Cardiovascular benefits of antidiabetic drugs: have we reached a conclusion?

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Disclosures

One world, one epidemic

Chinatown

Disneyland

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New-Onset Diabetes in Covid-19

TO THE EDITOR: There is a bidirectional relationship between Covid-19 and diabetes. On the one hand, diabetes is associated with an increased risk of severe Covid-19. On the other hand, new-onset diabetes and severe metabolic complications of preexisting diabetes, including diabetic ketoacidosis and hyperosmolarity for which exceptionally high doses of insulin are warranted, have been observed in patients with Covid-19.[1-3] These manifestations of diabetes pose challenges in clinical management and suggest a complex pathophysiology of Covid-19–related diabetes.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19, binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, and the kidneys.[4] Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of disease.

There are also several precedents for a viral cause of ketosis-prone diabetes, including other coronaviruses that bind to ACE2 receptors.[5] Greater incidences of fasting glycemia and acute-onset diabetes have been reported among patients with SARS coronavirus 1 pneumonia than among those with non-SARS pneumonia.[5]

In the aggregate, these observations provide support for the hypothesis of a potential diabetogenic effect of Covid-19, beyond the well-recognized stress response associated with severe illness. However, whether the alterations of glucose metabolism that occur with a sudden onset in severe Covid-19 persist or remit when the infection resolves is unclear. How frequent is the phenomenon of new-onset diabetes, and is it classic type 1 or type 2 diabetes or a new type of diabetes? Do these patients remain at higher risk for diabetes or diabetic ketoacidosis? In patients with preexisting diabetes, does Covid-19 change the underlying pathophysiology and the natural history of the disease? Answering these questions in order to inform the immediate clinical care, follow-up, and monitoring of affected patients is a priority.

To address these issues, an international group of leading diabetes researchers participating in the CoviDIAB Project have established a global registry of patients with Covid-19–related diabetes (covidiab.e-dendrite.com). The goal of the registry is to establish the extent and phenotype of new-onset diabetes that is defined by hyperglycemia, confirmed Covid-19, a negative history of diabetes, and a history of a normal glycated hemoglobin level. The registry, which will be expanded to include patients with preexisting diabetes who present with severe acute metabolic disturbance, may also be used to investigate the epidemiologic features and pathogenesis of Covid-19–related diabetes and to gain clues regarding appropriate care for patients during and after the course of Covid-19. Given the very short history of human infection with SARS-CoV-2, an understanding of how Covid-19–related diabetes develops, the natural history of this disease, and appropriate management will be helpful. The study of Covid-19–related diabetes may also uncover novel mechanisms of disease.

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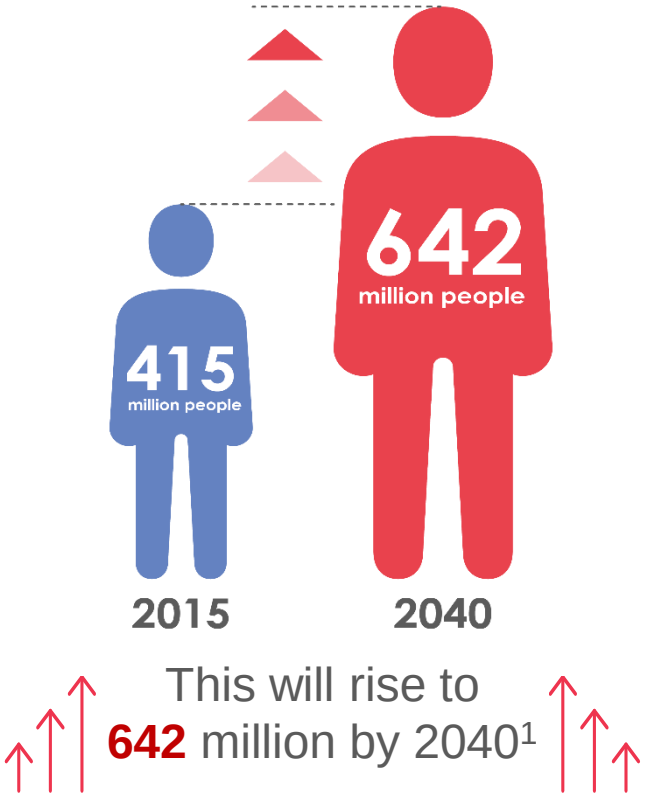
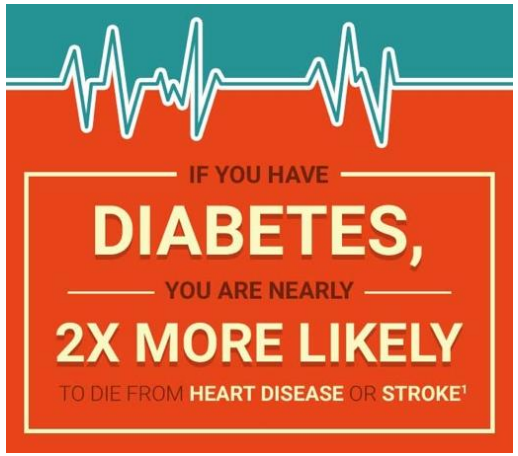
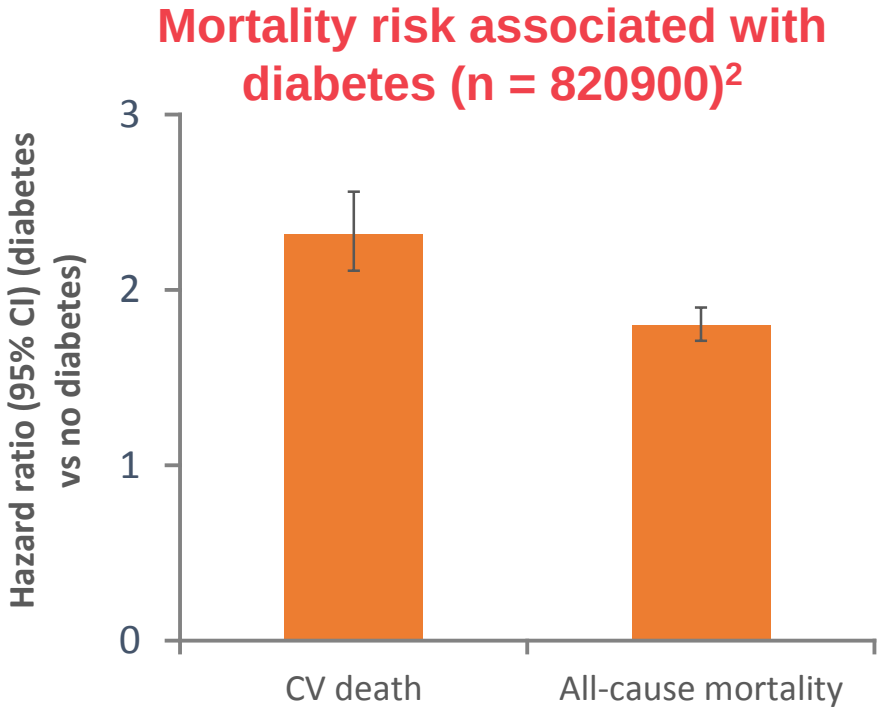
Type 2 diabetes mellitus (T2DM) is increasingly prevalent

- Globally, 415 million people are living with diabetes[1]







