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Guidelines for glucose lowering therapy in T2DM: roles of the ‘newer’ oral agents

Melanie Davies
Professor of Diabetes Medicine

University Hospitals of Leicester NHS
NHS Trust

University of Leicester

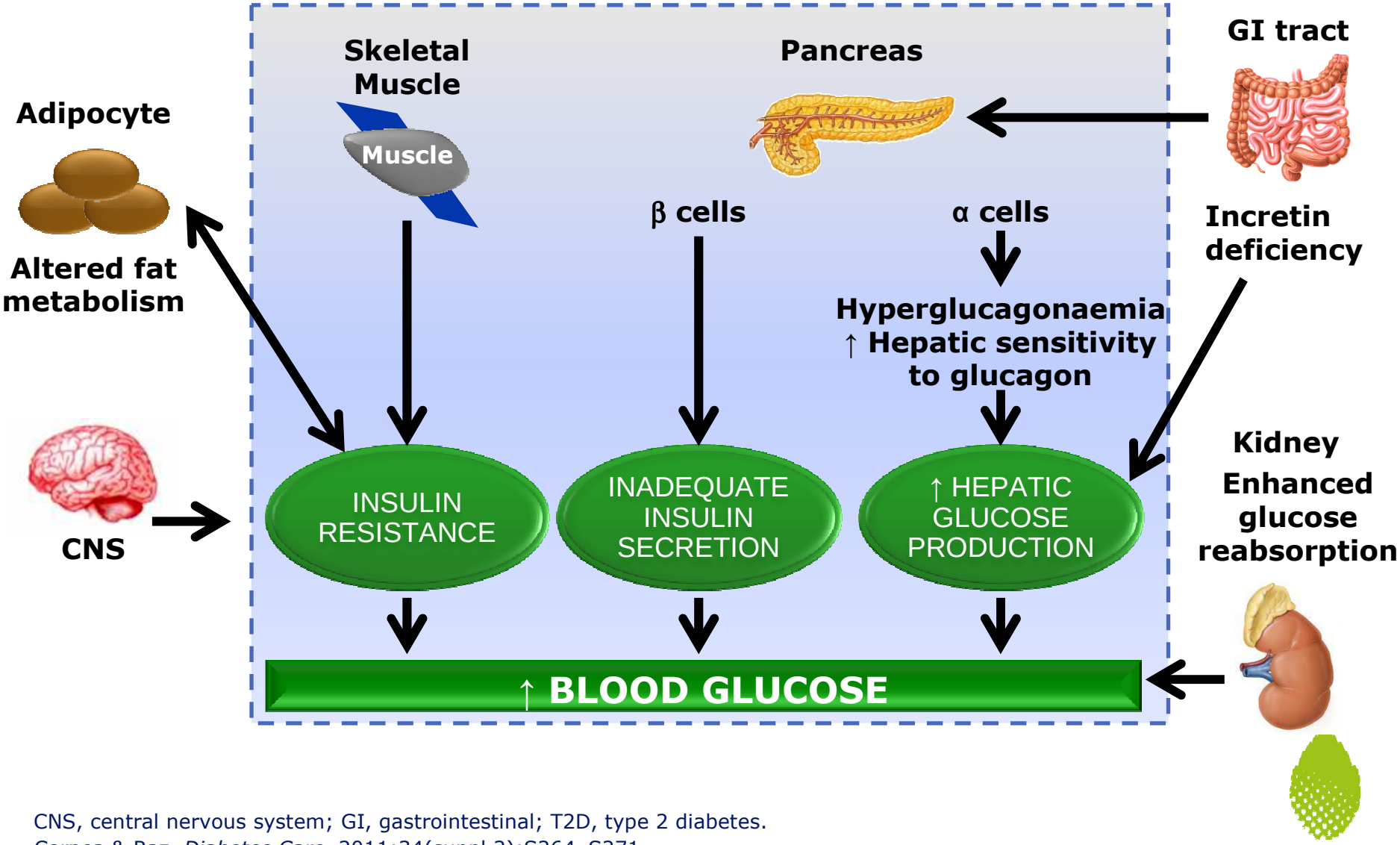
Disclosures of Interest

- I have acted as consultant, advisory board member and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim and Roche. I have received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme and GlaxoSmithKline

Outline

- The treatment algorithm for diabetes
- Clinical data with DPP-4 inhibitors and Linagliptin
- Clinical Data with the SGLT2 inhibitors
- Summary

T2D Is a Complex Multi-factorial Disease



CNS, central nervous system; GI, gastrointestinal; T2D, type 2 diabetes.

Cernea & Raz. *Diabetes Care.* 2011;34(suppl 2):S264–S271.

Complexity of treatment options in T2DM

Table 1 Combinatorics of multiple (eight) classes of therapeutic agents

Number of Medications	Number of combinations of therapeutic agents
0	1
1	8
2	28=(8×7)/(1×2)
3	56=(8×7×6)/(1×2×3)
4	70=(8×7×6×5)/(1×2×3×4)
Total	163

163 possible combinations

Even if we exclude combinations that are not approved (e.g. GLP-1 analogues combined with insulin) and combinations of agents that have similar mechanisms of action (e.g. sulfonylureas and glinides, or DPP-4 inhibitors and GLP-1 analogues) and exclude all but a few cases of quadruple therapy, we still obtain more than 60 different types of regimen [8]. This does not even take into account that there are at least three major sulfonylureas, two types of metformin (if one considers 'extended release' as a separate medication), two glinides, three commercially available DPP-4 inhibitors, two GLP-1 analogues, multiple forms of insulin (regular human insulin, NPH, insulin detemir [B29Lys(ε-tetradecanoyl),desB30 human insulin], insulin glargine [A21Gly,B31Arg,B32Arg human insulin], insulin aspart [B28Asp human insulin], insulin lispro [B28Lys,B29Pro human insulin], insulin glulisine, and several biphasic mixtures of regular human insulin and NPH and of insulin aspart or insulin lispro with protamine), and still more brand names for the generic compounds. When these options are considered, one encounters a further combinatorial explosion.

Rodbard. Diabetologia 2010;53:2456-2457

Impetus for 2012 ADA/EASD Joint Task Force

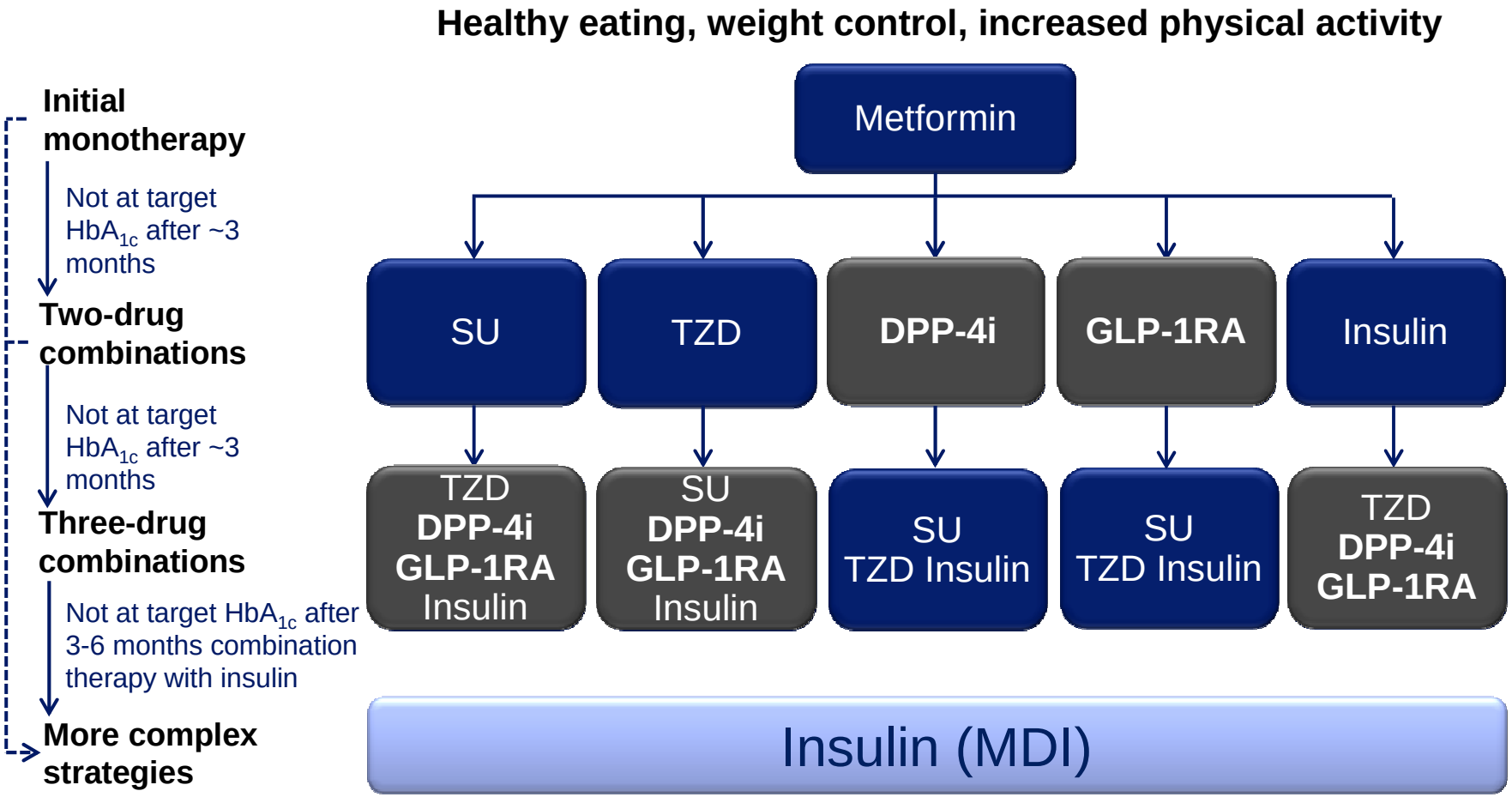
- T2D management complex
  - More available treatments
  - Risk-benefit profile concerns
  - Uncertainty about intensive glycaemic control and macrovascular complications
- The update addresses
  - Contemporary information
  - Efficacy/safety of new drug classes
  - Treatment withdrawal/restriction
  - Patient-centred care

ADA/EASD recommendations for anti-hyperglycaemic therapy in non-pregnant adults with T2D

'Improve clarity regarding optimal strategies for our patients'

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; T2D, type 2 diabetes.
Inzucchi et al. *Diabetologia.* 2012;55:1577–1596.

ADA/EASD position statement 2012

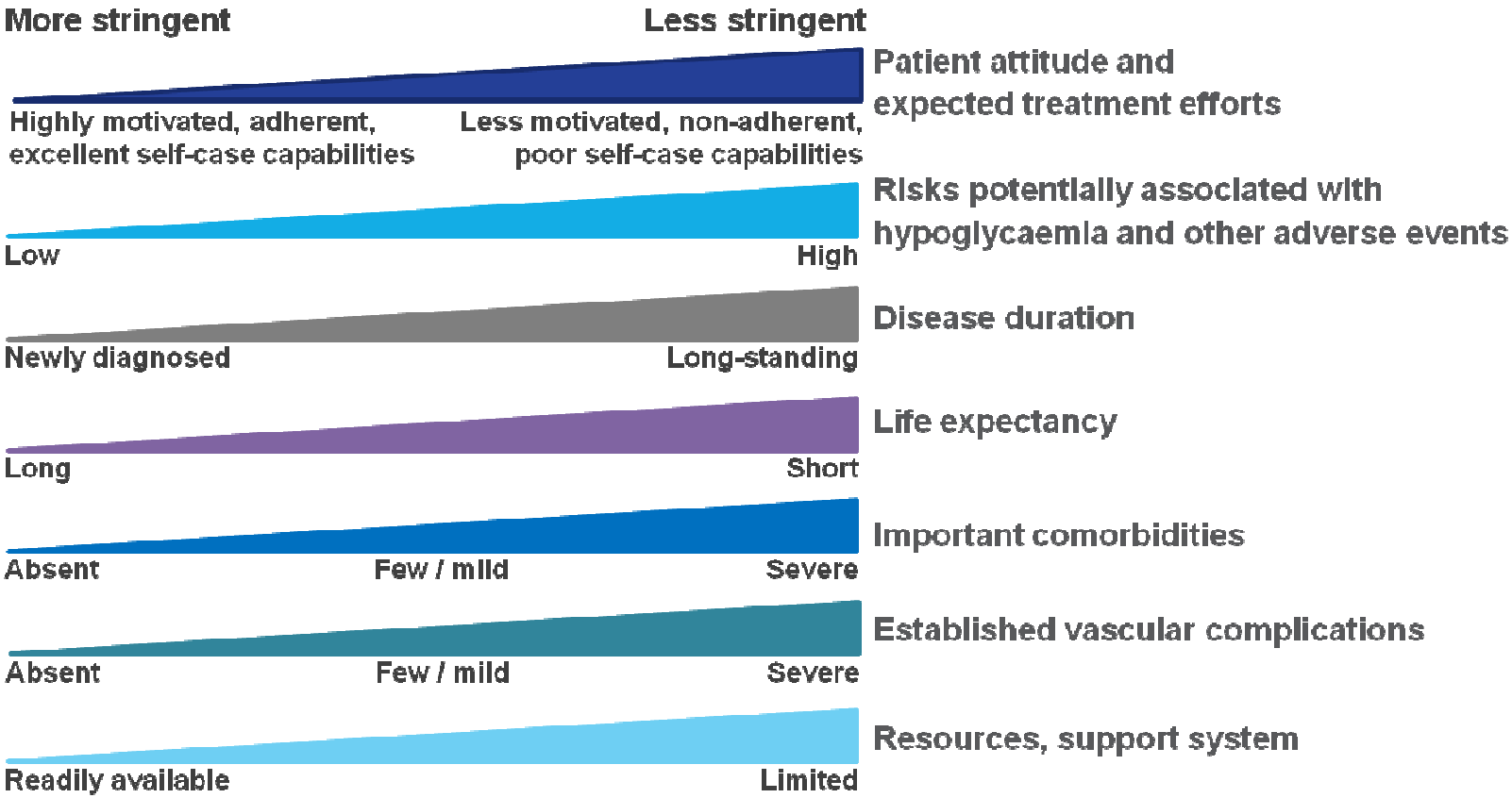


MDI, multiple daily injections; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SU, sulphonylurea; TZD, thiazolidinedione

Inzucchui SE et al, Diabetes Care (2012), 35 (6), 1364-1379

Individualisation of treatment goals is key

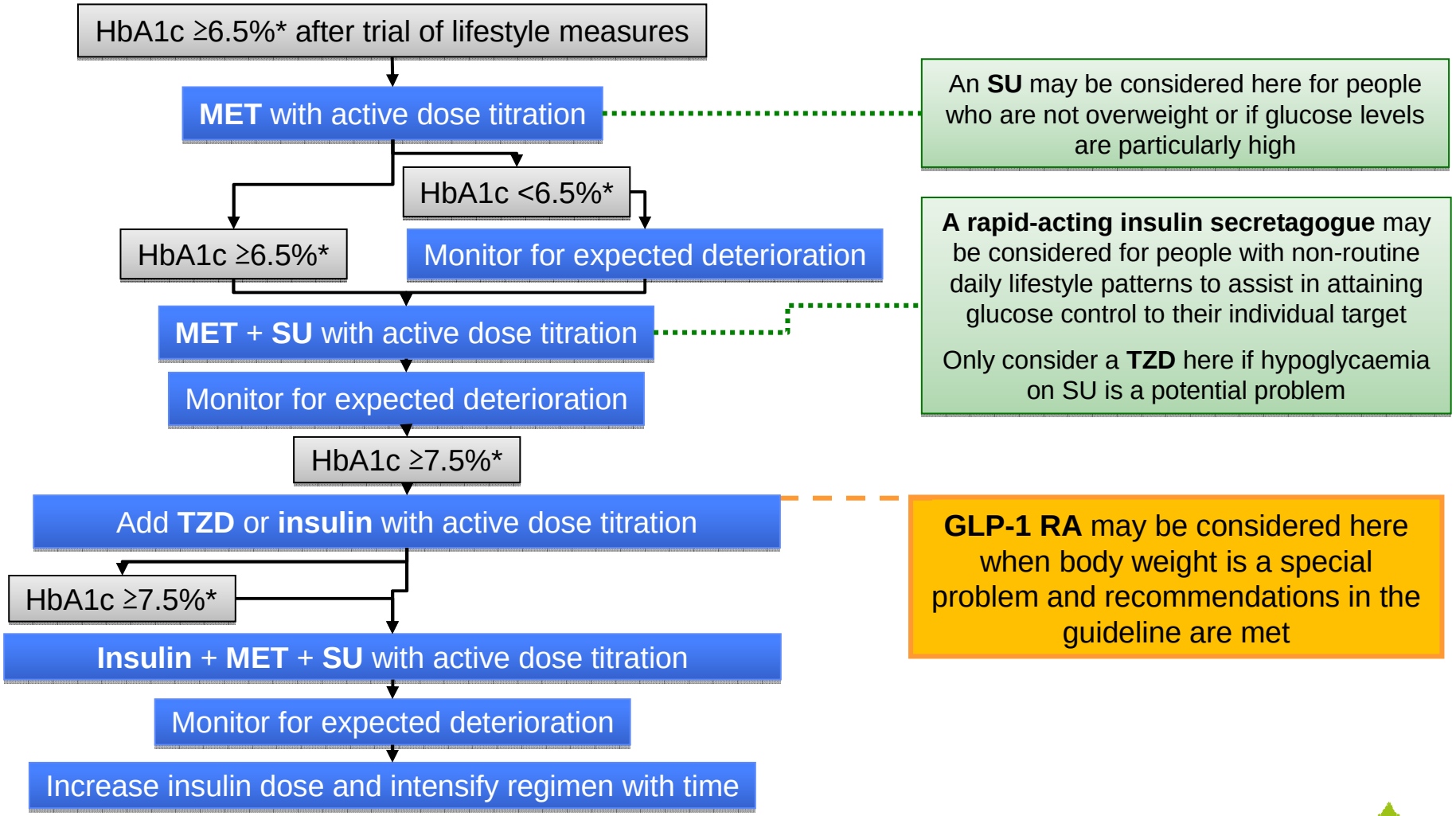
More (<6.5%) or less stringent (7.5-8%) goals



The figure depicts elements to consider when making decisions about HbA_{1c} targets for specific patients.
The scale is not designed to be applied rigidly but to serve as a broad framework to assist in determining glycaemic targets.

Adapted from: Ismail-Beigi F, *et al. Ann Intern Med* 2011;**154**:554–9; Inzucchi SE, *et al. Diabetes Care* 2012;**35**:1364–79.

NICE Algorithm: Glucose Lowering Pharmacotherapy in T2DM



*Or as individually agreed for each patient. MET: Metformin; NICE: National Institute for Health and Clinical Excellence; SU: Sulphonylurea; TZD: Thiazolidinedione National Collaborating Centre for Chronic Conditions. Type 2 diabetes: National clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008.

Metformin in overweight patients with Type 2 Diabetes

- Metformin reduced HbA1c by 0.6%, and reduced MI by 39% (UKPDS)
- Metformin should be first line monotherapy in patients with type 2 diabetes if tolerated and not contra-indicated

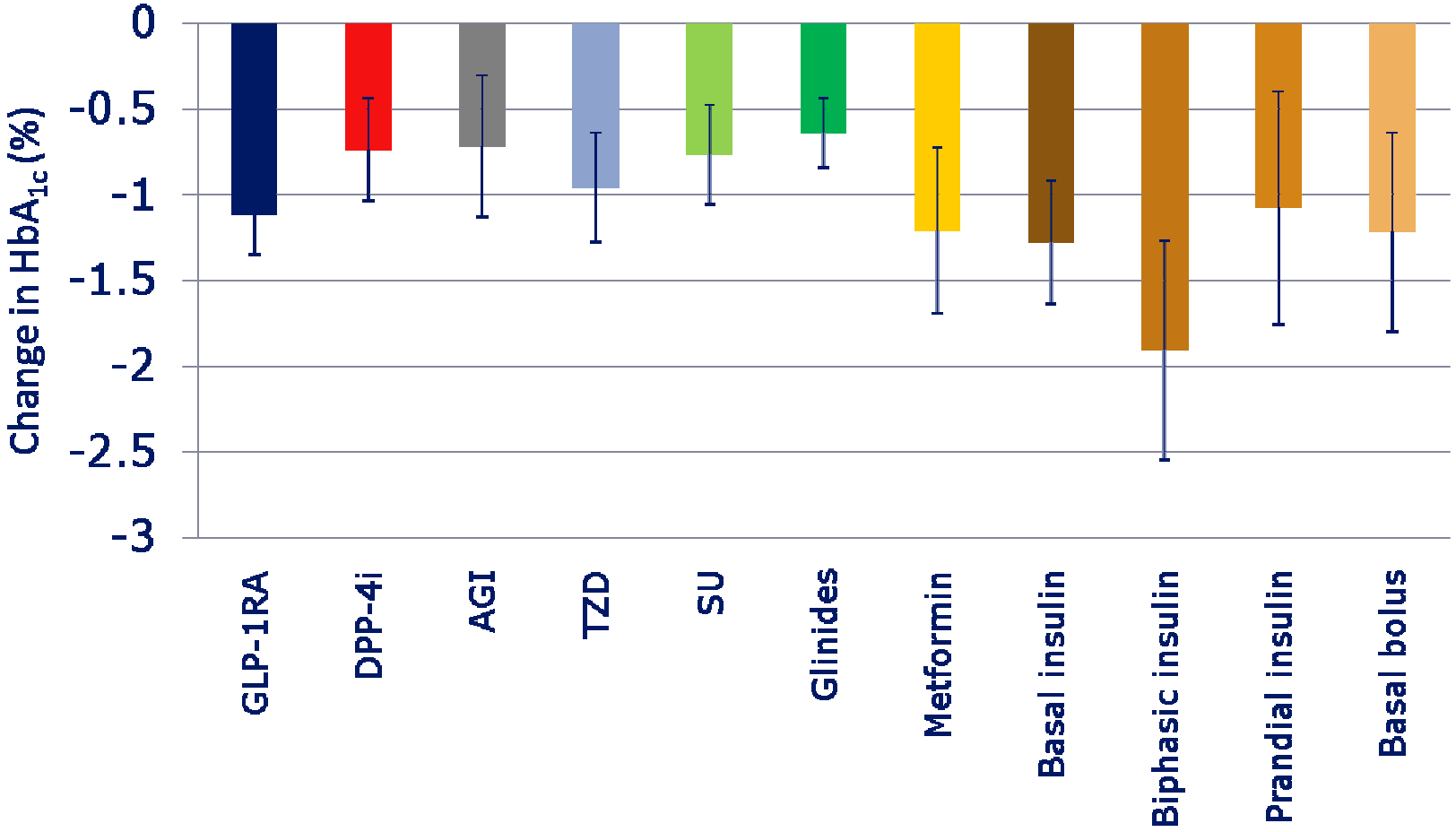
Choice of Therapy After Metformin: What We Know*

	SU	TZD	DPP-4i	GLP-1RA	Insulin (basal)
Physiological action(s)	↑ insulin secretion	↑ insulin sensitivity	↑ insulin secretion† ↓ glucagon secretion†	↑ insulin secretion† ↓ glucagon secretion† Slows gastric emptying ↑ satiety	↑ glucose disposal ↓ hepatic glucose production
Efficacy (↓HbA_{1c})	High	High	Intermediate	High	Highest
Hypoglycaemia risk	Moderate	Low	Low	Low	High
Weight effect	↑	↑	↔	↓	↑
Major side effects	Hypoglycaemia	Oedema Heart failure Bone fractures	Rare	GI	Hypoglycaemia

*Limited comparative data are available; †Glucose dependent.
DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; SU, sulphonylurea; TZD, thiazolidinedione; ↑, increase; ↓, decrease; ↔, neutral.

Adapted from Inzucchi et al. *Diabetologia.* 2012;55:1577–1596.

Variability in Achievable HbA_{1c} Reductions Among Drug Classes

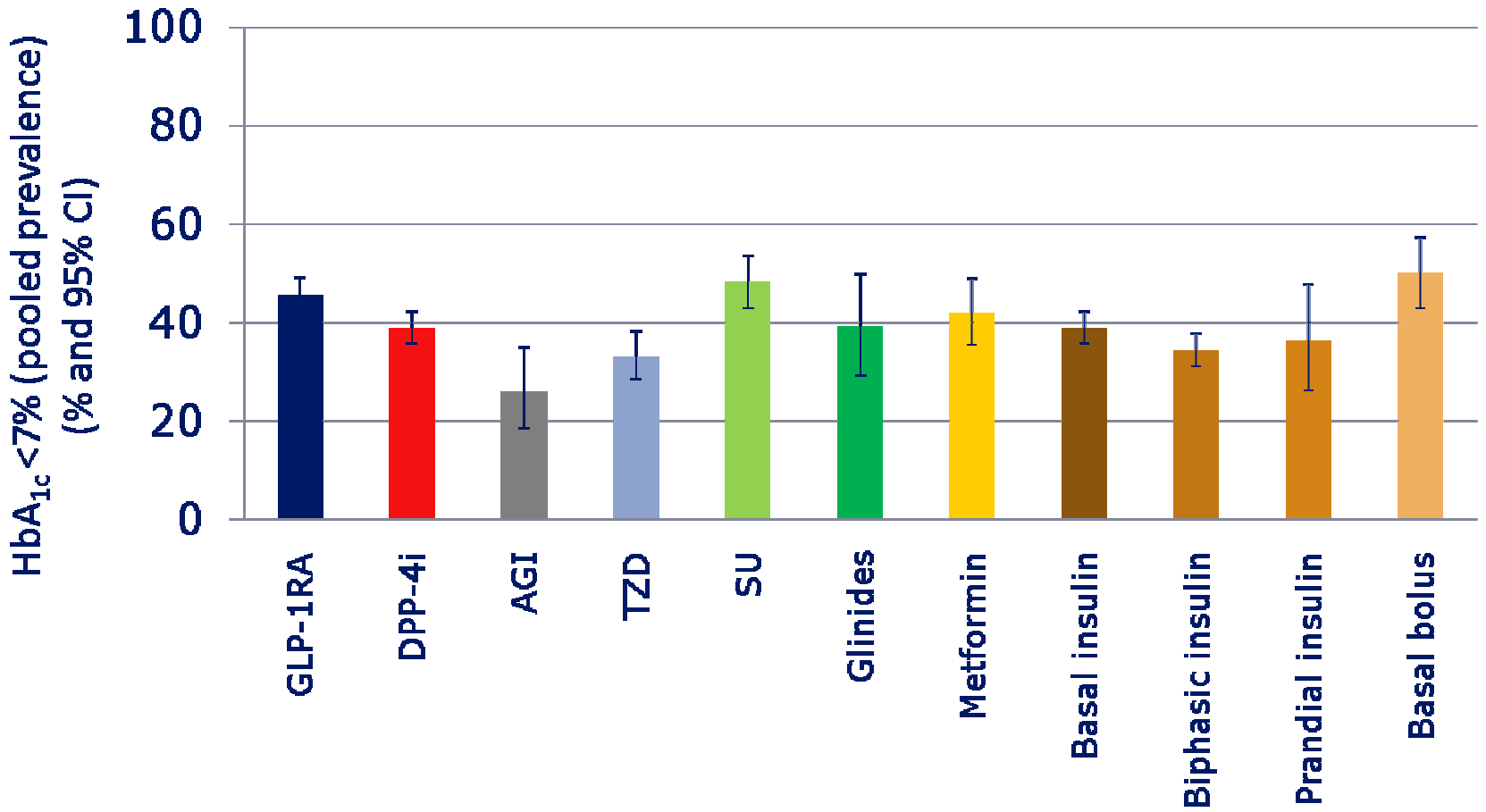


Subjects (n)	5783	13,847	1120	6655	5895	1050	4827	21,615	11,921	2597	2967

AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; SU, sulphonylurea; TZD, thiazolidinedione.

Esposito et al. *Diabetes Obes Metab.* 2012;14:228–233.

Variability in Reaching Goal Among Drug Classes

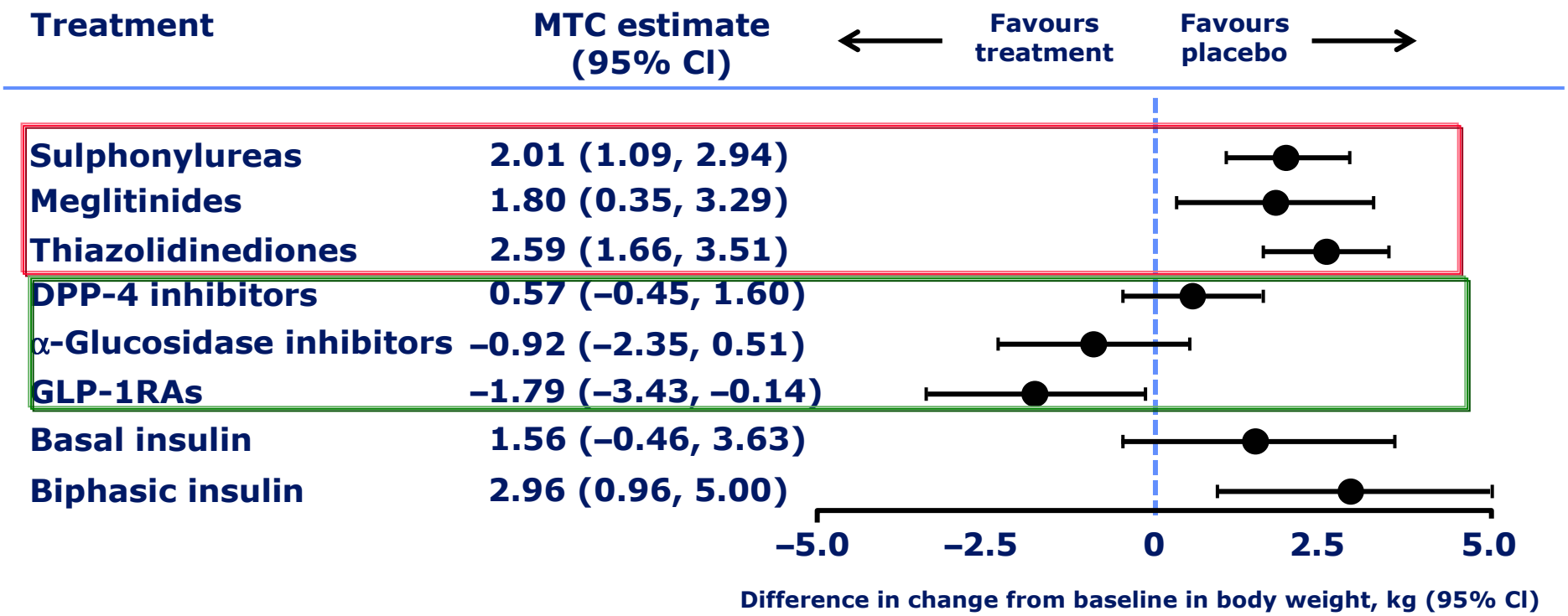


Subjects (n)	5783	13,847	1120	6655	5895	1050	4827	21,615	11,921	2597	2967

AGI, alpha-glucosidase inhibitor; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; SU, sulphonylurea; TZD, thiazolidinedione.

