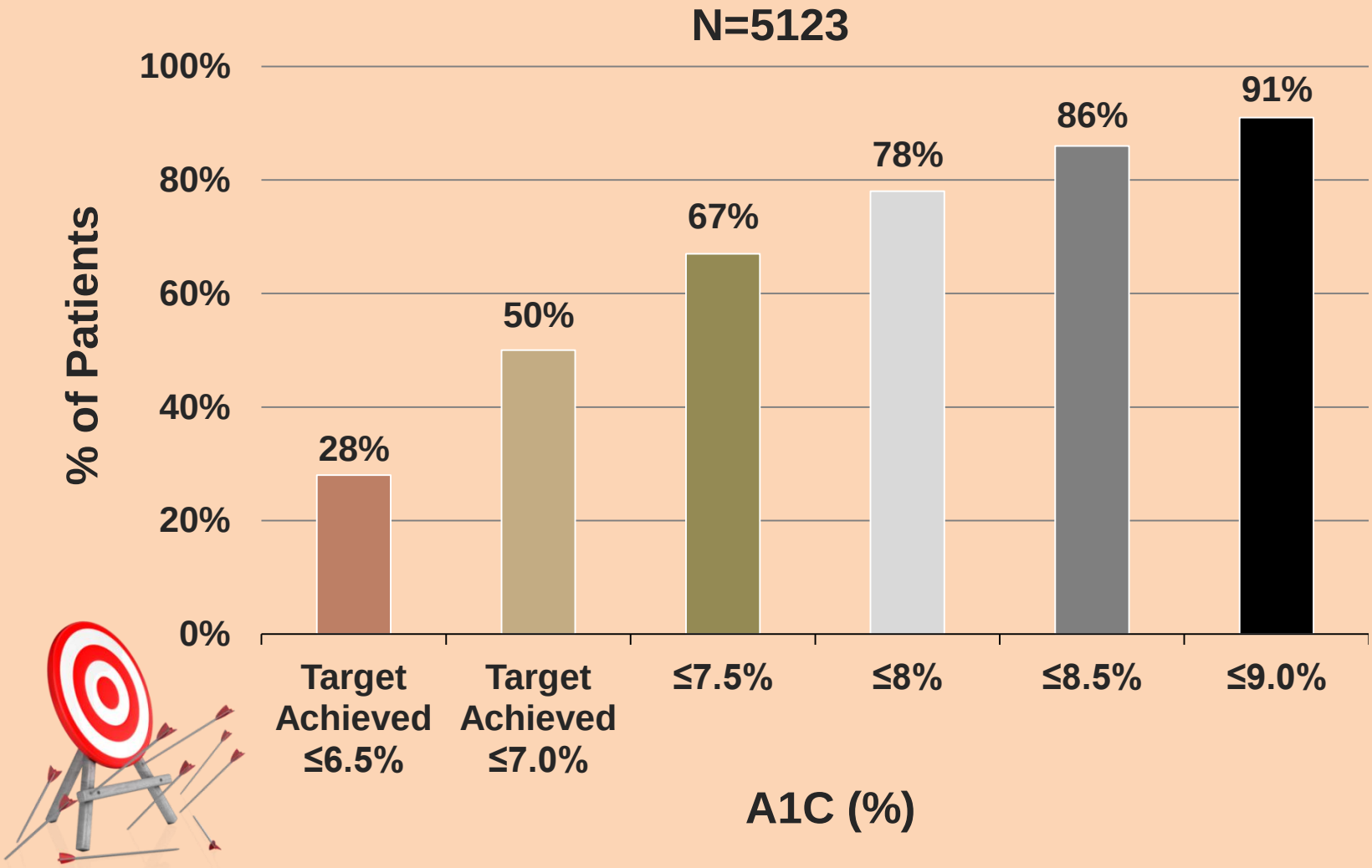
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** Astra Zeneca: Boehringer Ingelheim Pharmaceuticals, Inc.: Elil Lilly and Company: Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.: Novo Nordisk: Sanofi: Amgen Inc.: Abbott Laboratories:
  - **Consulting Fees:** Novo Nordisk; Boehringer Ingelheim Pharmaceuticals; Eli Lilly; Sanofi
  - **Other:** None

Disclosure of Commercial Support

- **This program has received financial support from** no *organization*.
- **This program may have received support indirectly because of inclusion of** materials I have used in previous talks sponsored by several Companies listed earlier.

- **<u>Potential for conflict(s) of interest</u>:**
  - Dr. Abu-Bakare has received no payments from any organization supporting this program <u>AND/OR</u> organization whose product(s) are being discussed in this program].

DM-SCAN: A1C Values Achieved in Primary Care

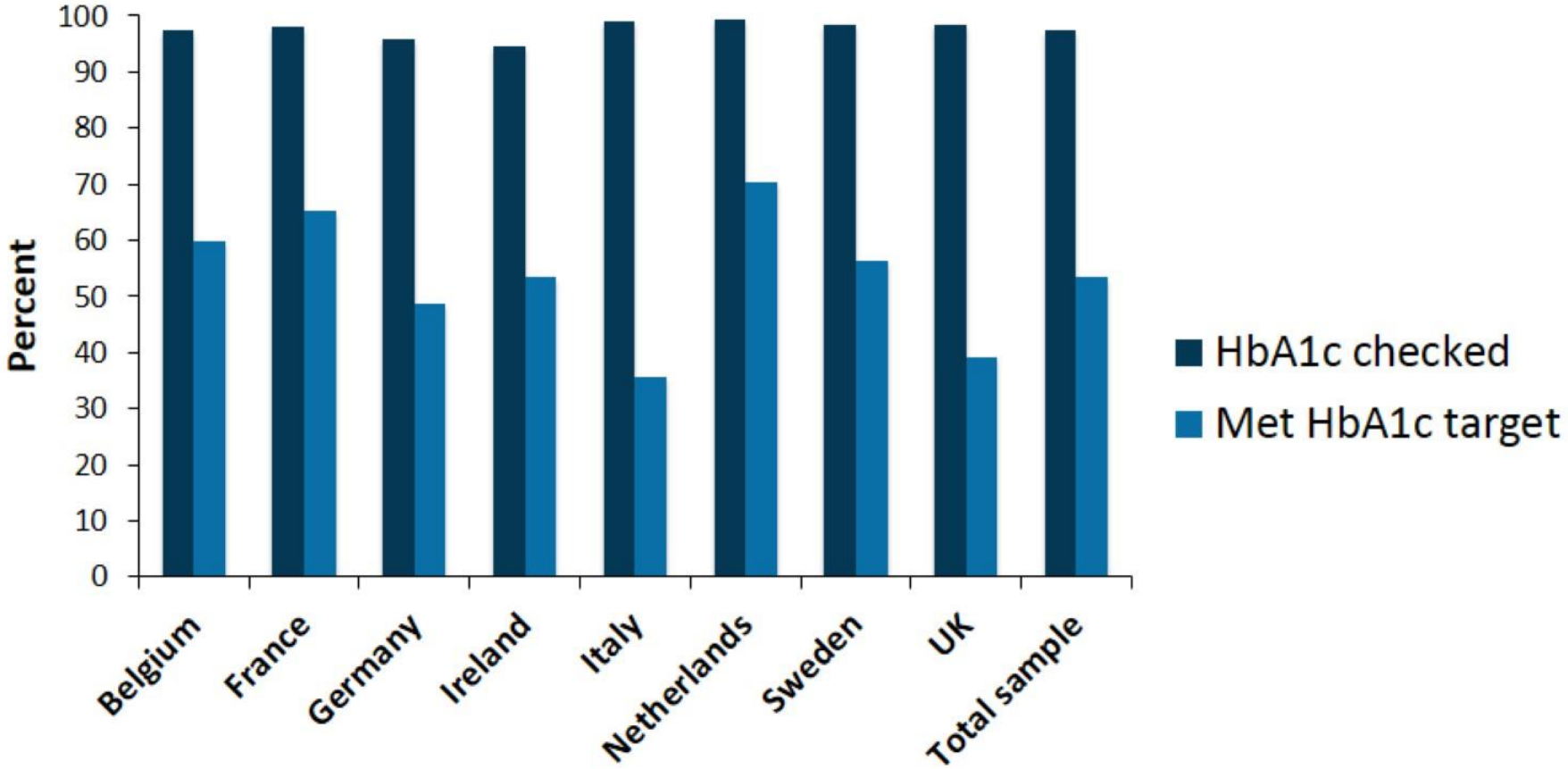


Leiter LA *et al. Can J Diabetes*. 2013;37(2):82-9.

Despite Advances in Treatment, a Significant Proportion of Patients With T2DM Still Fail to Reach Target HbA1c Levels

GUIDANCE Study; 7597 T2DM Patients

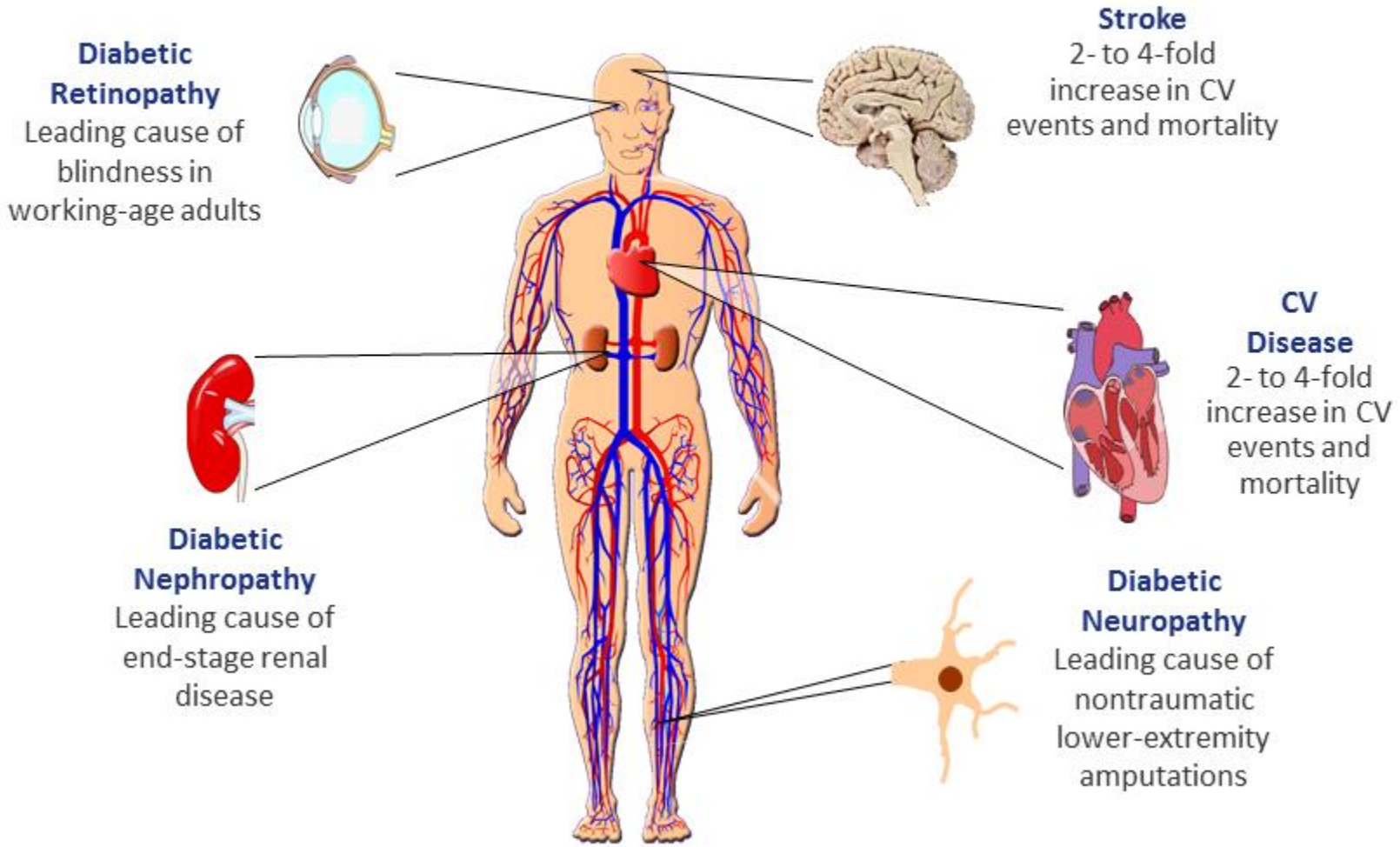
Gap exists between checking HbA1c and achieving target HbA1c <7%



Stone MA, et al. *Diabetes Care*. 2013;36:2628-2638.

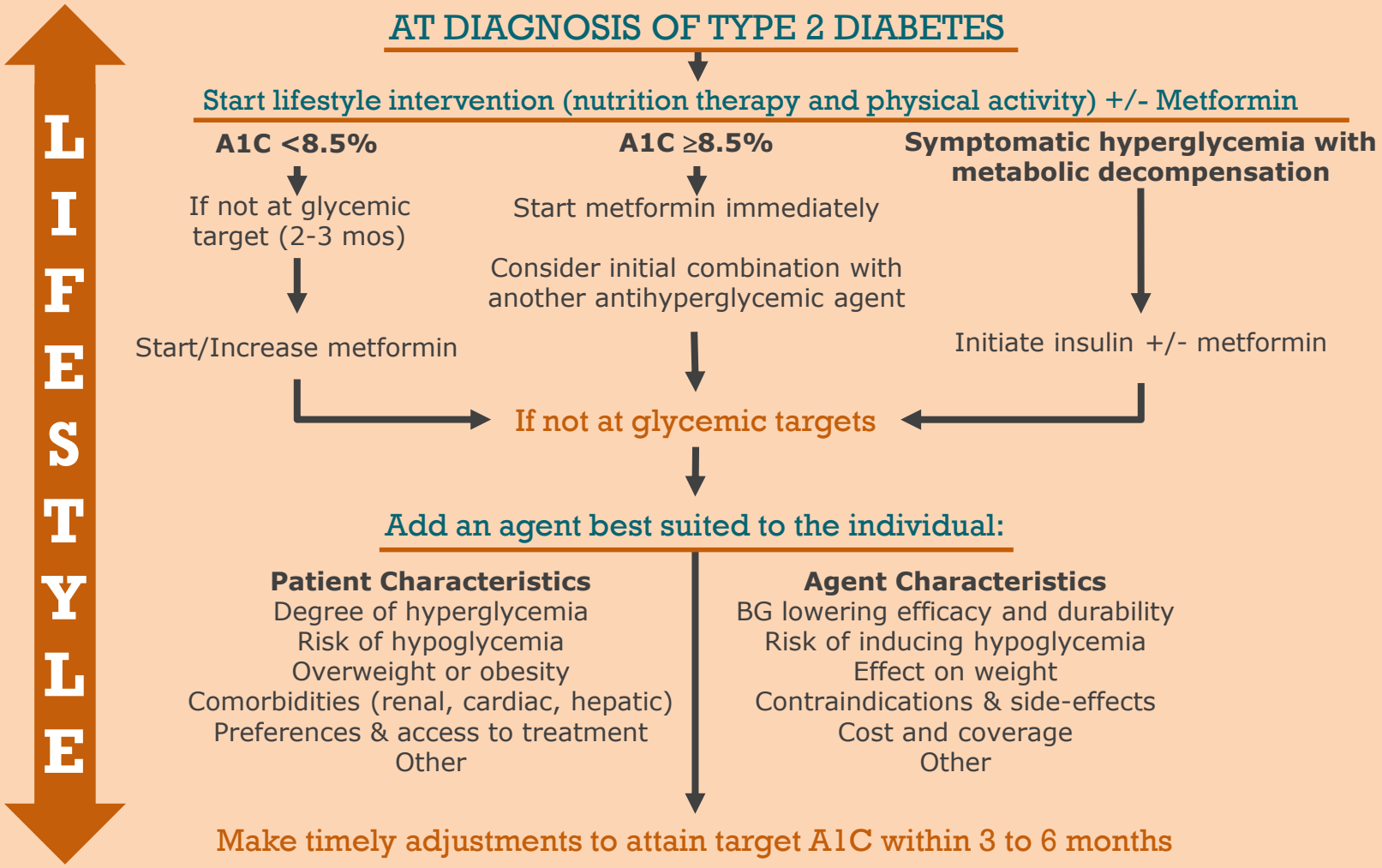
Long-term Complications of Diabetes

Consequences of Sustained Hyperglycemia



National Diabetes Statistics Report. 2014.

CDA Treatment Algorithm



CDA: Canadian Diabetes Association.

1. CDA. Can J Diabetes. 2013;37(suppl 1):S61-8.

2012 ADA/EASD Guidelines: Starting GLP-1 RAs

Healthy Eating, Weight Control, Increased Physical Activity

Initial antihyperglycemic monotherapy
Metformin

Efficacy (↓HbA1c)	Hypoglycemia	Weight	Side effects	Costs
high	low risk	neutral/loss	GI/lactic acidosis	low

After approximately 3 months proceed to a two-drug combination if needed to reach the individualized HbA1c target

Two-drug combination
(order not meant to denote any specific preference)

Metformin +	Efficacy (↓HbA1c)	Hypoglycemia	Weight	Major side effect(s)	Costs
TZD	high	low risk	gain	edema, HF, Fx	high
DPP-4i	intermediate	low risk	neutral	rare	high
GLP-1 RA	high	low risk	loss	GI	high

Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

Hyperglycemia Management: Multiple Combinations of Antihyperglycemic Therapy Can Work

Initial drug monotherapy

Proceed to next step if HbA1c not achieved after 3 months

Dual Therapy

Proceed to next step if HbA1c not achieved after 3 months

Triple Therapy

Proceed to next step if HbA1c not achieved after 3 months

Combination Injectable Therapy

Healthy eating, weight control, increased physical activity, and diabetes education

Metformin	Efficacy (↓HbA1c)	Hypoglycemia	Weight	Side effects	Costs
	high	low risk	neutral/loss	GI/lactic acidosis	low

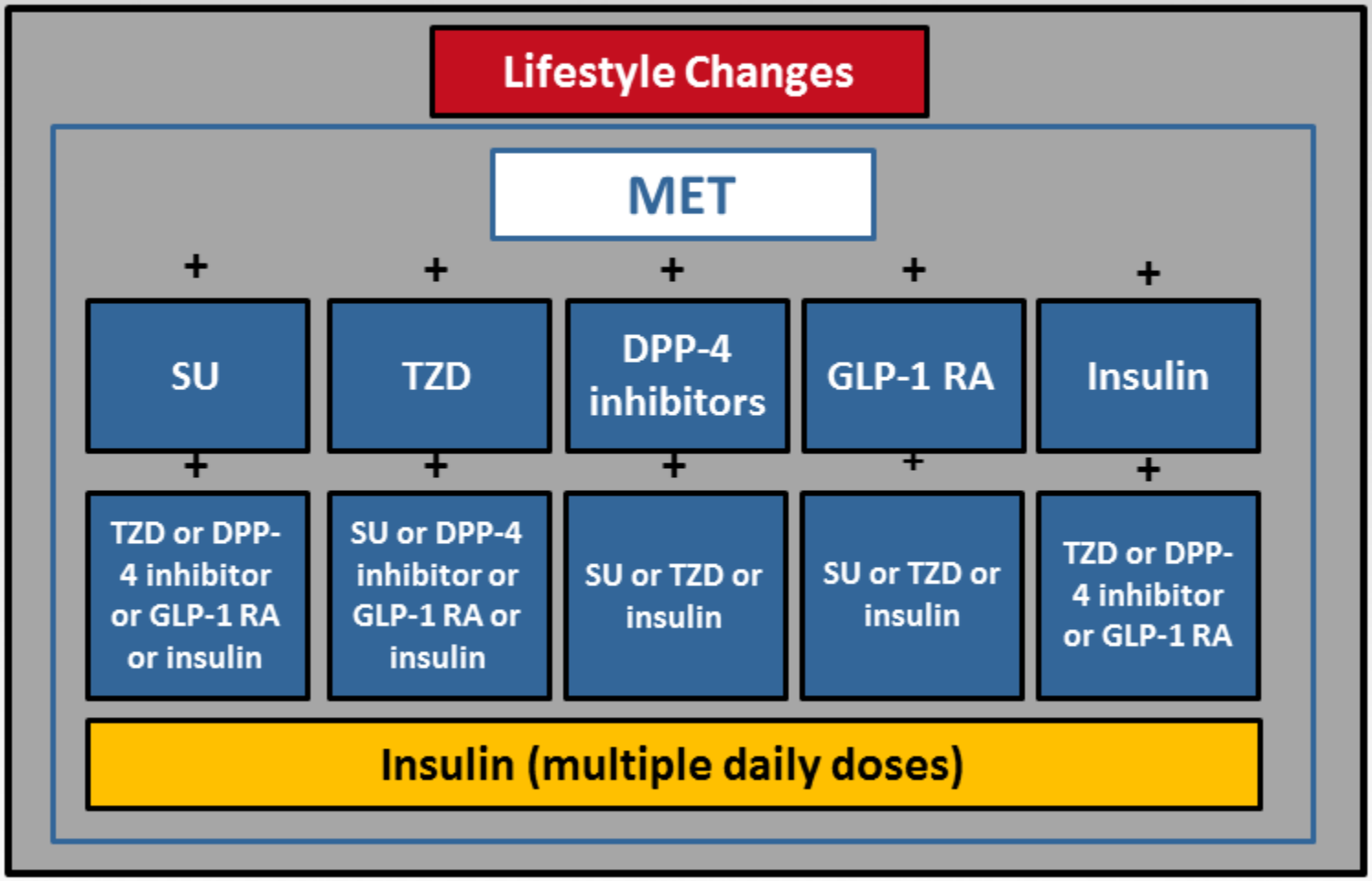
Metformin +	Efficacy (↓HbA1c)	Hypoglycemia	Weight	Side effect(s)	Costs
SU	high	moderate risk	gain	hypoglycemia	low
TZD	high	low risk	gain	edema, HF, Fxs	high
DPP-4i	intermediate	low risk	neutral	rare	high
SGLT2i	intermediate	low risk	loss	GU, dehydration	high
GLP-1 RA	high	low risk	loss	GI	high
Insulin (basal)	highest	high risk	loss	hypoglycemia	variable

Metformin +					
SU +	TZD or	DPP-4i or	SGLT2i	GLP-1 RA or	Insulin
TZD +	SU or	DPP-4i or	SGLT2i	GLP-1 RA or	Insulin
DPP-4i +	SU or	TZD or	SGLT2i	Insulin	
SGLT2i	SU or	TZD or	DPP-4i	Insulin	
GLP-1 RA +	SU or	TZD or	Insulin		
Insulin (basal) +	TZD or	DPP-4i or	SGLT2i	GLP-1 RA	

Metformin + Basal insulin + Mealtime insulin or GLP-1 RA

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

2012 ADA/EASD Position Statement



ADA = American Diabetes Association; DPP-4 = dipeptidyl peptidase-4; EASD = European Association for the Study of Diabetes; GLP-1 RA = glucagon-like peptide-1 receptor agonist; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione

Medscape EDUCATION

Inzucchi SE, et al. *Diabetes Care.* 2012;35(6):1364-1379.

Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
α-Glucosidase inhibitors	• Delay carbohydrate absorption from intestine	Acarbose Miglitol	Precose or generic Glyset
Amylin analogue	• Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Pramlintide	Symlin
Biguanide	• Decrease HGP • Increase glucose uptake in muscle	Metformin	Glucophage or generic
Bile acid sequestrant	• Decrease HGP? • Increase incretin levels?	Colesevelam	WelChol
DPP-4 inhibitors	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
Dopamine-2 agonist	• Activates dopaminergic receptors	Bromocriptine	Cycloset
Glinides	• Increase insulin secretion	Nateglinide Repaglinide	Starlix or generic Prandin

DPP-4 = dipeptidyl peptidase; HGP = hepatic glucose production.

Garber AJ, et al. *Endocr Pract*. 2013;19(suppl 2):1-48. Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.

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Noninsulin Agents Available for T2D

Class	Primary Mechanism of Action	Agent(s)	Available as
GLP-1 receptor agonists	• Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety	Albiglutide Dulaglutide Exenatide Exenatide XR Liraglutide	Tanzeum Trulicity Byetta Bydureon Victoza
SGLT2 inhibitors	• Increase urinary excretion of glucose	Canagliflozin Dapagliflozin Empagliflozin	Invokana Farxiga Jardiance
Sulfonylureas	• Increase insulin secretion	Glimepiride Glipizide Glyburide	Amaryl or generic Glucotrol or generic Diaβeta, Glynase, Micronase, or generic
Thiazolidinediones	• Increase glucose uptake in muscle and fat • Decrease HGP	Pioglitazone Rosiglitazone	Actos Avandia

GLP-1 = glucagon-like peptide; HGP = hepatic glucose production; SGLT2 = sodium glucose cotransporter 2.

Garber AJ, et al. *Endocr Pract*. 2013;19(suppl 2):1-48. Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.

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Effects of Agents Available for T2D

	Met	GLP1RA	SGLT2I	DPP4I	TZD	AGI	Coles	BCR-QR	SU/ Glinide	Insulin	Pram
Renal impair-ment/ GU	Contra-indicated in stage 3B, 4, 5 CKD	Exenatide contra-indicated CrCl <30 mg/mL	GU infection risk	Dose adjust-ment (except lina-gliptin)	May worsen fluid retention	Neutral	Neutral	Neutral	Increased hypo-glycemia risk	Increased risks of hypo-glycemia and fluid retention	Neutral
GI adverse effects	Mod	Mod*	Neutral	Neutral*	Neutral	Mod	Mild	Mod	Neutral	Neutral	Mod
CHF	Neutral	Neutral	Neutral	Neutral†	Mod	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Possible benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Safe	?	Neutral	Neutral
Bone	Neutral	Neutral	Bone loss	Neutral	Mod bone loss	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; Coles = colesevelam; CHF = congestive heart failure; CVD = cardiovascular disease; DPP4I = dipeptidyl peptidase 4 inhibitors; GI = gastrointestinal; GLP1RA = glucagon-like peptide 1 receptor agonists; GU = genitourinary; Met = metformin; Mod = moderate; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

*Caution in labeling about pancreatitis.
†Caution: possibly increased CHF hospitalization risk seen in CV safety trial.

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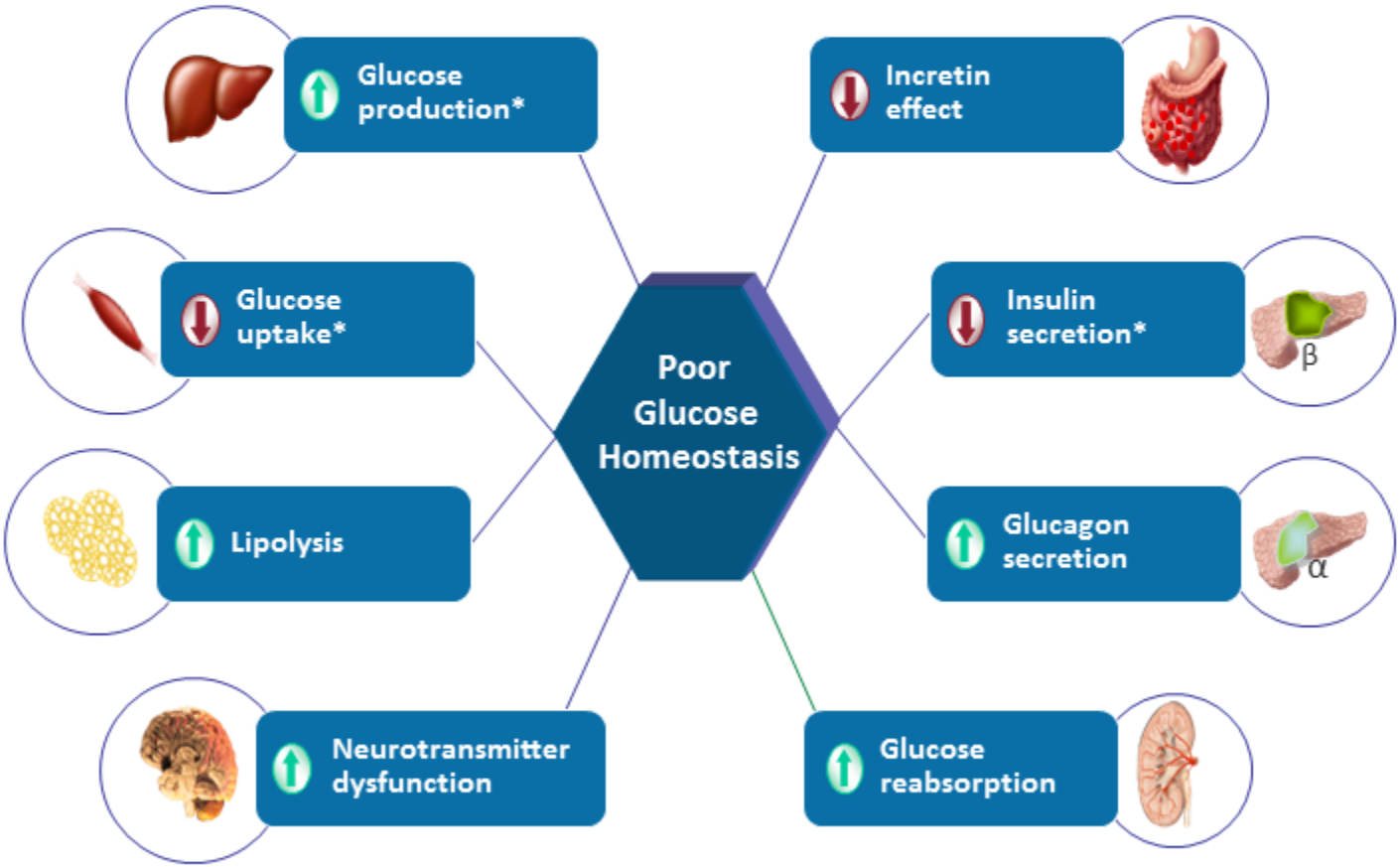
Current Evidence on the Pathophysiology of T2DM

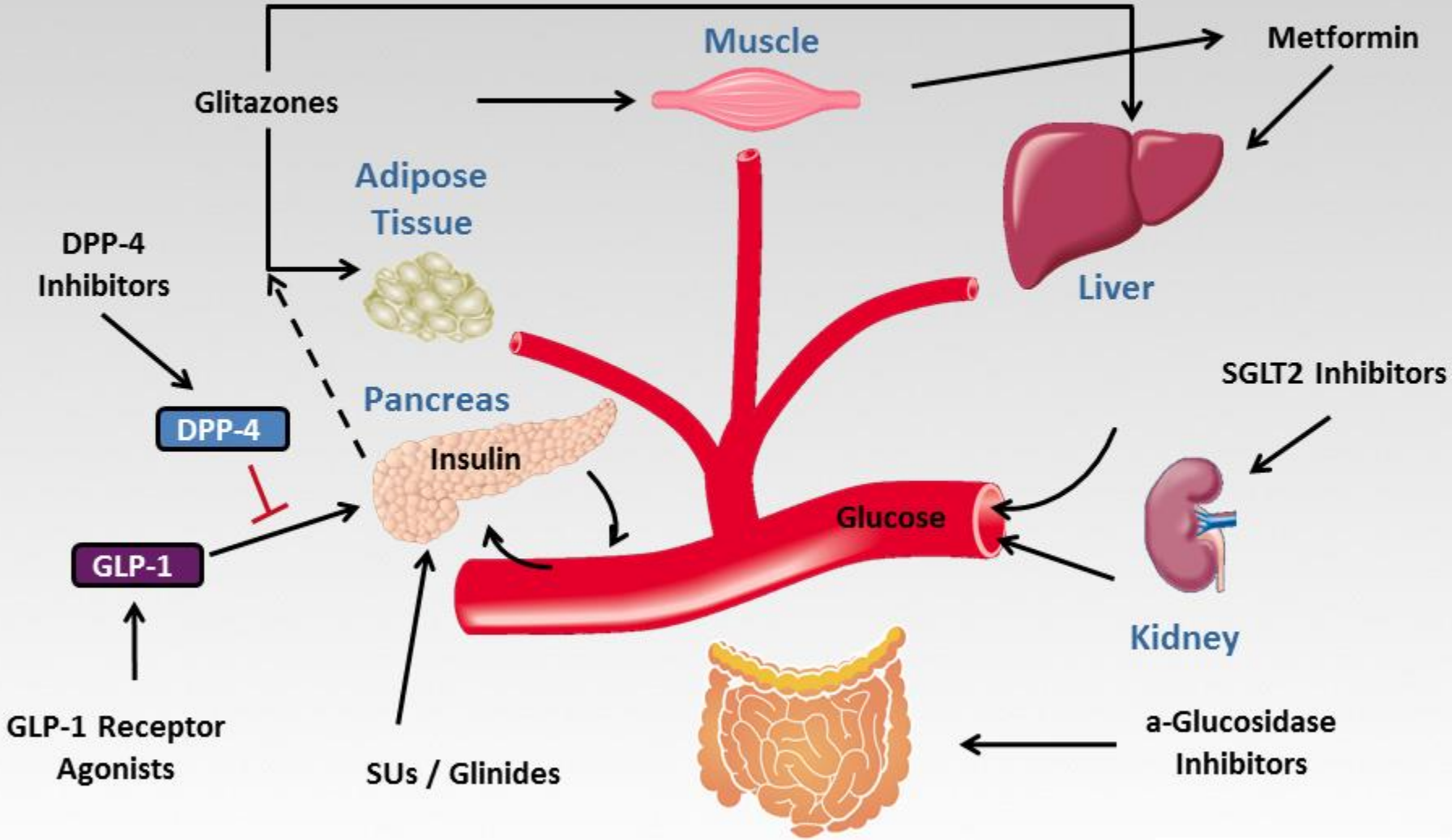
- Multiple drugs in combination may be required to improve glucose homeostasis
- Treatment should target underlying pathophysiology



