I Nuovi Farmaci Antidiabetici

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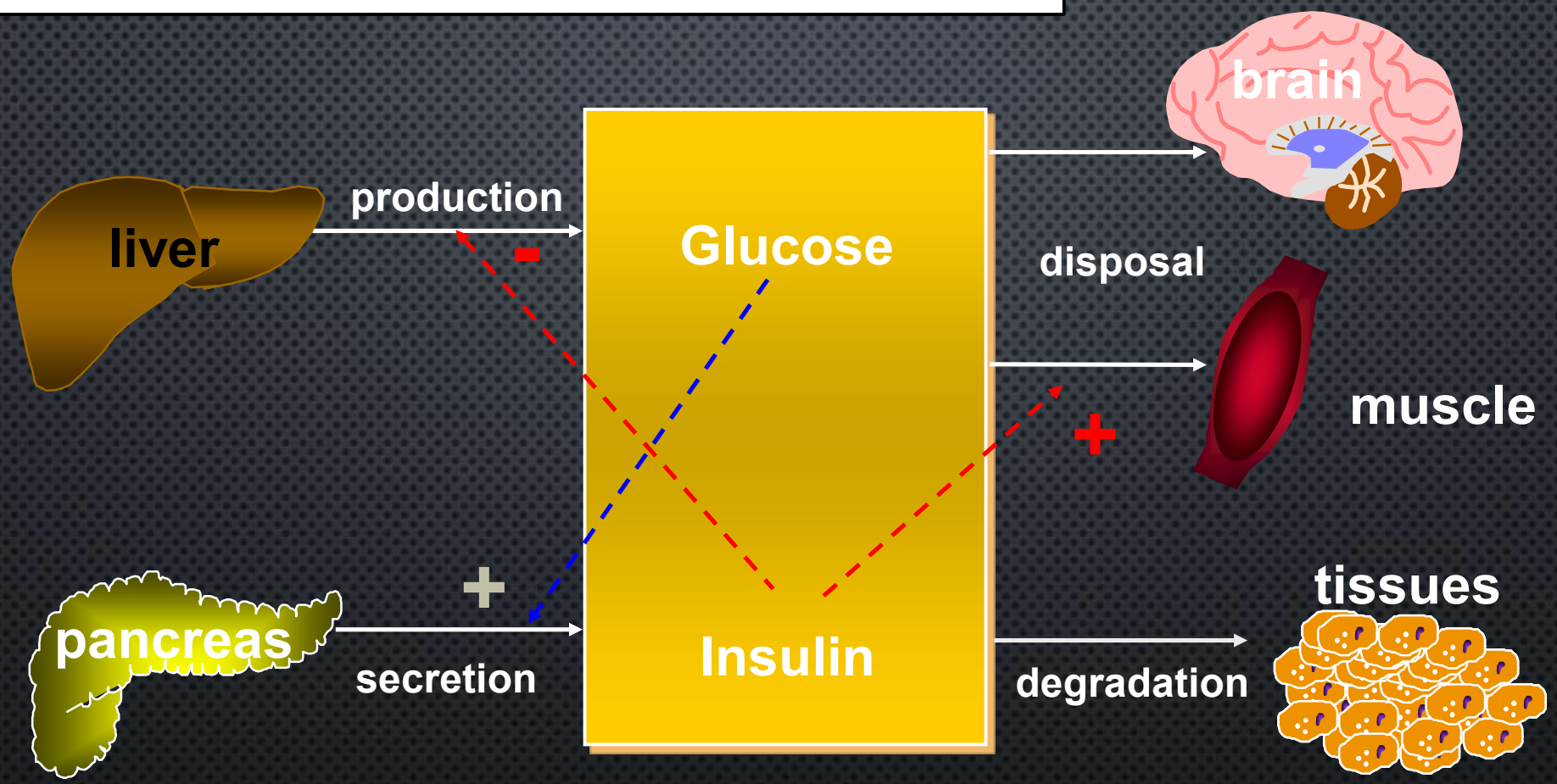
PRENDIAMOCI A CUORE IL RENE

Milano, 2 Dicembre 2016

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Astra Zeneca (Advisory Board)
- BMS (Advisory Board)
- Johnson & Johnson (Advisory Board)
- Gelesis (Research support)
- MOVI (Research support)
- Novo-Nordisk (Speaker, research support)
- Sunstar (Speaker, research support)
- Menarini Diagnostics(Speaker)
- Eli Lilly (Speaker)
- Sanofi (Speaker)
- Sigma Tau (Speaker)
- McKinsey & Co. (Consultant)

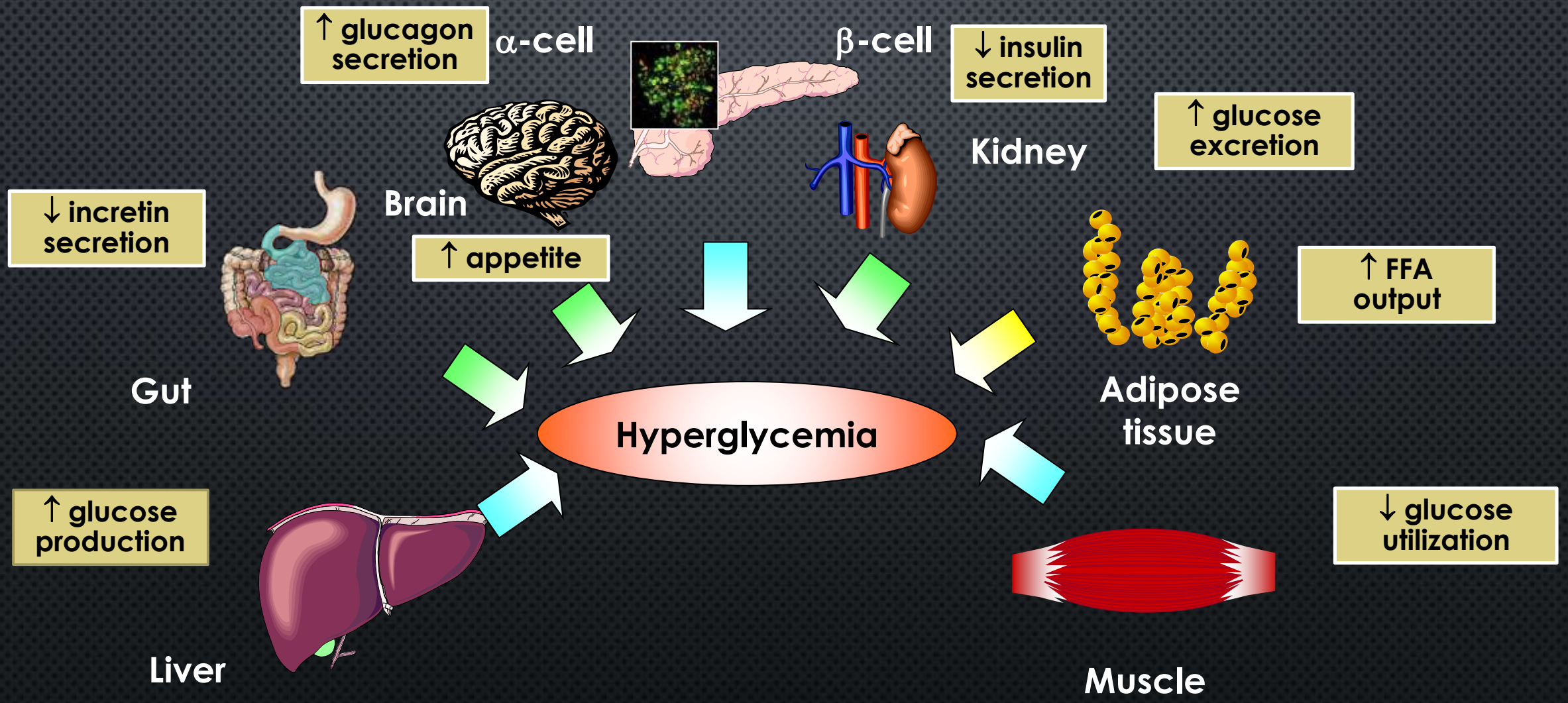
THE GLUCOSE - INSULIN SYSTEM



Beta-cell function: ϕ

Insulin sensitivity: S_I

Type 2 Diabetes Mellitus: Pathophysiology

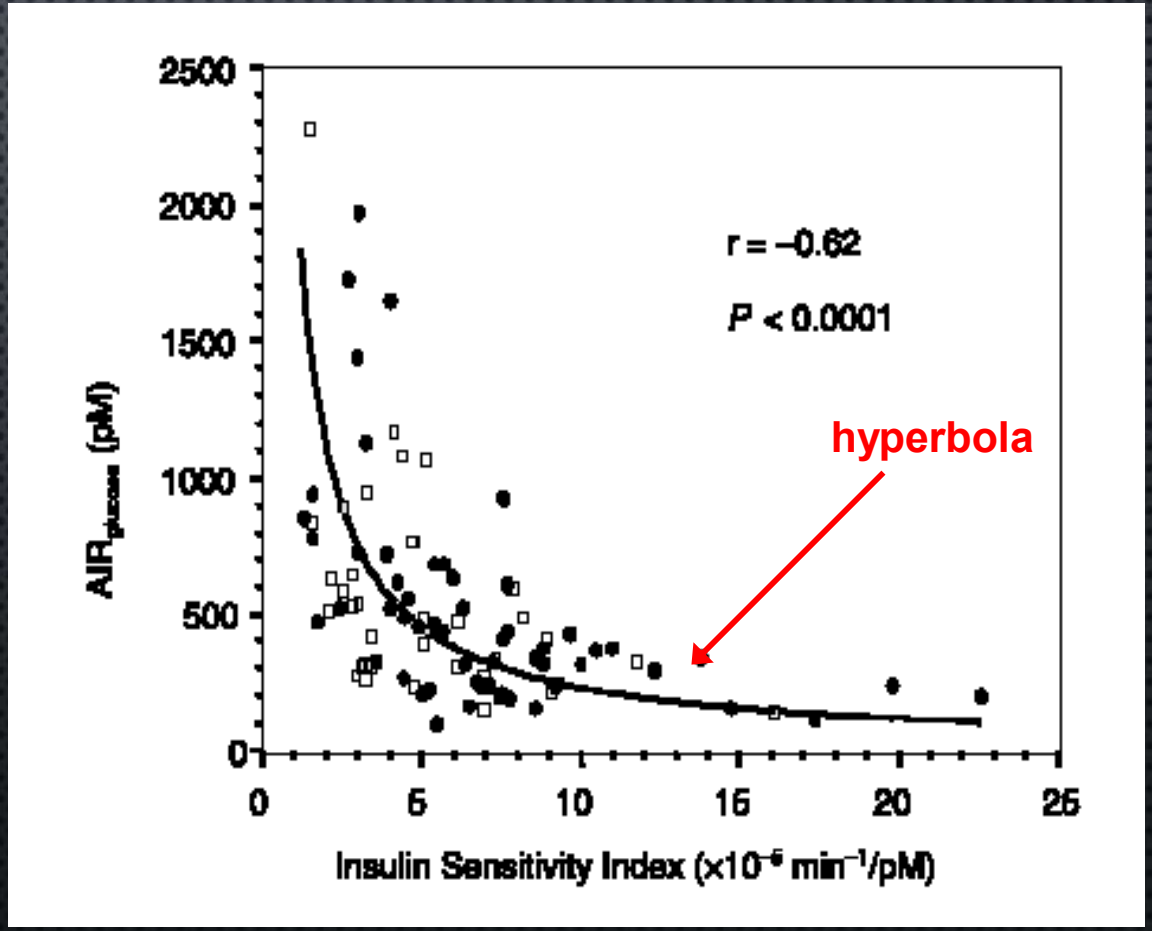


De Fronzo RA et al, Diabetes 2009; 58: 773–795

The Relationship between Insulin Sensitivity and Beta-cell Secretion is Hyperbolic