CV = cardiovascular

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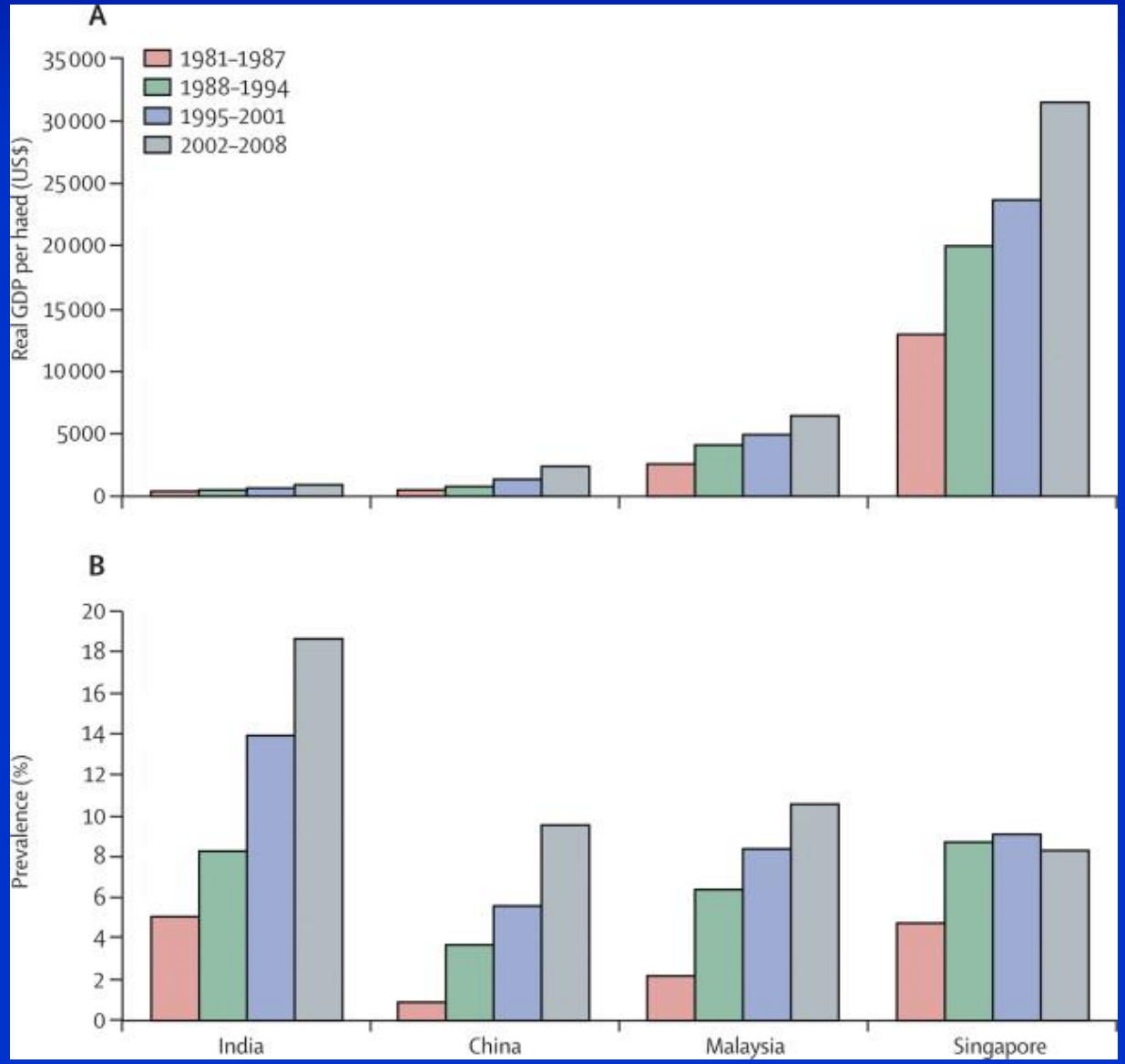
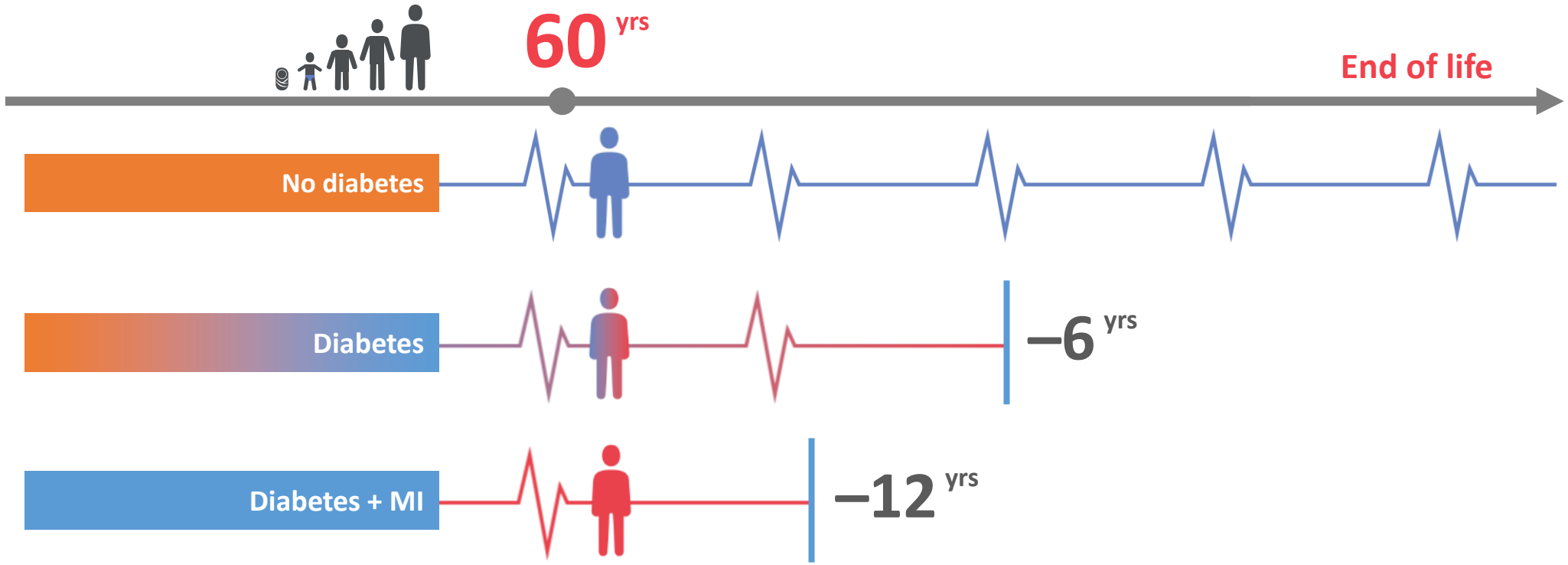
Diabetes in Asia



Lancet 2010; 375: 408-18

Reduced life expectancy

- At least 68% of people >65 years with diabetes die of heart disease



The Emerging Risk Factors Collaboration, et al. JAMA 2015;314:52

Reduced life expectancy

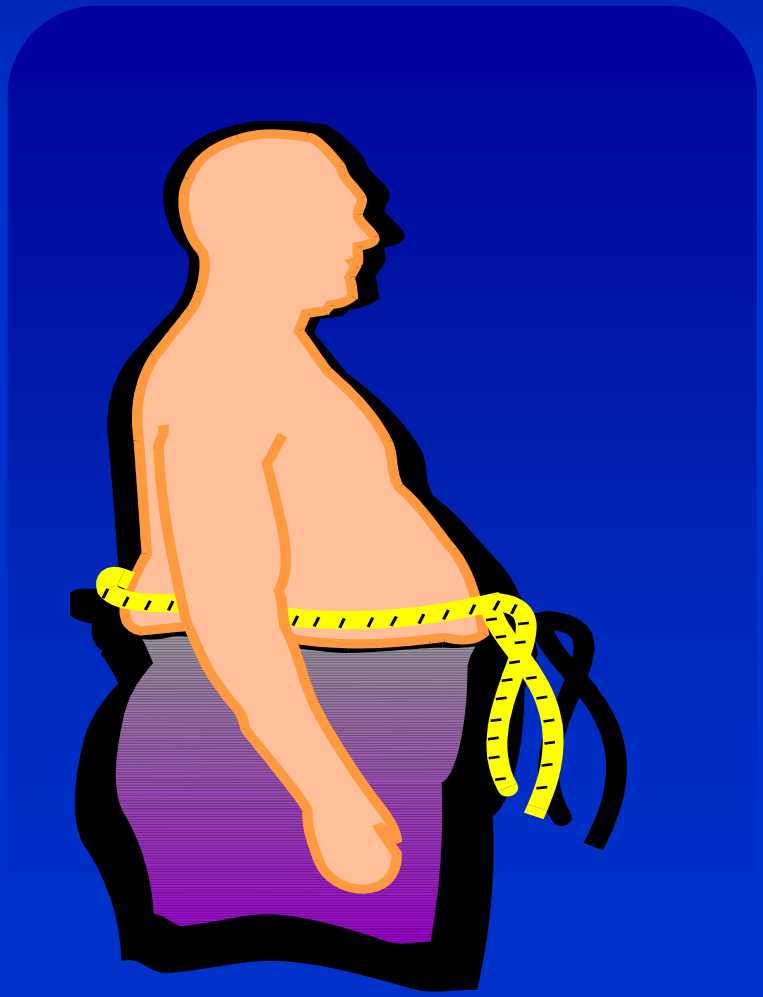
- At least 68% of people >65 years with diabetes die of heart disease[1]

