« ΝΕΟΤΕΡΑ ΔΕΔΟΜΕΝΑ ΓΙΑ ΤΟΝ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ ΤΥΠΟΥ ΙΙ »

ΘΕΟΔΩΡΑ ΣΤΡΑΤΗΓΟΥ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ

ΕΠΙΜΕΛΗΤΡΙΑ Β΄ Ε.Σ.Υ

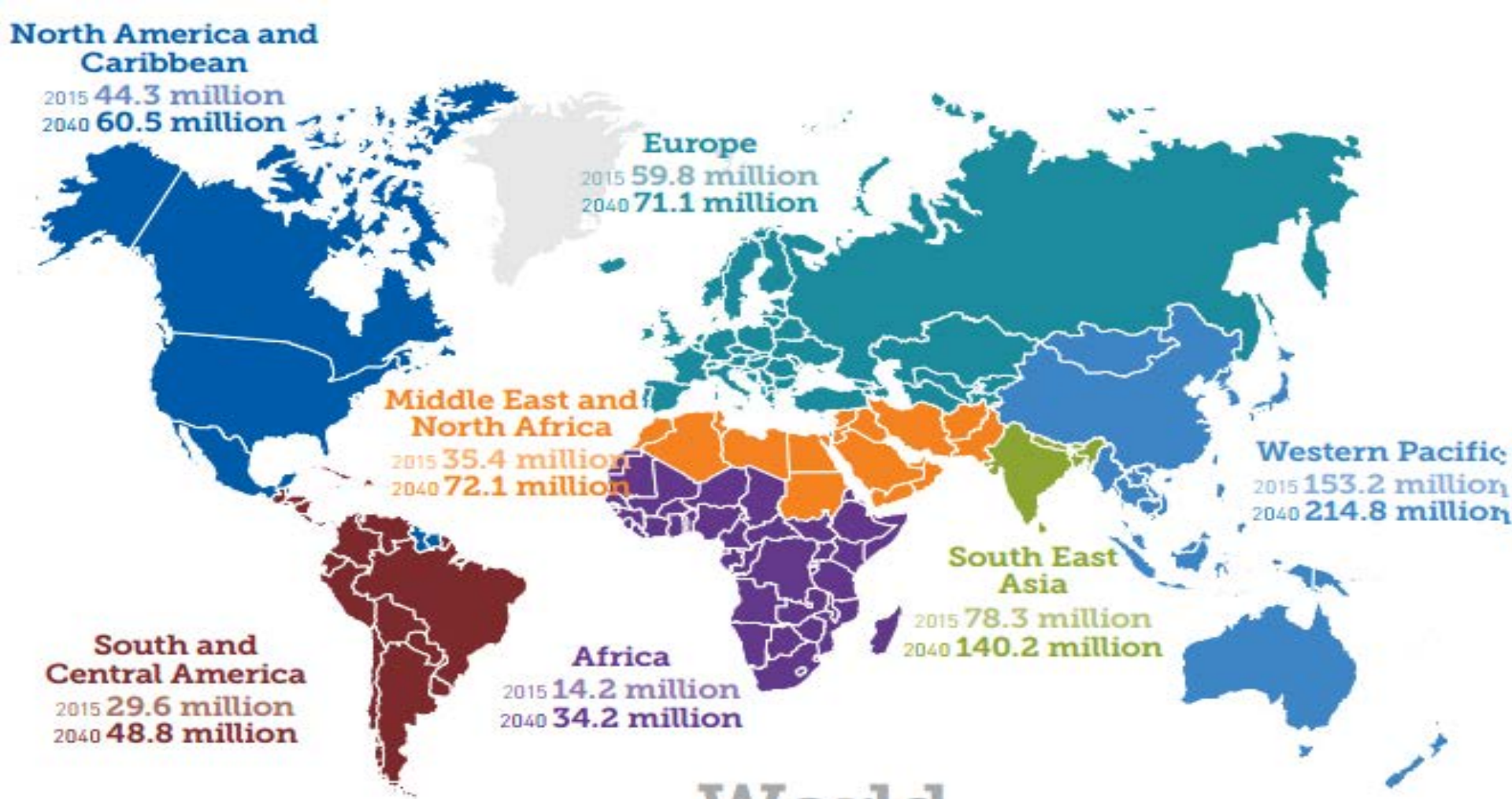
ΤΜΗΜΑ ΕΝΔΟΚΡΙΝΟΛΟΓΙΑΣ - ΔΙΑΒΗΤΟΛΟΓΙΚΟ ΚΕΝΤΡΟ

Γ.Ν.Α «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ»

24ο ΕΤΗΣΙΟ ΣΕΜΙΝΑΡΙΟ ΣΥΝΕΧΙΖΟΜΕΝΗΣ ΙΑΤΡΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ ΝΟΣΟΚΟΜΕΙΟΥ «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ»

Δεν υπάρχει σύγκρουση συμφερόντων με τις παρακάτω χορηγούς εταιρείες:

PFIZER, JANSSEN ONCOLOGY, SOFMEDICA, NOVARTIS, ABBVIE, MSD, WINMEDICA, GENESIS, ROCHE, TAKEDA, ASTELLAS, AMGEN, ANGELINI, ΑΝΤΙΣΕΛ, SERVIER, BRISTOL-MYERS SQUIBB, ABBOTT, GILEAD, SANDOZ, BIANEΞ, RONTIS, MAVROGENIS, AENORASIS, SPECIFAR, KARYO



World

2015 **415 million**

2040 **642 million**

Ο Σακχαρώδης Διαβήτης είναι ισόβια κατάσταση, που συσχετίζεται με σοβαρές ΜΙΚΡΟΑΓΓΕΙΑΚΕΣ **και** ΜΑΚΡΟΑΓΓΕΙΑΚΕΣ ΕΠΙΠΛΟΚΕΣ

Διαβητική Αμφιβληστροειδοπάθεια – 21% ΣΔ-2

Κύριο αίτιο τύφλωσης στους ενηλίκους[1,2]

Διαβητική Νεφροπάθεια – 18% ΣΔ-2

Κύριο αίτιο Νεφροπάθειας τελικού σταδίου[3,4]

Διαβητική νευροπάθεια – 12% ΣΔ-2

Κύριο αίτιο μη τραυματικών ακρωτηριασμών των κάτω άκρων[7,8]

Διπλάσια έως τετραπλάσια αύξηση της καρδιαγγειακής θνησιμότητας και των εγκεφαλικών επεισοδίων[5]

Εγκεφαλικό επεισόδιο

Καρδιαγγειακή Νόσος (75% των θανάτων του ΣΔ2)

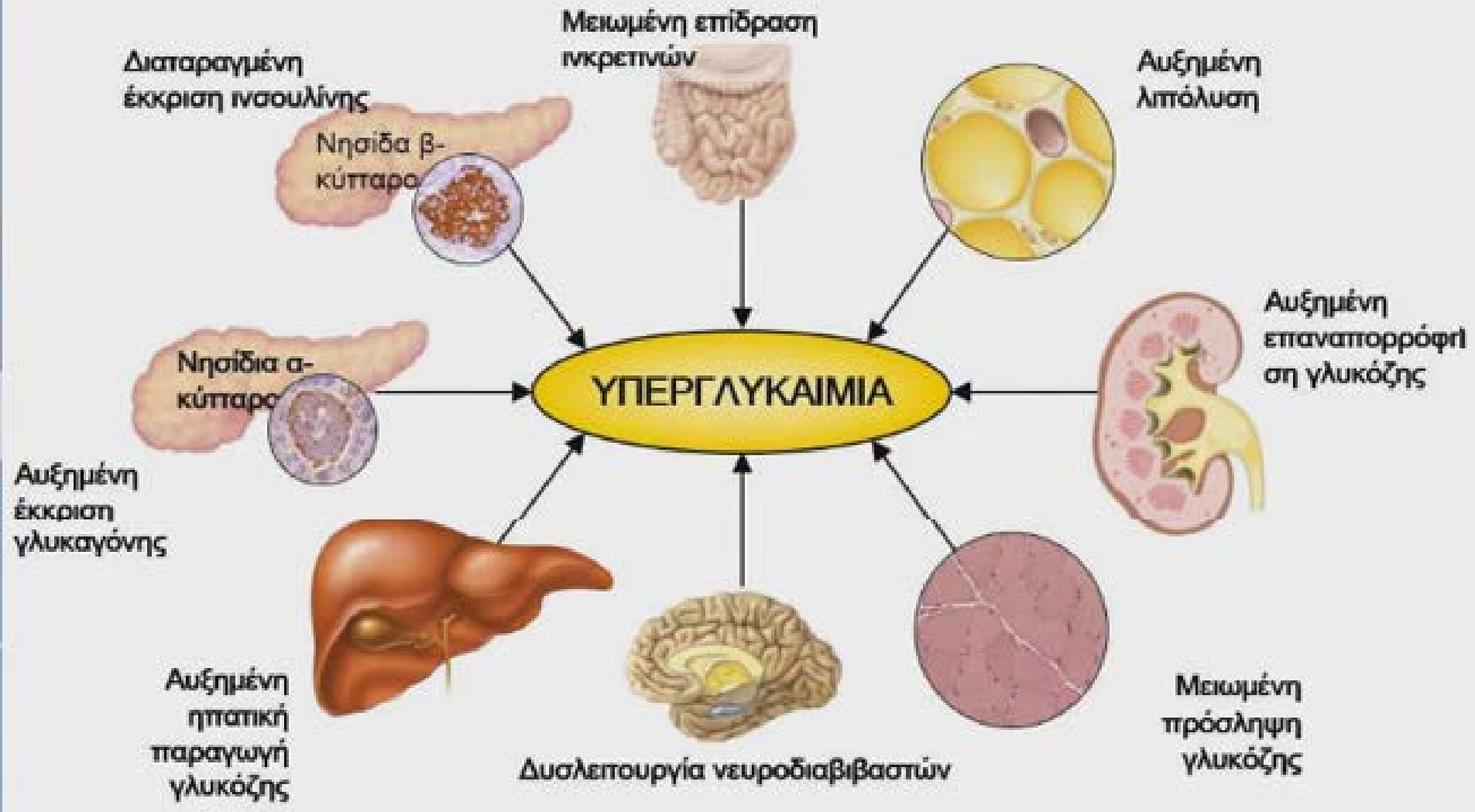
Οκτώ από τα δέκα άτομα με διαβήτη (80%) πεθαίνουν λόγω καρδιαγγειακών συμβαμάτων[6]

1. UKPDS Group. Diabetes Res 1990;13(1):1–11; 2. Fong DS, et al. Diabetes Care 2003;26(Suppl 1):S99–S102; 3. Hypertension in Diabetes Study. J Hypertens 1993;11(3):309–317; 4. Molitch ME, et al. Diabetes Care 2003;26(Suppl 1):S94–S98; 5. Kannel WB, et al. Am Heart J 1990;120(3):672–676; 6. Gray RP, et al. In Textbook of Diabetes 2nd Edition, 1997; 7. King's Fund. London: British Diabetic Association, 1996; 8. Mayfield JA, et al. Diabetes Care 2003;26(Suppl 1):S78–S79