Esposito et al. *Diabetes Obes Metab.* 2012;14:228–233.

Large Variability in Effect on Weight



CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; MTC, mixed treatment comparison.

McIntosh B et al. *Open Med.* 2011;5:e35–e48.

Approved Novel Non-insulin Therapies

SGLT2 inhibitors	Incretins	
	GLP-1 receptor agonists	DPP-4 inhibitors
Dapagliflozin	Exenatide twice daily	Sitagliptin
Canagliflozin	Liraglutide	Vildagliptin
	Exenatide once weekly	Saxagliptin
	Lixisenatide	Linagliptin
		Alogliptin (Japan and USA)
		Teneligliptin (Japan)

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

Outline

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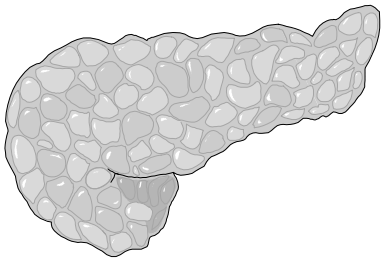
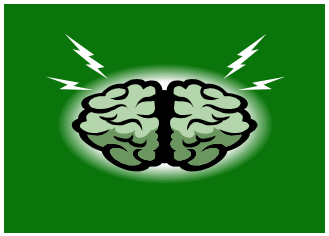
Effects of GLP-1 in humans and animals*



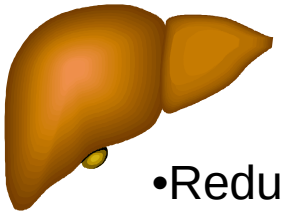
Pancreatic

- •Increase Glucose-dependent insulin secretion
- •Increase Proinsulin biosynthesis
- •Reduce Glucagon secretion
- •*increase beta cell mass
- •*reduces beta cell apoptosis
- •*increase neo-genesis



Central

- •Increase Satiety
- •Reduce Body weight

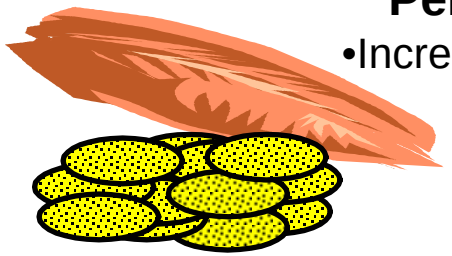


Hepatic*

- •Reduce Hepatic insulin extraction

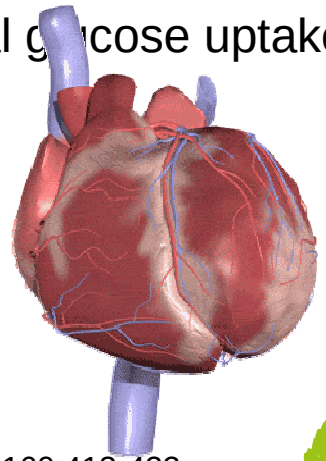
Cardiac*

- •Improved LVF (insulinomimetic effect on myocardial glucose uptake)



Peripheral Tissues*

- •Increase Glucose disposal?



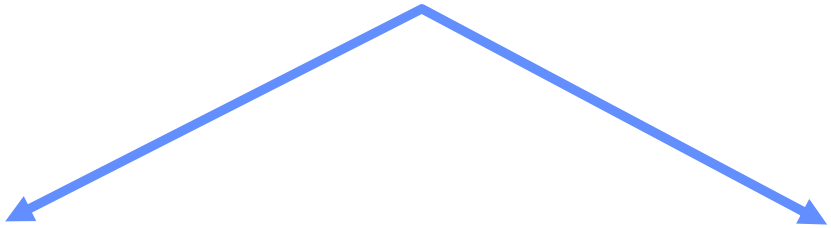
Gut

- •Reduce gastric emptying

Based on Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Drucker DJ. *Diabetes.* 1998;47:159-169. Green et al. *Diab Vasc Dis Res* 2006;3: 159-65

Restoring GLP-1 Response Is a Logical Target for Treatment

Incretin-based Treatment Options



DPP-4 Inhibitors
Prevent enzymatic degradation of native GLP-1 by DPP-4

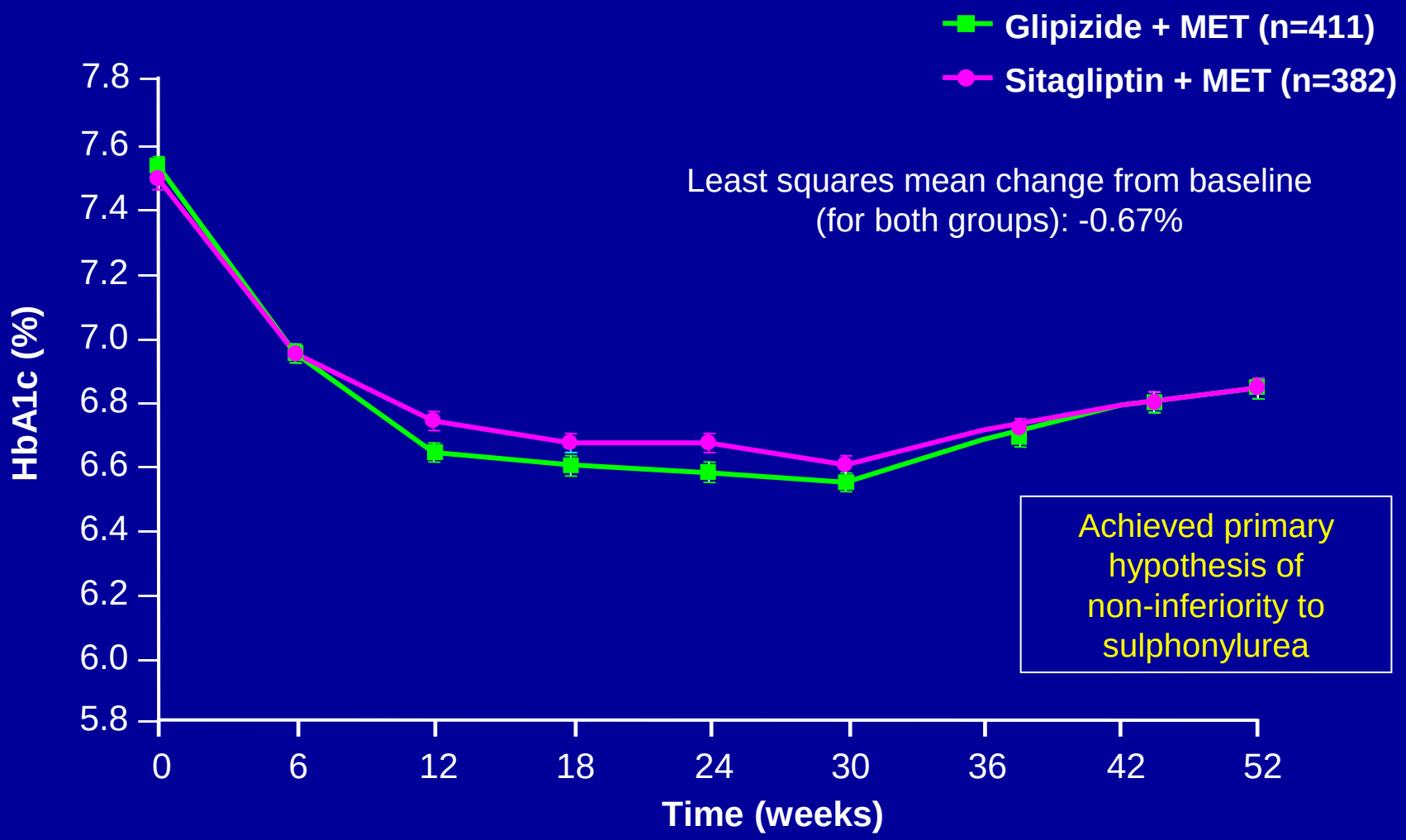
GLP-1 Receptor Agonists
Mimic native GLP-1 to restore GLP-1 activity

Incretin Enhancers

Incretin Mimetics

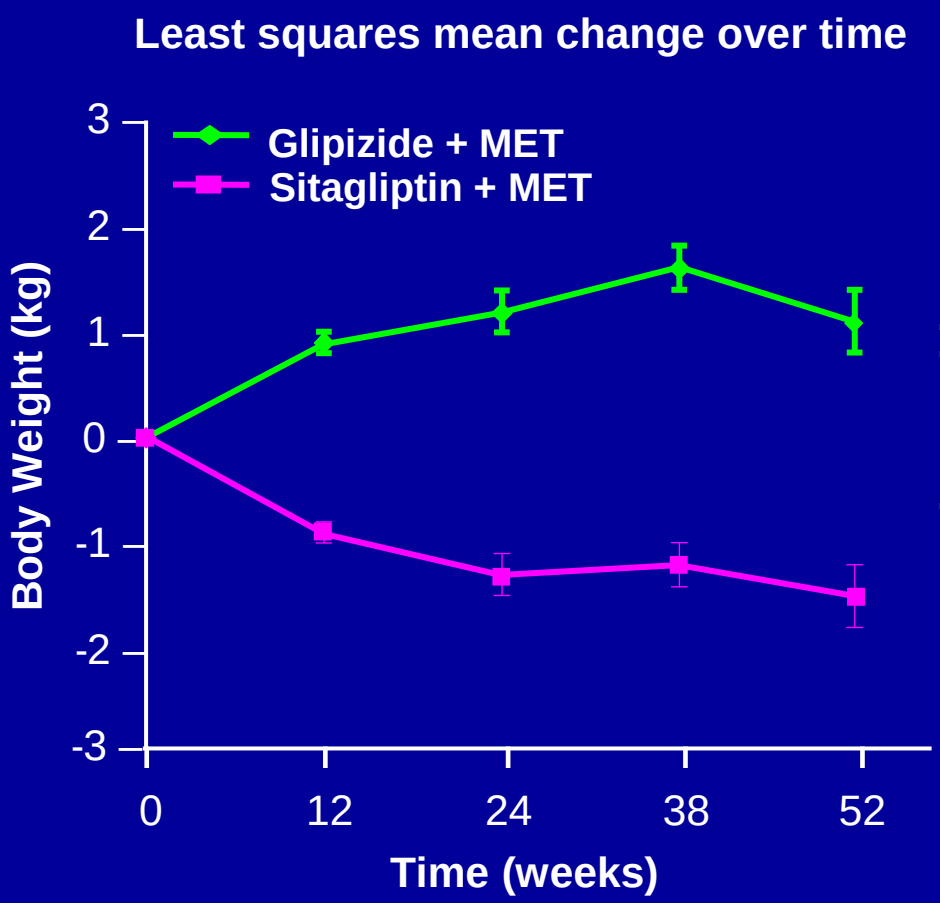
Developed from Holst JJ, Orskov C. *Diabetes*. 2004;53(suppl 3):S197-S204.

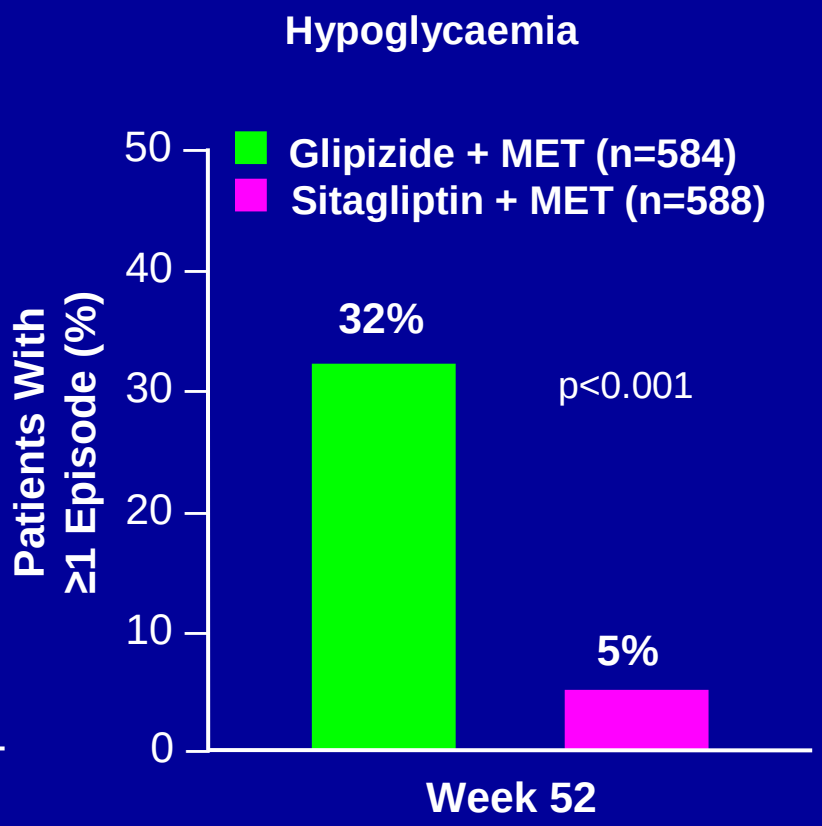
Sitagliptin with MET Showed Comparable Efficacy to Sulphonylurea with MET



MET: Metformin.
Per-protocol population. Data presented as mean ± SE
Adapted from Nauck et al. *Diabetes Obes Metab*. 2007;9:194–205.

Sitagliptin with MET Provided Weight Reduction (vs Weight Gain) and a Much Lower Incidence of Hypoglycaemia



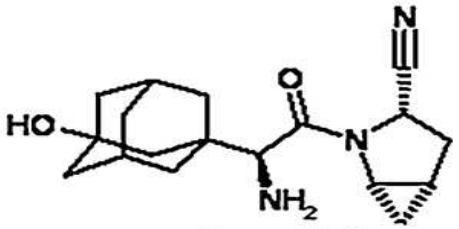


While this study demonstrated weight loss with sitagliptin, other studies have not shown significant weight loss, and sitagliptin is classed as weight neutral as per its SPC

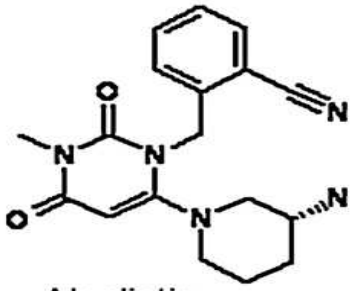
Least squares mean between-group diff|erence at Week 52 (95% CI): change in body weight = -2.5 kg [-3.1, -2.0] (p<0.001); Least squares mean change from baseline at Week 52: glipizide: +1.1 kg; sitagliptin: -1.5 kg. Per-protocol population. Data presented as mean ± SE.
SPC: Summary of Product Characteristics.
Adapted from Nauck MA, et al. *Diab Obes Metab.* 2007;9:194–205.

Structures of DPP-4 Inhibitors

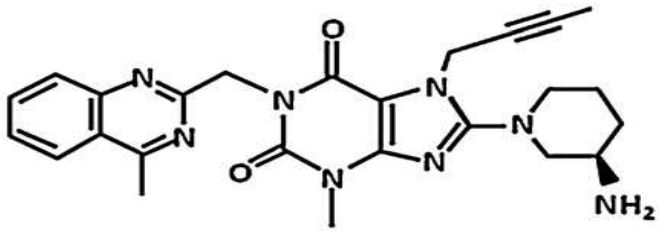
Sitagliptin



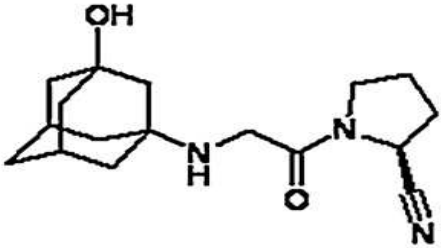
Saxagliptin



Alogliptin



Linagliptin



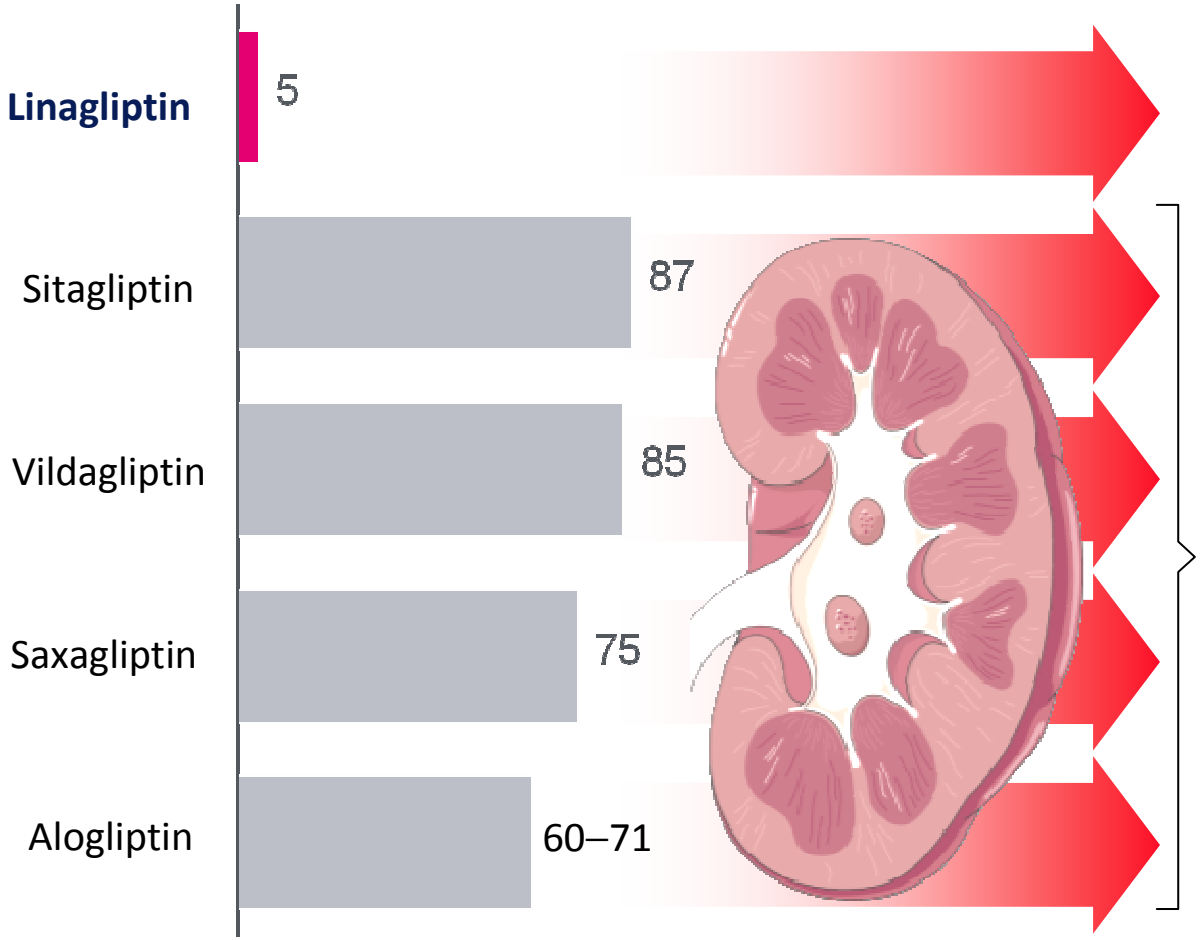
Vildagliptin

Feature	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Chemistry	Triazolopiperazine-based, substrate-like, non-covalent inhibitor	Cyanopyrrolidine-based, substrate-like, covalent inhibitor	Cyanopyrrolidine-based, substrate-like, covalent inhibitor	Pyrimidinedione-based, inhibitor, non-substrate-like, non-covalent inhibitor	Fused imidazole-based, non-substrate-like, non-covalent inhibitor

Gerich J. Dia Res Clin Pract 2010: 131-140, Baetta R and Corsini A, Drugs 2011:71(11);1441-1467

DPP-4 inhibitor excretion- Linagliptin by bile and gut[1]

Share of renal excretion[2], %



No dose adjustment and/or no additional drug monitoring required

Glucose lowering drugs with renal excretion increase the risk of hypoglycaemia in patients with renal impairment[3]

Dose adjustment required in patients with renal impairment and/or drug-related kidney monitoring

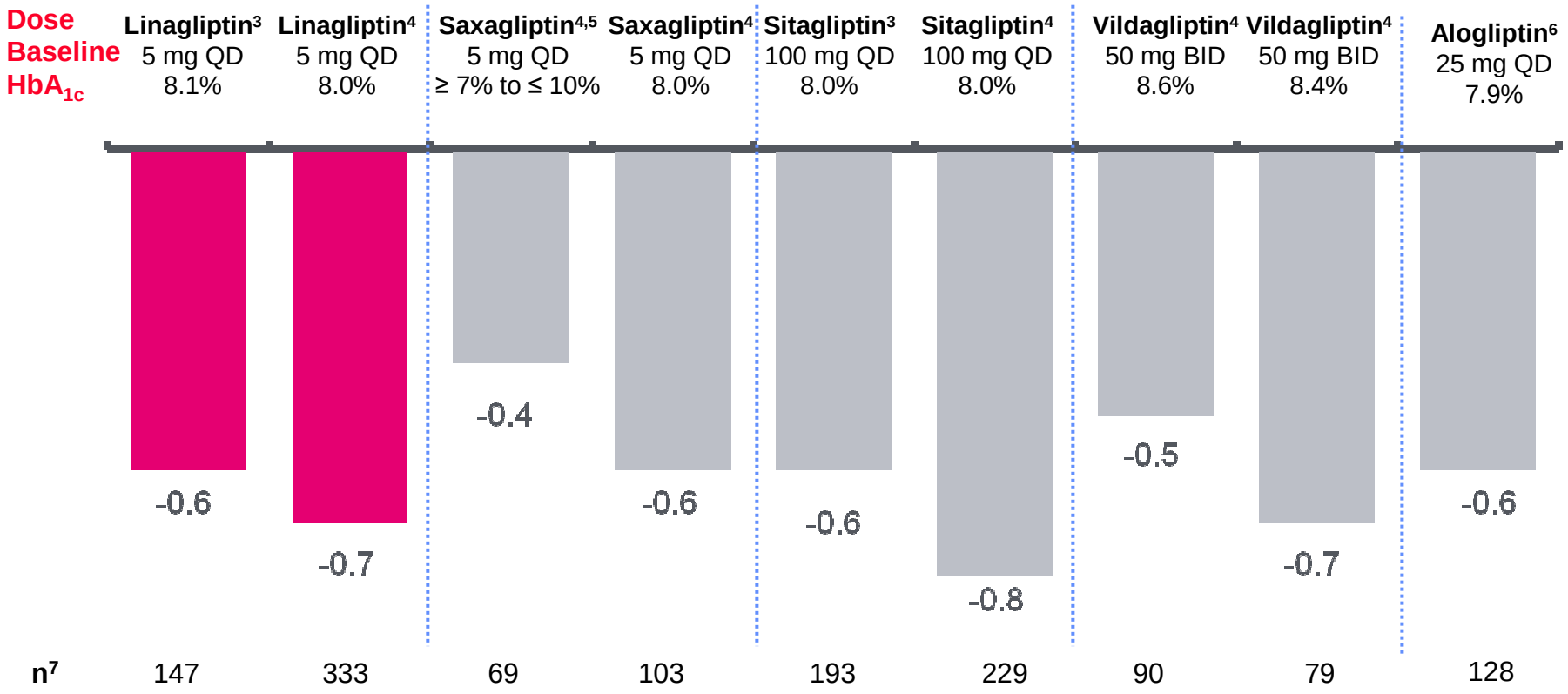
1. Of currently globally approved DPP-4 inhibitors. 2. Including metabolites and unchanged drug; excretion after single dose administration of C14 labeled drug.3. ADA/EASD Position Statement. *Diabetes Care*. 2012:doi:10.2337/dc12-0413.Source: US prescribing information linagliptin; Vincent SH, et al. *Drug Metab Dispos.* 2007;35:533–538; He H, et al. *Drug Metab Dispos.* 2009;37:536–544. US prescribing information saxagliptin. Christopher R, et al. *Clin Ther*. 2008;30:513–527.

Linagliptin – from preclinical attributes to clinical profile

Pharmacological attribute	Clinical correlate
▪ Tight binding to and slow dissociation (low k_{off}) from DPP-4 enzyme[1] ▪ Absorption of linagliptin not affected by food	+ Full 24-hour duration of action + Can be taken independent of food anytime of the day
▪ Highest biological potency	+ Low dose in man (5 mg once daily) + Small tablets (8 mm) + Suitable for combination tablets
▪ High selectivity (e.g., > 10,000-fold vs DPP-8/9[2]) ▪ No relevant inhibition or induction of P-gp	+ Large therapeutic window (> 100-fold) + No relevant drug–drug interactions with commonly used co-medications
▪ Very low free drug concentration	+ Very low likelihood of drug-related off target effect
▪ Primarily excreted via bile and gut ▪ High clearance of non-DPP-4 bound linagliptin	+ No dose adjustment in patients with renal impairment + One dose/one strength

1. More than 84% DPP4 inhibition after 24 hours.2 'Off-target' DPP inhibition (i.e., inhibition of DPP8/9) has shown severe toxicity in preclinical studies (Demuth HU, et al. *Biochim Biophys Acta*. 2005;1751:33–44).Source: Tradjenta® US prescribing information; Trajenta® EU summary of product characteristics; Thomas L, et al. *J Pharmacol Exp Ther.* 2008;325:175–182; Deacon CF. *Diabetes Obes Metab*. 2011;13:7–18; Scherntharner, et al. *Diabetes Obes Metab*. 2012;14:470–478.

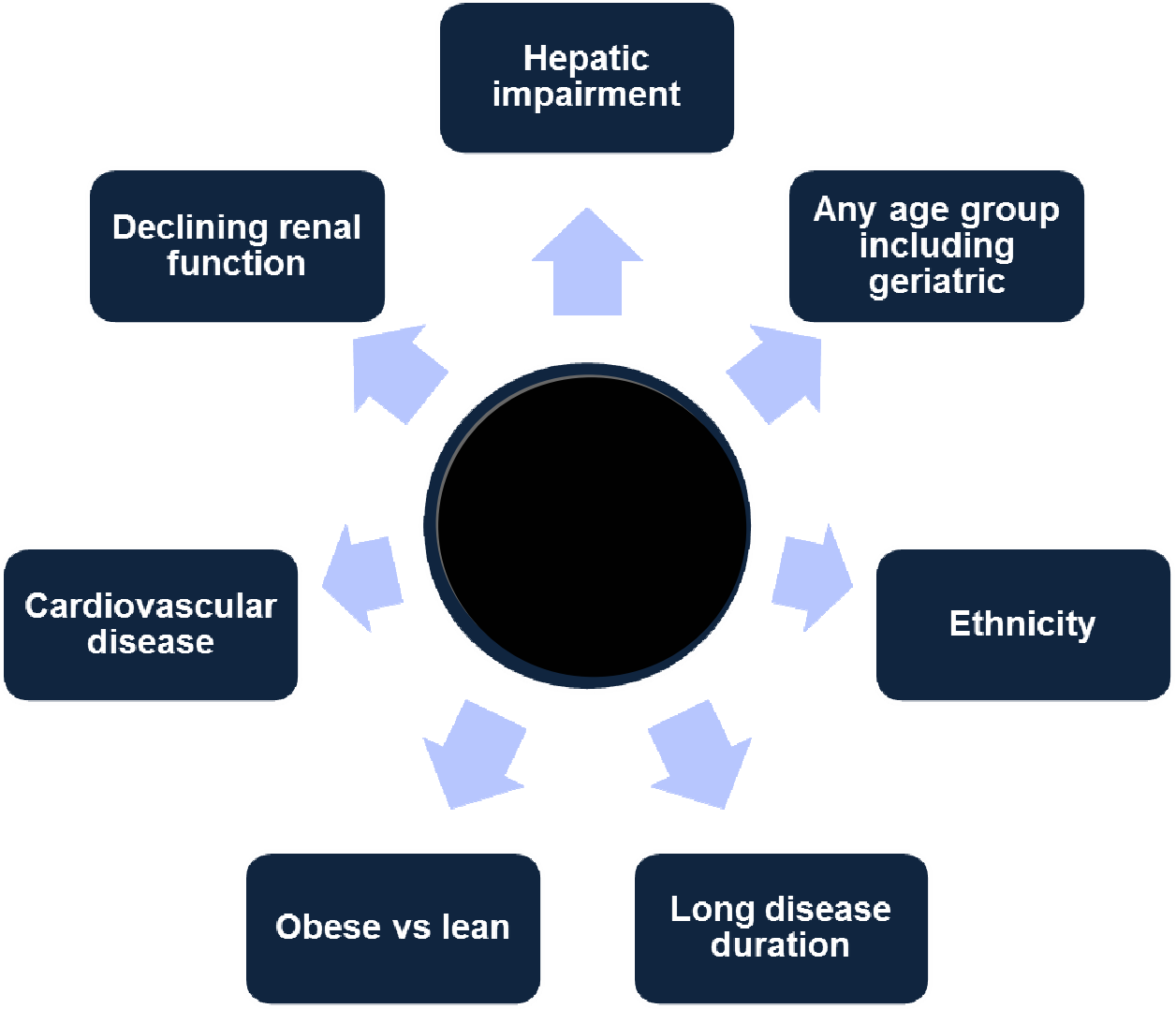
DPP4 inhibitors –US or EU label[1] monotherapy trials[1]



Treatment effect of various DPP4 inhibitors in monotherapy per US or EU[2] label
Placebo-corrected, adjusted mean change from baseline HbA_{1c} after 18/24/26 weeks of treatment

1. Data from the respective labels; 2. Trials listed in US prescribing information, except for vildagliptin, for which data from EU summary of product characteristics is shown; 3. 18 weeks' treatment duration; 4. 24 weeks' treatment duration; 5. Morning dosing; 6. 26 weeks' treatment duration; 7. DPP4 inhibitor group. Source: US prescribing information (linagliptin, saxagliptin , sitagliptin and alogliptin EU summary of product characteristics (saxagliptin, vildagliptin).

