Αντιδιαβητικά φάρμακα και καρδιαγγειακός κίνδυνος

Θεοχάρης Ι. Κουφάκης
Παθολόγος - Διαβητολόγος
Επίκουρος Καθηγητής Παθολογίας
Ιατρική Σχολή ΑΠΘ

ΙΠΠΟΚΡΑΤΕΙΟ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
ΘΕΣΣΑΛΟΝΙΚΗΣ

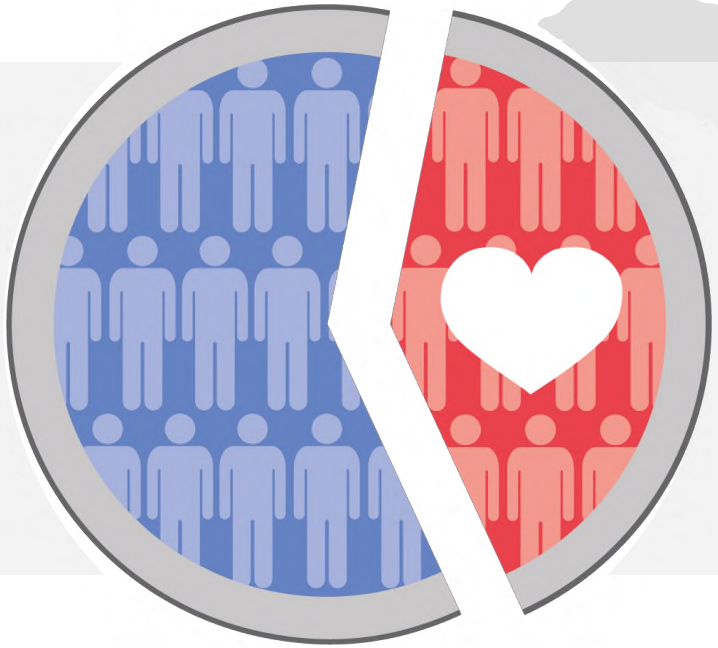
ARISTOTLE
UNIVERSITY OF
THESSALONIKI

Δήλωση συμφερόντων

- Grant/Research support: Ελληνική Διαβητολογική Εταιρεία, Boehringer Ingelheim
- Investigator in clinical trials funded by: El Lilly, NovoNordisk, AstraZeneca
- Speakers bureau: Pharmaserve Lilly, AstraZeneca, NovoNordisk, Boehringer Ingelheim

Γιατί είναι τόσο σημαντική η επίδραση των φαρμάκων στον ΚΔ κίνδυνο;

Ένα μεγάλο ποσοστό των ασθενών με ΣΔτ2 έχουν ΚΔ νόσο



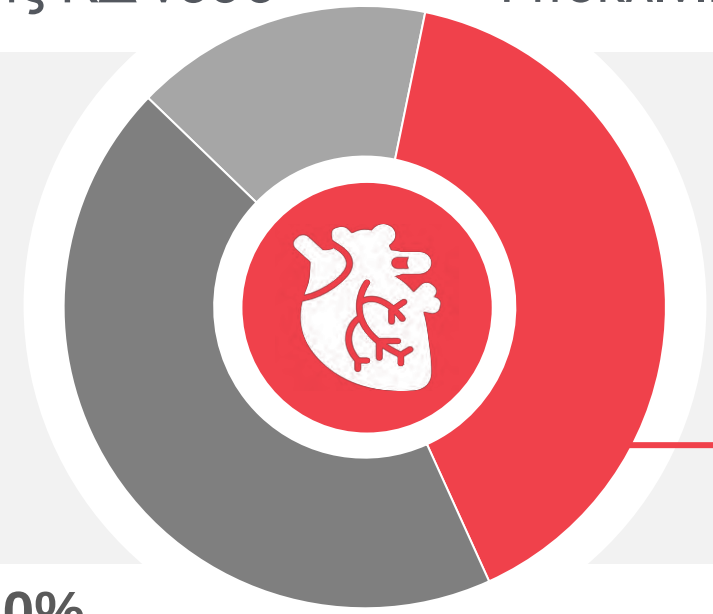
Παγκοσμίως, περίπου **1/3 των ασθενών** με ΣΔτ2 έχουν ΚΔ νόσο

Ανάλυση 60 μελετών με 4.549.481 ασθενείς με ΣΔτ2
ΚΔ: Καρδιαγγειακή, ΣΔτ2 Σακχαρώδης Διαβήτης τύπου 2
Einarson TR *et al. Cardiovasc Diabetol* 2018;17:83

Η ΚΔ Νόσος είναι συνήθως ασυμπωματική και αδιάγνωστη

16%
Χωρίς ΚΔ νόσο

44%
Υποκλινική ΚΔ νόσος



40%
Κλινική ΚΔ Νόσος

Σχεδόν οι μισοί ασθενείς με διαβήτη έχουν **Υποκλινική ΚΔ Νόσο***

Prevalence of subclinical CV disease across 1343 patients with diabetes aged ≥65 years in the US
*Absence of prevalent clinical disease at baseline: ankle–brachial index ≤0.9, internal carotid artery wall thickness >80th percentile, common carotid artery wall thickness >80th percentile, carotid stenosis >25%, major electrocardiogram abnormalities (based on the Minnesota code), and a Rose Questionnaire positive for claudication or angina pectoris in the absence of clinical diagnosis of angina pectoris or claudication
Kuller LH *et al. Arterioscler Thromb Vasc Biol* 2000;20:823

Η ΚΔ νόσος σε ασθενείς με ΣΔτ2 είναι υπεύθυνη για περισσότερους θανάτους από τον καρκίνο* στο γενικό πληθυσμό

2.5 φορές περισσότεροι θάνατοι από ότι ο καρκίνος*

Θάνατοι που οφείλονται στη ΚΔ νόσο σε ασθενείς με ΣΔτ2

Θάνατοι εξαιτίας καρκίνου* σε ασθενείς Με ΣΔτ2

24ετή παρακολούθηση 7461 ασθενών με ΣΔτ2 και 37.271 στην ομάδα ελέγχου από το Skaraborg Diabetes Register
*Solid tumour cancers only, ΚΔ: Καρδιαγγειακή, ΣΔτ2 Σακχαρώδης Διαβήτης τύπου 2,
Andersson T et al. Diabetes Res Clin Prac 2018;138:81

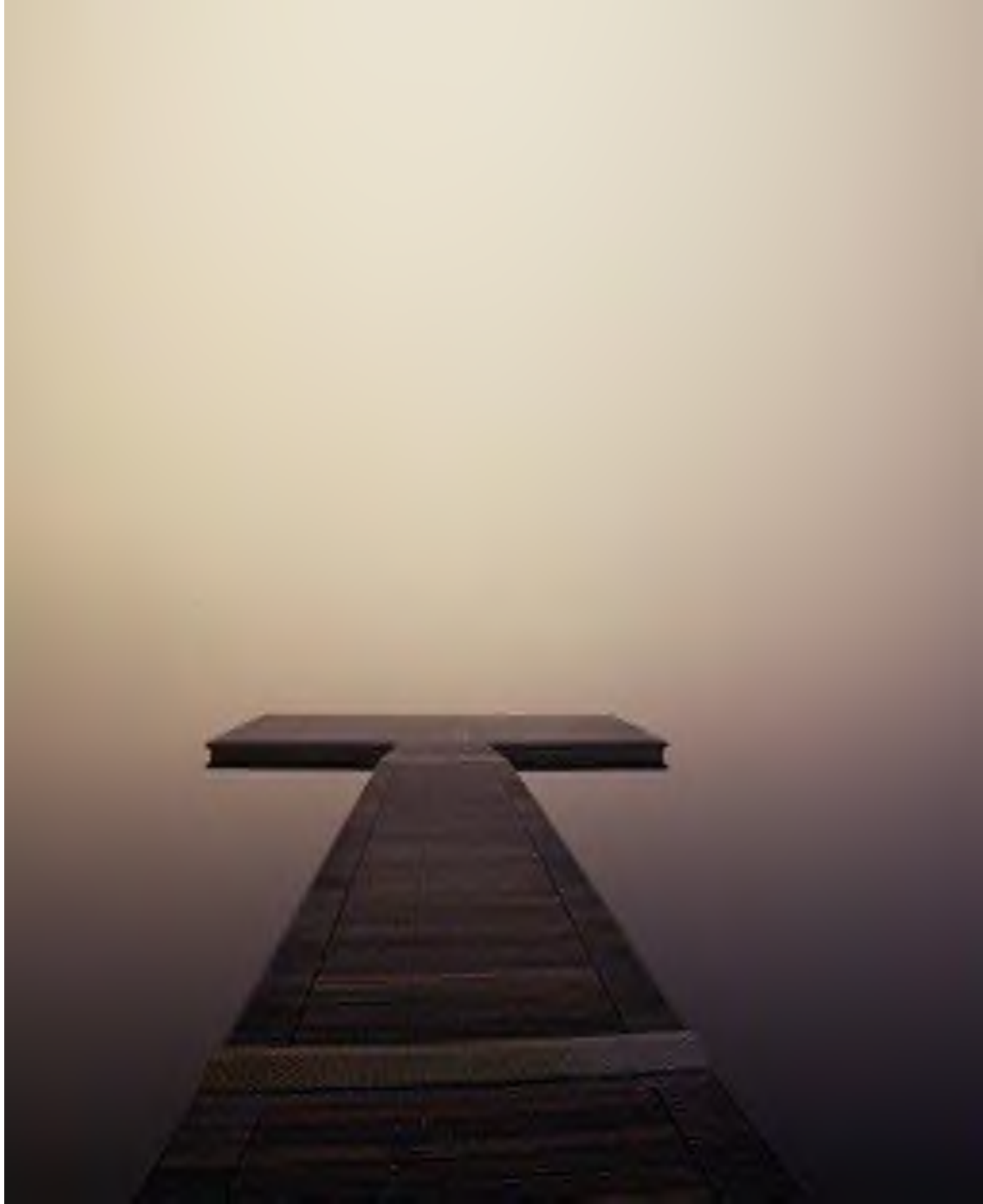
Η ΚΔ νόσος είναι επίσης ο μεγαλύτερος συντελεστής στη δαπάνη της διαχείρισης του ΣΔτ2

Η ΚΔ νόσος συνεισφέρει **έως 49%**
της συνολικής δαπάνης
της θεραπείας του ΣΔτ2

ΚΔ: Καρδιαγγειακή, ΣΔτ2 Σακχαρώδης Διαβήτης τύπου 2

Einarson TR *et al. Value Health* 2018;21:881

Γιατί να μην ρυθμίσω απλά τη HbA1c;



Περιορισμένα ΚΔ οφέλη έχουν παρατηρηθεί με τον εντατικό γλυκαιμικό έλεγχο σε ασθενείς με Δτ2

Μετανάλυση των μελετών ACCORD, ADVANCE, UKPDS και VADT

Στόχος: η δημιουργία ακριβούς εκτίμησης για τα οφέλη της θεραπείας μείωσης γλυκόζης στα κύρια ΚΑ συμβάντα

Ασθενείς με Δτ2 (N=27.049) οι οποίοι έχουν κατανεμηθεί στην κατηγορία 'Περισσότερο εντατικού' ή 'Λιγότερο Εντατικού' γλυκαιμικού ελέγχου

Κύρια ΚΑ συμβάντα
(ΚΑ θάνατος ή μη-θανατηφόρο εγκεφαλικό ή μη-θανατηφόρο ΜΙ)

Μέτριο όφελος
HR 0,91 (0,84, 0,99)

Θνησιμότητα οποιασδήποτε αιτιολογίας

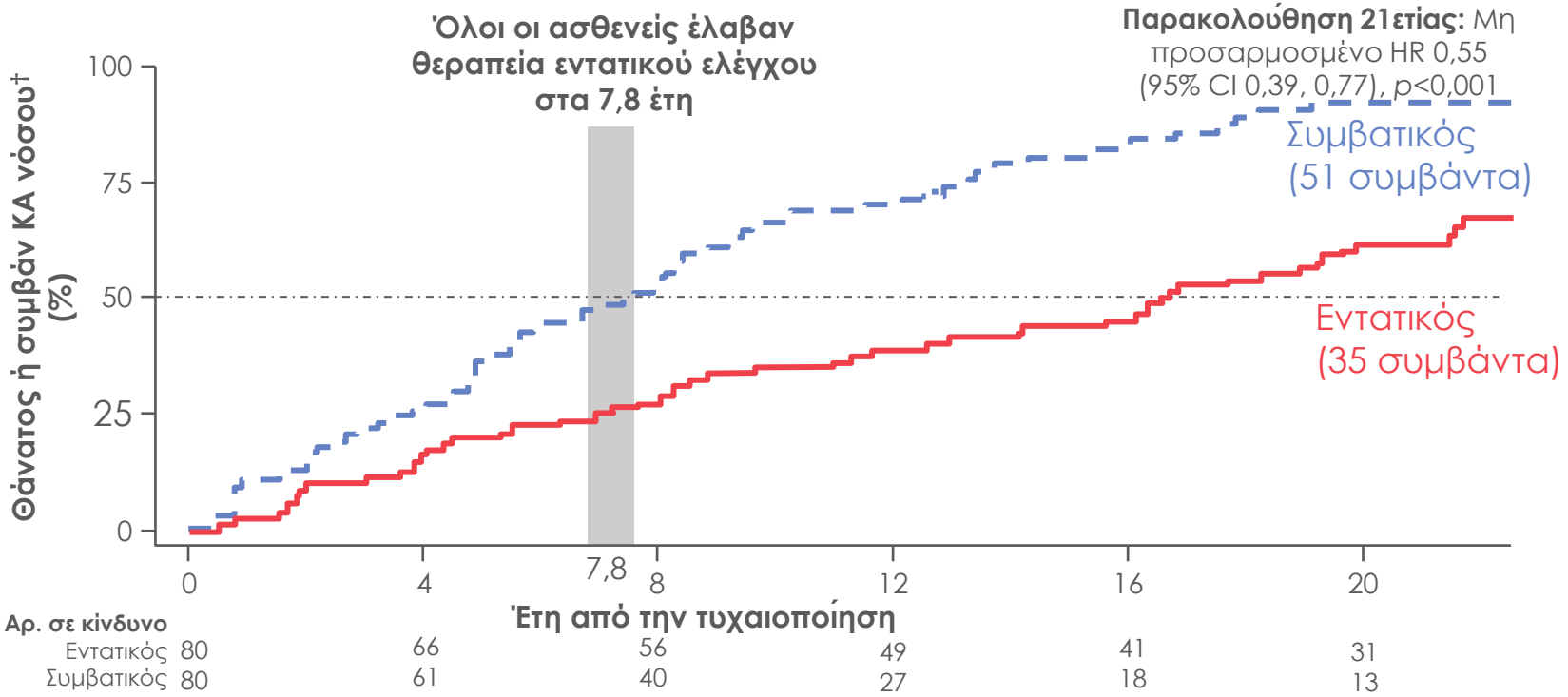
Καμία επίδραση
HR 1,04 (0,90, 1,20)

*Οι μελέτες διέφεραν στις θεραπείες μείωσης γλυκόζης και καρδιοπροστασίας στην παρακολούθηση. Οι μελέτες χρησιμοποίησαν μετφορμίνη, ινσουλίνη, σουλφονυλουρία, acarbose, glinide και θειαζολιδινεδιόνη ως παράγοντες μείωσης της γλυκόζης

Turnbull FM *et al. Diabetologia* 2009;52:2288

Ο πολυδιάστατος έλεγχος παραγόντων ΚΔ κινδύνου μείωσε τον ΚΔ κίνδυνο σε ασθενείς με Δτ2

Steno-2: Ο εντατικός πολυδιάστατος έλεγχος* παραγόντων ΚΑ κινδύνου μειώνει τον ΚΑ κίνδυνο σε ασθενείς με Δτ2 και μικρολευκωματινουρία[1,2]



Αλλαγές στις βασικές κλινικές και βιοχημικές μεταβλητές στα 7,8 έτη[2]

Μεταβλητή	Συμβατικός (n=63)	Εντατικός (n=67)	τιμή-*p*
Συστολική ΑΠ (mmHg)	-3 ± 3	-14 ± 2	<0,001
Διαστολική ΑΠ (mmHg)	-8 ± 2	-12 ± 2	0,006
LDL χοληστερόλη (mg/dl)	-13 ± 6	-47 ± 5	<0,001
HbA1c(%)	0,2 ± 0,3	-0,5 ± 0,2	<0,001
ΔΜΣ (άνδρες)	0,4 ± 0,4	0,7 ± 0,4	0,61
ΔΜΣ (γυναίκες)	1,3 ± 1,3	2,3 ± 1,2	0,29
Ενεργός καπνιστής (αρ. ασθενών)	-6	-5	0,73

Όφελος θεραπείας παρατηρήθηκε μετά από ~4 έτη. Οι συνεχιζόμενες ωφέλιμες επιδράσεις στην πάροδο του χρόνου ήταν άμεση συνέπεια της έγκαιρης εντατικοποίησης της θεραπείας στους ασθενείς

*Ο έντονος πολυδιάστατος έλεγχος περιλάμβανε μειωμένους στόχους για την αρτηριακή πίεση, τη χοληστερόλη, τα τριγλυκερίδια και την HbA1c, καθώς και θεραπεία με ασπιρίνη και ACEi. †Σύνθετο δευτερεύον τελικό σημείο: χρόνος έως την εμφάνιση ΚΑ νόσου, αριθμός ΚΑ συμβάντων, ποσοστά θνησιμότητας και ΚΔ νόσου.
ACEi, αναστολέας του μετατρεπτικού ενζύμου αγγειοτενσίνης. ΔΜΣ, δείκτης μάζας σώματος. LDL, λιποπρωτεΐνη χαμηλής πυκνότητας.
1. Gaede P *et al. Diabetologia* 2016;59:2298; 2. Gaede P *et al. N Engl J Med* 2003;348:383

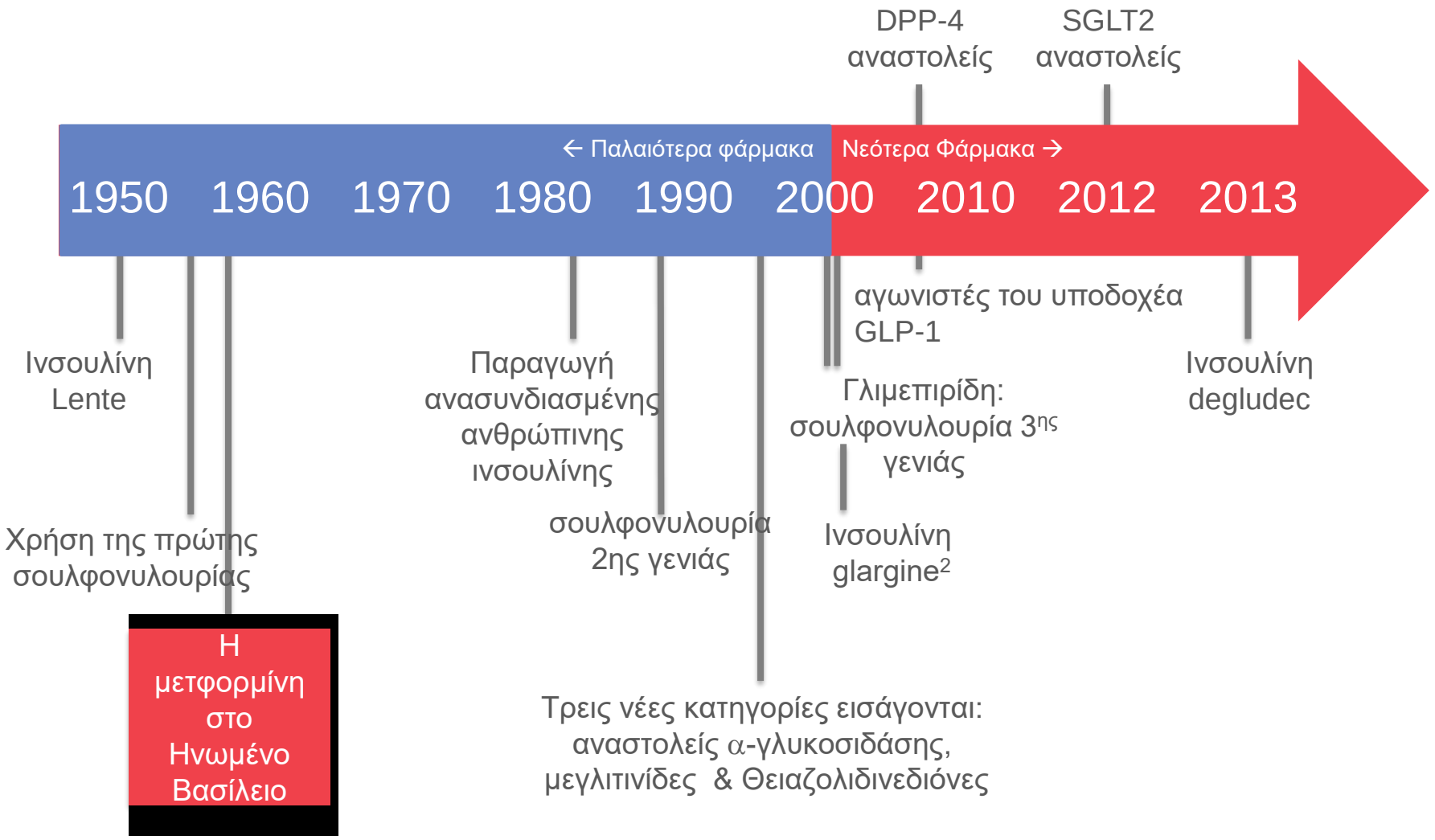
Οι επιδράσεις των παλαιότερων αντιδιαβητικών παραγόντων στον Καρδιαγγειακό κίνδυνο

Περιεχόμενα

Οι επιδράσεις των παλαιότερων αντιδιαβητικών παραγόντων στον Καρδιαγγειακό κίνδυνο

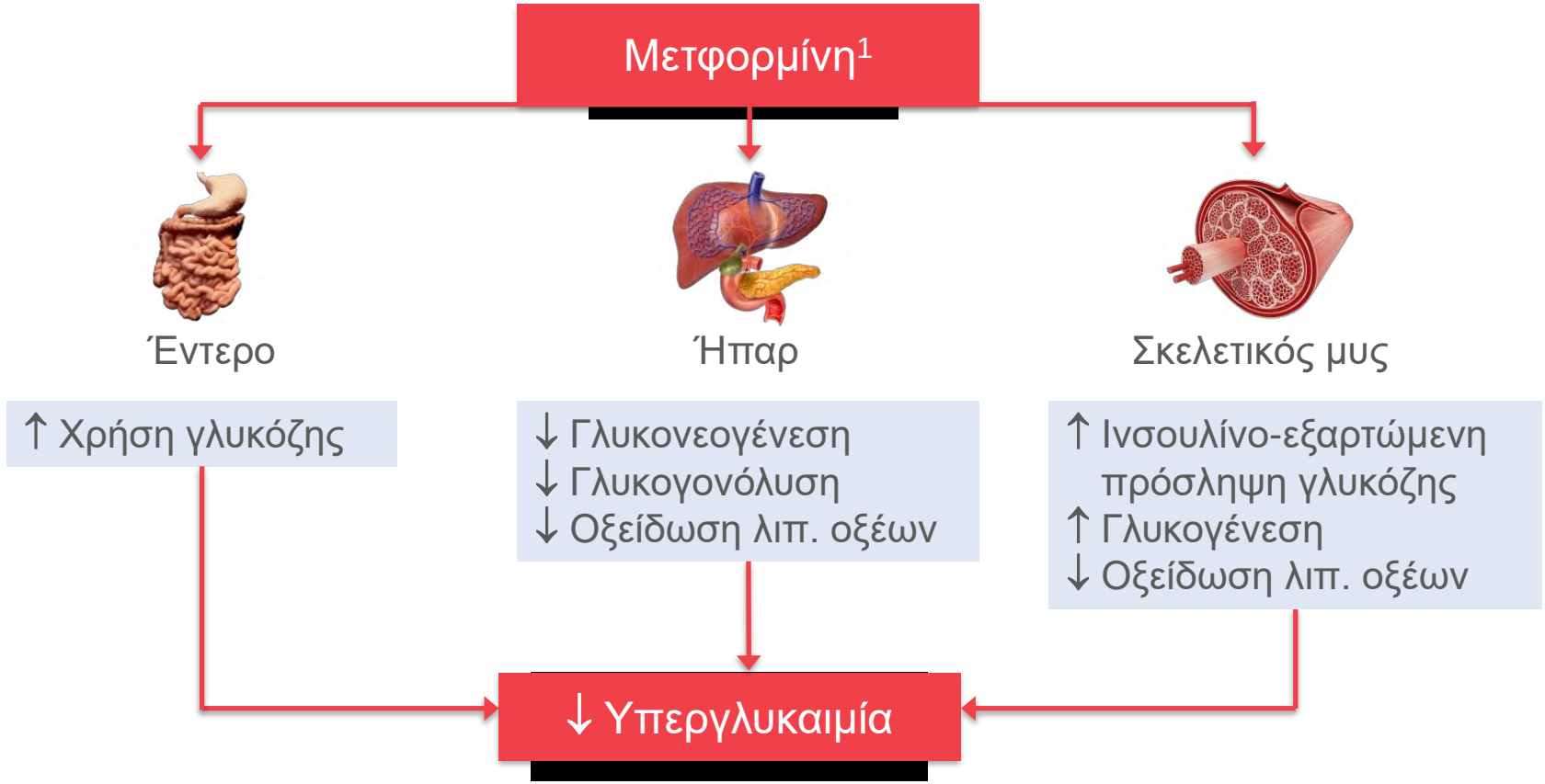
Περιεχόμενα

Εξέλιξη των Θεραπειών του ΣΔτ2



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter-2; ΣΔτ2, Σακχαρώδης Διαβήτης τύπου 2
Adapted from 1. Kirby MG. *Br J Diabetes Vasc Dis* 2012;12:315; 2. Lantus® SPC

Μετφορμίνη: Μηχανισμός δράσης



Επιπρόσθετα της δράσης της στη μείωση της γλυκόζης, η μετφορμίνη μπορεί να έχει πιθανές επιδράσεις στο ΚΔ σύστημα, π.χ. βελτίωση του προφίλ των λιπιδίων στο πλάσμα[2]

ΚΔ: Καρδιαγγειακό

Adapted from 1. Bailey CJ & Feher MD. *Therapies for Diabetes* 2004; 2. Batchuluun B *et al. J Endocrinol Diabetes Obes* 2014;2:1035

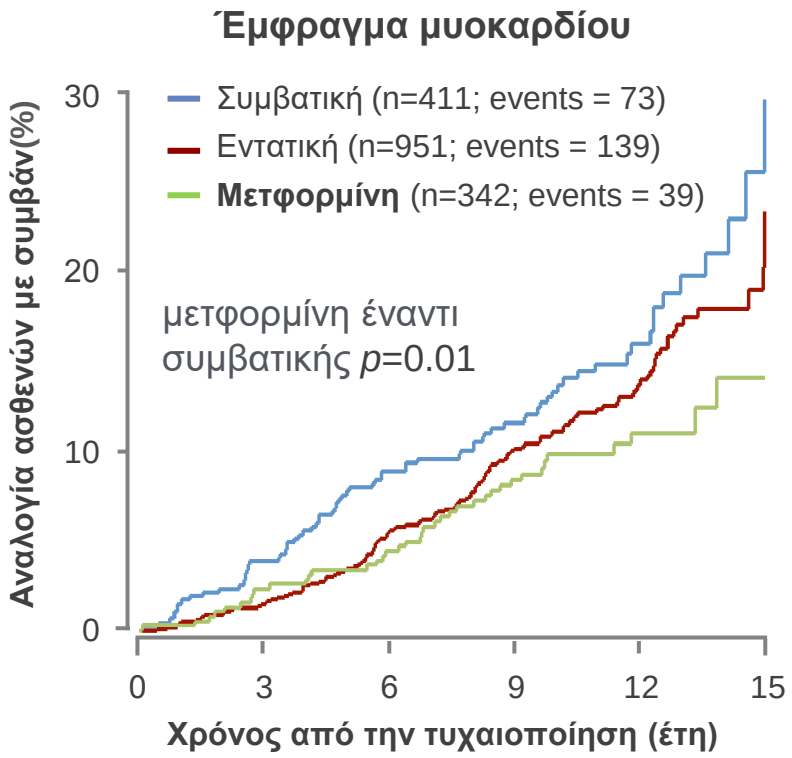
Metformin is recommended as first-line therapy in T2D

- Metformin is indicated for the treatment of T2D, and generally recommended as first-line therapy[1,2]
- Evidence for effect on CV risk cited in international prescribing information differs for US vs EU
  - US prescribing information[3]
    - States that there are no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin
  - EU prescribing information[1]
    - Cites UKPDS analysis from 342 overweight patients treated with metformin after failure of diet alone[1,4]
      - Metformin significantly reduced any diabetes-related complication, diabetes-related and overall mortality, and absolute risk of MI vs diet alone after 10.7 years

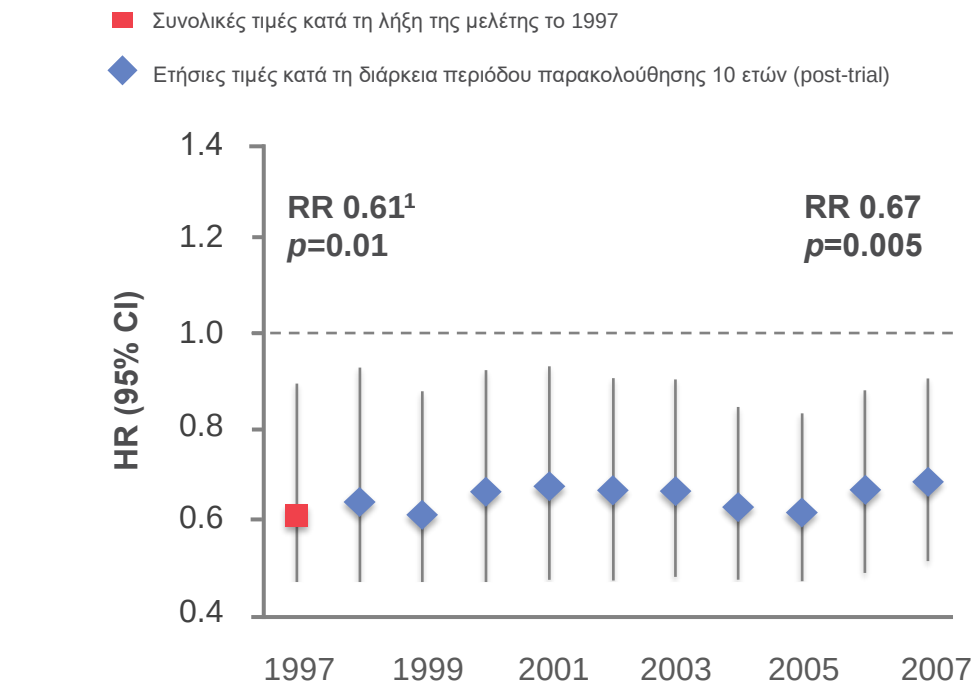
1. http://www.medicines.org.uk/emc/medicine/23244/SPC. 2. American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94.
3. http://www.drugs.com/pro/metformin.html 4. UKPDS 34. Lancet 1998;352:854–65.

