

Blood pressure effects of 'new' glucose-lowering drugs

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Amersfoort

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Disclosures

- Advisory board/Speaker:

Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck, Sanofi

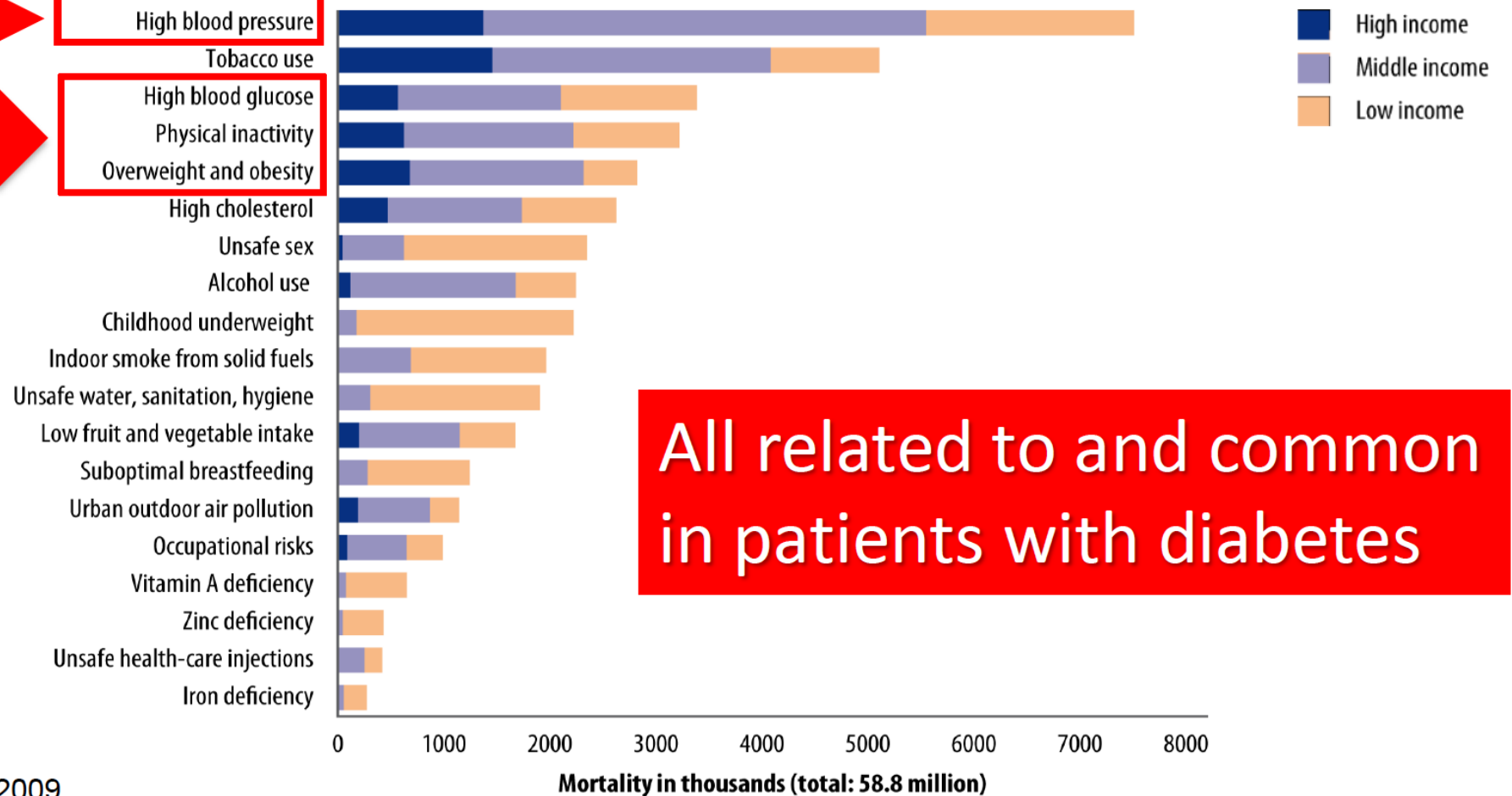
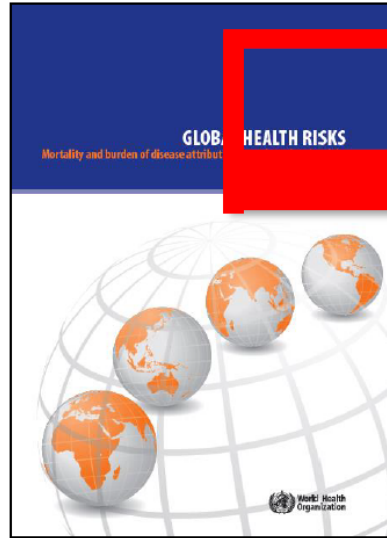
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Astra Zeneca, Boehringer Ingelheim, Merck, Sanofi

Honoraria transferred to employer VUMC

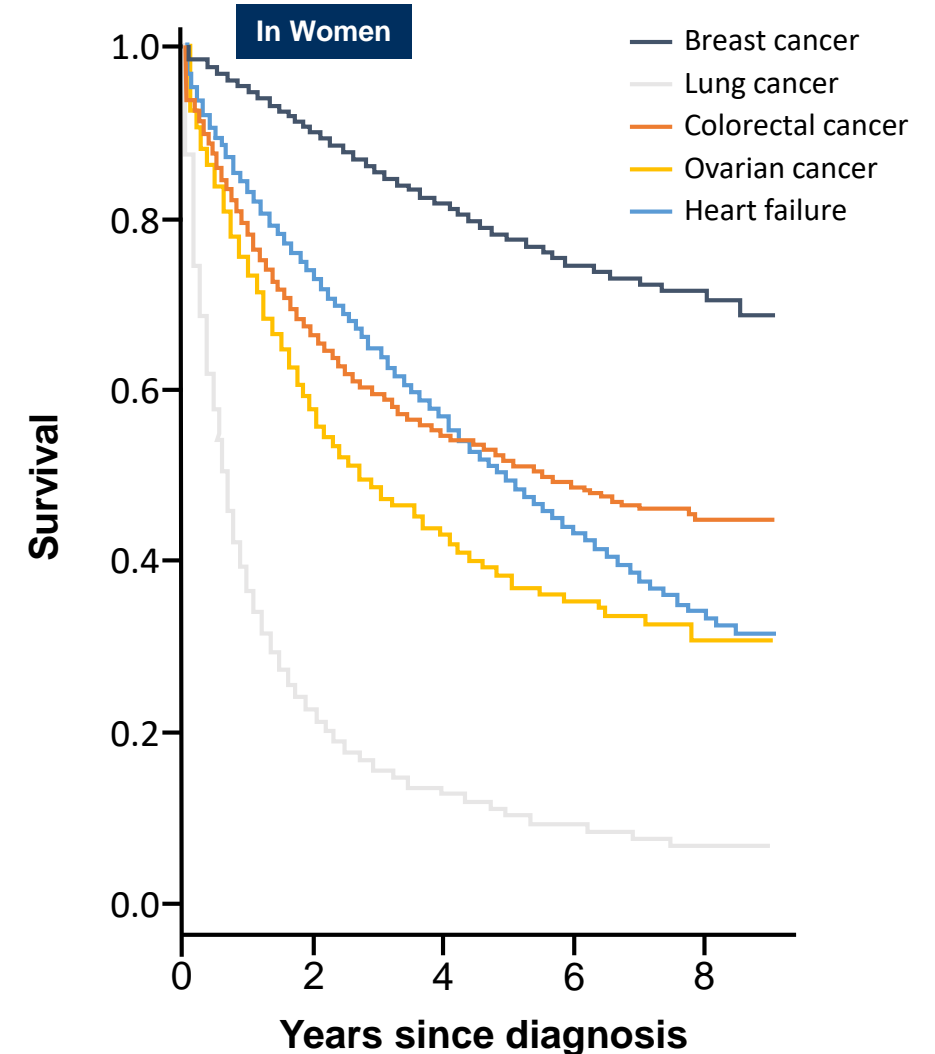
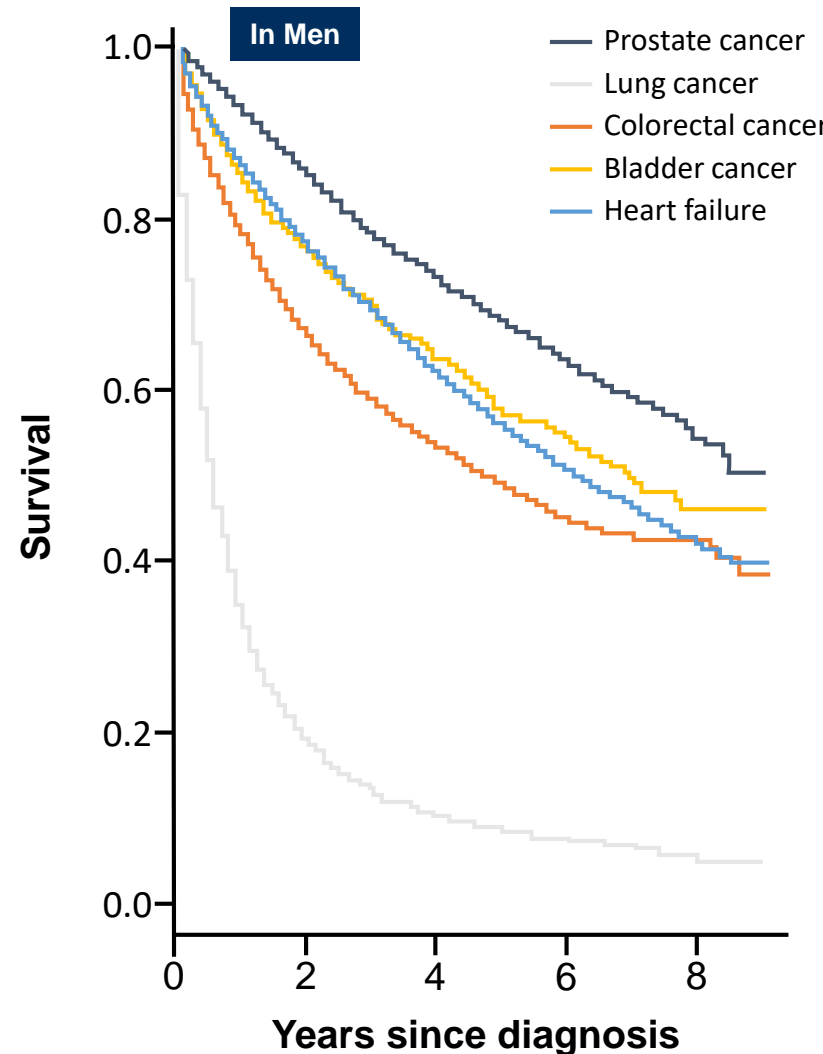
Global mortality attributed to 19 risk factors



WHO Global Health Risks 2009

Heart failure has a poor outcome in people with T2D

Despite advances in care, men and women with a diagnosis of HF continue to have worse survival than patients with one of several common cancers



Importance of risk factor control in T2D

Diabetologia (2018) 61:1724–1733
<https://doi.org/10.1007/s00125-018-4642-y>

ARTICLE



Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study

Jens Oelgaard^{1,2,3} · Peter Gæde^{1,2} · Peter Rossing^{3,4,5} · Rasmus Rørth⁶ · Lars Køber⁶ · Hans-Henrik Parving^{5,7} · Oluf Pedersen⁸

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Patients

Diabetes + microalbuminuria

Treatment

Intensive
Conventional

n=80
n=80

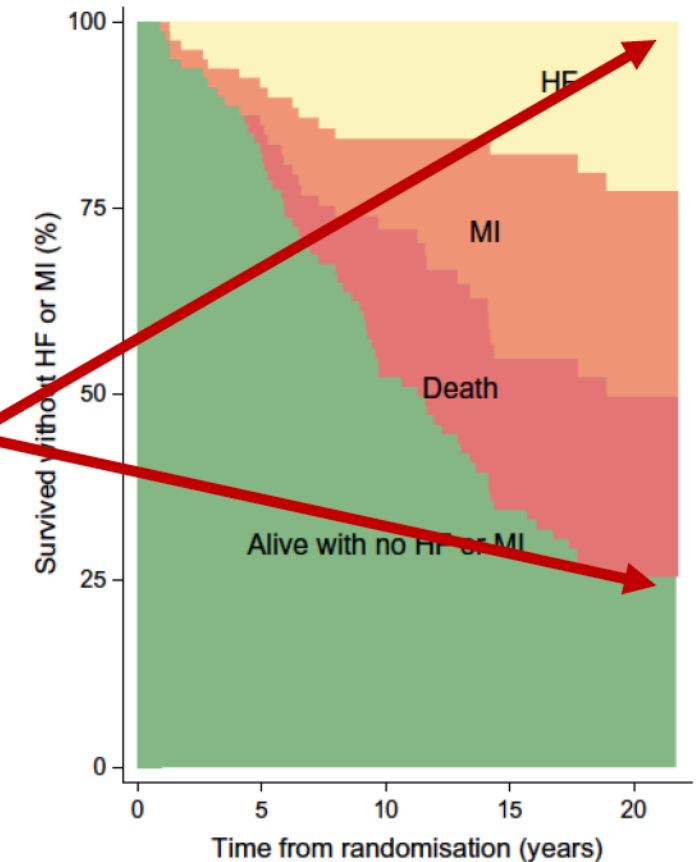
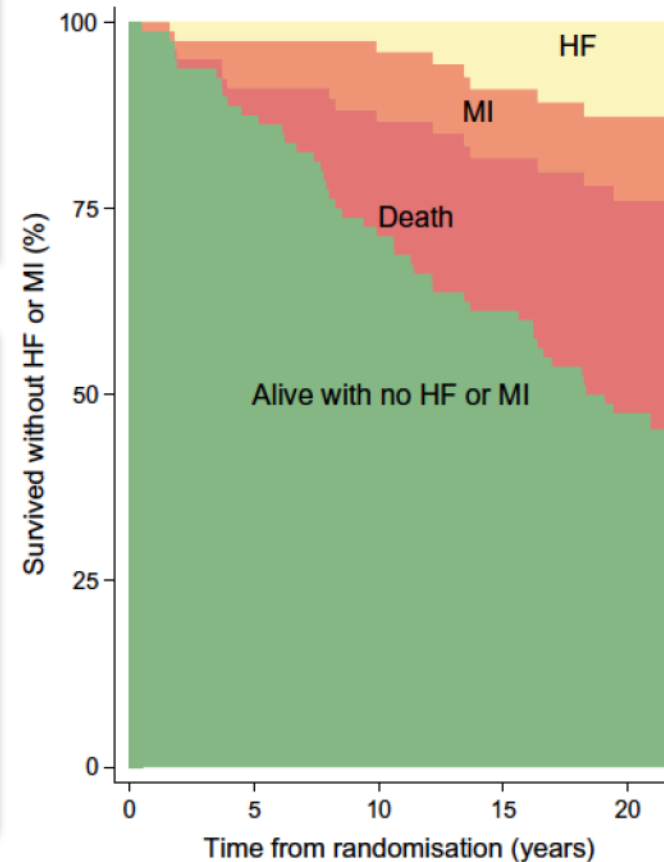
Trial design

