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Inibidores de SGLT2: do controle glicêmico ao tratamento da insuficiência cardíaca

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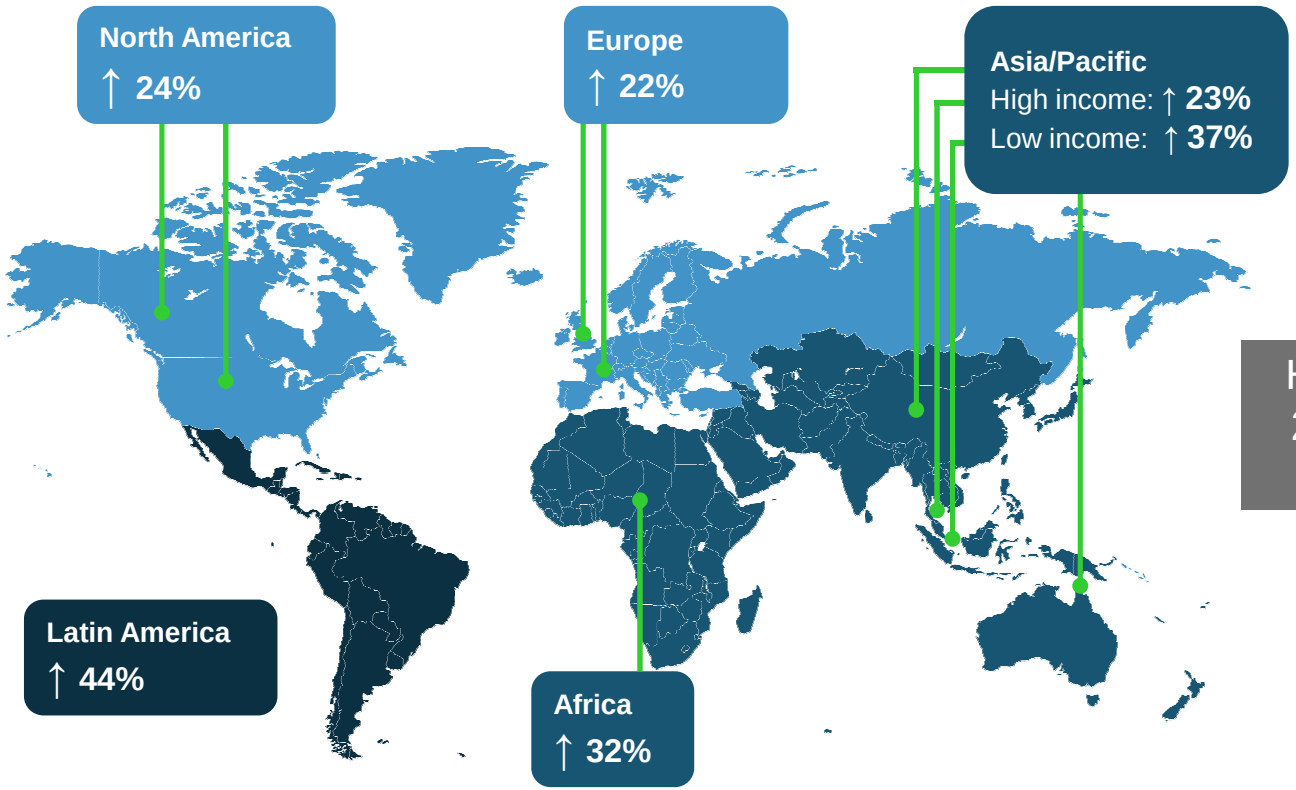
*Potenciais conflitos de interesse: Coordenador Nacional dos estudos DECLARE e DAPA-HF, citados na apresentação; relação completa no www.ACC.org

The global burden of heart failure is substantial and is on the rise

10 year growth in prevalent CHF cases from 2016[1]



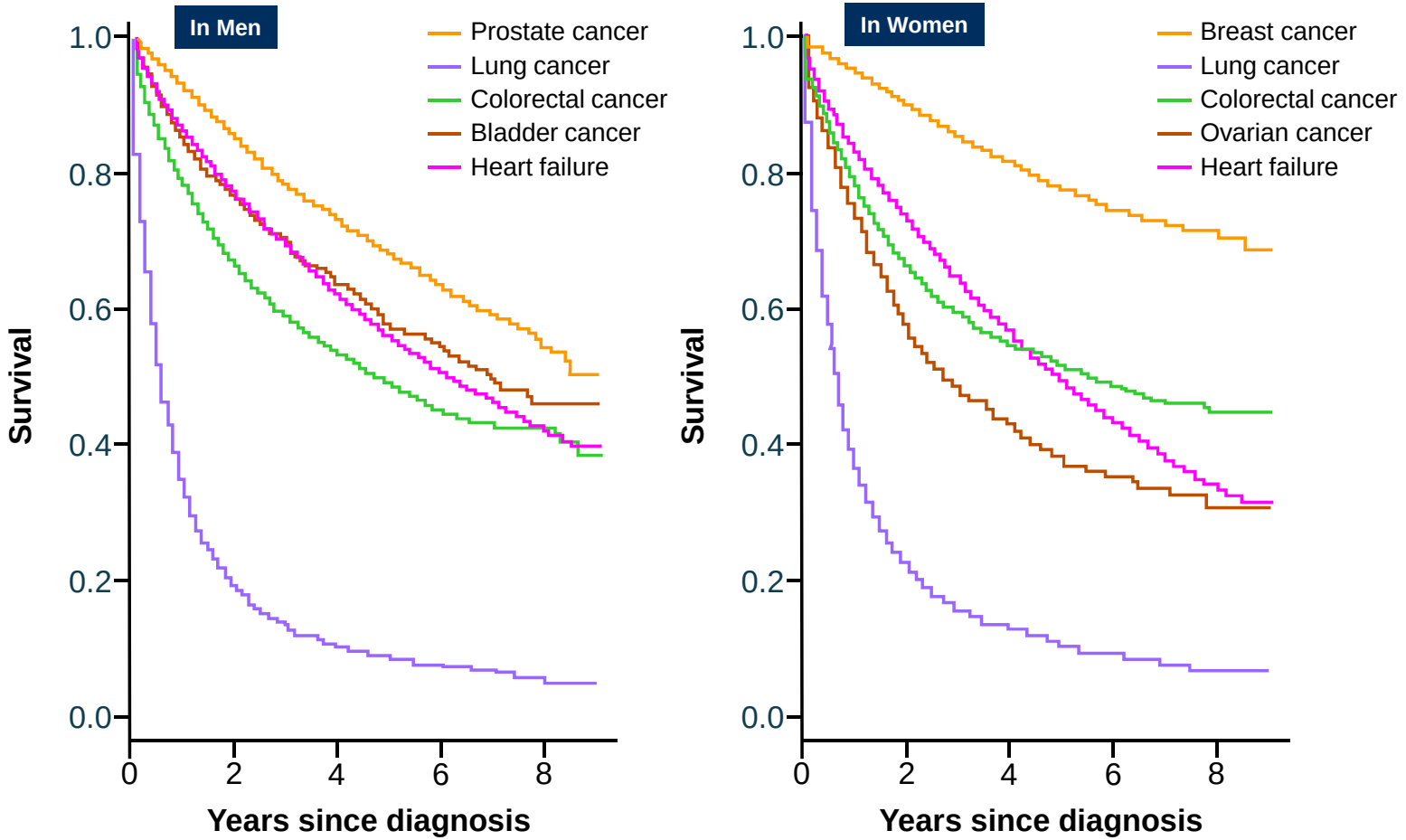
Heart failure currently affects at least 26 million people worldwide and this burden is projected to grow[2]

HF, heart failure

1. Kaur R, et al. *Eur Heart J* 2017;38:ehx502.P2452; 2.Savarese G and Lund LH. *Card Fail Rev* 2017;3:7–11

Despite advances in management, HF remains as ‘malignant’ as some of the common cancers in both men and women

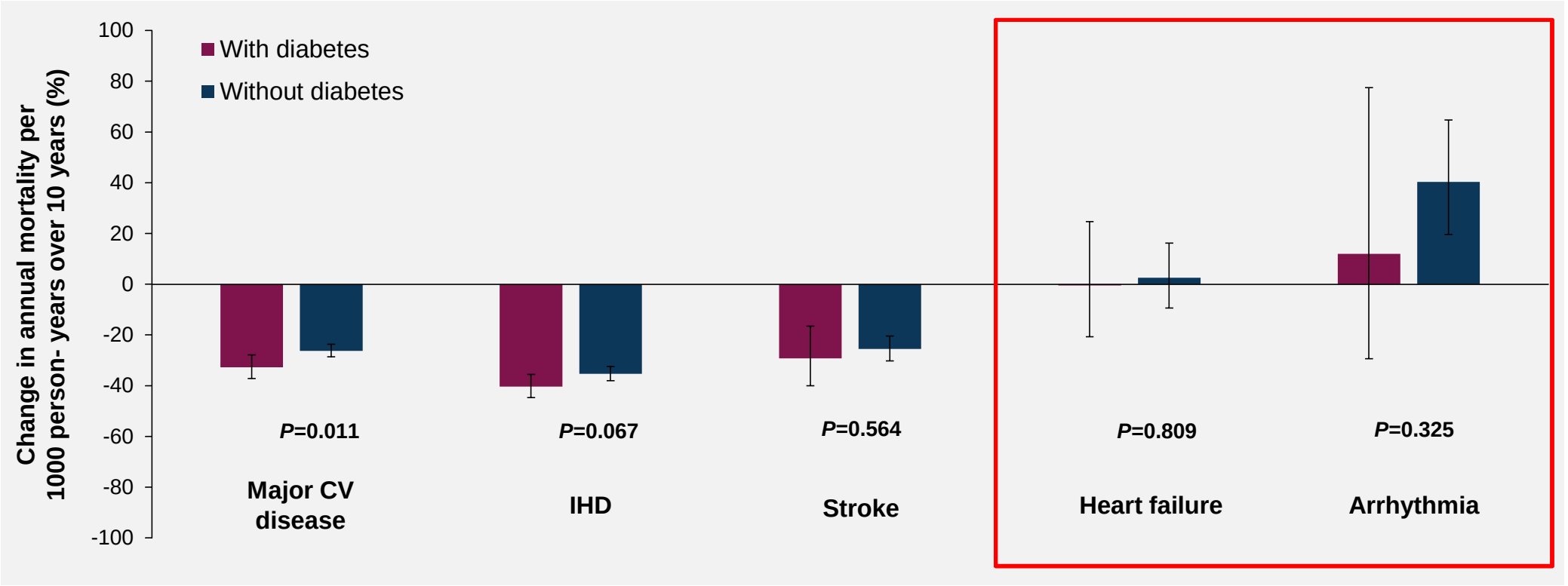
Despite advances in care, men and women with a diagnosis of HF continue to have worse survival than patients with one of several common cancers