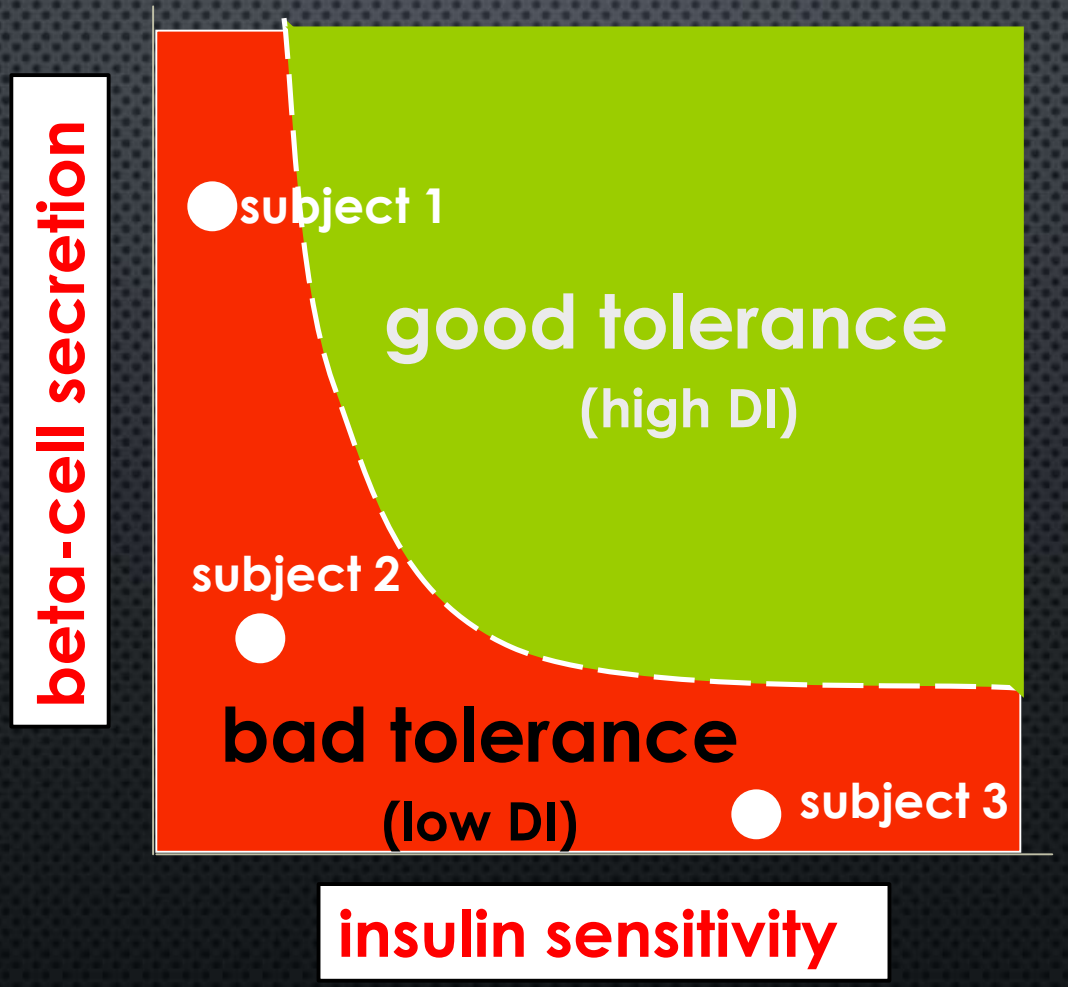
The product **insulin sensitivity** **x** **beta-cell function** tends to remain **CONSTANT** in normal subjects (*).

The relationship between insulin sensitivity and beta-cell function is thus **hyperbolic**.



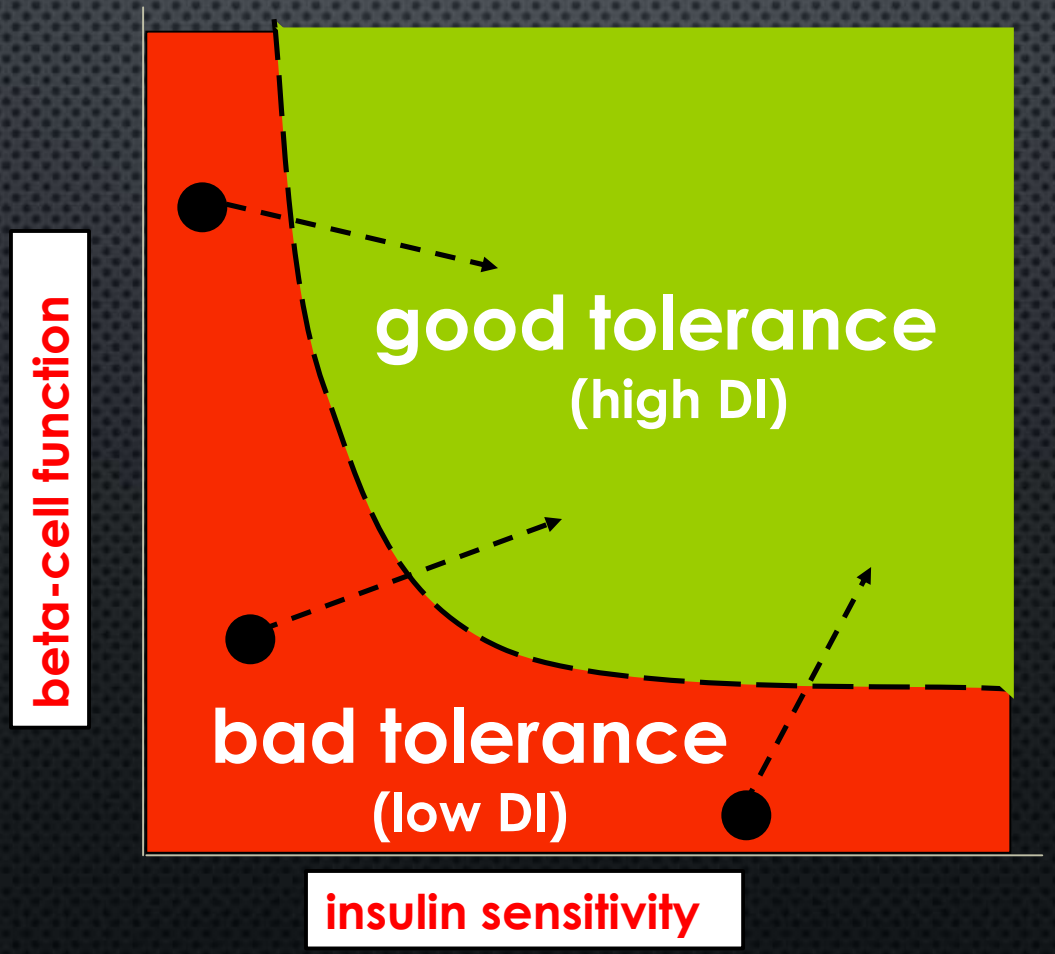
(*) Kahn et al. - *Diabetes*, 1993

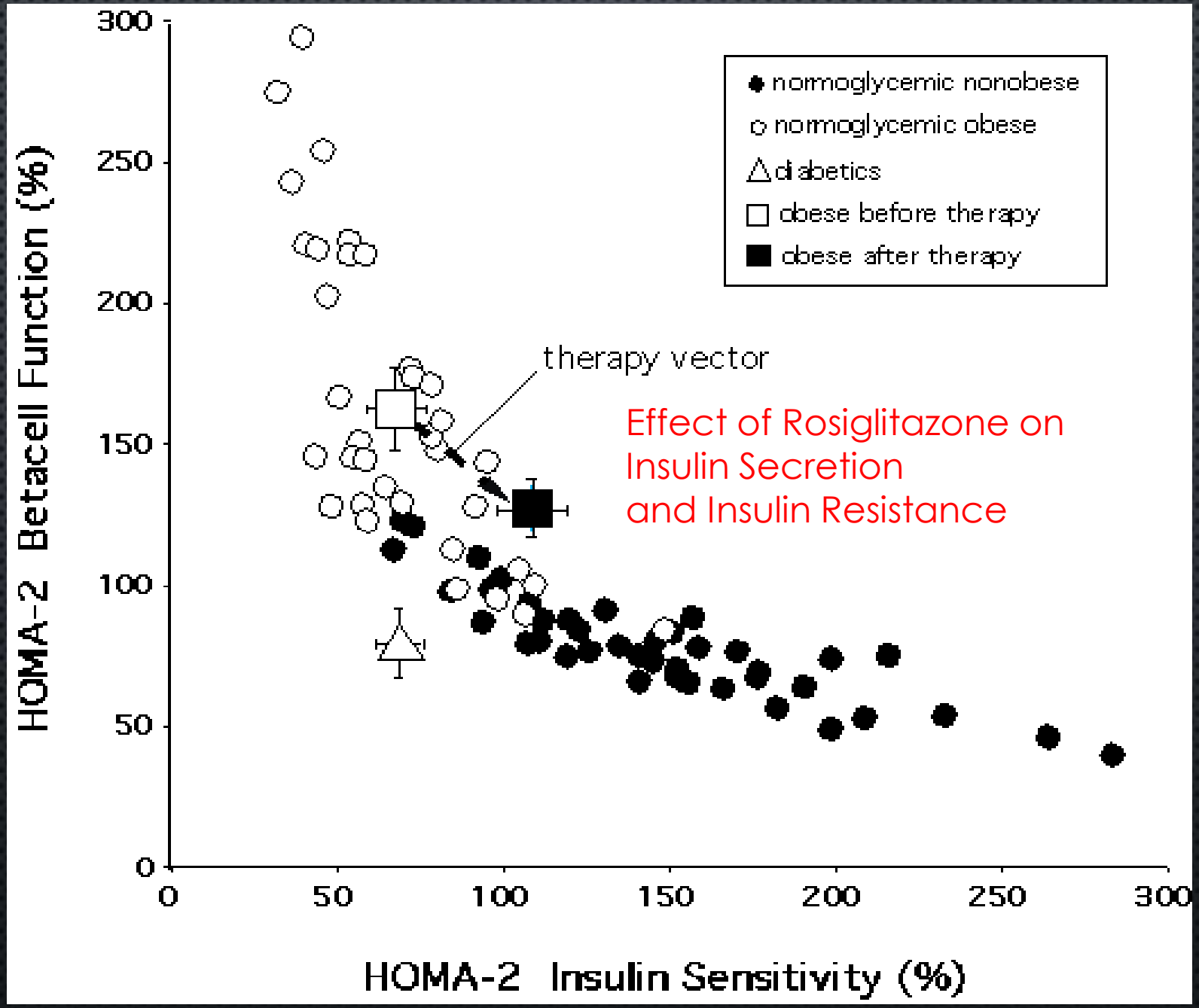
Bad tolerance: need for therapy



Aim of Therapy of Type 2 Diabetes

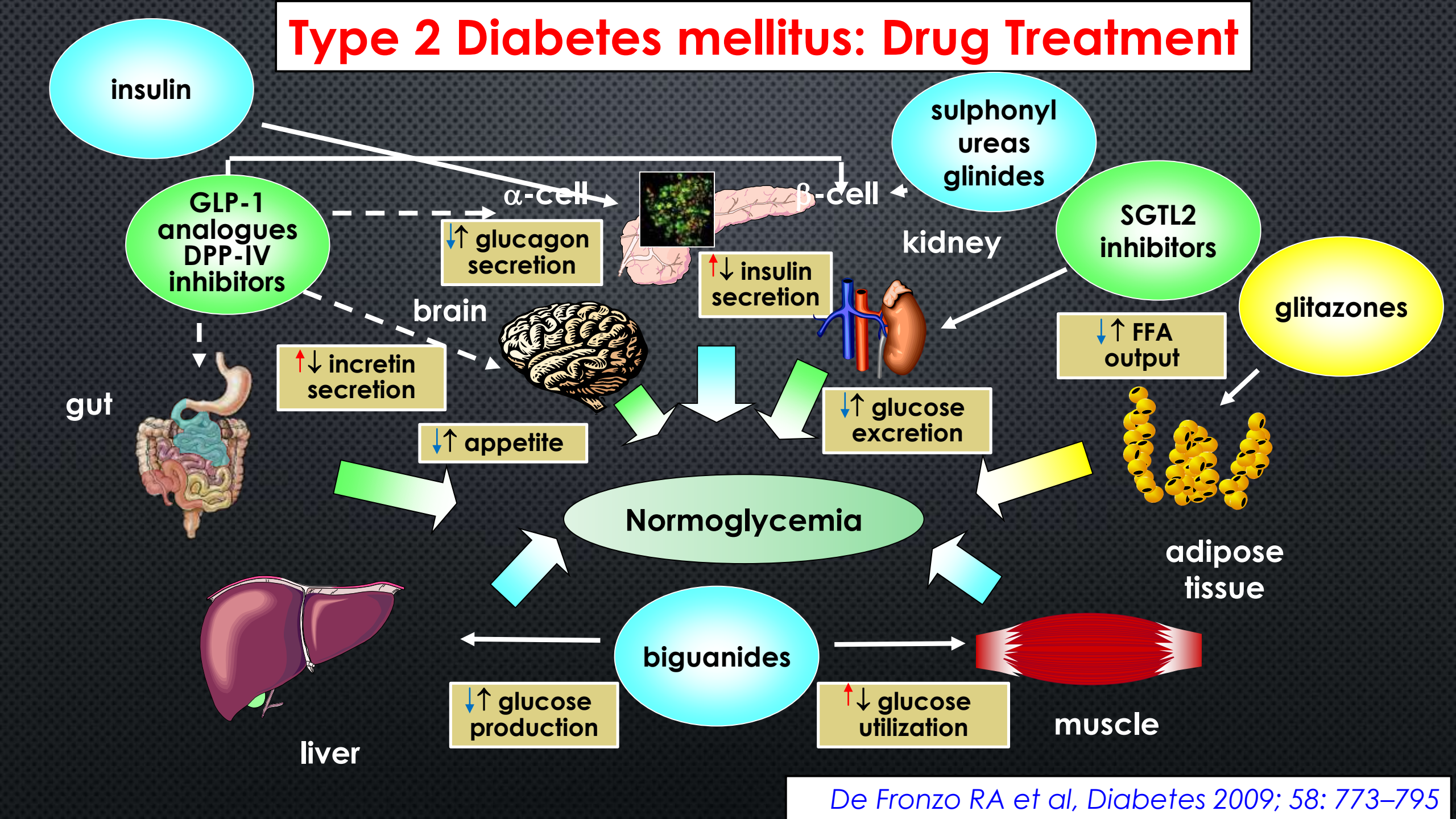
The aim of therapy is to **move** patients from the **bad** tolerance region to the **good** one