UKPDS 34 παρέχει ορισμένα στοιχεία για ευεργετικές ΚΔ επιδράσεις της μετφορμίνης σε υπέρβαρους ασθενείς

Ο κίνδυνος ΕΜ είναι 39% χαμηλότερος με μετφορμίνη έναντι της συμβατικής θεραπείας στους υπέρβαρους ασθενείς [1,2]



Σημαντική μείωση του ΕΜ διατηρήθηκε μετά από 10 χρόνια παρακολούθησης[3]



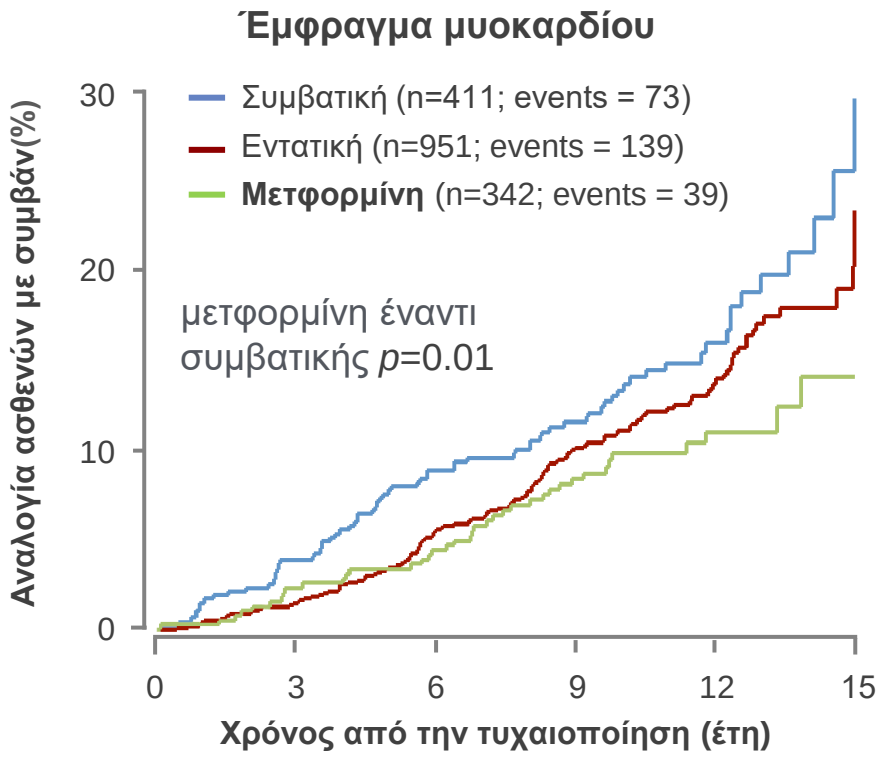
Αρ. συμβάντων:						
Συμβατική θεραπεία	73	83	92	106	118	126
Μετφορμίνη	39	45	55	64	68	81

ΚΔ: Καρδιαγγειακό, ΕΜ: Έμφραγμα του Μυοκαρδίου, RR, relative risk, UKPDS, United Kingdom Prospective Diabetes Study

1. UKPDS 34. *Lancet* 1998;352:854; 2. http://www.medicines.org.uk/emc/medicine/23244/SPC; 3. Holman RR *et al. N Engl J Med* 2008;359:1577

UKPDS 34: παρέχει ορισμένα στοιχεία για ευεργετικές ΚΔ επιδράσεις της μετφορμίνης σε υπέρβαρους ασθενείς

Ο κίνδυνος ΕΜ είναι 39% χαμηλότερος με μετφορμίνη έναντι της συμβατικής θεραπείας στους υπέρβαρους ασθενείς [1,2]



υπέρβαροι

n=342

Vs: conventional policy with diet (HbA1c 7.9%)

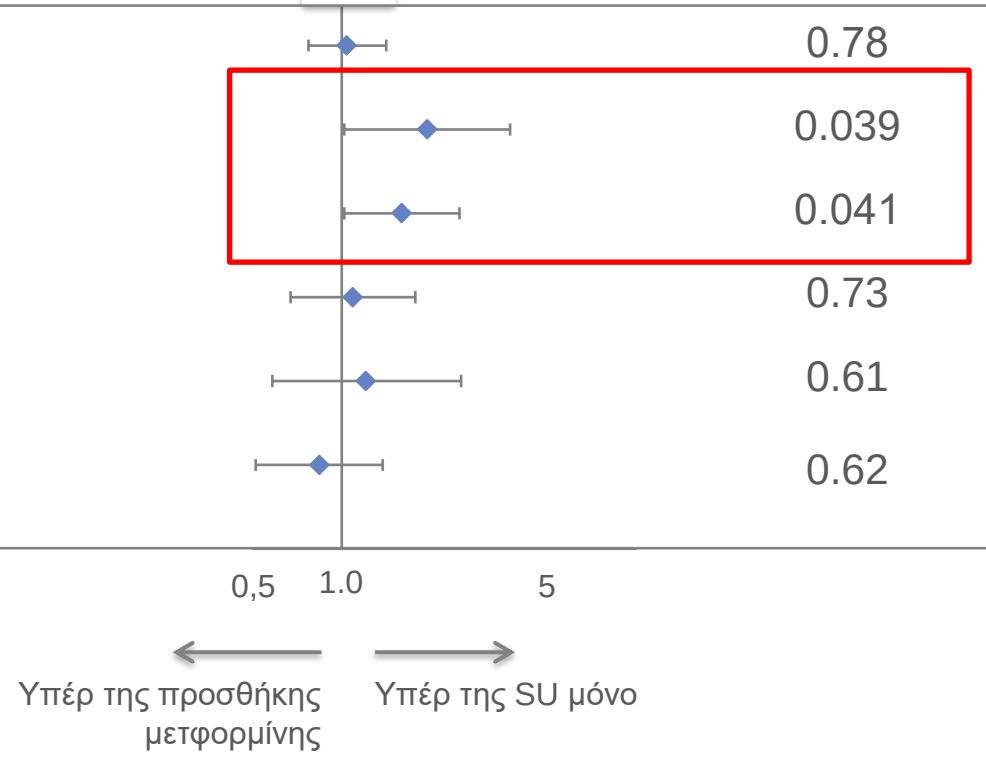
ΚΔ: Καρδιαγγειακό, ΕΜ: Έμφραγμα του Μυοκαρδίου, RR, relative risk, UKPDS, United Kingdom Prospective Diabetes Study

1. UKPDS 34. *Lancet* 1998;352:854; 2. http://www.medicines.org.uk/emc/medicine/23244/SPC; 3. Holman RR *et al. N Engl J Med* 2008;359:1577

UKPDS 34: ΚΔ επιδράσεις της μετφορμίνης προστιθέμενης σε σουλφονυλουρία

Η μετφορμίνη προστιθέμενη σε σουλφονυλουρία έναντι σουλφονυλουρίας μόνο, συσχετίστηκε με αυξημένο κίνδυνο θανάτου σχετιζόμενου με το διαβήτη και θνητότητας από κάθε αιτία

Διάμεση παρακολούθηση 6.6 έτη	RR	Σχετικός Κίνδυνος(95% CI)	*p*-value
Τελικό σημείο σχετιζόμενο με διαβήτη	1.04		0.78
Θάνατος σχετιζόμενος με το διαβήτη *	1.96		0.039
Θάνατος κάθε αίτιας*	1.60		0.041
Έμφραγμα του Μυοκαρδίου*	1.09		0.73
ΑΕΕ*	1.21		0.61
Μικροαγγειακό*	0.84		0.62



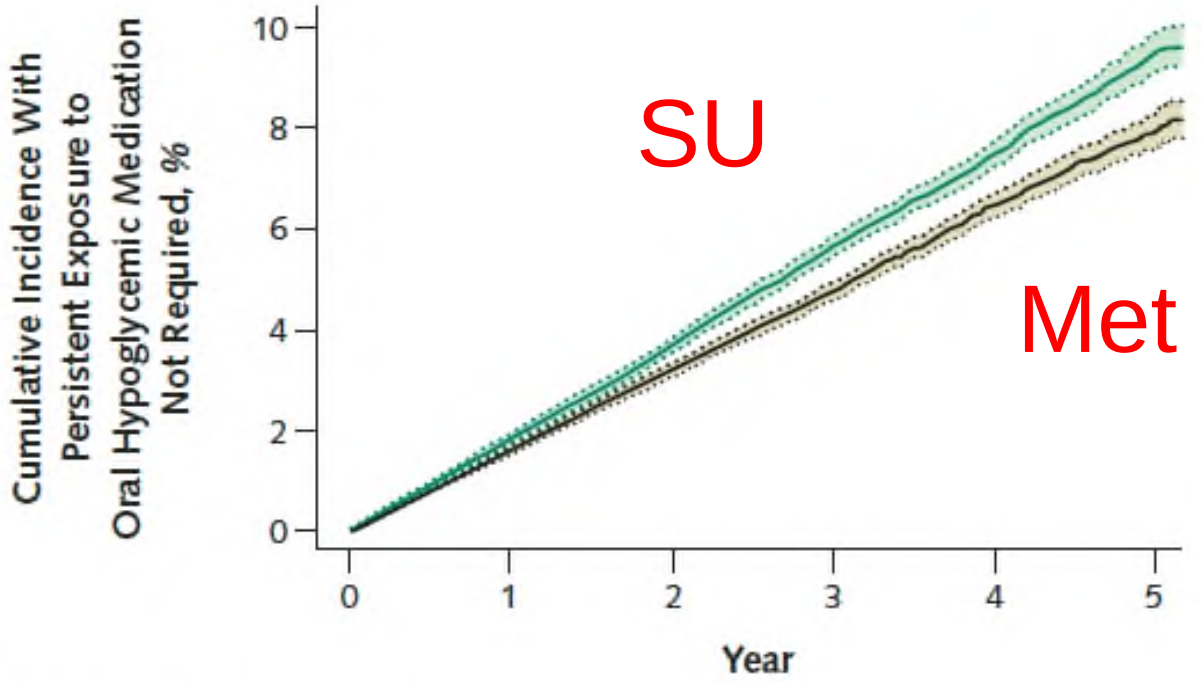
*Interpret with caution in view of small event numbers
ΚΔ: Καρδιαγγειακό, ΑΕΕ: Αγγειακό Εγκεφαλικό Επεισόδιο SU, sulphonylurea; UKPDS, United Kingdom Prospective Diabetes Study
UKPDS 34. *Lancet* 1998;352:854

Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus

A Cohort Study

Προβλήματα ερμηνείας

Π.χ. η SU επιβλαβής ή η μετφορμίνη επωφελής?



Patients receiving metformin, *n*	80 648	65 655	47 552	30 413	16 391	4637
Patients receiving sulfonylurea, *n*	80 648	64 757	45 982	29 104	15 513	4199

Roumie et al. Ann Intern Med 2012

Cardiovascular Drugs and Therapy
https://doi.org/10.1007/s10557-021-07249-0

REVIEW ARTICLE

Sodium-Glucose Co-transporter 2 Inhibitors Versus Metformin as the First-Line Treatment for Type 2 Diabetes: Is It Time for a Revolution?

Theocharis Koufakis[1] · Athanasia Papazafiropoulou[2] · Konstantinos Makrilakis[3] · Kalliopi Kotsa[1]

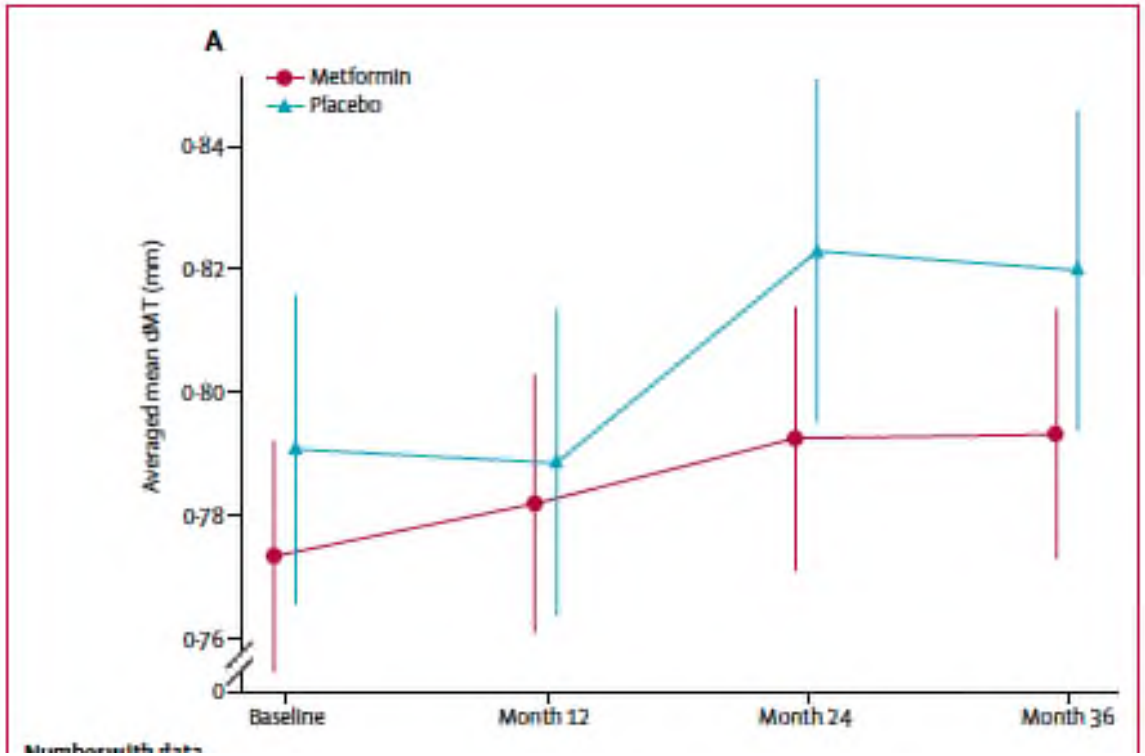
"Although metformin is generally believed to exert positive effects on cardiovascular outcomes, relevant data are mainly **observational** and potentially **overinterpreted**."

Koufakis et al. Cardiovasc Drugs Ther 2021

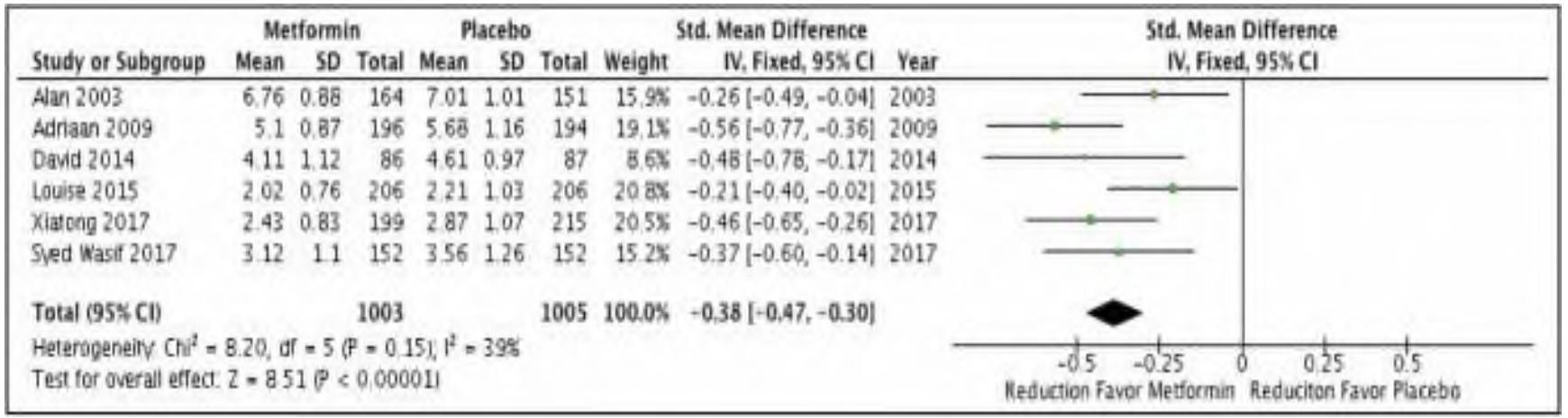
Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial

*John R Petrie, Nishi Chaturvedi, Ian Ford, Martijn C G J Brouwers, Nicola Greenlaw, Therese Tillin, Irene Hramiak, Alun D Hughes, Alicia J Jenkins, Barbara E K Klein, Ronald Klein, Teik C Ooi, Peter Rossing, Coen D A Stehouwer, Naveed Sattar, Helen M Colhoun, for the REMOVAL Study Group**

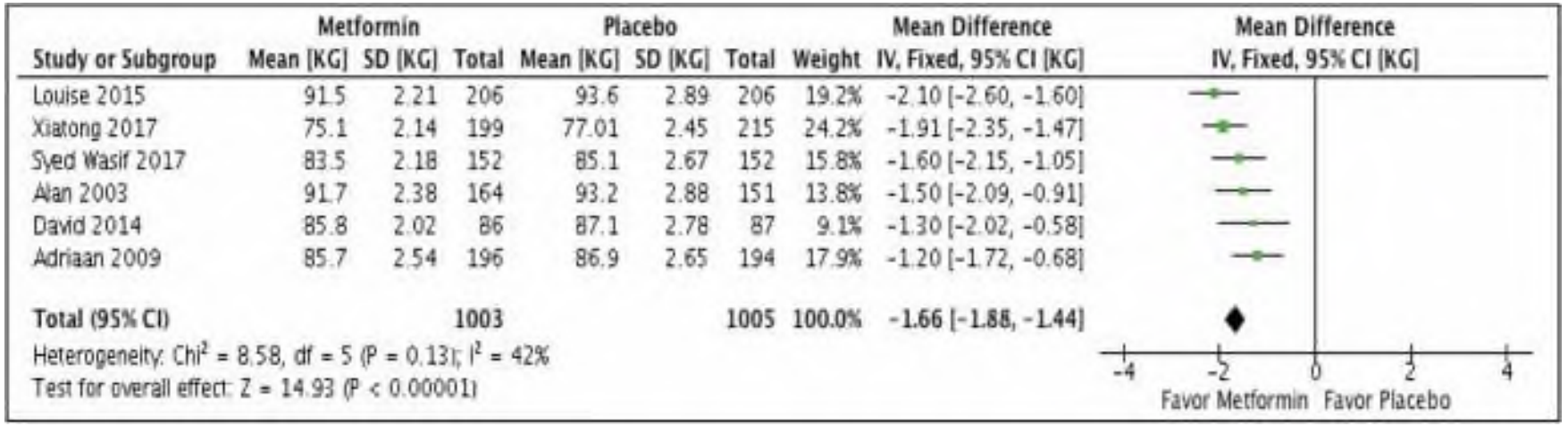
Maximal CIMT



Petrie et al. Lancet Diabetes Endocrinol 2017

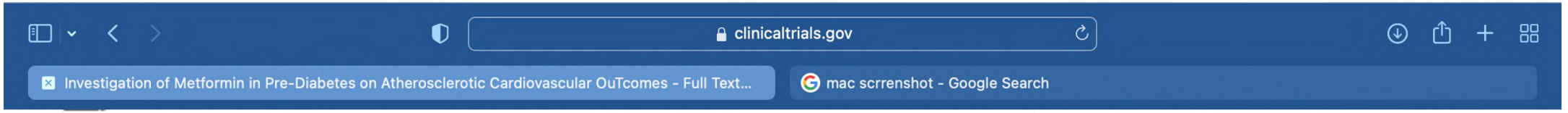


LDL-C



Body weight

Gillani et al. J Pharm Bioallied Sci 2021



ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login

Home > Search Results > Study Record Detail

Save this study

Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02915198

Recruitment Status : Active, not recruiting
First Posted : September 26, 2016
Last Update Posted : September 24, 2021

Sponsor:
VA Office of Research and Development

Information provided by (Responsible Party):
VA Office of Research and Development

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:
This research will help us to learn if the medicine called metformin reduces the risk of death, heart attacks, and/or strokes in patients who have pre-diabetes and heart or blood vessel problems.

Condition or disease	Intervention/treatment	Phase

- Πιθανά θετική επίδραση στο Κ/Δ σύστημα

- Μας λείπουν πολύ ισχυρά δεδομένα

Ποιος διάσημος θα ήταν η μετφορμίνη;

Οι επιδράσεις των παλαιότερων αντιδιαβητικών παραγόντων στον Καρδιαγγειακό κίνδυνο

Περιεχόμενα

Μετφορμίνη

Σουλφονυλουρίες

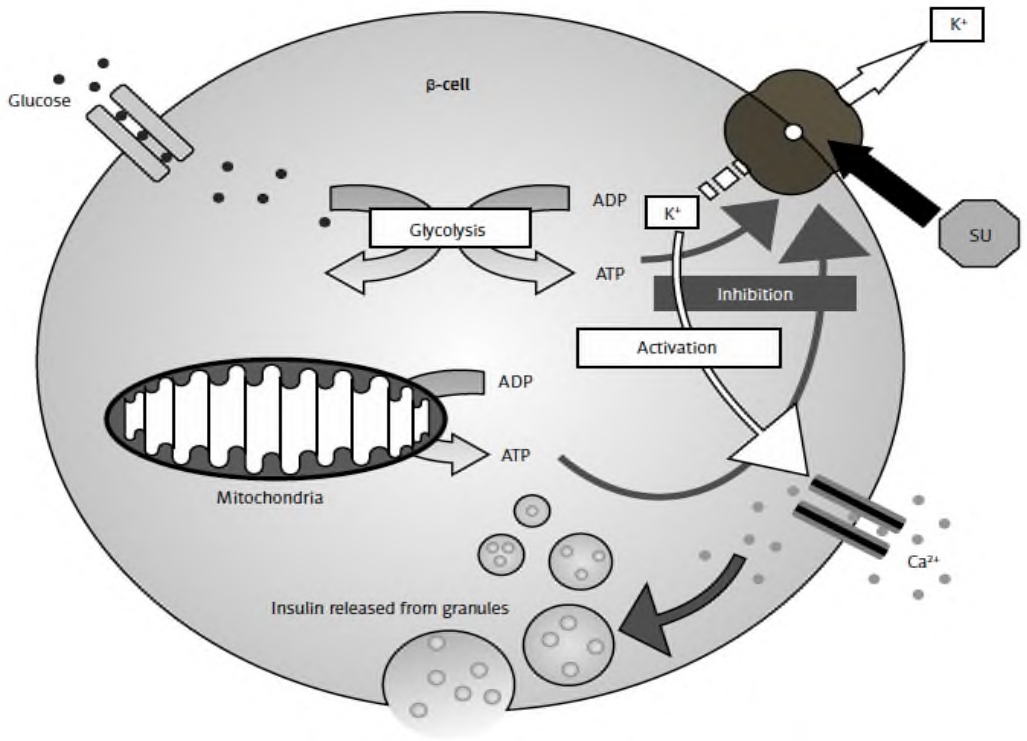
Θειαζολιδινεδιόνες

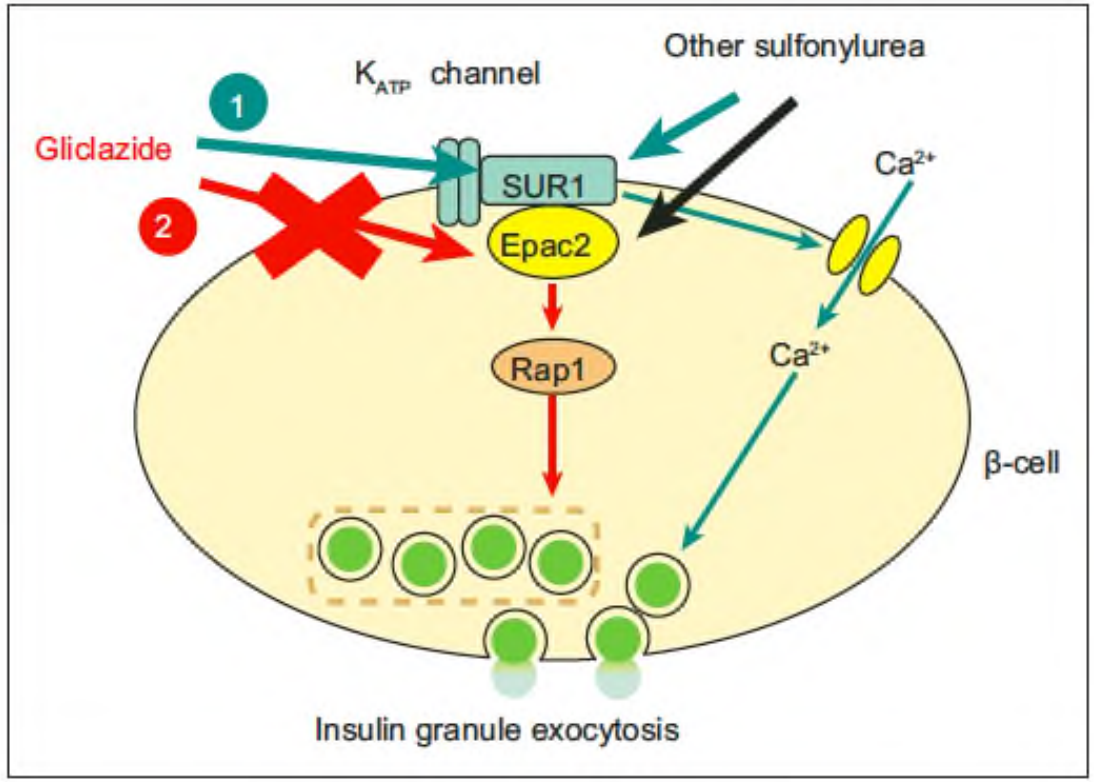
«Όταν το τραγικό τέλος μεταλλάσσεται σε αναζήτηση του απόλυτου»

Ευριπίδη Μήδεια, 431 π.Χ.

SU basics

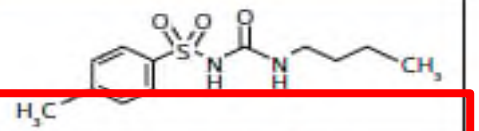
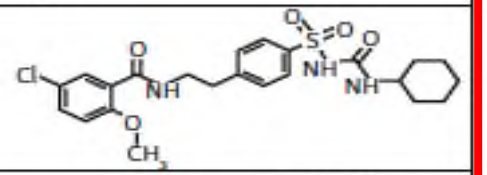
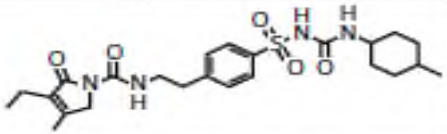
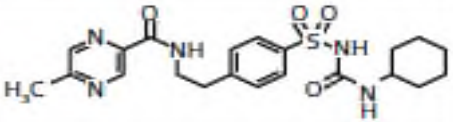
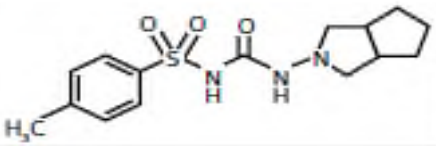
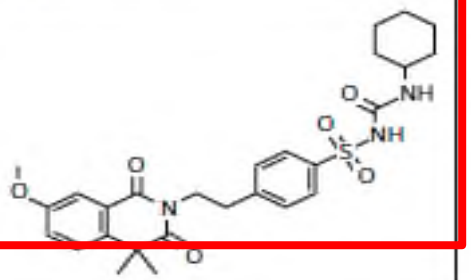
Μη γλυκοζοεξαρτώμενος





Sola et al. Arch Med Sci 2015

Table I. Various generations of sulfonylureas

Molecules	Gen.	Dose [mg]	Duration of action* T1/2	Activity of metabolites T1/2	Elimination	Structure
Tolbutamide	I	500–2000	Short 4.5 to 6.5 h	Inactive	Urine ≈ 100%	
Glibenclamide	II	2.5–15	Intermediate to long 5 to 7 h	Active 10 h	Bile ≈ 50%	
Glimepiride	II	1–6	Intermediate 5 to 8 h	Active 3 to 6 h	Urine ≈ 80%	
Glipizide	II	2.5–20	Short to intermediate 2 to 4 h	Inactive	Urine ≈ 70%	
Gliclazide	II	40–320	Intermediate 10 h	Inactive	Urine ≈ 65%	
Gliquidone	II	15–180	Short to intermediate 3 to 4 h	Inactive	Bile ≈ 95%	

**Short duration of activity means < 12 h, intermediate 12–24 h, long over 24 h.*

Sola et al. Arch Med Sci 2015

1970: University Group Diabetes Program

1998: UKPDS

Tolbutamide compared with placebo

	Tolbutamide	Placebo
All CVD deaths	26	10
Total deaths	30	21
N at risk	204	205

AGGREGATE ENDPOINTS	Difference between allocated intensive therapies	Patients with clinical endpoints	
		Intensive (n=2146)	Conventional (n=1896)
Any diabetes-related endpoint	p=0·36		
Chlorpropamide (n=619)		249	376
Glibenclamide (n=615)		221	376
Insulin (n=911)		349	376
Diabetes-related deaths	p=0·97		
Chlorpropamide (n=619)		73	113
Glibenclamide (n=615)		73	113
Insulin (n=911)		106	113

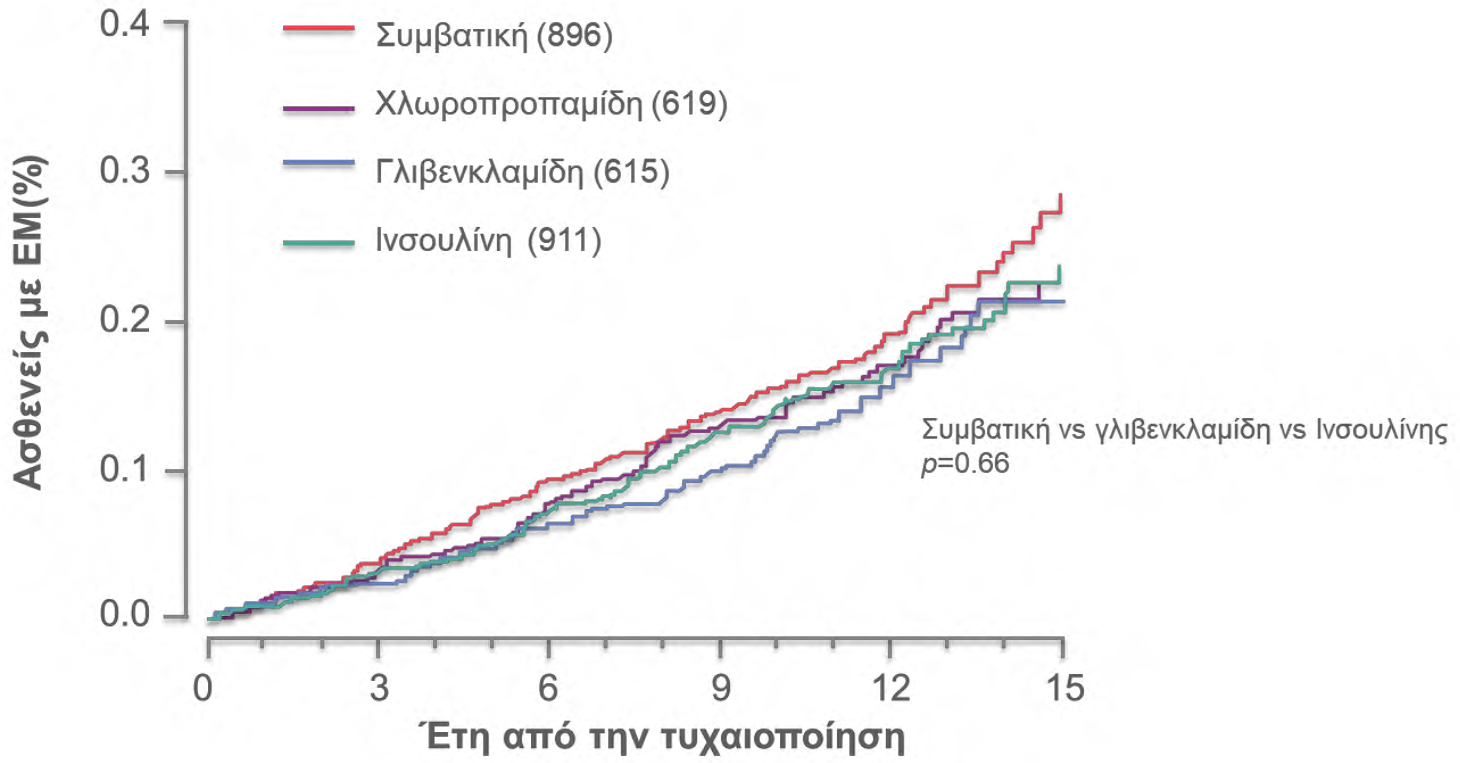
Σουλφονυλουρία και ΚΔ ασφάλεια

- Στις ΗΠΑ, για τις σουλφονυλουρίες υπάρχει ειδική προειδοποίηση αναφορικά με τον αυξημένο κίνδυνο ΚΔ Θανάτου[1–3]
  - Η προειδοποίηση βασίστηκε σε ευρήματα της μελέτης UGDP τα οποία αναφέρουν αύξηση στον αριθμό των ΚΔ θανάτων σε ασθενείς που ελάμβαναν tolbutamide έναντι placebo[4]
- Στην Ευρωπαϊκή ένωση για τις SUs δεν υπάρχει ειδική προειδοποίηση αναφορικά με τον αυξημένο κίνδυνο ΚΔ Θανάτου [5–7]

ΚΔ: Καρδιαγγειακό; SUs, Σουλφονυλουρίες; UGDP, University Group Diabetes Program

1. Glimepiride PI at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020496s021lbl.pdf;
2. Tolbutamide PI at http://www.drugs.com/pro/tolbutamide.html; 3. Glipizide PI at http://www.drugs.com/pro/glipizide.html;
4. Meinert M *et al. Diabetes* 1970;19 (suppl):789; 5. Glimepiride EU SmPC at http://www.medicines.org.uk/emc/medicine/27033;
6. Tolbutamide EU SmPC at http://www.medicines.org.uk/emc/medicine/26366; 7. Glipizide EU SmPC at http://www.medicines.org.uk/emc/medicine/9851