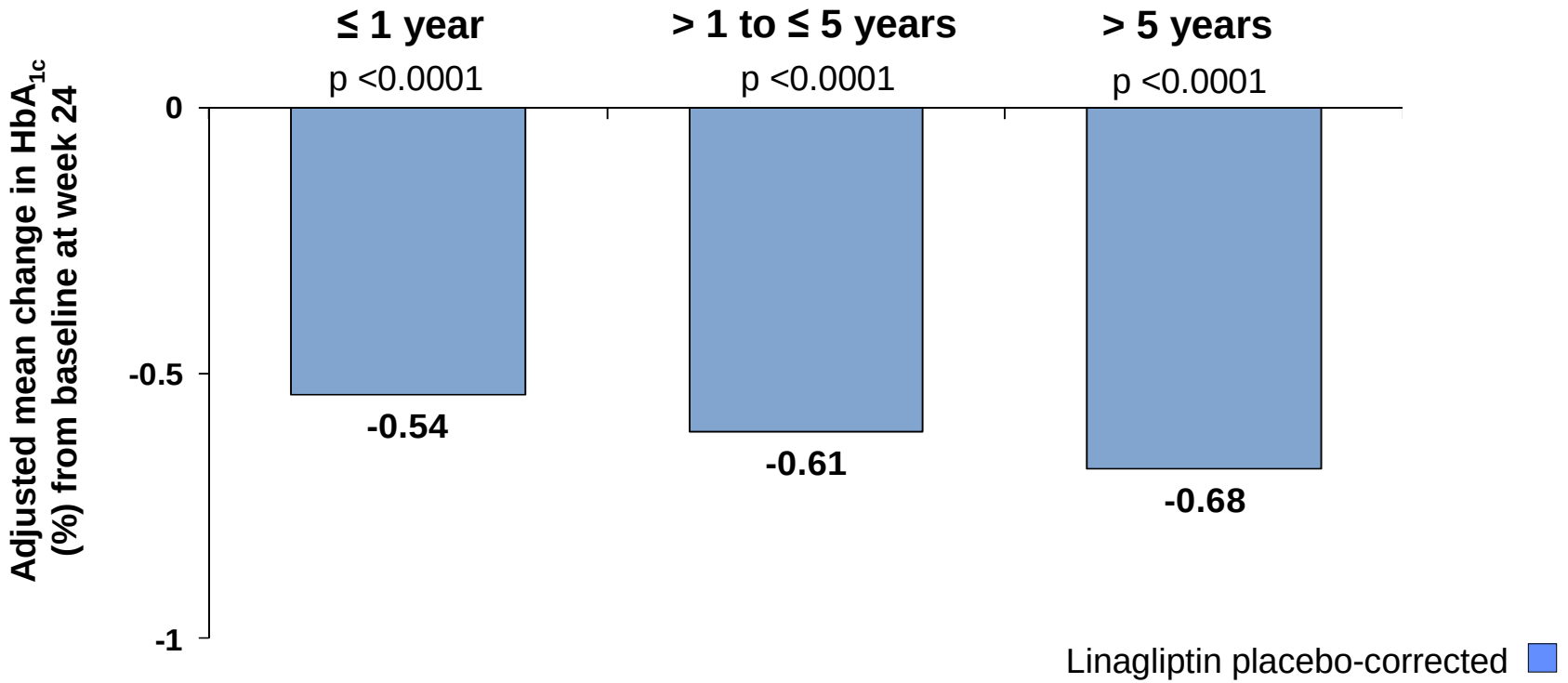
The patient spectrum



Linagliptin HbA_{1c} reductions independent of time since diagnosis of type 2 diabetes

Change from baseline HbA_{1c} by time since diagnosis of type 2 diabetes

Adjusted mean at 24 weeks of treatment, percent

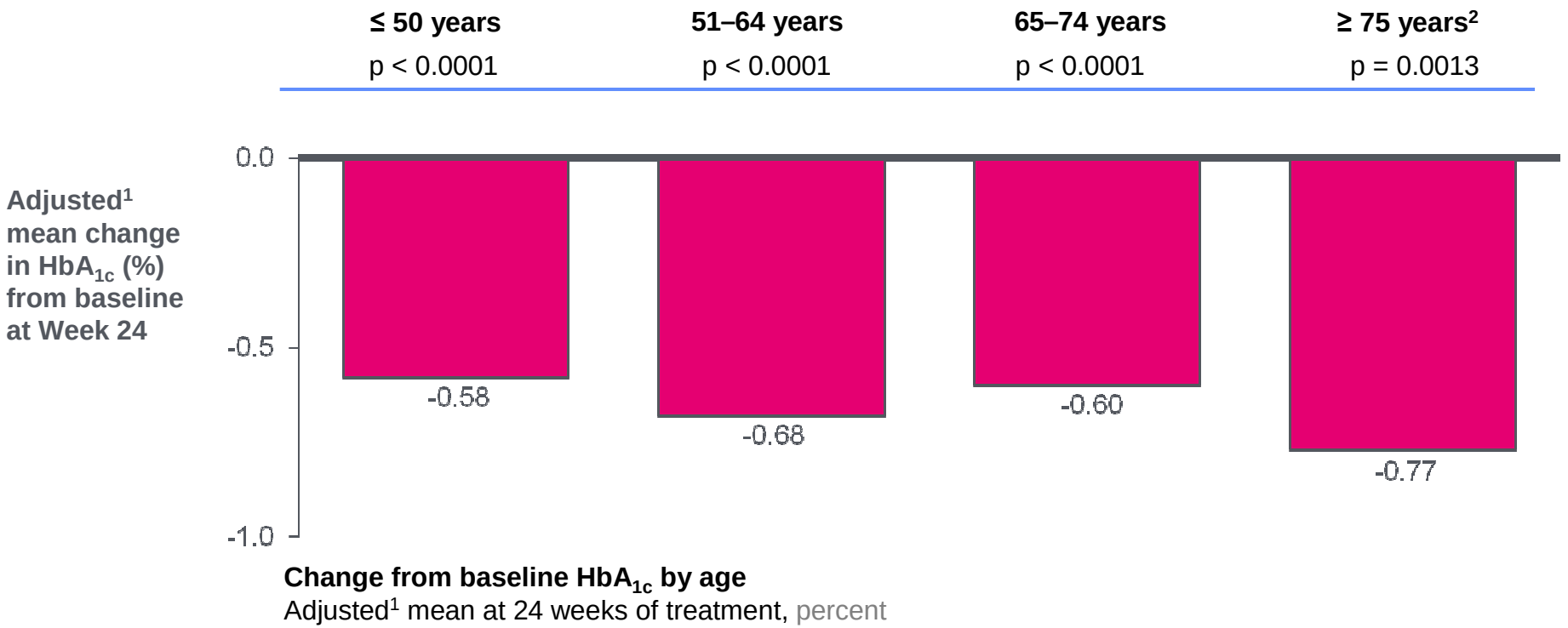


Pre-specified sub-group analysis on pooled data from 4 pivotal phase III randomized placebo-controlled trials: treatment in monotherapy, add-on to metformin, add-on to metformin + SU, initial combination with pioglitazone.

p-values for between group difference (versus placebo)

Patel 2011 EASD Poster P-832

Efficacy and age

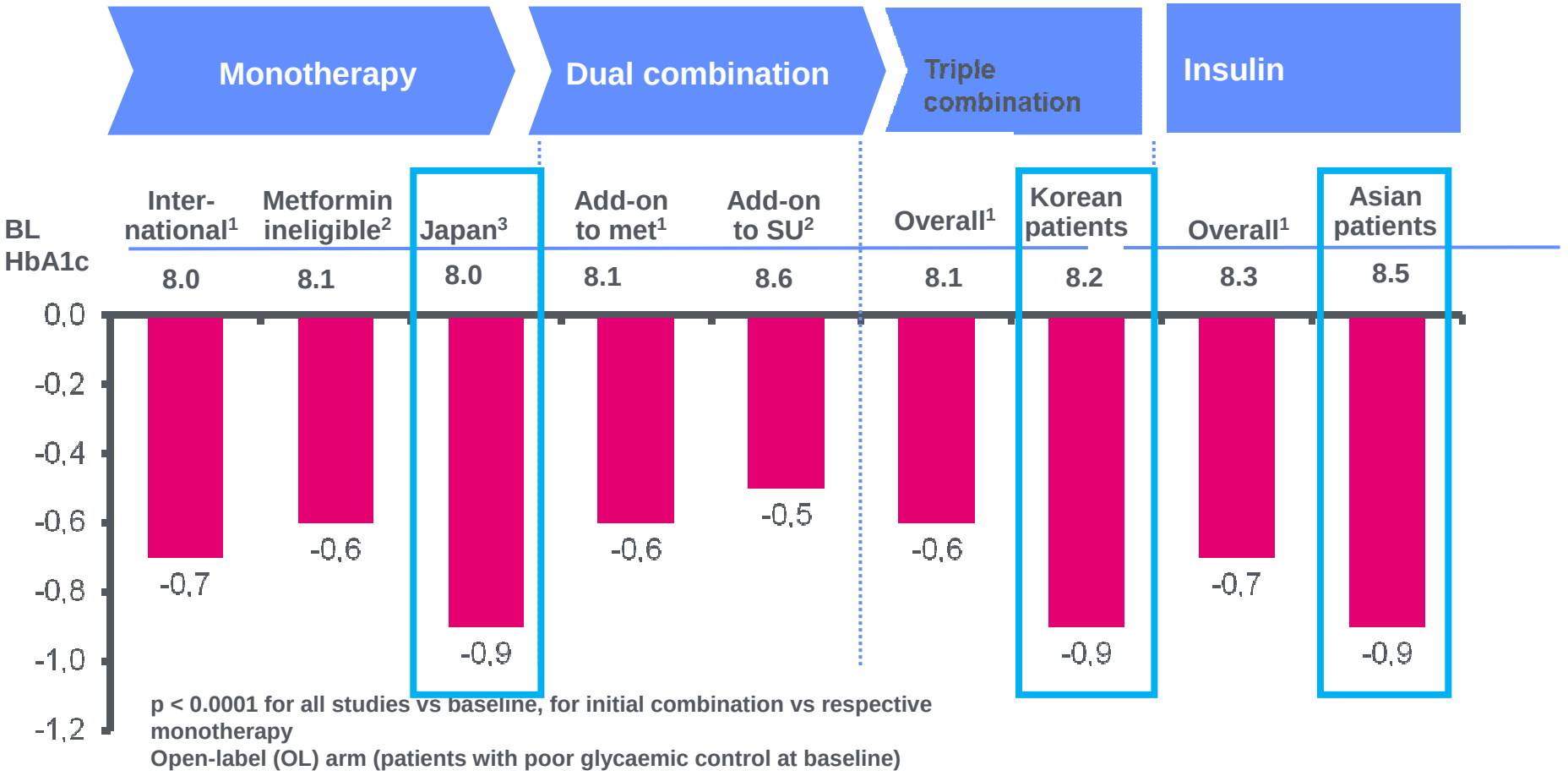


Change from baseline HbA_{1c} by age
Adjusted[1] mean at 24 weeks of treatment, percent

Note: Prespecified subgroup analysis on pooled data from three pivotal Phase III, randomized placebo-controlled trials: treatment in monotherapy, add-on to metformin, and add-on to metformin plus sulphonylurea. P-values for between-group differences (versus placebo). ANCOVA adjusted for continuous HbA_{1c}, BMI group, washout phase, treatment group, study, age group, sex, time since diagnosis of diabetes, race and age × treatment or T2DM × treatment interactions. Linagliptin should be used with caution when treating patients aged > 80 years, as experience in this patient group is limited.Source: Patel S, et al. EASD 2011, Poster P-832.

Meaningful efficacy across complete range of diabetes therapies

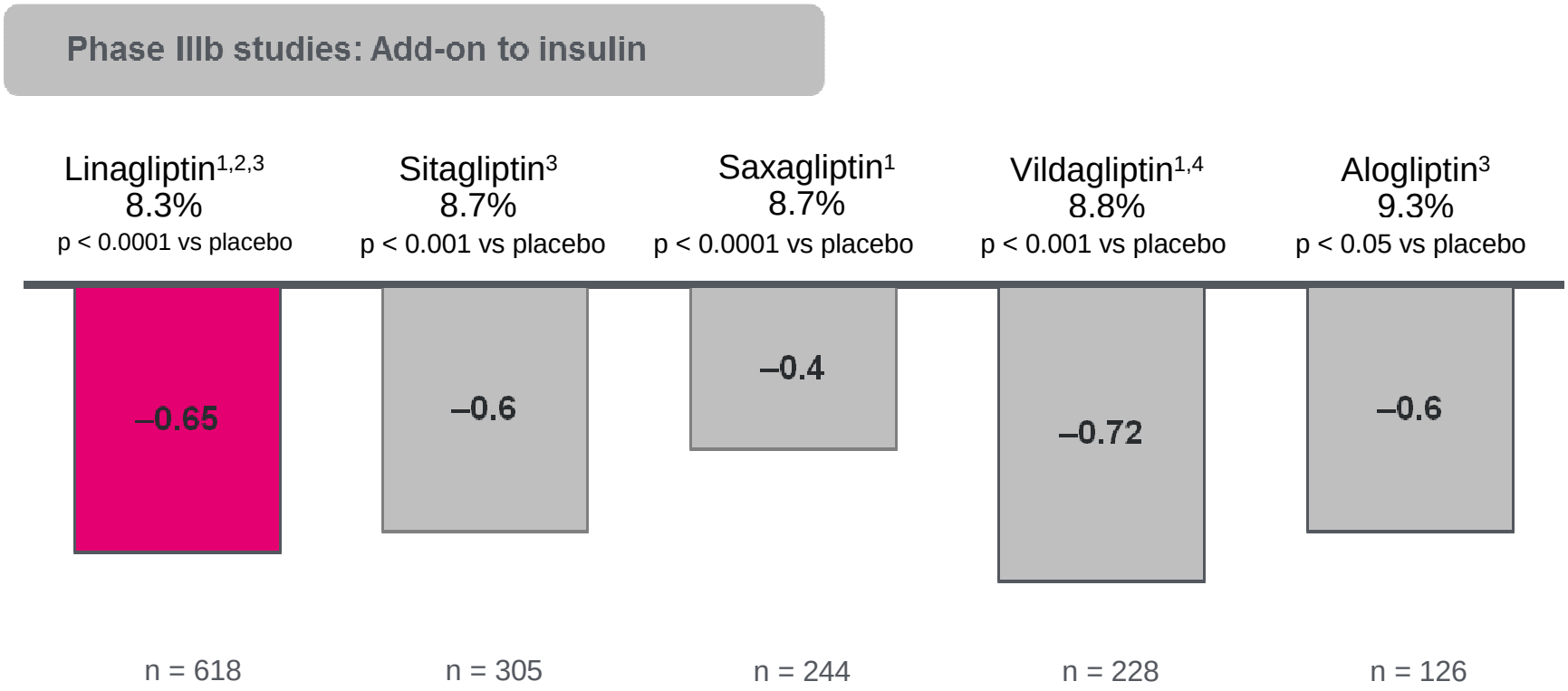
Linagliptin treatment effect across treatment lines
Adjusted mean change from baseline HbA1c, placebo-corrected



p < 0.0001 for all studies vs baseline, for initial combination vs respective monotherapy
Open-label (OL) arm (patients with poor glycaemic control at baseline)

- 1. 24 weeks' treatment duration; 2. 18 weeks' treatment duration; 3. 12 weeks' treatment duration.
- Source: Del Prato S, et al. *Diabetes Obes Metab*. 2011;13:258–267 (International); Barnett AH, et al. EASD 2010; Poster 823-P1 (Metformin ineligible); Kawamori, et al. *Diabetes Obes Metab*. 2011 [Epub ahead of print] (Japan); Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65–74 (Add-on to metformin); Lewin, et al. EASD 2010; Poster 821-P (Add-on to SU); Owens DR, et al. *Diabetic Med.* 2011;28:1352-1361 (Add-on to metformin+SU); Haak T, et al. *Diabetes Obes Metab*. 2012 Feb 22. doi: 10.1111/j.1463– 1326.2012.01590.x (Initial combined with met); Yki-Järvinen H, et al. accepted for presentation at ADA 999, P-(Add-on to basal insulin).

DPP4 inhibitors in combination with basal insulin



Treatment effect of linagliptin and other DPP4 inhibitors as add-on to basal insulin
Adjusted mean change from baseline HbA_{1c}, placebo-corrected

Note: Patient numbers are for the DPP4 inhibitors arm; 24-week data, except for alogliptin 26-week treatment duration ource: 1. SmPC (Traejtna®, Onglyza®, Galvus®); 2. Yki-Järvinen H, et al. 2013. Submitted; 3. US PI (Tradjenta®, Januvia®, Nesina®); 4. Kothny W, et al. *Diabetes Obes Metab*. 2013;15:252–257

Ethnicity and DPP-IV inhibitors

Diabetologia (2013) 56:696–708
DOI 10.1007/s00125-012-2827-3

META-ANALYSIS

Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis

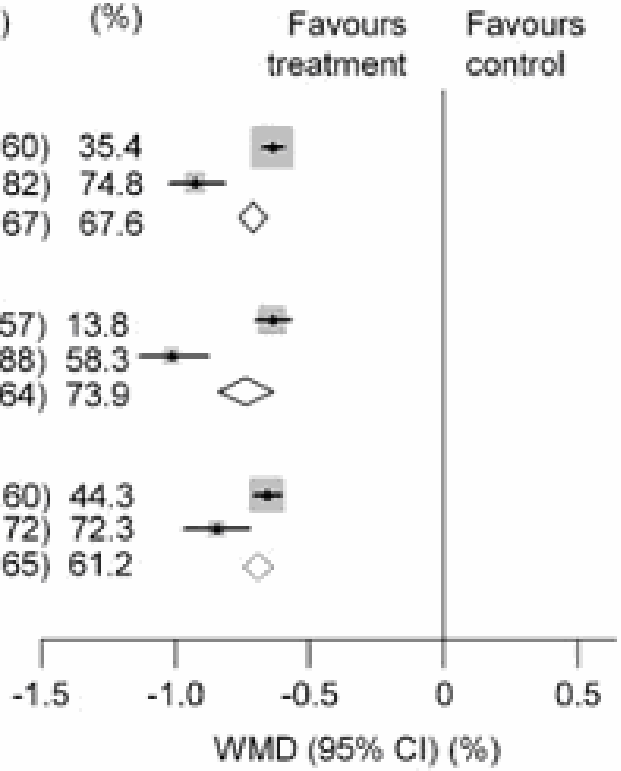
Y. G. Kim · S. Hahn · T. J. Oh · S. H. Kwak · K. S. Park · Y. M. Cho

Received: 16 November 2012 / Accepted: 19 December 2012 / Published online: 24 January 2013

Effects of DDP-IV on HbA1c

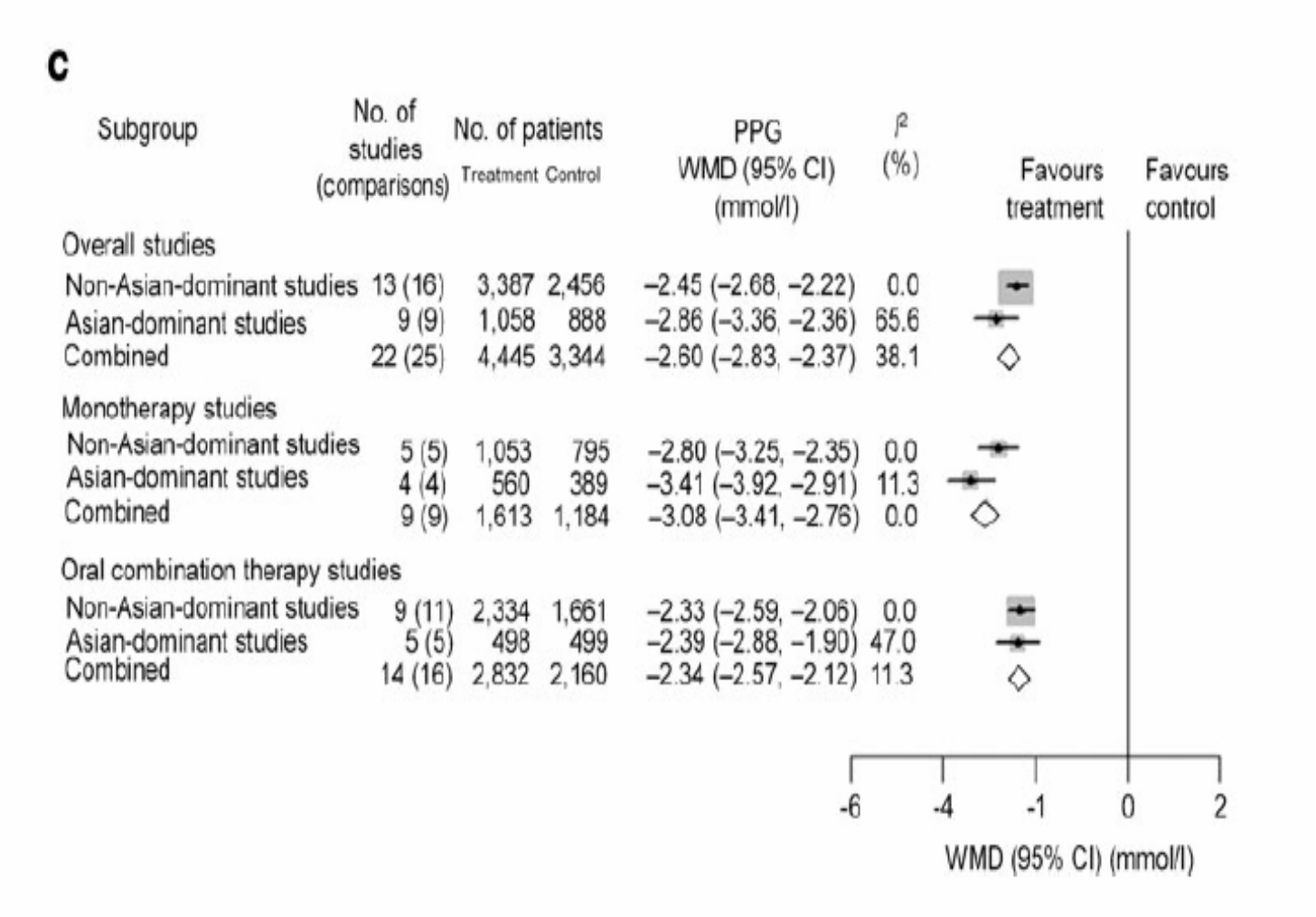
a

Subgroup	No. of studies (comparisons)	No. of patients Treatment	Control	HbA_{1c} WMD (95% CI) (%)	I^2 (%)
Overall studies					
Non-Asian-dominant studies	41 (44)	7,639	6,145	–0.65 (–0.69, –0.60)	35.4
Asian-dominant studies	13 (13)	2,050	1,357	–0.92 (–1.03, –0.82)	74.8
Combined	54 (57)	9,689	7,502	–0.72 (–0.77, –0.67)	67.6
Monotherapy studies					
Non-Asian-dominant studies	15 (15)	1,944	1,533	–0.64 (–0.70, –0.57)	13.8
Asian-dominant studies	6 (6)	675	498	–1.01 (–1.14, –0.88)	58.3
Combined	21 (21)	2,619	2,031	–0.74 (–0.84, –0.64)	73.9
Oral combination therapy studies					
Non-Asian-dominant studies	27 (29)	5,695	4,612	–0.66 (–0.71, –0.60)	44.3
Asian-dominant studies	7 (7)	1,375	859	–0.85 (–0.97, –0.72)	72.3
Combined	34 (36)	7,070	5,471	–0.70 (–0.76, –0.65)	61.2



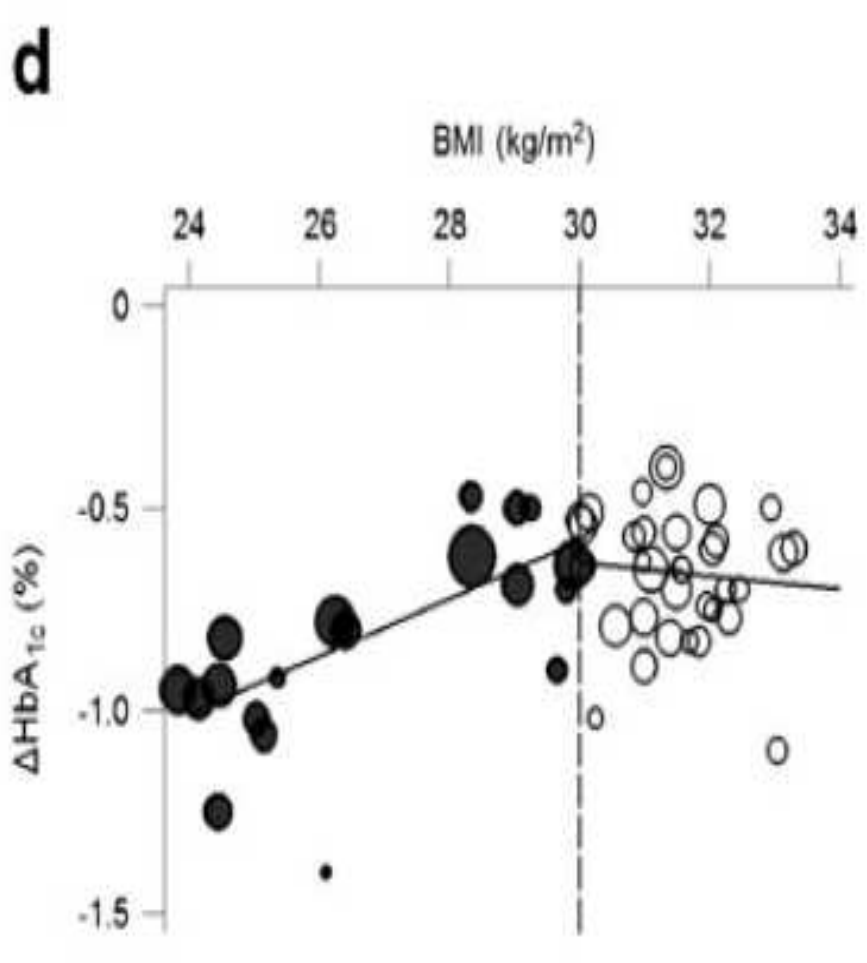
Kim YG et al Diabetologia 2013

Effect of ethnicity and PPG



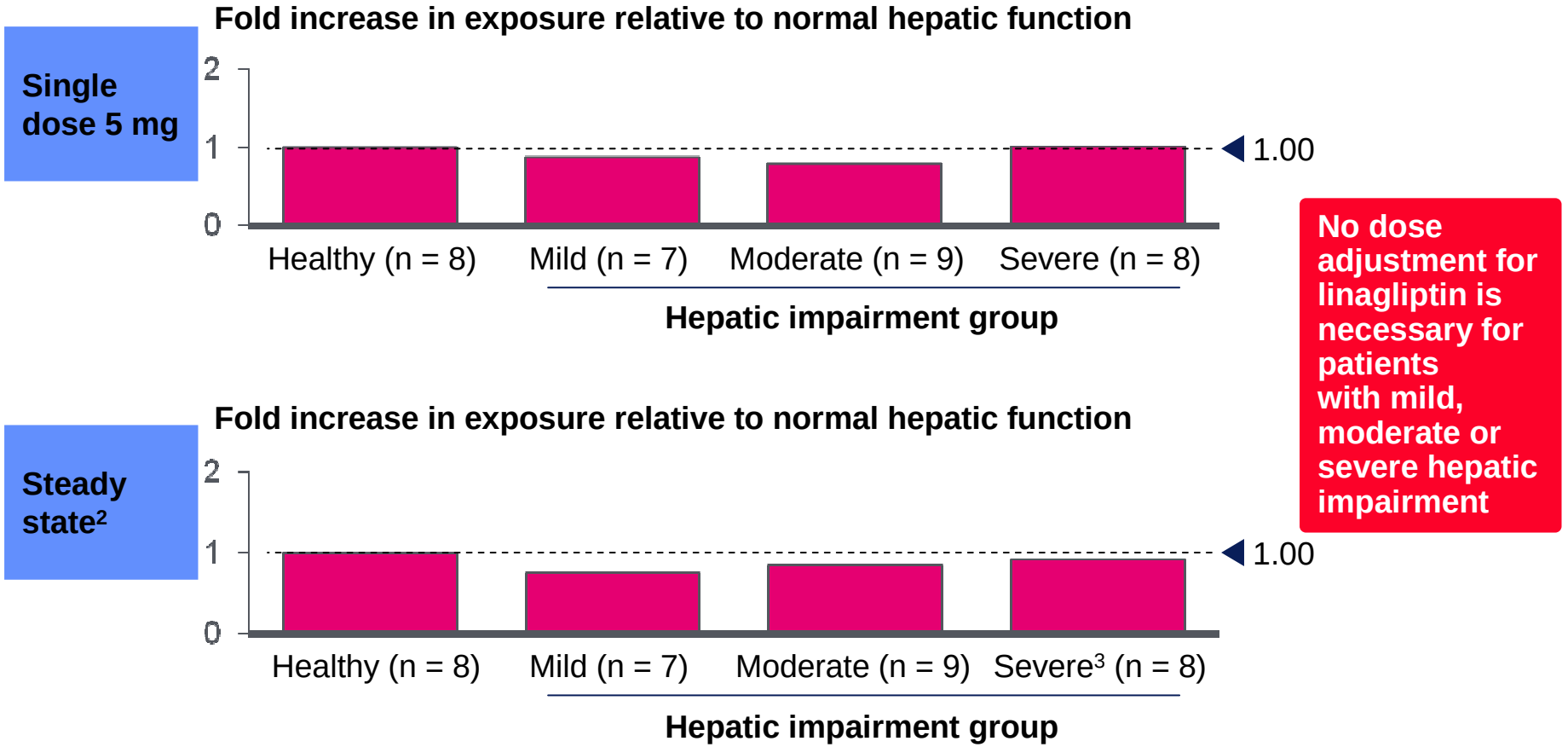
Kim YG et al Diabetologia 2013

Relationship between BMI and A1c lowering



Kim *et al. Diabetalogia* 2013;56:696–708

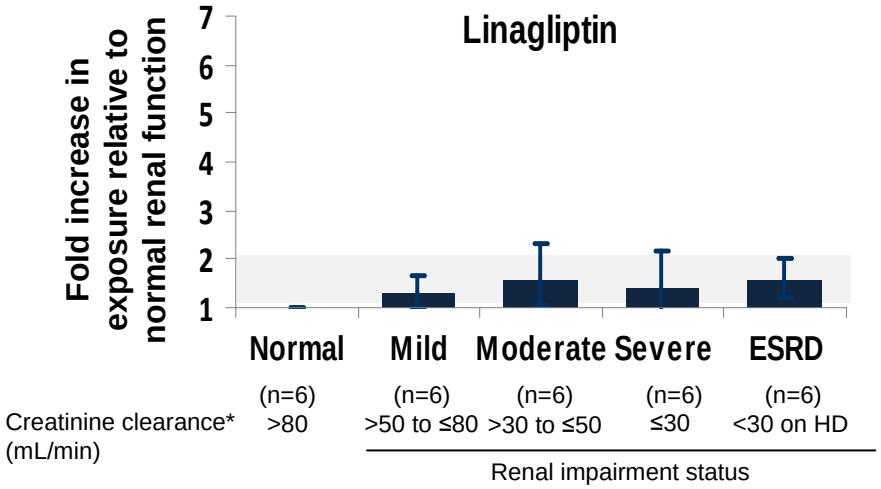
Influence of hepatic impairment on pharmacokinetics: No dose adjustment of linagliptin in patients with hepatic impairment

