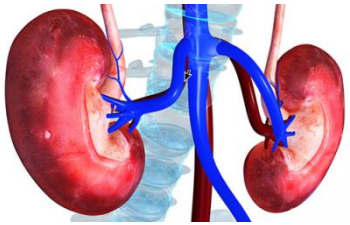
ΔΙΗΜΕΡΙΔΑ ΓΙΑ ΤΟ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ

Diabetes: Treating the gap

6-7 ΟΚΤΩΒΡΙΟΥ 2017
ΟΛΥΜΠΙΑΚΟ ΜΟΥΣΕΙΟ
ΘΕΣΣΑΛΟΝΙΚΗ

www.hellenicdiabetesacademy.gr

Αντιμετώπιση του σακχαρώδους διαβήτη



SGLT-2 ή φάρμακα που σχετίζονται με την

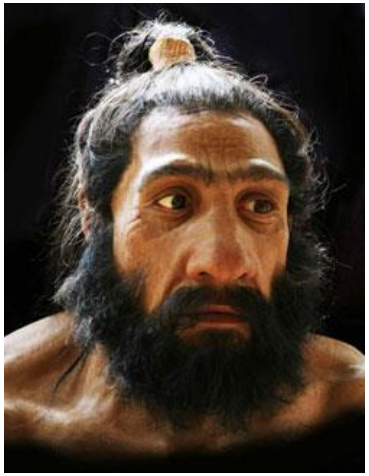
ινκρετίνη

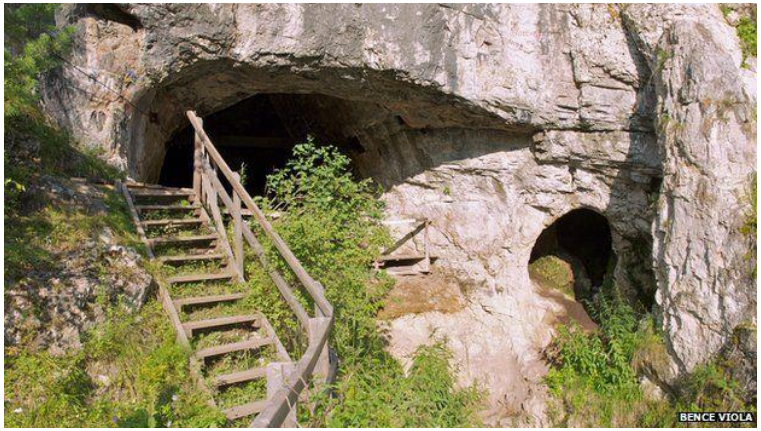
Παναγιώτης Χαλβατσιώτης
Β΄ Προπαιδευτική Παθολογική Κλινική - Μονάδα Έρευνας
& Διαβητολογικό Κέντρο Πανεπιστημίου Αθηνών
Πανεπιστημιακό Γενικό Νοσοκομείο «Αττικόν»

ΔΗΛΩΣΗ ΣΥΜΦΕΡΟΝΤΩΝ

Δεν υπάρχει οποιαδήποτε σύγκρουση συμφερόντων του ομιλητή.

NEANDERTHALS & DIABETES





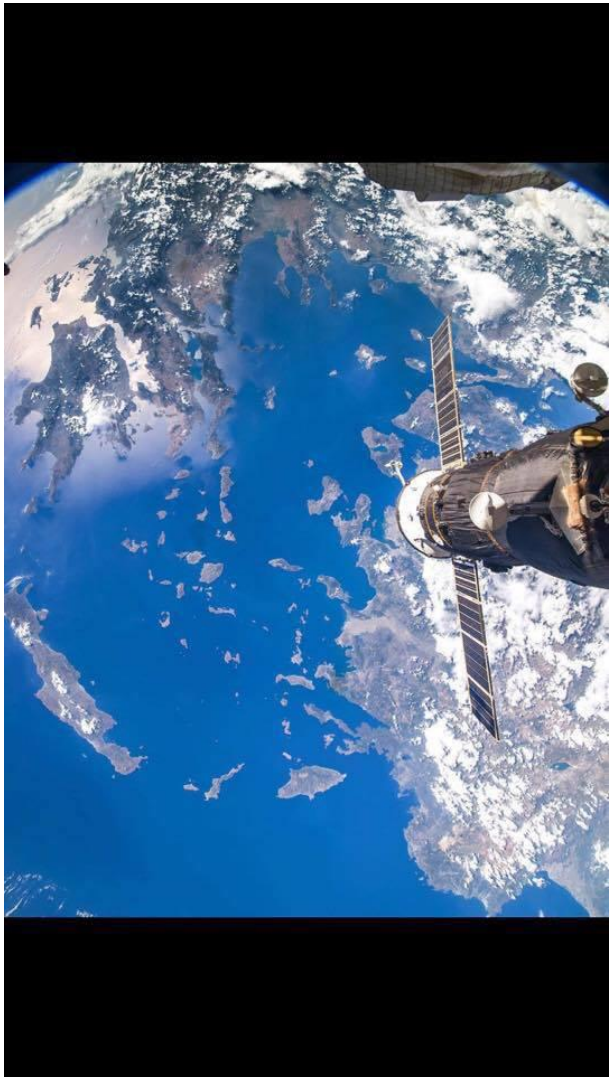
The gene variant was found in Neanderthal remains from Denisova Cave, Siberia

About **2% of the genomes** of non-Africans were inherited **from Neanderthals** which lived across Europe and western Asia from about 400,000-300,000 years ago.

A gene variant with the higher risk version of diabetes **SLC16A11** is inherited from Neanderthals

Nature. 2014 Feb 6;506(7486):97-101.

ΣΥΝΤΑΓΟΓΡΑΦΙΚΑ ΔΕΔΟΜΕΝΑ ΔΙΑΒΗΤΗ ΣΤΗΝ ΕΛΛΑΔΑ



- 10,222,779 ΑΜΚΑ, (95% πληθυσμού)
- Διαβητικοί 720,764 (7.0% του πληθυσμού)
- Επιπολασμός του ΣΔ1 0.24% (24.535 άτομα)

Liatis et al*Diabetes Res Clin Pract. 2016;118:162–7*

Diet, life-style and cardiovascular morbidity in the rural, free living population of Elafonisos island

Chris J. Kapelios, et al (The PERSEAS Study Group)

BMC Public HealthBMC series –2017**17**:147 **DOI:** 10.1186/s12889-017-4053-x

ΕΛΑΦΟΝΗΣΟΣ

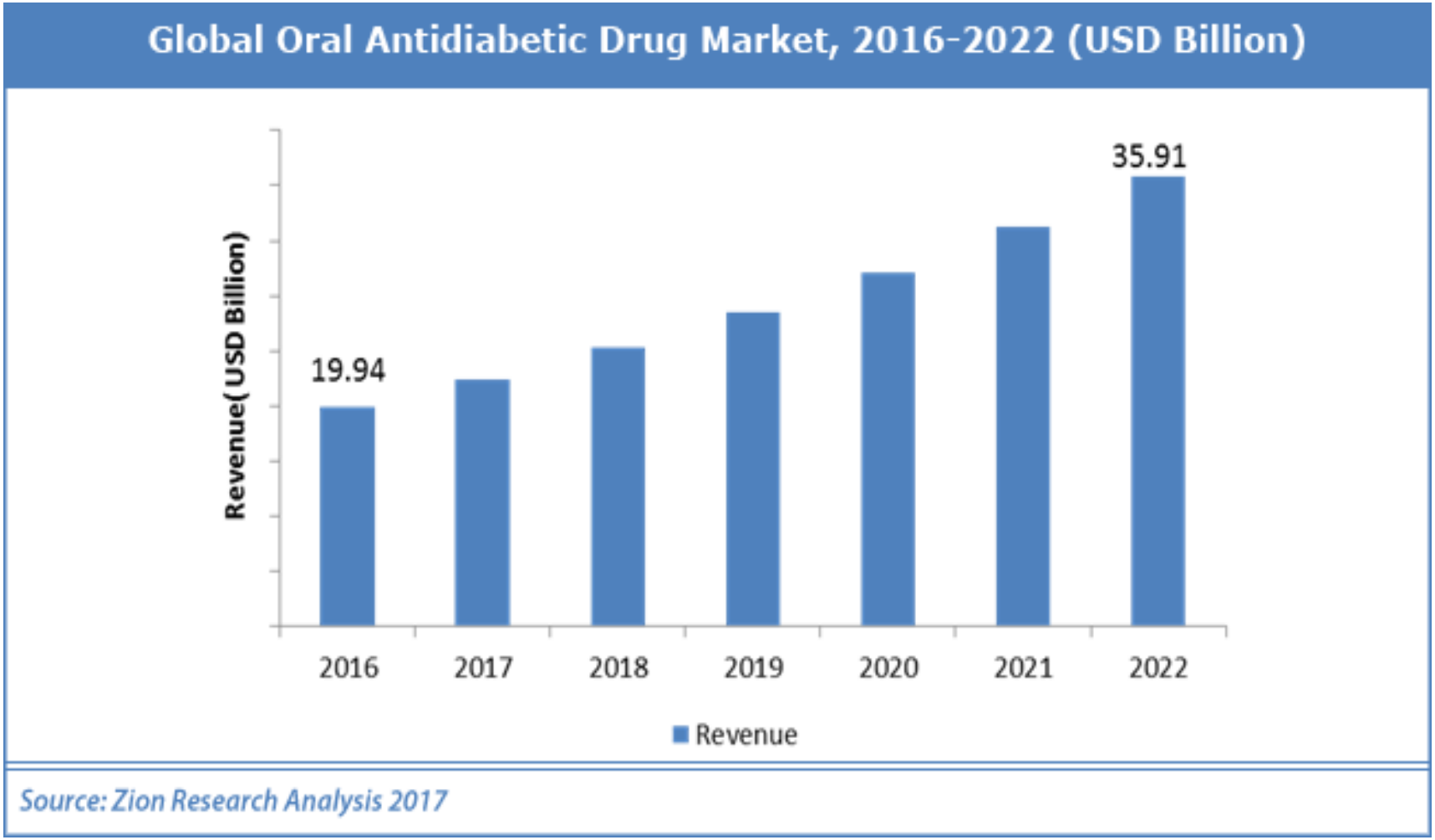
Prevalence of reported and screen detected classic cardiovascular risk factors stratified by sex[a]

Disease	Known	Medication-treated	Screen detected	Total
Diabetes mellitus	46 (7.7)	37 (6.2)	24 (4.0)	70 (11.7)
Men	20 (7.0)	16 (5.6)	15 (5.2)	35 (12.2)
Women	26 (8.4)	21 (6.8)	9 (2.9)	35 (11.3)
Arterial hypertension	184 (30.9)	171 (28.7)	77 (12.9)	261 (43.8)
Men	85 (29.6)	80 (27.9)	48 (16.7)	133 (46.3)
Women	99 (32.0)	91 (29.6)	29 (9.4)	128 (41.4)
Hypercholesterolemia	184 (30.9)	143 (24.0)	139 (23.3)	323 (54.2)
Men	72 (25.1)	59 (20.6)	67 (23.3)	139 (48.4)
Women	112 (36.2)	84 (27.4)	72 (23.3	184 (59.5)

Trends in Drug Utilization, Glycemic Control, and Rates of Severe Hypoglycemia, 2006-2013

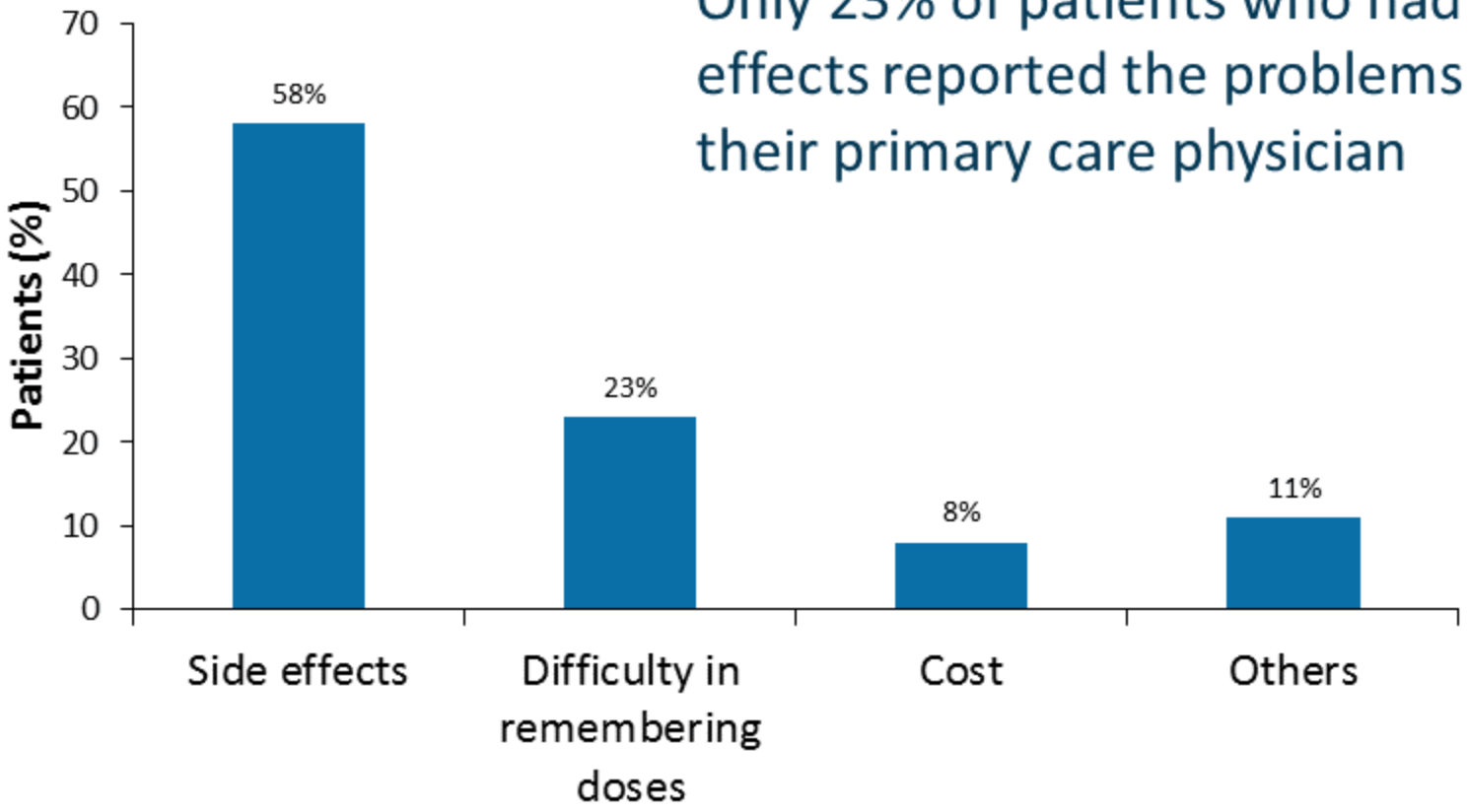
- **1.660.000 DM2 pts records from 2006 to 2013**
- **Metformin increased from 47.6 to 53.5%**
- **iDPP4 increased from 0.5 to 14.9%**
- **Insulin increased from 17.1 to 23.0%**
- **SU decreased from 38.8 to 30.8%**
- **TZD decreased from 28.5 to 5.6%**
- **Glycemic control was poor 23.3% of the youngest and 6.3% of the oldest patients**
- **Severe hypos remained same, declined modestly in oldest patients (2.9 to 2.3; *P* < 0.001), remained high among those with >2 comorbidities (3.2 to 3.5; *P* = 0.36)**

Diabetes Care. 2017 Apr;40(4):468-475.



the global oral antidiabetic drug market accounted for USD 19.94 billion in 2016 and is expected to reach USD 35.91 billion by 2022

Most Common Factors Related to Nonadherence in Patients With T2DM



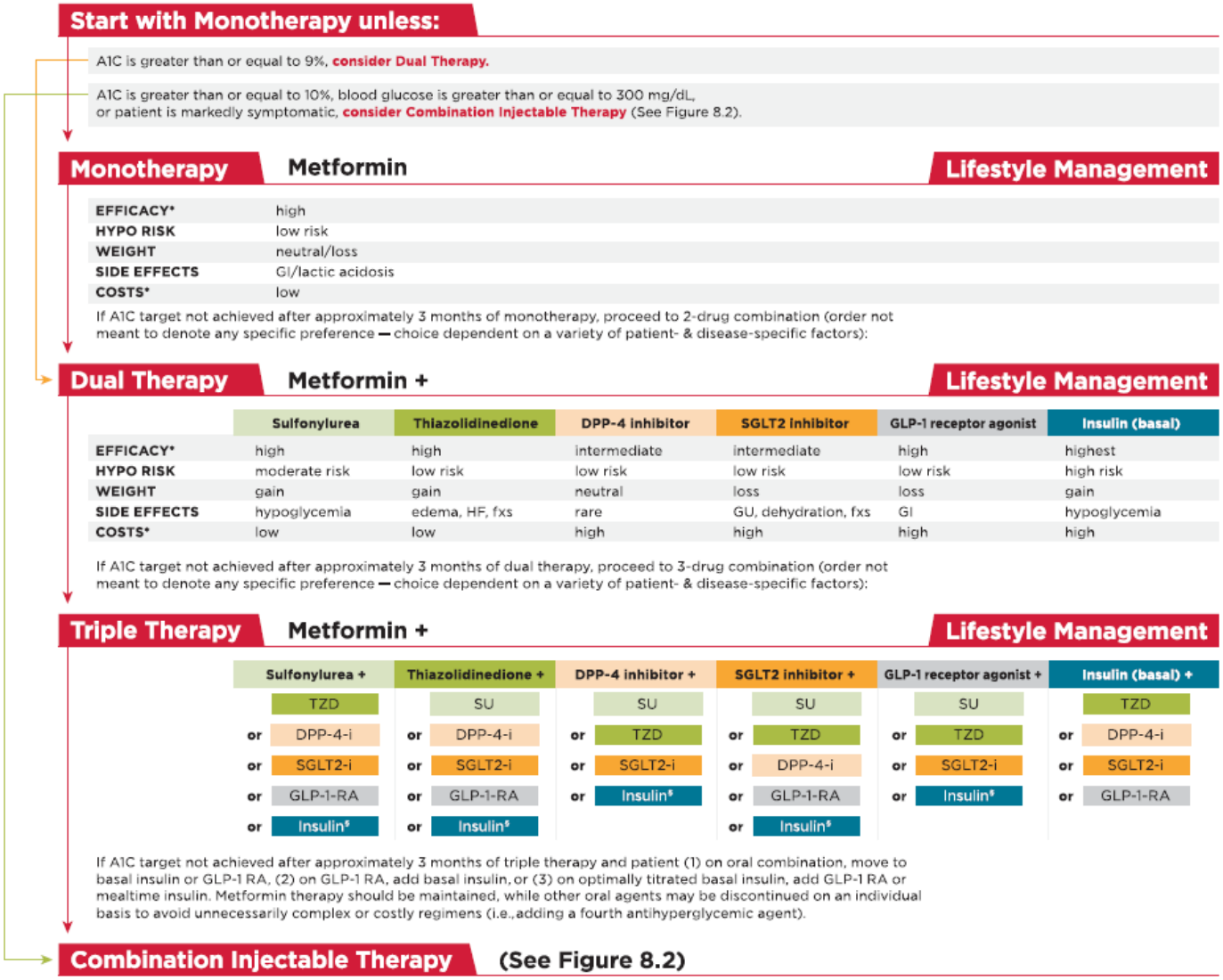
Grant RW, et al. *Diabetes Care*. 2003;26:1408-1412.