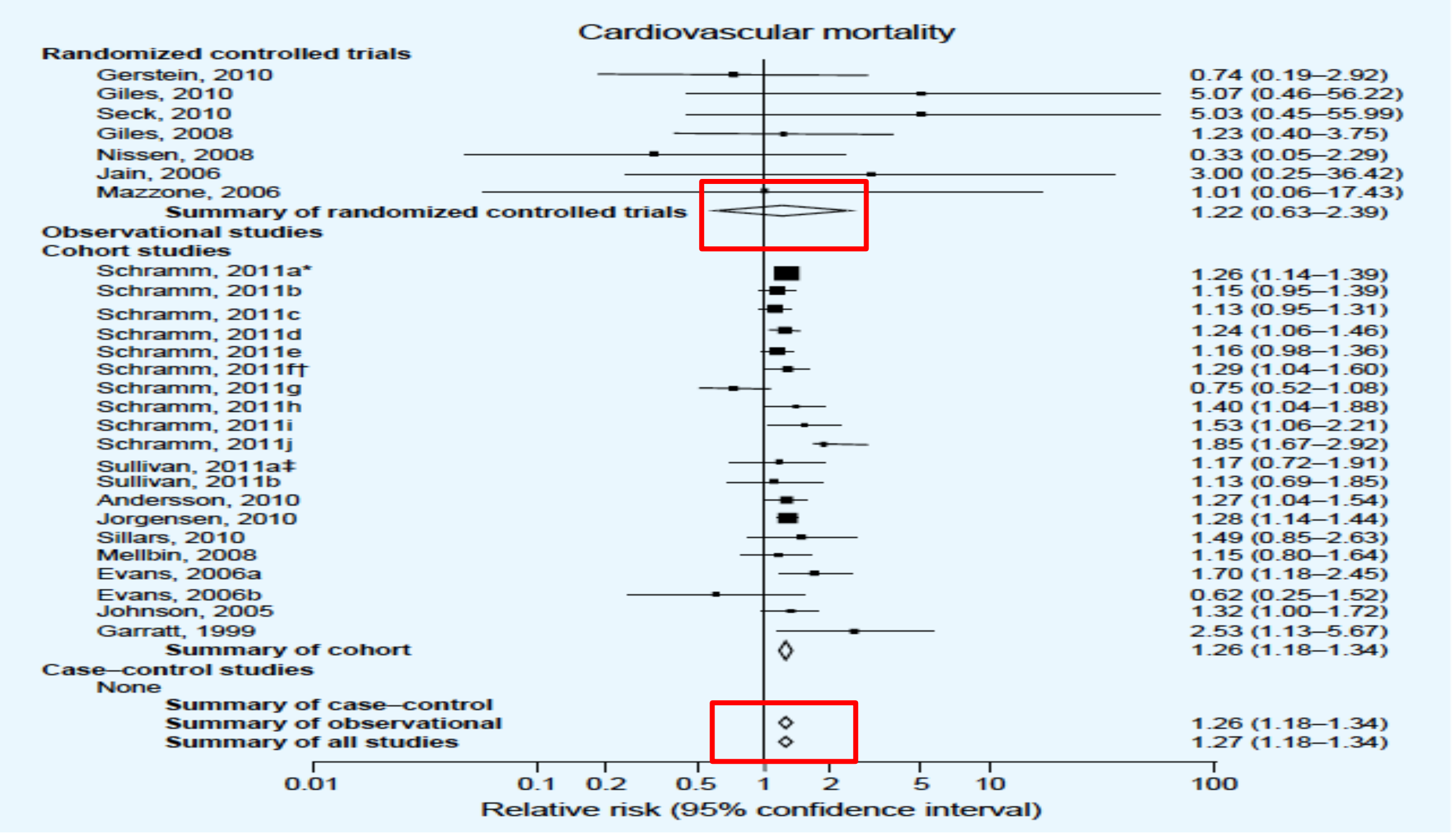
UKPDS 33: δεν παρατηρήθηκε επιβλαβής ΚΔ επίδραση των SUs έναντι ινσουλίνης ή συμβατικής θεραπείας[1]



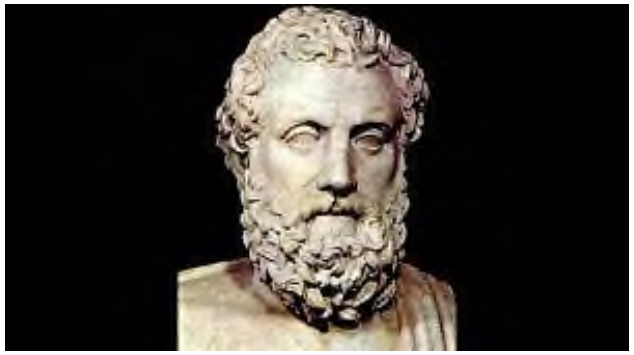
Επιπλέον, στη μελέτη ADVANCE, ο εντατικός γλυκαιμικός έλεγχος με τη γλικλαζίδη δεν συσχετίστηκε με επιβλαβείς ΚΔ επιδράσεις [2]

ΚΔ, Καρδιαγγειακό, ΕΜ: έμφραγμα του μυοκαρδίου, SUs, Σουλφονυλουρίες, UKPDS, UK Prospective Diabetes Study

1. UKPDS33. *Lancet* 1998;352:837; 2. Patel A *et al. N Engl J Med* 2008;358:2560



Phung et al. Diabet Med 2013

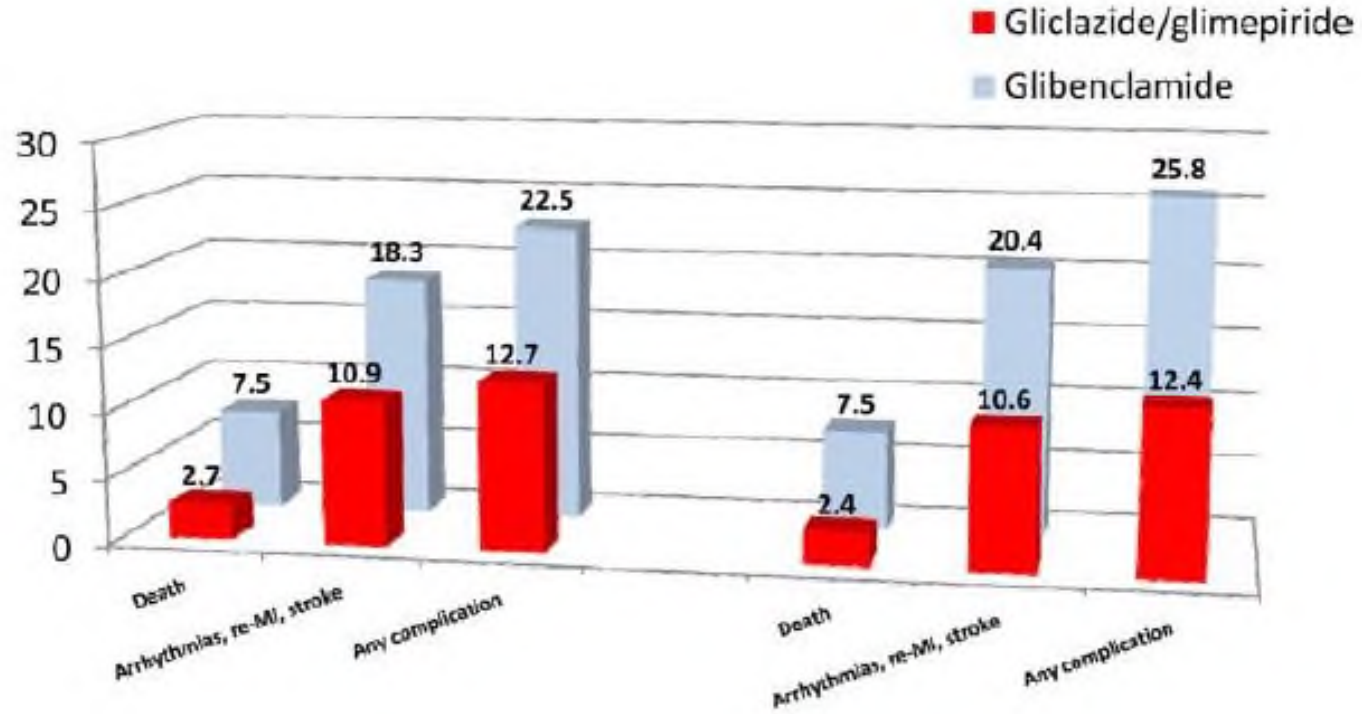


«Δεν μαθαίνει κανένας παρά μόνο τη μισή αλήθεια, όταν ακούει τη μία άποψη απ' τις δύο»

Αισχύλος

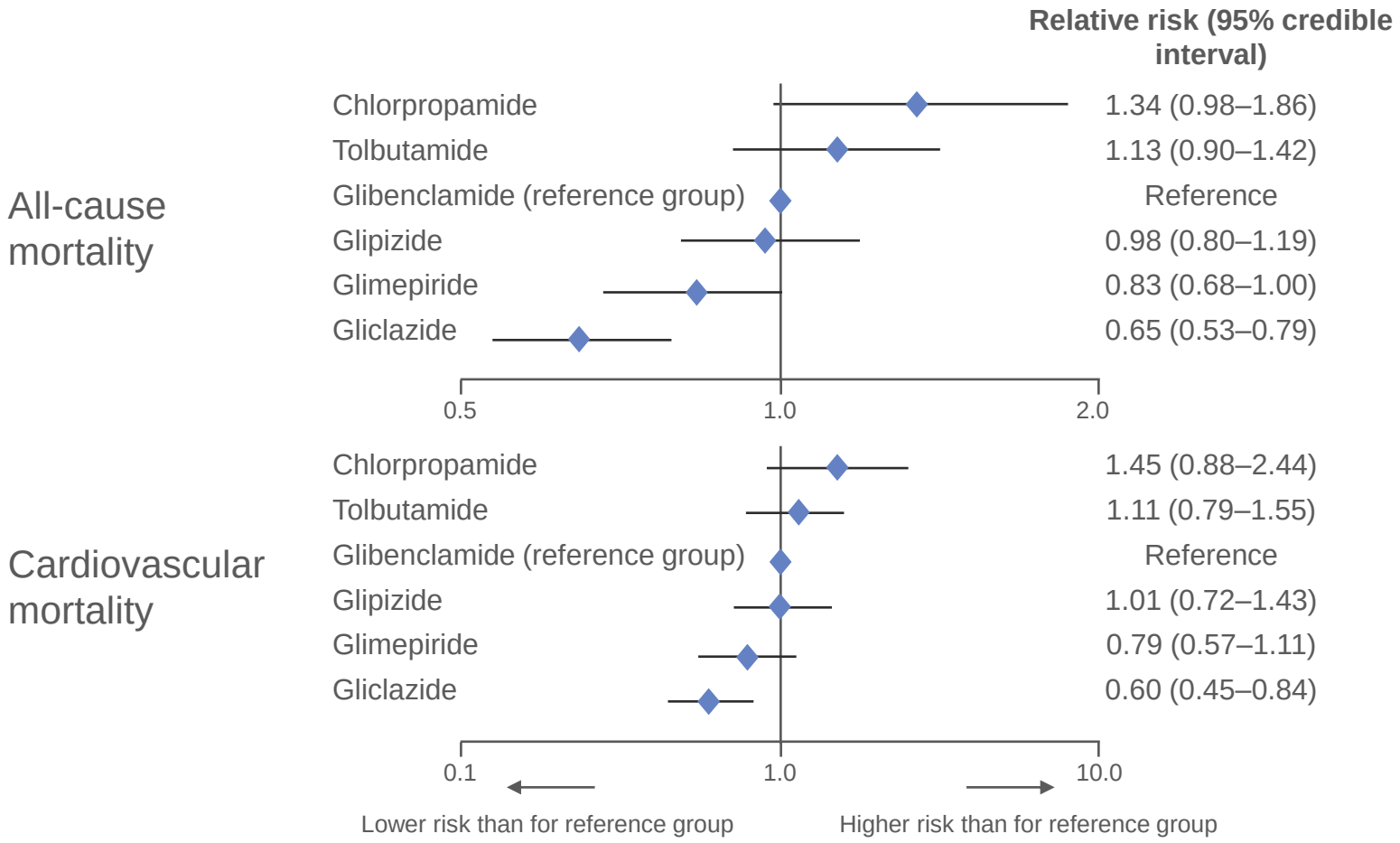
Impact of Type of Preadmission Sulfonylureas on Mortality and Cardiovascular Outcomes in Diabetic Patients with Acute Myocardial Infarction

- Ischemic Preconditioning
- Όχι για τη γλικλαζίδη και τη γλιμεπιρίδη



Zeller et al. J Clin Endocrinol Metab 2010

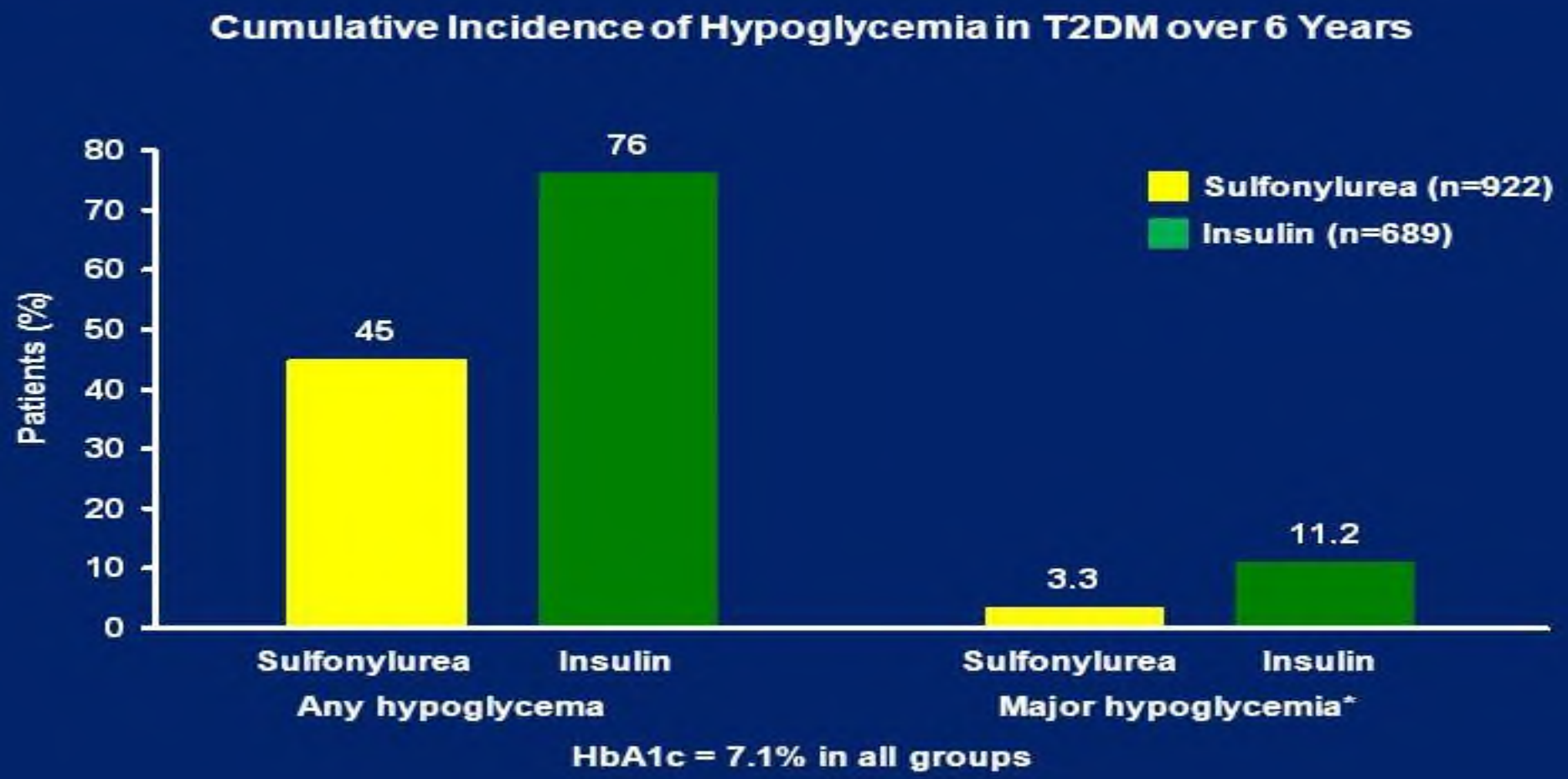
Network meta-analysis suggested possible variation between SUs in effects on mortality



Simpson et al. Lancet Diabetes Endocrinol 2015;3:43–51.

Υπογλυκαιμία και καρδιαγγειακή ασφάλεια

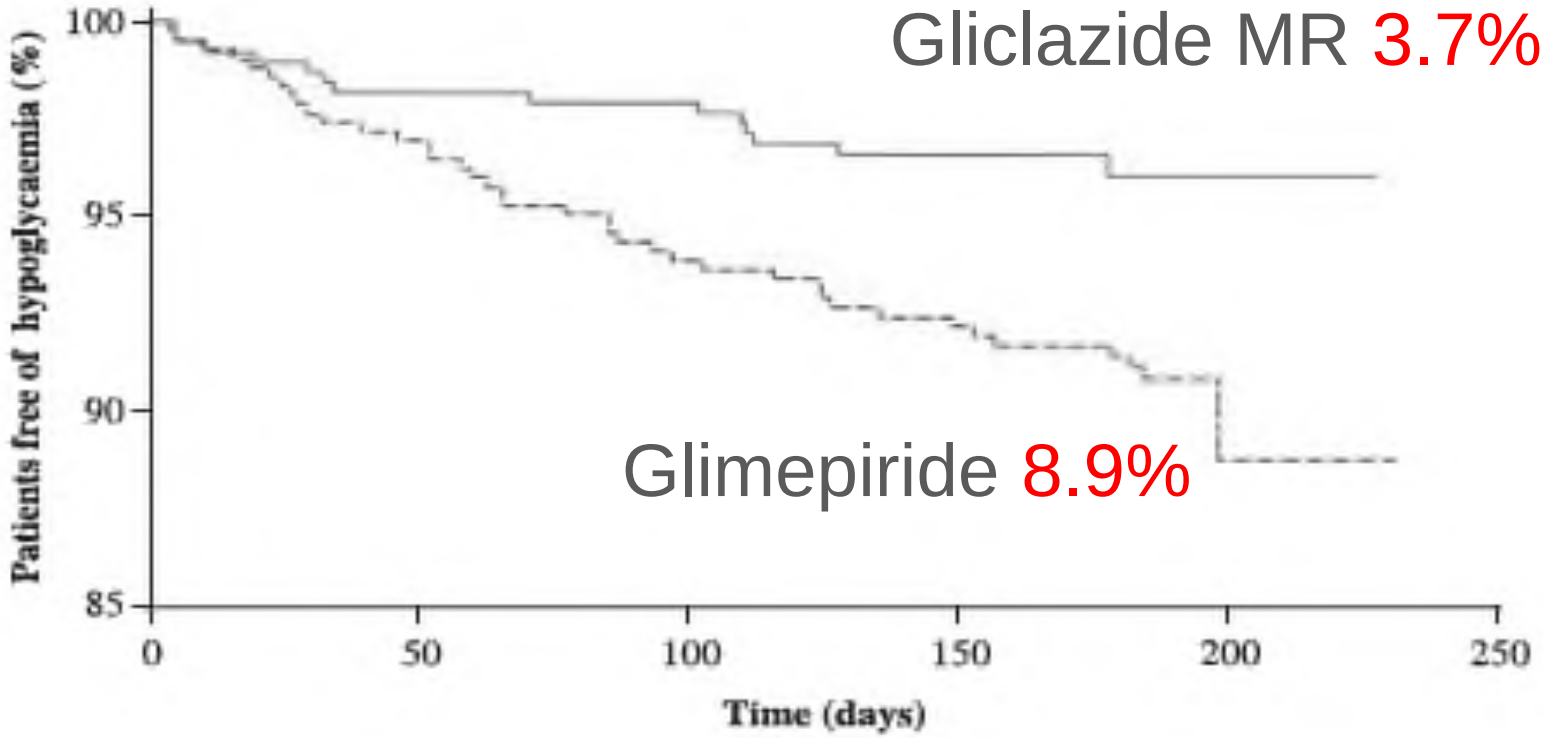
UKPDS – Treating to Targets Elevates the Risk of Hypoglycemia and Incidence can be High with SUs



SUs=sulfonylureas; T2DM=type 2 diabetes melllitus; *Requiring medical assistance or hospital admission

UK Prospective Diabetes Study Group. Diabetes.1995;44:1249–1258.

GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients



Schernthaner et al. Eur J Clin Invest 2004

Unexplained Deaths of Type 1 Diabetic Patients

R.B. Tattersall, G.V. Gill

Dead in Bed Syndrome: a New Manifestation of Nocturnal Hypoglycaemia?

'Sleep is a death, O make me try,
By sleeping what it is to die.
And as gently lay my head
On my grave, as now my bed.'

(Religio Medici; Sir Thomas Browne, 1605–1682)

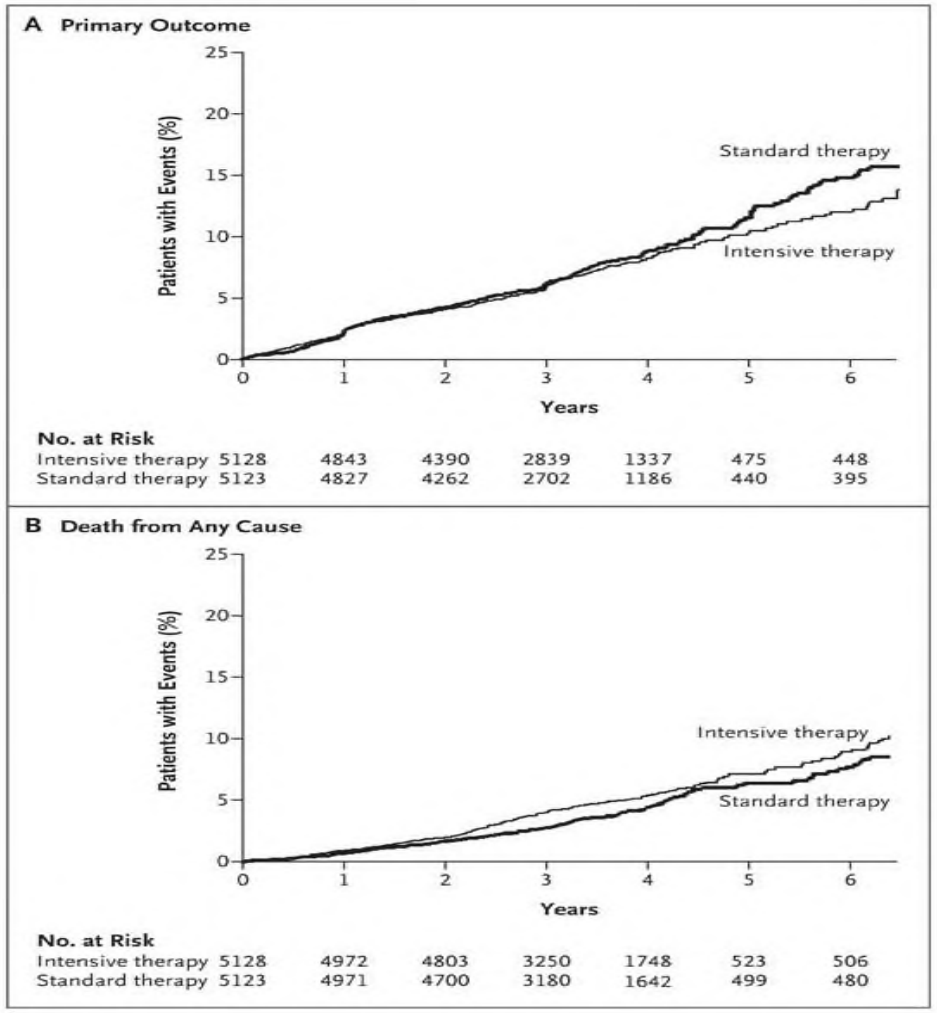
Campell I. Diabet Med 1991

Tattersal et al. Diabet Med 1990

Μελέτη ACCORD

TABLE 1. ACCORD 5-yr incidence of outcomes

	Intensive %	Standard %	Hazard ratio	*P*
Total mortality	7.5	6.5	1.19	0.02
CVD outcomes				
Primary composite[a]	10.0	10.8	0.91	NS
CVD death	3.5	3.0	1.29	0.02
Nonfatal MI	6.0	7.0	0.82	0.01
Stroke	2.0	2.0	0.86	NS
Microvascular outcomes				
Primary composite[b]	10.9	11.5	0.95	NS
Retinopathy progression[c]	9.1	13.0	0.67	0.003
Moderate vision loss[d]	29.8	32.9	0.88	0.06
Microalbuminuria[e]	12.5	15.3	0.79	0.0005
Macroalbuminuria[e]	2.7	3.9	0.68	0.0013
Severe hypoglycemia requiring medical aid[f]	10.5	3.5	3.00	<0.001

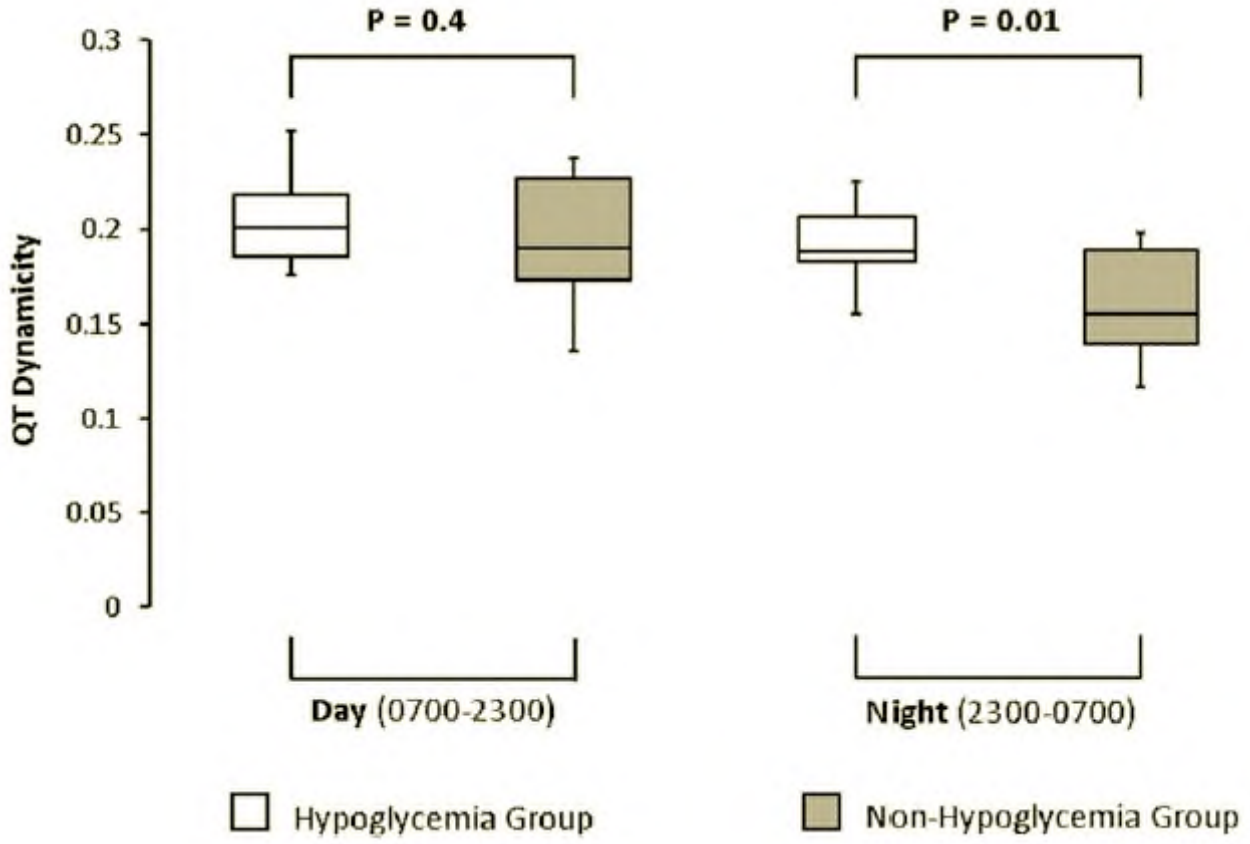


ACCORD Study GroupN Engl J Med 2008

Cardiac Effects of Sulfonylurea-Related Hypoglycemia

Diabetes Care 2017;40:663–670 | DOI: 10.2337/dc16-1972

- $HbA1_C$ 6.9 %
- 1/3 υπογλυκαιμία
- 73% ασυμπτωματική
- 67% νυχτερινή
- Παράταση QT



Middleton et al. Diabetes Care 2017

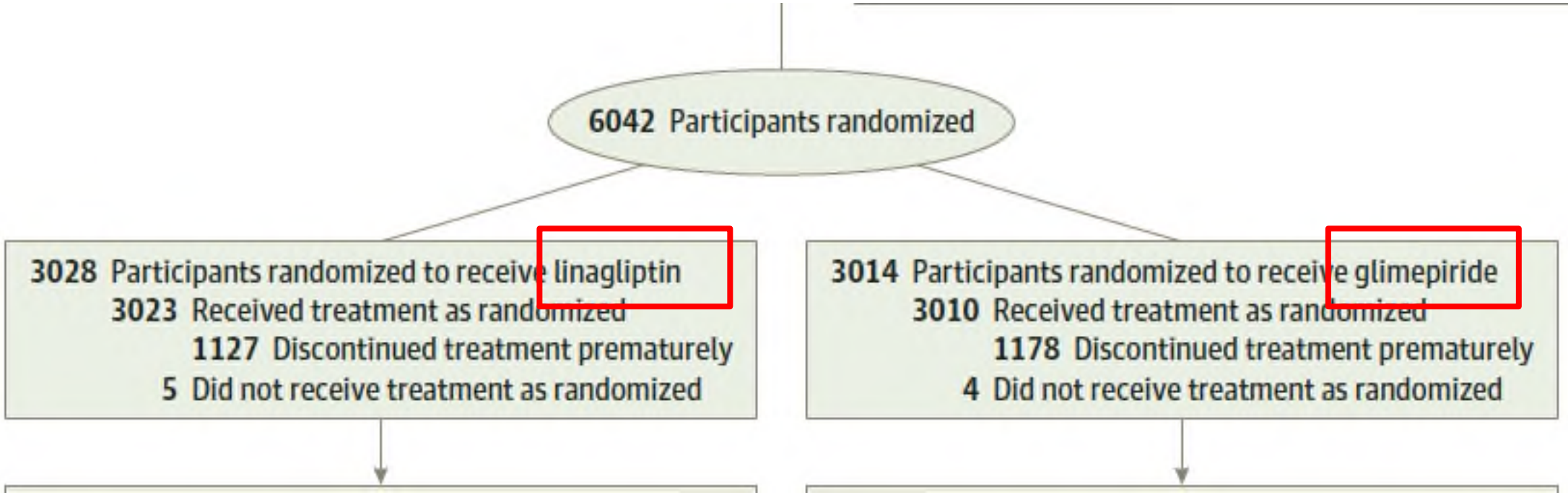
Δεν πεθαίνουν όλοι όσοι κάνουν υπογλυκαιμίες!