*3 core pathophysiologies of T2DM, known as the triumvirate

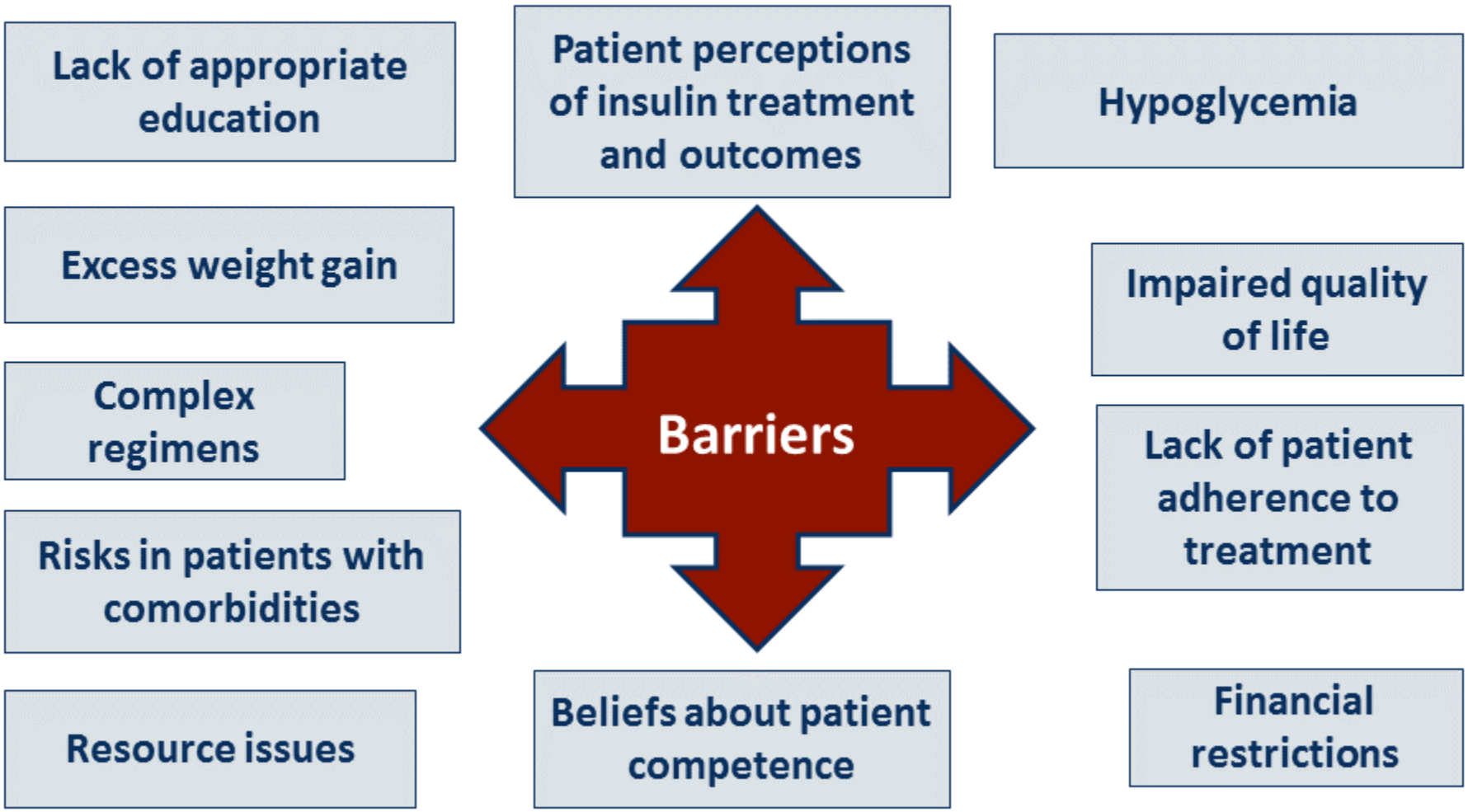
DeFronzo RA. *Diabetes*. 2009;58:773-795.

Antihyperglycemic Therapies:
Sites of Action



DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 ; SGLT2 = sodium glucose co-transporter 2

Clinical Inertia: Patient and Physician Barriers



Peyrot M, et al. *Diabetes Care.* 2005;28:2673-2679; Elgrably F, et al. *Diabetes Med.* 1991;8:773-777; Wallace TM, et al. *QJM.* 2000;93:369-374; Kunt T, et al. *Int J Clin Pract Suppl.* 2009;63:6-10.

The Way Forward(?): Personalizing/Individualizing Treatment for T2DM

- Patient-centered (personalized) care: an approach to *"providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions"*[a]
- Tailoring treatment to the individual: a central component
  - Heterogeneity of disease and treatment response in T2DM[a,b]

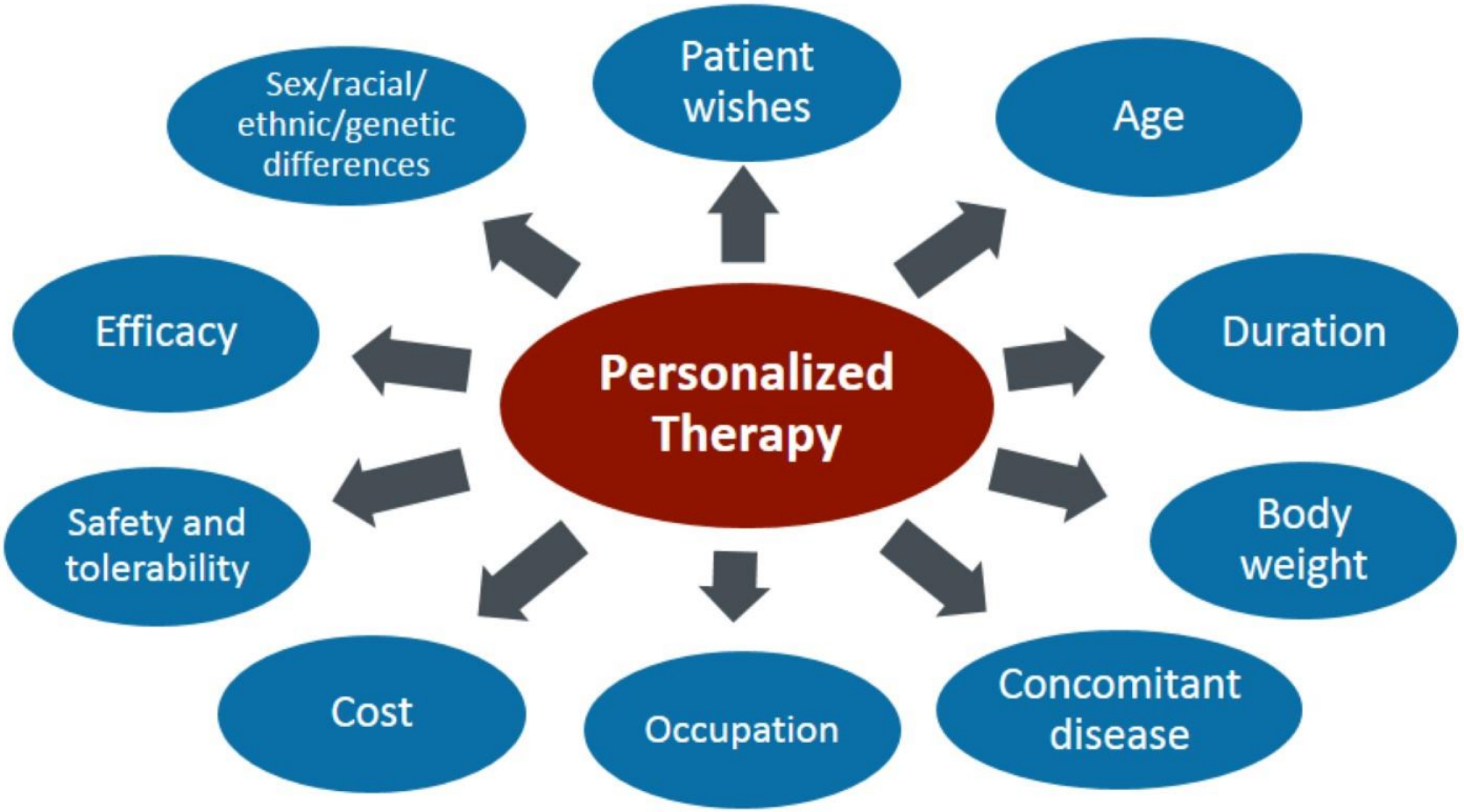
a. Inzucchi SE, et al. *Diabetologia.* 2012;55:1577-1596.
b. Smith RJ, et al. *J Clin Endocrinol Metab.* 2010;95:1566-1574.

Nonadherence a Problem of Epidemic Proportions

- Nonadherence in chronic diseases averages 50% at 12 months[a]
- In Europe, this issue costs 125 billion Euros and contributes to 200,000 deaths yearly[b]
- 3 in 10 stop taking their medicines before first supply runs out[c]
- 25% take less than recommended dose[c]
- 33% do not fill the prescriptions they are given[c]

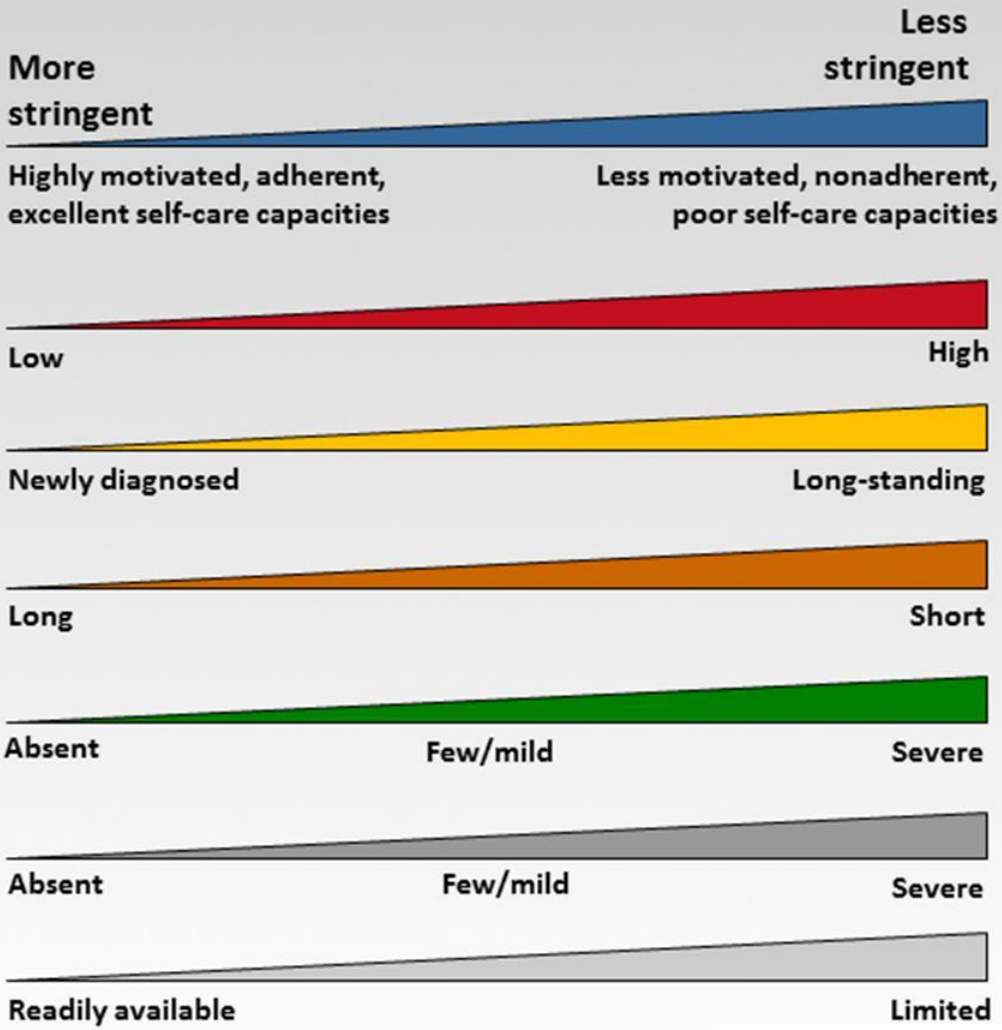
a. WHO. Adherence to Long-term Therapies: Evidence for Action. 2003.
b. Just What the Doctor Ordered: An EU Response to Medication Non-Adherence. Bibliotheque Solvay. 2010.
c. National Council on Patient Information and Education. Enhancing Prescription Medicine Adherence: A National Action National Plan. 2007.

Tailored Therapy in T2DM: Patient Considerations



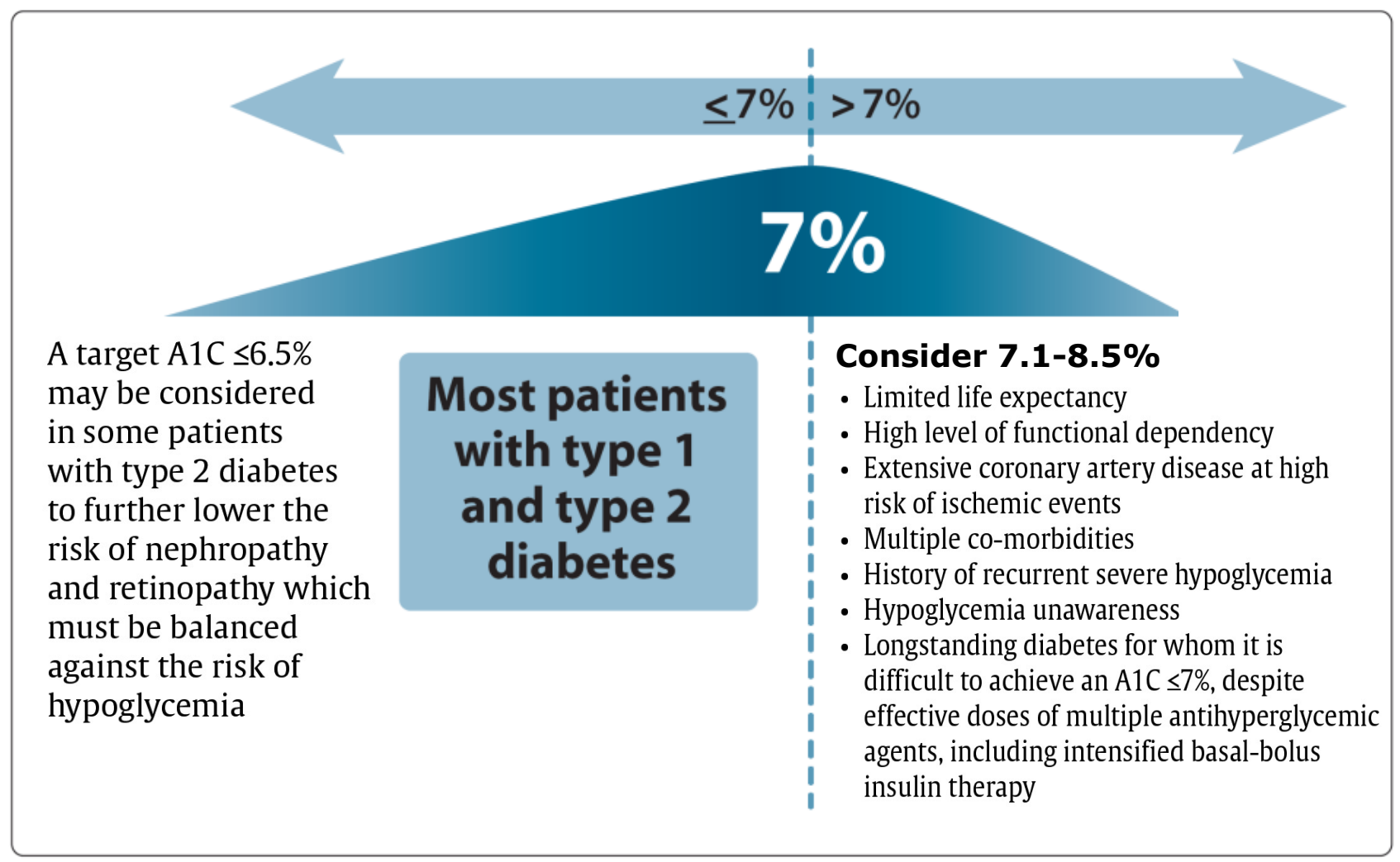
Pozzilli P, et al. *Diabetes Metab Res Rev.* 2010;26:239-244.
Reutens AT. *Nat Rev Endocrinol.* 2010;6:426-427.
Inzucchi SE, et al. *Diabetologia.* 2012;55:1577-1596.

ADA/EASD Position Statement: Approach to Hyperglycemia Management (cont)



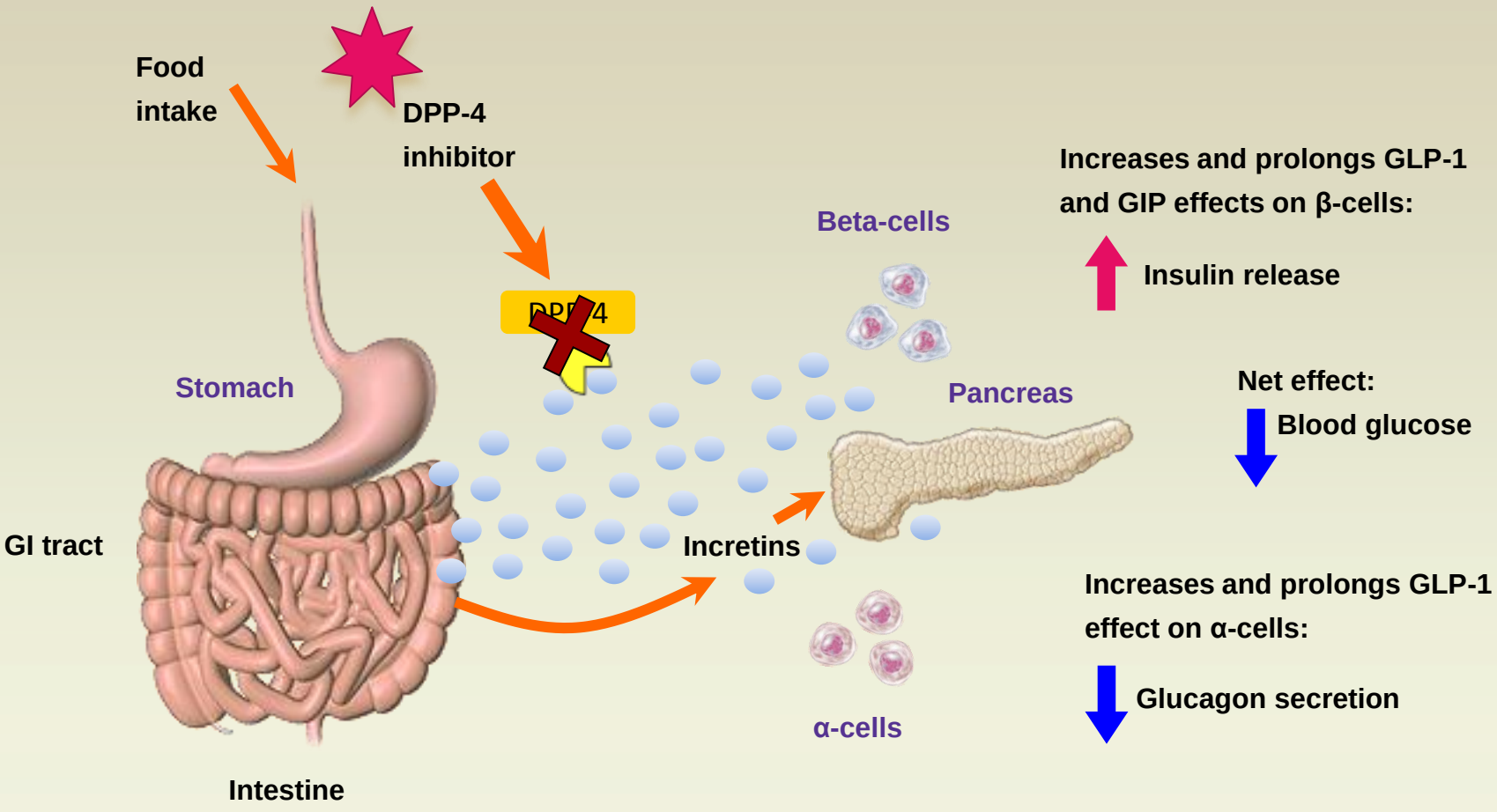
From Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

Individualizing A1C Targets



1. CDA. Can J Diabetes. 2013;37(suppl 1):S61-8.

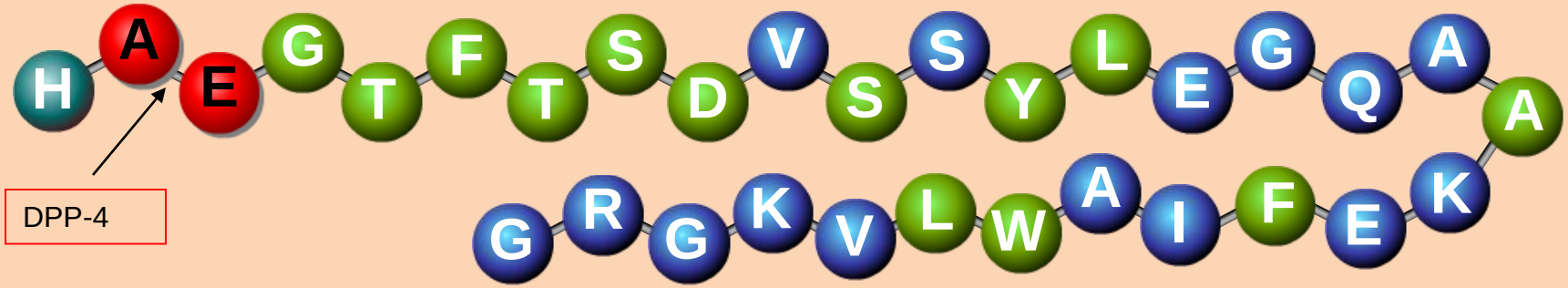
DPP-4 Inhibitors Enhance Incretin Activity



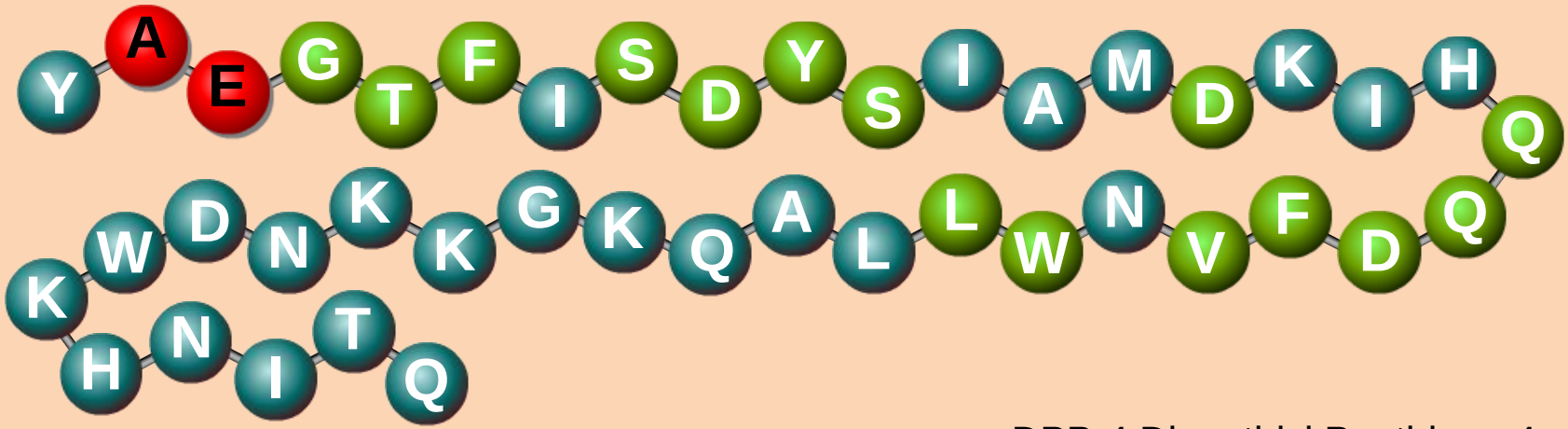
Adapted from: Barnett A. *Int J Clin Pract* 2006; 60:1454-70; Drucker DJ, Nauck MA. *Nature* 2006; 368:1696-705; Idris I, Donnelly R. *Diabetes Obes Metab* 2007; 9:153-65.

The Incretins

GLP-1: Glucagon-like peptide-1

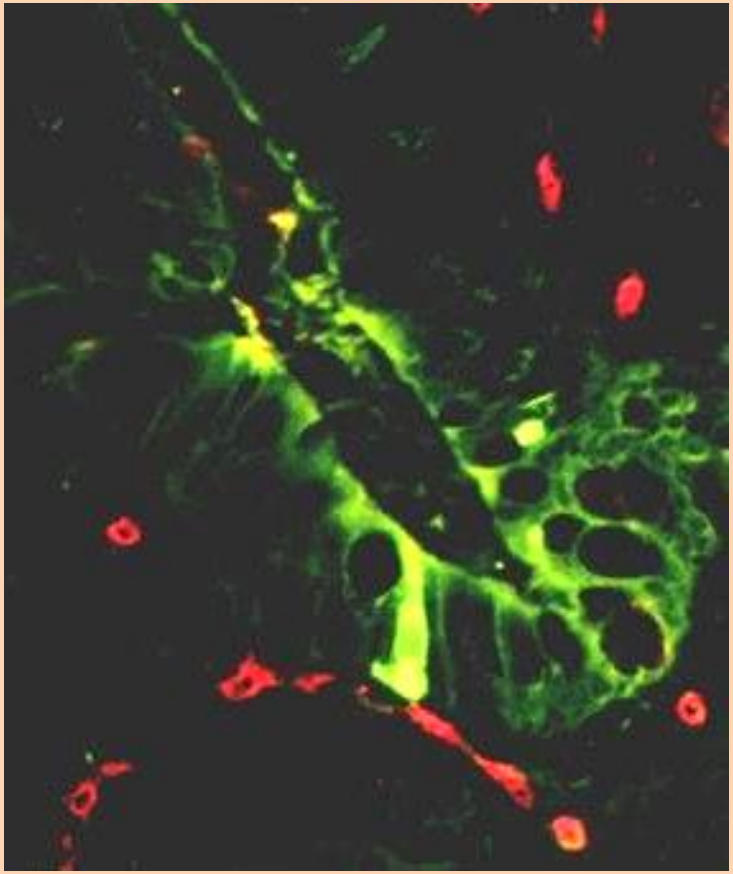


GIP: Glucose-dependent insulinotropic polypeptide



DPP-4 Dipeptidyl Peptidase-4

More Than 50% of Secreted GLP-1 Is Degraded Before Plasma Absorption

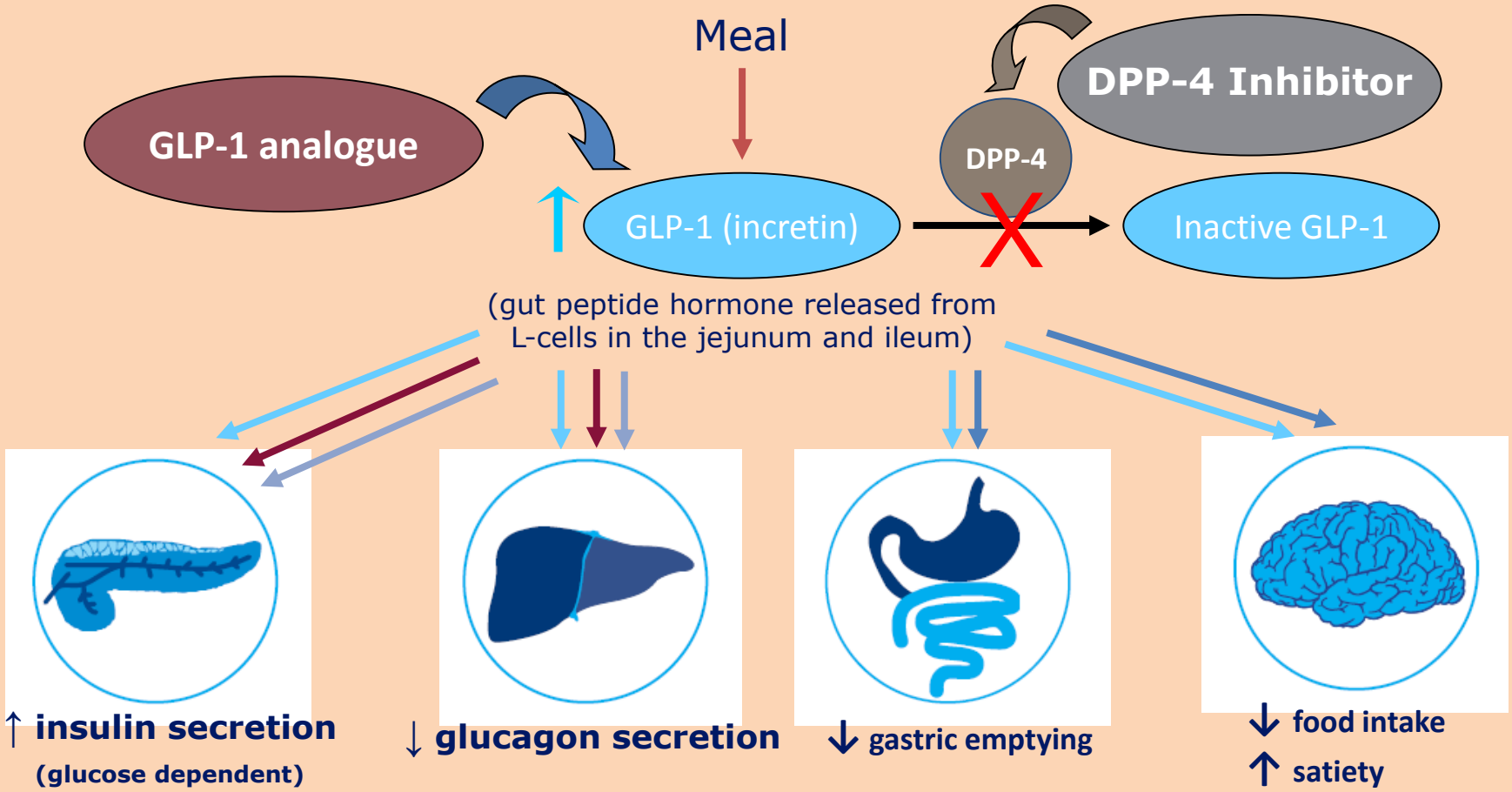


- GLP-1 (green) released into intestinal capillaries is immediately exposed to DPP-4 (red)[1]
- > 50% of secreted GLP-1 is already degraded before it reaches the general circulation[2]
- > 40% of circulating GLP-1 is already degraded before it reaches β-cells[2]

1. Hansen L, et al. *Endocrinology*. 1999;140:5356–5363; 2. Deacon CF, et al. *Am J Physiol*. 1996; 271(3 pt 1):E458–E464.