ΔΙΑΒΗΤΙΚΟΣ ΑΣΘΕΝΗΣ

- Θωμάς 64 ετών με τύπου 2 ΣΔ από το 2007
- Metformin 850 mg x2
  Glimepiride 4 mg x1
- GHbA1c: 8,5%
- Lisinopril & Atorvastatin
- Ύψος: 1,78 ΒΣ: 112,3 BMI: 35,4

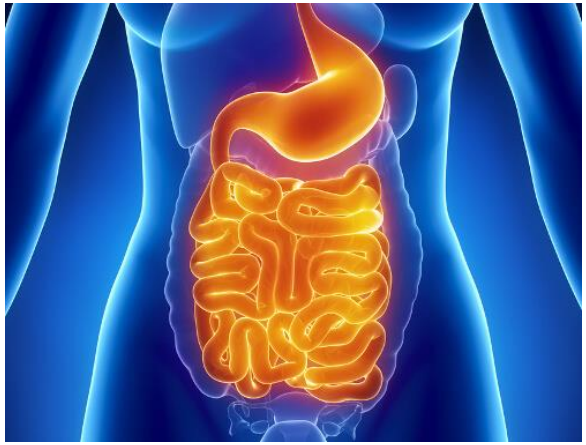
Tom Hanks

ADA STANDARDS OF MEDICAL CARE IN DIABETES—2017



GLP1s

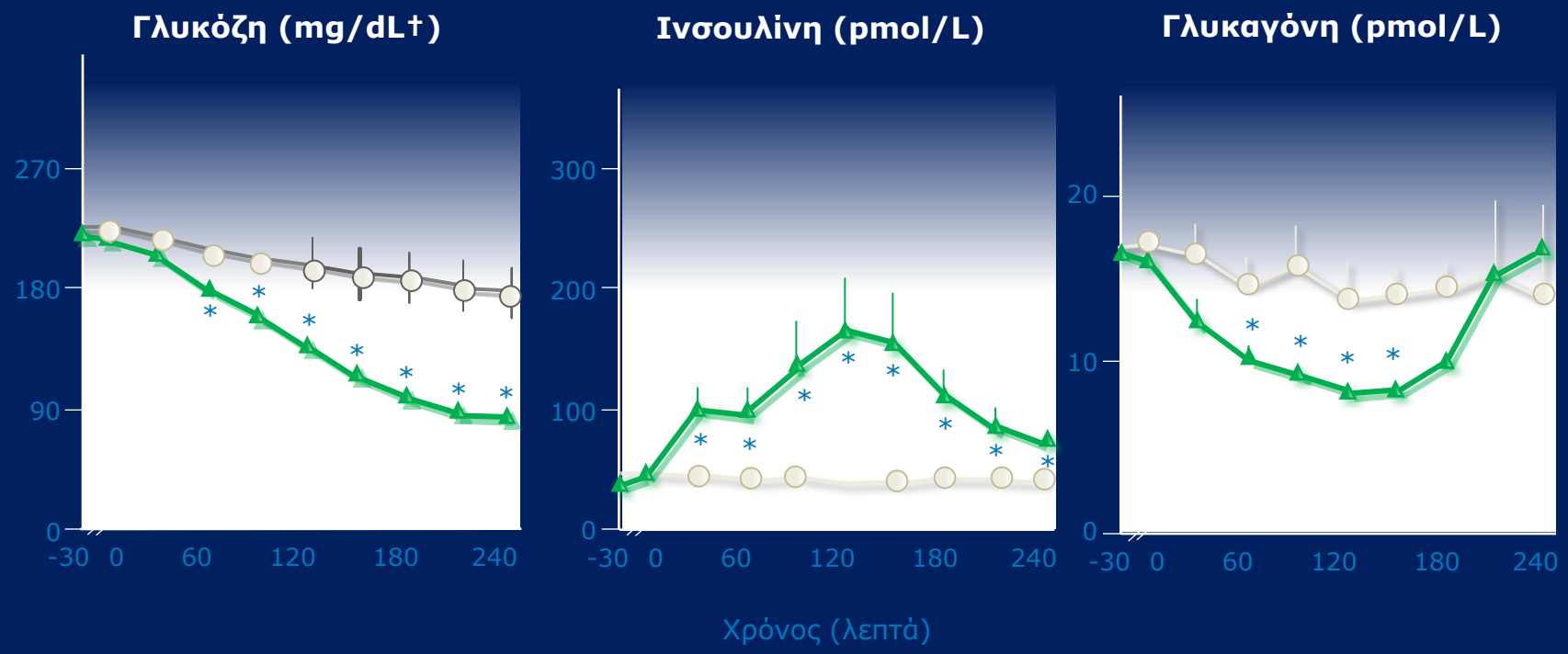
Meals vs Parenteral Nutrition



- **insulin response to oral** (and enteral) glucose is **substantially greater** than that to an **intravenous** glucose infusion
- **GIP & GLP-1** are predominantly released from **intestine** in response to enteral nutrients & stimulate insulin secretion in a **glucose-dependent manner**
- **GLP-1 agonists** and dipeptidyl peptidase 4 (**DPP-4**) inhibitors

Glucagon-like peptide-1 (GLP-1)
Γλυκοζοεξαρτώμενη έκκριση ινσουλίνης

Απάντηση σε IV χορήγηση GLP-1 σε τύπου 2 διαβητικούς (n=10)

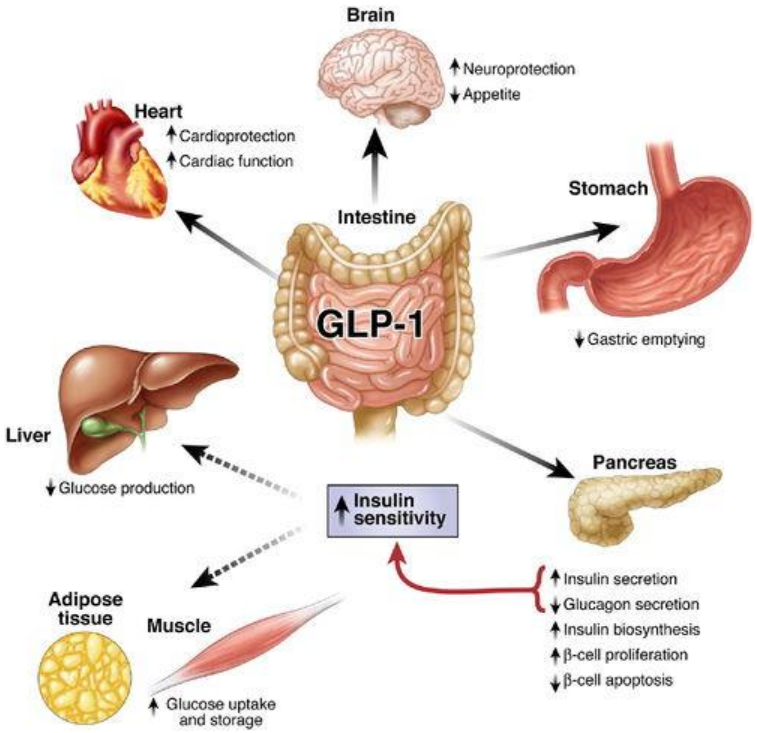


Mean (SE); *P<0.05
†για τη μετατροπή mg/dL of glucose σε mmol/L, διαιρέστε δια 18.

Placebo GLP-1

Adapted from: Nauck MA, et al. Diabetologia. 1993;36:741-4.

GLP-1 Agonists



- **Αυξάνεται η ινσουλινοέκκριση**
- **Μειώνεται η νεογλυκογένεση**
- **Αυξάνεται το αίσθημα κορεσμού**
- **Καθυστέρηση κένωσης στομάχου**
- **Απώλεια σωματικού βάρους**

GLP-1 Agonists

Human GLP1 based

- Daily LIRAGLUTIDE
- Weekly ALPIGLUTIDE
- Weekly DULAGLUTIDE

Exendin-4 based

- Daily EXENATIDE
- Weekly EXENATIDE LAR
- Daily LIXISENATIDE

INTRA GLP-1 VARIATION

- improvements in glycaemic control (LIRA)
- injection frequency
- tolerability (adverse reactions)
- CVD benefits (proved)

GLP-1 vs DPP4

Outcomes of Prospective Trials: GLP-1 RAs vs DPP-4 Inhibitors

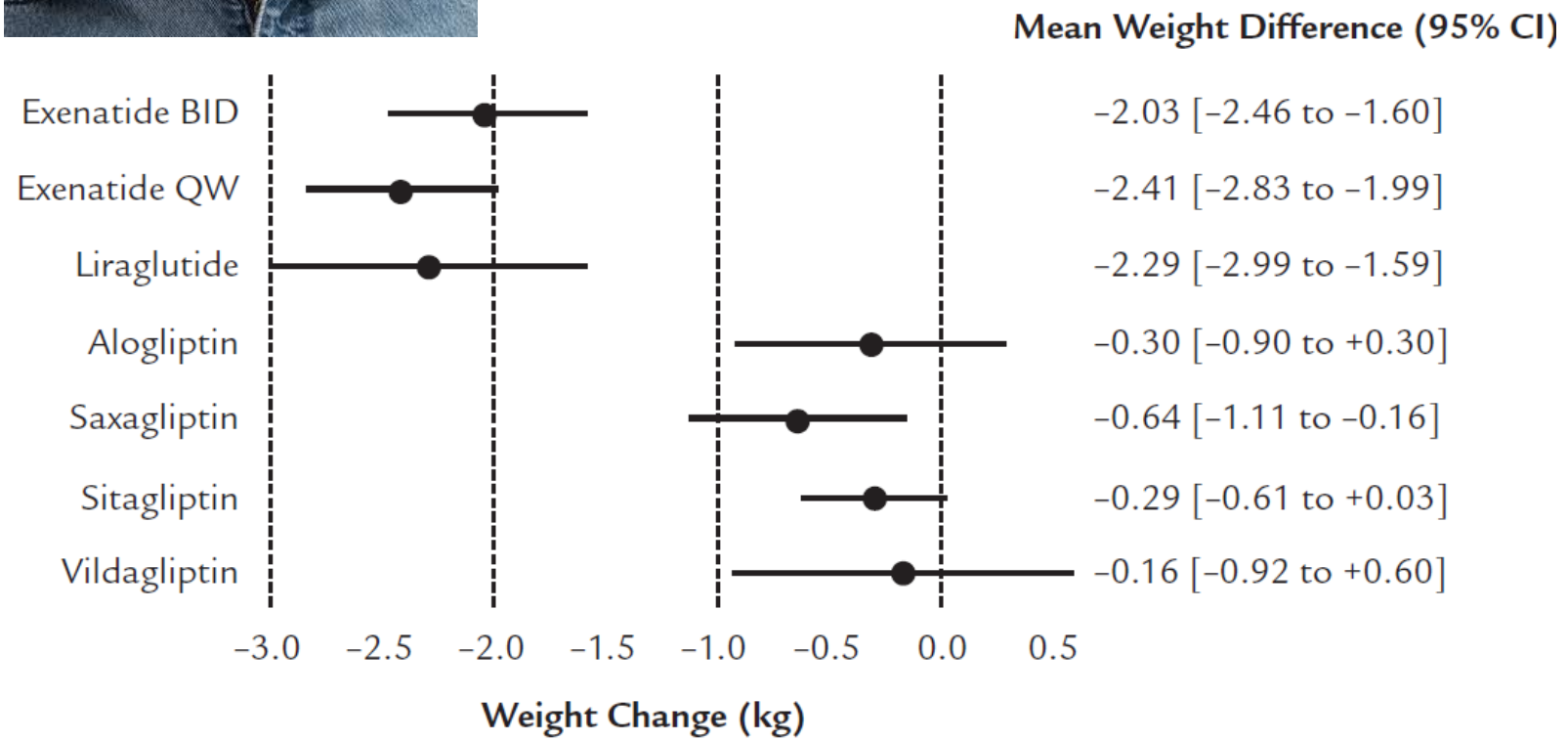
	Liraglutide vs Sitagliptin			Exenatide vs Sitagliptin		
Dosage	Liraglutide 1.2 mg qd	Liraglutide 1.8 mg qd	Sitagliptin 100 mg qd	Exenatide 5 mg bid x 2 weeks, then 10 mg bid x 2 weeks	Sitagliptin 100 mg qd	Glargine
HbA1c (%) baseline change	8.4 ($P \leq .0001$) -1.2* -1.3†	8.4 ($P \leq .0001$) -1.5* -1.5†	8.5 -0.9* -0.9†	8.4 ($P < .05$) -1.8	7.9 ($P < .05$) -1.5	7.9 ($P < .05$) -1.2
FPG (mg/dL) baseline change	182 ($P \leq .0001$) -34* -31†	178 ($P \leq .0001$) -39* -37†	180 -15* -11†	94 ($P < .05$) 12	96 ($P < .05$) 12	94 -5
△ Weight (kg)	-2.9* -2.8† ($P \leq .0001$)	-3.4* -3.7† ($P \leq .0001$)	-1.0* -1.2†	-0.9 ($P < .05$)	-0.1	0.4

*At the end of 26 wks; †At the end of 52 weeks.

Reid T. *Clin Diabetes*. 2012;30:3-12.