PROBE
Observational

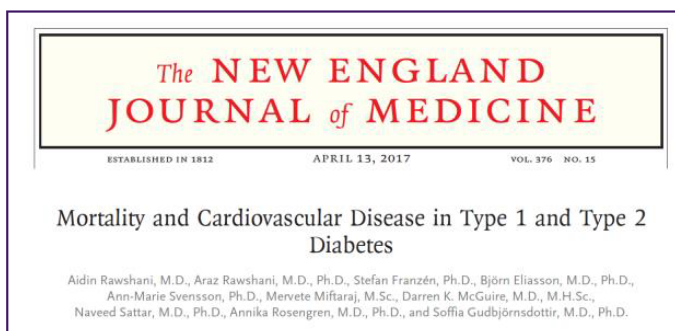
7.8 years
+13.4 years

Survival free from heart failure or myocardial infarction

Intensive therapy Conventional therapy

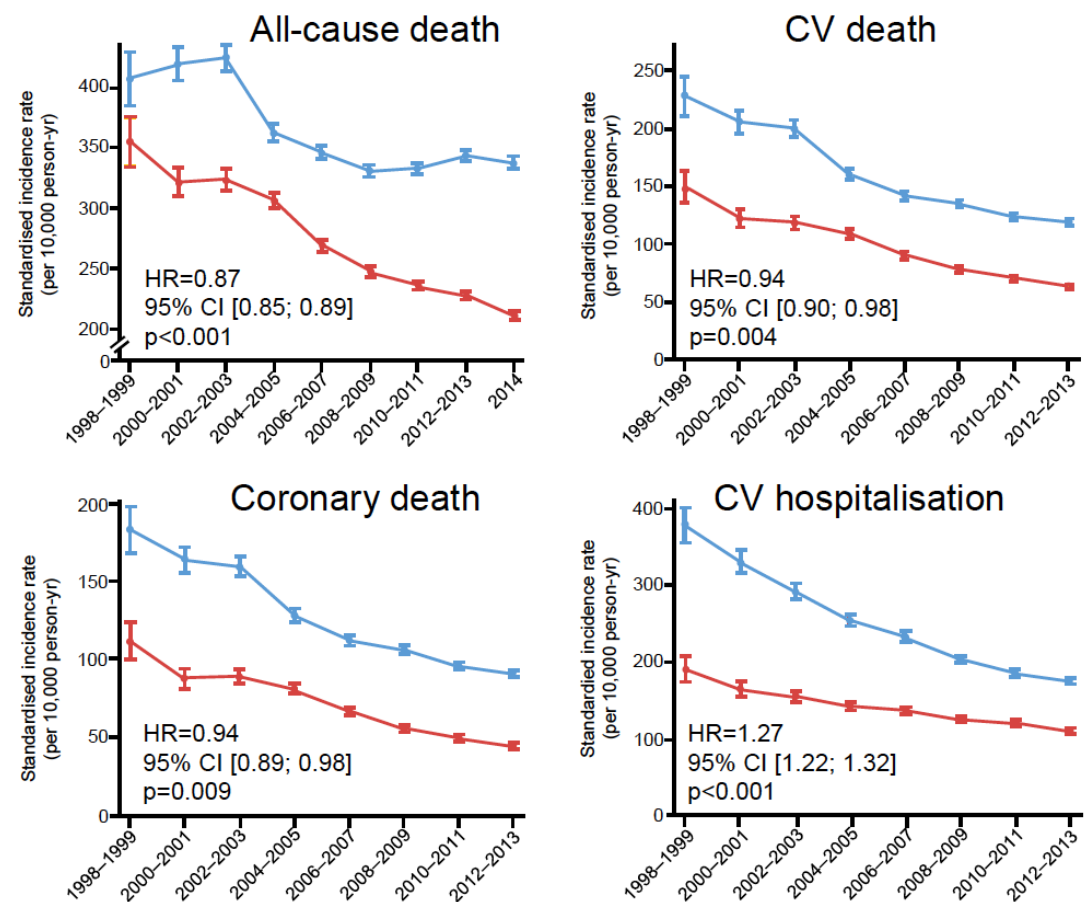


Residual risk: mortality and CVD in people with T2D

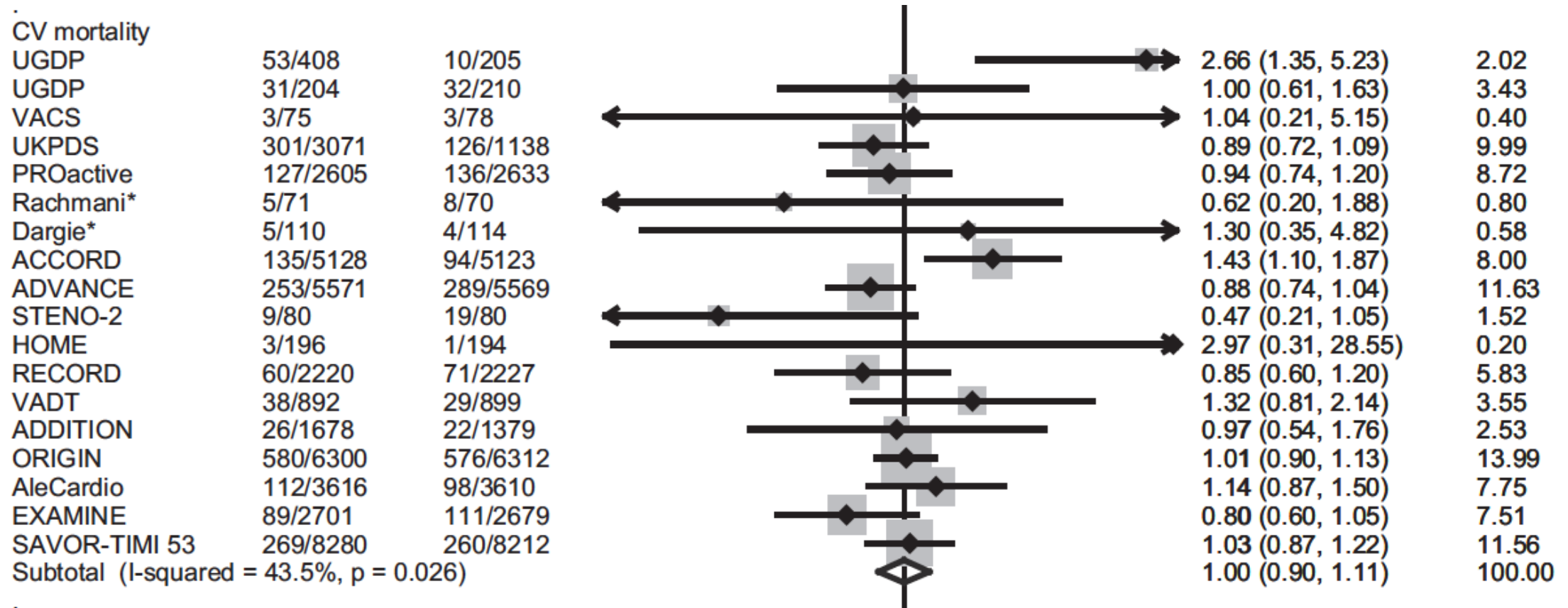


- **Patients**
From Swedish National Diabetes Register
- **Controls from population**
Matched for age, sex and county
- Trends in CV death and morbidity
- Standardised incidence rate per 10,000 person-years

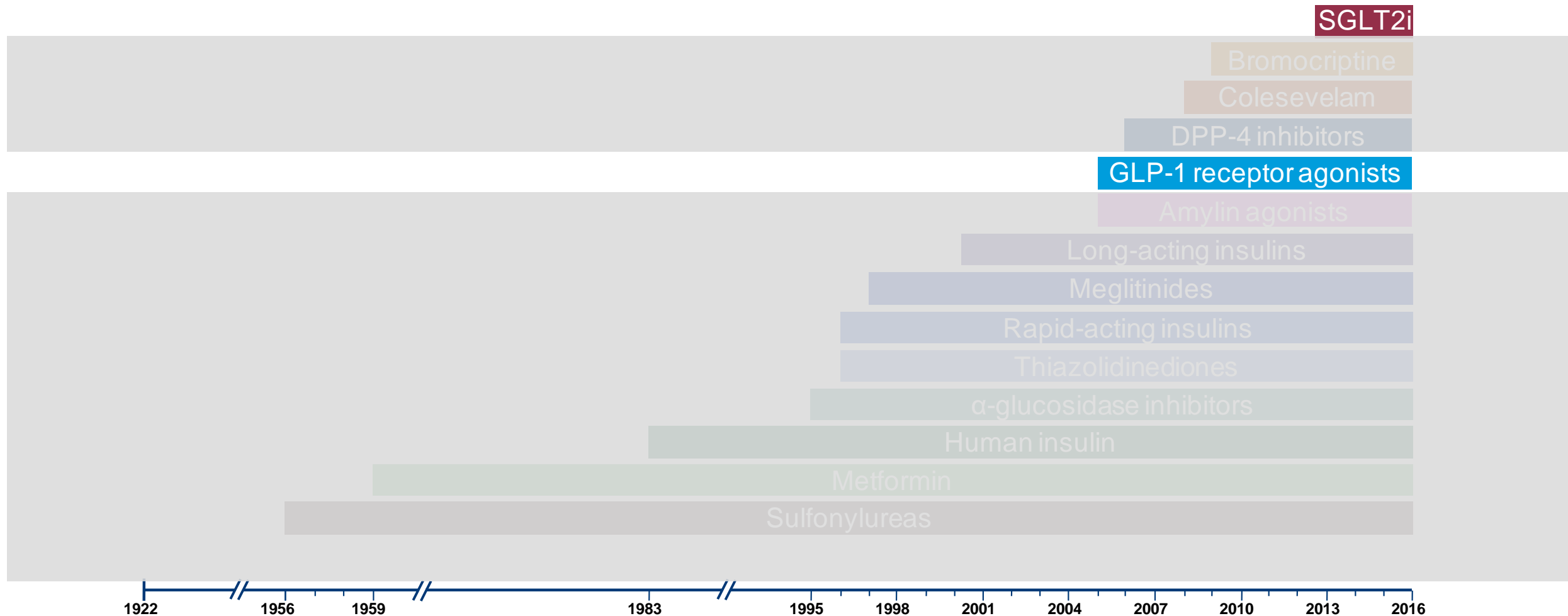
Rawshani A et al. *N Engl J Med* 2017;376:1407.