HF, heart failure
Mamas MA, et al. *Eur J of Heart Failure* 2017;19:1095–1104

Mortality improvements have been seen in major CV disease and atherosclerosis but not heart failure or arrhythmia in the US

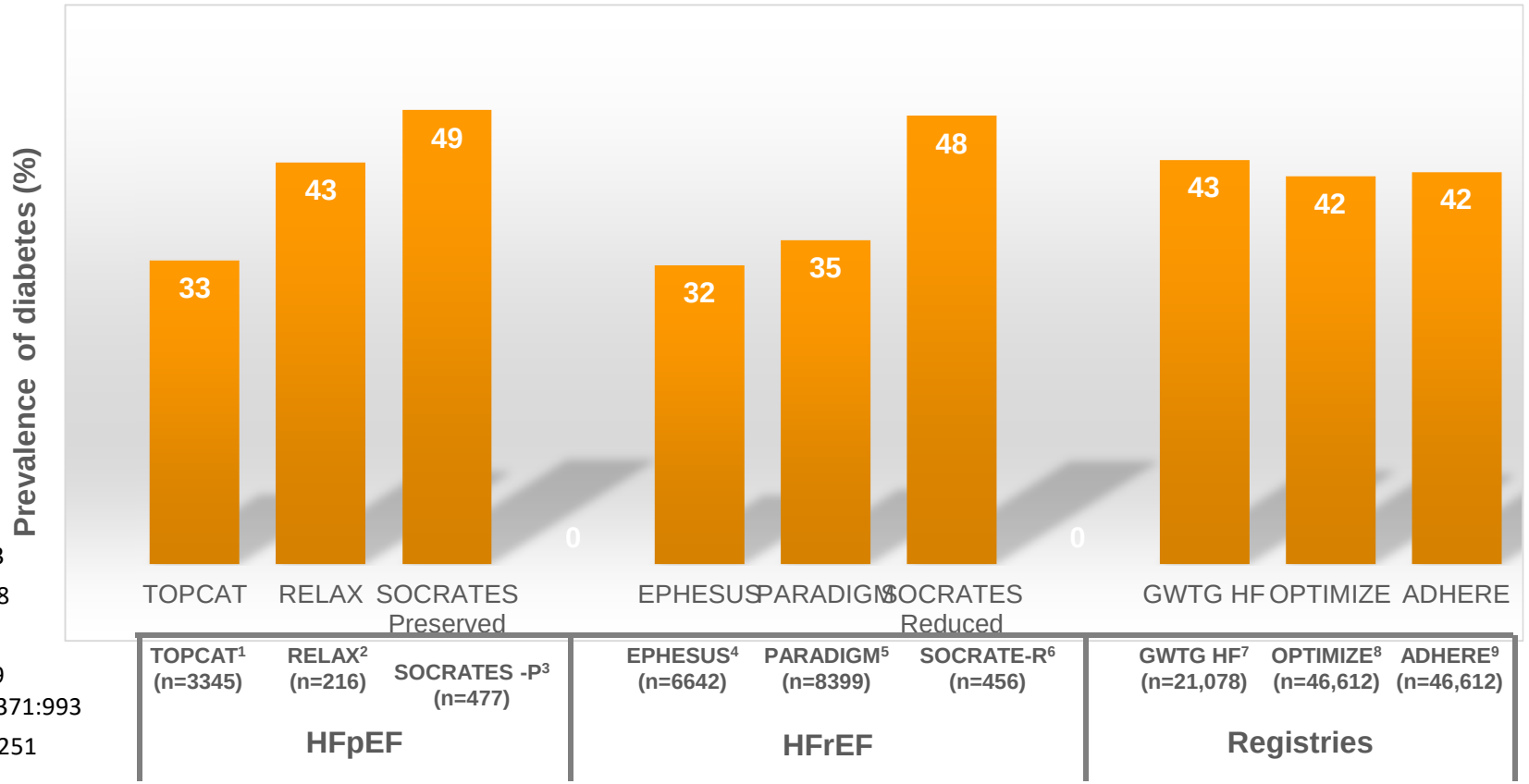
Data from the US National Health Interview Survey was used to analyze 677,051 adults over a mean follow-up period of 11.8 years from 1988 to 2015



CV = cardiovascular; IHD = ischemic heart disease; US = United States.
Cheng YJ et al. *Diabetes Care.* 2018;41:2306-2315.

Diabetes is Common Among Patients With HF

- Prevalence of diabetes at baseline: selected clinical trials and registries in patients with HF*



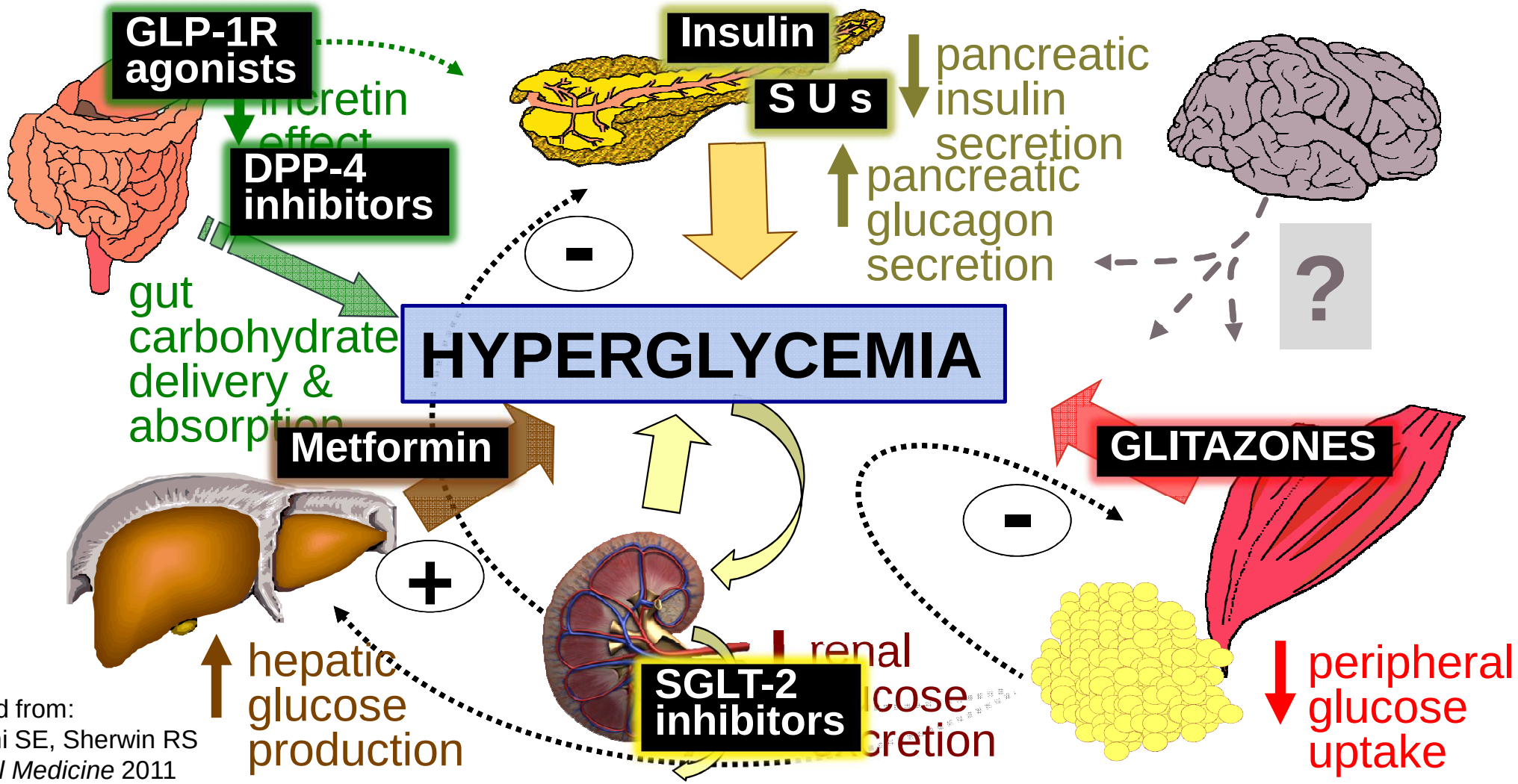
References

1. Pitt B *et al. N Engl J Med* 2014;390:1383
2. Redfield MM *et al. JAMA* 2013;309:1268
3. Pieske B *et al. Eur Heart J* 2016;38:1119
4. Pitt B *et al. N Engl J Med* 2003;348:1309
5. McMurray JJV *et al. N Engl J Med* 2014;371:993
6. Gheorghiade M *et al. JAMA* 2015;314:2251
7. Luo N *et al. JACC Heart Fail* 2017;5:305
8. Greenberg BH *et al. Heart J* 2007;154:277.e12277.e8

Of the non-diabetic HF patients, up to 50% have prediabetes

Study name	Study population	Country	N	Definition of prediabetes	Prediabetes* (%)
Goode 2009	Prospective, **stable** HF clinic **outpatients**	UK	970	**HbA1c** > 6.0	**50.0%**
Suskin 2000 (RESOLVD Study)	Baseline data of a multinational study; HF patients with **NYHA II-IV** & **EF <40%**	Multi	487	**FPG** > 6.1 mmol/L	**23.0%**
				Fasting **insulin resistance** index values ≥ 2·7	**33.0%**
Matsue 2011	Patients **admitted** with a diagnosis of congestive HF	Japan	94	**IGT:** FPG < 126 mg/dl + OGTT 2-h glucose ≥ 140 mg/dl OR FPG 110–125 mg/dl + OGTT 2-h glucose <140 mg/dl	**39.4%**
Witteles 2004	Clinic outpatients with stable HF and **IDCM**	US	43	**IGT**: OGTT 2-hour glucose level 140-199 mg/dl	**27.9%**
Egstrup 2011	Consecutive patients with SHF and **EF ≤ 45%** referred to a heart failure clinic	Denmark	227	**IGT:** FPG <7.0 mmol/L + OGTT 2-h glucose 7.8-11.1 mmol/L	**22.5%**

The 7 Major Glucose-Lowering Drug Classes in Use in Patients with T2DM in US & Europe