Efficacy of GLP-1 Agonists and iDPP-4

Body Weight

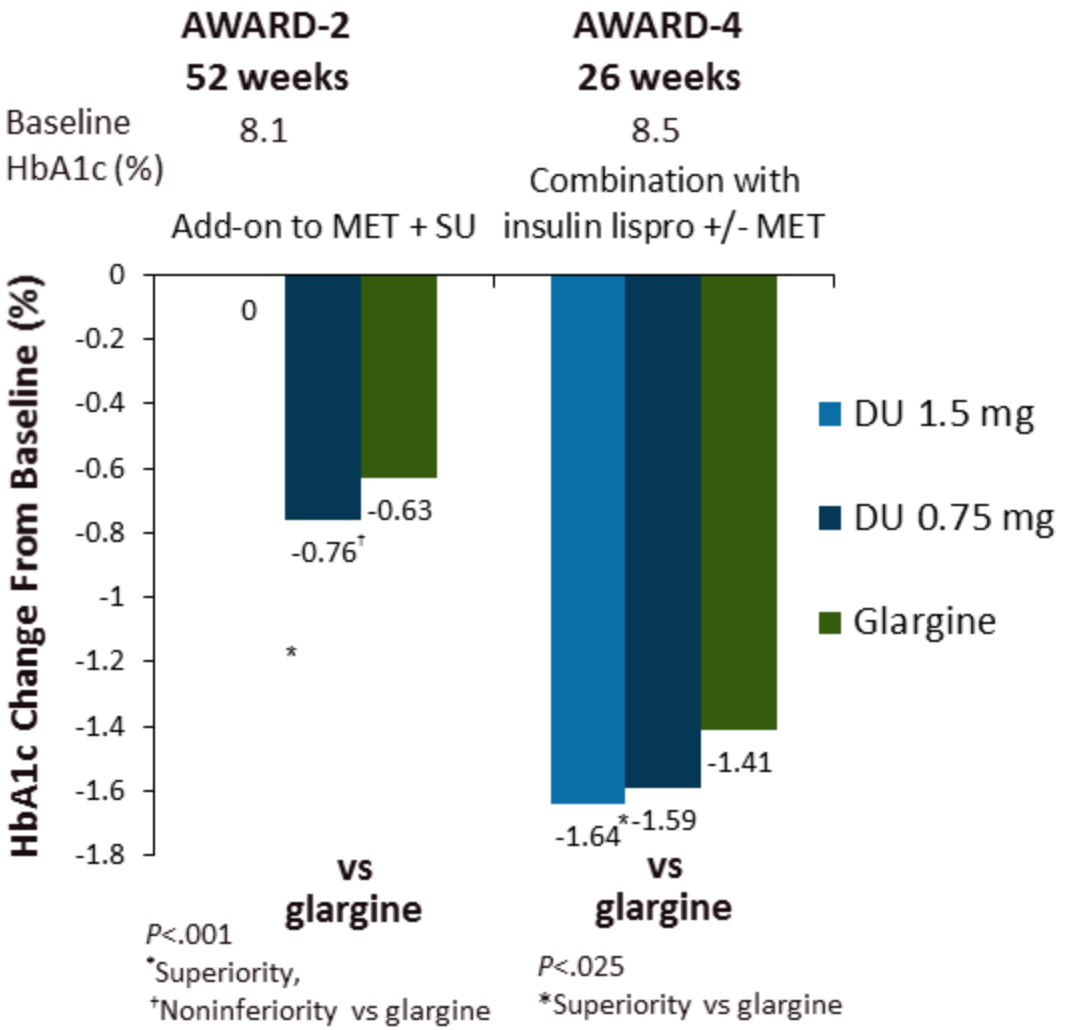


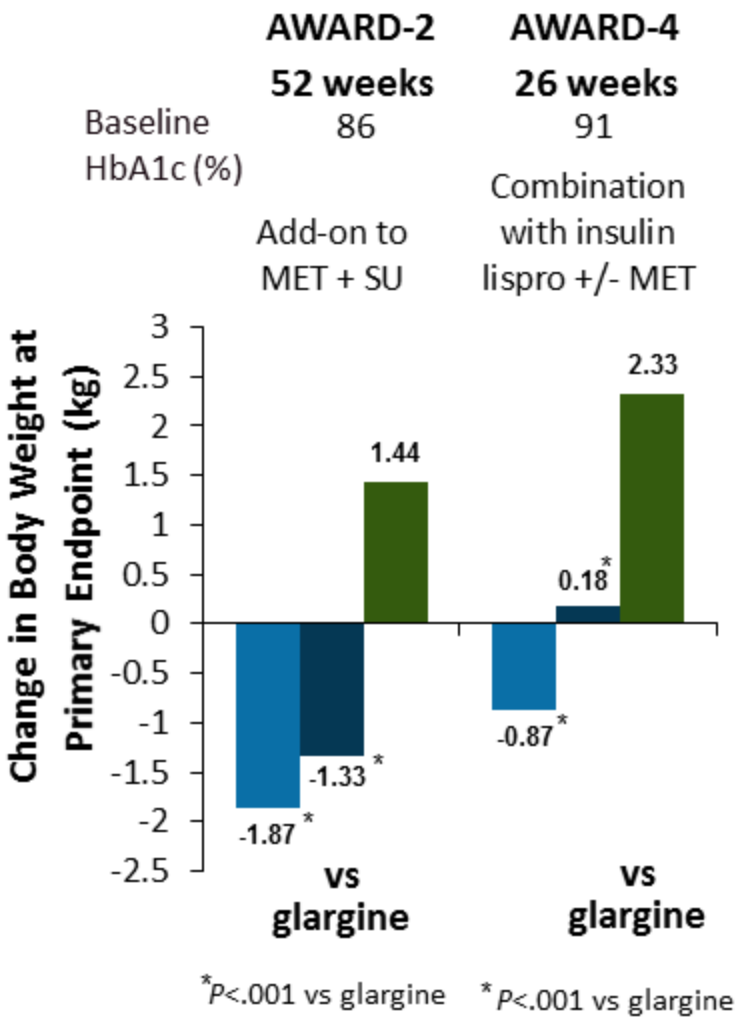
Short- and long-acting GLP-1RAs were associated with significant reductions from baseline in BW , whereas iDPP-4 only were associated **with a trend** toward weight loss

Clinical Therapeutics/Volume 34, Number 6, 2012

GLP-1 vs Ins

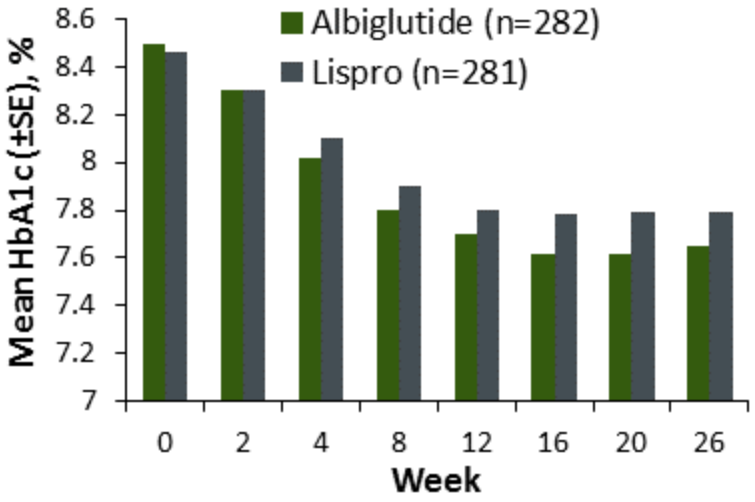
Dulaglutide AWARD-2, AWARD-4: HbA1c Change From Baseline and Weight Change From Baseline

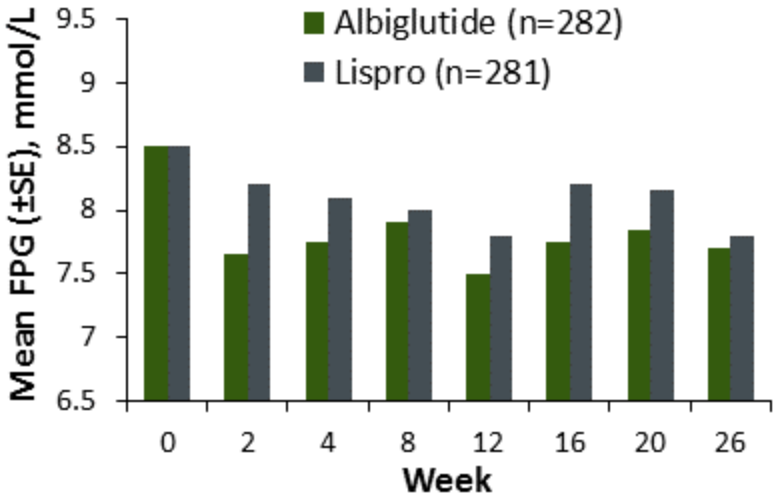


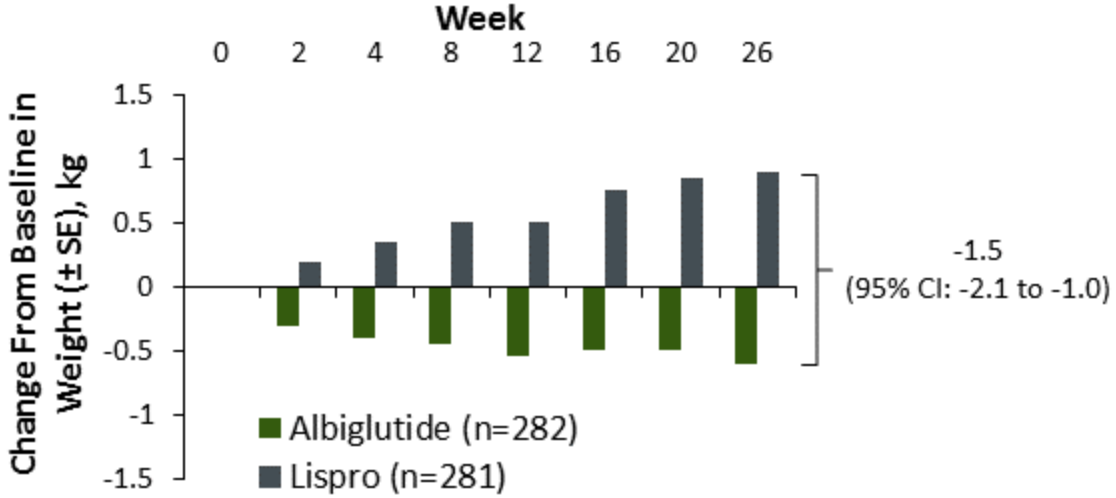


a. Giorgino F, et al. *Diabetes Care*. 2015;38:2241-2249.
b. Blonde L, et al. *Lancet*. 2015;385:2057-2066.

Advancing Basal Insulin Replacement in T2DM: qw Albiglutide vs tid Prandial Insulin Lispro: HbA1c, FPG, and Weight Change Results







- qw GLP-1 RA albiglutide, a simpler therapeutic option than tid prandial insulin, resulting in comparable glucose reduction with weight loss and lower hypoglycemia risk

Rosenstock J, et al. *Diabetes Care*. 2014;37:2317-2325.

DPP4s

Η σιταγλιπτίνη ενισχύει τα επίπεδα ενεργών ινκρετινών με αναστολή της DDP-4 [1–4]

Γλυκοζοεξαρτώμενη

Αυξάνοντας και παρατείνοντας τα επίπεδα ενεργών ινκρετινών, η σιταγλιπτίνη αυξάνει την έκκριση ινσουλίνης και μειώνει τα επίπεδα γλυκαγόνης στην κυκλοφορία με γλυκοζοεξαρτώμενο τρόπο.

Αναστολείς DPP-4: Αποτελεσματικότητα αναστολής του ενζύμου DPP-4

Inhibitor	DPP-4 inhibition*
Sitagliptin [9,27]	Max ~97%; >80% 24 h postdose
Vildagliptin [12,25]	Max ~95%; >80% 12 h postdose
Saxagliptin [14,26]	Max ~80%; ~70% 24 h postdose
Alogliptin [28]	Max ~90%; ~75% 24 h postdose
Linagliptin [29]	Max ~80%; ~70% 24 h postdose

Η αποτελεσματικότητα στην αναστολή του DPP-4 είναι παρόμοια

Deacon CF, Diabetes, Obesity and Metabolism 13: 7-18,2011

Αναστολείς DPP-4: Η σιταγλιπτίνη είναι ένας υψηλά εκλεκτικός αναστολέας

Inhibitor	Selectivity	QPP/DPP-2	PEP	FAPα	DPP-8	DPP-9
Sitagliptin [7]	High	>5550	>5550	>5550	>2660	>5550
Vildagliptin [10,20]	Moderate	>100 000	60 000	285	270	32
Saxagliptin [21]	Moderate	>50 000	Not reported	>4000	390	77
Alogliptin [15]	High	>14 000	>14 000	>14 000	>14 000	>14 000
Linagliptin [19]	Moderate	>100 000	>100 000	89	40 000	>10 000

QPP, quiescent cell proline dipeptidase; PEP, prolyl endopeptidase; FAPα, fibroblast activation protein-α.

C.F. Deacon. Diabetes, Obesity and Metabolism 13: 7–18, 2011

HbA1c response to different DPP-4 inhibitors in type 2 diabetes

Table 2 Effects of DPP-4 inhibitors and covariates on HbA1c reduction from baseline (Δ)

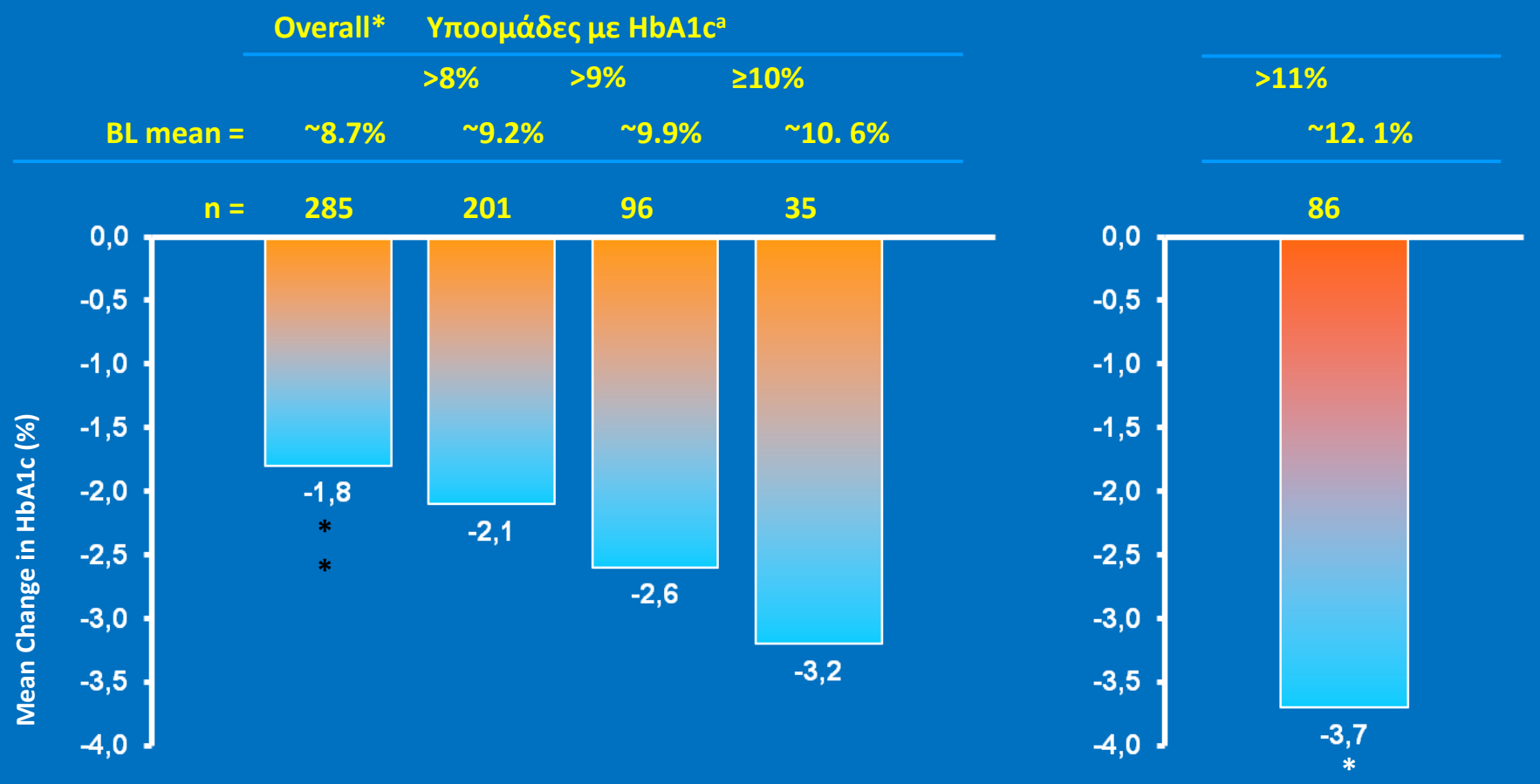
	Arms	Mean age*	Mean basal*	ΔHbA1c (%)	Low CI 95%	High CI 95%	p Value	I^2 (%)	Model
Vildagliptin 50 mg	26	56.3	8.06	−0.88	−1.00	−0.75	<0.0001	98	RE
Sitagliptin 100 mg	37	55.2	8.05	−0.79	−0.87	−0.71	<0.0001	94	RE
Saxagliptin 5 mg	13	55.4	8.01	−0.70	−0.79	−0.62	<0.0001	86	RE
Linagliptin 5 mg	13	59.0	8.05	−0.55	−0.65	−0.45	<0.0001	90	RE
Alogliptin 25 mg	11	55.2	8.14	−0.76	−0.86	−0.66	<0.0001	90	RE

24 163 participants

Baseline HbA1c & FPG explain most of the variance in HbA1c change in response to DPP-4 inhibitors due to their glucose dependent action

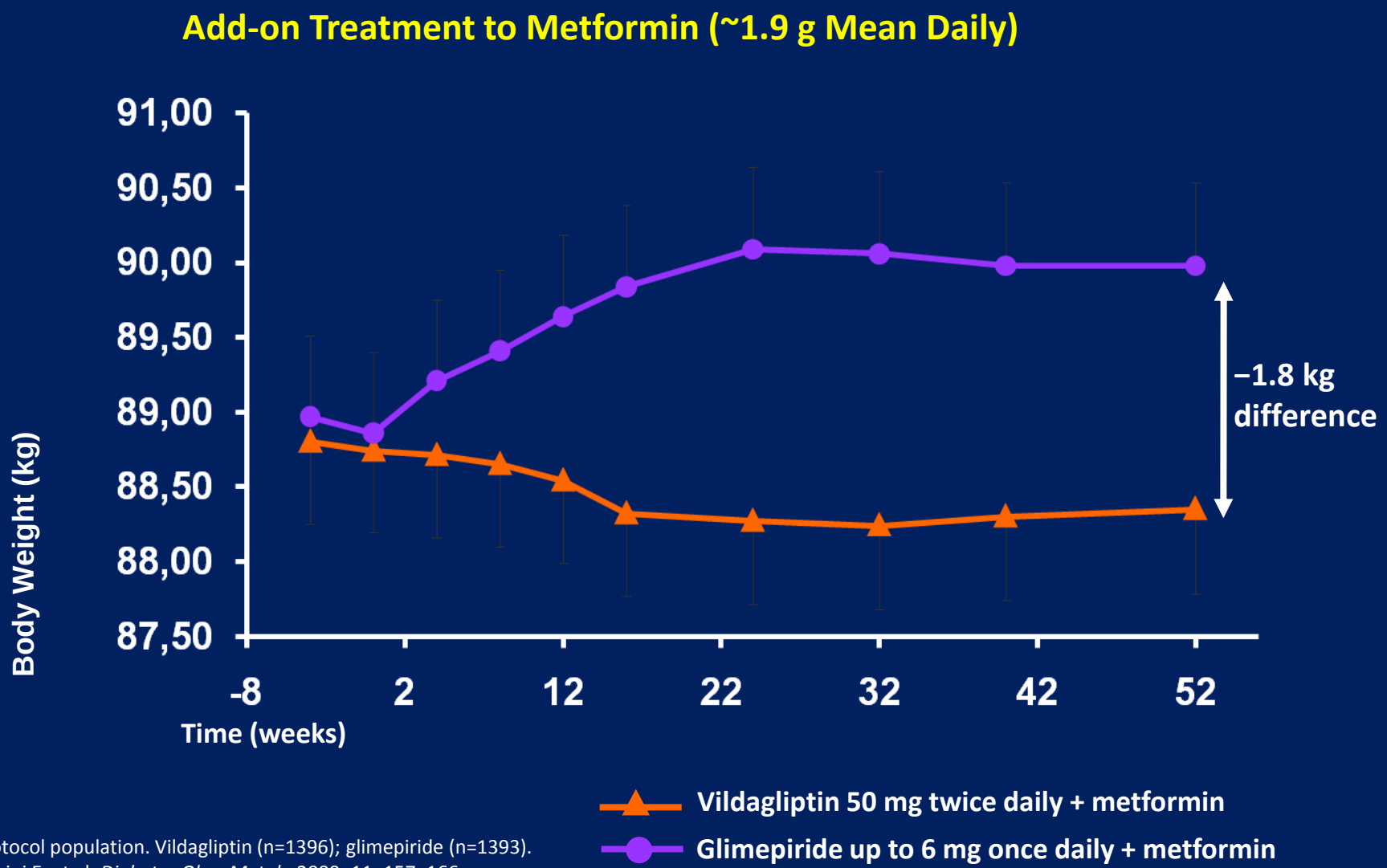
BMJ Open 2015;5:e005892. doi:10.1136/bmjopen-2014- 005892

Vildagliptin & Metformin: ΒΑΘΜΟΣ ΥΠΕΡΓΛΥΚΑΙΜΙΑΣ



BL=baseline; EP=end point; HbA1c=hemoglobin A1c; met=metformin; vilda=vildagliptin
*P <0.001 vs BL; **P <0.001 vs monotherapy components; [†]100 mg once daily is not an approved dose.
Intention-to-treat population. [a]Raw mean change from baseline; [b]Least-square mean change from baseline.
Bosi E, et al. *Diabetes Obes Metab* (in press); Data on file, Novartis Pharmaceuticals, [c]LMF237A2302 and [d]LMF237A2302S1.