- Διαβητική νευροπάθεια: παράταση QT
- Διάρκεια της υπογλυκαιμίας
- TSH
- Αντιβιοτικά, αντιϊσταμινικά

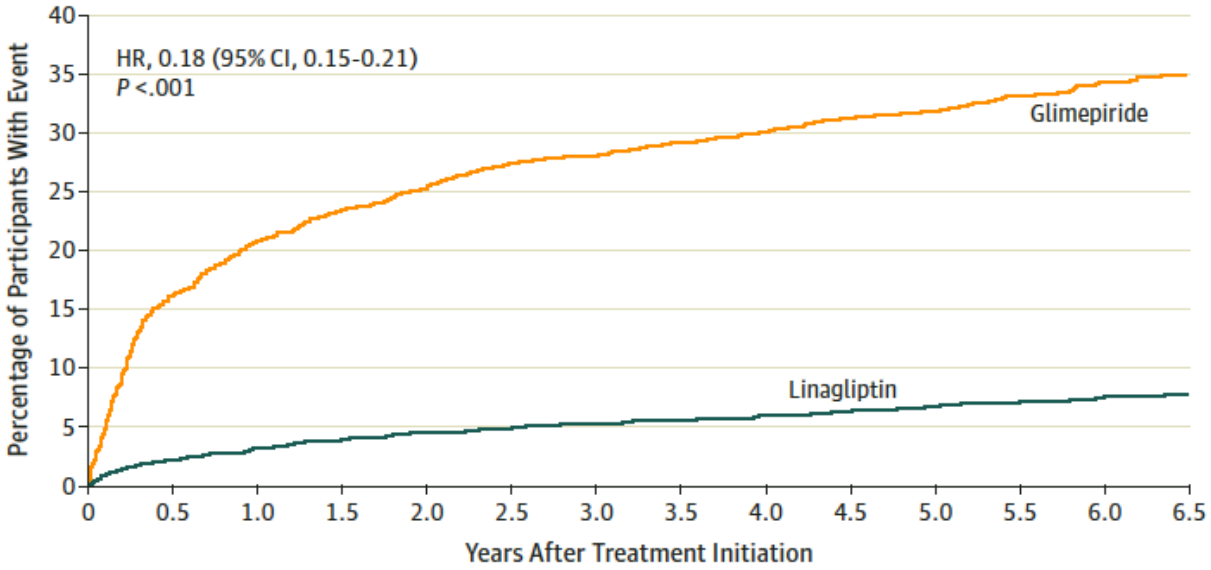
Pistrosch et al. Acta Diabetol 2015

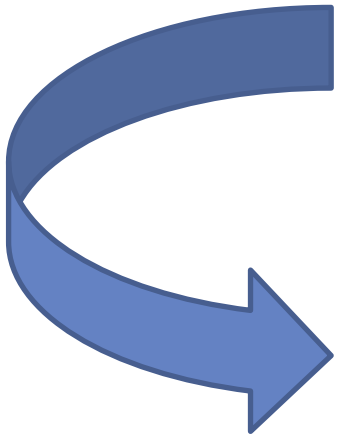
Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes

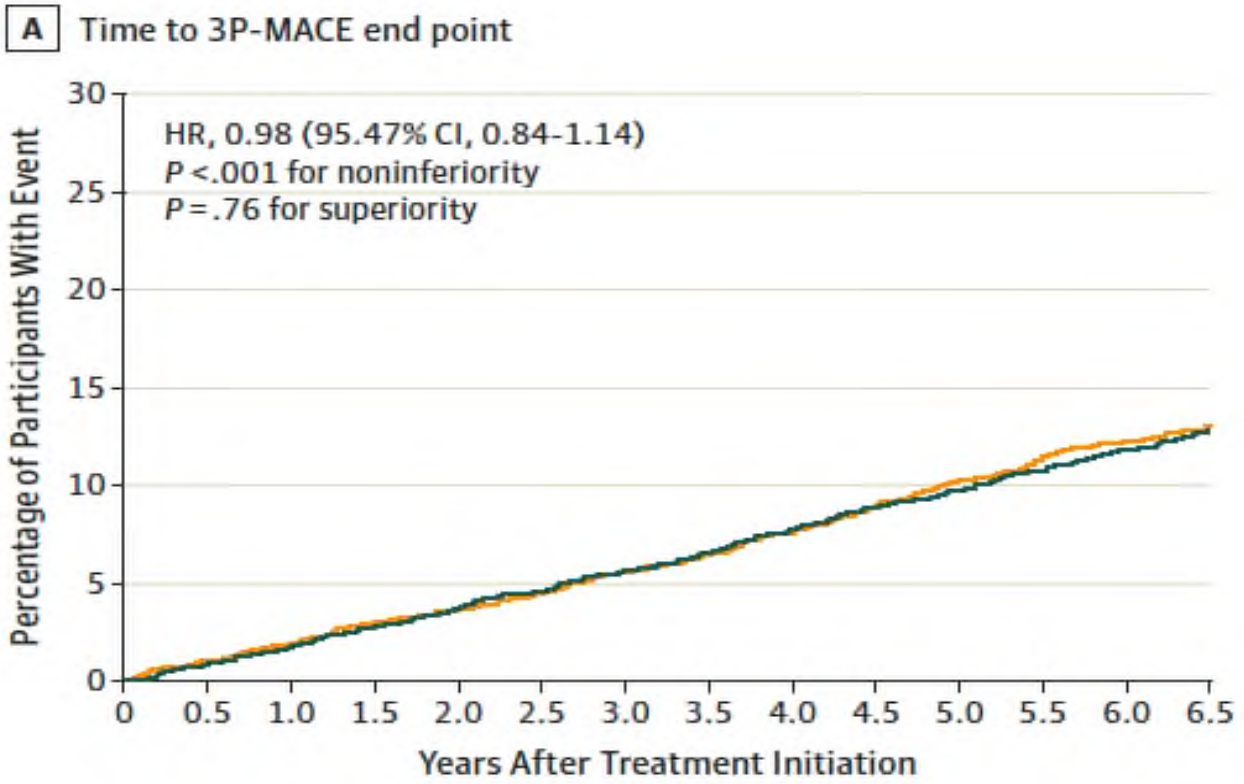
The CAROLINA Randomized Clinical Trial



Rosenstock et al. JAMA 2019

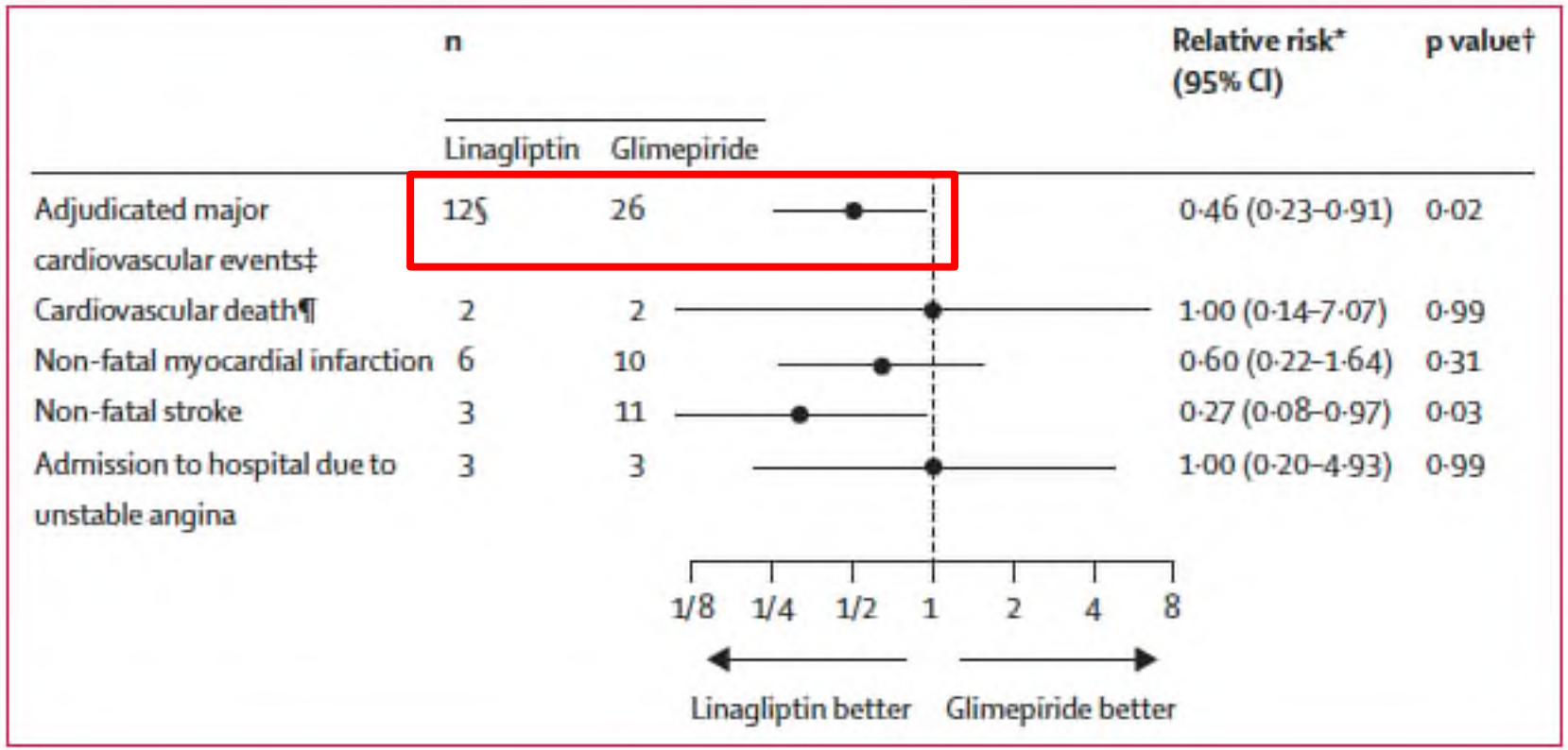






Rosenstock et al. JAMA 2019

2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial



Gallwitz et al. Lancet 2012

Άλμα στη λογική

Οι SUs κάνουν υπογλυκαιμίες

Οι υπογλυκαιμίες αυξάνουν τον ΚΑ κίνδυνο

Οι SUs δεν αυξάνουν τον ΚΑ κίνδυνο !

> J Diabetes. 2020 Jul;12(7):499-502. doi: 10.1111/1753-0407.13035. Epub 2020 Mar 23.

A lion in the room: Has the CAROLINA trial definitely resolved the issue of the cardiovascular safety of sulfonylureas?

Theocharis Koufakis [1], George Dimitriadis [2], Kalliopi Kotsa [1]

Affiliations + expand

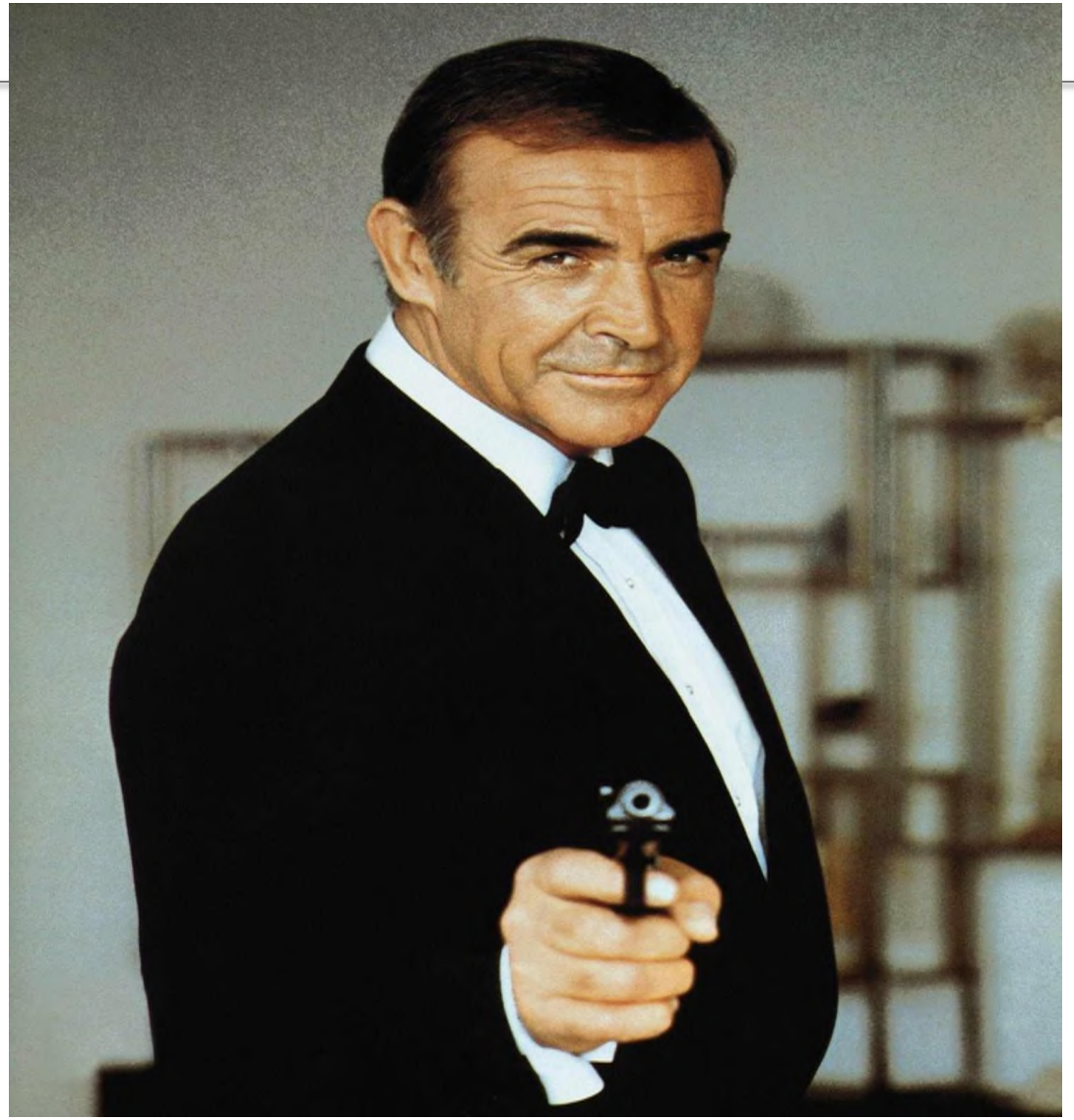
PMID: 32202061 DOI: 10.1111/1753-0407.13035

Koufakis et al. J Diabetes 2020

Συμπεράσματα

- Όλοι οι ασθενείς δεν είναι ίδιοι
- Όλες οι SUs δεν είναι ίδιες
- **Όλες προκαλούν υπογλυκαιμία!**

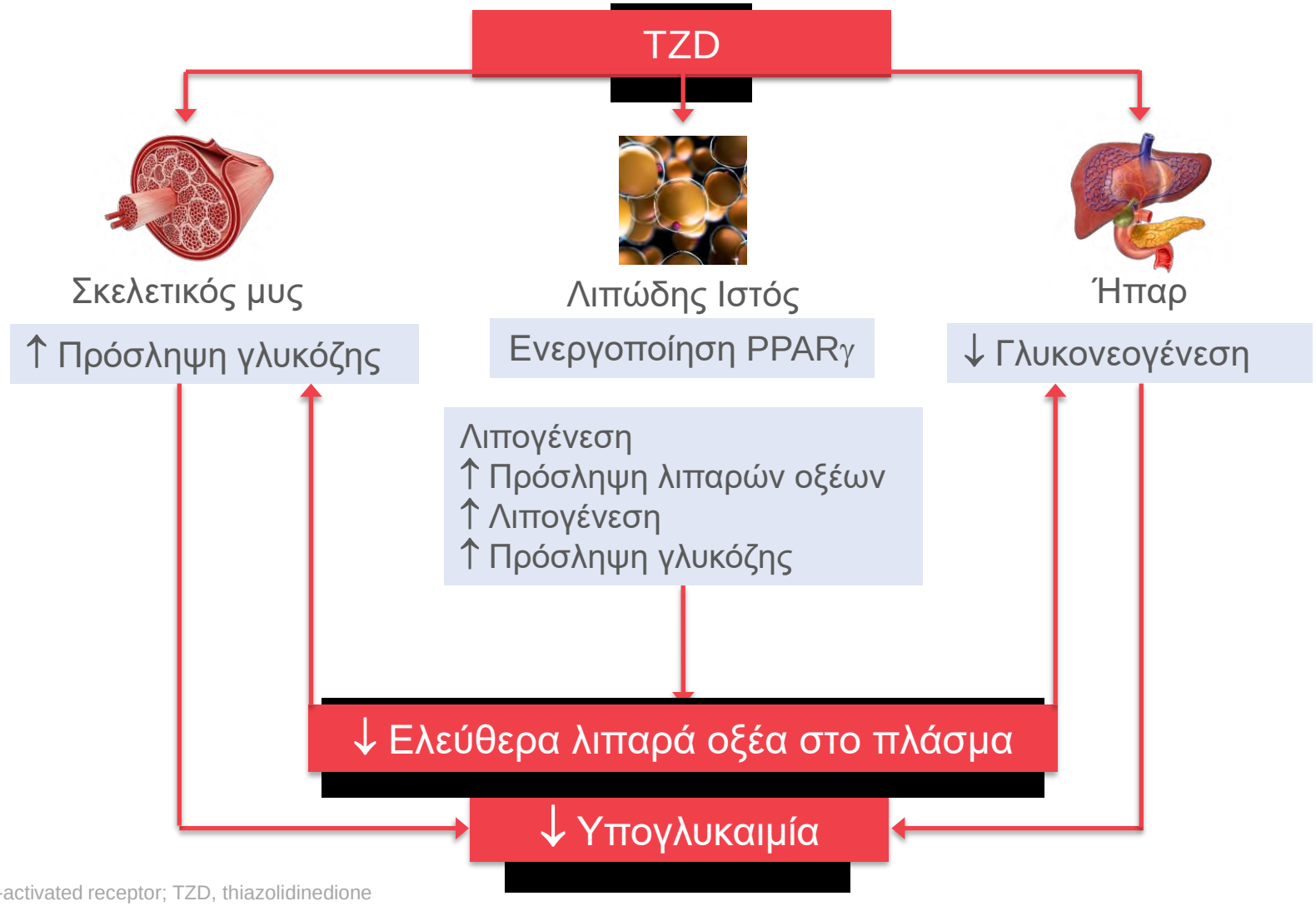
Ποιος διάσημος θα ήταν οι SUs;



Οι επιδράσεις των παλαιότερων αντιδιαβητικών παραγόντων στον Καρδιαγγειακό κίνδυνο

Περιεχόμενα

Θειαζολιδινεδιόνες (TZD; PPAR-γ αγωνιστές): Μηχανισμός δράσης

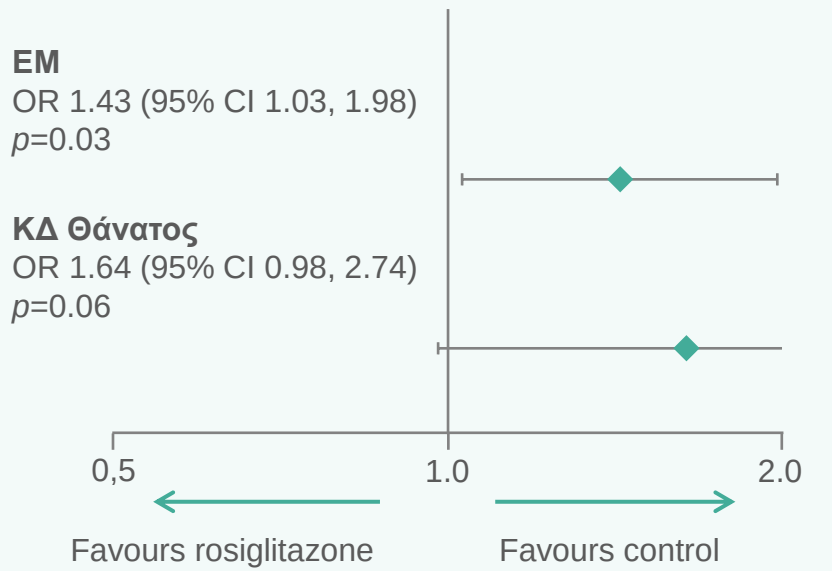


PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione

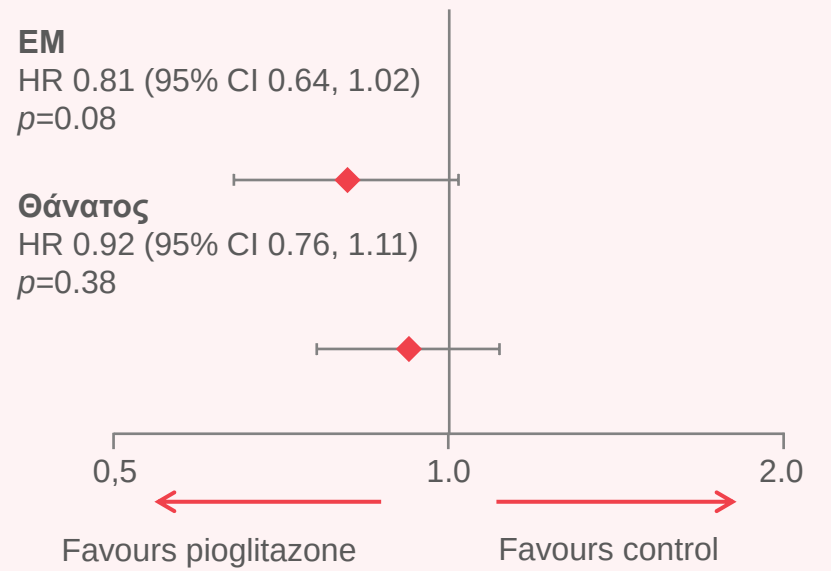
Προσαρμογή από Bailey CJ & Feher MD. Therapies for diabetes including oral agents and insulins. *Sherborne Gibbs Limited*, 2004

Το 2007, ξεχωριστές μετα-αναλύσεις πρότειναν διαφορετικές ΚΔ επιδράσεις των εκπροσώπων της κατηγορίας των TZDs

Μετα-αναλύση Ροσιγλιταζόνης [1]



Μετα-αναλύση Πιογλιταζόνης [2]



Δεν συγκρίθηκαν σε καμία RCT απευθείας οι ΚΔ επιδράσεις της Πιογλιταζόνης και της Ροσιγλιταζόνης

ΚΔ, Καρδιαγγειακό; ΕΜ: έμφραγμα του μυοκαρδίου; OR, odds ratio; TZD, thiazolidinedione

1. Nissen SE & Wolski K. *N Engl J Med* 2007;356:2457; 2. Lincoff AM *et al. JAMA* 2007;298:1180

Πιογλιταζόνη: Σχεδιασμός της μελέτης PROactive

Στόχος
Ο προσδιορισμός της επίδρασης της πιογλιταζόνης στη μακροαγγειακή νοσηρότητα και θνησιμότητα σε ασθενείς υψηλού κινδύνου με T2D

Κύρια κριτήρια εισαγωγής
1. Ασθενείς με ΣΔτ2 και ένδειξη μακροαγγειακής νόσου
2. Ηλικία 35–75 έτη
3. HbA1c >6.5%

Με ή χωρίς πρότερη θεραπεία

Πιογλιταζόνη vs Εικονικό Φάρμακο

N=5238; Μέση διάρκεια παρακολούθησης 34.5 μήνες

Πρωτεύον τελικό: χρόνος έως το πρώτο συμβάν θανάτου οποιασδήποτε αίτιας, μη θανατηφόρου ΕΜ, ΑΕΕ, ΟΣΣ, ενδοαγγειακή/χειρουργική επέμβαση στις στεφανιαίες αρτηρίες / αρτηρίες ποδιού, ακρωτηριασμός πάνω από τον αστράγαλο

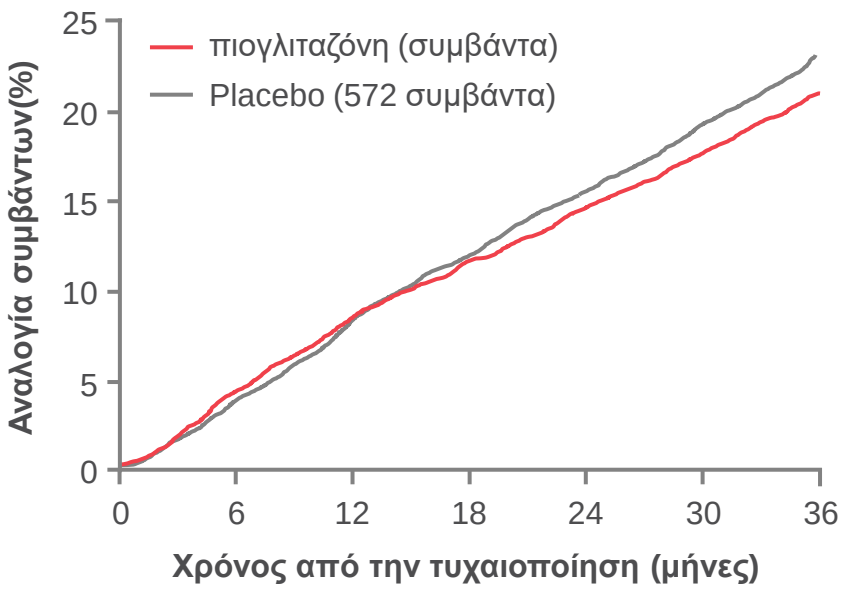
Δευτερεύον τελικό: χρόνος έως το πρώτο συμβάν θανάτου οποιασδήποτε αίτιας, μη θανατηφόρου ΕΜ, ΑΕΕ

Στατιστική Ανάλυση
- ≥760 ασθενείς με ≥1 τελικά συμβάντα
- Ο τελευταίος ασθενής που εντάχθηκε ακολουθήθηκε για 30 μήνες

ΕΜ: Έμφραγμα του Μυοκαρδίου, ΟΣΣ: Οξύ στεφανιαίο σύνδρομο; HbA1c, glycated haemoglobin; ΑΕΕ: Αγγειακό Εγκεφαλικό Επεισόδιο
PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; ΣΔτ2: Σακχαρώδης διαβήτης τύπου 2
Dormandy JA *et al. Lancet* 2005;366:1279

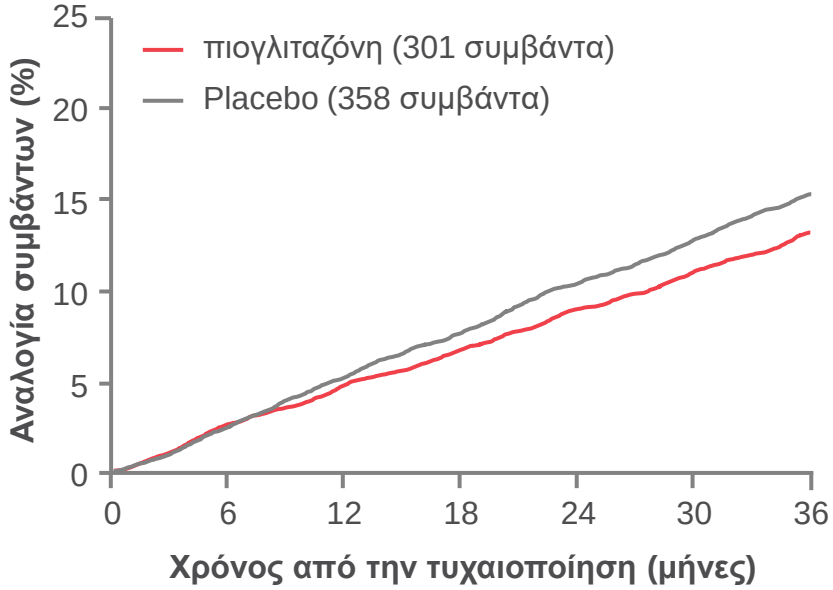
PROactive: Η πιογλιταζόνη ήταν ανώτερη του placebo για το κύριο δευτερεύον τελικό σημείο αλλά όχι για το πρωτεύον

Πρωτεύον τελικό σημείο *



HR 0.90 (95% CI 0.80, 1.02)
p=0.095

Χρόνος έως την εμφάνιση θανάτου οποιασδήποτε αίτιας, μη θανατηφόρου ΕΜ, ΑΕΕ



HR 0.84 (95% CI 0.72, 0.98)
p=0.027

Νοσηλεία για Καρδιακή Ανεπάρκεια:
6% (149 απο 2605) με πιογλιταζόνη vs 4% (108 από 2633) με placebo; *p*=0.007

*Θάνατος οποιασδήποτε αίτιας, μη θανατηφόρου ΕΜ (including silent MI), ΑΕΕ, ΟΣΣ, Ακρωτηριασμός ποδιού, στεφανιαία επαναγγείωση ή επαναγγείωση κάτω άκρου
ΕΜ: Έμφραγμα του Μυοκαρδίου, ΟΣΣ: Οξύ στεφανιαίο σύνδρομο; ΑΕΕ: Αγγειακό Εγκεφαλικό Επεισόδιο,
PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events, Dormandy JA *et al. Lancet* 2005;366:1279


bus stop
royal derby
Clear Channel
FIVE GET
THERE
FASTER
GWR
Great
Western
Railway

IRIS: Pioglitazone for Stroke Prevention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

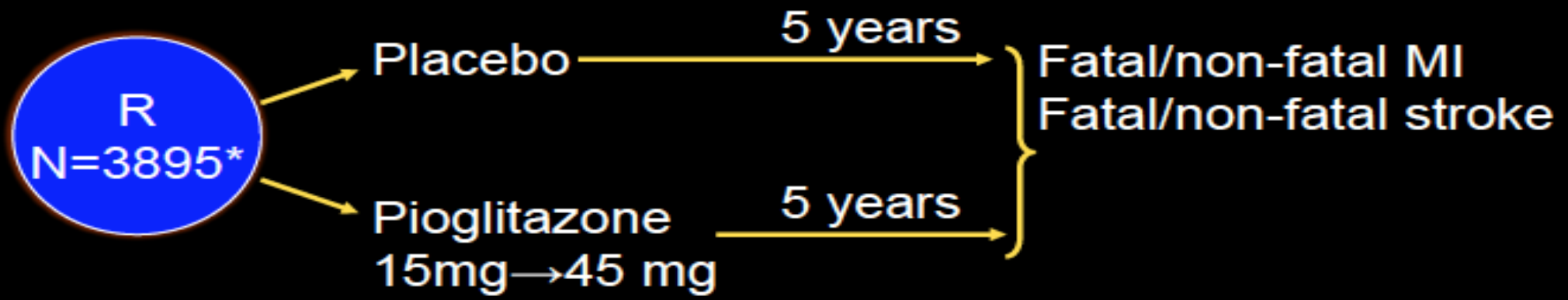
Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

NEJM: Published on-line: February 17, 2016 DOI: 10.1056/NEJMoa1506930

IRIS: Trial Design

Eligibility: Recent TIA or Ischemic Stroke
Non-Diabetic
Insulin Resistant (HOMA > 3.0)
No CHF

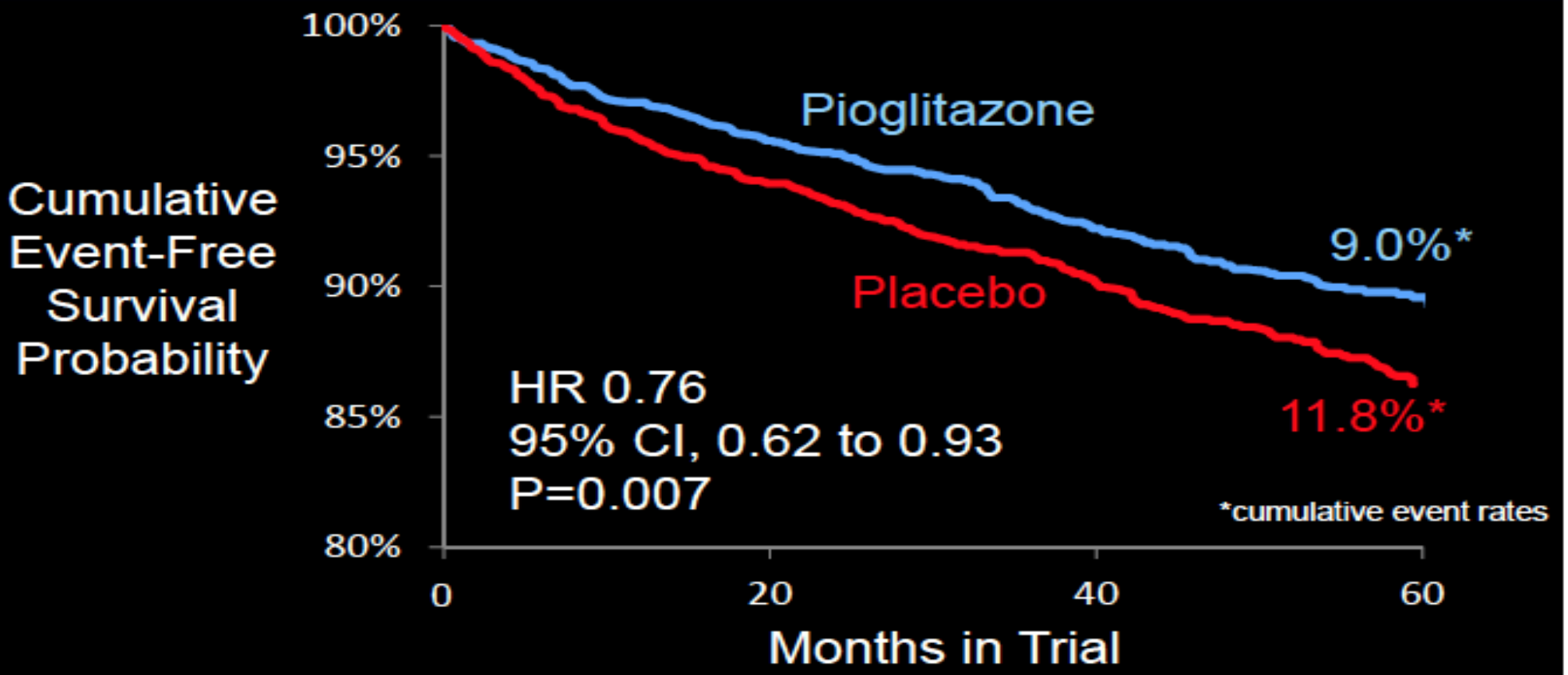


*90% power to detect a 20% RRR from 27% in the placebo group to 22% in the pioglitazone group at an alpha level of 0.05

Viscoli CM *et al. Am Heart J* 2014;168:823

ClinicalTrials.gov Identifier: NCT00091949

IRIS: Primary Outcome



Kernan WN *et al. N Engl J Med*, published on-line Feb 17, 2016 DOI: 10.1056/NEJMoa1506930

Filipova *et al. Diabetol Metab Syndr (2017) 9:90*
DOI 10.1186/s13098-017-0290-5

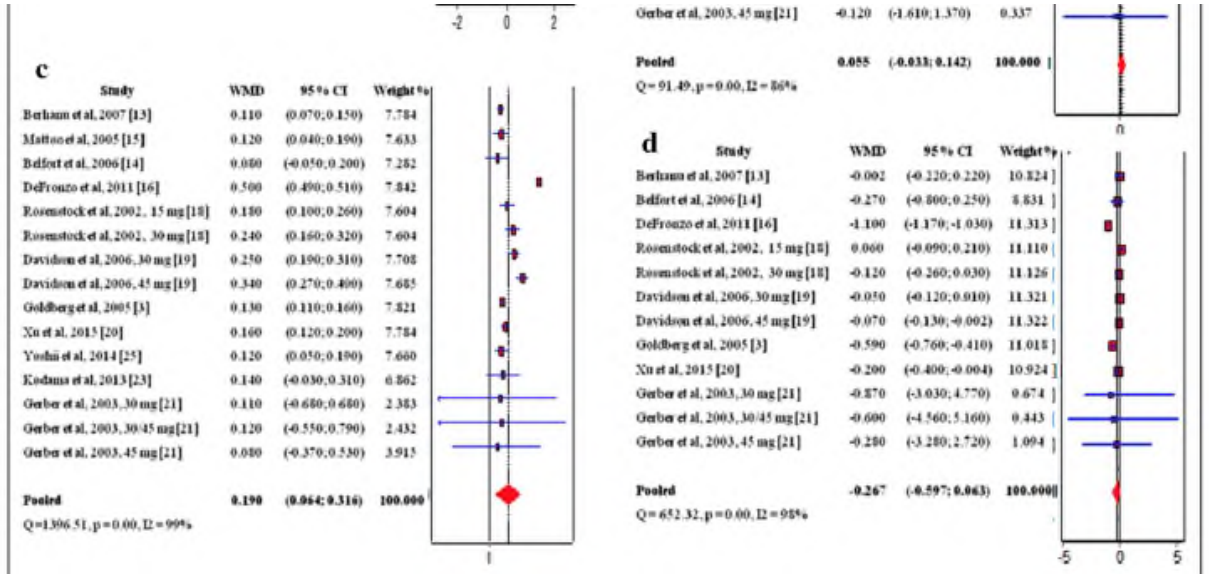
Diabetology & Metabolic Syndrome

REVIEW Open Access

Effects of pioglitazone therapy on blood parameters, weight and BMI: a meta-analysis

Elena Filipova[1*], Katya Uzunova[1], Krassimir Kalinov[2] and Toni Vekov[3]

HDL-C



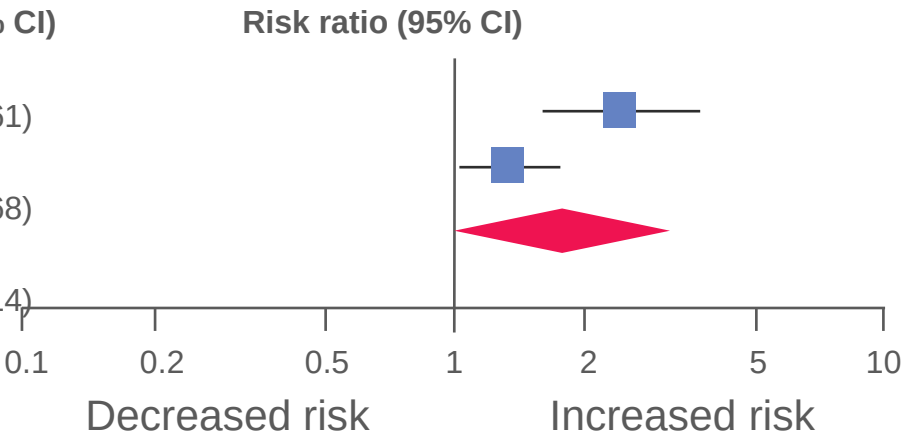
TG

Meta-analysis showed increased risk for congestive heart failure with both pioglitazone and rosiglitazone

Comparison of risk of congestive heart failure

	Weight	Risk ratio (95% CI)
Rosiglitazone trials	46.2%	2.41 (1.61–3.61)
Pioglitazone trials	53.8%	1.32 (1.04–1.68)
Total	100.0%	1.74 (0.97–3.14)

Test for overall effect: *Z* = 1.85 (p = 0.07)



- In a meta-analysis of 20,191 patients with pre-diabetes or T2D, the increased risk for congestive heart failure with TZDs did not differ between rosiglitazone and pioglitazone (p = 0.07)

NYHA III & IV

Lago et al. Lancet 2007;370:1129–36.