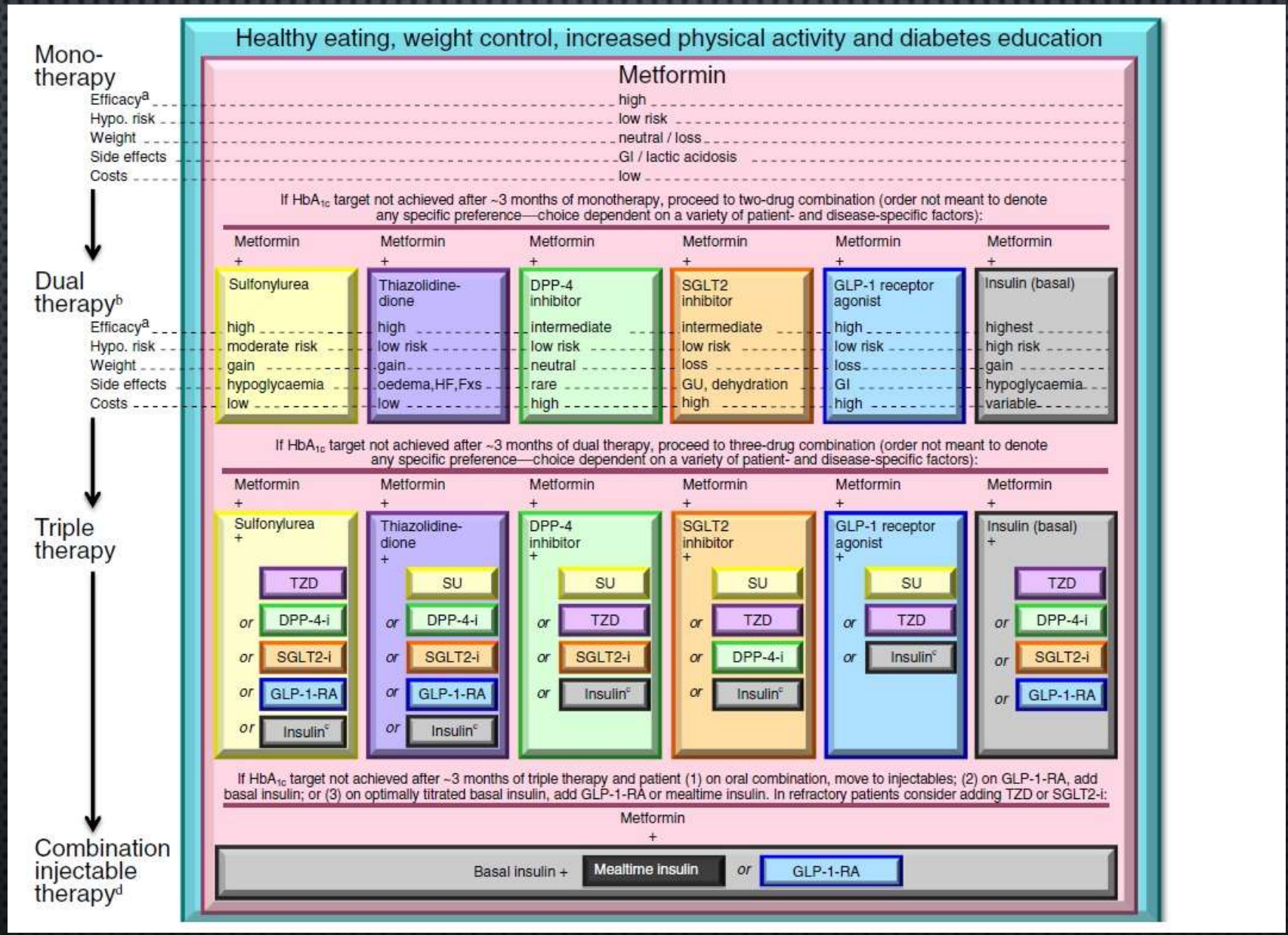


Caumo et al, Diabetes Care, 2006

Type 2 Diabetes mellitus: Drug Treatment



De Fronzo RA et al, Diabetes 2009; 58: 773–795

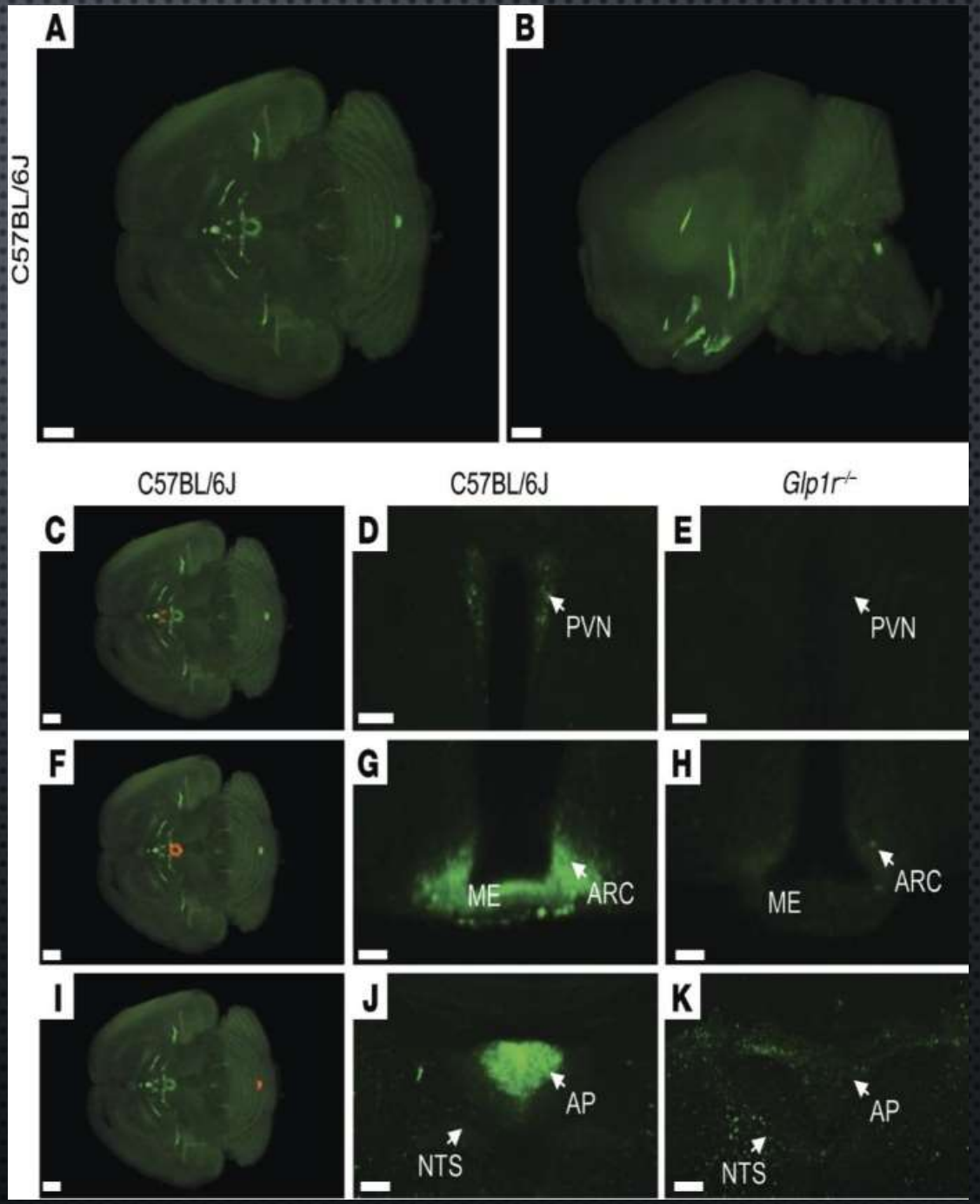


Diabetologia 2015;58:429-442

Analoghi GLP-1 ed Inibitori SGLT-2

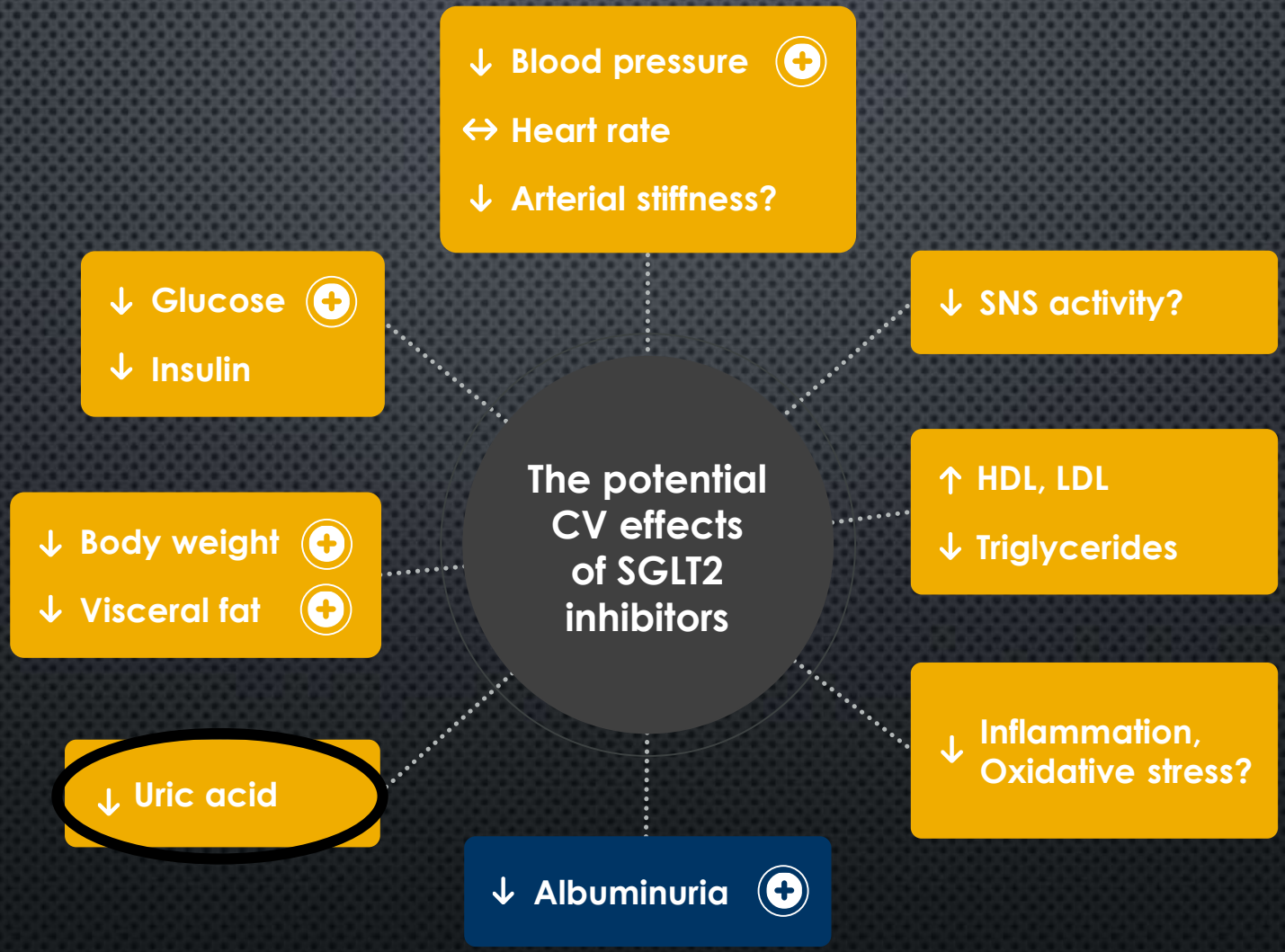
1. Effetto sui fattori di rischio cardiovascolari
2. Effetto sulla mortalità cardiovascolare
3. Effetto potenziale nefroprotettivo