Adapted from:
Inzucchi SE, Sherwin RS
in: *Cecil Medicine* 2011

2 + 2 + 2 + 1 = 7

GLP-1R agonists

DPP-4 inhibitors

"incretin enhancers"

Insulin

S U s

"insulin providers"

Metformin

"insulin sensitizers"

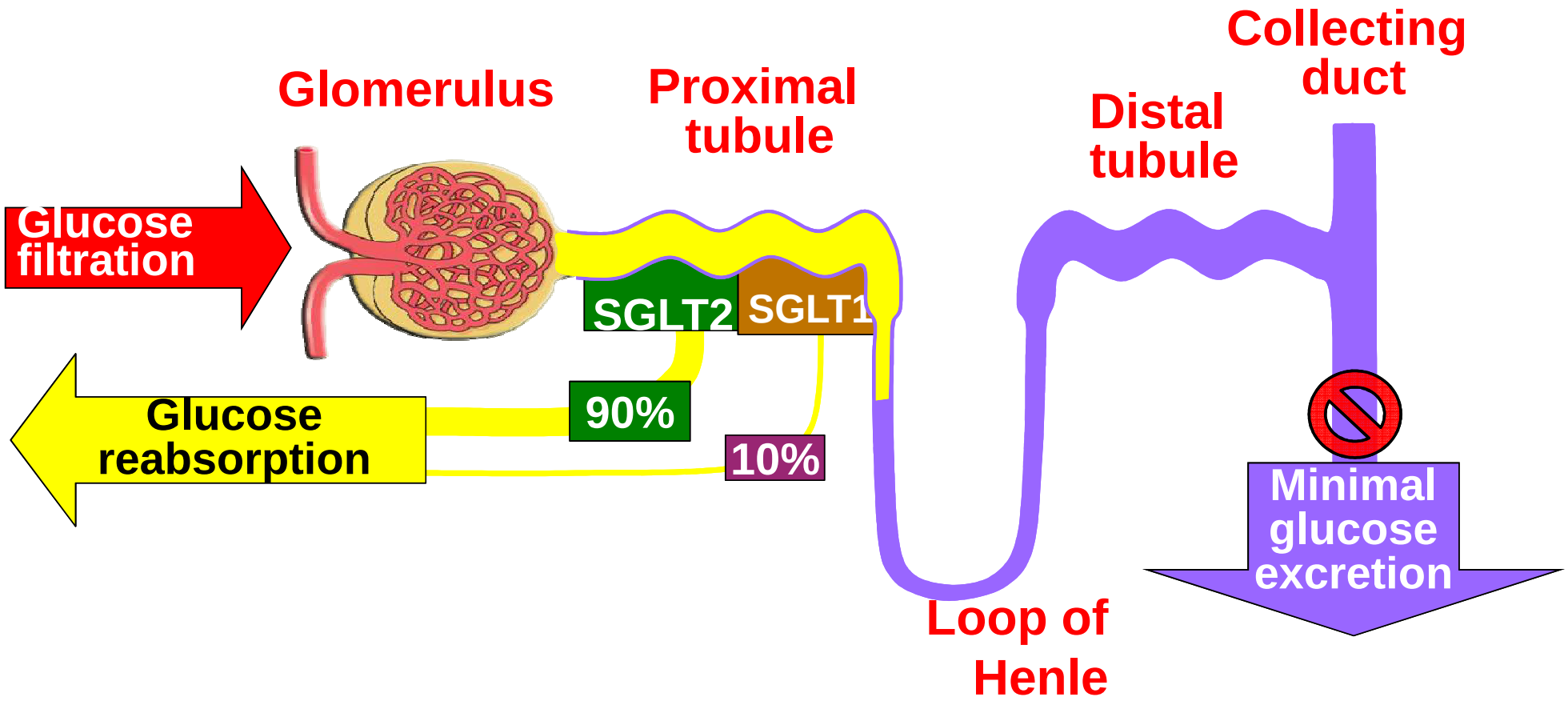
GLITAZONES

SGLT-2 inhibitors

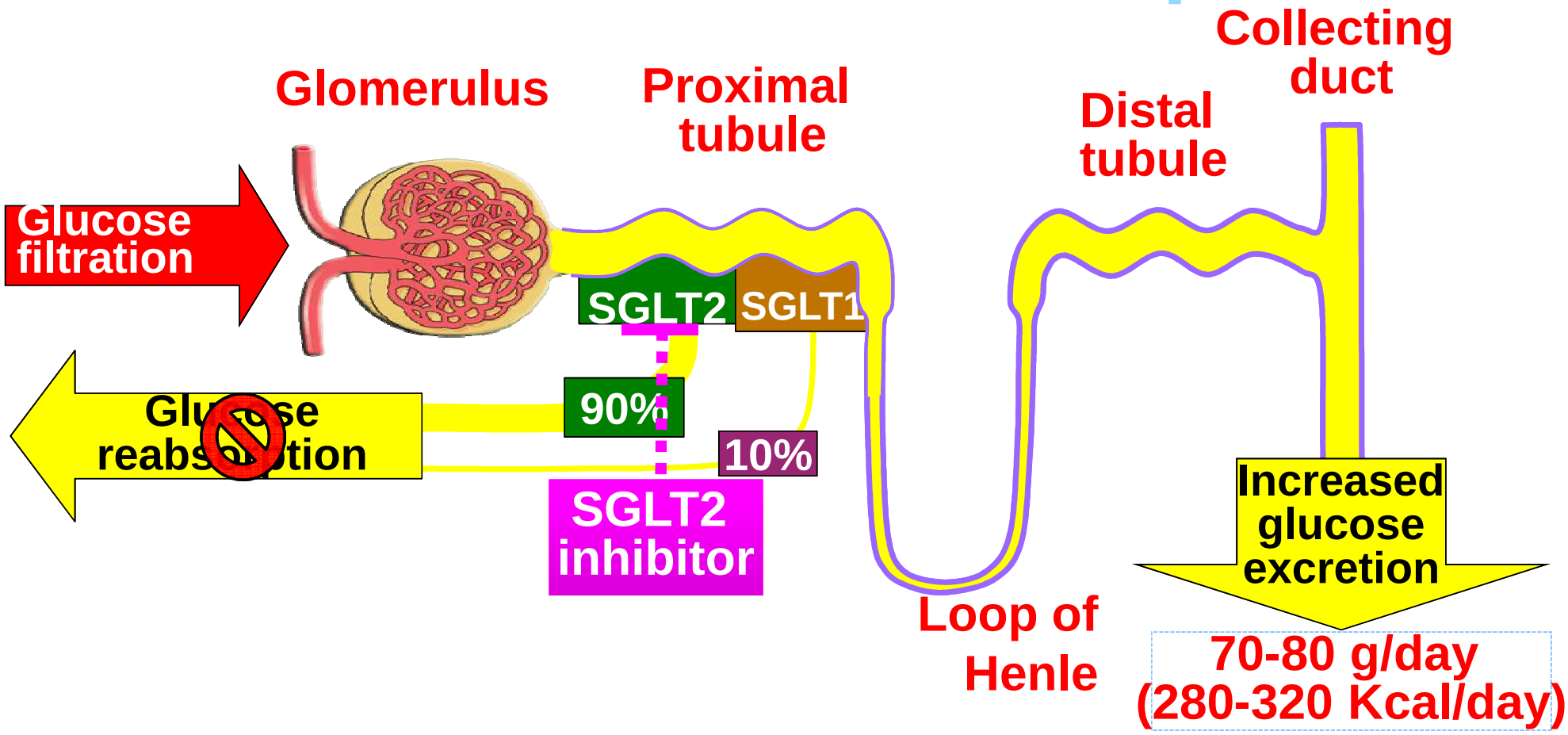
"glucose excreter"

Adapted from:
Inzucchi SE, Sherwin RS
in: *Cecil Medicine* 2011

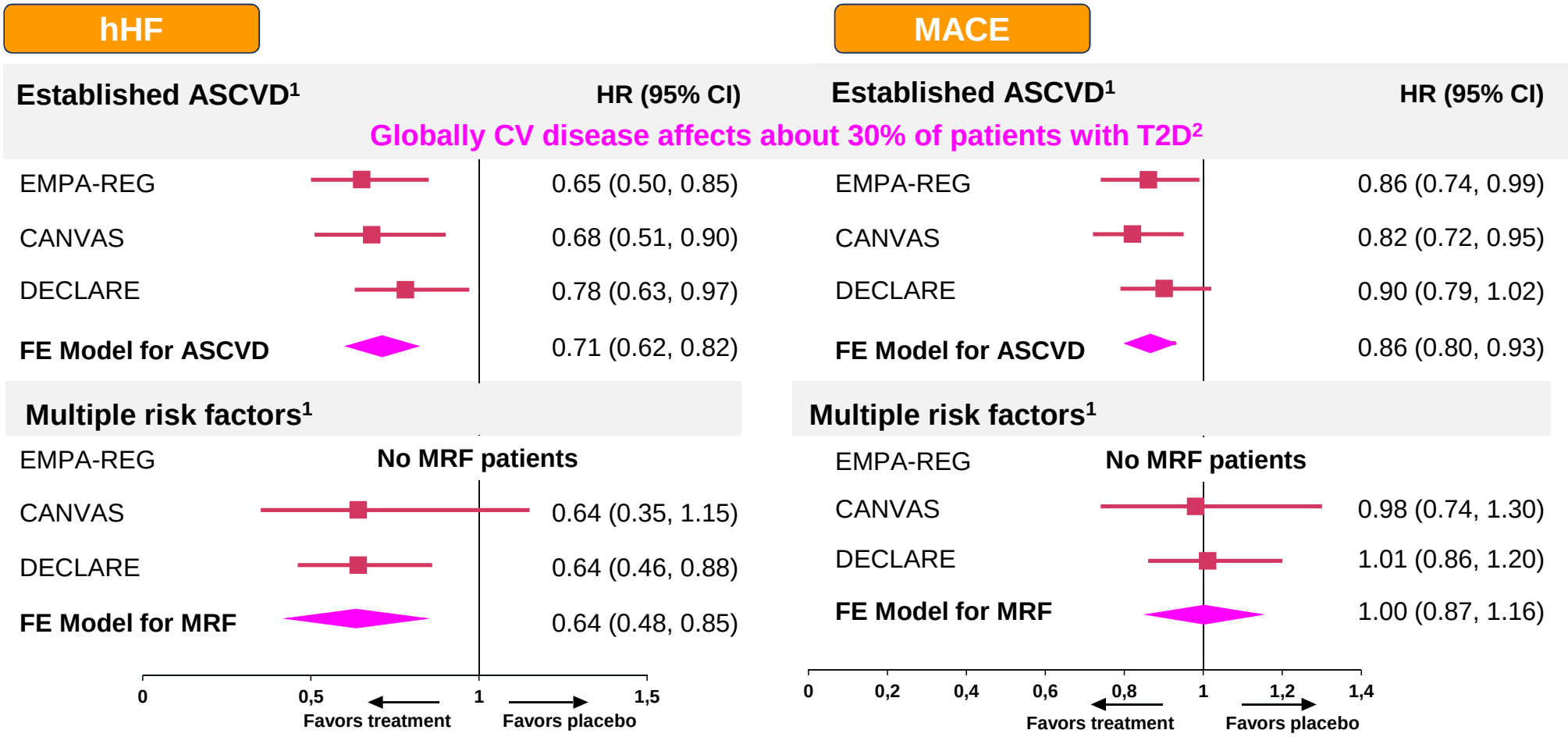
Normal Physiology of Renal Glucose Homeostasis