Histochemistry by C. Ørskov, Panum Institute, Copenhagen.

Effects of GLP-1 analogues and DPP-4 inhibitors

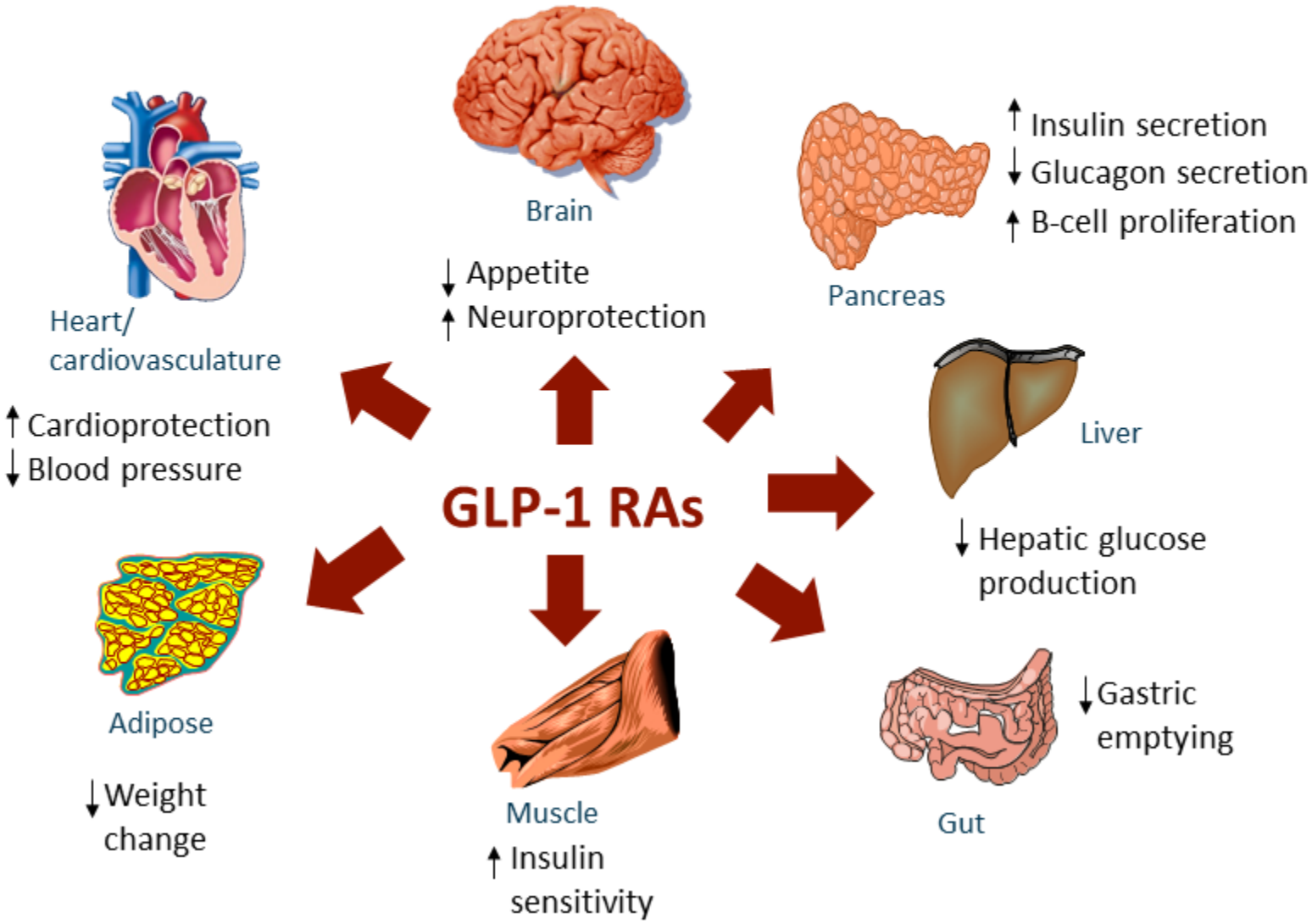


↑ β-cell mass
(long-term animal studies)

GLP-1 analogues → **pharmacological** level of GLP-1 action

DPP-4 inhibitors → **physiological** level of GLP-1 action

Pleiotropic Effects of GLP-1 RAs



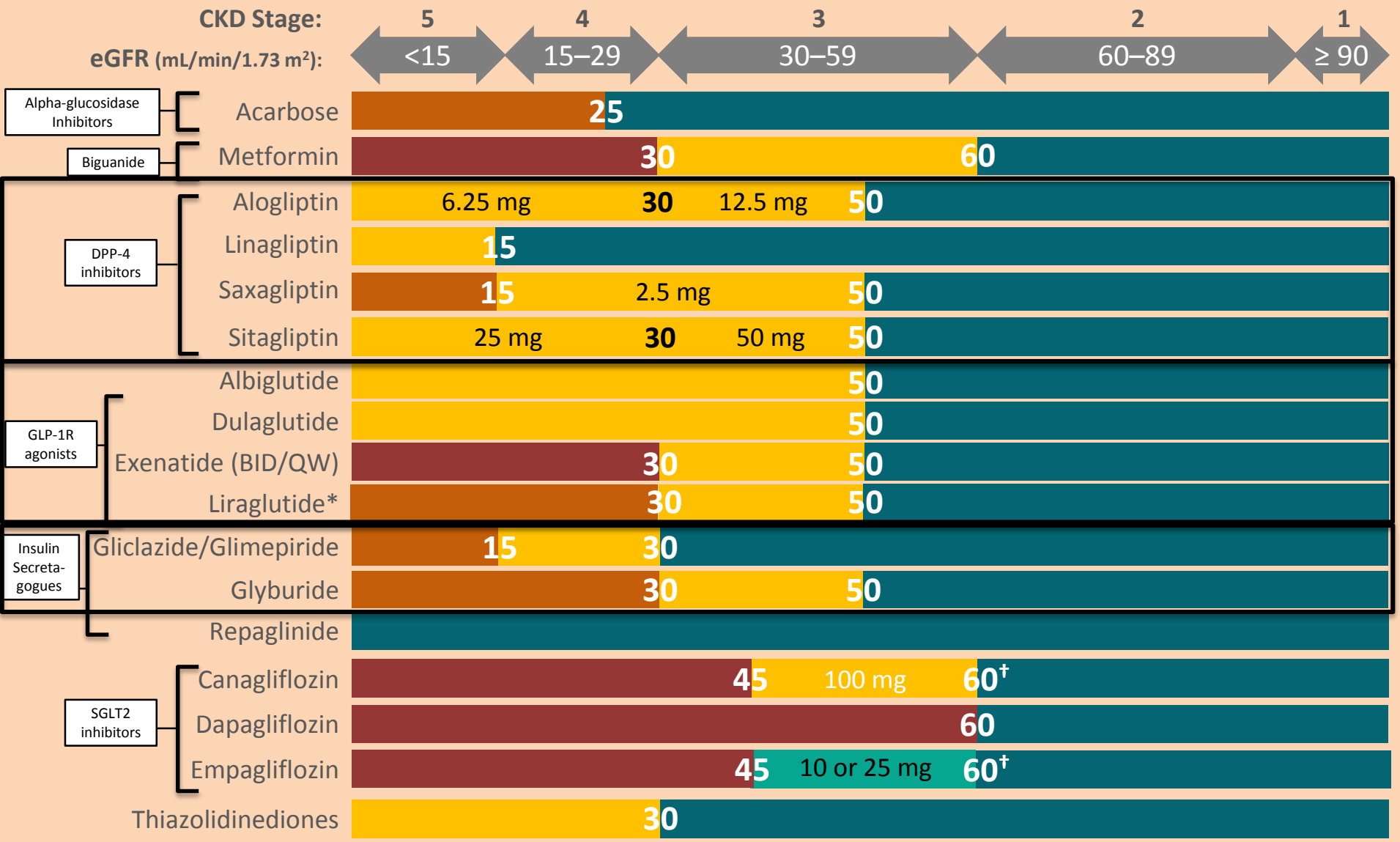
Currently Available DPP-4 Inhibitors Approved for Use in Patients with T2DM in Canada

	Sitagliptin	Saxagliptin	Linagliptin
Dosage	100 mg qd	5 mg qd	5 mg qd
Earliest approval	2005	2009	2011
Approximate half-life	12 hours	2 hours	> 120 hours
Elimination	Renal clearance (75%)	Hepatic metabolism to active metabolite(half as potent) Renal excretion (12% -29 % unchanged pant and 21%-52% as metabolite)	Entero-hepatic Eliminated unchanged in feces via biliary excretion (85%)
Important drug interactions	Low clinically meaningful interactions	Low clinically Meaningful interactions	Efficacy may be limited in patients receiving concurrent inducers of CYP3A4 or P-gp (eg, rifampicin)
Effect on weight	Neutral	Neutral	Neutral
Adverse events	Low	Low	Low

Summary of Dose Reductions Recommended in Patients With Renal Impairment

	Sitagliptin	Saxagliptin	Linagliptin
Usual dosage	100 mg qd	5 mg qd	5 mg qd
CrCl ≥ 50 mL/min	No dose adjustment required	No dose adjustment required	No dose adjustment required
CrCl ≥ 30 to <50 mL/min	Dose reduction to 50 mg/day	Dose reduction to 2.5 mg/day	No dose adjustment required
CrCl < 30 mL/min	Dose reduction to 25 mg/day	Dose reduction to 2.5 mg	No dose adjustment required
End-stage renal disease	Dose reduction to 25 mg/day	2.5 mg administered following dialysis	No dose adjustment required
Peritoneal dialysis	Dose reduction to 25 mg/day	No data available	No dose adjustment required

Antihyperglycemic Agents and Renal Function



*Based on Saxenda Product Monograph June 2015; †Do not initiate if eGFR <60 ml/min.

1. CDA. Can J Diabetes. 2015;39:250-252; 2. Respective Product Monographs as of Nov 2015.

GLP-1 RAs Currently Available

Medication	Dosing Frequency	Dosage
Exenatide BID[a]	Twice daily	• 5 µg or 10 µg dose in prefilled pen
Liraglutide[b]	Once daily	• Prefilled, multidose pen (0.6 mg, 1.2 mg, 1.8 mg)
Exenatide[c]	Once weekly	• Single dose tray with 2 mg vial • Single dose prefilled pen (2 mg)
Albiglutide[d]	Once weekly	• 30 mg or 50 mg powder in single-dose pen for reconstitution
Dulaglutide[e]	Once weekly	• Single-dose pen (0.75 mg or 1.5 mg) • Pre-filled single dose syringe (0.75 mg or 1.5 mg)

a. Byetta® PI 2015; b. Victoza® PI 2015; c. Bydureon® PI 2015; d. Tanzeum® PI 2015; e. Trulicity™ PI 2015.

Effects of GLP-1 RAs

Clinical Effects	Long-Acting GLP-1 RAs	Short-Acting GLP-1 RAs
	Liraglutide Exenatide-LAR, Albiglutide, Dulaglutide*, Semaglutide*	Exenatide, Lixisenatide
HbA1c reduction	~0.8%-1.9%	~0.5%-1.2%
FPG reduction	Up to 2.6 mmol/L	~0.8-1.4 mmol/L
PPG reduction	+	++
Gastric emptying deceleration	Neutral	++
Body weight reduction	~1-4 kg	~1-4 kg
Blood pressure reduction	Up to 6 mm Hg	~3-4 mm Hg
Heart rate increase	2-4 beats/min	Neutral

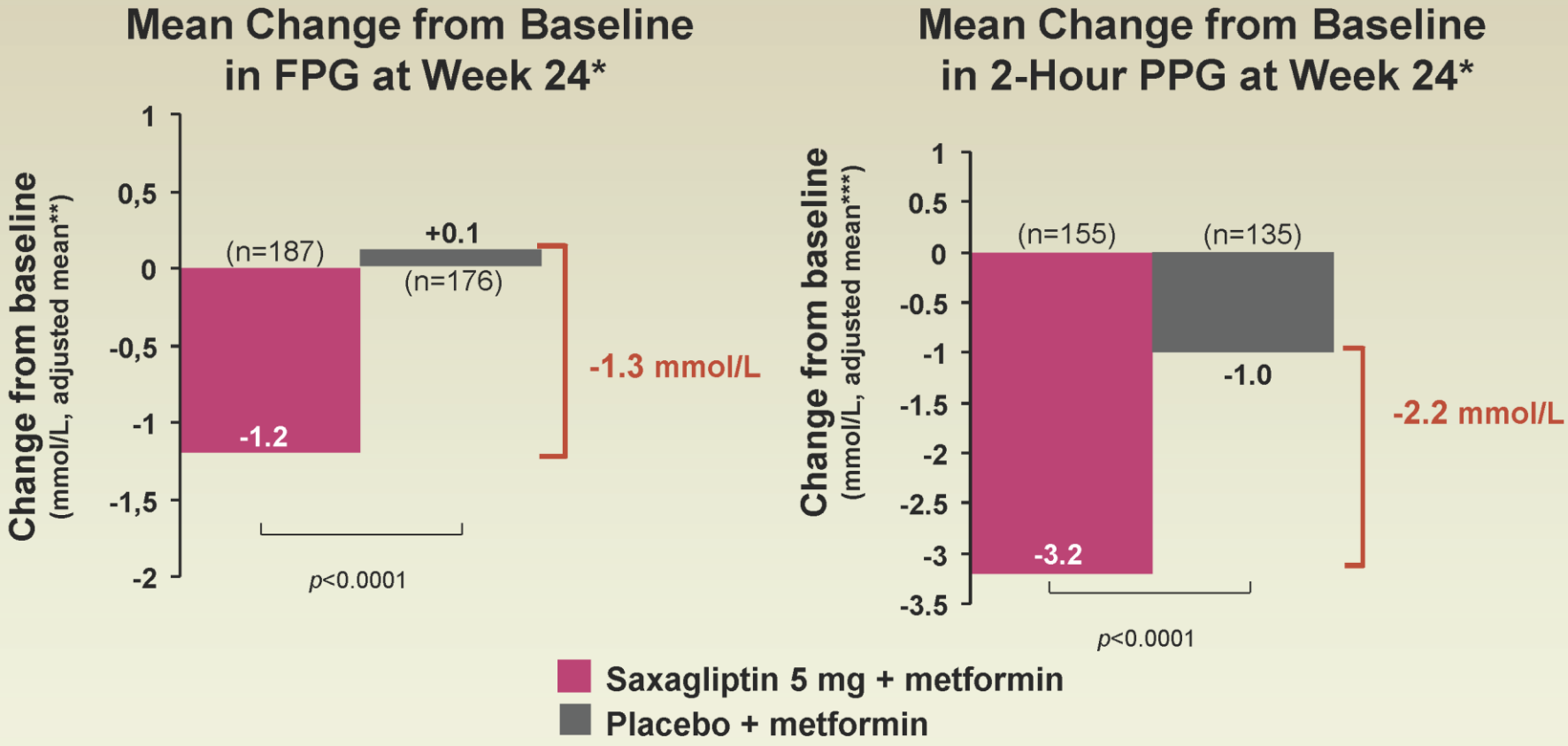
*Not approved for clinical use.

FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; LAR = long-acting release; PPG = postprandial plasma glucose; RA = receptor agonist

Medscape EDUCATION

Lund A et al. *Eur J Intern Med.* 2014;25:407-414.

Effect of Saxagliptin as Add-On Combination Therapy with Metformin on FPG and 2-Hour PPG

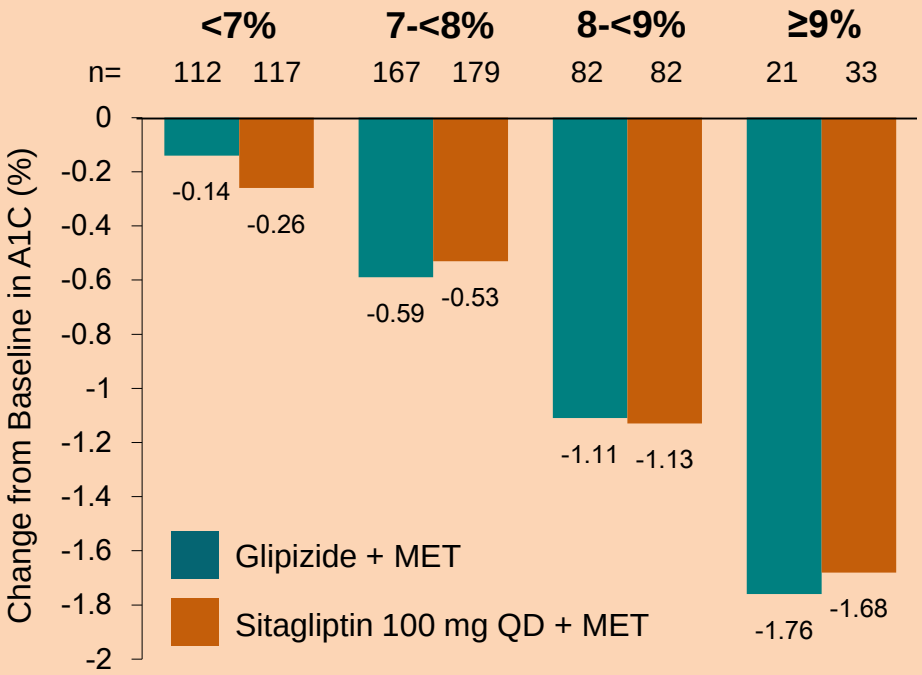


*Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy
**Least squares mean adjusted for baseline value (mean baseline FPG: saxagliptin 5 mg +metformin, 9.9 mmol/L; placebo +metformin, 9.7 mmol/L); ***mean baseline 2-hour PPG: saxagliptin 5 mg +metformin, 16.4 mmol/L; placebo +metformin, 16.4 mmol/L)
Bristol-Myers Squibb Canada and AstraZeneca Canada Inc. *ONGLYZA (Saxagliptin Tablets) Product Monograph*. 2009.

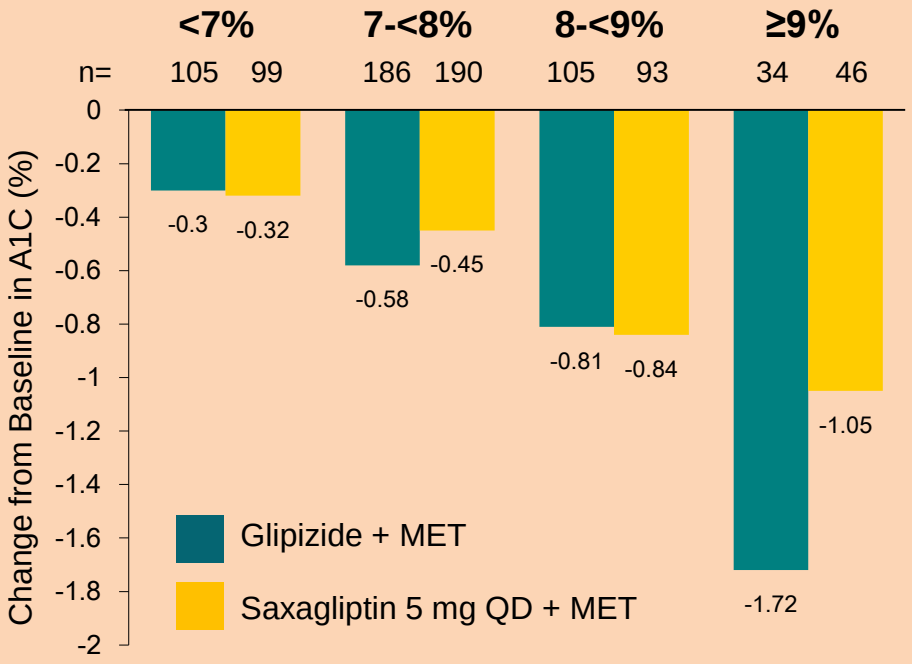
DPP-4 Inhibitors vs. Sulfonylureas (added to Metformin): Efficacy by Baseline A1C

Not head-to-head trials

Sitagliptin vs. Glipizide[1]
52 weeks (n=793)



Saxagliptin vs. Glipizide[2]
52 weeks (n=858)



p values not available.

1. Nauck et al. Diabetes Obes Metab. 2007;9:194-205; 2. Goke et al. Int J Clin Pract. 2010;64:1619-31.

HbA1c Reduction With GLP-1 RAs: Summary of Clinical Trial Data

Exenatide 10 µg twice daily	Change in HbA1c %*	Liraglutide 1.8 mg once daily[a]	Change in HbA1c %*	Exenatide 2 mg once weekly[a]	Change in HbA1c %*
+ None†[b]	–0.7	+ None*	–1.1	+ None*	–1.6
+ SU[c]	–1.0	+ SU	–1.1	+ SU	–1.9
+ MET[d]	–0.9	+ MET	–1.0	+ MET	–1.5
+ SU/MET[e]	–1.0	+ (MET + SU)	–1.3	+ (MET + SU)	–1.5
+ TZD ± MET[a]	–0.9	+ (MET +TZD)	–1.5		
		+ MET ± SU	–1.1		

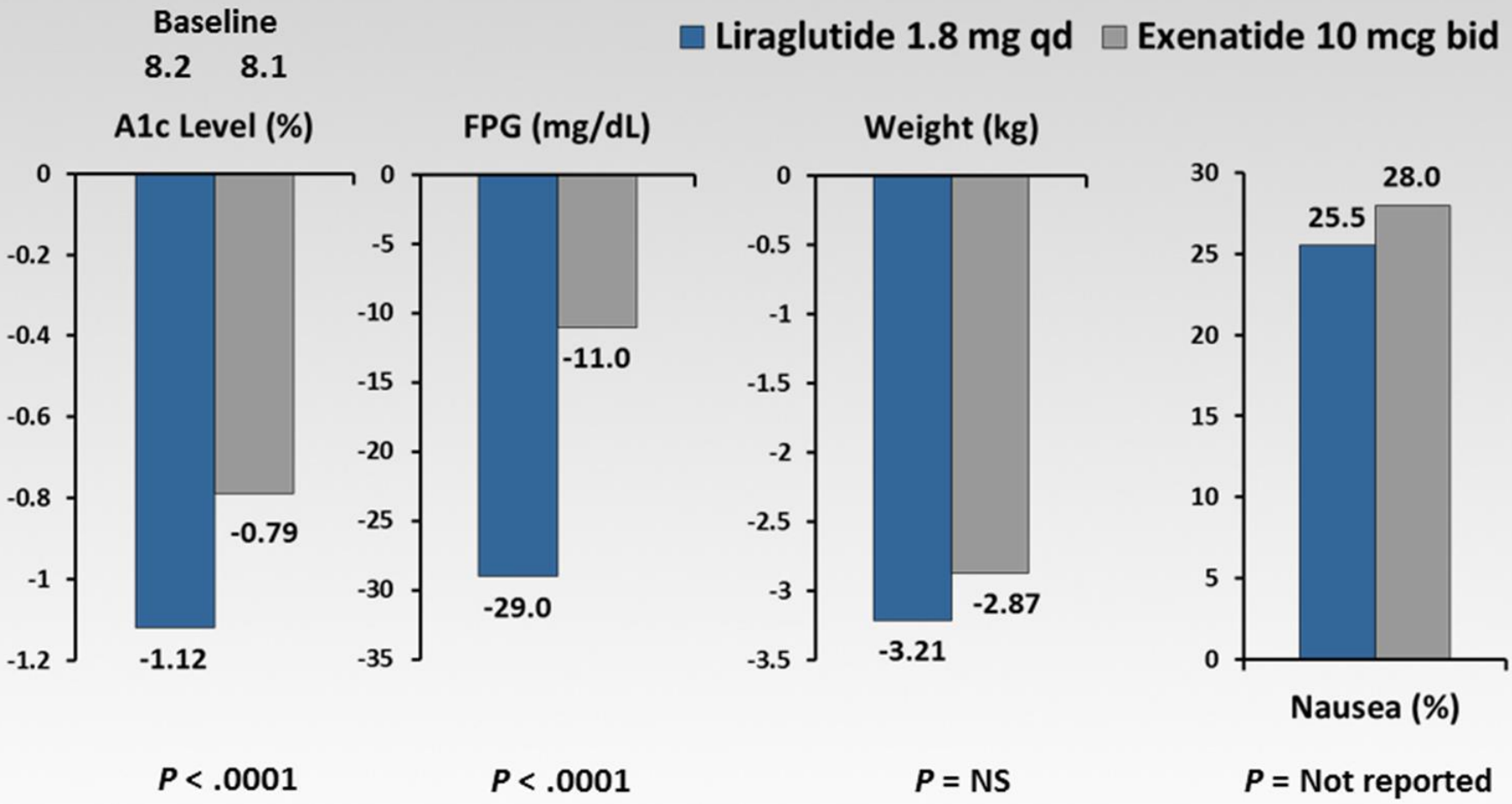
*Placebo-subtracted

†Background oral antihyperglycemic agent(s)

HbA1c = glycated hemoglobin; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione

a. Mundil D, et al. *Diab Vasc Dis Res*. 2012;9(2):95-108.
b. Poon T, et al. *Diabetes Technol Ther*. 2005;7(3):467-477.
c. Buse JB, et al. *Diabetes Care*. 2004;27(11):2628-2635.
d. DeFronzo RA, et al. *Diabetes Care*. 2005;28(5):1092-1100.
e. Kendall DM, et al. *Diabetes Care*. 2005;28(5):1083-1091.

Liraglutide vs Exenatide When Added to Metformin and/or SU in T2DM: LEAD-6



bid = twice daily; FPG = fasting plasma glucose; LEAD = Liraglutide Effect and Action in Diabetes; NS = not significant; qd = once daily

Adapted from Buse JB, et al. *Lancet*. 2009;374(9683):39-47.

Medscape EDUCATION

Short-Acting vs Long-Acting GLP-1 RAs

Parameter	Short-Acting GLP-1 RAs	Long-Acting GLP-1 RAs
	Exenatide Lixisenatide	Albiglutide Dulaglutide* Exenatide-LAR Liraglutide
Fasting plasma glucose	Modest reduction	Strong reduction
Postprandial glucose	Strong reduction	Modest reduction
SBP	Reduction	Reduction
Heart rate	No effect or small increase (0-2 beats/min)	Moderate increase (2-5 beats/min)
Body weight reduction	1-5 kg	2-5 kg

*Not approved for clinical use.

LAR = long-acting release; SBP = systolic blood pressure

Medscape EDUCATION

Meier JJ. *Nat Rev Endocrinol.* 2012;8(12):728-742.

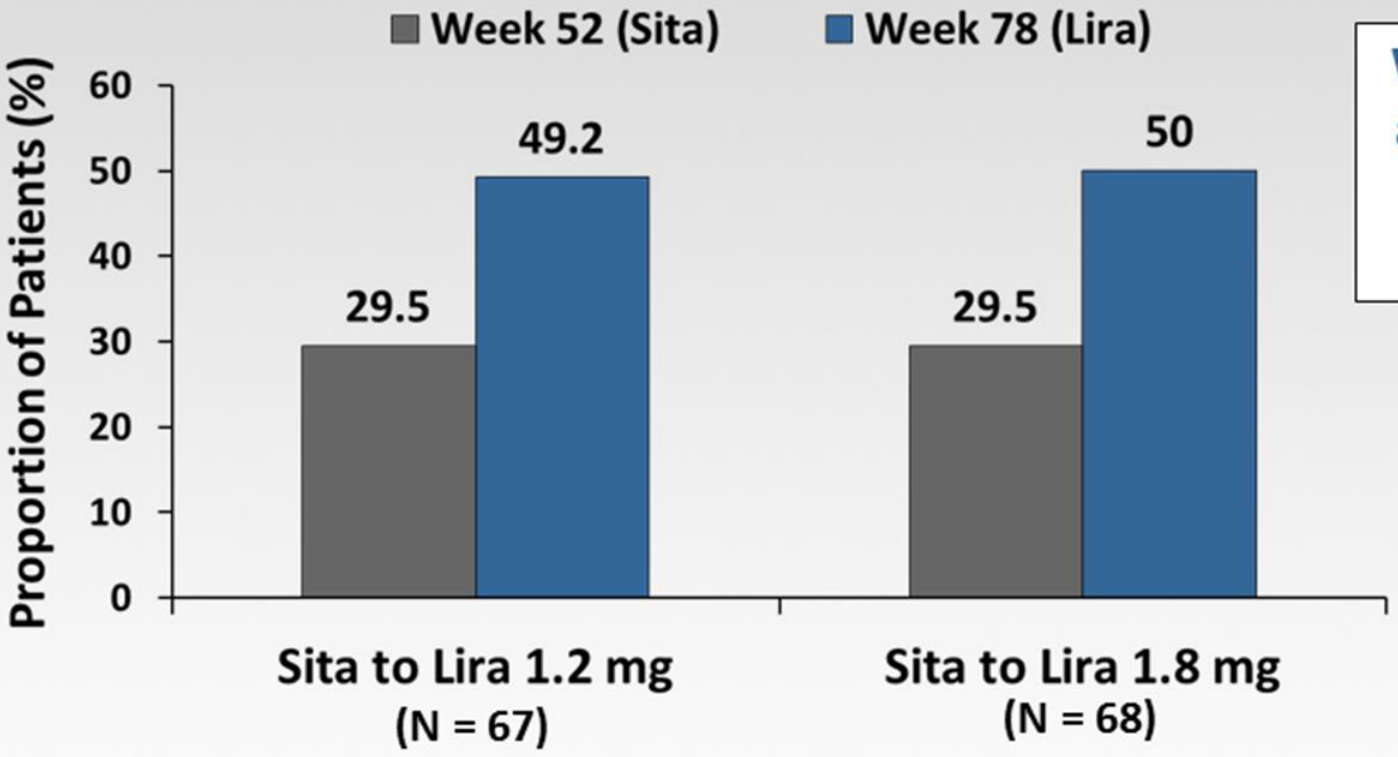
GLP-1 RAs and DPP-4 Inhibitors: A Comparison

Effects/Parameters	DPP-4 Inhibitors	GLP-1 RAs
Route of administration	PO	SC
Dosing/timing of administration	Once daily	Once or twice daily or once weekly
HbA1c reduction	0.5%-1.1%	0.6%-1.9%
Body weight	Neutral	Reduced
Hypoglycemia	Low incidence	Low incidence
Insulin secretion	Enhanced	Enhanced
Postprandial hyperglycemia	Reduced	Reduced
Glucagon secretion	Suppressed	Suppressed
Appetite	No effect	Suppressed
Gastric emptying	No effect	Slowed (shorter-acting agents)
Gastrointestinal	None	Nausea, diarrhea, vomiting

Reid T. *Clin Diabet.* 2012;30(1):3-12.
Scheen AJ. *Eur J Int Med.* 2012;23(2):126-131.
Rosenstock J, et al. *Int J Clin Pract Suppl.* 2008;(159):15-23.