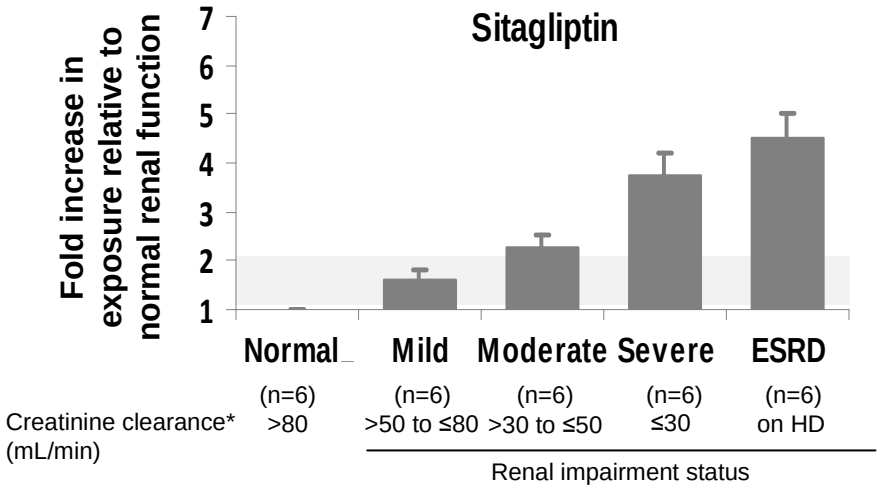


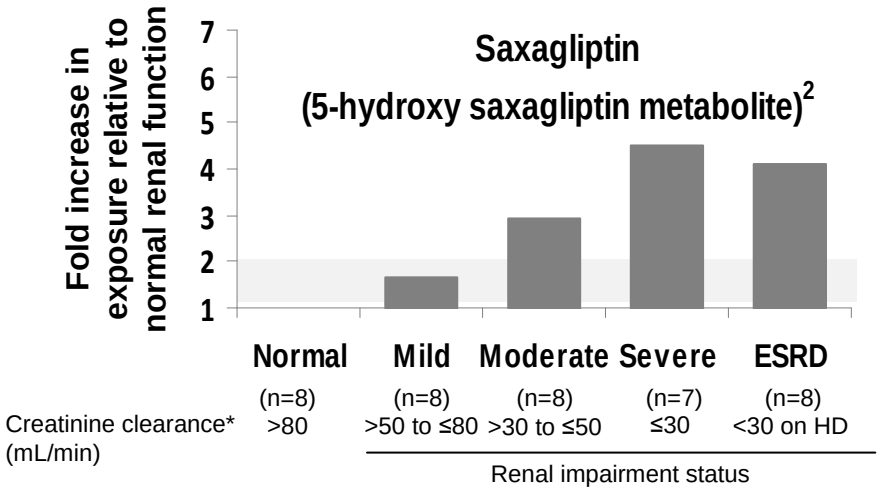
Linagliptin exposure in patients with mild, moderate, and severe hepatic impairment,[1] mean AUC

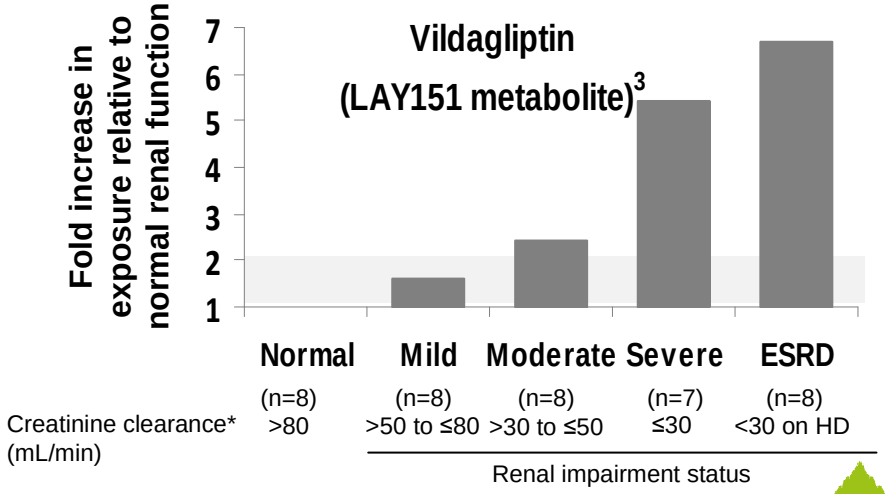
1. Following Child–Pugh Classification. 2. Application of six oral doses of 5-mg linagliptin at 24-h intervals. 3. Not measured; value estimated from single dose by pharmacokinetic modelling. Source: Graefe-Mody U, et al. *Br J Clin Pharmacol*. 2012;74:75–85.

DPP-4 inhibitor doses across renal function





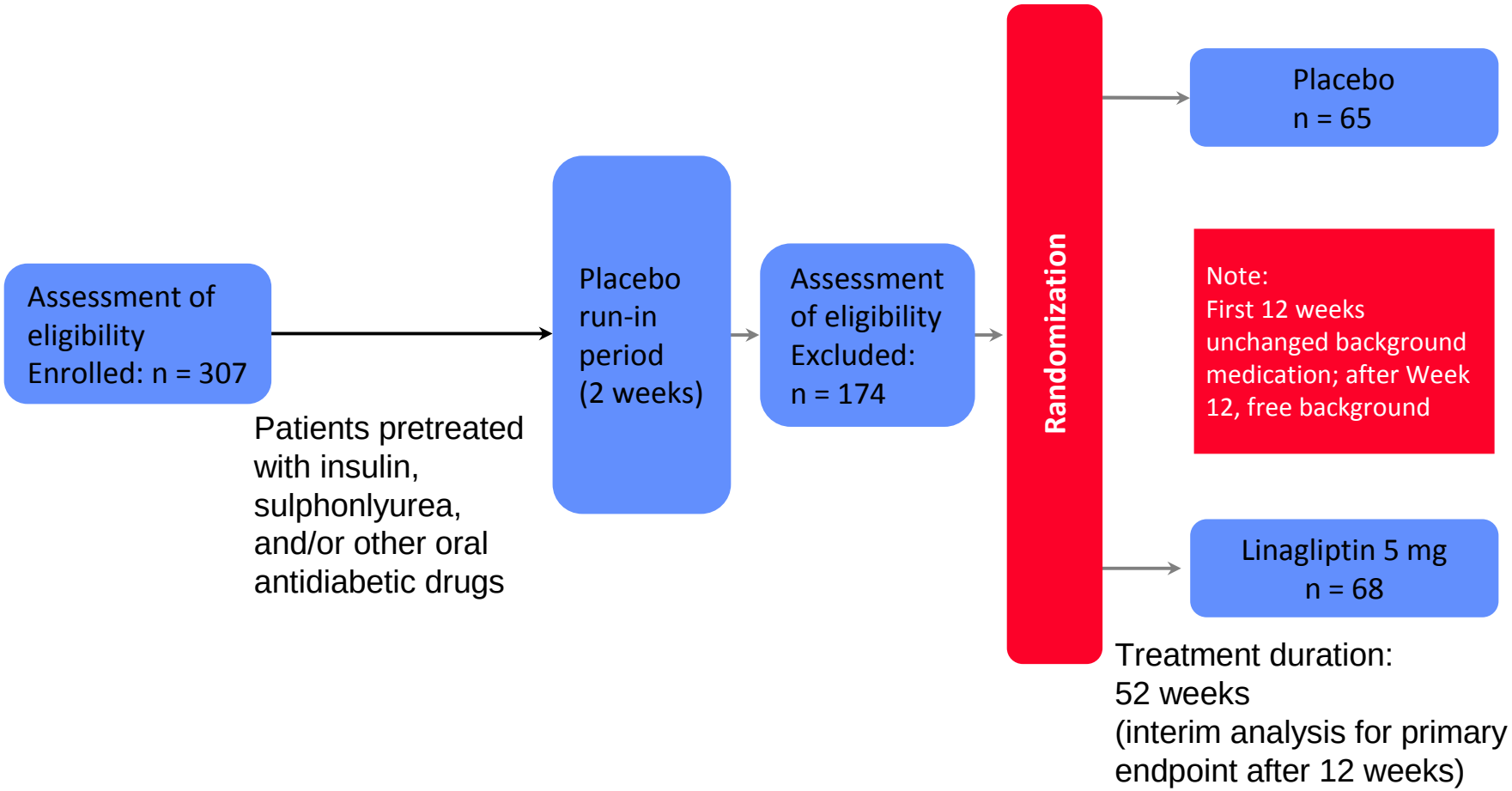




ESRD = end-stage renal disease; HD = Haemodialysis; * Estimated creatinine clearance values were calculated using the Cockcroft-Gault formula

Source: Graefe-Mody U, et al. *Diabetes Obes Metab.* 2011;13:939-946

Linagliptin in patients with severe renal impairment: Study design



Source: McGill JB, et al., *Diabetes Care.* 2013;36:237–244.

Baseline characteristics

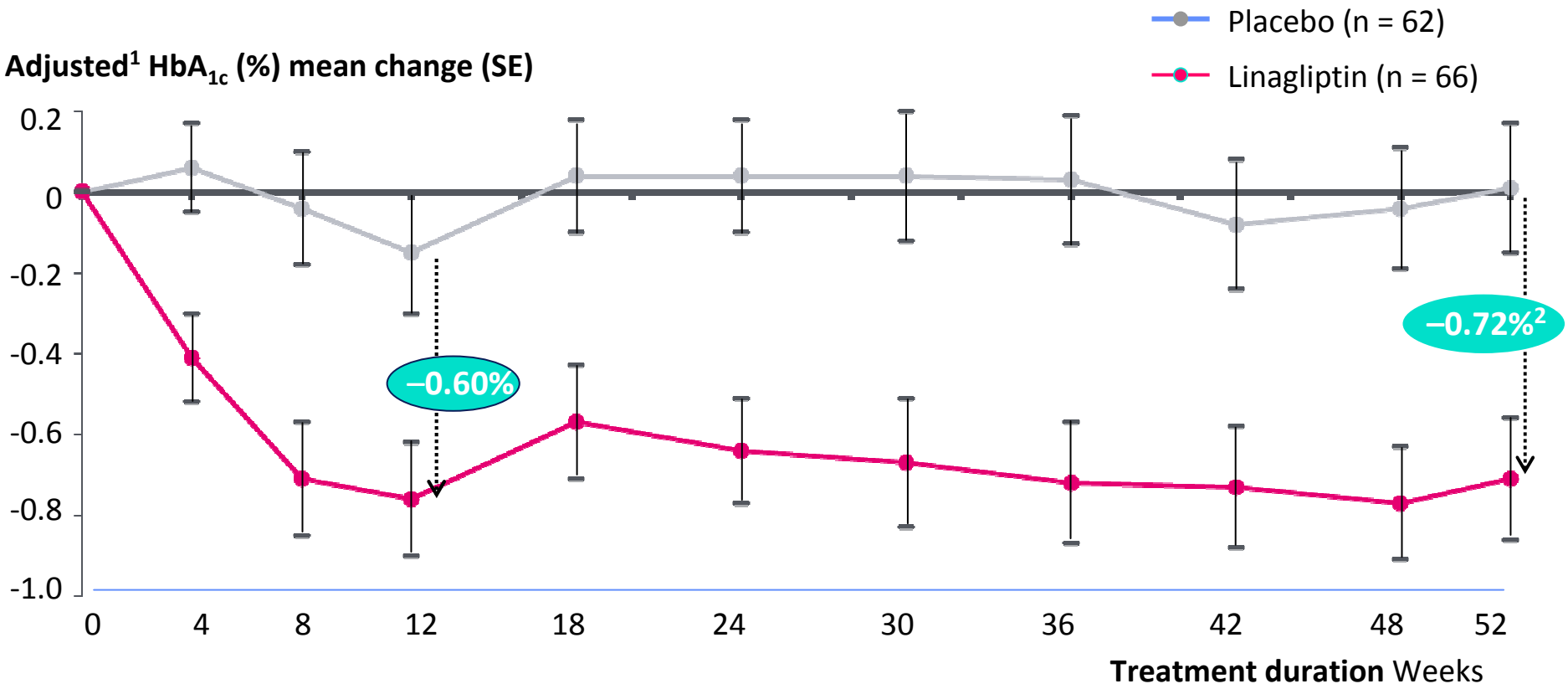
Treated set		
	Linagliptin (n = 68)	**Placebo (n = 65)**
Demographic parameter (mean ± SD)		
Age, years	64.0 ± 10.9	64.9 ± 9.6
Male, n (%)	45 (66.2)	35 (53.8)
Body weight, kg	89.9 ± 19.0	85.7 ± 17.6
BMI, kg/m^2	32.3 ± 5.8	31.7 ± 5.9
Duration of T2DM,[1] > 5 years, n (%)	64 (97.0)	59 (95.2)
Metabolic parameter (mean ± SD)		
HbA_{1c},[1] %	8.2 ± 1.1	8.2 ± 0.9
FPG[1], mmol/L	8.3 ± 4.4	8.9 ± 3.6
Baseline eGFR (MDRD), mL/min	22.1 ± 6.3	25.1 ± 6.9
Glucose-lowering regimen[1], n (%)		
Insulin therapy		
▪Monotherapy	39 (57.4)	46 (70.8)
▪Combination therapy	15 (22.1)	9 (13.8)
Sulphonylurea therapy		
▪Monotherapy	9 (13.2)	7 (10.8)
▪Combination therapy (other OADs)	4 (5.9)	3 (4.8)
Any other OADs	1 (1.5)	1 (1.6)

BMI, body mass index; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease equation.

Full analysis set (linagliptin, n = 66; placebo, n = 62).

Source: McGill JB, et al. *Diabetes Care.* 2013;36:237–244.

HbA_{1c} reductions maintained over 52 weeks



–0.7% adjusted mean HbA_{1c} change versus baseline at 52 weeks ($p < 0.0001$)

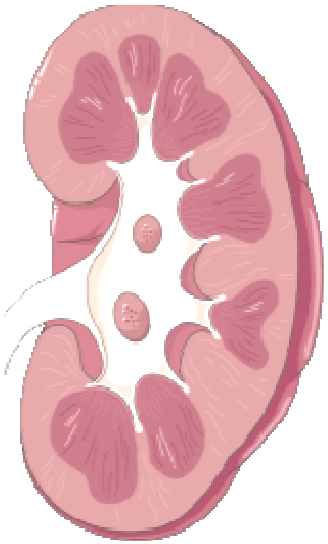
Note: Baseline HbA_{1c} linagliptin 8.2%, placebo 8.2%. Full analysis set, last observation carried forward.

1. Model includes treatment, continuous HbA_{1c}, creatinine clearance at baseline and background antidiabetes drugs. 2. Treatment difference after 52 weeks: –0.72 [95% CI –1.03, –0.41]; p<0.0001.

Source: McGill JB, et al. *Diabetes Care.* 2013;36:237–244.

Renal safety:Renal function is not affected by treatment with linagliptin[1]

Renal function	Renal function baseline[2]	Diabetes treatment	Renal function at end of trial[2]
Normal (GFR ≥ 80 mL/min) (n = 1,216)	120 ± 33	Linagliptin	119 ± 34
Mild impairment (GFR 50 to < 80 mL/min) (n = 314)	67 ± 8	Linagliptin	69 ± 13
Moderate impairment (GFR 30 to < 50 mL/min) (n = 27)	45 ± 5	Linagliptin	48 ± 8
Severe impairment (GFR ≤ 30 mL/min) (n = 68[3])	22 ± 6	Linagliptin	23 ± 8[4]

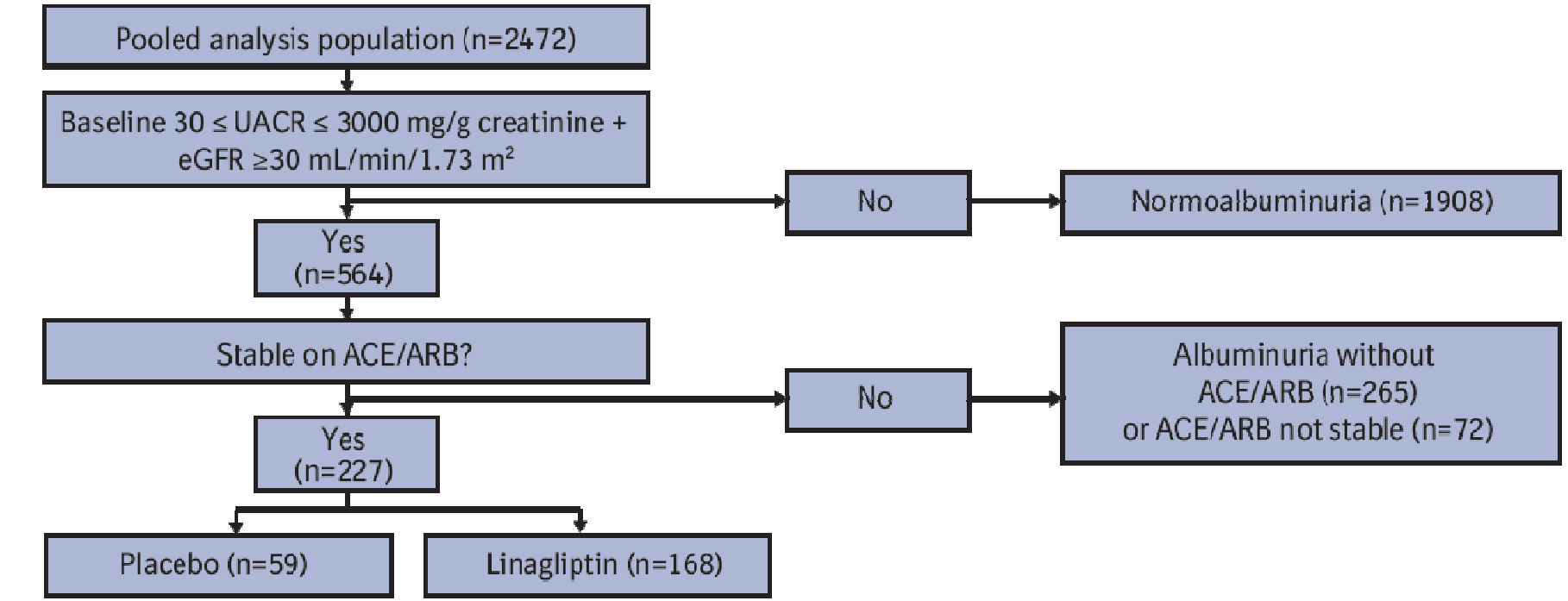


Mean GFR remains unchanged after treatment initiation with linagliptin up to 24 weeks

1. For fixed-dose combinations with metformin, similar contraindications and special precautions listed in metformin prescribing information apply; 2. Mean glomerular filtration rate (GFR) ± standard deviation (SD) according to Cockcroft–Gault in mL/min for normal, mild and moderate renal impairment (RI); mean GFR ± SD according to MDRD in mL/min for severe RI; 24 weeks' trial duration for normal, mild and moderate RI (pooled analysis of three Phase III trials), 12 weeks for severe RI; 3. Patients with severe RI at time of screening; 4. Median change in estimated (e)GFR from baseline was –0.8 and –2.2 mL/min/1.73m^2 for linagliptin and placebo, respectively. Source: Cooper M, et al. ADA 2011, Poster 1068-P; McGill JB, et al. *Diabetes Care.* 2012;36:237–244.

Study design

This was a pooled analysis of 4 Phase 3, randomized, double-blind, 24-week, placebo-controlled clinical trials of linagliptin 5 mg qd administered on a background of no, single, or dual oral glucose-lowering therapy in patients with T2DM



•Source: Groop PH, et al. ADA 2012 Poster: 953-P

Linagliptin significantly lowers albuminuria added to standard treatment for diabetic nephropathy

Albuminuria:

- Early marker for renal damage
- Marker for endothelial dysfunction
- Cardiovascular risk factor
- Lowering of albuminuria might be associated with kidney and cardiovascular protection

Definitions

Microalbuminuria

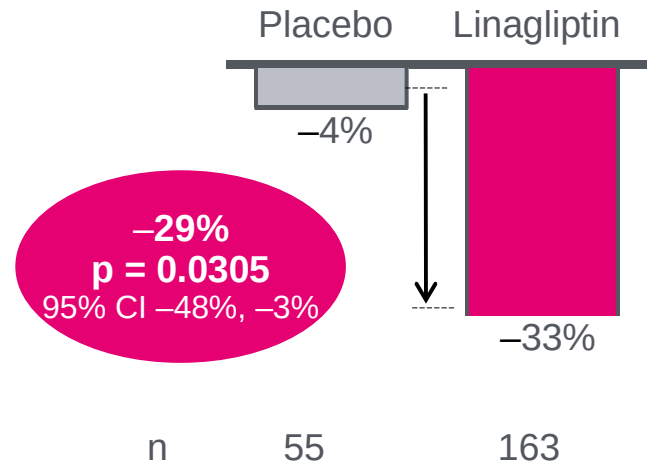
- UACR ≥ 30, < 300 mg/g creatinine

Macroalbuminuria

- UACR ≥ 300 mg/g creatinine

24 weeks' treatment
Effect of linagliptin on albuminuria in humans*

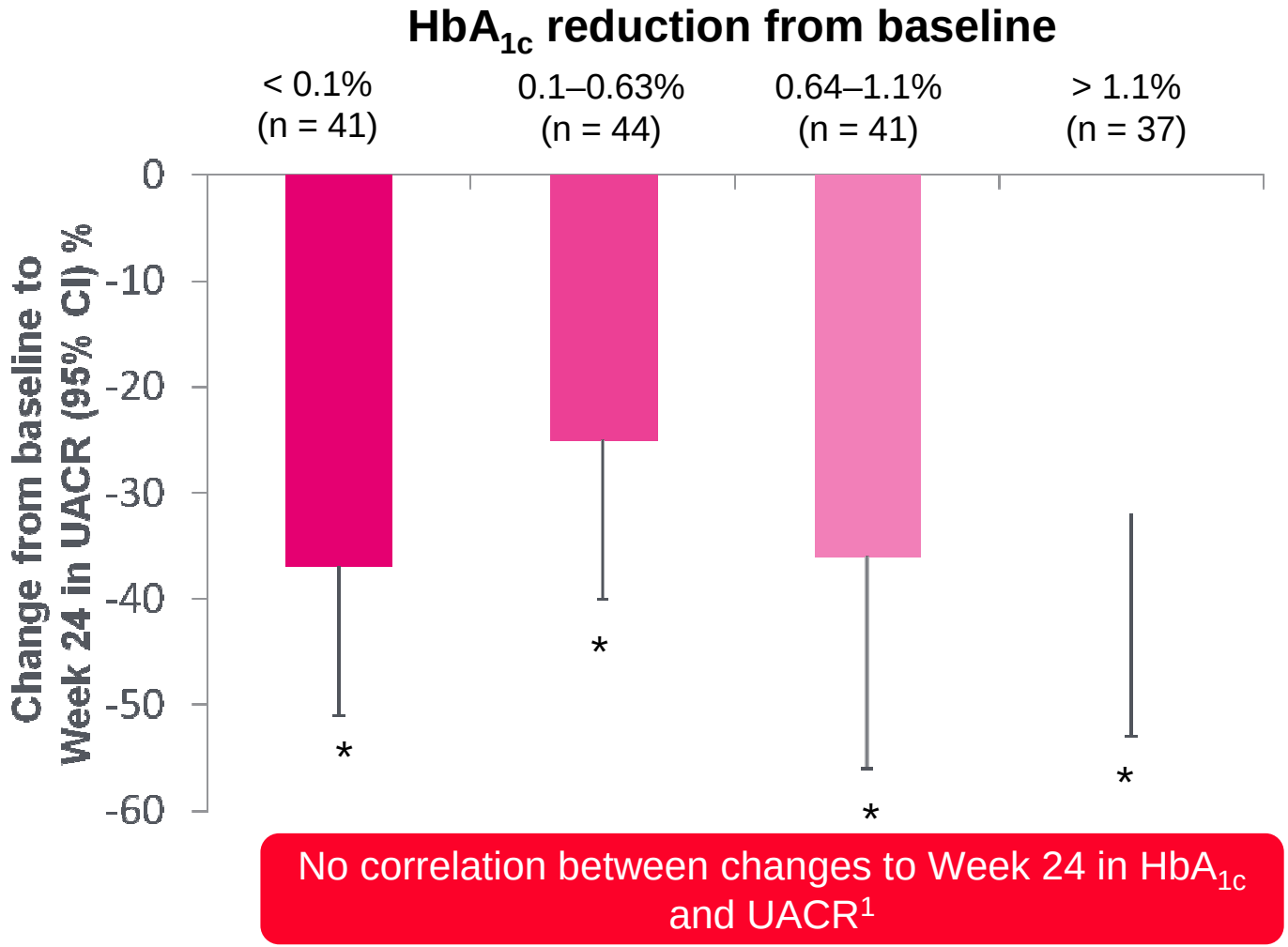
Adjusted mean change in albuminuria (24 weeks)[1]



–29% in albuminuria versus placebo after 24 weeks' treatment

1. Inclusion criteria: Stable ACE/ARB background; albuminuria 30–3000 mg/g creatinine; GFR > 30.
*MARLINA (1218.89) will aim to demonstrate albuminuria-lowering evidence for linagliptin.
Source: Groop P-H. EASD 2012, Oral presentation 06.

Albuminuria-lowering effects independent of HbA_{1c} reduction



No correlation between changes to Week 24 in HbA_{1c} and UACR[1]

* $p < 0.05$ versus baseline; includes all treated-set patients with a baseline and ≥1 on-treatment value for both HbA_{1c} and urine albumin-to-creatinine ratio (UACR). All patients (n = 218) Pearson's r = 0.073; Linagliptin-treated patients (n = 163) Pearson's r = 0.020.

Source: Groop P-H. EASD 2012, Oral presentation 06.