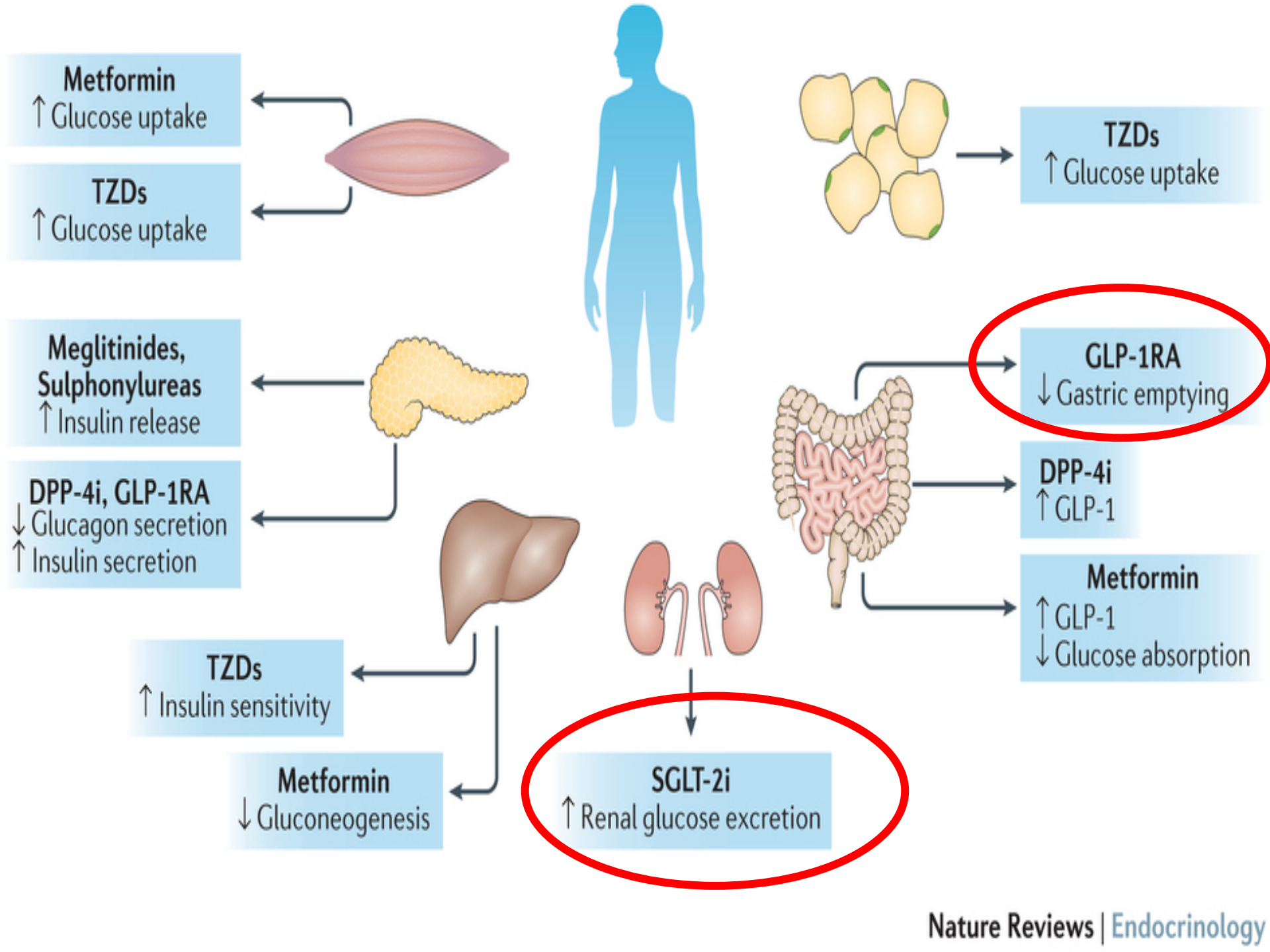
Παθογένεση του ΣΔ Τύπου 2

Η δυσοίωνη οκτάδα

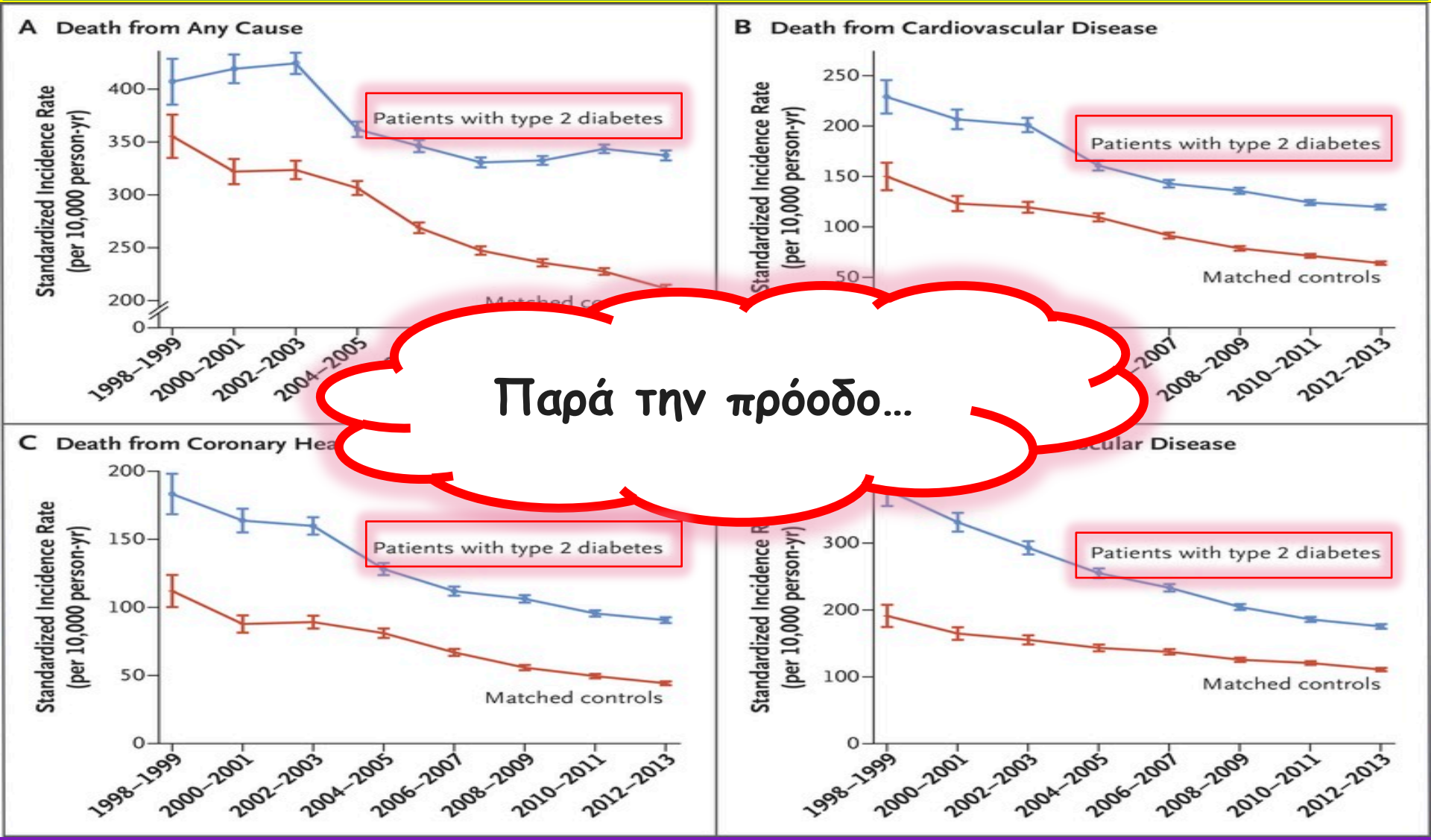
Πολλαπλές παθοφυσιολογικές αποτυχίες συντελούν στην υπεργλυκαιμία



Από DeFronzo RA. *Diabetes* 2009;58:773–95.


Metformin
↑ Glucose uptake
TZDs
↑ Glucose uptake
TZDs
↑ Glucose uptake
Meglitinides, Sulphonylureas
↑ Insulin release
DPP-4i, GLP-1RA
↓ Glucagon secretion
↑ Insulin secretion
GLP-1RA
↓ Gastric emptying
DPP-4i
↑ GLP-1
Metformin
↑ GLP-1
↓ Glucose absorption
TZDs
↑ Insulin sensitivity
Metformin
↓ Gluconeogenesis
SGLT-2i
↑ Renal glucose excretion
Nature Reviews | Endocrinology

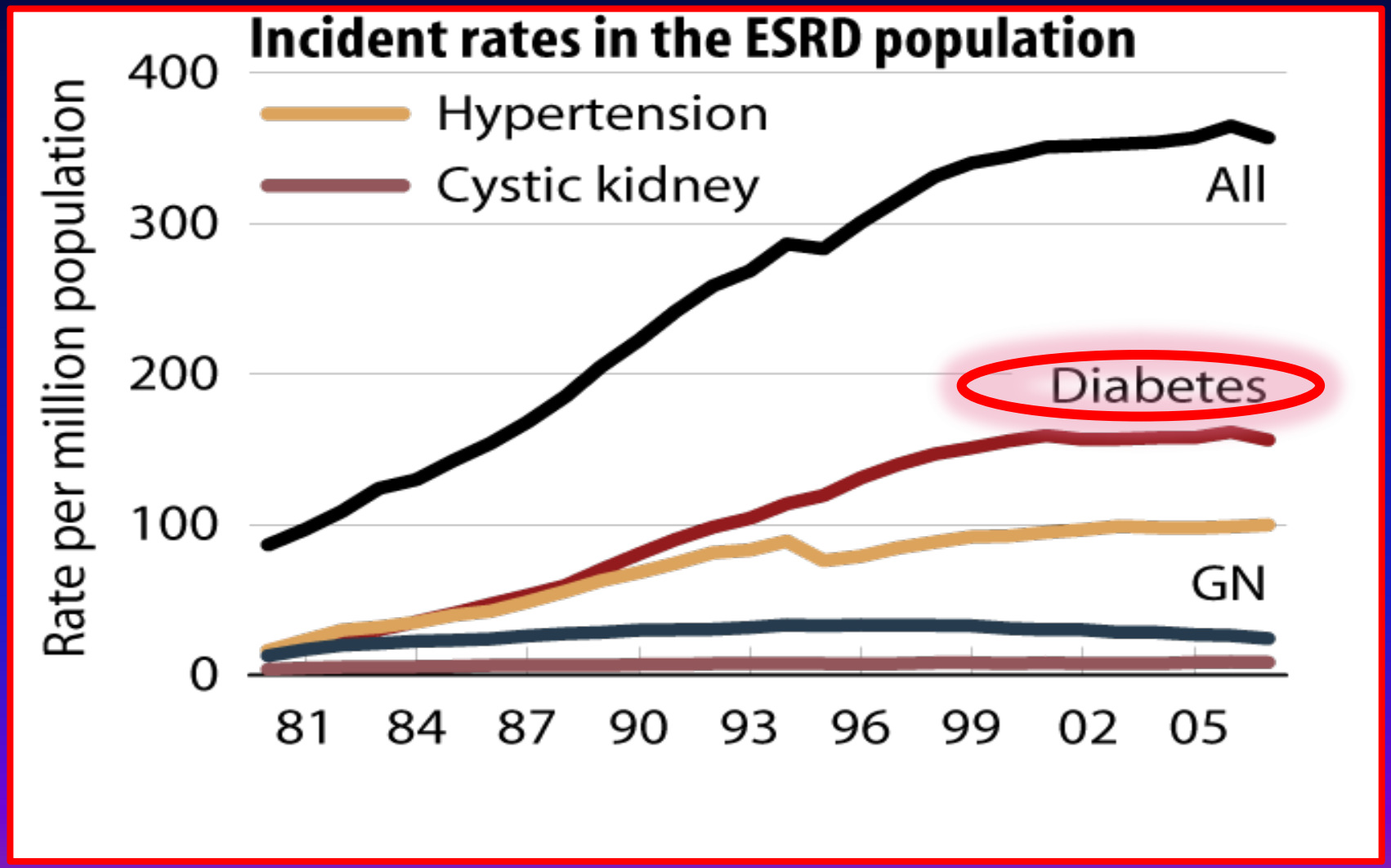
ΑΥΞΗΜΕΝΟΣ ΚΙΝΔΥΝΟΣ ΓΙΑ ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΝΟΣΟ ΣΕ ΑΤΟΜΑ ΜΕ ΣΔ



Παρά την πρόοδο…

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes ,Rawsani et al.New England J Med ,2017

Ο Σακχαρώδης Διαβήτης αποτελεί τη συχνότερη αιτία Χρόνιας Νεφρικής Νόσου (Διαβητική Νεφροπάθεια).



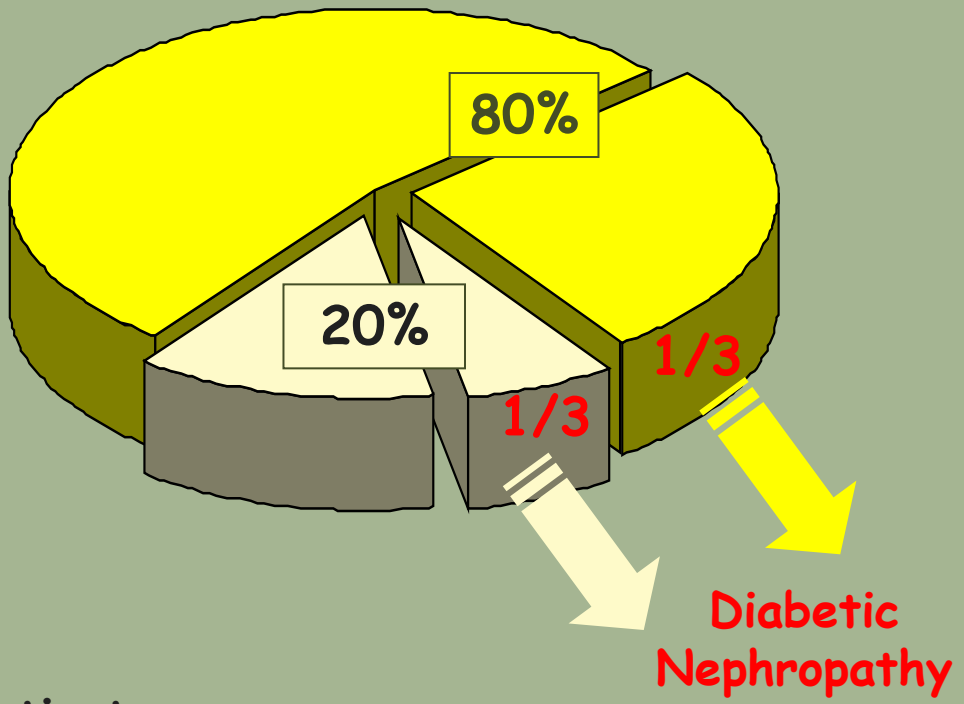
Seminars in Dialysis 23: 129–133, 2010

Εμφάνιση Δ.Ν σε ασθενείς με Σ.Δ

About 30% of the patients with DM type 1 or 2 will develop DN

type 1

type 2



60-90% of the diabetic patients are type 2

Diabetic Nephropathy, American Diabetes Association *Diabetes Care* 26:S94-S98, 2003

Η συνύπαρξη Χ.Ν.Ν και Σ.Δ

Χαρακτηρίζεται ως

«το δίδυμο που σκοτώνει»

- Διότι αυξάνει γεωμετρικά τον κίνδυνο για εμφάνιση καρδιαγγειακών επεισοδίων
- Οι περισσότεροι ασθενείς με ΧΝΝ σταδίου 3, ιδίως επί συνυπάρξεως ΣΔ, πεθαίνουν από κάποιο καρδιαγγειακό επεισόδιο πριν την εμφάνιση ΧΝΝ τελικού σταδίου

ΣΤΟΧΟΣ ΤΗΣ ΓΛΥΚΑΙΜΙΚΗΣ ΡΥΘΜΙΣΗΣ

Σε κάθε περίπτωση
«ο γλυκαιμικός στόχος εξατομικεύεται»

Ρύθμιση γλυκαιμίας

Επιβράδυνση

της εξέλιξης

CVD/CKD

Ασφάλεια ασθενούς

Επαγρύπνηση

για πιθανές

ανεπιθύμητες

ενέργειες

Το ζητούμενο είναι η
«διασφάλιση της ισορροπίας του οργανισμού»

ΣΤΟΧΟΣ ΤΗΣ ΓΛΥΚΑΙΜΙΚΗΣ ΡΥΘΜΙΣΗΣ

Summary of Glycemic Recommendations

Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2018; 40 (Suppl. 1): S13-S22

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Τι να προσέξουμε στα άτομα με ΣΔ2 ;;

Σκοπός μας εκτός από την γλυκαιμική ρύθμιση...