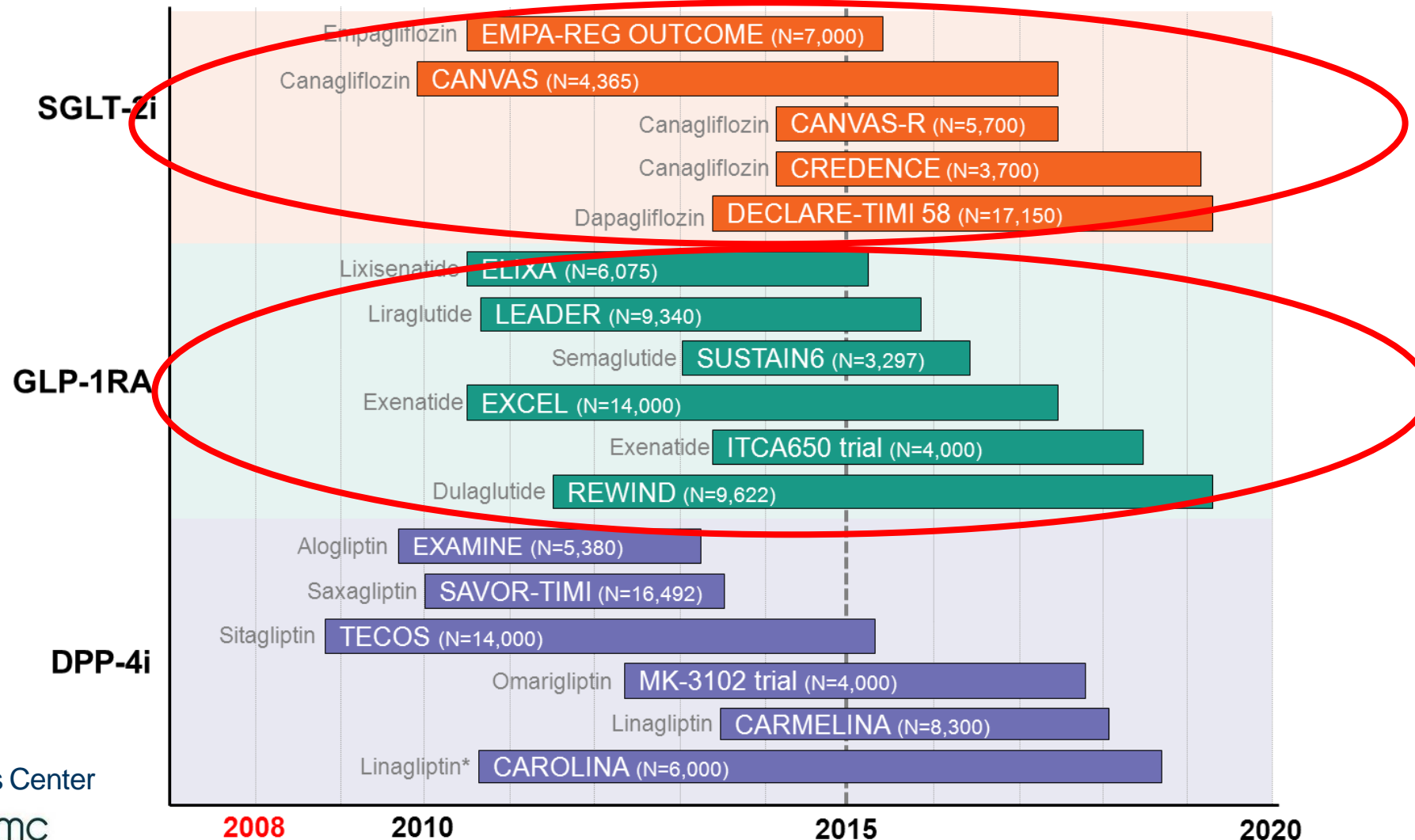
Glucose lowering and cardiovascular mortality



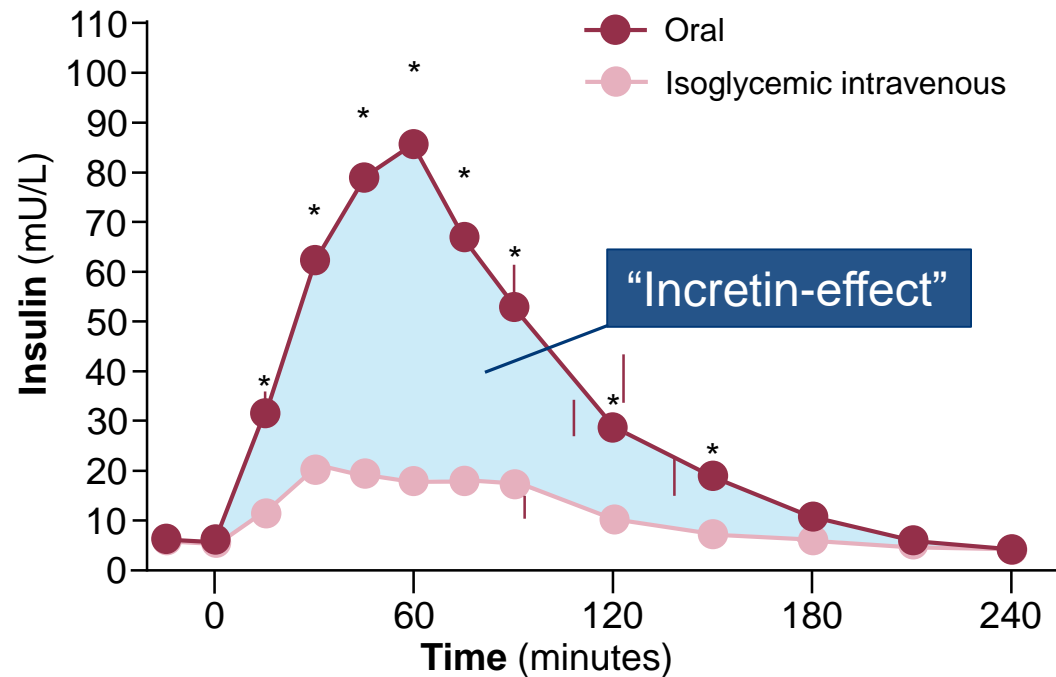
New glucose lowering agents



Cardiovascular Outcome Trials (CVOT) – 3 MACE

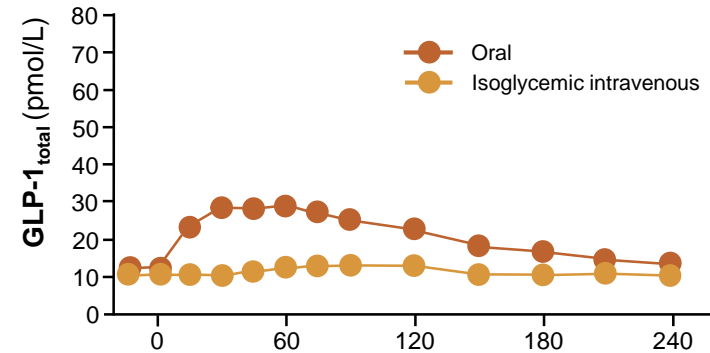
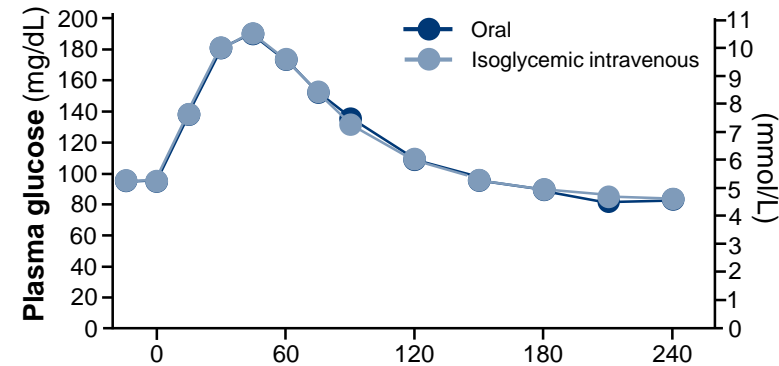


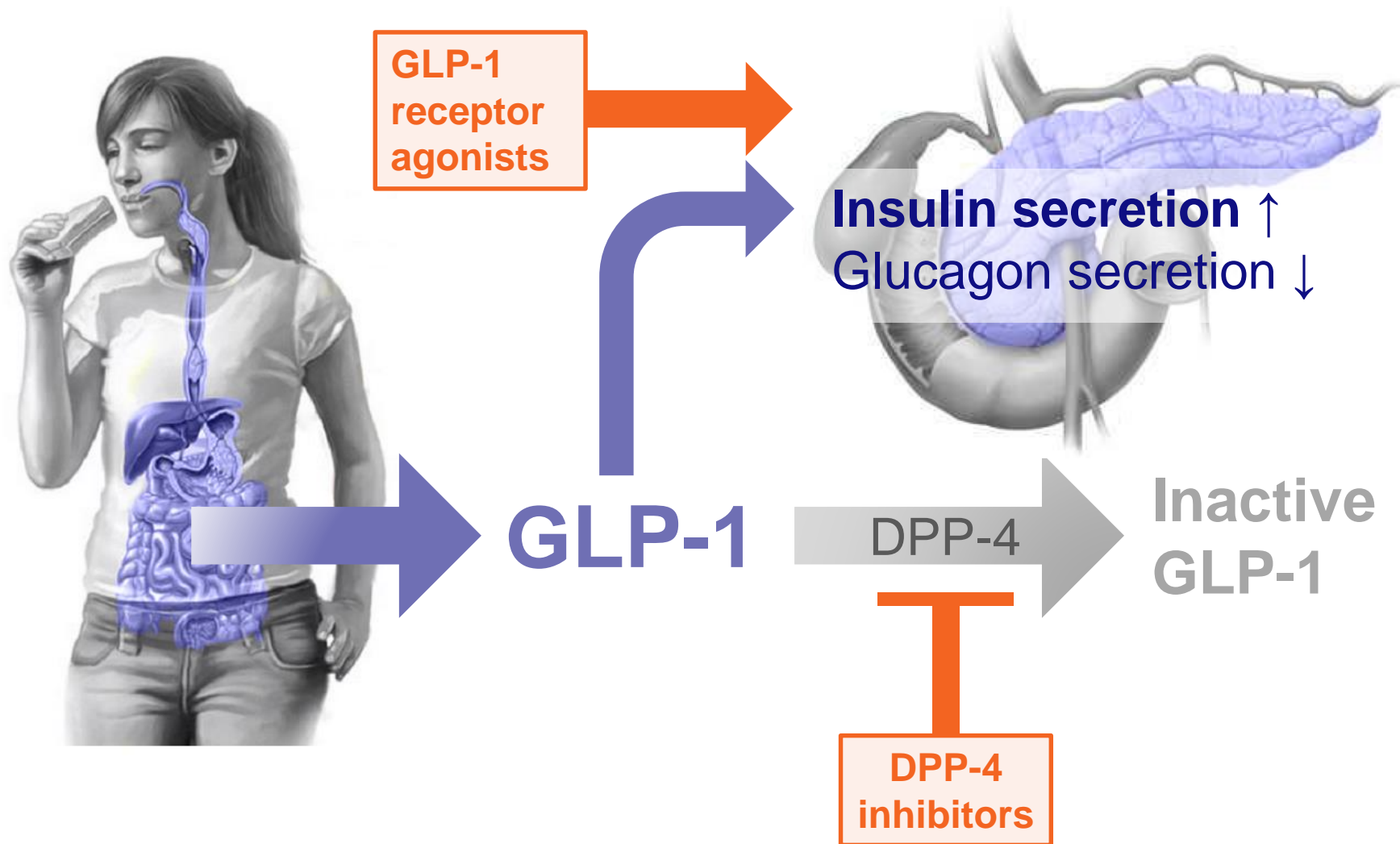
Gut hormones affect postprandial insulin secretion: Incretin effect



Two gut-derived incretin hormones have been identified:

- Glucagon-like peptide 1 (GLP-1)
- Glucose-dependent insulintropic polypeptide (GIP)





GLP-1: Effects in Humans— Understanding the Potential of Incretins

Normal GLP-1 secretion

- Stimulated by food intake
- Diminished in IGT, diabetes
- Response to GLP-1 preserved even in diabetes

Liver:
↓ Glucagon
reduces hepatic
glucose output

Alpha cell:
↓ Glucagon
secretion
postmeal

CNS:

Promotes satiety and
reduction of appetite

Beta cell:

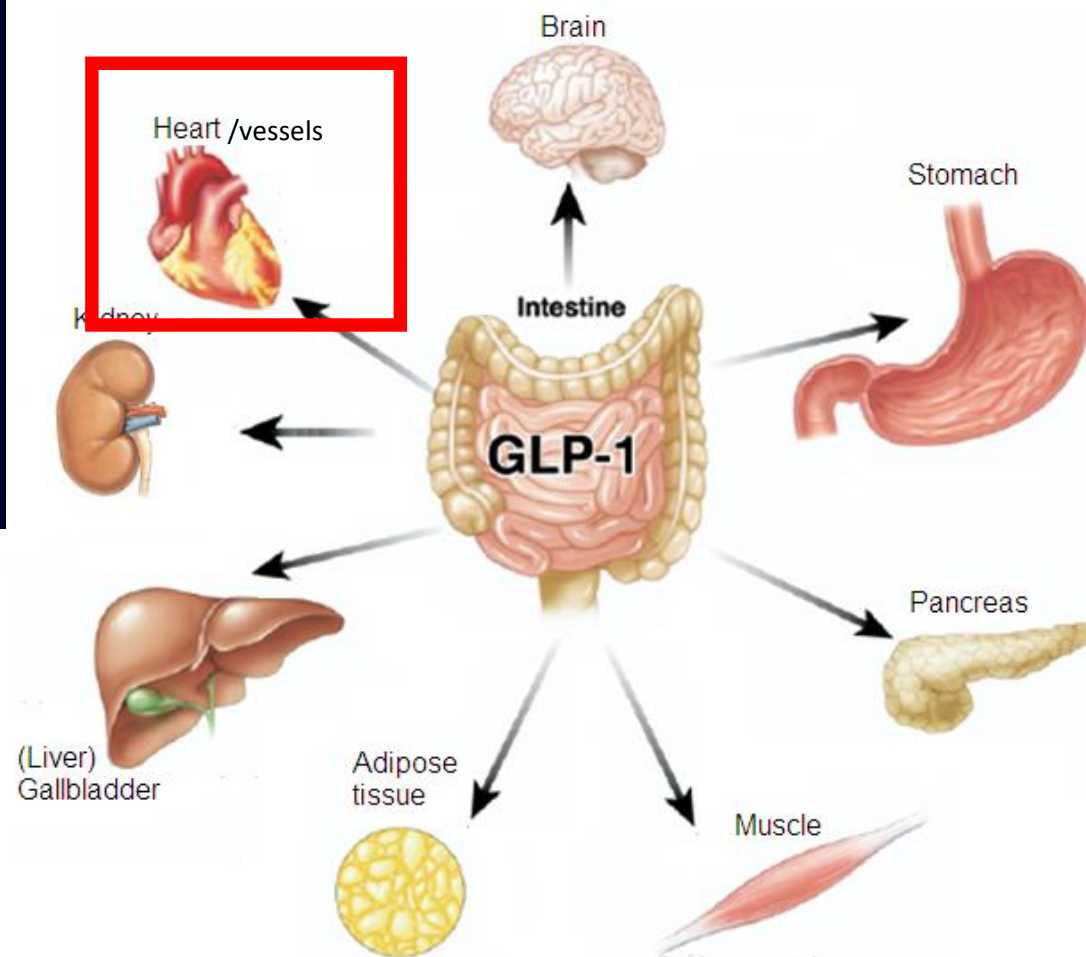
Enhances glucose-
dependent insulin
secretion