Liraglutide & weight loss

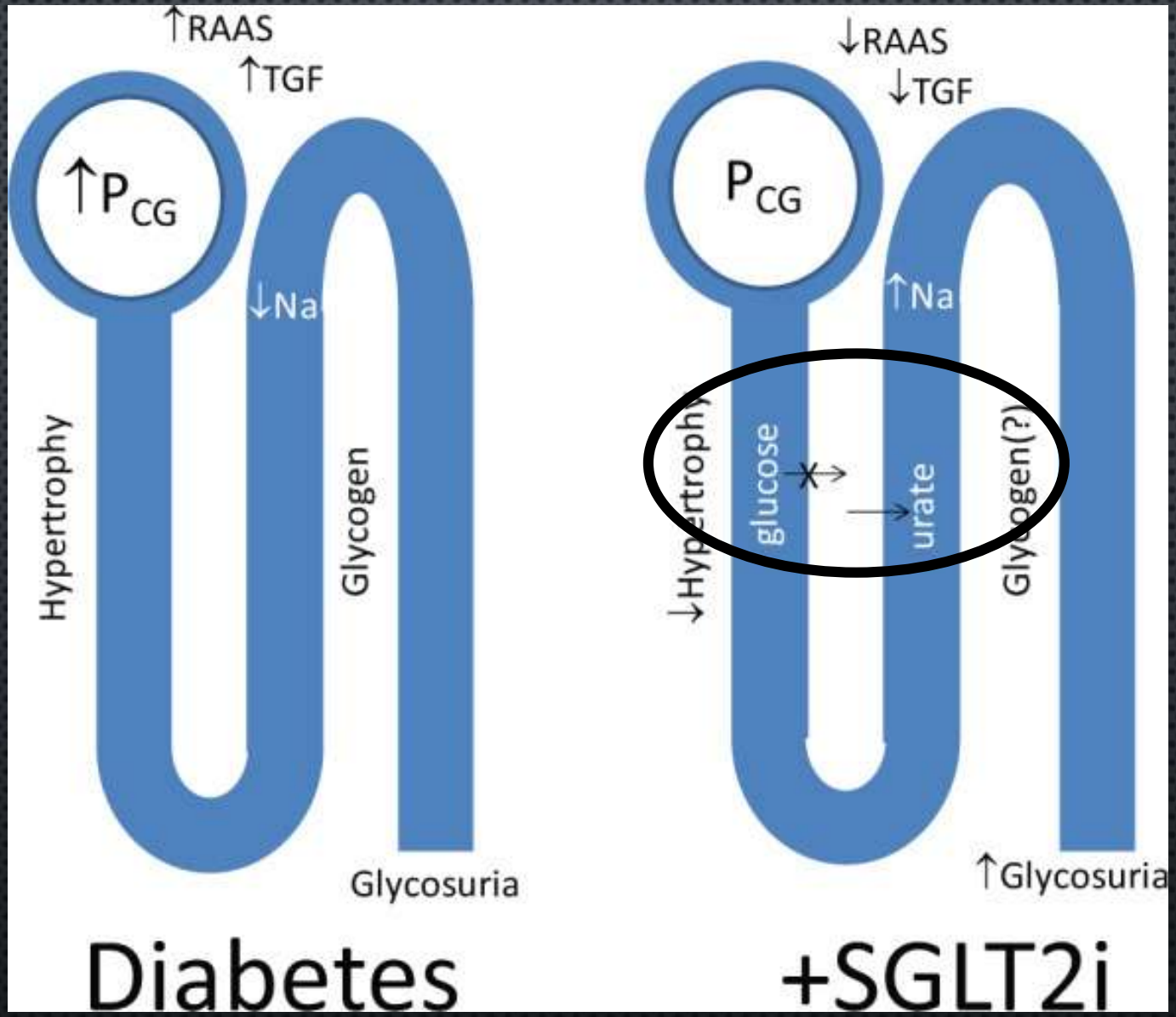


Secher A et al, J Clin Invest, 2014

SGLT2 inhibitors can reduce CV risk factors

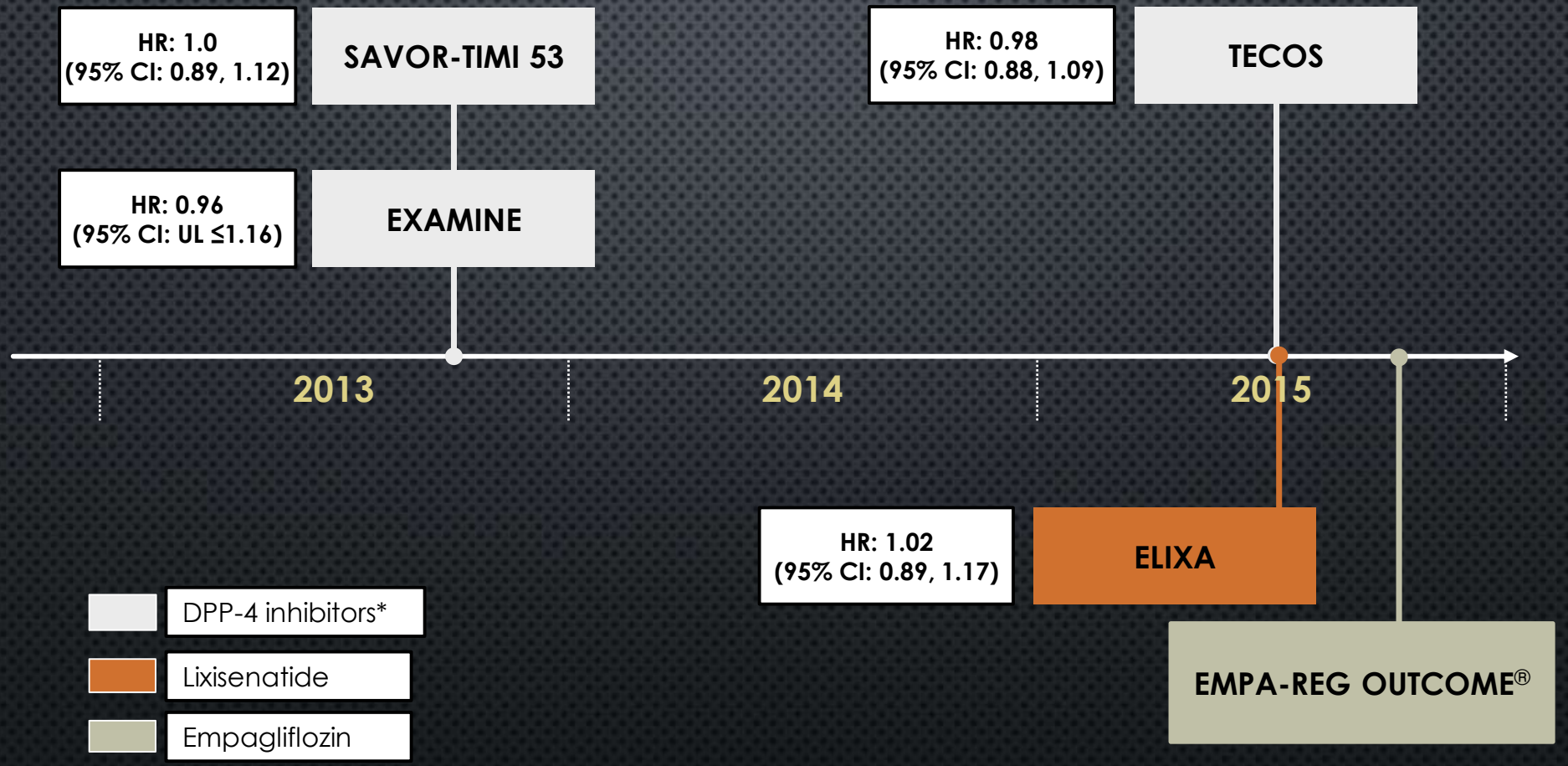


1. Inzucchi SE, *et al. Diab Vasc Dis Res.* 2015;12:90–100. 2. Majewski C *et al. Diabetes Care*. 2015;38:429-430. 3. Cherney DZ *et al. Cardiovascular Diabetology*. 2014,13:28–36.



Merlin CT, Ther. Adv. Endoc. Metab., 2014

Recent trials of newer glucose-lowering agents have been neutral on the primary CV outcome



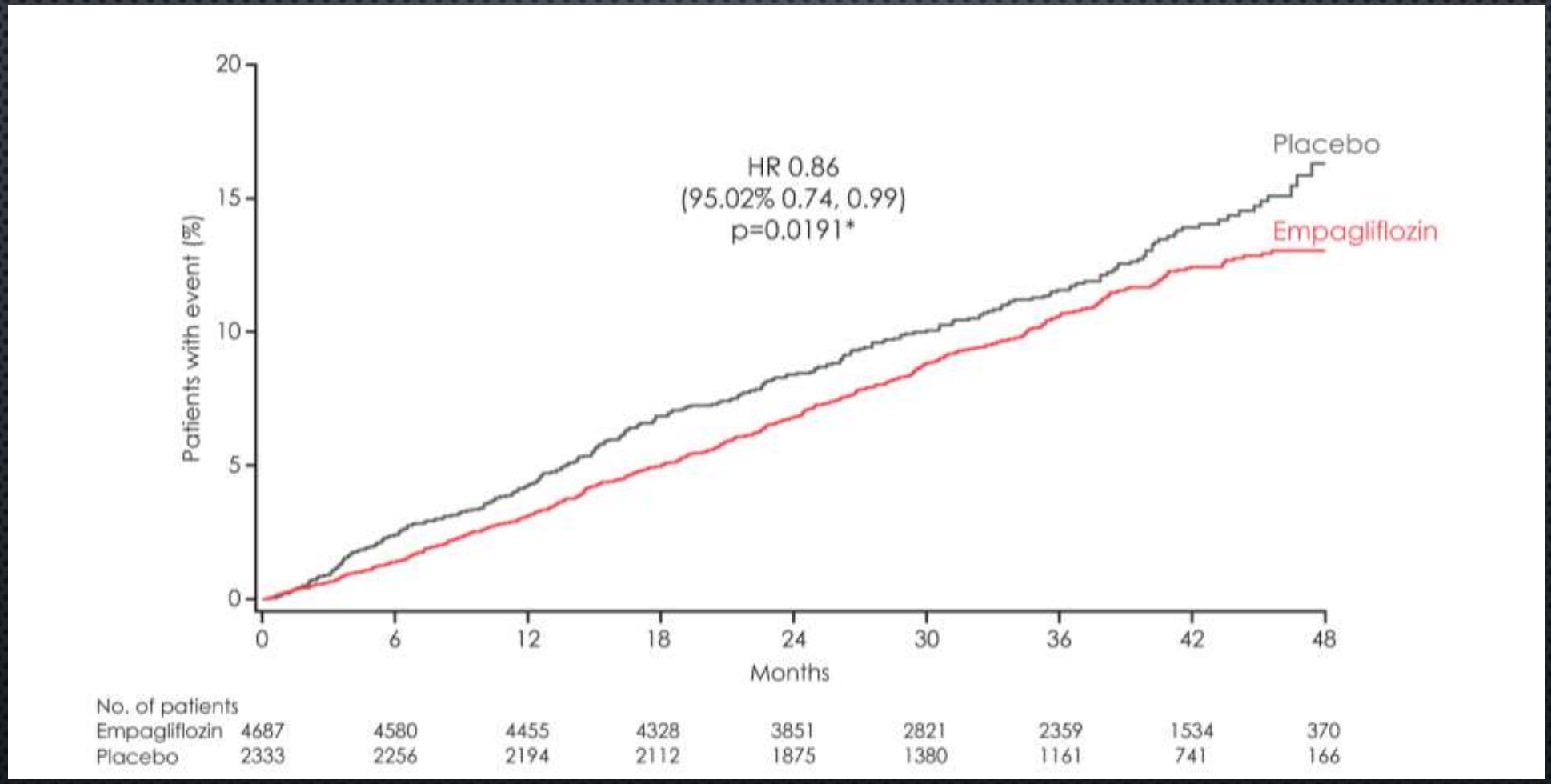
From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

CV, cardiovascular; HR, hazard ratio; DPP-4, dipeptidyl peptidase-4
*Saxagliptin, alogliptin, sitagliptin. Adapted from Johansen OE. World J Diabetes 2015;6:1092-96

Nuovi Farmaci per la Terapia del Diabete Mellito di Tipo 2
I Trials sugli Effetti Cardiovascolari: 2008-2016

- 1. Inibitori DPP-4
  - *SAVOR, TECOS, EXAMINE*
- 2. Analoghi recettoriali del GLP-1
  - *ELIXA, LEADER, SUSTAIN-6, REWIND*
- 3. Inibitori SGLT-2
  - *EMPA-REG, CANVAS, DECLARE*