είναι:

η βελτίωση της συνολικής έκβασης του ασθενούς

αλλά και

η επιλογή κατάλληλης θεραπευτικής αγωγής που μειώνει τον καρδιαγγειακό και νεφρικό κίνδυνο...

The new consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)for the Management of hyperglycaemia in type 2 diabetes, 2018

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

REVIEW AND AGREE ON MANAGEMENT PLAN

- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

Ο ασθενής ενημερώνεται για τις επιλογές θεραπείας και συναποφασίζει με την ομάδα...

ONGOING MONITORING AND SUPPORT INCLUDING:

- Emotional well-being
- Check tolerability of medication
- Monitor glycaemic status
- Biofeedback including SMBG, weight, step count, HbA_{1c}, BP, lipids

GOALS OF CARE

- Prevent complications
- Optimise quality of life

CONSIDER PATIENT FACTORS WHICH IMPACT CHOICE OF TREATMENT

- Individualised HbA_{1c} target
- Impact on weight and hypoglycaemia
- Side effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise adherence and persistence
- Access, cost and availability of medication

IMPLEMENT MANAGEMENT PLAN

- Patients not meeting goals generally should be seen at least every 3

SHARED DECISION-MAKING TO CREATE A MANAGEMENT PLAN

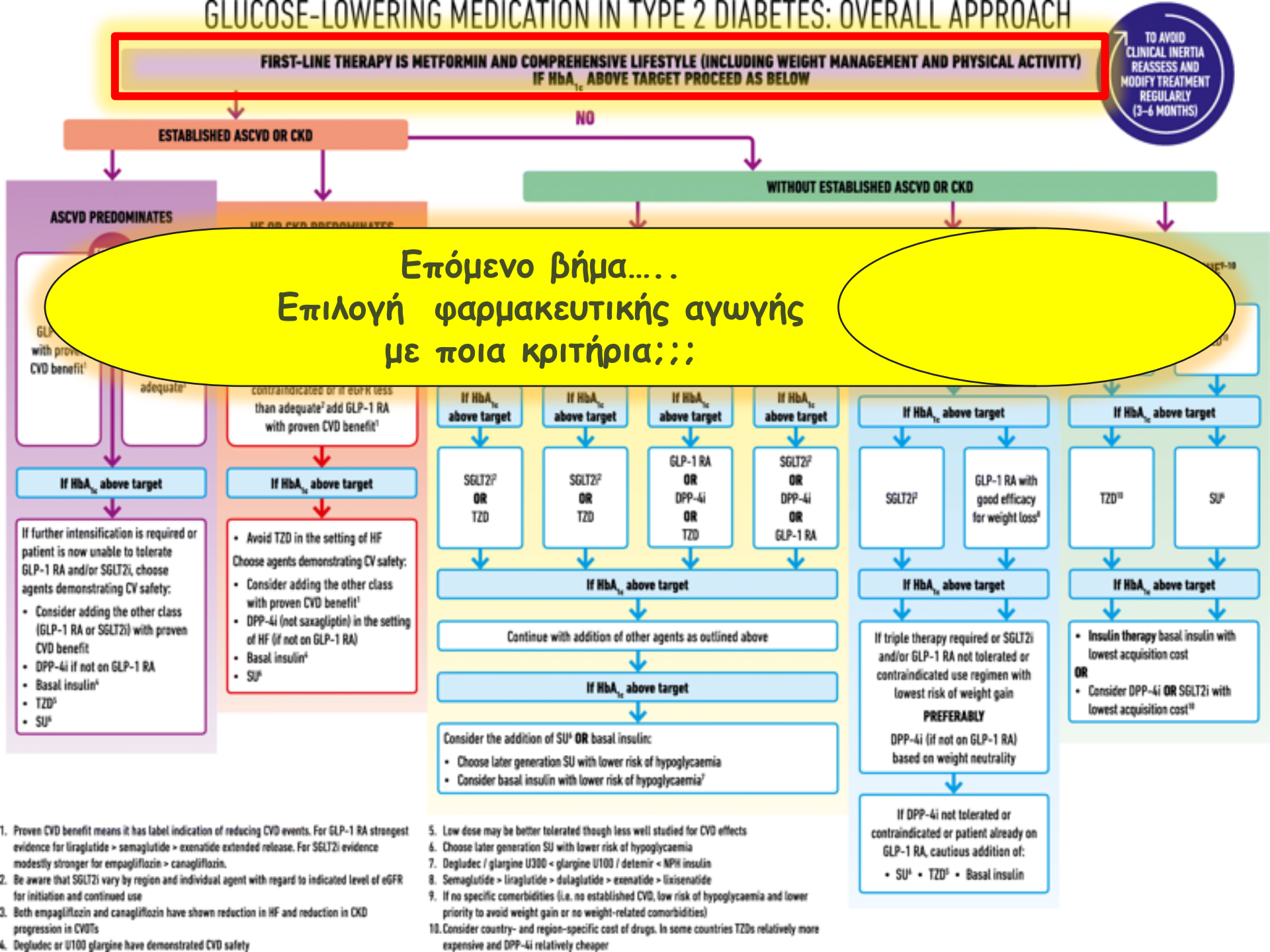
- Involves an educated and informed patient (and their family/caregiver)
- Ensures access to DSMES

Ασθενοκεντρική και εξατομικευμένη προσέγγιση

- Achievable
- Realistic
- Time limited

ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Περιορισμοί στη χορήγηση φαρμάκων που στοχεύουν στην γλυκαιμική ρύθμιση

Ερώτηση — **Γιατί;;;;;**

Απάντηση — **Λαμβάνουμε υπόψιν**

- Τον κίνδυνο υπογλυκαιμιών
- Την επίδραση στο σωματικό βάρος
- Την επίδραση στη νεφρική λειτουργία
- Τις ενδεχόμενες ευεργετικές επιδράσεις ιδίως στο καρδιαγγειακό σύστημα
- Την επίδραση στο ουρογεννητικό σύστημα,στα οστά,στο γαστρεντερικό (ανεπιθύμητες ενέργειες)
- Το κόστος /συμμόρφωση / προτίμηση ασθενούς

Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits

Use with caution

Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

COPYRIGHT © 2018 AACE MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE. DOI 10.4158/CS-2017-0153

Ερώτηση...

Ποια είναι η πρώτη ερώτηση
που πρέπει να απαντάται από το γιατρό
πριν την χορήγηση φαρμακευτικής αγωγής ;;

Γιατί πρέπει αυτό να ξεκαθαρίζεται από την αρχή;;

Απάντηση...

Υπάρχει ή δεν υπάρχει
εγκατεστημένη ή υφέρπουσα
καρδιαγγειακή νόσος
καθώς και χρόνια νεφρική νόσος;;

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

NO

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

further intensification is required or atient is now unable to tolerate LP-1 RA and/or SGLT2i, choose gents demonstrating CV safety:

Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
DPP-4i if not on GLP-1 RA
Basal insulin[4]
TZD[5]
SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9–10]

- SU[6]
- TZD[10]

If HbA_{1c} above target

- TZD[10]
- SU[6]

If HbA_{1c} above target

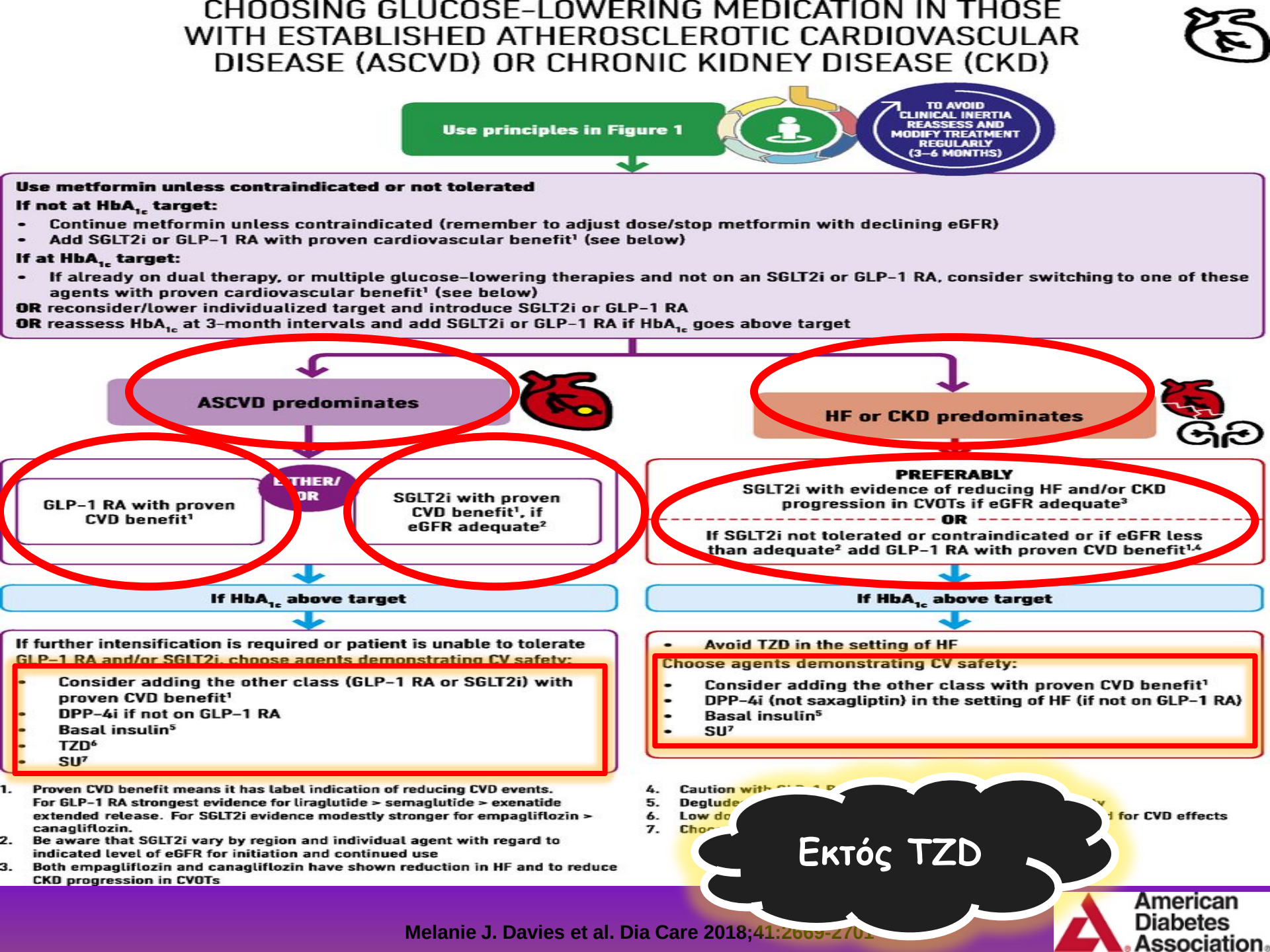
- **Insulin therapy** basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

SGLT2

ΜΕ ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΠΡΟΣΤΑΣΙΑ

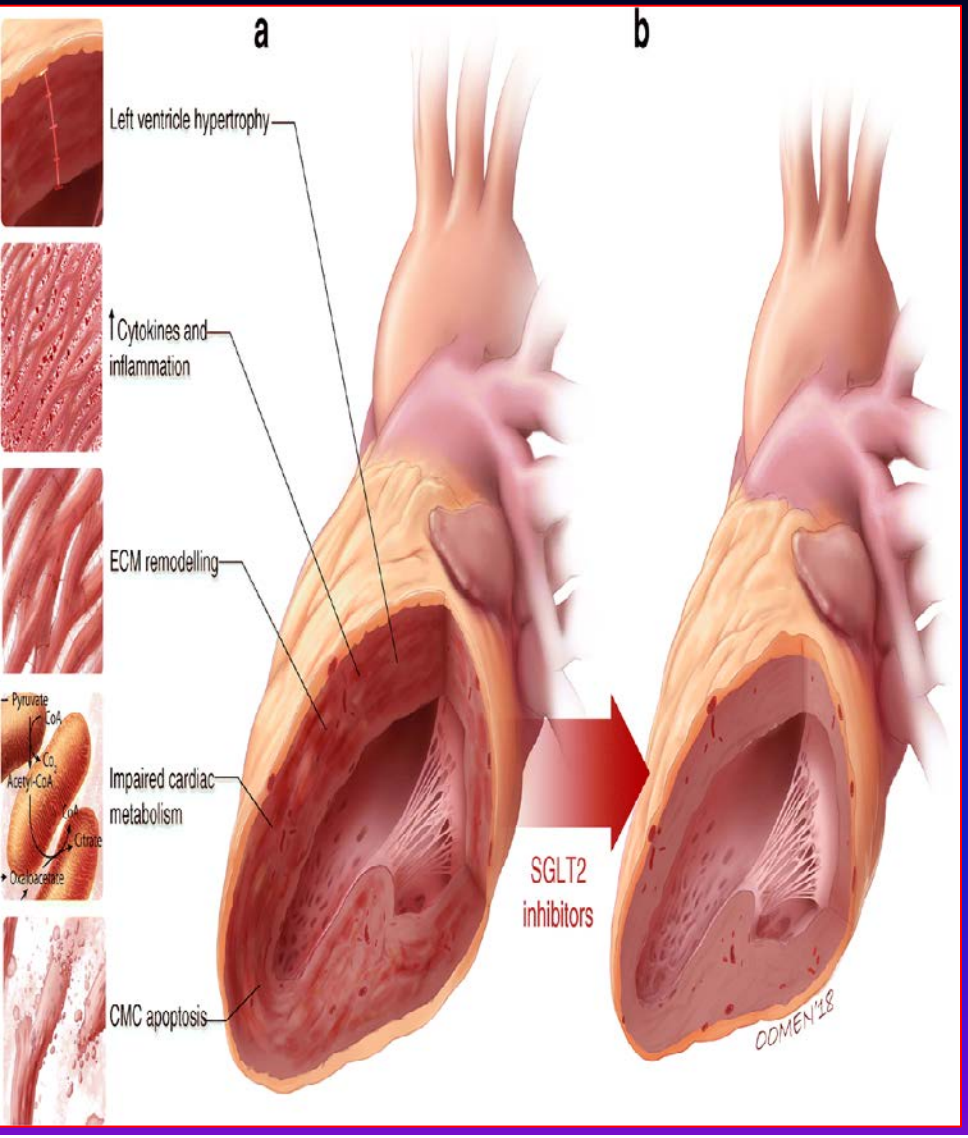
Εμπαγλιφλοζίνη > Καναγλιφλοζίνη….
Νταπαγλιφλοζίνη (Declare)…