SGLT2 Inhibition Reduces Renal Glucose Reabsorption



SGLT2i CVOT meta-analysis

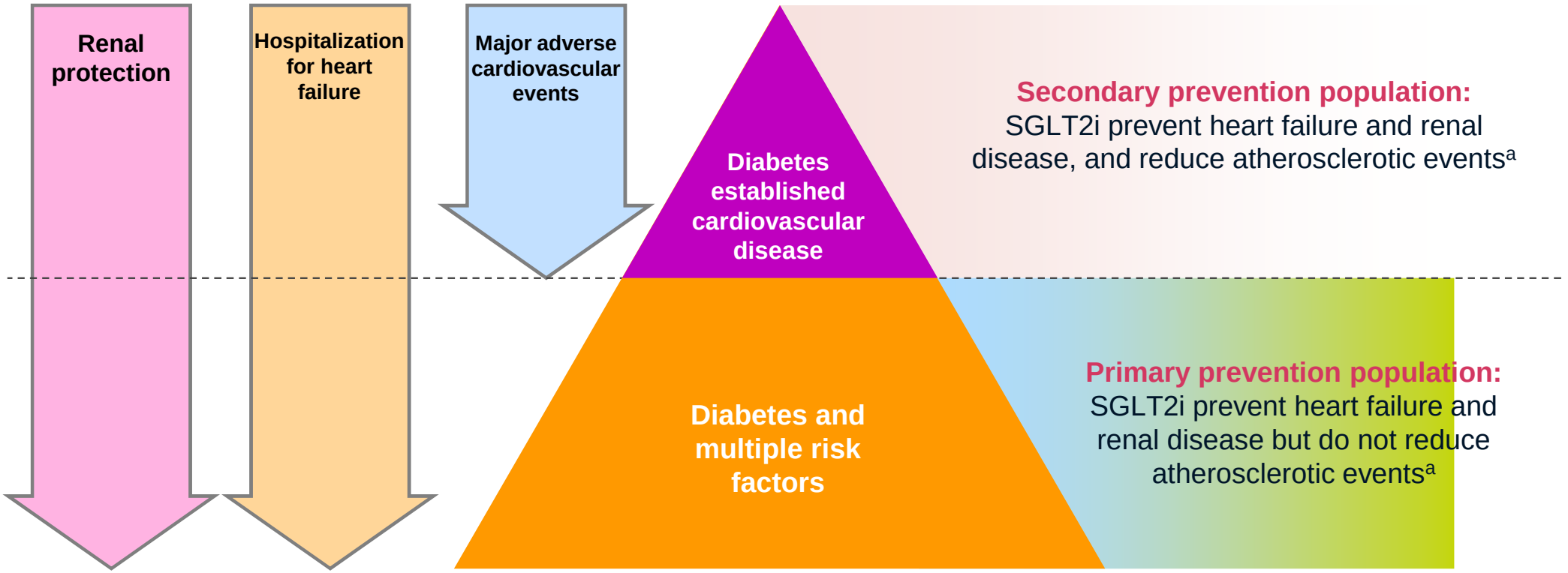


ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; hHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MRF, multiple risk factors; T2D, Type 2 diabetes

1. Zelniker TA, et al. *Lancet*. 2019;393:31–39; 2. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83

Pump, pipes and filter: SGLT2i covers it all

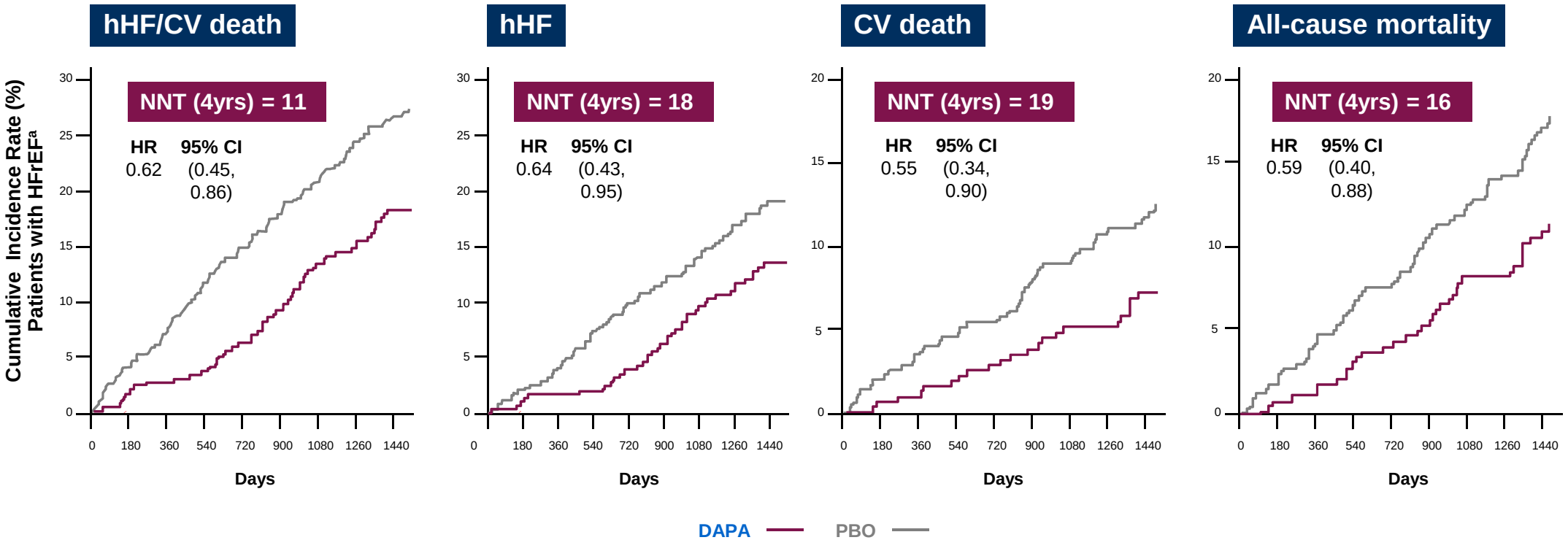
Cardiorenal efficacy of SGLT2i



[a]Defined as MACE
MACE, major adverse cardiovascular events; SGLT2i, sodium–glucose cotransporter 2 inhibitor
Verma S, et al. *Lancet* 2019;393:3–5

Kato et al, Circulation 3/19

The CV benefits of dapagliflozin appear early in T2D patients with HFrEF[a]



[a]Defined as EF <45% or severe/moderate LV systolic dysfunction, with or without history of HF. CV = cardiovascular; DAPA = dapagliflozin; EF =ejection fraction; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; HR = hazard ratio; LV = left ventricular; NNT = number needed to treat; PBO = placebo; T2D = type 2 diabetes; yrs = years.

Kato ET et al. Online ahead of print. *Circulation.* 2019.

Statins for the treatment of HF

- Statins help everyone and everything
- Great epidemiologic data that they help in HF
- Subgroups of statin trials of patients with HF showed substantial benefit
  - These subgroups were similar size to the subgroups with HF in the SGLT-trials
- It’s a no-brainer that it will help HF especially ischemic HF

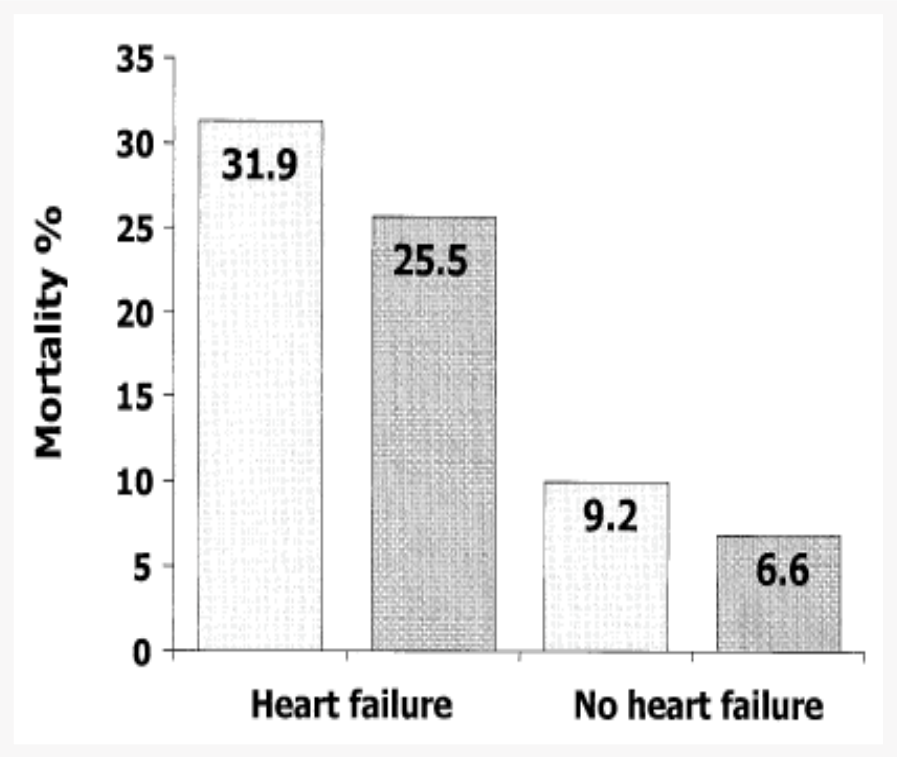
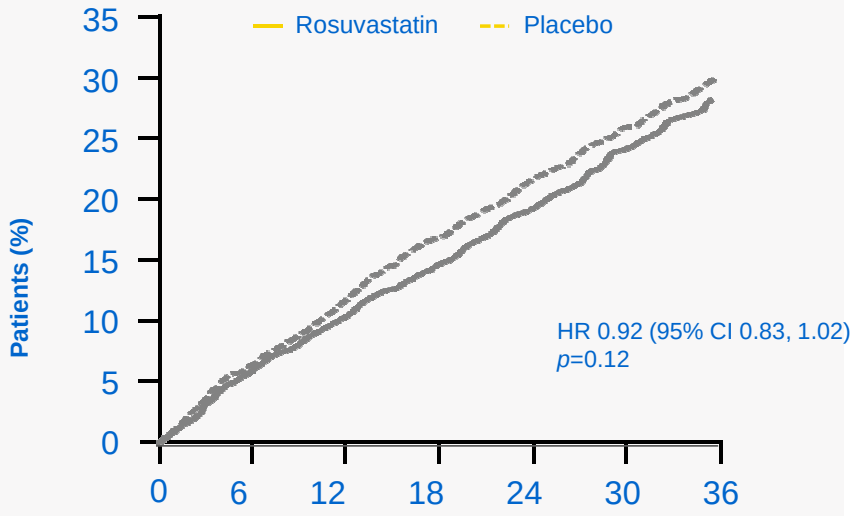


Figure: Effect of simvastatin on mortality among patients developing chronic heart failure (CHF) compared with those without clinical evidence of CHF in the Scandinavian Simvastatin Survival Study trial (1). White bar = placebo; shaded bar = simvastatin.