Ροσιγλιταζόνη: Σχεδιασμός της μελέτης RECORD

Στόχος
Μελέτη για τη σύγκριση της μακροαγγειακής νοσηρότητας και θνησιμότητας σε ασθενείς με ΣΔτ2 που έλαβαν θεραπεία με ροσιγλιταζόνη + μετφορμίνη / SU

Κύρια κριτήρια εισαγωγής
1. Ασθενείς με ΣΔτ2 σε θεραπεία με μέγιστες ανεκτές δόσεις μετφορμίνης ή SU
2. Ηλικία 40–75 έτη
3. BMI ≥25.0 mg/kg^2

OPEN-LABEL
Ροσιγλιταζόνη + μετφορμίνη
ή
Ροσιγλιταζόνη + SU

έναντι

OPEN-LABEL
Μετφορμινη + SU

N=4447; διάρκεια παρακολούθησης 5–7 έτη

Πρωτεύον τελικό:
Χρόνος μέχρι την πρώτη εμφάνιση καρδιαγγειακής νοσηλείας ή καρδιαγγειακού θανάτου

Δευτερεύον τελικό:
χρόνος έως το πρώτο συμβάν θανάτου οποιασδήποτε αίτιας, μη θανατηφόρου ΕΜ, ΑΕΕ

Στατιστική Ανάλυση

- Όριο μη κατωτερότητας 1,20 για HR
- 4000 συμμετέχοντες παρακολουθήθηκαν για ένα μέσο όρο 6 ετών προσδίδονται ισχύ στο 99%

ΕΜ: Έμφραγμα του Μυοκαρδίου; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes; SU, sulphonylurea;
ΑΕΕ: Αγγειακό Εγκεφαλικό Επεισόδιο ΣΔτ2: Σακχαρώδης διαβήτης τύπου 2
Home PD *et al. Lancet* 2009;373:2125

Ροσιγλιταζόνη: τα αποτελέσματα της μελέτης RECORD δεν έδειξαν αύξηση στο ΚΔ Θάνατο

ΚΔ εκβάσεις (original data)[1,2]	Ροσιγλιταζόνη N=2220	Παράγοντας ελέγχου N=2227	HR	95% CI
Πρωτεύον τελικό				
ΚΔ Θάνατος ή ΚΔ Νοσηλεία	321	323	0.99	0.85, 1.16
Δευτερεύον τελικό				
Θάνατος κάθε αιτίας	136	157	0.86	0.68, 1.08
ΚΔ Θάνατος	60	71	0.84	0.59, 1.18
ΕΜ	64	56	1.14	0.80, 1.63
ΑΕΕ	46	63	0.72	0.49, 1.06
ΚΔ θάνατος, ΕΜ or ΑΕΕ	154	165	0.93	0.74, 1.15
Καρδιακή Ανεπάρκεια	61	29	2.10	1.35, 3.27

- Το 2013, επιτροπή του FDA ψήφισε τη μείωση των περιορισμών ασφαλείας για τη ροσιγλιταζόνη[3]
- Ωστόσο, δεν υπάρχουν μακροπρόθεσμα προοπτικά δεδομένα σχετικά με την ΚΔ ασφάλεια, έτσι η αμφισβήτηση παραμένει [4]

ΚΔ: Καρδιαγγειακό; ΕΜ: Έμφραγμα του Μυοκαρδίου; ΑΕΕ: Αγγειακό Εγκεφαλικό Επεισόδιο
RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes
1. AVANDIA US Prescribing information; 2. Home PD *et al. Lancet* 2009;373:2125; 3. FDA Safety Information; 4. Rosenson RS *et al. Am Heart J* 2012;164:672

Section recap

CV safety of TZDs

- TZDs cause or exacerbate heart failure in some patients[1] (still no HF mortality)
- CV meta-analyses in 2007 suggested differing effects on CV outcomes
- Pioglitazone was associated with a significant 16% reduction in 3P-MACE (as a secondary endpoint) vs placebo in PROactive[2]
- Rosiglitazone open-label RECORD data showed no increase in CV death[1]
- FDA reduced the safety restrictions on rosiglitazone imposed following 2007 meta-analysis[3] but controversy over CV safety remains

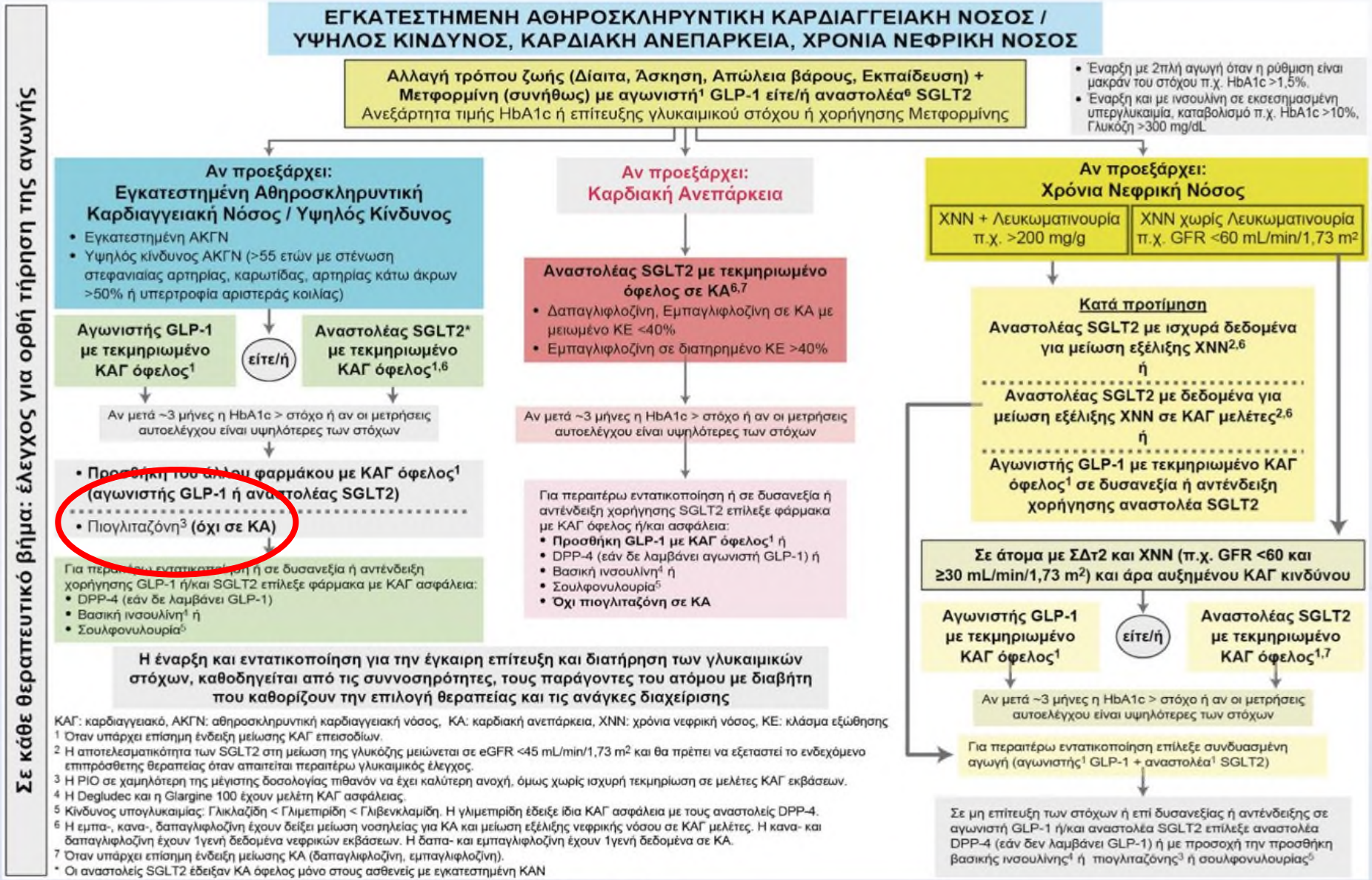
'Within the PPAR family, there is no "class effect" and each agent must be considered unique. The FDA has mandated that each agent within this class be evaluated individually in a variety of ways including clinical outcome studies'[4]

1. AVANDIA US Prescribing information. 2. Dormandy et al. Lancet 2005;366:1279–89. 3. FDA Safety Information.
4. Rosenson et al. Am Heart J. 2012;164:672–80.

ΘΕΡΑΠΕΥΤΙΚΗ ΔΙΑΧΕΙΡΙΣΗ ΑΣΘΕΝΩΝ ΜΕ ΣΔ ΤΥΠΟΥ 2

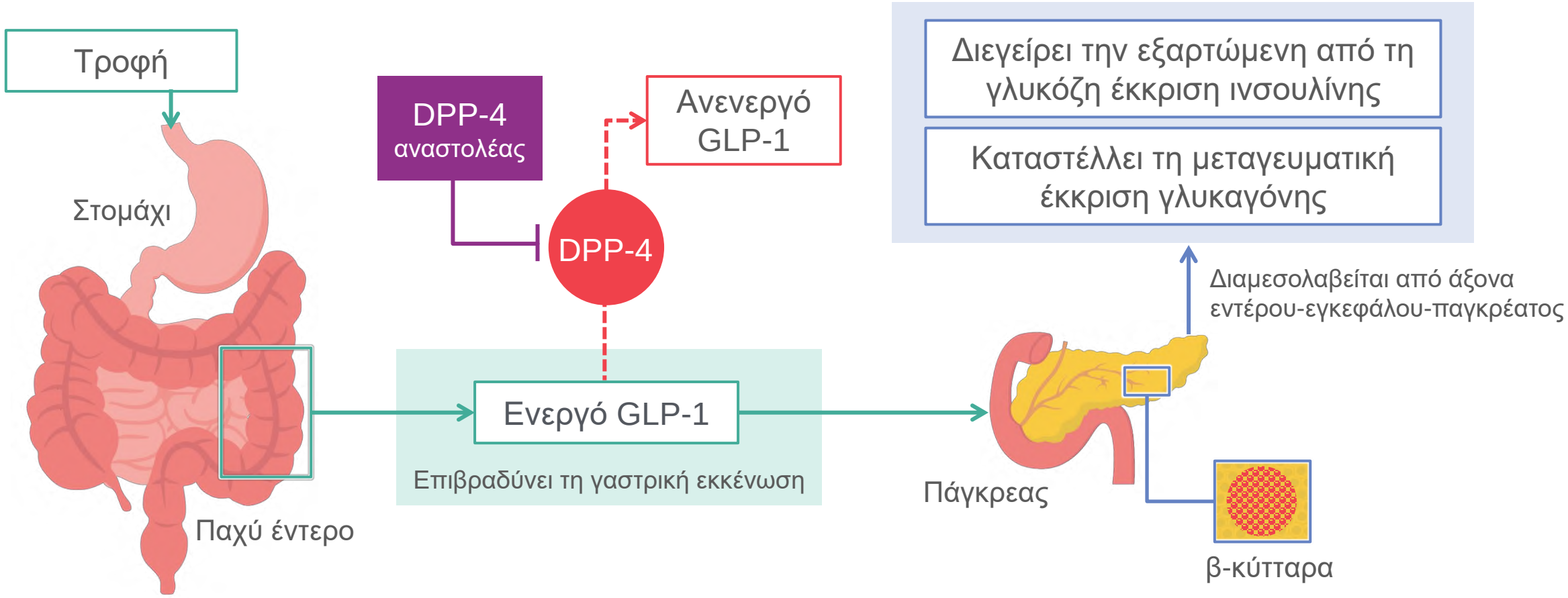
ΜΕ ΥΨΗΛΟ Κ/Α ΚΙΝΔΥΝΟ – ΕΓΚΑΤΕΣΤΗΜΕΝΗ ΑΚΝ – ΧΝΝ – ΚΑ ΜΕ ΜΕΙΩΜΕΝΟ ΚΕ

2022



Ποιος διάσημος θα ήταν η πιογλιταζόνη;

Μηχανισμός δράσης των DPP-4 αναστολέων

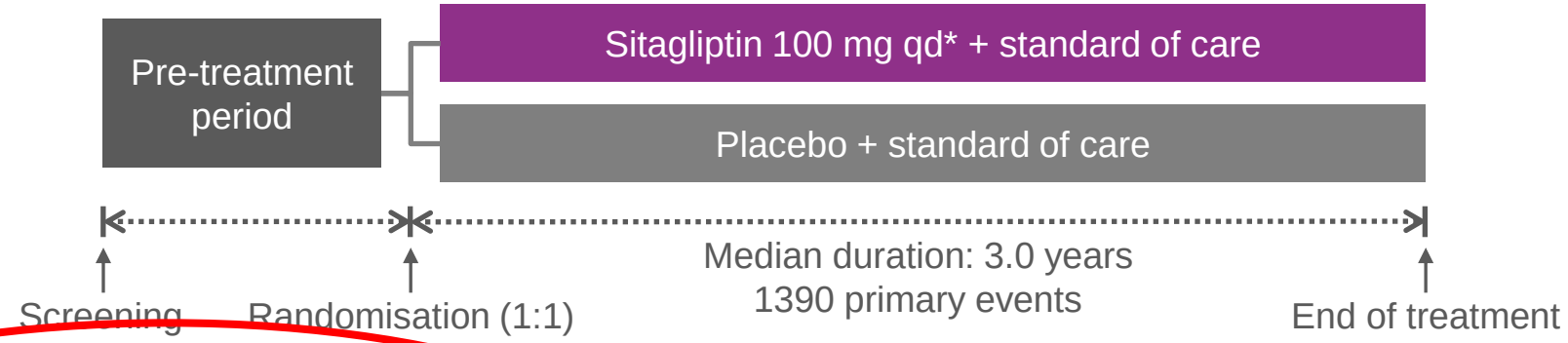


DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Προσαρμογή από: Drucker DJ. *Expert Opin Invest Drugs* 2003;12:87; Ahrén B. *Curr Diab Rep* 2003;3:365; Robinson LE *et al. BMJ Open* 2013;3:pii e001986

TECOS: Σχεδιασμός Μελέτης

Στόχος: Η αξιολόγηση της ΚΔ ασφάλειας της σιταγλιπτίνης έναντι του εικονικού φαρμάκου σε ασθενείς με ΣΔτ2 και εΚΔΝ



Key inclusion criteria

- Aged ≥50 years with T2D
- HbA1c 6.5–8.0% receiving stable oral glucose-lowering therapy or insulin, with or without metformin
- Established CV disease

Key exclusion criteria

- DPP-4 inhibitor, GLP-1 receptor agonist or TZD (other than pioglitazone) within the last 3 months
- ≥2 episodes of severe hypoglycaemia in the preceding 12 months
- T1D
- eGFR <30 ml/min/1.73 m^2

Primary endpoint	4P-MACE (3P-MACE or hospitalisation for unstable angina)
Key secondary endpoint	3P-MACE (CV death, non-fatal MI or non-fatal stroke)

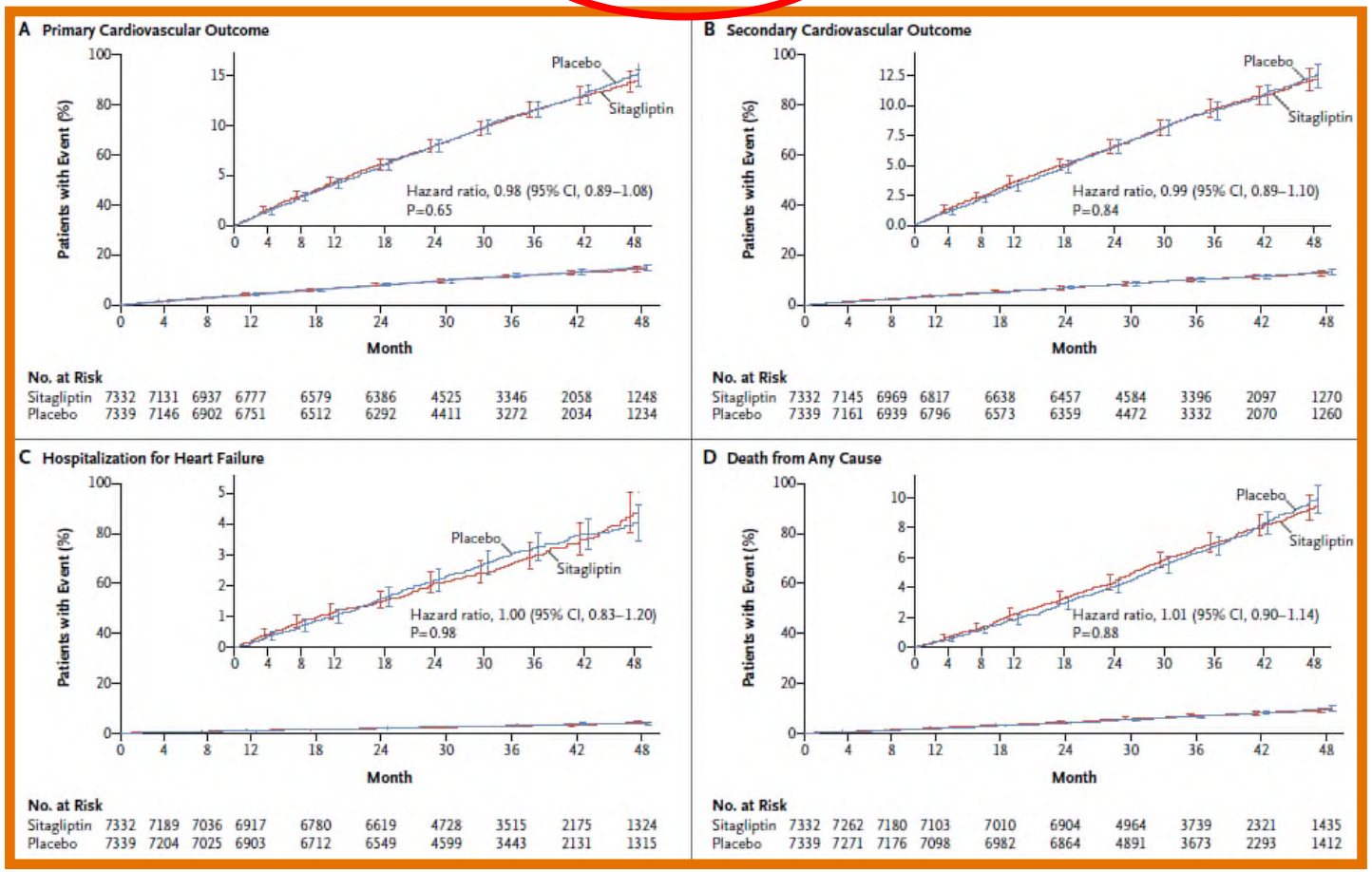
*50 mg qd for patients with baseline eGFR ≥30 to <50 ml/min/1.73 m^2

3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major adverse cardiovascular events; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MI, myocardial infarction; T1D, type 1 diabetes, T2D, type 2 diabetes; TZD, thiazolidinedione, εΚΔΝ: εγκατεστημένη Καρδιαγγειακή Νόσος

Green JB *et al. N Engl J Med* 2015;373:232

Clinical Outcomes with Sitagliptin

TECOS (n=14,671)



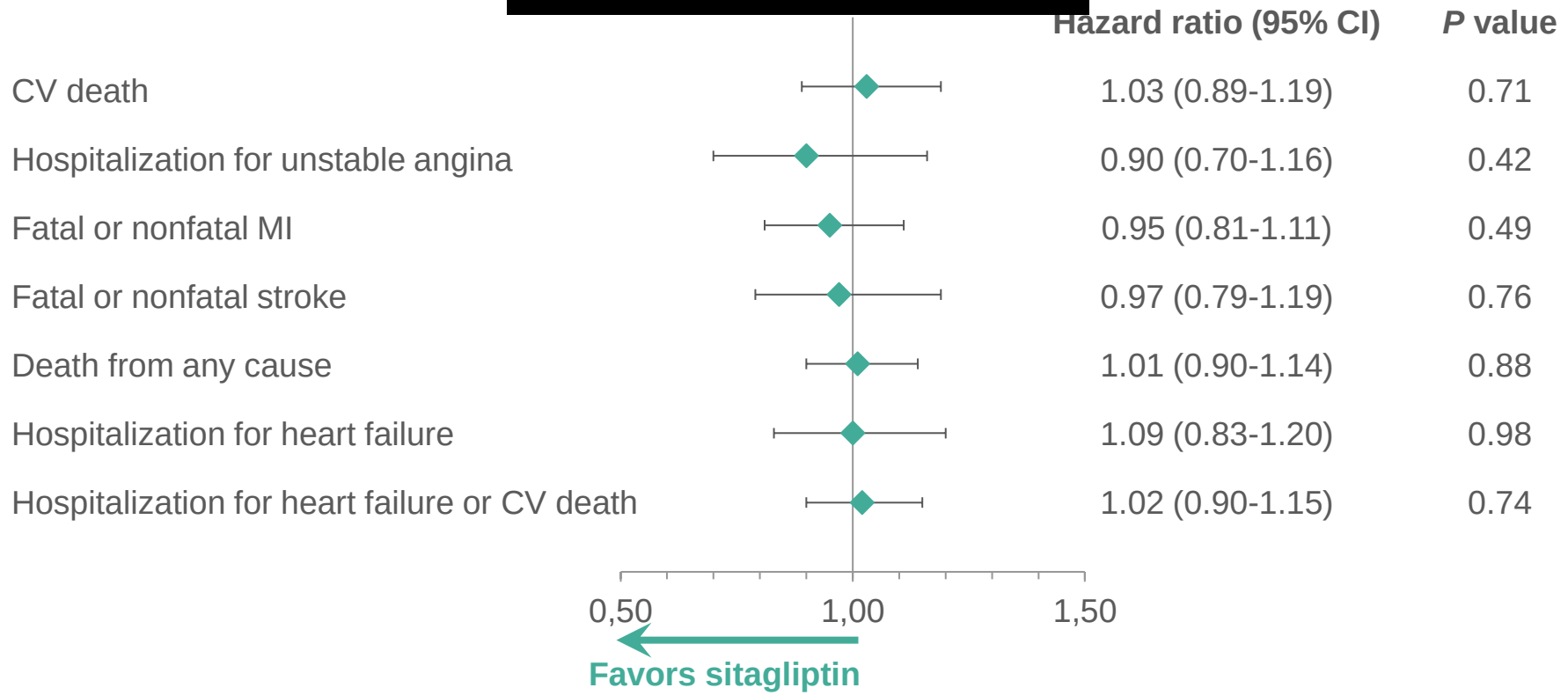
TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Individual Secondary Outcomes with Sitagliptin

TECOS Intent to Treat Analysis (n=14,671)

Median follow-up: 3.0 years



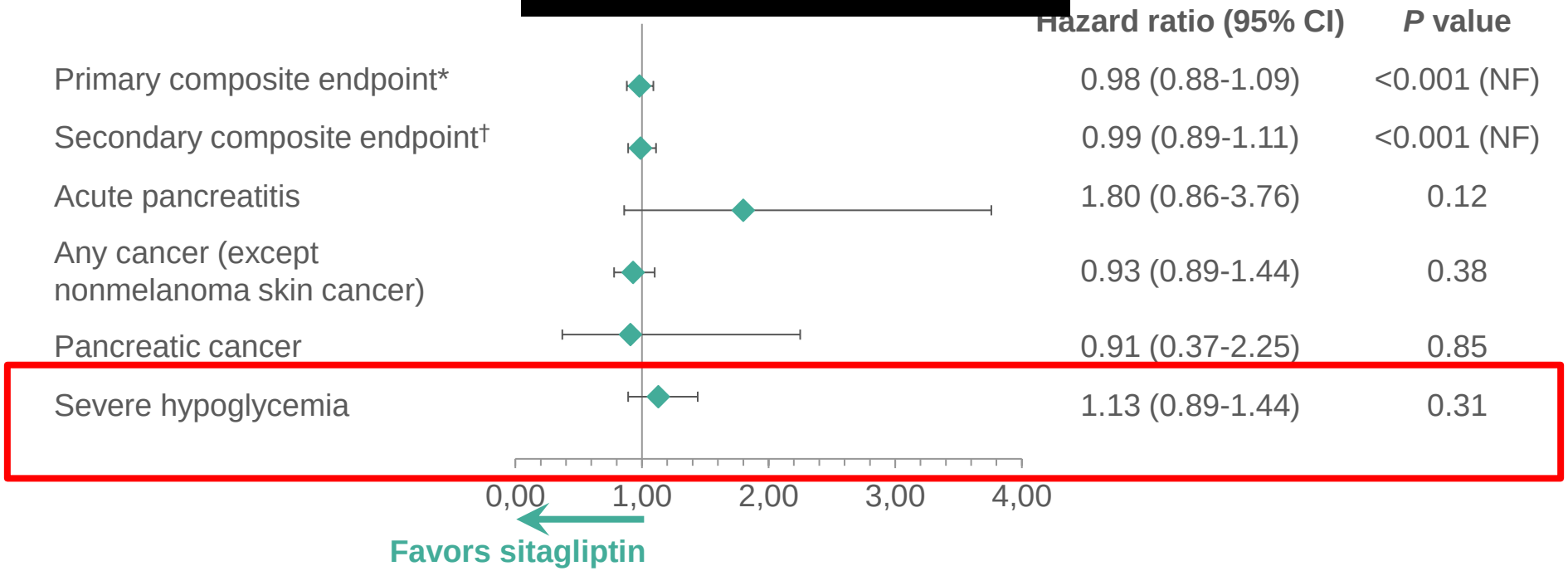
CV, cardiovascular; MI, myocardial infarction; NF, noninferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Primary and Secondary Outcomes with Sitagliptin

TECOS Per Protocol Analysis (n=14,523)

Median follow-up: 3.0 years



*Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

†Secondary composite: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

NF, noninferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

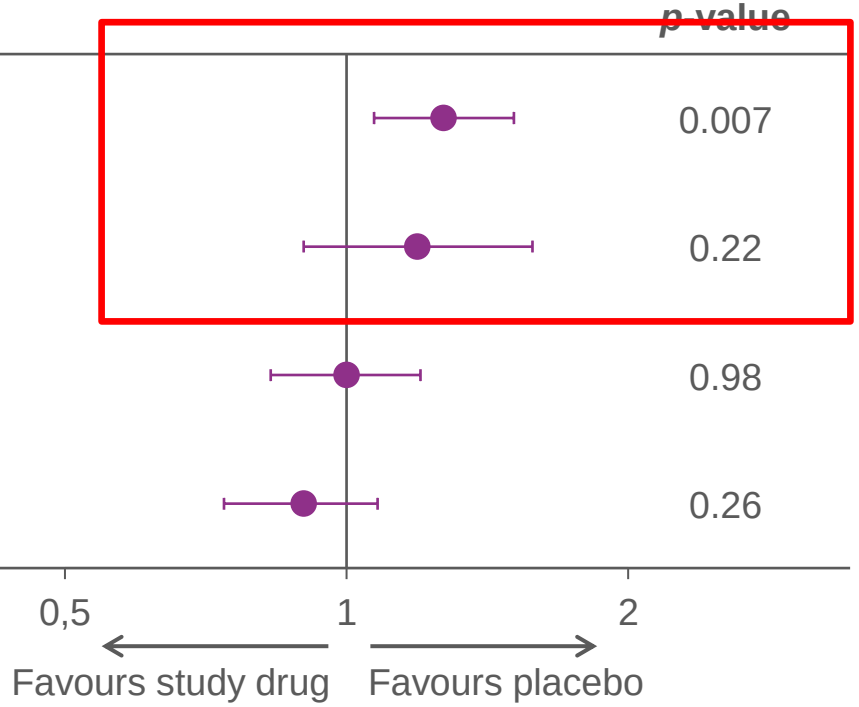
Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Είναι όλοι οι DPP4 αναστολείς ίδιοι;

Νοσηλεία για Καρδιακή Ανεπάρκεια στις μελέτες ΚΔ εκβάσεων των DPP-4 αναστολέων

Η σαξαγλιπτίνη συνδέθηκε με σημαντική αύξηση του κινδύνου για νοσηλεία από καρδιακή ανεπάρκεια συγκριτικά με το εικονικό φάρμακο

	Study drug	Placebo		
	n with event/N analysed (%)		HR (95% CI)	*p* value
SAVOR-TIMI 53*[1] (saxagliptin)	289/8280 (3.5)	228/8212 (2.8)	1.27 (1.07, 1.51)	0.007
EXAMINE*[2] (alogliptin)	106/2701 (3.9)	89/2679 (3.3)	1.19 (0.90, 1.58)	0.22
TECOS†[3] (sitagliptin)	228/7332 (3.1)	229/7339 (3.1)	1.00 (0.83, 1.20)	0.98
CARMELINA®[4] (linagliptin)	209/3494 (6.0)	226/3485 (6.5)	0.90 (0.74, 1.08)	0.26



Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

*According to an FDA safety review, saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. A warning has been added to the labels of these drugs[5]; †Heart failure risk was not assessed at the time of the trial

CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. Zannad F *et al. Lancet* 2015;385:2067; 3. Green JB *et al. N Engl J Med* 2015;73:232; 4. Rosenstock J *et al. JAMA* 2019;321:69; 5. FDA Drug Safety Communication. Feb 2014. https://www.fda.gov/drugs/drugsafety/ucm486096.htm (accessed Mar 2019)

Ποιος διάσημος θα ήταν οι DPP4i;

Οι επιδράσεις των παλαιότερων αντιδιαβητικών παραγόντων στον Καρδιαγγειακό κίνδυνο

Περιεχόμενα

Original Article

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators

N Engl J Med
Volume 367(4):319-328
July 26, 2012

The NEW ENGLAND JOURNAL of MEDICINE

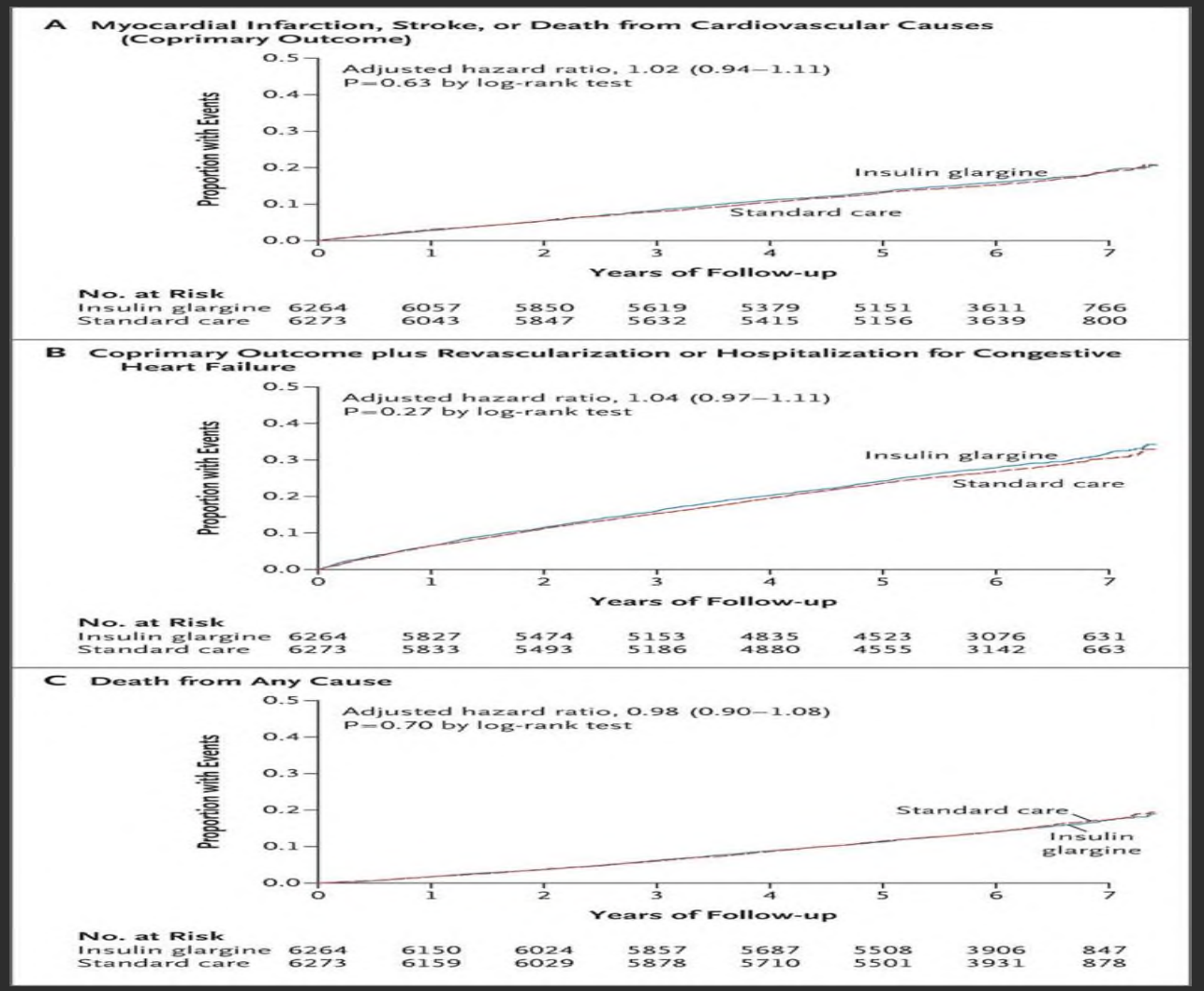
Study Overview

- In this study with a 2-by-2 factorial design, patients with cardiovascular risk factors and dysglycemia or type 2 diabetes received insulin glargine or standard care.