We need to look beyond glycemic control

Non-pharmacological and pharmacological intervention to reduce cardiovascular risk factors

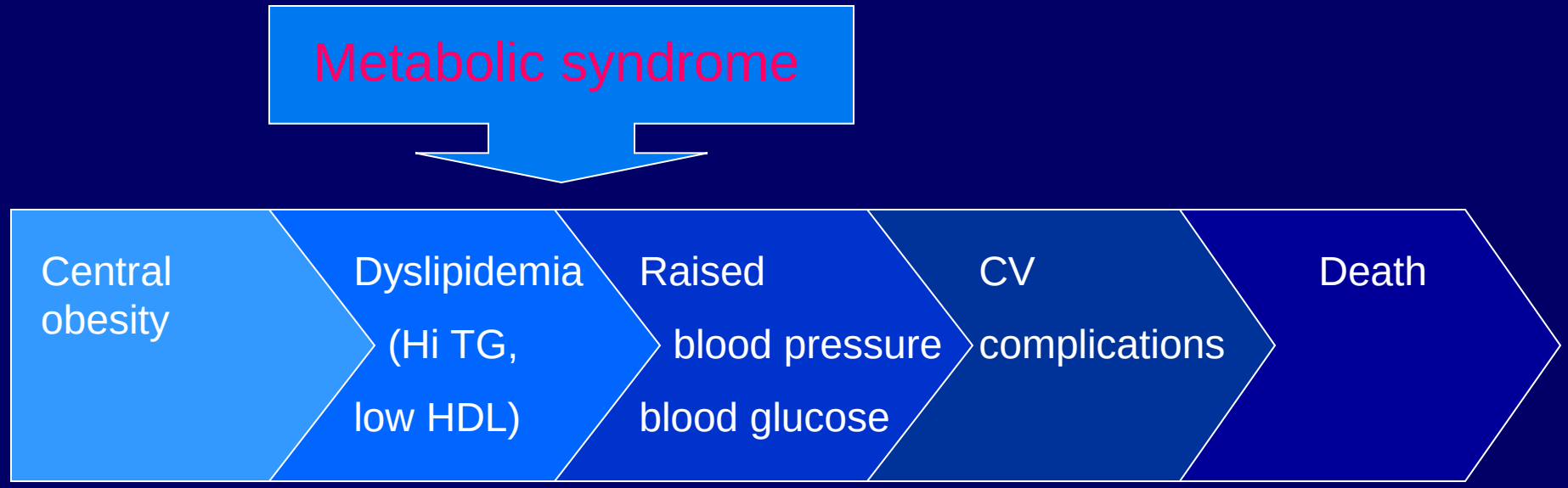
Cardiovascular effects of antidiabetic drugs

Metabolic Syndrome



- Abdominal obesity
- High blood pressure
- High fasting plasma glucose
- Hypertriglyceridemia
- Low HDL-cholesterol

The natural history of the metabolic syndrome



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Thomas et al. Clin Endocrinol 2007; 66: 666-71.

Effects of antihypertensive drugs on the risk of developing type 2 diabetes

Effect on insulin resistance	Drug
Increase	Thiazide diuretic Beta-blocker
Neutral	Calcium channel blocker
Decrease	ACE inhibitor Angiotensin receptor blocker

Antidiabetic drugs may increase cardiovascular risks[1-3]

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials

Jacob A Udell, Matthew A Cavender, Deepak L Bhatt, Saurav Chatterjee, Michael E Farkouh, Benjamin M Scirica

Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

Rodrigo M Lago, Premranjan P Singh, Richard W Nesto

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Cardiovascular safety of anti-diabetic drugs

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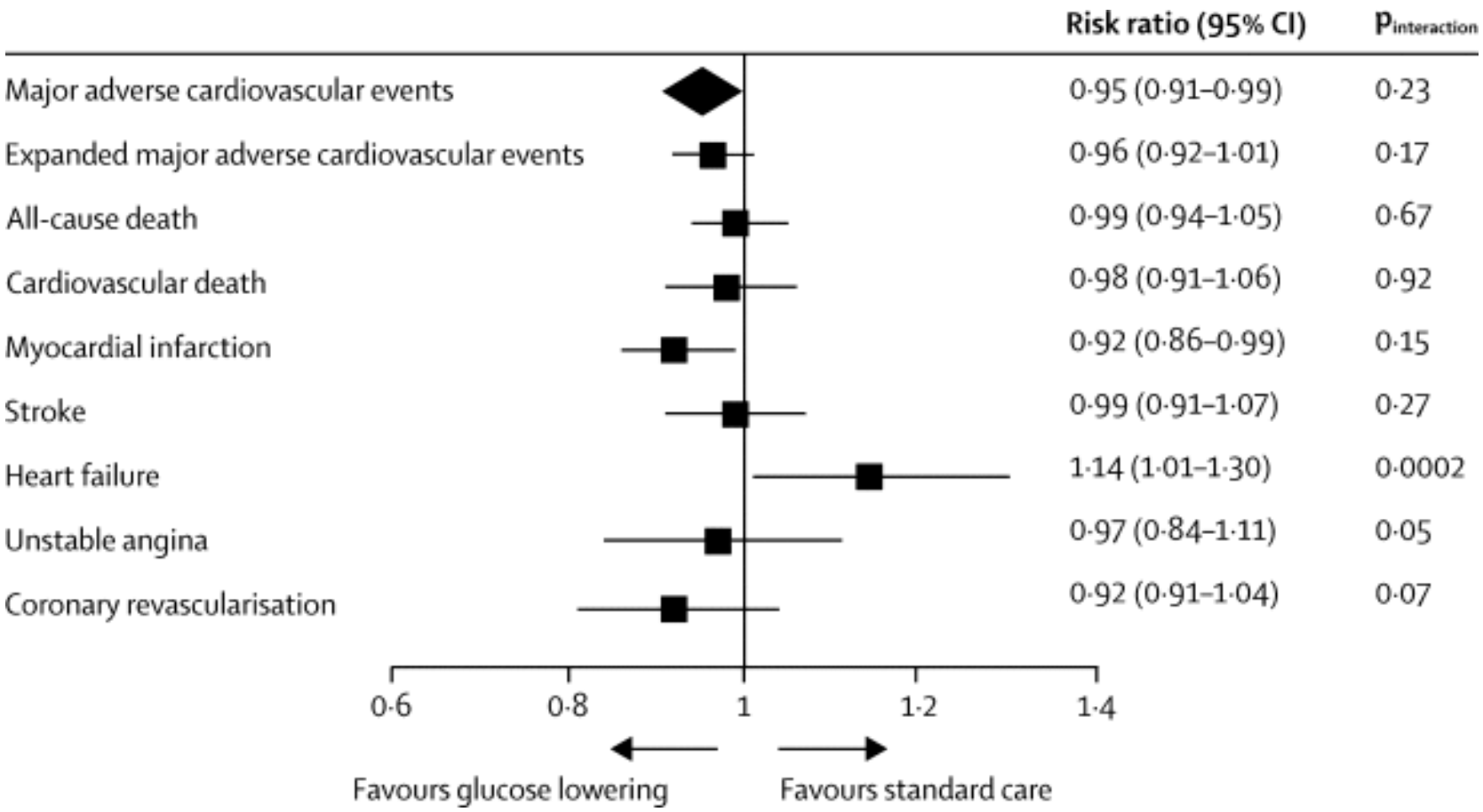