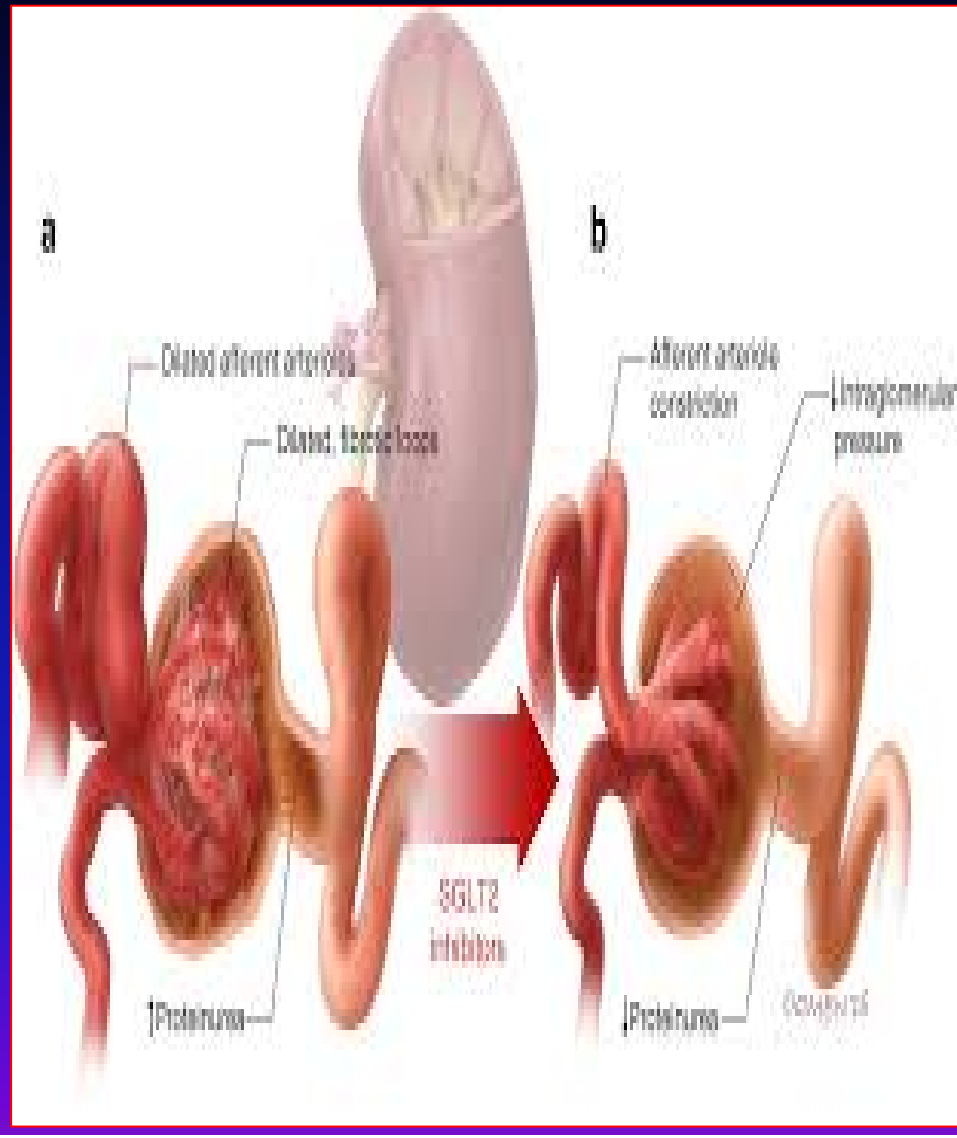
GLP1

ΜΕ ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΠΡΟΣΤΑΣΙΑ

Λιραγλουτίδη> Σεμαγλουτίδη> Εξανατίδη
LAR…ντουλαγλουτίδη
(Rewind… εν αναμονή)

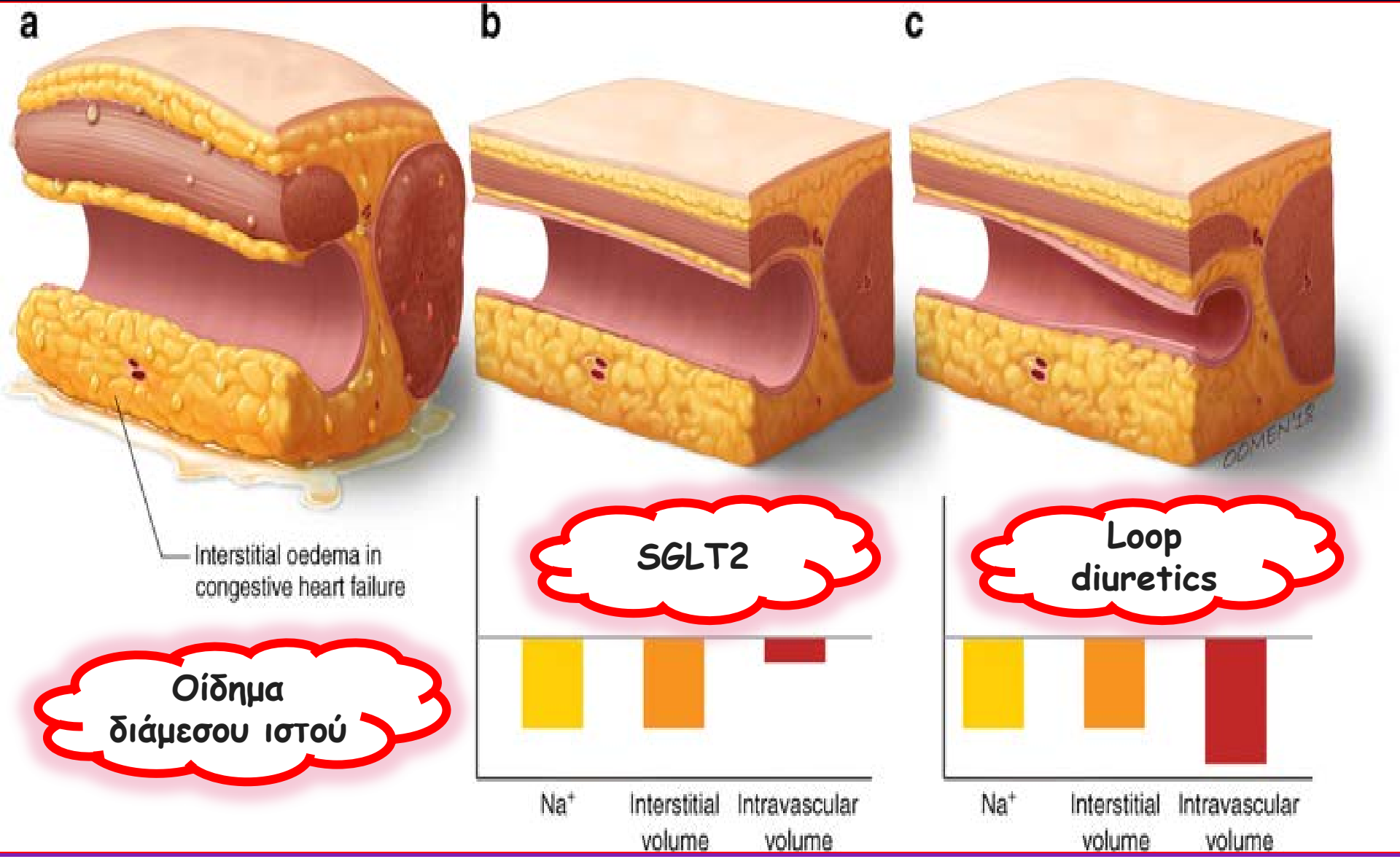
SGLT2 και καρδιο / νεφροπροστασία





SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review Diabetologia ,Octob 2018

SGLT2 και διουρητικά



Review Diabetologia ,Octob 2018

The NEW ENGLAND JOURNAL of MEDICINE

μελέτη EMBA - REG OUTCOME

ORIGINAL ARTICLE

Empagliflozin, [illegible]es, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. [illegible] Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Dev[illegible] Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the E[illegible] ors

N Engl J Med 2015; 373:2117-2128 | November 26, 2015 | DOI: 10.1056/NEJMo[illegible]

Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

3-point MACE

μελέτη EMBA - REG OUTCOME

	Ασθενείς με συμβάν/αναλύθηκαν Εμπανλιφλοζίνη	Placebo	HR	(95% CI)	τιμή p
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
ΚΔ Θάνατος	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Μη-θανατηφόρο ΕΜ	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Μη-θανατηφόρο ΑΕΕ	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638

Ανάλυση Cox regression. MACE, Major Adverse Cardiovascular Event; Μείζον καρδιαγγειακό Συμβάν
HR, hazard ratio; ΚΔ, καρδιαγγειακό; ΕΜ, έμφραγμα μυοκαρδίου
*95.02% CI

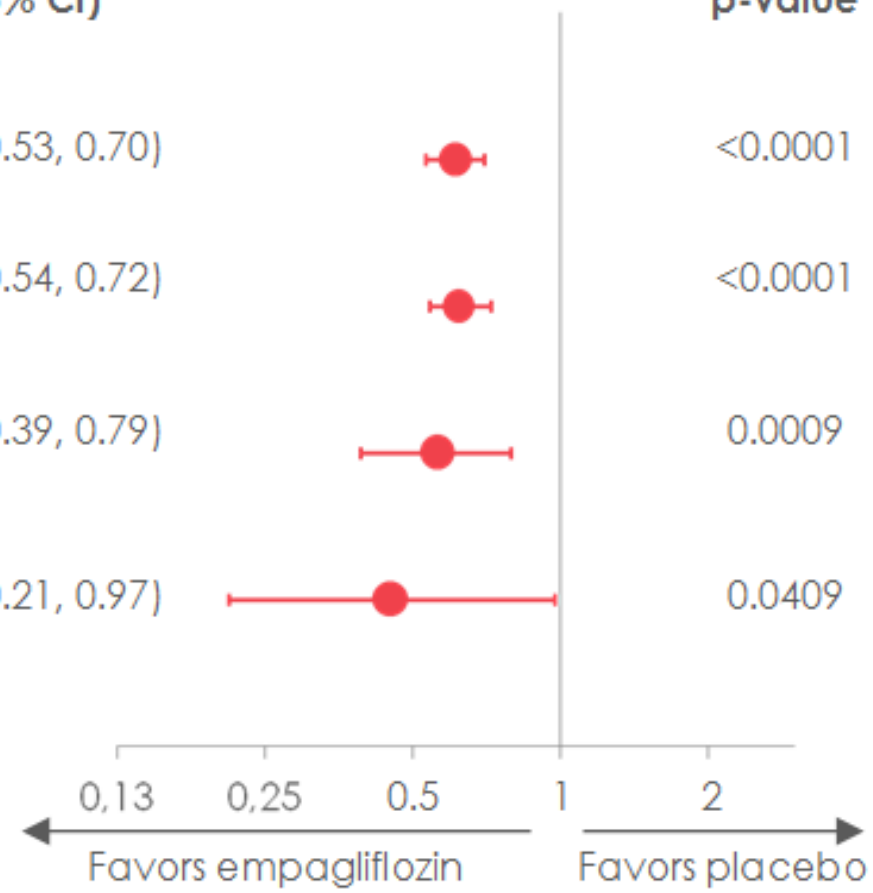
EMPA-REG OUTCOME®

ublished Online, September 17, 2015, at NEJM.org. DOI: 10.1056/NEJMoa1504720

Incident or worsening nephropathy and its components

μελέτη EMBA - REG OUTCOME

	Empagliflozin n with event/ N analyzed	Placebo n with event/ N analyzed	Hazard ratio (95% CI)	p-value
Incident or worsening nephropathy	525/4124	388/2061	0.61 (0.53, 0.70)	<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62 (0.54, 0.72)	<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56 (0.39, 0.79)	0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45 (0.21, 0.97)	0.0409



*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m^2.
Cox regression analyses.