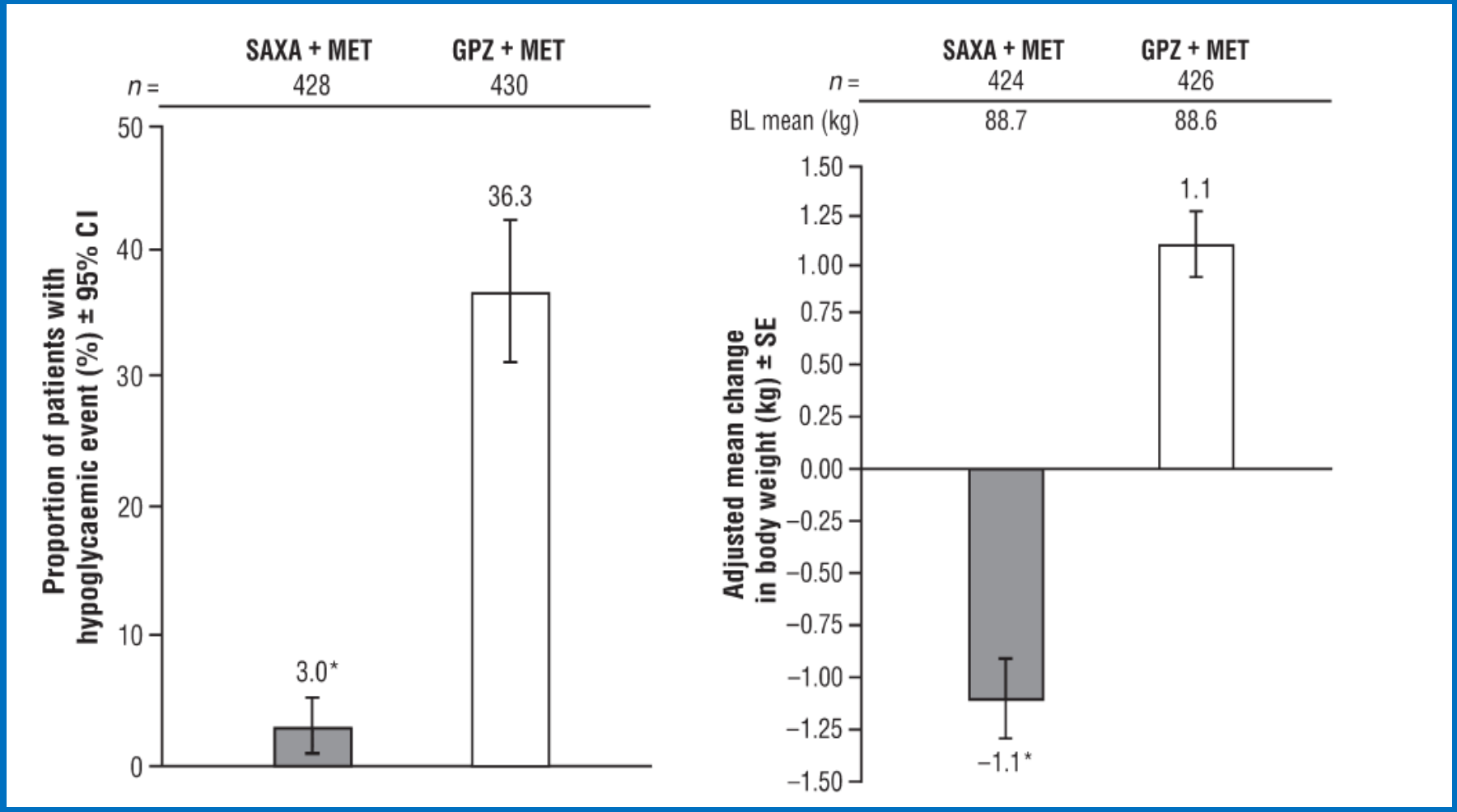
Vildagliptin vs Gimepiride σε συνδυασμό με Metformin: ΑΥΞΗΣΗ ΒΣ



Per protocol population. Vildagliptin (n=1396); glimepiride (n=1393).
Ferrannini E, et al. *Diabetes Obes Metab.* 2009; 11: 157–166.
Data on file, Novartis Pharmaceuticals, LAF237A2308.

ΥΠΟΓΛΥΚΑΙΜΙΑ

ΣΩΜΑΤΙΚΟ ΒΑΡΟΣ



Goeke B et al, Int J Clin Practice 2010

After a woman was taken to the hospital with hypoglycemia (low bloodsugar), two policemen stayed behind to prepare dinner for the five kids who were still in the house.
Afterwards, they also did the dishes. Respect.
(Eindhoven, Netherlands)

Hypoglycemia Incidence & Health Care Costs in DM2 Treated with Lina or Su After Met Monotherapy

TABLE 2 Incidence Rate of Hypoglycemic Events

	Total N = 11,536		Linagliptin n = 2,884		Sulfonylurea n = 8,652	
Rate in 100 person-years	3.37		2.51		3.63[a]	
Rate in 100 person-years by setting of care (% of overall rate)						
Hospital	0.26	(7.7)	0.14	(5.6)	0.30	(8.2)
Emergency room	0.34	(10.1)	0.07	(2.8)	0.42	(11.7)
Physician office	2.38	(70.6)	1.82	(72.2)	2.55	(70.2)
Other[b]	0.39	(11.6)	0.49	(19.4)	0.36	(9.9)

iDPP-4 with **lower hypoglycemia** and **costs** than SU

J Manag Care Spec Pharm. 2016;22(5):483-92

Ειδικοί πληθυσμοί: Νεφρική Δυσλειτουργία

	Νεφρική Δυσλειτουργία			
	Ήπια (Cl_{cr} >50 ml/min)	**Μέτρια (Cl_{cr} 30 -50 ml/min)**	**Σοβαρή (Cl_{cr} <30 ml/min)**	**Νεφρική Ανεπάρκεια Τελικού Σταδίου (ESRD)**
Σιταγλιπτίνη	✓	½ δόση	¼ δόση	¼ δόση
Βιλνταγλιπτίνη	✓	½ δόση	½ δόση	½ δόση (περιορισμένη εμπειρία σε ασθενείς με ESRD που υποβάλλονται σε αιμοδιύλιση γι αυτό το λόγο συνιστάται προσοχή σε αυτούς τους ασθενείς)
Σαξαγλιπτίνη	✓	½ δόση	½ δόση	**Δεν συνιστάται**
Λιναγλιπτίνη	✓	✓	✓	✓
Αλογλιπτίνη	✓	½ δόση	¼ δόση	¼ δόση Η αλογλιπτίνη δεν έχει μελετηθεί σε ασθενείς οι οποίοι υφίστανται περιτοναϊκή διύλιση

Ref: SPCs προϊόντων

Ειδικοί πληθυσμοί: Ηπατική Δυσλειτουργία

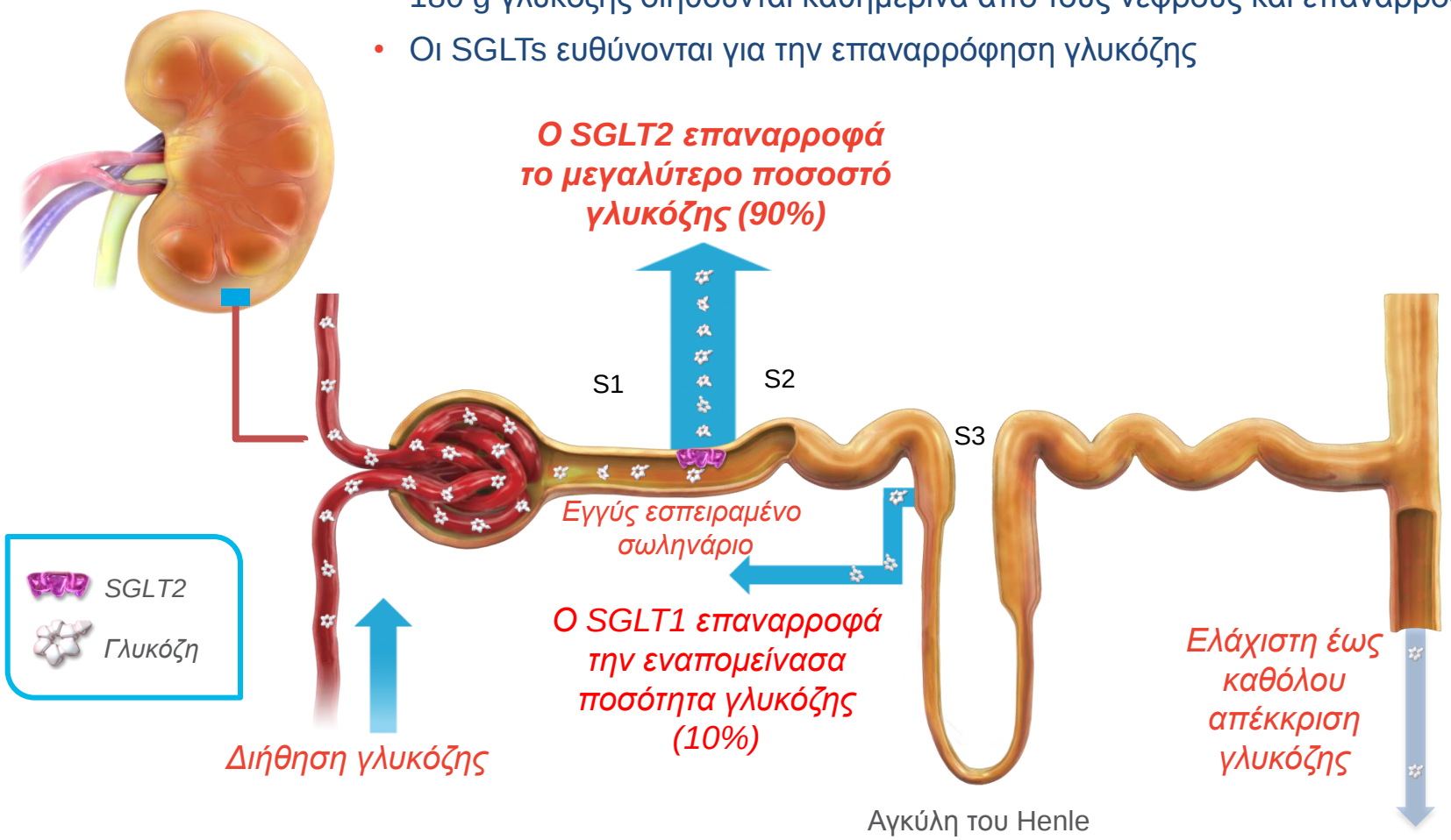
	Ηπατική δυσλειτουργία	
	Ήπια/ Μέτρια	**Σοβαρή**
Σιταγλιπτίνη	✓	Δεν συνιστάται
Βιλνταγλιπτίνη	**Δεν συνιστάται**	
Σαξαγλιπτίνη	✓ **(Μέτρια: με προσοχή)**	Δεν συνιστάται
Λιναγλιπτίνη	✓ **(περιορισμένη εμπειρία)**	✓ **(περιορισμένη εμπειρία)**
Αλογλιπτίνη	✓	Δεν συνιστάται

Ref: SPCs προϊόντων

SGLT2s

Φυσιολογική ρύθμιση γλυκόζης από τους νεφρούς

- 180 g γλυκόζης διηθούνται καθημερινά από τους νεφρούς και επαναρροφούνται
- Οι SGLTs ευθύνονται για την επαναρρόφηση γλυκόζης



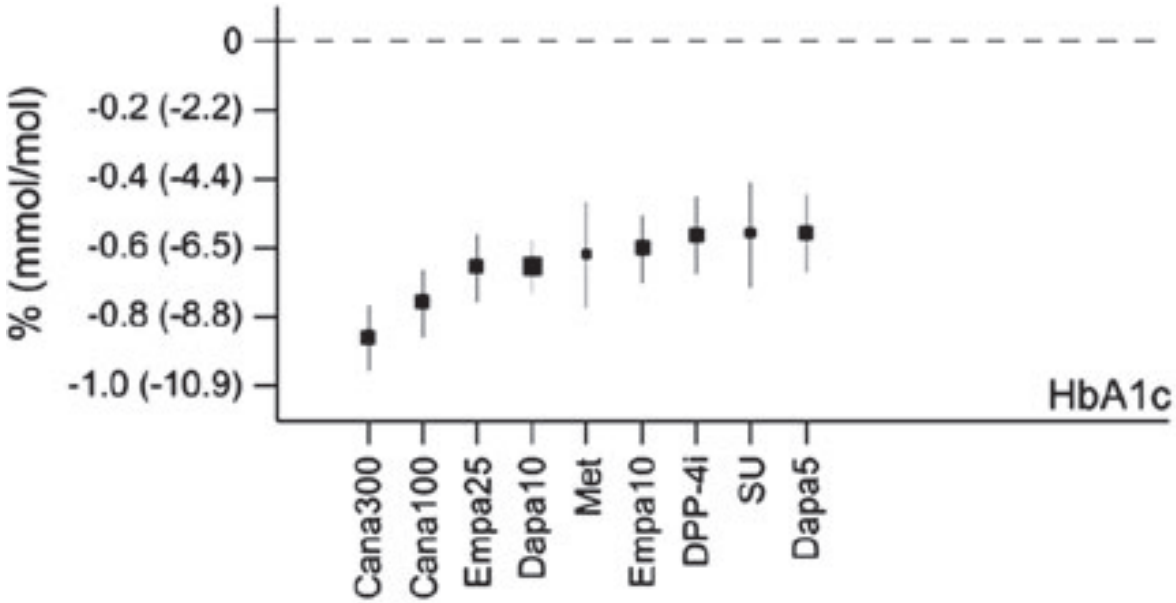
SGLT, συμμεταφορέας νατρίου-γλυκόζης.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21.

SGLT-2 Inhibitors

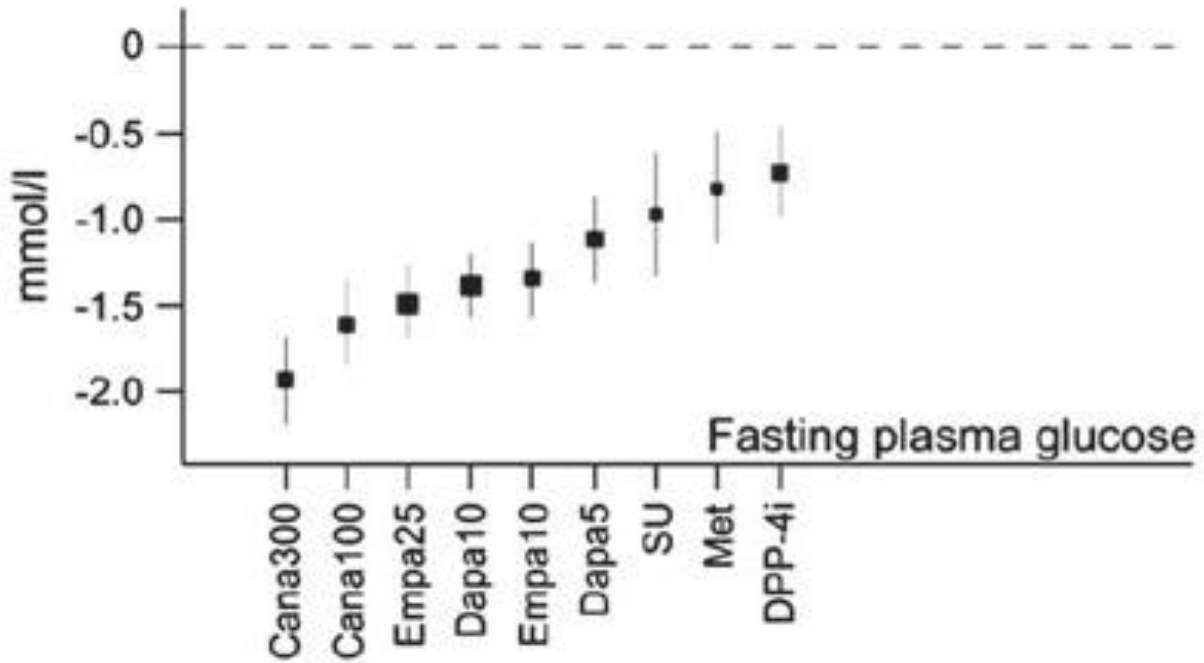
Drug	Dosing	Use in renal impairment
Canagliflozin	100 mg OD 300 mg OD	- eGFR <30 mL/min · 1.73 m^2 (avoid) - eGFR 45–60 mL/min · 1.73 m^2 (use 100 mg dose) - eGFR 30–45 mL/min · 1.73 m^2 (initial use not recommended; discontinue when <45 mL/min · 1.73 m^2 in patients already on canagliflozin)
Dapagliflozin	5 mg OD 10 mg OD	- eGFR >60 mL/min · 1.73 m^2 (no dose adjustment) - eGFR <60 mL/min · 1.73 m^2 (initial use not recommended; discontinue when <60 mL/min · 1.73 m^2 in patients already on dapagliflozin) - eGFR <30 mL/min · 1.73 m^2 (contraindicated)
Empagliflozin	10 mg OD 25 mg OD	- eGFR ≥45 mL/min · 1.73 m^2 (no dose adjustment) - eGFR <45 mL/min · 1.73 m^2 (initial use not recommended; discontinue when <45 mL/min · 1.73 m^2 in patients already on empagliflozin) - eGFR <30 mL/min · 1.73 m^2 (contraindicated)