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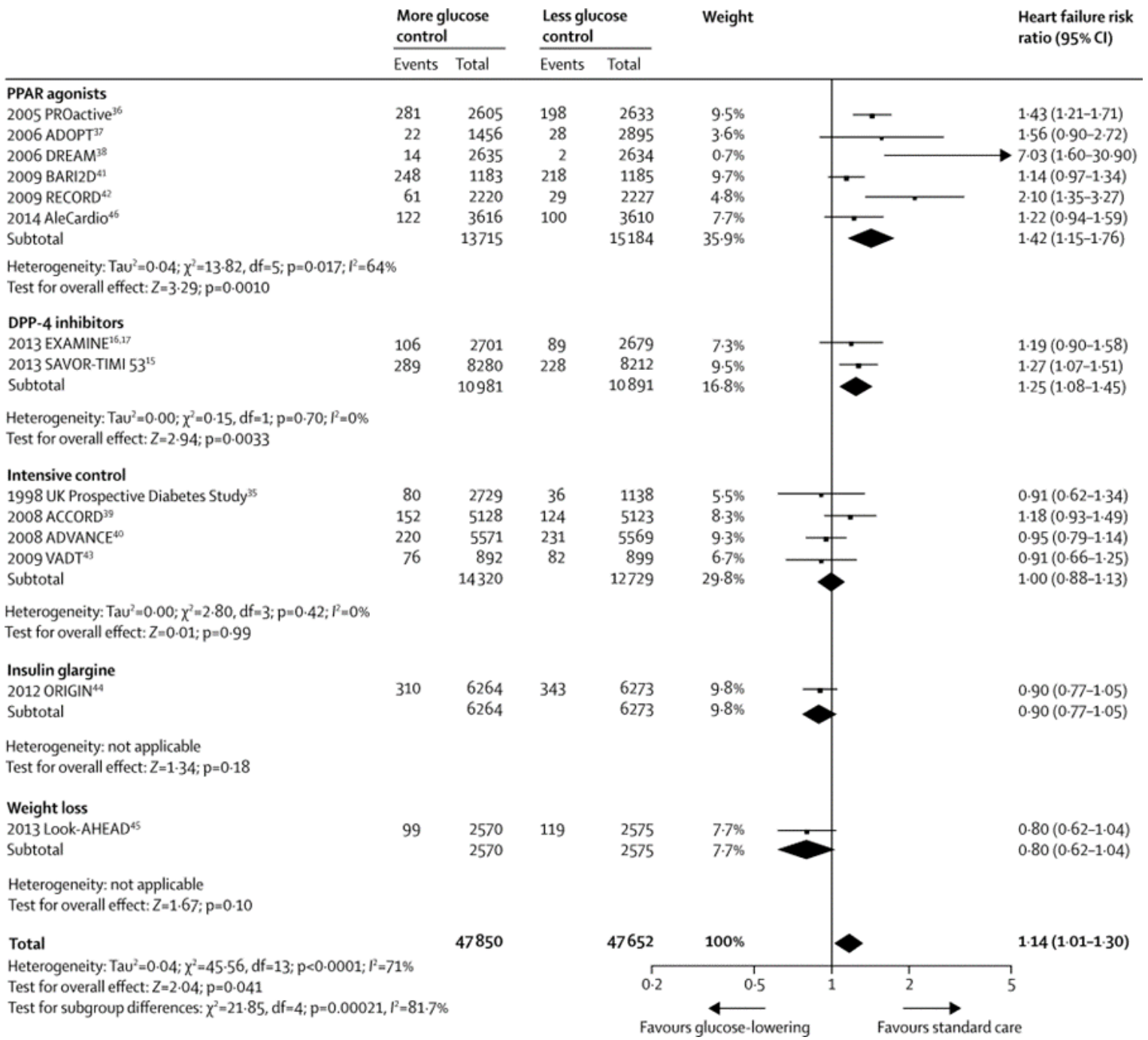

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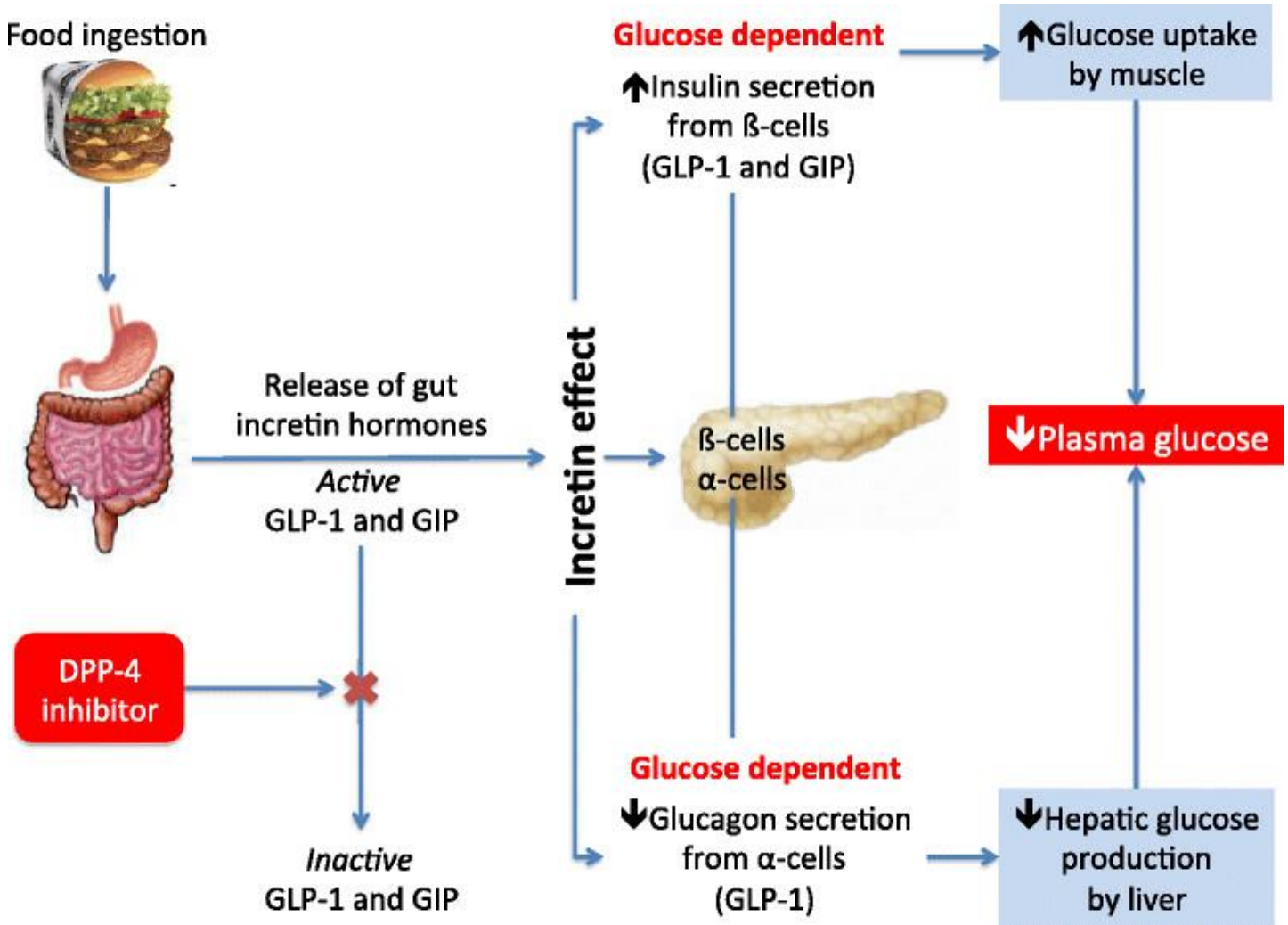