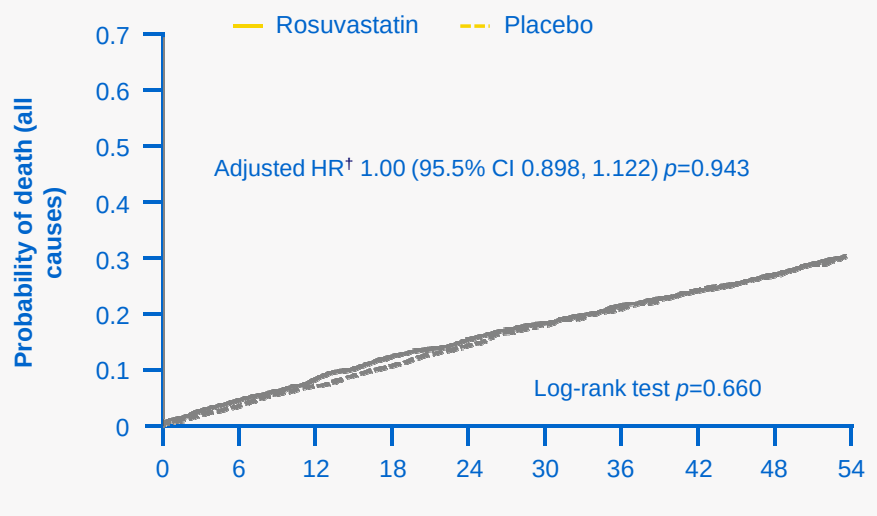
Oops…..Statins great for HF prevention not treatment

CORONA
Primary endpoint: 3P-MACE*



No. at risk							
Placebo	2497	2315	2156	2003	1851	1431	811
Rosuvastatin	2514	2345	2207	2068	1932	1484	855

GISSI-HF
Co-primary endpoint: all-cause death



No. at risk										
Placebo	2289	2202	2115	2028	1935	1848	1750	1397	1045	518
Rosuvastatin	2285	2180	2085	1987	1913	1841	1744	1436	1055	523

Courtesy SD Anker

Trial Design

- **Key inclusion criteria:** Symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
- **Key exclusion criteria:** eGFR <30 ml/min/1.73 m^2; symptomatic hypotension or SBP <95 mmHg; type 1 diabetes mellitus
- **Primary endpoint:** Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

For full details see McMurray JJV et al Eur J Heart Fail. 2019;21:665-675

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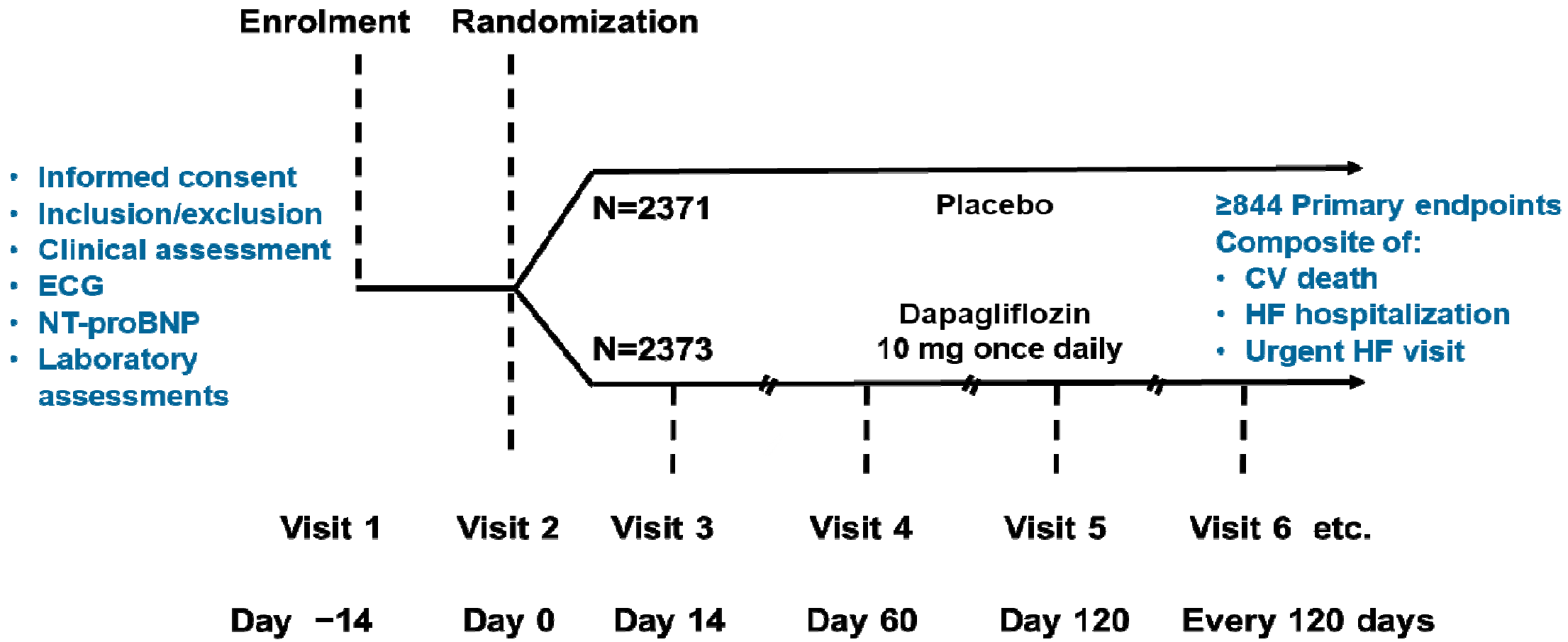
DAPA-HF Design



McMurray…Nicolau et al. NEJM Sept 19, 2019

DAPA-HF - A global trial

4,744 patients 20 countries

North America

Canada	223
USA	454

Western Europe

Denmark	99
Germany	186
Netherlands	135
Sweden	68
UK	62

Central/Eastern Europe

Bulgaria	266
Czech Rep.	210
Hungary	250
Poland	290
Slovakia	166
Russia	422

Latin America

Argentina	297
Brazil	520

Asia-Pacific

China	237
India	237
Japan	343
Taiwan	141
Vietnam	138

McMurray…Nicolau et al. NEJM Sept 19, 2019

Baseline treatment

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI+	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

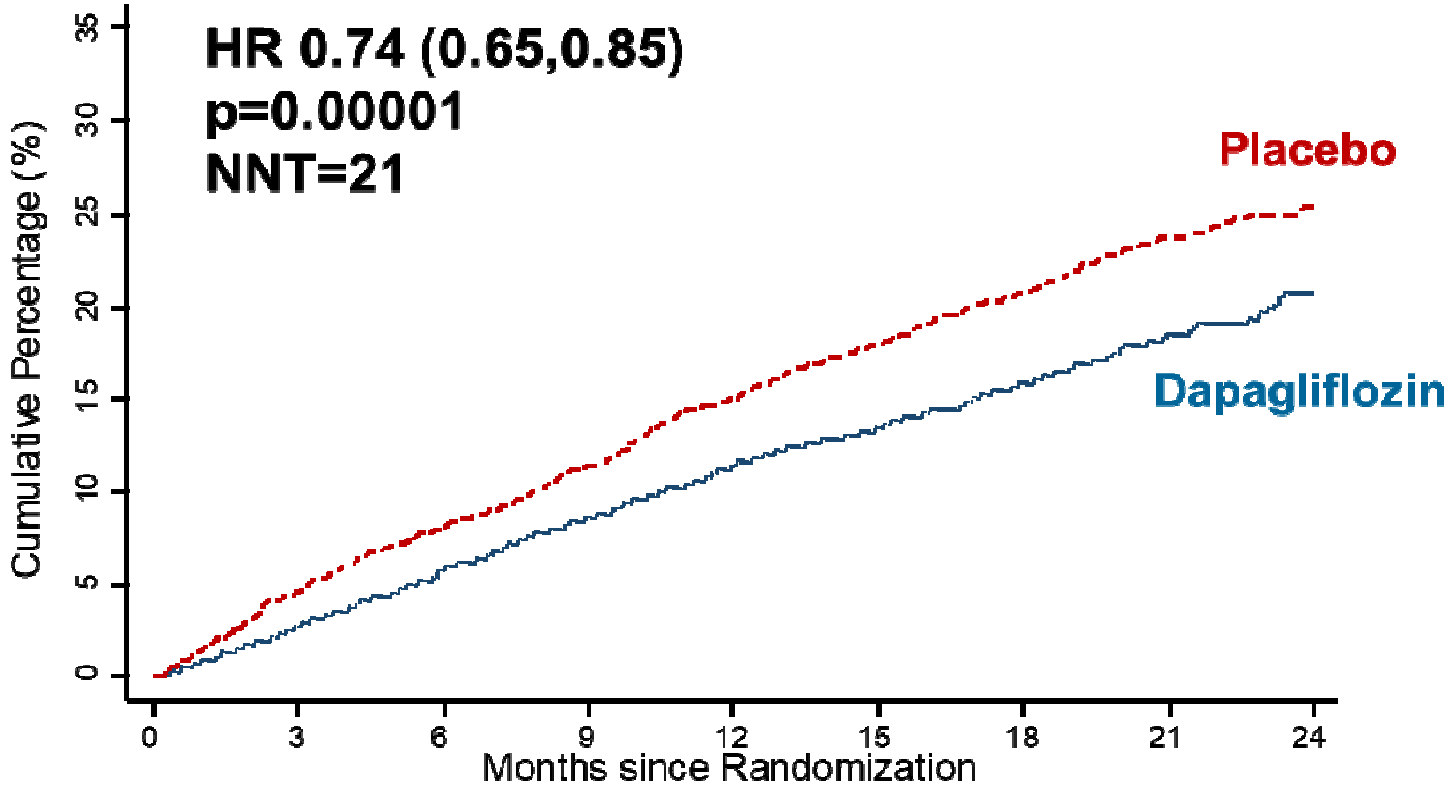
+ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