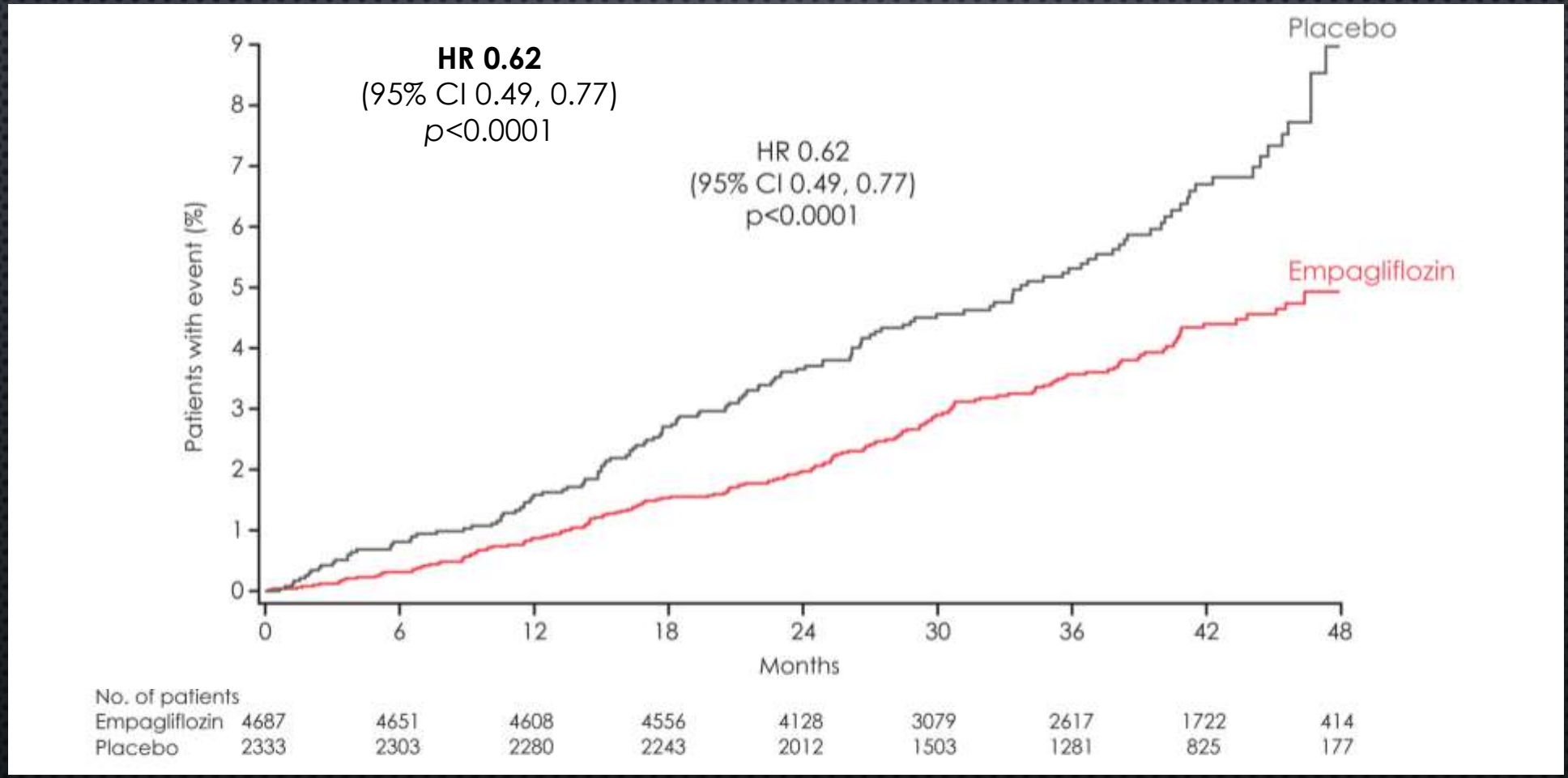
EMPA-REG primary outcome: 3-point MACE



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

EMPA-REG: CV death



Cumulative incidence function. HR, hazard ratio

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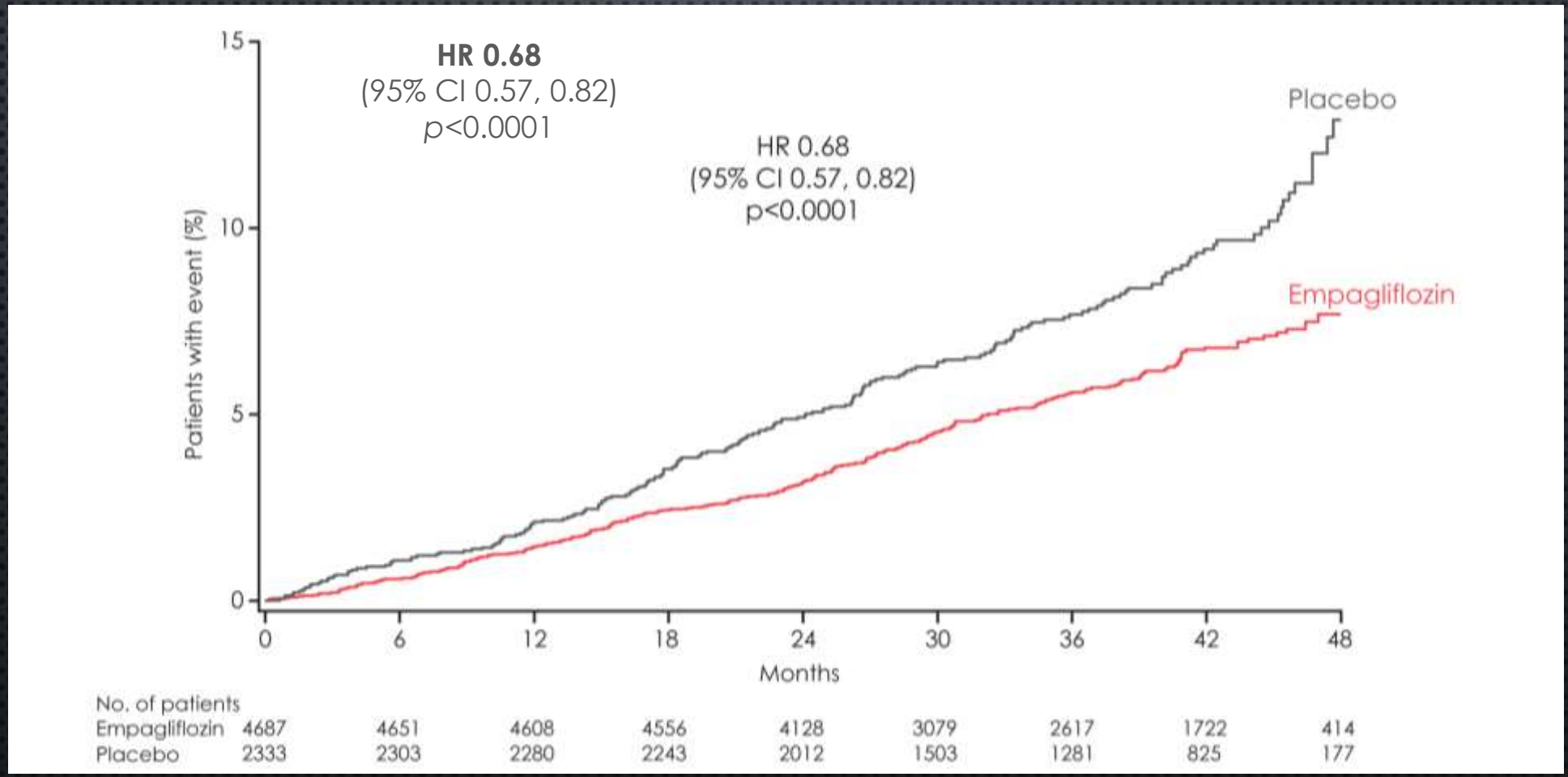
EMPA-REG: all-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Nuovi Farmaci per la Terapia del Diabete Mellito di Tipo 2
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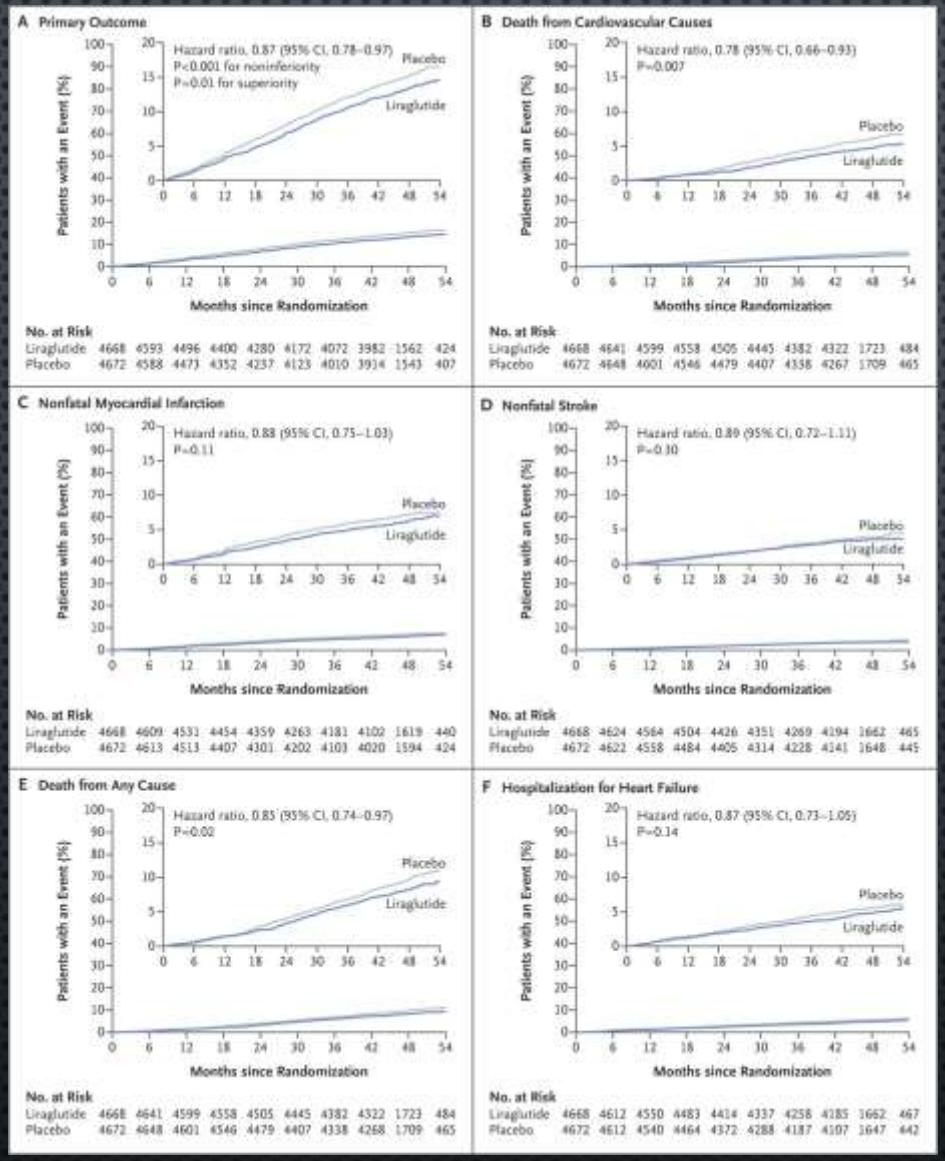
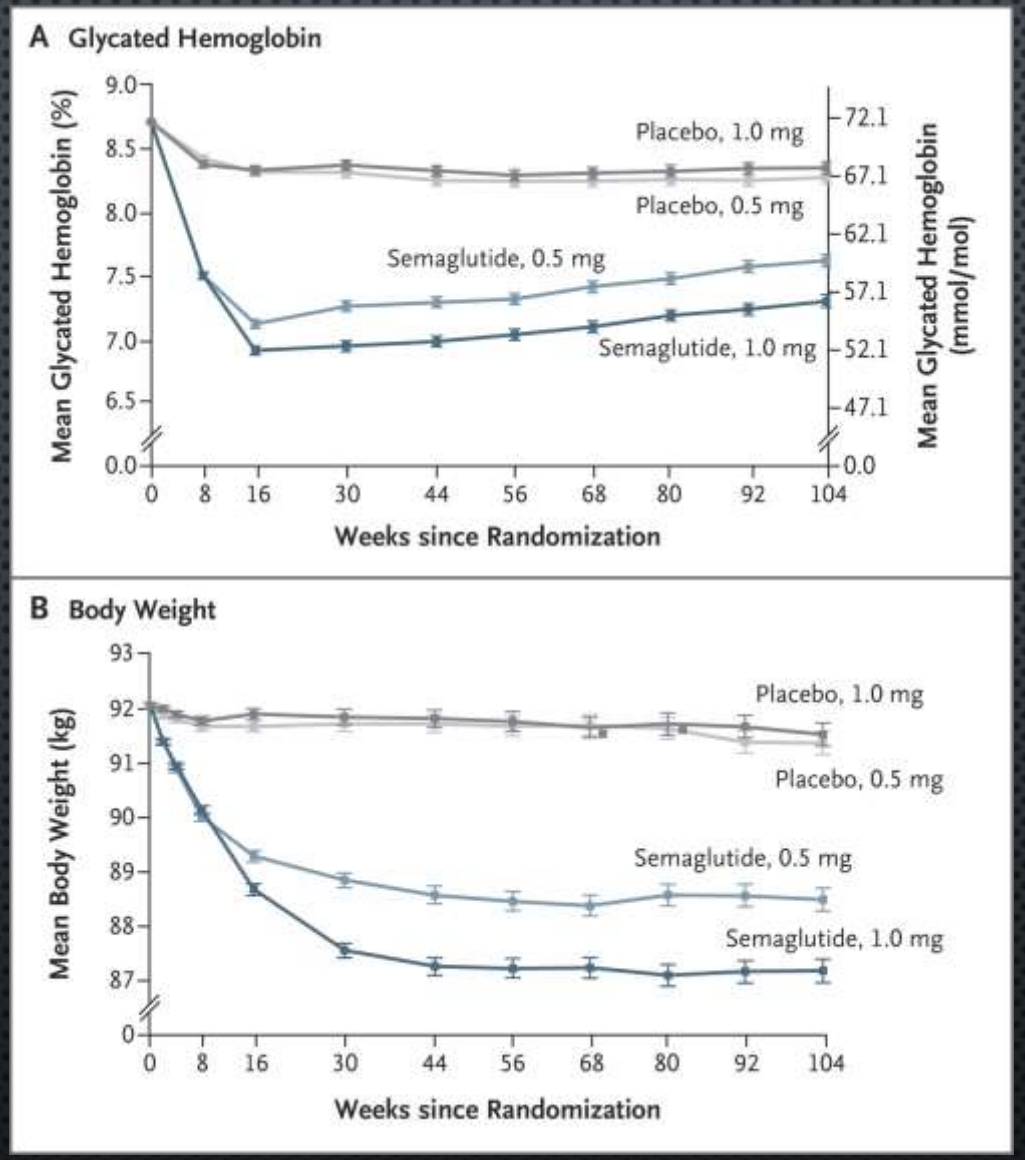
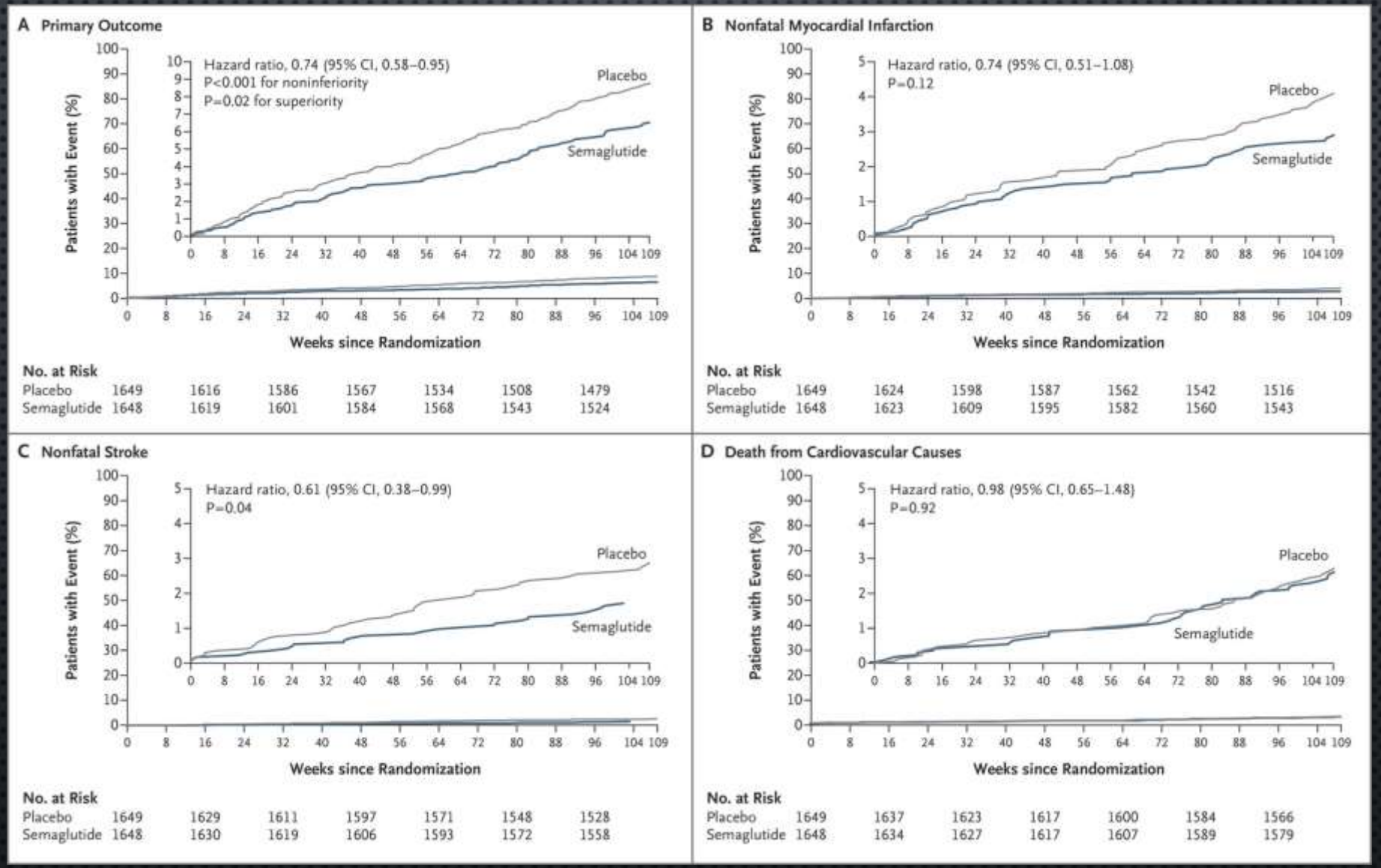