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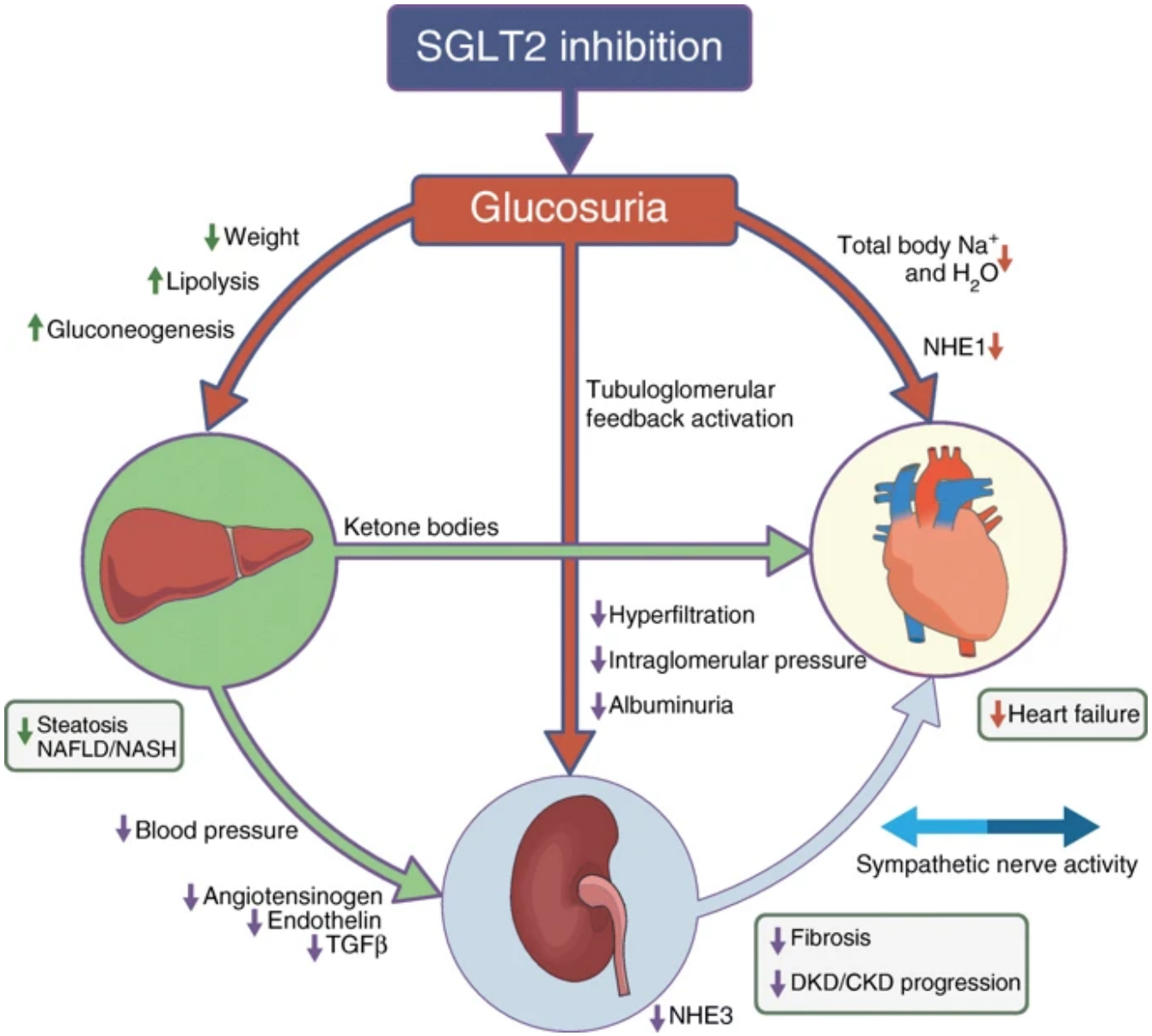
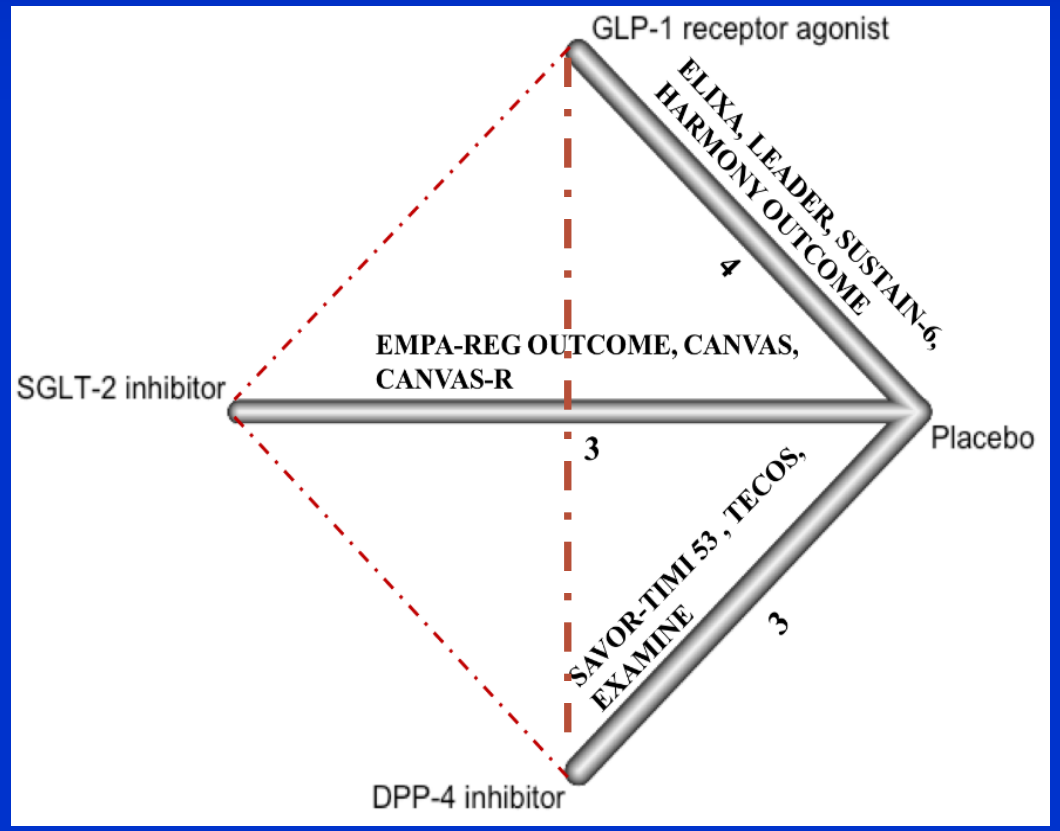