- Insulin treatment did not affect cardiovascular events, the primary outcome.

The NEW ENGLAND JOURNAL of MEDICINE

Proportion of Participants with Events over Time

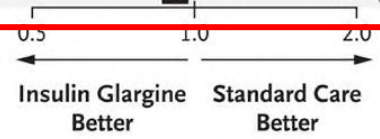


The ORIGIN Trial Investigators. N Engl J Med 2012;367:319-328

The NEW ENGLAND JOURNAL of MEDICINE

Hazard Ratios for the Coprimary and Other Outcomes

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



The ORIGIN Trial Investigators. N Engl J Med 2012;367:319-328

The NEW ENGLAND JOURNAL of MEDICINE

Incidence of a First Episode of Severe Hypoglycemia

Table 3. Incidence of a First Episode of Severe Hypoglycemia.

Variable	Insulin Glargine (N = 6264)	Standard Care (N = 6273)	P Value
Severe hypoglycemia*			
Participants with ≥1 episode — no. (no./100 person-yr)	359 (1.00)	113 (0.31)	<0.001
Total episodes during follow-up — no.	457	134	
Confirmed nonsevere symptomatic hypoglycemia†			
Participants with ≥1 episode — no. (no./100 person-yr)	2614 (9.83)	904 (2.68)	<0.001
Episodes/yr in participants with ≥1 episode — median (interquartile range)	0.5 (0.2–1.4)	0.3 (0.2–0.8)	<0.001
Participants with no confirmed episodes during follow-up — no. (%)	3650 (58.3)	5369 (85.6)	<0.001
Any nonsevere symptomatic hypoglycemia			
Participants with ≥1 episode — no. (no./100 person-yr)	3575 (16.72)	1580 (5.16)	<0.001
Episodes/yr in participants with ≥1 episode — median (interquartile range)	1.1 (0.4–3.1)	0.5 (0.2–1.3)	<0.001
Participants with no episodes during follow-up — no. (%)	2689 (42.9)	4693 (74.8)	<0.001

* This category included any episode of hypoglycemia for which the patient required assistance and that was confirmed by a self-measured or laboratory plasma glucose level of 2 mmol per liter (36 mg per deciliter) or less or from which the patient recovered promptly after oral carbohydrate, intravenous glucose, or glucagon administration.

† This category included any symptomatic nonsevere hypoglycemic episode that was confirmed by a self-measured glucose level of 3 mmol per liter (54 mg per deciliter) or less.

The ORIGIN Trial Investigators. N Engl J Med 2012;367:319-328

The NEW ENGLAND JOURNAL of MEDICINE

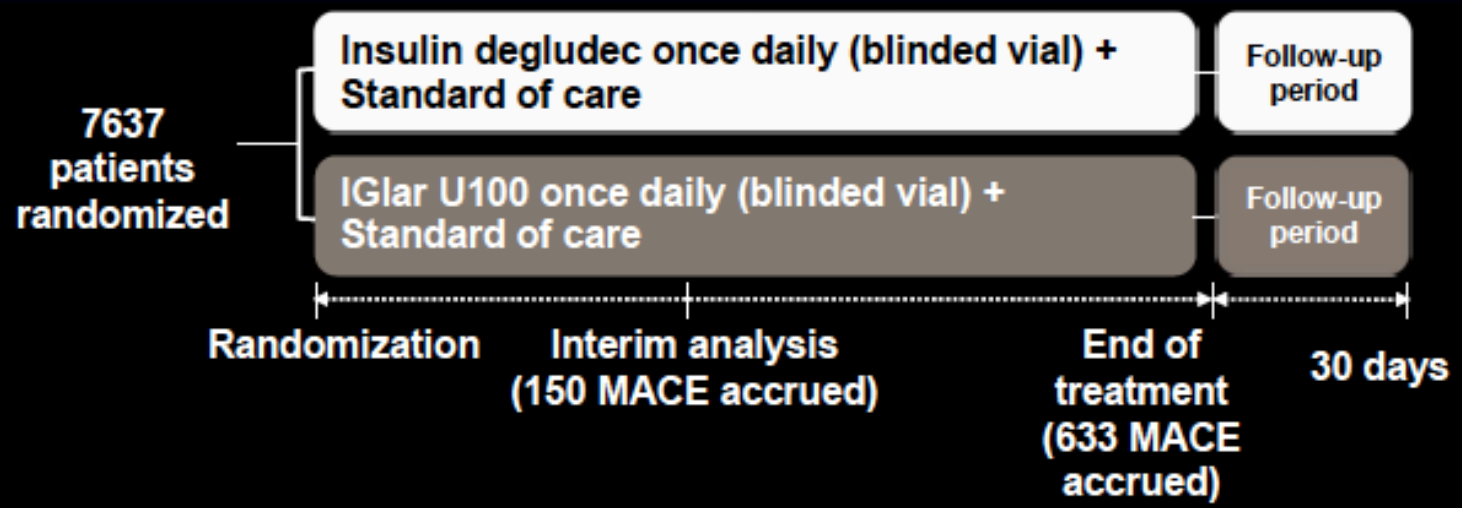
Conclusions

- When used to target normal fasting plasma glucose levels for more than 6 years, insulin glargine had a neutral effect on cardiovascular outcomes and cancers.

- Although it reduced new-onset diabetes, insulin glargine also increased hypoglycemia and modestly increased weight.

The NEW ENGLAND JOURNAL of MEDICINE

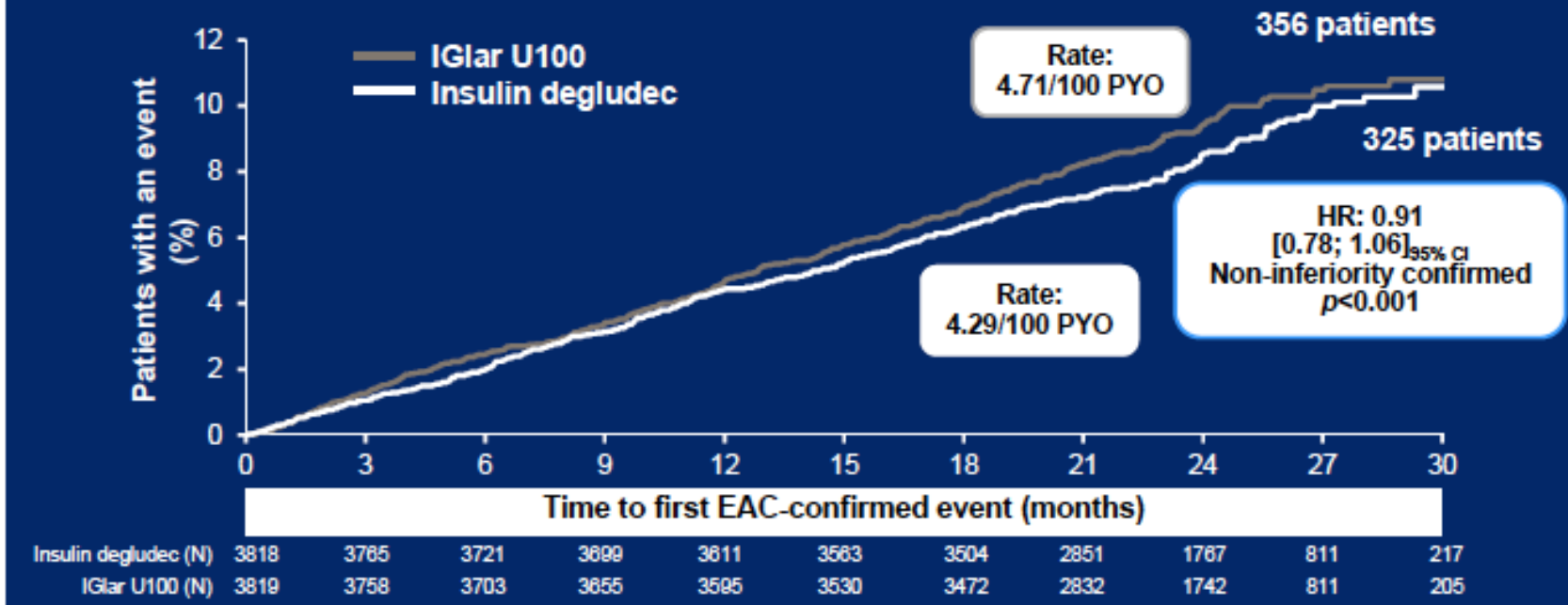
DEVOTE: Trial Design



Primary endpoint	Time from randomization to first occurrence of a 3-point MACE: cardiovascular death*†, non-fatal myocardial infarction* or non-fatal stroke*
Secondary endpoints	• Rate of severe hypoglycemic episodes*‡ • Incidence of severe hypoglycemic episodes*‡

Marso S. et al. NEJM, June14, 2017

DEVOTE: Time to First 3-point MACE



Insulin degludec (N)	3818	3765	3721	3699	3611	3563	3504	2851	1767	811	217
IGlar U100 (N)	3819	3758	3703	3655	3595	3530	3472	2832	1742	811	205

Full analysis set; Cox regression analysis accounting for treatment. Analysis includes events between randomization date and follow-up date. Patients without an event are censored at the time of last contact (phone or visit)
EAC, Event Adjudication Committee; N, number of patients at risk; PYO, patient-years of observation

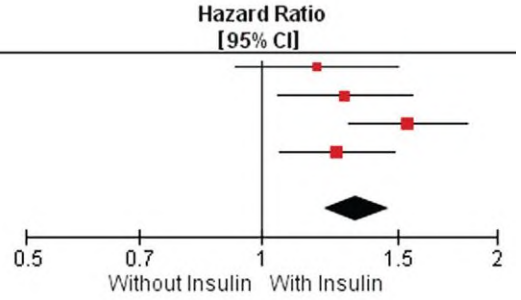
Marso S. et al. NEJM, June14, 2017

Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes

A

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Val-HeFT	0.1655	0.1219	15.8%	1.18 [0.93, 1.50]
CORONA	0.2469	0.101	23.0%	1.28 [1.05, 1.56]
GISSI-HF	0.4318	0.0892	29.4%	1.54 [1.29, 1.83]
ATMOSPHERE	0.2231	0.0858	31.8%	1.25 [1.05, 1.47]
Total (95% CI)			**100.0%**	**1.32 [1.20, 1.46]**

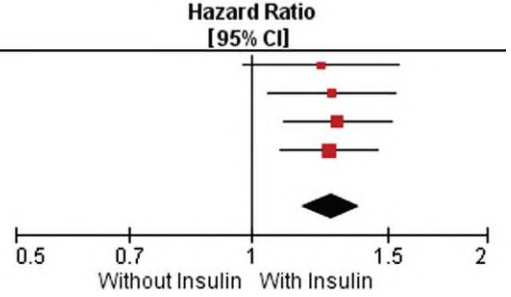
Heterogeneity: $Chi^2 = 4.33$, $df = 3$ ($P = 0.23$); $I^2 = 31\%$
Test for overall effect: $Z = 5.80$ ($P < 0.00001$)

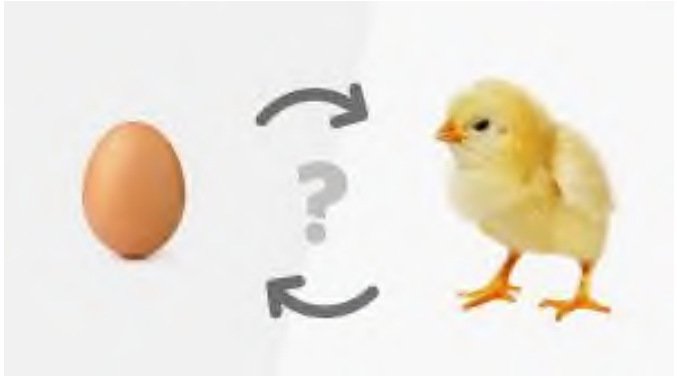


B

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Val-HeFT	0.207	0.117	14.0%	1.23 [0.98, 1.55]
CORONA	0.239	0.096	20.7%	1.27 [1.05, 1.53]
GISSI-HF	0.2546	0.0808	29.3%	1.29 [1.10, 1.51]
ATMOSPHERE	0.2311	0.0728	36.0%	1.26 [1.09, 1.45]
Total (95% CI)			**100.0%**	**1.27 [1.16, 1.38]**

Heterogeneity: $Chi^2 = 0.12$, $df = 3$ ($P = 0.99$); $I^2 = 0\%$
Test for overall effect: $Z = 5.41$ ($P < 0.00001$)





European Journal of Heart Failure, Volume: 20, Issue: 5, Pages: 888-895, First published: 28 February 2018, DOI: (10.1002/ejhf.1146)

Heart failure with insulin degludec versus glargine U100 in patients with type 2 diabetes at high risk of cardiovascular disease: DEVOTE 14

Richard E. Pratley, Mansoor Husain, Ildiko Lingvay, Thomas R. Pieber, Thomas Mark, Hans A. Saevereid, Daniel Vega Møller, Bernard Zinman, on behalf of the DEVOTE Study Group

Trial number: NCT01959529

Predictors of time to first hHF (SMQ definition)

Baseline predictor	Hazard ratio [95% CI]	Relative importance	P-value
Prior heart failure (Y vs N)	4.89 [3.90; 6.14]	54.6	<0.0001
Hepatic impairment (Y vs N)	3.08 [2.15; 4.41]	11.0	<0.0001
eGFR (log regression)	0.44 [0.34; 0.58]	10.0	<0.0001
Atrial fibrillation (Y vs N)	1.95 [1.50; 2.55]	7.2	<0.0001
Total insulin dose (U/kg) at week 1	1.53 [1.27; 1.84]	5.9	<0.0001
Prior myocardial infarction (Y vs N)	1.54 [1.23; 1.91]	4.3	0.0001
Macular edema (Y vs N)	3.77 [1.40; 10.2]	2.0	0.0087
A1C (squared regression)	1.00 [1.00; 1.01]	1.8	0.0137
Proteinuria (microalbuminuria and gross proteinuria)	1.36 [1.06; 1.73]	1.8	0.0140
Systolic blood pressure at baseline	1.01 [1.00; 1.01]	1.5	0.0251

Adapted from Table 2. Variables identified by stepwise selection – FAS. Relative importance is calculated as 100 x Chi-square/Total Chi-square, where the Chi squares are from a model simultaneously considering all effects mentioned in the table. CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; hHF, hospitalization for heart failure; N, no; SMQ, standardized Medical Dictionary for Regulatory Activities Query; U, units; Y, yes

Ποιος διάσημος θα ήταν η ινσουλίνη;

“***If you have always done it that way, it is probably wrong***”

Charles Kettering, 1876-1958

Ο ασκός του Αιόλου

Table I Timeline: the rise and fall of rosiglitazone

findings.[17]

21 May 2007	The meta-analysis of CV outcomes is published online.[18]
6 June 2007	The company publishes an unblinded interim analysis of the RECORD Trial.
30 July 2007	The FDA reveals its own meta-analysis of CV events with rosiglitazone, showing a statistically significant increase in risk (RR = 1.4).[17]
October 2007	The FDA adds a 'black box warning' to the rosiglitazone label for ischaemic events.
December 2008	The FDA issues a guidance requiring CV outcomes trials for diabetes drugs.[3]

DPP-4i

Saxagliptin and CV outcomes in patients with T2D

DPP-4i

Alogliptin after acute coronary syndrome in patients with T2D

DPP-4i

Effect of sitagliptin on CV outcomes in T2D

DPP-4i

Linagliptin CV and renal outcomes in T2D with vascular risk

DPP-4i

CV outcomes study of linagliptin vs glimepiride in patients with T2D

GLP-1RA

Lixisenatide in ACS, a long-term CV endpoint trial of lixisenatide vs placebo

GLP-1RA

Liraglutide and CV outcomes in T2D

GLP-1RA

SUSTAIN 6: CV and other long-term outcomes with semaglutide in patients with T2D

GLP-1RA

FREEDOM-CVO: CV outcomes study examining the safety of ITCA 650 vs placebo

GLP-1RA

CV outcomes after treatment with exenatide OW in patients with T2D

GLP-1RA

Effect of albiglutide on major CV events in patients with T2D

GLP-1RA

PIONEER 6: CV safety of oral semaglutide with SOC in patients with T2D

GLP-1RA

Effect of dulaglutide on major CV events in patients with T2D

SGLT-2i

Empagliflozin, CV outcomes and mortality in T2D

SGLT-2i

Canagliflozin and CV and renal events in T2D

SGLT-2i

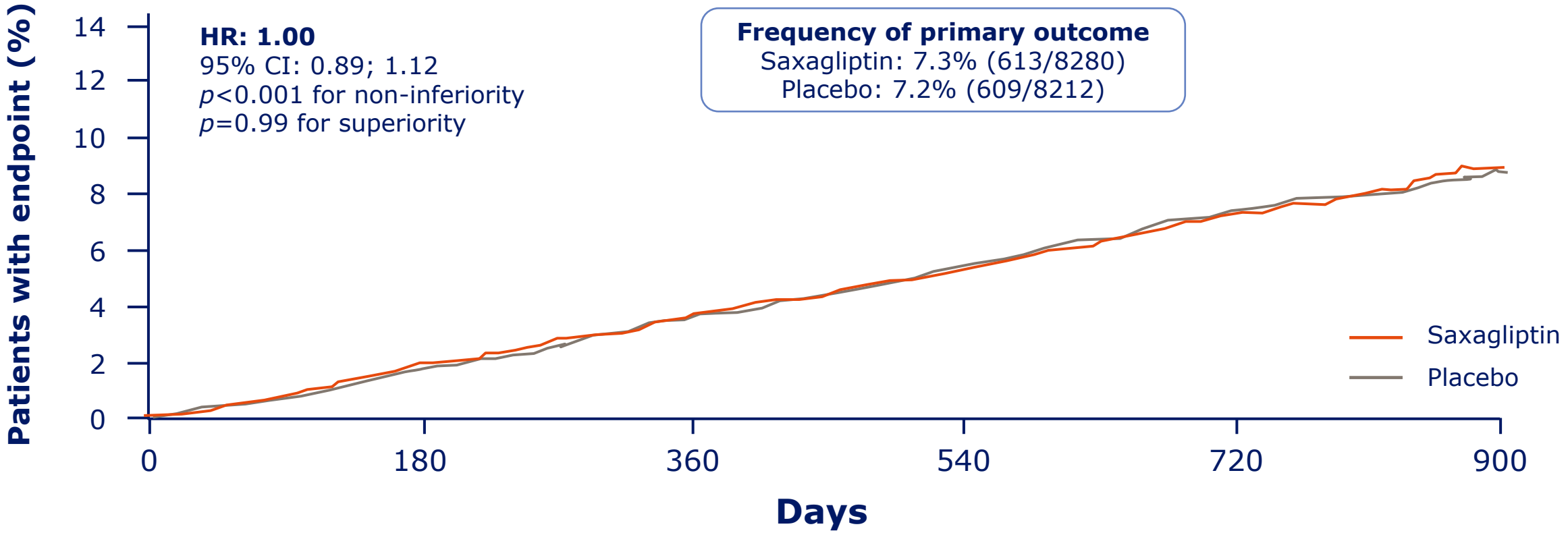
Effect of dapagliflozin on CV events in patients with T2D

Insulin

CV safety of IDeg vs IGlar in patients with T2D at high risk of CV events

ACS, acute coronary syndrome; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDeg, insulin degludec; IGlar, insulin glargine; SGLT-2i, sodium–glucose cotransporter-2 inhibitor; SOC, standard of care; T2D, type 2 diabetes

SAVOR-TIMI-53: Time to first CV death, non-fatal MI or non-fatal ischaemic stroke



Patients at risk

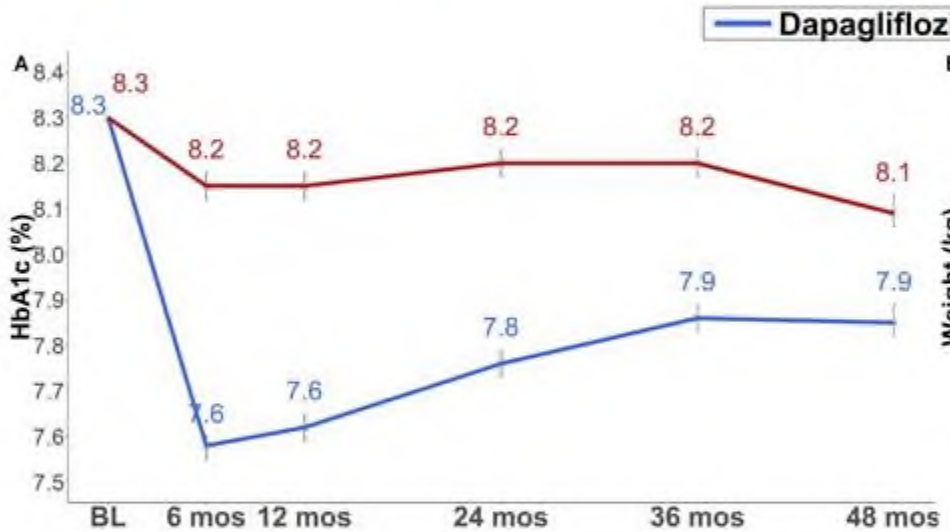
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction
Scirica BM et al. *N Engl J Med* 2013;369:1317–1326

Cardiovascular Risk Factors

HbA1c

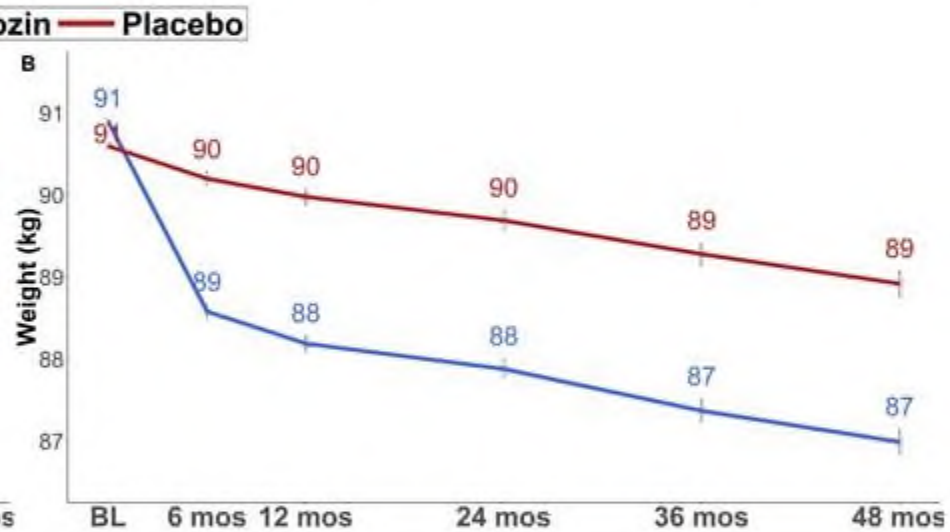
LSM Difference 0.42% (95% CI 0.40-0.45)



All P-values (except BL) <0.001

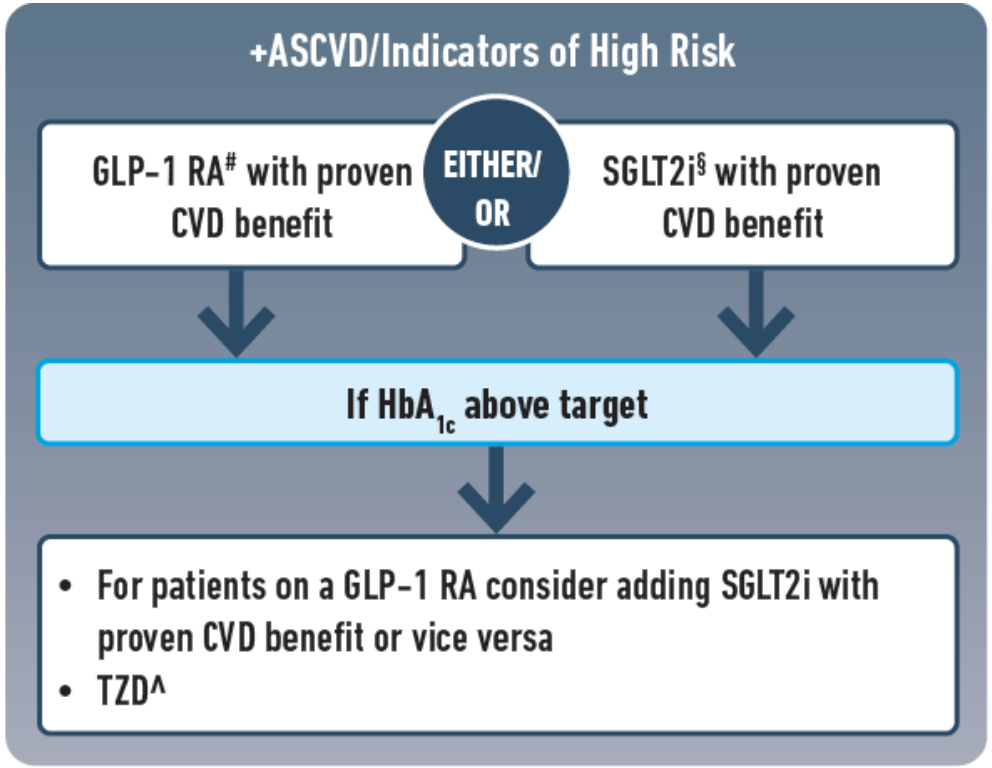
Weight

LSM Difference 1.8 kg (95% CI 1.7-2.0)



All P-values (except BL) <0.001

Choosing glucose-lowering medication in people with CVD



ASCVD = atherosclerotic cardiovascular disease

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

Consensus recommendations

- In people with established CVD, a GLP-1RA with proven benefit should be used to reduce MACE or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.
- In people without established CVD but with multiple cardiovascular risk factors (such as age ≥55, obesity, hypertension, smoking, dyslipidaemia, or albuminuria), a GLP-1RA with proven benefit could be used to reduce MACE or an SGLT2i with proven benefit could be used to reduce MACE and heart failure and improve kidney outcomes.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

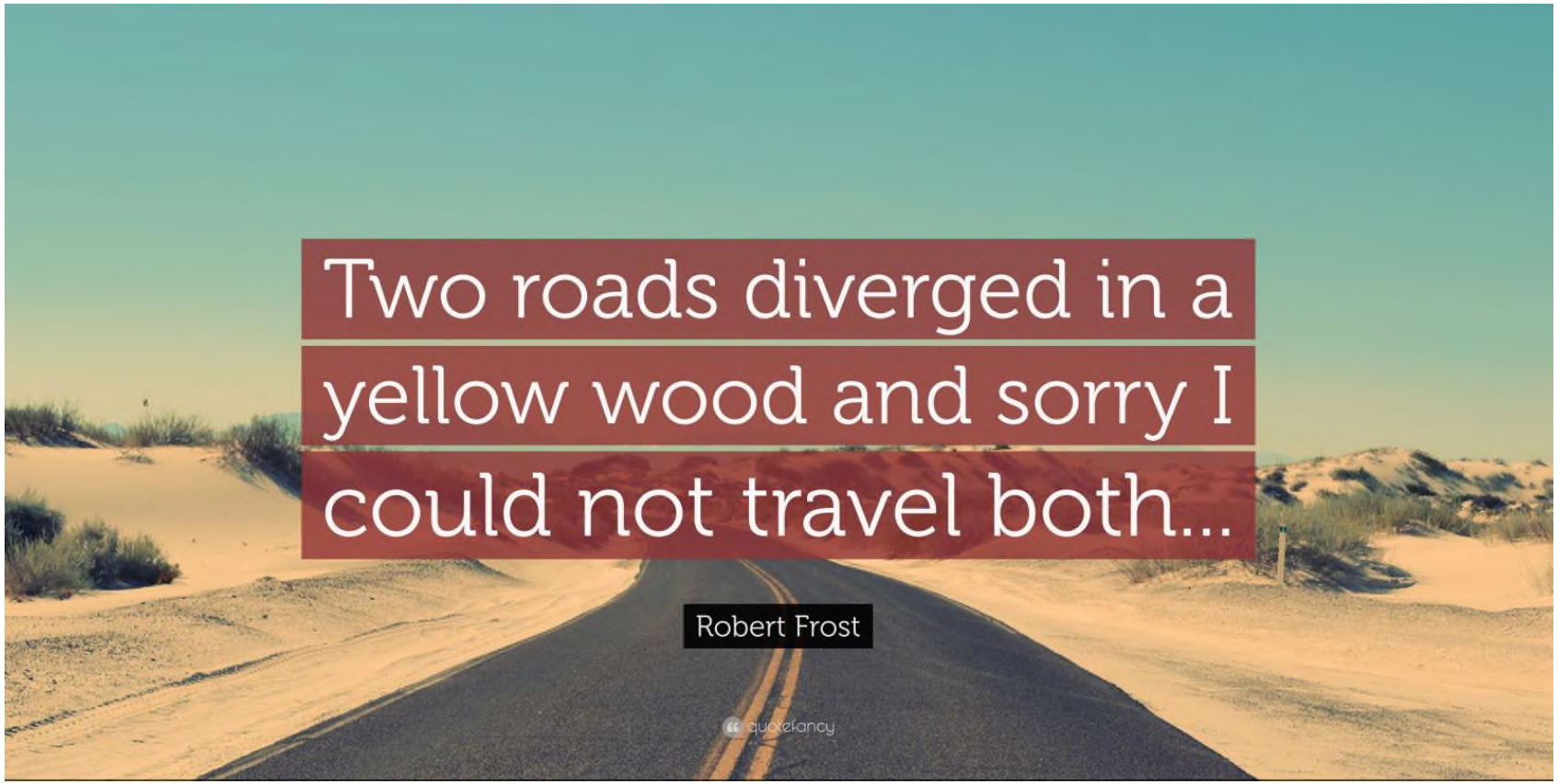
Consensus recommendations

- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of background use of metformin.