Stomach:

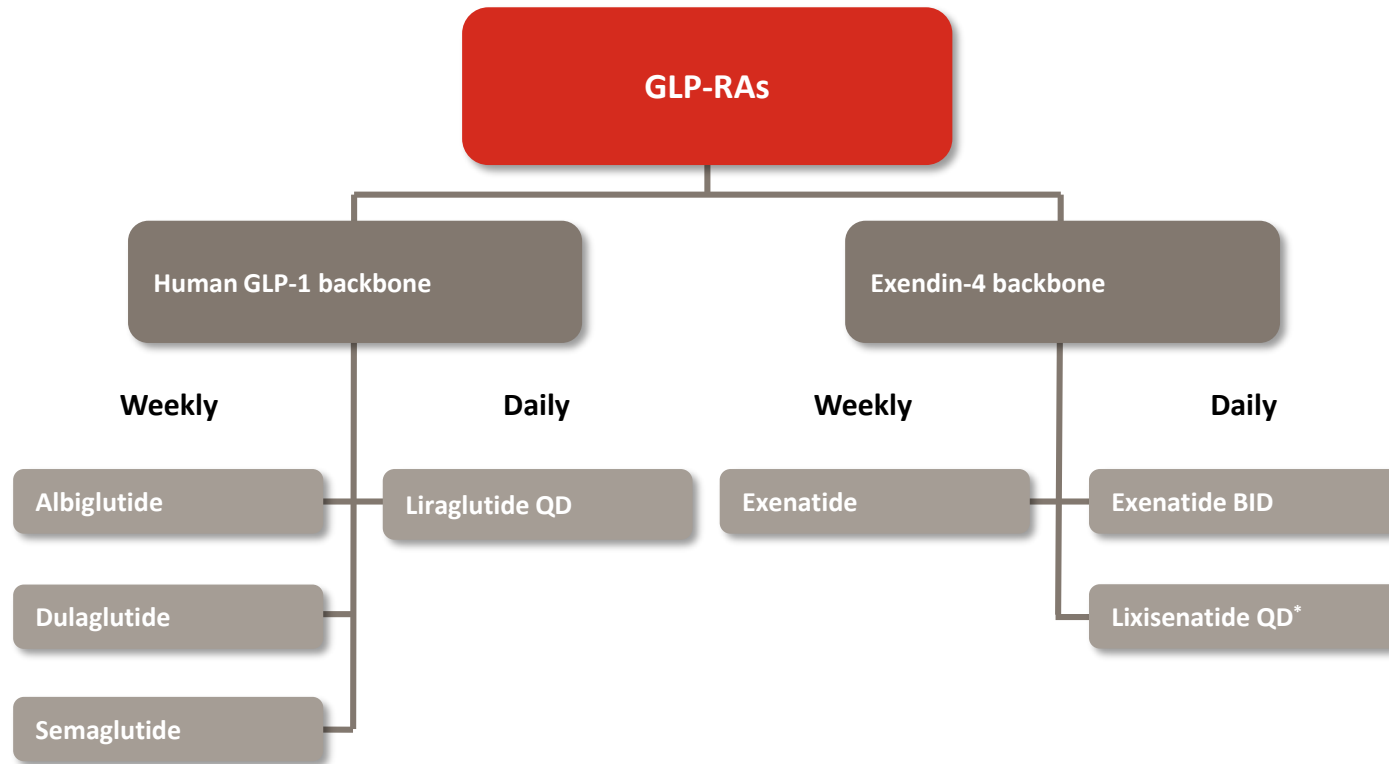
Regulates gastric
emptying



GLP-1 receptors present in:



Different GLP-1 RA compounds

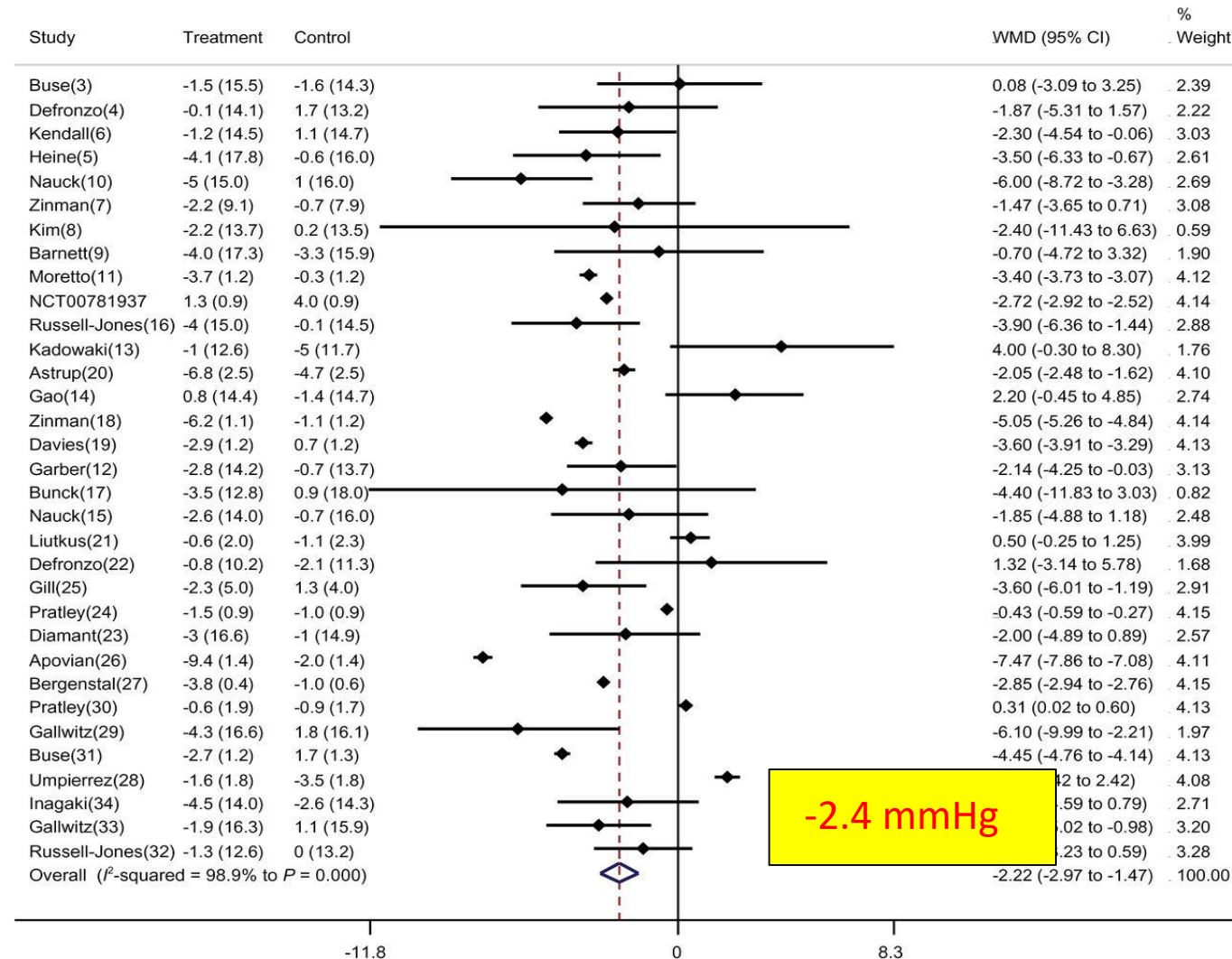


CV Outcome Trials of GLP-1 in T2D

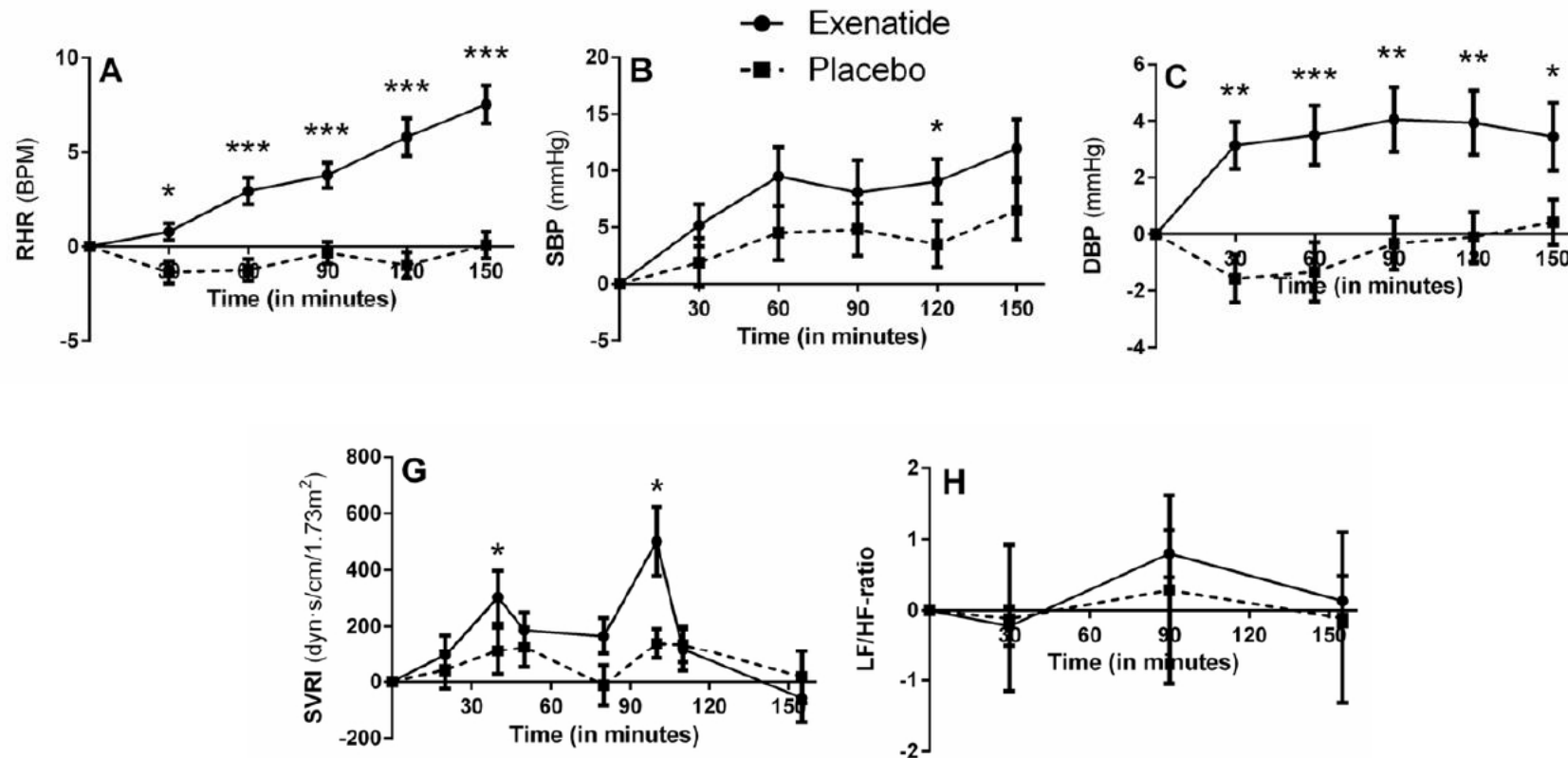


MACE	1.02 [0.89-1.17]	0.91 [0.83-1.00]	0.87 [0.78-0.97]	0.74 [0.58-0.95]	0.78 [0.68-0.90]
Non-fatal MI	1.03 [0.87-1.22]	0.97 [0.85-1.10]	0.88 [0.75-1.03]	0.74 [0.51-1.08]	0.75 [0.61-0.90]
Non-fatal stroke	1.12 [0.79-1.58]	0.85 [0.70-1.03]	0.89 [0.72-1.11]	0.61 [0.38-0.99]	0.86 [0.66-1.14]
CV death	0.98 [0.78-1.22]	0.88 [0.76-1.02]	0.78 [0.66-0.93]	0.98 [0.65-1.48]	0.93 [0.73-1.19]
All deaths	0.94 [0.78-1.13]	0.86 [0.77-0.97]	0.85 [0.74-0.97]	1.05 [0.74-1.50]	0.95 [0.78—1.16]
Heart failure	0.96 [0.75-1.23]	1.05 [0.94-1.18]	0.87 [0.73-1.05]	1.11 [0.77-1.61]	0.85 [0.70-1.04]