For full details see McMurray JJV et al Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548

McMurray…Nicolau et al. NEJM Sept 19, 2019

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



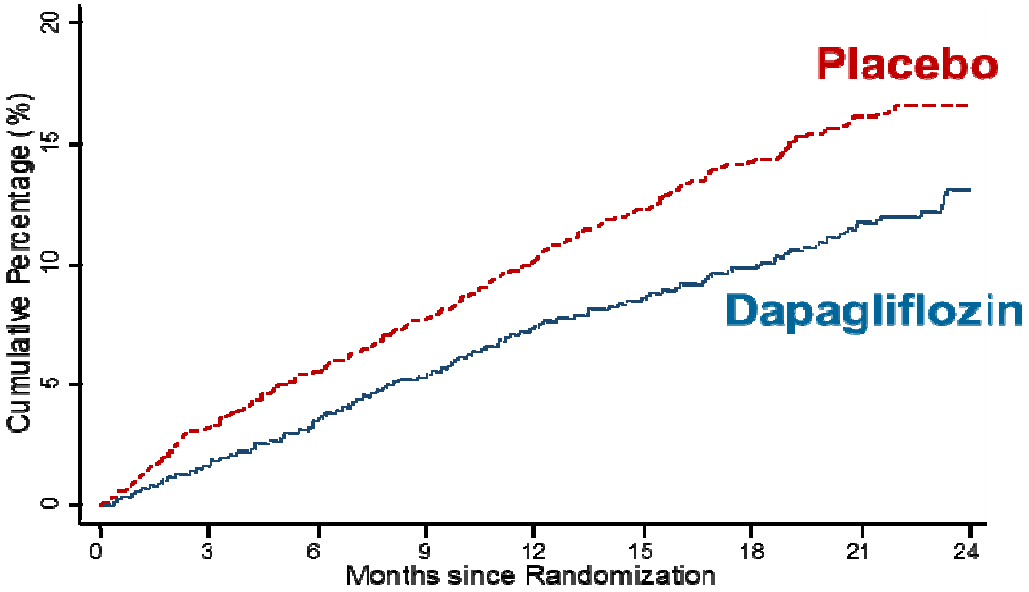
Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

McMurray…Nicolau et al. NEJM Sept 19, 2019

Components of primary outcome

Worsening HF event

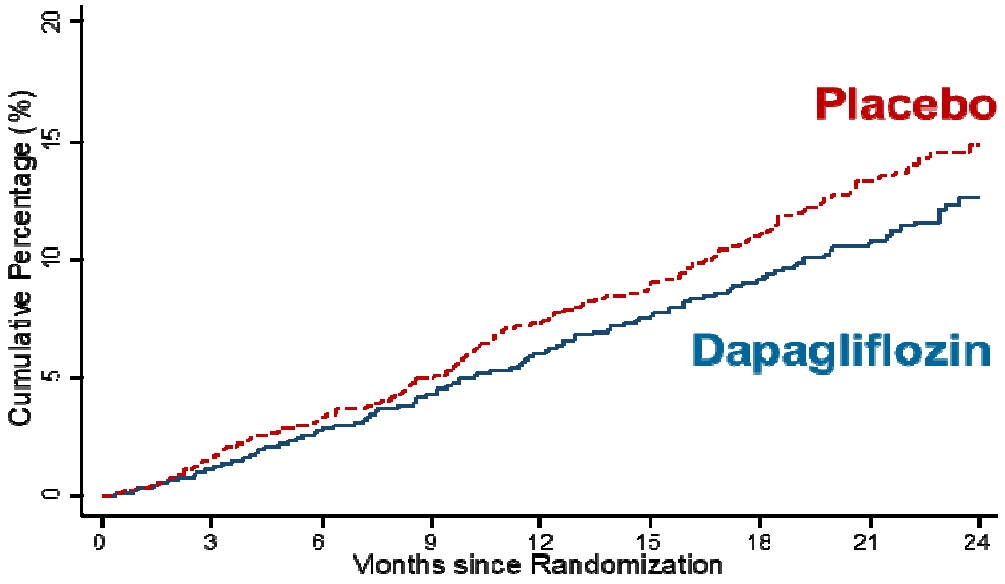
HR 0.70 (0.59, 0.83); p=0.00003



Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Cardiovascular death

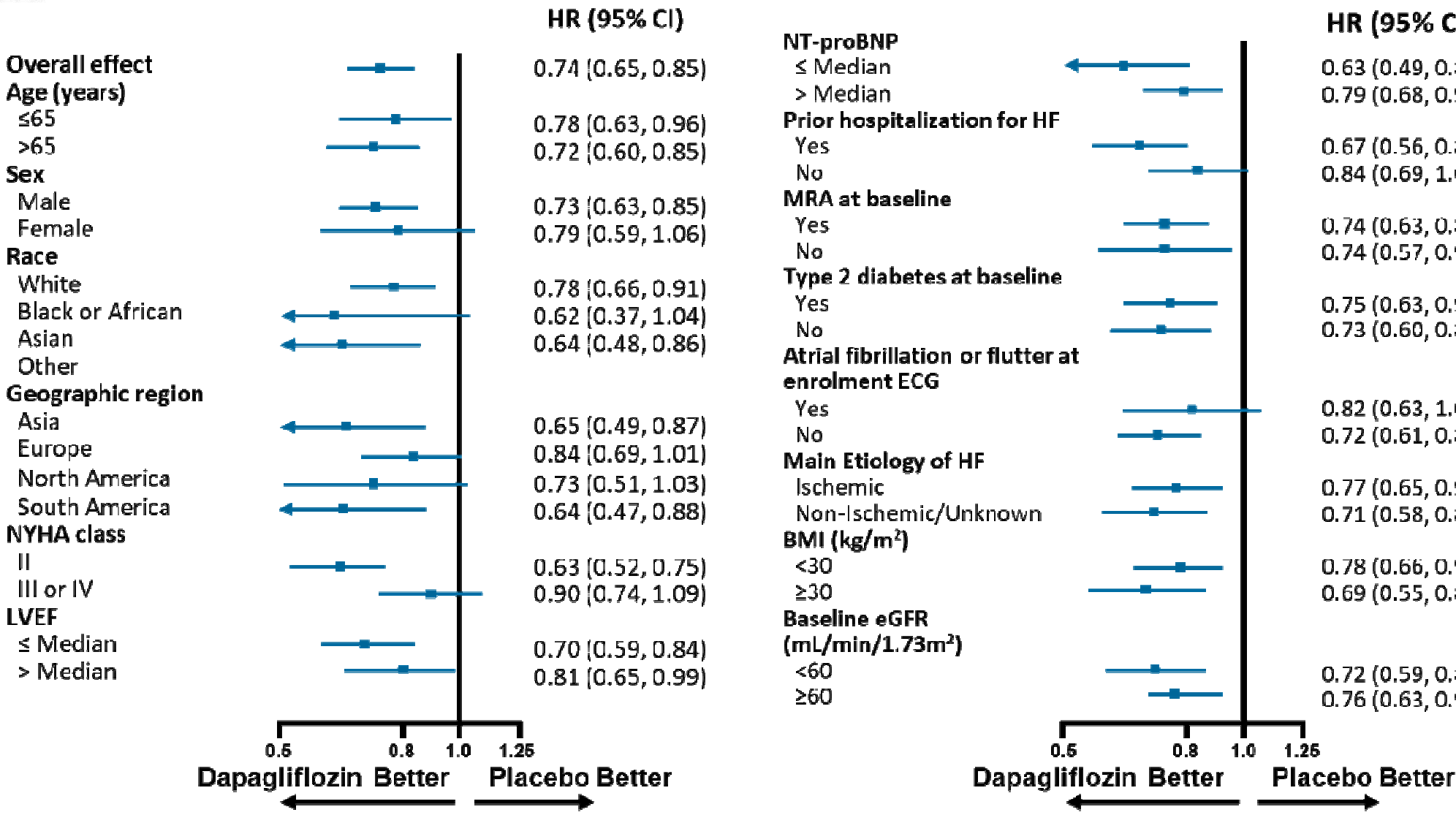
HR 0.82 (0.69, 0.98); p=0.029



	2373	2339	2293	2248	2127	1634	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

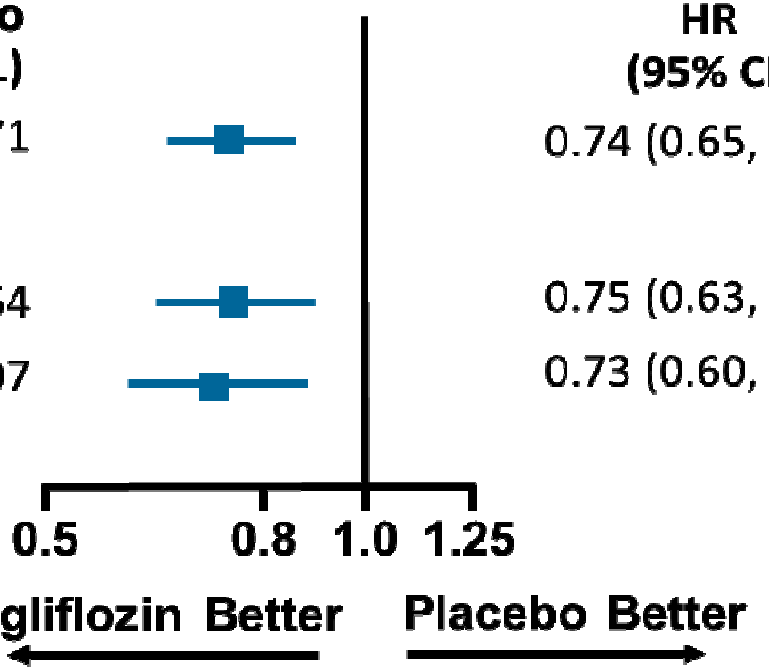
McMurray…Nicolau et al. NEJM Sept 19, 2019