Potential Mechanism for reno-protective effect

- Linagliptin has vascular protective properties- vasodilation in aortic ring seen with Vildagliptin but not other DPP-4 inhibitors
- Also effects ROS and inflammation - anti inflammatory and anti-oxidative
- Diabetic mice model of nephropathy Linagliptin added to ARB reduces albuminuria, reduces levels of osteopontin
- Reduces glomerulosclerosis and renal oxidative stress as measured by accumulation of malondialdehyde and reduced TNF-alpha

Alter et al kidney Blood Press 2012 Sortino et al Frontiers in Endocrinology 2013

Linagliptin and Kidney Endpoints

•Objective:

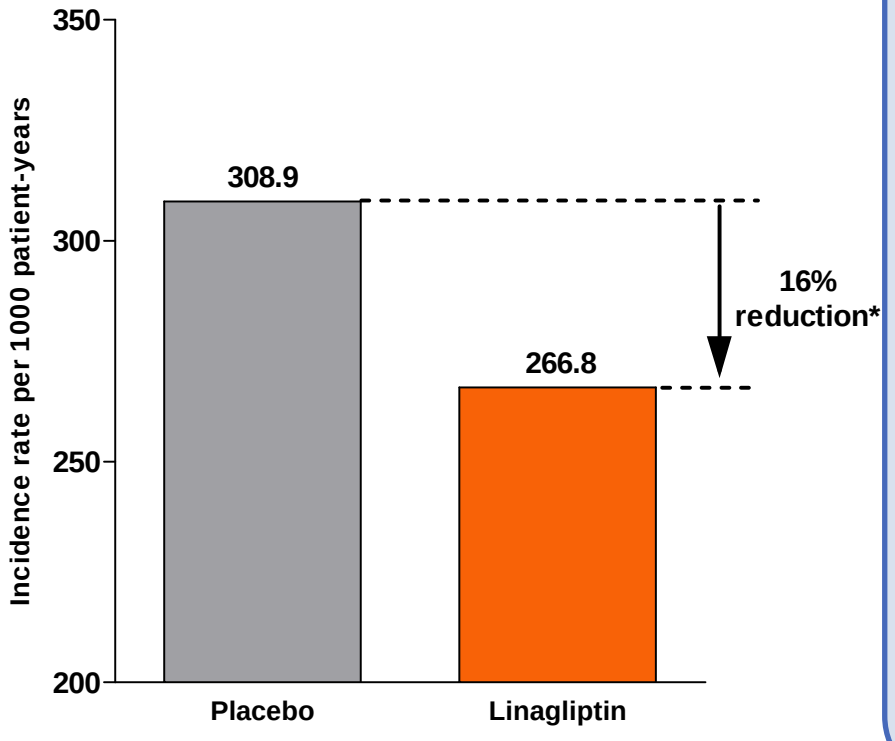
- To evaluate renal safety and outcomes with linagliptin in phase 3 studies≥12 weeks in trials across the global development program

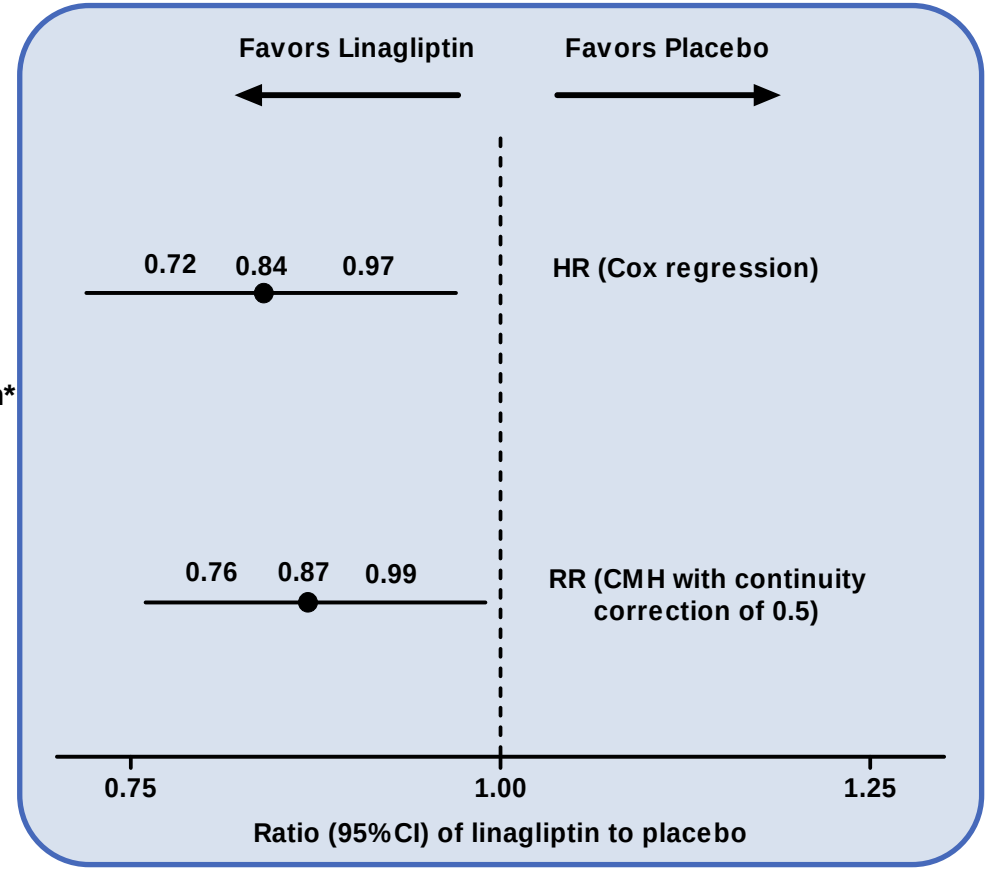
Study Endpoints:

- Predefined composite primary renal safety endpoint from 13 trials:
  - Microalbuminuria (first documented UACR ≥30 mg/g)
  - Macroalbuminuria (first documented UACR ≥300 mg/g)
  - CKD (first documented serum creatinine increase ≥2.83 mg/dL [250 µmol/L], at least 2 measurements)
  - Worsening of CKD (loss in eGFR >50% vs. baseline)*
  - Acute renal failure (based on standardized MedDRA query)
  - Death of any cause

Groop, EASD 2012

Primary Composite Renal Endpoint



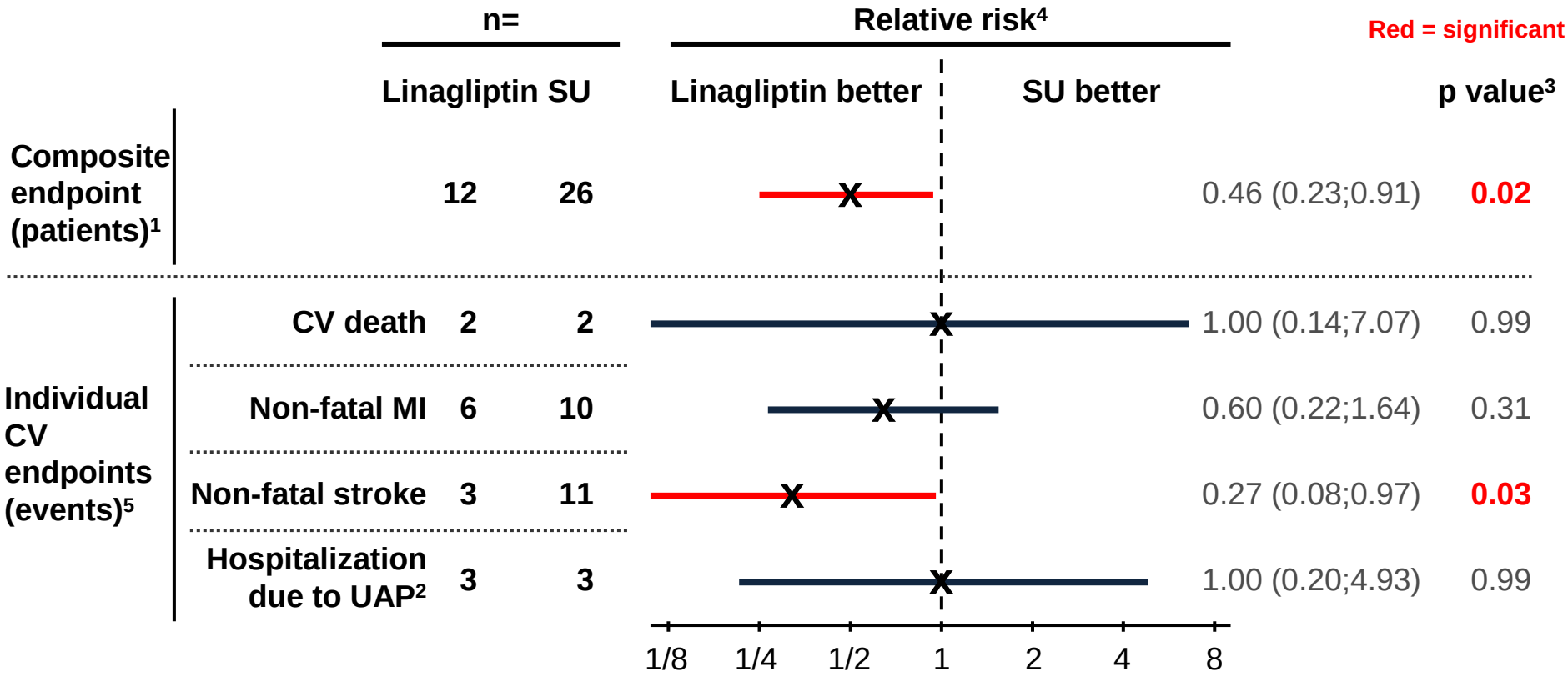


	Placebo	Linagliptin
Renal events	306	448
Time at risk, years	991	1679
Patients, n	1961	3505

*Significant reduction of 13–16% depending on statistical method applied

Significant relative risk reduction for CEC confirmed events for linagliptin compared to glimepiride

Linagliptin vs. glimepiride on metformin background over 2 years



Treated set: All events independently adjudicated by CEC, all endpoints pre-specified (also for individual studies) from CV-meta-analysis statistical plan. Patients may have suffered more than one individual CV endpoint event and therefore the number of patients reaching the composite end-point is less than the total number of events.

1. CV death, MI, stroke, hosp. due to unstable angina pectoris
2. UAP = Unstable angina pectoris
3. Chi-squared test
4. 2-sided 95% confidence interval on a logarithmic scale
5. Individual CV endpoints do not numerically add up to composite endpoint since a patient may experience more than one event

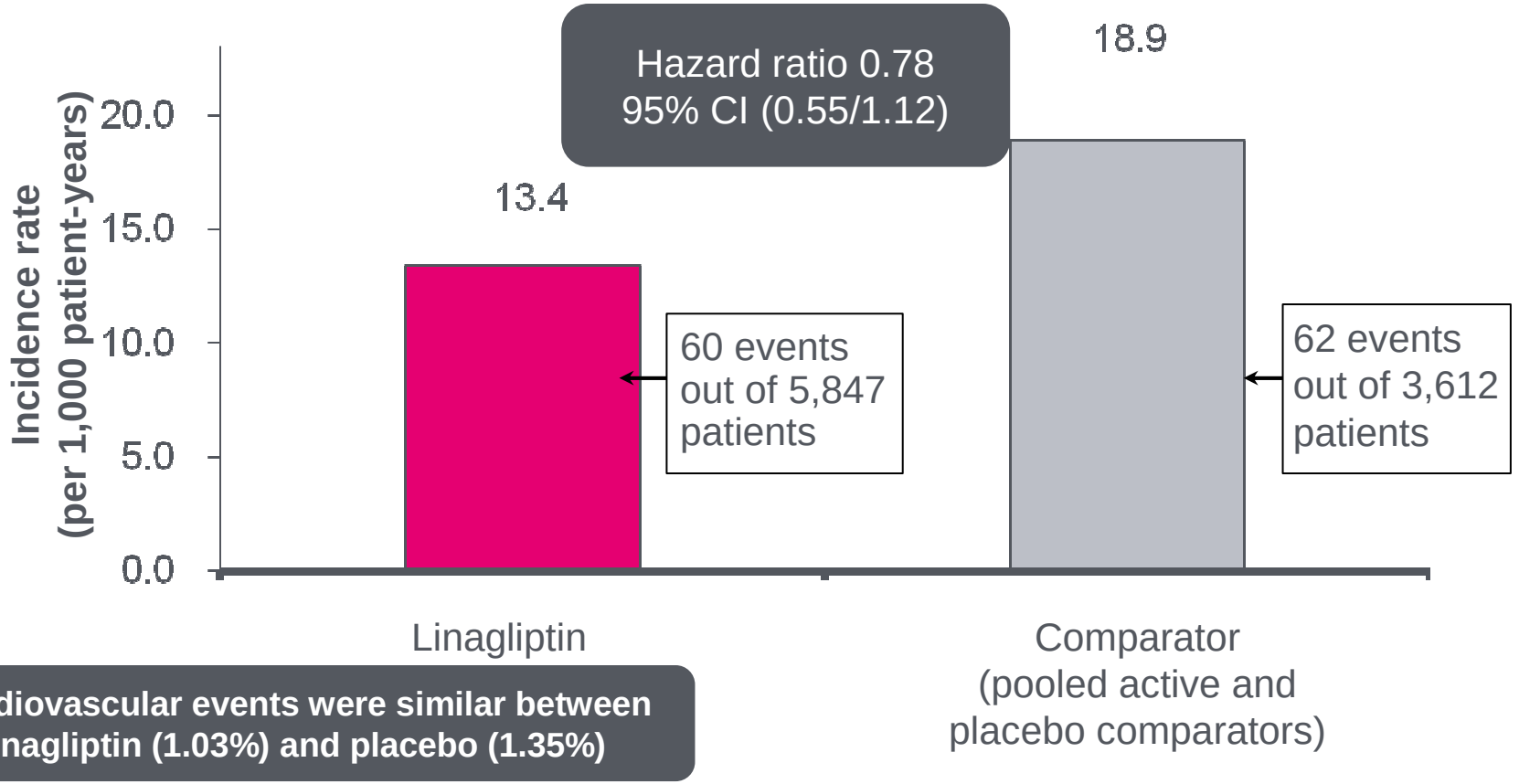
CEC = clinical events committee

Gallwitz B., et al. ADA 2011 Late Breaker 39-LB . Galllwitz et al Lancet 2012 ,;380,(9840):475 - 483,

In a prospective meta-analysis (19 trials), linagliptin and cardiovascular risk

Incidence rate of primary CV events[1]

Number and percentage of patients



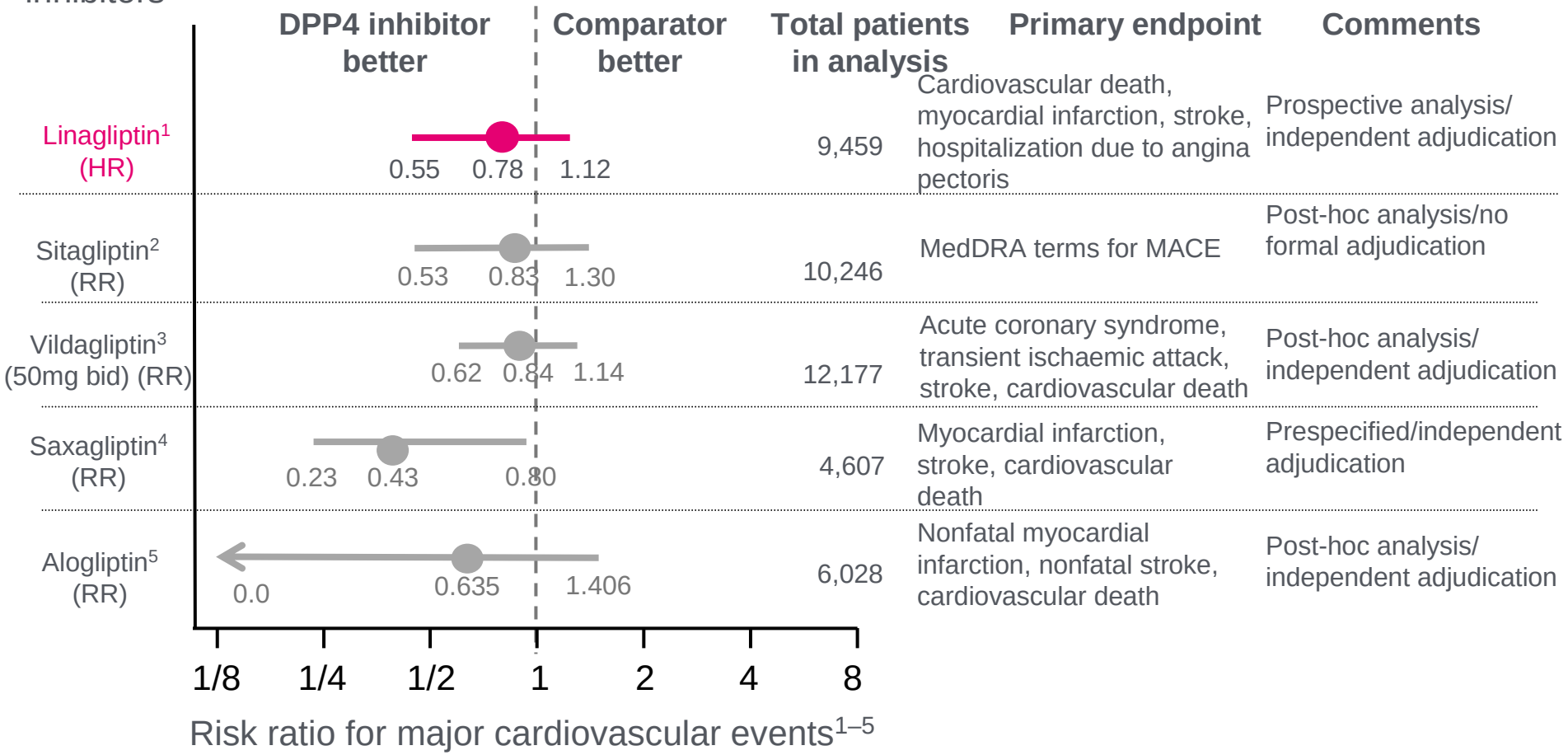
Cardiovascular events were similar between linagliptin (1.03%) and placebo (1.35%)

1. Primary endpoint, composite of: the occurrence or time to first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina.

Source: Trajenta® EU summary of product characteristics

DPP4 compounds and CVD

No increased risk of cardiovascular events was observed in patients randomly treated with DPP4 inhibitors



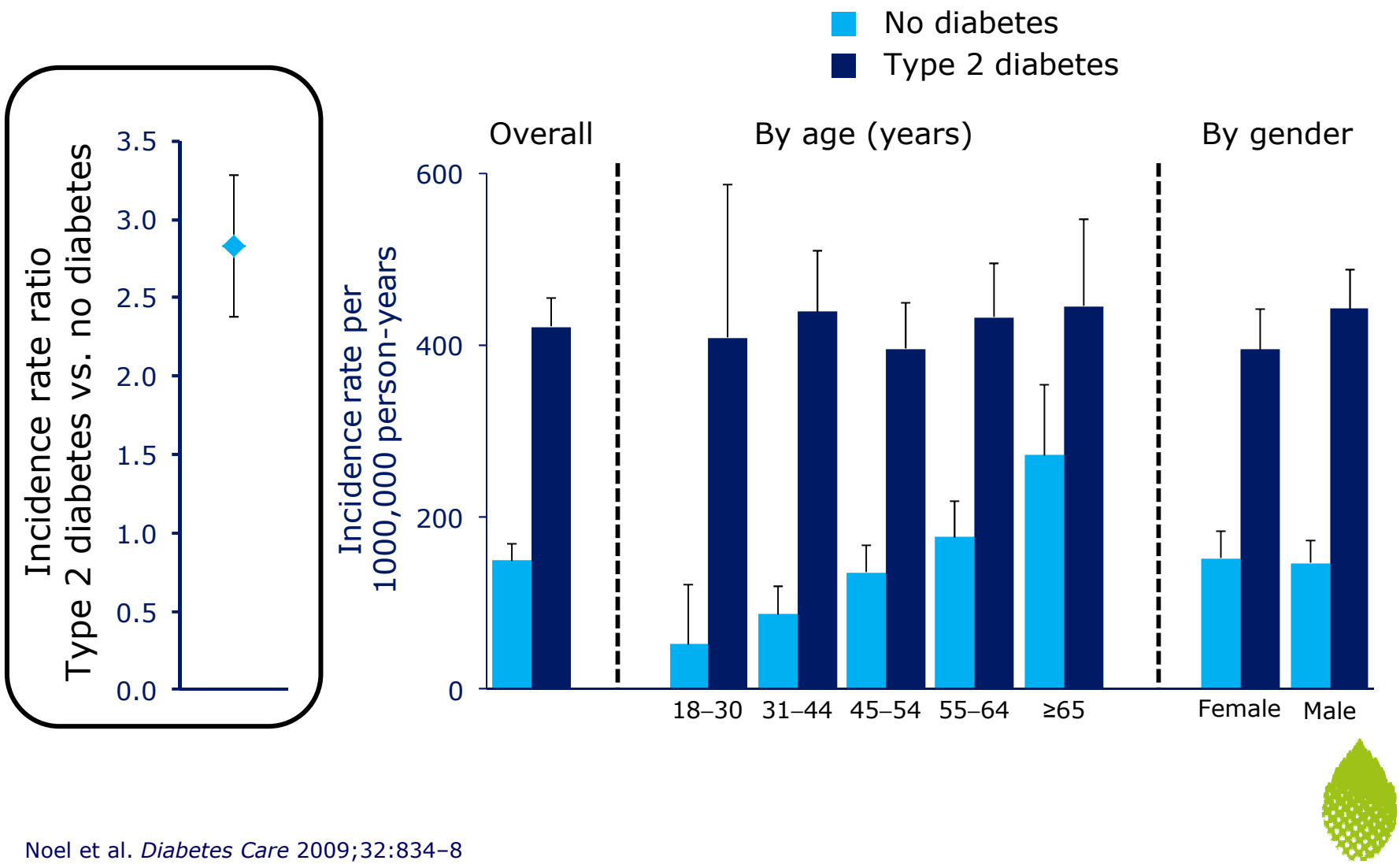
Source: 1. Trajenta EU SmPC; 2. Engel SS, et al. *Cardiovasc Diabetol.* 2013;12:3; doi: 10.1186/1475-2840-12-3; 3. Schweizer A, et al. *Diabetes Obes Metab*. 2010;12:485–494; 4 Frederich R, et al. *Postgrad Med.* 2010;122:16–27; 5. White WB, et al. *Diabetes Obes Metab.* 2013 Mar 12. doi: 10.1111/dom.12093. [Epub ahead of print]

Long-term CV studies of DPP-4is and GLP-1 RAs will also adjudicate cases of pancreatitis

Trial	Drug	Approximate study duration	Estimated enrolment (n)	Estimated year of completion
LEADER	Liraglutide	5 years	9341	2016
EXSCEL	Exenatide ER	5.5 years	9500	2017
ELIXA	Lixisenatide	Accumulation of ~844 CV events	6000	2014
REWIND	Dulaglutide	6.5 years	9600	2019
TECOS	Sitagliptin	Accumulation of 1,300 primary CV events	14000	2014
Savor-TIMI 53 **	Saxagliptin	4 years	12000	2015
CAROLINA	Linagliptin	7.7 years	6000	2018
EXAMINE **	Alogliptin	4.75 years	5400	2014

CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; RA, receptor agonist
Data compiled from clinicaltrials.gov

Incidence of acute pancreatitis in patients with and without type 2 diabetes



Noel et al. *Diabetes Care* 2009;32:834–8

Marketed Use of GLP-1-based Therapies: Pancreatitis Risk?

- Several large claims database studies have found no association between pancreatitis and exenatide and sitagliptin use in >1,000,000 patients

  - Garg et al. *Diabetes Care* 2010
  - Pendergrass et al. *Diabetes* 2010
  - Dore et al. *Curr Med Res Opin* 2009
  - Wenten et al. *Diabetes* 2010
  - Dore et al. *Diabetes Obes Metab* 2011
  - Romley et al. *Diab Techn Ther* 2012

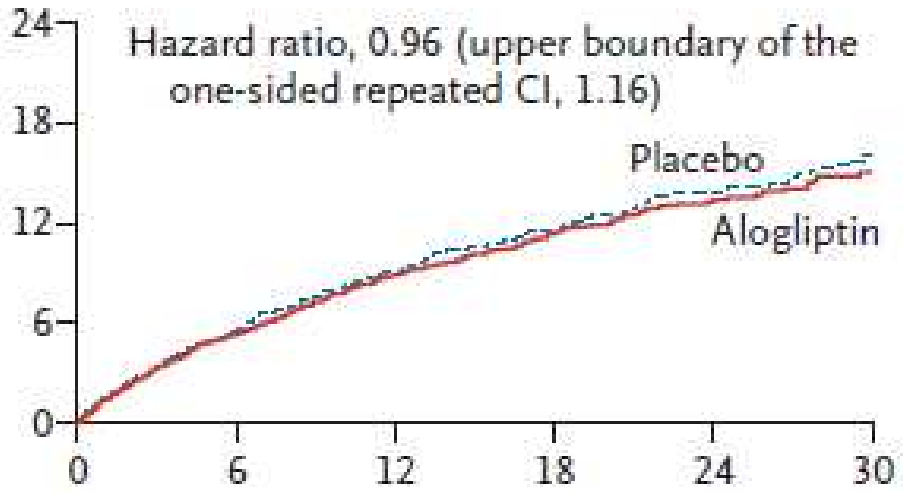
Garg et al. *Diabetes Care* 2010;33:2349–54; Pendergrass et al. *Diabetes* 2010;59(Suppl. 1):A160 (587-P);
Dore et al. *Curr Med Res Opin* 2009;25:1019–27; Wenten et al. *Diabetes* 2010;59(Suppl. 1):A163 (596-P);
Dore et al. *Diabetes Obes Metab* 2011;13:559–66; Romley et al. *Diab Techn Ther* 2012;DOI: 10.1089/dia.2012.0075

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*



Non-inferiority Trial
50% SU in both groups
No diff in Pancreatic Ca or pancreatitis

N Engl J Med 2013 DOI:10.1056/NEJMoa1305889

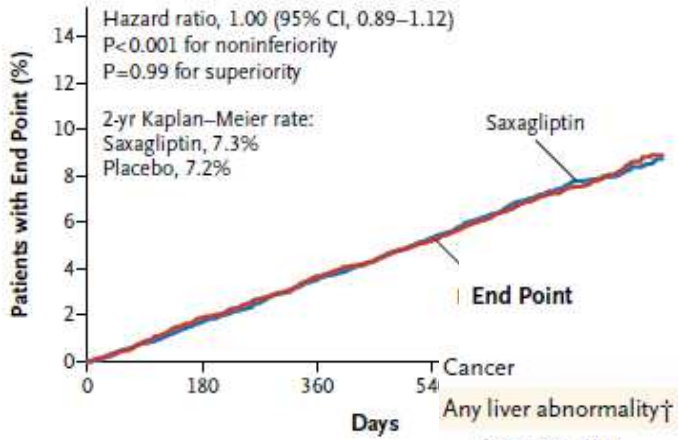
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mozenson, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

A Primary End Point

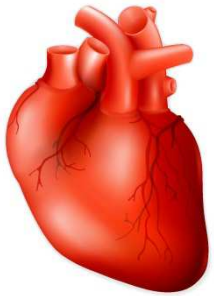


Superiority trial
Increased hypoglycaemia

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	P Value*
	no. (%)		
Cancer	327 (3.9)	362 (4.4)	0.15
Any liver abnormality†	55 (0.7)	67 (0.8)	0.28
AST >3× ULN	60 (0.7)	61 (0.7)	0.93
AST >10× ULN	12 (0.1)	15 (0.2)	0.57
ALT or AST >3× ULN and total bilirubin >2× ULN	13 (0.2)	23 (0.3)	0.097
Any pancreatitis†	24 (0.3)	21 (0.3)	0.77
Acute: definite or possible	22 (0.3)	16 (0.2)	0.42
Acute: definite	17 (0.2)	9 (0.1)	0.17
Acute: possible	6 (0.1)	7 (0.1)	0.79
Chronic	2 (<0.1)	6 (0.1)	0.18

N Engl J Med 2013 DOI:10.1056/NEJMoa1307684

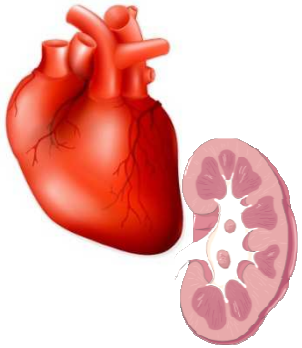
Long-term cardiovascular outcome trials



CAROLINA

Cardi**o**vascular safety of **Lina**gliptin or glimepiride in subjects with Type 2 Diabetes Mellitus at high cardiovascular risk

Linagliptin versus glimepiride as add-on to metformin



CARMELINA

CArdiovascular Safety and **R**enal **M**icrovascular outcom**E** study with **LINA**gliptin in patients with Type 2 Diabetes Mellitus at high vascular risk[1]

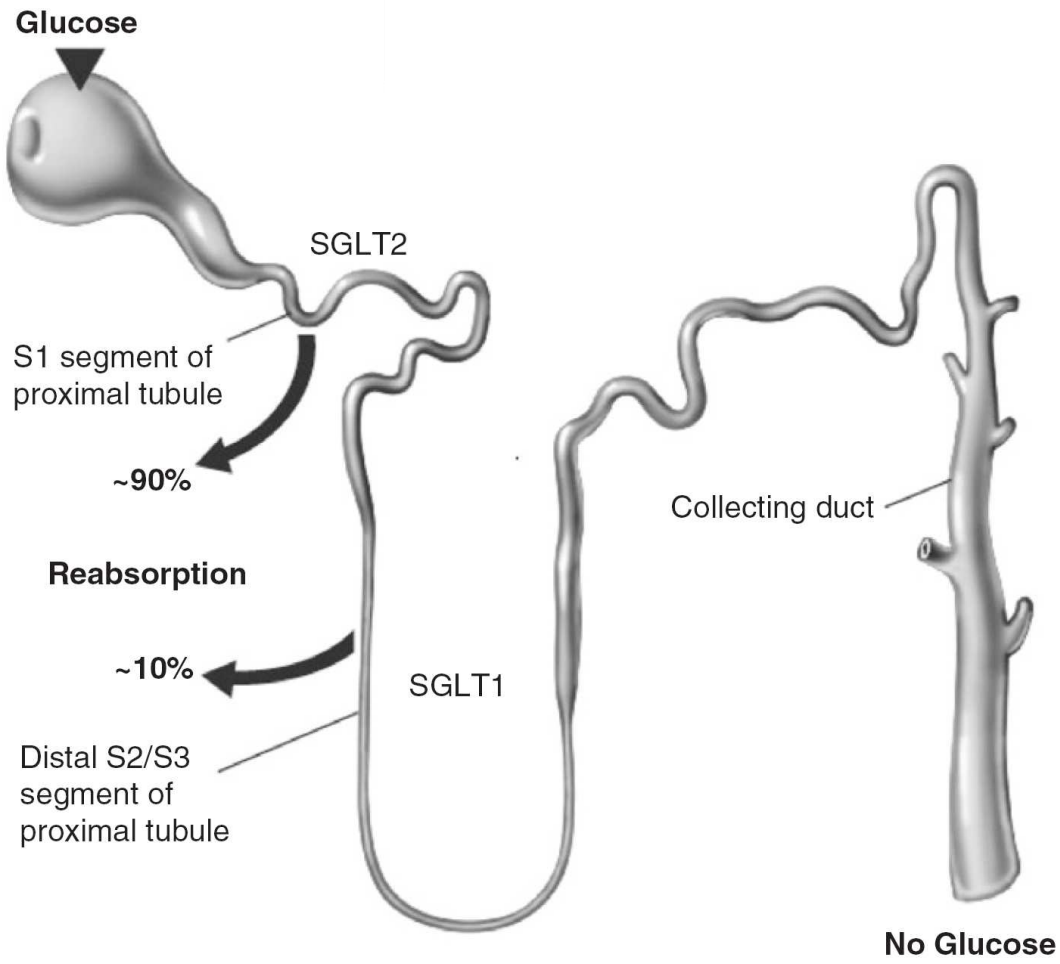
Linagliptin versus placebo on top of standard of care

1. Draft title, study protocol subject of FDA review.

Outline

- The treatment algorithm for diabetes
- Clinical data with DPP-4 inhibitors and Linagliptin
- Clinical Data with the SGLT2 inhibitors
- Summary

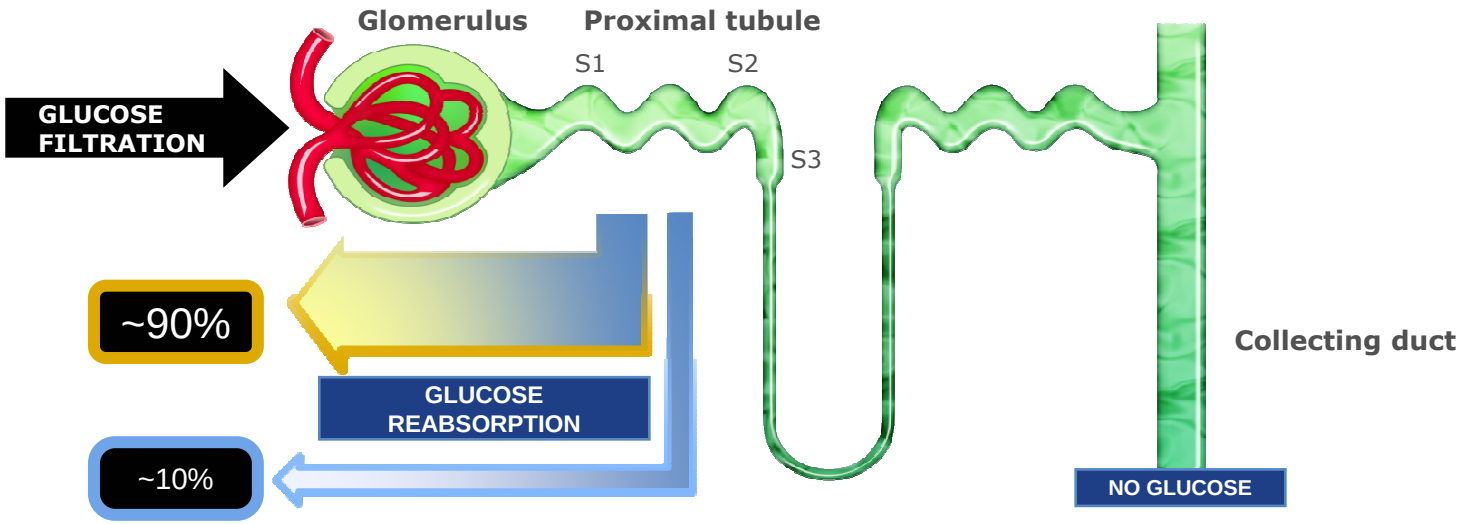
Glucose Transporters in the Renal Proximal Tubule



- Volume of plasma filtered daily = 180 L
- Normal glucose filtered daily =180 g
- Maximal reabsorptive capacity = 375 mg/min
- Normal subjects – no glycosuria
- Hyperglycaemia increases SGLT2 expression and absorption capacity

Bays H. CMRO. 2009;25:671-681.