Η αποτελεσματικότητα και η ασφάλεια των SGLT-2 αναστολέων σε σακχαρώδη διαβήτη τύπου 2: systematic review and network meta-analysis



Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis .Zaccardi_et_al-2016-Diabetes,_Obesity_and_Metabolism

Η αποτελεσματικότητα και η ασφάλεια των SGLT-2 αναστολέων σε σακχαρώδη διαβήτη τύπου 2: systematic review and network meta-analysis



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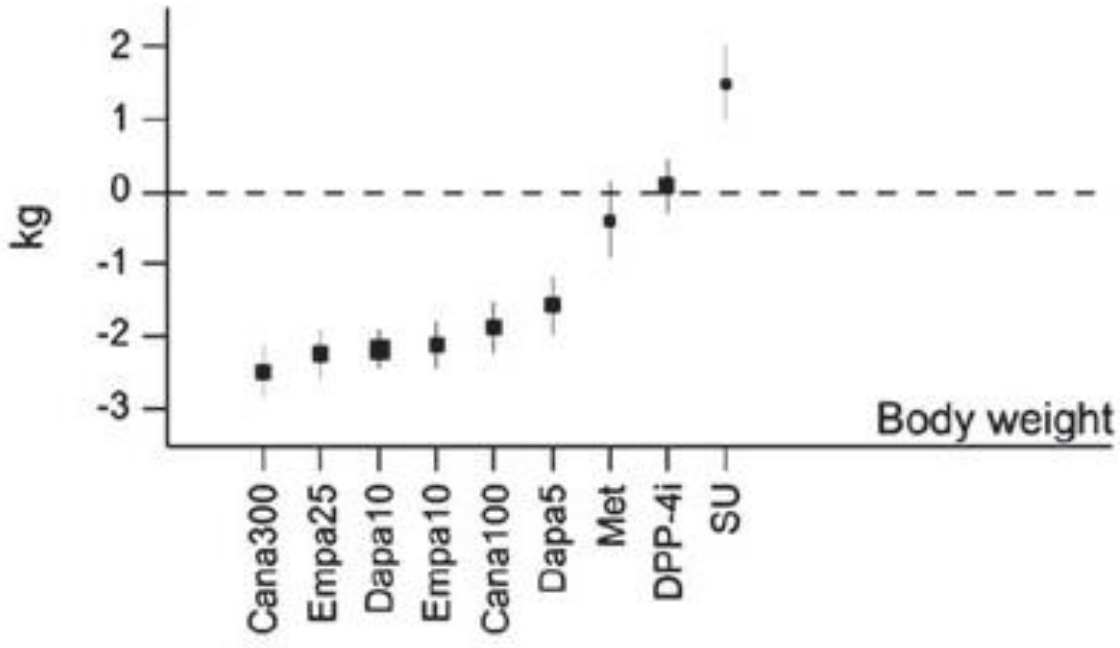

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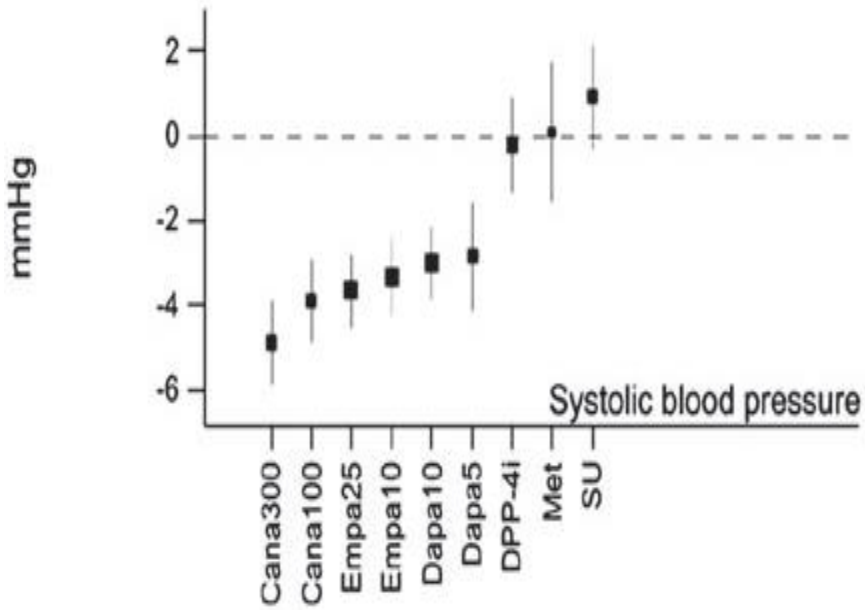
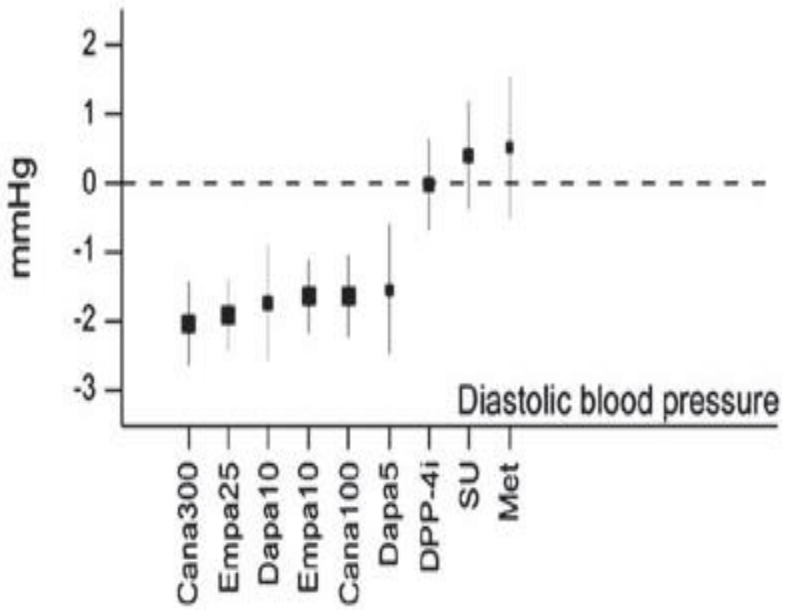




Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis .Zaccardi_et_al-2016-Diabetes,_Obesity_and_Metabolism

Επιπτώσεις στο Λιπιδαιμικό προφίλ

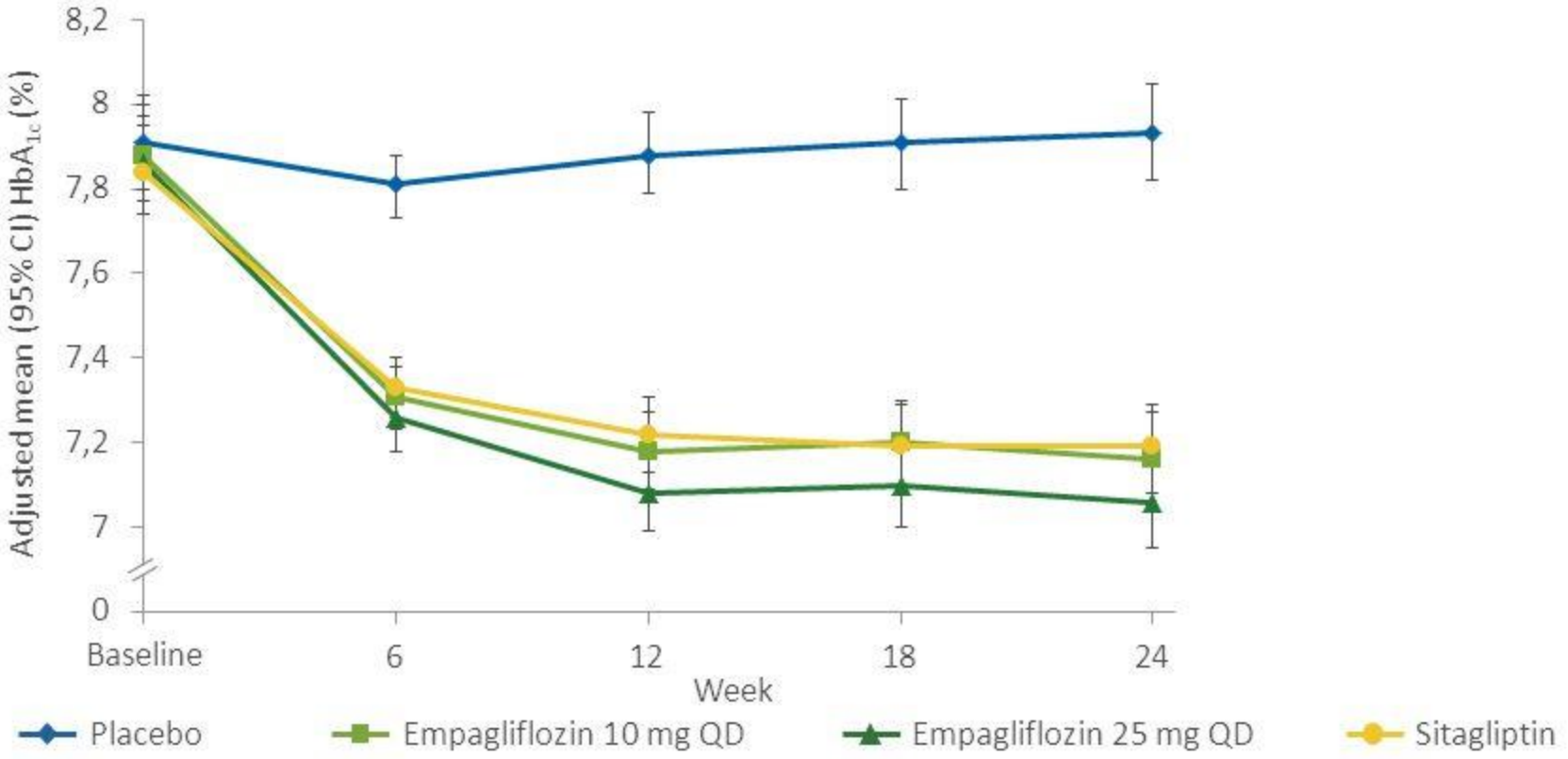
SGLT2 inhibitor

Compound	TGs	HDL-C	LDL-C
Canagliflozin	↓	↑	↑
Dapagliflozin	↔	↑	↑
Empagliflozin	↔	Slight ↑	↑

Common medications used by patients with type 2 diabetes mellitus: what are their effects on the lipid profile?
Paul D. Rosenblit *Cardiovascular Diabetology*2016**15**:95

DPP4 vs SGLT2

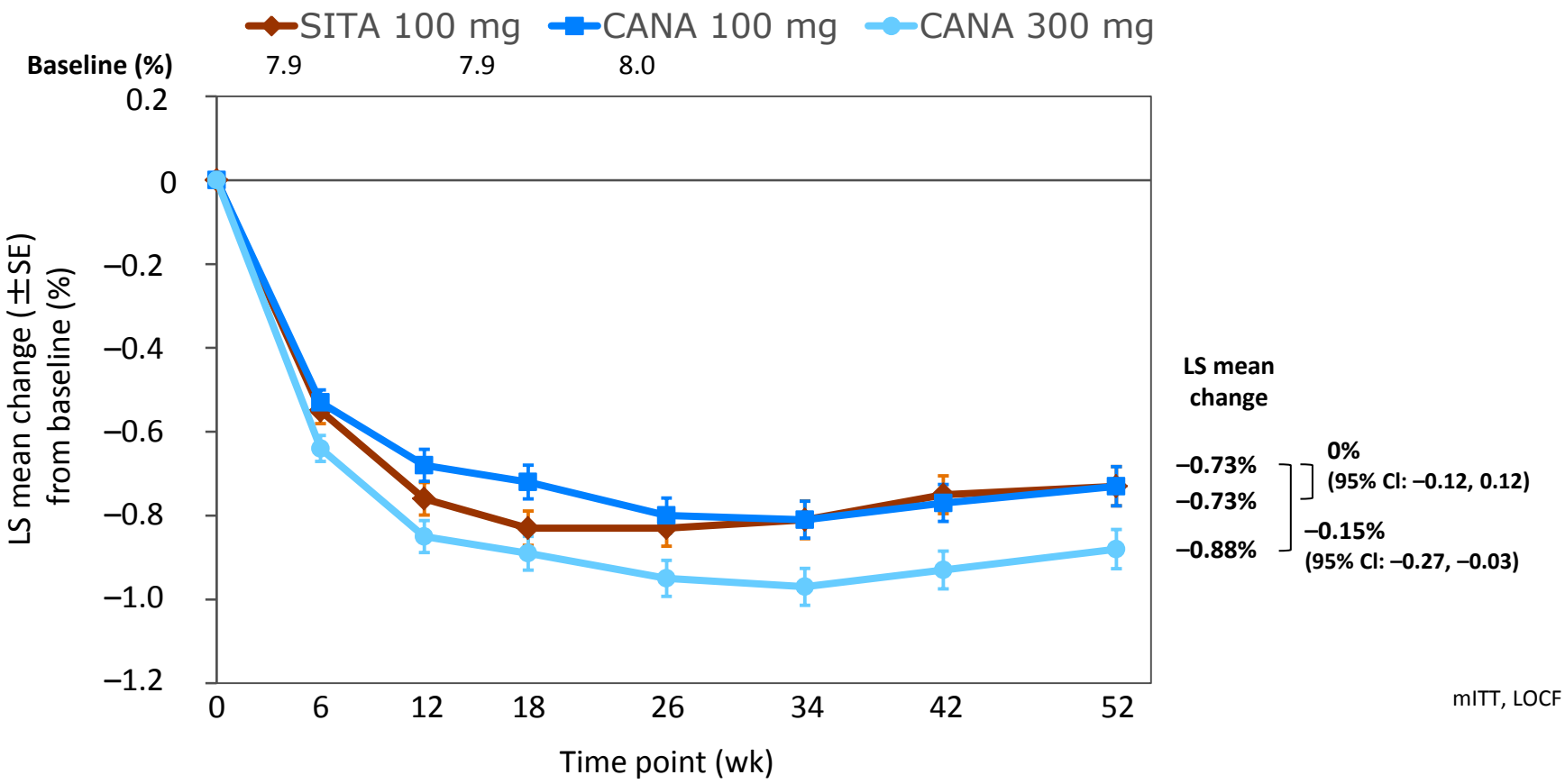
24-week empagliflozin monotherapy versus placebo and sitagliptin
Change from baseline in HbA_{1c} over time



Number of patients analysed					
Placebo	212	211	186	173	158
EMPA 10 mg QD	215	215	211	206	203
EMPA 25 mg QD	221	221	208	204	203
Sitagliptin	220	219	213	203	198

EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin; QD, once daily; SE, standard error.
MMRM results, FAS (OC).
Roden M, et al. *Lancet Diabetes Endocrinol.* 2013;1:208–219.