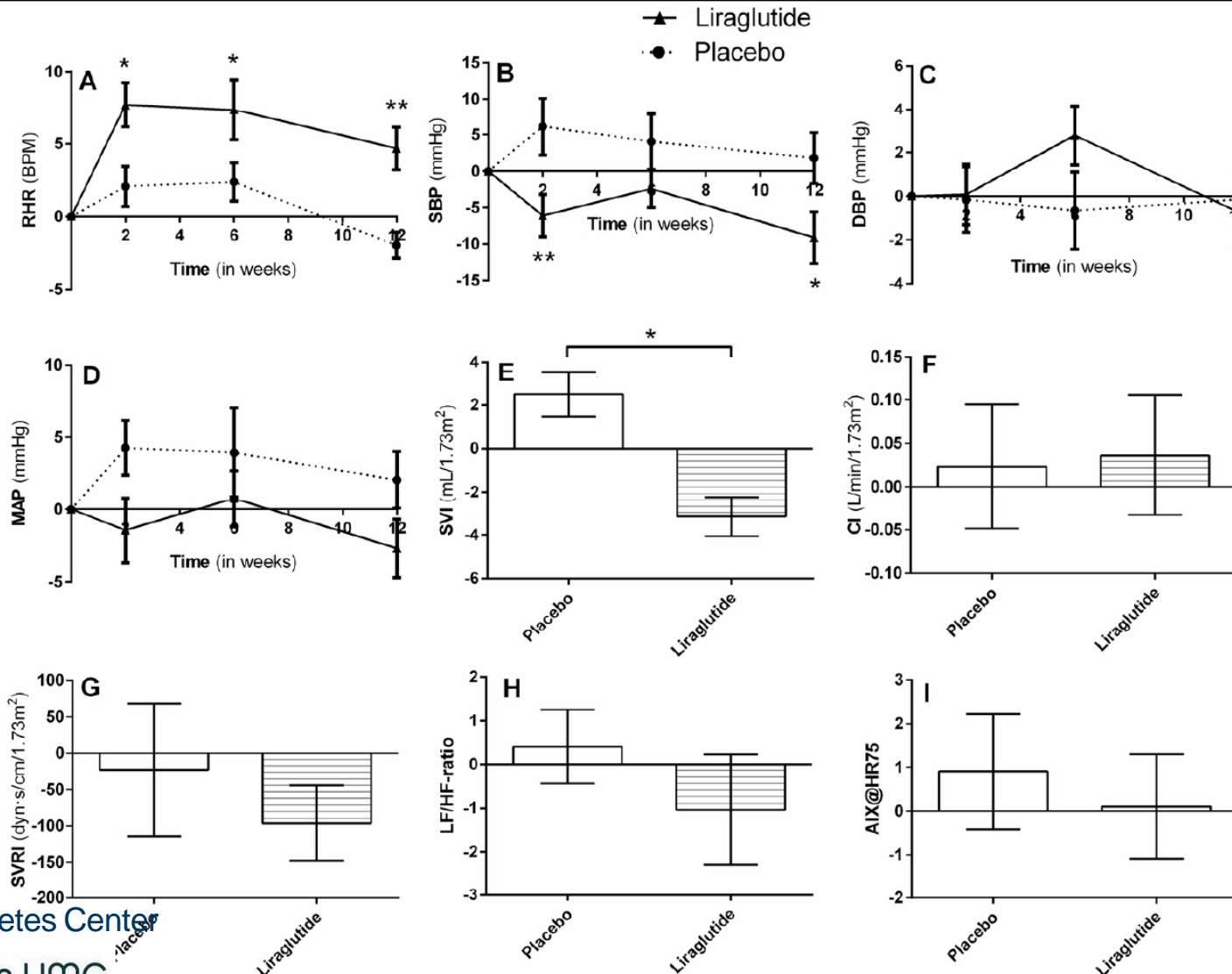
GLP-1 receptor agonist and blood pressure – long(er) term



Acute effects of GLP-1 RA on blood pressure



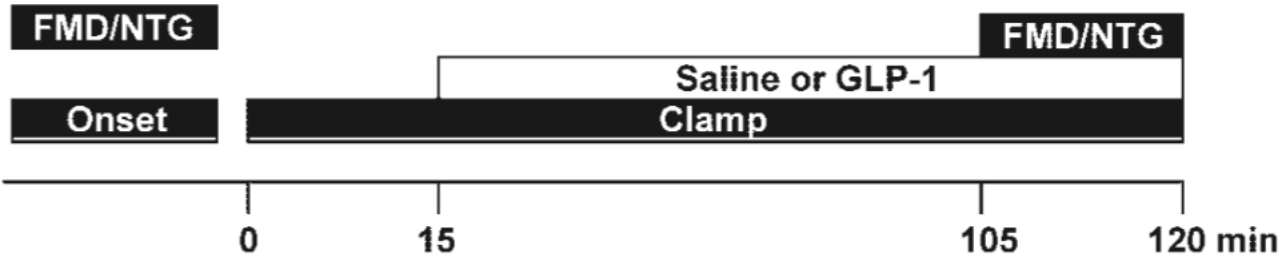
GLP-1 receptor agonist and blood pressure – long(er) term



Alternative hypotheses:

- Sodium excretion
- ANP secretion
- Smooth muscle relaxation
- Improvement endothelial function
- Secondary to weight loss

GLP-1 receptor agonists and endothelial function



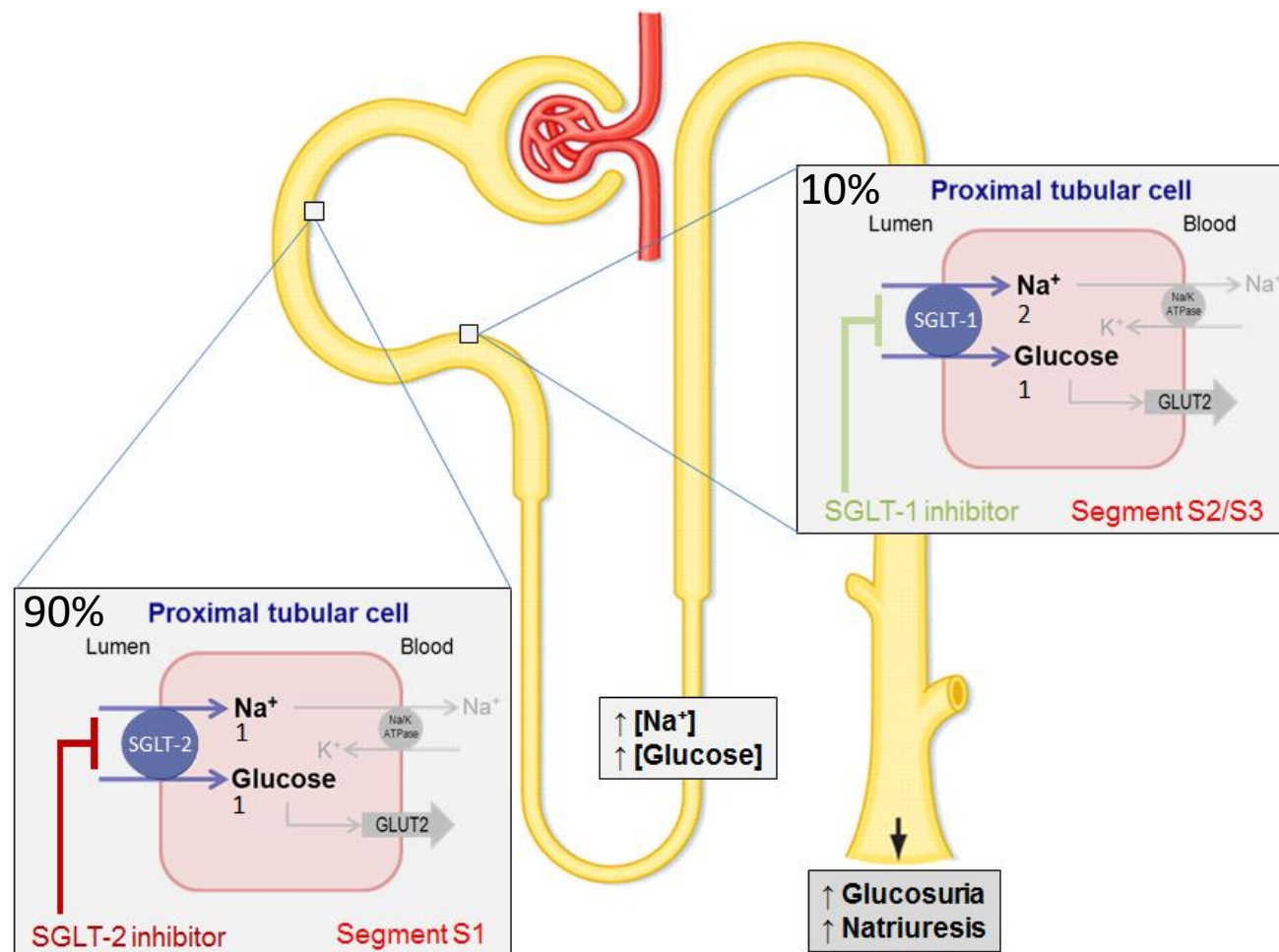
Variable	Saline		GLP-1	
	Onset	Clamp	Onset	Clamp
Baseline diameter FMD, mm	4.2±0.1	4.4±0.2	4.3±0.1	4.4±0.2
Maximal diameter FMD, mm	4.3±0.1	4.6±0.1	4.3±0.1	4.7±0.2
Δ FMD(%)	2.0±0.7	3.1±0.6	2.2±0.5	6.6±1.0*
Baseline diameter NTG, mm	4.3±0.1	4.5±0.2	4.3±0.1	4.5±0.2
Maximal diameter NTG, mm	5.0±0.1	5.1±0.1	5.0±0.1	5.2±0.1
Δ NTG(%)	17.5±2.0	14.5±2.0	16.7±1.5	16.5±2.4
Baseline flow FMD, ml/min	56±4	52±4	60±10	54±5
Maximal flow FMD, ml/min	166±9	161±11	162±12	167±18
Baseline flow NTG, ml/min	58±4	53±4	57±4	58±4
Maximal flow NTG, ml/min	64±4	62±3	67±4	69±4
Heart rate, beats/min	61±3	60±3	60±3	62±3
sBP, mmHg	127±5	125±4	124±4	127±3
dBP, mmHg	78±2	77±2	78±2	78±2

Conclusions - 1

- GLP-1 RA lower blood glucose levels by stimulating pancreatic islet-cell function while reducing body weight
- GLP-1 RA improve cardiovascular outcomes through uncertain mechanisms (atherosclerosis-related?)
- GLP-1 RA acutely increases blood pressure, while reducing it after more prolonged use, mechanisms remain poorly understood

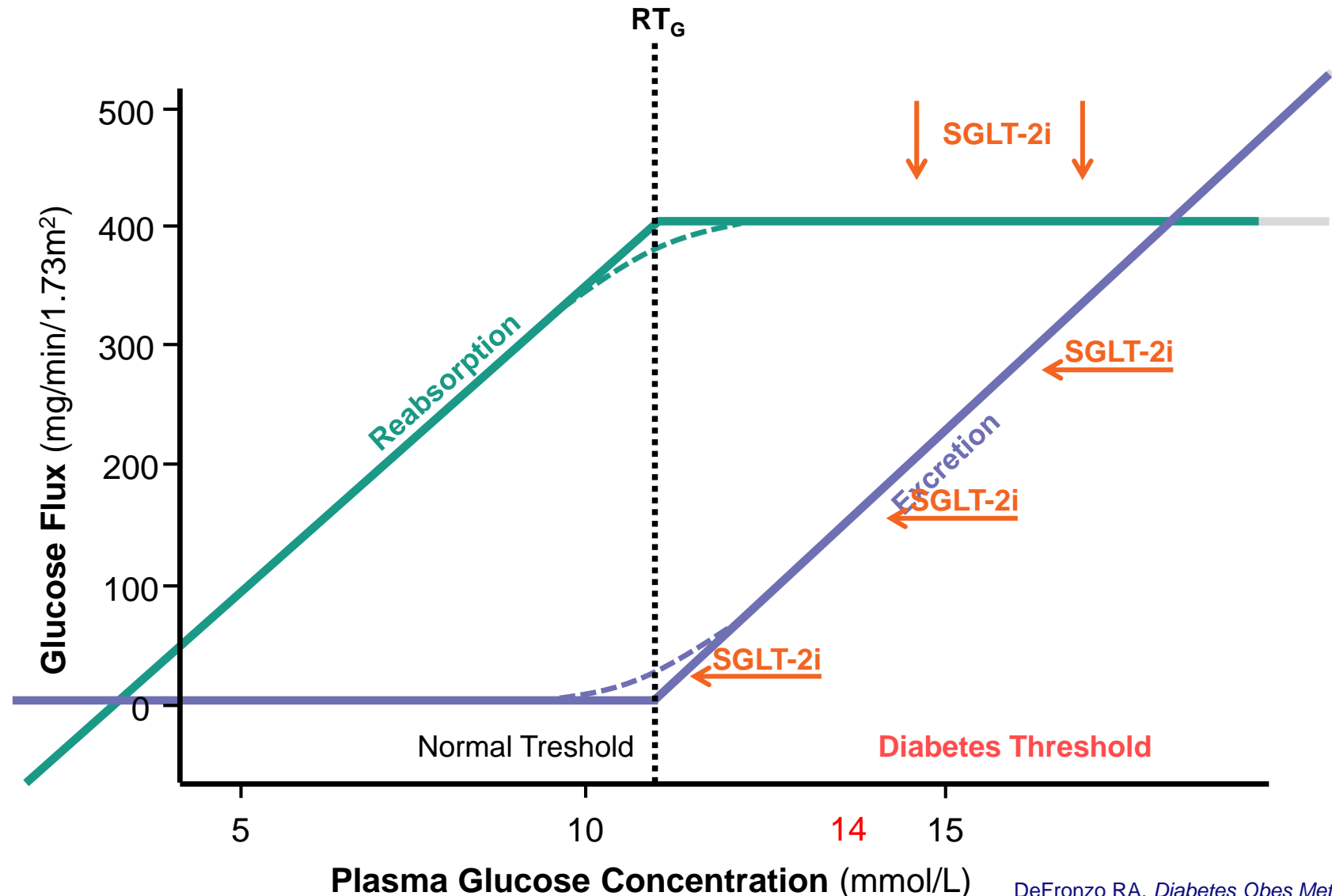
Sodium-glucose co-transporter 2 inhibitors