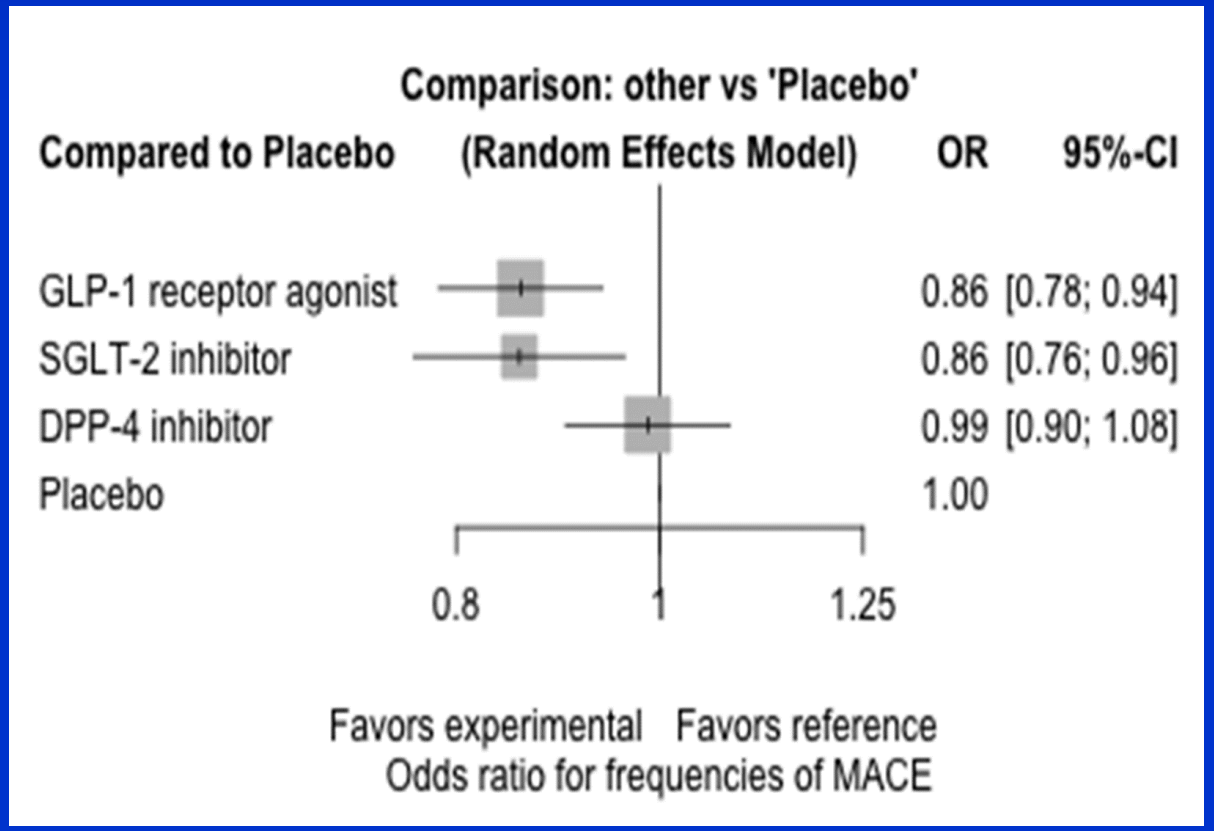
Wanner & Marx. Diabetologia 2018

Studies	Intervention (n)	Hazard ratio (95% CI) of MACE
SGLT-2 inhibitors vs. Placebo		
EMPA-REG OUTCOME 2015	Empagliflozin (4687) vs. placebo (2333)	**0.86 (0.74-0.99)**
CANVAS 2017	Canagliflozin (2888) vs. placebo (1442)	0.88 (0.75-1.03)
CANVAS-R 2017	Canagliflozin (2907) vs. placebo (2905)	0.82 (0.66-1.01)
DECLARE-TIMI 58 2018	Dapagliflozin (8582) vs. placebo (8578)	0.93 (0.84-1.03)
CREDENCE 2019	Canagliflozin (2202) vs. placebo (2199)	**0.80 (0.67-0.95)**
GLP-1 RAs vs. Placebo		
ELIXA 2015	Lixisenatide (3034) vs. placebo (3034)	1.02 (0.89-1.17)
LEADER 2016	Liraglutide (4668) vs. placebo (4672)	**0.87 (0.78-0.97)**
SUSTAIN-6 2016	Semaglutide (1648) vs. placebo (1649)	**0.74 (0.58-0.98)**
HARMONY OUTCOMES 2018	Albiglutide (4731) vs. placebo (4732)	**0.78 (0.68-0.90)**
EXSCEL 2018	Exenatide (5394) vs. placebo (5388)	0.91 (0.83-1.00)
REWIND 2019	Dulaglutide (4949) vs. placebo (4952)	**0.88 (0.79-0.99)**
PIONEER 2019	Semaglutide (1591) vs. placebo (1592)	0.79 (0.57-1.11)
DPP-4 inhibitors vs. Placebo		
SAVOR-TIMI 53 2013	Saxagliptin (8280) vs. placebo (8212)	1.00 (0.89-1.12)
EXAMINE 2015	Alogliptin (2701) vs. placebo (2679)	0.96 ($\leqq$1.16)*
TECOS 2015	Sitagliptin (7332) vs. placebo (7339)	0.99 (0.89-1.10)
CARMELINA 2018	Linagliptin (3494) vs. placebo (2485)	1.02 (0.89-1.17)

* Only upper bound of the one-sided 95% CI was reported (α=0.01)

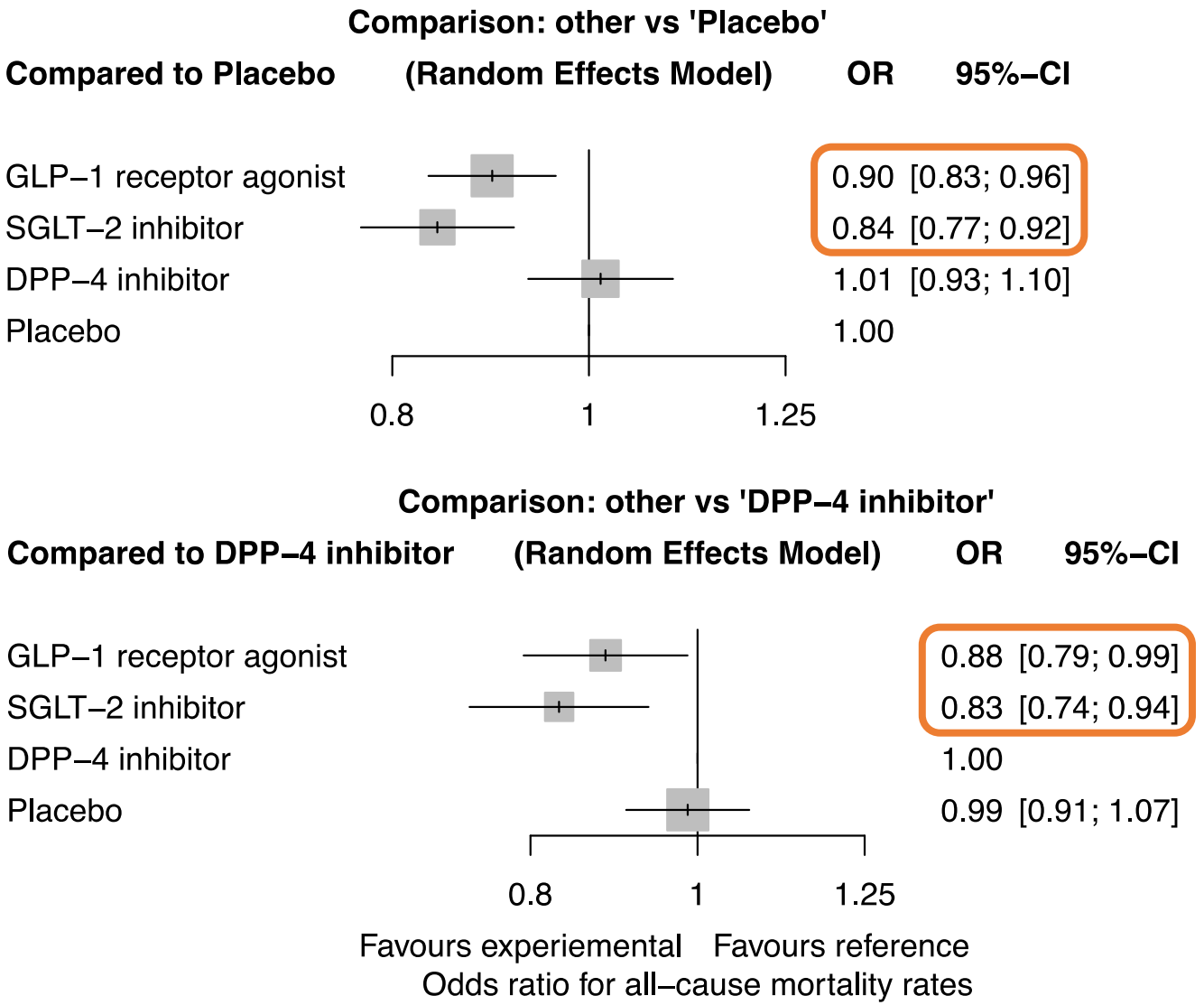
Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis