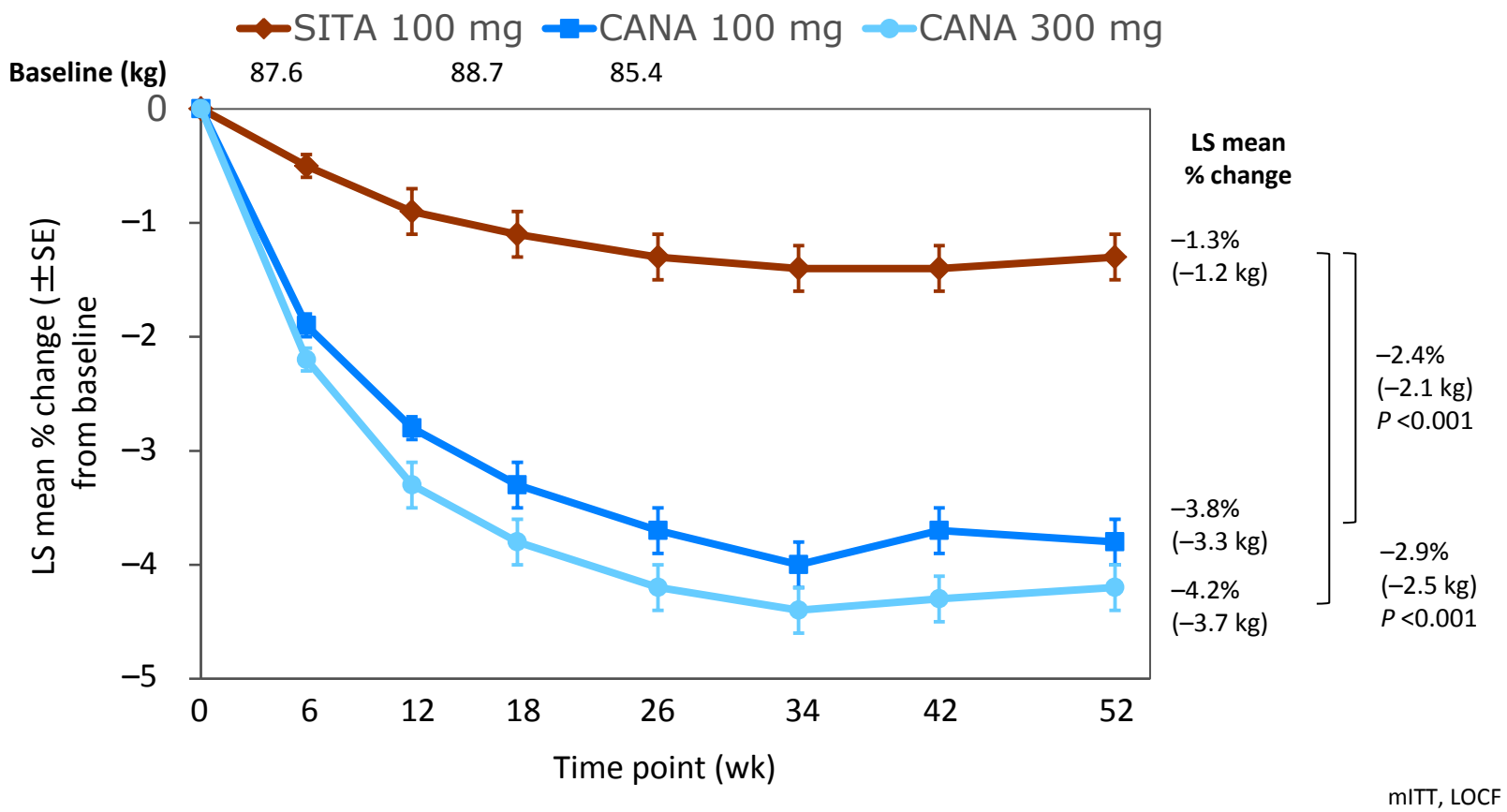
Επιπρόσθετη θεραπεία στη μετφορμίνη vs σιταγλιπτίνης (DIA3006): Μεταβολή της HbA1c



- Η CANA 100 και CANA 300 mg επέδειξαν μη κατωτερότητα σε σχέση με τη SITA 100 mg ως προς τη μείωση της HbA1c
- Η CANA 300 mg επέδειξε στατιστική ανωτερότητα σε σχέση με τη SITA 100 mg ως προς τη μείωση της HbA1c

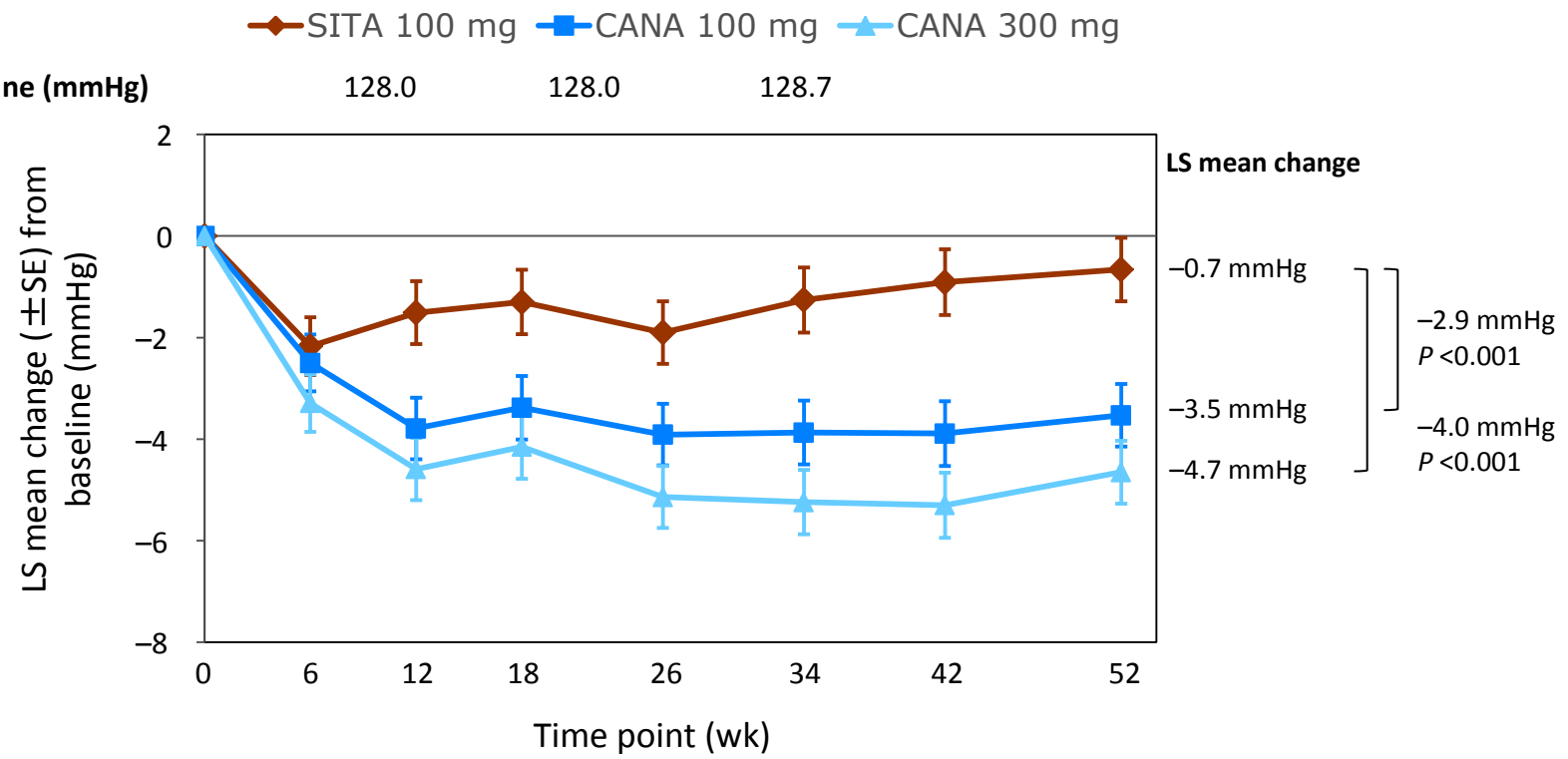
Lavalle-González FJ et al. Diabetologia. 2013 56:2582-2592

Επιπρόσθετη θεραπεία στη μετφορμίνη vs σιταγλιπτίνης (DIA3006): Μεταβολή του σωματικού βάρους



Lavalle González, et al. Poster presented at ADA 2013 Chicago, Illinois,
Lavalle-González FJ et al. Diabetologia. 2013 56:2582-2592

Επιπρόσθετη θεραπεία στη μετφορμίνη vs σιταγλιπτίνης (DIA3006): Μεταβολή της συστολικής αρτηριακής πίεσης



- Με την CANA 100 και 300 mg και τη SITA 100 mg, LS μέσες μεταβολές της διαστολικής ΑΠ από την τιμή αναφοράς ήταν −1.8, −1.8, και −0.3 mmHg, αντίστοιχα
- Μη αξιοσημείωτες μεταβολές στην καρδιακή συχνότητα παρατηρήθηκαν μεταξύ των ομάδων

mITT, LOCF

Lavalle González, et al. Poster presented at ADA 2013 Chicago, Illinois,
Lavalle-González FJ et al. Diabetologia. 2013 56:2582-2592

Επιλεγμένες AE

	Subjects, n (%)			
	PBO/SITA (n = 183)	SITA 100 mg (n = 366)	CANA 100 mg (n = 368)	CANA 300 mg (n = 367)
AEs				
UTI	12 (6.6)	23 (6.3)	29 (7.9)	18 (4.9)
Genital mycotic infection				
Male	1 (1.1)	2 (1.2)	9 (5.2)	4 (2.4)
Female	1 (1.1)	5 (2.6)	22 (11.3)	20 (9.9)
Osmotic diuresis-related AEs*	1 (0.5)	7 (1.9)	30 (8.2)	16 (4.4)
Volume-related AEs†	1 (0.5)	7 (1.9)	4 (1.1)	3 (0.8)
Documented hypoglycemia episodes‡	5 (2.7)	15 (4.1)	25 (6.8)	25 (6.8)
Severe episodes	0	1 (0.3)	1 (0.3)	0

*Includes dry mouth, micturition disorder, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased.
†Includes BP decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope, and urine output decreased.
‡**Includes episodes that were biochemically documented (≤70 mg/dL [3.9 mmol/L]) or severe (ie, requiring the assistance of another individual or resulting in seizure or loss of consciousness).**

Lavalle-González FJ et al. Diabetologia. 2013 56:2582-2592

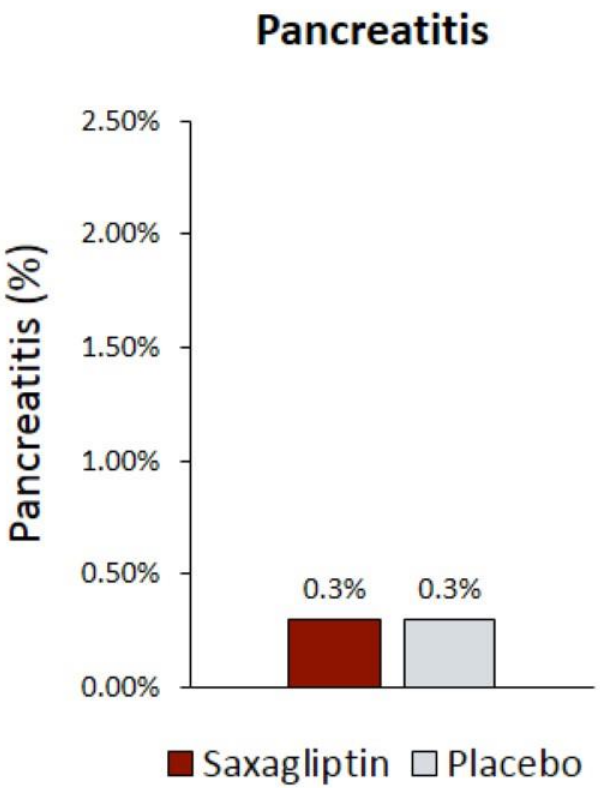
ANTIDIABETIC DRUGS & CVD

- In increased cardiovascular risk have demonstrated a cardiovascular benefit (significant reduction in time to first major adverse cardiovascular event) with the GLP-1R agonists **liraglutide (LEADER), semaglutide (SUSTAIN)** and SGLT2 inhibitors **canagliflozin (CANVAS) and Empagliflozin (EMPAREG).**

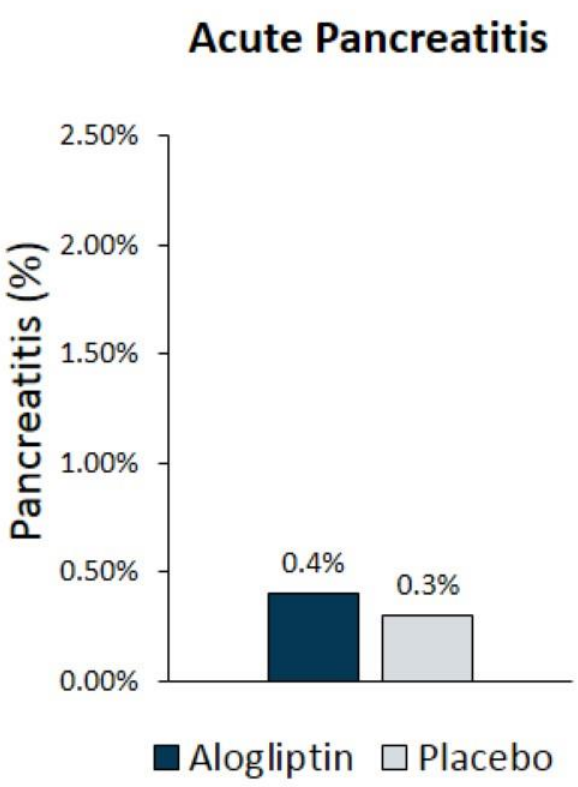
- **In contrast**, cardiovascular outcome trials examining the safety of the shorter-acting GLP-1R agonist **lixisenatide (ELIXA trial)** and the DPP-4 inhibitors **saxagliptin (SAVOR-TIMI 53 trial)**, **alogliptin (EXAMINE trial**), and **sitagliptin (TECOS)** found that **neither increased nor decreased** cardiovascular events.

DPP-4 Inhibitors: Pancreatitis

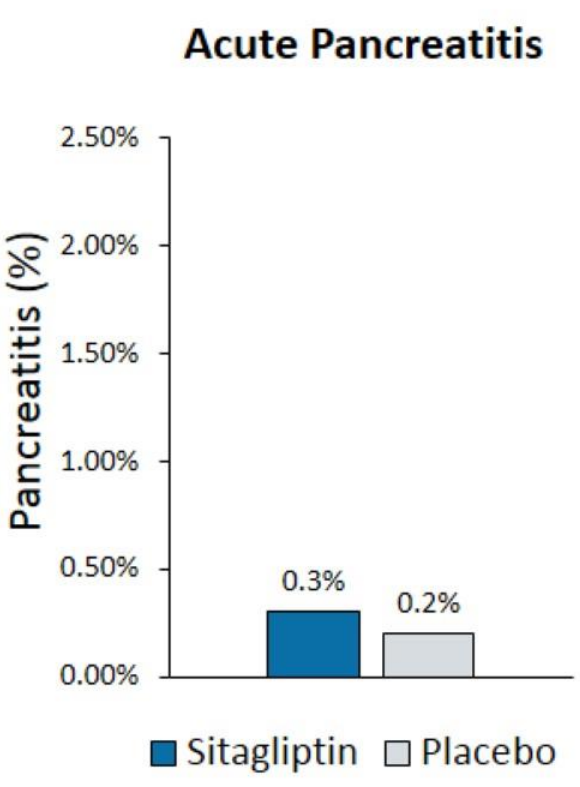
SAVOR-TIMI



EXAMINE



TECOS



Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.
White WB, et al. *N Engl J Med*. 2013;369:1327-1335.
Green JB, et al. *N Engl J Med*. 2015;373:232-242.

DPP-4 Inhibitor-Related Pancreatitis

Rare but Real

Diabetes Care 40, 284-6, Feb 2017

Study name	Pancreatitis / Total		Statistics for each study			
	Gliptin	Placebo	Odds ratio	Lower limit	Upper limit	p-Value
SAVOR	17 / 8280	9 / 8212	1.875	0.835	4.209	0.128
EXAMINE	12 / 2701	8 / 2679	1.490	0.608	3.651	0.383
TECOS	23 / 7257	12 / 7266	1.922	0.956	3.865	0.067
TOTAL	52 / 18238	29 / 18157	1.786	1.133	2.816	0.013

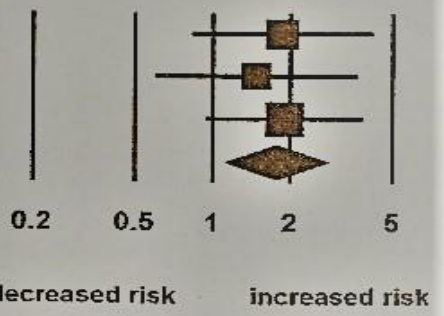


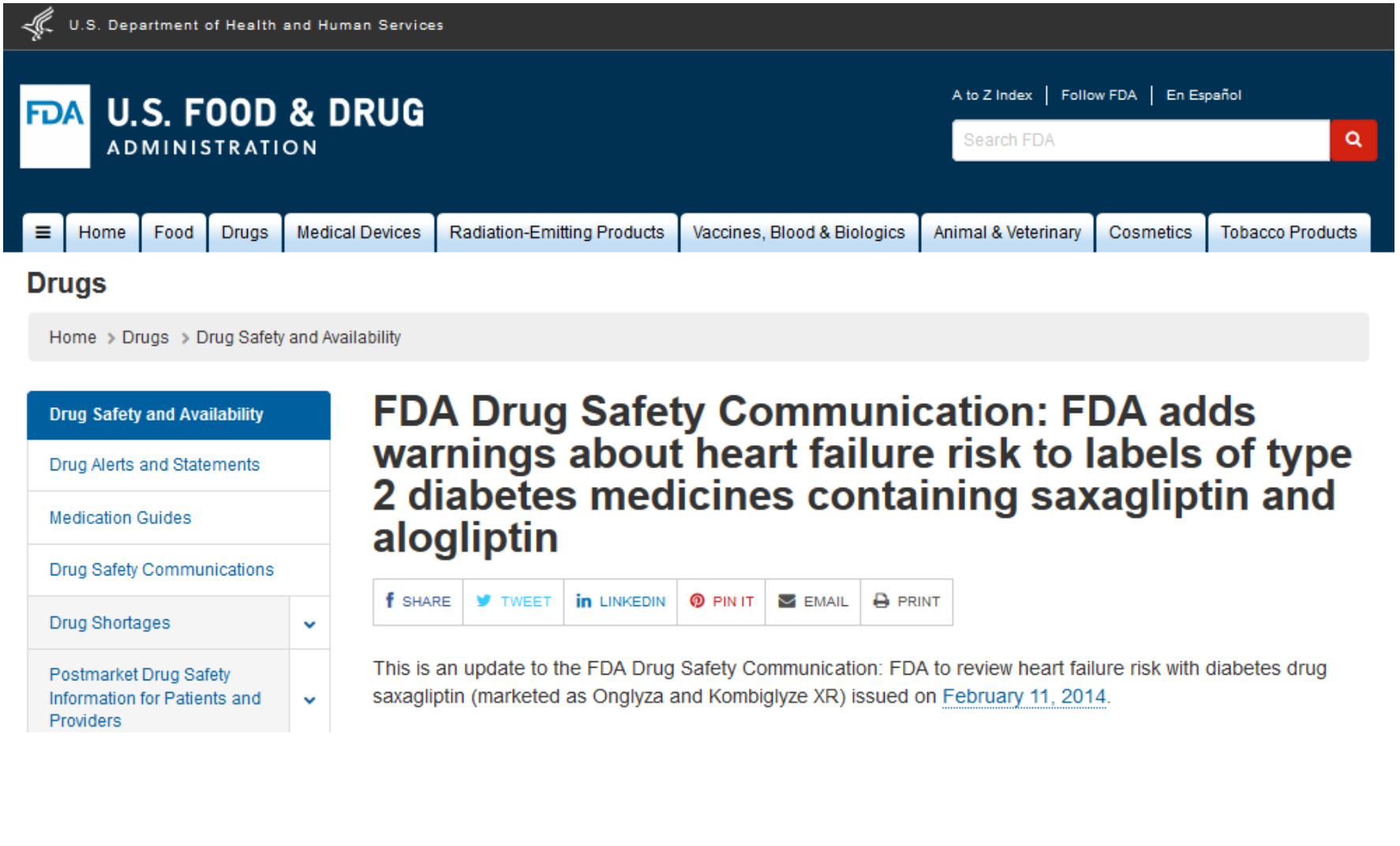
Figure 1—Combined analysis of the incidence of AP cases in the SAVOR-TIMI 53, EXAMINE, and TECOS studies.