- 180 g of glucose is filtered per day
- Complete tubular reabsorption
- Sodium-glucose linked transporters
- SGLT-1 and SGLT-2
- Upregulation of SGLT-2 in T2D

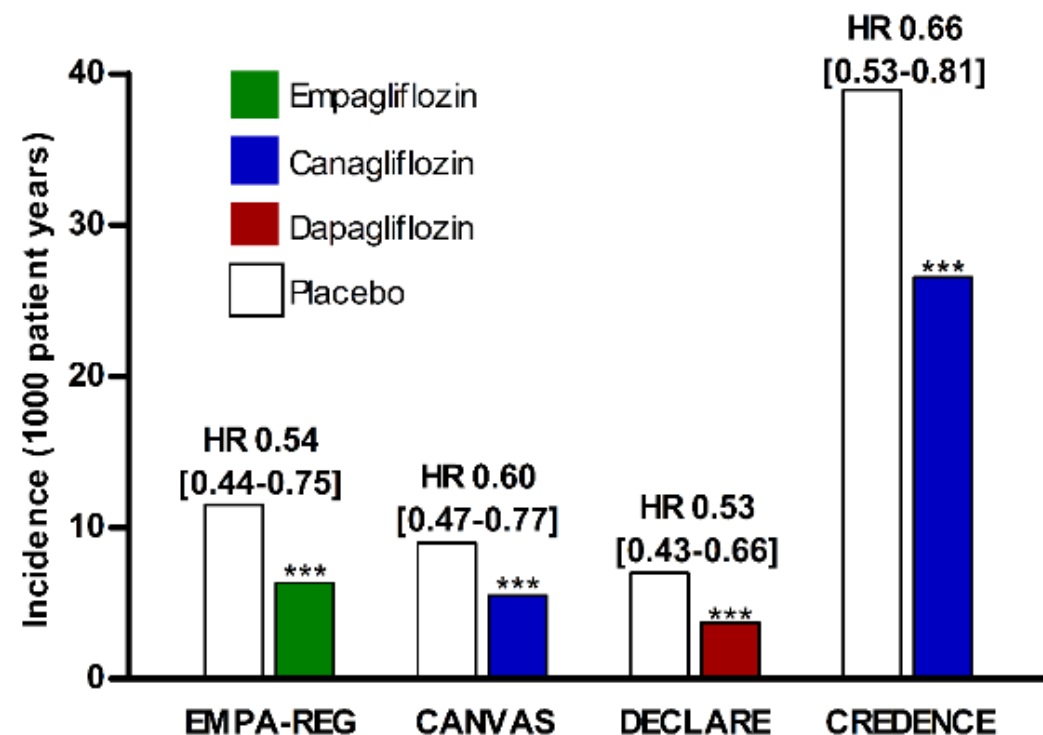
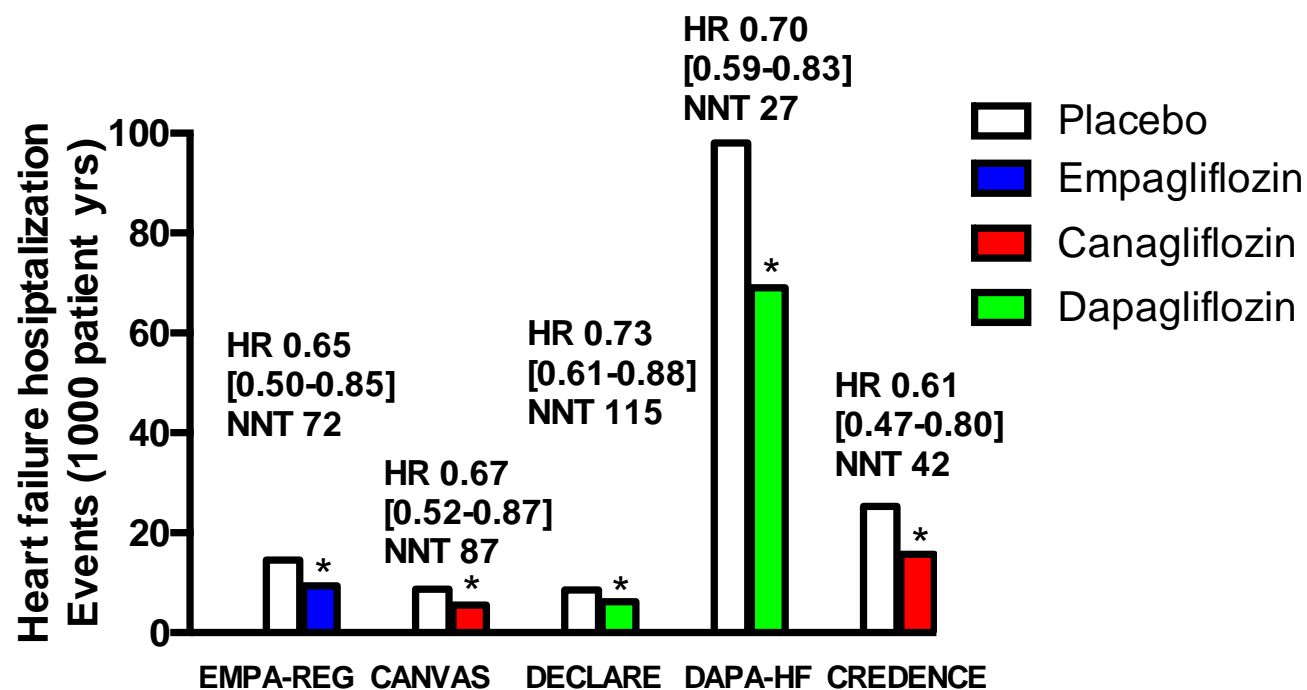


SGLT-2 inhibitors

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin

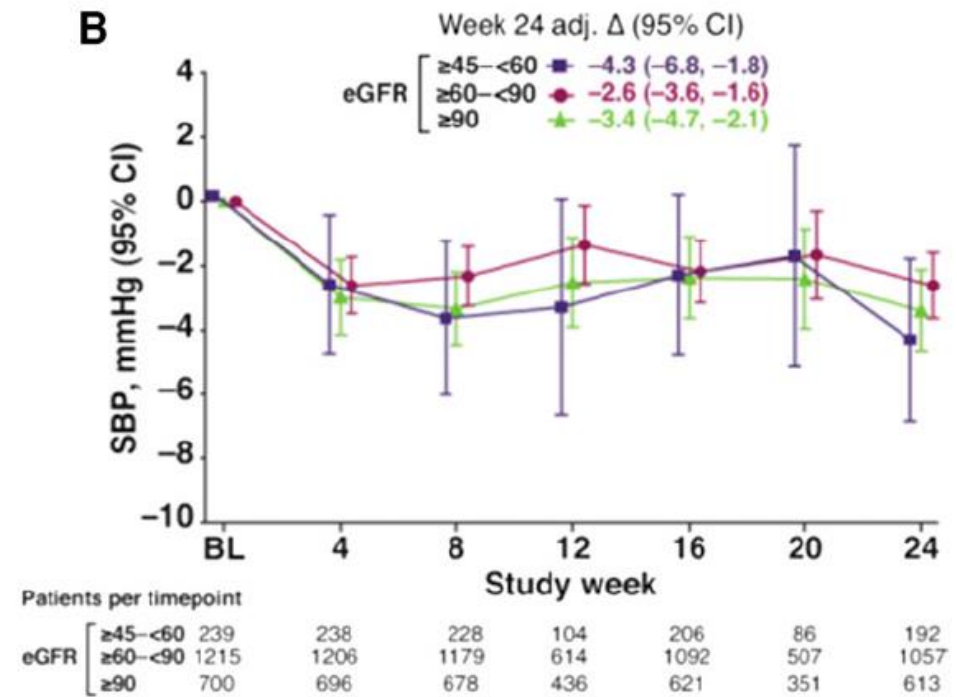
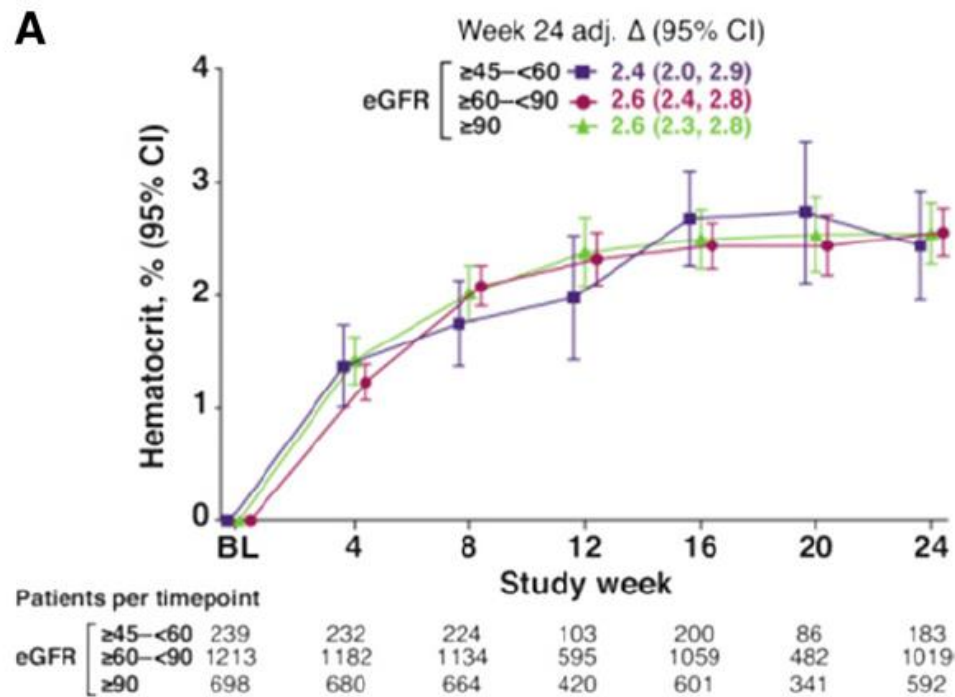