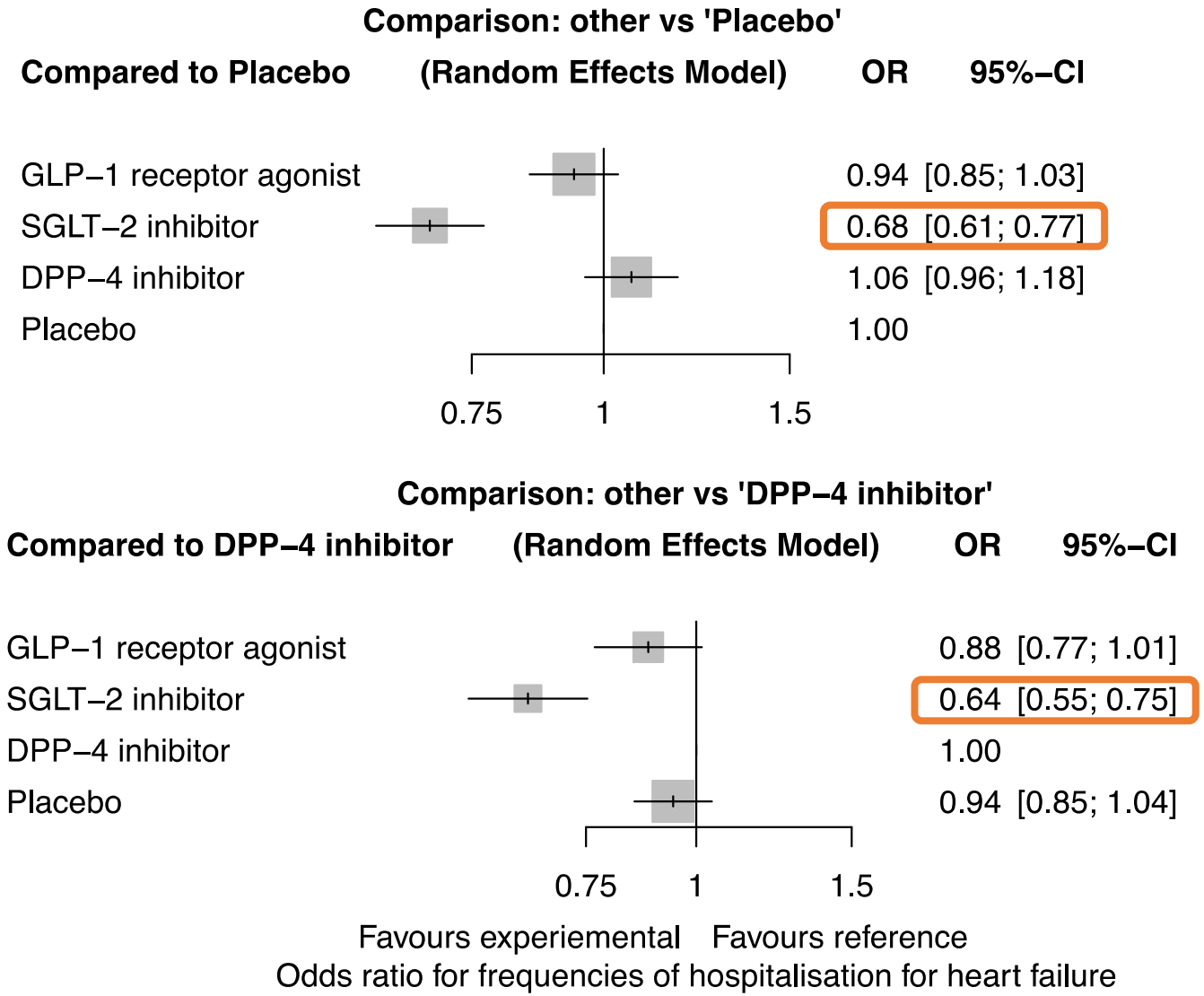


Fei Y, Tsoi MF, Kumana CR, Cheung TT, Cheung BMY. Int J Cardiol 2018
Fei Y, Tsoi MF, Cheung BMY. Cardiovasc Diabetol 2019

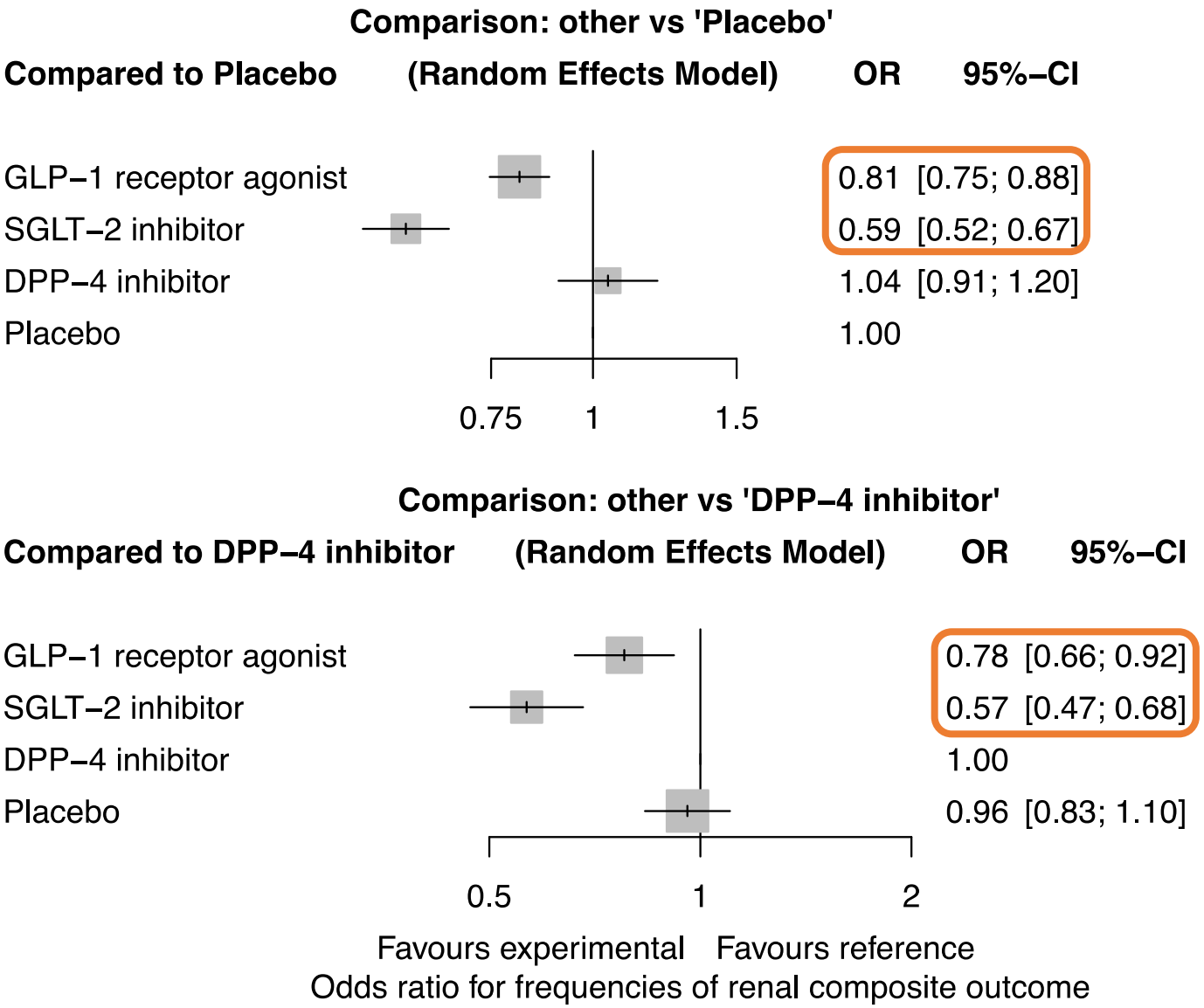
All-cause mortality in patients randomised to different classes of antidiabetic drugs



Hospitalisation for HF in patients randomised to different classes of antidiabetic drugs



Renal composite outcome in patients randomised to different classes of antidiabetic drugs



Ranking of antidiabetic drug classes

	Rank 1 (%)	Rank 2 (%)	Rank 3 (%)	Rank 4(%)
MACE				
GLP-1 RA	46.10	52.55	1.35	0.00
SGLT-2 inhibitor	**53.50**	44.85	1.60	0.05
DPP-4 inhibitor	0.40	2.50	49.40	47.70
Placebo	0.00	0.10	47.65	52.25
Nonfatal MI				
GLP-1 RA	25.85	61.50	10.25	2.40
SGLT-2 inhibitor	**72.20**	21.30	5.25	1.25
DPP-4 inhibitor	1.40	3.10	7.20	88.30
Placebo	0.55	14.10	77.30	8.05