Switching from a DPP-4 Inhibitor to a GLP-1 RA

Proportion of Patients Achieving HbA1c < 7% After Switching from Sitagliptin to Liraglutide



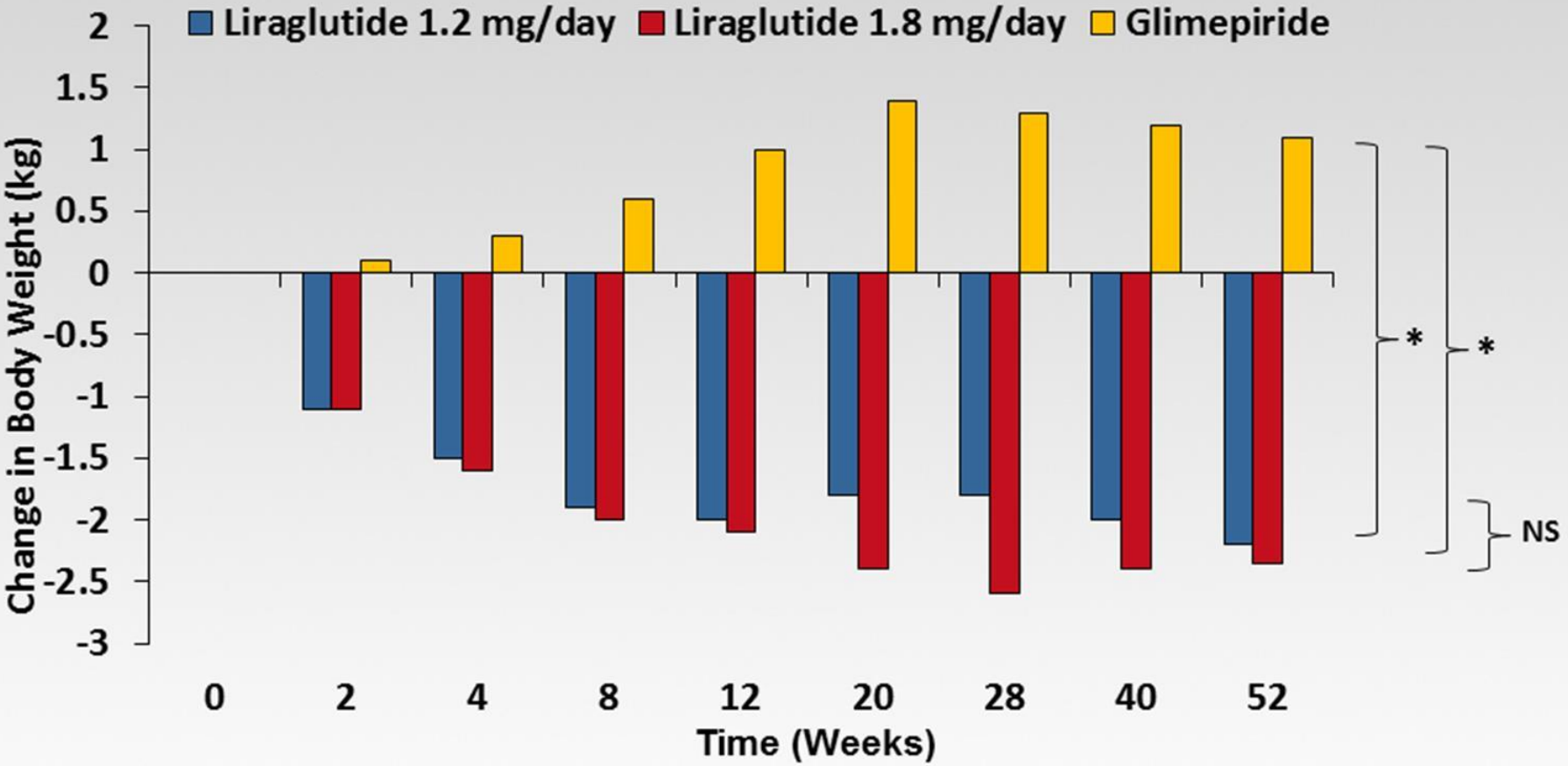
Weight change after switch to liraglutide: -1.6 kg

Lira = liraglutide; Sita = sitagliptin

Adapted from Pratley RE, et al. *Diabetes Care.* 2012;35(10):1986-1993.

Medscape EDUCATION

Evidence for Sustained Reduction in Body Weight: LEAD-3 Study



***P* values relate to estimated treatment difference for changes from baseline.**

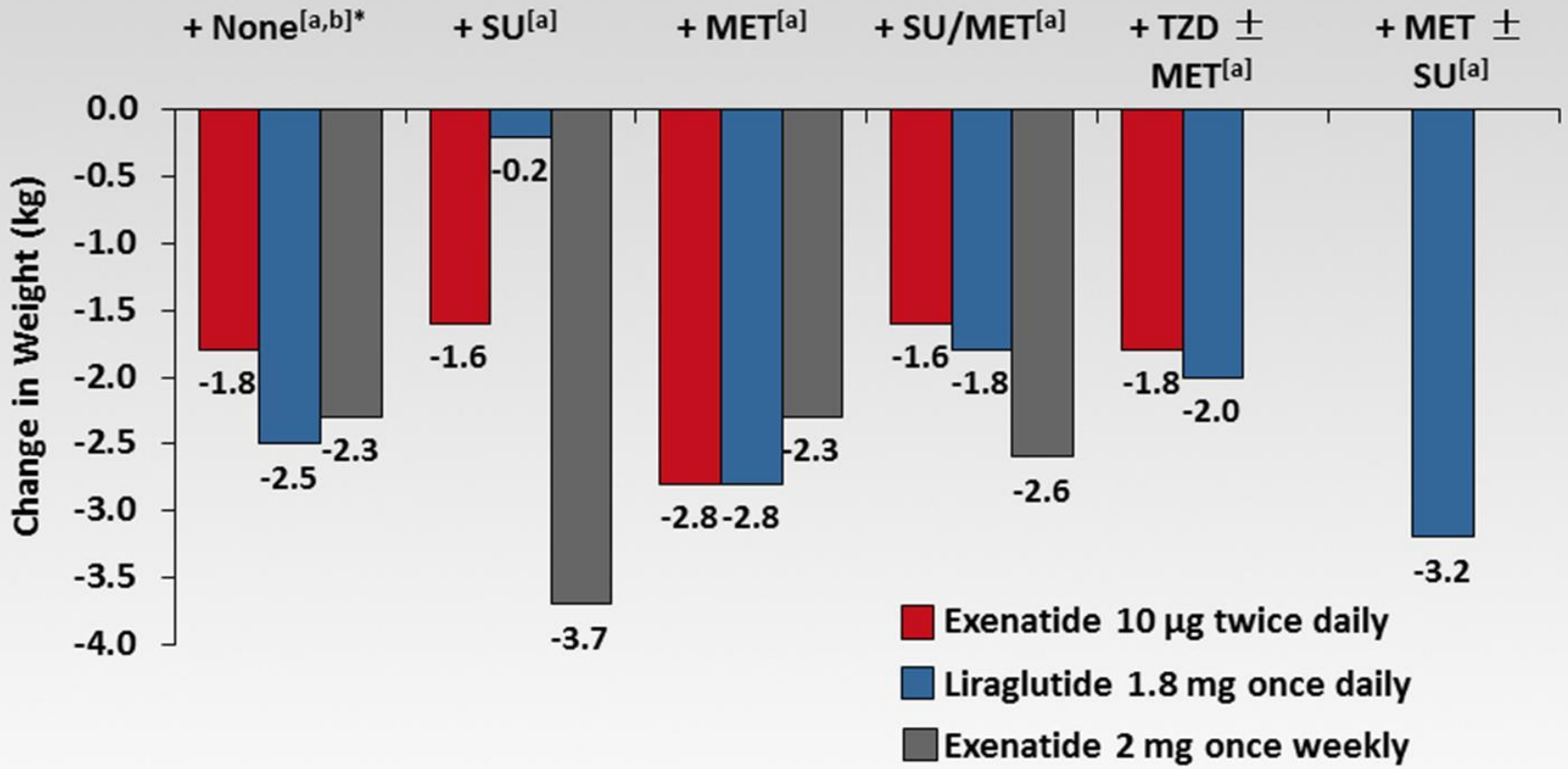
*** *P*<.0001.**

NS = not significant.

Garber A, et al. *Lancet*. 2009;373(9662):473-481.

Medscape EDUCATION

Weight Reduction With GLP-1 RAs: Summary of Clinical Trial Data



*Background oral antihyperglycemic agent(s)

a. Mundil D. *Diab Vasc Dis Res*. 2012;9(2):95-108.
b. Poon T, et al. *Diabetes Technol Ther*. 2005;7(3):467-477.

Medscape EDUCATION

SBP Reduction With GLP-1 RAs: Summary of Clinical Trial Data

Exenatide 2 mg Once Weekly	SBP (mm Hg)*	Liraglutide 1.8 mg Once Daily	SBP (mm Hg)*
+ None†	-2.9	+ None†	-3.6
+ SU	-4.7	+ SU	-2.8
+ MET	-4.0	+ MET	-2.3
+ MET ± SU	-3.0	+ MET + SU	-4.0
		+ MET + TZD	-5.5
		+ MET ± SU	-2.5

*Placebo subtracted

† Background oral antihyperglycemic agent(s)

SBP = systolic blood pressure

Mundil D, et al. *Diab Vasc Dis Res*. 2012;9(2):95-108.

Medscape EDUCATION

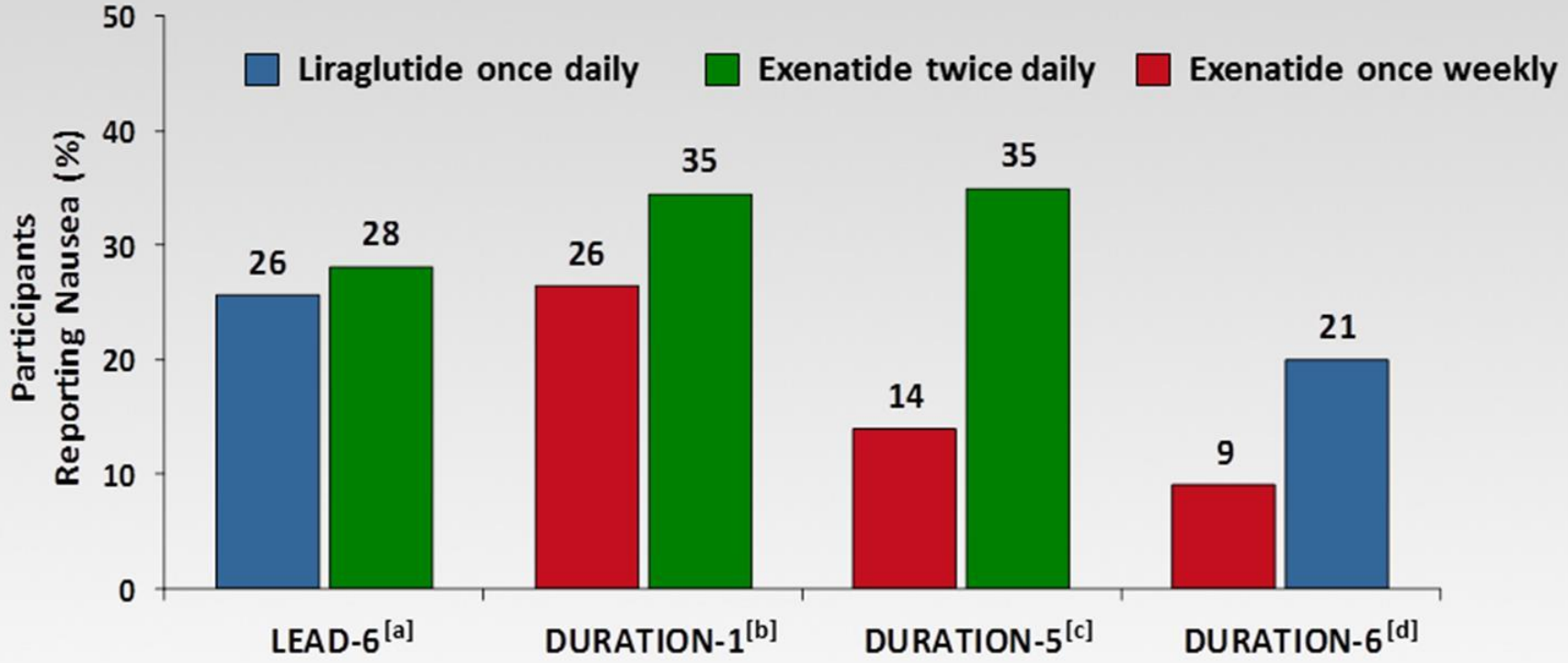
GLP-1 RAs: Safety Summary

- Most common side effects of GLP-1 RAs are transient nausea, vomiting and diarrhea, indigestion, and upper abdominal discomfort[a]
- Pancreatitis and pancreatic cancer: reports of association but no conclusive data[b]
  - Discontinue medication if signs/symptoms of pancreatitis develop; do not use if pancreatitis is confirmed
- Long-term activation of the GLP-1 receptor is associated with C-cell proliferation and tumor formation in rodents. This has not been shown in humans[c]
  - Two GLP-1 RAs (liraglutide and exenatide-LAR) are contraindicated in patients with MEN2 or family history of medullary thyroid cancer[d]
- Use in caution with patients with renal impairment, especially when initiating or escalating doses[d]
  - Exenatide and exenatide-LAR should not be used in patients with CrCl <30 mL/min

LAR = long-acting release; MEN2 = multiple endocrine neoplasia syndrome type 2; CrCl = creatinine clearance

a. Meier JJ. *Nat Rev Endocrinol*. 2012;8(12):728-742.
b. Thomsen RW, et al. ADA 2014. Abstract 154-OR.
c. Bjerre Knudsen L, et al. *Endocrinology*. 2010;151(4):1473-1486.
d. MHRA. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088117

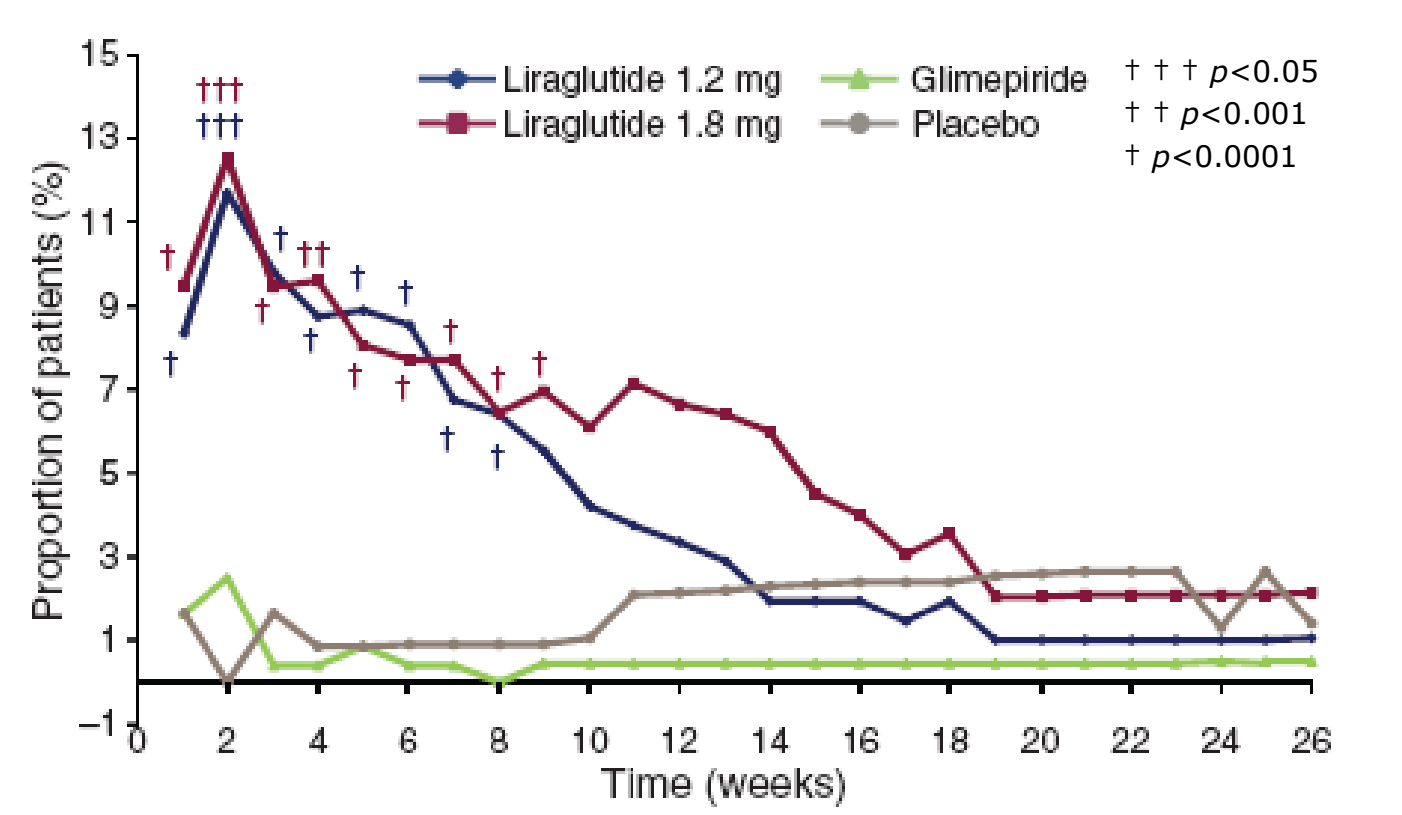
Nausea With GLP-1 RAs



a. Buse JB, et al. *Lancet*. 2009;374(9683):39-47.
b. Drucker D, et al. *Lancet*. 2008;372(9645):1240-1250.
c. Blevins T, et al. *J Clin Endocrinol Metab*. 2011;96(5):1301-1310.
d. Buse JB, et al. *Lancet*. 2013;381(9861):117-124.

Frequency of Nausea (LEAD 2)

Percentage of subjects with nausea through 26 weeks of treatment.



Nausea was generally ***mild to moderate***, ***transient*** and ***rarely led to discontinuation*** of therapy.

Nauck et al. *Diabetes Care* 2009;32:84–90;

Gallwitz B et al. *Int J Clin Pract.* 2010;64(2):267-276.

Adverse Events
Nausea/Vomiting

- Nausea is the most frequent adverse event of treatment
  - Usually dissipates within a few weeks
- 5%-10% of patients discontinue treatment due to nausea and vomiting
- Reduce nausea by
  - Co-administration with meals
  - Dose titration, especially with shorter-acting agents
  - Eat slowly and portion control

Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.

Use of GLP-1 RAs and Basal Insulin in Combination

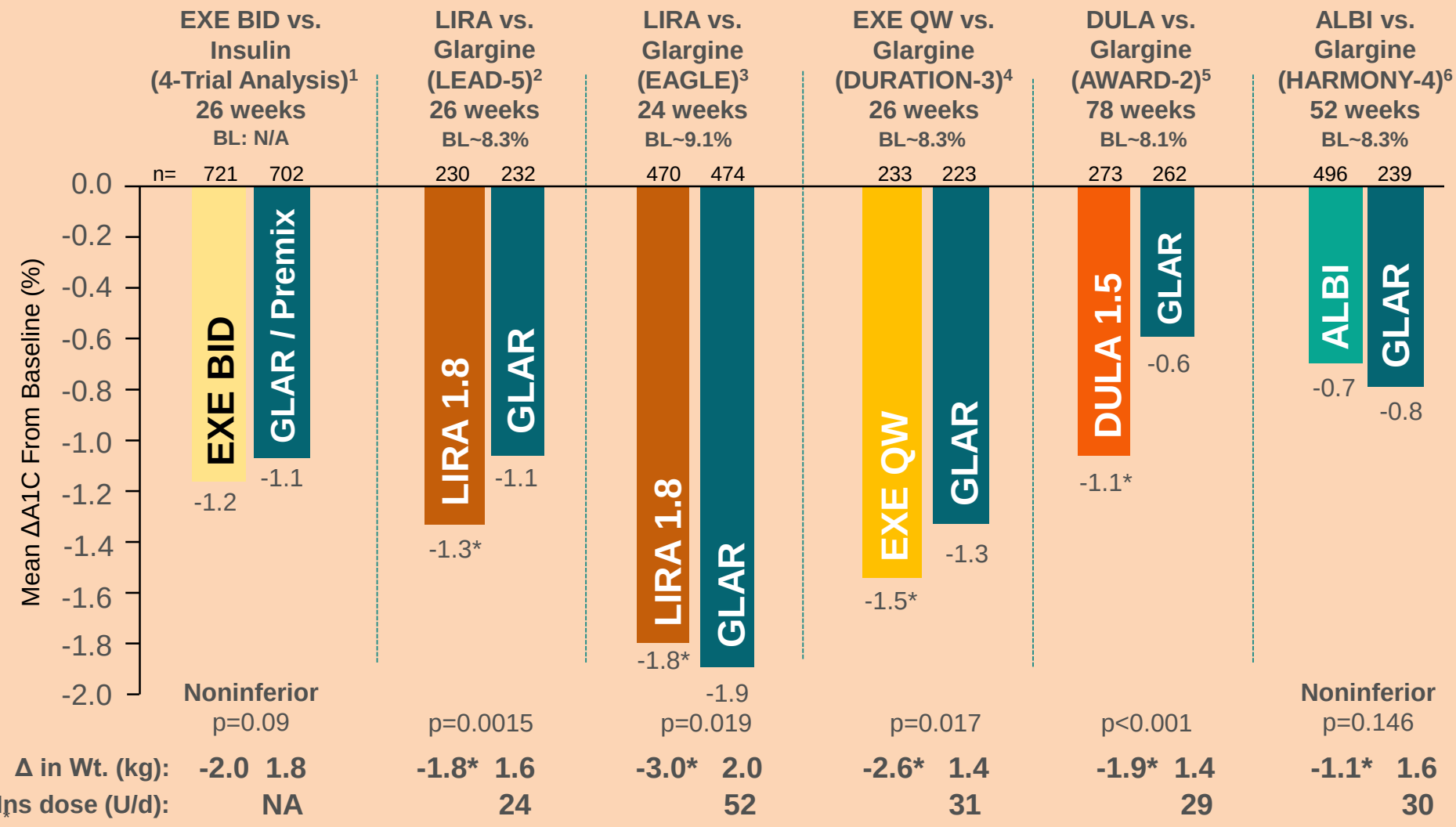
- GLP-1 RAs
  - Improve PPG levels without need for carbohydrate counting or frequent blood glucose monitoring
  - Are weight-reducing
- Basal insulin affects FPG primarily, whereas GLP-1 RAs improve both FPG and PPG
- Potential for better overall HbA1c control

FPG = fasting plasma glucose; PPG = postprandial glucose

Medscape EDUCATION

Vora J, et al. *Diabetes Metab*. 2013;39(1):6-15.

GLP-1R Agonists vs. Basal Insulin: Head-to-Head Trials



Significant vs. comparator.

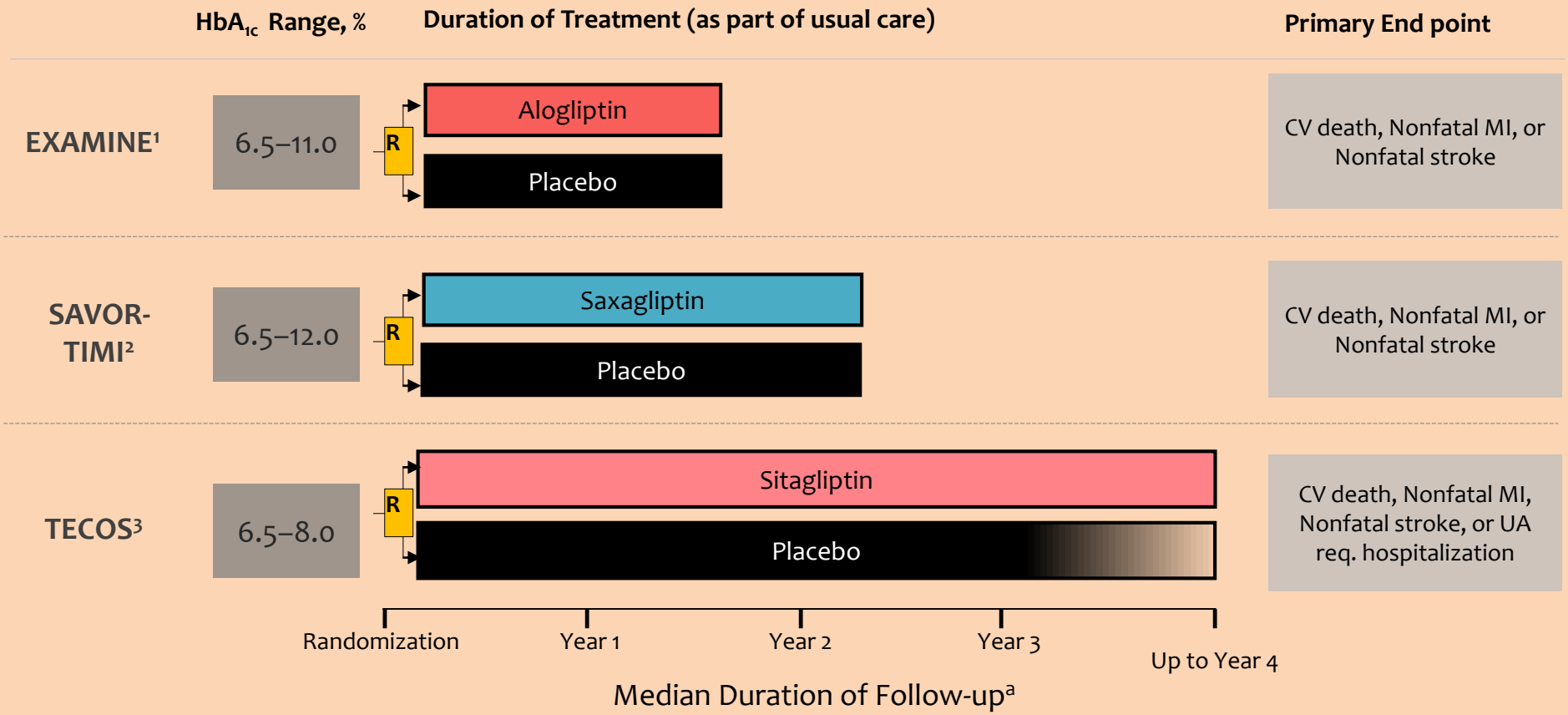
When Should GLP-1 RAs Be Considered?

- When hypoglycemia is particularly undesirable
- When weight loss is an important consideration
- When current therapy is failing to adequately control postprandial hyperglycemia

GLP-1 RA = glucagon-like peptide-1 receptor agonist

Inzucchi SE, et al. *Diabetes Care.* 2012;35(6):1364-1379.
Davidson JA. *Mayo Clin Proc.* 2010;85(12 Suppl):S27-S37.
Campbell RK. *Clin Ther.* 2011;33(5):511-527.

EXAMINE, SAVOR-TIMI, and TECOS



[a]Approximate median duration of follow-up for TECOS, based on the expected event rate at study initiation. EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome;SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin. CV = cardiovascular; MI = myocardial infarction; UA = unstable angina.

1. White WB et al. *N Engl J Med.* 2013;369:1327–1335. **2.** Scirica BM et al. *N Engl J Med* 2013;369:1317–1326. **3.** Green JB et al. *Am Heart J.* 2013;166:983–989.e7.

EXAMINE, SAVOR-TIMI, and TECOS

	EXAMINE[1]	SAVOR-TIMI[2]	TECOS[3]
	Alogliptin vs Placebo	*Saxagliptin vs Placebo*	*Sitagliptin vs Placebo*
Sample size, N	5,380	16,492	14,724
Median duration of diabetes, y	≈7.2	10.3	9.4
Baseline HbA_{1c}, %	8.0	8.0	7.3
Number of events	621	1,222	>1,300
Median duration of exposure, y	1.5	2.1	≈ 3.0

EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

SAVOR TIMI-53: Individual Endpoints

Endpoint	2-year KM rate (%)		HR	*p* value for superiority
	Placebo (n = 8,212)	Saxagliptin (n = 8,280)		
CV death	2.9	3.2	1.03 (0.87-1.22)	0.72
MI	3.4	3.2	0.95 (0.80-1.12)	0.52
Ischemic stroke	1.7	1.9	1.11 (0.88-1.39)	0.38
Hosp. for cor. revasc.	5.6	5.2	0.91 (0.80-1.04)	0.18
Hosp. for UA	1.0	1.2	1.19 (0.89-1.60)	0.24
Hosp. for HF	2.8	3.5	1.27 (1.07-1.51)	0.007
All-cause mortality	4.2	4.9	1.11 (0.96-1.27)	0.15

Scirica BM, et al. *N Engl J Med* 2013; 369(14):1317-26.

Relevant Baseline Characteristics

Characteristic	SAVOR-TIMI[1]	EXAMINE[2]	TECOS[3]
# patients	16492	5380	14724
Males (%)	67	68	71
Mean age (SD)	68.1 (8.5)	61	66 (8)
BMI	31.1 (5.5)	28.7	30.2 (5.7)
A1C %	8.0	8.0	7.3 +/-0.7
Duration of DM	10.3	7.2	9.4
North America	31.9%	15.9	18%
Western Europe	26.0%	11.3*	14%

* Western Europe, Australia, New Zealand, and Middle East ** Eastern Europe, Western Europe

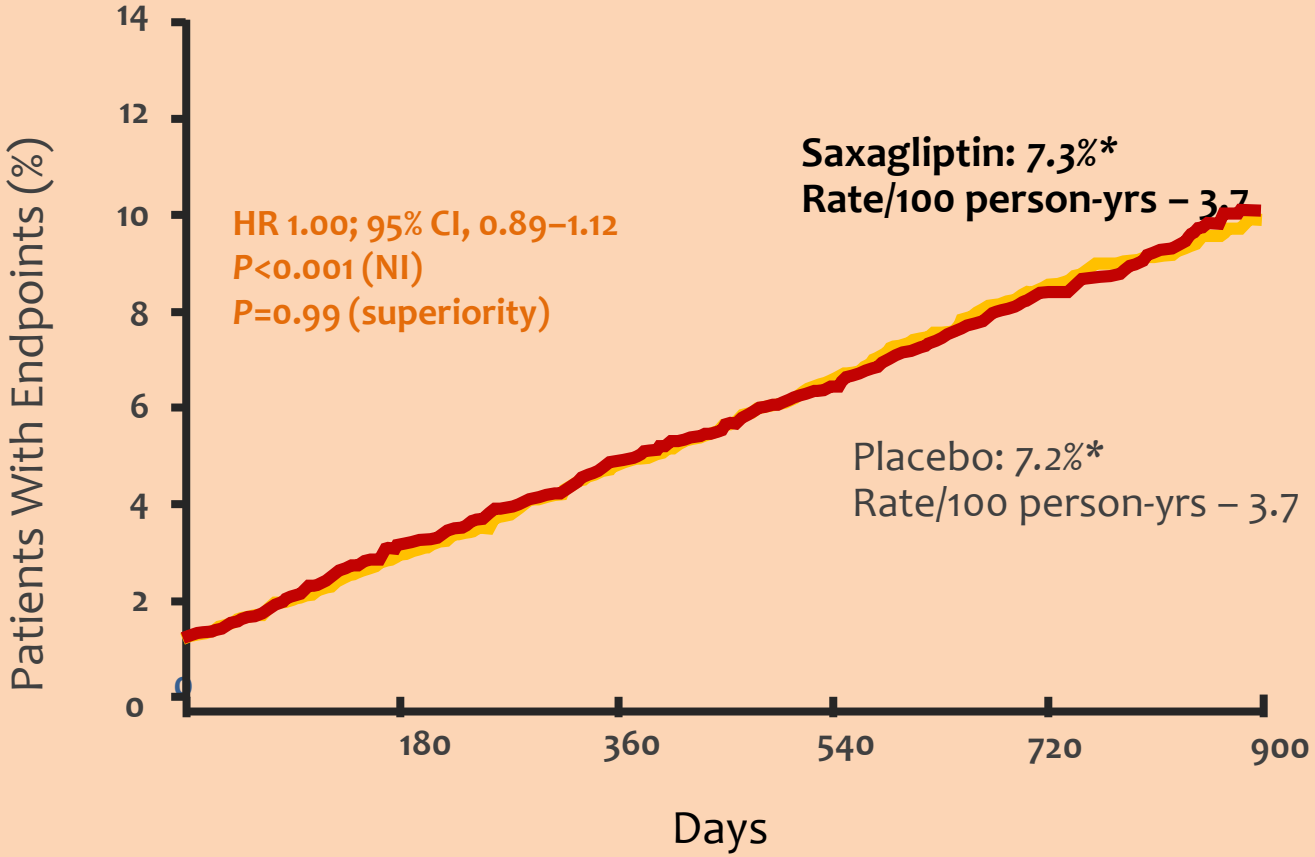
1.Scirica BM et al, N Engl J Med 2013. DOI: 10.1056/NEJMoa1307684. 2.White W. et al N Engl J Med 2013. DOI: 10.1056/NEJMoa1305889.
3.Bethel M.A. et al. DOM 2015 Jan 20. doi: 10.1111/dom.12441.