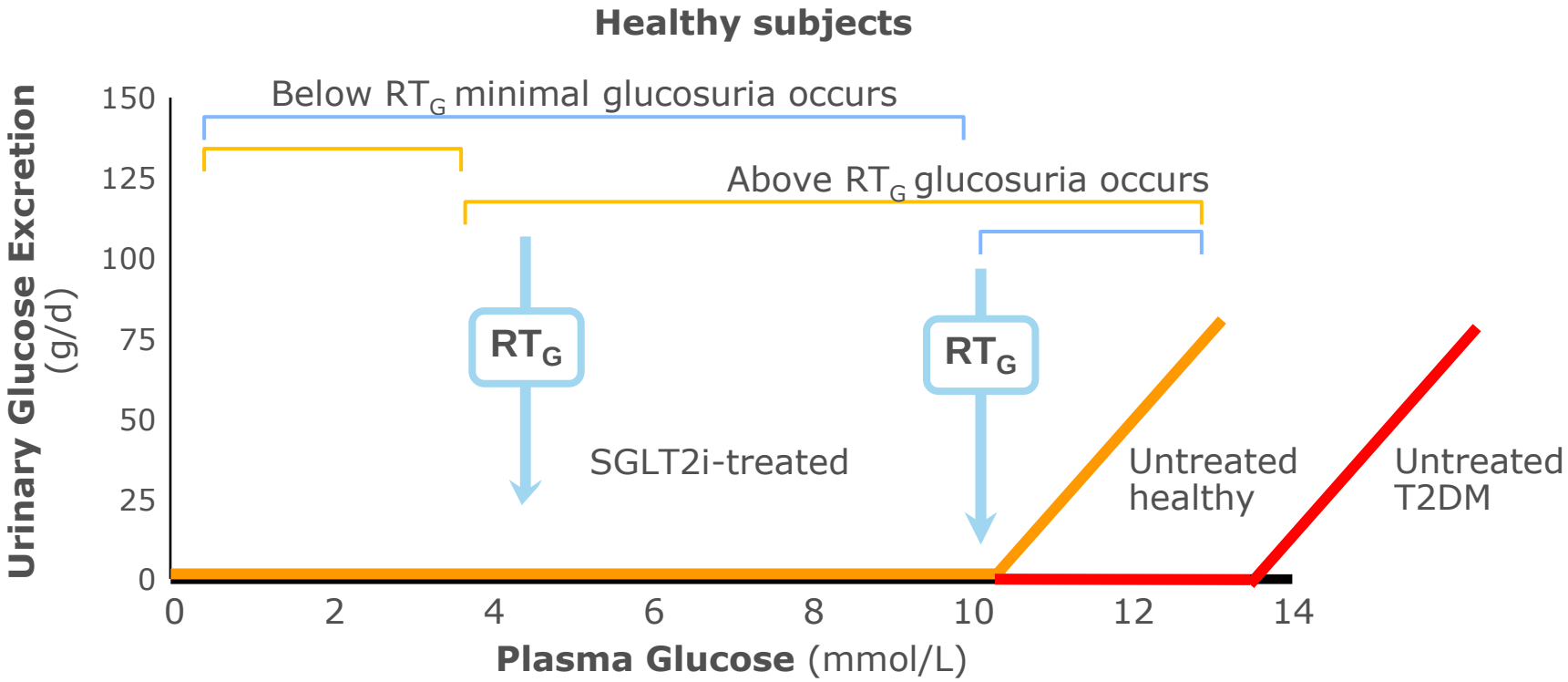
Renal Glucose Reabsorption in the Proximal Tubule



- Up to 180 g glucose filtered/24 h[2]. Almost all filtered glucose is reabsorbed until the filtered load exceeds the glucose resorptive capacity[1,2]
- The plasma glucose concentration at which renal resorptive capacity is exceeded and urinary glucose excretion (UGE) ensues is called the renal threshold for glucose (RT_G)[1,2]
- Renal glucose resorptive capacity is increased in type 2 diabetes mellitus (T2DM), contributing to the worsening of hyperglycemia[1-3]

1. Ruhnau B. et al. Diabetes Res Clin Pract 1997; 36: 27–33. 2. DeFronzo R. *Diabetes*. 2009;58(4):773-795.
3. Polidori D. et al. Poster presented at IDF, 2011 (D-0992).

SGLT2 Inhibition Lowers RT_G



SGLT2 inhibition lowers RTG

Appreciable UGE occurs only when plasma glucose exceeds RTG

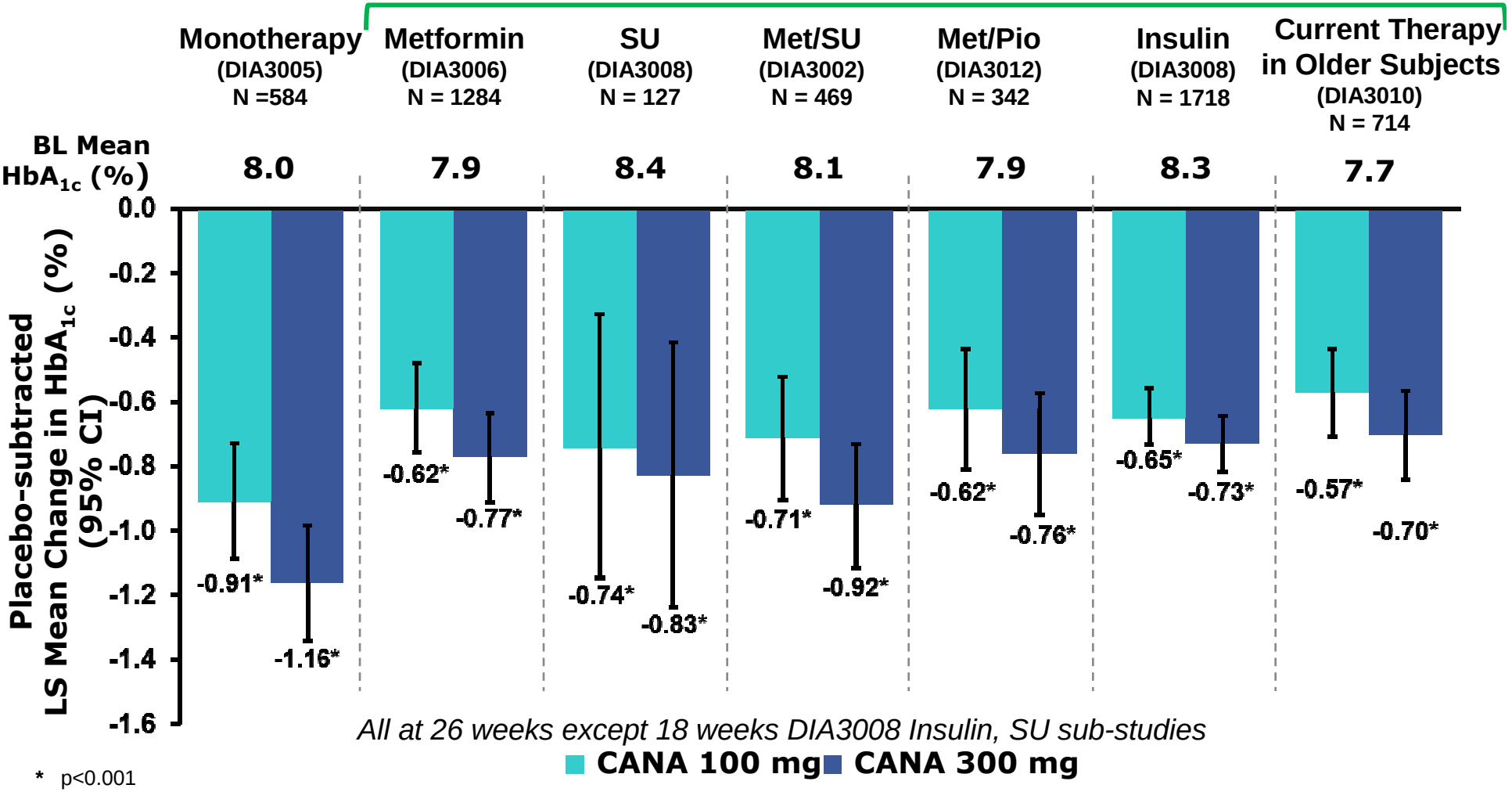
SGLT2, sodium glucose co-transporter 2; RTG, renal threshold for glucose excretion; UGE, urinary glucose excretion.

Polidori D et al. 2010. Abstract 2186-PO. *Presented at: American Diabetes Association*. ADA 2010.

Polidori D et al. 2010. Abstract 875. *Presented at: European Association for the Study of Diabetes*. EASD 2010.

HbA_{1c} : Placebo-controlled Phase 3 Studies

Add-on Combinations with



All at 26 weeks except 18 weeks DIA3008 Insulin, SU sub-studies

CANA 100 mg **CANA 300 mg**

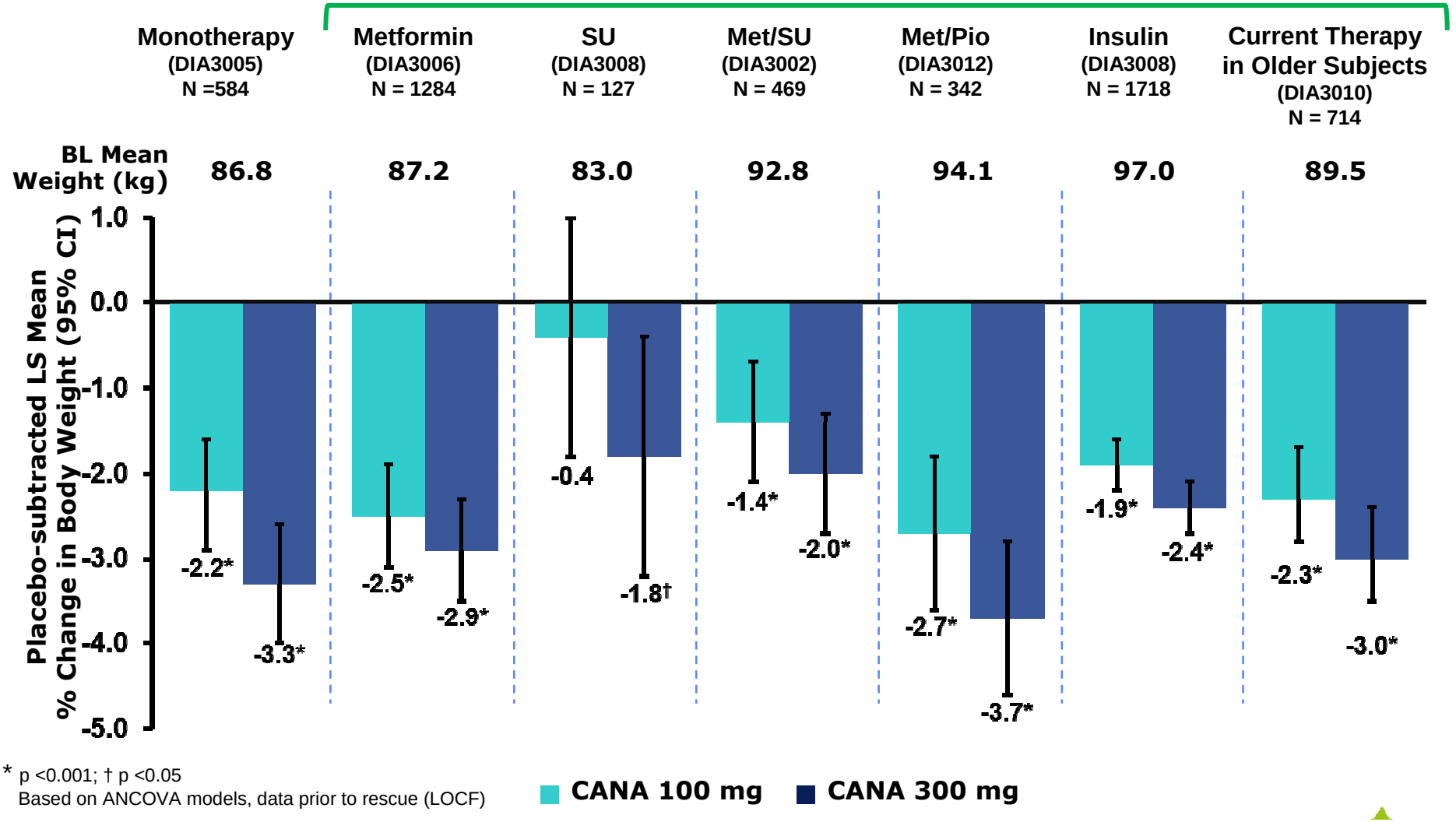
* p<0.001

Based on ANCOVA models, data prior to rescue (LOCF)

Stenlof et al. Diabetes Obes Metab. 2013;15(4):372-82.
Lavalle-González FJ et al. Diabetologia. 2013 Sep 13. [Epub ahead of print]
Wilding JP et al. Int J Clin Pract. 2013 Oct 13. [Epub ahead of print]
Matthews D. et al. Poster presented at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (P764).
Bode B et al. Hosp Pract. 2013;41(2):72-84.
Forst T et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P64).
Fulcher G et al. Poster presented at the 73rd Scientific sessions of the American Diabetes Association (ADA), 2013; Jun. 21-25; Chicago, Illinois, (P1124).

Body Weight % Change from Baseline
Placebo-controlled Phase 3 Studies

Add-on combinations with



* p <0.001; † p <0.05
Based on ANCOVA models, data prior to rescue (LOCF)

Stenlof et al. Diabetes Obes Metab. 2013;15(4):372-82.
Lavalle-González FJ et al. Diabetologia. 2013 Sep 13. [Epub ahead of print]
Wilding JP et al. Int J Clin Pract. 2013 Oct 13. [Epub ahead of print]
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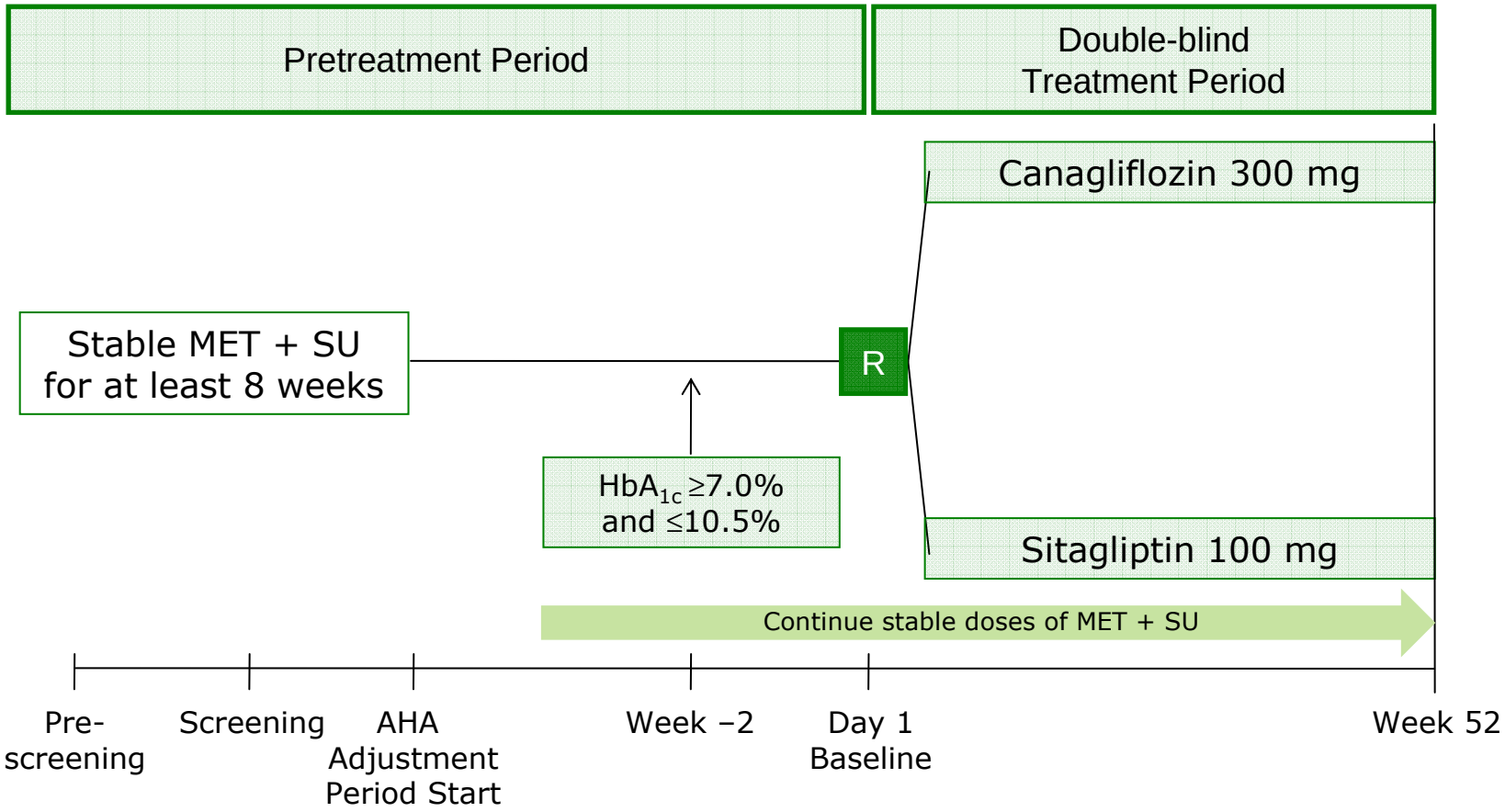
Fulcher G et al. Poster presented at the 73rd Scientific sessions of the American Diabetes Association (ADA), 2013; Jun. 21-25; Chicago, Illinois, (P1124).

Add-on to MET + SU :
Canagliflozin vs Sitagliptin Study Design



Schernthaner G. et al. Data presentation at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (OP43)
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

Schernthaner G etal, Diabetes Care 36:2508-2515, 2013

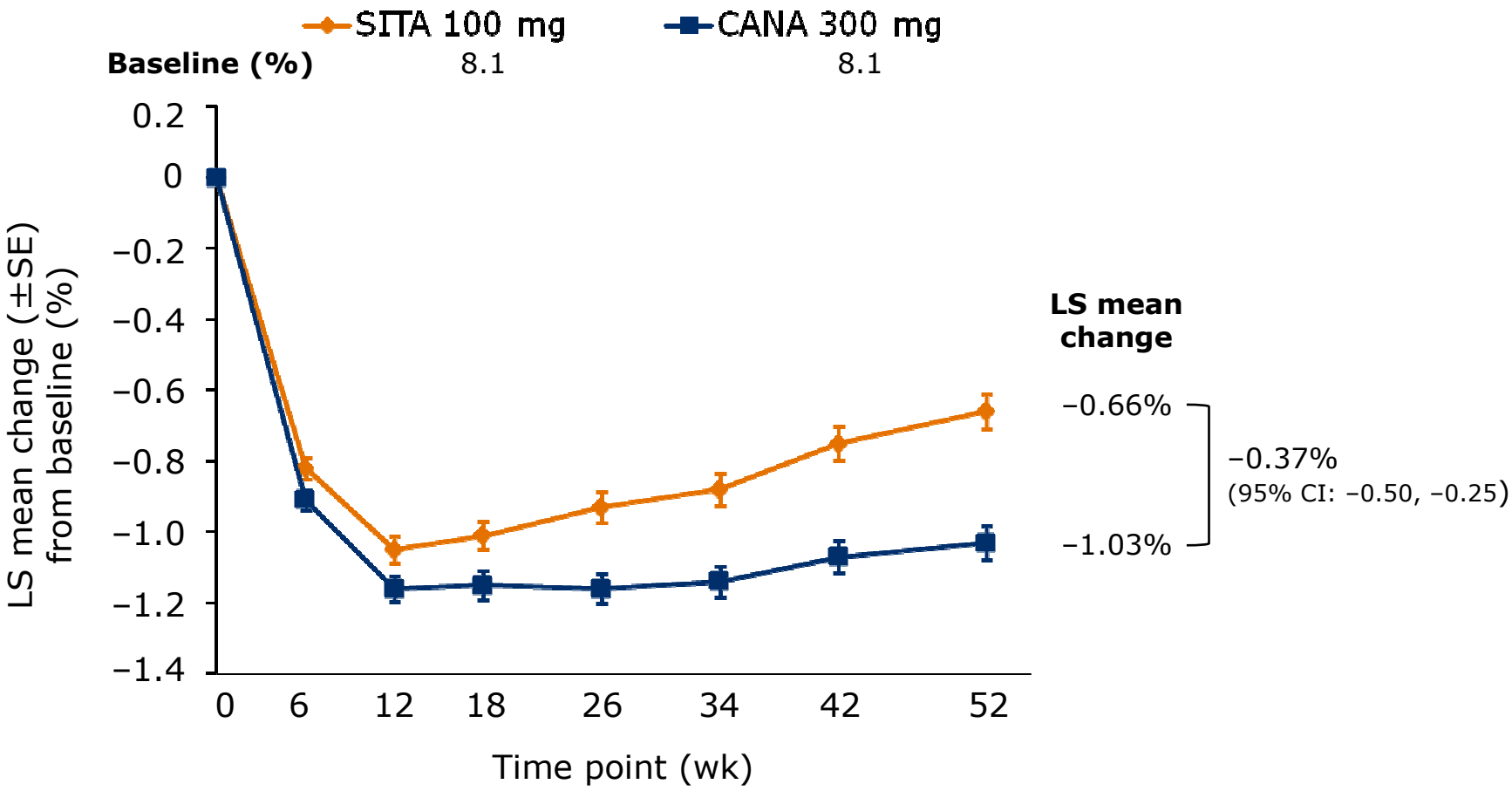
Baseline Characteristics

Characteristic	SITA 100 mg (n = 378)	CANA 300 mg (n = 377)	Total (N = 755)
Sex, n (%)			
Male	215 (56.9)	207 (54.9)	422 (55.9)
Female	163 (43.1)	170 (45.1)	333 (44.1)
Mean (SD) age, y	56.7 (9.3)	56.6 (9.6)	56.7 (9.5)
Race, n (%)			
White	240 (63.5)	245 (65.0)	485 (64.2)
Black or African American	45 (11.9)	43 (11.4)	88 (11.7)
Asian	65 (17.2)	67 (17.8)	132 (17.5)
Other*	28 (7.4)	22 (5.8)	50 (6.6)
Mean (SD) HbA_{1c}, %	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
Mean (SD) FPG, mmol/L	9.2 (2.5)	9.4 (2.6)	9.3 (2.6)
Mean (SD) body weight, kg	89.1 (23.2)	87.4 (23.2)	88.3 (23.2)
Mean (SD) BMI, kg/m^2	31.7 (6.9)	31.5 (6.9)	31.6 (6.9)
Mean (SD) T2DM duration, y	9.7 (6.3)	9.4 (6.1)	9.6 (6.2)

SITA, sitagliptin; CANA, canagliflozin; SD, standard deviation; FPG, fasting plasma glucose; BMI, body mass index; T2DM, type 2 diabetes mellitus.
*Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Schernthaner G. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P70).
Schernthaner G. et al. Data presentation at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (OP43)
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

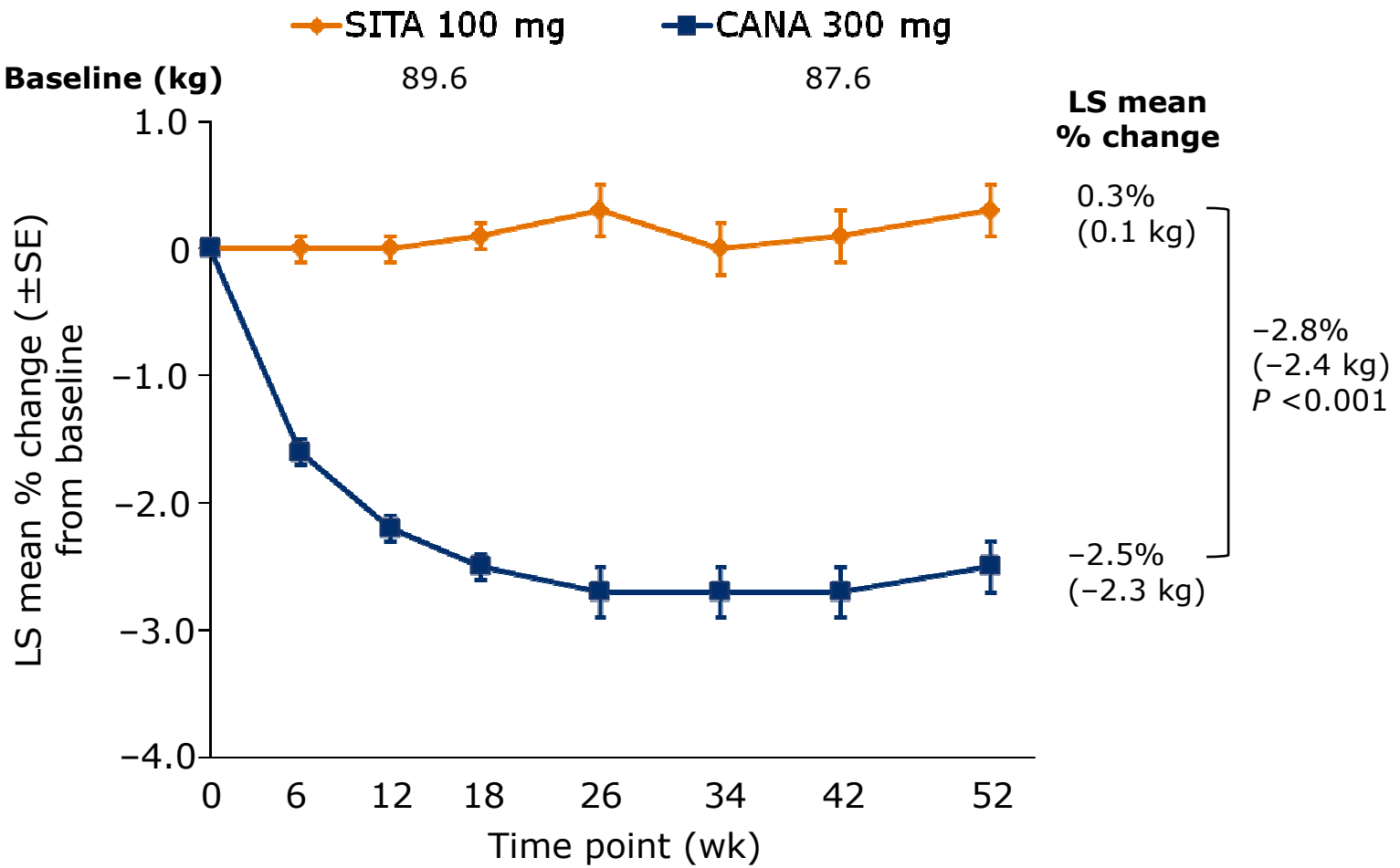
Change in HbA_{1c} (LOCF)



LOCF, last observation carried forward ; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

Schernthaner G. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P70).
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

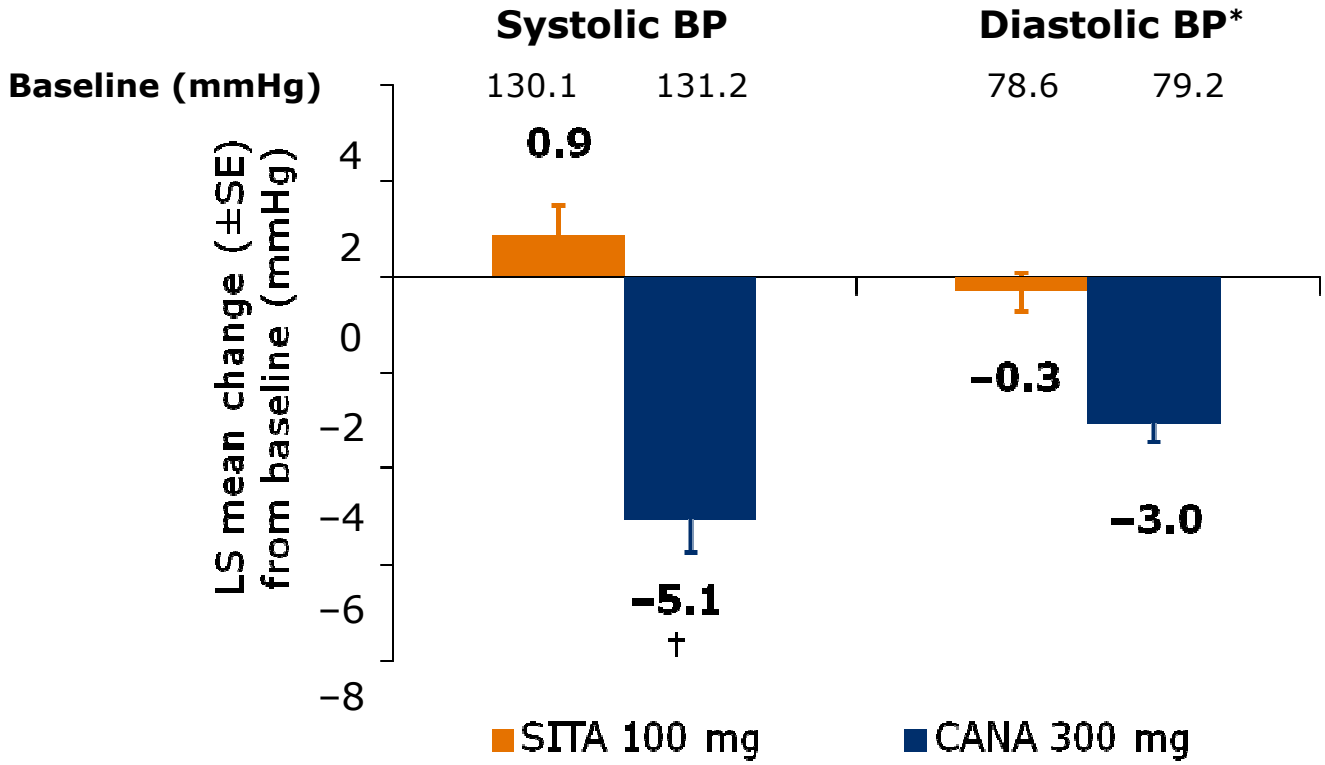
%Change in Body Weight (LOCF)



LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error.