The NEW ENGLAND JOURNAL of MEDICINE

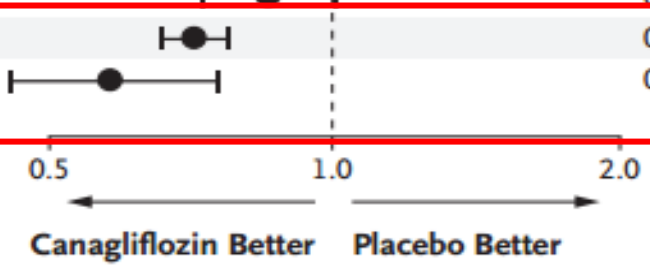
ORIGINAL ARTICLE

μελέτη CANVAS

Canagliflo… …rdiovascular and Renal Even… …2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vla… …Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, … …her, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D… …h.D., Mehul Desai, M.D., and David R. Matthews, D… …h., for the CANVAS Program Collaborative G…

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

nejm.org on June 25, 2017

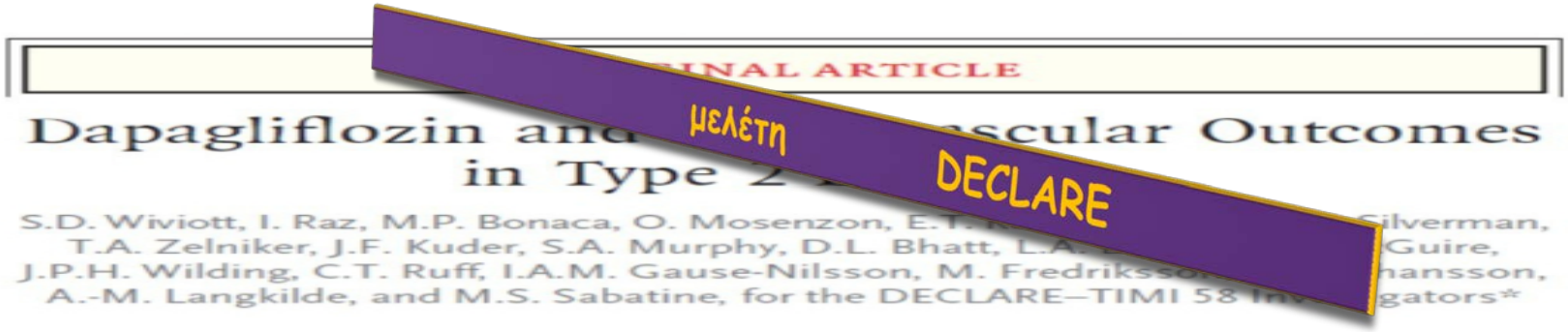


Table. DECLARE-TIMI 58: Results

Efficacy outcomes		
MACE	Similar rates	8.8% vs 9.4% ; HR 0.93; P=0.17
Composite of CV death or hospitalization for HF	Lower for dapagliflozin	4.9% vs. 5.8%; HR 0.83; P=0.005
Renal composite	24% lower risk with dapagliflozin	4.3% vs 5.6%, respectively, HR 0.76
Death from CV cause	Similar	2.9% vs 2.9% HR 0.98
Death from any cause	Similar	6.2% vs 6.6%, HR 0.93
Safety outcomes		
MACE	Dapagliflozin no worse vs placebo	P<.001 for noninferiority

The NEW ENGLAND JOURNAL of MEDICINE

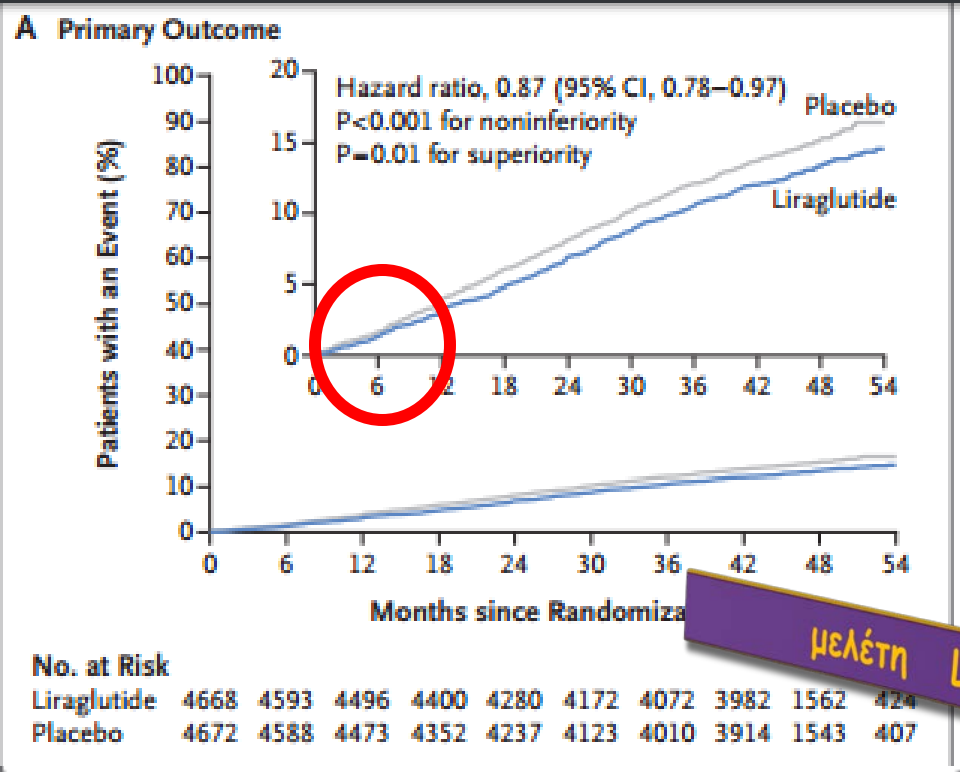
ORIGINAL ARTICLE

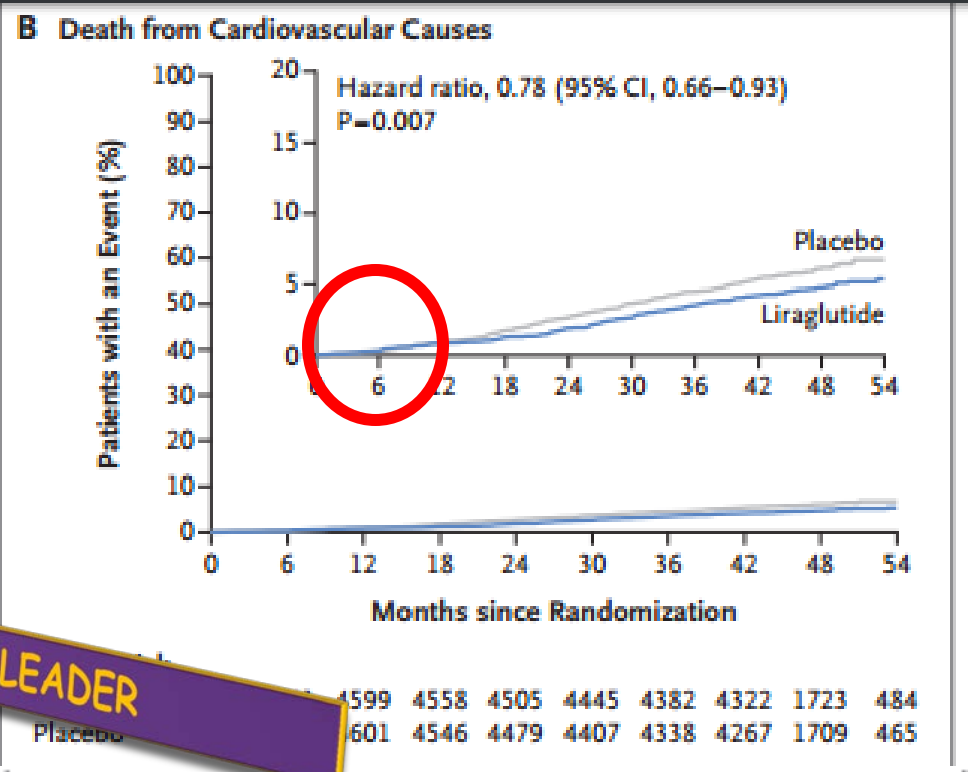
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Λιραγλουτίδη

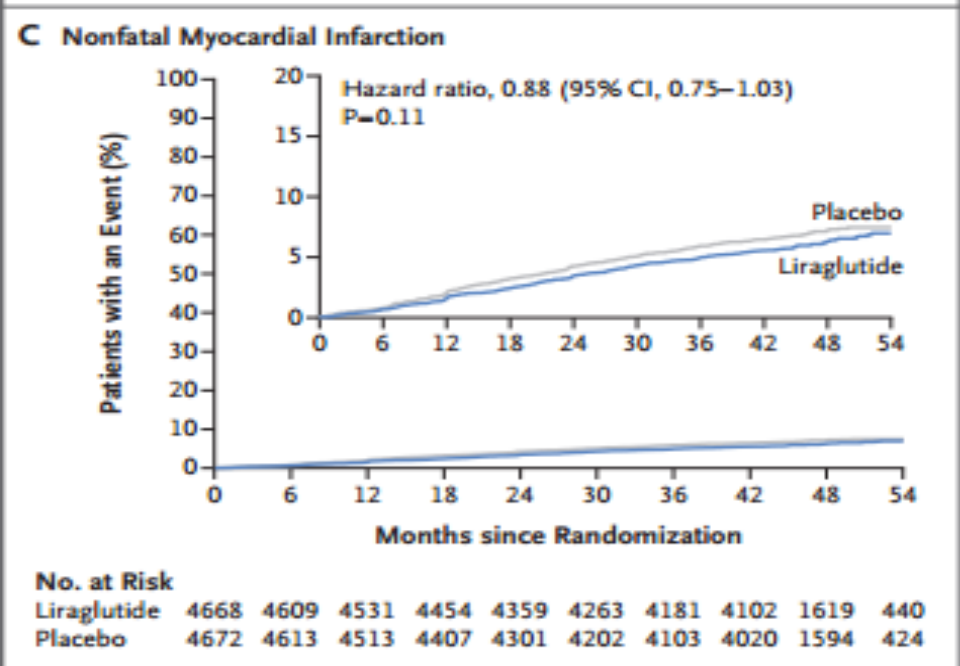
μελέτη LEADER

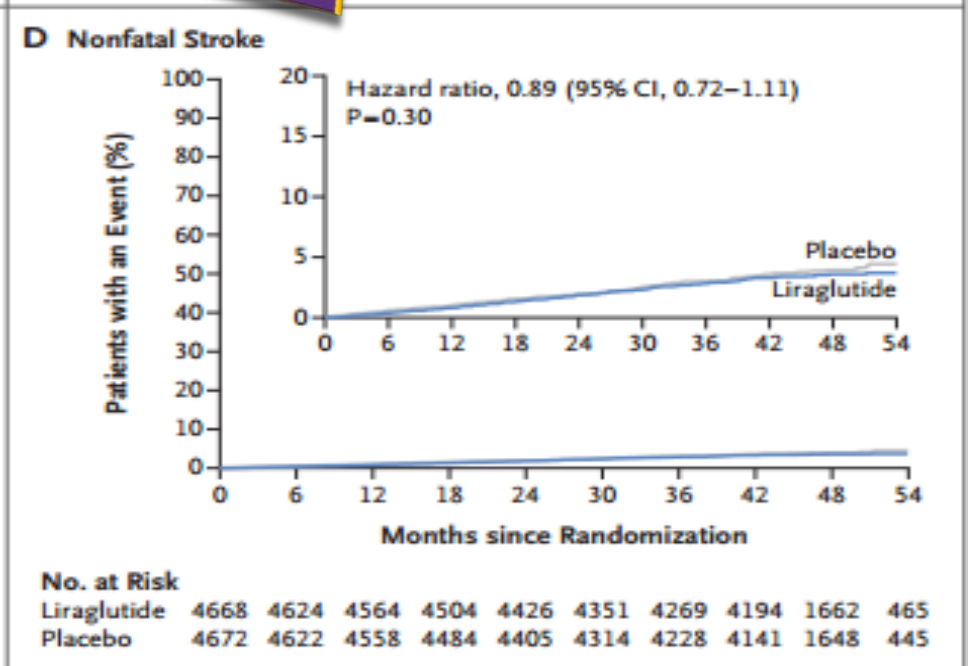
- μείωση κινδύνου νεφροπάθειας
- μείωση κινδύνου θανάτου από κάθε καρδιαγγειακό αίτιο
- έγκριση χορήγησης για μείωση κινδύνου μη θανατηφόρου ΑΕΕ & εμφράγματος μυοκαρδίου σε άτομα με ΣΔ και εγκατεστημένη CVD