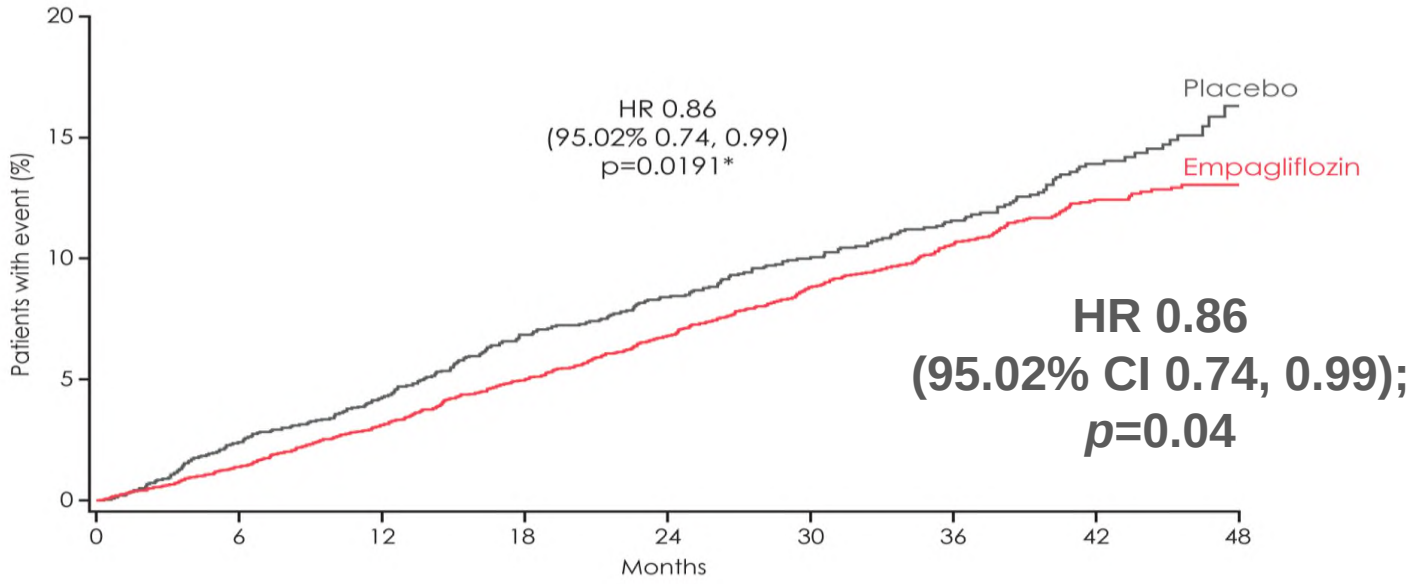
- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.


Two roads diverged in a
yellow wood and sorry I
could not travel both...
Robert Frost
quotefancy

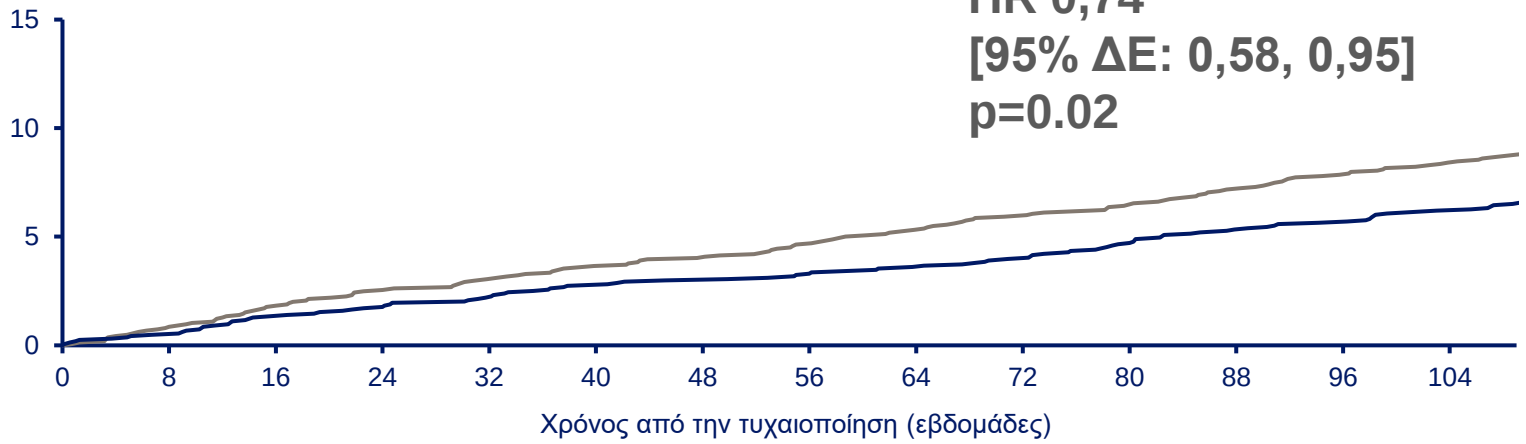
SGLT2i



HR 0.86
(95.02% CI 0.74, 0.99);
***p*=0.04**

EMPA-REG

GLP-1 RAs

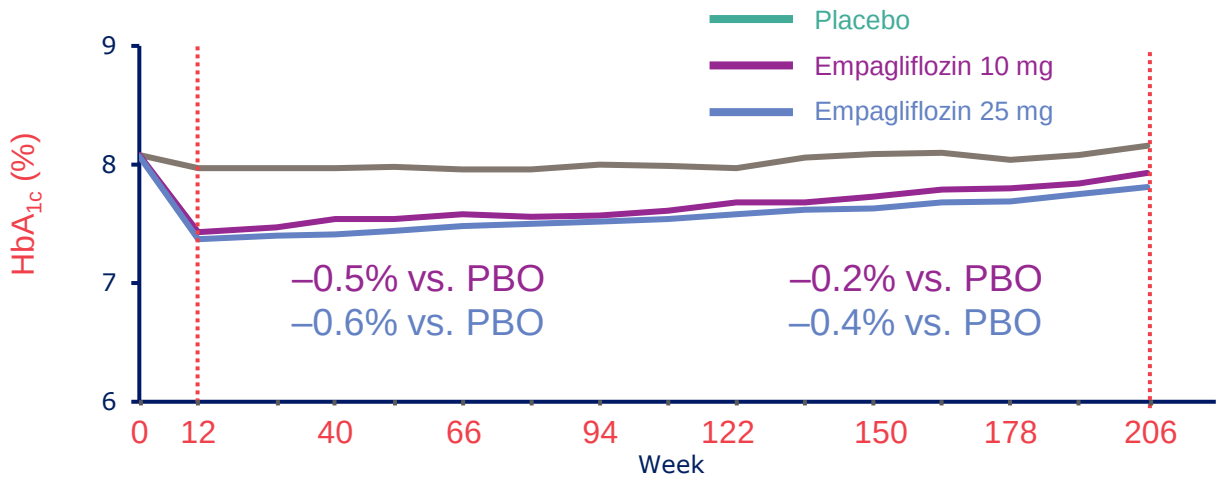


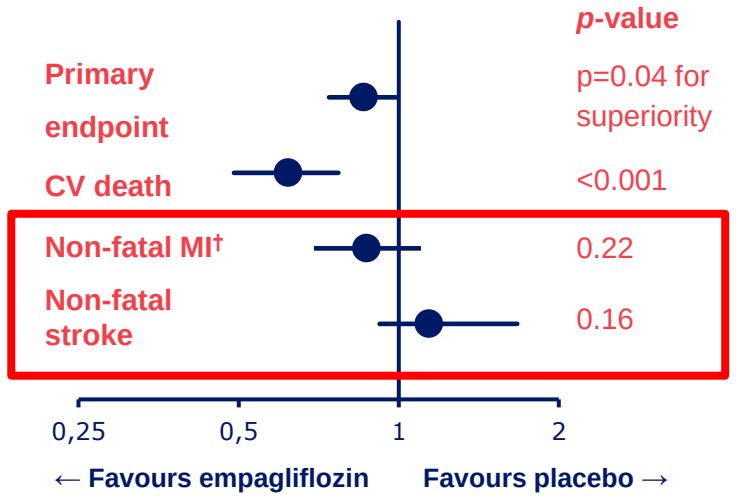
HR 0,74
[95% ΔΕ: 0,58, 0,95]
p=0.02

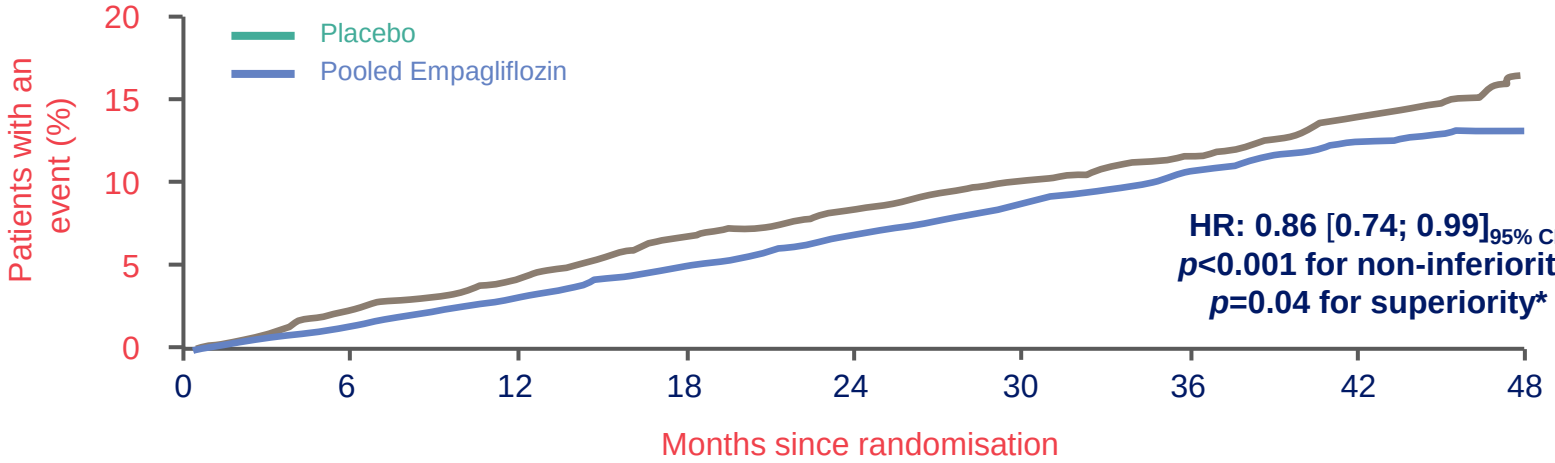
SUSTAIN 6

Empagliflozin: EMPA-REG results

HbA_{1c} reductions and macrovascular outcomes







Heart failure

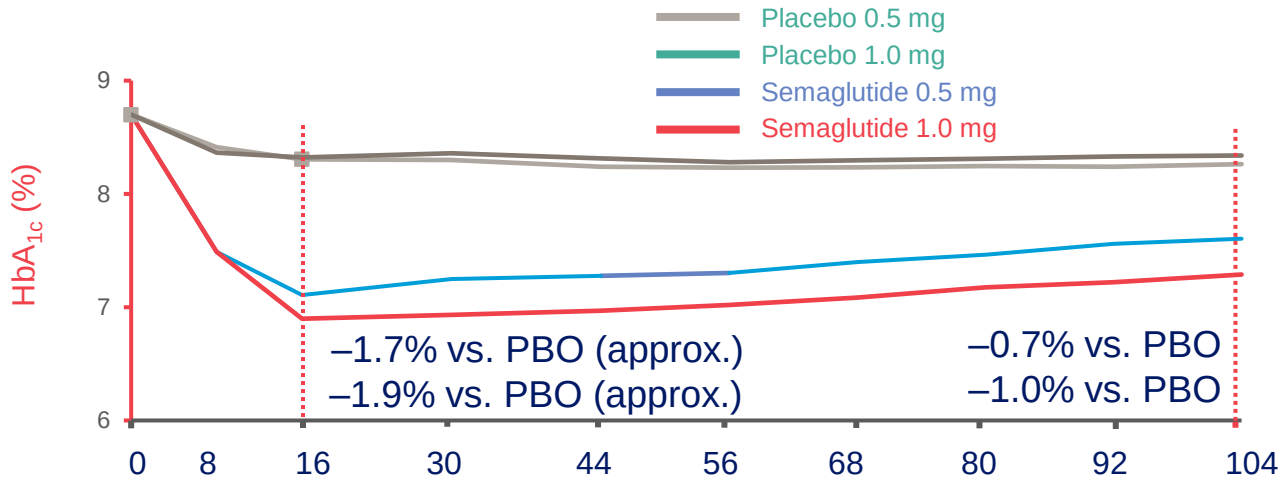
As compared with placebo, empagliflozin resulted in a significantly lower risk of hospitalisation for heart failure

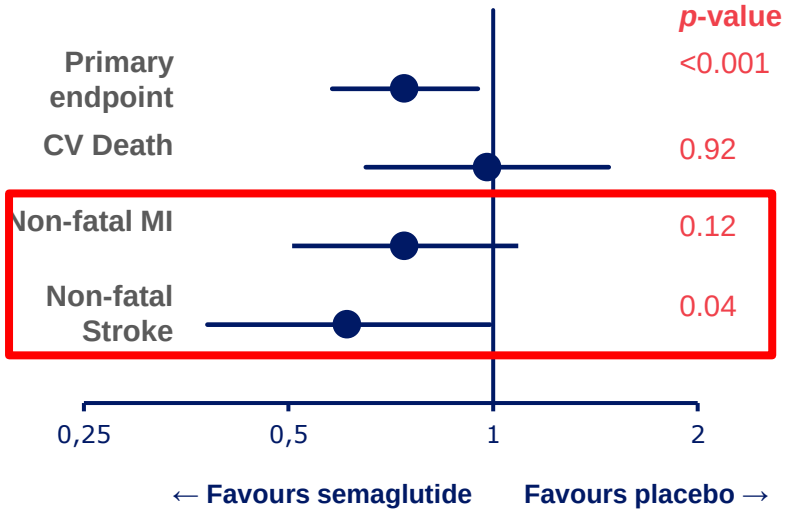
HR: 0.65
[0.50; 0.85]$_{95\%\ CI}$, *p*=0.002

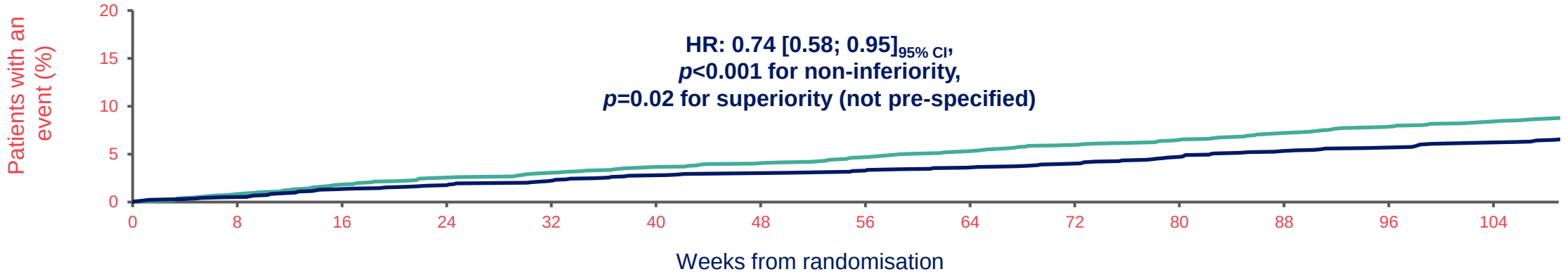
The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empaglif lozin group vs. the placebo group. *Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498); †Excluding silent MI. CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin; ERR, estimated rate ratio; HR, hazard ratio; MI, myocardial infarction; PBO, placebo; PE, primary endpoint; SGLT-2i, sodium glucose co-transporter 2 inhibitor. 1. Zinman et al. *N Engl J Med* 2015;373:2117–28.

Semaglutide: SUSTAIN-6 results

HbA_{1c} reductions and macrovascular outcomes







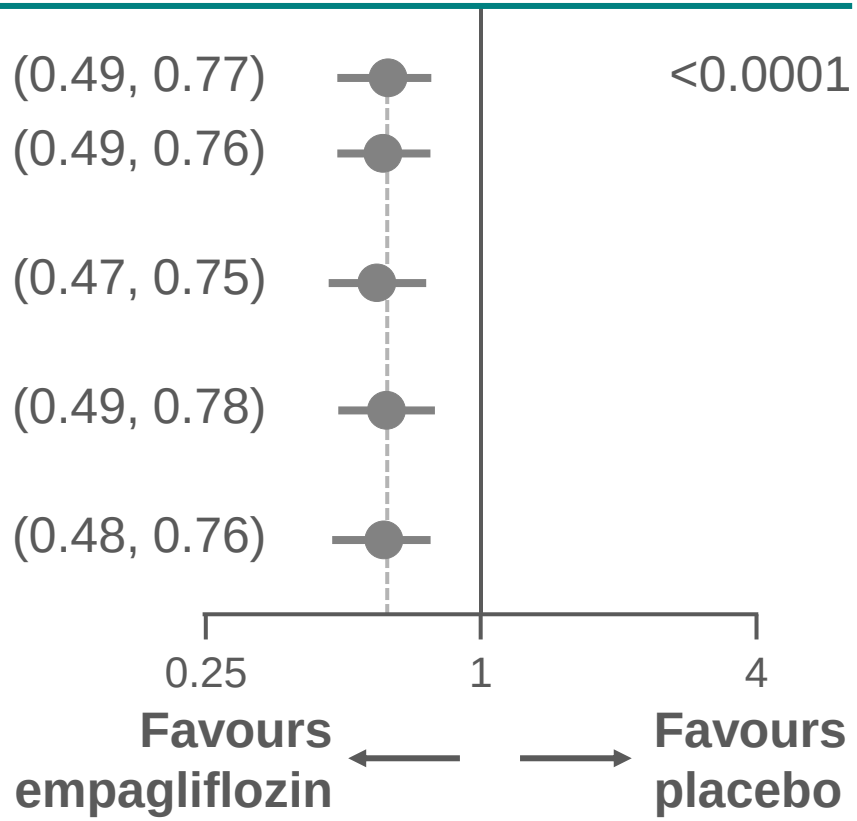
Semaglutide is under development and not approved. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Primary endpoint analysed using Cox proportional hazard regression with pooled treatment (semaglutide vs. placebo) as a fixed factor. Change at week 104 is shown for metabolic and CV risk factors. CV, cardiovascular; HbA1c, glycated haemoglobin; HR, hazard ratio; PBO, placebo; MI, myocardial infarction; Sema, semaglutide.

Marso et al. *New Engl J Med* 2016;375:1834–44.

Το κλειδί βρίσκεται στους μηχανισμούς

Reduced risk of CV death was not associated with BP, LDL-cholesterol or HbA_{1c} control over time

CV death	Patients with event/analysed (%) Empagliflozin	Placebo	HR (95% CI)	*p* value
Main analysis	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	<0.0001
Adjusted for time-dependent control of BP*	172/4687 (3.7)	137/2333 (5.9)	0.61 (0.49, 0.76)	
Adjusted for time-dependent control of LDL-C †	167/4615 (3.6)	136/2308 (5.9)	0.59 (0.47, 0.75)	
Adjusted for time-dependent control of HbA_{1c} ‡	172/4685 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.78)	
Adjusted for time-dependent control of BP, LDL-C and HbA_{1c}	167/4614 (3.6)	136/2308 (5.9)	0.61 (0.48, 0.76)	

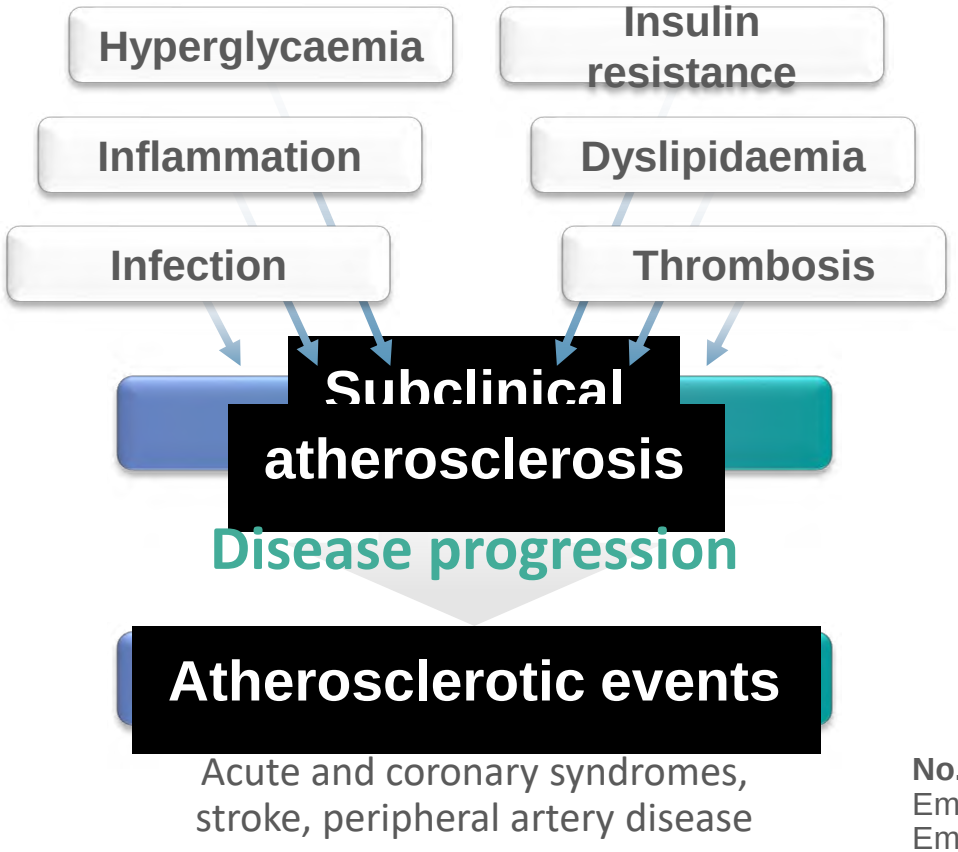


***(SBP <140 mmHg and DBP <90mmHg). †(LDL-cholesterol <100mg/dl). ‡(HbA_{1c}<7.5%).**
Post-hoc analysis. Cox regression analysis in patients treated with ≥1 dose of study drug.
Main analysis did not adjust for baseline or time-dependent control of BP, LDL-cholesterol or HbA1c.

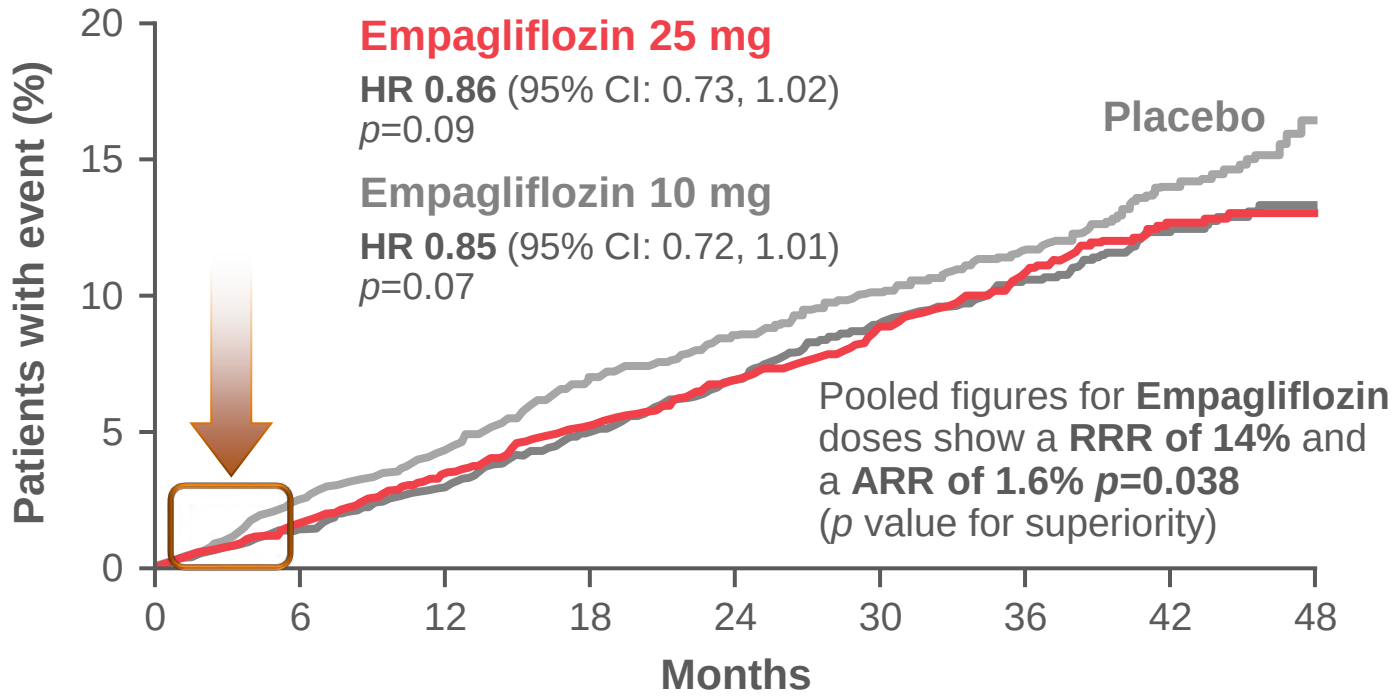
Fitchett D, et al. Poster presented at Diabetes UK Professional Conference, 14-16 March 2018, London, UK.

SGLT2i CVOT study results challenge the classical model of cardiovascular risk

Classic CV risk model[1]



EMPA-REG OUTCOME study: major adverse cardiac event (MACE)[2]



No. of patients:

Empagliflozin 10 mg	2345	2292	2233	2167	1918	1415	1177	753	178
Empagliflozin 25 mg	2342	2288	2222	2161	1933	1406	1182	781	192
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

1. Biondi-Zoccai GGL, *et al. J Am Coll Cardiol* 2003;41:1071–7; 2. Zinman B, *et al. N Engl J Med* 2015;373:2117–28.

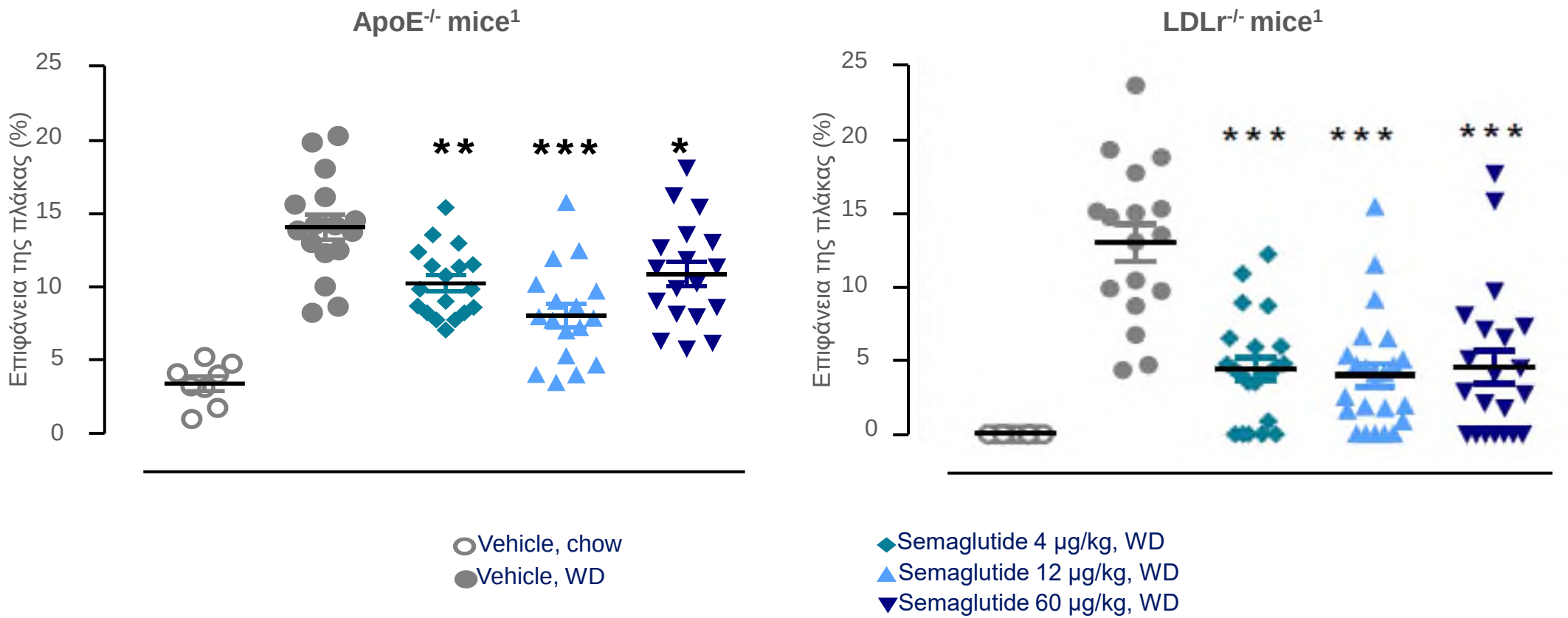
Στην EMPA-REG OUTCOME, τα οφέλη της θεραπείας με την εμπαγλιφλοζίνη προέκυψαν εντός λίγων εβδομάδων μετά την έναρξη

Τα οφέλη παρατηρήθηκαν πολύ νωρίς με τη μείωση κινδύνου να φτάνει τη στατιστική σημαντικότητα την :

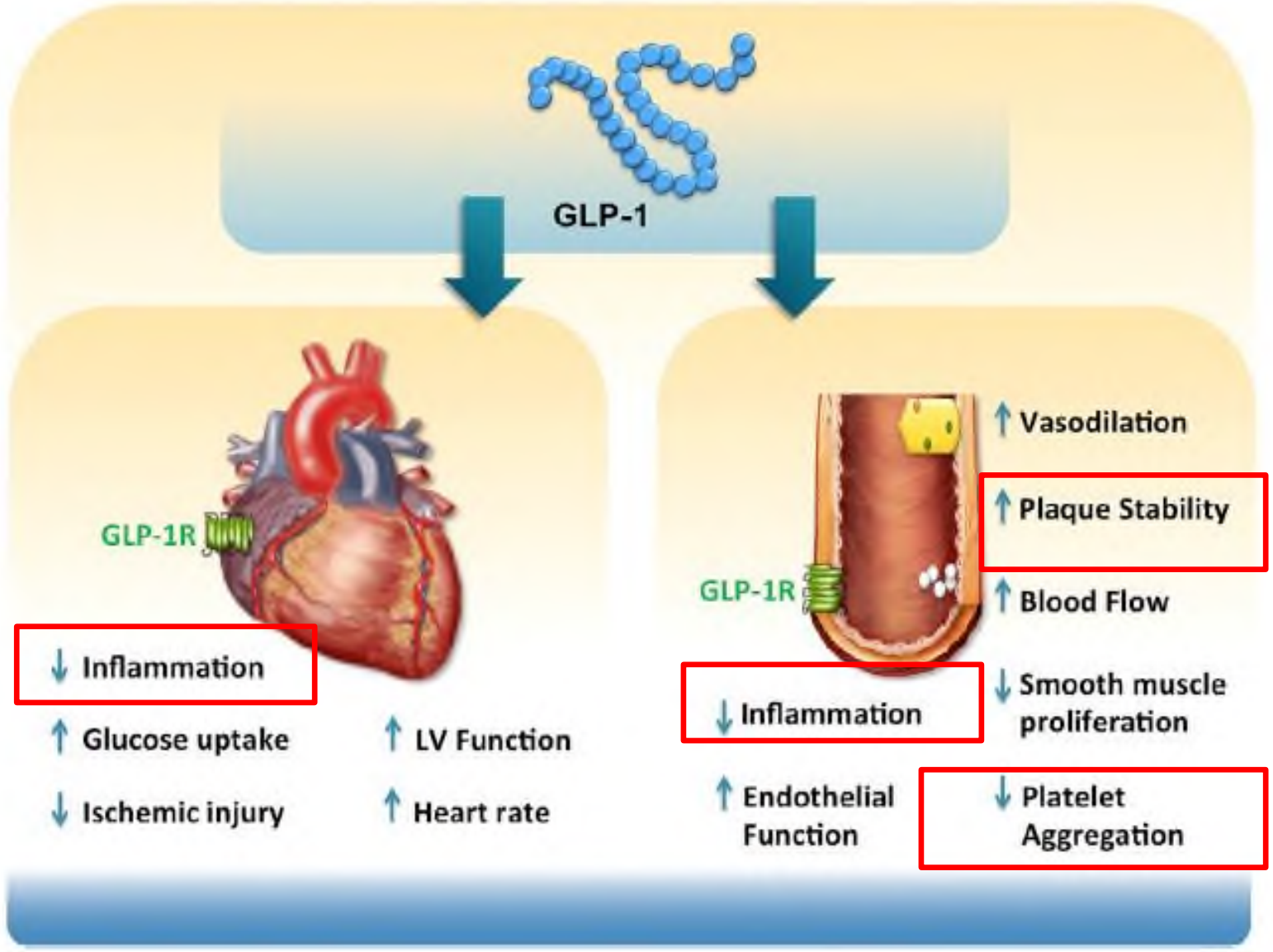
CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio.
Verma S, et al. ESC Heart Fail 2021; 8:2603–2607.