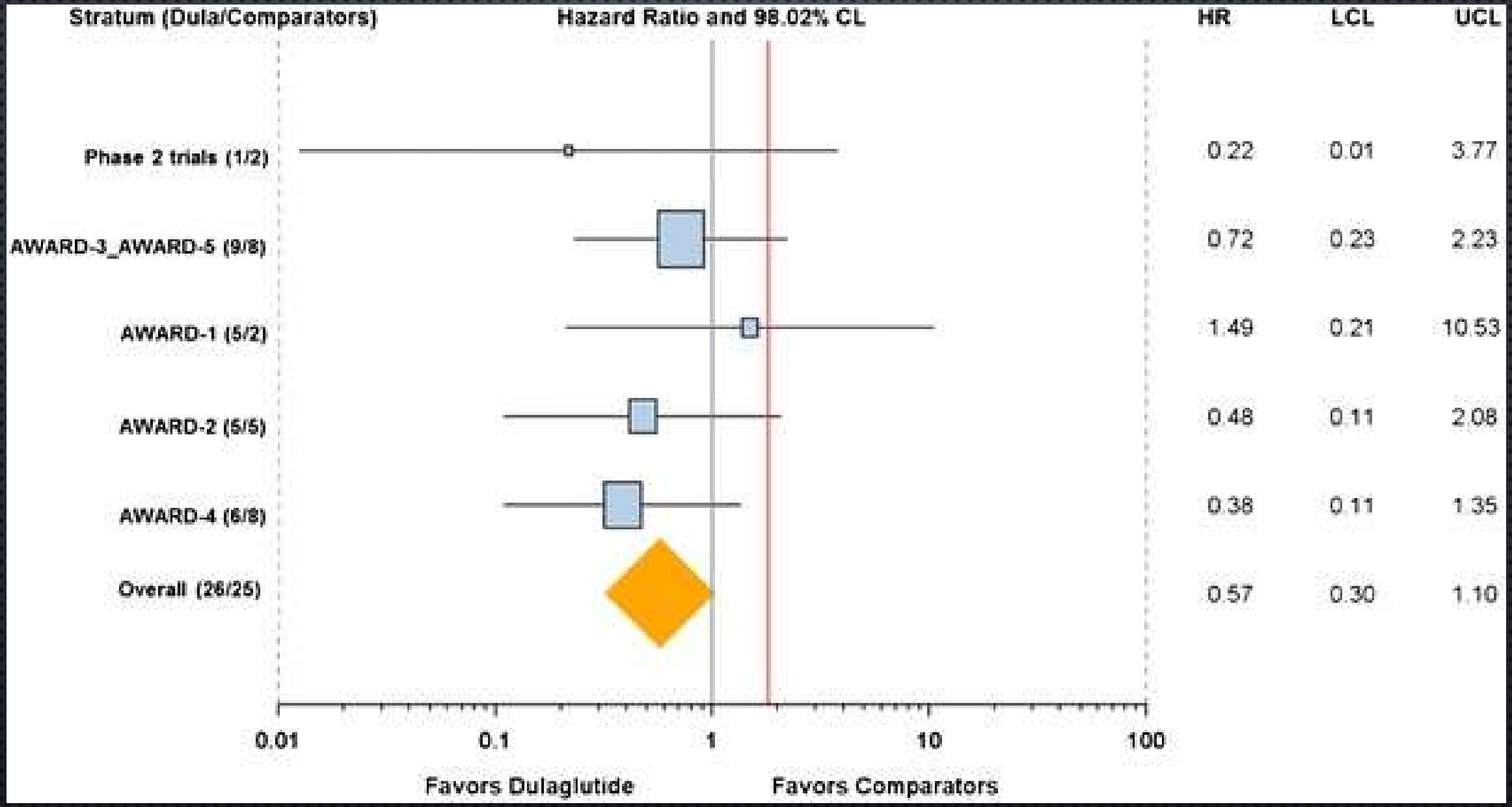
Marso et al, New Engl J Med, 2016



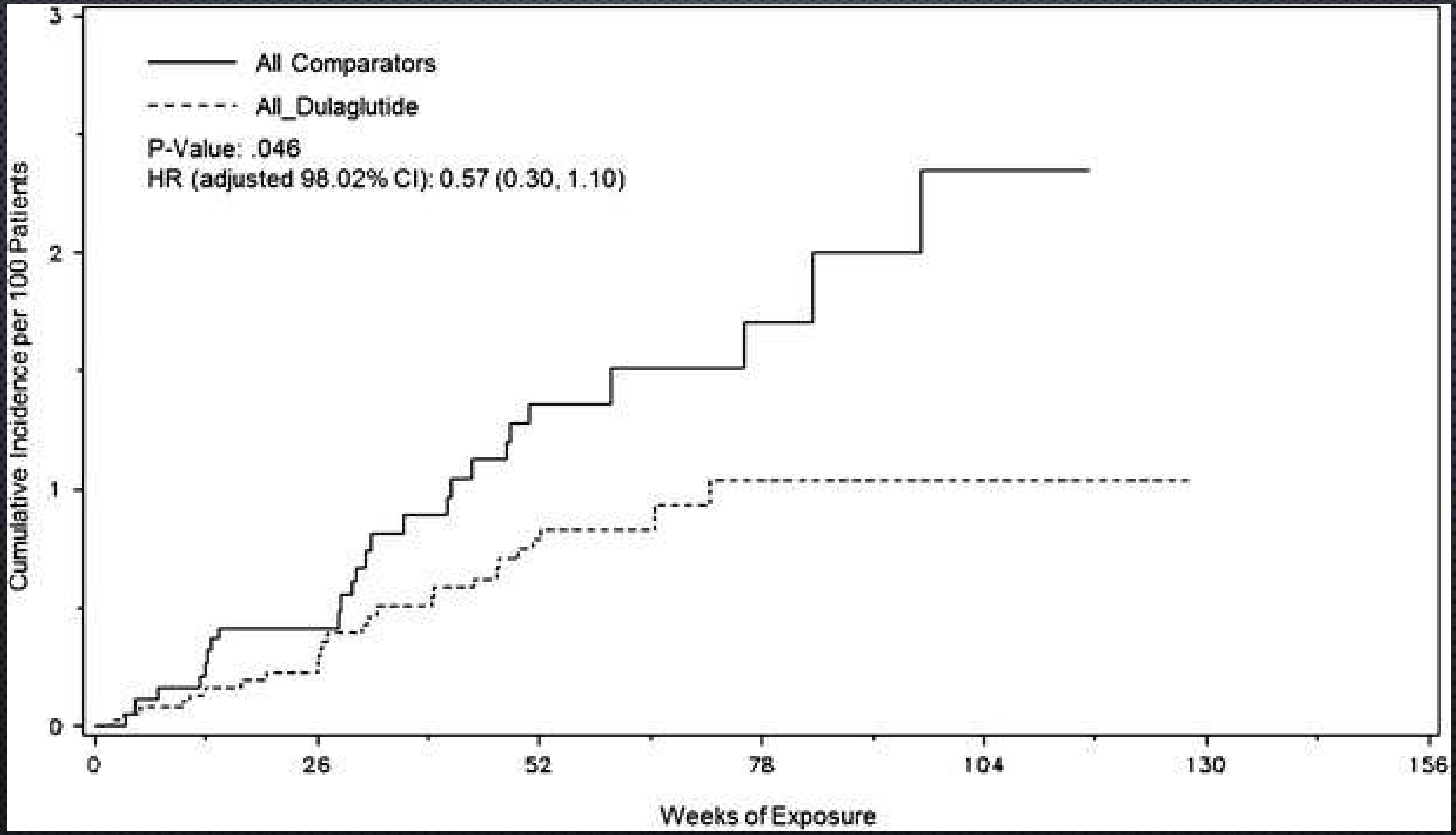
Marso et al, N Engl J Med, 2016



Marso et al, N Engl J Med, 2016



Ferdinand, Cardiovascular Diabetol, 2016



Ferdinand, Cardiovascular Diabetol, 2016

Nuovi Farmaci per la Terapia del Diabete Mellito di Tipo 2: Analisi degli Effetti sul Rene

- 1. Inibitori DPP-4
  - *SAVOR, TECOS, EXAMINE*
- 2. Analoghi recettoriali del GLP-1
  - *ELIXA, LEADER, SUSTAIN-6, REWIND*
- 3. Inibitori SGLT-2
  - *EMPA-REG, CANVAS, DECLARE*