Relevant Baseline Characteristics (2)

Characteristic	SAVOR-TIMI[1]	EXAMINE[2]	TECOS[3]
Established CVD	78.4%	100%	100%
MI	37.8%	88%	43%
CABG	TBD	12.8%	25%
Stroke/TIA	TBD	7.2%	21%
PAD	TBD	9.6%	17%
CHF (all patients)	12.8%	28.5%[4]	18%
CHF (NYHA Class 3-4)	1.4%	5.65%[4]	2.5%

1-Scirica BM et al, N Engl J Med 2013. DOI: 10.1056/NEJMoa1307684. 2-White W. et al N Engl J Med 2013. DOI: 10.1056/NEJMoa1305889
3- Bethel M.A. et al. DOM 2015 Jan 20. doi: 10.1111/dom.12441. 4-Zannad F. et al. Lancet 2015. Published online March 10, 2015.
http://dx.doi.org/10.1016/S0140-6736(14)62225-X

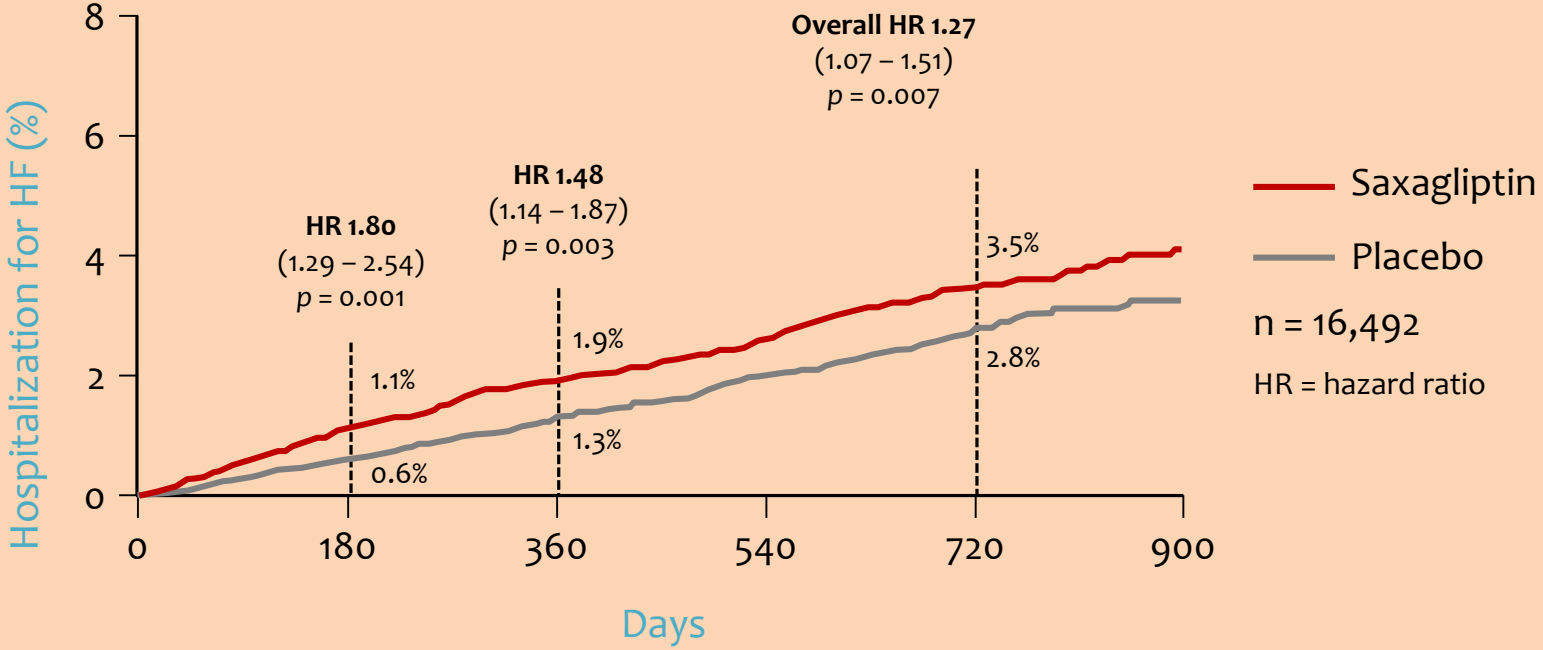
SAVOR: Kaplan – Meier Rates of the Primary Composite Endpoint – CV Death, MI, or Stroke



SAVOR: n = 16,492 patients (mean age 65 years) with type 2 diabetes (median duration 10.3 years) and established CVD or multiple risk factors. Median duration of follow-up: 2.1 years. A1C at 2 yrs: Saxa, 7.6%, PBO 7.9%

*K-M event rates are presented after 2 yrs., HR: hazard ratio; K-M: Kaplan-Meier; Pbo: placebo; Saxa: saxagliptin,
Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.

SAVOR TIMI – 53: Rates of Risk of Hospitalization For Heart Failure Over Time



- Saxagliptin neither increased nor decreased the risk of the 1° and 2° endpoints in these high-risk populations
- There were no specific subgroups in which the RR associated with saxagliptin was particularly high or low
- The absolute risk with saxagliptin was smallest in patients at low risk of HF and correspondingly larger in patients at highest risk

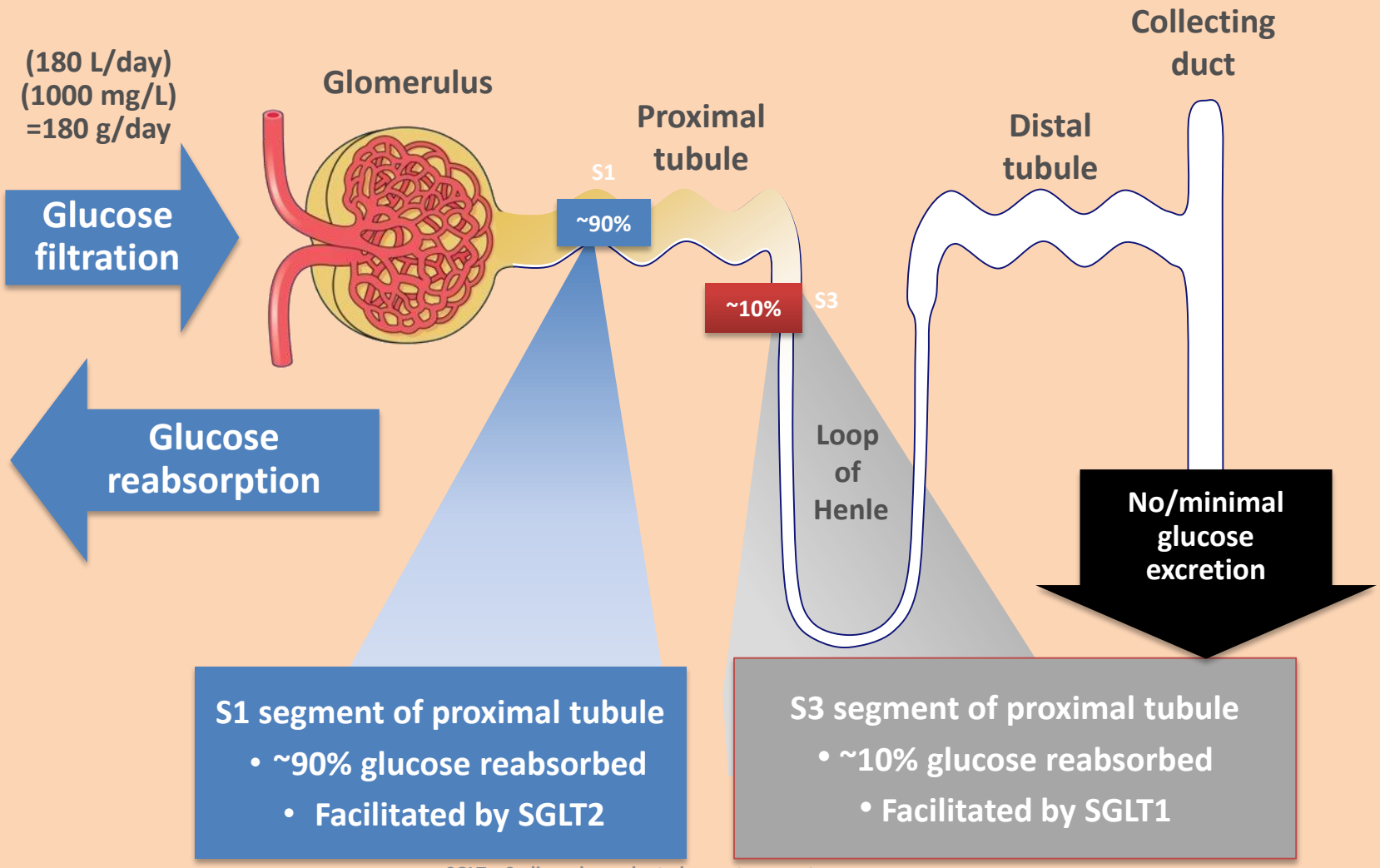
HF, heart failure. Scirica BM et al. Circulation. 2014; 130:1579-88.

Conclusions

- **GLP-1 RAs offer the opportunity to achieve both improved glycemic control and a reduction in body weight**
- **GLP-1 RAs may be used alone (monotherapy) or in combination with other antihyperglycemic therapies (dual or triple therapy)**
- **Renal impairment affects the clearance of exenatide but not that of liraglutide[a,b]**
- **Hypovolemia due to nausea and vomiting may worsen renal function**

a. Linnebjerg H, et al. *Br J Clin Pharmacol*. 2007;64(3):317-327.
b. Jacobsen L, et al. *Br J Clin Pharmacol*. 2009;68(6):898-905.

Renal Handling of Glucose in Healthy Patients



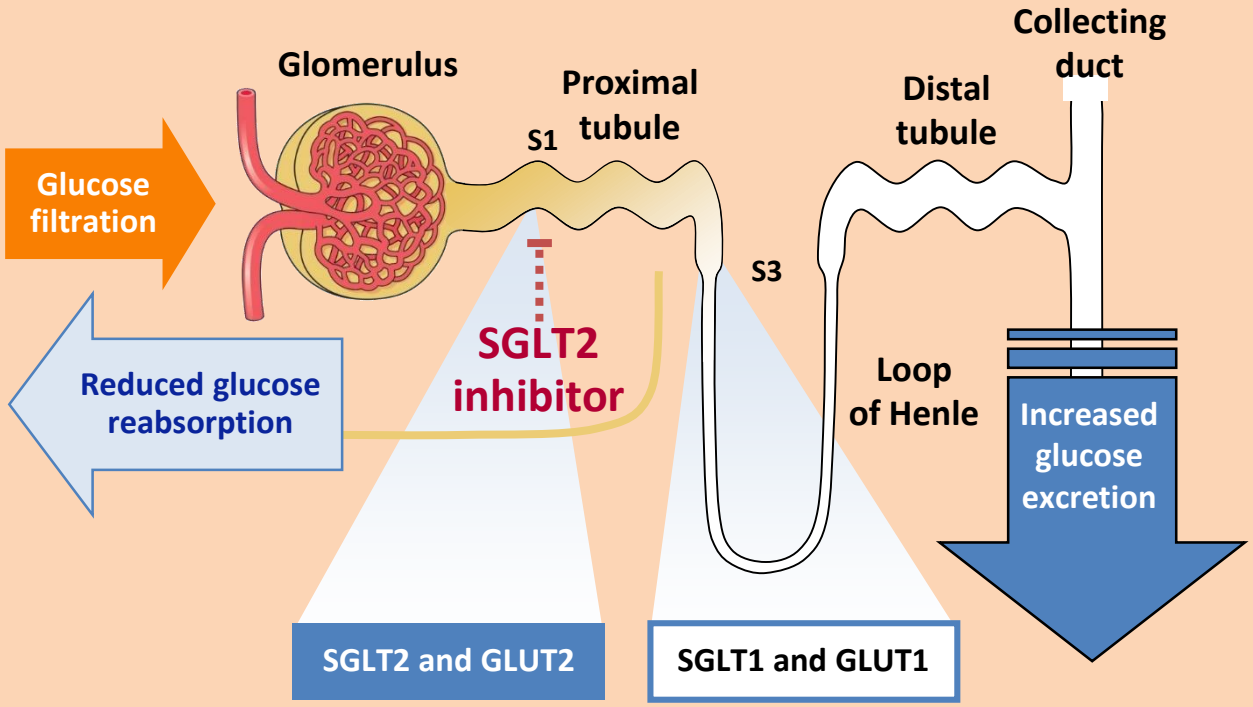
SGLT = Sodium-dependent glucose transporter

Adapted from:

1. Bailey CJ. *Trends in Pharmacol Sci.* 2011;32:63-71.
2. Chao EC. *Core Evid.* 2012:7:21-28.

SGLT2 Inhibitors: Mechanism of Action

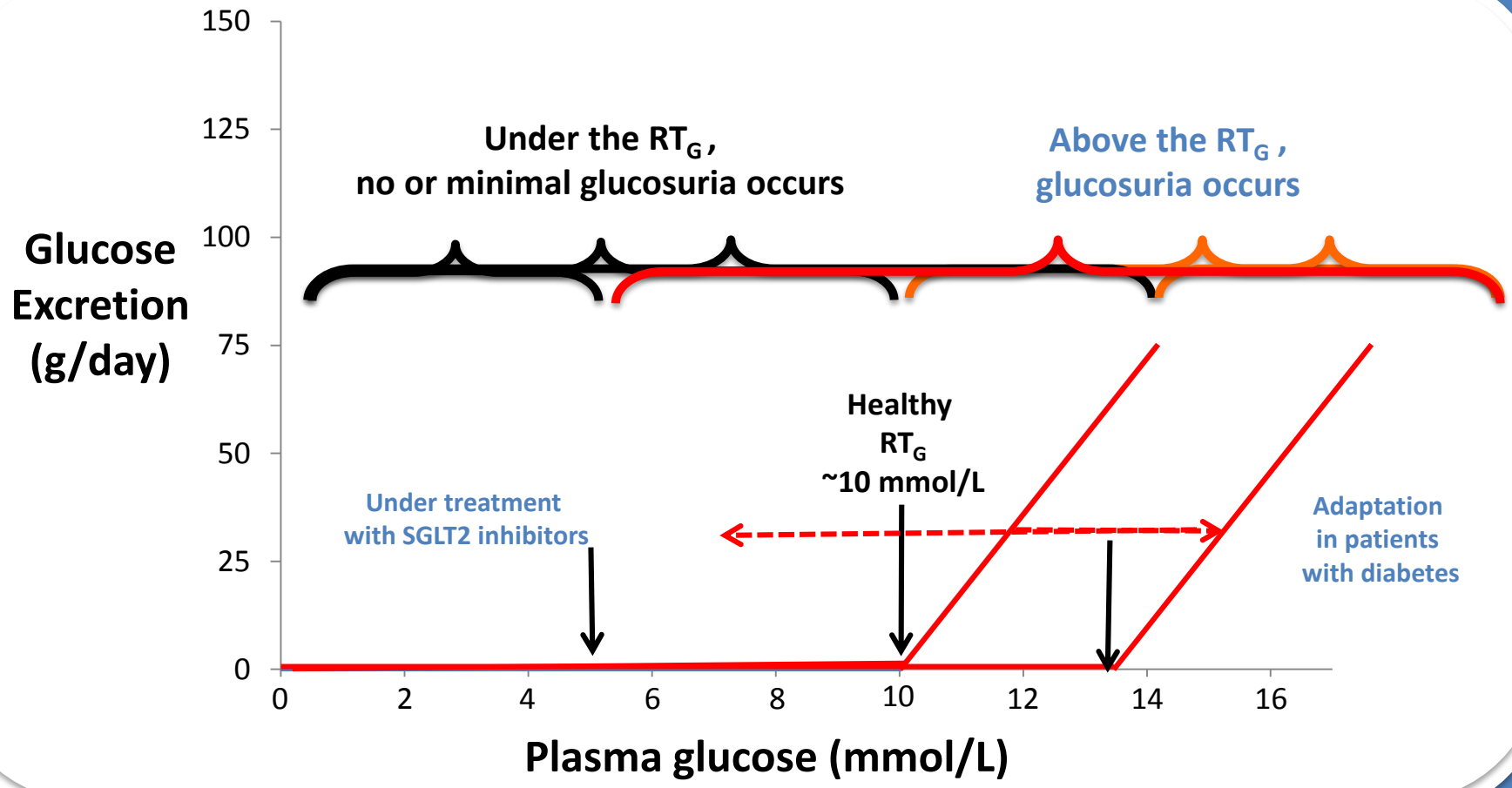
SGLT2 inhibition reduces renal glucose reabsorption and increases glucose elimination



GLU = facilitative glucose transporter. SGLT = sodium-dependent glucose transporter.

Adapted from: Abdul-Ghani MA, et al. Endocr Pract 2008; 14(6):782-90. Bays H. Curr Med Res Opin 2009; 25(3):671-81. Wright EM. Am J Physiol Renal Physiol 2001; 280(1):F10-8. Lee YJ, et al. Kidney Int Suppl 2007; 106:S27-35. Han S, et al. Diabetes 2008 ; 57:1723-9.

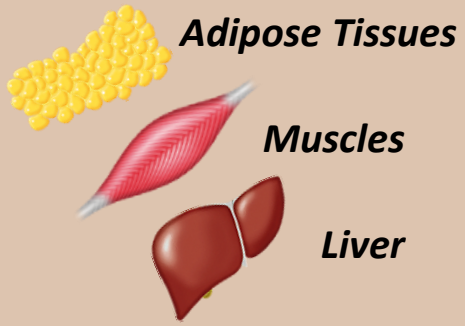
Effects of SGLT2 Inhibitors on RT_G



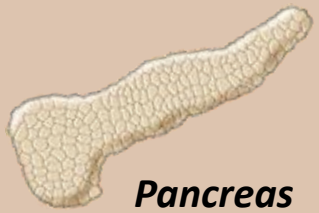
RT_G= Renal Threshold of Glucose

Targeting Hyperglycemia: Insulin-Dependent vs Insulin-Independent Approaches

Insulin-Dependent Mechanisms



Insulin action
- TZDs
- Metformin

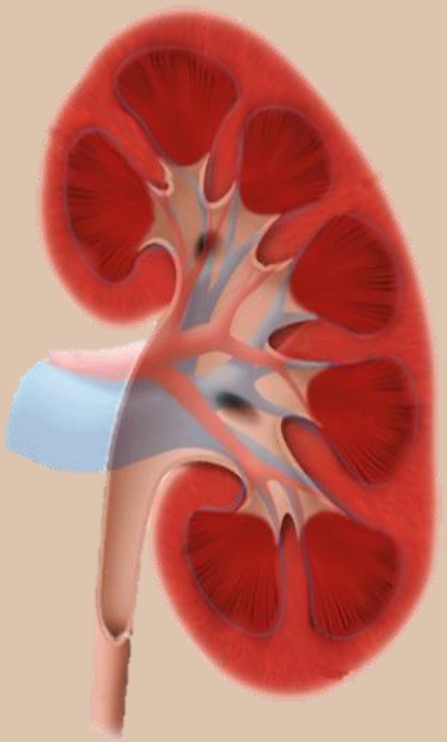


Insulin release
- Sulfonylureas
- GLP-1R agonists
- DPP-4 inhibitors
- Meglitinides

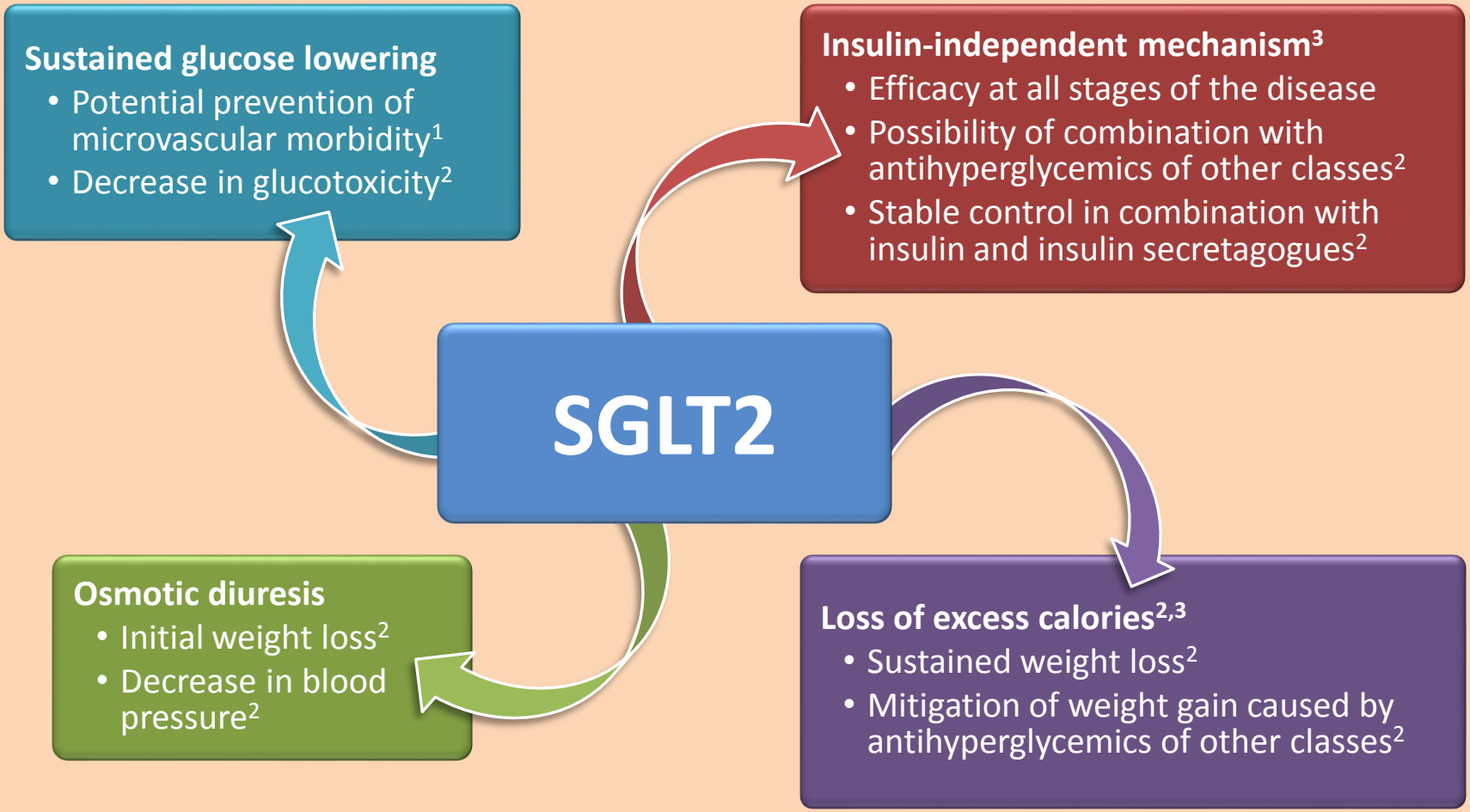
Insulin replacement
- Insulin

Insulin-Independent Mechanism

Insulin-independent renal SGLT2



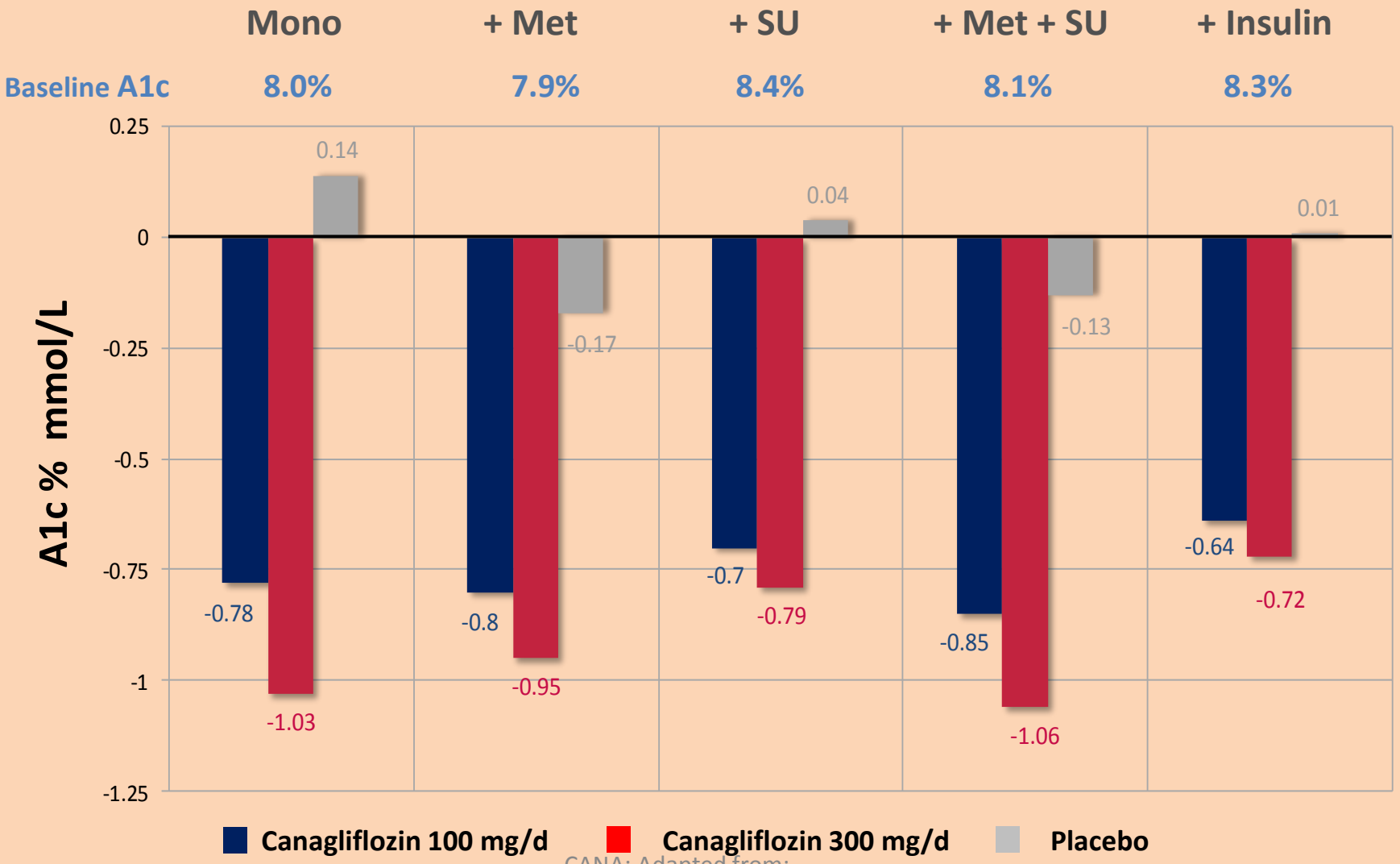
Treatment with an SGLT2 Inhibitor: Clinical Benefits in T2DM



1. Holman RR, et al. N Engl J Med 2008; 359:1577-89. 2. Neumiller JJ. Drugs 2010; 70:377-85.
3. Lo MC, et al. Am J Ther 2013; 20(6):638-653.

Canagliflozin – Summary of Clinical Studies

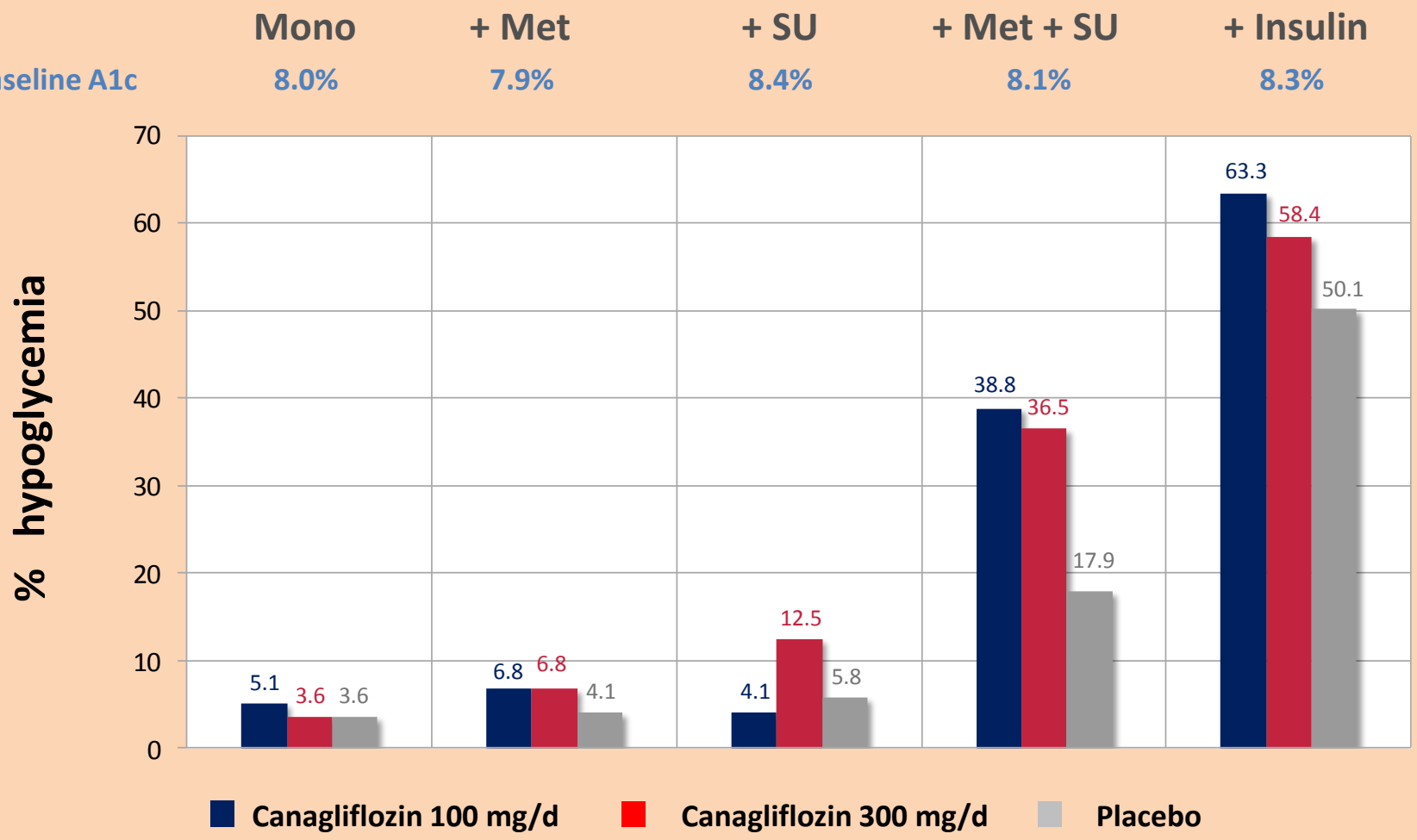
A1c Reduced: 0.64 to 1.06% (0.63 to 1.17% PBO Corrected)