Schernthaner G. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P70).
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

Change in BP at Week 52 (LOCF)



- Mean change from baseline in heart rate with CANA versus SITA was −0.1 and 0.7 beats/min, respectively

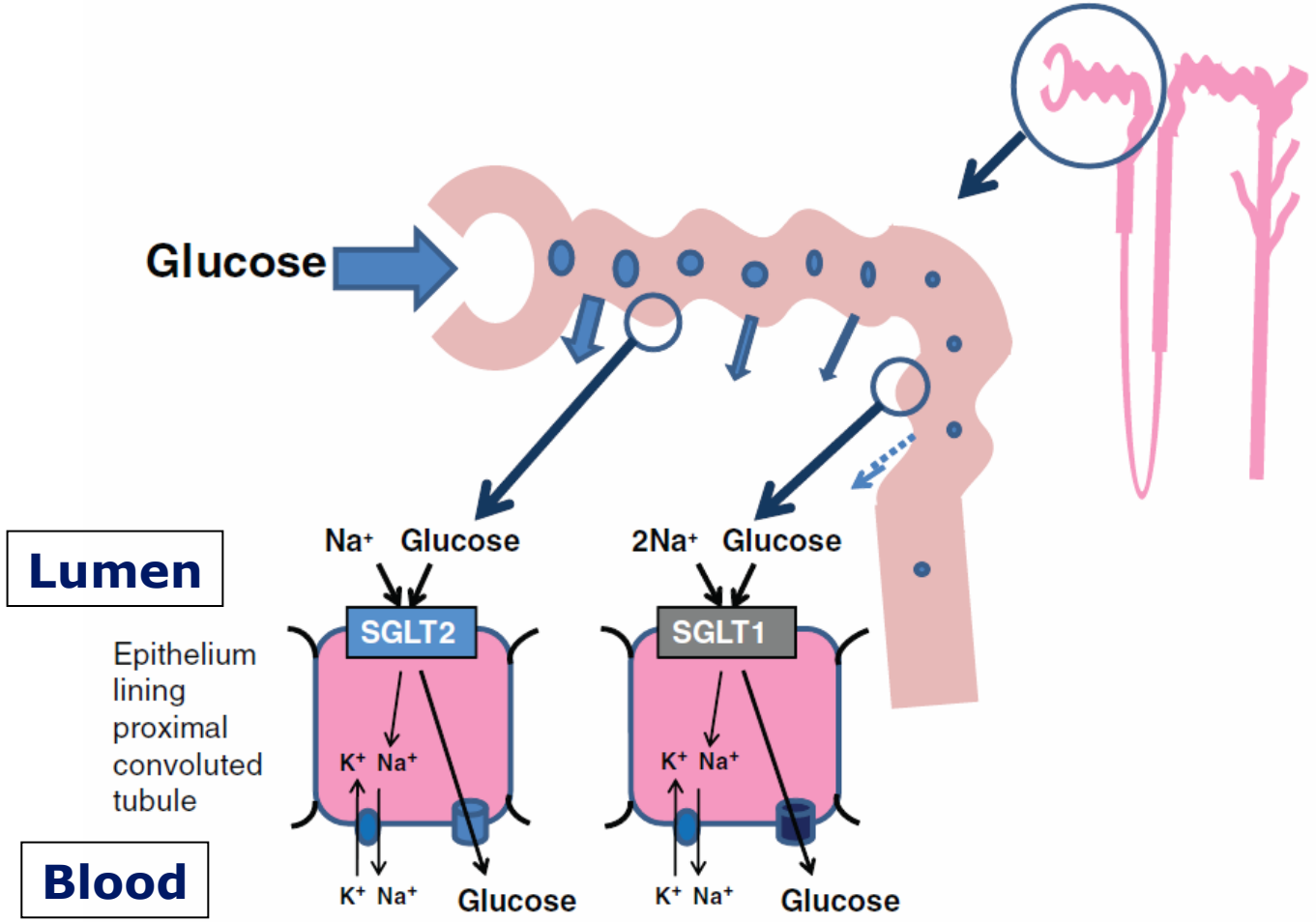
*Statistical comparison for CANA 300 mg vs SITA 100 mg not performed (not pre-specified).
†*P* <0.001 vs SITA 100 mg.

BP, blood pressure; LOCF, last observation carried forward; LS, least squares; SE, standard error; SITA, sitagliptin; CANA, canagliflozin.

Schernthaner G. et al. Data presentation at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (OP43)
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

SGLT2 Inhibitors: Indirect Effects on Glucose Metabolism

- **SGLT2 inhibitors increase glycosuria to reduce hyperglycaemia**



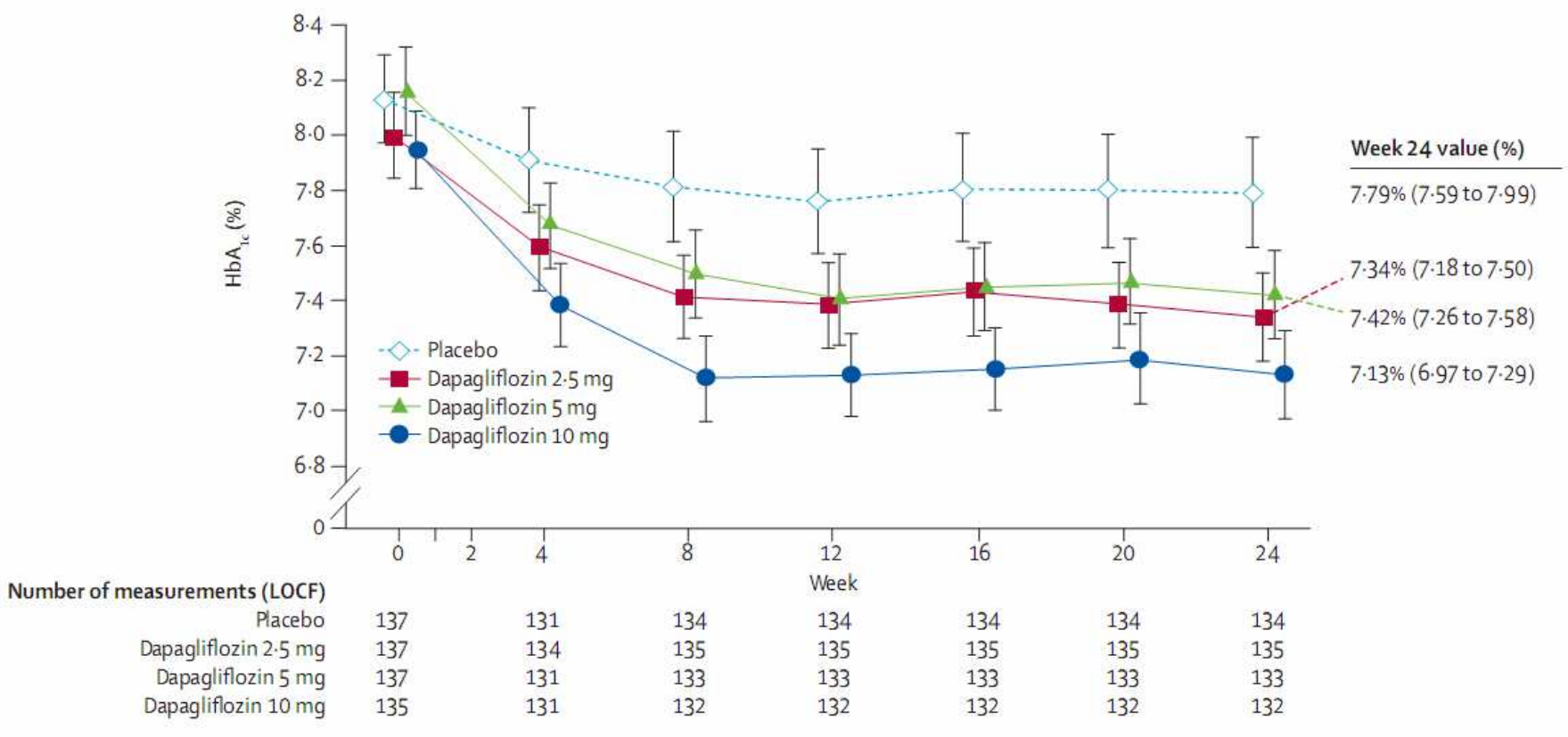
SGLT1, sodium glucose co-transporter 1; SGLT2, sodium glucose co-transporter 2.
Figure adapted from Bailey et al. *Br J Diabetes Vasc Dis.* 2010;10:193–199.

Dapagliflozin

- 24 week study – Dapa added to insulin in people with T2DM, baseline HbA1c 8.5% MDD 77IU
- Placebo subtracted ↓ HbA1c 2.5 – 10 mg dose 1- 1.7%
- Wt. ↓1- 1.7Kg
- IDD ↓ 5- 7IU
- Discontinuation rates similar in both groups, more UG symptoms in Dapa group
- Small ↓in SBP – no orthostatic hypotension

Wilding JP et al 78 OR Diabetes Suppl1, 2010 A21

Change from baseline in HbA1c

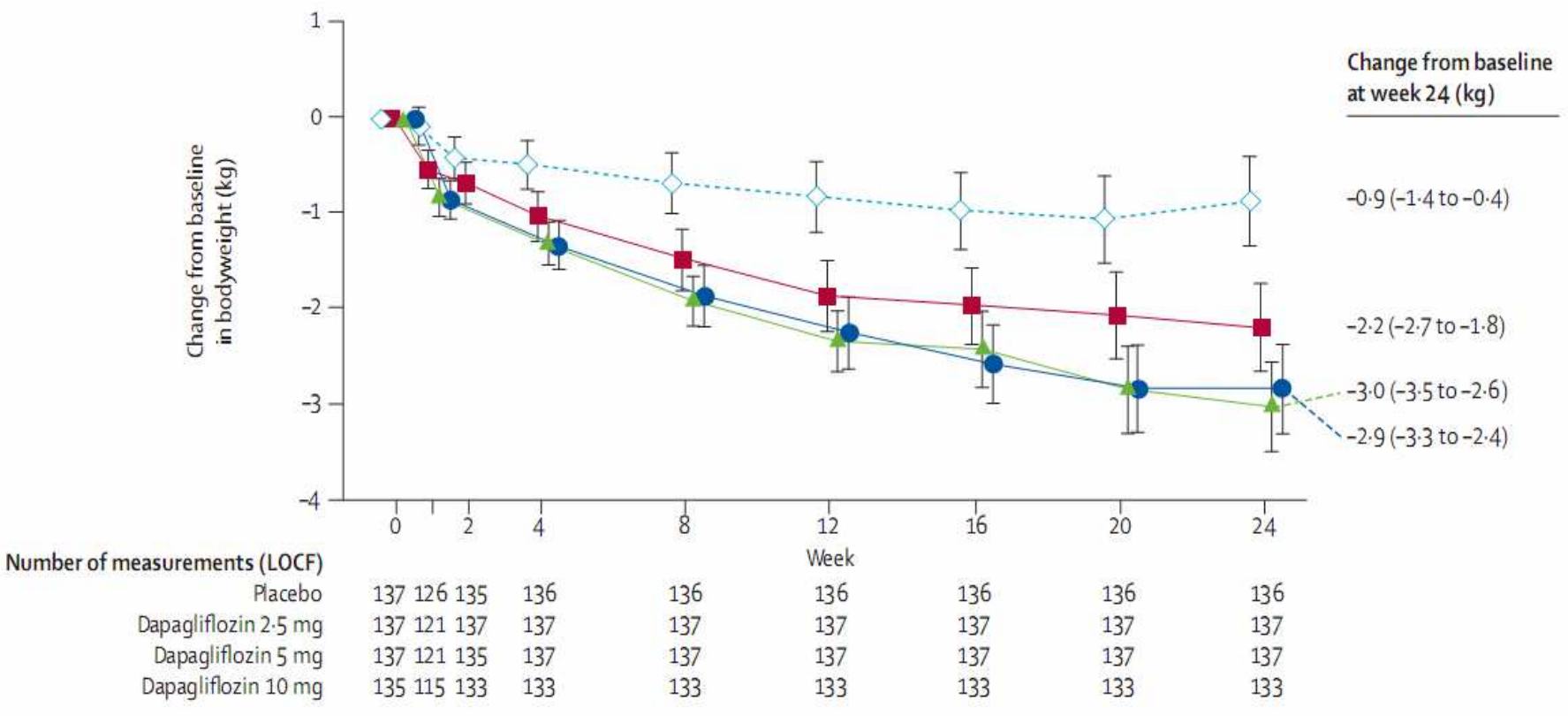


Number of measurements (LOCF)							
Placebo	137	131	134	134	134	134	134
Dapagliflozin 2·5 mg	137	134	135	135	135	135	135
Dapagliflozin 5 mg	137	131	133	133	133	133	133
Dapagliflozin 10 mg	135	131	132	132	132	132	132

Statistically significant reductions at week 24 from baseline in all groups vs pbo:

- Dapa 2.5 mg: -0.67%
- Dapa 5 mg: -0.70%
- Dapa 10 mg: -0.84%

Change from baseline in weight



Statistically significant reductions at week 24 from baseline in all groups vs pbo:

- Dapa 2.5 mg: -2.2kg
- Dapa 5 mg: -3.0kg
- Dapa 10 mg: -2.9kg

Adverse events

	Placebo group (n=137)	Dapagliflozin 2·5 mg group (n=137)	Dapagliflozin 5 mg group (n=137)	Dapagliflozin 10 mg group (n=135)
One or more adverse event	88 (64%)	89 (65%)	95 (69%)	98 (73%)
One or more drug-related adverse event*	22 (16%)	22 (16%)	25 (18%)	31 (23%)
Adverse event leading to discontinuation	5 (4%)	3 (2%)	3 (2%)	4 (3%)
One or more serious adverse event†	5 (4%)	4 (3%)	4 (3%)	4 (3%)
Deaths	0	0	0	0
Adverse events with frequency ≥5% in any group (by preferred term)				
Headache	6 (4%)	4 (3%)	10 (7%)	11 (8%)
Back pain	7 (5%)	5 (4%)	3 (2%)	10 (7%)
Diarrhoea	7 (5%)	3 (2%)	5 (4%)	10 (7%)
Urinary tract infection	7 (5%)	4 (3%)	7 (5%)	9 (7%)
Influenza	10 (7%)	13 (9%)	13 (9%)	8 (6%)
Nasopharyngitis	11 (8%)	12 (9%)	4 (3%)	8 (6%)
Hypertension	6 (4%)	9 (7%)	4 (3%)	5 (4%)
Upper respiratory tract infection	10 (7%)	5 (4%)	4 (3%)	3 (2%)
Cough	7 (5%)	4 (3%)	4 (3%)	1 (<1%)
Special interest categories				
Hypoglycaemia‡§	4 (3%)	3 (2%)	5 (4%)	5 (4%)
Events suggestive of urinary tract infection¶	11 (8%)	6 (4%)	10 (7%)	11 (8%)
Events suggestive of genital infection‡‖	7 (5%)	11 (8%)	18 (13%)	12 (9%)
Hypotension or syncope‡	1 (<1%)	0	2 (1%)	0

Summary of Adverse Drug Reactions in the Placebo-controlled Studies Dataset

	Placebo N=646 n (%)	CANA 100 mg N=833 n (%)	CANA 300 mg N=834 n (%)
Gastrointestinal Disorders			
Constipation	6 (0.9)	15 (1.8)	19 (2.3)
Thirst	1 (0.2)	23 (2.8)	19 (2.3)
Renal and Urinary Disorders			
Polyuria or pollakiuria	5 (0.8)	44 (5.3)	38 (4.6)
Urinary tract infection	26 (4.0)	48 (5.8)	36 (4.3)
Reproductive System and Breast Disorders			
Balanitis or balanoposthitis	2 (0.6)	17 (4.2)	15 (3.7)
Vulvovaginal candidiasis	10 (3.2)	44 (10.4)	49 (11.4)

Other ADR's: Hypotension, Impaired renal function, Hypoglycemia with concomitant insulin or insulin secretatgoues, Hypersensitivty reactions, Increased LDL-C, Pancreatitis, Bone fractures
Increases in: Potassium, Magnesium, Phosphate, and Hemoglobin

Schernthaner G etal, Diabetes Care 36:2508-2515, 2013

Add-on therapy to metformin + SU: canagliflozin CANTATA-D2 52-week data

Baseline characteristics	Canagliflozin 300 mg n=377	Sitagliptin 100 mg n=378
	Patients on metformin + SU Baseline HbA_{1c}: 8.1% Baseline weight: 88.3 kg	
ΔHbA_{1c} (%)	–1.03	–0.66
% to target HbA_{1c} <7.0%	47.6	35.3
Δweight (%)	–2.5[a]	0.3
ΔSBP (mmHg)	–5.1[a]	0.9
Δtriglycerides (%)	9.6	11.9
ΔHDL-C (%)	7.6	0.6
ΔLDL-C (%)	11.7	5.2
AEs (%)	76.7	77.5
SAEs (%)	6.4	5.6
AE-related discontinuations (%)	5.3	2.9
Superficial genital fungal infections (%)[b]	15.3/9.2	4.3/0.5
≥1 hypoglycaemic episode	43.2	40.7

[a]*P*<0.001 vs sitagliptin; [b]values given for women/men.
AEs, adverse events; HbA_{1c}, glycosylated haemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SAEs, serious adverse events; SBP, systolic blood pressure; SU, sulphonylurea
Gross JL et al. ADA 2012. Abst 50-LB

Comparison of Incretin-based Therapies and SGLT2 Inhibitor Characteristics

	Incretin-based therapies		SGLT2 inhibitors
	GLP-1 receptor agonists	DPP-4 inhibitors	
Administration	SC	PO	PO
MOA	Direct	Direct	Indirect
Glycaemic control	Good	Moderate	Good
Body weight	Decreased	Neutral	Decreased
sBP	Decreased	Neutral	Decreased
Lipid profile	Improved	Improved	Increased LDL
β-Cell function	Improved	Improved	Improved
Side effect profile	Well tolerated	Very Well tolerated	Well tolerated
Common AEs	GI	URTI, headache	GU infection

AEs, adverse events; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GU, genitourinary; LDL, low density lipoprotein; MOA, mechanism of action; PO, orally; sBP, systolic blood pressure; SC, subcutaneously; SGLT2, sodium glucose co-transporter 2; URTI, upper respiratory tract infection.

Brown et al. *J Nutr Metab.* 2012; doi:10.1155/201/381713. Kim et al. *Diab Metab Synd Obes.* 2012;5:313–327.

Outline

- The treatment algorithm for diabetes
- Clinical data with DPP-4 inhibitors and Linagliptin
- Clinical Data with the SGLT2 inhibitors
- Summary

Some factors to consider when choosing an appropriate therapy

- Patient priorities
- HbA1c
- Hypoglycaemia
- Weight
- Renal function
- Co-morbidities

- Cost of therapies and local circumstances

Summary

- DPP-4 as a class offer effective glucose lowering with weight neutrality and very low risk of hypoglycaemia
- Linagliptin is the first DPP-4 which is excreted predominantly via the bile and gut and can be used across spectrum of CKD and liver disease
- SGLT2 Inhibitors offer effective glucose lowering with weight loss
- Different patients may benefit from these newer therapies
- Long term safety needs to be established

Case Studies and discussion

Melanie Davies
Professor of Diabetes Medicine

University Hospitals of Leicester NHS
NHS Trust

University of Leicester

Outline

- MCQs
- Case Study 1
- Case Study 2
- Summary

Question 1- DPP-4 Inhibitors :

A Have low risk of hypoglycaemia and are weight losing

B Have the same risk of hypoglycaemia as an SU and are associated with weight loss

C Are weight neutral with a low risk of hypoglycaemia

D Compared to an SU are associated with weight loss, a low risk of hypoglycaemia but less HbA1c reduction

Question 1- DPP-4 Inhibitors :

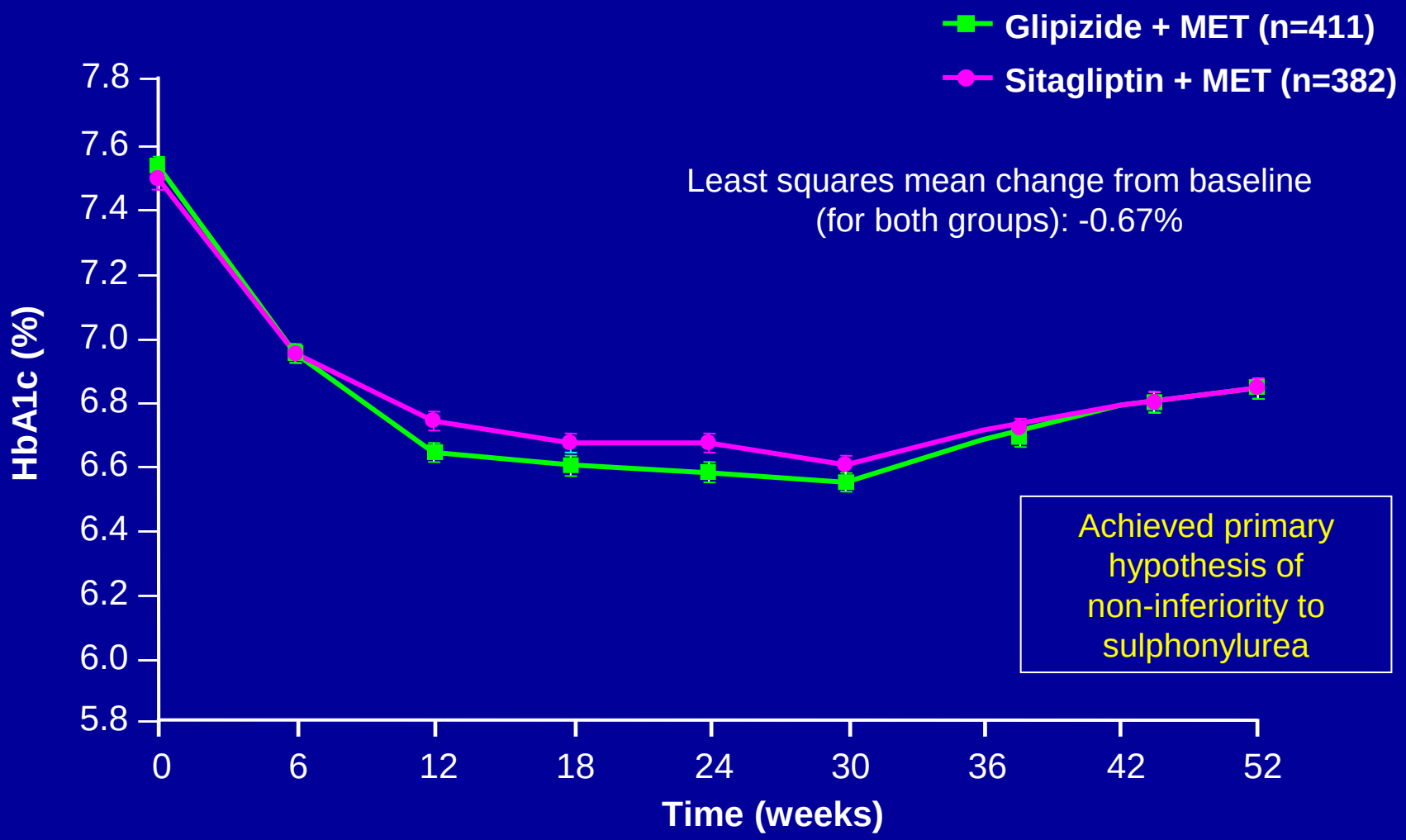
A Have low risk of hypoglycaemia and are weight losing

B Have the same risk of hypoglycaemia as an SU and are associated with weight loss

C Are weight neutral with a low risk of hypoglycaemia

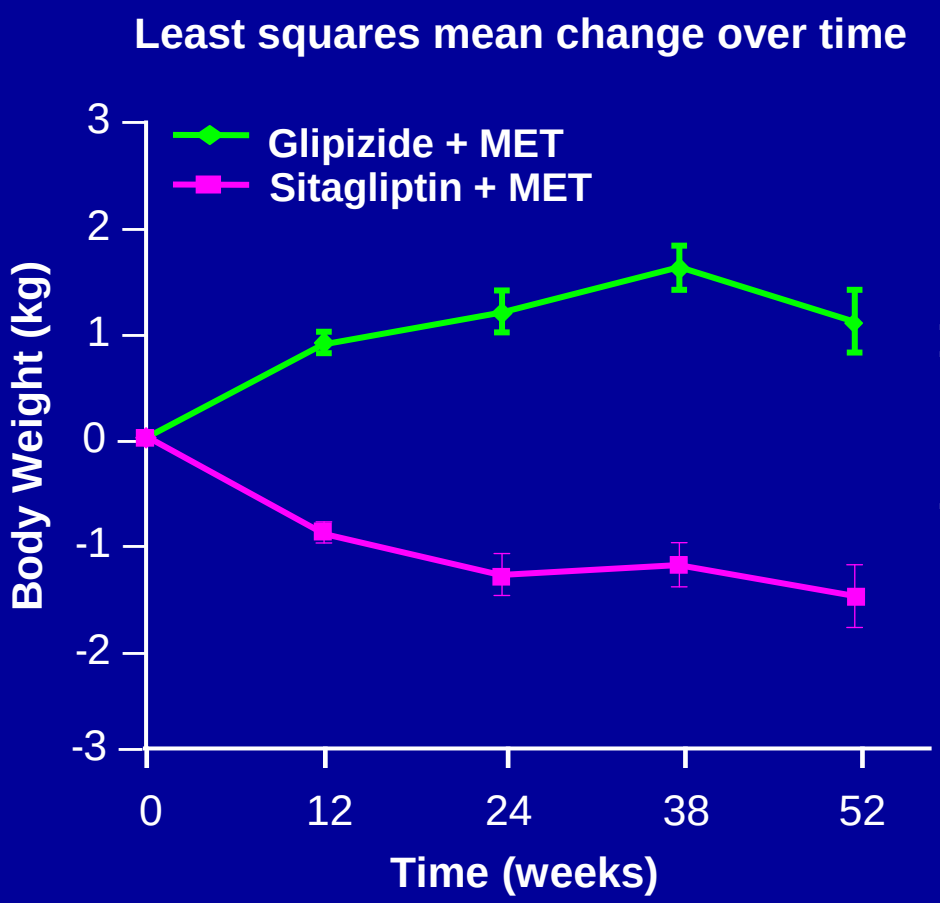
D Compared to an SU are associated with weight loss, a low risk of hypoglycaemia but less HbA1c reduction

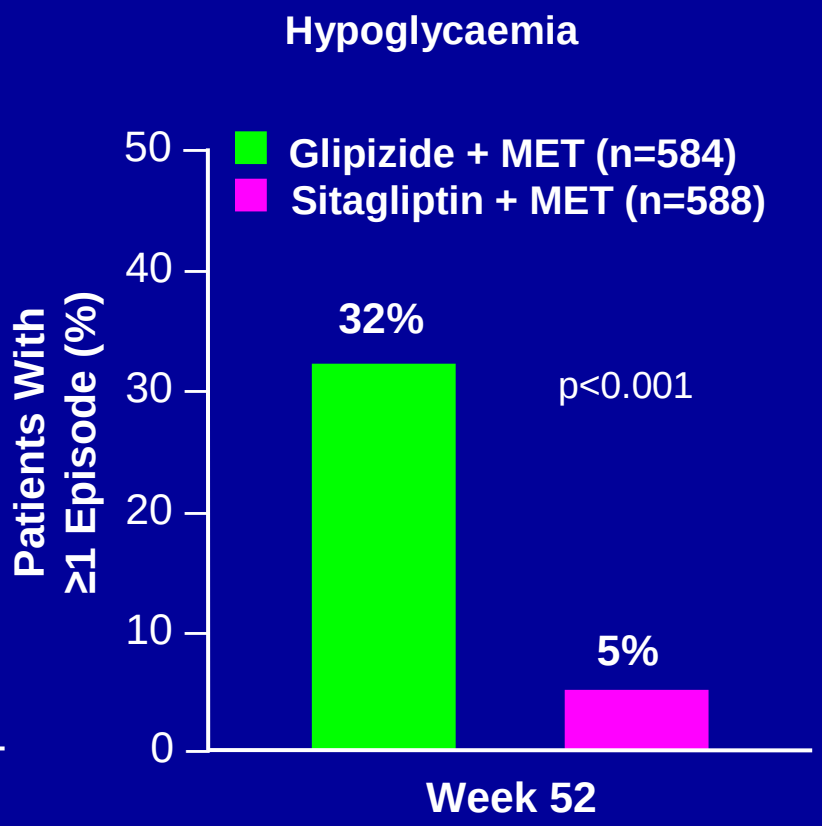
Sitagliptin with MET Showed Comparable Efficacy to Sulphonylurea with MET



MET: Metformin.
Per-protocol population. Data presented as mean ± SE
Adapted from Nauck et al. *Diabetes Obes Metab*. 2007;9:194–205.