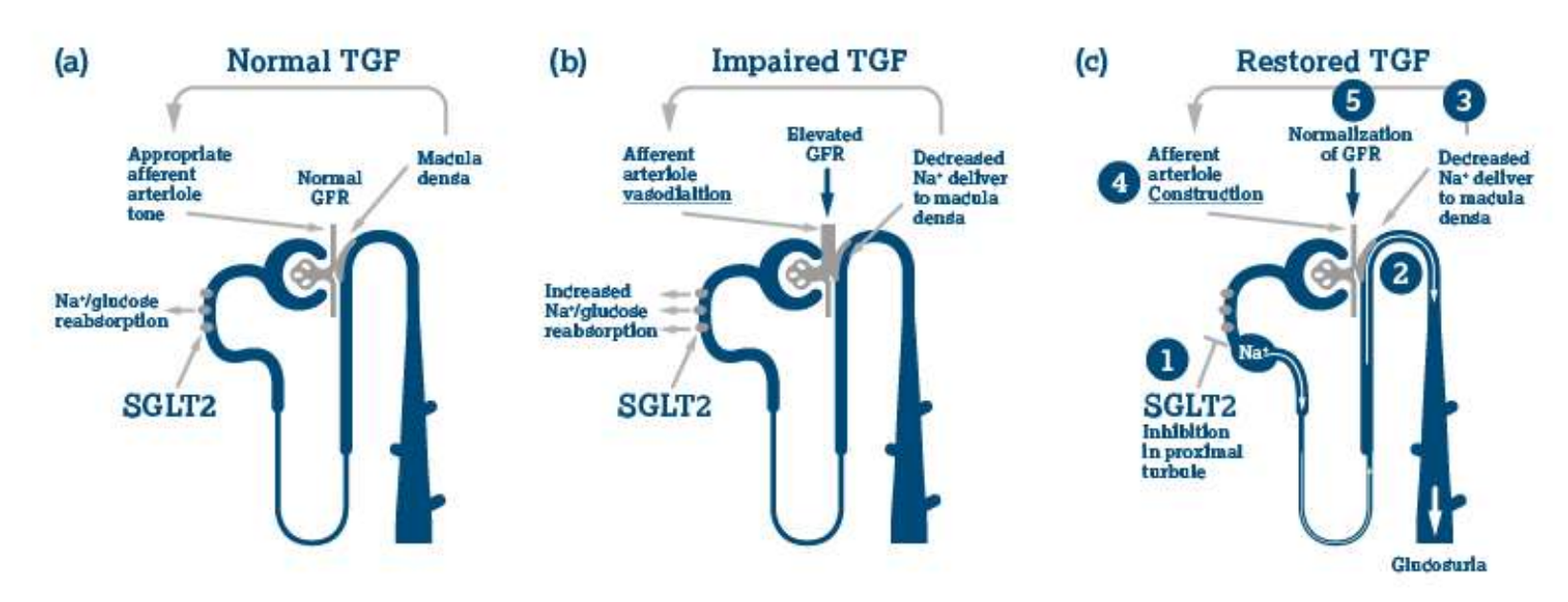
Possible mechanism for SGLT2-i nephroprotection

Tubuloglomerular feedback and sodium-glucose cotransporter-2 inhibition[1]

Normal physiology

Diabetes
Hyperfiltration in early stages of diabetic nephropathy

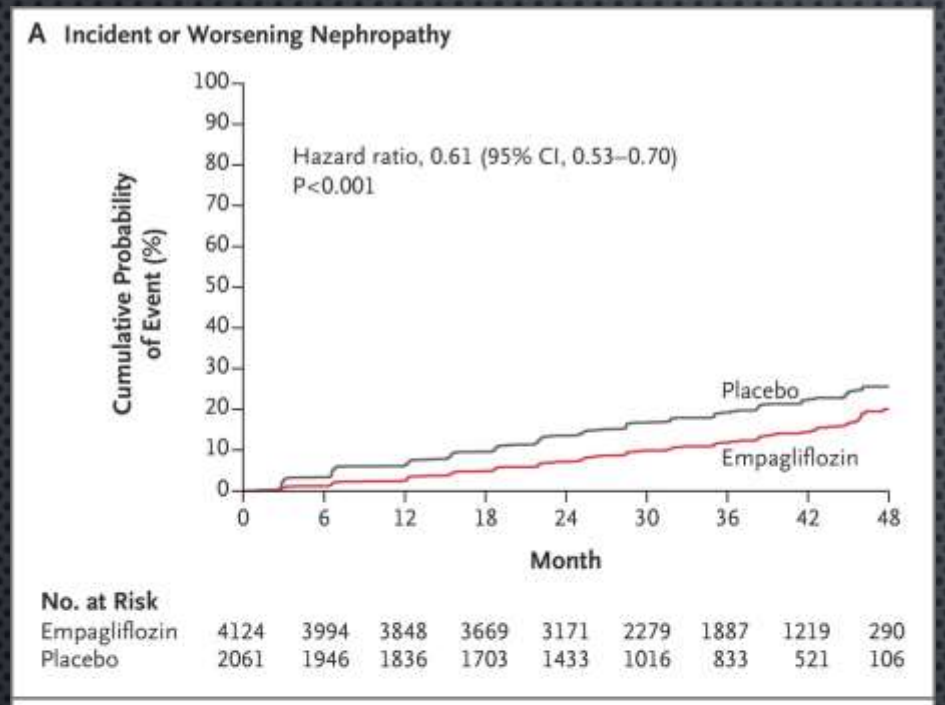
Diabetes after treatment with SGLT2 inhibition
Reduction of hyperfiltration via TGF

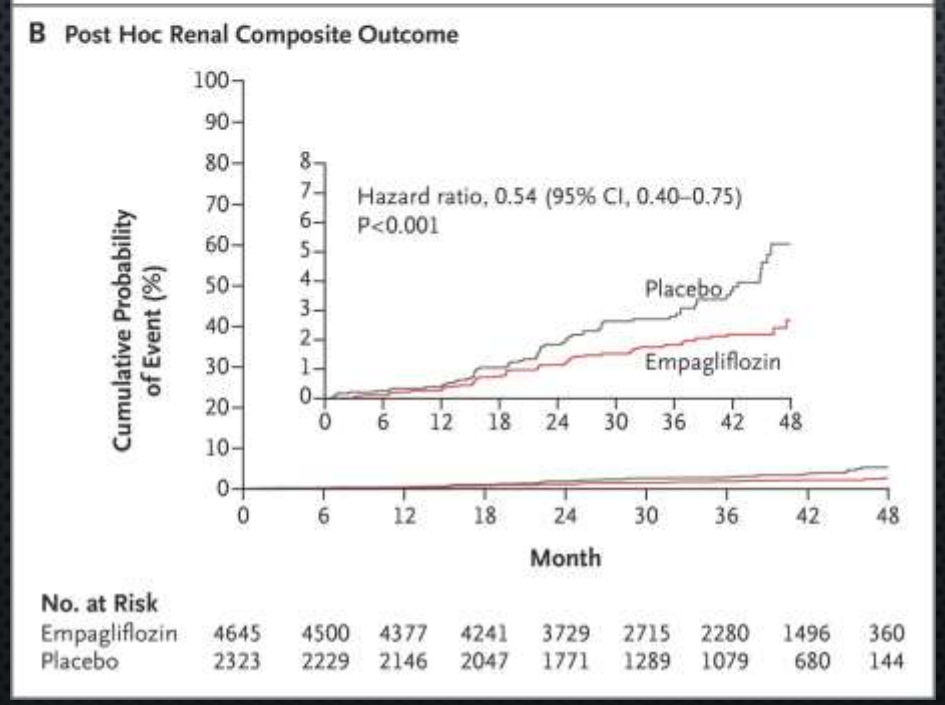


Taken from Skrtic M, *et al.* 2015.

GFR=glomerular filtration rate; SGLT2=sodium-glucose transporter-2; TGF=tubuloglomerular feedback.

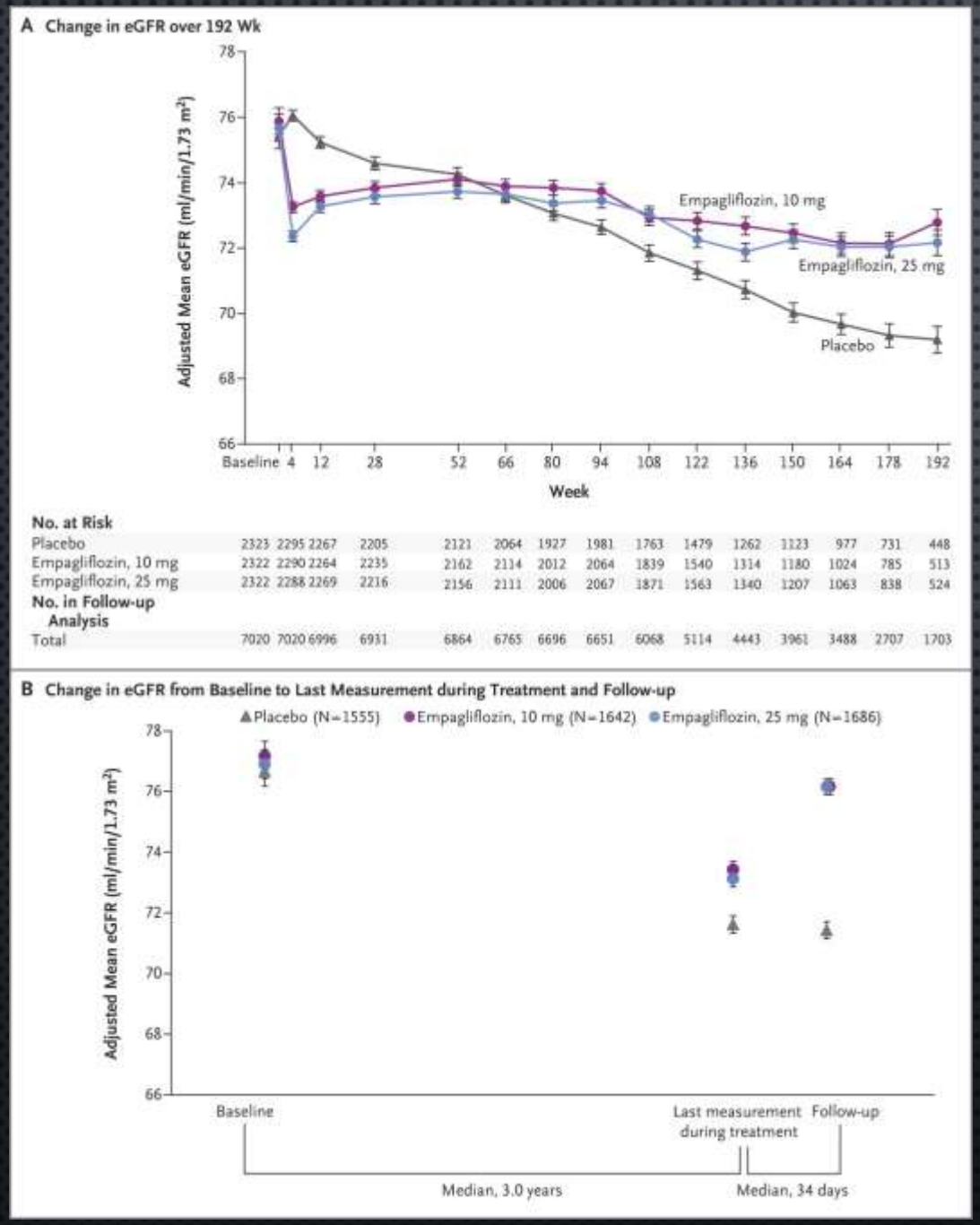
1. Skrtic M *et al. Curr Opin Nephrol Hypertens.* 2015, 24:96–103





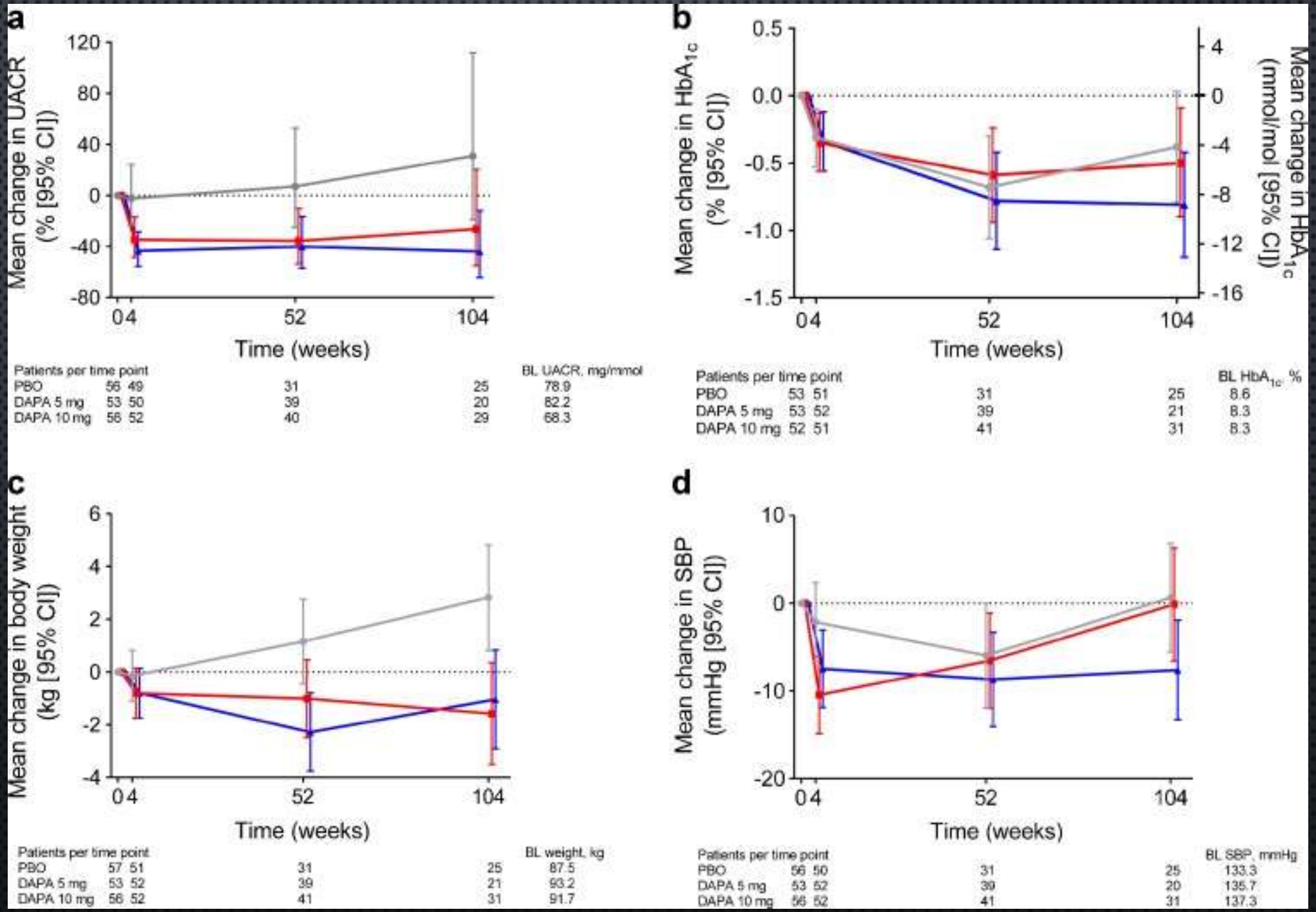
Empaglifozin: Incident or Worsening Nephropathy