Primary Endpoint: Prespecified subgroups



No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)

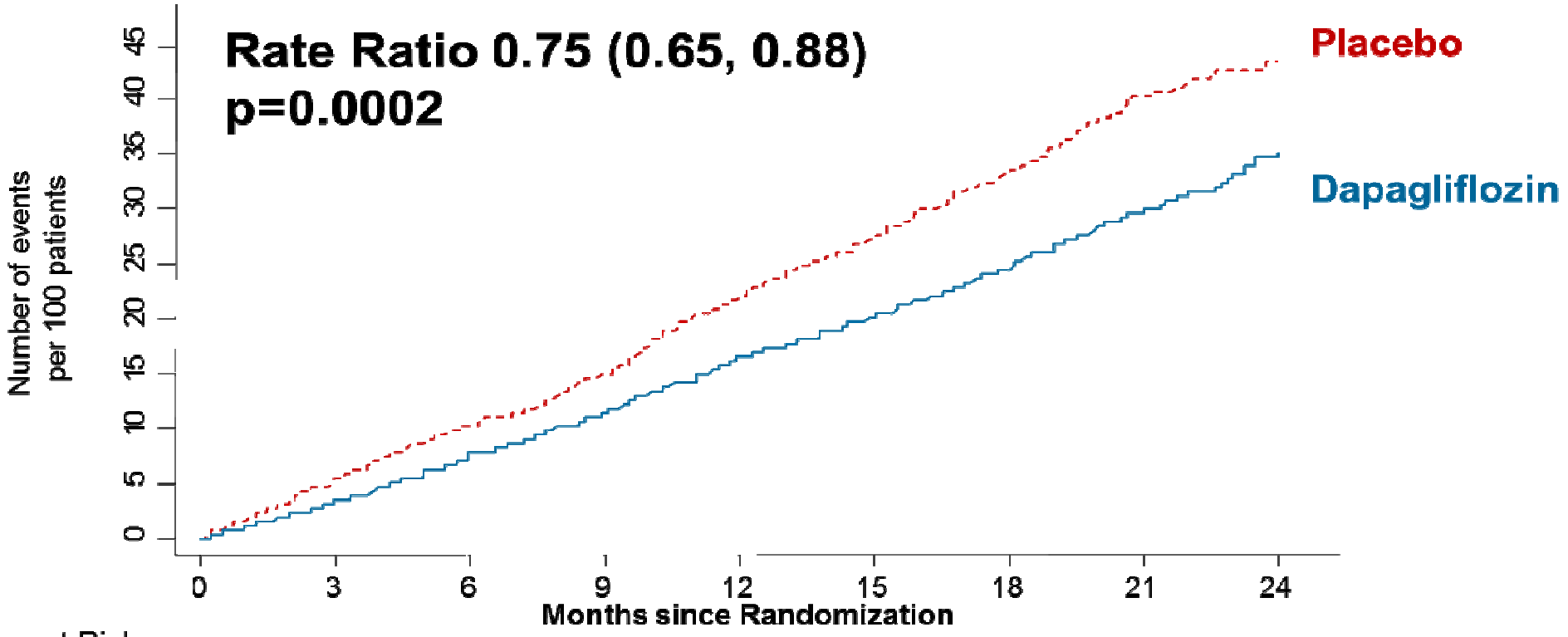


*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

McMurray…Nicolau et al. NEJM Sept 19, 2019

Total HF hospitalizations and CV death

Including first and repeat hospitalizations



Number at Risk									
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

McMurray…Nicolau et al. NEJM Sept 19, 2019

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

Treatment	Change
Dapagliflozin	**+6.1** ± 18.6
Placebo	**+3.3** ± 19.2

Difference
2.8 points (95% CI 1.6, 4.0)
p<0.001*

Increase in score indicates an improvement

*Calculated from win ratio, incorporating death. Win ratio = 1.18 (CI 1.11, 1.26). Win ratio >1 indicates superiority of dapagliflozin over placebo

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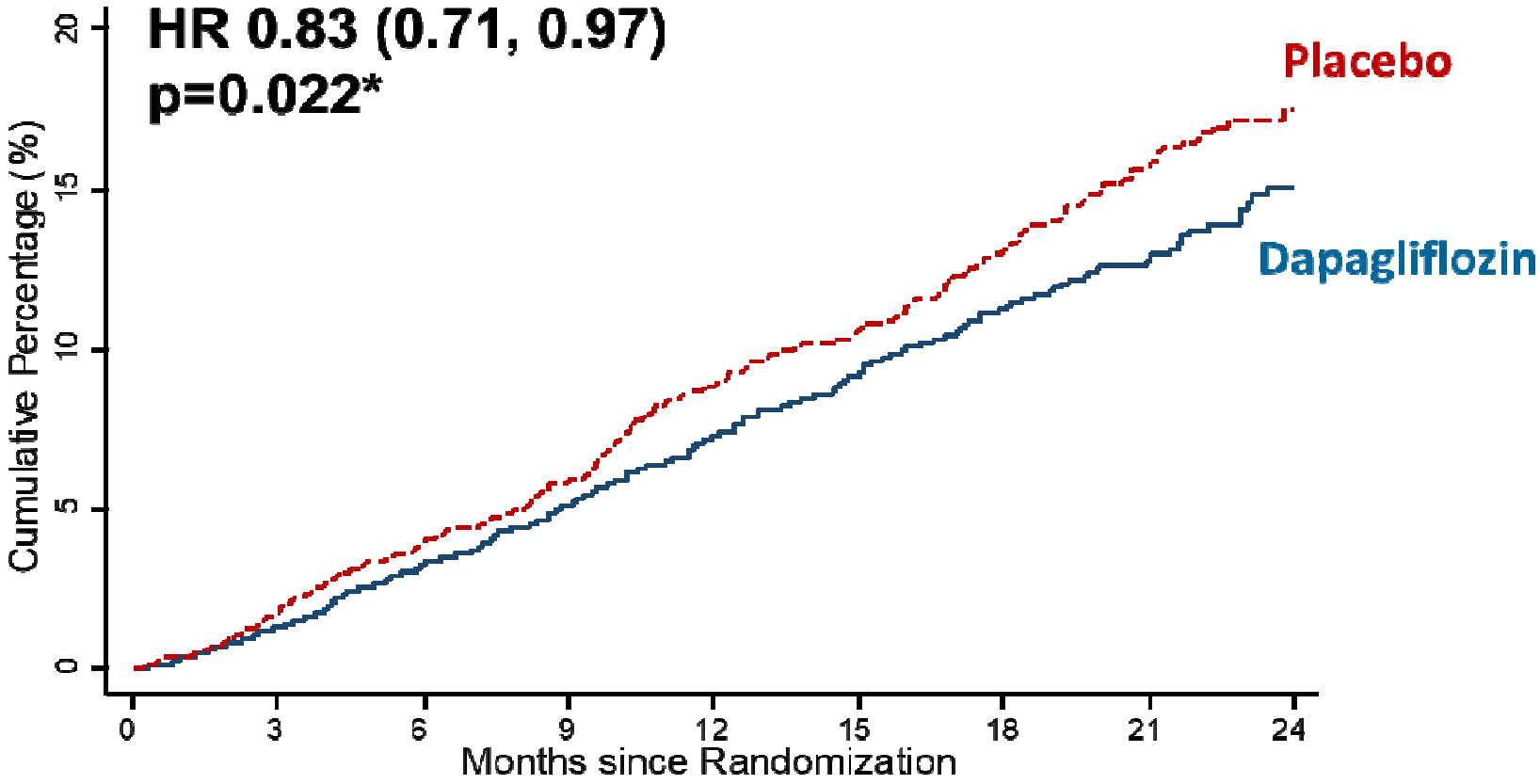
All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

McMurray…Nicolau et al. NEJM Sept 19, 2019

Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion⁺	7.5	6.8	0.40
Renal AE‡	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

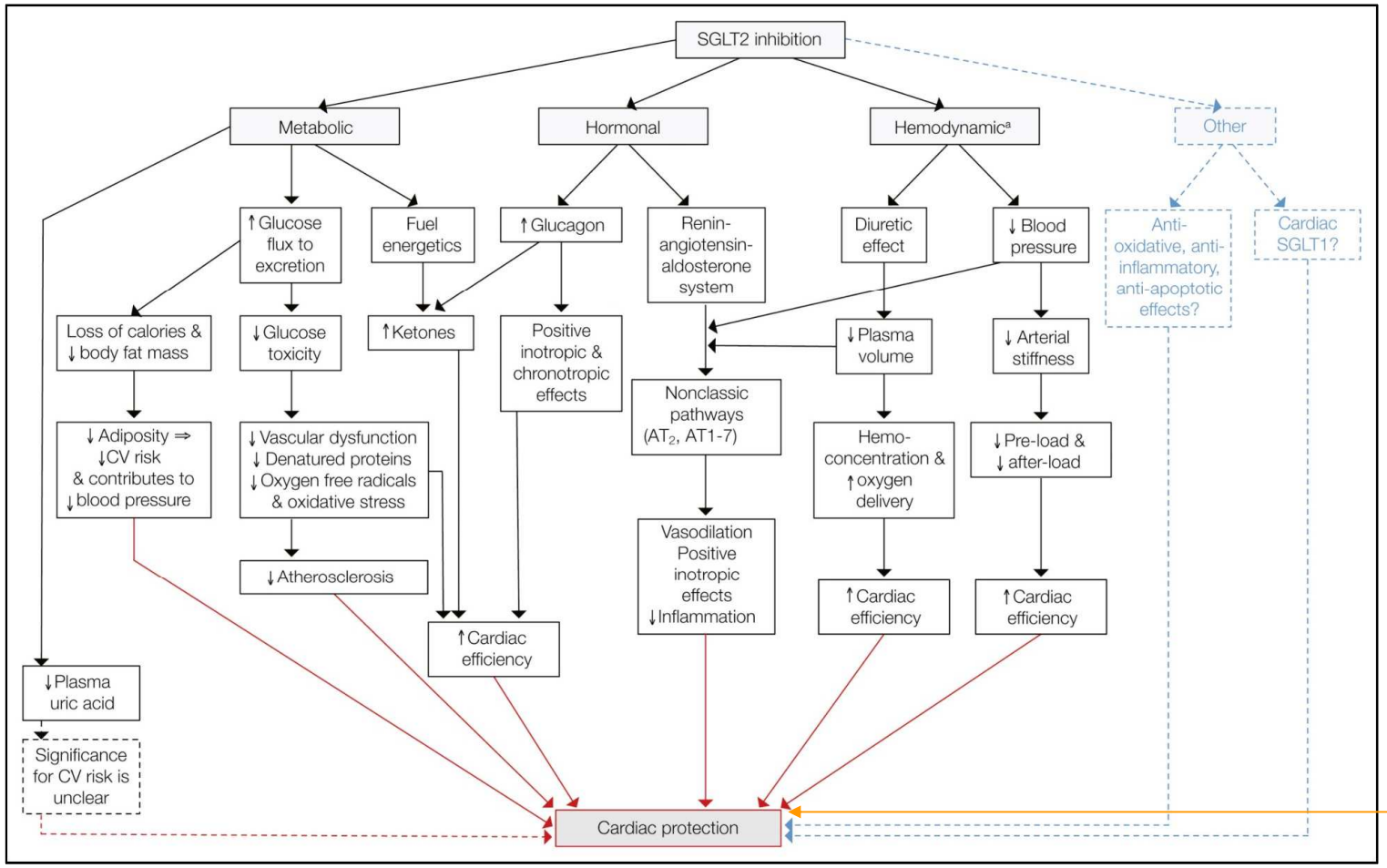
⁺Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