Increased Risk 1.79- Absolute increased Risk 0.13% - **2 pt every 1000 pt for 2 y treatment**
Translated to 1.000.000 users results to **~ 750 new pancreatitis cases /year**

Contributing factor to **gallstones** (hypertriglyceridemia – diabetes)
Avoid pt with **pancreatitis history**, **gallstones** and **fluctuating 3x lipase** levels

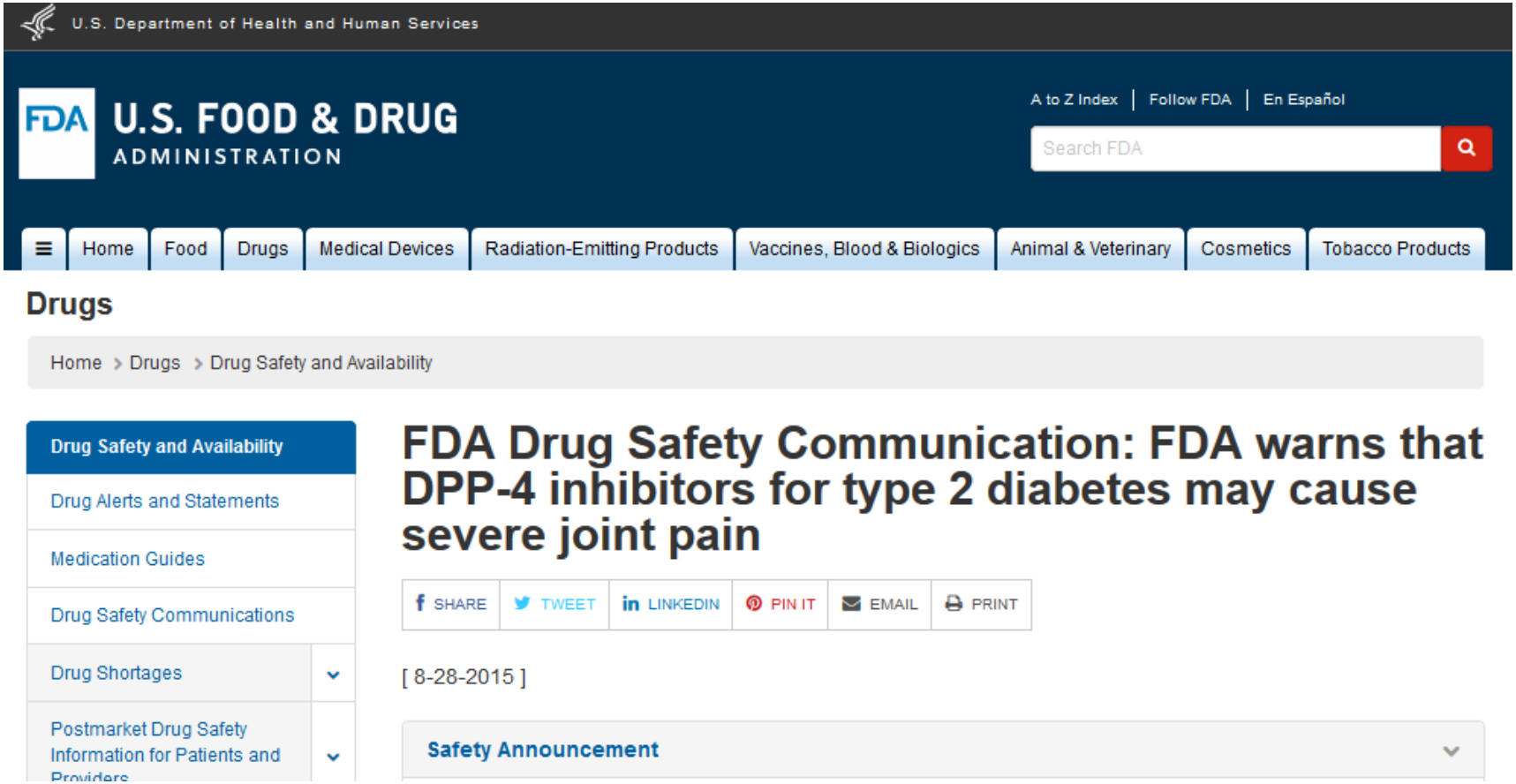
FDA WARNINGS

HF admissions



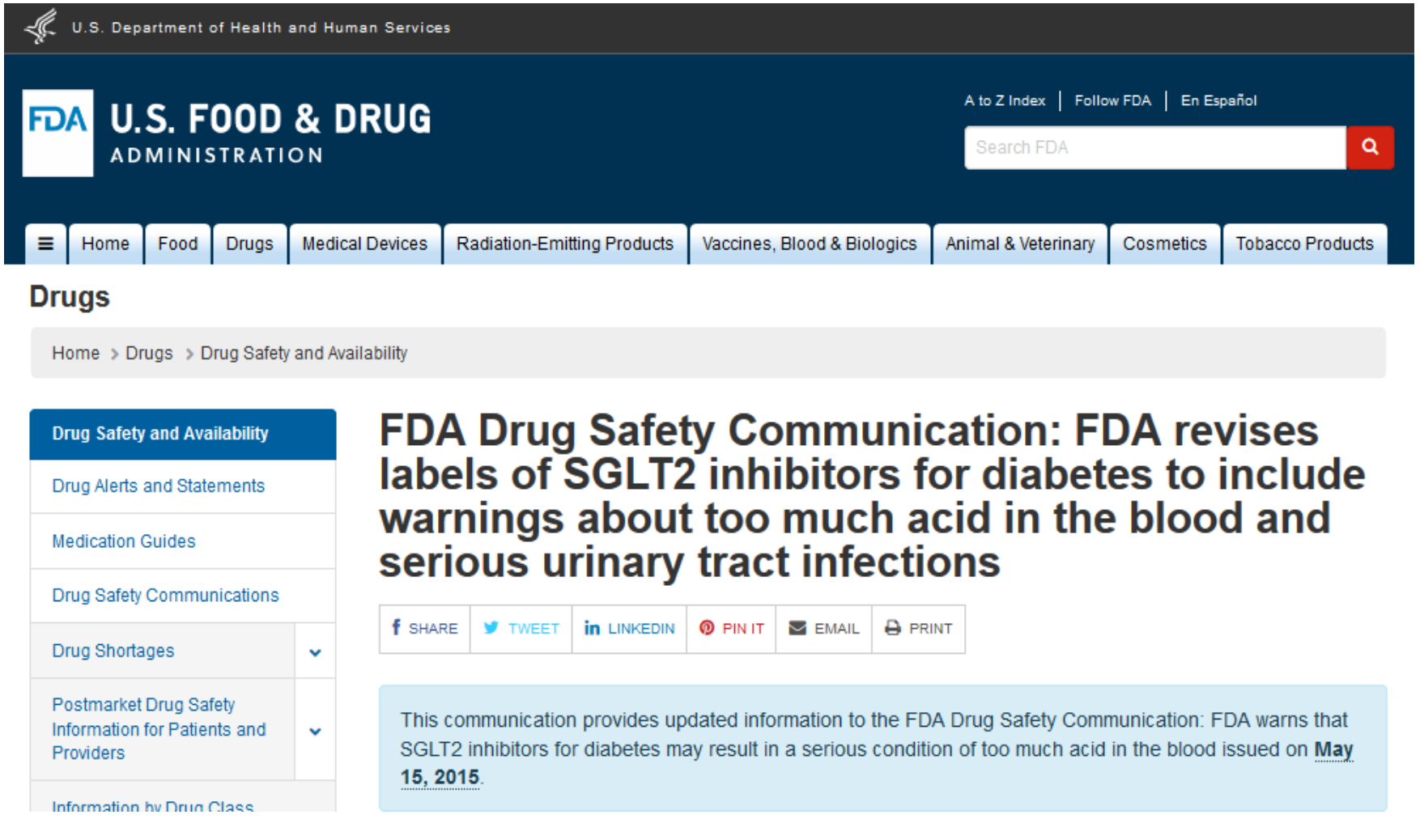
FDA WARNINGS

Joint pain



FDA WARNINGS

DKA

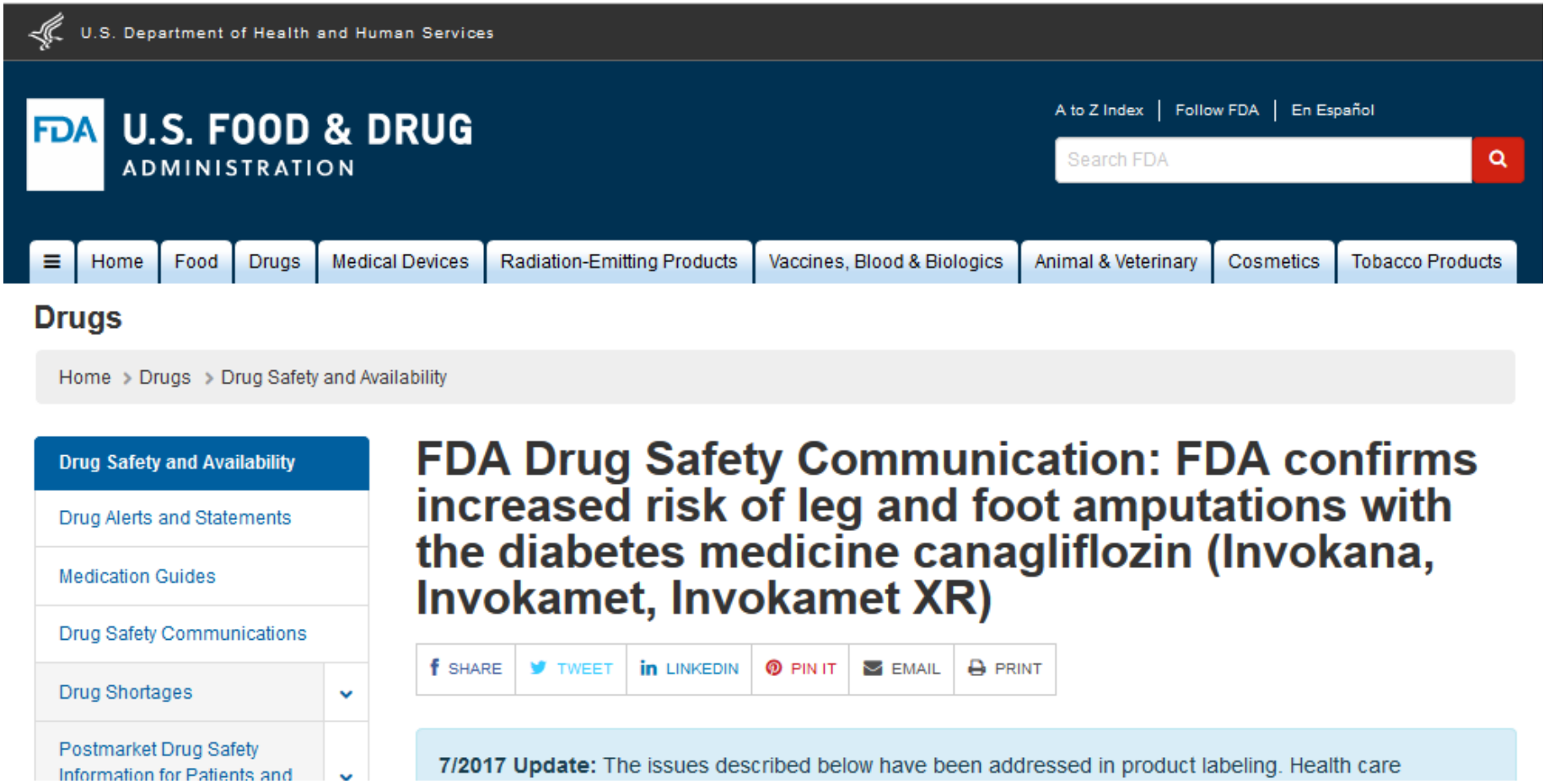


FDA WARNINGS

Renal

FDA WARNINGS

amputations



DIABETES MALPRACTICE

ΓΙΑΤΙ ΠΡΕΠΕΙ ΝΑ ΕΙΝΑΙ ΕΞΑΤΟΜΙΚΕΥΜΕΝΗ Η ΙΑΤΡΙΚΗ

Η ΥΓΕΙΑ ΕΙΝΑΙ ΚΑΤΙ ΤΟ ΠΡΟΣΩΠΙΚΟ:

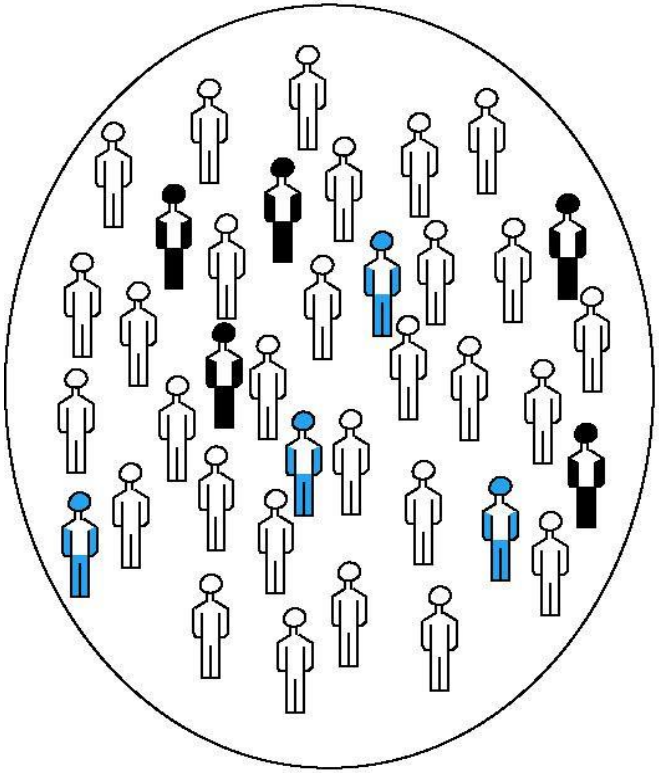
Υπάρχουν ασθενείς που δεν απαντούν στην θεραπεία