Η σεμαγλουτίδη έχει αντι-αθηροσκληρυντική δράση

ΕΛΑΤΤΩΣΗ ΤΟΥ ΕΜΒΑΔΟΥ ΤΗΣ ΠΛΑΚΑΣ ΣΕ ΠΕΙΡΑΜΑΤΙΚΑ ΜΟΝΤΕΛΑ ΤΗΣ ΑΘΗΡΟΣΚΛΗΡΥΝΣΗΣ



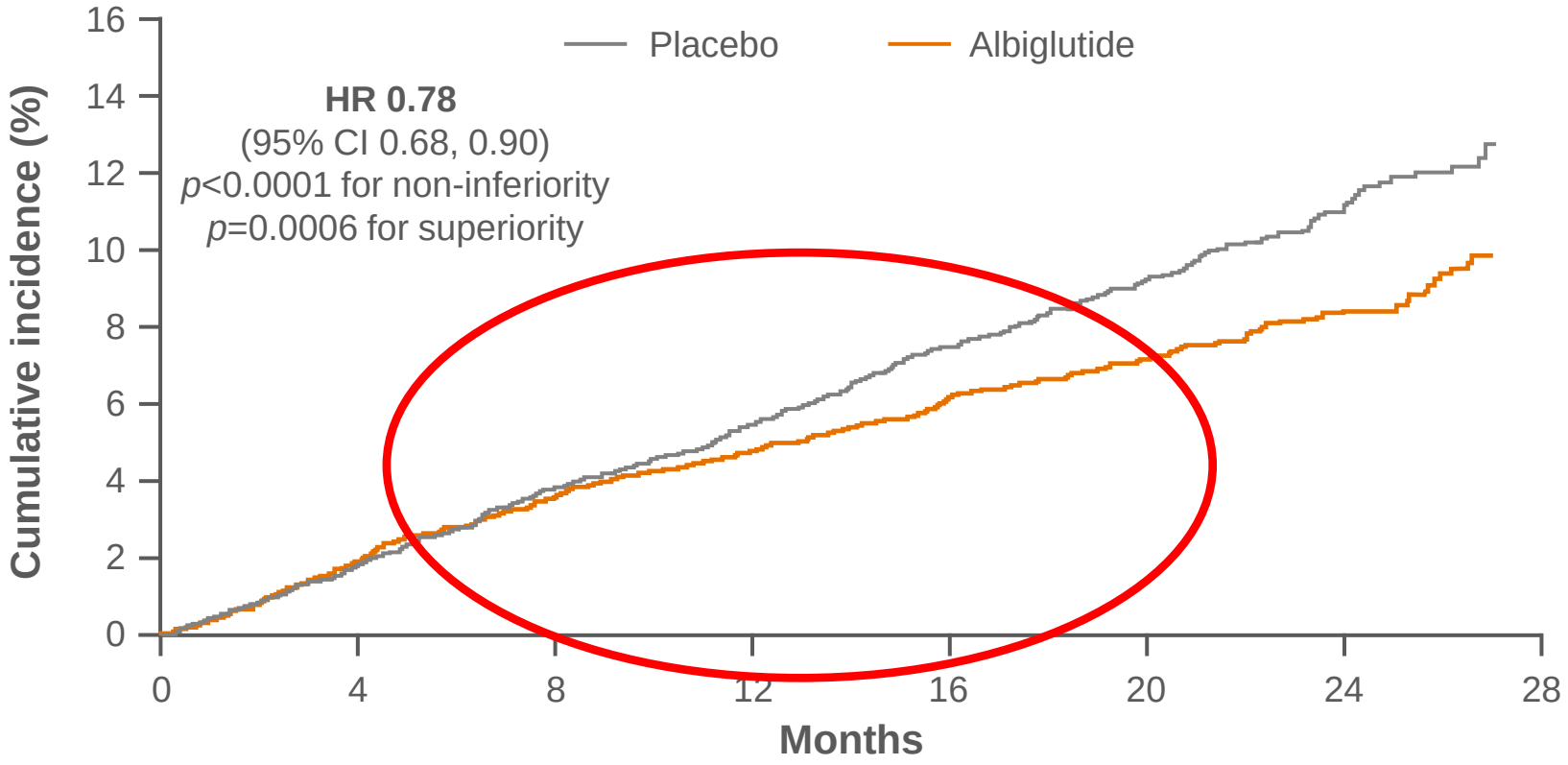
*p<0.05 vs vehicle WD; **p<0.01 vs vehicle WD; ***p<0.001 vs vehicle WD.
ApoE, apolipoprotein E; ApoE$^{-/-}$, ApoE knockout; LDLr, low-density lipoprotein receptor; LDLr$^{-/-}$, LDLr knockout; WD, western diet.
Rakipovski G et al. *JACC Basic Transl Sci* 2018;3:844–57.



Drucker D. Cell Metabol. 2016

Harmony Outcomes: Πρωτεύον τελικό σημείο

Η αλμπιγλουτίδη επέδειξε ανωτερότητα ως προς το 3P-MACE



No. at risk								
Placebo	4732	4603	4460	4208	3074	2077	1030	..
Albiglutide	4731	4613	4503	4239	3148	2142	1064	..

Intention-to-treat population. 3P-MACE, 3-point major adverse cardiovascular events; MI, myocardial infarction

Hernandez AF *et al. Lancet* 2018;392:1519

CV Outcome Trials of New T2D ADD (HR[95% CI])

	EMPA-REG OUTCOME®	CANVAS Program	DECLARE-TIMI 58	LEADER	SUSTAIN#	EXSCEL	Harmony Outcomes	REWIND	PIONEER 6##
3p-MACE	0.86 [0.74-0.99]	0.86 [0.75-0.97]	0,93 0,84-1,03	0.87 [0.78-0.97]	0.74 [0.58-0.95]	0.91 [0.83-1.00]	0.78 [0.68-0.90]	0.88 [0.79-0.99]	0.79 [0.57-1.11]
Non Fatal MI	0.87 [0.70-1.09]	0.85 [0.69-1.05]	0,89 [0,77-1,01]	0.88 [0.75-1,03]	0.74 [0.51-1.08]	0.95 [0.84-1.09]	0.75* [0.61-0.90]	0.96 [0.79-1.16]	1.18 [0.73- 1.90]
Non Fatal Stroke	1.24 [0.92-1.67]	0.90 [0.71-1.15]	1,01 [0,84-1,21]	0.89 [0.72-1.11]	0.61 [0.38-0.99]	0.86 [0.70-1.07]	0.86** [0.66-1.14]	0.76 [0.61-0.95]	0.74 [0.35-1.57]
CV Death	0.62 [0.49-0.77]	0.87 [0.72-1.06]	0,98 [0,82-1,17]	0.78 [0.66-0.93]	0.98 [0.65-1.48]	0.88 [0.76-1.02]	0.93 [0.73-1.19]	0.91 [0.78-1.06]	0.49 [0.27-0.92]
All Cause Mortality	0.68 [0.57-0.82]	0.87 [0.74-1.01]	0,93 [0,82-1,04]	0.85 [0.74-0.97]	1.05 [0.74-1.50]	0.86 [0.77-0.97]	0.95 [0.79-1.16]	0.90 [0.80-1.01]	0.51 [0.31-0.84]
Hospitalization for Heart Failure	0.65 [0.50-0.85]	0.67 [0.52-0.87]	0,73 [0,61-0,88]	0.87 [0.73-1.05]	1.11 [0.77-1.61]	0.94 [0.78-1.13]	0.85† [0.70-1.04]	0.93 [0.77-1.12]	0.86 [0.48-1.55]
Nephropathy	0.61 [0.53-0.70]	0.60 [0.47-0.77]	0,76 [0,67-0,87]	0.78 [0.67-0.92]	0.64 [0.46, 0.88]	---	---	0.85 [0.77-0.93]	---

Direct comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

SUSTAIN 6: Non-Inferiority Trial. Testing for superiority was not pre-specified.

PIONEER 6: Non-Inferiority Trial.

* Fatal or non-fatal myocardial infarction

** Fatal or non-fatal stroke

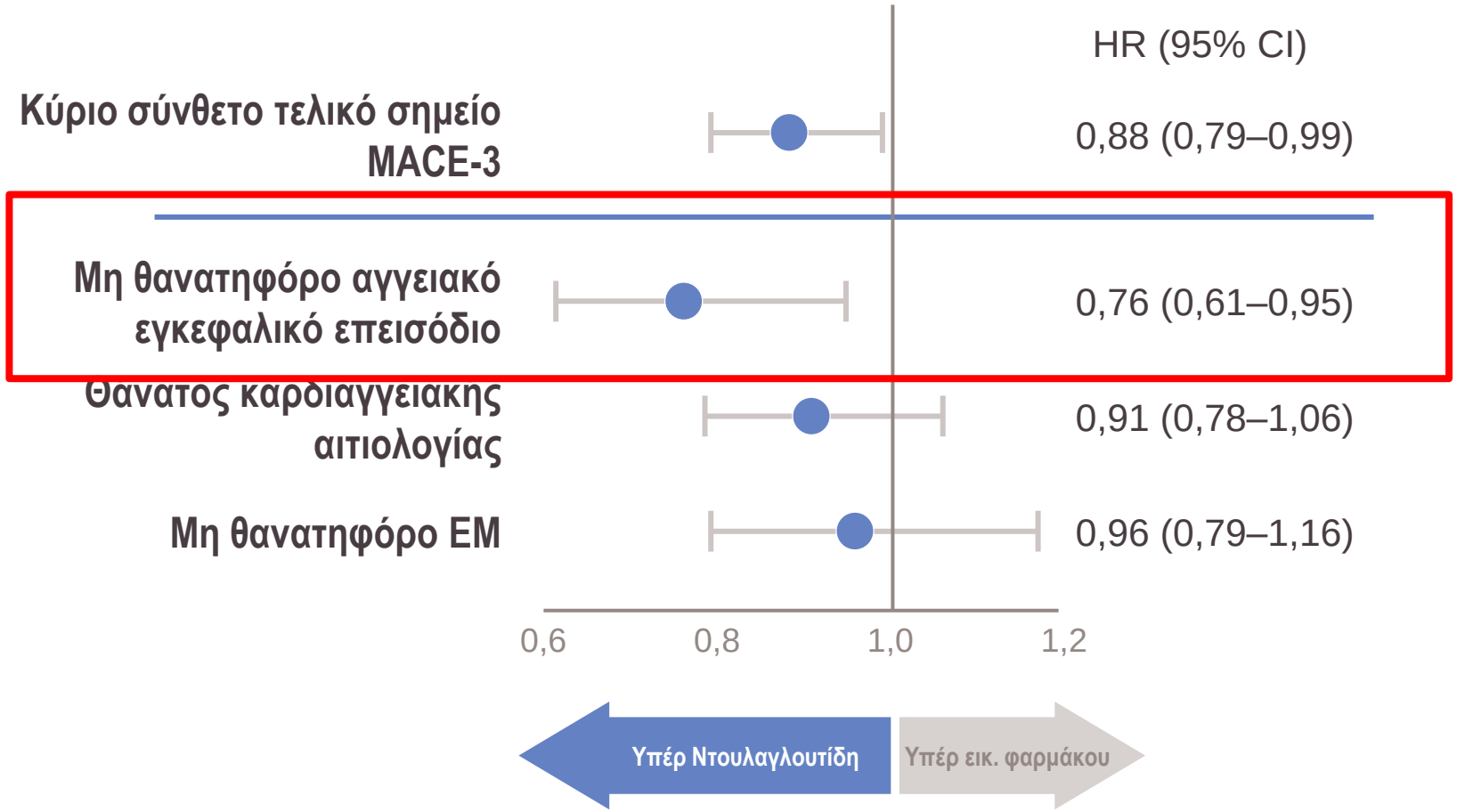
† Composite of Death from Cardiovascular causes or hospital admission for heart failure

Statistically significant

NOT Statistically significant

NOT Statistically tested for Superiority

REWIND



Βιβλιογραφική Αναφορά: 1. Gerstein HC et al. Lancet. 2019 Jun 7. pii: S0140-6736(19)31149-3. doi: 10.1016/S0140-6736(19)31149-3. [Epub ahead of print].

J Clin Endocrinol Metab. 2022 Mar 5;dgac116. doi: 10.1210/clinem/dgac116. Online ahead of print.

Antiatherosclerotic effects of sodium–glucose cotransporter 2 inhibitors: An underrecognized piece of the big puzzle?

Theocharis Koufakis [1], Prashanth Vas [2 3 4], Giuseppe Maltese [5 6], Kalliopi Kotsa [1]

Affiliations – collapse

Affiliations

1 Division of Endocrinology and Metabolism and Diabetes Centre, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece.
2 King's College NHS Foundation Trust, London, UK.
3 King's Health Partners' Institute of Diabetes, Endocrinology and Obesity, London, UK.
4 Department of Diabetes, School of Life Course Sciences, King's College London, London, UK.
5 Department of Diabetes and Endocrinology, Epsom & St Helier University Hospitals, Surrey, UK.
6 Unit for Metabolic Medicine, Cardiovascular Division, Faculty of Life Sciences & Medicine, King's College, London, UK.

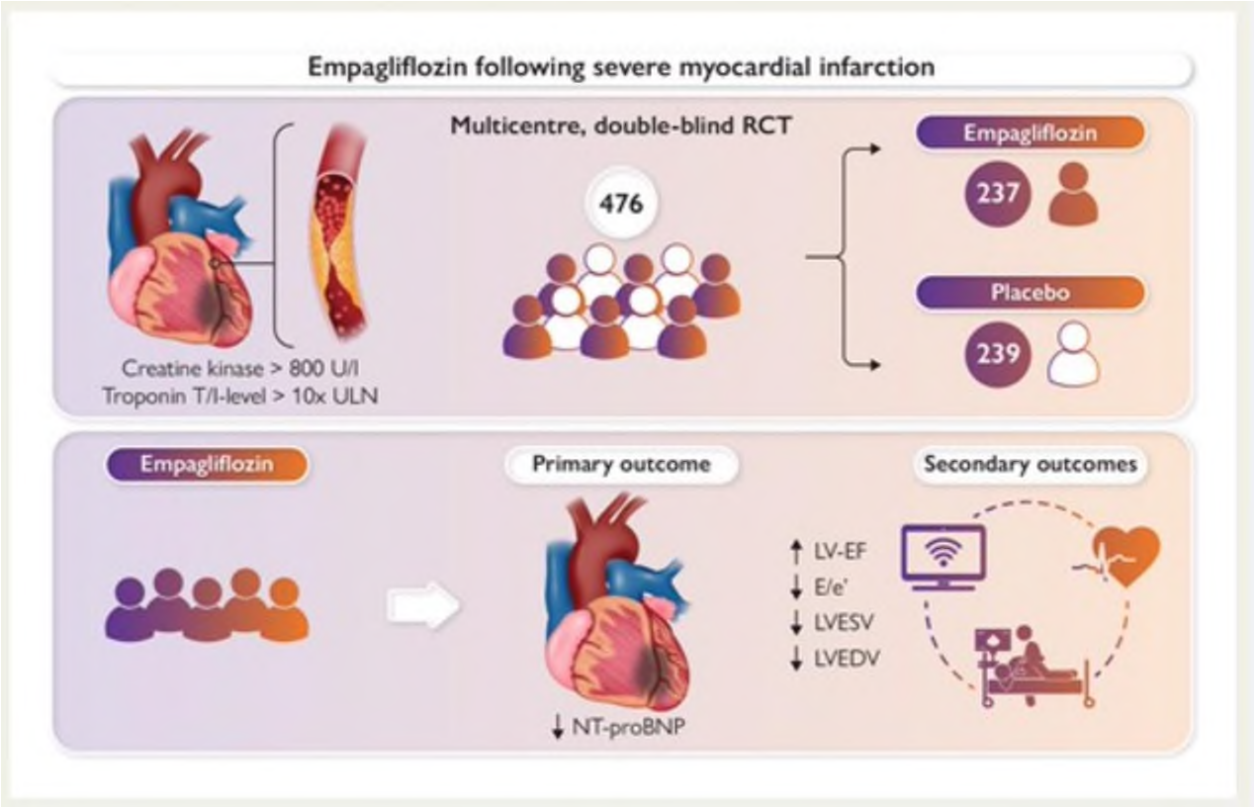
JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Empagliflozin in acute Myocardial Infarction: the EMMY trial

Dirk von Lewinski ✉, Ewald Kolesnik, Norbert J Tripolt, Peter N Pferschy, Martin Benedikt, Markus Wallner, Hannes Alber, Rudolf Berger, Michael Lichtenauer, Christoph H Saely ... Show more

European Heart Journal, ehac494, https://doi.org/10.1093/eurheartj/ehac494

Published: 29 August 2022 **Article history** ▾



EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2022.2113385

Taylor & Francis
Taylor & Francis Group

SPECIAL REPORT

Dual sodium-glucose cotransporter (SGLT) 1/2 versus pure SGLT2 inhibitors: two distinct drug categories or one class with multiple faces?

Theocharis Koufakis [a], Michael Doumas[b], Pantelis Zebekakis [a] and Kalliopi Kotsa [a]

[a]Division of Endocrinology and Metabolism and Diabetes Center, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece; [b]Second Propedeutic Department of Internal Medicine, Hippokration General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

ABSTRACT

Introduction: According to their selectivity for sodium-glucose cotransporters (SGLT) 1 and 2, gliflozins could be subdivided into two additional categories: pure SGLT2 inhibitors, which are highly selective for SGLT2, and dual SGLT1/2 inhibitors which, in addition to SGLT2, exhibit strong inhibitory activity for SGLT1.

Areas covered: This article aims to discuss whether the pharmacological differences between the two subtypes of gliflozins could be translated into different efficacy and safety characteristics that might be important for clinical practice.

Expert Opinion: In large cardiovascular outcome trials, dual inhibitors have shown a unique efficacy profile in terms of reducing glycemia in patients with severe renal impairment and decreasing the risk of atherosclerotic outcomes. These features do not characterize selective SGLT2 inhibitors and could be attributed to the parallel inhibition of SGLT1. The increased risk of diarrhea and severe hypoglycemia observed only with dual inhibitors is probably related to their action in the gut and brain, respectively. However, differences in populations included in various studies should be considered when attempting to translate their findings into clinical practice; therefore, head-to-head trials are needed to shed more light on this issue and provide clear guidance to clinicians.

ARTICLE HISTORY

Received 25 May 2022
Accepted 11 August 2022

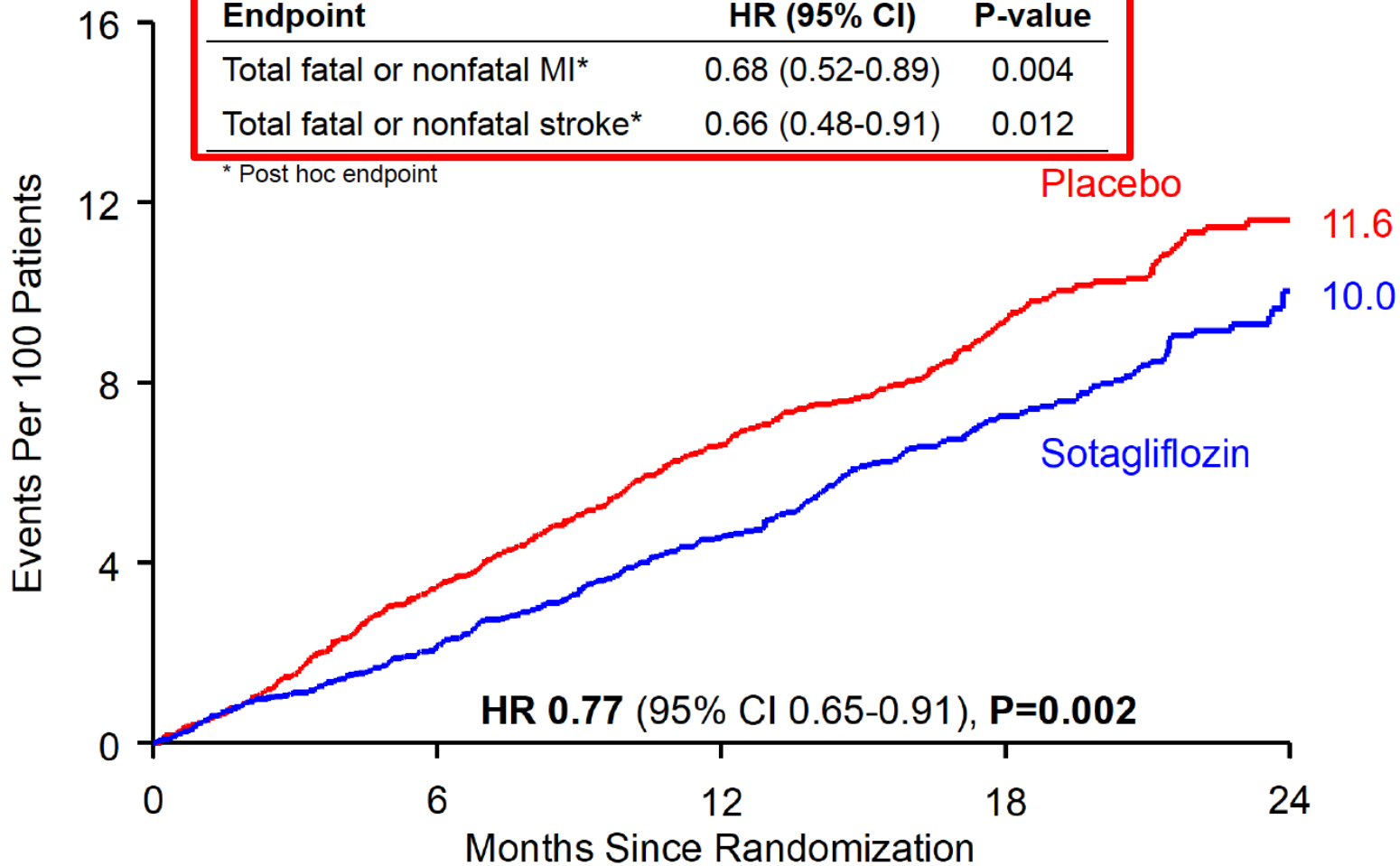
KEYWORDS

SGLT2 inhibitors; cardiometabolic outcomes; hypoglycemia; sotagliflozin

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

Endpoint	HR (95% CI)	P-value
Total fatal or nonfatal MI*	0.68 (0.52-0.89)	0.004
Total fatal or nonfatal stroke*	0.66 (0.48-0.91)	0.012

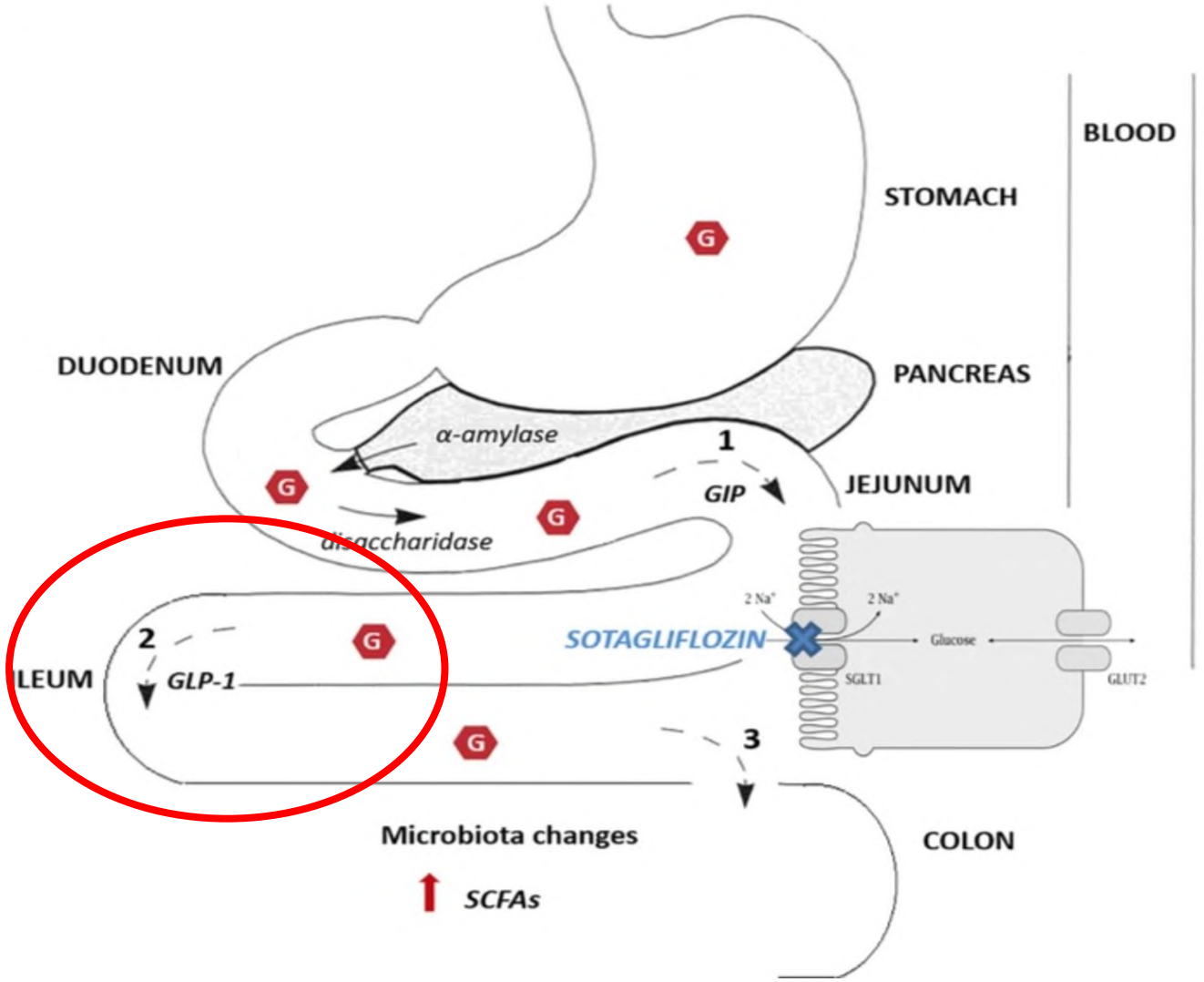
* Post hoc endpoint



Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Αύξηση ενδογενούς GLP-1

Fig. 3



Cefalo et al. Cardiovasc Diabetol 2019

Drugs. 2021 Aug;81(12):1365-1371. doi: 10.1007/s40265-021-01559-1. Epub 2021 Jul 7.

Insights Into the Results of Sotagliflozin Cardiovascular Outcome Trials: Is Dual Inhibition the Cherry on the Cake of Cardiorenal Protection?

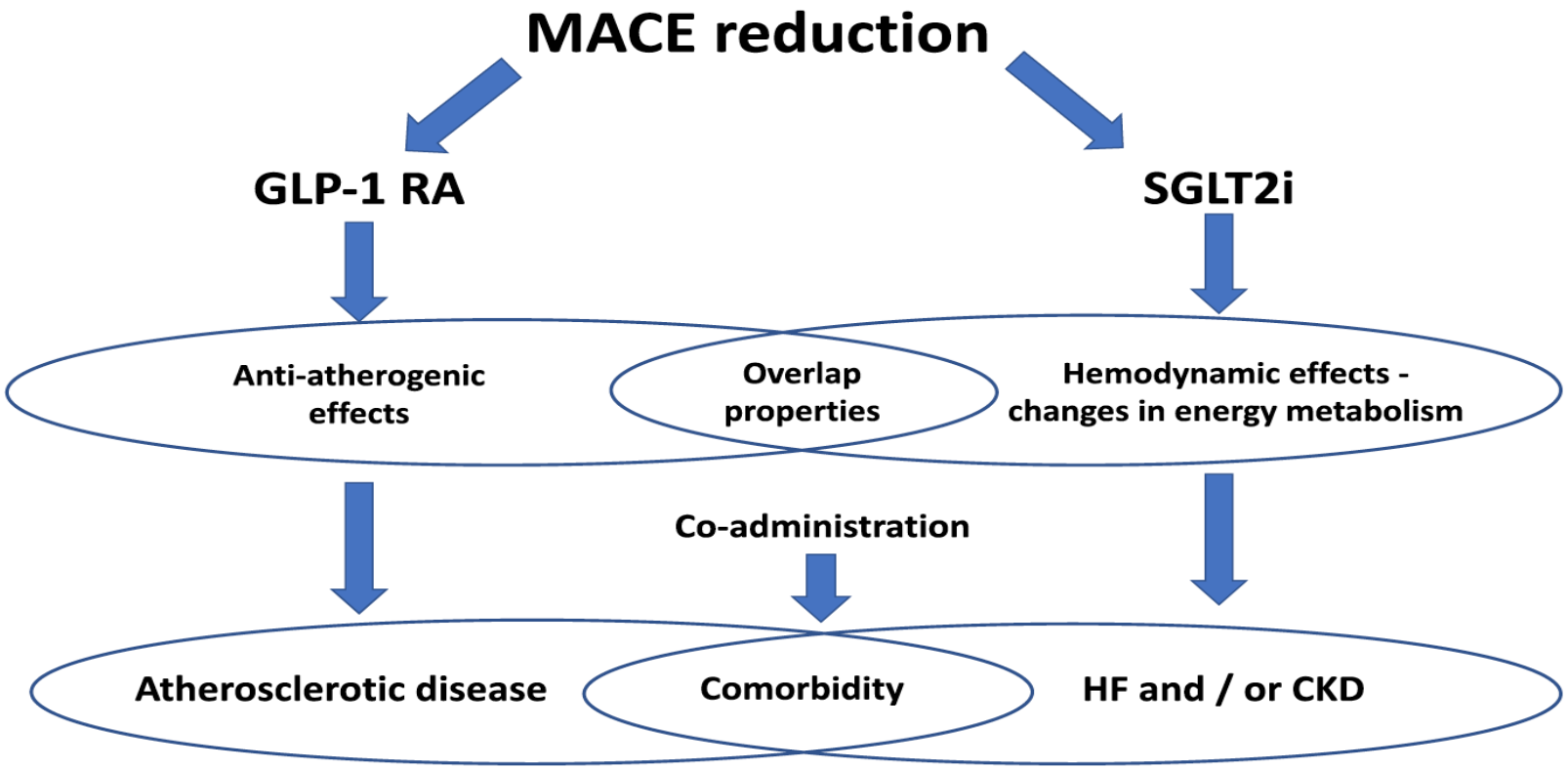
Theocharis Koufakis [1], Omar G Mustafa [2], Vasilios Tsimihodimos [3], Ramzi A Ajjan [4], Kalliopi Kotsa [5]

Key Points
SOLOIST-WHF and SCORED explored the effects of sotagliflozin on cardiorenal outcomes.
The results reconfirm the class effects of SGLT2i but also differentiate sotagliflozin from other agents.
Dual SGLT inhibition might contribute to the unique safety and efficacy profile of the drug.

> Am J Cardiovasc Drugs. 2022 Mar 15. doi: 10.1007/s40256-022-00527-8. Online ahead of print.

A Horse, a Jockey, and a Therapeutic Dilemma: Choosing the Best Option for a Patient with Diabetes and Coronary Artery Disease

Theocharis Koufakis [1], Evangelos N Liberopoulos [2], Kalliopi Kotsa [3]



Koufakis et al. Am J Cardiovasc Drugs 2022

Editorial > Expert Rev Clin Pharmacol. 2021 Oct;14(10):1189-1192.
doi: 10.1080/17512433.2021.1942843. Epub 2021 Jun 19.

Treatment options following metformin in primary prevention populations with type 2 diabetes: which is the right road to take?

Theocharis Koufakis [1], Nikolaos Papanas [2], Pantelis Zebekakis [1], Kalliopi Kotsa [1]

"*Considering that life with diabetes is more of a **marathon** than a sprint, many people with T2D will eventually need **both classes** to control their **blood glucose levels** and address **cardiorenal complications***"

Koufakis et al. Expert Rev Clin Pharmacol 2021

Circulation

EDITORIAL

Why Choose Between SGLT2 Inhibitors and GLP1-RA When You Can Use Both?

The Time to Act Is Now

Article, see p 770

Alice Y.Y. Cheng, MD

SGLT2i ή GLP-1 RA ?

Ποιος διάσημος θα ήταν οι SGLT2i;

Ποιος διάσημος θα ήταν οι GLP-1 RA;


6

Συμπεράσματα

- **Μετφορμίνη:** πιθανά ωφέλιμη ή τουλάχιστον ασφαλής
- Έλλειψη δεδομένων από μεγάλες RCTs

- **SUs:** Μεγάλη ετερογένεια
- Πρόβλημα η υπογλυκαιμία
- Καλό είναι να αποφεύγονται σε high risk

- **TZDs:** Pio ωφέλιμη vs Rosi επιβλαβής;
- Προσοχή στην ΚΑ

- **Ινσουλίνη:** ουδέτερη
- Προσοχή σε ΚΑ και υπογλυκαιμία

Take home messages

- Η προστασία από τις καρδιαγγειακές επιπλοκές έχει κεντρικό ρόλο στο νέο μοντέλο διαχείρισης της νόσου

- Τα GLP-1 ανάλογα αποτελούν την πρώτη θεραπευτική επιλογή σε ασθενείς με ΑΕΕ-ΣΝ

- Οι SGLT2i χορηγούνται σαν 2η επιλογή ή συγχορηγούνται σε περίπτωση συννοσηροτήτων (πχ ΚΑ, ΧΝΝ)

Koufakis et al. Pharmacol Res 2022

Koufakis et al. Cardiovasc Drugs Ther 2021

Review > Cardiovasc Drugs Ther. 2023 Apr;37(2):315-321. doi: 10.1007/s10557-021-07249-0.
Epub 2021 Sep 3.

Sodium-Glucose Co-transporter 2 Inhibitors Versus Metformin as the First-Line Treatment for Type 2 Diabetes: Is It Time for a Revolution?

Theocharis Koufakis [1], Athanasia Papazafiropoulou [2], Konstantinos Makrilakis [3], Kalliopi Kotsa [4]

Affiliations + expand

PMID: 34476668 DOI: 10.1007/s10557-021-07249-0

Γιατί να χρησιμοποιήσω φάρμακα:

- Χωρίς καρδιονεφρικά οφέλη
- Με μεγάλο κίνδυνο υπογλυκαιμίας
- Με αρνητική ή ουδέτερη επίδραση στο βάρος

Koufakis et al. Cardiovasc Drugs Ther 2021

“***If you have always done it that way, it is probably wrong***”

Charles Kettering, 1876-1958