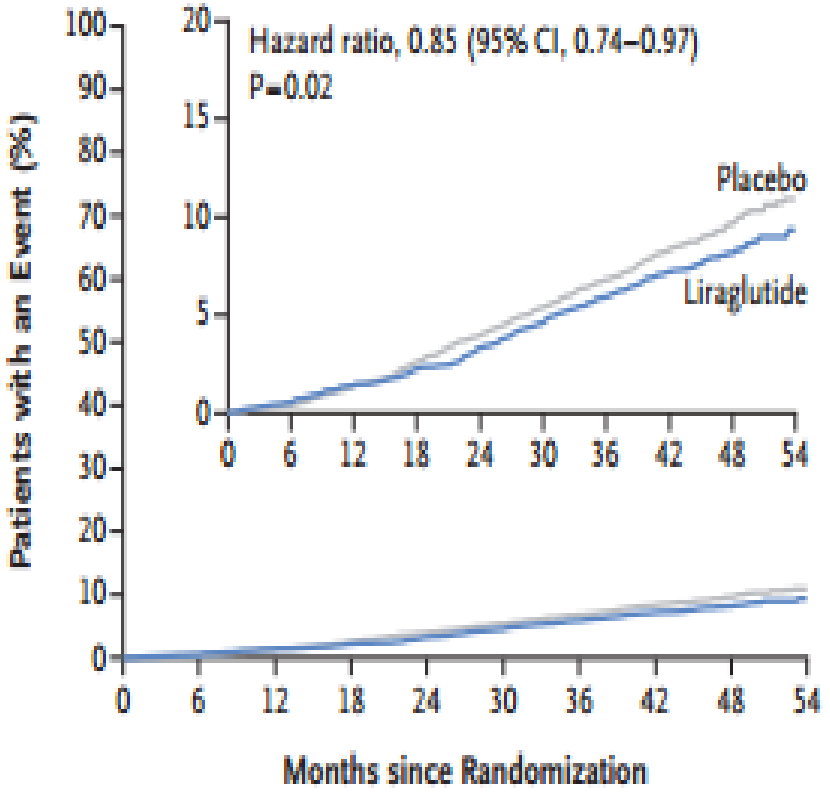


μελέτη LEADER





E Death from Any Cause

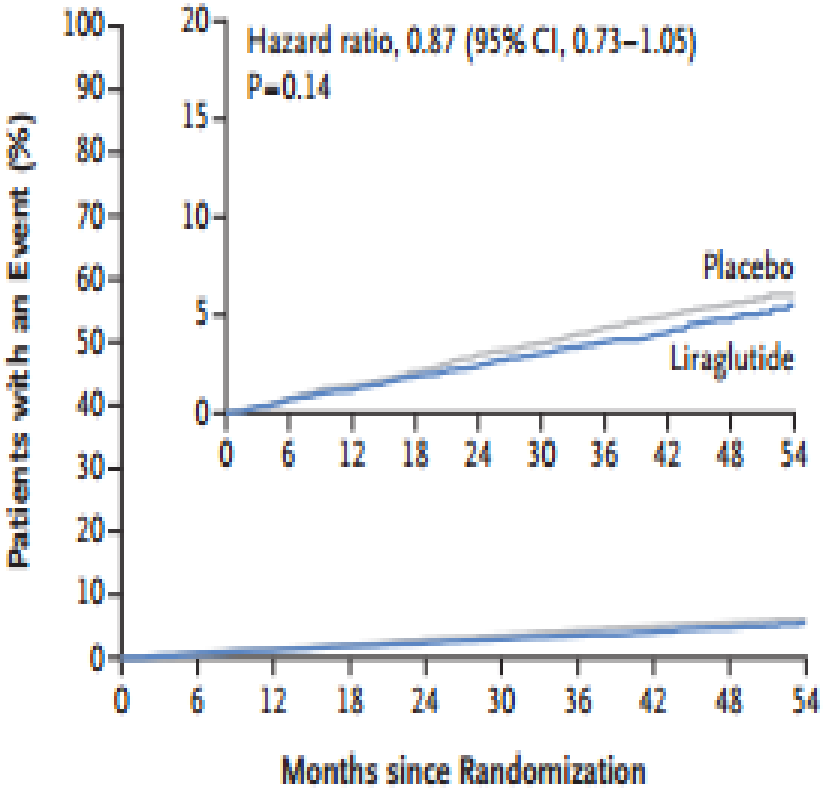


No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F Hospitalization for Heart Failure

χωρίς



No. at Risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

μελέτη LEADER

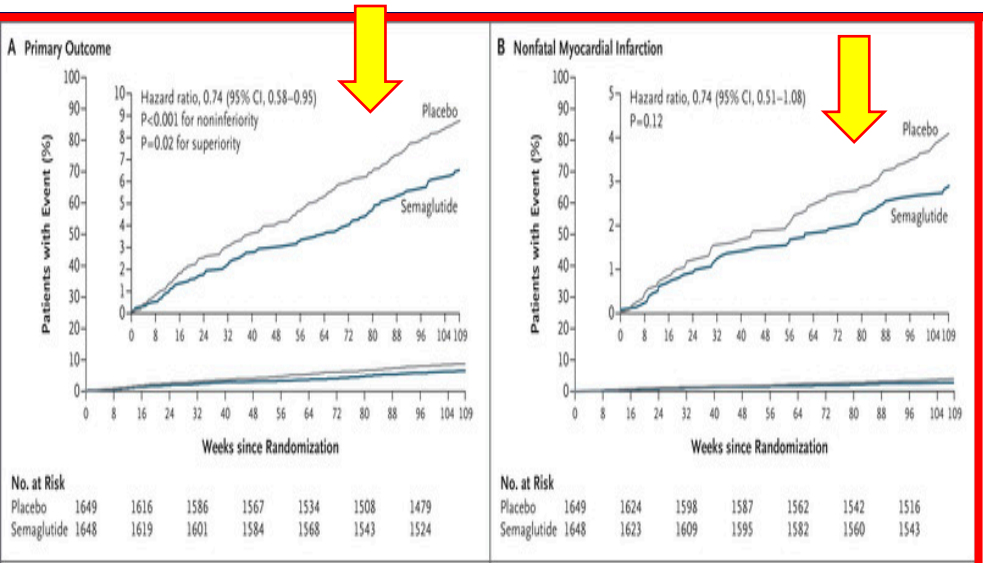
The NEW ENGLAND JOURNAL of MEDICINE

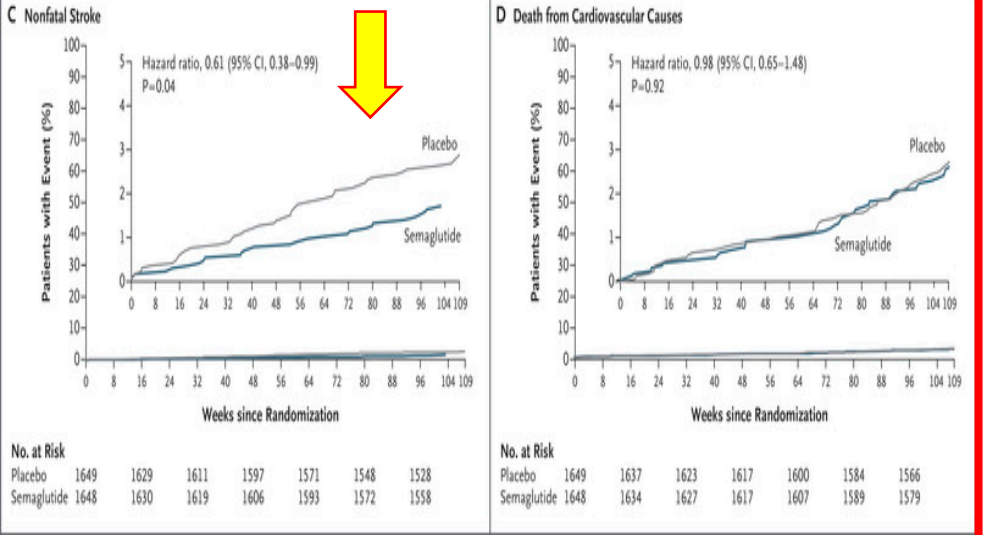
ORIGINAL ARTICLE

Semaglutide an[illegible]iovascular Outcomes in Patients w[illegible] 2 Diabetes

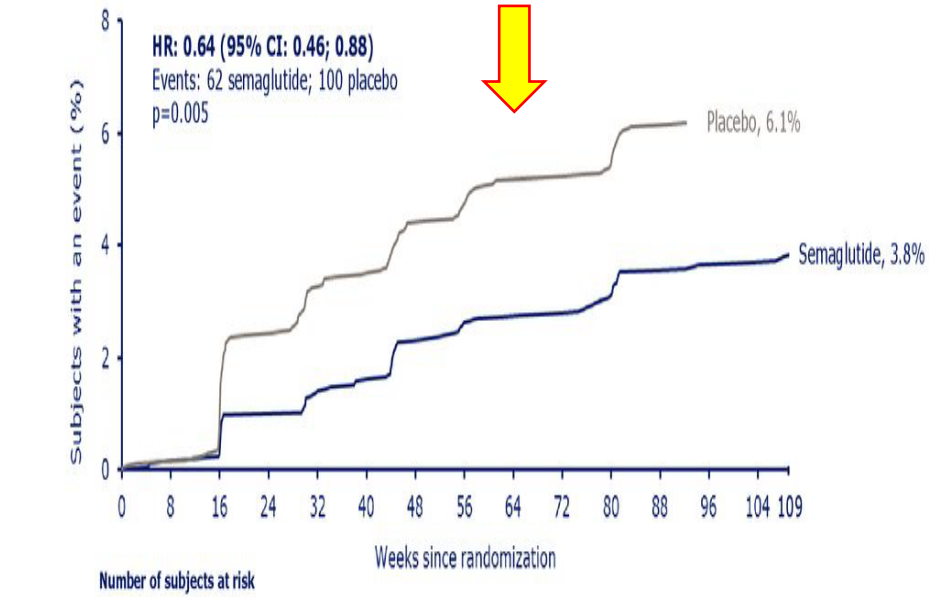
μελέτη SUSTAIN 6

Steven P. Marso, M.D., Stephen C. Bain[illegible]o Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar[illegible]A. Lester, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., [illegible]D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., [illegible]M.D., Ole Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas [illegible]Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 [illegible]