Συχνά απαιτείται διαφορετική δοσολογία

Κάποιοι εμφανίζουν ανεπιθύμητες αντιδράσεις

Ο καθένας έχει την διαφορετικότητά του

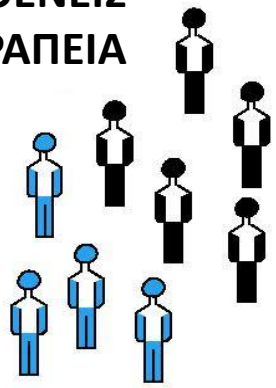
ΔΙΑΧΕΙΡΙΣΗ ΤΩΝ ΘΕΡΑΠΕΥΤΙΚΩΝ ΕΠΙΛΟΓΩΝ



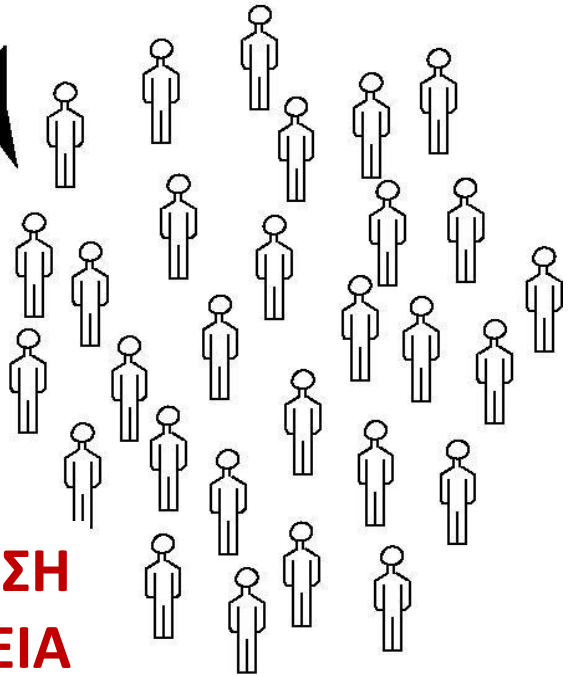
ΑΣΘΕΝΕΙΣ
ΜΕ ΤΟΝ ΙΔΙΟ ΦΑΙΝΟΤΥΠΟ
ΝΟΣΗΜΑΤΟΣ

ΓΟΝΙΔΙΑΚΟΣ
ΕΛΕΓΧΟΣ

ΑΣΘΕΝΕΙΣ
ΠΟΥ ΔΕΝ ΑΠΑΝΤΟΥΝ ΣΤΗ ΘΕΡΑΠΕΙΑ



ΑΣΘΕΝΕΙΣ
ΜΕ ΠΑΡΕΝΕΡΓΕΙΕΣ



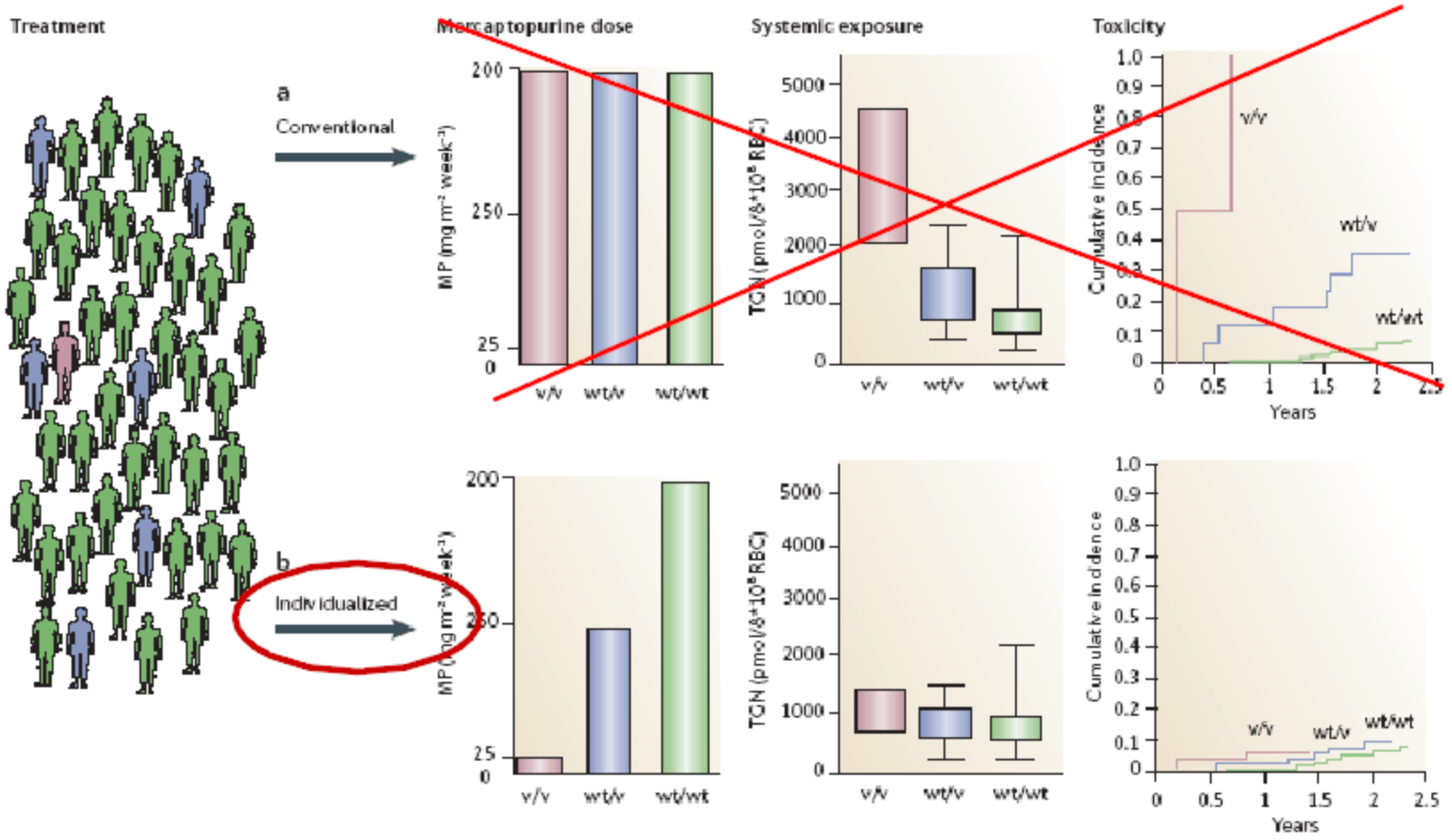
ΑΣΘΕΝΕΙΣ ΜΕ ΑΠΑΝΤΗΣΗ
ΣΤΗ ΘΕΡΑΠΕΙΑ

ΤΟ ΠΑΡΑΔΟΞΟ ΤΗΣ ΑΝΑΠΤΥΞΗΣ ΝΕΩΝ ΦΑΡΜΑΚΩΝ

Οι **κλινικές μελέτες** υποδεικνύουν τη **συνήθη δοσολογία** που ένα φάρμακο είναι δραστικό με τις ελάχιστες παρενέργειες **για κάθε ασθενή**

Χορηγούμε σε κάθε ασθενή που η **απάντηση του στη θεραπεία μπορεί να διαφέρει** την ίδια δόση

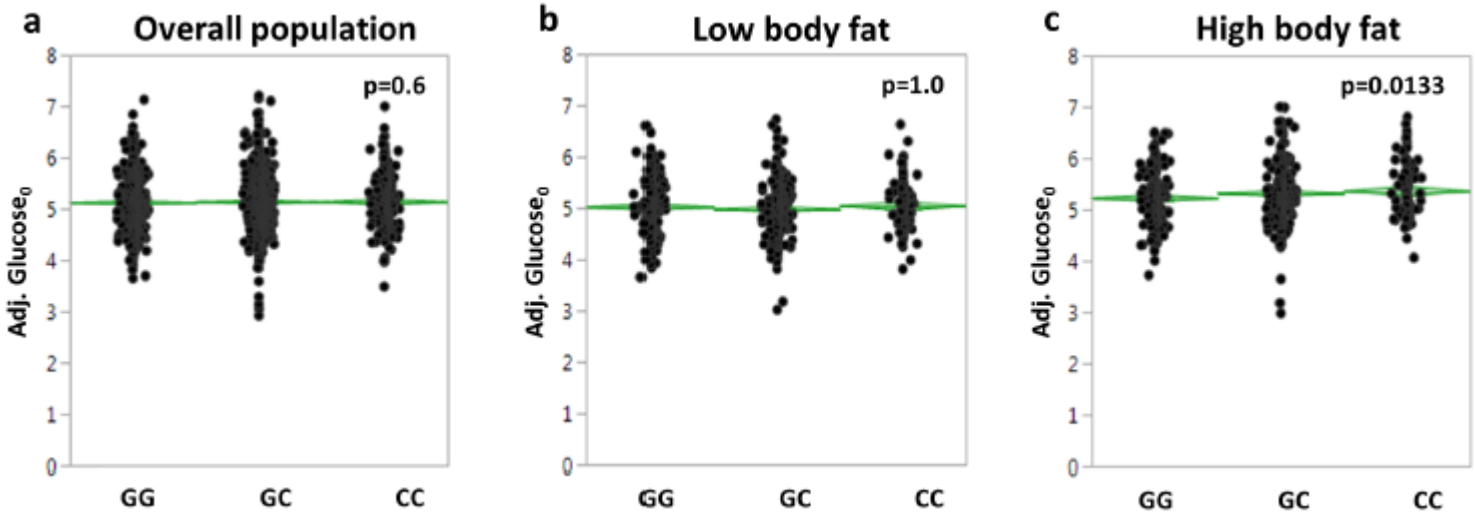
Dosing 6MP *with* pharmacogenetics



Evans Nature Reviews Cancer 2006

DPP4 gene variation affects GLP-1 secretion, insulin secretion, and glucose tolerance in humans with high body adiposity

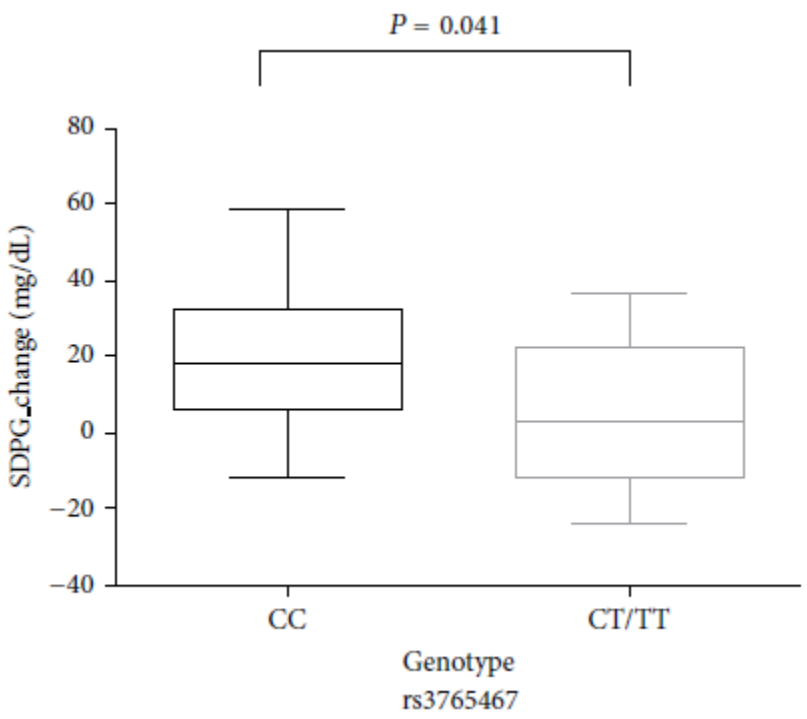
PLOS ONE | https://doi.org/10.1371/journal.pone.0181880 July 27, 2017

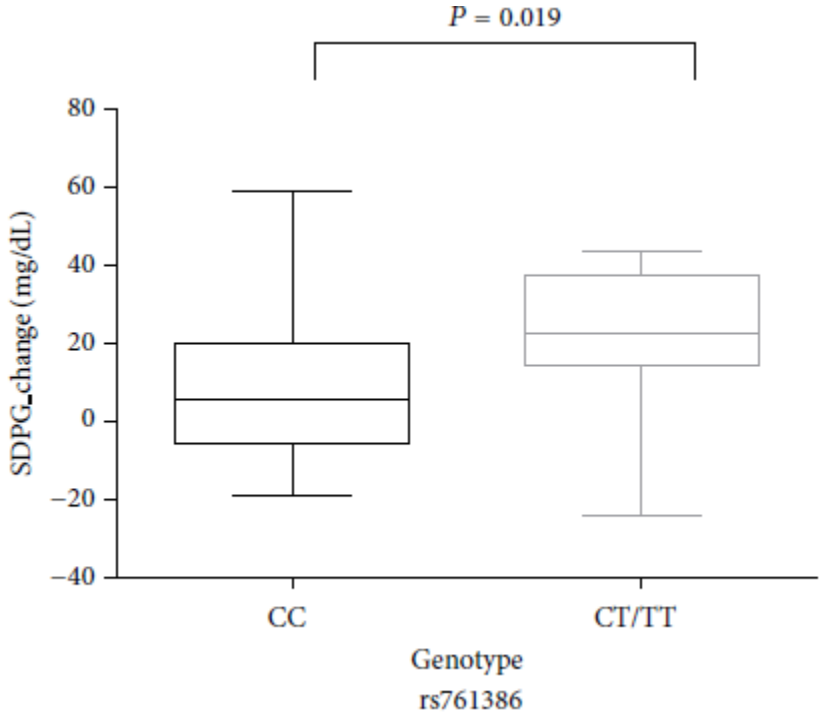


A fat interaction on GLP-1 levels, insulin secretion and plasma glucose levels

Rs6741949 chr 2

Polymorphisms of GLP-1 Receptor Gene and Response to GLP-1 Analogue in Patients with Poorly Controlled Type 2 Diabetes





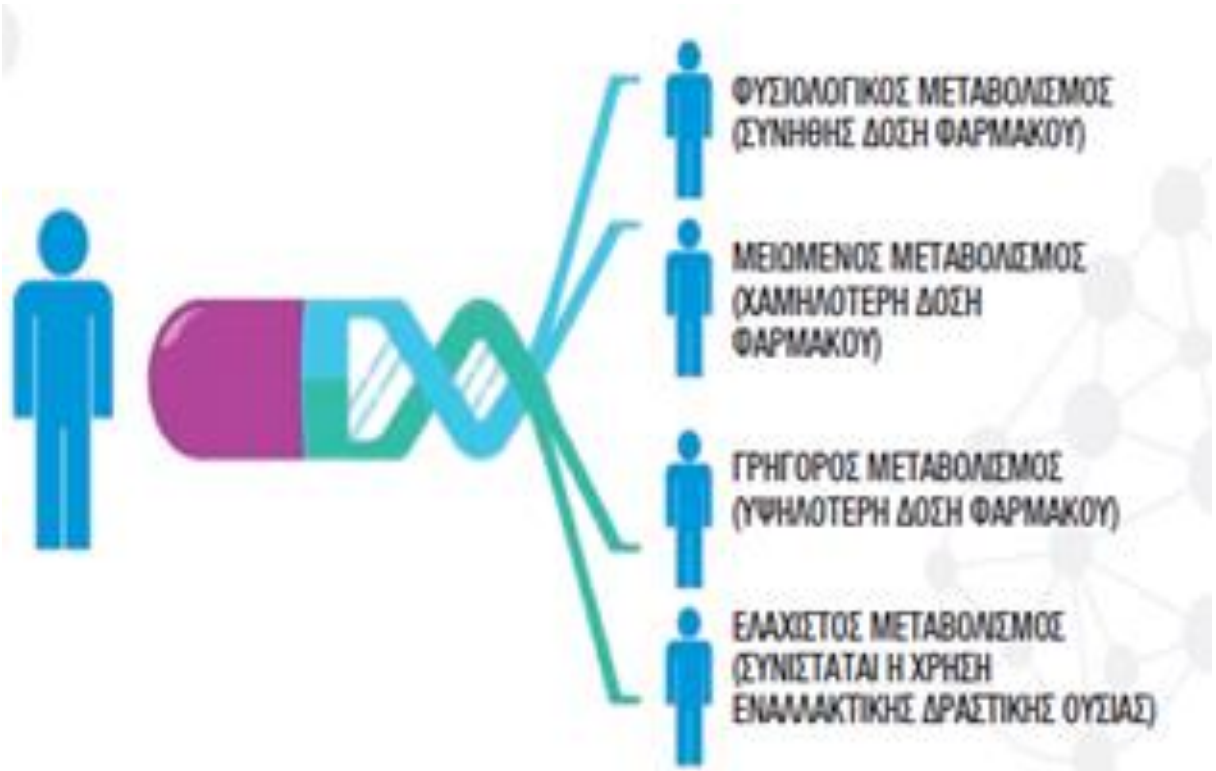
Hindawi Publishing Corporation
Journal of Diabetes Research
Volume 2015, Article ID 176949, 10 pages
http://dx.doi.org/10.1155/2015/176949

SGLT2: A potential target for the pharmacogenetics of Type 2 diabetes

- SGLT2 is coded by the **SLC5A2 gene**, which maps on chromosome 16
- **Mutations** in SLC5A2 cause **familial renal glucosuria**
- SLC5A2 **polymorphisms** might therefore represent potential candidates for pharmacogenomic studies

Pharmacogenomics. 2011;12(8):1119-1126.

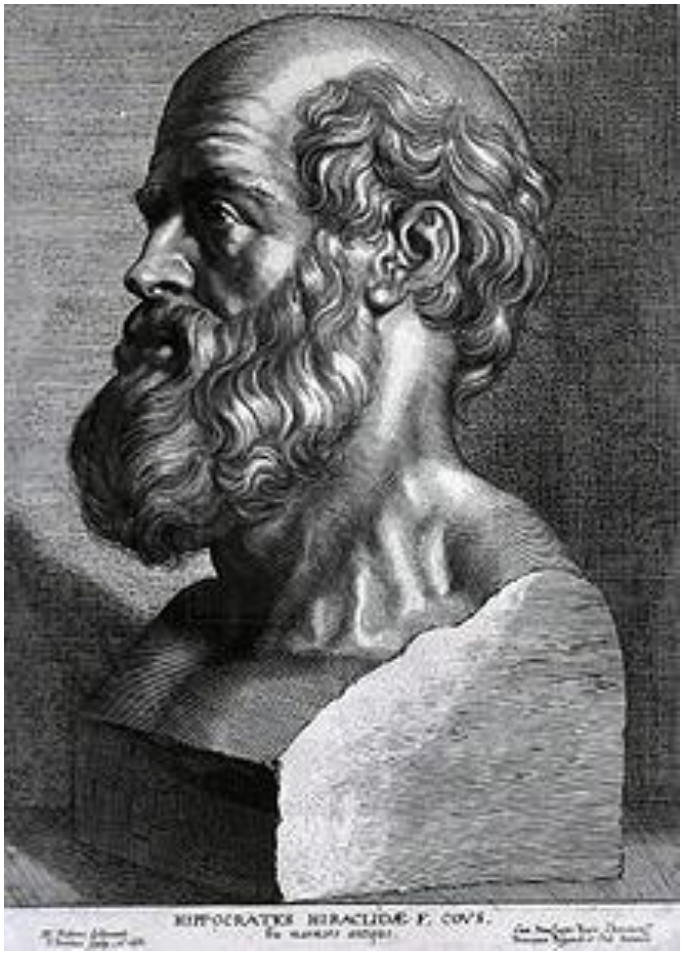
PHARMACOGENOMICS



«Είναι πιο σημαντικό να γνωρίζουμε ποιος είναι αυτός που νοσεί από το τι ακριβώς νόσημα έχει»

-Ιπποκράτης

(460 π.Χ. – 370 π.Χ.)



	GLP1 agonist	DPP4 inhibitors	SGLT2 inhibitors
ΔΡΑΣΤΙΚΟΤΗΤΑ	Υψηλή	Ενδιάμεση	Ενδιάμεση
ΥΠΟΓΛΥΚΑΙΜΙΑ	Χαμηλή	Χαμηλή	Χαμηλή
ΒΑΡΟΣ	Απώλεια	Ουδέτερο	Απώλεια
ΠΑΡΕΝΕΡΓΕΙΕΣ	Γαστρεντερικο	Σπάνιες	Αρκετές (οξέωση, αφυδάτωση κα)
ΚΟΣΤΟΣ	Υψηλό	Υψηλό	Υψηλό

Only true professional can diagnose without even putting stethoscope in his ears

ΣΥΜΠΕΡΑΣΜΑΤΙΚΑ

- **Η επιλογή εξατομικευμένα:**
  - Σύγχρονα «έξυπνα» φάρμακα
  - Ενέσιμη μορφή
  - Απώλεια ΒΣ
  - ΑΠ, Λιπίδια
  - Νεφρική δυσλειτουργία
  - Καρδιαγγειακά οφέλη
  - Μη αλκοολική στεατοηπατίτιδα
  - Παρενέργειες (γαστρεντερικό, λοιμώξεις, κετοξεώσεις, ακρωτηριασμοί δακτύλων)

Famous People
Who Died of Diabetes Mellitus

- Alexander Graham Bell
- Ella Fitzgerald
- Jules Verne
- Curtis Mayfield
- Laura Ingalls Wilder
- Johnny Cash
- James Cagney

- Aretha Franklin
- B. B. King
- Elvis Presley
- Ernest Hemingway
- Ray Kroc (McDonalds)
- Fahd bin Abdulaziz Al Saud
- Tito, Josip Broz