‡Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

McMurray…Nicolau et al. NEJM Sept 19, 2019

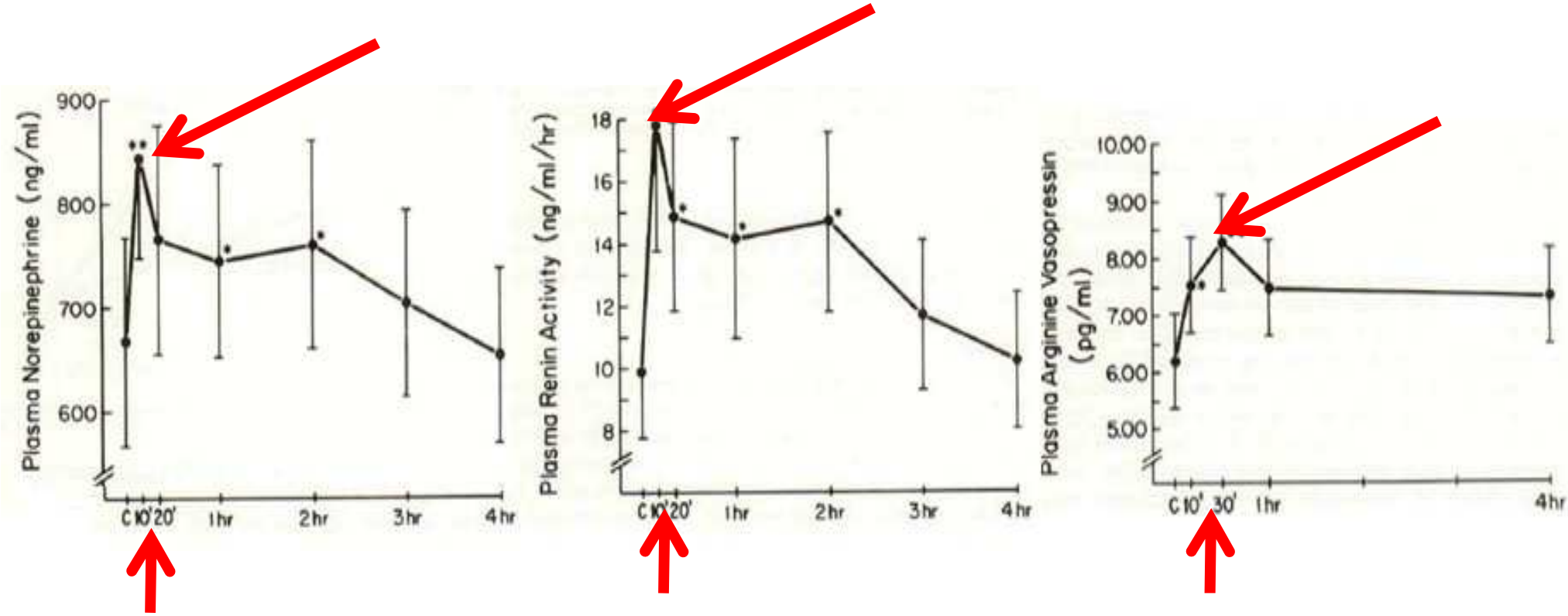
So how do SGLT-i's work?

……..nobody knows the all picture



Cardiac and renal NHE3 blockade?

Loop diuretics are particularly bad:



Francis et al, *Ann Intern Med* 1985;103:1

SGLT2-i reduces sympathetic activity

J Hypertens 2017 10. 35:2059-2068. 10.1097/HJH.0000000000001434

Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2.

Matthews, VB, Elliot, RH, Rudnicka, C, Hricova, J, Herat, L, Schlaich, MP

BACKGROUND: The sympathetic nervous system (SNS) regulates glucose metabolism in various organs including the kidneys. The sodium glucose cotransporter 2 (SGLT2) mediates glucose reabsorption in renal proximal tubules and its inhibition has been shown to improve glucose control, cardiovascular and renal outcomes. We hypothesized that SNS-induced alterations of glucose metabolism may be mediated via regulation of SGLT2. METHOD: We used human renal proximal tubule cells to investigate the effects of noradrenaline on SGLT2 regulation. Mice fed a high-fat diet were oral gavaged with dapagliflozin and the expression of noradrenaline and tyrosine hydroxylase was measured in the kidney and heart.
RESULTS: Noradrenaline treatment resulted in a pronounced increase in SGLT2 and interleukin (IL)-6 expression in HK2 cells and promoted translocation of SGLT2 to the cell surface. In vivo, dapagliflozin treatment resulted in marked glucosuria in high-fat diet-fed mice. SGLT2 inhibition significantly reduced high-fat diet-induced elevations of tyrosine hydroxylase and noradrenaline in the kidney and heart. We also aimed to assess the levels of hypertension-related cytokines in the kidneys of our mice treated with and without dapagliflozin. Excitingly, we demonstrate that SGLT2 inhibition with dapagliflozin promoted a trend towards reduced tumour necrosis factor-alpha and elevated IL-1β protein levels in the kidney.
CONCLUSION: Our in-vitro and in-vivo studies provide first evidence for an important cross-talk between the SNS and SGLT2 regulation that may not only account for SNS-induced alterations of glucose metabolism but potentially contribute to cardiovascular and renal protection observed with SGLT2 inhibitors.

SGLT2-i reduces sympathetic activity

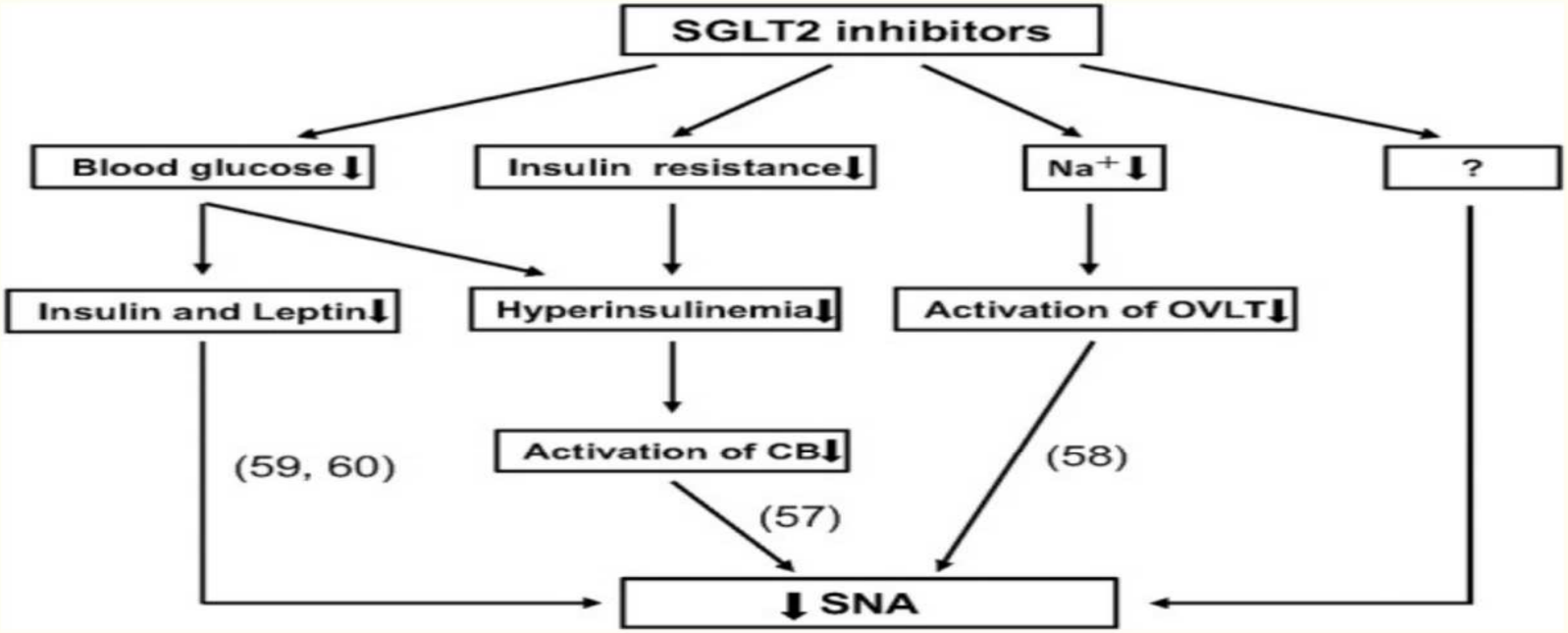


Figure 3

Possible mechanisms for reducing sympathetic nervous activity (SNA) through use of sodium-glucose cotransporter 2 (SGLT2) inhibitors. Recent studies have suggested that SGLT2 inhibitors elicit a reduction in SNA by decreasing insulin, leptin (59, 60) and blood glucose levels; and by improving insulin resistance and hyperinsulinemia, which could reduce the activation of carotid body (CB) (57); as well as by reducing sodium volume, which inhibits the activation of organum vasculosum laminae terminalis (OVLT) (58). Importantly, there are likely to be other mechanisms that have not been described.

Wan et al, Front Endorinol 2018; 10.3389/fendo.2018.00421

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