SUSTAIN 6: New or worsening nephropathy

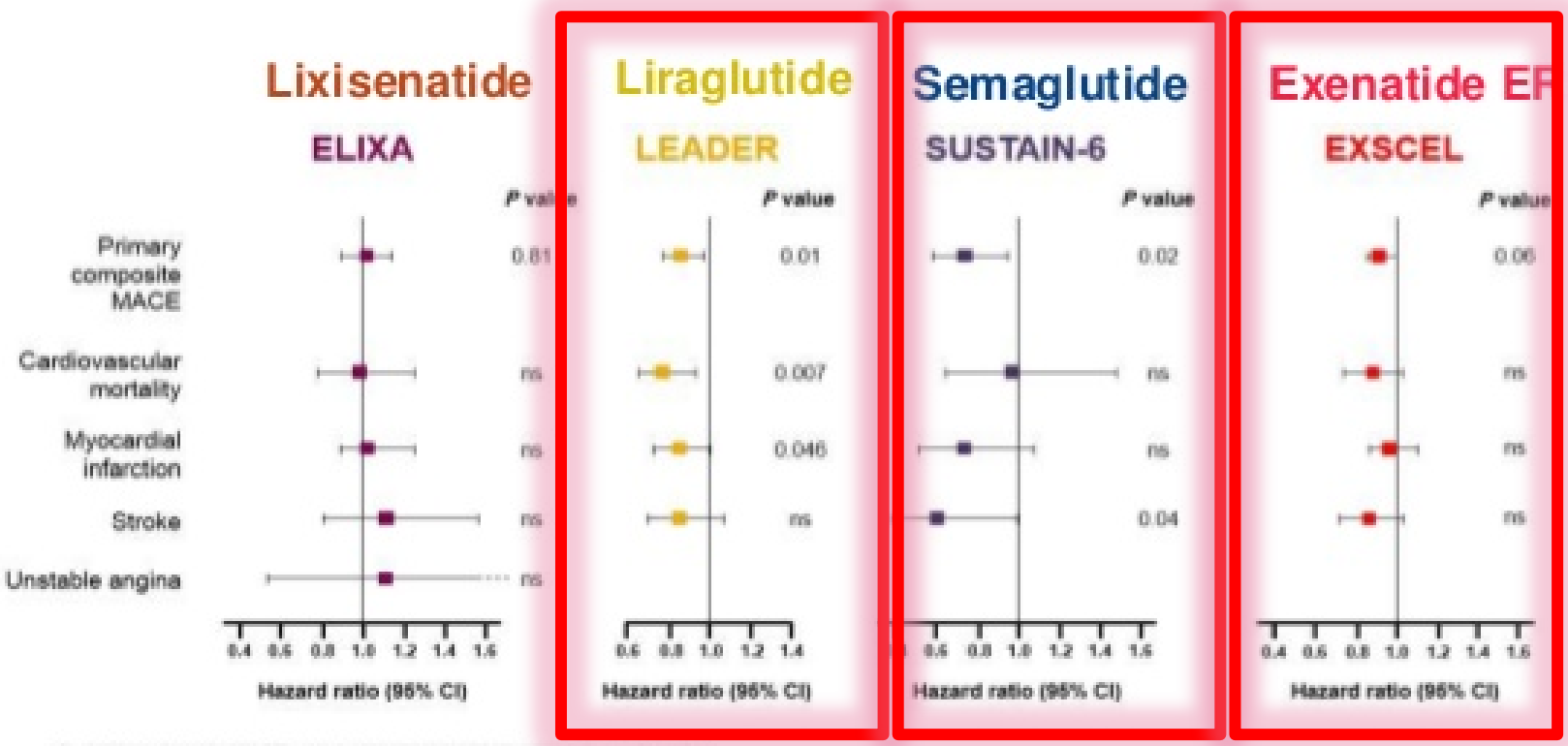


Number of subjects at risk

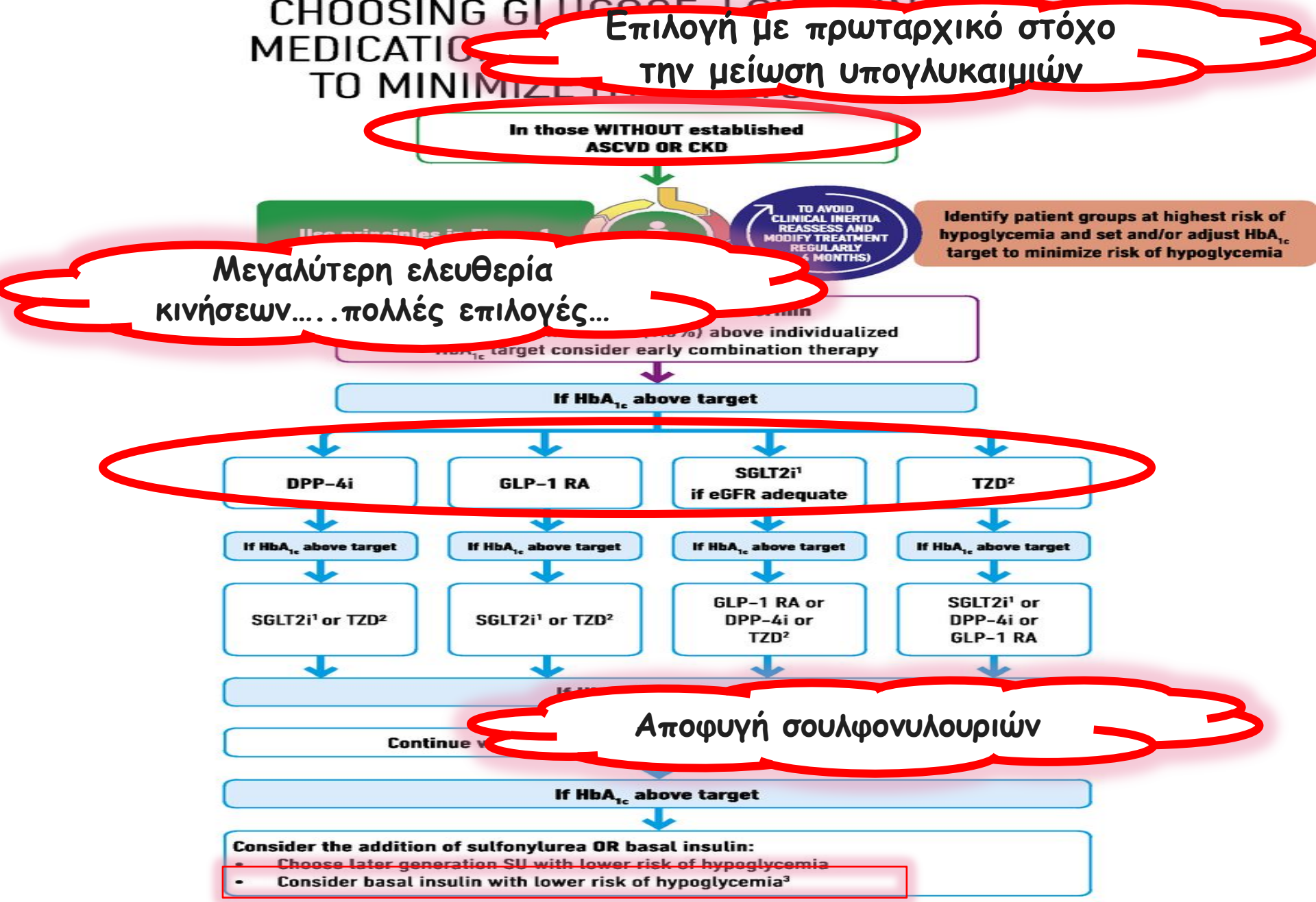
Semaglutide	1648	1630	1605	1580	1563	1541	1525	1518
Placebo	1649	1629	1570	1545	1518	1498	1471	1465

Kaplan-Meier plot for time from randomization to first (external) event adjudication committee-confirmed new or worsening nephropathy using "in-trial" data from subjects in the full analysis set. HR is from a proportional hazard model.
Marso SP et al. *N Engl J Med.* 2016;375(19):1834–1844.
HR, hazard ratio; CI, confidence interval.

GLP1 Receptor Agonist Trials



CI, confidence interval; MACE, major adverse cardiovascular event; ns, not significant.
Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016;375:1834-1844; Holman RR et al., *N Engl J Med*, in press.

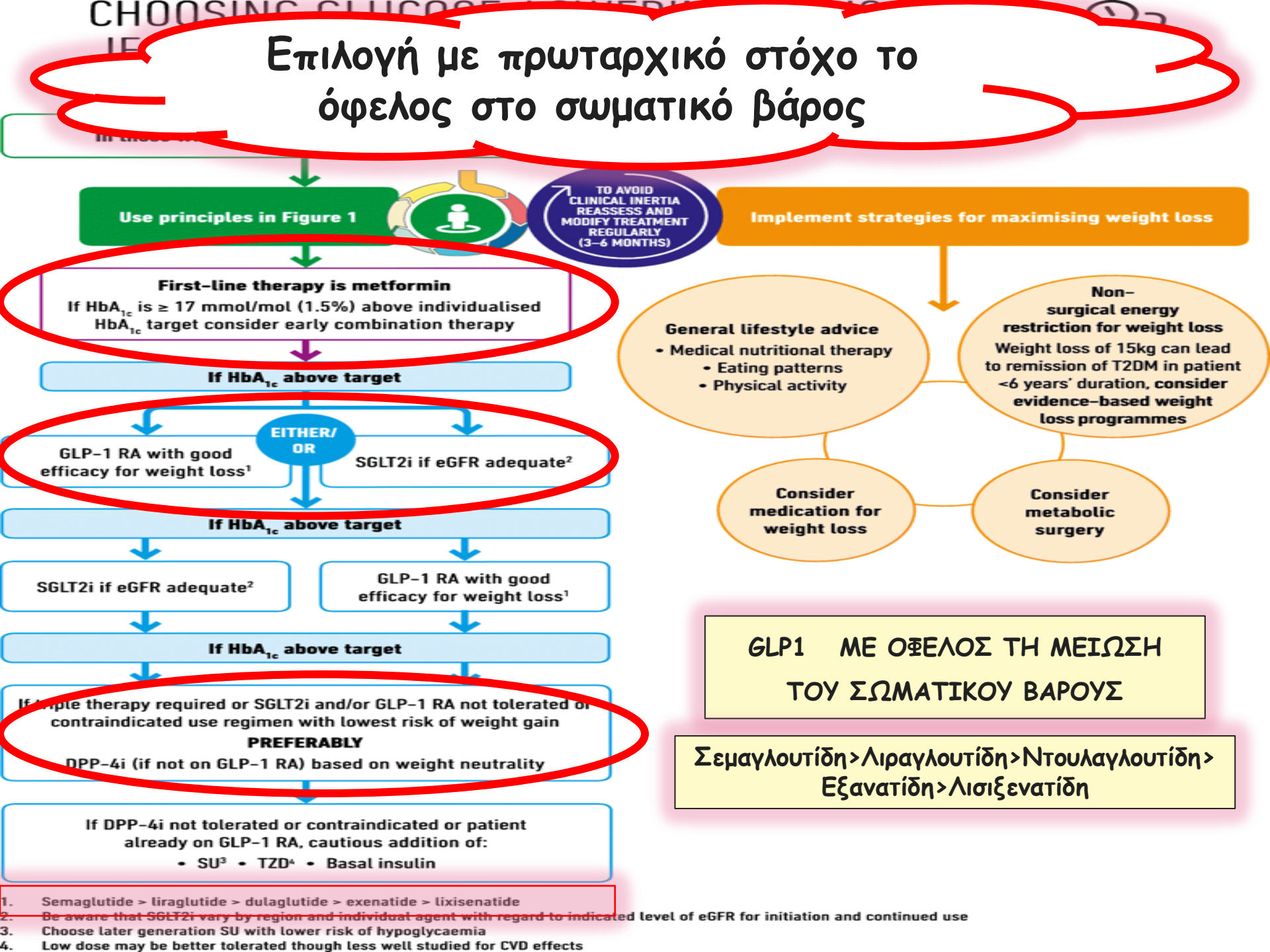


1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

Επιλογή με πρωταρχικό στόχο το όφελος στο σωματικό βάρος



GLP1 ΜΕ ΟΦΕΛΟΣ ΤΗ ΜΕΙΩΣΗ ΤΟΥ ΣΩΜΑΤΙΚΟΥ ΒΑΡΟΥΣ

Σεμαγλουτίδη>Λιραγλουτίδη>Ντουλαγλουτίδη>Εξανατίδη>Λισιξενατίδη

1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycaemia
4. Low dose may be better tolerated though less well studied for CVD effects

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

Επιλογή με πρωταρχικό στόχο το κόστος

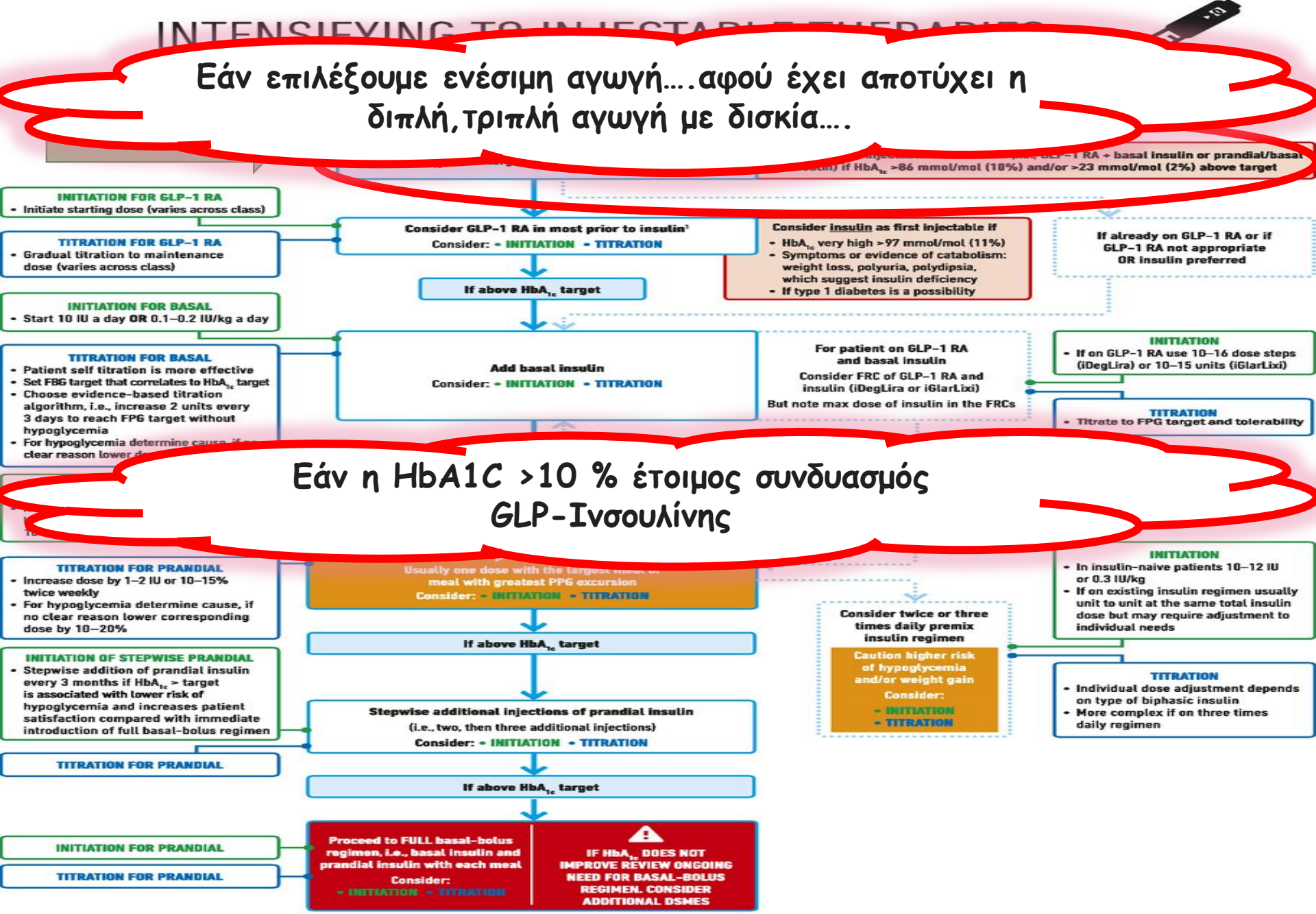
Πιθανή χρήση σουλφονυλουριών

1. Choose later generation SU to minimize risk of hypoglycemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper
3. Low-dose TZDs are better tolerated

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

Εάν επιλέξουμε ενέσιμη αγωγή….αφού έχει αποτύχει η διπλή,τριπλή αγωγή με δισκία….