Sitagliptin with MET Provided Weight Reduction (vs Weight Gain) and a Much Lower Incidence of Hypoglycaemia





While this study demonstrated weight loss with sitagliptin, other studies have not shown significant weight loss, and sitagliptin is classed as weight neutral as per its SPC

Least squares mean between-group diff|erence at Week 52 (95% CI): change in body weight = -2.5 kg [-3.1, -2.0] (p<0.001); Least squares mean change from baseline at Week 52: glipizide: +1.1 kg; sitagliptin: -1.5 kg. Per-protocol population. Data presented as mean ± SE.
SPC: Summary of Product Characteristics.
Adapted from Nauck MA, et al. *Diab Obes Metab.* 2007;9:194–205.

Question 2- DPP-4 Inhibitors :

A Are all oral agents with similar chemical structures

B Inhibit the degradation of GLP-1 and increase GLP-1 levels

C Are all excreted predominantly through the kidney

D Have varying effects on lowering HbA1c

Question 2- DPP-4 Inhibitors :

A Are all oral agents with similar chemical structures

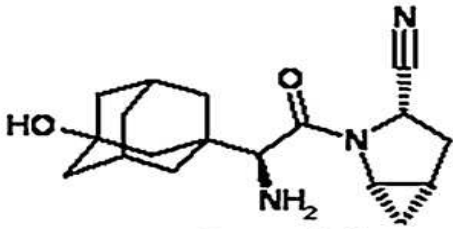
B **Inhibit the degradation of GLP-1 and increase GLP-1 levels**

C Are all excreted predominantly through the kidney

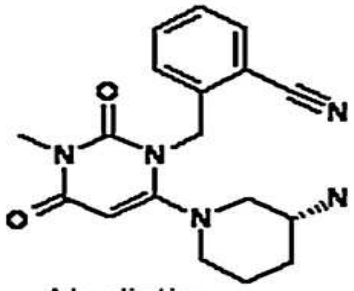
D Have varying effects on lowering HbA1c

Structures of DPP-4 Inhibitors

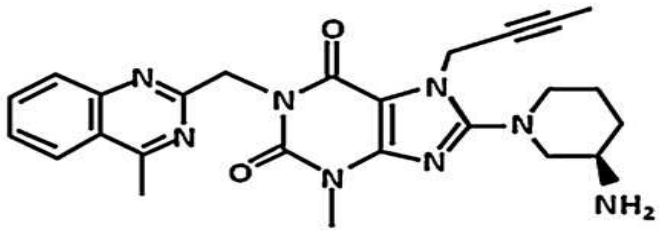
Sitagliptin



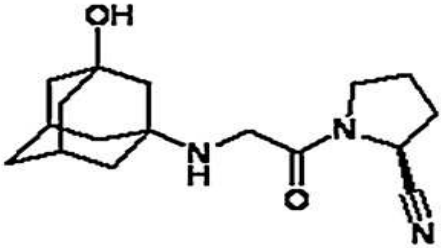
Saxagliptin



Alogliptin



Linagliptin



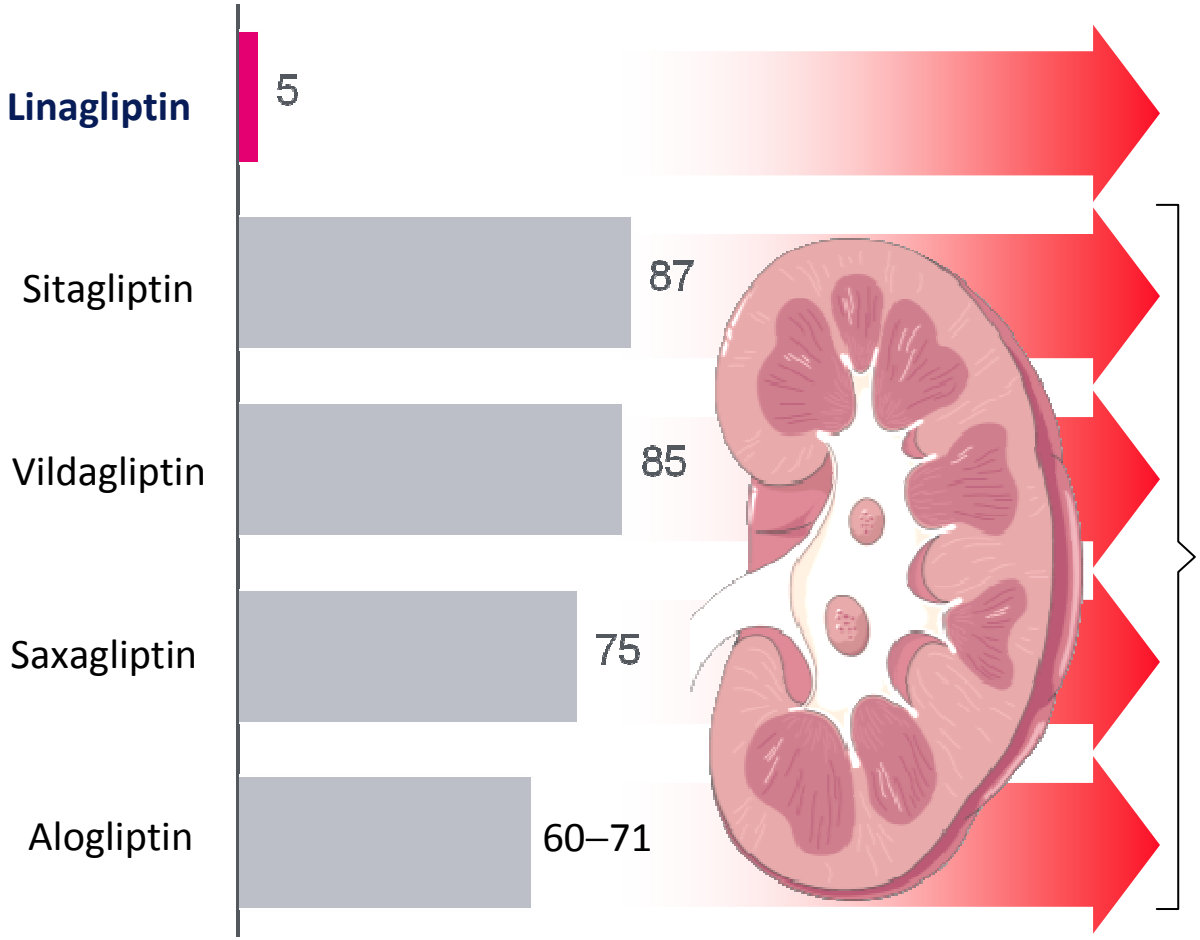
Vildagliptin

Feature	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Chemistry	Triazolopiperazine-based, substrate-like, non-covalent inhibitor	Cyanopyrrolidine-based, substrate-like, covalent inhibitor	Cyanopyrrolidine-based, substrate-like, covalent inhibitor	Pyrimidinedione-based, inhibitor, non-substrate-like, non-covalent inhibitor	Fused imidazole-based, non-substrate-like, non-covalent inhibitor

Gerich J. Dia Res Clin Pract 2010: 131-140, Baetta R and Corsini A, Drugs 2011:71(11);1441-1467

DPP-4 inhibitor excretion- Linagliptin by bile and gut[1]

Share of renal excretion[2], %



No dose adjustment and/or no additional drug monitoring required

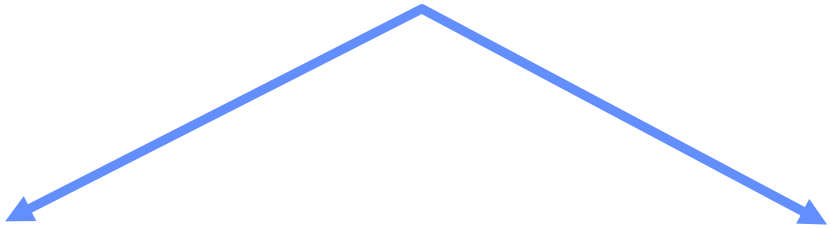
Glucose lowering drugs with renal excretion increase the risk of hypoglycaemia in patients with renal impairment[3]

Dose adjustment required in patients with renal impairment and/or drug-related kidney monitoring

1. Of currently globally approved DPP-4 inhibitors. 2. Including metabolites and unchanged drug; excretion after single dose administration of C14 labeled drug.3. ADA/EASD Position Statement. *Diabetes Care*. 2012:doi:10.2337/dc12-0413.Source: US prescribing information linagliptin; Vincent SH, et al. *Drug Metab Dispos.* 2007;35:533–538; He H, et al. *Drug Metab Dispos.* 2009;37:536–544. US prescribing information saxagliptin. Christopher R, et al. *Clin Ther*. 2008;30:513–527.

Restoring GLP-1 Response Is a Logical Target for Treatment

Incretin-based Treatment Options



DPP-4 Inhibitors
Prevent enzymatic degradation of native GLP-1 by DPP-4

GLP-1 Receptor Agonists
Mimic native GLP-1 to restore GLP-1 activity

Incretin Enhancers

Incretin Mimetics

Developed from Holst JJ, Orskov C. *Diabetes*. 2004;53(suppl 3):S197-S204.

Case Study 1

- Agnes
- 51 yr old Widow
- T2DM for 10 years
- HbA1c climbed to 9%
- On MF at max tolerated dose
- Gym and treadmill
- Weight 75 kg
- BP on ACE
- LDL Chol 2.2 mmol/l
- HbA1c currently 8%

NEJM 2013:369:1370-2

Case Study 1 (cont)

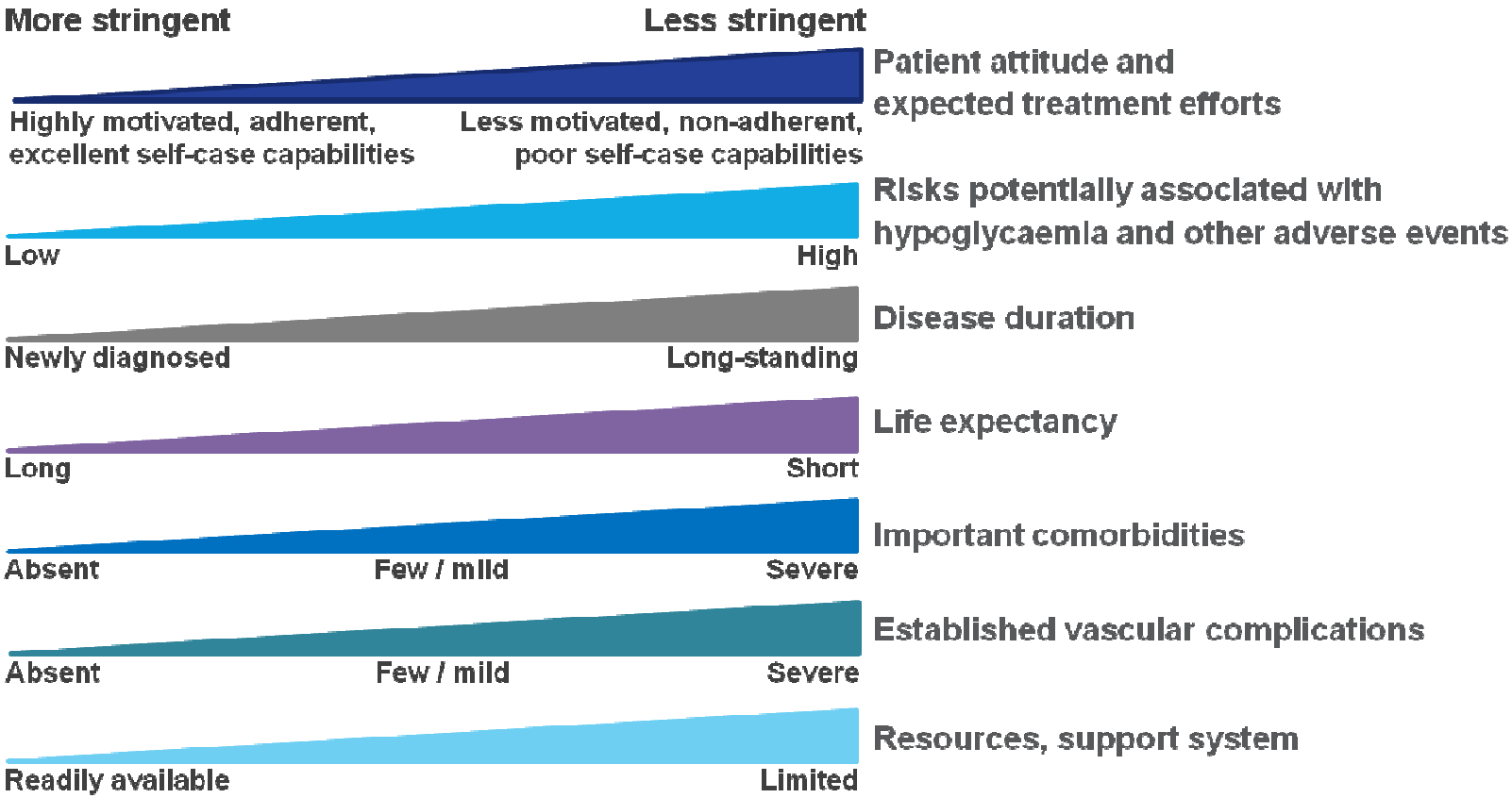
- Agnes
- Not keen on injectable therapy
- Her sister has been on SU and experienced hypos
- She is keen to avoid hypos and weight gain
- She has heard of new treatments – ‘gliptins’ and also a drug that works on the kidney

- Case posed in Clinical Decision series in NEJM 2013 and readers asked to ‘vote’ for gliptin or gliflozin

NEJM 2013:369:1370-2

Individualisation of treatment goals is key

More (<6.5%) or less stringent (7.5-8%) goals



The figure depicts elements to consider when making decisions about HbA_{1c} targets for specific patients.
The scale is not designed to be applied rigidly but to serve as a broad framework to assist in determining glycaemic targets.

Adapted from: Ismail-Beigi F, *et al. Ann Intern Med* 2011;**154**:554–9; Inzucchi SE, *et al. Diabetes Care* 2012;**35**:1364–79.

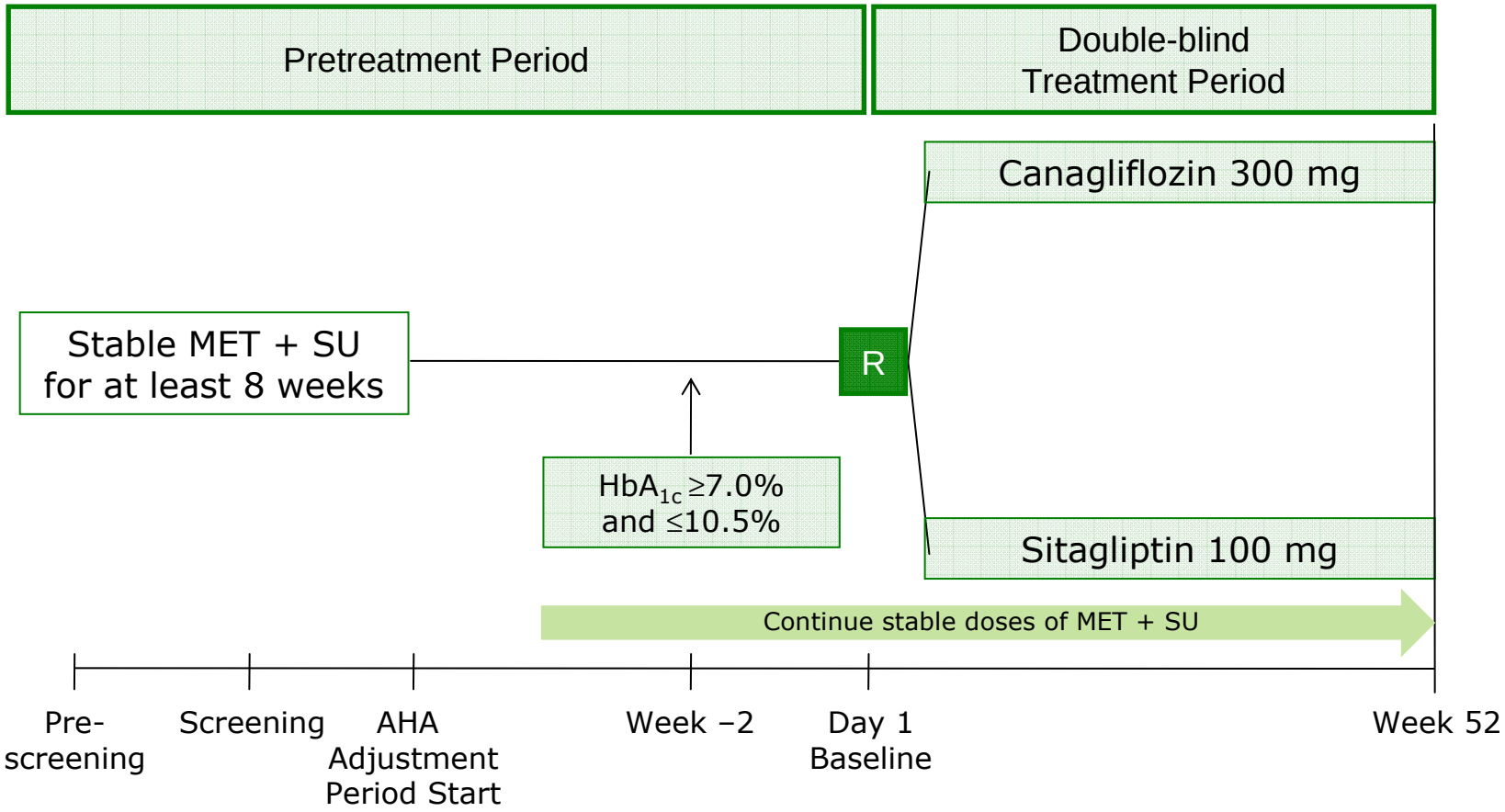
Result of Poll

- 1353 voted from 95 countries

- 72.3% voted GLIPTIN
- 27.7% voted GLIFLOZIN

- Specific issues
- Need more focus on Education diet and Exercise
- Focus more on CVD RF
- Choose other options SU Insulin GLP-1
- Needle phobis can be overcome

Add-on to MET + SU : Canagliflozin vs Sitagliptin Study Design



Schernthaner G. et al. Data presentation at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (OP43)
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

Schernthaner G etal, Diabetes Care 36:2508-2515, 2013

Baseline Characteristics

Characteristic	SITA 100 mg (n = 378)	CANA 300 mg (n = 377)	Total (N = 755)
Sex, n (%)			
Male	215 (56.9)	207 (54.9)	422 (55.9)
Female	163 (43.1)	170 (45.1)	333 (44.1)
Mean (SD) age, y	56.7 (9.3)	56.6 (9.6)	56.7 (9.5)
Race, n (%)			
White	240 (63.5)	245 (65.0)	485 (64.2)
Black or African American	45 (11.9)	43 (11.4)	88 (11.7)
Asian	65 (17.2)	67 (17.8)	132 (17.5)
Other*	28 (7.4)	22 (5.8)	50 (6.6)
Mean (SD) HbA_{1c}, %	8.1 (0.9)	8.1 (0.9)	8.1 (0.9)
Mean (SD) FPG, mmol/L	9.2 (2.5)	9.4 (2.6)	9.3 (2.6)
Mean (SD) body weight, kg	89.1 (23.2)	87.4 (23.2)	88.3 (23.2)
Mean (SD) BMI, kg/m^2	31.7 (6.9)	31.5 (6.9)	31.6 (6.9)
Mean (SD) T2DM duration, y	9.7 (6.3)	9.4 (6.1)	9.6 (6.2)

SITA, sitagliptin; CANA, canagliflozin; SD, standard deviation; FPG, fasting plasma glucose; BMI, body mass index; T2DM, type 2 diabetes mellitus.
*Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported.

Schernthaner G. et al. Poster presented at the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), 2012;Nov.8-11; Barcelona, Spain, (P70).
Schernthaner G. et al. Data presentation at the 48th European Association for the Study of Diabetes (EASD);2012;Oct.1-5: Berlin, Germany, (OP43)
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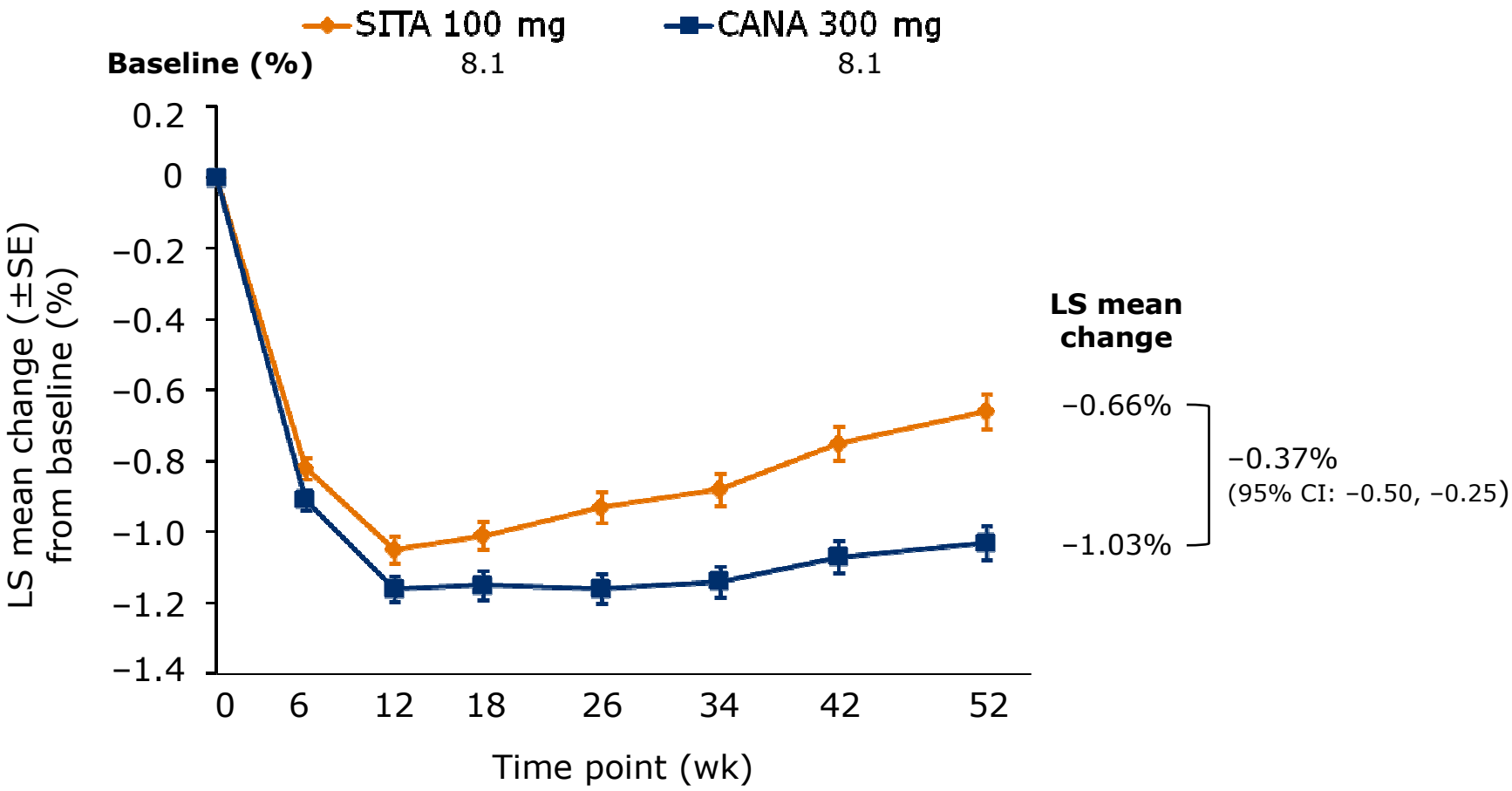
Change in HbA_{1c} (LOCF)



LOCF, last observation carried forward ; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

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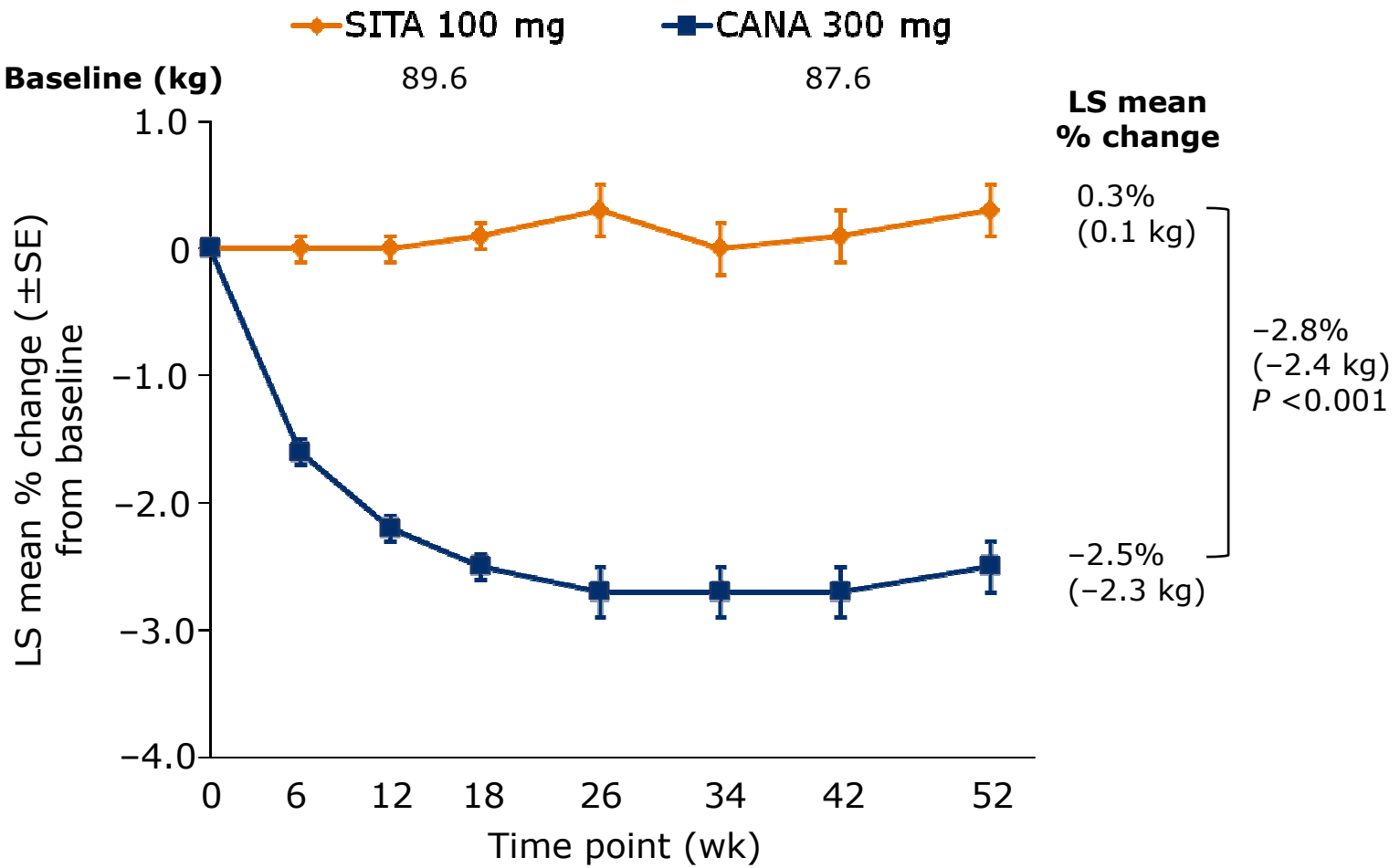
Schernthaner G et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print]

%Change in Body Weight (LOCF)



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Question 3- DPP-4 Inhibitors and SGLT 2 inhibitors

A Both classes can be used in patients with impaired renal function

B DPP-4 inhibitors are more likely to induce hypoglycaemia

C In head to head studies DPP-4 inhibitors have a greater effect on lowering HbA1c

D SGLT 2 inhibitors are more likely to induce wt loss

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Comparison of Incretin-based Therapies and SGLT2 Inhibitor Characteristics

	Incretin-based therapies		SGLT2 inhibitors
	GLP-1 receptor agonists	DPP-4 inhibitors	
Administration	SC	PO	PO
MOA	Direct	Direct	Indirect
Glycaemic control	Good	Moderate	Good
Body weight	Decreased	Neutral	Decreased
sBP	Decreased	Neutral	Decreased
Lipid profile	Improved	Improved	Increased LDL
β-Cell function	Improved	Improved	Improved
Side effect profile	Well tolerated	Very Well tolerated	Well tolerated
Common AEs	GI	URTI, headache	GU infection

AEs, adverse events; DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GU, genitourinary; LDL, low density lipoprotein; MOA, mechanism of action; PO, orally; sBP, systolic blood pressure; SC, subcutaneously; SGLT2, sodium glucose co-transporter 2; URTI, upper respiratory tract infection.

Brown et al. *J Nutr Metab.* 2012; doi:10.1155/201/381713. Kim et al. *Diab Metab Synd Obes.* 2012;5:313–327.

Case Study 2

- Maria
- 75 yr old Widow
- T2DM for 10 years
- BMI 27
- Was on MF but even at lowest dose and MR unable to tolerate
- Active and fit for her age
- BP well controlled
- eGFR 50 (CKD3a)
- HbA1c climbed from 7.3% to 8.2%
- Lives alone
- Occ nocturia

Case Study 2

- What treatment strategies are important
- What factors in her specific case influence your choice of treatment
- What is your preferred treatment option

Case Study 3

- David
- 42 yr old Man –Desk Job -Accountant
- T2DM for 6 years
- BMI 35
- HbA1c climbed to 7.8%
- On MF at max tolerated dose
- Struggled with weight loss and exercise
- BP controlled on ACE
- Hyperlipidaemia
- eGFR Normal
- Married with 2 children age 10 and 15 yrs
- FH of DM and early CVD

Case Study 3

- What are the important management strategies

- More extreme phenotype- very high long term CVD risk and poor outcomes
- Diet and Exercise and Lifestyle
- Education and Self-management
- Compliance

Case Study 3

- After more intense self-management programme and lifestyle intervention
- Weight loss 6 Kg and A1c falls to 7.3%

Case Study 3

- What is your preferred options re Glucose lowering therapies

- Nothing else
- SU
- TZD
- DPP-4 inhibitor
- GLP-1 RA
- SGLT2 inhibitor
- Insulin

Summary

- There is more choice for glucose lowering therapies
- In T2DM the phenotype is becoming more varied
- Management options are becoming more complex
- Personalised management strategies are required