SGLT2 inhibitors improve CV and renal outcomes in T2D

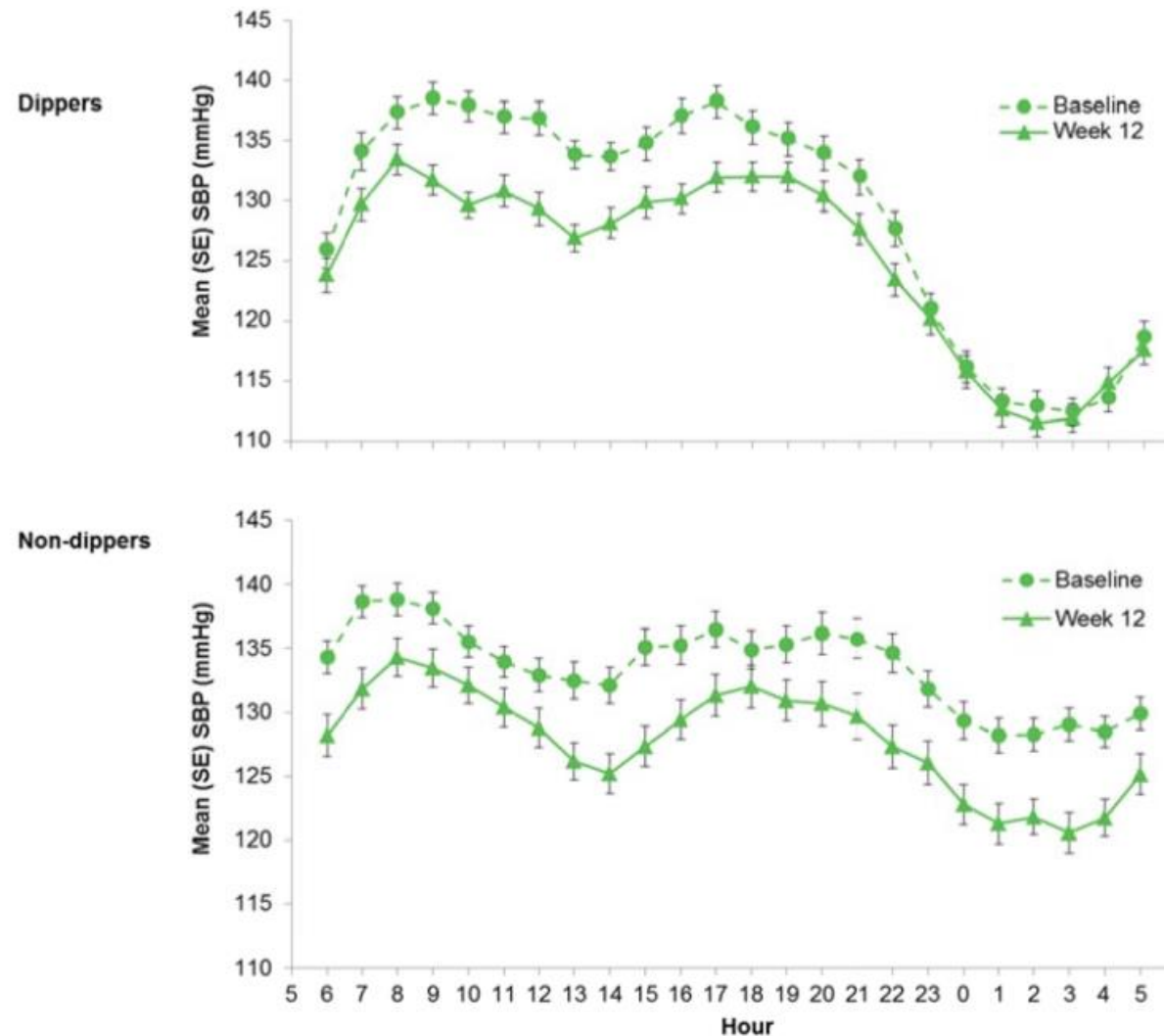


(40-50% eGFR reduction; end-stage renal disease; renal death)

SGLT2 inhibitors lower blood pressure

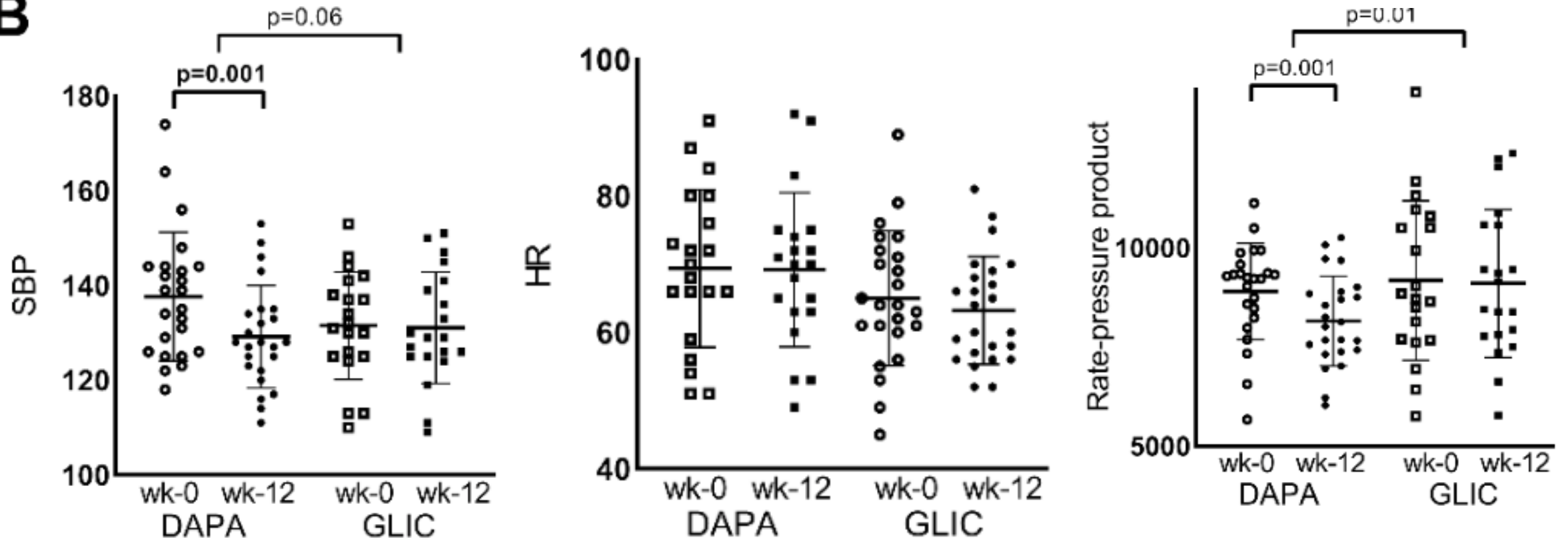


Blood pressure effects – restoration of dipping pattern

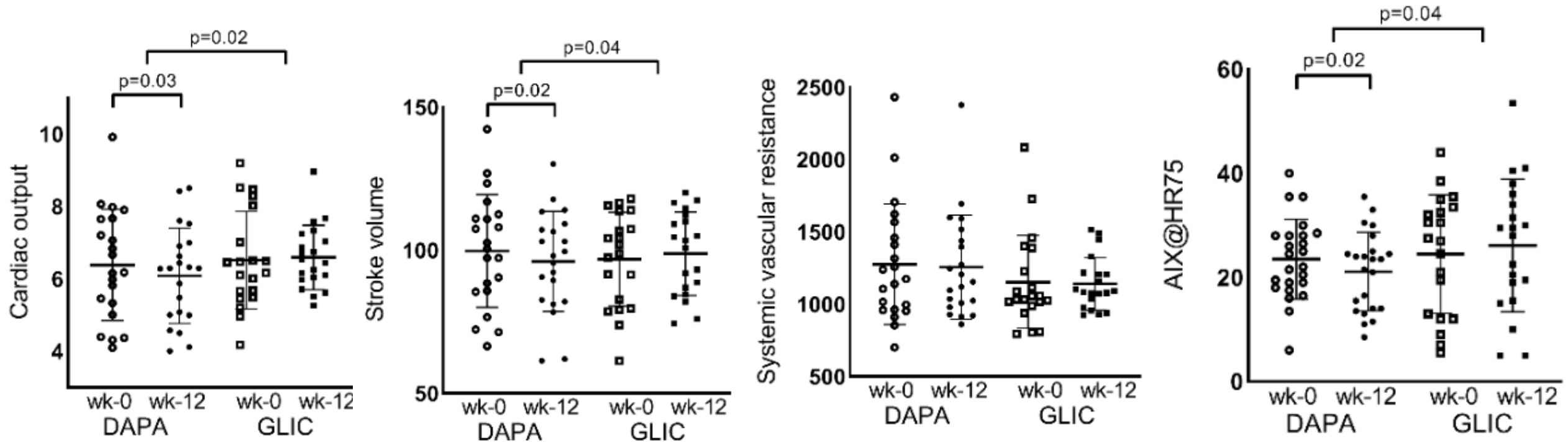


SGLT2 inhibition and systemic hemodynamics

B

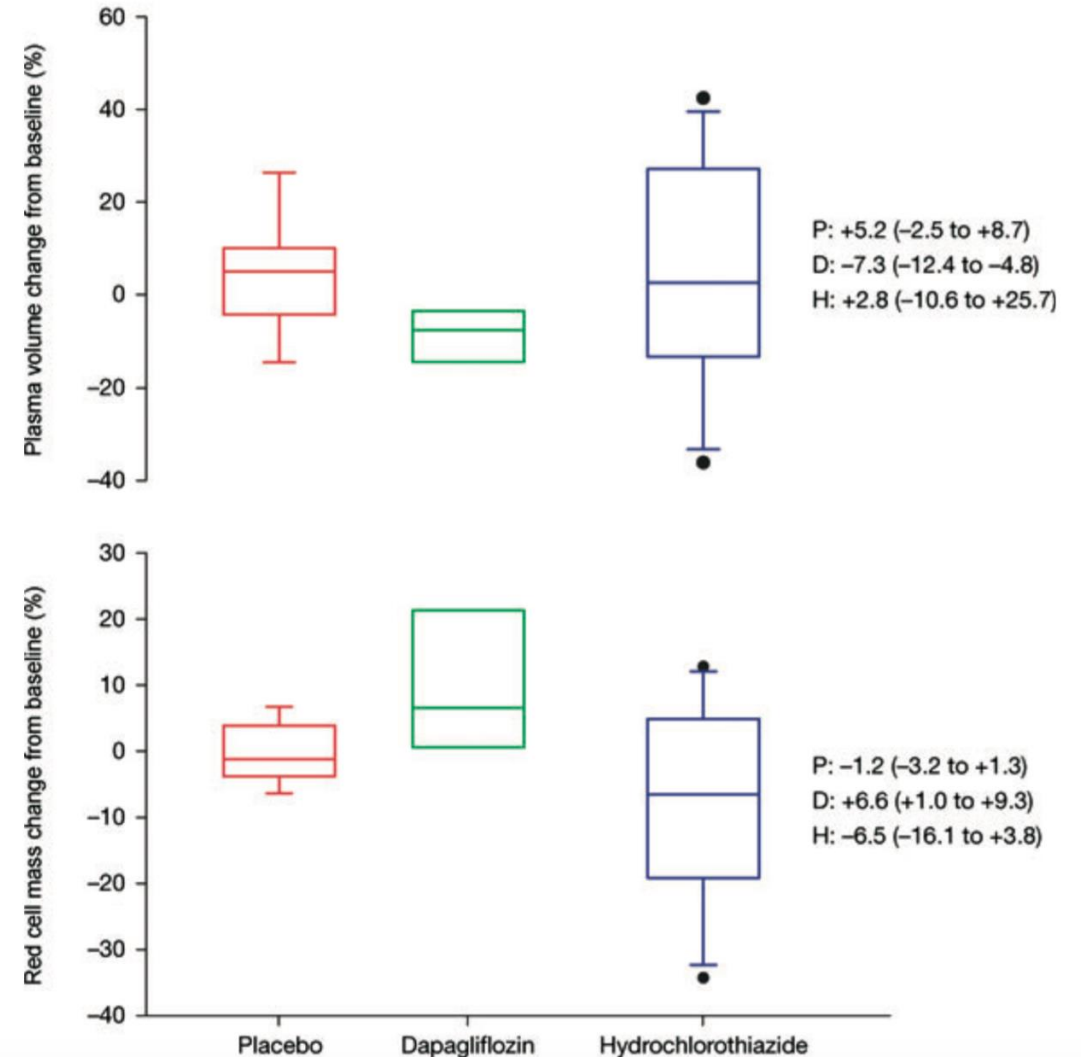
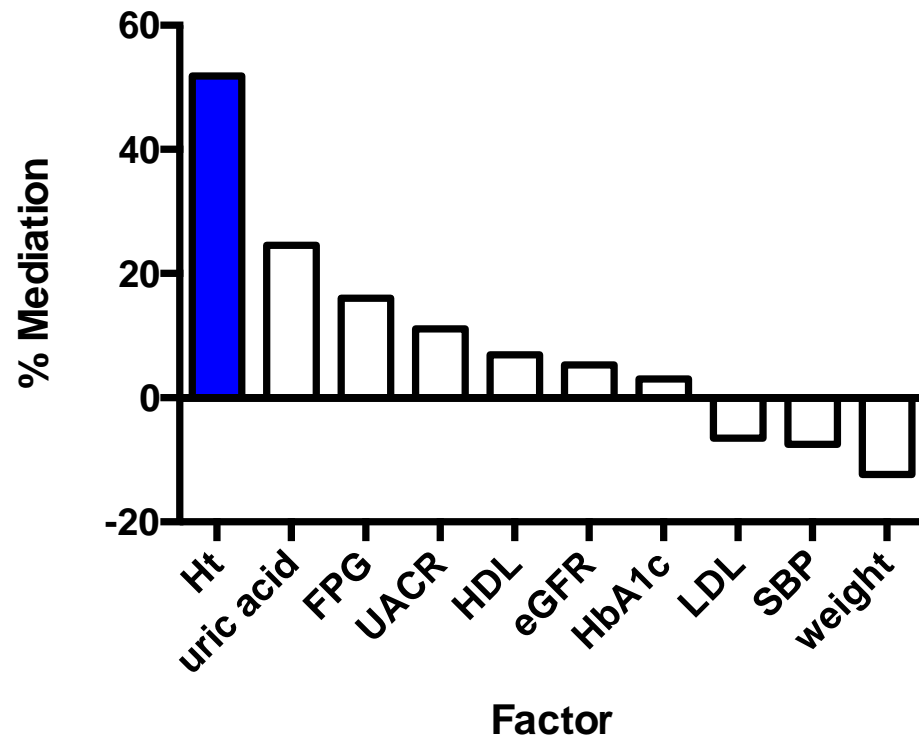