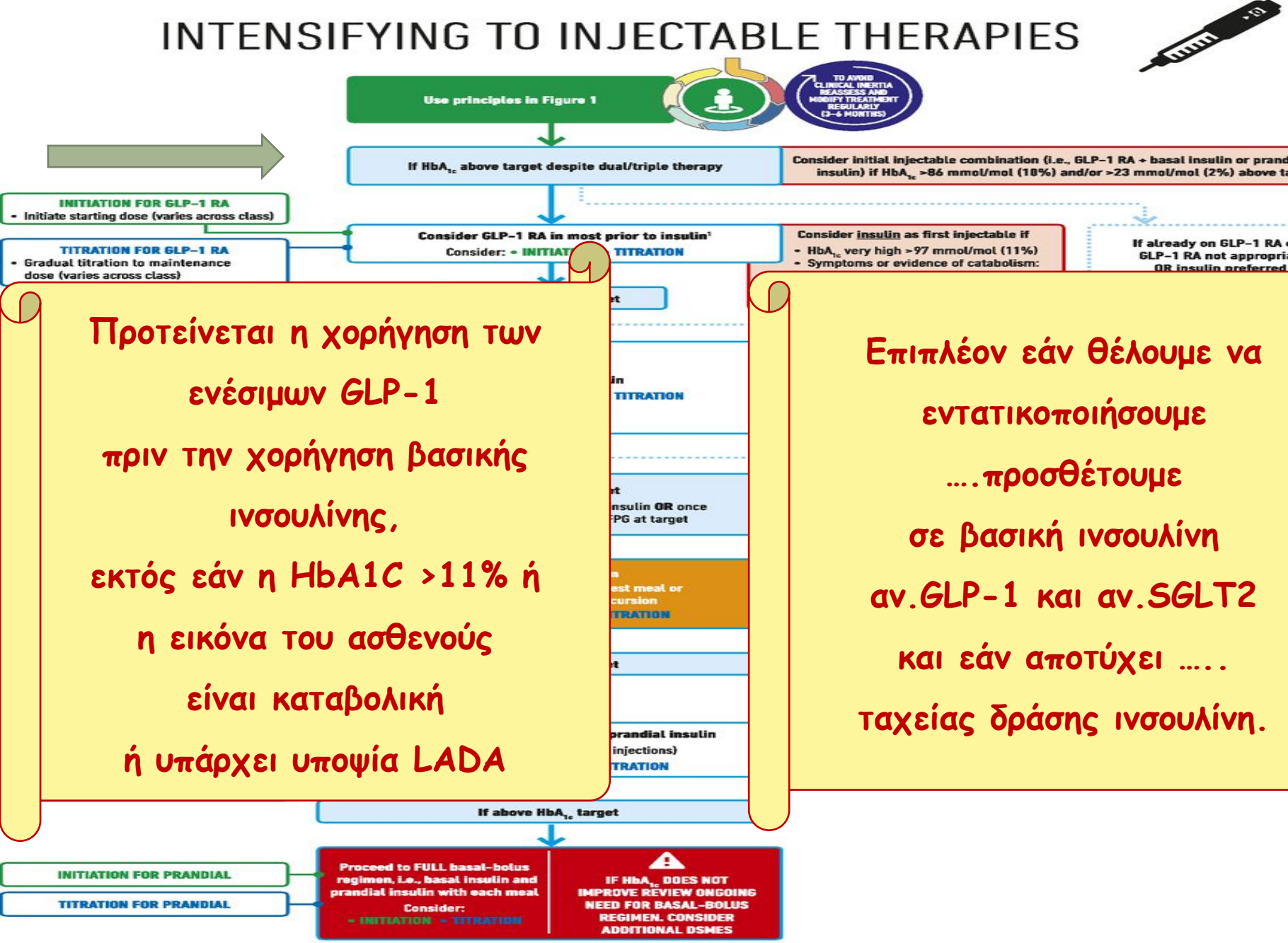


Εάν η HbA1C >10 % έτοιμος συνδυασμός GLP-Ινσουλίνης

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

INTENSIFYING TO INJECTABLE THERAPIES



Προτείνεται η χορήγηση των ενέσιμων GLP-1 πριν την χορήγηση βασικής ινσουλίνης, εκτός εάν η HbA1C >11% ή η εικόνα του ασθενούς είναι καταβολική ή υπάρχει υποψία LADA

Επιπλέον εάν θέλουμε να εντατικοποιήσουμε ….προσθέτουμε σε βασική ινσουλίνη αν.GLP-1 και αν.SGLT2 και εάν αποτύχει ….. ταχείας δράσης ινσουλίνη.

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

METFORMIN

Continue treatment

OR reduce dose

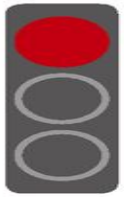
Τονίζεται η δυνατότητα συγχορήγησης ενέσιμης αγωγής με peros αγωγή…

SGLT2i

If on SGLT2i, continue treatment

Consider adding SGLT2i if

- Established CVD
- If HbA_{1c} above target or as weight reduction aid

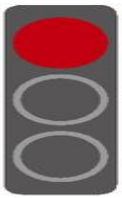


Beware

- DKA (euglycemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

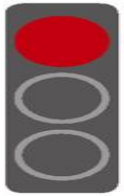
SULFONYLUREA

If on SU, stop or reduce dose by 50% when basal insulin initiated



Consider stopping SU if prandial insulin initiated or on a premix regimen

DPP-4i



Stop DPP-4i if GLP-1 RA initiated

1. Contraindicated in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain

Melanie J. Davies et al. Dia Care 2018;41:2669-2701

American Diabetes Association.

ΕΠΙΛΟΓΙΖΟΝΤΑΣ …….

Για πρώτη φορά προτείνονται συγκεκριμένα φάρμακα κατάλληλα για τον ασθενή, με βάση:

- το καρδιαγγειακό ιστορικό του (αθηρωματική νόσο, καρδιακή ανεπάρκεια, νεφρική νόσο)
- την επιθυμητή απώλεια σωματικού βάρους, τον κίνδυνο υπογλυκαιμιών και το οικονομικό κόστος.

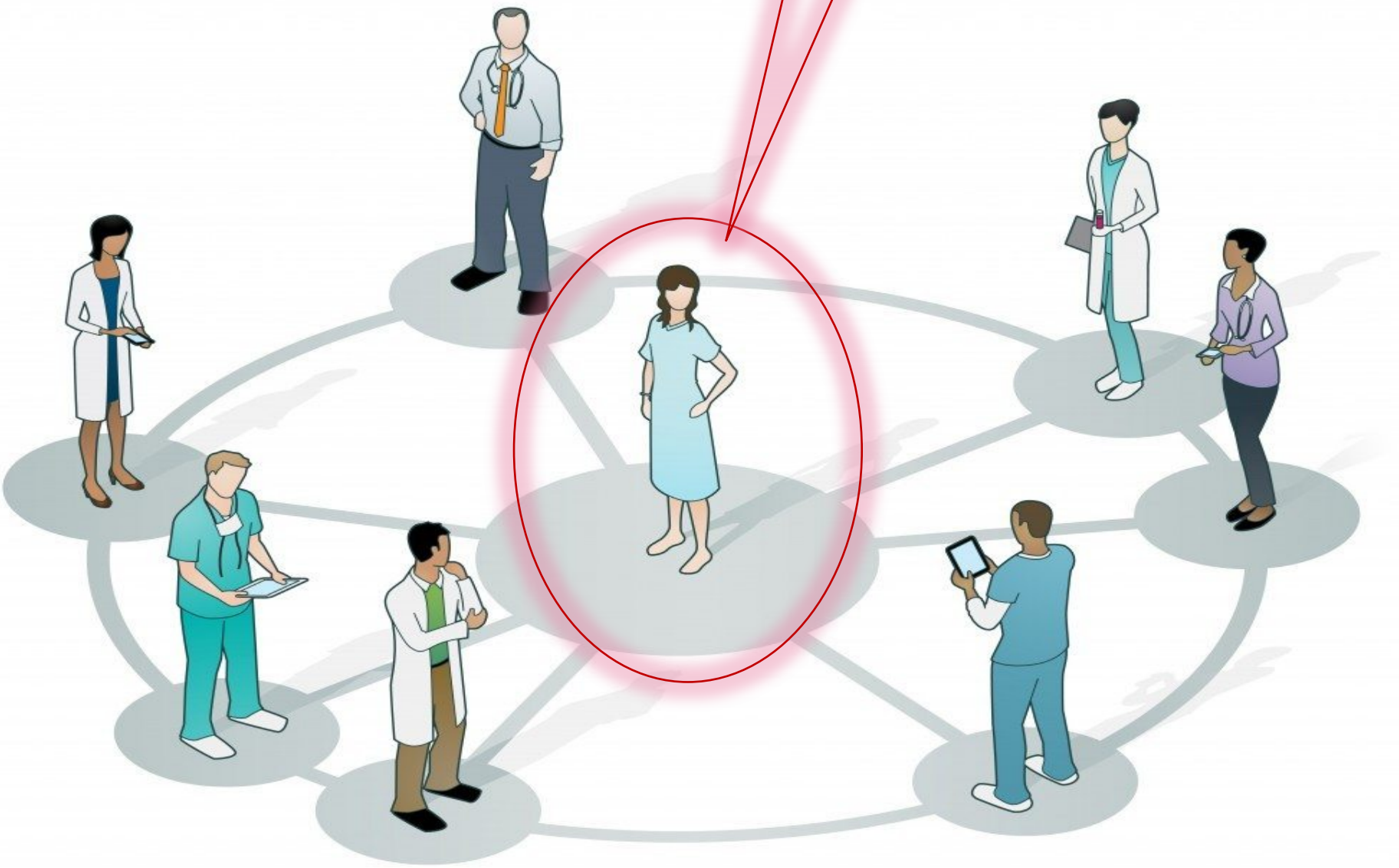
ΕΠΙΛΟΓΙΖΟΝΤΑΣ …….

Αποφυγή σουλφονυλουριών
εκτός εάν μείζον κριτήριο επιλογής
φαρμάκου αποτελεί το κόστος….

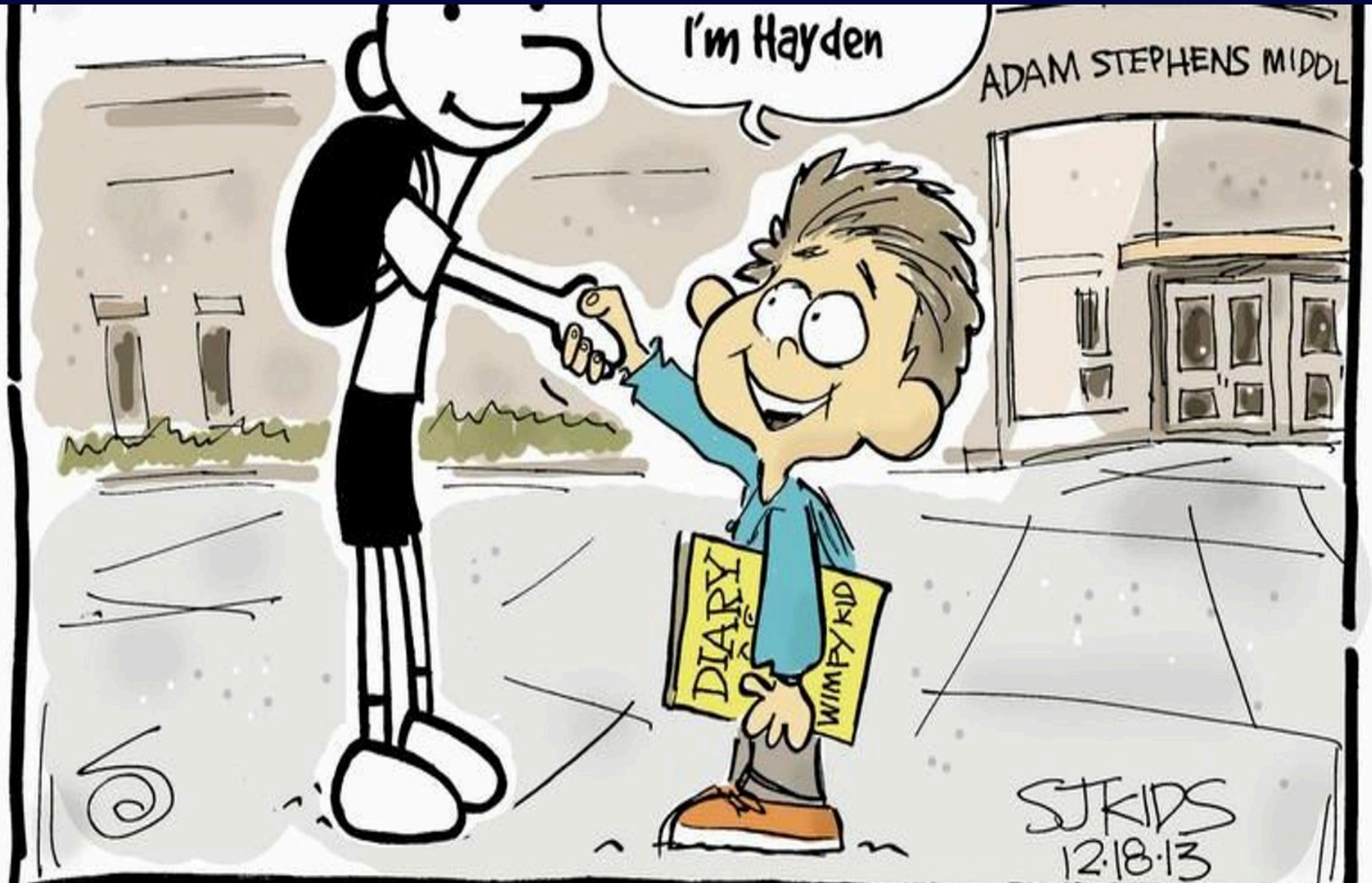
Προτείνετ[illegible]ηση βασικής ινσουλίνης, εκτός εάν η HbA1C >11% ή η εικόνα του ασθενούς είναι καταβολική ή υπάρχει [illegible]AD

Επιλογή φαρμάκων με καρδιακό όφελος
δηλαδή με προστατευτική δράση
όπως GLP-I και αν.SGLT2 που έχουν
συνεργική δράση.

Ο ασθενής είναι στο κέντρο



Συναποφασίζει με τον θεράποντα….



Type 2 diabetes
More than hyperglycaemia

Most important
Treat the patient!
Not the HbA_{1c}

Thanks for your attention!!!

ΣΑΣ ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