Wanner, New Engl J Med, 2016



Empaglifozin: Renal Function over Time

Wanner, New Engl J Med, 2016



Fioretto, Diabetologia, 2016

Ethnicity and Drug Efficacy

Ethnic Differences in the Relationship Between Insulin Sensitivity and Insulin Response

DIABETES CARE, VOLUME 36, JUNE 2013 1789

META-ANALYSIS

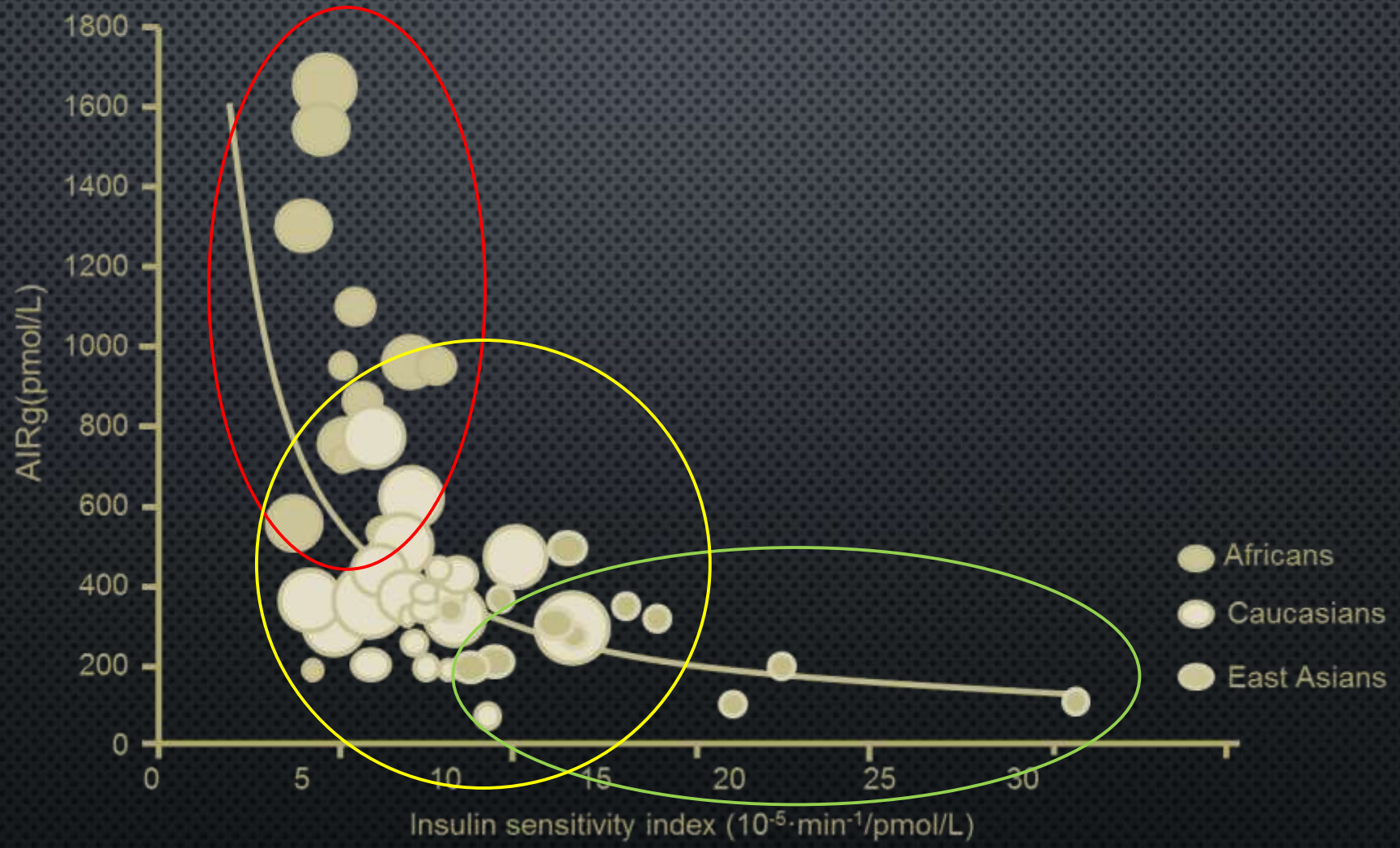
Ethnic Differences in the Relationship Between Insulin Sensitivity and Insulin Response

A systematic review and meta-analysis

74 study cohorts comprising 3,813 individuals (19 African cohorts, 31 Caucasian, and 24 East Asian)

Kodama K , et al. Diabetes Care. 2013;36(6):1789-96.

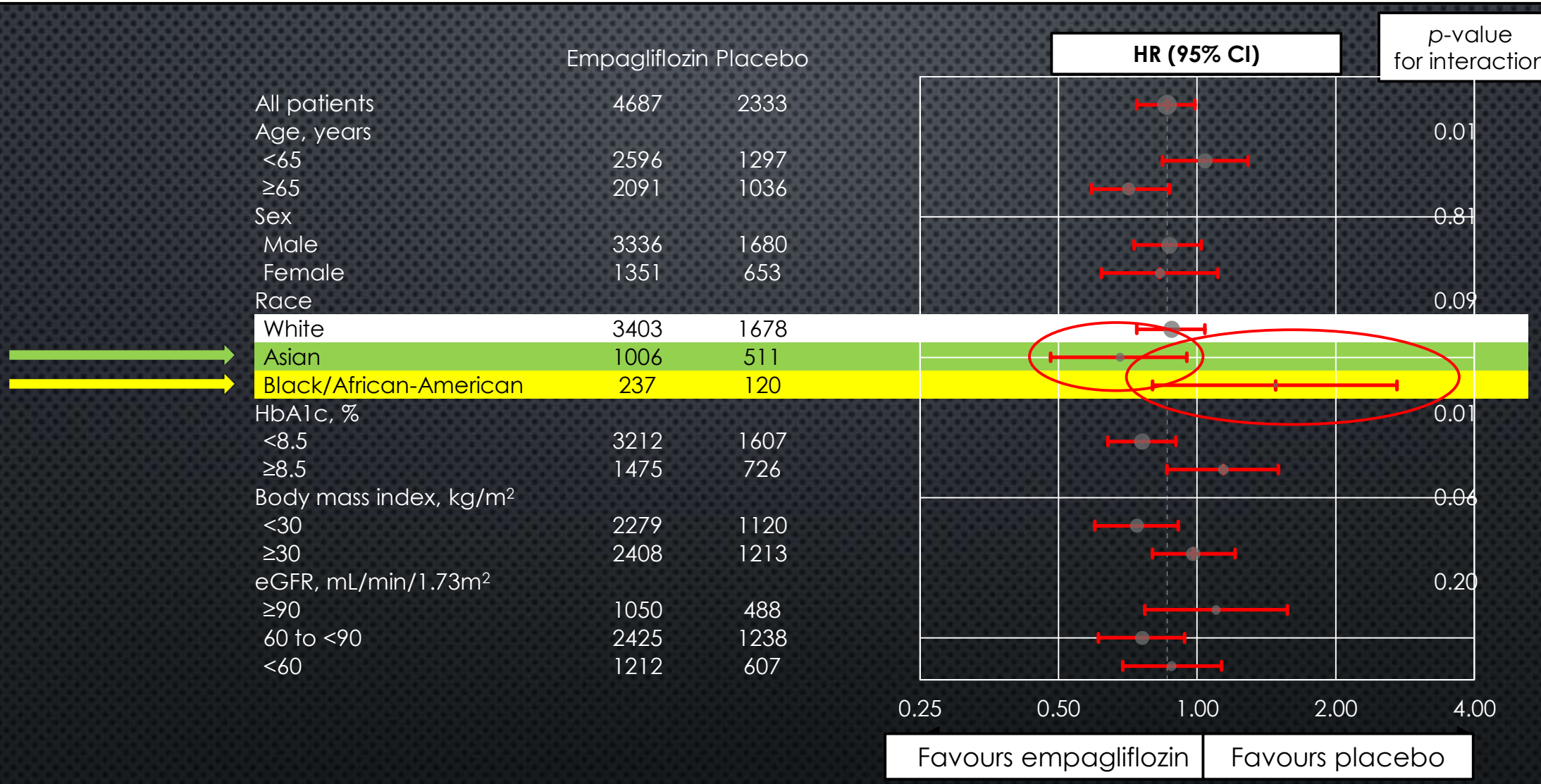
First phase insulin response in East Asians was much lower than that of Africans and Caucasians in NGT



Kodama K , et al. Diabetes Care. 2013;36(6):1789-96.

EMPA-REG: 3-point MACE: subgroup analysis

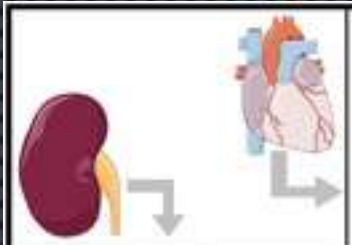
	Empagliflozin	Placebo
All patients	4687	2333
Age, years		
<65	2596	1297
≥65	2091	1036
Sex		
Male	3336	1680
Female	1351	653
Race		
White	3403	1678
Asian	1006	511
Black/African-American	237	120
HbA1c, %		
<8.5	3212	1607
≥8.5	1475	726
Body mass index, kg/m^2		
<30	2279	1120
≥30	2408	1213
eGFR, mL/min/1.73m^2		
≥90	1050	488
60 to <90	2425	1238
<60	1212	607



From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Conclusioni

1. Inibitori di DPP-4 sono farmaci sicuri dal punto di vista cardiovascolare e renale, e si sono dimostrati efficaci nel migliorare il compenso glicemico;
2. Sia Analoghi recettoriali del GLP-1 che inibitori di SGLT-2 si sono dimostrati efficaci nel ridurre la mortalità cardiovascolare, sebbene il meccanismo d'azione per SGLT-2i sia ancora in massima parte da chiarire;
3. Gli inibitori di SGLT-2, hanno dimostrato numerosi altri effetti metabolici oltre a quelli sulla glicemia (quadro lipidico ed acido urico tra i principali);
4. Gli inibitori di SGLT-2 hanno un potenziale effetto nefroprotettivo;



	Normal or subclinical ENDOTHELIAL DYSFUNCTION	ESTABLISHED ATHERO-SCLEROSIS	ACUTE CORONARY SYNDROME	HEART FAILURE
Stage I-II CKD **eGFR 90-60 ml/min/1.73 m²**	Metformin[a], Pioglitazone[b] DPP4-I[c-e], GLP-1 RA[f], SGLT2-I[g], Insulin[1h] SUs[1]	Metformin, SGLT2-I[g], GLP-1RA[f], Pioglitazone[b], DPP4-I[c-e], Insulin[h] Gliclazide[k]	Insulin[m] DPP4-I[e], GLP-1RA[f],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage III CKD **eGFR 59-30 ml/min/1.73 m²**	Metformin[2], Pioglitazone[3b], SLGT2-I[4g], GLP-1RA[f], DPP4-I[2c-e], Gliclazide[2k], Insulin[h]	Metformin[2], GLP-1RA[f], SGLT2-I[4g], Pioglitazone[3b], DPP4-I[2c-e], Insulin[h], Gliclazide[2k]	Insulin[m] DPP4-I[e], GLP-1RA[f],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage IV CKD **eGFR 29-15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]
Stage V CKD **eGFR <15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]

Evidence of efficacy **Evidence of safety** **Author consensus**

Avogaro et al, Cardiovasc. Diabetol., 2016