CANA: Adapted from:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

Canagliflozin – Summary of Clinical Studies

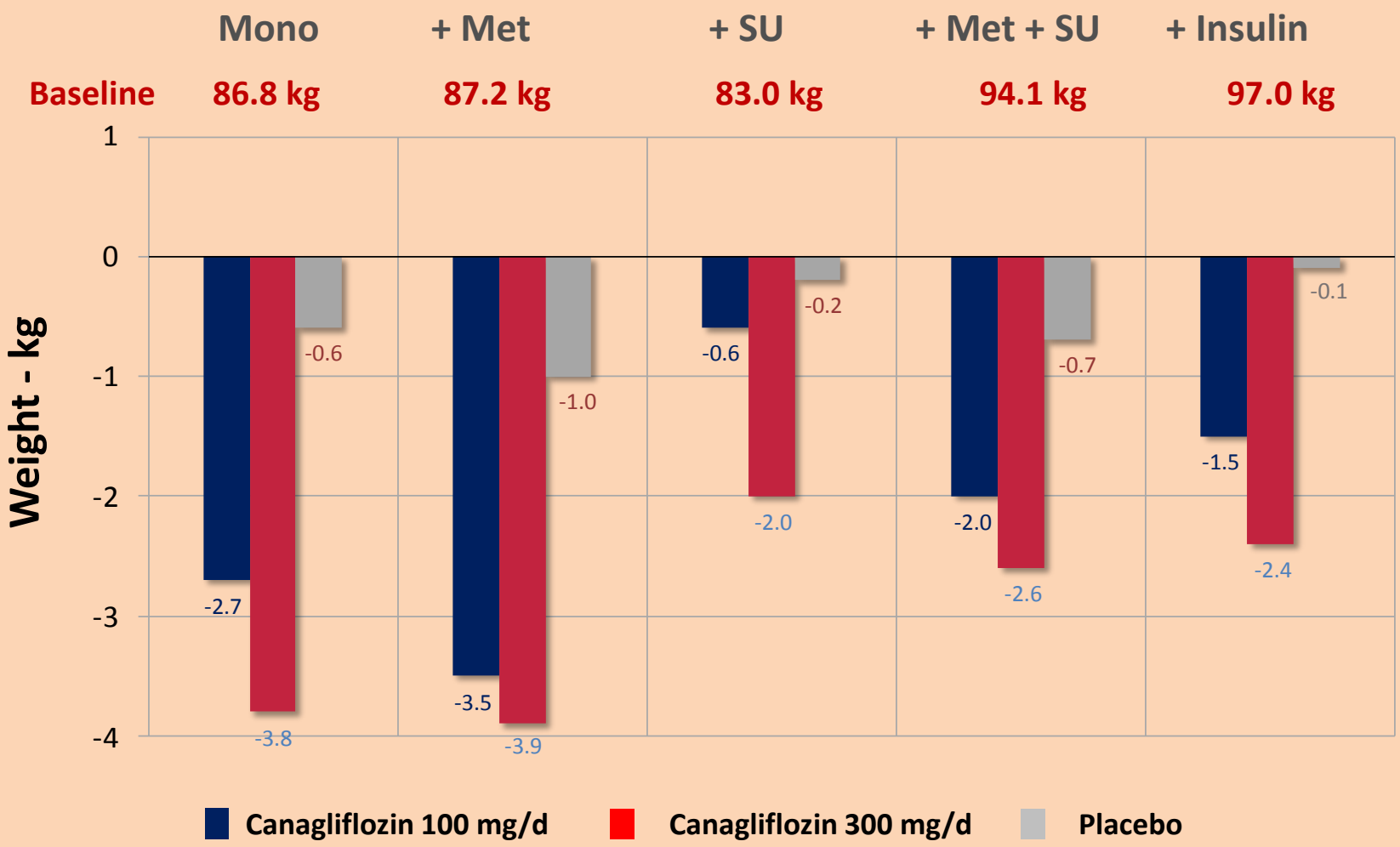
Rare Hypoglycemia Except When Combined with Secretagogues or Insulin



CANA: Adapted from:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

Canagliflozin – Summary of Clinical Studies

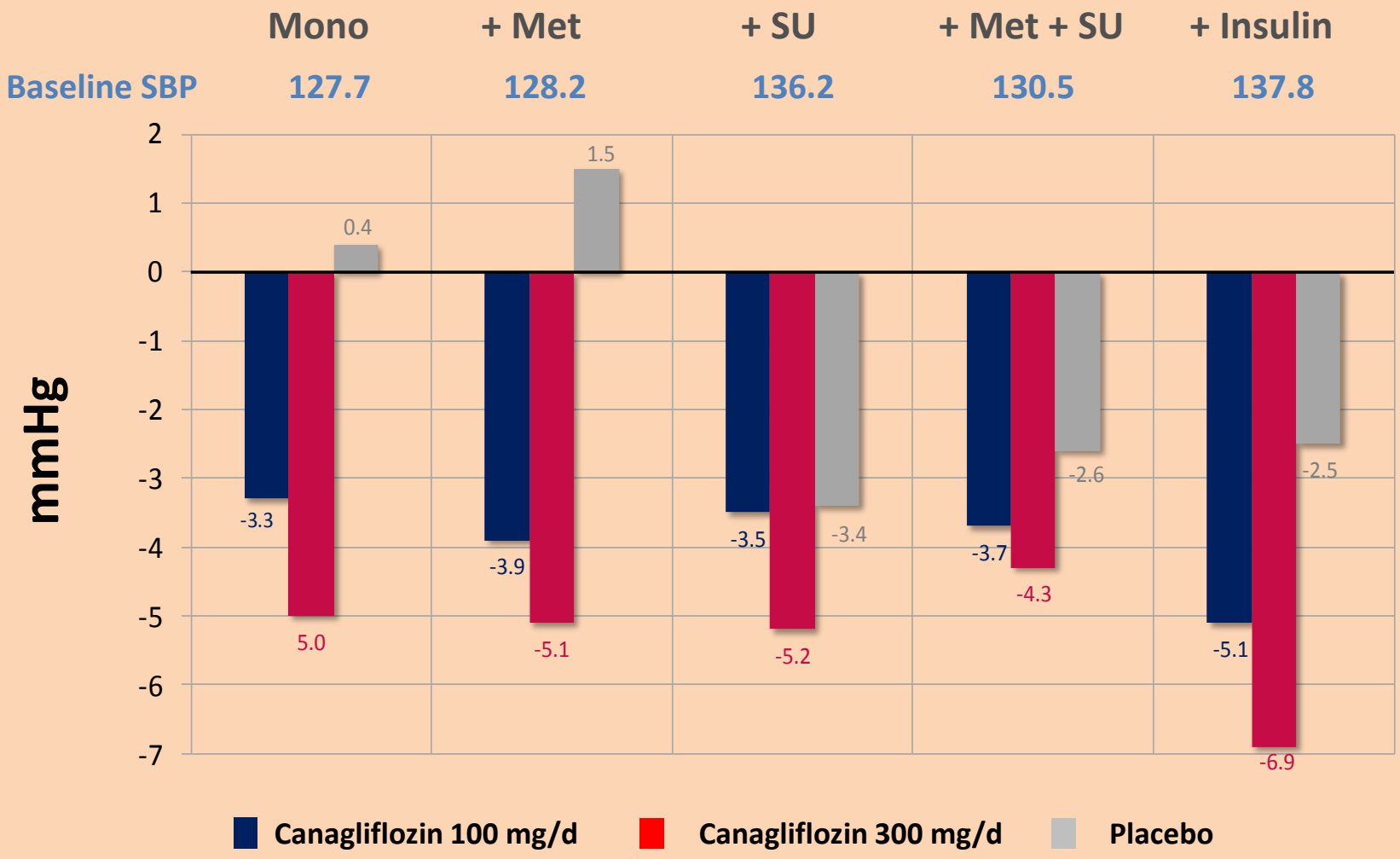
Weight Reduced by 0.6 to 3.9 kg (0.4-3.2 kg PBO Corrected)



CANA: Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

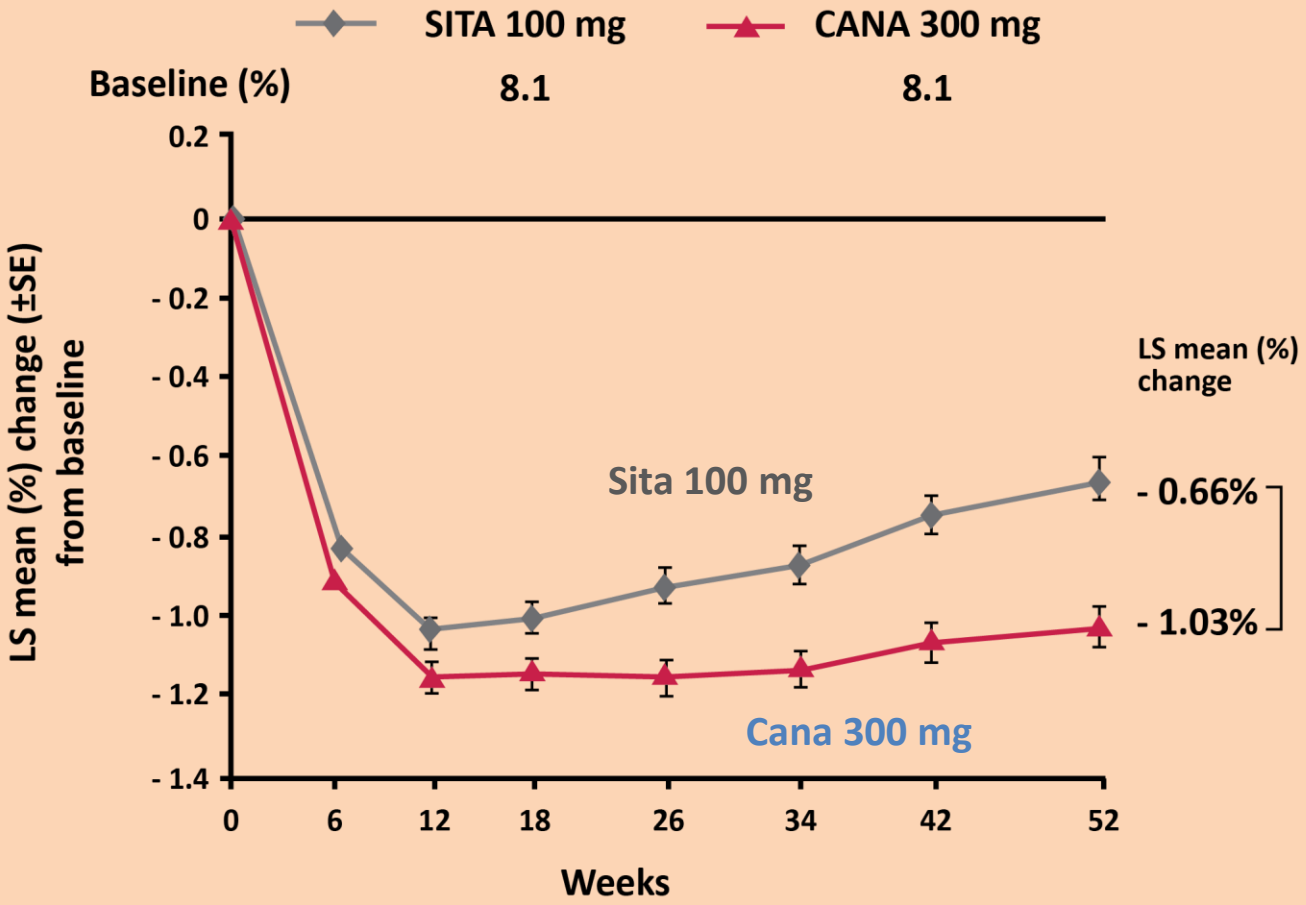
Canagliflozin – Summary of Clinical Studies

Systolic BP Decreased by 3.3 - 6.9 mmHg (0.1-6.6 PBO Corrected)



CANA: Adapted from:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013

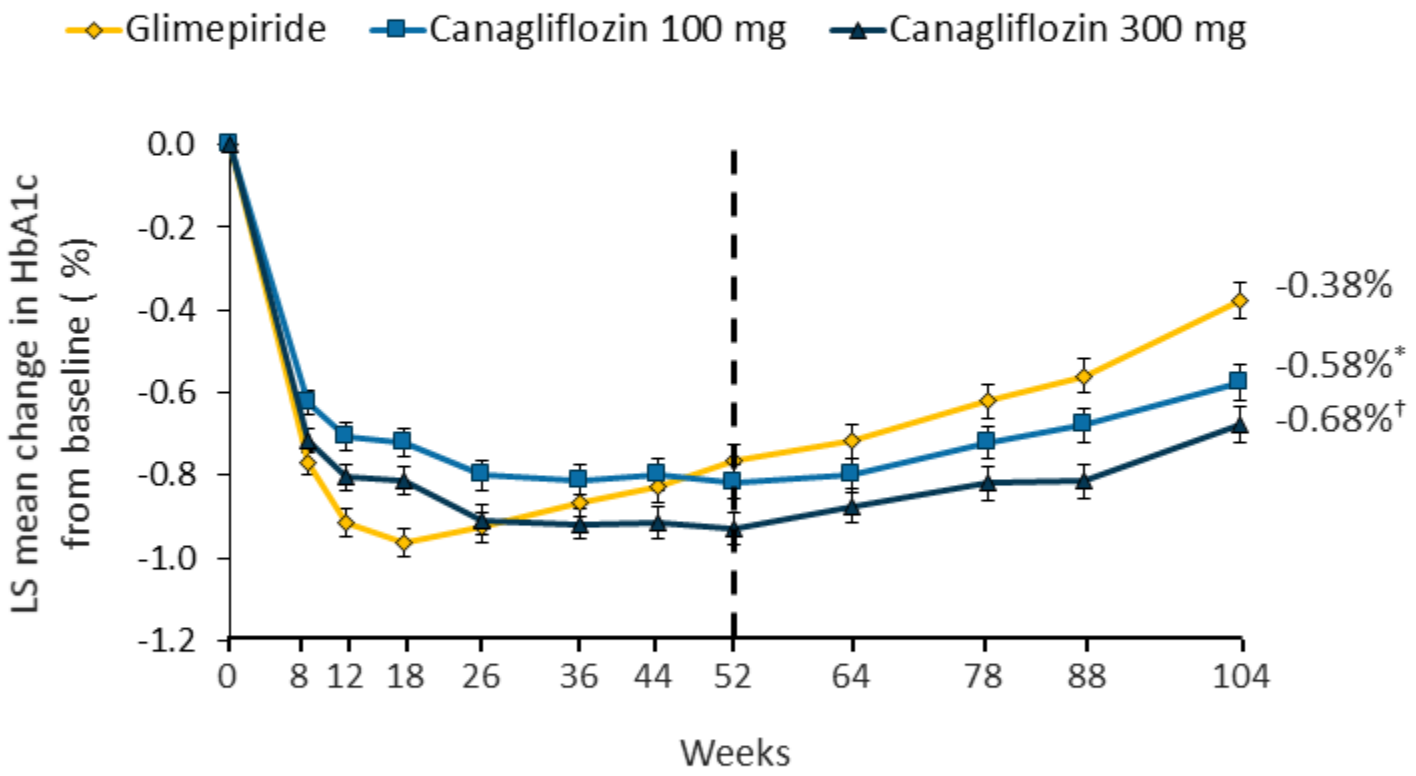
A1c - Comparative Data
Canagliflozin vs Sitagliptin in Triple Therapy MET + SU



Superior A1c reduction observed with CANA compared to SITA

	Cana	Sita
% achieving A1c < 7.0%	47.6%	35.3%

Long-term Change in HbA1c: SGLT2 Inhibitor vs SU as Add-on to Metformin Over 104 Weeks

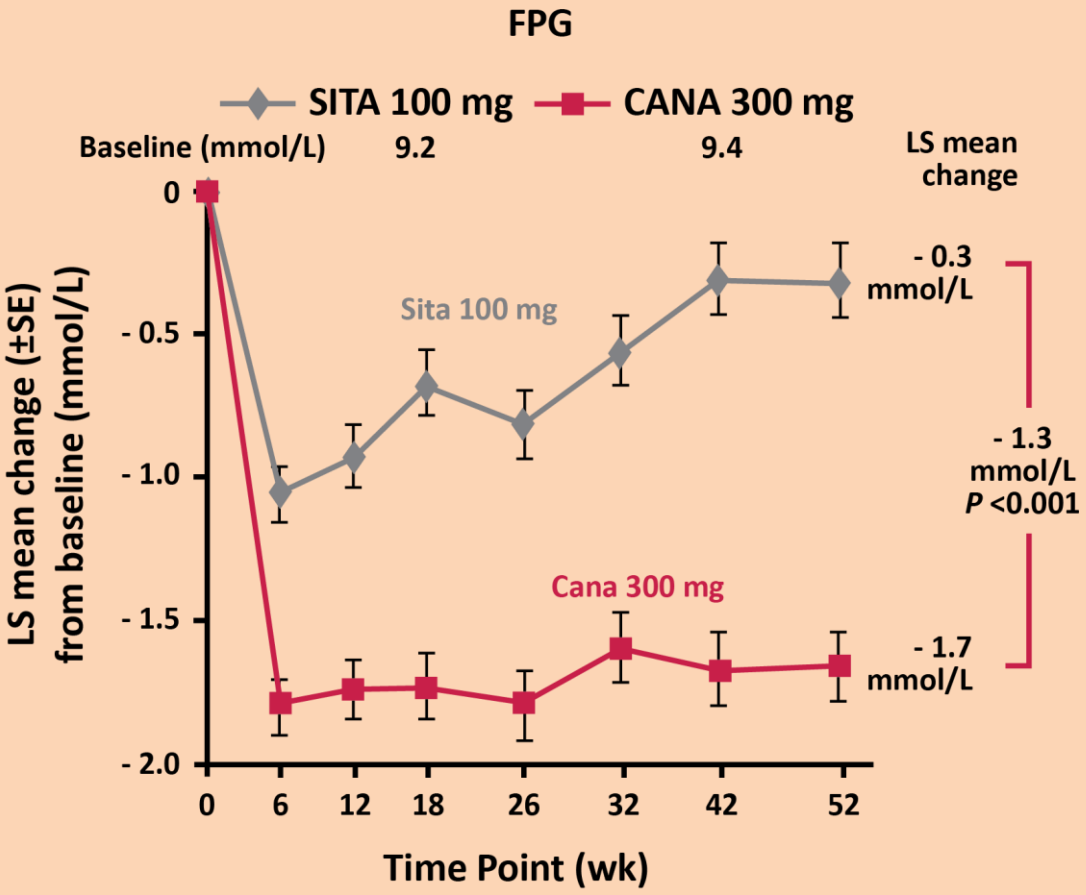


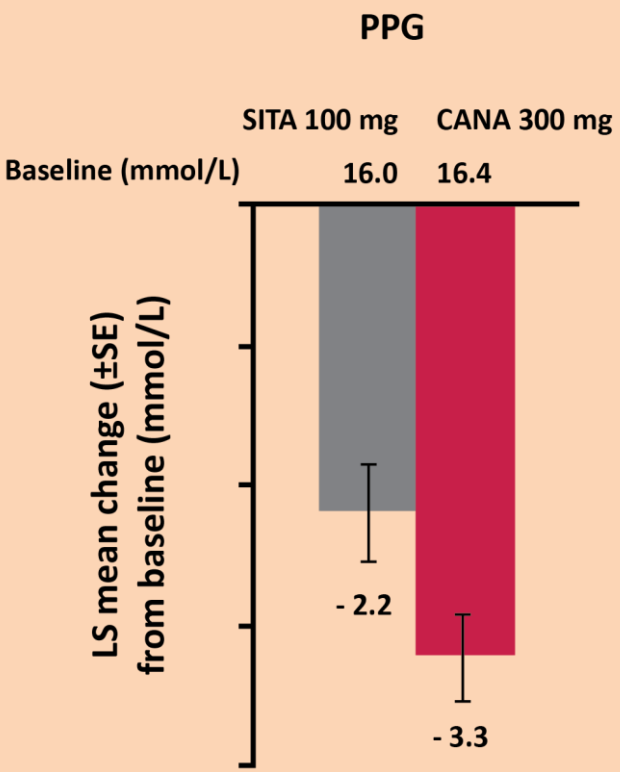
*Difference in LS mean change vs GLIM: -0.20%; 95% CI: -0.34 to -0.06

†Difference in LS mean change vs GLIM: -0.30%; 95% CI: -0.44 to -0.16

Leiter LA, et al. *Diabetes Care*. 2015;38:355-364.

Mean Change in FPG and PPG
Canagliflozin vs Sitagliptin in Triple Therapy MET + SU

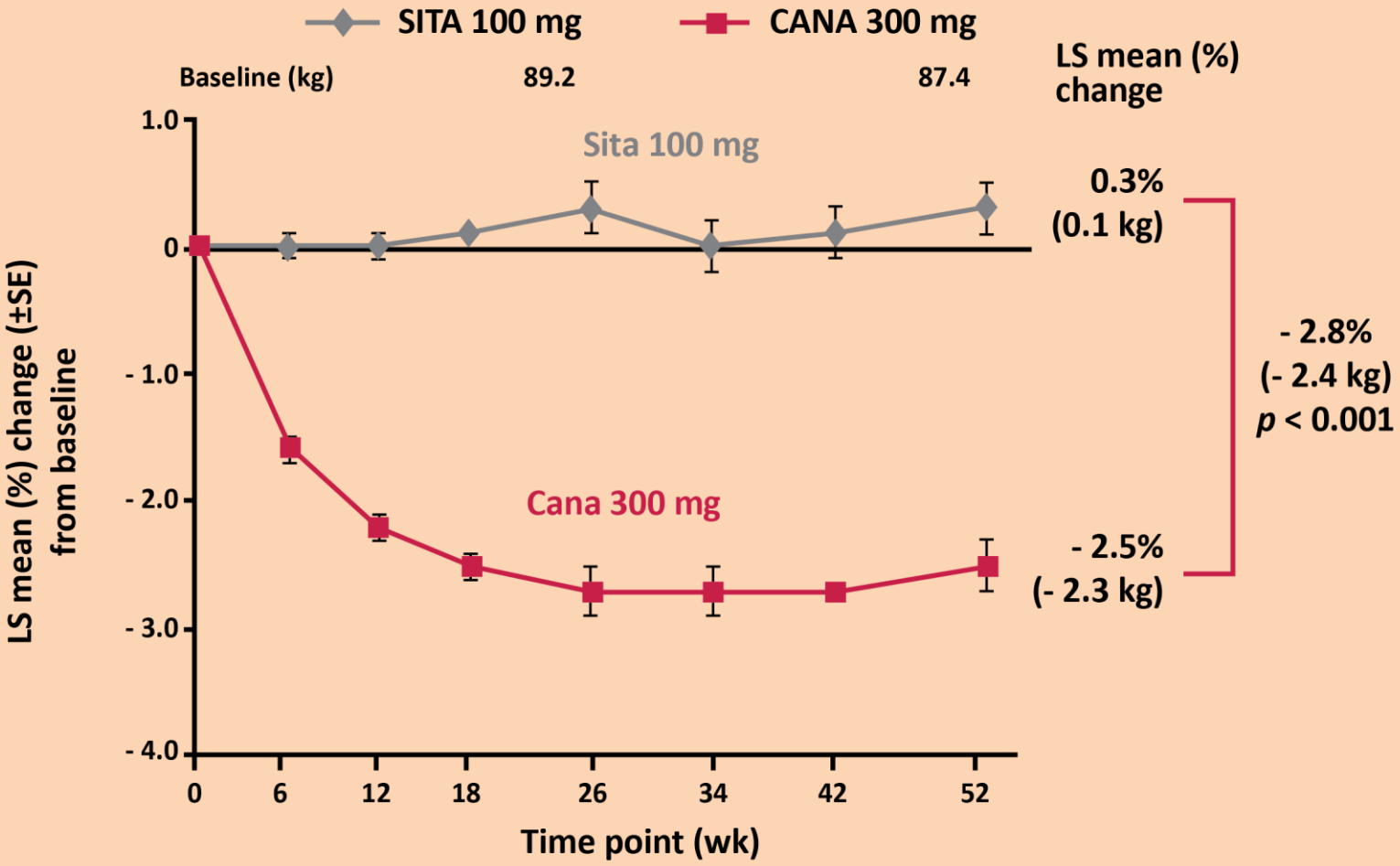




Schernthaner G, *et al. Diabetes Care*. 2013;36(9):2508-2515.

Weight - Comparative Data

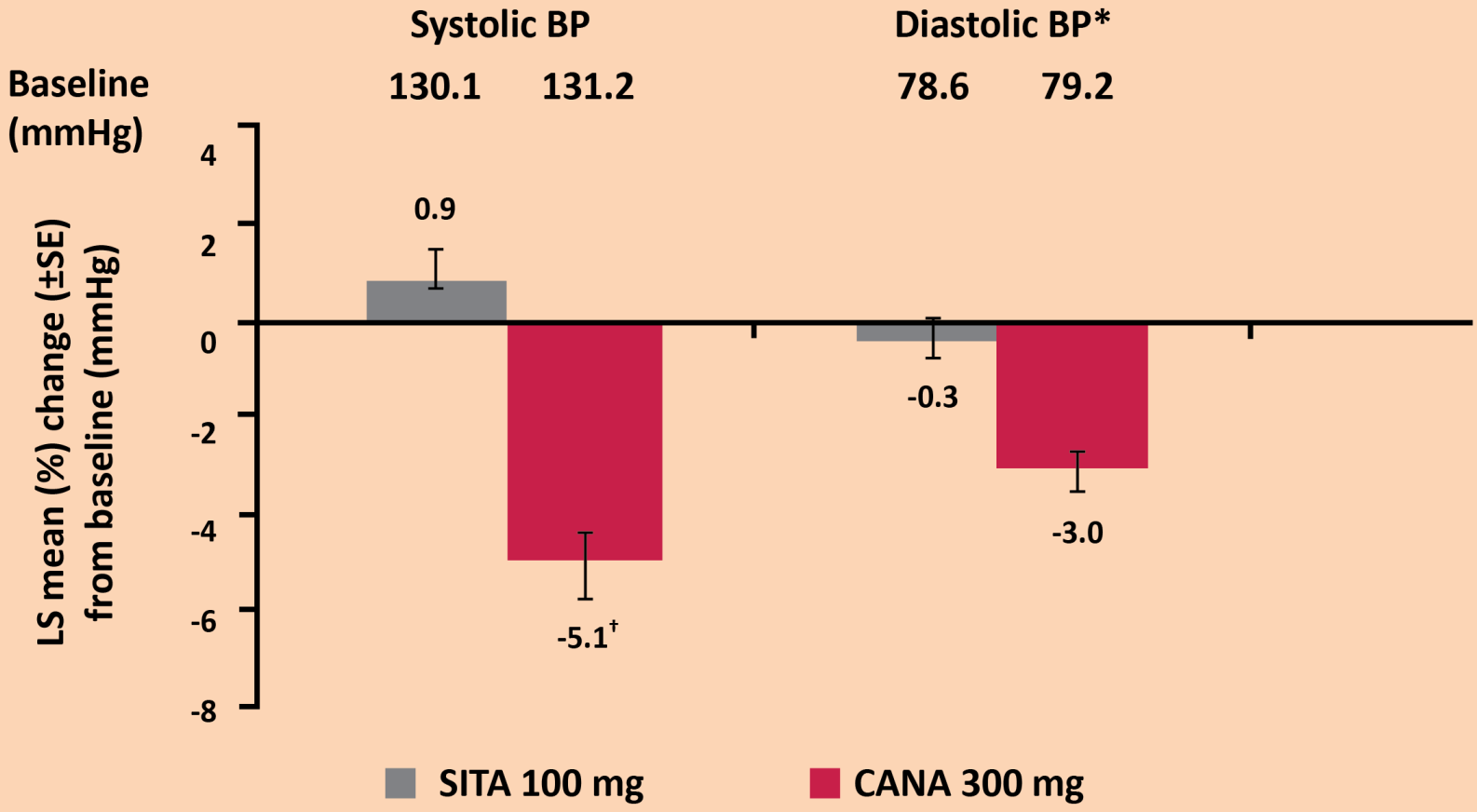
Canagliflozin vs Sitagliptin in Triple Therapy MET + SU



Schernthaner G, *et al*. Presentation 243. Presented at: The 48th Annual EASD Meeting, Oct. 2012.

Blood Pressure - Comparative Data

Canagliflozin vs Sitagliptin in Triple Therapy MET + SU

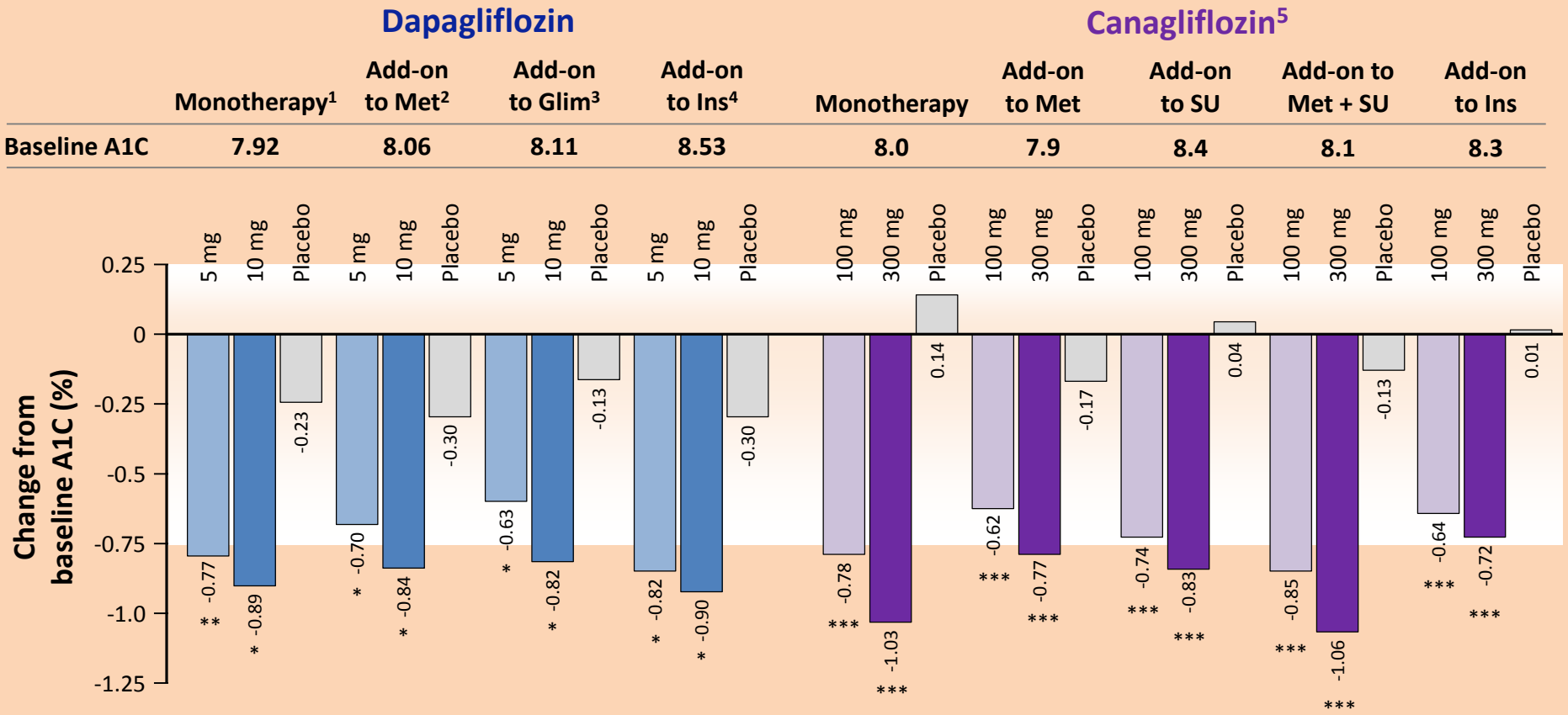


* Statistical comparison for CANA 300 mg vs SITA 100 mg not performed (not pre-specified)
†$p < 0.001$ vs PBO.
mITT, LOCF

Schernthaner G, *et al*. Presentation 243.
Presented at: The 48th Annual EASD Meeting, Oct. 2012.