SGLT2 inhibition and systemic hemodynamics

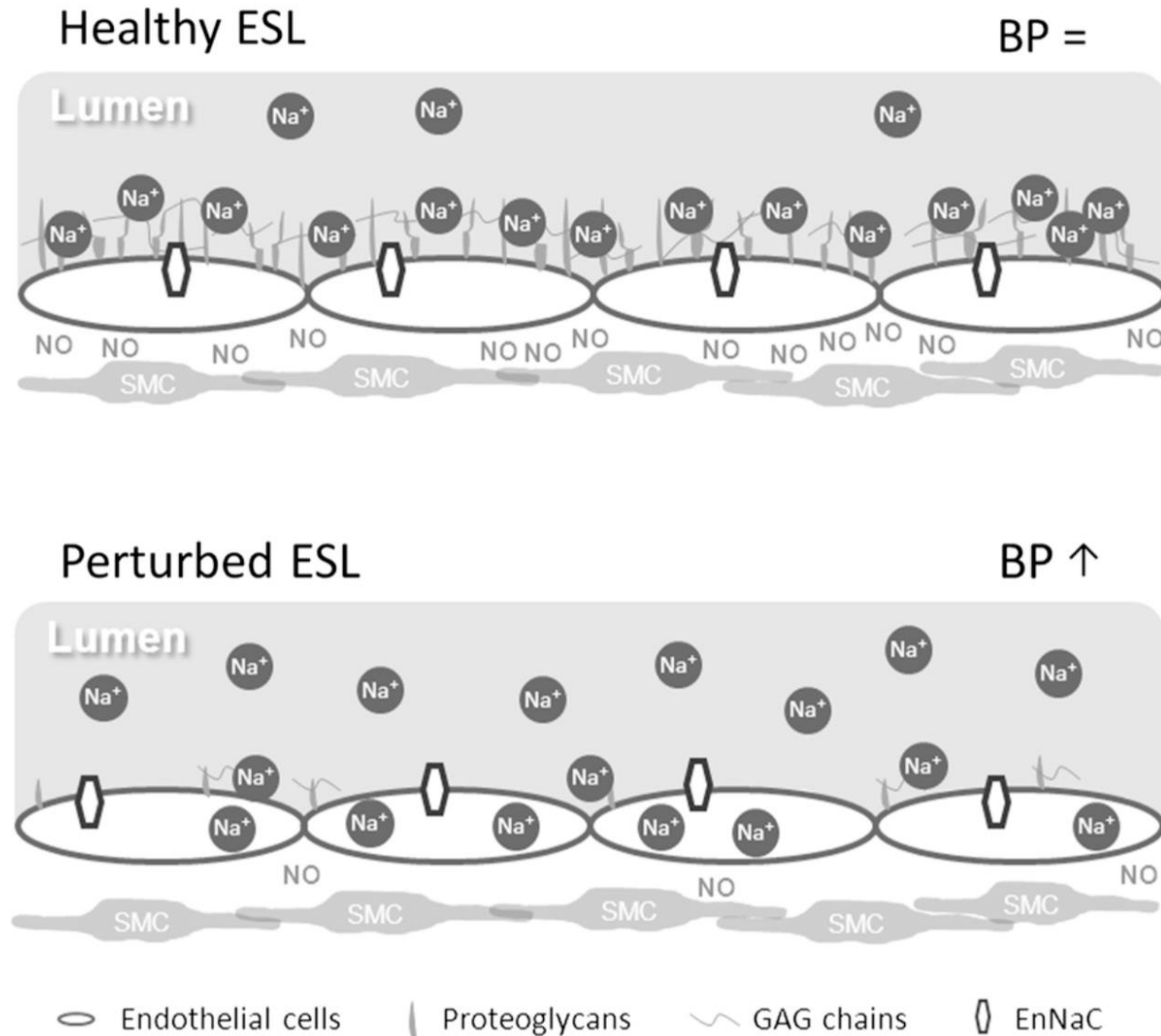


SGLT2 inhibition and plasma volume

EMPA REG OUTCOME trial empagliflozin



Non-osmotic sodium storage



Tissue sodium content

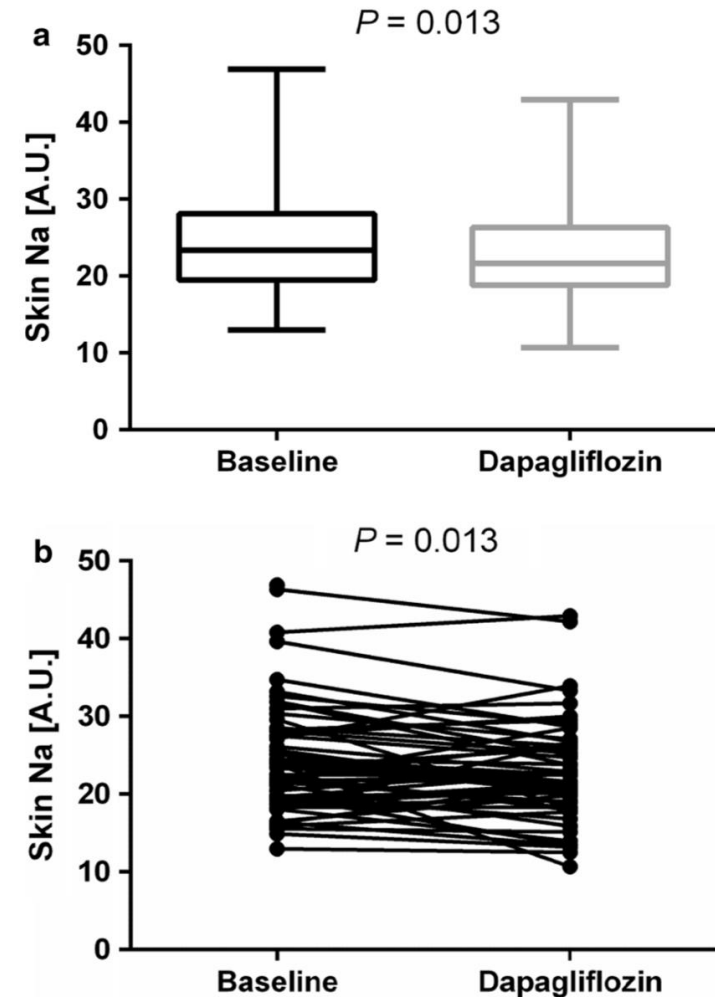
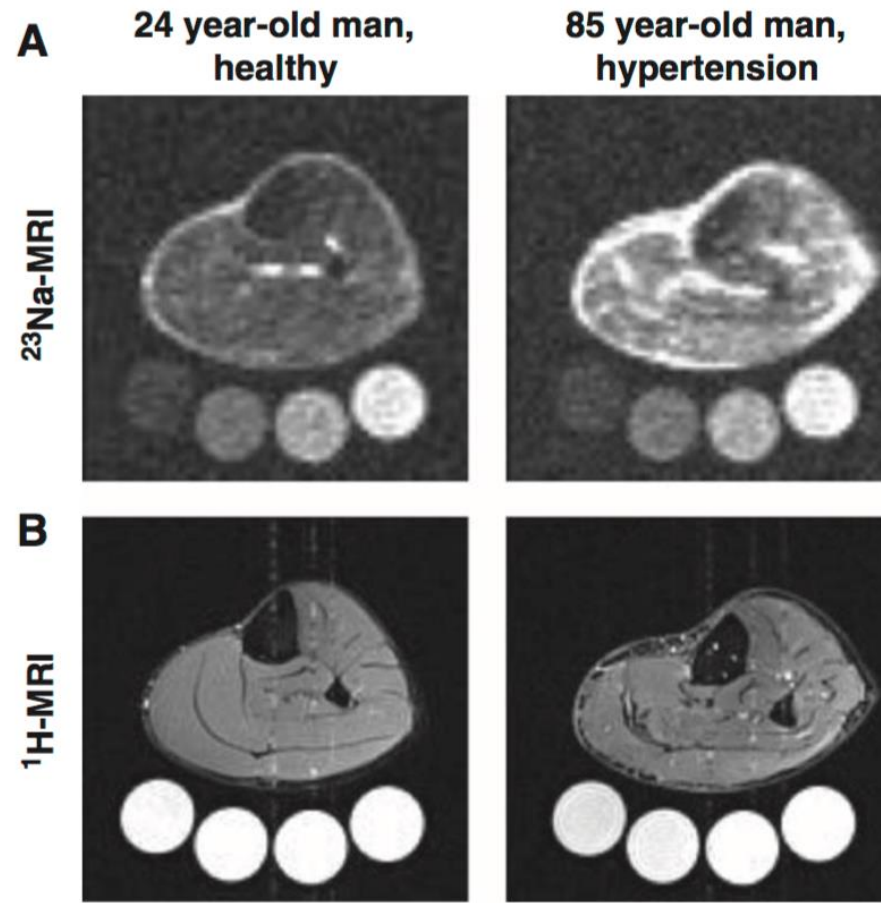


Fig. 1 Box and whisker plot (**a**) and linear graphic (**b**) of changes in skin sodium content after 6 weeks treatment with dapagliflozin

Conclusions - 2

- SGLT-2 lower blood glucose levels through glucosuria
- SGLT-2 cardiorenal outcomes likely through alterations in sodium handling
- SGLT-2 inhibitors reduce blood pressure; maybe by reducing body sodium content or direct cardiovascular actions

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

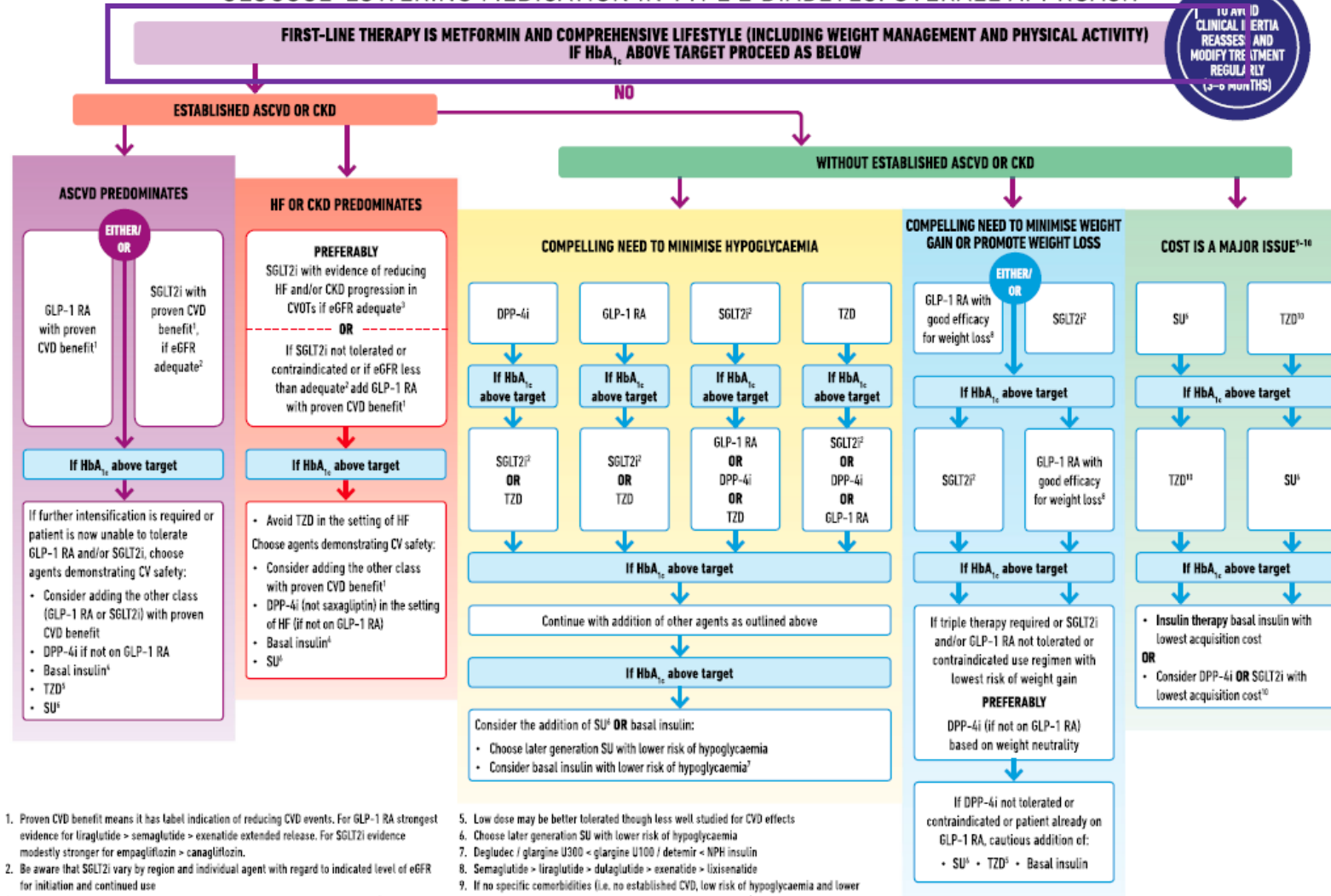


Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

+ indication for DKD by FDA
For SGLT2 inhibitors

Future perspectives

- Await further cardiovascular and heart failure outcome trials including patients without diabetes (SGLT2)
- Outcome in non-diabetes CKD (EMPA-KIDNEY and DAPA CKD) for SGLT2
- Effects of combination therapies (particularly with GLP-1 receptor agonists)
- Novel molecules that are in development (Combined GLP-1/GIP agonists)
- More mechanistic studies that may provide further guidance

Diet and exercise (education) remain crucial...