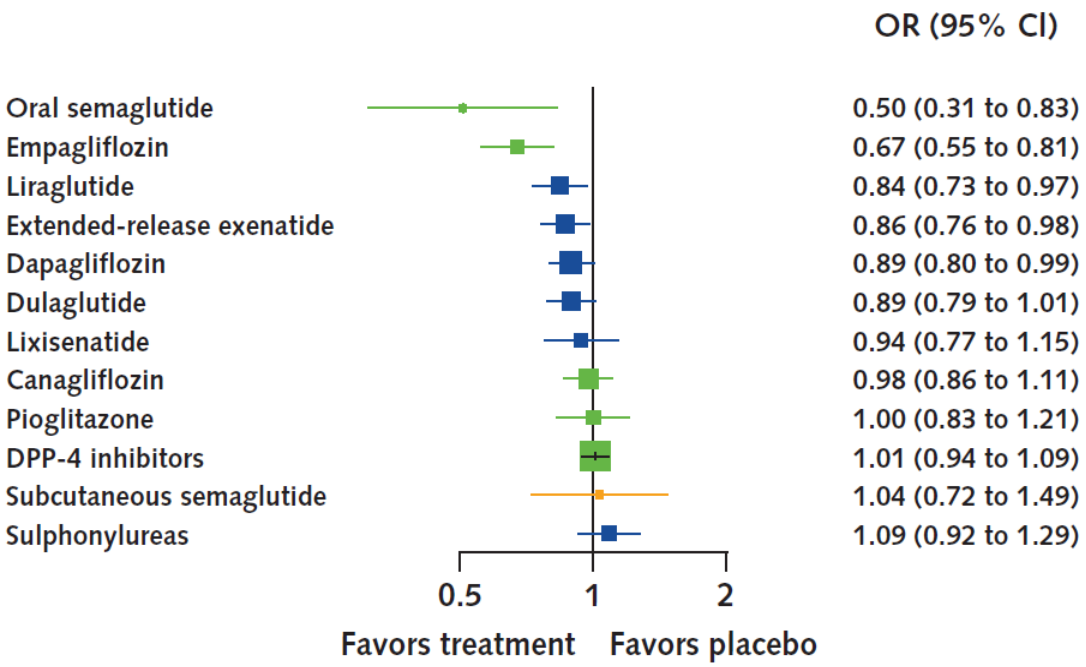
Ranking of antidiabetic drug classes

	Rank 1 (%)	Rank 2 (%)	Rank 3 (%)	Rank 4(%)
Cardiovascular mortality				
GLP-1 RA	16.50	68.80	11.65	3.05
SGLT-2 inhibitor	**81.05**	16.30	2.45	0.20
DPP-4 inhibitor	2.45	13.45	45.10	39.00
Placebo	0.00	1.45	40.80	57.75
All-cause mortality				
GLP-1 RA	16.25	79.30	3.65	0.80
SGLT-2 inhibitor	**83.30**	16.10	0.60	0.00
DPP-4 inhibitor	0.45	4.05	36.20	59.30
Placebo	0.00	0.55	59.55	39.90

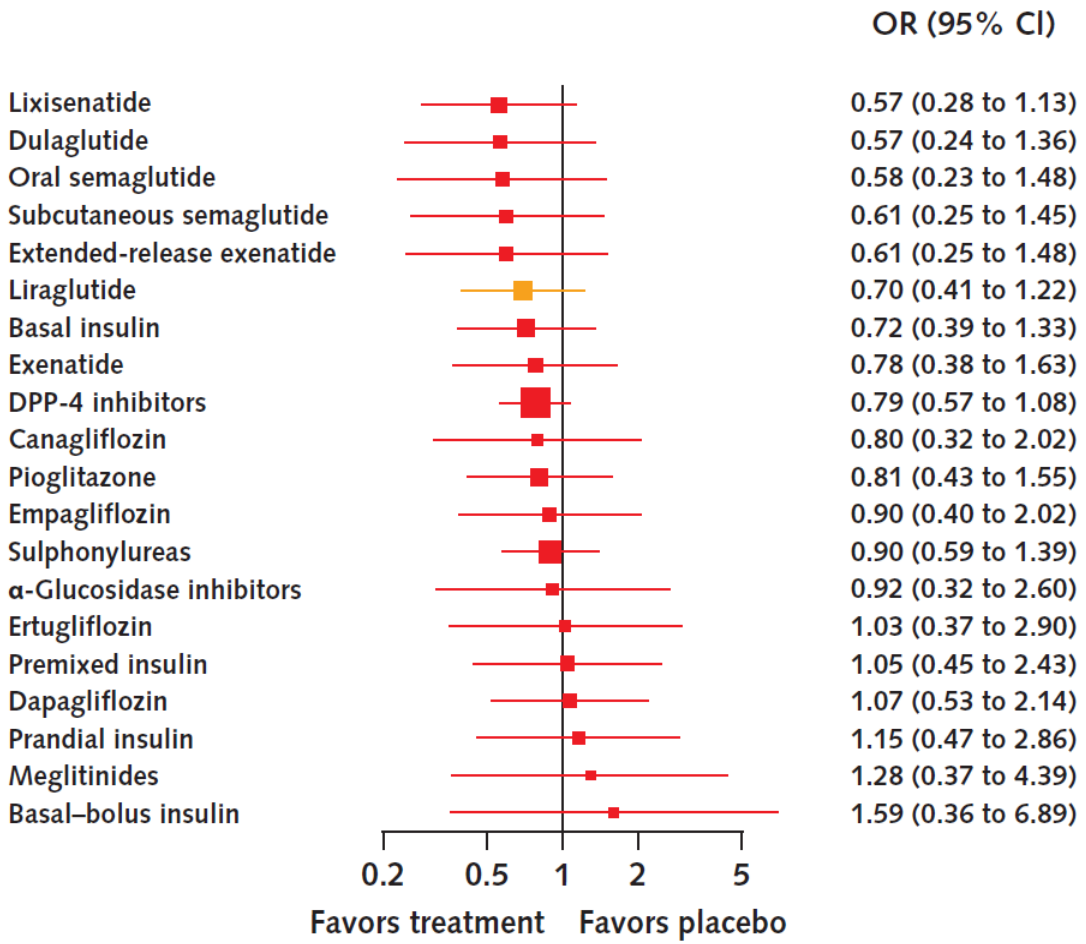
Ranking of antidiabetic drug classes

	Rank 1 (%)	Rank 2 (%)	Rank 3 (%)	Rank 4(%)
Hospitalisation for heart failure				
GLP-1 RA	0.05	77.20	15.45	7.30
SGLT-2 inhibitor	**99.95**	0.05	0.00	0.00
DPP-4 inhibitor	0.00	7.40	16.20	76.40
Placebo	0.00	15.35	68.35	16.30
Renal composite outcome				
GLP-1 RA	0.35	95.80	3.10	0.75
SGLT-2 inhibitor	**99.65**	0.35	0.00	0.00
DPP-4 inhibitor	0.00	3.20	28.35	68.45
Placebo	0.00	0.65	68.55	30.80

C. All-Cause Mortality in Patients at Increased Cardiovascular Risk Receiving Metformin-Based Background Therapy



D. All-Cause Mortality in Patients at Low Cardiovascular Risk Receiving Metformin-Based Background Therapy

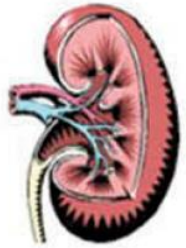


Tsapas et al. Ann Intern Med June 30, 2020

Putative mechanisms of cardiovascular and renal benefits with GLP-1 agonists and SGLTs inhibitors

GLP-1 agonists

- ■ Relaxation of vascular smooth muscle
- ■ Improvement in lipids
- ■ Increases myocardial contractility
- ■ Improved angiogenesis
- ■ Decrease platelet aggregation
- ■ Increase plaque stability
- ■ Decreased apoptosis and extracellular matrix remodeling
- ▲ Natriuresis
- ▲ Weight loss
- ▲ Decreased blood pressure
- ▲ Improved endothelial function
- ▲ Anti-inflammatory effects



SGLT2 inhibitors

- ■ Impact ion homeostasis of cardiac myocytes
- ■ Decreased insulin resistance
- ■ Decrease myocardial fibrosis
- ■ Increase in HDL cholesterol and decrease in triglycerides
- ■ Increase ketone body oxidation
- ■ Decrease epicardial fat
- ▲ Reduction in uric acid levels
- ▲ Diuresis
- ▲ Natriuresis
- ▲ Weight loss
- ▲ Decreased blood pressure
- ▲ Reduction in arterial stiffness
- ▲ Reduction in inflammation and oxidative stress
- ● Nephron remodeling
- ● Decrease albuminuria

■ Cardiovascular
▲ Both
● Renal

Munir & Davis Expert Opin Pharmacother 2018

Adverse effects of GLP-1 agonists and SGLT2 inhibitors

GLP-1 agonists	SGLT2 inhibitors
Nausea and vomiting	Urinary frequency
Risk of acute kidney injury	Genital and urinary infection
Pancreatitis	Volume depletion
Contraindicated in medullary thyroid cancer	Risk of acute kidney injury
	Euglycemic diabetic ketoacidosis

Comparison of non-insulin treatments for T2DM

	A1c reduction	Weight	CV benefits	Renal benefits	Cost
Sulfonylureas	≤ 1%	↑	no	no	low
Metformin	≤ 2%	--	possible	no	low
Pioglitazone	≤ 1.4%	↑	may worsen CHF	no	low
DPP-4 inhibitors	≤ 1%	--	may worsen CHF	no	moderate
GLP-1 agonists	≤ 2%	↓	yes	yes	high
SGLT2 inhibitors	≤ 1%	↓	yes	yes	moderate

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