A1C Reductions Across Continuum of T2DM

= 0.6-1.1% from Baseline with Dapa and Cana

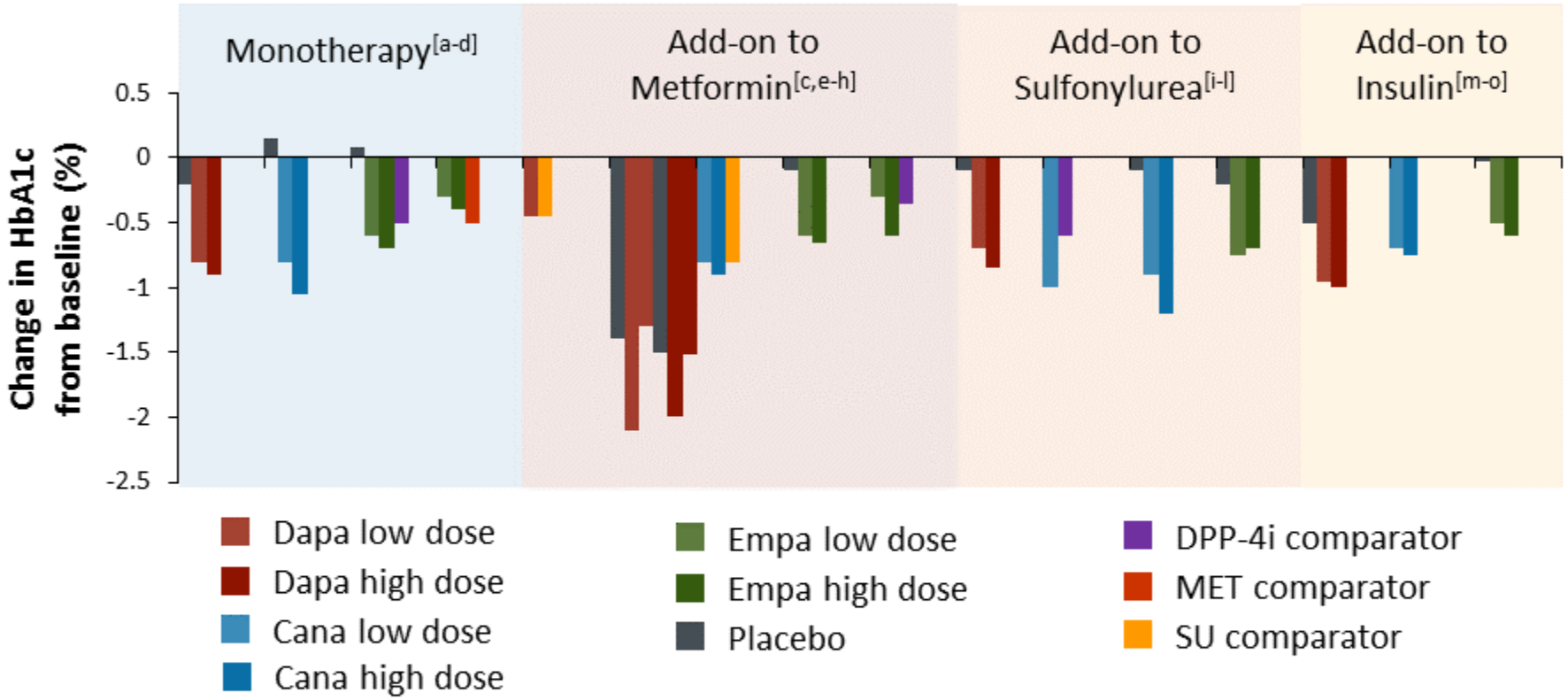


*p < 0.0001 vs. placebo. **p = 0.0005 vs. placebo. ***p < 0.001 vs. placebo.

Bargraph denotes individual trials and is not intended for comparisons between dapagliflozin and canagliflozin.

1. Ferrannini E, et al. Diabetes Care 2010; 33:2217-24. 2. Bailey CJ, et al. Lancet 2010; 375:2223-33. 3. Strojek K, et al. Diabetes Obes Metab 2011; 13:928-38.
4. Wilding JP, et al. Ann Intern Med. 2012 Mar 20;156(6):405-15. 5. INVOKANA Product Monograph. Janssen Inc., November 2014.

SGLT2 Inhibition: Glycemic Control*

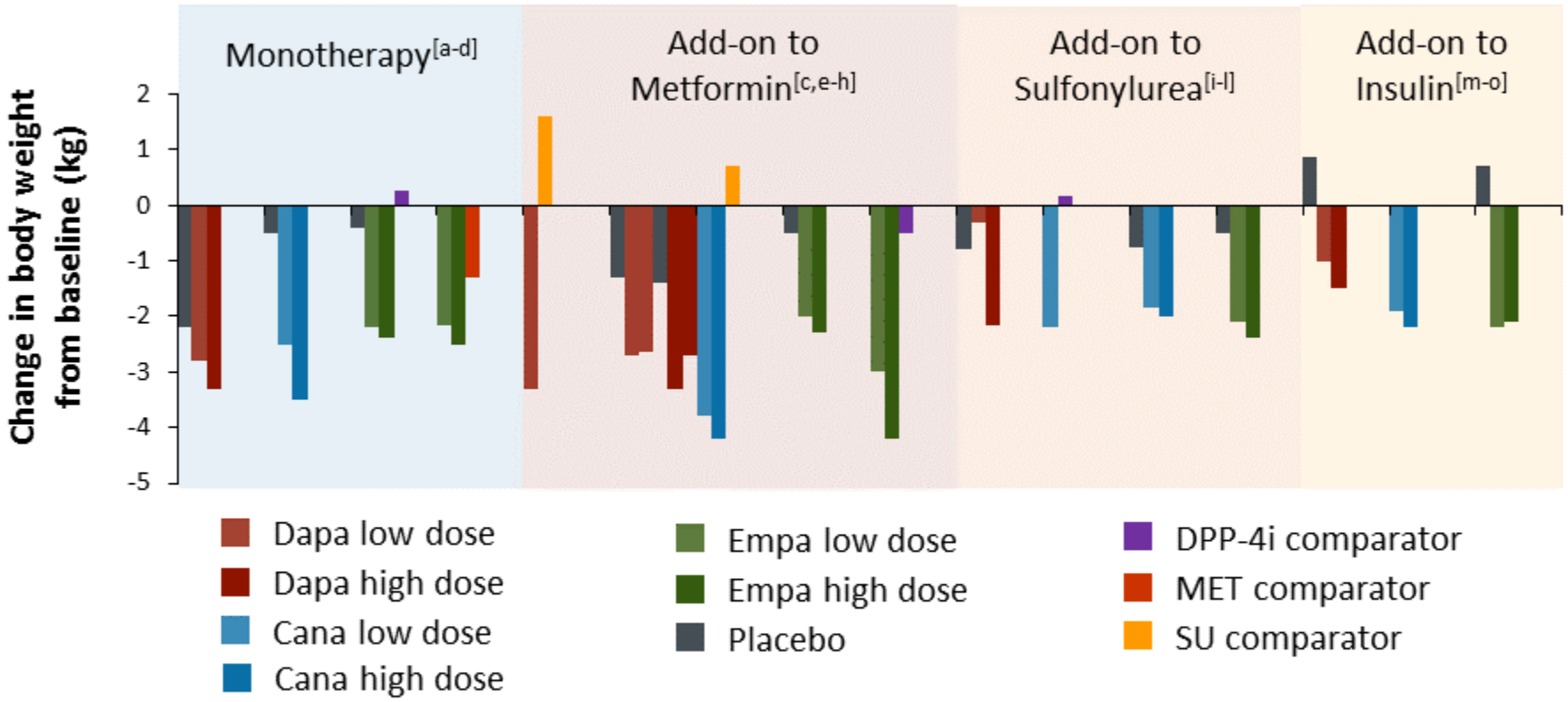


*Not head-to-head trials. Data shown is for informational purposes only and not meant to be direct comparisons, as study designs and populations may be different.

Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.

a. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224; b. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382; c. Ferrannini E, et al. *Diabetes Care*. 2013;36:4015-4021; d. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219; e. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022; f. Henry RR, et al. *Int J Clin Pract*. 2012;66:446-456; g. Cefalu WT, et al. *Lancet*. 2013;382:941-950; h. Häring HU, et al. *Diabetes Care*. 2014;37:1650-1659; i. Strojek K, et al. *Diabets Obes Metab*. 2011;13:928-938; j. Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515; k. Wilding JP, et al. *Int J Clin Pract*. 2013;67:1267-1282; l. Häring HU, et al. *Diabetes Care*. 2013;36:3396-3404; m. Wilding JP, et al. *Ann Intern Med*. 2012;156:405-415; n. Neal B, et al. *Diabetes Care*. 2015;38:403-411; o. Rosenstock J, et al. *Diabetes Obes Metab*. 2015 June 4 [epub ahead of print].

SGLT2 Inhibition: Reduction in Body Weight

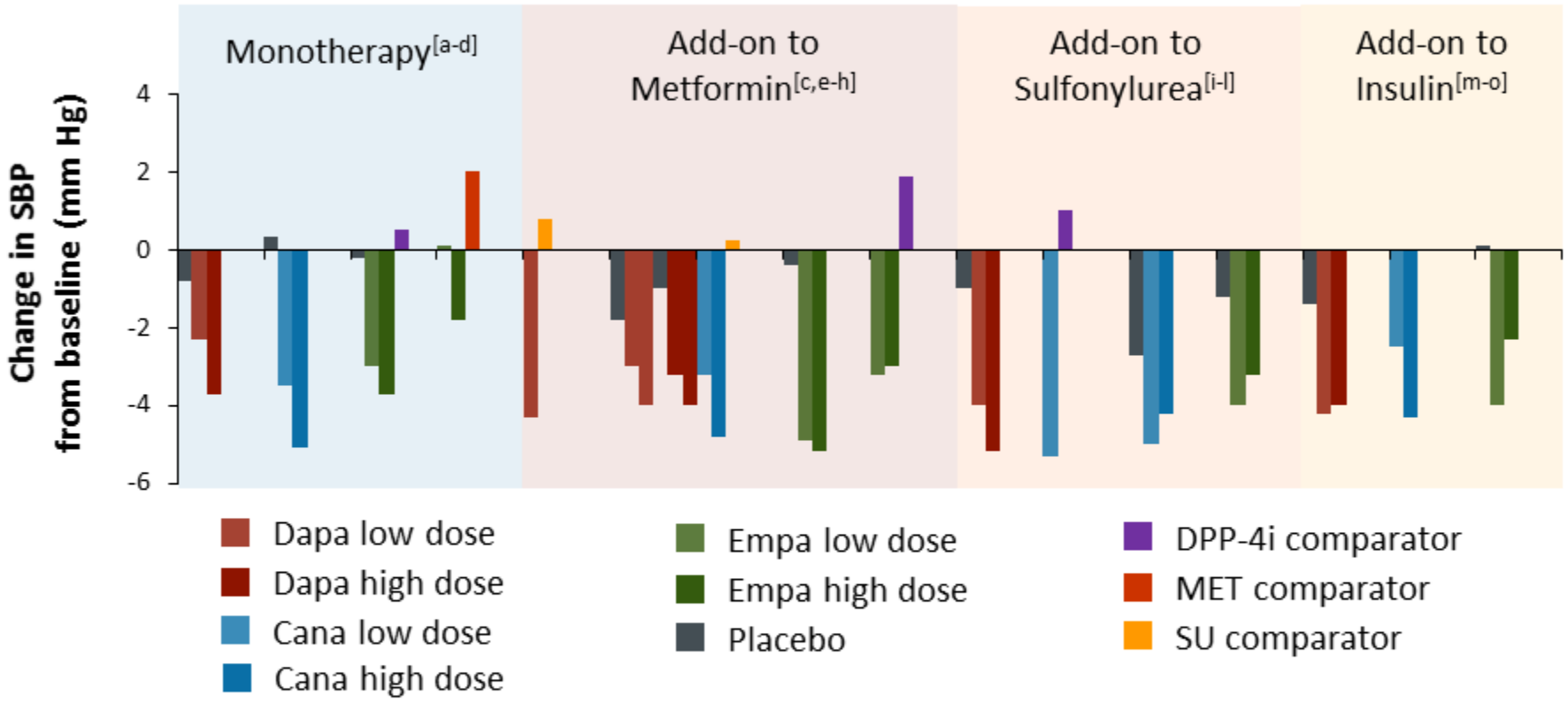


*Not head-to-head trials. Data shown is for informational purposes only and not meant to be direct comparisons, as study designs and populations may be different.

Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.

a. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224; b. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382; c. Ferrannini E, et al. *Diabetes Care*. 2013;36:4015-4021; d. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219; e. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022; f. Henry RR, et al. *Int J Clin Pract*. 2012;66:446-456; g. Cefalu WT, et al. *Lancet*. 2013;382:941-950; h. Häring HU, et al. *Diabetes Care*. 2014;37:1650-1659; i. Strojek K, et al. *Diabets Obes Metab*. 2011;13:928-938; j. Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515; k. Wilding JP, et al. *Int J Clin Pract*. 2013;67:1267-1282; l. Häring HU, et al. *Diabetes Care*. 2013;36:3396-3404; m. Wilding JP, et al. *Ann Intern Med*. 2012;156:405-415; n. Neal B, et al. *Diabetes Care*. 2015;38:403-411; o. Rosenstock J, et al. *Diabetes Obes Metab*. 2015 June 4 [epub ahead of print].

SGLT2 Inhibition: Reduction in SBP



*Not head-to-head trials. Data shown is for informational purposes only and not meant to be direct comparisons, as study designs and populations may be different.

Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.

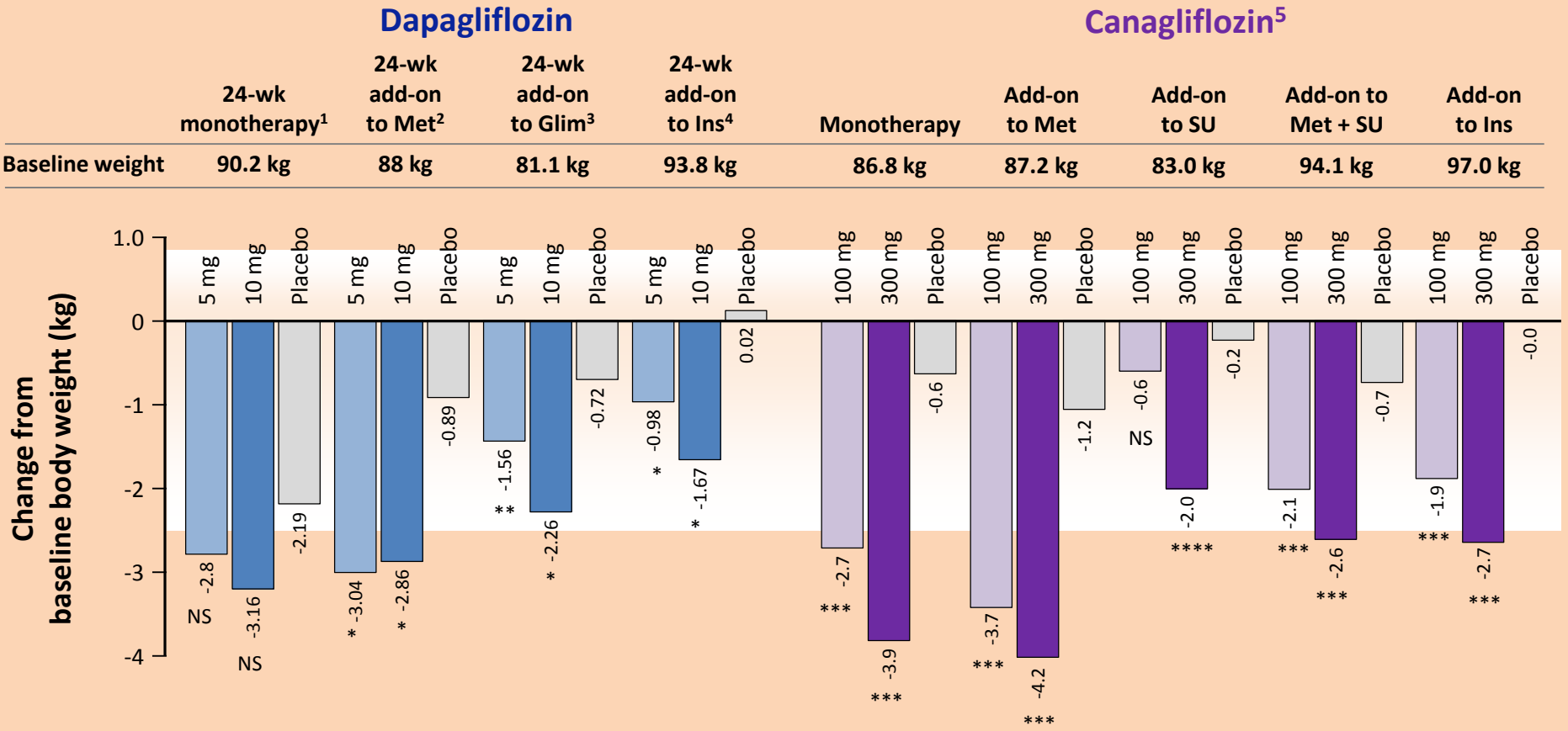
a. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224; b. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382; c. Ferrannini E, et al. *Diabetes Care*. 2013;36:4015-4021; d. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219; e. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022; f. Henry RR, et al. *Int J Clin Pract*. 2012;66:446-456; g. Cefalu WT, et al. *Lancet*. 2013;382:941-950; h. Häring HU, et al. *Diabetes Care*. 2014;37:1650-1659; i. Strojek K, et al. *Diabets Obes Metab*. 2011;13:928-938; j. Schernthaner G, et al. *Diabetes Care*. 2013;36:2508-2515; k. Wilding JP, et al. *Int J Clin Pract*. 2013;67:1267-1282; l. Häring HU, et al. *Diabetes Care*. 2013;36:3396-3404; m. Wilding JP, et al. *Ann Intern Med*. 2012;156:405-415; n. Neal B, et al. *Diabetes Care*. 2015;38:403-411; o. Rosenstock J, et al. *Diabetes Obes Metab*. 2015 June 4 [epub ahead of print].

SGLT2 Inhibitors vs Other Antihyperglycemic Agents in T2DM

Class	HbA1c reduction (%)	SBP (mm Hg)	Body weight (kg)	Hypoglycemia risk[c]
Metformin[a]	~1.5	+7 to -5	↓	Low
DPP-4 inhibitors[a]	0.15–1.1	0 to -3	↔	Low
GLP-1 RAs[a]	0.8–1.4	-1 to -8	↓	Low
TZDs[a]	0.5–1.4	-5	↑	Low
SUs[a]	~1.5	-5 to +7	↑	High
Insulin[a]	1.5–3.5	0 to +2	↑	High
SGLT2 inhibitors[b]	0.5–1.0	-3 to -5	↓	Low

a. Niswender K. *Diabetes Obes Metab*. 2010;12:267-287.
b. Chao EC. *Core Evid*. 2012;7:21-28.
c. Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

Body Weight Reductions Across Continuum of T2DM = 1.0 - 3.9 kg from Baseline with Dapa and Cana



*p < 0.0001 vs. placebo. **p = 0.0091 vs. placebo. ***p < 0.001 vs. placebo. ****p < 0.05.

Bargraph denotes individual trials and is not intended for comparisons between dapagliflozin and canagliflozin.

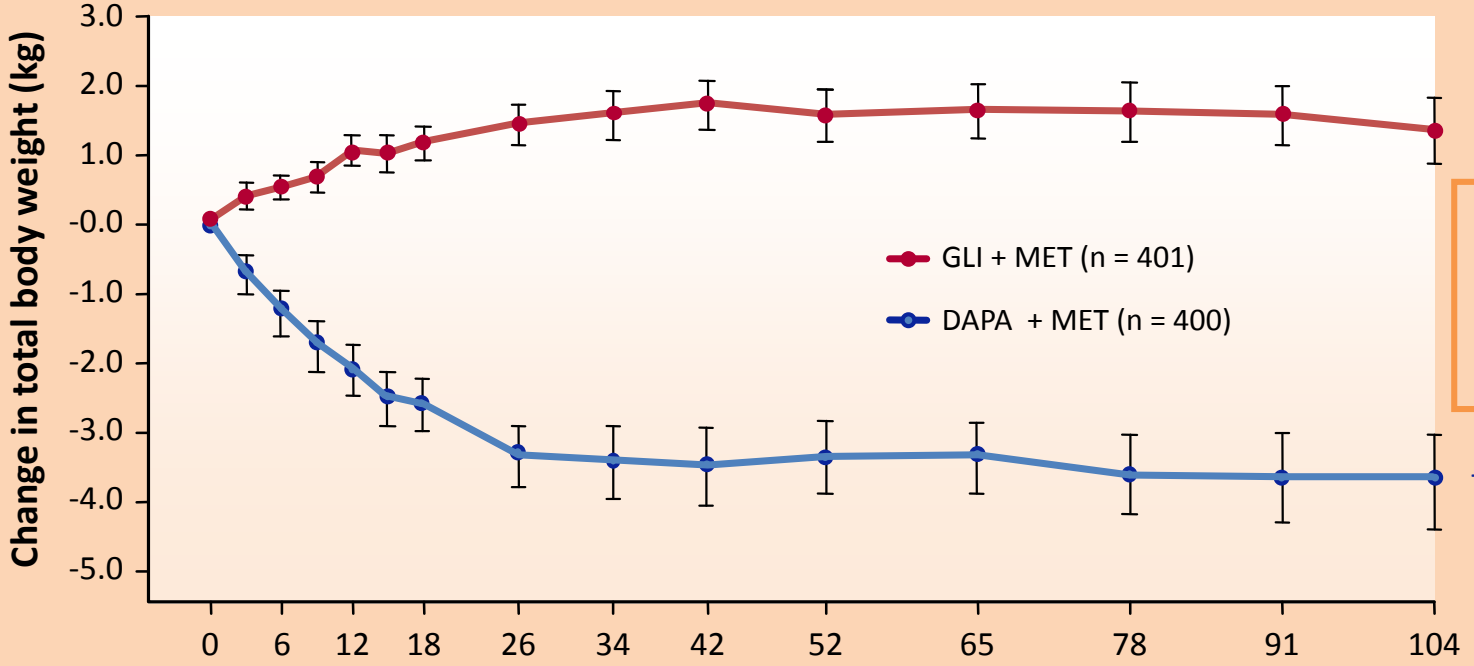
1. Ferrannini E, et al. Diabetes Care 2010; 33:2217-24. 2. Bailey CJ, et al. Lancet 2010; 375:2223-33. 3. Strojek K, et al. Diabetes Obes Metab 2011; 13:928-38.
4. Wilding JP, et al. Ann Intern Med. 2012 Mar 20;156(6):405-15. 5. . INVOKANA Product Monograph. Janssen Inc., November 2014.

Sustained Body Weight Reduction with Add-on Dapagliflozin vs. Add-on Glipizide* in Patients Taking Metformin (104 weeks)

Baseline weight

DAPA + MET: 88.4 kg

Sulfonylrea + MET: 87.6 kg



Week 104 weight

+1.36 kg (0.88, 1.84)

Between-group difference:
–5.06 kg
(95% CI; –5.73, –4.4)

-3.70kg (-4.16, -3.24)

Sample size per time point

DAPA + MET	400			369				323			234
SU + MET	401			361				315			211

*Glipizide is approved and authorized for use but is not marketed in Canada.

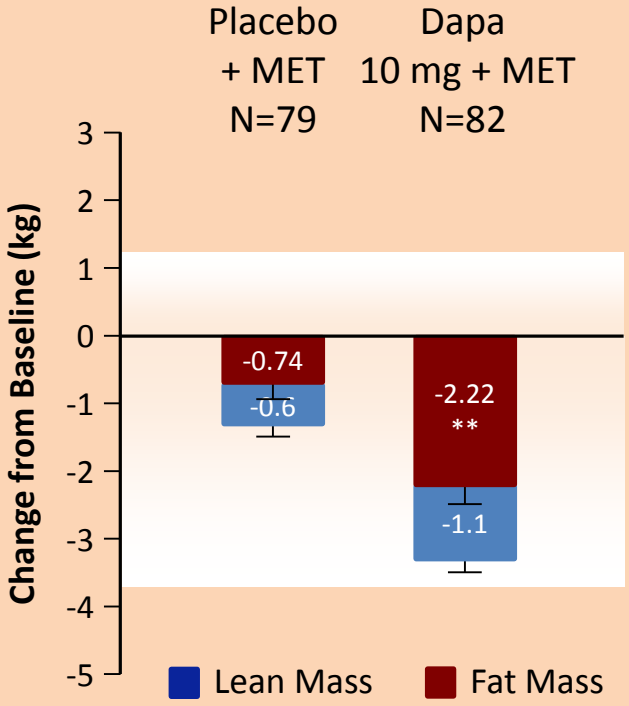
Nauck M, et al. Diabetes Obes Metab 2014; 16(11):1111-20.

SGLT2 Inhibitors:

Predominant Fat Loss

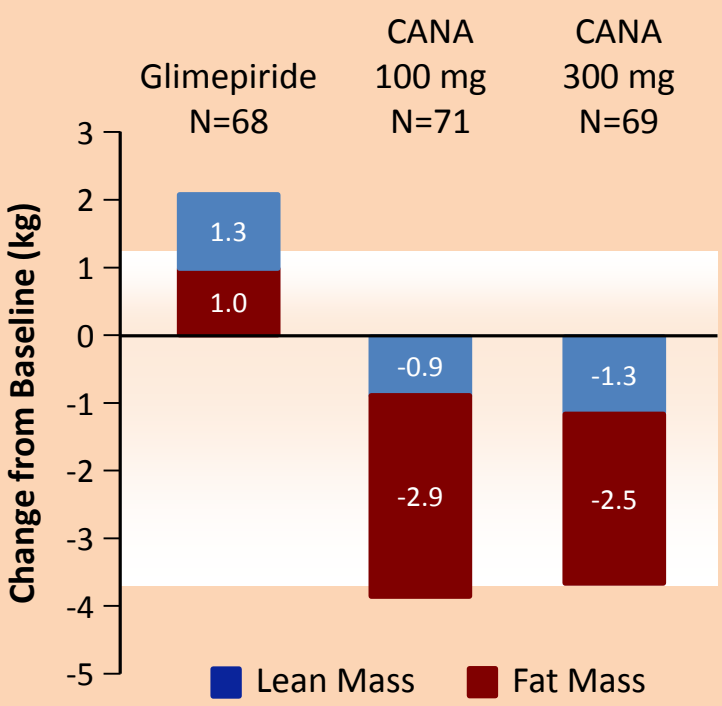
Dapagliflozin[2]

Δ Body Fat and Lean Mass (kg) at Week 24 by DXA (SE)



Canagliflozin[1]

Δ Body Fat and Lean Mass (kg) at Week 52 by DXA



DXA= Dual-energy X-ray Absorptiometry.

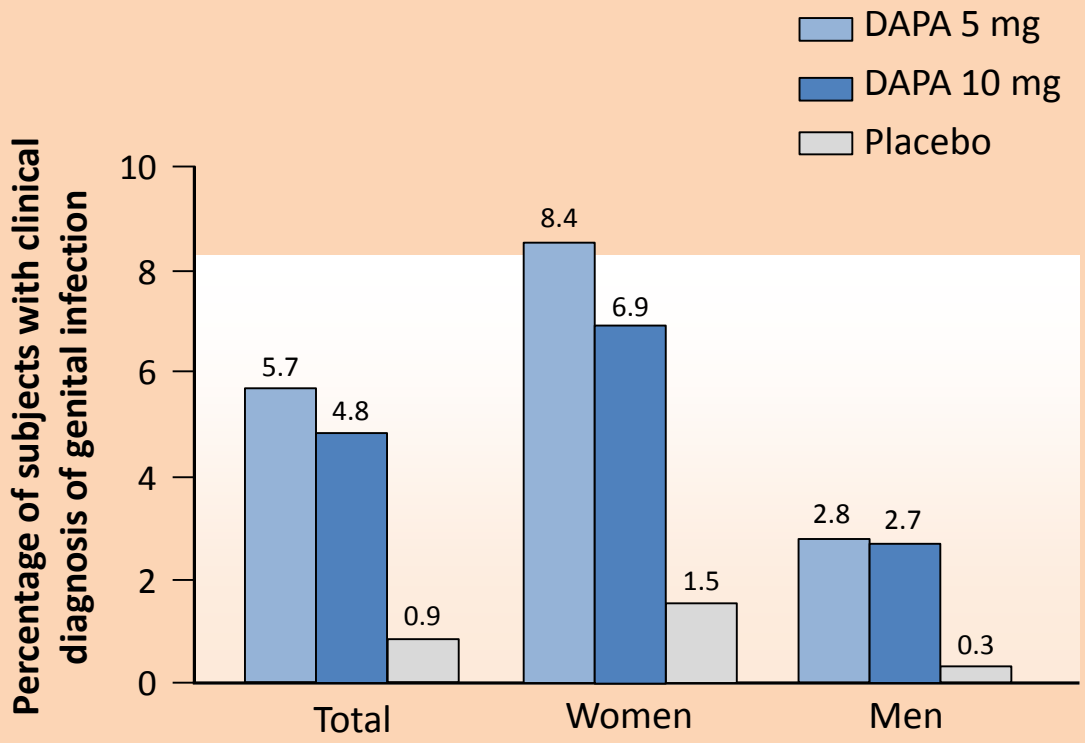
** Statistically significant vs. placebo by Hochberg's method (p<0.001)

1. Toubro S et al. EASD Annual Meeting 2012. Poster 762.
2. Bolinder J et al. J Clin Endocrinol Metab 2012;97:1020-1031.

Dapagliflozin Pooled Data: Genital Mycotic Infections

Higher rates of GMI in dapagliflozin treatment groups than placebo

- More in women than men
- All events were mild to moderate in intensity
- Rarely led to discontinuation (0.2%)
- Most events responded to the initial course of standard therapy and rarely re-occurred

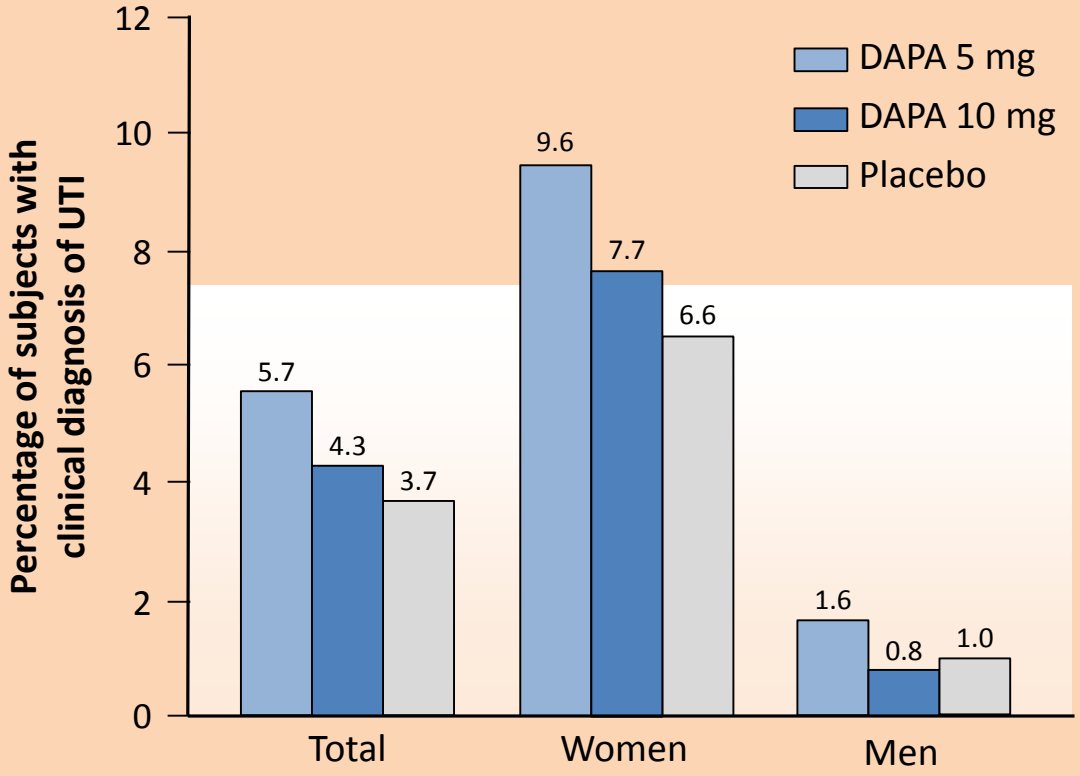


Johnsson KM, et al. J Diabetes Complications 2013; 27(5):479-84.

Dapagliflozin Pooled Data: UTI

Rates of clinically diagnosed UTI higher in the dapa groups than placebo
Upper UTI were rare and balanced between groups

- More frequent in women than men
- All events were mild to moderate in intensity
- Rarely led to treatment discontinuation (0.3%)
- Most events responded to the initial course of standard therapy and rarely reccurred



Johnsson KM, et al. J Diabetes Complications 2013; 27(5):473-8.

Volume-related AEs

- Polyuria → dapagliflozin 10 mg (0.9%) vs. placebo (0.2%)
- Pollakiuria → dapagliflozin 10 mg (2.1%) vs. placebo (0.7%)
- Rarely led to discontinuation from dapagliflozin

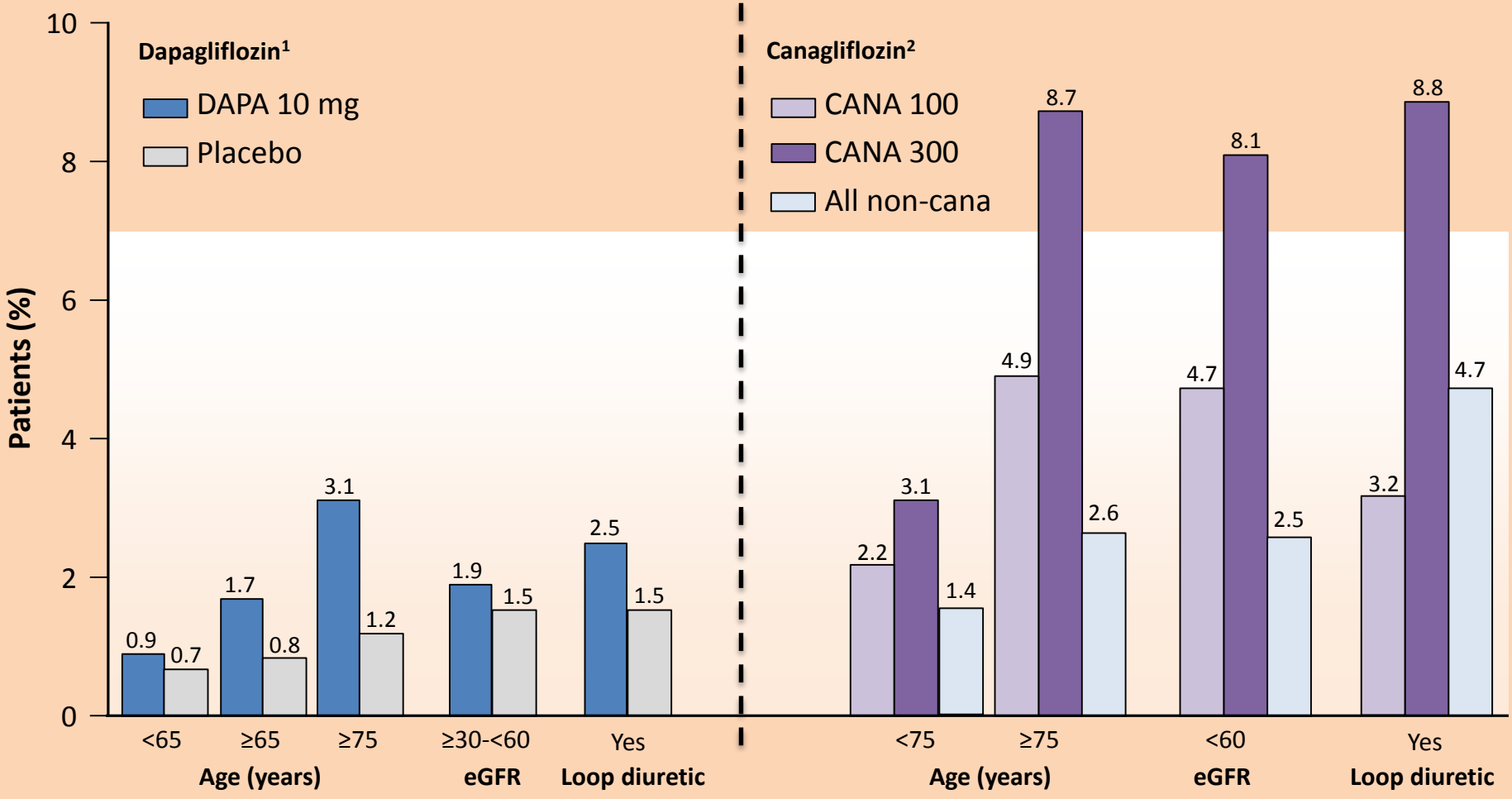
Johnsson et al. Presented at EASD 2014. Abstract 800-P.

Events of Volume Depletion with SGLT2 Inhibitors: Pooled Analyses

- SGLT2 inhibitors not recommended for initiation in volume depleted patients.
- Temporary interruption of SGLT2 inhibitors is recommended for patients who develop volume depletion until the depletion is corrected.

INVOKANA Product Monograph. Janssen Inc., November 2014.
FORXIGA Product Monograph. AstraZeneca. December 2014.

Volume-related Adverse Effects: Which Patients Are More At Risk?



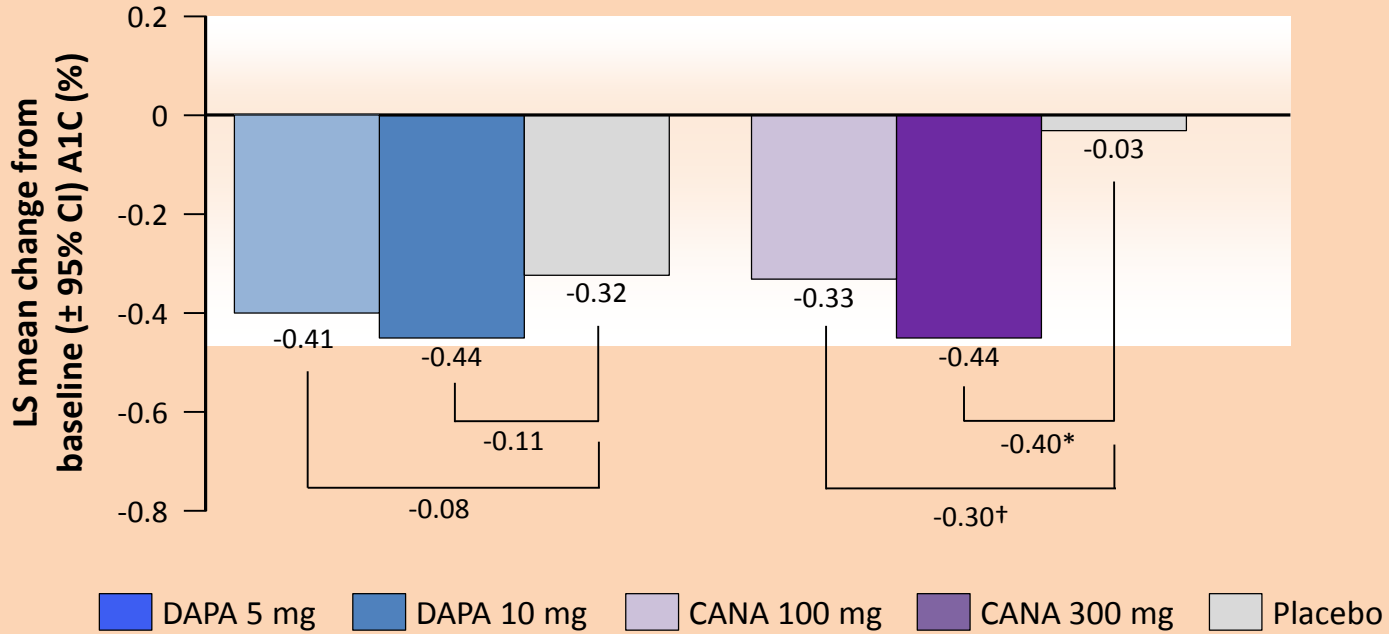
Not intended for comparisons between trials

eGFR measured in mL/min/1.73m^2

1. Johnsson et al. Presented at EASD 2014. Abstract 800-P.
2. Adapted from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013.

Efficacy of SGLT2 Inhibitors is Reduced in Patients with Moderate Renal Impairment

	Dapagliflozin in eGFR 30 to < 60 (N = 252)[2]	Canagliflozin in eGFR 30 to < 50 (N = 269)[1]
BL Mean A1C (%)	8.4	8.0
BL Mean eGFR (mL/min/1.73m^2)	44.6	39.4



*$p < 0.001$; †$p < 0.05$

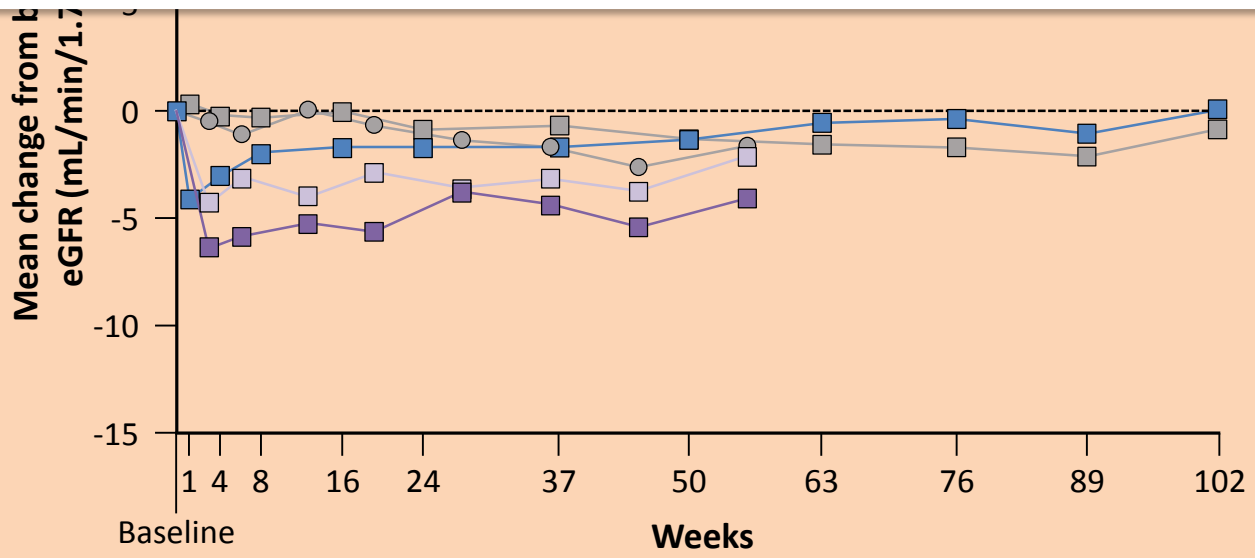
1. Kohan D et al. Kidney Int. 2014;85: 962-971.
2. Yale JF et al. Diabetes Obesity & Metabolism 2013;15:463-473.

eGFR Changes in Normal Renal Function and in CKD

Dapagliflozin in normal eGFR[1] **Canagliflozin in low eGFR[2]**

BL Mean eGFR (mL/min/1.73m²)	80.7	81.0	40.1	39.4	38.5

eGFR decreases slightly at initiation of SGLT2 inhibitors, then returns slowly towards baseline



Note: These are separate pooled analysis for Dapagliflozin and Canagliflozin.

1. Ptaszynska, et al. Presented at EASD 2014. 2. Yale JF, et al. Presented at ADA 2013. Abstract 1075-P.

Canagliflozin Pooled Analysis: Hyperkalemia-related Endpoints

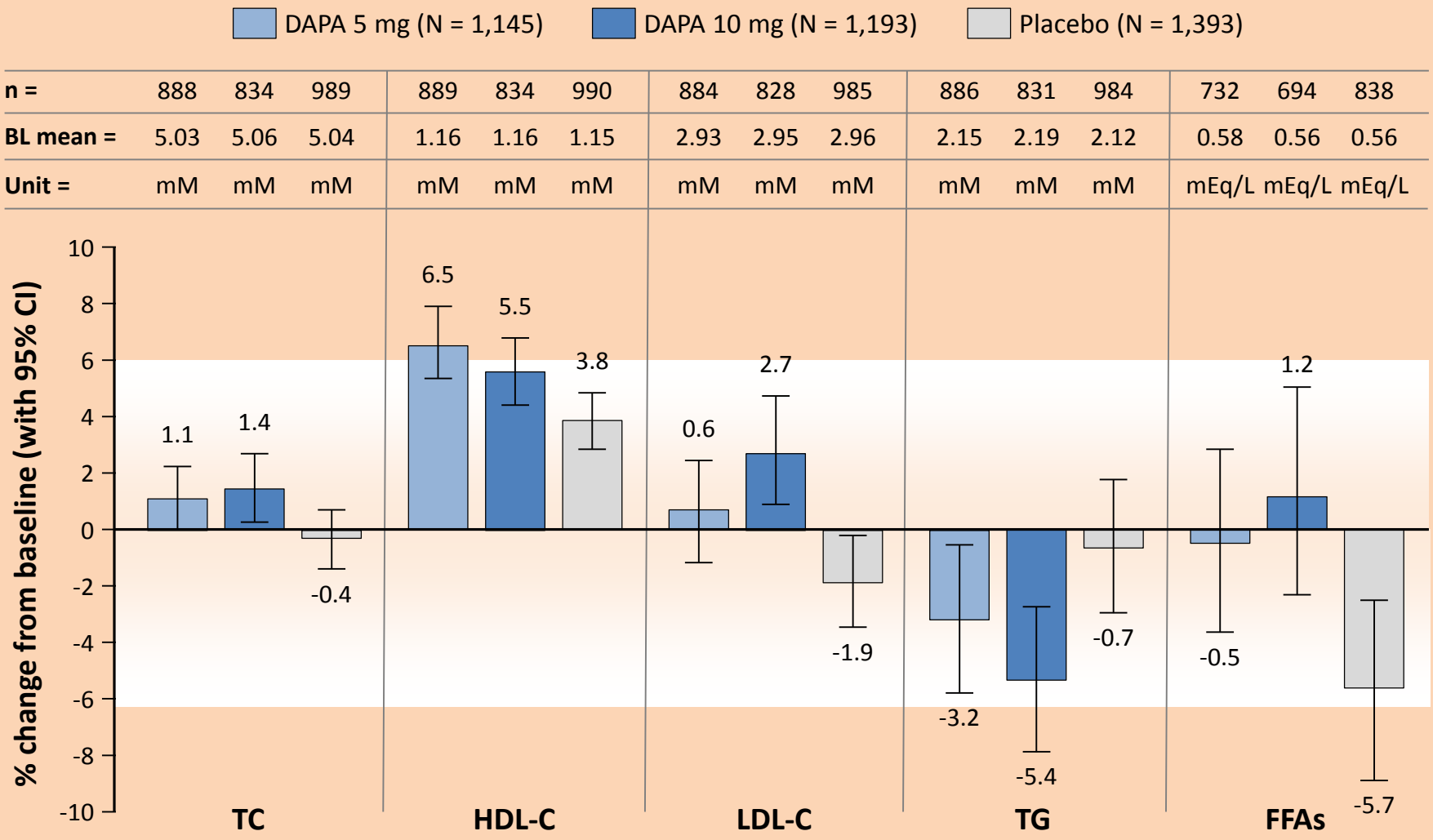
	eGFR ≥ 60			eGFR ≥ 45 and < 60		
	PBO	Cana 100	Cana 300	PBO	Cana 100	Cana 300
Mean % change from BL	0.5%	0.6%	1.0%	0.7%	1.7%	2.8%
AE – blood K^+ increased	0.2%	0.8%	0.7%	1.5%	1.4%	2.1%
K^+ level meeting outlier criteria*	4.7%	4.5%	6.8%	5.5%	5.2%	9.1%
K^+ level meeting outlier criteria* among patients on RAAS blockers or K-sparing diuretics	4.6%	5.1%	6.1%	5.6%	4.9%	10.5%

*outlier criteria = potassium > 5.4 mmol/L with a > 15% increase from baseline

- In both populations, K^+ elevations were usually < 6.5 mmol/L
- Elevations ≥ 6.5 mmol/L were rare but more frequent in patients taking antihypertensive agents that affect K^+ excretion, in both the canagliflozin and placebo groups

Weir MR, et al. Curr Med Res Opin 2014; 30:1759-68.

Dapa: Changes in Lipids From Baseline



Hardy E, et al. Presented at ADA 2013. Poster 1188-P.

Bladder Cancer

- Across 22 clinical trials, newly diagnosed cases of bladder cancer were reported in 10/6,045 patients treated with dapagliflozin (0.17%) and 1/3,612 patient (0.03%) treated with placebo/comparator.
- Risk factors: 10/11 were male, 9/11 were > 55 years and 8/11 had smoking history.
- Pre-existing?
  - 8/11 had hematuria at baseline
  - 6/11 were diagnosed within 6 months of the start of treatment

PM: Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.

DAPAGLIFLOZIN BMS-512148 NDA 202293. US Food & Drug Administration (FDA) Endocrinologic & Metabolic Drug Advisory Committee (EMDAC) Background Document. 2013. Available at: http://www.fda.gov/downloads/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf.
FORXIGA Product Monograph. AstraZeneca. December 2014.

Potential Adverse Events of SGLT2 Inhibitors[a-c]

Hypo-glycemia
- Low incidence when used as monotherapy or as add-on therapy to metformin

GU infections
- Increased incidence of mild to moderate genitourinary tract infections vs comparators

Polyuria and volume depletion
- Rare, but use cautioned in the elderly, those with moderate/severe renal impairment or using loop diuretics, and in patients who are volume-depleted or with concomitant illness as they may be at higher risk

Lipids
- Small increase in LDL-C, but not in TC/LDL-C ratio, without meaningful clinical significance

Keto-acidosis
- Recent US FDA warning[d]
- May appear more likely in insulin-deficient patients with severe intercurrent illness if insulin dose is not adjusted (SGLT2 inhibitors are not approved for use in T1DM)

a. Dapagliflozin SPC. http://ec.europa.eu/health/documents/community-register/2012/20121112124487/anx_124487_en.pdf.
b. Canagliflozin SPC. http://ec.europa.eu/health/documents/community-register/2015/20150408131591/anx_131591_en.pdf.
c. Empagliflozin SPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf.
d. FDA. http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm.

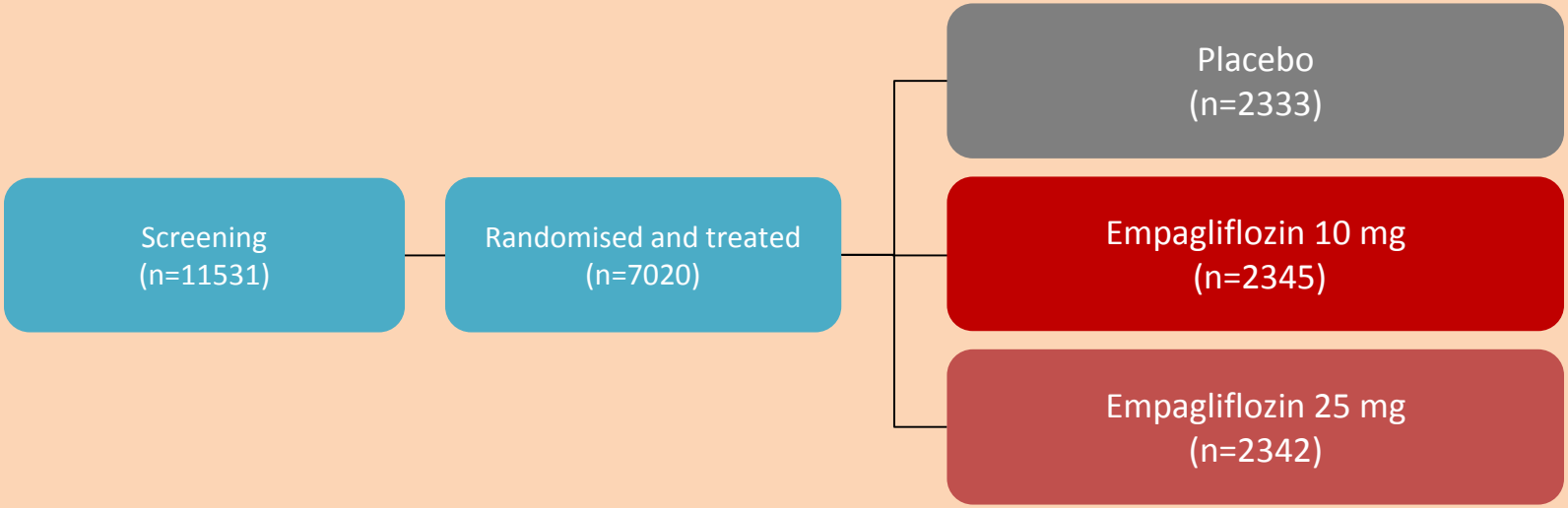
SGLT2 Inhibitors: Ongoing CV Outcome Trials

	Treatment	n	Population	Endpoints	Results
CANVAS	Canagliflozin vs. Placebo	4,363	CVD or high risk for CVD	CV death, nonfatal MI or nonfatal CVA	June 2018
EMPA-REG OUTCOMES	Empagliflozin vs. Placebo	7,000	CVD	CV death, nonfatal MI or nonfatal CVA	April 2015
DECLARE	Dapagliflozin vs. Placebo	17,150	CVD or high risk for CVD	CV death, nonfatal MI or nonfatal CVA	April 2019

www.clinicaltrials.gov.

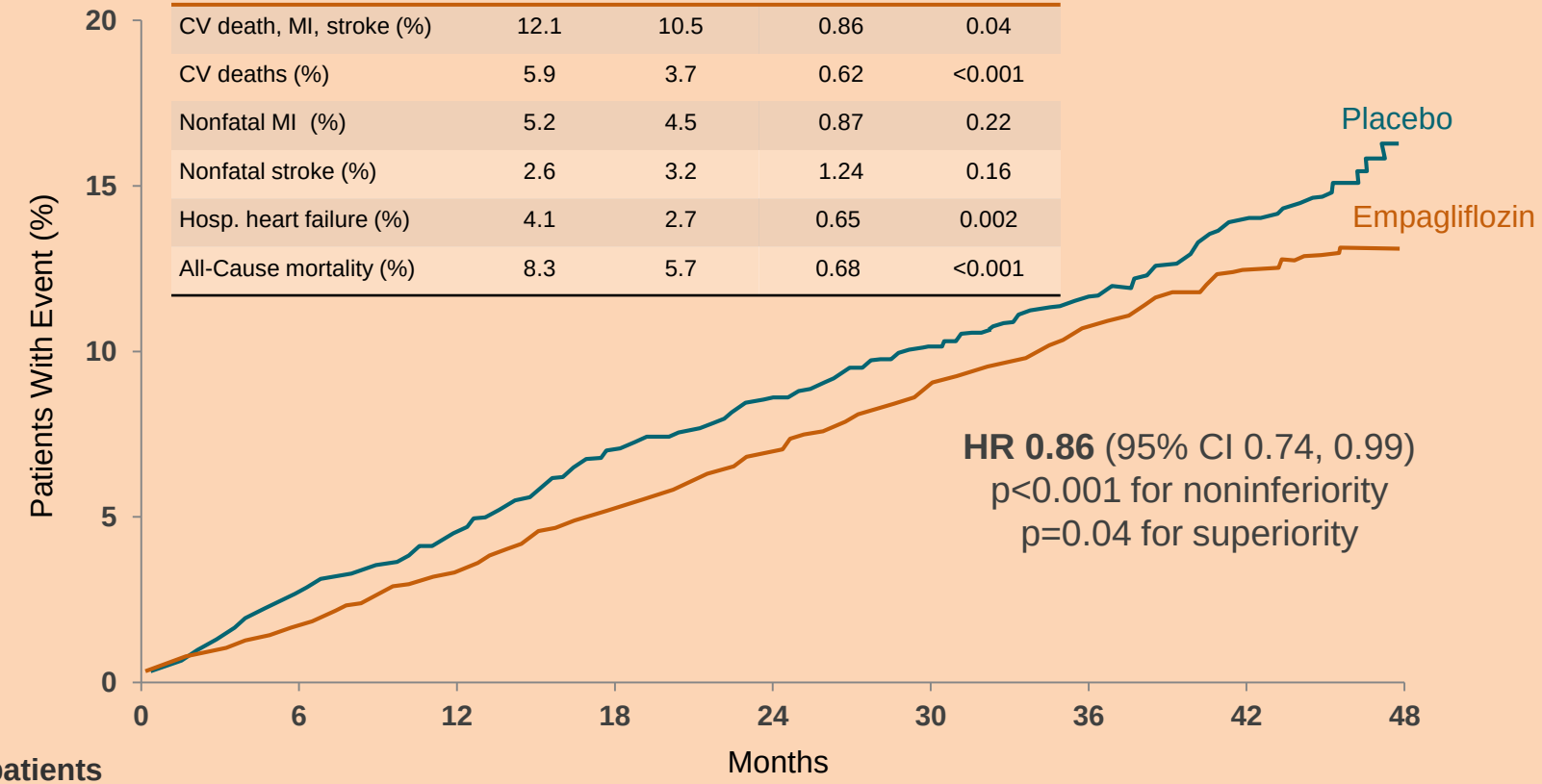
EMPA-REG OUTCOMES: Trial design

- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event



EMPA-REG Outcome: Primary Composite Endpoint CV Death, MI, or Stroke

	PBO	EMPA	HR	p value
CV death, MI, stroke (%)	12.1	10.5	0.86	0.04
CV deaths (%)	5.9	3.7	0.62	<0.001
Nonfatal MI (%)	5.2	4.5	0.87	0.22
Nonfatal stroke (%)	2.6	3.2	1.24	0.16
Hosp. heart failure (%)	4.1	2.7	0.65	0.002
All-Cause mortality (%)	8.3	5.7	0.68	<0.001



No. of patients

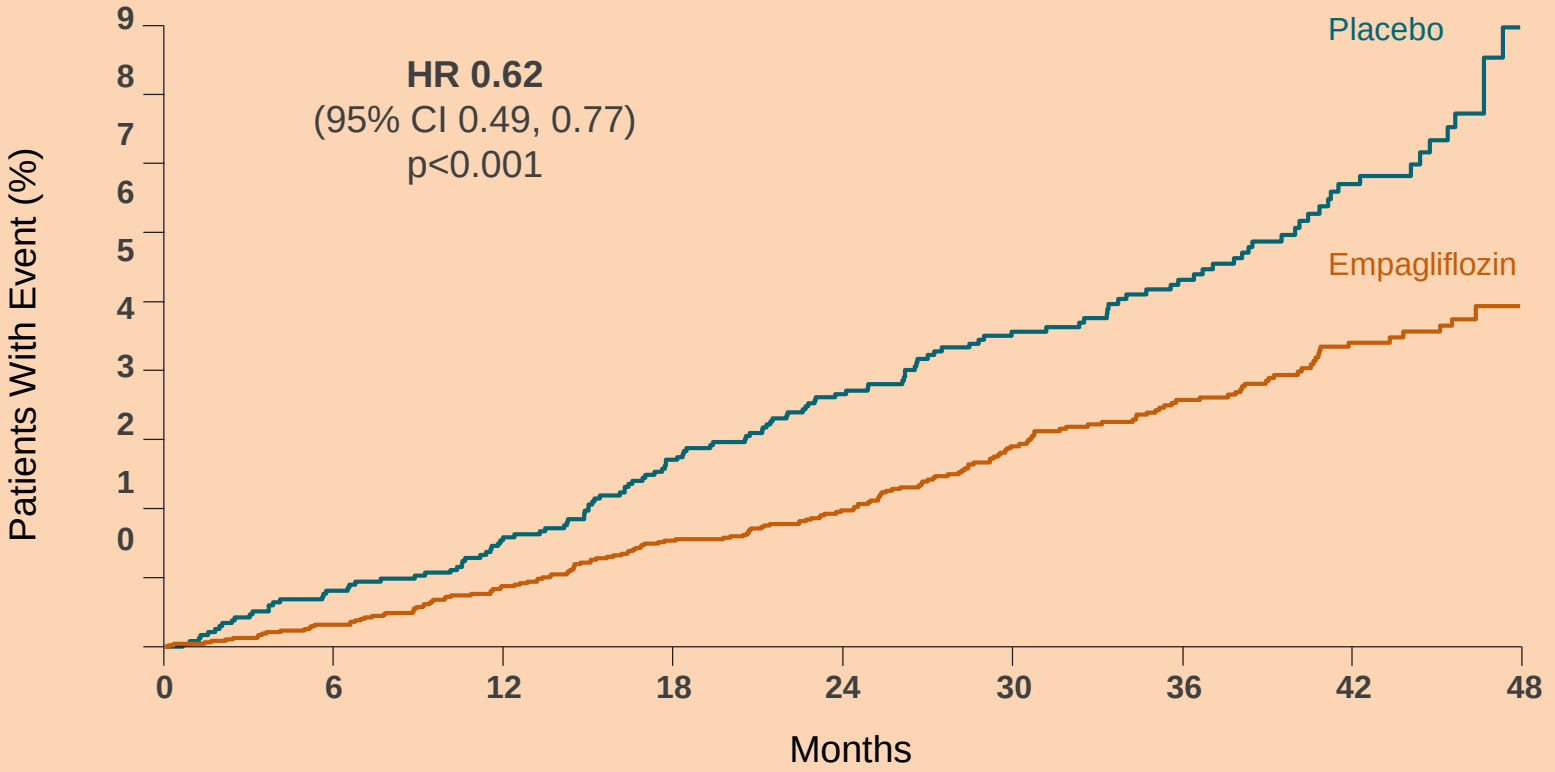
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	875	1380	1161	741	166

EMPA-REG Outcome: n=7020 patients (mean age 63 years) with type 2 diabetes and established CVD.
Median duration of follow-up: 3.1 years. Mean diff in A1C: 0.4% at wk 94. Mean diff in SBP 4 mm Hg.

CI: confidence interval; CV: cardiovascular; EMPA: empagliflozin; HR: hazard ratio; MI: myocardial infarction; PBO: placebo.

1. Zinman B et al. N Engl J Med. 2015;373:2117-28.

EMPA-REG Outcome: Death from CV cause



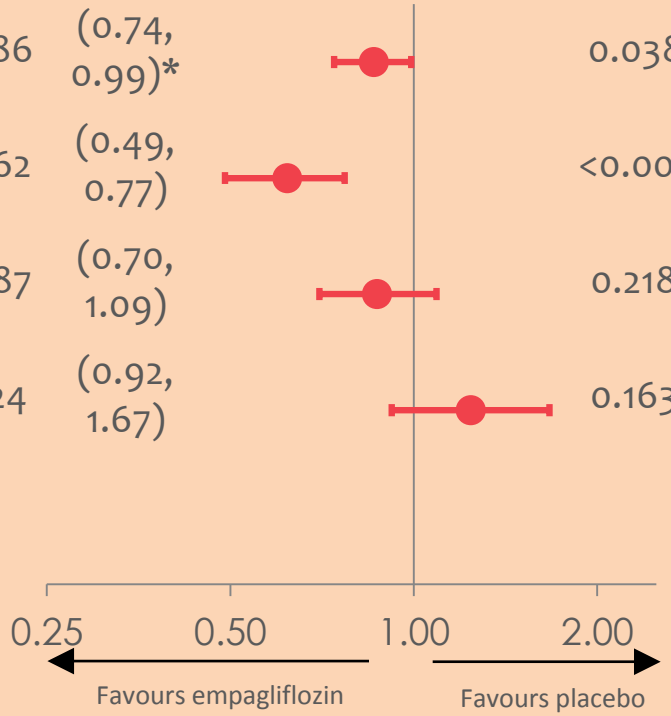
No. at risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR: hazard ratio.

1. Zinman B et al. N Engl J Med. 2015;373:2117-28.

EMPA-REG OUTCOMES: CV death, MI and stroke

	Patients with event/analysed				
	Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction *95.02% CI

Summary

- T2DM is associated with considerable CV risk
- Some classes of antihyperglycemics are associated with off-target effects (eg, weight gain, fluid retention, hypoglycemia) that may elevate CV risk
  - Other classes(e.g., GLP-1 RAs, SGLT2 inhibitors) have shown benefit on those risk factors (eg, weight loss, BP reduction)
- CV safety studies in DPP-4 inhibitors have demonstrated CV neutrality, with perhaps a slight HF signal
- EMPA-REG, the first trial in the SGLT2 inhibitor class, reported a substantial reduction in CV mortality
- The first GLP-1 RA trial, with lixisenatide, showed CV neutrality
- All CV safety studies have been conducted in high risk populations
- A number of other GLP-1 RA CV safety trials (eg, LEADER) will be reporting soon

ANY QUESTIONS OR COMMENTS?